

INFORMATION TO USERS

This was produced from a copy of a document sent to us for microfilming. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help you understand markings or notations which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure you of complete continuity.
2. When an image on the film is obliterated with a round black mark it is an indication that the film inspector noticed either blurred copy because of movement during exposure, or duplicate copy. Unless we meant to delete copyrighted materials that should not have been filmed, you will find a good image of the page in the adjacent frame. If copyrighted materials were deleted you will find a target note listing the pages in the adjacent frame.
3. When a map, drawing or chart, etc., is part of the material being photographed the photographer has followed a definite method in "sectioning" the material. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.
4. For any illustrations that cannot be reproduced satisfactorily by xerography, photographic prints can be purchased at additional cost and tipped into your xerographic copy. Requests can be made to our Dissertations Customer Services Department.
5. Some pages in any document may have indistinct print. In all cases we have filmed the best available copy.

University
Microfilms
International

300 N. ZEEB RD., ANN ARBOR, MI 48106

8203322

SARANAK, JUREEPAN

EFFECTS OF LESIONS AND DRUGS ON ROTATION ELICITED BY
ELECTRICAL STIMULATION OF THE RAT SUBSTANTIA NIGRA

City University of New York

PH.D. 1981

University
Microfilms
International 300 N. Zeeb Road, Ann Arbor, MI 48106

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy.
Problems encountered with this document have been identified here with a check mark ✓.

1. Glossy photographs or pages ✓
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages ✓
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Other _____

University
Microfilms
International

EFFECTS OF LESIONS AND DRUGS ON ROTATION ELICITED BY ELECTRICAL
STIMULATION OF THE RAT SUBSTANTIA NIGRA

by

JUREEPAN SARANAK

A dissertation submitted to the Graduate Faculty
in the Biomedical Sciences in partial fulfillment
of the requirements for the degree of Doctor of
Philosophy, The City University of New York.

1981

This manuscript has been read and accepted for the Graduate Faculty
in the Biomedical Sciences in satisfaction of the dissertation
requirement for the degree of Doctor of Philosophy.

June 18, 1981
date

Joseph Goldfarb
Joseph Goldfarb, Ph. D.
Chairman of Examining Committee

June 18, 1981
date

Terry A. Krulwich
Terry A. Krulwich, Ph. D.
Executive Officer

Joseph S. Eisenman
Joseph S. Eisenman, Ph. D.

Stanley D. Glick
Stanley D. Glick, Ph. D., M.D.

Thomas P. Jerussi
Thomas P. Jerussi, Ph. D.

Sherwin Wilk
Sherwin Wilk, Ph. D.

Supervisory Committee

ABSTRACT

EFFECTS OF LESIONS AND DRUGS ON ROTATION ELICITED BY ELECTRICAL
STIMULATION OF THE RAT SUBSTANTIA NIGRA

by

Jureepan Saranak

Adviser: Professor Joseph Goldfarb

Contralateral rotation evoked by electrical stimulation of the substantia nigra has generally been attributed to release of dopamine in the striatum. However, dopamine released in the substantia nigra, as well as activation of nondopaminergic nigral afferents and efferent could be involved. The present experiments were designed to identify the pathway(s) responsible for nigral-evoked rotation. The effects on nigral-evoked rotation of electrolytic lesions of the lateral hypothalamus, caudate-putamen and globus pallidus, and 6-OHDA lesions of the lateral hypothalamus, were investigated. Electrolytic lesions (2 mA DC, 15 sec) at the ipsilateral lateral hypothalamus which produced mean ipsilateral striatal dopamine depletion of 58 % partially decreased nigral-evoked rotation from 2 hours to 14 days postlesion. 6-OHDA (8 ug in 4 ul) which produced mean ipsilateral striatal dopamine depletion of 93 % significantly increased the rotation from 3 to 14 days postlesion. Neither electrolytic nor 6-OHDA lesions of the lateral hypothalamus altered rotation evoked by stimulation of the contralateral substantia nigra. The lesion effects on stimulus-induced rotation parallel those on rotation evoked by the predominantly directly acting dopamine agonist, apomorphine,

rather than those on rotation evoked by the indirect (presynaptic) action of amphetamine. The time course of reduction in the rotation by electrolytic lesions of the lateral hypothalamus and the lack of reduction by 6-OHDA lesions do not support the possibility that dopamine release in the substantia nigra mediates the rotation. Rather, they suggest that dopaminergic neurons may not be essential for nigral-evoked rotation. 6-OHDA lesions at the ipsilateral lateral hypothalamus that produced partial striatal dopamine depletion equivalent to that produced by electrolytic lesions, had no effect on nigral-evoked rotation. Furthermore, electrolytic lesions at the lateral hypothalamus produced equivalent reduction in the rotation in rats pretreated with either 6-OHDA (8 ug in 4 ul) or vehicle. Thus, the reduction of nigral-evoked rotation by electrolytic lesion of the lateral hypothalamus is due to destruction of nondopaminergic neurons.

Whereas the persistence and even enhancement of nigral-evoked rotation following 6-OHDA lesions at the lateral hypothalamus suggested that ascending dopaminergic neurons were not crucial, pharmacological data are somewhat conflicting. Haloperidol 0.5 mg/kg i.p. reduced nigral-evoked rotation by 50 %, but was equally potent in lesioned and nonlesioned rats. The tyrosine hydroxylase inhibitor, alpha-methyl-p-tyrosine, which reduces all catecholamine synthesis decreased the rotation, however, a similar effect was obtained with the dopamine-beta-hydroxylase inhibitor, sodium diethyldithiocarbamate, which depletes only norepinephrine and epinephrine. Furthermore in rats given desipramine, prior to the 6-OHDA lesions to spare the noradrenergic fibers, there was no increase in nigral-evoked rota-

tion following the lesions. However, desipramine acutely depressed rotation. Further experiments are necessary to determine whether noradrenergic pathways play a role in nigral-evoked rotation.

Large electrolytic lesions (5 mA DC, 30 sec) of the ipsilateral caudate-putamen had no immediate effect but markedly decreased nigral-evoked rotation by 3 days postlesion. In contrast, electrolytic lesions (2 mA DC, 20 sec) of the ipsilateral globus pallidus caused an immediate reduction in nigral-evoked rotation and in some rats a reversal in direction of rotation. The delayed reduction in nigral-evoked rotation by caudate-putamen lesions suggests that the primary synapses for the rotation are not in the caudate-putamen. They may be in the globus pallidus or the pallidum may contain fibers of passage critical for nigral-evoked rotation. Antidromic activation of nigral afferents from corpus striatum is suggested as a probable substrate, although orthodromic activation of nigral efferents synapsing or passing through the globus pallidus with supporting collaterals in the caudate-putamen has not been excluded.

ACKNOWLEDGEMENTS

So much effort and so much help in unforgettable way during my training and preparation of this dissertation that individual acknowledgements are difficult and insufficient to express my appreciation. However, I owe my deepest gratitude and affection to Joe Goldfarb for being very understanding advisor. His constant support, encouragement and enlightened discussion led to the completion of this work.

I am indebted to Stan Glick, who introduced me to the interesting world of rotational behavior, for his initiation and his generosity with facilities which enabled me to generate the data.

I am also indebted to Sherwin Wilk, who introduced me to GC, for his assistance in solving my problems and his willingness to answer my naive questions in neurochemistry.

My appreciation is extended to Tom Jerussi for his critical reading of this thesis, to Richard Meibach for his comments on neuroanatomy part, to Lindsay Hough for his help in programming my favorite procedure.

I also wish to thank all the previous and present members of the behavior lab. and the GC lab. for their help in my experiments.

My gratitude is extended to Department of Pharmacology and Mount Sinai for providing financial support and facilities throughout my training, most of all to Dr. Kuperman who sent me to Sinai.

Lastly, this thesis is dedicated to my parents who are always with me no matter how far away I am.

TABLE OF CONTENTS

	Page
ABSTRACT.....	iii
LIST OF TABLES.....	x
LIST OF ILLUSTRATIONS.....	xi
LIST OF ABBREVIATIONS.....	xiv
 INTRODUCTION.....	 1
Turning or circling induced by electrical stimulation of the brain.....	 4
Telencephalic stimulation.....	4
Diencephalic stimulation.....	10
Mesencephalic stimulation.....	12
Anatomy of the rat substantia nigra.....	17
Morphology.....	17
Nigral afferents.....	20
Nigral efferents.....	28
Dopaminergic projections.....	28
Nondopaminergic projections.....	32
Responses following substantia nigra stimulation.....	38
Responses of striatal neurons.....	38
Stimulus-evoked release of DA.....	42
Responses of nonstriatal neurons.....	45
Rotational behavior in rodents.....	47
Classical model.....	47
Mesolimbic dopamine and rotation.....	48
Striatonigral system and rotation.....	50
GABA and rotation.....	53
Substance P and rotation.....	58
Acetylcholine and rotation.....	59
Serotonin and rotation.....	61
Norepinephrine and rotation.....	66
Morphine, opiod peptides and rotation.....	70
Present experiments.....	72

	Page
MATERIALS AND METHODS.....	76
Surgery.....	76
Prelesion stimulus-rotation curves.....	78
Lesions.....	80
Postlesion stimulus-rotation curves.....	82
Drug preparation and administration.....	82
Dopamine assay.....	83
Histology.....	85
Statistics.....	86
RESULTS.....	87
Correlation between stimulus-induced rotation and electrode placements.....	94
Effects of electrolytic lesions of the LH on NER.....	95
Effects of 6-OHDA 8 ug at the LH on NER.....	101
Effects of DMI pretreatment and 6-OHDA lesions of the LH on NER.....	104
Effects of haloperidol on nonlesioned and lesioned rats.....	109
Effects of electrolytic lesions of the LH on rotation evoked by electrical stimulation of the contralateral SN.....	120
Effects of 6-OHDA lesions of the LH on rotation evoked by electrical stimulation of the contralateral SN.....	127
Effects of sequential 6-OHDA 4 and 1 ug at the LH on NER.....	127
Effects of sequential 6-OHDA and electrolytic lesions at the LH on NER.....	132
Effects of electrolytic lesions of the CP on NER.....	141
Effects of electrolytic lesions of the GP on NER.....	156
Rotation evoked by stimulation of the globus pallidus.....	162
Effects of ibotenic acid lesions at the CP on NER.....	165
Effects of electrolytic lesions of nuclei receiving nigral and/or mesocortical efferents on NER.....	173
Effects of AMPT and DDTC on NER.....	176

	Page
DISCUSSION.....	183
Summary and Conclusions.....	215
BIBLIOGRAPHY.....	220

LIST OF TABLES

	Page
Table I Stereotaxic coordinates.....	77
Table II Haloperidol sensitivity of nigral-evoked rotation in nonlesioned and lesioned rats.....	115
Table III Haloperidol sensitivity of nigral-evoked rotation and lateral hypothalamus-evoked rotation in nonlesioned rats.....	119

LIST OF ILLUSTRATIONS

	Page
Figure 1	Contralateral rotation evoked upon stimulation of the left SN in a rat with stimulating electrode at border between the ventral SN and the cerebral peduncle..... 89
Figure 2	Contralateral rotation evoked upon stimulation of the left SN..... 91
Figure 3	Contralateral rotation evoked upon stimulation of the left SN..... 93
Figure 4	Alteration of contralateral rotation evoked by electrical stimulation of the SN following electrolytic lesions of the LH..... 97
Figure 5	A. Location of stimulating electrode tips..... 100 B. Extent of electrolytic lesions of the LH
Figure 6	Alteration of contralateral rotation evoked by electrical stimulation of the SN following microinjection of 6-OHDA (8 ug) at the ipsilateral LH..... 103
Figure 7	Mean contralateral rotation evoked by electrical stimulation of the SN following microinjection of 6-OHDA (8 ug) at the ipsilateral LH in rats pre-treated with DMI 30 mg/kg i.p..... 106
Figure 8	Mean contralateral rotation evoked by electrical stimulation of the SN in 3 nonlesioned rats tested before and after DMI 30 mg/kg i.p..... 108
Figure 9	Effects of haloperidol on nigral-evoked rotation from 6-OHDA (8 ug) lesioned rats..... 112
Figure 10	Effects of haloperidol on nigral-evoked rotation from 3 nonlesioned rats..... 114
Figure 11	Effects of haloperidol on rotation evoked by electrical stimulation of the LH from 3 nonlesioned rats.... 118
Figure 12	Contralateral rotation evoked by electrical stimulation of the right SN following electrolytic lesions of the left LH..... 121
Figure 13	A. Extent of electrolytic lesions of the left LH..... 124 B. Location of stimulating electrode tips in the right SN

	Page
Figure 14 Contralateral rotation evoked by electrical stimulation of the right SN following 6-OHDA (8 ug) lesions at the left LH.....	126
Figure 15 Contralateral rotation evoked by electrical stimulation of the SN before and after 6-OHDA (4 ug) at the ipsilateral LH.....	129
Figure 16 Contralateral rotation evoked by electrical stimulation of the SN before and after 6-OHDA (1 ug) at the ipsilateral LH.....	131
Figure 17 Effects of ipsilateral electrolytic lesions at the LH in rats microinjected 10 to 14 days previously with 6-OHDA 8 ug.....	136
Figure 18 Effects of ipsilateral electrolytic lesions at the LH in rats microinjected 10 to 14 days previously with vehicle.....	138
Figure 19 A. Localization of stimulating electrode tips in the SN B. & C. Extent of electrolytic lesions from rats preinjected with 6-OHDA or vehicle	140
Figure 20 Contralateral rotation evoked by electrical stimulation of the SN before and after small electrolytic lesions at the center of the ipsilateral caudate-putamen.....	143
Figure 21 Alteration of rotation evoked by electrical stimulation of the SN following large electrolytic lesions of the ipsilateral caudate-putamen.....	145
Figure 22 Nigral-evoked rotation before and after sham lesion at the caudate-putamen.....	147
Figure 23 A. Location of stimulating electrode tips in the SN.. B., C. & D. Extent of electrolytic lesion at the caudate-putamen and globus pallidus	149
Figure 24 Time course of the alteration of nigral-evoked rotation following large electrolytic lesions of the ipsilateral caudate-putamen.....	153
Figure 25 A. Extent of large electrolytic lesions at the caudate-putamen..... B. Location of stimulating electrode tips	155
Figure 26 Alteration of nigral-evoked contralateral rotation following electrolytic lesions at the ipsilateral globus pallidus.....	159

	Page
Figure 27 Mean nigral-evoked rotation in 6 rats with sham lesions of the globus pallidus.....	161
Figure 28 Contralateral rotation evoked upon electrical stimulation of the globus pallidus.....	164
Figure 29 Effects of ibotenic acid (10 and 20 ug) microinjected to the ipsilateral caudate-putamen on nigral-evoked contralateral rotation.....	167
Figure 30 A representative coronal 40 u section through the caudate-putamen lesioned by ibotenic acid.....	169
Figure 31 Nigral-evoked rotation before and after intrastriatal injections of phosphate buffered saline.....	171
Figure 32 Extent of electrolytic lesions of the nucleus accumbens and the reticular formation.....	175
Figure 33 Nigral-evoked rotation before and after AMPT.....	178
Figure 34 Nigral-evoked rotation before and after DDTC.....	180
Figure 35 Nigral-evoked rotation before and after saline.....	182

LIST OF ABBREVIATIONS

ACh	Acetylcholine
AMPT	alpha-Methyl-p-tyrosine
CAT	Choline acetyltransferase
CM	Centromedian thalamic nucleus
CP	Caudate-putamen
DA	Dopamine
DC	Direct current
DOPA	3-(3,4-dihydroxyphenyl) alanine
DOPAC	3,4-dihydroxyphenyl acetic acid
5-DMT	5-methoxy-N,N-dimethyltryptamine
EOS	Ethanolamine-O-sulfate
GABA	gamma-Aminobutyric acid
GAD	GABA decarboxylase
GP	Globus pallidus
HRP	Horseradish peroxidase
5-HT	5-hydroxytryptamine
5-HTP	5-hydroxytryptophan
HVA	Homovanillic acid
i.m.	Intramuscular injection
i.p.	Intraperitoneal injection
i.v.	Intravenous injection
LH	Lateral hypothalamus
MFB	Medial forebrain bundle
NE	Norepinephrine
NER	Nigral-evoked rotation
6-OHDA	6-hydroxydopamine
PC	Pars compacta
PCPA	para-Chlorophenylalanine
PF	Parafascicular thalamic nucleus
PL	Pars lateralis
PR	Pars reticulata
s.c.	Subcutaneous injection
SN	substantia nigra
STN	Subthalamic nucleus
VM	Ventromedial thalamic nucleus
VTA	Ventral tegmental area

INTRODUCTION

The rotating rodent is one of the animal models used to investigate the functional properties of the nigrostriatal system. This animal model is based on the hypothesis that manipulations which increase the asymmetry of the dopaminergic nigrostriatal system cause rotation away from the side with more dopaminergic activity (Arbuthnott and Crow, 1971; Costall et al., 1972; Glick et al., 1976; Ungerstedt, 1971b, 1971c; Ungerstedt and Arbuthnott, 1970). Animals with unilateral 6-OHDA lesions of the nigrostriatal pathway are commonly used to screen and differentiate directly and indirectly acting dopamine (DA) agonists. Amphetamine and other indirectly acting DA agonists cause rotation ipsilateral to the lesion (the release of DA is greater on the intact side) (Christie and Crow, 1971; Ungerstedt, 1971b; Von Voigtlander and Moore, 1973), while apomorphine and other directly acting DA agonists cause contralateral rotation if sufficient time is allowed for development of postsynaptic denervation supersensitivity (Ungerstedt, 1971c). Striatal asymmetries are also inherent in normal non-lesioned rats. Left and right striatal dopamine levels in individual naive rats differ by 10 to 15 percent and spontaneous as well as amphetamine-induced rotation is consistently away from the side with the higher DA content (Glick et al., 1974; Jerussi and Glick, 1974, 1976).

Another way to asymmetrically activate the nigrostriatal system is to unilaterally stimulate along the pathway. Unilateral electrical stimulation of the substantia nigra (SN) (Arbuthnott and Crow, 1971;

Roffman et al., 1978), the lateral hypothalamus (LH) (Arbuthnott and Ungerstedt, 1975) the medial forebrain bundle (MFB) (Barghon and Costentin, 1980) and the caudate nucleus (Zimmerberg and Glick, 1974) in rats produced contralateral rotation which was attributed to the activation of the dopaminergic synapses in the striatum. This inference was based on the assumption that the synaptic connections of the dopaminergic nigrostriatal neurons were restricted to the striatum, and on pharmacological data suggesting that the rotation was reduced by various DA receptor antagonists. However, evidence for spontaneous (Nieoullon et al., 1977b), electrically evoked (Korf et al., 1976b) and potassium evoked (Geffen et al., 1976) release of DA in the SN has been reported as has a nigral DA-sensitive adenylate cyclase (Gale et al., 1977a; Kebebian and Saavedra, 1976; Phillipson and Horn, 1976; Spano et al., 1976, 1977; Traficante et al., 1976). Furthermore, there are neurons other than dopaminergic nigrostriatal cells that are involved in rotational behavior. The striatonigral system has been shown to be essential for the expression of rotation (Garcia-Munoz et al., 1977; Marshall and Ungerstedt, 1977a, 1977b; Olanas et al., 1978b; Ungerstedt and Marshall, 1975). Dopamine-independent contralateral rotation has been reported following unilateral intranigral injection of kainic acid (DiChiara et al., 1977; Olanas et al., 1978a) or gamma-aminobutyric acid (GABA) agonists (eg. Kelly and Moore, 1978; Scheel-Krüger et al., 1977). A role of the nucleus accumbens in the motor component of rotational behavior has been proposed (Kelly and Moore, 1976, 1977; Pycock and Marsden, 1978).

The present study describes the acute and chronic effects of electrolytic and/or chemical lesions at the lateral hypothalamus, the caudate-putamen (CP), and the globus pallidus (GP) as well as the effects of drugs modifying catecholaminergic transmission on rotation induced by electrical stimulation of the SN in rats. The goal was to determine whether the rotation was due to stimulation of the dopaminergic nigrostriatal neurons, as was previously assumed, and if not to identify the pathways subserving the rotation. Rotation or head turning induced by electrical stimulation of the brain has been reported in various species and this is reviewed below. Since all experiments in the present study were done in rats, the morphology of the rat SN as well as current knowledge of nigral afferents and efferents is also reviewed, as are electrophysiological and neurochemical responses evoked by nigral stimulation. Since the bulk of data on these latter responses have been obtained in cats, results in this species are included in the review. Although the dopaminergic basis for rotation in rodents has been widely accepted and rotating rodents have been used to investigate dopaminergic drugs, many aspects of rotational behavior including the involvement of nondopaminergic pathways are still unclear and are currently subjects of active investigation. A review of possible roles of various transmitters in pathways related to rotation forms the penultimate section of the introduction. Lastly, hypotheses, rationales and results of the present experiments are briefly summarized.

TURNING OR CIRCLING INDUCED BY ELECTRICAL STIMULATION OF THE BRAIN

Turning behavior induced by unilateral electrical stimulation of the brain has been reported since the late nineteenth century. Ferrier (1873) reported that unilateral electrical stimulation of the corpus striatum in the anesthetized dog caused a strong contralateral bending of the body so that the head approached the tail. In the early twentieth century, stimulus-induced turning behavior was still studied in anesthetized animals with acute implantation of electrodes. More recently, unanesthetized animals with chronically implanted electrodes have been used for studying stimulus-induced turning or circling behavior. The direction of turning varies with species and electrode location.

Turning induced by electrical stimulation of the telencephalon

Cortical stimulation. Contralateral head turning (among other behaviors) was commonly observed following unilateral electrical stimulation of particular cortical structures. In rabbit, electrical stimulation through surface electrodes on the motor cortex yielded contralateral head turning and a simultaneous contralateral posturing (White and Himwich, 1957). No head turning or posturing was observed when the surface stimulating electrode was 6 mm. posterior to the motor cortex electrode (White and Himwich, 1957). In cats, stimulation of the medial aspects of the cortex including the retrosplenial cortex on the border between the cerebral cortex and subjacent white matter, the anterior limbic cortex, the medial prefrontal cortex, the

anterior portion of the hippocampal gyrus, and the hippocampus proper caused contralateral head turning that progressed to circling movements upon strong stimulation (Kaada et al., 1953). Head turning upon hippocampal stimulation, but not circling was confirmed by MacLean (1955, 1957). Contralateral turning was not observed with control stimulation of other cortical areas including temporal, parietal, occipital and sensorimotor regions (Kaada et al., 1953). Contralateral head turning was also reported following electrical stimulation of the cat anteromedial and basolateral amygdala (Anand and Dua, 1955; Gloor, 1960).

It was clear that cortical-induced contralateral head turning or circling behavior was not due to generalized activation of one cerebral hemisphere. Although in some studies stimulus parameters could not be set to selectively elicit turning without other motor responses, there appeared to be specific sites in the cortex where electrical stimulation led to contralateral head turning and circling.

Corpus striatum stimulation. Unilateral electrical stimulation of the caudate nucleus in cats, rats, rabbits and monkeys consistently produced turning away from the stimulated side. There have been many reports in cats that electrical stimulation of the caudate nucleus caused head and neck turning which progressed to complete contraversive circling upon increasing stimulus intensity (Buchwald and Ervin, 1957; Cools, 1973; Forman and Ward, 1957; Laursen, 1962; McLennan et al., 1964; Stevens et al., 1961). The contralateral head turning and circling appeared to be of caudate origin since stimulation of the internal capsule or the corpus callosum with the same stimulus para-

meters was ineffective (Forman and Ward, 1957; McLennan et al., 1964), (consequences of spread of stimulation from caudate to nucleus accumbens in rats is described below). Neither response was changed by removal of the ipsilateral sensorimotor cortex (Laursen, 1962; McLennan et al., 1964), but both were abolished by caudate lesion (Laursen, 1962). The contralateral limb flexion observed in some studies (Cools, 1973; Forman and Ward, 1957; Laursen, 1962) was shown to be due to activation of corticofugal fibers. It was elicited with the lowest threshold when the internal capsule was stimulated (Laursen, 1962) and it was abolished following ipsilateral lesion of either the motor area or the internal capsule (Forman and Ward, 1957; Laursen, 1962). Contralateral head turning persisted following these lesions. Chemical stimulation of the caudate nucleus in cats also induced contralateral turning. Unilateral injections of DA (10 ug), d-amphetamine (10 ug), apomorphine (0.6 ug) to the cat caudate nucleus resulted in contralateral head turning and facilitated effects of electrical stimulation (Cools, 1973). Caudate stimuli which were subthreshold in controls, caused head turning following the drugs. In contrast, unilateral intracaudate haloperidol, alpha-methyl-para-tyrosine (AMPT) or procaine resulted in ipsilateral head turning, and inhibited contralateral head turning produced by threshold electrical stimulation of caudate (Cools, 1973). Unilateral electrical stimulation of the caudate nucleus also produced contraversive circling in rabbits (White and Himwich, 1957) and monkeys (Delgado et al., 1975). Stimulation of the internal capsule, the corona radiata or the septum was ineffective (White and Himwich, 1957).

Although contralateral rotation has been reported following caudate stimulation in rats (Zimmerberg and Glick, 1974), the most commonly observed response is contralateral head turning (Barnett and Goldstein, 1975; Crossman et al., 1977; Lee et al., 1980; Slater et al., 1980; Wheeler, 1980). The discrepancy could be explained by the different stimulus parameters used. Zimmerberg and Glick (1974) used trains of 5 msec monophasic pulses, a pulse width ten times greater than the longest of those used by other investigators. It is noteworthy that circling in cats (discussed above) was also obtained by using wide stimulus pulses [10 sec trains of 1 msec pulses at 25 to 60 Hz (Buchwald and Ervin, 1957; McLennan et al., 1964; Stevens et al., 1961)]. The lowest threshold for head turning in rats was obtained from the center of the caudate (Slater et al., 1980). Stimulation of the nucleus accumbens, cortex, internal capsule or septum using the same stimulus parameters effective in caudate stimulation did not cause head turning (Lee et al., 1980). However, when the stimulating electrode was in the ventral caudate close to the nucleus accumbens rats circled contralaterally without head turning (Slater et al., 1980). These observations are consonant with the view that in circling behavior activation of the caudate nucleus produces the asymmetry while the accumbens provides the motor component to amplify the asymmetry (Kelly and Moore, 1977; Pycock and Marsden, 1978). Ipsilateral sensorimotor cortex lesions increased the threshold but did not increase the latency of head turning upon caudate stimulation (Lee et al., 1980). Electrolytic (Lee et al., 1980; Slater et al., 1980) or kainic acid lesions (Slater et al., 1980) of the ipsilateral globus pallidus abolished contralateral head turning

evoked by caudate stimulation. Rats occasionally showed ipsilateral head turning following the pallidal lesions (Lee et al., 1980; Slater et al., 1980). Small electrolytic lesions of the ipsilateral SN increased the latency for contralateral head turning and large lesions reversed the direction (Lee et al., 1980). Microinjection of picrotoxin into the ipsilateral globus pallidus enhanced the head turning (Crossman et al., 1977; Slater et al., 1980; Wheeler, 1980). Pallidal microinjection of muscimol, a GABA-transaminase inhibitor, gamma-acetylenic GABA (Crossman et al., 1977; Slater et al., 1980; Wheeler, 1980), and systemic administration of DA agonists (L-DOPA, amantadine and apomorphine) and anticholinergic drugs (trihexyphenidyl and benztropine) (Barnett and Goldstein, 1975) reduced it. Contralateral head turning in rats following electrical stimulation of the caudate nucleus has been proposed as a model for screening putative GABA-like compounds (Crossman et al., 1977; Slater et al., 1980; Wheeler et al., 1980) and antiparkinson drugs (Barnett and Goldstein, 1975).

Most recent experiments on stimulus-induced or drug-induced rotation have been done in rodents where there is no distinct anatomical separation of caudate and putamen. There is one study, however, of electrical stimulation of the putamen in cats, demonstrating ipsilateral head turning (Hassler and Dieckmann, 1968).

Electrical stimulation of the globus pallidus-entopeduncular nucleus complex in cats has been reported to produce contraversive head turning (Buchwald and Ervin, 1957; Montanelli and Hassler, 1964; McLennan et al., 1964) and contralateral circling (Hassler, 1979; Hassler and Dieckmann, 1968; Montanelli and Hassler, 1964). The former was frequently obtained when electrodes were in the pallidum

and the latter was predominant when electrodes were in the entopeduncular nucleus (Montanelli and Hassler, 1964). Contralateral head turning following electrical stimulation of the pallidum has also been reported in rats (Slater et al., 1980) and monkeys (Delgado et al., 1975).

Consonant with the contralateral head turning or circling following unilateral activation of the globus pallidus-entopeduncular nucleus complex, unilateral electrocoagulation involving the external pallidum and internal capsule in rats or the entopeduncular nucleus in rats and cats caused immediate ipsiversive circling movements which persisted up to 21 days postlesion (Dankova et al., 1975).

Since electrical stimulation of either caudate or pallidum produced contralateral head turning and the caudate-induced contralateral head turning was abolished by electrolytic or kainic acid lesions of the ipsilateral globus pallidus, Slater et al. (1980) hypothesized that caudate-evoked contralateral head turning was relayed across synapses in the pallidum via GABAergic striatopallidal fibers. However, the enhancement of caudate-evoked contralateral head turning by intrapallidal picrotoxin and the reduction by intrapallidal muscimol or gamma-acetylenic GABA (Crossman et al., 1977; Slater et al., 1980; Wheeler, 1980) would argue against this hypothesis unless one supposes that the consequence of electrical stimulation in the caudate is to decrease the firing of caudate GABAergic efferents. Rather, the data are more consistent with the view that striatal stimulation produces head turning consequent to activation of pallidal neurons.

Turning induced by electrical stimulation of the diencephalon

Thalamic stimulation. The direction of head turning and circling following thalamic stimulation depends on the nucleus stimulated. In cats, contraversive head turning was observed following stimulation of the anterior ventral thalamus (Mussen, 1934), centromedian nucleus (Hunter and Jasper, 1949), ventral thalamic nucleus and the region between the entopeduncular nucleus and the ventral thalamus (Montanelli and Hassler, 1964). In addition, Mussen (1934) and Hunter and Jasper (1949) were also able to evoke contralateral circling. Stimulation of the ventral posterolateral nucleus, on the other hand, resulted in ipsilateral head turning (Montanelli and Hassler, 1964).

In rats, contralateral posturing has been reported following electrical stimulation of the nucleus reticularis near the internal capsule (Vierck Jr. et al., 1968). Ipsiversive posturing and rolling were obtained upon electrical stimulation of the ventral nucleus of thalamus, and a slow ipsiversive circling and running upon stimulation of the midline nuclei (Vierck Jr. et al., 1968). In rabbits, electrical stimulation of the ventromedial nucleus also caused ipsiversive circling (White and Himwich, 1957).

Hypothalamic stimulation. Unilateral electrical stimulation of the lateral hypothalamus (Christie et al., 1973), the posterior-lateral hypothalamus (Arbuthnott and Ungerstedt, 1969, 1975) or the medial forebrain bundle (Barghon and Costentin, 1980) in rats caused contralateral rotation or tight circling. Increasing stimulus intensity eventually resulted in high frequency contralateral forelimb

tremor and body roll over (Arbuthnott and Ungerstedt, 1975). The dopaminergic nigrostriatal axons course through the posterior-lateral hypothalamus and the MFB (Andén et al., 1964; Fuxe, 1965) and electrical stimulation of the nigrostriatal pathway causes release of ^3H -DA in the caudate nucleus (Von Voigtlander and Moore, 1971a, 1971b). Thus, rotation obtained by stimulation at these sites was postulated to be due to activation of the dopaminergic nigrostriatal system. This hypothesis was supported by the demonstration by Arbuthnott and Ungerstedt (1975) that the maximum rotation obtained from electrical stimulation of the posterior lateral hypothalamus was reduced by DA antagonists: haloperidol 0.5 mg/kg i.p. (90 % block at 1 hour), pimozide 1 mg/kg i.p. (75 % block at 24 hours), fluphenazine 0.5 mg/kg i.p. (50 % block at 4 hours) and tetrabenazine 5 mg/kg i.p. (75 % block at 1 hour). Barghon and Costentin (1980) also reported that MFB-evoked rotation was haloperidol sensitive, and was almost completely inhibited at 0.05 mg/kg s.c. Turning induced by submaximal LH stimulation was increased by amphetamine 0.5 mg/kg i.p. (Arbuthnott and Ungerstedt, 1975). This result is consistent with the postulation that amphetamine enhances impulse evoked release of DA (Von Voigtlander and Moore, 1973). An attempt to block rotation by 6-OHDA was, however, less successful. Injections of 6-OHDA 8 μg at the ipsilateral SN abolished LH-evoked rotation in only 4 out of 11 rats (Christie et al., 1973).

Turning induced by electrical stimulation of the mesencephalon

Mesencephalic reticular formation stimulation. Both ipsilateral and contralateral head turning or circling have been reported in cats and rats following electrical stimulation of the midbrain reticular formation. In cats, McLennan et al. (1964) reported only ipsilateral head turning and Buchwald and Ervin (1957) ipsilateral circling following stimulation of the reticular formation. Skultety (1962), however, observed ipsilateral head turning and circling upon stimulation of ventromedial midbrain reticular formation but contralateral circling when stimulating dorsal or lateral midbrain reticular formation and the periaqueductal gray. Hyde (1965) also produced contralateral head turning upon stimulation of these sites, but ipsilateral head turning upon stimulation of the zona incerta. When cats were lesioned through electrodes that yielded contralateral turning, they commenced spontaneous ipsilateral head turning or circling which lasted until 6 days after the lesions (Skultety, 1962).

In rats, the topographic distribution of the sites eliciting ipsilateral and contralateral evoked-rotation appeared the same as in cats. Stimulation of the ventromedial mesencephalic reticular formation primarily resulted in ipsiversive circling, while contralateral rotation was obtained from dorsolateral sites (Vierck Jr. et al., 1968). Cobbin and Atrens (1976) similarly showed that electrodes which produced ipsilateral rotation on stimulation were generally located in the ventromedial mesencephalon. Three of the four electrodes from which contralateral rotation was obtained were located dorsal or lateral to the ipsiversive sites. Of seven sites eliciting

ipsilateral rotation, rotation from 6 sites was sensitive to haloperidol 0.1 to 0.5 mg/kg i.p. (Cobbin and Atrens, 1976). Ipsilateral circling has also been reported in rabbits following electrical stimulation of the midbrain tegmentum (White and Himwich, 1957).

Apparent contradictory results upon electrical stimulation of the "mesencephalic reticular formation" is a good example of how confusion can result when a single anatomical name is used to describe a heterogeneous region of the brain. The reticular formation consists of numerous nerve fascicles originating, ending or passing through this region. In addition, decussation of many groups of nerve fibers including the superior cerebellar peduncle, the rubospinal fibers, the tectospinal fibers occurs at this level (Zeman and Innes, 1963). Conceivably, different directions of rotation might be due to activation of the same pathway but before or after decussation. Hassler (1979) and McLennan et al. (1964) suggested that the connection between caudate and spinal motor neurons was via a pallidal link to the contralateral reticular formation and then through the reticulospinal tracts.

Red nucleus stimulation. Stimulation of the red nucleus in cats resulted in ipsilateral flexion of the head and body and ipsilateral rotation in a small circle with pivoting on hindlegs (Mussen, 1934). Lesions of the anterior region of the red nucleus reversed the direction of curvature and rotation. In monkeys, however, contralateral head turning and contralateral circling (among other behaviours) have been reported following stimulation at the rostromedial part of the red nucleus (Delgado, 1965). The contralateral head turning and

circling were not blocked by atropine alone or by a combination of atropine, phentolamine and propranolol (Delgado, 1965). Chlorpromazine 1 mg/kg i.p., however, blocked all behaviors but head turning (Delgado, 1965). It is not clear whether this discrepancy reflects a species difference or functional differences within the red nucleus.

Substantia nigra stimulation. Rotational behavior following electrical stimulation of the SN was first reported by Mettler et al. (1939). SN stimulation caused swinging of the head away from the side stimulated and contralateral curving of the spine in cats and monkeys fixed in the stereotaxic instrument (Mettler et al., 1939). Contralateral head turning has been observed following stimulation of the lateral SN in freely moving cats and acute ipsilateral turning or circling was obtained when lesions were made at the stimulating electrodes (Skultety, 1962). York (1973) observed progressive behavioral changes when the frequency of nigral stimulation was increased: arrest movement at 1 - 5 Hz, contralateral head turning at 5 - 25 Hz, and contraversive circling movements at 25 - 60 Hz. Haloperidol 1.4 mg/kg i.m. 15 hours or chlorpromazine 4 mg/kg i.p. 1 hour prior to testing completely blocked the arrest and turning responses with recovery in 3 to 5 days (York, 1973).

Arbuthnott and Crow (1971), Arbuthnott et al. (1970b) and Roffman et al. (1978) reported contralateral rotation following electrical stimulation of the SN in freely moving rats. Following lesions through the stimulating electrodes, DA fluorescence in the ipsilateral striatum was reduced in comparison with that in the adjacent accumbens and methamphetamine 5 mg/kg produced ipsiversive rotation (Arbuthnott

and Crow, 1971). Roffman et al. (1978) showed that contralateral rotation was also induced by stimulation of the ventral tegmental area (VTA) in rats. Contralateral rotation induced by stimulation of the SN or the VTA was reduced by haloperidol and clozapine in a dose related manner (Roffman et al., 1978). Based on these results nigral and VTA -evoked rotation was presumed to be due to activation of the A₉ and A₁₀ neurons respectively. Ipsilateral rotation has been observed upon nigral stimulation but was not so identified by the authors. Among the 36 electrode placements in the "mesencephalic reticular formation" that yielded ipsiversive rotation in the study by Cobbin and Atrens (1976), 7 were in the caudal SN. One of the 4 sites yielding contraversive rotation was also in the caudal SN.

Raphe stimulation. In spite of many reports of spontaneous contraversive rotation induced by median raphe lesions (Costall and Naylor, 1974a; Costall et al., 1976b; Giambalvo and Snodgrass, 1978a; Hodge and Butcher, 1979; Nicolaou et al., 1979), there is only one report on rotation induced by raphe stimulation. Miliaressis and Rompré (1980) reported that electrical stimulation of the median raphe in rats induced ipsilateral rotation. However, three out of 4 electrodes from which ipsilateral rotation was obtained were at the periphery of the median raphe and the remaining one was outside the median raphe.

In conclusion, unilateral electrical stimulation of the various cortical and subcortical structures yielded head turning and/or circling behavior. In most of the studies, head turning progressed to

circling with increased stimulation. Circling without head turning has also been observed. Increasing stimulus amplitude can alter responses by increasing the number and type of neurons stimulated (both increase in effective volume of brain stimulated and recruitment of higher threshold cells and fibers); increasing pulse width can do the same, although the effective increase in volume of tissue stimulated would depend on the chronaxie curves of the neuronal elements at the fringe of the stimulated region; increasing pulse frequency would increase the rate of firing of a specific group of neurons and therefore increase temporal summation at the first and possibly subsequent synapses.

Stimulation of the motor cortex, the medial aspects of cortex, the hippocampus, the amygdala, the caudate nucleus, the globus pallidus, the lateral hypothalamus and the substantia nigra yield predominantly contralateral rotation, while stimulation of the thalamus and the mesencephalic reticular formation causes ipsilateral or contralateral rotation depending on the location of electrodes. The neuronal circuits involved have not been elucidated, and it is not known if the different sites from which rotation has been elicited form a single series circuit or are involved in multiple parallel circuits.

ANATOMY OF THE RAT SUBSTANTIA NIGRA

Morphology

The SN lies dorsal and parallel to the crus cerebri and extends the length of the midbrain. Three zones of the SN are commonly recognized: The pars compacta (PC), the pars reticulata (PR) and the pars lateralis (PL). Three types of neurons were identified in the SN (Gulley and Wood, 1971; Juraska et al., 1977). Large oval or elongated neurons (25 - 40 u) found scattered in the PR and PL give rise to non-DA nigral efferents; medium oval or multipolar neurons (15 - 20 u), the predominant type in the PC with some cells in the PR, give rise to the dopaminergic nigrostriatal fibers; small cells (8 - 12 u) are possibly interneurons in both the PC and PR.

The PC, a cell rich region in the medial and dorsal part of the SN is composed mainly of the dopaminergic nigrostriatal cell bodies (Moore and Bloom, 1978). The DA cell bodies (A_9 of Dahlström and Fuxe, 1964) form a thin compact cell layer extending from above the caudal mamillary complex to the lateral edge of the medial lemniscus (Moore and Bloom, 1978). Caudal to the mamillary complex large numbers of DA cells continuously extend to the VTA A_{10} (Dahlström and Fuxe, 1964; Moore and Bloom, 1978). The dendrites of the A_9 cells extend ventrally into the PR (Juraska et al., 1977) where they ramify extensively to form a DA-containing varicose dendritic network (Björklund and Lindvall, 1975). The A_{10} cell bodies are generally more elongated with horizontal dendrites (Moore and Bloom, 1978). The PC, in addition, contains some small non DA cells with nondirectional den-

dritic fields restricted to the PC (Gulley and Wood, 1971; Juraska et al., 1977; Moore and Bloom, 1978).

The PR, which forms the bulk of the SN, is a cell poor region adjacent to the crus cerebri. It is characterized by an extensive well organized neuropil with scattered neurons and glial elements (Gulley and Wood, 1971). The bulk of the cell bodies are large-sized nondopaminergic nigral efferents (Dray, 1979) with dendrites oriented mediolaterally (Juraska et al., 1977). There are also medium-sized cells whose dendrites course rostrocaudally and small neurons with thin dendrites and a small dendritic field (Juraska et al., 1977). Some PR cells have axon collaterals while others remain unbranched for their observable length (Juraska et al., 1977).

The PL, the phylogenetically oldest part of the SN (Dray, 1979), includes most of the lateral part of the PC and PR and contains large, medium and small cells (Juraska et al., 1977). The large- and medium-sized cells send axons dorsomedially and dendrites into the PR (Juraska et al., 1977).

There appears to be considerable overlapping of cell types within all regions of the SN. Just as the PC is not comprised solely of DA cells, the rest of the nigra is not devoid of them. DA cell bodies are also found scattered in the caudal, ventrolateral part of the PR and PL (Björklund and Lindvall, 1975; Dahlström and Fuxe, 1964; Fuxe et al., 1977; Moore and Bloom, 1978). Small-sized cells having thin dendrites and small nondirectional dendritic fields, considered to be interneurons, are found in all regions of the SN (Juraska et al., 1977). On the basis of dendritic organization, an alternative anatomical division of the SN into three layers has been suggested: the

superior layer (cellular PC), the intermediate layer (dorsomedial area of the PR) where both the PC and PR dendrites run rostrocaudally and dorsoventrally, and the peripeduncular layer where dendrites from all regions including DA dendrites run parallel to the crus cerebri (Juraska et al., 1977).

Synaptic organization

Electron microscopic studies revealed various types of synaptic boutons in the SN. The most common type, boutons with pleomorphic vesicles, are terminals of caudate-putamen cells that form symmetrical axosomatic or proximal axodendritic synapses (Bak et al., 1975; Hadju et al., 1973). The pallidonigral pathway has also been shown to make symmetrical axodendritic or, less often, axosomatic synapses in the SN (Hattori et al., 1975). The least commonly found terminals have large dense core vesicles and belong to axons from the raphe nuclei that form axodendritic synapses in both the PC and PR (Bak et al., 1975; Parizek et al., 1971). In addition, dendrodendritic (Hajdu et al., 1973; Wilson et al., 1977) or dendro-axonic (Hattori et al., 1979) synapses have been morphologically identified. It has been suggested that the DA compacta cells synapse with each other (dendrodendritic) (Wilson et al., 1977) and with terminals of striatonigral or pallidonigral neurons (dendroaxonic) (McGeer et al., 1979).

Nigral Afferents

The SN receives major inputs from the ipsilateral caudate putamen, globus pallidus, subthalamic nucleus, and raphe nuclei. Other inputs include those from the ipsilateral nucleus accumbens, cerebral motor cortex and the amygdaloid nuclear complex.

Striatonigral projection. It has been consistently shown by degeneration (Hajdu et al., 1973), anterograde transport of ^3H -leucine (Hattori et al., 1975; Nagy et al., 1978; Tulloch et al., 1978) and retrograde transport of horseradish peroxidase (HRP) (Bunney and Aghajanian, 1976c) that the striatum projects ipsilaterally to the SN. The medium-sized cells (12 -20 μ) in all parts of the striatum except the medial core project to the SN terminating primarily in the PR (Bunney and Aghajanian, 1976c; Hattori et al., 1975; Tulloch et al., 1978). Consistent with the above, retrograde transport of the intranigral ^3H -GABA labeled only the medium-sized cells in the external part of the CP (Streit et al., 1979). [Retrograde transport of HRP (Nagy et al., 1978) and electrophysiological data (Richardson et al., 1977) indicate that the central core of the CP projects to the GP.] Electron microscopy following anterograde transport of ^3H -leucine showed autoradiographic grains in boutons terminating as symmetrical synaptic contacts on nondopaminergic dendrites (Hattori et al., 1975). The striatonigral projection appears to be topographically arranged so that the dorsal part of the anterior striatum innervates the anterior and medial portion of the PR, while the ventral of the striatum innervates the more posterior SN; the tail of the

caudate projects to the lateral and dorsal parts of the SN including the PC as shown by orthograde ^3H leucine injection (Tulloch et al., 1978) and confirmed by retrograde HRP transport (Bunney and Aghajanian, 1976c; Tulloch et al., 1978).

Evidence is accumulating suggesting that the most likely transmitters for the striatonigral pathway are GABA and substance P (Brownstein et al., 1977; Fonnum et al., 1978; Gale et al., 1977c; Hong et al., 1977b; Jessell et al., 1978; Kanazawa et al., 1977; Mroz et al., 1977; Nagy et al., 1978; Staines et al., 1980). Substance P containing cell bodies tend to be located more anteriorly in caudate, the GABA containing striatonigral cell bodies are located mainly at the body of the caudate rostromedial to the GP (Brownstein et al., 1977; Gale et al., 1977; Jessell et al., 1978; Nagy and Fibiger, 1980; Porceddu et al., 1980; Staines et al., 1980). Descending projections from the substance P cell bodies innervate both the PC and PR (Brownstein et al., 1977; Jessell et al., 1978). GABA cell bodies from the anterior CP innervate only the PR while the GABA cell bodies from the posterior CP project to both the PC and PR (Jessell et al., 1978). The CP projections to the pallidum also contain GABA (Fonnum et al., 1978; Nagy et al., 1978) and substance P (Staines et al., 1980). Some striatonigral neurons may send collaterals to pallidum (Preston et al., 1980).

Electrical stimulation of the ipsilateral CP inhibited spontaneous firing of neurons in the ipsilateral SN, the inhibitions were antagonized by iontophoresis of picrotoxin (Crossman et al., 1973) or bicuculline (Dray and Gonye, 1975). A reciprocal relationship between striatonigral GABA and nigrostriatal DA has been demonstrated.

Unilateral knife cuts at the crus cerebri which depleted nigral GABA by 60 % without affecting striatal DA caused a significant increase in striatal 3-methoxytyramine; increasing nigral GABA by intranigral or intracerebroventricular injections of a GABA-transaminase inhibitor, ethanolamine-O-sulfate (EOS), decreased striatal 3-methoxytyramine (Racagni et al., 1977). The predominant effect of substance P iontophoresed onto PC and PR neurons was to increase neuronal activity (Davies and Dray, 1976; Pinnock et al., 1979; Walker et al., 1976). There is still no study which correlates the ability to excite single nigral neurons with substance P with the ability to evoke excitation by caudate stimulation.

Pallidonigral projection. The globus pallidus, a major output nucleus of the basal ganglia, projects directly to the ipsilateral SN. Injection of ^3H -leucine into the GP results in a major accumulation of autoradiographic grains in the SN (Carter and Fibiger, 1978). Injection of HRP into the PC or the posterior PR labels cells in the GP (Tulloch et al., 1978). Bunney and Aghajanian (1976c) reported more HRP reactive cells in the GP following injection of HRP to the PR than to the PC, while the reverse was reported by Hattori et al. (1975) and Kanazawa et al. (1976). The latter investigators also noted that pallidal HRP positive neurons were large triangular neurons as opposed to medium round striatal HRP positive neurons. GABA (Brownstein et al., 1977; Jessell et al., 1978) and substance P (Jessell et al., 1978; Kanazawa et al., 1977) have been postulated as neurotransmitters for the pallidonigral pathway. However, the existence of a GABAergic pallidonigral pathway has been seriously questioned by DiChiara et al.

(1980), Fonnum et al. (1978) and Nagy and Fibiger (1980) who proposed that the cells of origin of the GABA containing terminals in the SN were in the caudate rather than the GP. This hypothesis is based on experiments showing that oblique hemitransections which separated the head and body of the caudate nucleus from the GP and SN caused a substantial reduction of glutamic acid decarboxylase (GAD) in the GP and SN (Fonnum et al., 1978). In addition, kainic acid lesions of the GP which reduced pallidal GAD and choline acetyltransferase (CAT) by 42 % did not significantly reduce nigral GAD (DiChiara et al., 1980; Nagy and Fibiger, 1980; Porceddu et al., 1980).

Substance P like immunoreactive neurons in the GP (Kanazawa et al., 1977) might be the cells of origin of some pallidonigral projections. Although it has been shown that radiofrequency lesions of the GP substantially reduced nigral substance P (Kanazawa et al., 1977), the fact that striatonigral axons pass through the GP makes it impossible to ascribe the loss of substance P to destruction of pallidal neurons. A crucial experiment to corroborate the existence of a substance P pallidonigral system would be to examine the effects of chemical lesions of pallidal cell bodies on nigral substance P.

Subthalamonigral projection. In addition to reciprocal connections with the ipsilateral GP (Perkins and Stone, 1980), the subthalamic nucleus (STN) also projects to the ipsilateral SN as shown by retrograde transport of HRP (Kanazawa et al., 1976; Tulloch et al., 1978). Both studies showed maximum HRP labeled cells in the STN following injection to posterior SN. Kanazawa et al. (1976) found more labeled cells following injection to the PC while Tulloch et al. (1978)

emphasized the STN projection to the PR. Electrophysiological studies confirmed the existence of a subthalamonigral pathway. Antidromic spikes were recorded in STN following electrical stimulation of the SN but not of the adjacent areas. The antidromic response was present in rats whose sensorimotor cortex had previously been removed (Hammond et al., 1978). In addition, Hammond et al. (1978) also demonstrated monosynaptic orthodromic excitation of cells in both the PC and PR following STN stimulation, even following chronic hemitransection rostral to the STN.

Raphe-nigral projection. Both retrograde and anterograde tracing techniques demonstrate that the dorsal raphe projects to the SN. HRP (Bunney and Aghajanian, 1976c; Fibiger and Miller, 1977; Kanazawa et al., 1976; Pasquier et al., 1977; Tulloch et al., 1978) or ^3H -serotonin (Streit et al., 1979) injections into the SN resulted in the labeled cells in the ipsilateral dorsal raphe. The region of termination of the raphe projection has not been unambiguously established. Lesions of the raphe resulted in a few degenerating boutons forming axodendritic synapses in both PC and PR (Bak et al., 1975). Fibiger and Miller (1977) studying transport of ^3H -leucine from dorsal raphe and Moore et al. (1978) studying ^3H -proline transport from both median and dorsal raphe also describe projections to both PC and PR with the predominant projection to the latter. Azmitia and Segal (1978) and Conrad et al. (1974) using smaller injection volumes of ^3H -proline reported only a projection to the PC.

The raphe nuclei contain serotonin (5-HT) cell bodies (Dahlström and Fuxe, 1964) which give rise to ascending and descending 5-HT path-

ways (Ungerstedt, 1971a). The SN contains high concentrations of 5-HT (higher in PR than PC) and calcium dependent potassium evoked release of 5-HT from SN slices (PC and PR) has been shown (Reubi and Emson, 1978). This release was diminished when studies were done 10 days after raphe lesions (Reubi and Emson, 1978). Electrolytic lesions of the dorsal raphe significantly reduced nigral (and striatal) 5-HT (Dray et al., 1978; Fibiger and Miller, 1977) and significantly increased nigral homovanillic acid (HVA) (Dray et al., 1978).

Although no projection from the median raphe to the SN was demonstrable with HRP (Bunney and Aghajanian, 1976c; Fibiger and Miller, 1977; Tulloch et al., 1978), and injection of labeled amino acid into the median raphe alone did not result in transport to the SN (Azmitia and Segal, 1978), it has been suggested on the basis of biochemical and electrophysiological studies that the median raphe in addition to projecting to the hippocampus (Lorens and Gulberg, 1974) also sends an ascending 5-HT projection to the SN (Dray et al., 1976b, 1976c, 1978; Dray and Oakley, 1977) but not to the CP (Lorens and Gulberg, 1974; Olpe and Koella, 1977a). Electrolytic lesions of the median raphe significantly reduced nigral but not striatal 5-HT (Dray et al., 1976b, 1978) and significantly increased nigral HVA (Dray et al., 1978) and striatal DA (Dray et al., 1976b, 1976c). The existence of a median raphe projection to the SN was also proposed on the basis of antidromic activation of cells in both dorsal and median raphe (Dray et al., 1978). Dray et al. (1976b, 1976c) noted that electrical stimulation of the median raphe generally produced inhibition of nigral (PC and PR) neurons, but excitation or mixed excitation inhibition was also observed. Fibiger and Miller

(1977) found similar responses in a few cells, but the majority of nigral cells in their study did not respond to median raphe stimulation. The discrepancy might reflect different loci of recording electrodes in the SN and the small cell sample studied by Fibiger and Miller (1977). Spontaneous firing of the PC and PR neurons was inhibited by iontophoresis of 5-HT as well as electrical stimulation of the median raphe (Dray et al., 1976a; Dray and Oakley, 1977). Furthermore, the median raphe- and the exogenous 5-HT- evoked inhibitions in the same neurons were antagonized by a 5-HT antagonist, methiothepin (Dray and Oakley, 1977). Stimulation of the dorsal raphe also inhibited PC and PR neurons (Dray et al., 1978; Fibiger and Miller, 1977), an effect which was blocked by pretreatment with the 5-HT synthesis inhibitor, para-chlorophenylalanine (PCPA). Unlike median raphe stimulation, however, there was no clear relationship between dorsal raphe- and 5-HT- evoked inhibition of nigral neurons; among 16 cells studied only 4 cells were depressed by both (Dray et al., 1978).

Positive electrophysiological and neurochemical but negative anatomical evidence of the median raphe - nigral projection could be reconciled if the positive results reflected the effects of electrical stimulation or lesions of the axons passing through or near the median raphe and the SN. The studies on antidromic excitation of median raphe cells for example could have reflected stimulation of axons rather than terminals in nigra. Ascending axons have been identified between the SN and the medial lemniscus following ^3H -proline injections into the median and/or dorsal raphe (Azmitia and Segal, 1978; Conrad et al., 1974; Moore et al., 1978), and in the ventral tegmental area following

^3H -leucine injections into the dorsal raphe (Fibiger and Miller, 1977). Axons of dorsal raphe cells appear in median raphe and vice versa. Injection of ^3H -proline into one nucleus results in grains in the other (Azmitia and Segal, 1978). HRP injection into the dorsal raphe resulted in labeled cells in the median raphe (Aghajanian and Wang, 1977; Bobillier et al., 1976). These findings illustrate the difficulties in determining the exact origin of raphe projections.

Accumbens-nigral projection. The nucleus accumbens projects ipsilaterally to the dorsomedial part of the SN and the adjacent ventral tegmental area as shown by degeneration (Williams et al., 1977), anterograde transport of ^3H -leucine or ^3H -proline (Conrad and Pfaff, 1976; Nauta et al., 1978; Powell and Leman, 1976; Swanson and Cowan, 1975) and retrograde transport of HRP (Bunney and Aghajanian, 1976c). The projection terminates both in the PC and PR (Conrad and Pfaff, 1976; Nauta et al., 1978; Williams et al., 1977).

Corticonigral projection. A corticonigral projection in rats was suggested on the basis of retrograde transport of HRP (Bunney and Aghajanian, 1976c; Tulloch et al., 1978). HRP injection into the anterior PR led to a few labeled cells in the ipsilateral prefrontal cortex at the level of the genu of the corpus callosum (Tulloch et al., 1978). Bunney and Aghajanian (1976c) reported in addition to labeled cells in layer V of the prefrontal cortex, HRP reactive cells in layer V of the parietal, insular and temporal cortices. Labeled pyramidal cells in layer V of the cortex was also observed following injections of ^3H -5-HT into the SN regardless of the chemospecificity of the

retrograde transport (Streit et al., 1979). In cats, however, although anatomical (Rinvik, 1966) and functional (Glowinski et al., 1978) connections from motor cortex to ipsilateral SN have been suggested, electron microscopic examination revealed only degenerating myelinated axons not boutons in the SN (Rinvik and Walberg, 1969). In addition, no monosynaptic responses of nigral neurons were obtained upon cortical stimulation (Goswell and Sedgwick, 1973). The positive results from retrograde HRP transport in rats may reflect HRP uptake by axons passing through or near the SN, and if the projection exists it is likely to be a minor one.

Amygdalonigral projection. HRP injections into the lateral one-third of the SN along the entire anterior-posterior extent resulted in many highly labeled cells within the central nucleus of the amygdaloid complex (Bunney and Aghajanian, 1976c). However, Tulloch et al. (1978) did not observe any HRP labeled cells in the amygdala following HRP injection to the entire SN.

Nigral Efferents

Nigral efferents are organized into two major groups: the dopaminergic projections originating mainly from the PC, and the non-dopaminergic projections originating mainly from the PR.

Dopaminergic projections

A large uncrossed nigrostriatal DA pathway has been mapped by

means of the histofluorescent and neurochemical techniques with and without discrete brain lesions to generate anterograde and retrograde neuronal changes (Andén et al., 1964, 1965; Dahlström and Fuxe, 1964; Hökfelt and Ungerstedt, 1969). The DA cells in the PC give rise to small unmyelinated ascending axons of slow conduction velocity (0.6 m/sec) to the ipsilateral CP (Deniau et al., 1978b; Guyenet and Aghajanian, 1978). The dopaminergic nigrostriatal axons ascend through the LH and undergo a massive collateralization in the striatum and each branch contains numerous small varicosities (Andén et al., 1966c). Each nigral DA neuron innervating the CP has an estimated total axon length between 55 and 77 cm. and about 500,000 axonal varicosities which could serve as transmitter release sites (Andén et al., 1966c). Electron microscopic autoradiography combined with intraventricular 6-OHDA lesions revealed that the dopaminergic nigrostriatal terminals formed asymmetrical synaptic contacts with dendritic spines or major dendrites of the striatal neurons (Hattori et al., 1979). The presynaptic terminals contained moderately packed pleomorphic vesicles (Hattori et al., 1973, 1979). The DA projection is denser in the anterior CP as shown by a regular decrease in ^3H -DA uptake and DA content as one progresses rostro-caudally (Tassin et al., 1976). There is also a sparse projection to the GP and the entopeduncular nucleus that consists of scattered fine DA terminals (Moore and Bloom, 1978).

The ascending DA pathways were originally described as 2 separate systems: the nigrostriatal originating from the SN (A_9) and terminating in the CP, the mesolimbic originating from the VTA (A_{10}) and terminating in the nucleus accumbens and olfactory tubercle.

Subsequent studies show no distinct anatomical border between cells in A₉ and A₁₀ or between cells in A₉ and A₈ (a DA cell group in the mesencephalic reticular formation lateral to the SN) (Dahlström and Fuxe, 1964). Nor is there a clear division in their projection fields. They can be considered as a single mesencephalic DA cell group with a topographic projection to the telencephalon (Moore and Bloom, 1978). Anterograde transport of ³H-leucine and retrograde transport of HRP combined with the glyoxylic acid fluorescence histochemical technique demonstrated that the projection from the mesencephalic DA cell group to the telencephalic areas shows topographic specificity in all three stereotaxic planes: an inverse dorsal-ventral projection and direct medial-lateral and anterior-posterior projections (Fallon and Moore, 1978a, 1978b; Fallon et al., 1978a; Moore and Bloom, 1978).

Ventral cells of the PC and VTA project to the dorsal structures of the septum, nucleus accumbens, CP, and frontal cortex; dorsal cells project to the ventral structures such as olfactory tubercle and amygdala (Fallon and Moore, 1978b). Although the SN projects to both the CP and the allocortex, the projections were shown by Golgi and HRP techniques to exhibit further topographic specificity. The DA neurons located dorsally in the SN having horizontally oriented dendrites project principally to the basal forebrain allocortex, the ventrally located DA neurons having dendrites extending into the PR project principally to the CP (Fallon et al., 1978b).

The medial sectors of the SN-VTA project to the medial part of the basal forebrain nuclei and CP whereas lateral sectors of the SN-VTA project to the lateral parts (Fallon and Moore, 1978a). Collaterals from the SN-VTA axons which project to the medial CP form a

sparse plexus throughout the pallidal gray matter and make synaptic contacts with non-fluorescent pallidal neurons as shown by glyoxylic acid-vibratome technique (Lindvall and Björklund, 1979). Neurons in the lateral VTA and medial PC project to the amygdala primarily to the central and basal nuclei and intercalated cell groups (Fallon et al., 1978a). The piriform-suprarhinal area is innervated by more lateral cells of the SN with a rostrocaudal topography (Moore and Bloom, 1978).

As one moves posteriorly in the SN-VTA cell group the cortical projection area moves from anterior medial frontal cortex to anterior cingulate, piriform and suprarhinal cortices, to entorhinal cortex (innervated by the more posterior DA cells) (Fallon and Moore, 1978a). Scatton et al. (1980) have reported a DA projection to the hippocampus. Electrolytic and 6-OHDA lesions in midbrain reduced hippocampal DA and 3,4-dihydroxyphenyl acetic acid (DOPAC). The topography of this projection resembles that of other projections, 'anterior' hippocampus receiving DA input from the anterior-medial part of the VTA (A₁₀), whereas the 'posterior' hippocampal formation is innervated by more posterior-lateral DA cells (A₉ and A₁₀) (Scatton et al., 1980).

Although it has not been confirmed, electrolytic lesions of the A₈, A₉ and A₁₀ resulted in a significant reduction of DA in the median eminence (Kizer et al., 1976), thus suggesting an ascending projection in addition to the classic DA input from cells in the arcuate nucleus (A₁₂) (Ungerstedt, 1971a).

An uncrossed DA nigrospinal pathway was proposed following the demonstration of a reduction of DA in the ipsilateral thoracic spinal cord 10 days after 6-OHDA lesions of the SN, and a significant in-

crease in ipsilateral spinal HVA after electrical stimulation of the SN in chloral hydrate anesthetized rats (Commissiong et al., 1979). However, the proposed DA nigrospinal pathway was not confirmed in other studies. Retrograde transport of a fluorescent dye, primuline, injected into the lower thoracic and the upper lumbar spinal cord in rats demonstrated that the DA projections were from a group of cells in the periventricular area at the border between the mesencephalon and the hypothalamus (Hökfelt et al., 1979). These cells corresponded to the diencephalic catecholamine cell group (A₁₁) described by Dahlström and Fuxe (1964). No labeled neurons were observed in the SN after spinal injections of HRP in rats (Hopkins and Niessen, 1976). It is possible that Commissiong et al. (1979) might have lesioned and stimulated the descending projections from this other cell group.

Nondopaminergic projections

Nigrostriatal projection. In addition to the dopaminergic nigrostriatal projection, the SN also sends a separate non DA projection to the ipsilateral CP. Degenerating axons and granules stained by the Fink-Heimer method were observed in the CP following SN electrolytic lesions 2 months after intracerebroventricular injections of 6-OHDA 200 ug which caused degeneration of the mesencephalic DA cell bodies (Hedreen, 1971; Hedreen and Chalmers, 1972). Some of the nigral neurons which contained HRP after CP microinjection did not contain tyrosine hydroxylase, suggesting that they were not dopaminergic (Ljungdahl et al., 1975). Intracerebroventricular 6-OHDA decreased

the nigrostriatal axonal transport of the ^{14}C -protein (-69 %) less than striatal tyrosine hydroxylase activity (-92 %) while electrolytic lesions of the MFB produced equivalent decreases in both, [axonal transport (-75 %), striatal tyrosine hydroxylase activity (-81 %)] (Fibiger et al., 1972). This suggests that some 20 % of the nigrostriatal axons are non DA. The non DA nigrostriatal projection appears to originate from the PR cells giving rise to myelinated small diameter fibers with an estimated conduction velocity of 3 - 4 m/sec (Deniau et al., 1978b; Guyenet and Aghajanian, 1978). A single PR neuron might send branching projections to 2 or 3 different structures, since there is electrophysiological evidence that the single PR cells antidromically activated from the ipsilateral CP were also antidromically activated from the ipsilateral ventromedial thalamic nucleus (9/14, Deniau et al., 1978b; 5/7, Guyenet and Aghajanian, 1978) and the contralateral superior colliculus (2/14, Deniau et al., 1978b). However, the existence of these collateral projections were not supported by retrograde double labeling experiments (Bentivoglio et al., 1979).

Nigrothalamic projection. A nigrothalamic projection has been demonstrated by means of HRP retrograde transport (Clavier et al., 1976; Faull and Mehler, 1978; Herkenham, 1979), ^3H -leucine or ^3H -proline orthograde transport (Beckstead et al., 1979; Clavier et al., 1976) and terminal degeneration following nigral kainic acid (DiChiara et al., 1979b) or electrolytic (Faull and Carman, 1968) lesions. HRP injection into the ventromedial nucleus (VM) labeled multipolar cells (20 u) throughout the dorsal and central regions of

the ipsilateral PR with the highest proportion in the rostromedial and caudomedial aspects of the nucleus (Clavier et al., 1976; Faull and Mehler, 1978). There appeared to be a rostrocaudal (Faull and Mehler, 1978), mediolateral and dorsoventral (Herkenham, 1979) topographic organization of the nigral projection to the VM (Faull and Mehler, 1978). HRP injection into the parafascicular nucleus (PF) led to weak but consistent retrograde labeling of fusiform cells (20 - 25 μ) in the medial PR (Clavier et al., 1976). Anterograde transport of ^3H -leucine confirmed that the major nigral input is to the ipsilateral VM with a small projection to the ipsilateral PF (Beckstead et al., 1979; Clavier et al., 1976) and the paralamellar zone of the ipsilateral and to some extent contralateral mediodorsal nucleus (Beckstead et al., 1979). Double labeling suggests that in addition to an unbranched projection to the VM, some neurons in ventral PR project to both ipsilateral VM and superior colliculus (Bentivoglio et al., 1979). This result supports electrophysiological data by Deniau et al. (1978b) suggesting that 25 % of nigrothalamic cells send collaterals to the ipsilateral superior colliculus. Collaterals to the contralateral superior colliculus (3/30) and contralateral VM (2/25) have also been suggested (Deniau et al., 1978b).

Nigral kainic acid injections or electrocoagulation reduced GAD (DiChiara et al., 1979b; Kilpatrick et al., 1980), and GABA (Kilpatrick et al., 1980) in the ipsilateral VM suggesting that GABA might be a neurotransmitter in the nigrothalamic pathway (DiChiara et al., 1979b). Consonant with this suggestion electrophysiological experiments in cats demonstrated monosynaptic IPSPs in neurons in the VM following electrical stimulation of the PR (Ueki et al., 1977).

Extracellular recording of the VM and PF in rats revealed correlation of inhibitory effects following SN stimulation and iontophoresis of GABA, and both were readily blocked by iontophoresis of bicuculline (MacLeod et al., 1980). The nigral evoked inhibitions were presumed to be monosynaptic since the latencies (4 msec) were comparable to the antidromic latencies for this pathway (1 - 5 msec) (MacLeod et al., 1980), although this argument is weak.

Nigrotectal projection. The nigral projection to the superior colliculus has been demonstrated by retrograde transport of HRP (Beckstead et al., 1981; Bentivoglio et al., 1979; Faull and Mehler, 1978; Hopkins and Niessen, 1976) as well as orthograde transport of ^3H -leucine and ^3H -proline (Beckstead et al., 1979; Hedreen, 1978; Wright and Arbuthnott, 1980). The projection is mainly ipsilateral with a small contralateral component (Beckstead et al., 1981; Deniau et al., 1977, 1978a, 1978b, Faull and Mehler, 1978; Hedreen, 1978; Hopkins and Niessen, 1976; Wright and Arbuthnott, 1980). The nigrotectal cells are medium-sized (15 - 20 μ) fusiform or multipolar somata located exclusively in the PR forming a prominent ventral longitudinal cell lamina adjacent to the cerebral peduncle (Beckstead et al., 1981; Bentivoglio et al., 1979; Deniau et al., 1977; Faull and Mehler, 1978). The projection terminates in the intermediate and deep layers (Beckstead et al., 1979; Bentivoglio et al., 1979; Chevalier et al., 1981; Deniau et al., 1977; Hedreen, 1978) of the caudal two-thirds of the superior colliculus (Faull and Mehler, 1978). As mentioned above, some nigrotectal neurons in rats send collaterals to the ipsilateral VM; the possible branching of nigrotectal neurons to the contralateral

VM has not been studied with double labeling. Electrophysiological data supports the view that the nigrotectal pathway is inhibitory (Chevalier et al., 1981; Deniau et al., 1978a) and that GABA is a nigrotectal transmitter (Chevalier et al., 1981). Biochemical evidence that GAD in the superior colliculus and VM was decreased following nigral kainic acid or electrolytic lesions (DiChiara et al., 1979b) also support this suggestion. There are no data, however, showing that those neurons which send collaterals to both tectum and thalamus are GABA containing cells.

Nigrosegmental projection. Using retrograde transport of HRP Hopkins and Niessen (1976) demonstrated a predominantly ipsilateral projection from the PR to the medial and lateral tegmental fields. Anterograde transport of ^3H -leucine and ^3H -proline indicates a small descending nigral projection terminating in the area of the ipsilateral tegmentum pedunculopontine nucleus (Beckstead et al., 1979; Hedreen, 1978), the most posterior of the PR projections (Wright and Arbuthnott, 1980). Antidromic activation of PR cells has been observed upon electrical stimulation of the pontine reticular formation (Guyenet and Aghajanian, 1978). Electrical stimulation of the SN evoked monosynaptic IPSPs in neurons in the area of nucleus reticularis gigantocellularis in the reticular formation (González-Vegas, 1981).

Other possible nigral projections. Pasquier et al. (1977) postulated a direct projection from the mediodorsal PC to the rostral dorsal raphe nucleus upon demonstration of retrograde transport of

HRP. The specificity of these data is doubtful since Aghajanian and Wang (1977) showed HRP transport to nigra when HRP was iontophoresed into both the dorsal raphe and the adjacent reticular formation. More recently, however, Beckstead et al. (1979) reported anterograde transport of ^3H -leucine and ^3H -proline from medial nigra to the dorsal raphe and, to a lesser extent to the median raphe. Whether or not distinct nigral pathways exist, there are functional differences, since electrical stimulation of nigra suppresses firing of anterior raphe neurons but excites most cells in the adjacent reticular formation (Stern et al., 1979).

The existence of a nigro-coeruleus projection has been proposed in cats following the observation of HRP labeled cells in the ipsilateral SN after injections into the ventrolateral locus coeruleus (Sakai et al., 1977). In rats, bilateral projections from the VTA to the locus coeruleus have been shown by ^3H -leucine autoradiography (Simon et al., 1979) and by Fink-Heimer staining for degenerating terminals (Simon and Le Moal, 1977). The transmitter of the VTA-locus coeruleus projections is presumed to be DA (Simon and Le Moal, 1977; Simon et al., 1979). A direct projection from the SN to the locus coeruleus has not been shown in rats.

Bilateral nigrocerebellar projections have been proposed in rhesus monkeys. HRP labeled cells were observed bilaterally in the SN following unilateral HRP injections into the dentate nucleus, the interpositus nucleus and the overlying cerebellar cortex (Chan-Palay, 1977). This nigral efferent has not been shown in rats.

RESPONSES FOLLOWING SUBSTANTIA NIGRA STIMULATION

This section includes both electrophysiological and neurochemical (release, synthesis, turnover) responses of related nuclei following electrical stimulation (and sometimes chemical stimulation) of the SN. Since most electrophysiological experiments and measurements of transmitter release have been done in cats, the discussion of these particular topics includes data from cats as well as from rats when available.

Responses of striatal neurons

The interpretation of extracellular and intracellular recordings from caudate neurons following electrical stimulation of the SN has been complicated by uncertainty of connectivity between nigral neurons and caudate cells, the presence of collateral arborization of both the caudate afferents and efferents, and the existence of dual projections of DA and non-DA neurons from the SN.

When the SN is stimulated and striatal cells are recorded extracellularly both excitations and inhibitions and commonly both, are recorded (Connor, 1968; Dafny, 1975; Davies and Tongroach, 1978; Feltz and MacKenzie, 1969). Both haloperidol sensitive excitations (Richardson et al., 1977) presumed to be dopaminergic, as well as excitations which persisted following 98 % depletion of brain DA (Feltz and DeChamplain, 1972) have been described. Intracellular recording revealed apparent monosynaptic EPSPs and EPSP-IPSP sequences (Hull et al., 1970; Kitai et al., 1975), dual EPSP sequences (Hull et al.,

1970; Kocsis and Kitai, 1977) and IPSPs (Hull et al., 1970) in cat caudate neurons. The nigral evoked EPSP-IPSP (Hull et al., 1970; Kitai et al., 1975) or EPSP-EPSP (Kocsis and Kitai, 1977) in the cat caudate and the DA-independent nigral-evoked inhibition of spikes in some rat caudate cells associated with burst responses in others (Richardson et al., 1977) suggest that the caudate responses following SN stimulation are complicated by antidromic activation of the collaterals of the striatonigral pathway. These collaterals might synapse onto striatal inhibitory interneurons (Richardson et al., 1977) or striatal medium spiny neurons (Park et al., 1980). There is little doubt that electrical stimulation of the SN can evoke monosynaptic excitatory responses in caudate neurons. Among the cells in which these responses have been recorded are striatopallidal neurons (Richardson et al., 1977) and medium spiny output neurons with numerous axon collaterals in the CP and GP (Preston et al., 1980) in rats; and similar cells (Fuller et al., 1975; Kitai et al., 1976a; Matsuda and Jinnai, 1980) or medium intrinsic spiny cells (Kitai et al., 1976b) in cats. PSPs which are not monosynaptic could involve either orthodromic polysynaptic pathways, or recurrent pathways activated either orthodromically or antidromically. A complete description of synaptic organization of the caudate remains to be elucidated. It has been suggested, however, that in rats, the recurrent collaterals are GABAergic and directly inhibit the striatonigral neurons in the caudate (Park et al., 1980).

Effects of iontophoresed DA on striatal neurons. There appears to be a parallelism between the recorded effects of nigral stimulation

and of iontophoresis of DA on striatal neurons. With intracellular recording (and extracellular iontophoresis), DA caused membrane depolarization and spikes in cat striatal neurons that showed EPSPs and action potentials in response to nigral stimulation. Iontophoresed chlorpromazine suppressed both the nigral-induced EPSPs and spikes (Kitai et al., 1976b). Iontophoretically applied haloperidol, chlorpromazine or fluphenazine selectively blocked action potentials in caudate cells elicited by stimulation of the SN without affecting the response to cortical or thalamic stimulation (Norcross and Spehlmann, 1977). Excitation by both iontophoresed DA and nigral stimulation was also reported for putamen cells in cats (York, 1970, 1976). In general, in experiments in which iontophoresis of DA was coupled with extracellular recording, DA decreased the firing rates of unidentified caudate neurons in both cats (Connor, 1970; McLennan and York, 1966, 1967) and rats (Davies and Tongroach, 1978; McCarthy et al., 1977). Those striatal neurons depressed by iontophoretic DA were also consistently depressed by nigral stimulation (Connor, 1970; Davies and Tongroach, 1978).

These data have fueled a controversy for many years over whether DA in caudate is an excitatory or inhibitory transmitter. One can perhaps rationalize the conflicting results by considering the differences in techniques used and neurons sampled. DA mimics and DA receptor blockers antagonize the monosynaptic excitatory effects of nigral stimulation intracellularly recorded in striatal neurons, supporting the view that the dopaminergic nigrostriatal pathway exerts direct excitatory effects on striatal cells, many of which appear to be striatal output cells. In these experiments, the duration of the

iontophoretic current is brief, and it is likely that the action of DA is primarily on the cell being recorded. When iontophoresis is coupled with extracellular recording, ejection times are long leaving ample time and quantity of drug ejected for spread of DA to neighboring neurons which might inhibit the cell being recorded. In an attempt to exclude this mechanism McCarthy et al. (1977) showed that the decreased firing rate produced by iontophoresed DA was blocked by alpha-flupenthixol but not by iontophoresed picrotoxin or strychnine. They concluded that DA inhibition was not mediated by GABA or glycine. This experiment, however, cannot distinguish between direct vs. indirect DA inhibition of striatal neurons since the location of presumed GABA or glycine synapses need not have been within diffusion distance of the amino acid antagonists. Systemic administration of the antagonists might have answered this criticism. Multiple DA receptors have been postulated and described in terms of physiological effects [one mediating excitation, the other mediating inhibition (Cools and Van Rossum, 1976, 1980)], effector mechanism [one linked to adenylate cyclase, D₁; one not, D₂ (Garau et al., 1978; Kebabian and Calne, 1979; Schwarcz et al., 1978)], and location [presynaptic or postsynaptic (Bunney and Aghajanian, 1977, 1978)]. One location of noncyclase-linked DA receptors is on terminals of corticostriatal neurons (Garau et al., 1978; Schwarcz et al., 1978). DA and DA agonists inhibited potassium-evoked release of endogenous glutamate from rat striatal slices (Rowlands and Roberts, 1980). Repetitive nigral stimulation inhibits cortical-evoked potentials in rat caudate. This effect can be antagonized by i.p. administrations of pimozide (0.1 - 0.2 mg/kg), haloperidol (0.1 - 0.5 mg/kg), chlorpromazine

(0.5 - 2 mg/kg) and thioridazine (0.5 - 4 mg/kg) (Olpe and Koella, 1978).

Stimulus evoked release of DA

Electrical stimulation of the LH (400 uA, 0.5 msec square wave pulses of 30 Hz for 30 min) increased the levels of endogenously synthesized as well as exogenously administered ^3H -DA in the cerebrospinal fluid in cats (Chiueh and Moore, 1973). The release was mimicked by intracerebroventricular d-amphetamine (Chiueh and Moore, 1973). The release of exogenously administered DA to the cerebrospinal fluid in cats by electrical stimulation (100 - 400 uA, 1 msec pulses of 3 to 100 Hz) of the LH (Von Voigtlander and Moore, 1971a) or the SN (Von Voigtlander and Moore, 1971b) was dependent on amplitude and frequency of stimulation with an optimum frequency of 30 Hz. In these experiments labeled tyrosine or DA was injected into the lateral ventricle and cerebrospinal fluid samples were collected from the aqueduct. It was assumed that the ^3H -DA in the samples reflected DA release from the caudate. An alternative indirect demonstration of release is to examine DA levels before and after stimulation of the nigrostriatal pathway. In rats pretreated with tyrosine hydroxylase inhibitor, stimulation increased the rate of DA depletion in all parts of the striatum (Arbuthnott et al., 1970a). Studies of the release in cat caudate of endogenously synthesized DA have been done using the push-pull cannula technique. Electrical stimulation (0.1 Hz trains of 100 msec duration of 100 uA 0.5 msec pulses at 300 Hz, for 15 min) or potassium depolarization of the SN caused an increase in DA release

in the ipsilateral caudate (Nieoullon et al., 1977b). Intranigral DA, d-amphetamine, and benztropine caused immediate reduction and intranigral haloperidol caused potentiation of the in vivo release of endogenously synthesized ^3H -DA at 3 hours after superfusion of DA terminals with ^3H -tyrosine in cats (Chéramy et al., 1978a). Intranigral perfusion of glycine reduced (Chéramy et al., 1978b) but intranigral perfusion of GABA, GABA agonists (muscimol, baclofen, gamma-hydroxybutyrate, GABA-choline) (Chéramy et al., 1978c) or strychnine (Chéramy et al., 1978b) increased the spontaneous release of endogenously synthesized ^3H -DA in the ipsilateral caudate. The GABA-induced increase in striatal DA release was antagonized by simultaneous intranigral perfusion of picrotoxin (Chéramy et al., 1978c).

There is anatomical (Björklund and Lindvall, 1975; Hattori et al., 1979; Wilson et al., 1977) and biochemical (Geffen et al., 1976; Hattori et al., 1979) evidence indicating that dendrites of DA neurons in the rat SN contain physiological releasable pools of DA. Potassium-evoked release of DA from both the SN and the CP in rats were inhibited by low calcium or high magnesium concentrations (Geffen et al., 1976). Intranigral d-amphetamine (Chéramy et al., 1978a; Nieoullon et al., 1977a), muscimol, baclofen, and gamma-hydroxybutyrate (Chéramy et al., 1978c) increased the release of endogenously synthesized ^3H -DA from DA dendrites in the cat SN. Intranigral perfusion of substance P decreased the release of endogenously synthesized ^3H -DA in the ipsilateral SN but increased the release in the ipsilateral caudate in cats (Michelot et al., 1979). The function of DA in nigra may be both as a direct feedback autotransmitter onto the DA cells (Aghajanian and Bunney, 1973, 1975, 1977; Bunney and

Aghajanian, 1978; Ruffieux and Schultz, 1980) and as a feed forward transmitter to other elements. A DA-sensitive adenylate cyclase has been localized in the rat SN (Phillipson and Horn, 1976; Spano et al., 1976; Traficante et al., 1976) associated with the axon terminals of nigral afferents (Gale et al., 1977; González-Vegas and Pardey, 1979; Phillipson et al., 1977; Spano et al., 1977). DA, as well as amphetamine, evoked calcium-dependent, haloperidol and alpha-flupenthixol-sensitive GABA release from slices of rat SN (Reubi et al., 1977).

Stimulus-evoked increase in DA synthesis and turnover. Electrical stimulation of the rat MFB (at the level of the rostral end of the supramammillary decussation) with 200 uA monophasic 1.5 msec pulses at 5 to 30 Hz for 20 min increased the synthesis of DA (measured by an increase in the specific activity of ^3H -DA after i.v. ^3H -tyrosine) in the striatum and olfactory tubercle with the maximum increase at a frequency of 15 Hz (Murrin and Roth, 1976). The level of DA in the striatum remained unchanged during prolonged electrical stimulation of the MFB (Korf et al., 1976a; Murrin and Roth, 1976). There were, however, increases in striatal DOPAC (Korf et al., 1976a, 1977; Roth et al., 1976) and striatal HVA (Korf et al., 1976a, 1977). In addition to the changes in caudate, MFB stimulation also increased nigral DOPAC and HVA (Korf et al., 1976a, 1977). In these stimulation studies the optimum stimuli were 200 to 300 uA biphasic symmetrical 1 msec pulses at 15 to 30 Hz.

Responses of nonstriatal neurons

Yoshida et al. (1971) recorded IPSPs in entopeduncular neurons in cats upon SN stimulation. These were presumed to be monosynaptic because of their constant latency. Since these potentials were absent following ipsilateral caudate lesions they might well be evoked by antidromic activation of striatonigral fibers whose collaterals synapse in the entopeduncular nucleus.

Monosynaptic responses of thalamic neurons to nigral stimulation are predominantly inhibitory. IPSPs were recorded in neurons of the ipsilateral VM in cats (Ueki et al., 1977). In the cat CM-PF, a short latency, brief EPSP followed by a 200-350 msec long IPSP was recorded (Dalsass and Krauthamer, 1981). Extracellular recordings revealed short latency excitation and inhibition in cat VL-VA cells (Deniau et al., 1978c) and rat VM and PF cells (MacLeod et al., 1980) following SN stimulation. The short latency nigral-evoked excitatory response of thalamic neurons may be mediated via collaterals of corticofugal fibers since it was absent in pericruciate decorticated cats (Deniau et al., 1978c). The monosynaptic inhibition has been attributed to activation of GABAergic nigrothalamic neurons (MacLeod et al., 1980).

Studies of the nigrotectal projection in rats revealed that stimulation of the pars reticulata predominantly caused monosynaptic inhibition of cells within the intermediate and deep layers of the ipsilateral superior colliculus (Chevalier et al., 1981; Deniau et al., 1978a). This inhibition was present in rats with previous transections of internal capsule and optic tract rostral to the SN (Cheva-

lier et al., 1981). There is evidence that the pathway is mediated by GABA. Whereas both GABA and glycine inhibited tectal cells, the inhibition evoked from the SN was reversed by iontophoresed bicuculline but not by strychnine (Chevalier et al., 1981). There was a report of monosynaptic activation of collicular neurons following stimulation of the lateral SN and antidromic activation following stimulation of the medial SN in rats (York and Faber, 1977). This study, unlike the one above did not control for stimulation of adjacent pathways.

Electrical stimulation of the rat SN decreased the firing rate of the ipsilateral dorsal raphe neurons but activated the majority of cells in the adjacent pontine reticular formation (Stern et al., 1979). There was no evidence to demonstrate that these effects were monosynaptic or that they were secondary to antidromic activation of 5-HT afferents or fibers of passage. Intracellular recording in nucleus reticularis gigantocellularis revealed IPSPs following SN stimulation. These were not the results of stimulating cortical efferents since stimulation of these fibers produced EPSPs (González-vegas, 1981). Electrical stimulation of the pars reticulata in rats evoked a contralateral cervical dorsal root potential and decreased the amplitude of cervical-evoked dorsal root potentials (Motamedi and York, 1980). Again there are no data to support monosynapticity.

ROTATIONAL BEHAVIOR IN RODENTS

Classical model

Rotational behavior in rodents is correlated with striatal DA asymmetry (Glick et al., 1976; Ungerstedt et al., 1971b, 1971c). This asymmetry can be produced by experimenter induced lesions, but an asymmetry exists in naive rats as well (the two striata differing in DA content by 10 to 15 %, Glick et al., 1974). Spontaneous rotation in naive rats (Glick and Cox, 1978), unilateral nigrostriatal 6-OHDA (Ungerstedt, 1971b) or electrolytic (Andén et al., 1966a) lesioned rats is always toward the side with lower striatal DA, with the exception of initial ipsiversive turning accompanying degeneration release of DA. Spontaneous rotation in naive rats while easily discernable at night, is not marked during daylight hours (Glick and Cox, 1978). Manipulations which amplify the dopaminergic nigrostriatal asymmetry e.g. amphetamine or unilateral caudate lesion induce measurable day time rotation (Glick and Cox, 1978; Glick et al., 1974; Jerussi and Glick, 1974). Unilateral intrastriatal injection of DA or drugs with DA agonistic actions (apomorphine, amphetamine, amantadine) to rats pretreated with a monoamine oxidase inhibitor and/or reserpine induces contralateral postural asymmetry (Costall and Naylor, 1974b; Ungerstedt et al., 1969) or contralateral rotation (Sato et al., 1976; Setler et al., 1978; Ungerstedt et al., 1969). The contralateral turning is blocked by a prior bilateral intrastriatal injection of chlorpromazine (Ungerstedt et al., 1969).

Systemic administration of indirectly acting DA agonists, e.g. amphetamine, causes ipsilateral rotation in animals with 6-OHDA or electrolytic lesions of the nigrostriatal system (Christie and Crow, 1971; Crow, 1971; Pycock et al., 1975b; Stawarz et al., 1975; Ungerstedt, 1971b; Ungerstedt and Arbuthnott, 1970). The ipsilateral rotation is due to the release of DA on the intact side (Von Voigtlander and Moore, 1973) and is abolished by a tyrosine hydroxylase inhibitor (Christie and Crow, 1971; Ungerstedt, 1971b) or haloperidol (Pycock et al., 1975b; Stawarz et al., 1975; Ungerstedt, 1971b). Systemic administration of directly acting DA agonists, e.g. apomorphine, causes contralateral rotation in nigrostriatal 6-OHDA lesioned animals which is ascribed to the development of postsynaptic dopamine receptor supersensitivity on the lesioned side (Pycock et al., 1975; Ungerstedt 1971c). The rotation is reduced by haloperidol (Pycock et al., 1975b; Ungerstedt 1971c).

Mesolimbic dopamine and rotation

The DA cells of VTA that predominantly innervate the nucleus accumbens and the olfactory tubercle (Ungerstedt, 1971a) have been shown to contribute to the locomotor component of rotation (Kelly and Moore, 1976, 1977; Pycock and Marsden, 1978). Rotational behavior is viewed as the expression of two factors, an asymmetry or gating function controlled by the imbalance of the dopaminergic nigrostriatal system, and a locomotor function (which is operated on by the gate) controlled by the dopaminergic mesolimbic system. The mesolimbic component is not postulated to contribute to the directionality since

amphetamine or apomorphine did not induce rotation in unilateral mesolimbic 6-OHDA lesioned rats (Kelly, 1975). Additionally, unilateral electrical stimulation of the nucleus accumbens did not result in head turning or circling (Lee et al., 1980). Bilateral 6-OHDA lesions that resulted in 76 % depletion of accumbens DA and 70 % depletion of DA in the olfactory tubercle reduced amphetamine-induced ipsilateral rotation and enhanced apomorphine-induced contralateral rotation in rats with unilateral striatal 6-OHDA lesions (Kelly and Moore, 1976, 1977). Pretreatment with desipramine did not alter the effect of the mesolimbic 6-OHDA lesions suggesting that the reduction of forebrain norepinephrine was not the cause (Kelly and Moore, 1977). Bilateral electrolytic lesions of the nucleus accumbens reduced both amphetamine-induced ipsilateral rotation and apomorphine-induced contralateral rotation in unilateral LH 6-OHDA lesioned rats (Pycock and Marsden, 1978). The differential effect of 6-OHDA and electrolytic lesions of the accumbens on apomorphine-induced rotation are analogous to the differences in direction of apomorphine-induced rotation in animals with 6-OHDA (contralateral, Kelly and Moore, 1976, 1977; Pycock, 1975b) vs. electrolytic (ipsilateral, Andén, 1970) lesions of the striatum. The 6-OHDA lesion allows expression of supersensitivity, the electrolytic lesion removes the output pathway. Bilateral microinjections of haloperidol 5 ug in 1 ul to the nucleus accumbens reduced both the amphetamine-induced ipsilateral rotation and the apomorphine-induced contralateral rotation in unilateral striatal 6-OHDA lesioned rats (Kelly and Moore, 1977).

The two component hypothesis of rotational behavior is supported by experiments on striatal-induced rotation. Slater et al. (1980)

observed contralateral head turning following electrical stimulation of the rat caudate nucleus, and contralateral circling when stimulating in ventral caudate close to the accumbens. Unilateral intrastriatal injection of DA in a volume of 1 ul induced contralateral head turning (Costall and Naylor, 1972, 1974b), while contralateral rotation was observed following intrastriatal injection of 5 ul or more (Sato et al., 1976; Ungerstedt et al., 1969). The larger volume of injection probably spread to accumbens since the diameter of spread of 4 ul of ^3H -DA injected to rat SN is about 4.6 mm. (Agid et al., 1973). Contralateral circling upon electrical stimulation has been observed following stimulation at the medial SN (Arbuthnott and Crow, 1971; Arbuthnott et al., 1970; Roffman et al., 1978), the ventromedial tegmentum (Roffman et al., 1978), the posterior-lateral hypothalamus (Arbuthnott and Ungerstedt, 1969, 1975) and the MFB (Barghon and Costentin, 1980). Stimulation of all these sites could activate both "nigrostriatal" and "mesolimbic" neurons.

Striatonigral system and rotation

The differential effects of electrolytic and 6-OHDA lesions of the striatum on apomorphine-induced rotation are not restricted to lesions of the striatum. Apomorphine induces contralateral rotation in animals following 6-OHDA lesions at the LH (Wright and Arbuthnott, 1980), the MFB (Oberlander et al., 1980) or the SN (Costall et al., 1976a; Iwamoto et al., 1976a; Ungerstedt, 1971c; Watanabe and Watanabe, 1979); but ipsilateral rotation following electrolytic lesions of the crus cerebri at the hypothalamic level (Garcia-Munoz

et al., 1977; Marshall and Ungerstedt, 1977a) or the SN (Costall et al., 1976a; Costall and Naylor, 1974a; Dray et al., 1977; Iwamoto et al., 1976a; Oberlander et al., 1980; Watanabe and Watanabe, 1979). This suggests that just as postsynaptic striatal DA receptors are necessary for the expression of apomorphine effects, so are descending nondopaminergic neurons (presumed to be striatonigral cells). This hypothesis was supported by serial lesion studies. After unilateral 6-OHDA lesions of the dopaminergic nigrostriatal neurons, apomorphine caused contralateral rotation which was abolished by ipsilateral electrocoagulation or knife cut of the internal capsule at the level of the caudal hypothalamus (Marshall and Ungerstedt, 1977b; Ungerstedt and Marshall, 1975). Unilateral electrocoagulation of the internal capsule at the diencephalic level caused apomorphine-induced ipsilateral rotation which was potentiated by 6-OHDA lesions of the contralateral ascending DA axons (Marshall and Ungerstedt, 1977a). Yet another indication of the role of the SN as a striatal output was the observation that contralateral asymmetry induced by intrastriatal DA could be abolished by electrolytic lesion of the SN (Costall and Naylor, 1974b). A predominant view of the striatonigral system prior to these findings was that it served as a feedback system controlling activity of nigrostriatal DA cells. Systemic administration of DA agonists slows the firing rate of nigral DA cells and decreases striatal DA metabolites (DOPAC and HVA), while DA antagonists increase firing rate of the nigral DA cells which in turn increases striatal DOPAC and HVA levels (Bunney et al., 1973). D-amphetamine, DA or c-AMP iontophoresed in the striatum or the accumbens depresses the firing rate of the DA cells (Bunney and

Aghajanian, 1973). The existence of a long loop negative feedback pathway was supported by the demonstration that discrete knife cuts of the crus cerebri or radiofrequency lesions at the tail of the caudate and a small portion of the lateral border of the internal capsule (which damaged the striatonigral but spared the nigrostriatal fibers) reduced the depressant effect of systemic d-amphetamine on the firing rate of compacta neurons (Bunney and Aghajanian, 1973, 1976a, 1976b). That the feedback loop involved GABA was supported by the results that picrotoxin i.v. completely reversed d-amphetamine induced depression of the DA neurons in intact animals (Bunney and Aghajanian, 1976b, 1978). However, the long loop negative feedback regulation of the dopaminergic nigrostriatal neurons was seriously questioned by Groves et al.(1975) who favored a positive feedback loop based on their results that amphetamine infusion to the SN decreased firing rate of the compacta neurons and excited the caudate neurons while infusion of amphetamine to the caudate caused prolonged inhibition of the caudate neurons and prolonged excitation of the compacta neurons. The presence of DA receptors on the DA neurons and on other elements of the SN provide an explanation for the results obtained with nigral injection of agonists. The discrepancy with intracaudate drugs might reflect the presence of two physiologically different striatonigral projections (GABA and substance P). The studies by the two groups might have involved either spread of drug to different regions of the striatum or different populations of nigral cells thus favoring the recording of effects of a facilitatory system in one case and an inhibitory in the other.

GABA and rotation

If one assumes the striatonigral pathway includes a GABAergic negative feedback loop on the dopaminergic nigrostriatal system, one would expect ipsilateral rotation after microinjections of GABA or GABA agonists to the SN and contralateral rotation after microinjections of GABA antagonists. There have been, however, many reports of contralateral rotation in rats upon SN microinjections of GABA (Kelly and Moore, 1978; Olpe et al., 1977; Scheel-Krüger et al., 1977); or drugs with direct or indirect GABA agonistic effects: muscimol (Gale and Iadarola, 1980; Oberlander et al., 1977; Olpe et al., 1977; Waddington, 1978a; Waddington and Crow, 1977), baclofen (Kelly and Moore, 1978; Waddington, 1977b, 1978a; Waddington and Cross, 1979; Waddington and Crow, 1977), gamma-hydroxybutyrate (Kelly and Moore, 1978; Olpe et al., 1977), the GABA-transaminase inhibitor, ethanolamine-O-sulfate (Koob et al., 1976; Tanner, 1978).

In some experiments both ipsilateral and contralateral rotation, depending on the site of injection, have been reported following unilateral intranigral injections of GABA agonists and antagonists. Muscimol (Arnt and Scheel-Krüger, 1979a; Reavill et al., 1979) or a GABA uptake inhibitor, cis -1,3-aminocyclohexane carboxylic acid (ACHC) (James and Starr, 1978; Straughan and James, 1978) induced ipsilateral rotation following microinjections to the 'rostral' SN (A-P 2.1 to 2.5, König and Klippel atlas), but contralateral rotation following microinjections to the 'caudal' SN (A-P 1.6, König and Klippel atlas). Intranigral picrotoxin (James and Starr, 1978; Olpe et al., 1977; Reavill et al., 1979; Scheel-Krüger et al.,

1977; Straughan and James, 1978; Tarsy et al., 1975), bicuculline (Olpe et al., 1977), or tetanus toxin (James and Starr, 1978; Straughan and James, 1978) yielded just the reverse i.e. contralateral rotation following 'rostral' injection and ipsilateral rotation following 'caudal' injection (or 'rostral' injection of 2 ul as opposed to 0.5 ul). The direction of rotation following 'rostral' intranigral injection of GABA related drugs fits the model of a reciprocal DA-GABA circuit. GABA mimetic drugs decrease dopaminergic nigrostriatal activity, and lead to ipsilateral rotation while GABA-lytic drugs increase dopaminergic nigrostriatal activity and lead to contralateral rotation. The involvement of the dopamine neurons in this response is supported by the reports that ipsilateral rotation induced by muscimol (Kilpatrick and Starr, 1981; Reavill et al., 1979) or ACHC (James and Starr, 1978) was blocked by systemic haloperidol. ACHC-induced ipsilateral rotation was also blocked by 6-OHDA lesions of the ipsilateral MFB. Similarly, contralateral rotation produced by picrotoxin (James and Starr, 1978) or tetanus toxin (Straughan and James, 1978) was blocked by either systemic haloperidol or 6-OHDA lesion of the ipsilateral MFB. Striatal HVA was increased following 'rostral' intranigral picrotoxin (James and Starr, 1978) or tetanus toxin (James and Collingridge, 1979), and was decreased following 'rostral' intranigral ACHC (James and Starr, 1978).

The direction as well as the characteristics of rotation induced by 'caudal' intranigral injections of GABAergic drugs appear to be somewhat independent of the nigrostriatal dopamine system. Contralateral rotation induced by intranigral muscimol was not reduced by ipsilateral hemitransection rostral to the SN (Gale and Iadarola,

1980). Contralateral rotation induced by intranigral injections of muscimol (Arnt and Scheel-Krüger, 1979a; Oberlander et al., 1977; Olpe et al., 1977; Waddington, 1978a), ACHC (James and Starr, 1978), or the benzodiazepine, flurazepam (Waddington, 1978b), was not blocked by systemic haloperidol. Ipsilateral rotation induced by intranigral picrotoxin (James and Starr, 1978) was similarly insensitive. 6-OHDA lesions of the nigrostriatal system ipsilateral to drug microinjection had minimal effects on ipsilateral rotation induced by picrotoxin (James and Starr, 1978) or contralateral rotation induced by muscimol or ACHC (James and Starr, 1978; Waddington, 1980). Flurazepam-induced contralateral rotation was increased following 6-OHDA (Waddington, 1978b). 'Caudal' intranigral injections of picrotoxin, ACHC or tetanus toxin did not change striatal HVA levels (James and Collingridge, 1979; James and Starr, 1978). However, following intranigral muscimol, an increase in ipsilateral striatal ^3H -DA release from ^3H -tyrosine perfusion through push-pull cannulae during contralateral rotation has been reported (Martin and Haubrich, 1978). Furthermore, muscimol-induced contralateral rotation obtained by Martin et al. (1978) was reduced by approximately 50 % following haloperidol 1 mg/kg i.p. A very recent study of discrete microinjections of muscimol (40 ng in 0.2 μl , injection time 3 min) into different sites in the SN revealed that there were 2 different kinds of contralateral rotation induced by intranigral muscimol: DA-independent contralateral rotation (insensitive to nigrostriatal 6-OHDA lesion, haloperidol and pimozide i.p.) following injection to the ventral or lateral PR, and 'partial' DA-dependent contralateral rotation (72 % reduction by nigrostriatal 6-OHDA lesion, 80 % reduction by haloperidol 0.1

mg/kg i.p. and 66 % reduction by pimozide 0.25 mg/kg i.p.) following injection to the central PR (Kilpatrick and Starr, 1981; Kilpatrick et al., 1980; Starr and Kilpatrick, 1981). These findings might explain the conflicting results with muscimol-induced contralateral rotation since the sites of intranigral injections shown by Martin et al. (1978) were mostly in central PR with only 4 out of 11 sites in the ventral PR.

A probable explanation for DA-independent GABAergic rotation is that GABA inhibits non DA neurons in the PR which mediate ipsilateral rotation. This interpretation is supported by the finding that unilateral intranigral injections of kainic acid (0.25 to 1 ug) caused dose-related spontaneous contralateral rotation (DiChiara et al., 1977; Olanas et al., 1978a). This rotation seemed to involve neurons other than dopaminergic nigrostriatal neurons since bilateral intranigral injections of 6-OHDA (8 ug) did not change the rotation, and haloperidol i.p. potentiated it (DiChiara et al., 1977; Olanas et al., 1978a). Surgical removal of the telencephalic forebrain did not block intranigral kainic acid induced contralateral rotation (Papadopoulos et al., 1980). Contralateral rotation induced by intranigral muscimol was not attenuated by either removal of the telencephalon (Papadopoulos and Huston, 1980) or ipsilateral knife cut rostral to the SN (Gale and Iadarola, 1980; Reavill et al., 1981).

The anatomical basis for the different effects observed with GABA agonists and antagonists is unclear. A rostro-caudal topography of nigral projections in rats is clearly shown only in the ascending DA projections to the telencephalic structures which mainly originate from the PC, and the PC is dorsal (not rostral) to the PR. It is

conceivable, however, that with 'rostral' intranigral injection drugs might gain greater access to the DA cells in the PC since there are more cells in the rostral than the caudal SN. Furthermore, Kilpatrick and Starr (1981) reported that ipsilateral rotation which could be abolished by haloperidol 0.1 mg/kg i.p. was obtained only following injection of muscimol to the rostral PC; there was no rostro-caudal difference in either direction or rate of rotation when injections were made into the PR. It seems reasonable to suggest that the DA dependent rotation obtained from 'rostral' intranigral injections of GABA-related drugs can be attributed to the GABA-DA feedback loop. However, rotation induced by injections of GABA-related drugs to the PR might be attributed to more than one mechanism. While contralateral rotation was always obtained from injections of muscimol to the PR, that obtained with injection at ventral and lateral PR was DA independent and might be due to inhibition of nigral output cells responsible for ipsiversive rotation, but that obtained from injection at central PR was partially DA dependent and might include a component due to disinhibition of the dopaminergic nigrostriatal neurons (Kilpatrick and Starr, 1981; Starr and Kilpatrick, 1981). Disinhibition of GABAergic nigrothalamic cells in the PR might be another mechanism of intranigral muscimol induced DA-independent contralateral rotation since this rotation was blocked by electrolytic lesions or ethanolamine O-sulfate (a GABA-transaminase inhibitor) microinjection to the ipsilateral VM and was increased by picrotoxin microinjection to the ipsilateral VM (Kilpatrick et al., 1980). Furthermore, microinjection of muscimol to the VM or PF induced haloperidol resistant ipsiversive rotation (Kilpatrick et al., 1980),

or ipsilateral posturing (DiChiara et al., 1979a).

Substance P and rotation

The SN contains a higher concentration of substance P than any other CNS structure studied (Hökfelt et al., 1975; Kanazawa and Jessell, 1976; Ljungdahl et al., 1978). Most substance P is associated with efferents of the corpus striatum (Brownstein et al., 1977; Gale et al., 1977b; Mroz et al., 1977). Unilateral intranigral injection of substance P or a substance P derivative, eleodoisin (2.5 to 10 ug in 2 ul) caused a dose-related contralateral rotation which was described as the combination of on the spot ('watch hand') and head to tail rotation (Olpe and Koella, 1977b). As with GABA agonists and antagonists the direction of rotation following intranigral substance P varies with the site of injection. Contralateral rotation was observed following substance P injection to the PR (James and Starr, 1977, 1979) or to the caudal PR (Arnt and Scheel-Krüger, 1979b), but ipsilateral rotation following injection into the PC and PL (James and Starr, 1977, 1979) or the rostral PR (Arnt and Scheel-Krüger, 1979b; James and Starr, 1977). Unlike the responses to GABA agonists and antagonists, however, all responses to substance P were blocked by haloperidol 0.5 mg/kg i.p. and increased by nialamide 100 mg/kg i.p. (James and Starr, 1979). Rats exhibiting contralateral rotation had an increase in striatal HVA (James and Starr, 1977, 1979) and a decrease in striatal DA (James and Starr, 1979), while rats exhibiting ipsilateral rotation had a decrease in striatal HVA (James and Starr, 1977, 1979) and an increase in striatal

DA and hydroxyindole acetic acid (James and Starr, 1979). There is, however, no comparable electrophysiological differentiation of substance P actions in nigra.

Acetylcholine and rotation

The corpus striatum contains cholinergic interneurons (Lehmann et al., 1979; McGeer et al., 1971). Acetylcholine (ACh) (Jacobowitz and Goldberg, 1971), acetylcholinesterase (Butcher et al., 1975) and choline acetyltransferase (Fonnum, 1975) occur in the rat SN. Reciprocal DA and ACh functions have been proposed, for example in Parkinson's disease which can be treated by cholinergic antagonists as well as dopaminergic agonists. The actions of cholinergic drugs on rotation in rodents reflect this cholinergic-dopaminergic interaction, but not always in the simplest sense. This is partly because ACh interaction with nigral DA cells is both pre- and post-synaptic. Intranigral injection of the ACh agonists, carbachol (De Montis et al., 1979; James and Massey, 1978) and arecoline (Costall et al., 1972) induces ipsilateral rotation. Intranigral injection of the antimuscarinics, scopolamine (De Montis et al., 1979) and atropine (Costall et al., 1972) or the choline uptake blocker, hemicholinium (James and Massey, 1978) induces contralateral rotation. Similarly, when injected directly into the corpus striatum (CP or GP), the agonist arecoline (Costall et al., 1972) yields ipsilateral and the antagonist atropine (Costall et al., 1972; McKenzie et al., 1972) yields contralateral circling. The actions of drugs in SN appeared linked to alterations in DA function. A decrease in ipsilateral

striatal HVA accompanied the ipsilateral rotation induced by intranigral carbachol, and an increase in HVA accompanied the contralateral rotation induced by intranigral hemicholinium (James and Massey, 1978). Effects of intranigral carbachol on rotation and striatal HVA were specifically blocked by simultaneous intranigral injection of alpha-flupenthixol (James and Massey, 1978). Rotation induced by intranigral hemicholinium was reduced by haloperidol 2.5 mg/kg i.p. (James and Starr, 1978), the dose higher than that causes catalepsy (Carter and Pycock, 1979; Kostowski et al., 1977)

In rats with unilateral 6-OHDA lesions of the nigrostriatal system, ipsilateral rotation was observed following systemic scopolamine (Kelly and Miller, 1975; Ungerstedt et al., 1973) or atropine (Ungerstedt et al., 1973; Iwamoto et al., 1976a) and contralateral rotation following arecoline (Iwamoto et al., 1976a). Similar results were reported with scopolamine and benztropine in mice (Pycock et al., 1978). Scopolamine also potentiated amphetamine-induced ipsilateral rotation but not apomorphine-induced contralateral rotation in 6-OHDA lesioned mice (Pycock et al., 1978) and produced the same direction of rotation as 1 mg/kg amphetamine in naive rats (Jerussi and Glick, 1976). Atropine resembled amphetamine in that ipsilateral rotation occurred following either 6-OHDA or electrolytic lesions of the SN, while arecoline resembled apomorphine in that contralateral rotation occurred in rats with 6-OHDA lesions and ipsilateral rotation in rats with electrolytic SN lesions (Iwamoto et al., 1976a). Turning induced by scopolamine in animals with unilateral 6-OHDA lesions was abolished by AMPT, haloperidol (Pycock et al., 1978), alpha-flupenthixol and pimozide (Kelly and Miller, 1975) reinforcing the suggestion that DA

synapses mediated the behavior. Turning induced by methamphetamine (ipsilateral) and apomorphine (contralateral) following 6-OHDA were both blocked by the cholinergic agonist oxotremorine (Kelly and Miller, 1975).

The cholinergic-dopaminergic interaction, then, is clearly reciprocal rather than simply sequential, and the experiments done thus far have not clearly delineated sites of action of systemically administered drugs.

Serotonin and rotation

The dorsal raphe and median raphe are the major sources of ascending 5-HT projections (Dahlström and Fuxe, 1964; Ungerstedt, 1971a). Anatomical evidence (reviewed above) favors the dorsal raphe as the primary source of nigral and striatal 5-HT, biochemical and electrophysiological evidence suggest a median raphe projection to nigra. Rotation induced by systemic administration of 5-HT related drugs has been generally explained by assuming a uniform inhibitory effect of all serotonergic input on dopaminergic function. Systemically administered 5-HT precursors, tryptophan or 5-hydroxytryptophan (5-HTP), decreased apomorphine-induced contralateral rotation in 6-OHDA lesioned rats (Baldessarini et al., 1975) and mice (Milson and Pycock, 1976), or amphetamine-induced ipsilateral rotation in 6-OHDA lesioned mice (Milson and Pycock, 1976). 5-HT antagonists have opposite effects. Apomorphine- or amphetamine-induced rotation in lesioned animals was increased by methysergide (Baldessarini et al., 1975; Milson and Pycock, 1976), or a 5-HT synthesis blocker,

para-chlorophenylalanine (PCPA) (Baldessarini et al., 1975). In non-lesioned rats, the direction of d-LSD induced rotation was the same as that of amphetamine and the combination of LSD and amphetamine was synergistic (Fleisher and Glick, 1979). LSD-induced rotation was increased by PCPA pretreatment and decreased by AMPT pretreatment (Fleisher and Glick, 1979). All consistent with 5-HT agonists opposing and antagonists enhancing DA function. However, discrete lesions at two major 5-HT nuclei yielded different effects on rotation induced by systemic drugs.

Unilateral 5,7-DHT lesions of the median raphe or the SN in DMI pretreated rats (Giambalvo and Snodgrass, 1978a, 1978b) caused an immediate spontaneous contralateral rotation which was haloperidol sensitive. In addition, systemic apomorphine or amphetamine given 3 to 7 days postlesion also induced haloperidol sensitive contralateral rotation (Giambalvo and Snodgrass, 1978a, 1978b). Both median raphe and SN 5,7-DHT lesions resulted in increased ipsilateral striatal DA turnover (as measured by the increase in DOPA accumulation following decarboxylase inhibition) and decreased cortical 5-HT turnover (as measured by the decrease in 5-HTP accumulation following decarboxylase inhibition) (Giambalvo and Snodgrass, 1978a, 1978b). The rate of apomorphine- or amphetamine-induced contralateral rotation in the lesioned rats was correlated with the increase in striatal DA turnover and the decrease in cortical 5-HT turnover (Giambalvo and Snodgrass, 1978a, 1978b). Unilateral electrolytic lesion of the median raphe also resulted in spontaneous haloperidol sensitive contralateral rotation (Costall and Naylor, 1974a; Costall et al., 1976b; Hodge and Butcher, 1979; Nicolaou et al., 1979), contralateral rota-

tion upon administration of apomorphine or amphetamine (Costall and Naylor, 1974a; Costall et al., 1976b) and increases in ipsilateral striatal HVA and DOPAC (Nicolaou et al., 1979).

It seems reasonable to suggest that median raphe lesions remove a tonic serotonergic inhibition of the dopaminergic nigrostriatal neurons in the SN. Electrophysiological data indicate that the predominant effect of 5-HT iontophoresed on SN cells was a depression of the PC cells which was antagonized by iontophoresis of a 5-HT antagonist, methiothepin (Dray and Straughan, 1976). Consonant with this suggestion, unilateral intranigral injection of 5-HT caused ipsilateral circling and a decrease in ipsilateral striatal HVA (Straughan and James, 1978). The opposite effects were obtained following intranigral injection of a 5-HT antagonist, methysergide. The rate of apomorphine-induced contralateral rotation in median raphe or SN 5,7-DHT lesioned rats was not correlated with the decrease in striatal 5-HT turnover (Giambalvo and Snodgrass, 1978a) suggesting that the site of 5-HT action was not in the striatum. Although nigral 5-HT turnover was not measured in any study, the similarity of the rotational and biochemical profile following 5,7-DHT lesions of the SN and the median raphe suggests that the median raphe 5-HT neurons modulate rotational behavior by exerting tonic inhibitory input directly to the dopaminergic nigrostriatal neurons at the level of the SN.

In contrast to median raphe lesions, unilateral 5,7-DHT lesions of the dorsal raphe caused transient spontaneous ipsilateral rotation that disappeared 2 days after the lesion (Blackburn et al., 1979). Apomorphine and amphetamine induced ipsilateral rotation and a 5-HT

agonist, 5-methoxy-N,N-dimethyltryptamine (5-DMT) induced contralateral rotation 1 week following electrolytic lesions (Nicolaou et al., 1979) or 3 days after 5,7-DHT lesion (Blackburn et al., 1979) of the dorsal raphe. All drug-induced rotation was reduced by haloperidol (Blackburn et al., 1979). Consonant with the known projections of the dorsal raphe, apomorphine or amphetamine also caused haloperidol sensitive ipsilateral rotation in rats with 5,7-DHT lesions of the MFB (Giambalvo and Snodgrass, 1978b; Waddington and Crow, 1979) or the ventrocaudal (5-HT rich area) striatum or the GP (Giambalvo and Snodgrass, 1978b). The 5-HT agonists, 5-DMT and fenfluramine (Waddington and Crow, 1979) or 5-HTP (Azmitia and Segal., 1978; Jacob et al., 1977) induced contralateral rotation in MFB 5,7-DHT lesioned rats. 5,7-DHT lesions of the dorsal raphe or MFB produced an ipsilateral striatum reduction in 5-HT, 5-HT turnover, 5-HT uptake and DA turnover and an ipsilateral cortex reduction in 5-HT and 5-HT uptake (Blackburn et al., 1979; Giambalvo and Snodgrass, 1978b; Jacobs et al., 1977; Waddington and Crow, 1979).

The data suggest that rotation resulting from dorsal raphe or MFB lesions is mediated through a different mechanism from that resulting from median raphe or SN lesions. The dorsal raphe 5-HT neurons might indirectly exert a tonic facilitatory input on DA neurons in the striatum. In agreement with this suggestion, intrastriatal injection of 5-HT evoked contralateral circling in nonlesioned rats (Costall and Naylor, 1974b) and intrastriatal injection of the 5-HT antagonist, cyproheptadine, caused ipsilateral head turning in response to noxious stimuli (McKenzie et al., 1972). However, intrastriatal 5-HT induced contralateral circling might be independent

from dopaminergic nigrostriatal neurons, since this rotation was also shown in rats with prior 6-OHDA lesions of the ipsilateral nigrostriatal system (Costall et al., 1976c; Setler et al., 1978). A DA-independent 5-HT rotation in rats with 5,7-DHT lesions of the MFB may exist since neither direct nor indirect DA agonists induced rotation, while 5-HTP and para-chloroamphetamine induced contralateral rotation (Jacobs et al., 1977). The parachloroamphetamine effect was blocked by pretreatment with the 5-HT synthesis inhibitor, para-chlorophenylalanine (Jacobs et al., 1977). Similar results were also obtained from rats with 5,7-DHT lesions of rostral striatum. These animals rotated contralaterally in response to 5-DMT (Waddington and Crow, 1979) but did not rotate following apomorphine or amphetamine (Giambalvo and Snodgrass, 1978b; Waddington and Crow, 1979).

A 5,6-DHT lesion of the MFB which in addition to reducing striatal 5-HT also caused a substantial reduction of striatal DA, yielded the same rotational profile as 6-OHDA lesion of the MFB, i.e. contralateral rotation to apomorphine and ipsilateral rotation to amphetamine (Pieri et al., 1975; Waddington, 1977a; Waddington and Crow, 1979). The additional ipsilateral striatal 5-HT depletion by 5,6-DHT might account for the faster onset of apomorphine-induced contralateral rotation (Crow and Waddington, 1977; Waddington, 1977a) and the attenuation of amphetamine-induced ipsilateral rotation (Waddington, 1977a).

While it is certain that the 5-HT system modulates rotational behavior, it appears that not all 5-HT neurons have similar effects on rotation. The median raphe seems to influence rotation linked to DA probably by tonically inhibiting the nigral DA neurons. Dorsal

raphe cells, on the other hand, have an opposite influence on rotation and might be indirectly linked to the DA system in the caudate. The opposite results on spontaneous as well as drug-induced rotation obtained from 5,7-DHT lesions of the median raphe/SN and dorsal raphe/MFB/CP make it unlikely that only one of the raphe nuclei influences rotation and that lesions of the other reflect damage to axons of passage. However, the possibility that the two nuclei have synaptic interactions such that one normally inhibits the other has not been excluded.

Norepinephrine and rotation

The role of noradrenergic neurons in rotational behavior is still uncertain. There is no anatomical evidence demonstrating direct interconnection between the dopaminergic nigrostriatal system and the noradrenergic system. Norepinephrine (NE) levels in the CP are relatively low compared to DA, ACh, GABA and 5-HT. Effects on rotation of drugs modifying noradrenergic transmission can generally be accounted for by their actions on DA receptors or by their nonselective effects. Unilateral intrastriatal injection of NE caused contralateral rotation in rats pretreated with a monoamine oxidase inhibitor or reserpine and a monoamine oxidase inhibitor (Sato et al., 1976; Setler et al., 1976; Ungerstedt et al., 1969), but not in nonpretreated rats (Costall and Naylor, 1974b; Costall et al., 1974; Donaldson et al., 1976a). Contralateral rotation was also obtained following intrastriatal injection of NE ipsilateral to a prior 6-OHDA lesion after DA supersensitivity developed (Costall et al., 1976c;

Setler et al., 1978). These effects were presumed to be due to actions of NE on DA receptors (Sato et al., 1976; Ungerstedt et al., 1969). There is recent evidence, however, of the presence of β_1 -adrenergic receptors in the rat striatum (Palacios and Kuhar, 1980).

NE reuptake blockers, meprotiline, clomipramine, and amitriptyline, suppressed apomorphine-induced contralateral rotation in 6-OHDA lesioned rats (Delini-Stula and Vassout, 1979). Amitriptyline also suppressed amphetamine-induced ipsilateral rotation in 6-OHDA lesioned mice while low dose increased it (Pycock et al., 1976). The suppression of apomorphine- or amphetamine-induced rotation might be due to DA receptor blocking properties of these drugs (Delini-Stula and Vassout, 1979; Pycock et al., 1976). Amitriptyline and clomipramine have been shown to inhibit DA activated adenylate cyclase from rat striatum (Karobath, 1975). Although alpha and beta adrenergic receptor antagonists have been reported to alter rotation, it is difficult to ascribe their effects to specific receptors. Propranolol reduced apomorphine induced circling (Luscombe et al., 1979) but large doses were required, and there was no stereospecificity for l- and d-isomers. The "alpha-blocker", phenoxybenzamine, attenuated apomorphine-induced rotation (Pycock et al., 1975b) in 6-OHDA lesioned mice but only at doses that caused sedation. The pharmacological interaction that remains unexplained is the action of the α_2 receptor agonist, clonidine, in increasing apomorphine- or amphetamine-induced rotation in 6-OHDA lesioned mice (Pycock et al., 1977).

A direct approach to the role of noradrenergic systems on rotation has been attempted by lesioning the locus coeruleus. Unilateral electrolytic or 6-OHDA lesions of the locus coeruleus which caused a permanent reduction of ipsilateral cortical NE by 55 % yielded rats in which apomorphine or amphetamine induced contralateral rotation. The increased drug sensitivity lasted for approximately 1 month after the lesion (Donaldson et al., 1976a, 1976b; Pycock et al., 1975a). Although the lesions were presumably placed in the noradrenergic system, the apomorphine or amphetamine -induced contralateral rotation in these lesioned rats was not attenuated by phenoxybenzamine or propranolol (Donaldson et al., 1976a), which might be expected to minimize the surgically induced noradrenalin asymmetry. Unilateral electrolytic lesions of the ascending ventral noradrenergic bundle mimicked the effects of locus coeruleus electrolytic lesions (Donaldson et al., 1976c, 1978). The possibility of a noradrenergic facilitatory input to the ipsilateral dopaminergic nigrostriatal system (probably at the SN) has been suggested. It is supported by the results that intranigral NE (Donaldson et al., 1976a) or alpha-agonists, clonidine and oxymetazoline (Arnt and Scheel-Krüger, 1979b) caused contralateral rotation. Neither clonidine (Pycock et al., 1977; Setler et al., 1976) nor NE (Donaldson et al., 1976a) caused rotation following unilateral intrastriatal injections. In addition, the prediction is consonant with the finding that electrical stimulation of the locus coeruleus did excite dopaminergic nigrostriatal neurons, although the excitation was followed by inhibition (Collingridge et al., 1979). Sodium-dependent uptake and potassium-evoked calcium dependent release of ^3H -NE from rat SN slices in vitro have

been shown (Collingridge et al., 1979). The release was reduced by 6-OHDA lesions of the ipsilateral locus coeruleus.

The possibility that electrolytic lesion at the locus coeruleus or the ventral noradrenergic bundle might have also included 5-HT axons, and that it was the latter that was critical seems unlikely since neither locus coeruleus (Jenner et al., 1977) nor ventral noradrenergic bundle (Donaldson et al., 1978) lesions reduced cortical 5-HT. However, dorsal noradrenergic bundle lesions which caused apomorphine or amphetamine -induced ipsilateral rotation (Donaldson et al., 1976c, 1978) were accompanied by a reduction in both cortical NE and 5-HT (Donaldson et al., 1978). The direction of apomorphine or amphetamine -induced rotation as well as the reduction in cortical 5-HT were similar to those obtained from electrolytic or 5,7-DHT lesions of the dorsal raphe (Blackburn et al., 1979; Nicolaou et al., 1979). This suggests that lesions of 5-HT neurons might be responsible for the rotational effects following lesions aimed at the dorsal noradrenergic bundle. Whether NE directly modulates the dopaminergic nigrostriatal system, and if so, how the two systems are linked is still unclear. It should be noted that hemispheric asymmetry of NE distribution in human thalamus (Oke et al., 1978) and rat thalamus (Oke et al., 1980) has been shown. Whether the NE hemispheric asymmetry is involved in lateralization and rotational behavior is unknown.

Morphine, opioid peptides and rotation

The brain areas with the highest content of enkephalins are the caudate putamen and globus pallidus (Hong et al., 1977a), and opiate binding sites are highly localized in the caudate putamen (Atweh and Kuhar, 1977; Kuhar et al., 1973) and the central pars compacta (Pert et al., 1976). Systemic morphine and other narcotic analgesics produced ipsilateral circling in rats with unilateral electrolytic or 6-OHDA lesion of the SN (Iwamoto et al., 1976b). The inactive isomer of levorphanol, dextrophan, was ineffective supporting a specific opiate effect, however, high doses of naloxone (20 - 30 mg/kg) were required to block morphine-induced rotation (Iwamoto et al., 1976b). Unilateral intranigral beta-endorphin, morphine and other narcotic analgesics caused contralateral circling (Iwamoto and Way, 1977). The microinjected drugs were ineffective following prior 6-OHDA lesions of the ipsilateral SN, a supramaximal dose (20 mg/kg i.p.) of naloxone or a high dose (2 mg/kg i.p.) of haloperidol which induced catalepsy in all rats (Iwamoto and Way, 1977). The doses of both naloxone and haloperidol, however, were high and render judgements about specific drug effects difficult. The effects of morphine either administered locally to nonlesioned rats or systemically to unilateral nigrostriatal lesioned rats might be via modulation of the dopaminergic nigrostriatal system. In fact, systemic morphine increased the firing rate of the dopaminergic nigrostriatal neurons (Iwatsubo and Clouet, 1977) and increased striatal DA turnover (Papeschi et al., 1975). These effects were not due to a neuroleptic-like action since morphine did not antagonize the decrease in firing rate of the DA neurons following

systemic apomorphine or l-DOPA (Iwatsubo and Clouet, 1977) nor did it block DA activated adenylate cyclase in the rat CP in vitro (Iwatsubo and Clouet, 1975). Since unilateral intrastriatal injection of even large doses of morphine did not result in circling or asymmetry (Iwamoto and Way, 1977), it was presumed that morphine facilitated dopaminergic nigrostriatal activity via an action in the SN.

Some actions of morphine and other narcotic analgesics show significant species variation. For example, in rats with unilateral 6-OHDA caudate lesions, morphine blocks amphetamine-induced turning (Slater et al., 1980), whereas in mice this turning is augmented by morphine (Slater and Blundell, 1979). The species difference was also evident neurochemically in that systemic morphine significantly decreased striatal cAMP in rats and increased it in mice (Slater and Blundell, 1979). In contrast to amphetamine-induced rotation, apomorphine-induced contralateral rotation in SN 6-OHDA lesioned rats was only modestly reduced by systemic morphine (Slater et al., 1980). One possible mechanism of morphine action in rats is that it suppresses the release of DA (Celsen and Kuschinsky, 1974; Loh et al., 1976) possibly by stimulating specific opiate receptors on the pre-synaptic terminals of dopaminergic nigrostriatal neurons (Biggio et al., 1978). This action would account for the effects of morphine on amphetamine-induced rotation.

Morphine microinjections outside the nigrostriatal system also resulted in rotation. Morphine and heroin (but not other opiates) unilaterally microinjected to the midbrain reticular formation induced a tight ipsilateral circling in response to previously neutral auditory or visual stimuli (Jacquet et al., 1976). Unlike intranigral

morphine-induced contralateral circling, ipsilateral circling upon sensory stimuli that followed intrareticular morphine was potentiated by systemically or locally administered naloxone but was not affected by systemic pimozide (Jacquet et al., 1976).

PRESENT EXPERIMENTS

The SN has been shown to have a major role in rotational behavior. Contralateral rotation evoked by electrical stimulation of the SN (nigral-evoked rotation, NER) has often been presumed to be due to activation of the striatal synapses made by DA neurons of the SN pars compacta. To verify the DA hypothesis of the NER and to study the physiology and pharmacology of the nigral afferents and efferents, effects of lesions and drugs on rotation evoked by electrical stimulation of the SN in rats were examined. The initial hypothesis was that nigral DA synapses (by the release of DA from dendrites) rather than striatal synapses were of prime importance in controlling rotation. The hypothesis was first tested by studying the immediate and delayed effects of electrolytic and/or 6-OHDA lesions of the LH on NER. If NER were due to DA release in the SN, there should be no immediate change following an electrolytic lesion at the LH. Rotation would decrease with time as retrograde degeneration in the SN impaired DA release. Similarly, 6-OHDA lesions at the LH should have had no immediate effect but rotation should decrease as DA cell bodies in the SN degenerated. The results of initial experiments were that

LH electrolytic lesions which produced a mean ipsilateral striatal DA depletion of 58 % caused immediate deficits in NER with no further reduction with time after lesion, while 6-OHDA lesions which produced mean ipsilateral striatal DA depletion of 93 % caused an increase in NER from 3 to 24 days. These findings not only did not meet either of the initial expectations, but raised the question of whether the rotation evoked by SN stimulation even required activation of the DA neurons. Subsequent experiments sought to examine the reasons for the differential lesion effect and to identify the pathway involved in stimulus induced rotation. The differential effects of the two types of lesion might reflect differences in the extent of striatal DA depletion in the neurons destroyed. If LH electrolytic lesions reduced NER by partial reduction of striatal DA, 6-OHDA lesions at the LH producing striatal DA depletion equivalent to that occurring with electrolytic lesions should have reduced NER to the same extent. However, 6-OHDA lesions which produced mean ipsilateral striatal DA depletion of 57 and 40 % had no effect on NER. Conversely if the reduction in NER upon electrolytic lesion of LH resulted from destruction of nondopaminergic axons, then such lesions should have equivalent effects with and without prior 6-OHDA lesions. This hypothesis was tested and electrolytic lesions at the LH reduced NER to an equivalent extent in both 6-OHDA and vehicle pretreated rats. Consistent with the view that the effects of electrolytic lesions were independent of the loss of DA cells, there were no correlation between percent reduction of NER and percent depletion of ipsilateral striatal DA in any lesioned group.

The opposite direction of alteration in NER following electrolytic and 6-OHDA lesions of the LH is similar to the opposite direction of apomorphine-induced rotation following electrolytic and 6-OHDA lesions of the SN (i.e. electrolytic lesions reduced NER -- equivalent to apomorphine-induced ipsilateral rotation; 6-OHDA lesions increased NER -- equivalent to apomorphine-induced contralateral rotation). Thus, NER resembles apomorphine rather than amphetamine, which implies that the rotation may be evoked by orthodromic or antidromic activation of non DA neuronal elements postsynaptic to the dopaminergic nigrostriatal system.

Although reduction of striatal DA did not reduce NER, the question of whether the CP is essential for NER remained to be answered. Small electrolytic lesions which destroyed the center of the CP had no effect on NER until 14 days postlesion. Large caudate lesions which destroyed the major part of the head of CP did not immediately reduce NER but gradually reduced it with maximum reduction at 3 days after the lesions. In contrast to CP lesions, however, electrolytic lesions of the globus pallidus immediately reduced NER, and the effect persisted for the two weeks of testing. Lesions of other structures which receive nigral efferents did not change rotation. The delayed effects of CP lesions and immediate effects of GP lesions suggest that NER requires pallidal synapses of axon collaterals from striato-nigral or nigrostriatal pathways. An attempt was made to distinguish these two models by using ibotenic acid lesions of the CP. An ibotenic acid lesion which destroyed only cell bodies in the CP was expected to reduce NER if striatal efferents were being antidromically activated. and to have minimal effects if nigral efferents were being

orthodromically activated. The latter was the case in the present results, however, the conclusion would be premature since histology revealed that extent of the lesion was less than that of the effective electrolytic lesions.

The contribution of DA to the NER remains questionable. The persistence and even enhancement of NER following 6-OHDA lesions which in some rats reduced striatal DA to undetectable levels argues against it. Haloperidol, on the other hand, did partially reduce NER in doses which produced no grossly observable motor deficits. Since it produced equivalent effects in lesioned and nonlesioned rats the specificity of its actions as a DA antagonist might be questioned. Effects of generalized reduction of brain catecholamines by synthesis blockers, alpha-methyl para-tyrosine and diethyldithiocarbamate on NER were studied. Both drugs reduced NER. Desipramine pretreatment to prevent depletion of forebrain NE by 6-OHDA 8 ug also prevented the increase in NER. These results suggest some role for the noradrenergic system in rotation evoked by electrical stimulation of the SN.

MATERIALS AND METHODS

Surgery

Female Sprague-Dawley rats weighing 250 to 300 g. at surgery were used throughout the experiments. Surgical instruments, electrodes, cannulae and screws were immersed in benzalkonium chloride (1:750 solution) for at least 30 minutes before use. Rats were anesthetized with methohexital (Brevital, Lilly) 50 mg/kg i.p. and were placed in a Kopf stereotaxic apparatus with the mouth piece 5 mm. above the interaural line. A midsagittal cut through the skin above the skull was made, the skull was exposed and cleaned. Adrenalin chloride 1 mg/ml solution (Parke-Davis) was applied at the cut to minimize bleeding. The intersection of bregma and the sagittal suture was used to reference electrodes and cannulae. The stereotaxic coordinates (Pellegrino and Cushman, 1967) used in this study are shown in Table I. Guide cannulae and lesioning and stimulating electrodes were generally implanted in the left hemisphere. In the study of lesion effects on rotation evoked by stimulation of the contralateral SN, stimulating electrodes were implanted in the right SN. Electrodes and/or cannulae were fixed to the skull by dental cement anchored to the 3 stainless steel screws. Bacitracin-neomycin-polymyxin ointment (E. Fougera & Co.) was applied to the area surrounding the dental cement at surgery and every day after testing for rotation. Cut skin anterior and posterior to the cement cap was closed with wound clips. Iodine 1% solution was applied at the cut edge. Procaine penicillin suspension 12,000,000 units was given intramuscularly at the end of surgery. Rats were housed individually with free access to Purina rat chow and water.

Table I

Stereotaxic coordinates (Pellegrino and Cushman, 1967) for electrodes and guide cannulae, parameters for electrolytic and chemical lesions.

Sites	Implanted	A-P*	L**	H***	Lesions
Substantia nigra	Electrode	-3.2	2.0	7.8	
Lateral hypothalamus	Electrode	-1.6	2.0	7.5	2 mA DC, 15 sec
	Cannula	-1.6	2.0	6.5	6-OHDA 8,4,1 ug
Caudate putamen	Electrode	+2.0	3.0	5.0	2 mA DC, 30 sec
		+3.0	2.5	5.5	2 mA DC, 30 sec
					5 mA DC, 30 sec
	Cannula	+3.0	2.5	4.5	Ibotenic acid 10, 20 ug
Globus pallidus	Electrode	+0.8	3.0	6.5	2 mA DC, 20 sec
Nucleus accumbens	Electrode	+3.4	1.5	6.5	2 mA DC, 20 sec
Thalamic nuclei:					
Ventral anterior	Electrode	-0.4	1.7	6.7	2 mA DC, 15 sec
Ventromedial	Electrode	-1.0	1.2	6.7	2 mA DC, 20 sec
Dorsomedial	Electrode	-1.2	1.0	5.4	2 mA DC, 25 sec
Parafascicular	Electrode	-2.2	1.2	5.7	2 mA DC, 15 sec
Amygdala nuclei:					
Central	Electrode	0.0	4.7	7.8	2 mA DC, 20 sec
Lateral	Electrode	-1.0	5.3	7.8	2 mA DC, 25 sec
Olfactory tubercle	Electrode	+3.4	3.2	9.2	2 mA DC, 30 sec
Piriform cortex	Electrode	+1.0	5.8	8.0	2 mA DC, 30 sec
superior colliculus	Electrode	-5.2	1.2	3.2	2 mA DC, 20 sec
Mesencephalic reticular formation	Electrode	-5.0	2.0	6.0	2 mA DC, 20 sec
Periventricular gray matter	Electrode	-5.0	0.8	5.1	2 mA DC, 20 sec

* mm. anterior (+) or posterior (-) from bregma

** mm. from midsagittal line

*** mm. from dura

Electrodes

Stimulating and lesioning electrodes were bipolar twisted stainless steel wires, 0.25 mm. in diameter insulated except at the tips (Plastic Products Co.). Electrodes were cut to the appropriate length (about 3 mm. longer than the vertical coordinates) and were tested for continuity of insulation prior to use. Electrodes for large lesions in the CP had 1.5 mm. of the tip exposed and had a tip separation of 1.5 mm.

Cannulae

The cannulation system was constructed according to the method of Crane and Glick (1979). Guide cannulae were made of g 26 stainless steel hypodermic tubing cut to appropriate length and notched at the upper end. Stylets were g 32 stainless steel hypodermic tubing inserted through the guide cannulae with 1 mm. bent outward over the notch of the guide cannulae. The opposite ends of the guide cannulae with stylets were sharply bevelled for penetration of the dura and also to seal off the end of the stylet tubing. Injection cannulae were g 33 stainless steel hypodermic tubing that extended 1 mm. beyond the guide cannula tip when seated in the guide. The length of the g 33 tubing was set using a short piece of g 26 tubing, and polyethylene tubing (PE 10) was attached to each cannula with a drop of epoxy glue.

Prelesion stimulus-rotation curves

Rats were allowed to recover from surgery for at least one week. Stimulus-rotation curves were done during the light part of the 12 hr.

-dark-light cycle. The rat was placed in a plexiglass cylinder (12 inches in diameter and height) with a grid aluminum plate floor. The electrode was connected to the stimulator via a mercury commutator installed above the cylinder so the rat could freely move in the cylinder. A Grass S48 stimulator equipped with a photoelectric constant current isolation unit (Grass PSIU 6B) was used to generate constant current 10 second trains of 1 msec pulses at 30 Hz. Current amplitude was increased stepwise in 40 uA increments from 40 to 400 uA (or until excessive body torsion precluded rotation) at 1 minute intervals. The first stimulus was delivered 3 to 5 minutes after the rat was placed in the chamber. The number of contralateral rotations was counted to the closest quarter turn. Stimulus-rotation curves were initially plotted as stimulus amplitude versus number of evoked turns. These are referred to as amplitude-rotation curves (A-R). Altering stimulus frequency at a fixed amplitude can also generate a graded rotation response. These were included in later experiments by selecting a stimulus amplitude for each rat that produced half to two-thirds of the maximum rotation. Stimulus frequency was altered in 10 Hz increments from 10 to 100 Hz (or until excessive body torsion precluded rotation) once per minute. These plots are referred to as frequency-rotation curves (F-R). F-R curves were always done 45 minutes after the A-R curve was completed. Rats were tested daily until rotation stabilized before beginning experiments. Rats with reproducible rotation of 2 turns or more at any control test and with a consistent stimulus response relationship were included in the experiments. Lesions or drug administration to nonlesioned rats were done on the day after the last control. The prelesion stimulus-rotation

control for each rat was the average of 3 stable curves tested on 3 different days (Fig. 2B). The predrug curve for each rat was the one obtained on the day of drug administration.

Lesions

Electrolytic lesions

Rats were lightly anesthetized with methohexital 25 mg/kg i.p. and the electrodes were connected bipolarly to a Grass D.C.LM5 lesion maker. Current parameters for lesions are shown in Table I. To prevent inadvertent lesion of the GP, one group of rats who were to have large CP lesions received monopolar anodal current through the anterior pole of the lesioning electrode using a metallic plate underneath the rat body as an indifferent. Sham lesions were done under conditions identical to that of the lesions except no current was passed through the electrodes.

6-OHDA lesions

6-OHDA HBr (Regis) 2 ug/1 ul solution calculated as free base was freshly prepared in ice-cold sterile saline with 0.2 mg/ml ascorbic acid (Fisher) as an antioxidant. The vehicle for control injections was ascorbic acid 0.2 mg/ml in sterile ice-cold saline. A 10 ul microsyringe connected to an injection cannula via a PE 10 tubing was prefilled to the tip of the injection cannula. The microsyringe was attached to a syringe pump (Sage 341). Micro-injections were done in nonanesthetized rats restrained in an uncovered plexiglass cylinder (8 inches in diameter, and 6 inches

in height). The stylet was replaced by the injection cannula and the solution was injected at a rate of 1 ul per 64 seconds. The injection cannula was left intact for 1 minute after completion of the injection, and the stylet was returned to the guide cannula. DMI pretreated rats received desipramine HCl (USV Pharmaceutical Corp., 15 mg/ml in water for injection) 30 mg/kg i.p. 30 minutes before 6-OHDA 8 ug in 4 ul microinjections.

Rats in sequential lesioned groups (6-OHDA + electrolytic lesion, vehicle + electrolytic lesion) received 6-OHDA 8 ug in 4 ul or vehicle 4 ul microinjections to the LH at the initial surgery before implanting lesioning electrodes at that site. Acute microinjections were done by attaching a 5 ul microsyringe with a blunt tip needle (g 26, 5 cm. long) filled with 6-OHDA or vehicle solution to a stereotaxic electrode holder. The microsyringe was lowered to the LH and the solution was injected manually at a rate of about 1 ul per minute. The microsyringe was withdrawn 1 minute after completion of the injection, and replaced by a bipolar electrode which was chronically implanted (see above).

Ibotenic acid lesions

Ibotenic acid (Regis, batch no. L1818,330401) 20 ug/0.5 ul or 10 ug/0.5 ul was freshly prepared in phosphate buffered saline (8 g. NaCl, 0.2 g. KH_2PO_4 , 1.5 g. Na_2HPO_4 , distilled water to 1 liter, pH 7.2 to 7.4). Cannulae were the same as those used for 6-OHDA. The injection rate was 0.39 ul per minute. Phosphate buffered saline 1.0 or 0.5 ul was injected as a control. The injection cannula was left intact for 1 minute after the injection.

Postlesion stimulus-rotation curves

All lesioned and sham rats except ibotenic acid lesioned rats were tested at 2 - 3 hours, 3, 7 and 14 days after the lesions. One group of rats with large CP lesions was followed up to 28 days after the lesions, another was tested at 2 - 3 hours, 6 - 7 hours, 1, 2, 3, 7 and 14 days postlesion. Ibotenic acid lesioned rats were tested at 2 - 3 hours, 1, 2, 3, 5, 7, 10 and 14 days postlesion. Methods and stimulus parameters for postlesion tests were identical to those for prelesion tests.

Drug preparation and administration

Haloperidol (McNeil) was prepared as a 1 mg/ml solution. The drug was dissolved in a few drops of glacial acetic acid, water for injection was added and the pH was adjusted to 4 - 5 using NaOH. The solution was diluted to 0.1 and 0.5 mg/ml before injection. Water for injection at pH 4 - 5 was used as the vehicle control. The same regimen of doses was used in all rats. Haloperidol 0.1 mg/kg was given first, followed by a control trial with vehicle 7 days later. Haloperidol 0.5 mg/kg was given last on day 3 after control. Post-haloperidol rotation was tested at 2 and 3 hours after the injections using same stimulus parameters as in the predrug test.

AMPT (DL-alpha-methyltyrosine methyl ester HCl, Regis) and DDTC (sodium diethyldithiocarbamate trihydrate, E. Merck) were prepared as 150 and 200 mg/ml solutions respectively in normal saline. AMPT 150 mg/kg, DDTC 200 mg/kg and an equivalent volume of saline i.p. were given to 8 rats. Three rats received saline first, AMPT 1 day after

saline, and DDTC 8 days after AMPT. Five rats received DDTC first, then saline 5 to 8 days after DDTC, and AMPT 3 days after saline. Rats were tested at 1 to 3 hours after DDTC, 4 to 5 hours after AMPT and 2 to 5 hours after saline. In all studies in which more than one dose of a drug or more than one drug was given to an individual rat, the interval between experiments was sufficient so that predrug rotation returned to the original control.

Dopamine assay

The extent of lesion damage to the DA-NS system was ascertained by measuring striatal DA levels using a gas chromatographic method (Wilk and Stanley, 1977). Rats were decapitated 2 to 3 days after the last stimulation test or 7 days after the last drug administration. The whole brain was quickly removed and dissected on an ice-cold glass plate. A coronal cut was made at the optic chiasm. The caudal part of the brain was kept in 10% formalin for verification of lesion size and stimulating electrode placement. The rostral part was cut in the midsagittal plane, and left and right striata were dissected, weighed and homogenized in 1 ml cold 1 N HCl. (Striatal samples from 4 rats in the initial electrolytic lesioned group and 6 rats in the sham group were originally prepared for a spectrofluorometric assay of DA. These samples were homogenized in 5 ml cold 0.4 N perchloric acid). Homogenized samples were centrifuged for 20 minutes at 15,000 rpm in a Sorvall RC-2B refrigerated centrifuge. Striatal supernatants were kept at -80°C until assay. An aliquot of 0.2 ml supernatant from intact striata or 0.4 ml from striata ipsilateral to lesions was added to 15 ml ground glass stoppered centrifuge tubes containing 100 mg

alumina, 4 ml 0.5 M pH 8.5 Tris-chloride buffer, 0.1 ml 10% EDTA pH 7.2 and 50 ng alpha-methyl dopamine (Hoffman La Roche) as an internal standard. Two standards containing 100 ng DA (Sigma) were processed in parallel with samples. The total volume of each tube was brought to 4.5 ml by adding 1 N HCl. (In the samples originally prepared for spectrofluorometric assay the procedure was modified by using 1 ml of 1 M pH 8.63 Tris-chloride buffer, 3.0 and 1.5 ml of perchloric acid supernatants from lesioned and intact side respectively, and the volumes equalized with 0.4 N perchloric acid).

Catecholamines were adsorbed onto the alumina by gently agitating the tubes by hand for 3 minutes. The supernatant was removed by aspiration after centrifugation. The alumina was washed 3 times with 5 ml water by shaking for 1 minute each time, centrifuging and removing the water by aspiration. The adsorbed catecholamines were eluted by shaking for 3 minutes with 1 ml 0.25 N acetic acid in methanol. After centrifugation the eluate was transferred to a 3 ml ground glass stoppered centrifuge tube and 10 μ l of a 1.25 mg/ml sodium diethyldithiocarbamate was added. The contents were evaporated to dryness under nitrogen. The residue was reacted with 5 μ l pentafluoropropionic anhydride (Pierce Chemicals) in 100 μ l ethyl ether for 5 minutes at room temperature. The reagents were then evaporated under a gentle stream of nitrogen and the derivatives dissolved in 250 μ l toluene for chromatographic analysis. Appropriate volumes were injected on a 3% OV-17 or 3% JXR column coated on gas chrom Q 100/120 mesh at a column temperature of 135 to 140°C in a Packard 7400 series gas chromatography, and a flow rate of 20 to 30 ml/minute nitrogen. The dimensions of the chromatographic columns were 6 feet

x 4 mm. I. D. The detector and inlet ports were maintained at a temperature 20° greater than the column temperature. The electron capture detectors contained 150 mCi ³H foils as source of electrons.

The calculation of the amount of DA was based on the ratio between DA and alpha-methyl DA in the sample (R sample) and in the standard (R standard).

$R = \text{DA peak height} / \text{alpha-methyl DA peak height}$

$DA = R \text{ sample} / R \text{ standard} \times 100 \text{ ng}$

Striatal DA was expressed as ug/g of tissue wet weight.

Percent DA depletion = $\frac{\text{contralateral} - \text{ipsilateral}}{\text{contralateral}} \times 100$

Histology

Nonlesioned and lesioned rats not subjected to striatal DA determinations were anesthetized with methohexital and perfused with saline followed by 10% buffered formalin. The whole brains were removed and kept under 10% formalin for at least 2 days. Frozen sections of 40 u thickness were sliced and one of every three was mounted and stained with luxol blue and cresyl violet. Mapping of the lesions and electrode placements was done by superimposing the magnified section on the stereotaxic atlas outline at the appropriate anterior-posterior plane. Caudate lesion volume was estimated by planimetric measurement of the lesion area in one of every three 40 u sections throughout the entire rostrocaudal extent of the lesion. Stimulating electrode tips in approximately 50% of the rats used in this study were the middle points between cathode and anode. In the remaining rats the polarity of stimulating electrodes was determined, and the middle of the cathode was localized as the electrode tip.

In rats microinjected with ibotenic acid serial 40 u sections of the CP were stained with neutral red (1%) and microscopic examination for degenerated cell bodies and glial reaction on the lesioned side was done.

Statistics

Data was stored, analyzed and graphs were produced using the PROPHEET, time sharing computer system of the National Institutes of Health. Statistical comparison of stimulus-rotation curves before and at various times after lesion or after drugs was done using the multifactor analysis of variance (ANOVA) program (Baig and Reid-Miller, 1980). Comparison of percent changes in mean rotation at selected stimuli or of DA levels in different groups of rats was done using the Newman-Keuls or Kruskal-Wallis multiple range test program (Baig and Reid-Miller, 1980). A paired t-test or Wilcoxon rank test was used to determine the significance of depletion of striatal DA. The extent of various lesions at the CP was compared by using t-tests. Correlation coefficients were determined between percent striatal DA depletion and percent change in mean rotation. Chi-square tests were used to determine the association between stimulating electrode placements and the rotation response.

RESULTS

Electrical stimulation of the SN in rats caused stimulus bound head to tail contralateral rotation. At subthreshold currents rats appeared to have normal spontaneous activity. Contralateral head turning was observed as the current approached threshold for rotation, and progressed to tight circling when the threshold current was reached. A few rats demonstrated head to tail rotation at the onset of stimulation which changed to wide circling by the end of the ten second stimulus train. The magnitude of the response could be altered by changing either stimulus amplitude or frequency. In general, inverted U shaped curves were obtained when the number of turns was plotted as a function of frequency (Fig. 1B, 3B). When the number of turns was plotted as a function of amplitude, curves ranged from a narrow inverted U (Fig. 1A) to broad inverted U curves (Fig. 2A) or curves that plateaued at 160 to 240 uA (Fig. 2B), to curves which continued to show increased rotation at and above 280 uA (Fig. 3A). Other behaviors were observed when stimulus amplitude or frequency was higher than the optimum for rotation. These behaviors were contralateral front paw tremor and body torsion which progressed to roll over around the longitudinal body axis. In inverted U shaped stimulus-rotation curves contralateral front paw tremor and body torsion were always associated with the descending part of the curves. Six rats did not show paw tremor or body torsion at stimuli up to 400 uA. These rats had sigmoidal amplitude-rotation curves (Fig. 3). Stimulus evoked rotational behavior stabilized in individual rats between 7 and 14 days post-surgery. There was generally reasonable stability when rats

Figure 1

Contralateral rotation evoked upon stimulation of the left substantia nigra in a rat with stimulating electrode at the border between the ventral substantia nigra and the cerebral peduncle. The ordinates show the number of 360° turns during a ten second train of 1 msec pulses at 1 minute interval.

A. Amplitude-rotation curve (A-R) tested at 40 days after surgery. Stimulus amplitude was increased by 40 uA increments at a frequency of 30 Hz. Contralateral front paw tremor and body torsion increasing the stimulus amplitude beyond 120 uA.

B. Frequency-rotation curve (F-R) from the same rat tested 45 minutes following the amplitude-rotation curve. Stimulus frequency was increased by 10 Hz increments from 10 to 100 Hz at an amplitude of 40 uA.

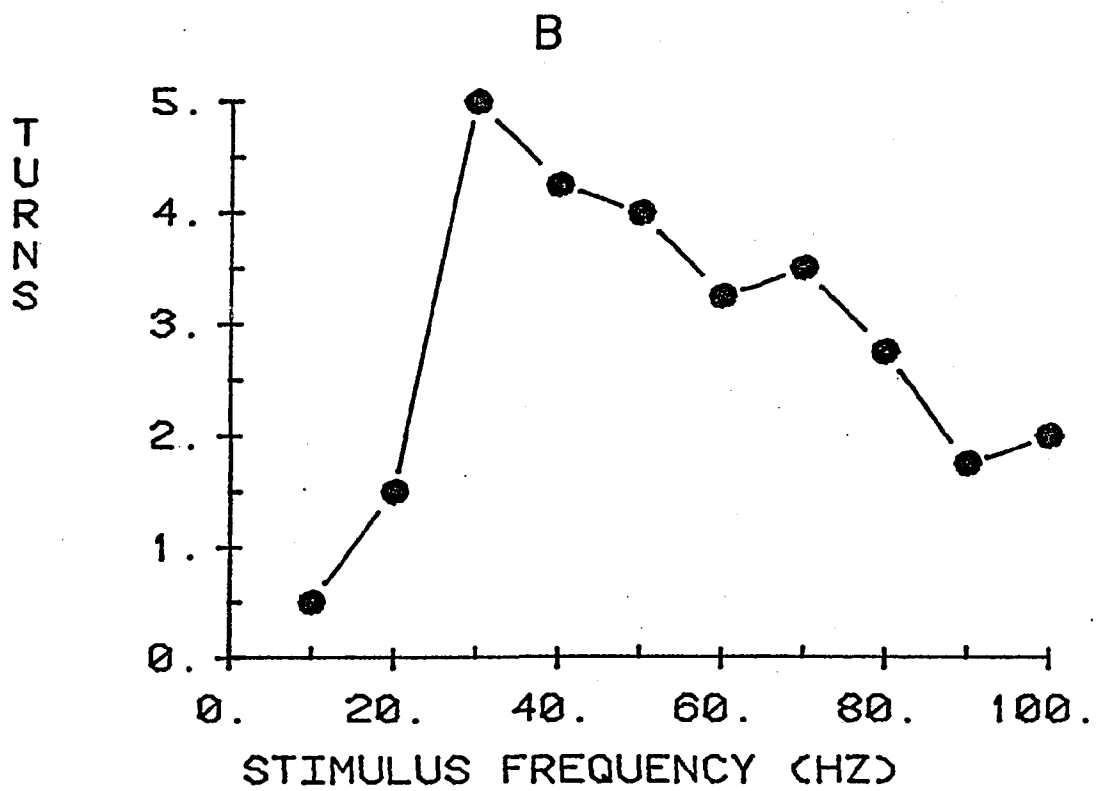
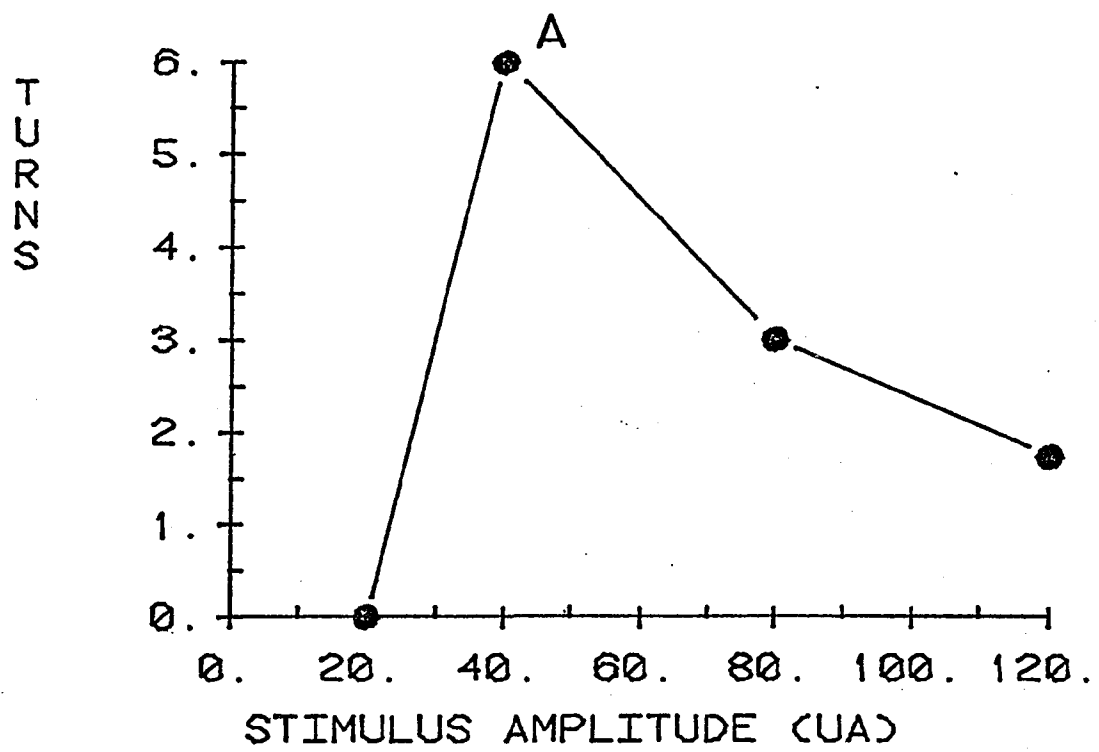


Figure 2

Contralateral rotation evoked upon stimulation of the left substantia nigra. The ordinates show the numbers of 360° turns during a ten second train of 1 msec pulses at 1 minute interval.

A. Broad inverted-U amplitude-rotation curve (A-R), from a control rat tested on day 40 after surgery. Stimulus amplitude was increased by 40 uA increments from 40 to 280 uA at a frequency of 30 Hz. Four complete stimulus-response curves were obtained at 45 minute intervals (O, 0 min; Δ , 45 min; $\square$, 90 min; $\diamond$, 135 min). The line connects the means of the 4 values at each stimulus amplitude.

B. Amplitude-rotation curve that plateaued at 200 uA from another rat tested at 8 (O), 9 (Δ) and 10 ($\square$) days after surgery. The line connected the means of the 3 values at each stimulus amplitude.

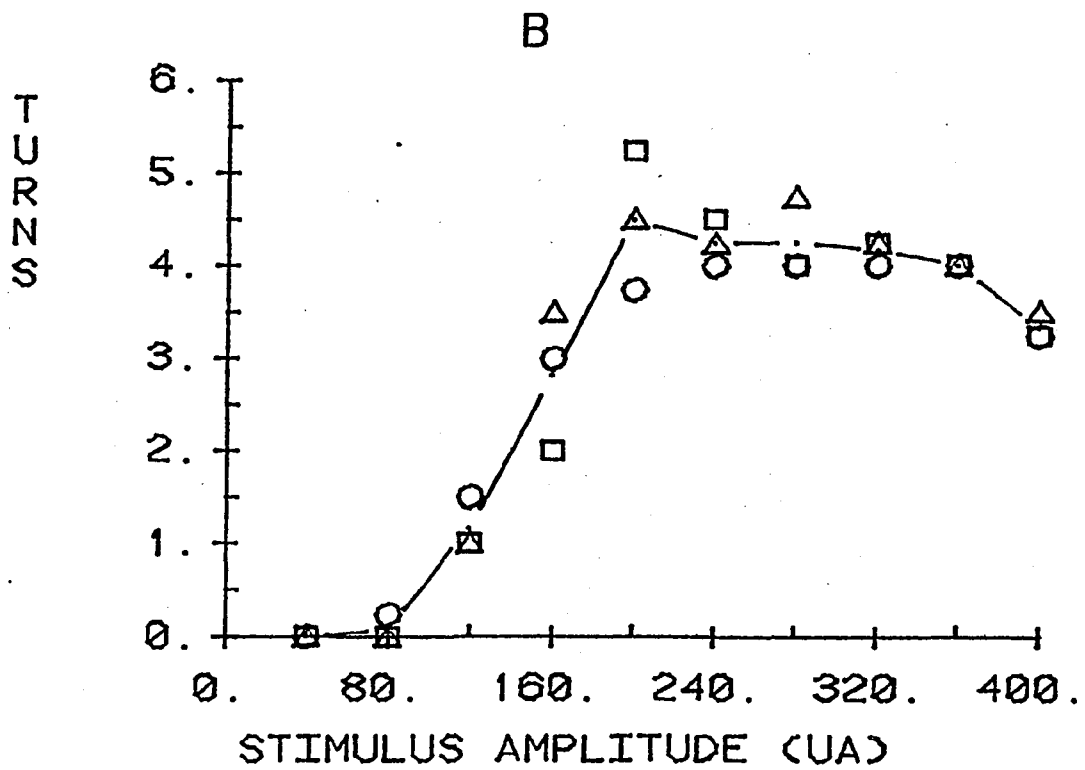
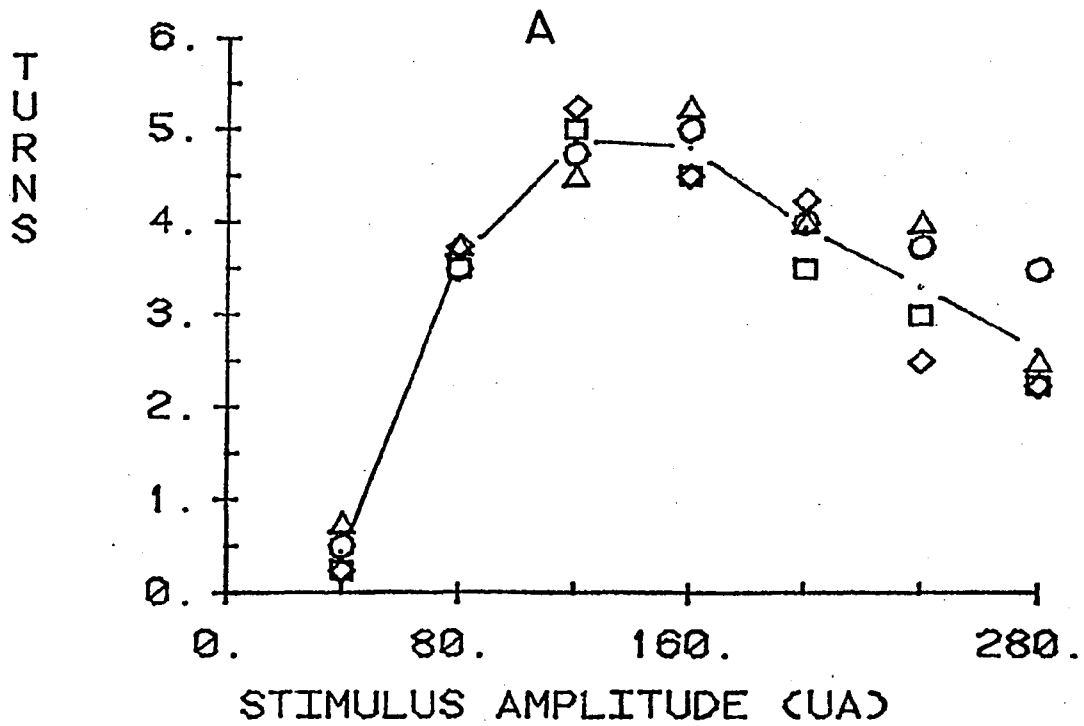
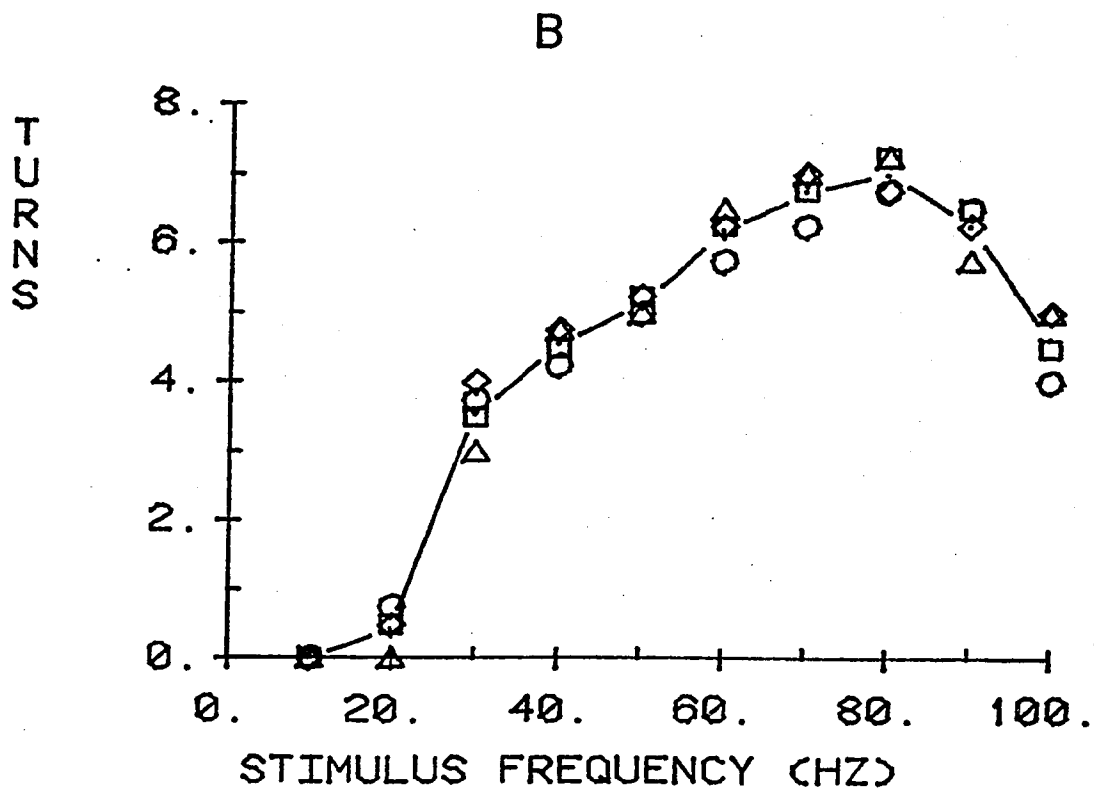
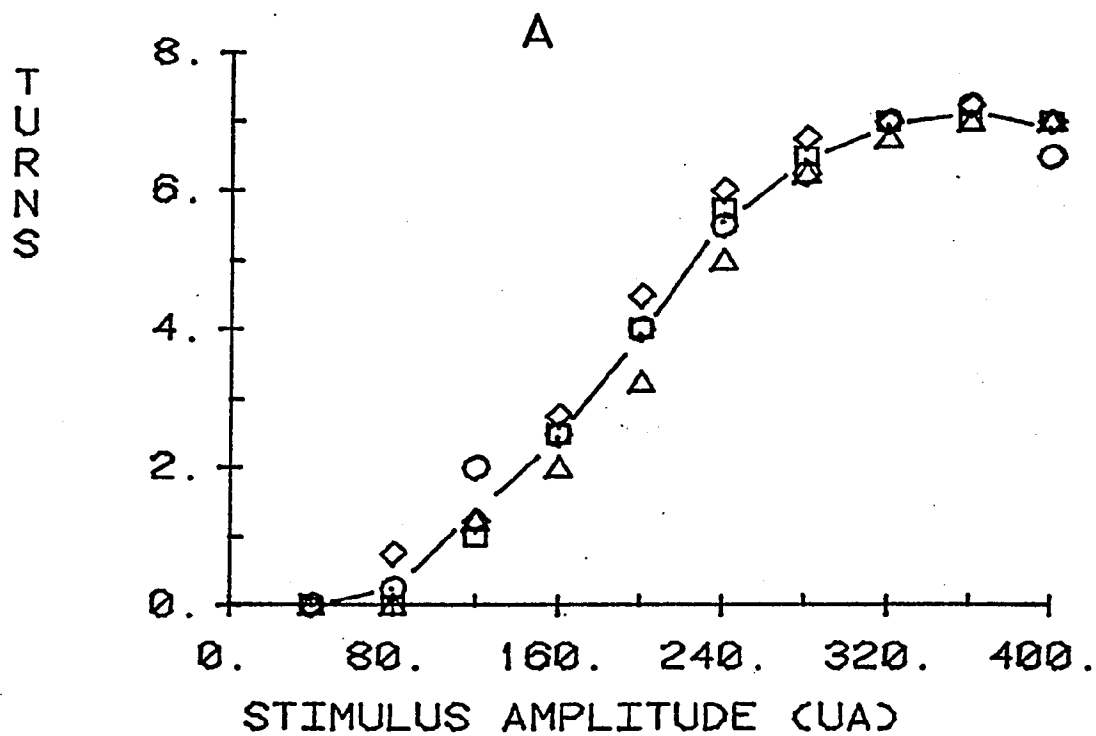


Figure 3

Contralateral rotation evoked upon stimulation of the left substantia nigra in a control rat tested at 45 minute intervals on the same day. The ordinates show the numbers of 360° turns during a ten second train of 1 msec pulses delivered every 1 minute. Four complete stimulus-response curves were obtained at 45 minute intervals (o, 0 min; Δ , 45 min; $\square$, 90 min; $\diamond$, 135 min). The lines connect the means of the four values at each stimulus intensity.

A. Amplitude-rotation curve tested at 36 days after surgery. Stimulus amplitude was increased by 40 uA increments from 40 to 400 uA at a frequency of 30 Hz.

B. Frequency-rotation curve tested at 47 days after surgery. Stimulus frequency was increased by 10 Hz increments from 10 to 100 Hz at an amplitude of 200 uA.



were repeatedly tested either on the same day (Fig. 2A, 3) or once per day (Fig. 2B).

Correlation between stimulus-induced rotation and electrode placement

Rats exhibiting maximum rotation of 2 or more turns with a consistent stimulus response relationship generally had electrode tips in the SN or the adjacent VTA (154 out of 175 rats). Among the poor rotators (less than 2 turns, no demonstrable stimulus response relationship) and non-rotators (no turns upon stimulus amplitudes up to 400 uA) 31 out of 47 rats had electrode tips outside the SN or VTA. Evaluation of the total 222 electrode placements with respect to ability to evoke rotation shows a significant correlation between electrode placement in the SN and rotation ($\chi^2 = 60.14$, $P < 0.005$). Rats showed considerable variation in the maximum number of turns that could be evoked (from 2 to 10.5 turns in 10 seconds) as well as in the lowest stimulus amplitude producing one full turn [40 uA (20% of total rats studied), 80 uA (40 %), 120 uA (17 %), 160 uA (13 %), 200 uA (6 %) and 240 uA (4 %)]. Rats with thresholds for 1 full turn of 120 and 160 uA had a higher maximum number of turns [$\bar{x} \pm \text{SEM} (n) = 5.44 \pm 0.35 (32)$ and $5.36 \pm 0.49 (23)$ respectively] than rats with threshold for one full turn of 240 uA [$\bar{x} \pm \text{SEM} (n) = 3.39 \pm 0.41 (7)$] (Newman-Keuls test, $P < 0.05$). Of the group of "acceptable rotators", evaluation of 84 electrode placements which generated rotation of low (40 or 80 uA) or high (200 or 240 uA) threshold for 1 full turn showed that the probability of the electrode being in the SN was higher for low threshold than for high threshold rats [61 of 65 low thresh-

hold rats (94 %) and 12 of 19 high threshold rats (63 %) had electrode tips in the SN] ($\chi^2 = 12.17$, $P < 0.005$).

Forty two rats had particularly narrow inverted U amplitude-rotation curves such as that illustrated in Figure 1. The response at high stimulus amplitudes was dominated by contralateral front paw tremor and body torsion. These behaviors were less apparent when stimulus amplitude was selected on the ascending limb of the curve and the stimulus frequency was varied from 10 to 100 Hz. In these rats the locations of electrode tips were in ventral SN or at the border between the ventral SN and the cerebral peduncle, (15 out of 42 rats with narrow A-R curves vs. 17 out of 133 rats with wide A-R curves had electrode tips on the ventral edge of the SN, $\chi^2 = 11.23$, $P < 0.005$). Consistent with the above, all 6 rats with amplitude-rotation curves that showed no decline in rotation at high stimuli had electrode tips in the dorsal half of the SN. All rats with narrow amplitude-response curves exhibited thresholds for a full turn at 40 to 80 μ A.

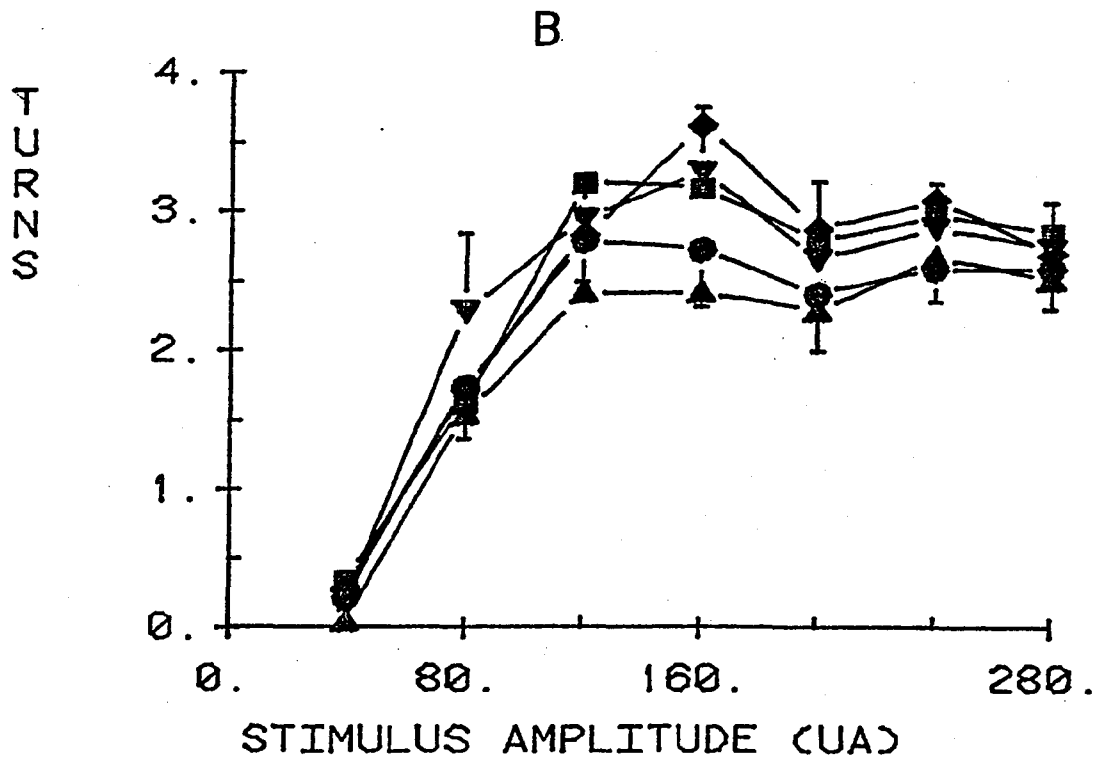
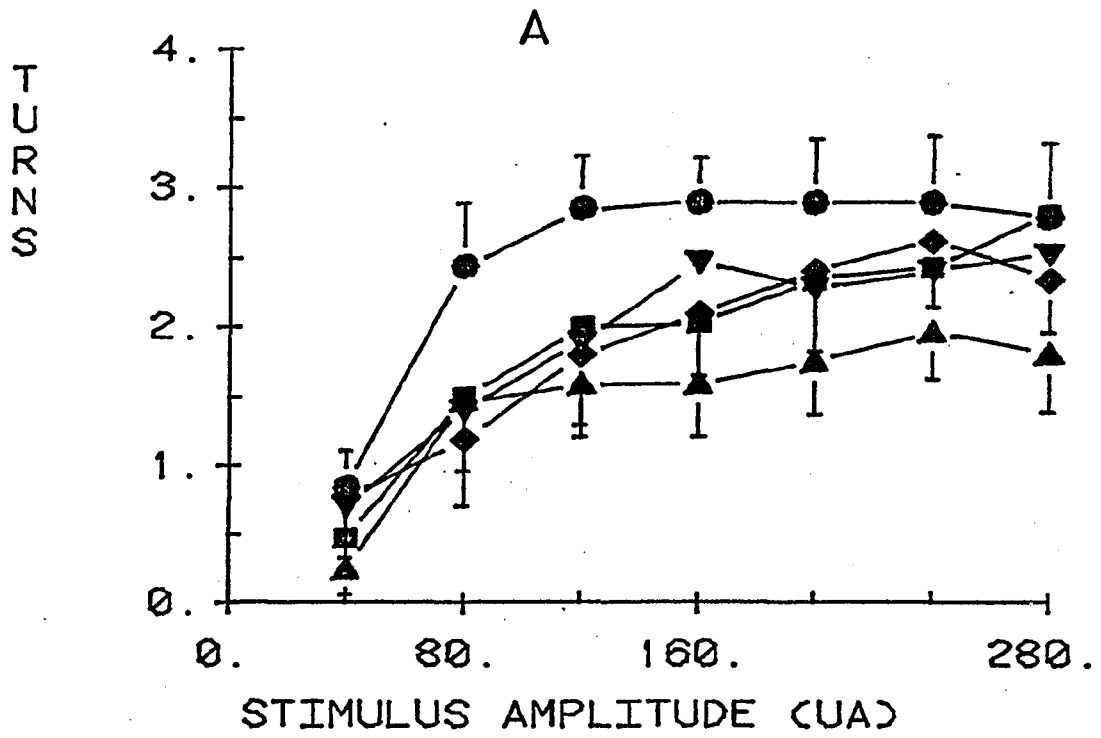
Effects of electrolytic lesions of the LH on NER

Electrolytic lesions (2 mA DC, 15 sec) at the LH in 8 rats significantly reduced NER tested at 2 hours and 14 days after the lesions (ANOVA, $F = 5.57$, $P < 0.005$) (Fig. 4A). NER at 2 hours, 3, 7 and 14 days postlesion was significantly lower than prelesion (ANOVA, $F = 29.90$, $P < 0.005$; $F = 8.41$, $P < 0.005$; $F = 7.12$, $P < 0.025$ and $F = 8.95$, $P < 0.005$ respectively). Acute (2 hours) post-

Figure 4

A. Alteration of contralateral rotation evoked by electrical stimulation of the substantia nigra following electrolytic lesions (2 mA DC, 15 sec) of the ipsilateral lateral hypothalamus. Lesions are diagrammed in Figure 5. Each point represents the mean rotation from 8 rats tested before (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM. There was a significant decrease in rotation after the lesions (ANOVA, $F = 5.57$, $P < 0.005$). For further statistical analysis see text. Mean ipsilateral striatal DA depletion was $58 \pm 7\%$, SEM.

B. Mean contralateral rotation of a group of 6 sham lesioned rats tested at equivalent times. Symbols as in A. There was no significant effect of sham lesion on rotation (ANOVA, $F = 2.17$, $P > 0.05$).



lesion NER was significantly lower than that 3, 7 and 14 days post-lesion ($F = 6.18$, $P < 0.025$; $F = 6.03$, $P < 0.025$ and $F = 4.57$, $P < 0.05$ respectively). Chronic (3, 7 and 14 days) postlesion NER was not significantly changed with time after the lesions ($F = 0.08$, $P > 0.25$). F-R curves were not studied in this group.

Ipsilateral striatal DA was significantly reduced following electrolytic lesions of the LH (paired t-test, $P < 0.001$). DA content of the lesioned and intact sides was 4.4 ± 0.7 and 10.2 ± 0.7 ug/g ($\bar{x} \pm \text{SEM}$, $n = 8$) respectively. DA depletion ranged from 34 to 80 % ($\bar{x} \pm \text{SEM} = 58 \pm 7$ %, $n = 8$). Striatal DA depletion was not correlated with degree of reduction in rotation (expressed as percent change from prelesion of mean rotation evoked at 80 to 280 uA) at any time tested ($r = 0.054$, -0.335 , -0.212 and -0.310 at 2 hours, 3, 7 and 14 days respectively, $P > 0.05$).

There was no significant change in rotation in 6 control rats tested at 2 hours, 3, 7 and 14 days after sham lesions (0 mA, 15 sec) (ANOVA, $F = 2.17$, $P > 0.05$) as shown in Fig. 4B. Ipsilateral and contralateral striatal DA content was 9.5 ± 0.8 and 10.3 ± 0.6 ug/g ($\bar{x} \pm \text{SEM}$, $n = 6$) respectively. There was no significant difference in DA content between ipsilateral and contralateral striatum (paired t-test, $P > 0.10$), or between the contralateral side of lesioned and either side of sham rats (Newman-Keuls test, $P > 0.05$).

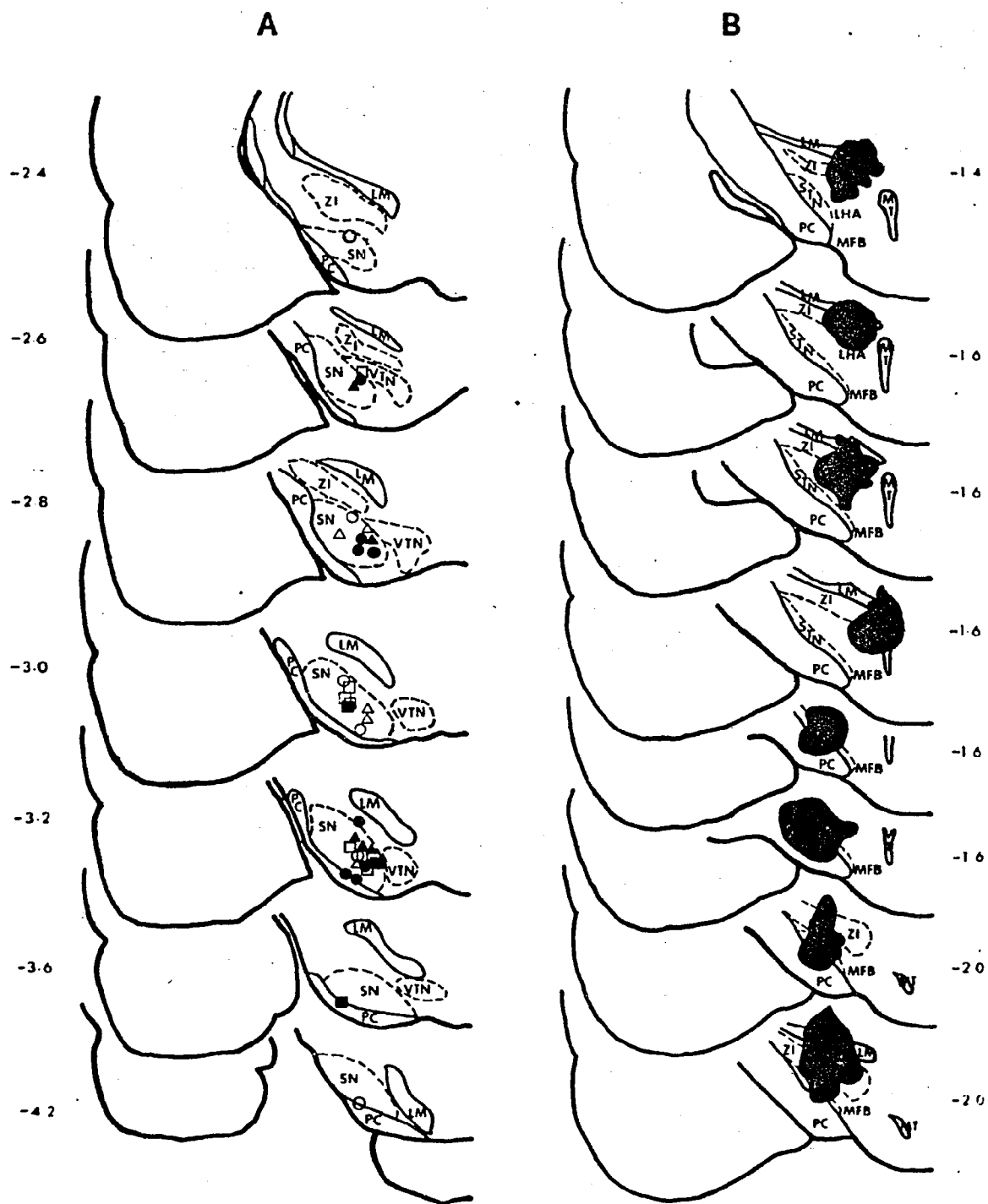
Electrode placements and extent of the lesions are diagrammed in Fig. 5. The lesions were mapped at the anterior-posterior plane with the largest lesion size. Among the LH lesions in 8 rats, 4 were at lateral and encroached upon the mediodorsal part of the crus cerebri and part of the subthalamic nucleus. The other 4 were more medial

Figure 5

A. Localization of stimulating electrode tips in the left substantia nigra from electrolytic lesioned (●), sham (○), 6-OHDA lesioned (▲), vehicle (△), DMI + 6-OHDA lesioned (□) and nonlesioned (■) rats.

B. Extent of electrolytic lesions (2 mA DC, 15 sec) at the anterior-posterior plane with the largest lesion size in each of 8 rats.

Sections are redrawn from Pellegrino and Cushman (1967). The numbers represent mm. posterior to bregma. Abbreviations: LHA, lateral hypothalamic area; LM, medial lemniscus; MFB, medial forebrain bundle; MT, mamillothalamic tract; PC, cerebral peduncle; SN, substantia nigra; STN, subthalamic nucleus; VTN, ventral tegmental nucleus; ZI, zona incerta.



and spared the crus cerebri and the subthalamic nucleus. There was no significant difference in either percent reduction of rotation at 2 hours postlesion (t-test, $P > 0.20$) or percent striatal DA depletion (t-test, $P > 0.50$) between the lateral and the medial lesions. The dorsal part of the mamillothalamic tract was damaged in 1 rat. The medial part of the medial lemniscus and the zona incerta above the LH was lesioned in 6 rats. Sham rats showed no lesions other than the electrode tract itself.

Before lesions, contralateral rotation or circling could be evoked from the 4 medial lesioning electrodes using stimulus parameters described for SN stimulation at amplitudes of 80, 120 and 160 uA. LH-evoked rotation was not tested in the 4 rats with lateral lesions, but A-R and F-R curves could be generated from the same placement in another group of rats (Fig. 11). Rats exhibited contralateral head to tail rotation as they did during stimulation of the SN. Contralateral front paw tremor and body torsion were rare, and A-R curves from all rats tested were wide inverted Us. Seven out of nine rats had higher number of turns in F-R than in A-R curves, and those F-R curves were sigmoidal rather than inverted U-shape. One of the remaining two rats had body roll over at high stimulus frequencies. Three out of the seven rats with sigmoidal F-R curves rotated in a wide circle when tested for F-R curves.

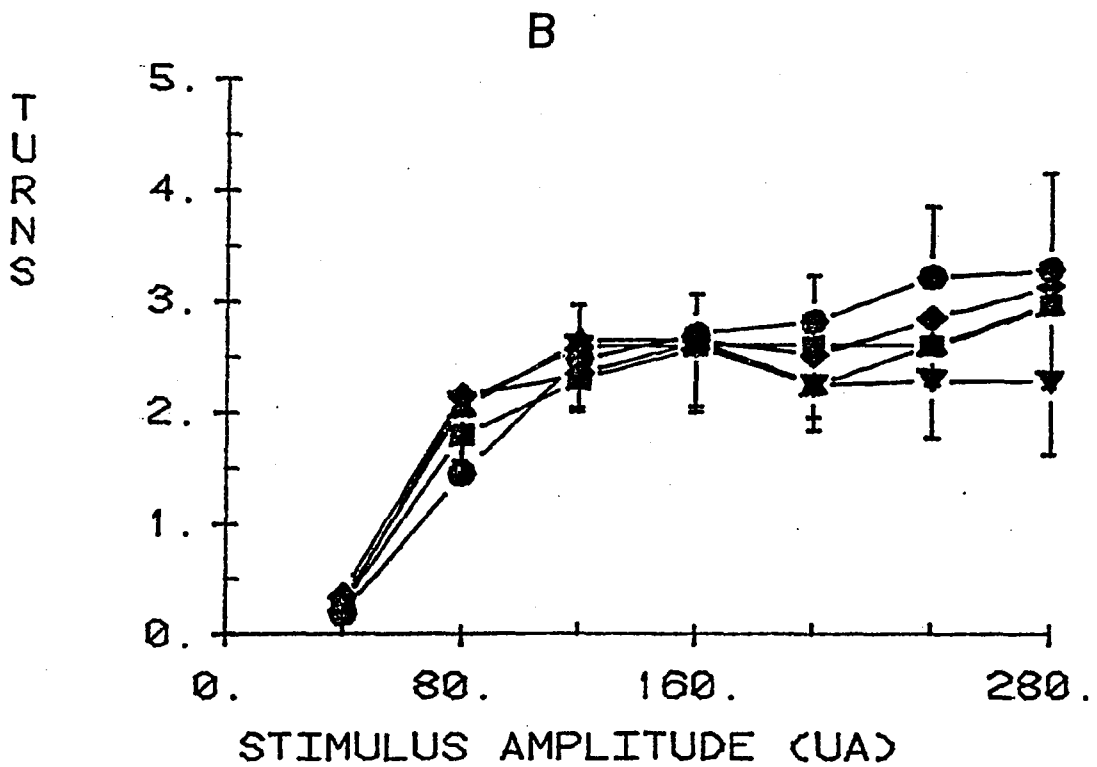
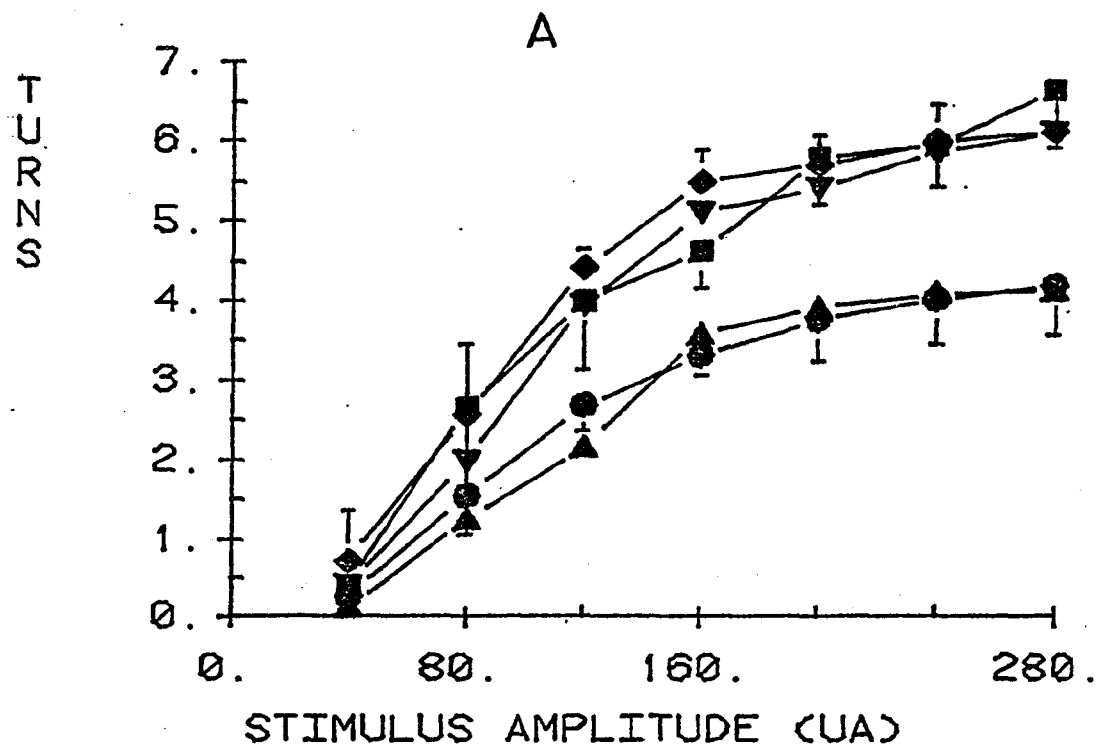
Effects of 6-OHDA 8 ug in 4 ul at the LH on NER

6-OHDA 8 ug in 4 ul microinjected to the LH in 6 rats did not significantly change NER at 2 hours postlesion (ANOVA, $F = 0.12$,

Figure 6

A. Alteration of contralateral rotation evoked by electrical stimulation of the substantia nigra following microinjection of 6-OHDA (8 ug in 4 ul) at the ipsilateral lateral hypothalamus. Each point represents the mean rotation from 6 rats tested before (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postmicroinjection. Error bars represent SEM. There was a significant increase in rotation after the lesions (ANOVA, $F = 17.05$, $P < 0.005$). For further statistical analysis see text. Mean ipsilateral striatal DA depletion was $93 \pm 1\%$, SEM.

B. Mean contralateral rotation in 5 rats microinjected with vehicle (4 ul) tested at equivalent times. Symbols as in A. There was no significant effect of vehicle microinjection on rotation (ANOVA, $F = 0.43$, $P > 0.25$). There was no significant difference in striatal DA ipsilateral and contralateral to vehicle microinjection (paired t-test, $P > 0.50$).



$P > 0.25$) but significantly increased NER at 3, 7 and 14 days post-lesion ($F = 22.76, 28.10$ and 43.88 respectively, $P < 0.005$) (Fig. 6A). Postlesion rotation did not significantly change from day 3 to 14 ($F = 0.57, P > 0.25$). Ipsilateral striatal DA was undetectable in 3 rats and $0.7, 1.0$ and 1.7 ug/g in 3 rats. Contralateral striatal DA content was 11.9 ± 0.3 ug/g ($\bar{x} \pm \text{SEM}, n = 6$). There was a significant difference between ipsilateral and contralateral striatal DA (Wilcoxon test, $P < 0.025$). If undetectable DA was conservatively estimated to be equivalent to 0.5 ug/g, the mean percent DA depletion following 6-OHDA 8 ug in 4 ul was 93 ± 1 % ($\bar{x} \pm \text{SEM}, n = 6$).

Five rats microinjected with 4 ul of vehicle at the LH showed no significant change in NER tested at 2 hours, 3, 7 and 14 days post-injection (ANOVA, $F = 0.43, P > 0.25$). Ipsilateral and contralateral striatal DA content in these rats was 11.9 ± 1.1 and 12.7 ± 0.6 ug/g ($\bar{x} \pm \text{SEM}, n = 5$) respectively. There was no significant difference in striatal DA between ipsilateral and contralateral sides of vehicle injected rats (paired t-test, $P > 0.50$), or between the contralateral side of 6-OHDA lesioned and either side of vehicle injected rats (Newman-Keuls test, $P > 0.05$).

Electrode placements in the SN of these 2 groups are diagrammed in fig. 5A.

Effects of DMI pretreatment and 6-OHDA 8 ug in 4 ul lesions of the LH on NER

In rats pretreated with DMI (30 mg/kg i.p.) 30 minutes before microinjection of 6-OHDA 8 ug in 4 ul at the LH (Fig. 7), NER was

Figure 7

Mean contralateral rotation evoked by electrical stimulation of the substantia nigra following microinjection of 6-OHDA (8 ug in 4 ul) at the ipsilateral lateral hypothalamus in rats pretreated with DMI 30 mg/kg i.p. 30 minutes previously. Each point represents the mean rotation from 7 rats tested before (●) and 2-3 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postmicroinjection. Error bars represent SEM. Mean ipsilateral striatal DA depletion ($93 \pm 2\%$) was equivalent to that in nonpretreated 6-OHDA 8 ug lesioned groups.

A. Amplitude-rotation curves: there was a significant reduction of rotation at 2 hours after the lesion (2.5 hours after DMI) (ANOVA, $F = 20.51$, $P < 0.005$) but rotation at 3, 7 and 14 days was not significantly different from control ($F = 2.15$, $P > 0.01$; $F = 1.32$, $P > 0.25$ and $F = 0.81$, $P > 0.25$ respectively).

B. Frequency-rotation curves: there was a significant decrease in rotation at 3 hours after the lesion (3.5 hours after DMI) (ANOVA, $F = 111.24$, $P < 0.005$) and a slight but significant increase in rotation at 3 and 14 days after the lesion ($F = 7.36$, $P < 0.01$; $F = 4.05$, $P < 0.05$ respectively) but no change at 7 days ($F = 0.37$, $P > 0.25$).

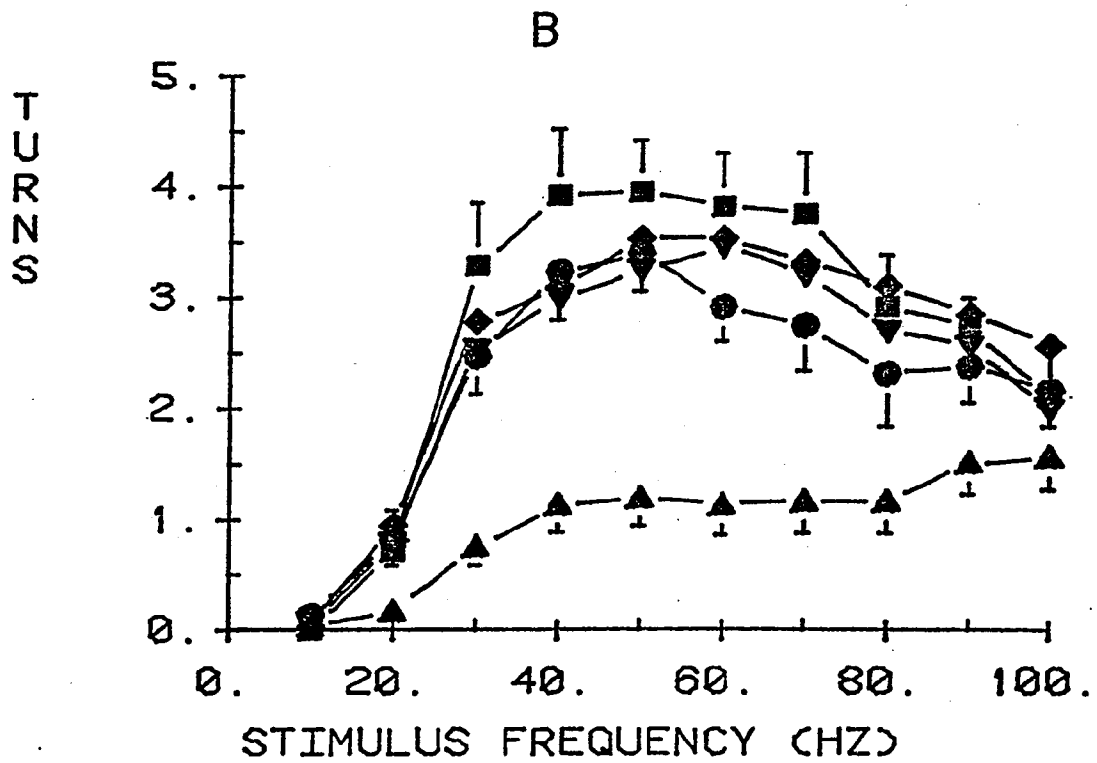
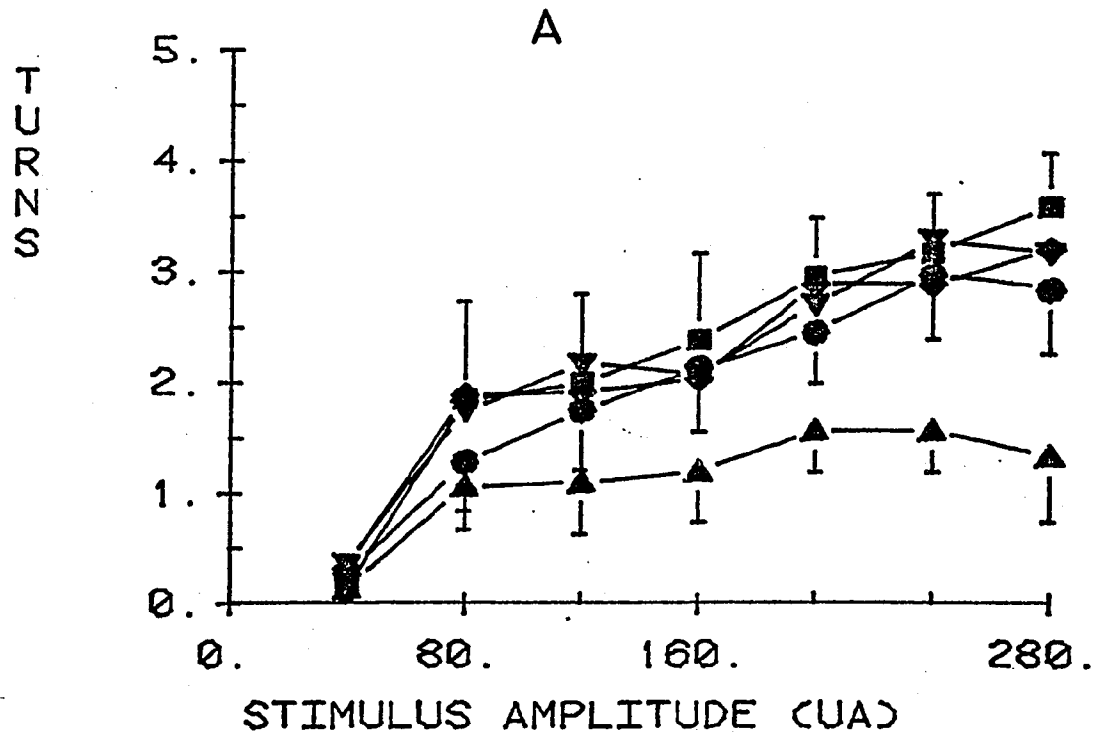
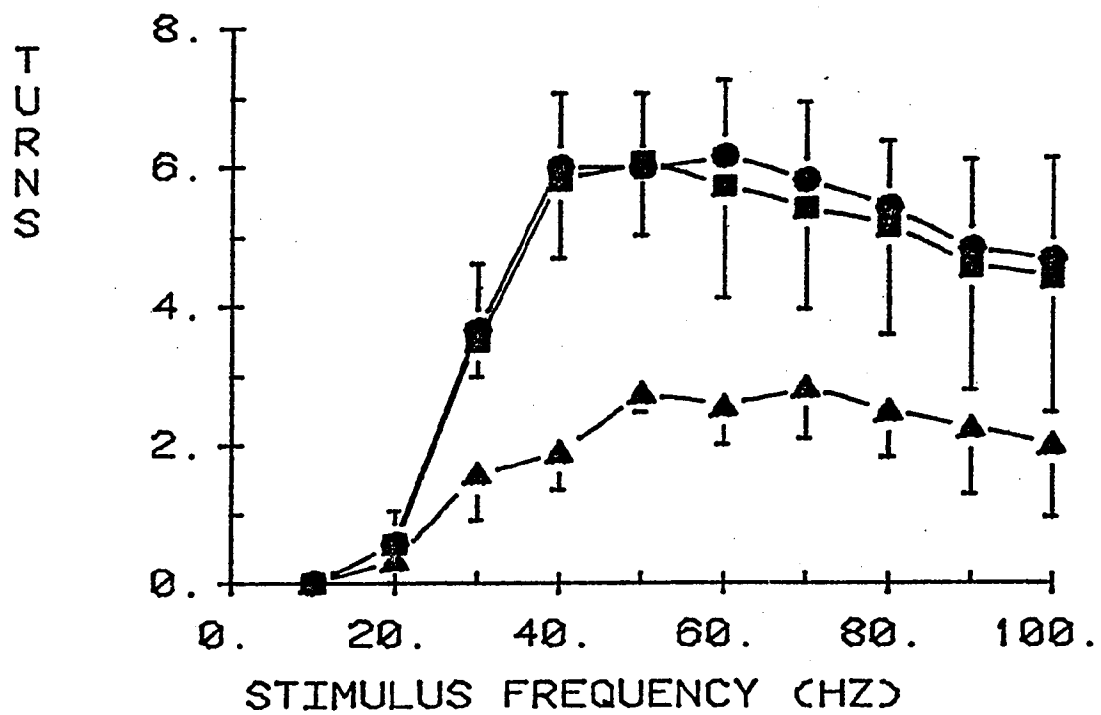
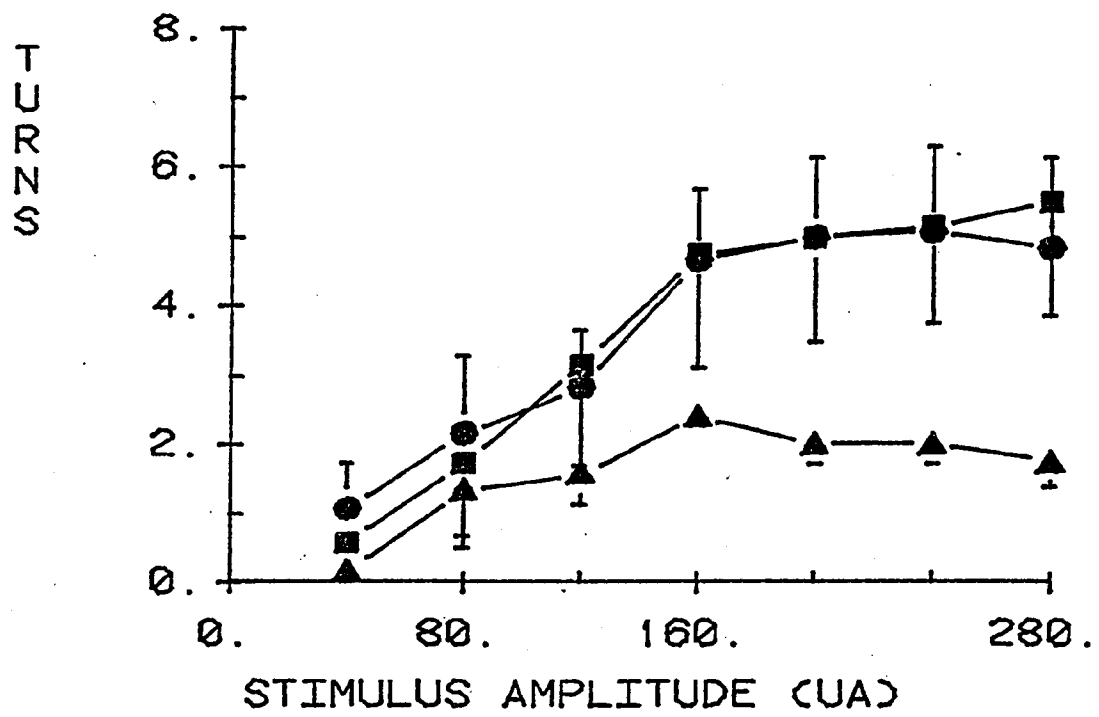


Figure 8

Mean contralateral rotation evoked by electrical stimulation of the substantia nigra in 3 nonlesioned rats tested prior to (●) and 2.5 - 3.5 hours (▲) and 7 days (■) after DMI 30 mg/kg i.p. Error bars represent SEM. There was a significant reduction of rotation at 2.5 hours in amplitude-rotation curve and at 3.5 hours in frequency-rotation curve (ANOVA, $F = 66.48$ and 140.42 respectively, $P < 0.005$) but not at 7 days ($F = 0.02$ and 0.38 respectively, $P > 0.25$) postlesion.



significantly reduced at 2 - 3 hours postlesion (ANOVA, $F = 20.51$, for A-R and $F = 111.24$ for F-R, $P < 0.005$). At 3, 7 and 14 days postlesion NER was not different from control when stimulus amplitude was varied ($F = 2.15$, $P > 0.10$; $F = 1.32$, $P > 0.25$ and $F = 0.80$, $P > 0.25$ respectively). When frequency was varied there was a slight but significant increase over control rotation at 3 and 14 days ($F = 7.36$, $P < 0.01$; $F = 4.05$, $P < 0.05$) but it was unchanged at 7 days ($F = 0.37$, $P > 0.25$).

Ipsilateral striatal DA levels were undetectable in 5 rats, 1.5 and 1.6 ug/g in the remaining 2 rats. Contralateral striatal DA was 13.0 ± 0.6 ug/g ($\bar{x} \pm \text{SEM}$, $n = 7$). There was a significant difference in striatal DA between ipsilateral and contralateral sides (Wilcoxon test, $P < 0.025$). DA depletion ranged from 86 to 96 % ($\bar{x} \pm \text{SEM} = 93 \pm 2$ %, $n = 7$). There was no significant difference in percent depletion of ipsilateral striatal DA between DMI-pretreated and non pretreated groups (Kruskal-Wallis test, $P > 0.05$).

Electrode placements in these rats are shown in Fig. 5.

DMI 30 mg/kg i.p. significantly reduced NER in 3 nonlesioned rats tested at 2.5 to 3.5 hours (ANOVA, $F = 66.48$ and 140.42 for A-R and F-R curves respectively, $P < 0.005$) but not at 7 days after the injections ($F = 0.02$ and 0.38 respectively, $P > 0.25$) (Fig. 8). This accounts for the immediate decrease in NER in the DMI pretreated 6-OHDA rats.

Effects of haloperidol on nonlesioned and lesioned rats

The effects of haloperidol 0.1 and 0.5 mg/kg i.p. on NER was tested in nonlesioned, vehicle injected, electrolytic lesioned and

6-OHDA lesioned rats. Each rat received both doses of haloperidol 10 days apart separated by a control trial in which haloperidol vehicle was injected. There was a significant decrease in NER following haloperidol 0.1 mg/kg (ANOVA, $F = 6.97$, $P < 0.025$; $F = 7.93$, $P < 0.025$; $F = 6.46$, $P < 0.025$ and $F = 22.63$, $P < 0.005$) and 0.5 mg/kg ($F = 57.45$, $P < 0.005$; $F = 5.08$, $P < 0.05$; $F = 11.34$, $P < 0.005$ and $F = 54.18$, $P < 0.005$) but not following water i.p. ($F = 0.58$, $P > 0.25$; $F = 0.91$, $P > 0.25$; $F = 2.75$, $P > 0.10$ and $F = 0.74$, $P > 0.25$) in nonlesioned, vehicle, electrolytic lesioned and 6-OHDA lesioned rats respectively. Effects of haloperidol in 6-OHDA lesioned and nonlesioned rats are shown in Figures 9 and 10. Haloperidol effects in rats given vehicle or electrolytic lesions were similar and are not illustrated. Numerical data from all groups are included in Table II. Although the time course of recovery was not followed, the equivalence of the predrug NER for the three tests was achieved since there were no significant differences in preinjection curves from the 4 groups ($F = 1.13$, 0.26, 0.18 and 0.92 respectively, $P > 0.25$) (Fig. 9B). To compare the sensitivity to haloperidol of the 4 experimental groups, the mean of percent response to haloperidol at 120, 160, 200 and 240 μ A which was at the plateau part of pre- and post-injection curves was computed for each group (Table II). Analysis of variance showed a significant drug effect ($F = 20.95$, $P < 0.005$) which was dose-dependent; haloperidol at 0.5 mg/kg had a greater effect than that at 0.1 mg/kg ($F = 10.11$, $P < 0.025$) and haloperidol 0.1 mg/kg had a greater effect than water ($F = 14.40$, $P < 0.005$). However, there was no significant difference in haloperidol sensitivity among the 4 groups ($F = 1.90$ and 0.28, $P > 0.25$; for lesions, and lesion x drug dose interactions

Figure 9

A. Effects of haloperidol on contralateral nigral-evoked rotation from 6-OHDA (8 ug) lesioned rats tested 2 hours after haloperidol 0.1 (▲), 0.5 (■) mg/kg and water (◆) i.p. See methods for schedule of drug administration. Rotation prior to the 0.1 mg/kg dose (●) is shown as an example of preinjection curves.

B. Preinjection stimulus-rotation curves of the 6-OHDA lesioned rats in A. Prehaloperidol 0.1 (●), 0.5 (■) mg/kg and prewater (◆) were tested on day 14, 21 and 24 after 6-OHDA lesion respectively.

Each point represents mean rotation from 3 rats, error bars represent SEM. There was no significant difference in the 3 preinjection curves (ANOVA, $F = 0.92$, $P > 0.25$). There was a significant difference before and after haloperidol 0.1 and 0.5 mg/kg ($F = 22.63$ and 54.18 respectively, $P < 0.005$) but not water ($F = 0.74$, $P > 0.25$). For further statistical analysis see text.

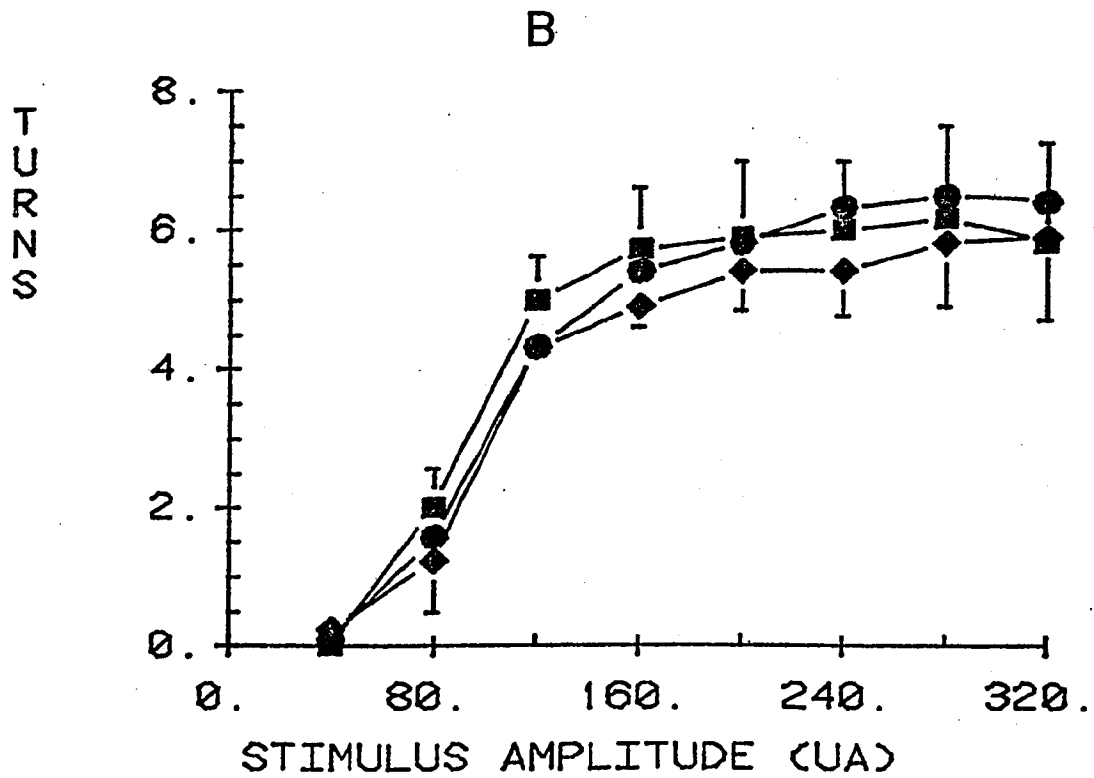
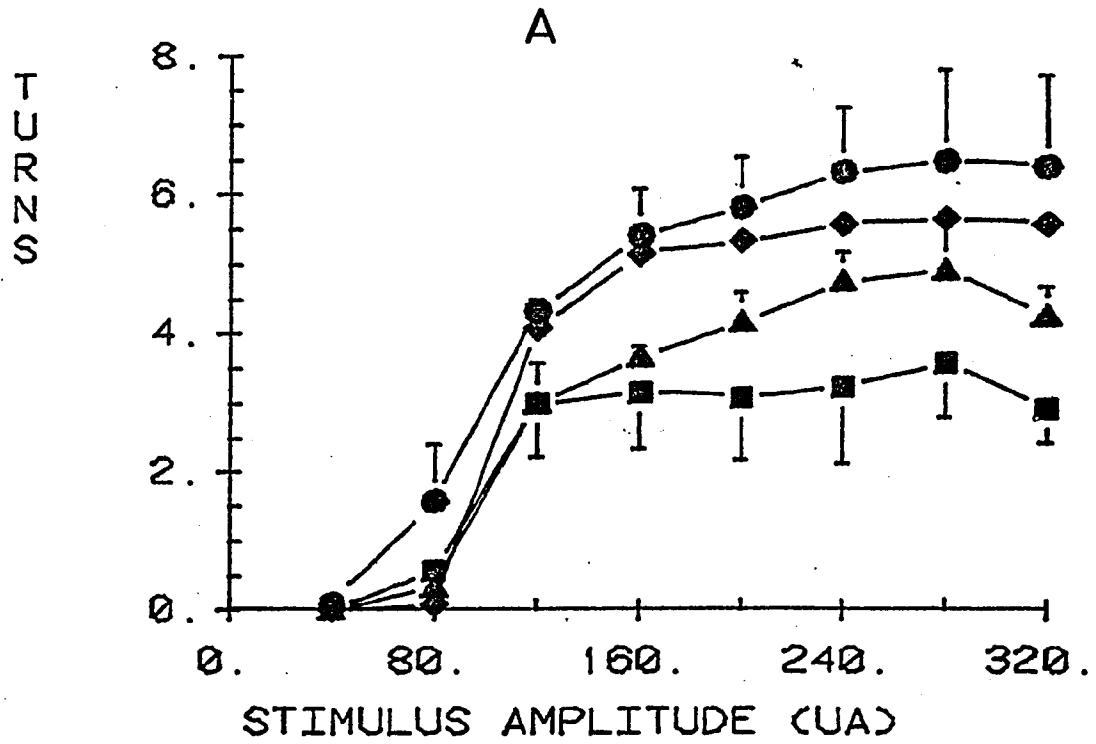


Figure 10

Effects of haloperidol on rotation evoked by electrical stimulation of the substantia nigra from 3 nonlesioned rats. (A) Amplitude-rotation curve measured at 2 hours and (B) frequency-rotation curve measured at 3 hours after haloperidol 0.1 ($\blacktriangle$), 0.5 ($\blacksquare$) mg/kg and water ($\blacklozenge$) i.p. See methods for schedule of drug administration. Control stimulus-response curves were determined before each injection, and were not significantly different from each other (ANOVA, $F = 1.13$ and 0.56 for A-R and F-R respectively, $P > 0.25$). Rotation prior to the 0.1 mg/kg dose is shown as an example ($\bullet$). Error bars represent SEM. There was a significant reduction in rotation following haloperidol 0.1 mg/kg ($F = 6.97$, A-R and 6.12 , F-R, $P < 0.025$), 0.5 mg/kg ($F = 57.45$, A-R and 100.31 , F-R, $P < 0.005$) but not following water i.p. ($F = 0.58$, A-R and 0.30 , F-R, $P > 0.25$). For further statistical analysis see text.

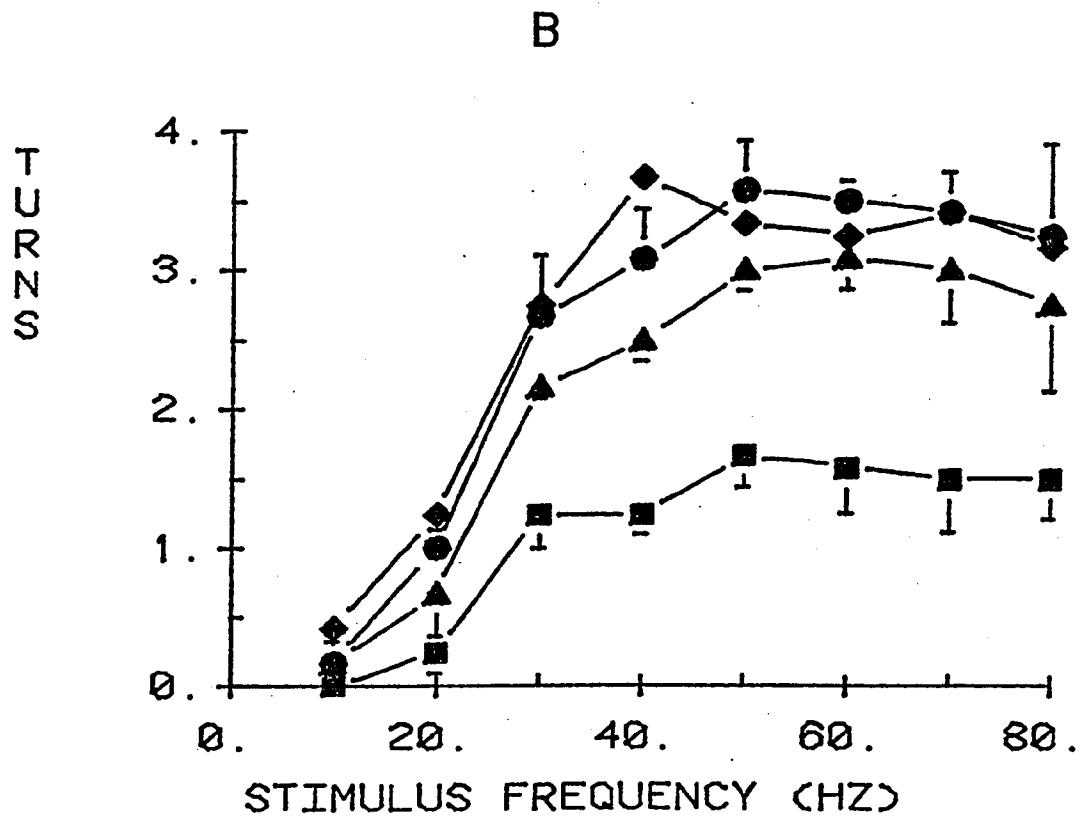
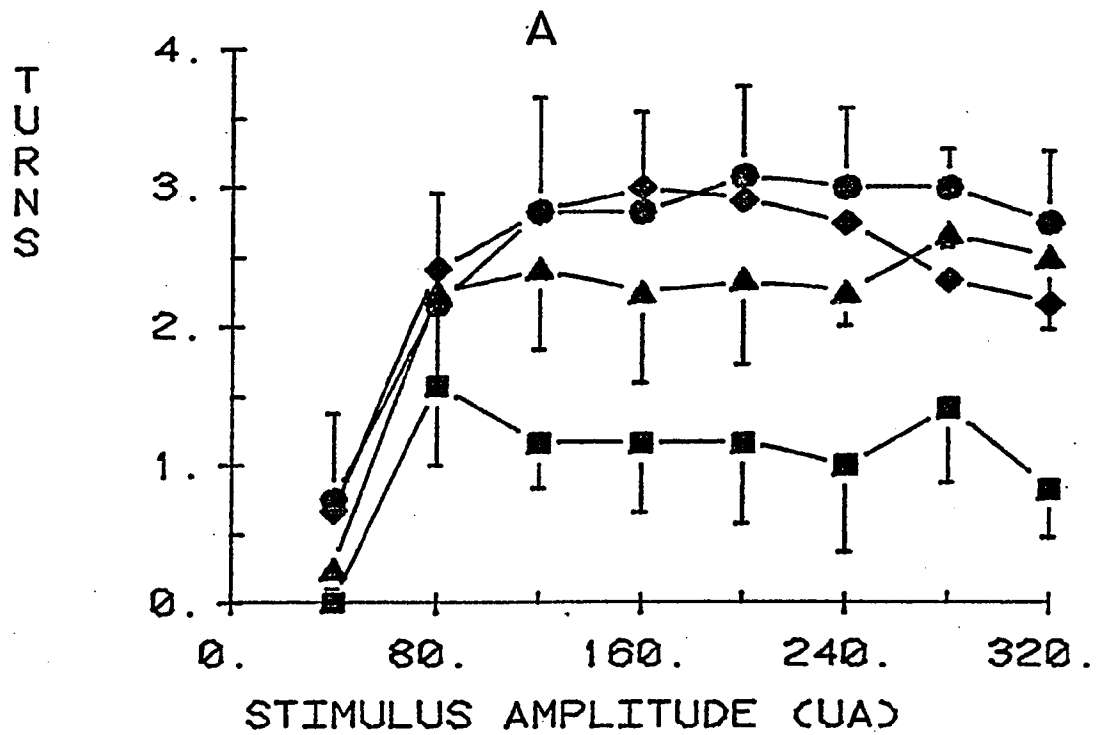


Table II

Haloperidol sensitivity of nigral-evoked rotation in nonlesioned and lesioned rats

Mean rotation at 120, 160, 200 and 240 uA was determined before and 2 hours after each drug dose. The values in the table are percent changes in mean rotation from preinjection controls. No significant lesion effect on haloperidol sensitivity (ANOVA, $F = 1.90$, $P > 0.25$). Drug effects were significant (ANOVA, $F = 20.90$, $P < 0.005$), haloperidol 0.5 > haloperidol 0.1 ($F = 10.11$, $P < 0.025$), haloperidol 0.1 > haloperidol 0.0 ($F = 14.40$, $P < 0.005$).

Treatments	Percent change in rotation $\bar{x} \pm$ SEM (n = 3)			
	Nonlesioned	Vehicle	2 mA DC, 15 sec	6-OHDA 8 ug
Haloperidol 0.0 mg/kg i.p.	-4 $\pm$ 8	-8 $\pm$ 18	-20 $\pm$ 5	+1 $\pm$ 11
haloperidol 0.1 mg/kg i.p.	-20 $\pm$ 5	-42 $\pm$ 5	-43 $\pm$ 9	-27 $\pm$ 10
Haloperidol 0.5 mg/kg i.p.	-59 $\pm$ 14	-56 $\pm$ 14	-68 $\pm$ 11	-46 $\pm$ 14

respectively).

Haloperidol effects on F-R curves from 3 nonlesioned rats were the same as the effects on A-R curves i.e. reduction of maximum rotation (Fig. 10B). Haloperidol 0.1 and 0.5 mg/kg significantly reduced NER (ANOVA, $F = 6.12$, $P < 0.025$ and $F = 100.31$, $P < 0.005$ respectively while a water control was without effect ($F = 0.30$, $P > 0.25$). Haloperidol 0.5 mg/kg had a greater effect than 0.1 mg/kg ($F = 54.25$, $P < 0.005$), and haloperidol 0.1 mg/kg had a greater effect than water ($F = 4.65$, $P < 0.05$). There was no significant difference in the 3 pre-injection curves ($F = 0.56$, $P > 0.25$).

Haloperidol 0.1 and 0.5 mg/kg and water i.p. were given to 3 rats tested for LH-evoked rotation (LHER). Haloperidol effects on A-R and F-R curves are shown in Fig. 11. Haloperidol 0.5 mg/kg significantly reduced LHER (ANOVA, $F = 19.04$ and 50.45 for A-R and F-R curves respectively, $P < 0.005$), the effect was greater than haloperidol 0.1 mg/kg and water ($F = 5.33$, $P < 0.05$; $F = 15.16$, $P < 0.005$ respectively for A-R curves; $F = 35.73$ and 31.48 respectively for F-R curves, $P < 0.005$). There was no significant effect of haloperidol 0.1 mg/kg or water ($F = 0.52$ and 0.55 respectively for A-R curves; $F = 0.46$ and 0.59 respectively for F-R curves, $P > 0.25$). There was no significant difference among the preinjection curves ($F = 1.82$, $P > 0.10$; $F = 0.07$, $P > 0.25$ for A-R and F-R curves respectively).

The relative haloperidol sensitivity of NER and LHER was assessed by comparing the percent change in mean rotation evoked at 120 to 240 uA or 40 to 80 Hz for NER, and 200 to 320 uA and 60 to 100 Hz for LHER produced by 0.0, 0.1 and 0.5 mg/kg haloperidol (Table III). Analysis of variance showed no significant difference in haloperidol

Figure 11

Effects of haloperidol on rotation evoked by electrical stimulation of the lateral hypothalamus from 3 nonlesioned rats. (A) Amplitude-rotation curve measured at 2 hours and (B) frequency-rotation curve measured at 3 hours after haloperidol 0.1 (▲), 0.5 (■) mg/kg and water (◆) i.p. Stimulus parameters and schedule of drug administration were the same as that used for nigral-evoked rotation. Control stimulus response curves were determined before each injection, and were not significantly different from each other (ANOVA, $F = 1.82$, $P > 0.10$, A-R; $F = 0.07$, $P > 0.25$, F-R). Rotation prior to the 0.1 mg/kg dose is shown as an example (●). Error bars represent SEM. There was a significant reduction in rotation from that preinjection following haloperidol 0.5 mg/kg ($F = 19.04$, A-R and 50.45 , F-R, $P < 0.005$) but not following haloperidol 0.1 mg/kg and water i.p. ($F = 0.52$ and 0.55 , A-R, $F = 0.46$ and 0.59 , F-R respectively, $P > 0.25$). For further statistical analysis see text.

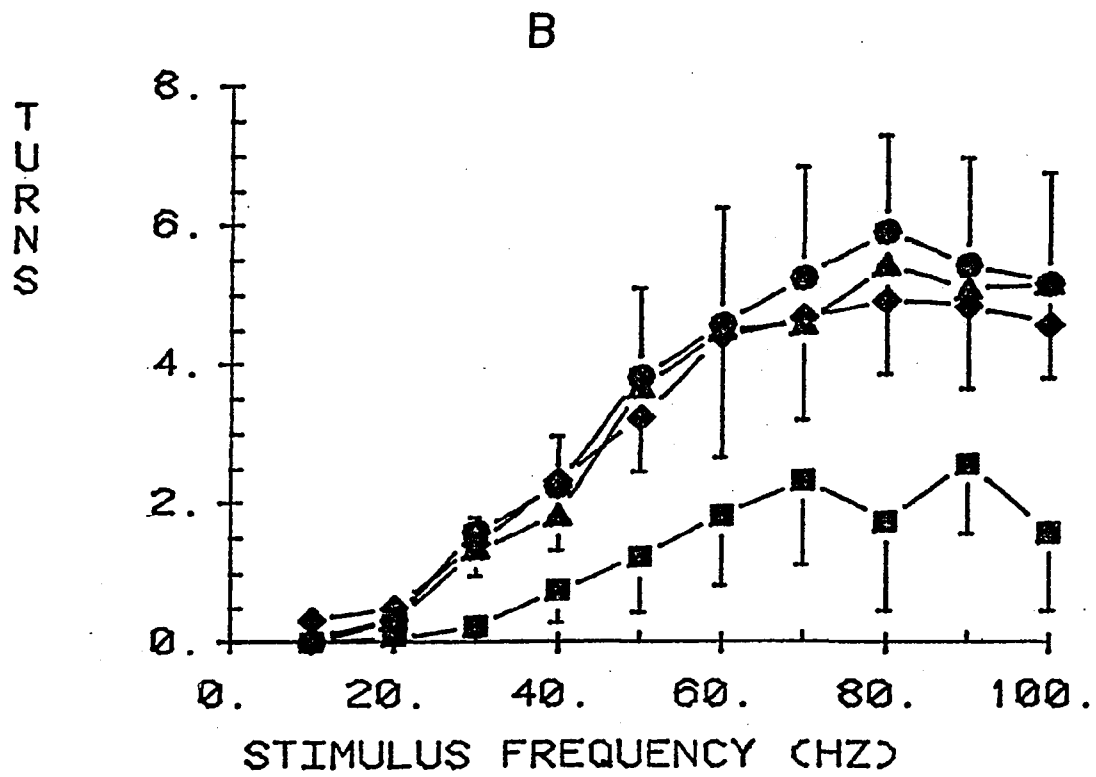
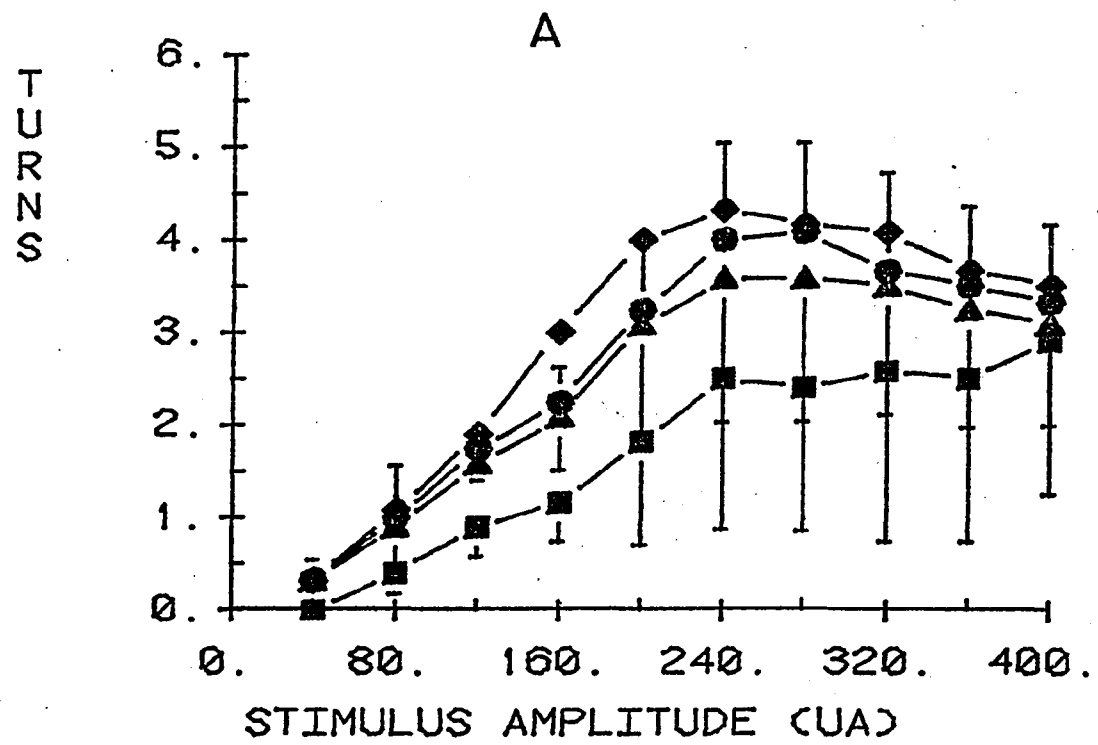


Table III

Haloperidol sensitivity of nigral-evoked rotation and lateral hypothalamus-evoked rotation in nonlesioned rats.

Mean rotation at 120 to 240 μ A or 40 to 80 Hz for NER, 200 to 320 μ A or 60 to 100 Hz for LHER was determined before and 2 or 3 hours after each drug dose. The values in the table are percent changes in mean rotation from preinjection controls. There were no significant differences between stimulus sites (ANOVA, $F = 0.38$, A-R and 0.00, F-R, $P > 0.25$) and no significant site $\times$ dose interactions ($F = 0.01$, A-R and 0.40, F-R, $P > 0.25$). Drug effects were significant (ANOVA, $F = 10.98$, A-R and 20.70, F-R, $P < 0.005$).

Treatments	Percent change in mean rotation $\bar{x} \pm$ SEM (n = 3)			
	NER, A-R	NER, F-R	LHER, A-R	LHER, F-R
Haloperidol 0.0 mg/kg i.p.	-4 $\pm$ 8	-4 $\pm$ 6	0 $\pm$ 0	-10 $\pm$ 9
Haloperidol 0.1 mg/kg i.p.	-20 $\pm$ 5	-14 $\pm$ 4	-14 $\pm$ 13	-5 $\pm$ 4
Haloperidol 0.5 mg/kg i.p.	-59 $\pm$ 14	-57 $\pm$ 2	-52 $\pm$ 17	-59 $\pm$ 18

sensitivity (ANOVA, $F = 0.38$ and 0.00 for A-R and F-R curves respectively; and $F = 0.01$ and 0.40 for stimulus site $\times$ drug dose interactions in A-R and F-R curves respectively, $P > 0.25$). There was a significant drug effect ($F = 10.98$ and 20.70 for A-R and F-R curves respectively, $P < 0.005$), haloperidol at 0.5 mg/kg had a greater effect than that at 0.1 and 0.0 mg/kg ($F = 7.46$, $P < 0.05$ and $F = 18.29$, $P < 0.005$ respectively for A-R curves; $F = 25.65$ and 23.50 respectively for F-R curves, $P < 0.005$). Although haloperidol at 0.1 mg/kg did not significantly decrease LHER and did significantly decrease NER, analysis of variance at each haloperidol dose revealed nonsignificant differences in haloperidol sensitivity between NER and LHER at either the 0.1 or 0.5 mg/kg dose ($F = 0.11$ and 0.08 respectively, $P > 0.25$ for A-R curves; $F = 2.89$, $P > 0.01$ and $F = 0.03$, $P > 0.25$ respectively for F-R curves).

Effects of electrolytic lesions of the LH on rotation evoked by electrical stimulation of the contralateral SN

Electrolytic lesions (2 mA DC, 15 sec) at the left LH in 6 rats did not significantly change rotation evoked by stimulation of the right SN (ANOVA, $F = 1.00$ and 0.67 for A-R and F-R curves respectively, $P > 0.25$) (Fig. 12). Striatal DA content was 8.8 ± 3.9 ipsilateral, and 14.8 ± 6.6 ug/g contralateral to the lesions ($\bar{x} \pm$ SEM, $n = 6$). There was a significant reduction of ipsilateral striatal DA (paired t-test, $P < 0.025$). Striatal DA depletion ranged from 8 to 90 % ($\bar{x} \pm$ SEM = 42 ± 12 %, $n = 6$).

Electrode placements in the SN and extent of lesions in the LH

Figure 12

Contralateral rotation evoked by electrical stimulation of the right substantia nigra following electrolytic lesions (2 mA DC, 15 sec) of the left lateral hypothalamus. Lesions are diagrammed in Figure 13. Each point represents the mean rotation from 6 rats tested for control (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM. There was no significant change in rotation following the lesions (ANOVA, $F = 1.00$, A-R and 0.67, F-R, $P > 0.25$). Mean ipsilateral striatal DA depletion was $42 \pm 12 \%$, SEM.

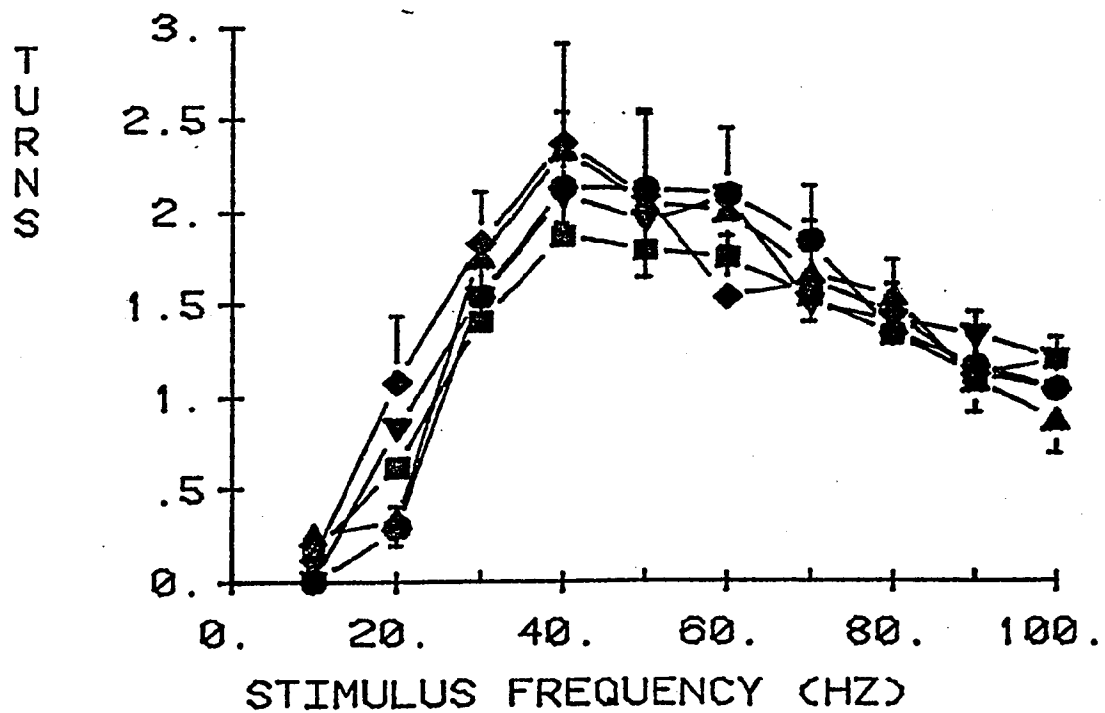
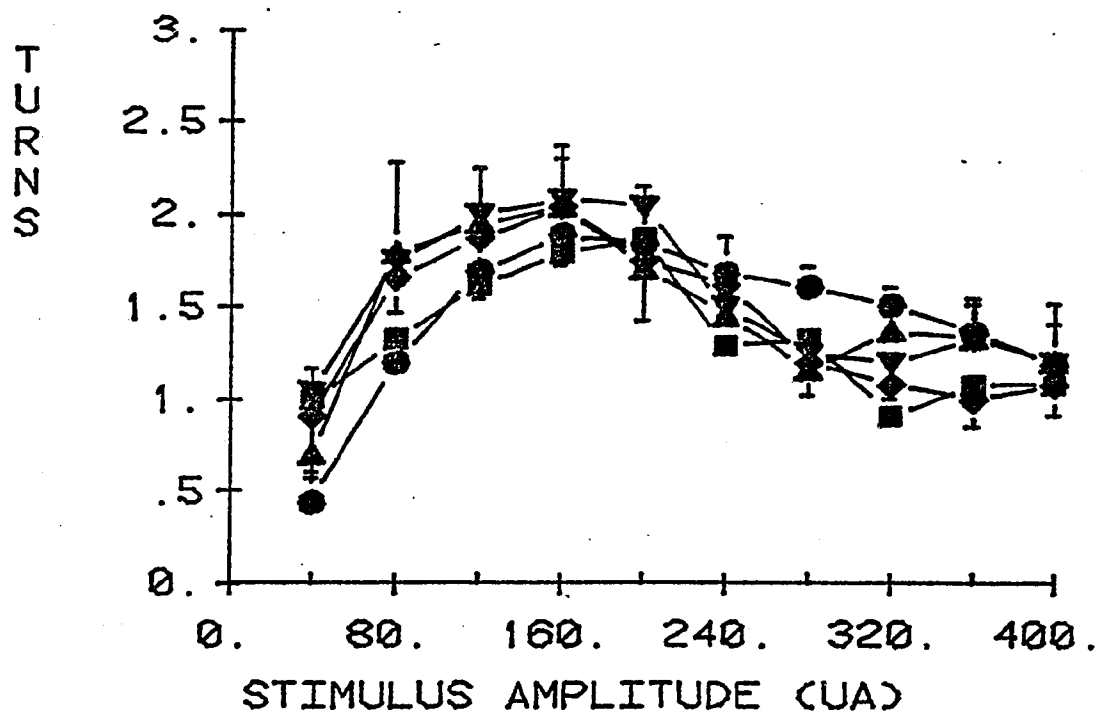


Figure 13

A. Extent of electrolytic lesions (2 mA DC, 15 sec) of the left lateral hypothalamus at the anterior-posterior plane with the largest lesion size in each of 6 rats.

B. Location of stimulating electrode tips in the right substantia nigra from electrolytic lesioned (●), 6-OHDA lesioned (□) and vehicle rats (■).

Sections are redrawn from Pellegrino and Cushman (1967). The numbers represent mm. posterior to bregma. Abbreviations: LHA, lateral hypothalamic area; LM, medial lemniscus; MFB, medial forebrain bundle; MT, mamillothalamic tract; PC, cerebral peduncle; SN, substantia nigra; STN, subthalamic nucleus; ZI, zona incerta.

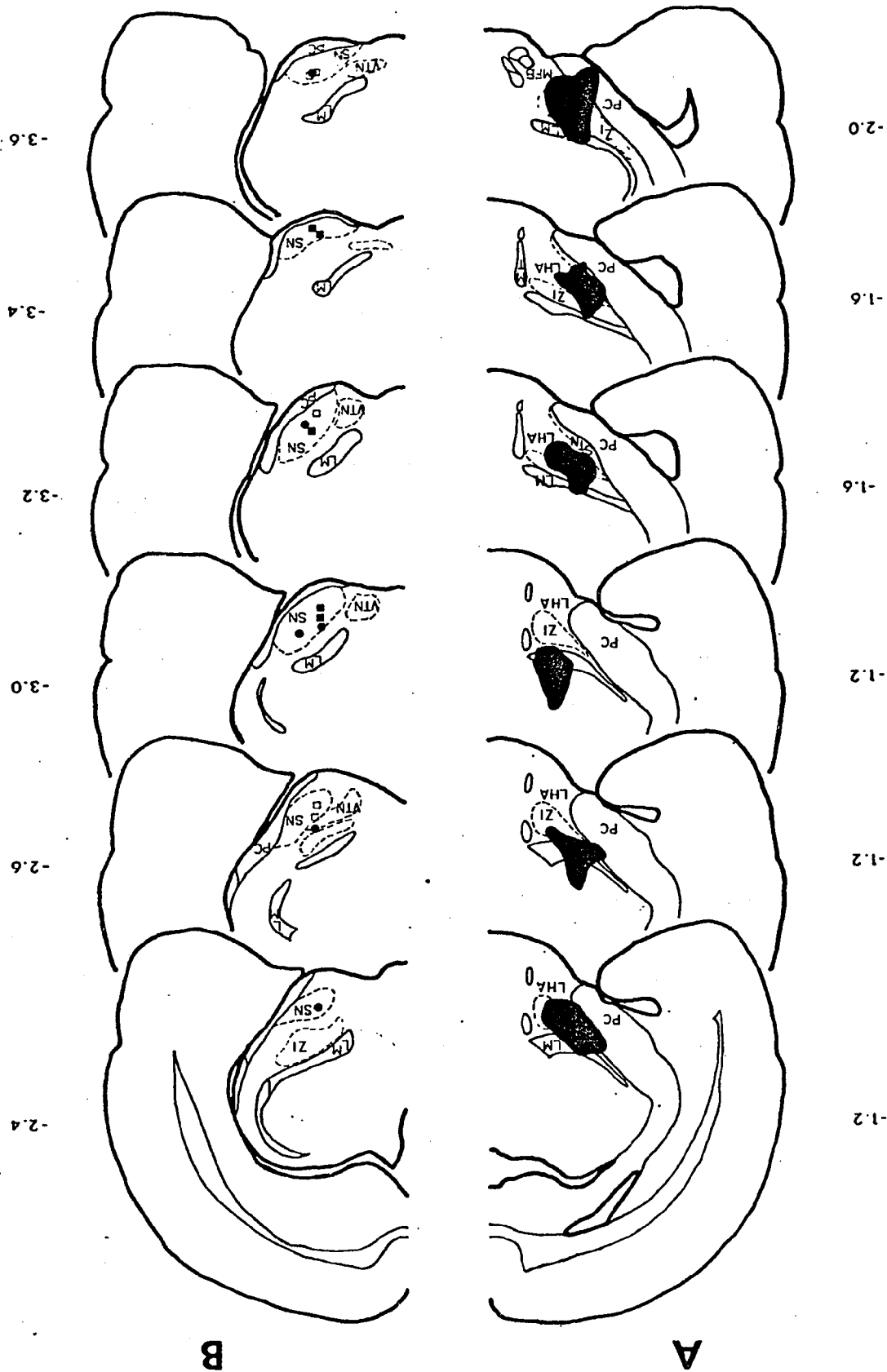
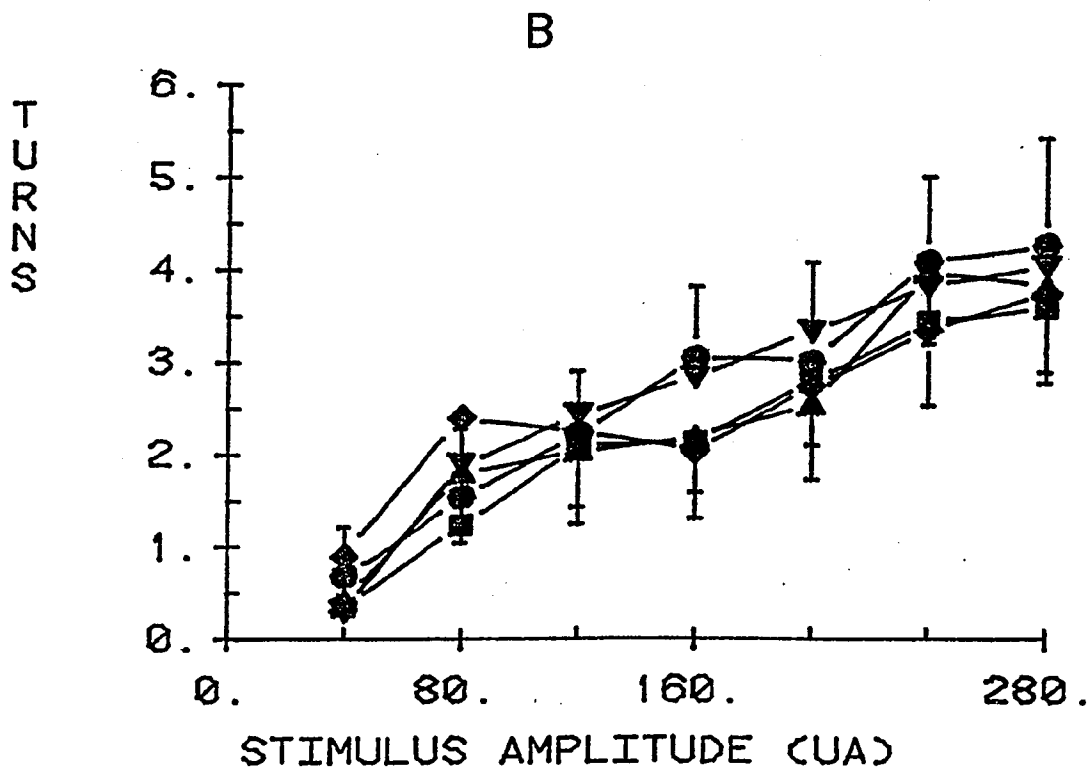
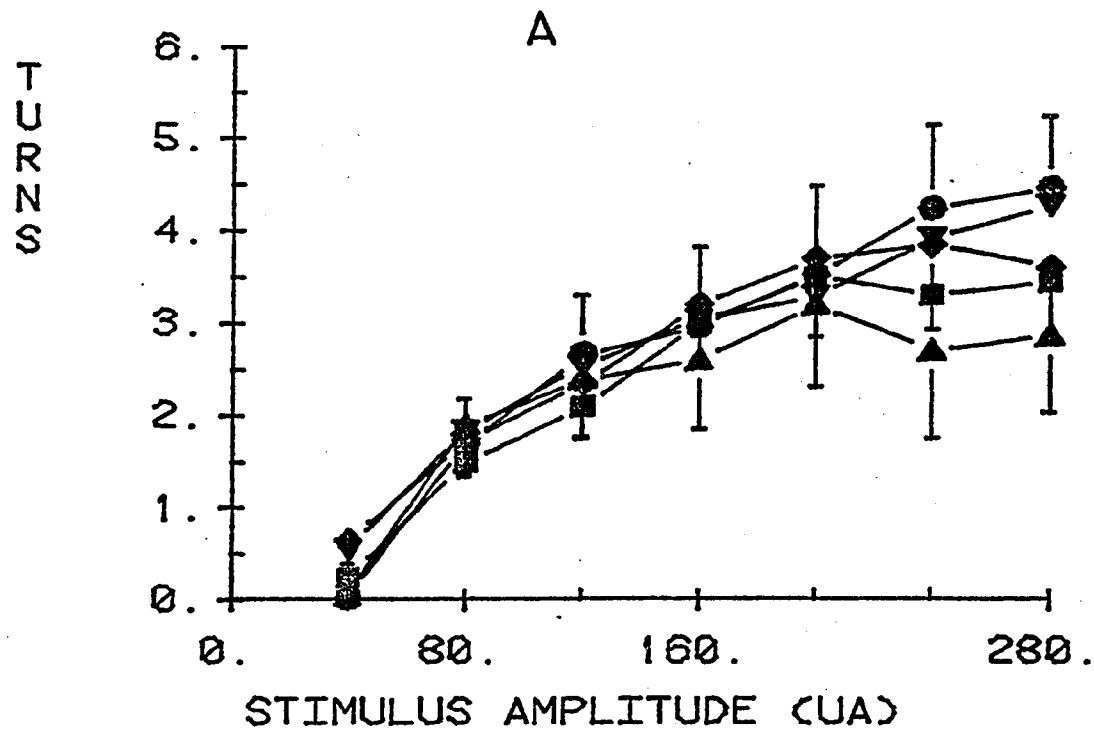


Figure 14

Contralateral rotation evoked by electrical stimulation of the right substantia nigra following 6-OHDA (8 ug in 4 ul) lesions (A) or vehicle (4 ul) (B) microinjection at the left lateral hypothalamus. Each point represents the mean contralateral rotation from 5 rats tested before (●), and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM. There was no significant change in rotation following the contralateral 6-OHDA or vehicle (ANOVA, $F = 2.01$, $P > 0.05$ for A and $F = 0.46$, $P > 0.25$ for B). The mean ipsilateral striatal DA depletion in the 6-OHDA lesioned group was 92 ± 4 %, SEM. There was no significant difference in striatal DA between left and right sides of vehicle group (paired t-test, $P > 0.40$).



are diagrammed in Fig. 13.

Effects of 6-OHDA lesions of the LH on rotation evoked by electrical stimulation of the contralateral SN

Neither 6-OHDA (8 ug in 4 ul) nor vehicle (4 ul) microinjections at the left LH significantly changed rotation evoked by stimulation of the right SN (ANOVA, $F = 2.01$, $P > 0.05$; $F = 0.46$, $P > 0.25$ respectively) (Fig. 14). Left striatal DA in 6-OHDA lesioned rats was undetectable in 4 rats and 3.6 ug/g in 1 rat, with a mean depletion of $92 \pm 4\%$ ($\bar{x} \pm \text{SEM}$, $n = 5$). Right striatal DA was 13.1 ± 0.9 ug/g ($\bar{x} \pm \text{SEM}$, $n = 5$), which was significantly different from the left side (Wilcoxon test, $P < 0.05$). Left and right striatal DA from the vehicle group were 14.0 ± 1 and 14.8 ± 0.4 ug/g respectively ($\bar{x} \pm \text{SEM}$, $n = 5$). There was no significant difference in striatal DA between the left and right sides of the vehicle group (paired t-test, $P > 0.40$) or between the right side of the 6-OHDA group and either side of vehicle group (Newman-Keuls test, $P > 0.50$). Electrode placements in both groups are shown in Fig. 13.

Effects of 6-OHDA 4 ug in 2 ul and 1 ug in 0.5 ul at the LH on NER

To determine whether the difference between electrolytic and 6-OHDA lesions was the degree of DA depletion, the dose of 6-OHDA was reduced. There was no significant change in NER tested at 2 hours 3, 7 and 14 days after 6-OHDA 4 ug in 2 ul (ANOVA, $F = 1.86$ and 1.62 for A-R and F-R curves respectively, $P > 0.10$) or 1 ug in 0.5 ul (F

Figure 15

Contralateral rotation evoked by electrical stimulation of the substantia nigra prior to (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days after 6-OHDA 4 ug in 2 ul at the ipsilateral lateral hypothalamus. Each point represents the mean rotation from 5 rats, error bars represent SEM. There was no significant change in the rotation following 6-OHDA (ANOVA, $F = 1.86$, A-R and 1.62 , F-R, $P > 0.10$). Mean ipsilateral striatal DA depletion was $57 \pm 9 \%$, SEM.

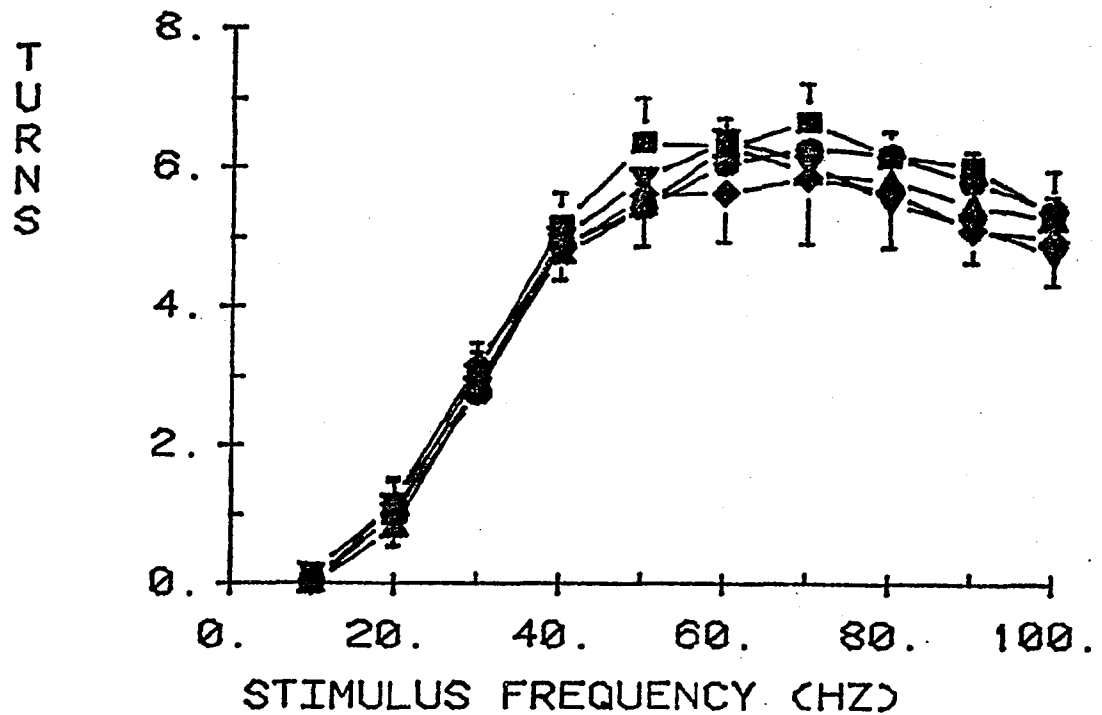
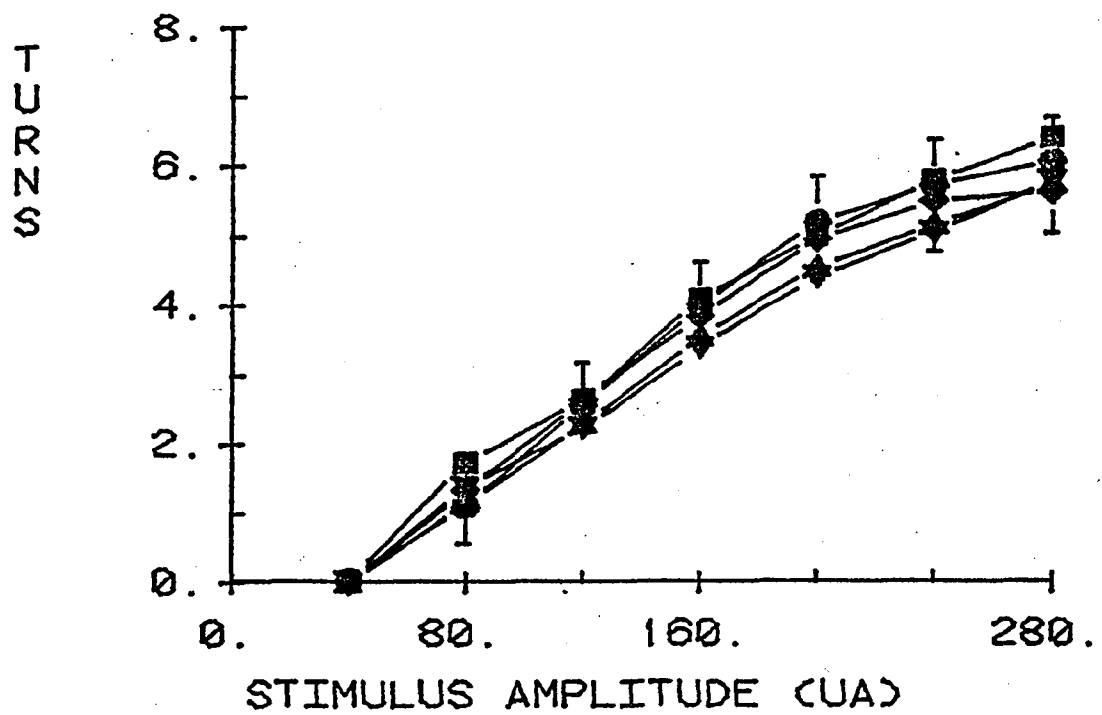
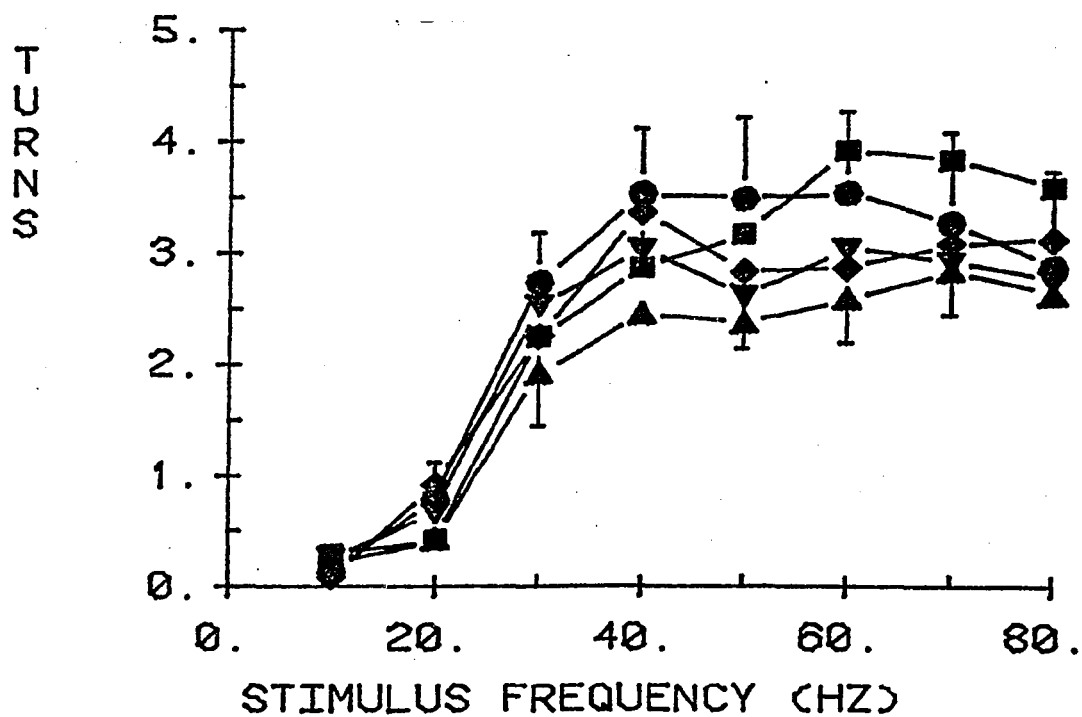
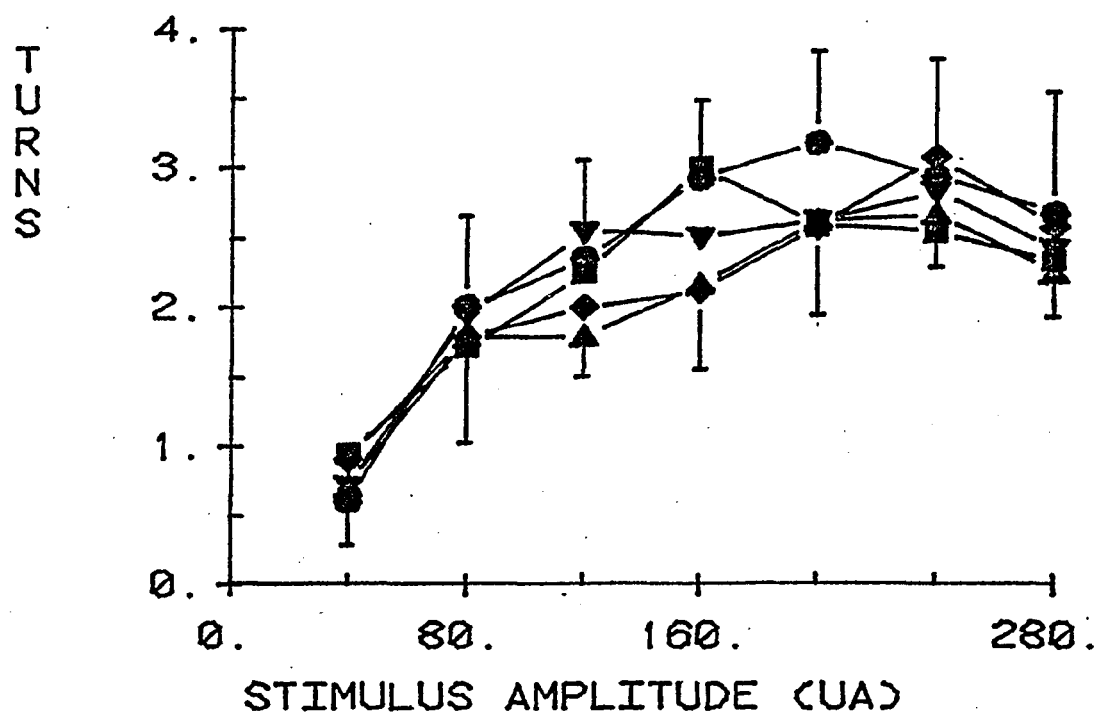


Figure 16

Contralateral rotation evoked by electrical stimulation of the substantia nigra prior to (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days after 6-OHDA 1 ug in 0.5 ul at the ipsilateral lateral hypothalamus. Each point represents the mean rotation from 6 rats, error bars represent SEM. There was no significant change in the rotation following 6-OHDA (ANOVA, $F = 0.35$, $P > 0.25$, A-R; $F = 1.90$, $P > 0.10$, F-R). Mean ipsilateral striatal DA depletion was 40 ± 7 %, SEM.



= 0.35, $P > 0.25$ and $F = 1.90$, $P > 0.10$ for A-R and F-R curves respectively (Fig. 15, 16). Ipsilateral and contralateral striatal DA were 6.5 ± 1.4 and 14.6 ± 0.8 ug/g ($\bar{x} \pm$ SEM, $n = 5$) respectively (paired t-test, $P < 0.001$) for 6-OHDA 4 ug lesioned rats; 8.7 ± 1 and 14.5 ± 0.7 ug/g ($\bar{x} \pm$ SEM, $n = 6$) respectively (paired t-test, $P < 0.01$) for 6-OHDA 1 ug lesioned rats. Striatal DA depletion ranged from 42 to 89 % ($\bar{x} \pm$ SEM = 57 ± 9 %, $n = 5$) and from 20 to 67 % ($\bar{x} \pm$ SEM = 40 ± 7 %, $n = 6$) for 6-OHDA 4 and 1 ug lesioned rats respectively. These DA depletions were similar in magnitude to those produced by electrolytic lesions (Newman-Keuls test, $P > 0.05$). Electrode placements are shown in Fig. 19.

Effects of sequential 6-OHDA and electrolytic lesions at the LH on NER

Electrolytic lesions (2 mA DC, 15 sec) at the LH in rats previously treated with 6-OHDA (8 ug in 4 ul) significantly reduced NER (ANOVA, $F = 5.10$ and 6.45 for A-R and F-R curves respectively, $P < 0.005$) (Fig. 17). NER at 2 to 3 hours, 3 and 7 days postlesion was significantly less than prelesion NER ($F = 13.19, 11.40, 9.23$ respectively for A-R curves, $F = 11.22, 24.62, 9.63$ respectively for F-R curves, $P < 0.005$). NER at 14 days postlesion was not different from prelesion in A-R curves ($F = 2.98$, $P > 0.05$), but significantly less than prelesion in F-R curves ($F = 5.32$, $P < 0.025$).

Ipsilateral striatal DA was undetectable in 2 rats and 1.5 ± 0.2 ug/g ($\bar{x} \pm$ SEM) in 6 rats. Contralateral striatal DA was 14.1 ± 0.4 ug/g ($\bar{x} \pm$ SEM, $n = 8$). There was a significant reduction of ipsilateral striatal DA (Wilcoxon test, $P < 0.01$). The DA depletion ranged

from 86 to 96 % ($\bar{x} \pm \text{SEM} = 91 \pm 2 \%$, $n = 8$). There was no correlation between percent depletion of striatal DA and percent reduction of NER (expressed as percent change from prelesion of mean rotation evoked at 80 to 280 uA) at any time tested ($r = -0.033$, -0.613 , -0.660 and -0.128 at 2 hours, 3, 7 and 14 days respectively, $P > 0.05$).

Electrolytic lesions (2 mA DC, 15 sec) reduced NER in rats with prior microinjection of 4 ul vehicle (ANOVA, $F = 7.47$ and 9.38 for A-R and F-R curves respectively, $P < 0.005$) (Fig. 18). NER at 2 to 3 hours, 3, 7 and 14 days postlesion was significantly less than that prelesion ($F = 22.90$, $P < 0.005$; $F = 12.57$, $P < 0.005$; $F = 8.50$, $P < 0.005$ and $F = 4.83$, $P < 0.05$ respectively for A-R curves; $F = 36.41$, $P < 0.005$; $F = 22.38$, $P < 0.005$; $F = 20.48$, $P < 0.005$ and $F = 7.43$, $P < 0.01$ respectively for F-R curves). The reduction in NER was most marked at 2 - 3 hours postlesion and both amplitude and frequency curves at this time are significantly lower than that at 14 days ($F = 7.88$, $P < 0.025$ for A-R; $F = 8.57$, $P < 0.005$ for F-R). There were no significant differences in rotation from 3 to 14 days postlesion ($F = 1.18$, $P > 0.25$ for A-R; $F = 2.39$, $P > 0.05$ for F-R).

DA levels were 6.8 ± 1.1 ug/g ($\bar{x} \pm \text{SEM}$, $n = 8$) ipsilateral and 13.4 ± 0.4 ug/g contralateral to the lesions (paired t-test, $P < 0.001$). The DA depletion ranged from 16 to 93 % ($\bar{x} \pm \text{SEM} = 49 \pm 8 \%$, $n = 8$). Striatal DA content contralateral to the 6-OHDA lesion was not significantly different from that contralateral to the vehicle injection (Newman-Keuls test, $P > 0.05$). There was no correlation between percent reduction of striatal DA and percent reduction of NER (expressed as percent change from prelesion of mean rotation evoked at 80 to 280 uA) at 2 hours, 3 and 7 days ($r = 0.360$, 0.067 and 0.375

respectively, $P > 0.05$). The correlation was significant at 14 days postlesion ($r = 0.738$, $P < 0.05$).

There was a significant difference in percent depletion of ipsilateral striatal DA between 6-OHDA preinjected and vehicle preinjected groups (Newman-Keuls test, $P < 0.01$), but there were no significant differences in percent reduction of rotation (expressed as percent change from prelesion of mean rotation evoked at 80 to 280 μ A) tested at 2 hours, 3, 7 and 14 days after electrolytic lesions between the two groups (Newman-Keuls test, $P > 0.05$).

Striatal DA depletions in rats with electrolytic lesions only were similar regardless of whether there had been prior injection of vehicle to the LH (Newman-Keuls test, $P > 0.05$). There were no significant differences in percent reduction of rotation (expressed as percent change from prelesion of mean rotation evoked at 80 to 280 μ A) between nonpreinjected and 6-OHDA preinjected groups tested at 2 hours, 3, 7 and 14 days postelectrolytic lesion (Newman-Keuls test, $P > 0.05$), or between nonpreinjected and vehicle preinjected groups tested at 2 hours, 3, 7 and 14 days postelectrolytic lesion (Newman-Keuls test, $P > 0.05$).

Stimulating electrode placements and extent of electrolytic lesions of 6-OHDA and vehicle preinjected rats are diagrammed in Fig. 19. LH electrolytic lesions were mapped at the anterior-posterior plane with the largest lesion size. The size of the lesions varied among rats but there was no major difference between the two groups. Lesions encroached upon the dorsal part of the crus cerebri and part of the subthalamic nucleus in 5 6-OHDA rats and 7 vehicle rats. The medial lemniscus and/or the zona incerta were partially damaged in 7

Figure 17

Effects of ipsilateral electrolytic lesions (2 mA DC, 15 sec) at the lateral hypothalamus in rats microinjected 10 to 14 days previously with 6-OHDA 8 ug in 4 ul. Each point represents the mean nigral-evoked rotation from 8 rats tested prior to electrolytic lesion (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM.

A. Amplitude-rotation was significantly decreased at 2 hours, 3 and 7 days after electrolytic lesions (ANOVA, $F = 13.19$, 11.40 and 9.23 respectively, $P < 0.005$).

B. Frequency-rotation was significantly decreased at 3 hours, 3, 7 and 14 days after electrolytic lesions (ANOVA, $F = 11.22$, $P < 0.005$; $F = 24.62$, $P < 0.005$; $F = 9.63$, $P < 0.005$ and $F = 5.32$, $P < 0.025$ respectively).

Lesions and electrode placements are diagrammed in Figure 19. Mean ipsilateral striatal DA depletion was $91 \pm 2\%$, SEM. For further statistical analysis see text.

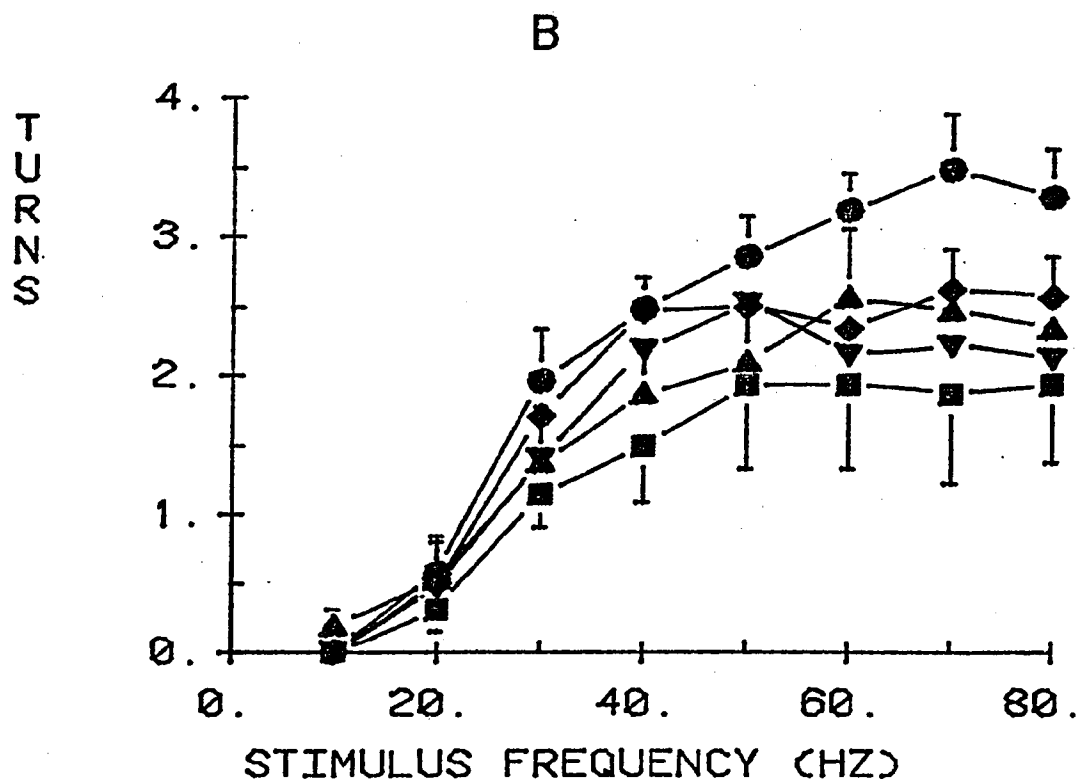
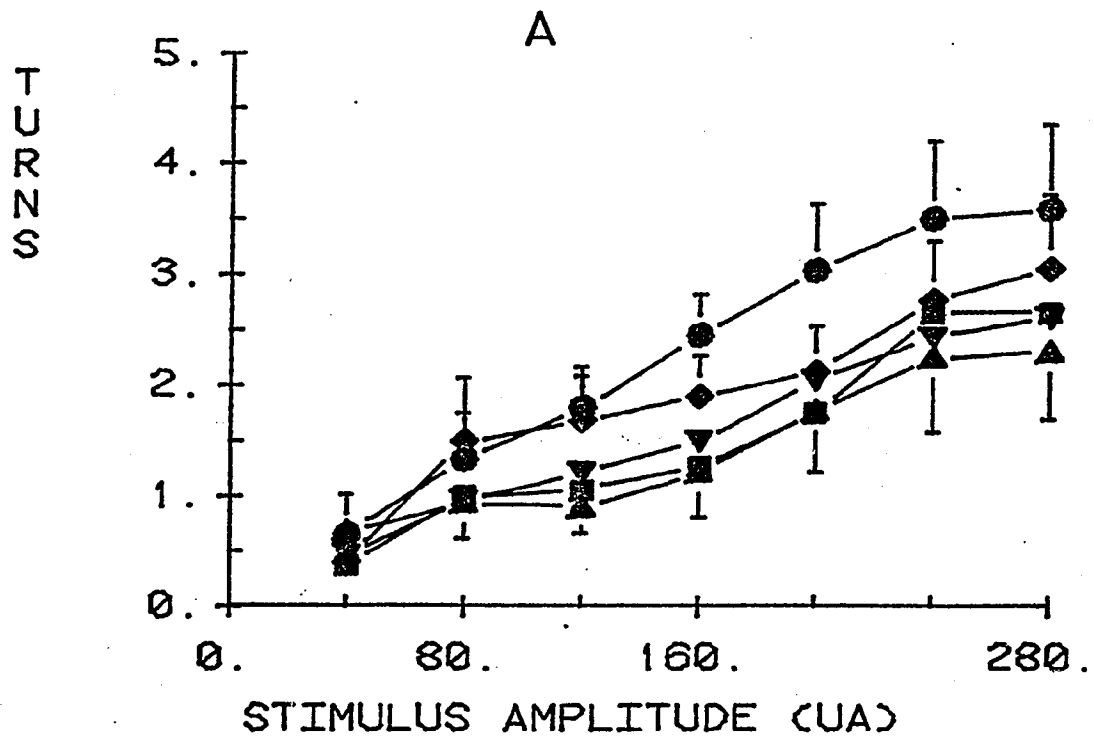


Figure 18

Effects of ipsilateral electrolytic lesions (2 mA DC, 15 sec) at the lateral hypothalamus in rats microinjected 10 to 14 days previously with vehicle (4 ul). Each point represents the mean nigral-evoked rotation from 8 rats tested prior to electrolytic lesion (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM. Rotation was significantly decreased at 2-3 hours, 3, 7 and 14 days after electrolytic lesions (ANOVA, $F = 22.90$, $P < 0.005$; $F = 12.57$, $P < 0.005$; $F = 8.50$, $P < 0.005$ and $F = 4.83$, $P < 0.05$ respectively for A-R; $F = 36.41$, $P < 0.005$; $F = 22.38$, $P < 0.005$; $F = 20.48$, $P < 0.005$ and $F = 7.43$, $P < 0.01$ respectively for F-R). Lesions and electrode placements are diagrammed in Figure 19. Mean ipsilateral striatal DA depletion was $49 \pm 8\%$, SEM. For further statistical analysis see text.

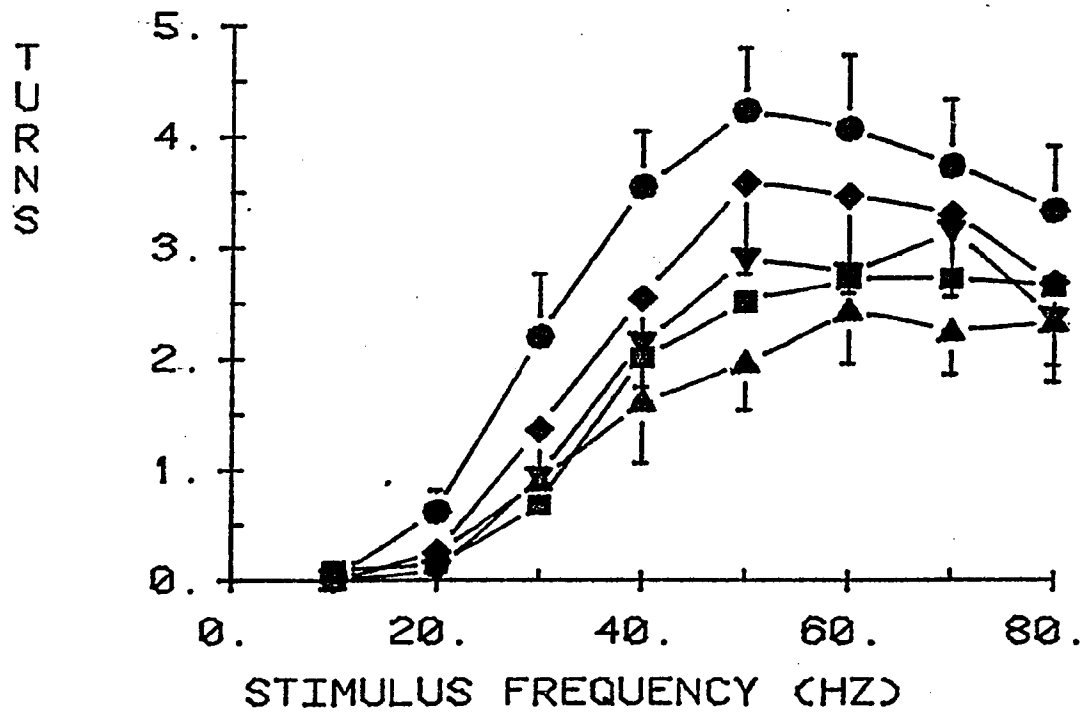
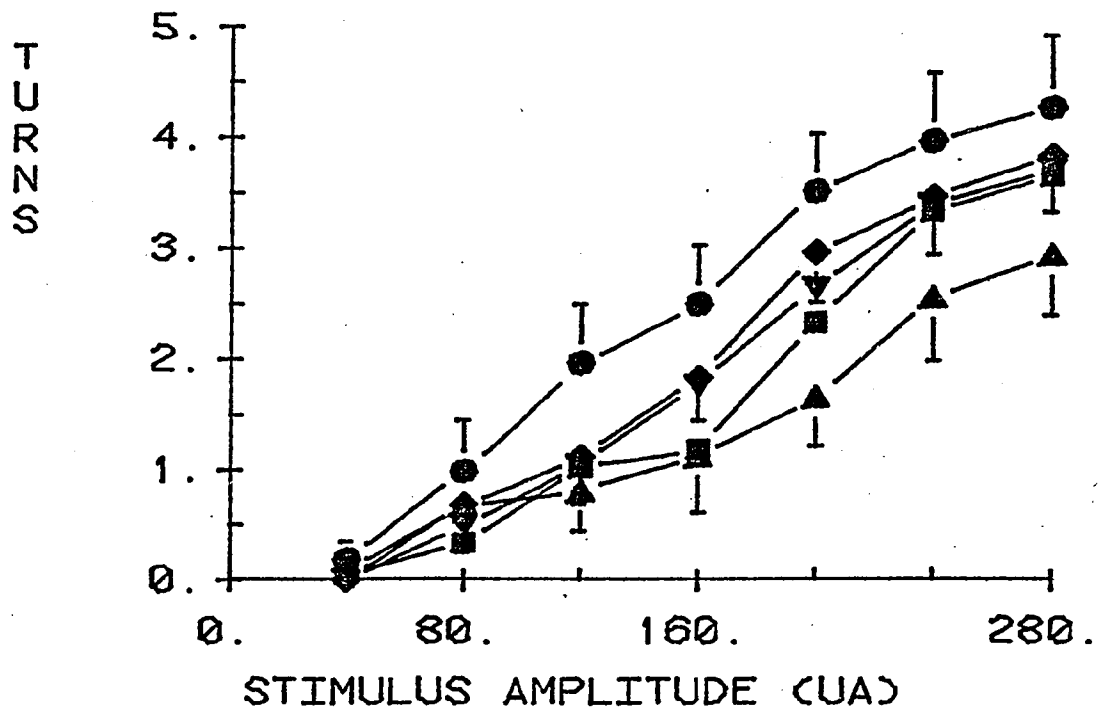
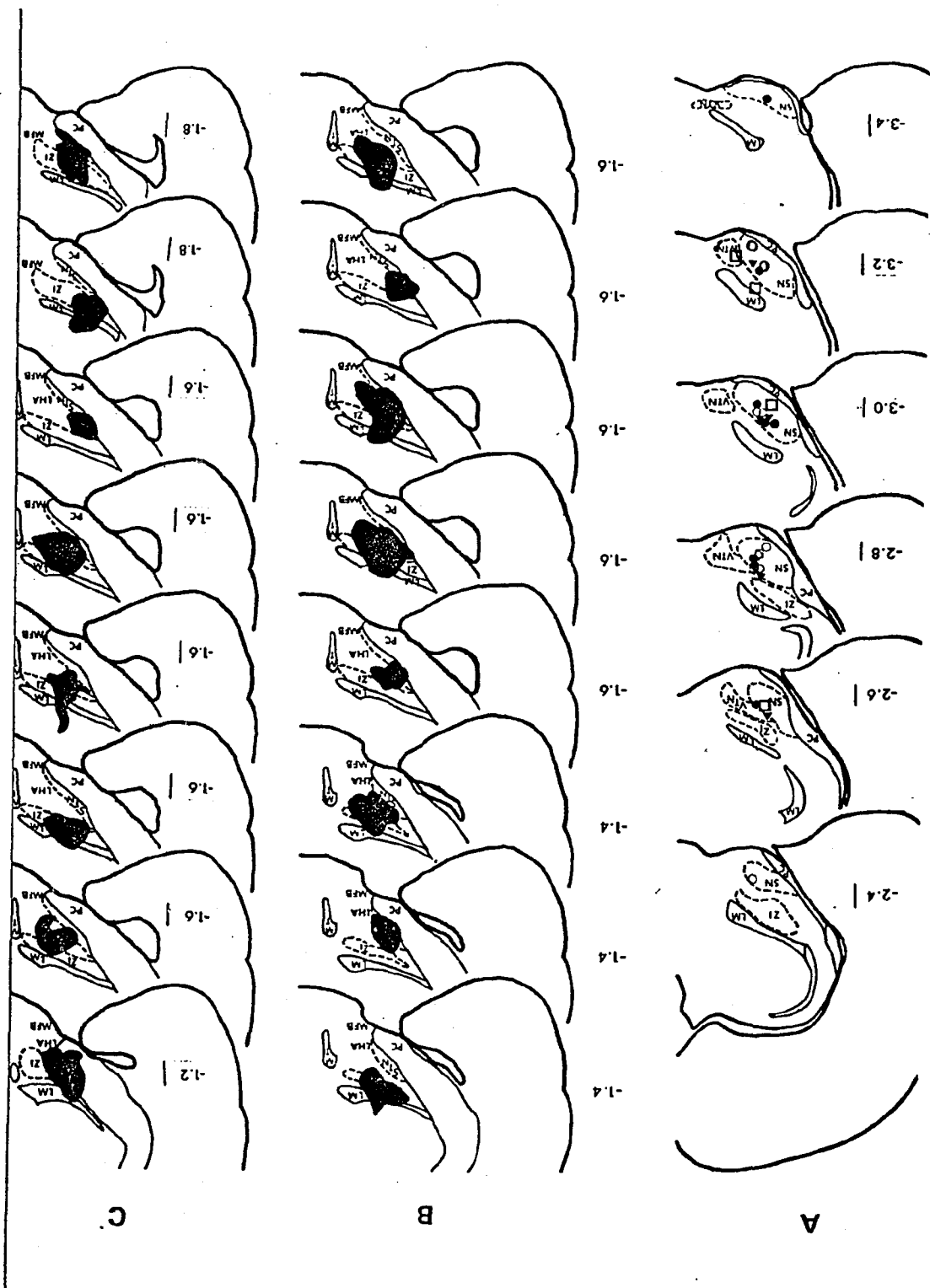


Figure 19

A. Localization of stimulating electrode tips in the substantia nigra of rats with 4 ug 6-OHDA lesions ($\blacktriangle$), 1 ug 6-OHDA lesions ($\square$), 8 ug 6-OHDA plus electrolytic lesions (O), and vehicle plus electrolytic lesions ($\bullet$).

B and C. Extent of electrolytic lesions (2 mA DC, 15 sec) at anterior-posterior plane with the largest lesion size from each of 8 rats preinjected with 6-OHDA (B), and each of 8 rats preinjected with vehicle (C).

The numbers represent mm. posterior to bregma. Abbreviations: LHA, lateral hypothalamic area; LM, medial lemniscus; MFB, medial forebrain bundle; MT, mamillothalamic tract; PC, cerebral peduncle; SN, substantia nigra; STN, subthalamic nucleus; VTN, ventral tegmental nucleus; ZI, zona incerta.



out of 8 rats in each group.

Effects of electrolytic lesions of the CP on NER

Small electrolytic lesions (2 mA DC, 30 sec) at the middle of the CP (as diagrammed in Fig. 23) in 6 rats did not significantly change NER tested at 2 hours, 3, 7 and 14 days postlesion (ANOVA, $F = 2.22$, $P > 0.05$) (Fig. 20).

Large electrolytic lesions (5 mA DC, 30 sec), through bipolar electrodes (tips separated by 1.5 mm rostrocaudally with 1.5 mm. exposed) at the CP (diagrammed in Fig. 23) in 5 rats significantly reduced NER tested at 3, 7, 14, 21 and 28 days postlesion (ANOVA, $F = 408.81, 215.66, 181.68, 268.38$ and 241.24 respectively, $P < 0.005$ for A-R curves; $F = 224.47, 128.74, 165.76, 203.50$ and 97.91 respectively, $P < 0.005$ for F-R curves) (Fig. 21). Postlesion NER at 2 and 3 hours was not significantly different from prelesion ($F = 2.22$ and 2.08 for A-R and F-R curves respectively, $P > 0.10$). NER did not significantly change from 1 to 4 weeks postlesion ($F = 0.46$ and 0.07 for A-R and F-R curves respectively, $P > 0.25$). Rotation at 3 days, however, was significantly lower than that at 7, 14, 21 or 28 days ($F = 23.57, 12.90, 12.95$ and 19.09 respectively for A-R curves, $F = 15.43, 16.41, 9.05$ and 12.95 respectively for F-R curves, $P < 0.005$).

Five rats implanted with similar bipolar electrodes but sham lesioned (0 mA DC, 30 sec) showed no significant change in NER tested at equivalent postlesion times (ANOVA, $F = 0.41$, $P > 0.25$; $F = 1.44$, $P > 0.10$ for A-R and F-R curves respectively) (Fig. 22).

Figure 20

Contralateral rotation evoked by electrical stimulation of the substantia nigra prior to (●) and 2 hours (▲), 3 (■), 7 (▼) and 14 (◆) days after small electrolytic lesions (2 mA DC, 30 sec) at the center of the ipsilateral caudate putamen. Each point represents the mean rotation from 6 rats, error bars represent SEM. There was no significant change in nigral-evoked rotation following the lesions (ANOVA, $F = 2.22$, $P > 0.05$). Lesions and electrode placements are diagrammed in Figure 23.

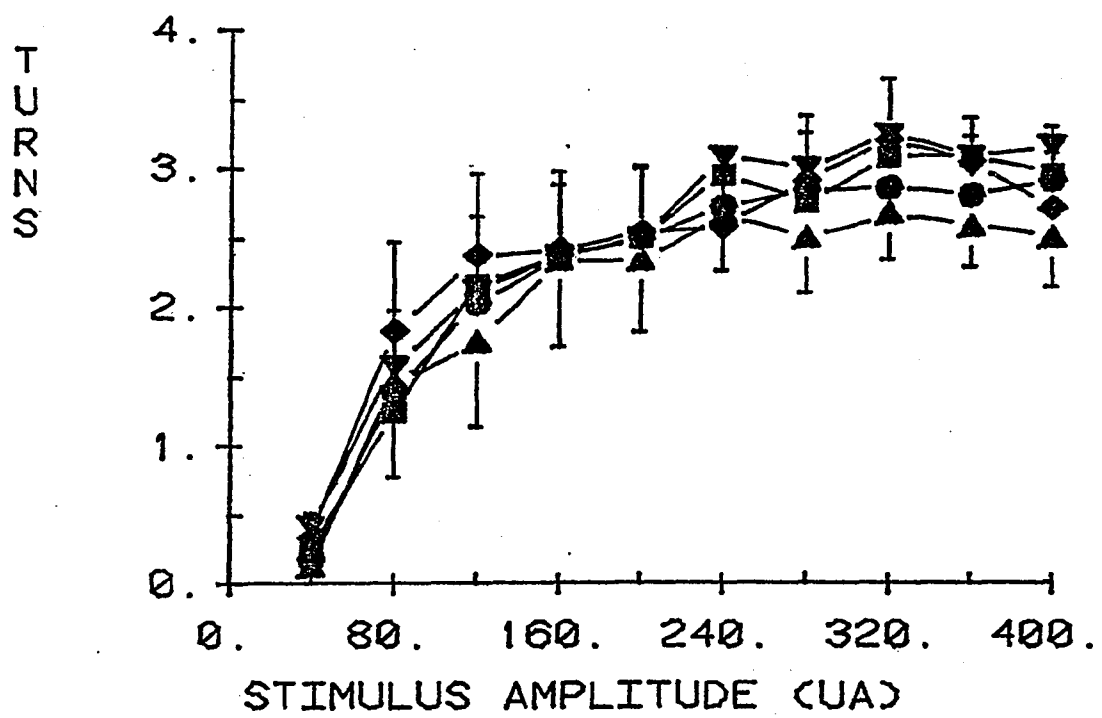


Figure 21

Alteration of rotation evoked by electrical stimulation of the substantia nigra following large electrolytic lesions (5 mA DC, 30 sec) of the ipsilateral caudate putamen. Each point represents the mean rotation from 5 rats tested for control (●) and 2 - 3 hours (▲), 3 (■), 7 (▼), 14 (◆), 21 (○) and 28 (△) days postlesion. Error bars represent SEM. There was no significant reduction of the rotation at 2 - 3 hours postlesion (ANOVA, $F = 2.22$, A-R and 2.08 , F-R, $P > 0.10$). Rotation at 3, 7, 14, 21 and 28 days postlesion was lower than control ($F = 408.81$, 215.66 , 181.68 , 268.38 and 241.24 respectively for A-R; $F = 224.47$, 128.74 , 165.76 , 203.50 and 97.91 respectively for F-R; $P < 0.005$). For further statistical analysis see text. Lesions and electrode placements are diagrammed in Figure 23.

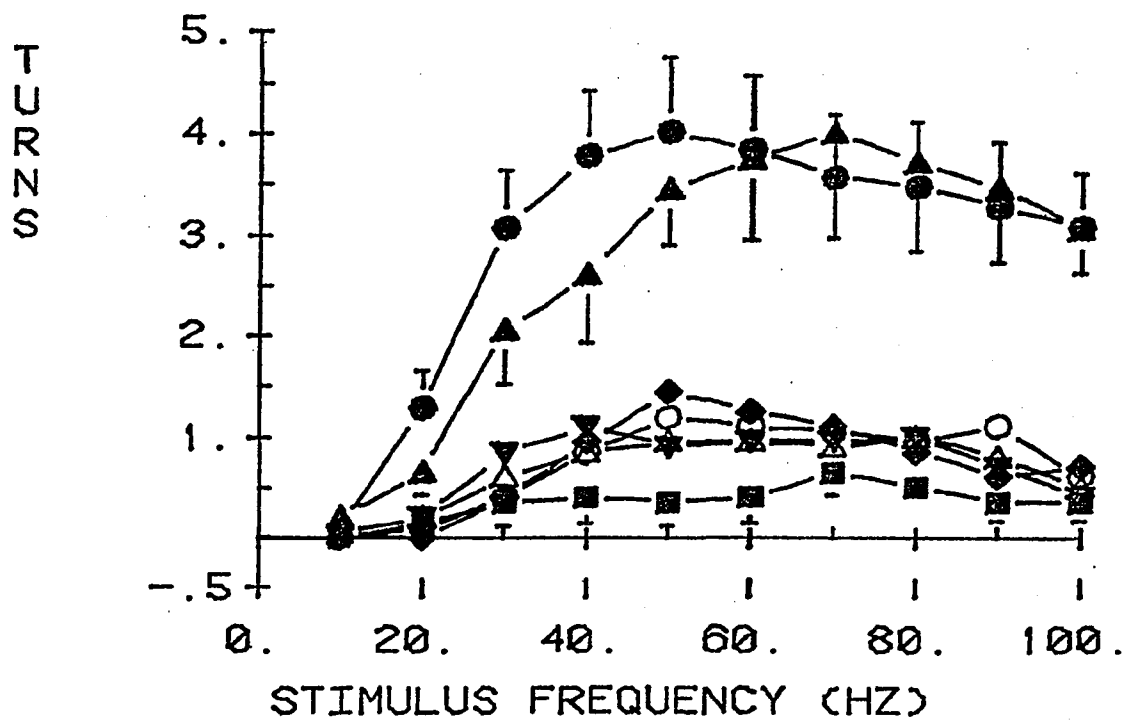
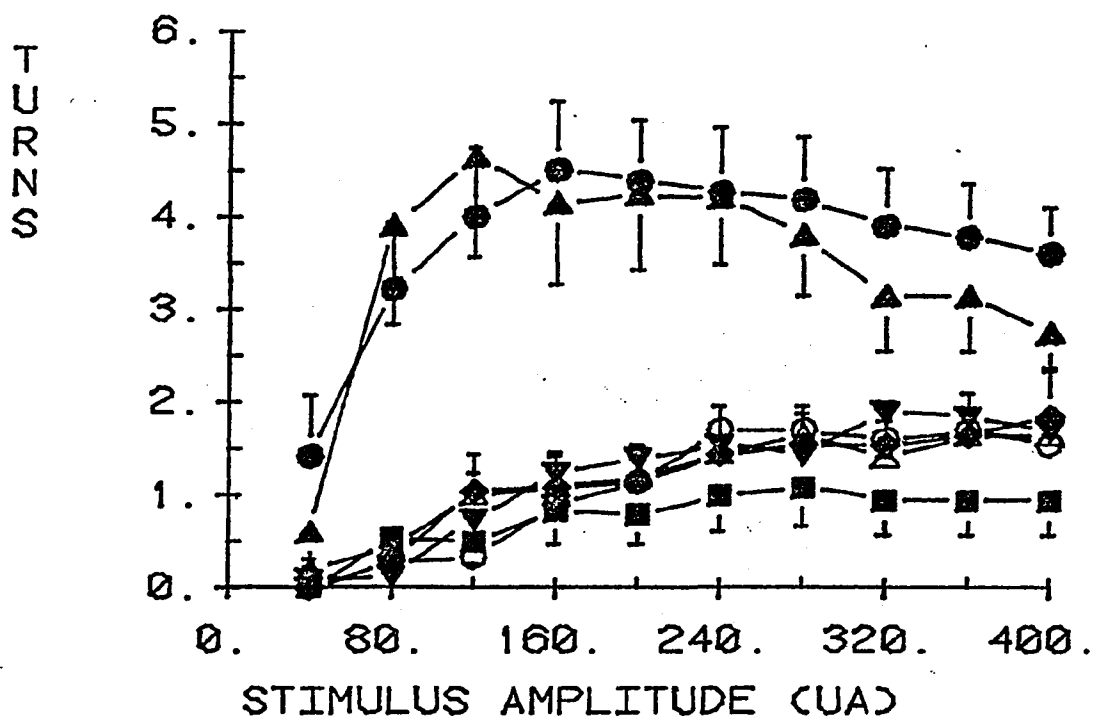


Figure 22

Nigral-evoked contralateral rotation prior to (●) and 2 - 3 hours (▲), 3 (■), 7 (▼), 14 (◆), 21 (○) and 28 (△) days after sham lesion at the caudate putamen. Each point represents the mean rotation from 5 rats, error bars represent SEM. There was no significant change in nigral-evoked rotation following sham lesion (ANOVA, $F = 0.41$, $P > 0.25$; $F = 1.44$, $P > 0.10$ for A-R and F-R respectively).

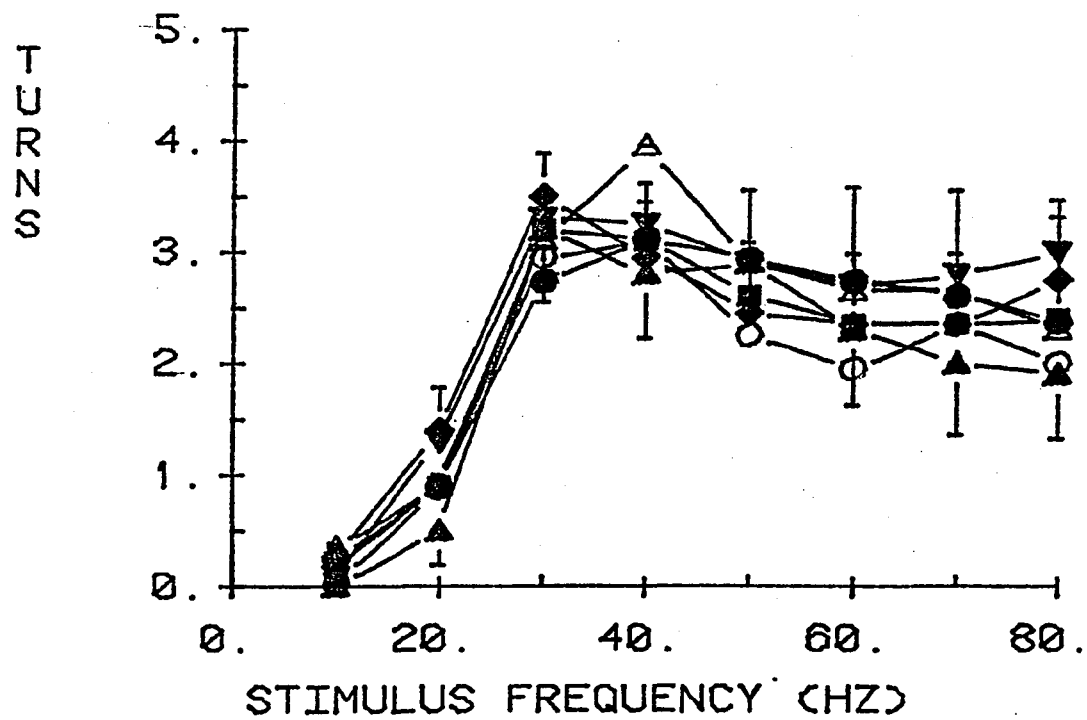
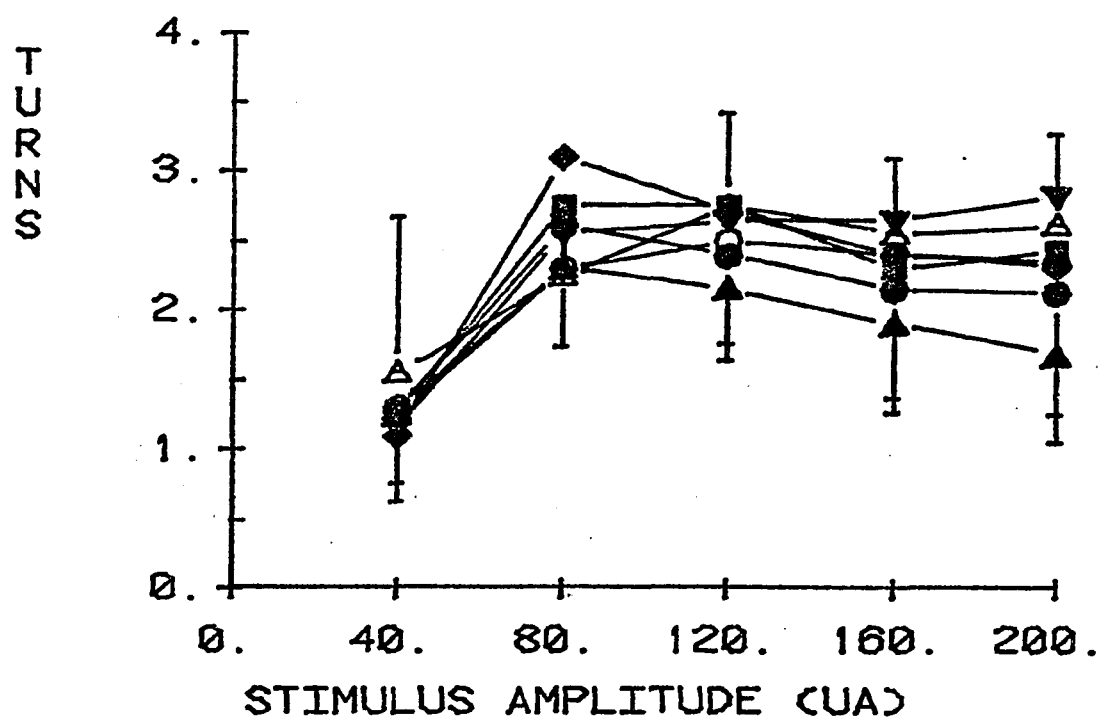


Figure 23

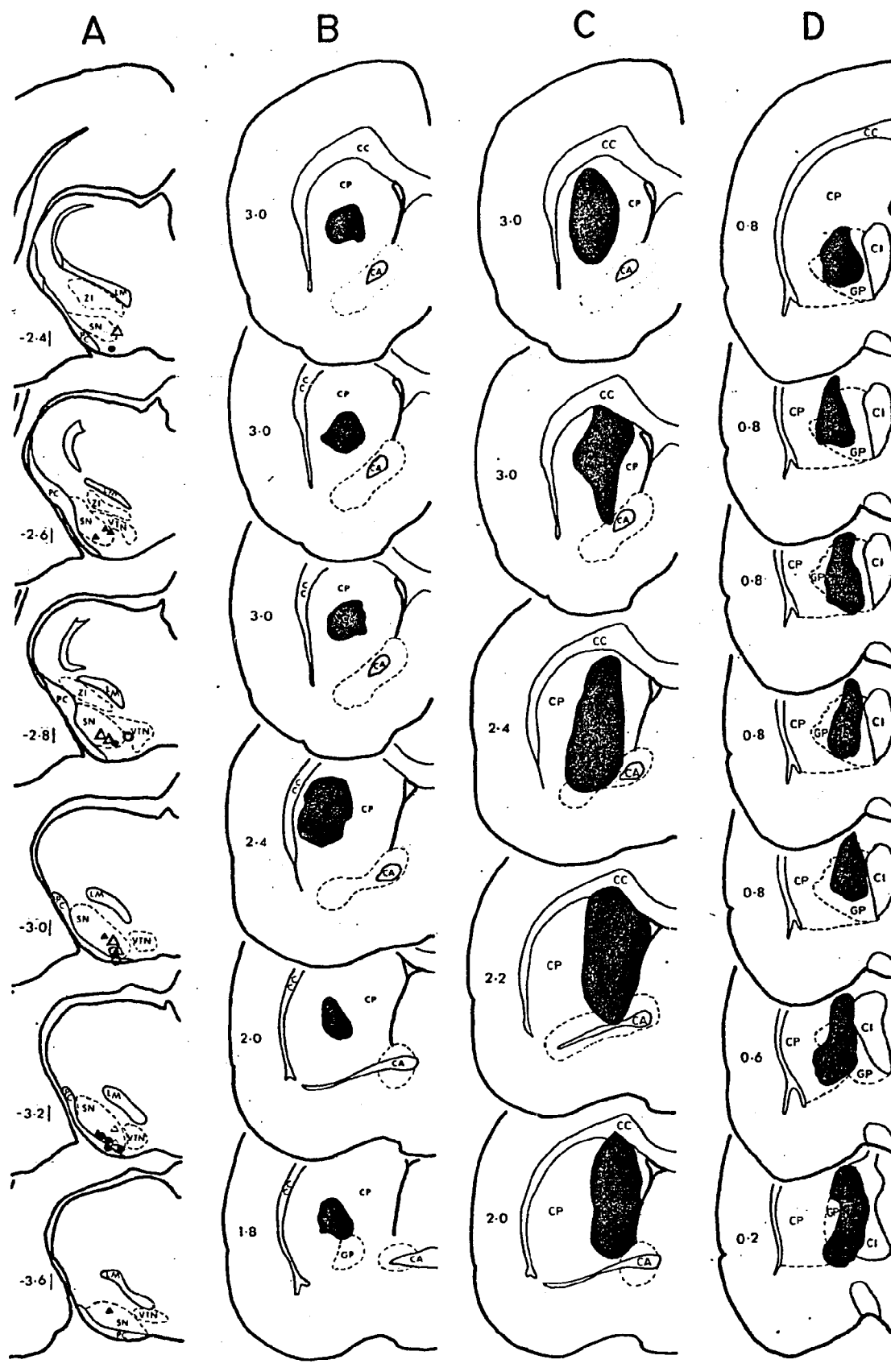
A. Localization of stimulating electrode tips in the left substantia nigra in rats with caudate lesions (●, small; ○, large), and globus pallidus lesions (▲, sham; △, lesion).

B. Anterior-posterior plane showing maximum extent of small electrolytic lesions in each of 6 rats (2 mA DC, 30 sec) at the caudate putamen.

C. Anterior-posterior plane showing maximum extent of large electrolytic lesions in each of 5 rats (5 mA DC, 30 sec) at the caudate putamen.

D. Anterior-posterior plane showing maximum extent of electrolytic lesion in each of 7 rats (2 mA DC, 20 sec) at the globus pallidus.

The numbers represent mm. anterior or posterior (-) to bregma. Abbreviations: CA, anterior commissure; CC, corpus callosum; CI, internal capsule; CP, caudate putamen; GP, globus pallidus; IM, medial lemniscus; PC, cerebral peduncle; SN, substantia nigra; VTN, ventral tegmental nucleus; ZI, zona incerta.



Examination of the lesions at the CP revealed that small CP lesions destroyed only the middle core of the CP without invasion of any adjacent structures as shown in Fig. 23. The extent of the large CP lesions was estimated by summing the planimetric measured areas of one of every three serial 40 μ sections through the entire rostro-caudal extent of the CP lesions at a constant magnification. The lesion volume (mm^3) was calculated from sum of the areas (mm^2) x thickness of 3 sections (0.12 mm). The lesion volume from 5 rats ranged from 4.4 to 9.6 mm^3 ($\bar{x} \pm \text{SEM} = 6.8 \pm 0.9 \text{ mm}^3$). These lesions destroyed approximately 18 to 39 % ($28 \pm 4 \%$, $\bar{x} \pm \text{SEM}$) of the total volume of the CP (24.6 mm^3) as estimated from the Pellegrino and Cushman atlas (Andén et al., 1966c). Corpus callosum and adjacent cortex, the dorsal part of the nucleus accumbens and part of anterior commissure were also destroyed (Fig. 23). These extrastriatal lesions were not included in the planimetric measurement. One rat had a cortical lesion anterior and adjacent to the rostral end of the CP, one rat had more damage of the ipsilateral accumbens than the other rats. The time course of lesion effects in these two rats was indistinguishable from that of the others. In one rat the lesion extended posteriorly to the rostral part of the GP. This rat evidenced slight depression of A-R curve at 2 hours postlesion, and approximately 50 % depression of F-R curve at 3 hours postlesion. Two rats with lesions substantially encroaching on the GP showed marked immediate reduction in NER, and were excluded from this group. Pallidal lesions are considered separately below.

A second group of rats was prepared to study in great detail the time course of the reduction in NER following large lesions of the

CP. To avoid destruction of the GP, lesions were made monopolarly through the anterior pole of the bipolar electrodes in 3 rats, and bipolarly with the anterior pole as an anode in 3 rats. The lesions (Fig. 25) were more anterior than the lesions in the previous group, and in the rats with monopolar lesions there was substantial damage to cortex anterior to CP and to the corpus callosum. The caudate lesion itself was primarily in the rostral and dorsal CP. The volume of the CP lesions estimated by the method described above ranged from 2.5 to 8.3 mm³ ($\bar{x} \pm \text{SEM} = 5.0 \pm 0.9 \text{ mm}^3$, $n = 6$) and was not significantly different from the previous group (Fig. 23C) (t-test, $P > 0.10$). The lesions destroyed approximately 10 to 34 % of the total volume of the CP ($20 \pm 4 \%$, $\bar{x} \pm \text{SEM}$). Effects of the lesions on NER at 2 hours to 3 days are shown in Fig. 24. NER was not significantly different from control at 2 hours postlesion in A-R curve (ANOVA, $F = 1.15$, $P > 0.25$) but was significantly decreased at 3 hours postlesion in F-R curve ($F = 6.29$, $P < 0.025$). For A-R curves, there was a gradual reduction of NER from 6 hours to 3 days postlesion: NER at 6 hours postlesion was significantly less than that at 2 hours ($F = 25.98$, $P < 0.005$) and NER at 1 day postlesion was significantly lower than that at 6 hours ($F = 10.45$, $P < 0.005$). NER at 1 and 2 days postlesion was not significantly different ($F = 0.99$, $P > 0.25$), but NER at 3 days was significantly lower than that at 1 day postlesion ($F = 7.13$, $P < 0.01$). For F-R curves, NER at 7 hours postlesion was significantly lower than that at 3 hours ($F = 44.60$, $P < 0.005$) and NER at 2 days was significantly lower than NER at 7 hours and 1 day postlesion ($F = 5.23$, $P < 0.05$; $F = 5.80$, $P < 0.025$ respectively). NER at 2 days was not significantly

Figure 24

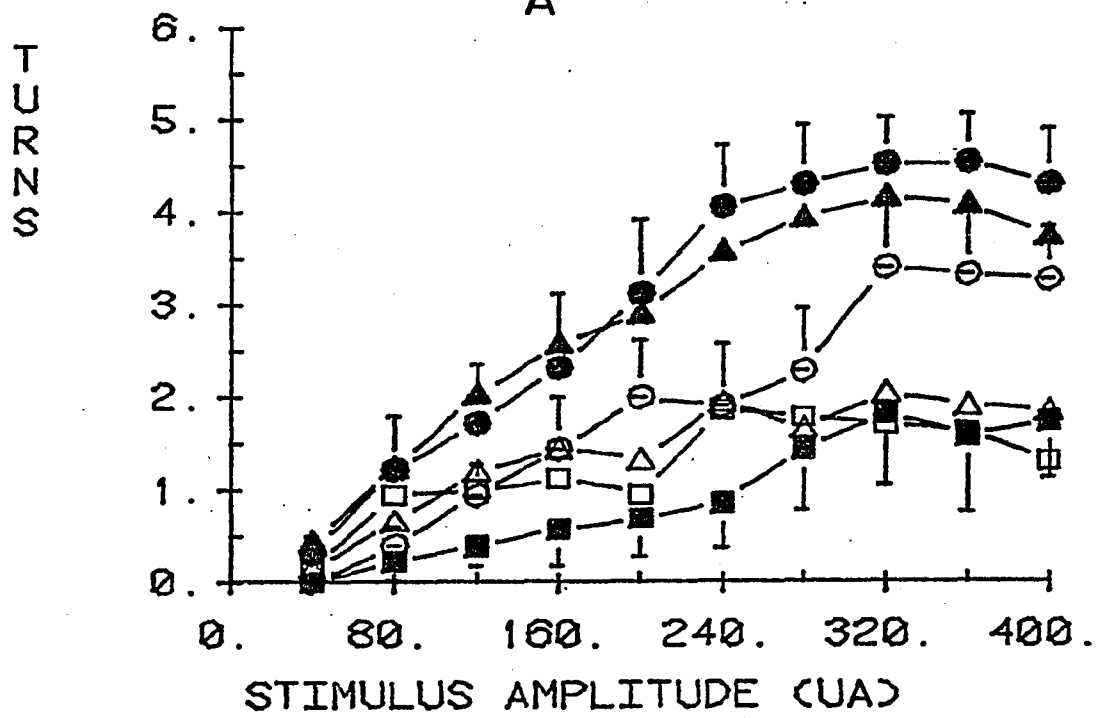
Time course of the alteration of nigral-evoked rotation following large electrolytic lesions (5 mA DC, 30 sec) of the ipsilateral caudate putamen. Each point represents the mean rotation at control tests (●) and at 2 - 3 (▲), 6 - 7 (○) hours, 1 (△), 2 (□), and 3 (■) days postlesion, error bars represent SEM.

A, amplitude-rotation curves. There was no significant change in the rotation at 2 hours (ANOVA, $F = 1.15$, $P > 0.25$). Rotation at 6 hours was lower than that at 2 hours ($F = 25.98$, $P < 0.005$), rotation at 1 day was lower than that at 6 hours ($F = 10.45$, $P < 0.005$) and higher than that at 3 days ($F = 7.13$, $P < 0.01$).

B, frequency-rotation curves, rotation was significantly decreased at 3 hours (ANOVA, $F = 6.29$, $P < 0.025$). Rotation at 7 hours was lower than 3 hours ($F = 44.60$, $P < 0.005$), rotation at 2 days was significantly lower than that at 7 hours ($F = 5.23$, $P < 0.05$) and 1 day ($F = 5.80$, $P < 0.025$) postlesion.

Lesions and electrode placements are diagrammed in Figure 25. Volume of the caudate putamen lesion was not significantly different from that in the original caudate putamen lesioned group (t-test, $P > 0.10$). See text for further statistical analysis.

A



B

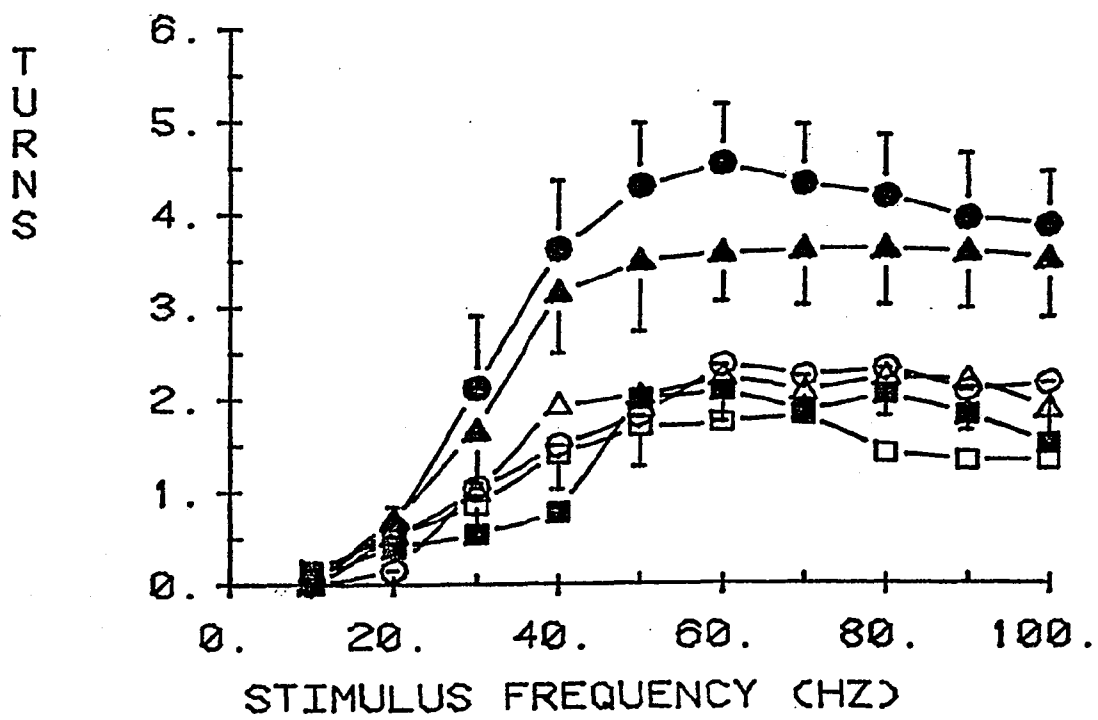
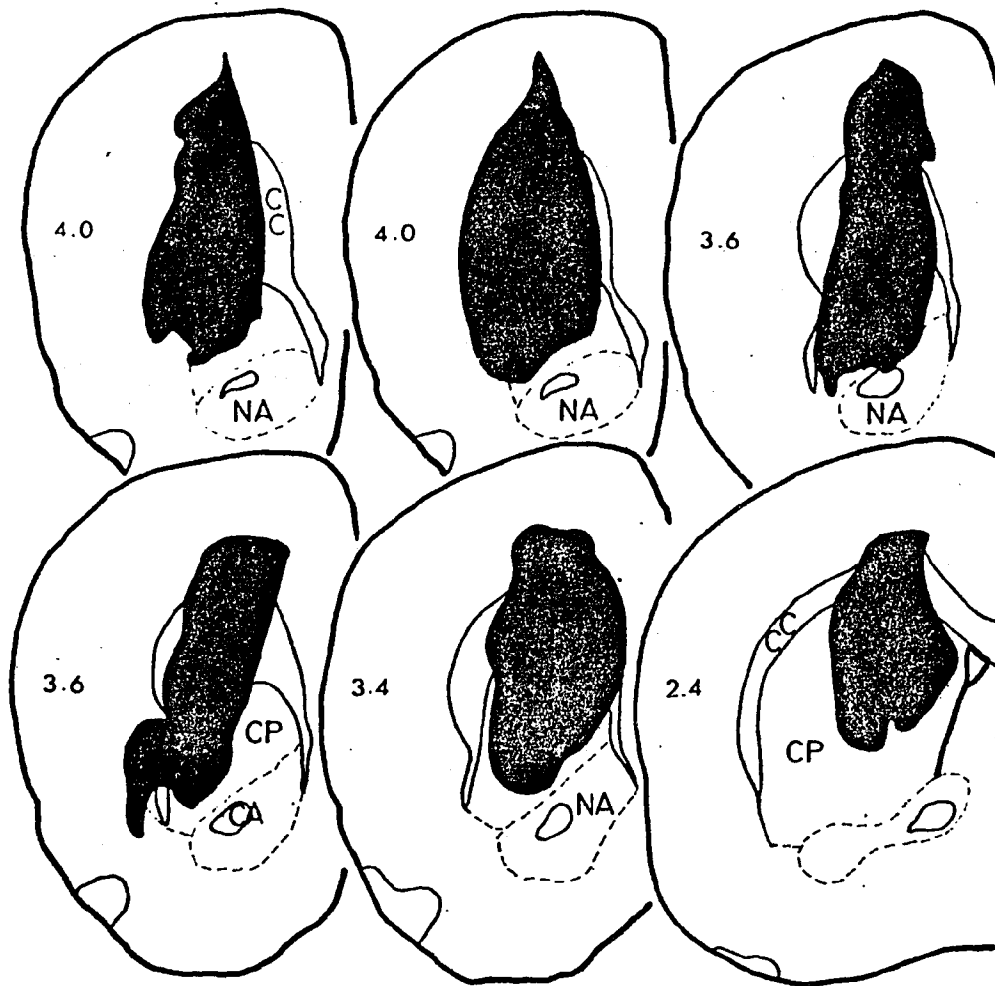
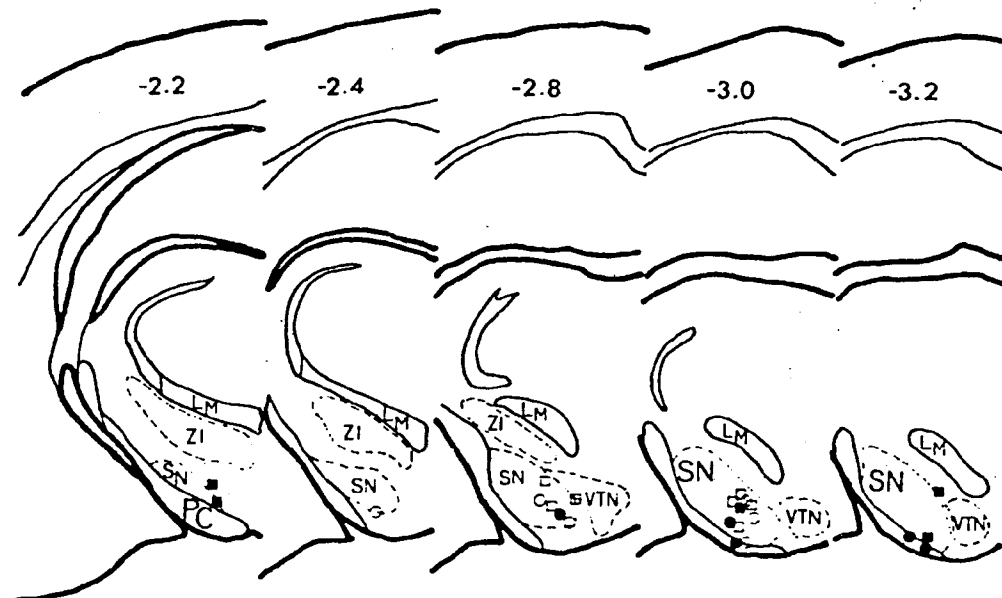


Figure 25

A. Extent of large electrolytic lesions (5 mA DC, 30 sec) at the caudate putamen drawn at the anterior-posterior plane showing maximum size of the lesions in each of 6 rats. Top - Lesions were made monopolarly through the anterior pole of the separated tips bipolar electrodes. Bottom - Lesions were made bipolarly with anodal current passing through the anterior pole.

B. Location of stimulating electrode tips in the left substantia nigra of caudate lesioned rats: O, large electrolytic lesion; ●, sham; □, ibotenic lesion and ■, phosphate buffered saline.

The numbers represent mm. anterior or posterior (-) to bregma. Abbreviations: CA, anterior commissure; CC, corpus callosum; CP, caudate putamen; LM, medial lemniscus; NA, nucleus accumbens; PC, cerebral peduncle; SN, substantia nigra; VTN, ventral tegmental nucleus; ZI, zona incerta.

**A****B**

different from that at 3 days postlesion ($F = 0.29$, $P > 0.25$). NER in this group was also tested at 7 and 14 days postlesion which was significantly lower than prelesion ($F = 40.44$ and 25.69 for C-R, $F = 35.23$ and 13.90 for F-R, $P < 0.005$) and was significantly higher than that at 3 days ($F = 10.49$ and 29.15 , $P < 0.005$ for A-R; $F = 6.45$, $P < 0.025$ and $F = 17.58$, $P < 0.005$ for F-R). NER at 14 days was slightly higher than at 7 days ($F = 3.51$ and 4.29 for A-R and F-R respectively, $P < 0.05$).

The rat in this group with the highest threshold for 1 full contralateral turn (240 uA) during prelesion tests occasionally showed direction reversal of NER evoked at stimulus amplitudes from 40 to 200 uA on days 2 to 14 postlesion. The maximum stimulus bound ipsilateral rotation in this rat was one and three quarter turns. Ipsilateral turns were assigned negative values in statistical analysis.

The 11 rats with large CP lesions showed no significant correlation between the CP lesion volume and the percent reduction of mean rotation (evoked at 40 to 400 uA) at 3, 7 and 14 days postlesion ($r = -0.392$, -0.202 and -0.469 respectively, $P > 0.05$).

Effects of electrolytic lesions of the GP on NER

Electrolytic lesions (2 mA DC, 20 sec) at the GP in 7 rats significantly reduced NER from 2 hours to 14 days postlesion (ANOVA, $F = 45.46$ and 41.42 for A-R and F-R curves respectively, $P < 0.005$) (Fig. 26). NER at 2 hours, 3, 7 and 14 days postlesion were significantly lower than prelesion NER ($F = 191.36$, 72.99 , 86.74 and 46.23 respectively for A-R curves; $F = 73.05$, 176.78 , 65.41 and 61.83 res-

pectively for F-R curves, $P < 0.005$). When stimulus amplitude was varied the maximum reduction of NER was at 2 hours postlesion. NER at 3, 7 and 14 days postlesion was significantly higher than that at 2 hours ($F = 18.05, 32.63$ and 47.58 respectively, $P < 0.005$). NER at 14 days postlesion was significantly higher than that at 3 and 7 days ($F = 7.95, P < 0.025$ and $F = 4.25, P < 0.05$ respectively). When stimulus frequency was varied there was also a marked reduction in NER at 3 hours postlesion but further reduction was observed at 3 days. NER at 3 days was significantly lower than that at 3 hours, 7 and 14 days postlesion ($F = 33.13, 19.11$ and 32.05 respectively, $P < 0.005$). NER did not differ at 3 hours, 7 and 14 days postlesion ($F = 0.25, P > 0.25$).

As is obvious from Figure 26, reversal of direction of NER was consistent enough to be revealed in the averaged rotation response from the seven rats in the GP lesioned group. In two of the rats all postlesion rotation was contralateral. In two of the 5 remaining rats all rotation at two hours postlesion was ipsilateral, in the other rotation was ipsilateral at low stimulus amplitudes and contralateral at higher amplitudes. On subsequent days there was generally a similar pattern, three rats maintaining some ipsilateral rotation up to 14 days postlesion. The maximum number of ipsilateral turns during a ten second stimulus train was two turns. The three rats displaying ipsilateral rotation over the widest stimulus range and which had at least one test day in which all turning was ipsilateral had electrode implantations in the caudal SN (A-P -3.0, -3.2, -3.2, Pellegrino and Cushman, 1967), and their amplitude response curves had a shallow slope at the initial ascending portion. The two rats that did not

Figure 26

Alteration of nigral-evoked contralateral rotation following electrolytic lesions (2 mA DC, 20 sec) at the ipsilateral globus pallidus. Lesions and electrode placements are diagrammed in Figure 23. Each point represents the mean rotation from 7 rats tested before lesions (●) and 2 - 3 hours (▲), 3 (■), 7 (▼) and 14 (◆) days postlesion. Contralateral turns are assigned positive and ipsilateral turns negative values. Error bars represent SEM. There was a significant alteration of rotation after the lesions (ANOVA, $F = 45.46$, A-R and 41.42 , F-R, $P < 0.005$). See text for further statistical analysis and reversal of nigral-evoked rotation after the lesions.

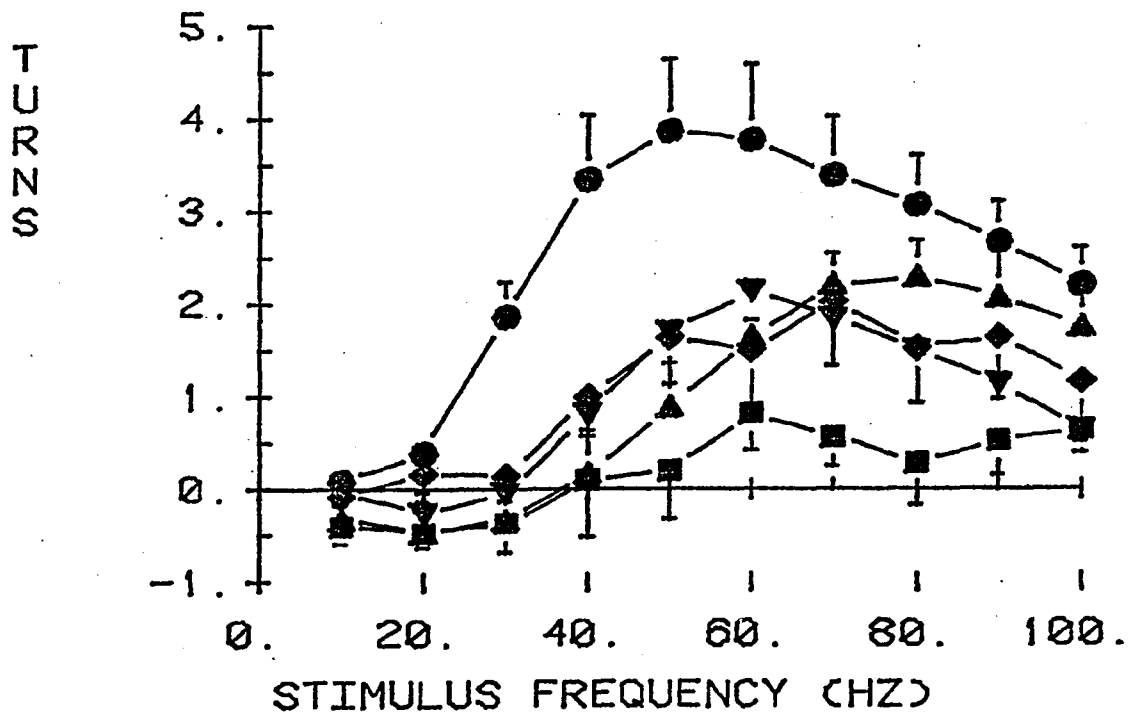
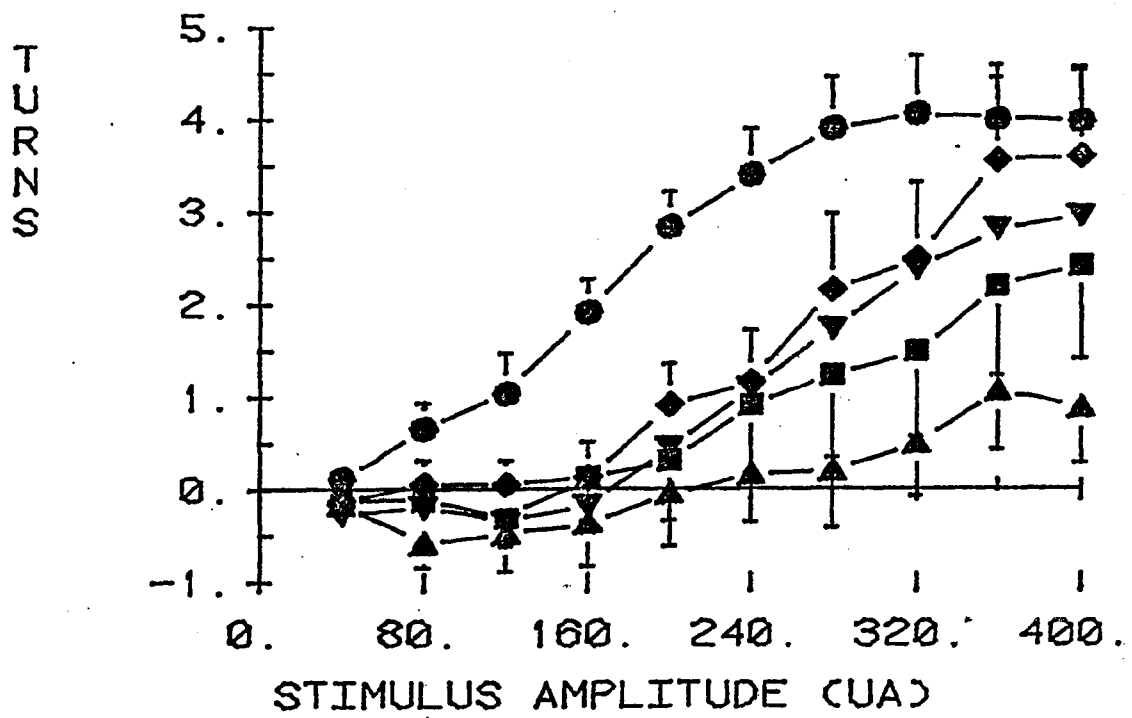
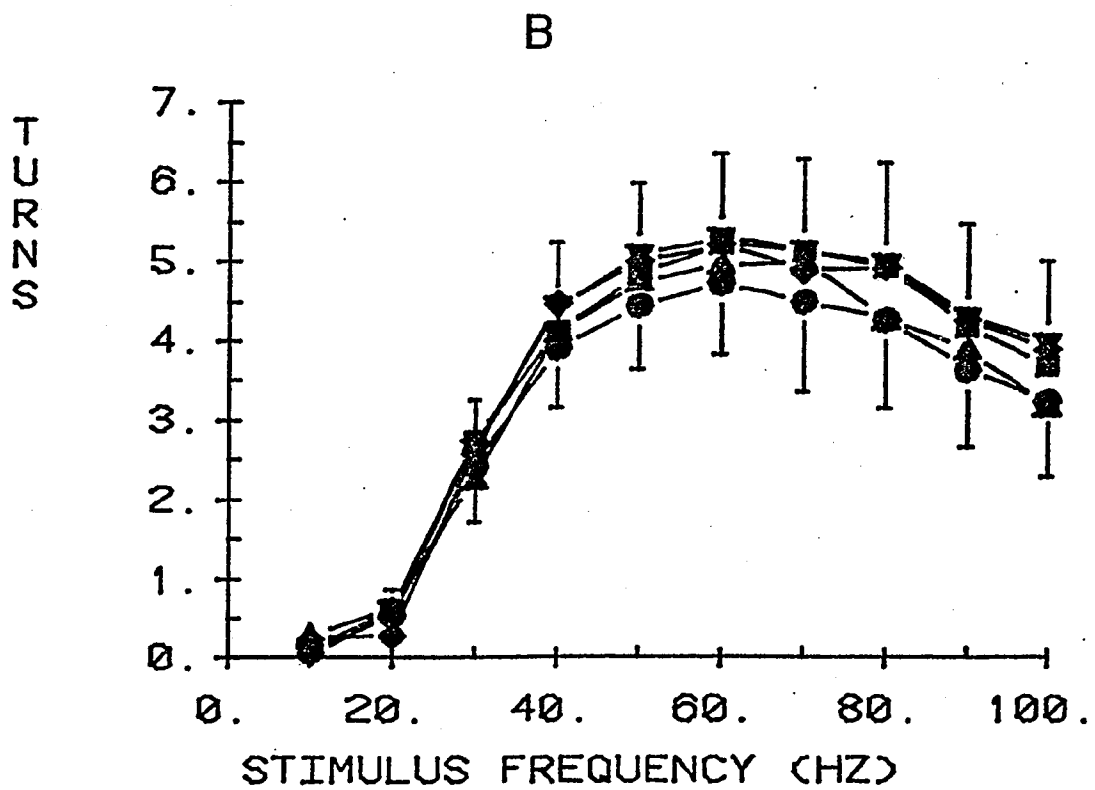
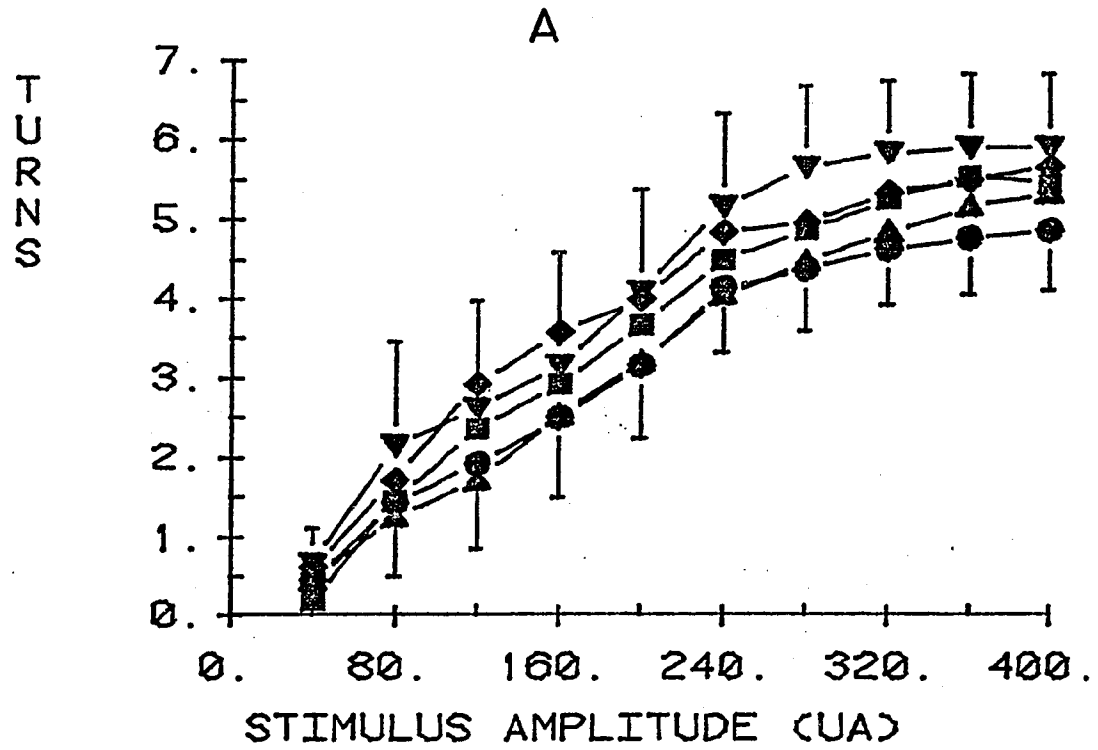


Figure 27

Mean nigral-evoked rotation in 6 rats with sham lesions of the globus pallidus. Rats were tested before (●) and 2 - 3 hours (▲), 3 (■), 7 (▼) and 14 (▣) days after sham lesions. In A-R curves, there was a small but significant increase in the rotation at 3, 7 and 14 days (ANOVA, $F = 4.19$, $P < 0.05$; $F = 16.35$, $P < 0.005$ and $F = 13.01$, $P < 0.005$ respectively) but not at 2 hours ($F = 0.15$, $P > 0.25$) postsham. There was no significant change of the rotation in F-R curves ($F = 1.51$, $P > 0.10$).



rotate ipsilaterally had the lowest thresholds for 1 full contralateral turn (80 and 120 uA) during prelesion tests.

When stimulus frequency was varied, rats rotating contralaterally at the stimulus amplitude chosen (at 30 Hz), rotated contralaterally at all frequencies. Rats rotating ipsilaterally at the selected stimulus amplitude would generally change to contralateral rotation at higher frequencies. At transitional frequencies the rats would often make discrete turning movements in both directions. There was no consistent order of turning direction during the ten second stimulus train in these trials. For statistical analysis of these data, ipsilateral turns were assigned negative values and net rotation was used when rats turned in two directions.

There was no significant change in F-R curves from 6 sham GP rats tested at equivalent times (ANOVA, $F = 1.51$, $P > 0.10$) (Fig. 27B). There was no significant change in A-R curves at 2 hours postsham ($F = 0.15$, $P > 0.25$), but A-R curves at 3, 7 and 14 days postsham was slightly but significantly higher than control ($F = 4.19$, $P < 0.05$; $F = 16.35$, $P < 0.005$ and $F = 13.01$, $P < 0.005$ respectively) (Fig. 27A).

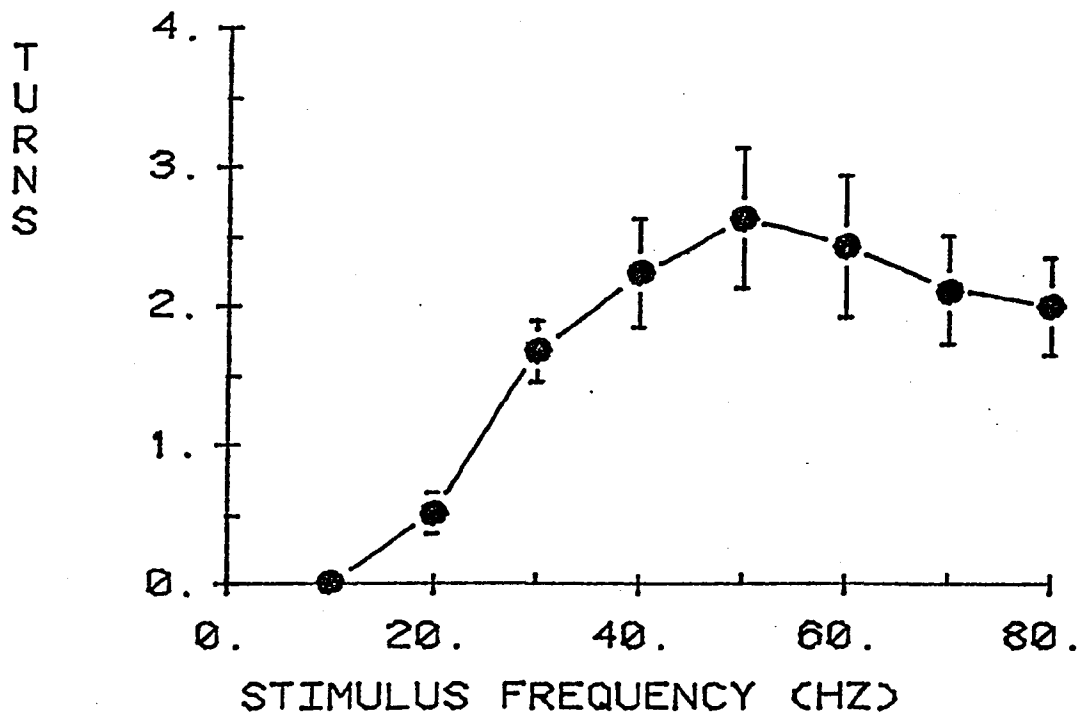
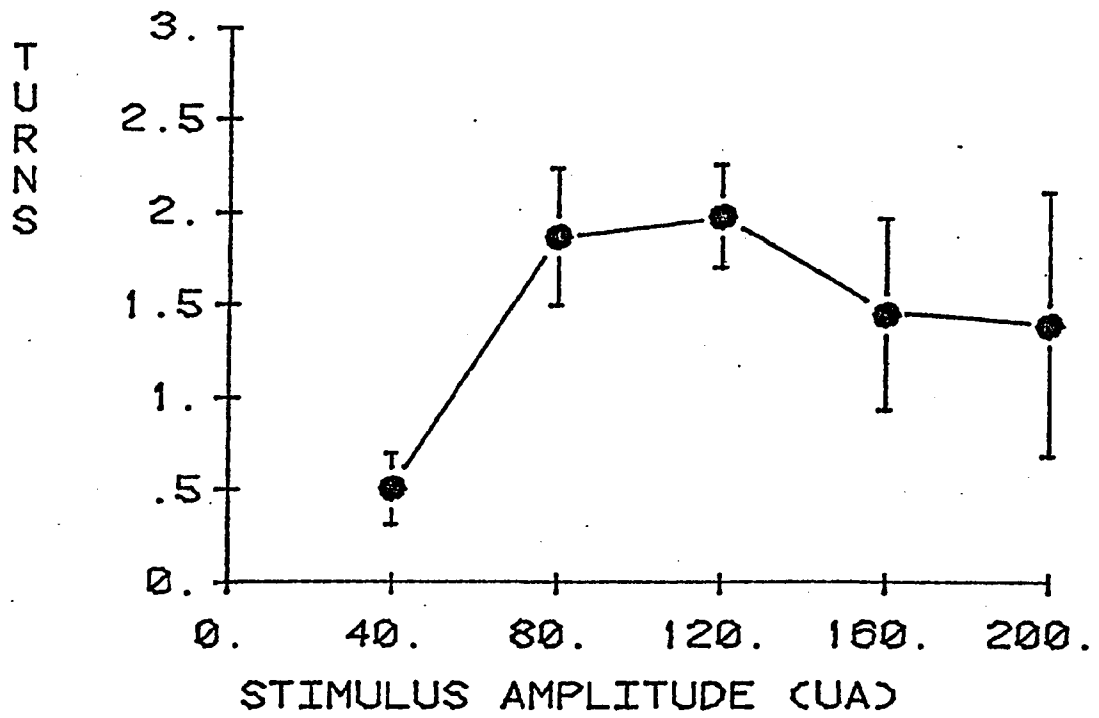
Diagrams of electrode placements and GP lesions are shown in Fig. 23. The lesions destroyed 1/2 to 2/3 of the GP at the level of the largest lesion. The adjacent CP or the internal capsule was slightly damaged in some rats. Sham rats showed no GP damage other than the electrode tract.

Rotation evoked by stimulation of the globus pallidus

Stimulus bound contralateral rotation was obtained from electrical stimulation of the GP in 4 rats (Fig. 28). In these rats

Figure 28

Contralateral rotation evoked upon electrical stimulation of the globus pallidus. Stimulus parameters and paradigm were the same as that used for nigral-evoked rotation. Each point represents the mean rotation from 4 nonlesioned rats, error bars represent SEM.



front paw tremor and body torsion occurred at low stimulus amplitudes (160 uA) and were severe enough that no attempt was made to study rotation at stimuli greater than 200 uA. The amplitude response pattern is reminiscent of rats with "nigral" electrodes near the cerebral peduncle, and probably reflects spread of stimulus to the adjacent internal capsule. The interfering motor behaviors relative to magnitude of rotation were less when stimulus frequency was varied.

Effects of ibotenic acid lesions at the CP on NER

Ibotenic acid [20 ug in 0.5 ul (5 rats) and 10 ug in 0.5 ul (2 rats)] microinjections to the CP significantly reduced NER at 2 to 3 hours and 1 day postlesion (ANOVA, $F = 81.06$ and 78.34 respectively, $P < 0.005$ for A-R curves; $F = 94.86$, $P < 0.005$ and $F = 8.10$, $P < 0.025$ respectively for F-R curves) (Fig. 29). NER recovered to control after 1 day postlesion. There were no significant changes in NER at 3, 5, 7, 10 and 14 days postlesion ($F = 2.48$, $P > 0.10$; $F = 0.02$, $P > 0.25$; $F = 0.11$, $P > 0.25$; $F = 0.03$, $P > 0.25$ and $F = 1.72$, $P > 0.10$ respectively for A-R curves; $F = 1.84$, $P > 0.10$; $F = 0.001$, $P > 0.25$; $F = 0.08$, $P > 0.25$; $F = 0.29$, $P > 0.25$ and $F = 2.62$, $P > 0.10$ respectively for F-R curves).

Two rats receiving 20 ug ibotenic acid showed strong stimulus bound ipsilateral rotation at 2 to 3 hours after the microinjections, one of them still rotated ipsilaterally when tested on day 1 postlesion. These two rats had stimulating electrodes at A-P -3.0 and had thresholds for 1 full contralateral turn in prelesion tests of 200 and 160 uA. One additional rat showed ipsilateral turning at

Figure 29

Effects of ibotenic acid 10 and 20 ug in 0.5 ul microinjected to the ipsilateral caudate putamen on nigral-evoked contralateral rotation. Each point represents the mean rotation from 7 rats tested for control (●), and 2 - 3 hours (▲), 1 (○), 3 (■), 7 (▼) and 14 (◆) days postlesion. Error bars represent SEM. There was a significant reduction in rotation at 2 - 3 hours and 1 day after ibotenic acid (ANOVA, $F = 81.06$ and 78.34 , $P < 0.005$ for A-R; $F = 94.86$, $P < 0.005$ and $F = 8.10$, $P < 0.025$ for F-R). There were no significant changes in rotation at 3, 7, and 14 days postlesion ($F = 2.48$, $P > 0.10$; $F = 0.11$, $P > 0.25$ and $F = 1.72$, $P > 0.10$ respectively for A-R; $F = 1.84$, $P > 0.10$; $F = 0.08$, $P > 0.25$ and $F = 2.62$, $P > 0.10$ respectively for F-R).

A representative lesion is shown in Fig. 30, electrode placements are diagrammed in Figure 25.

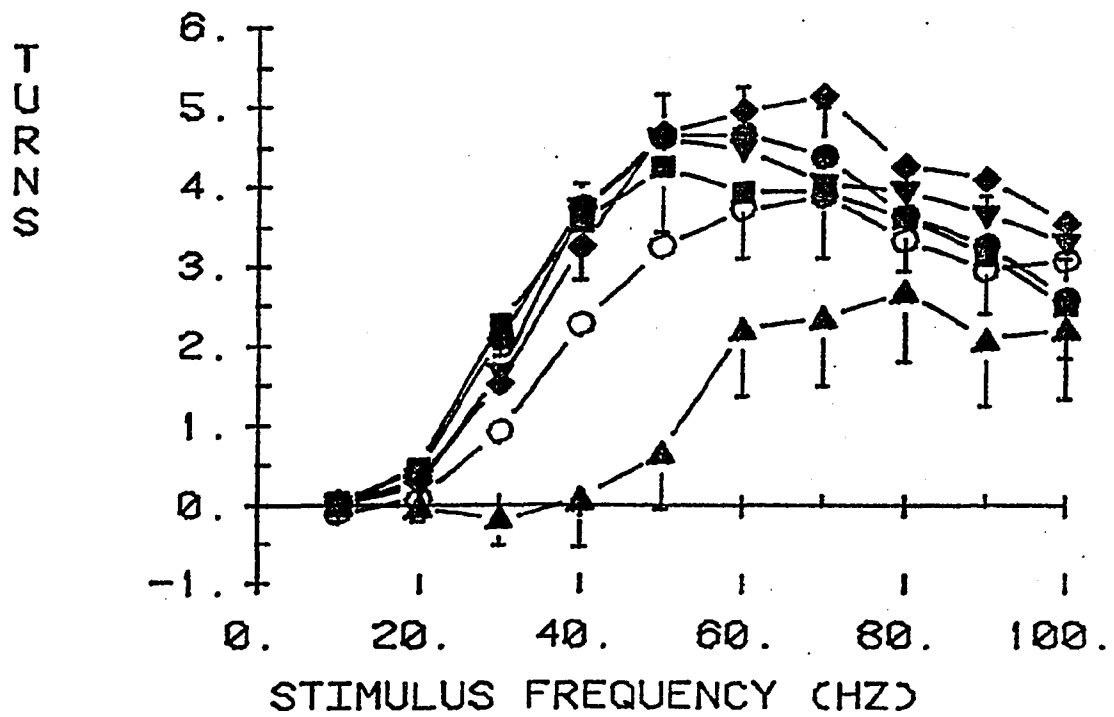
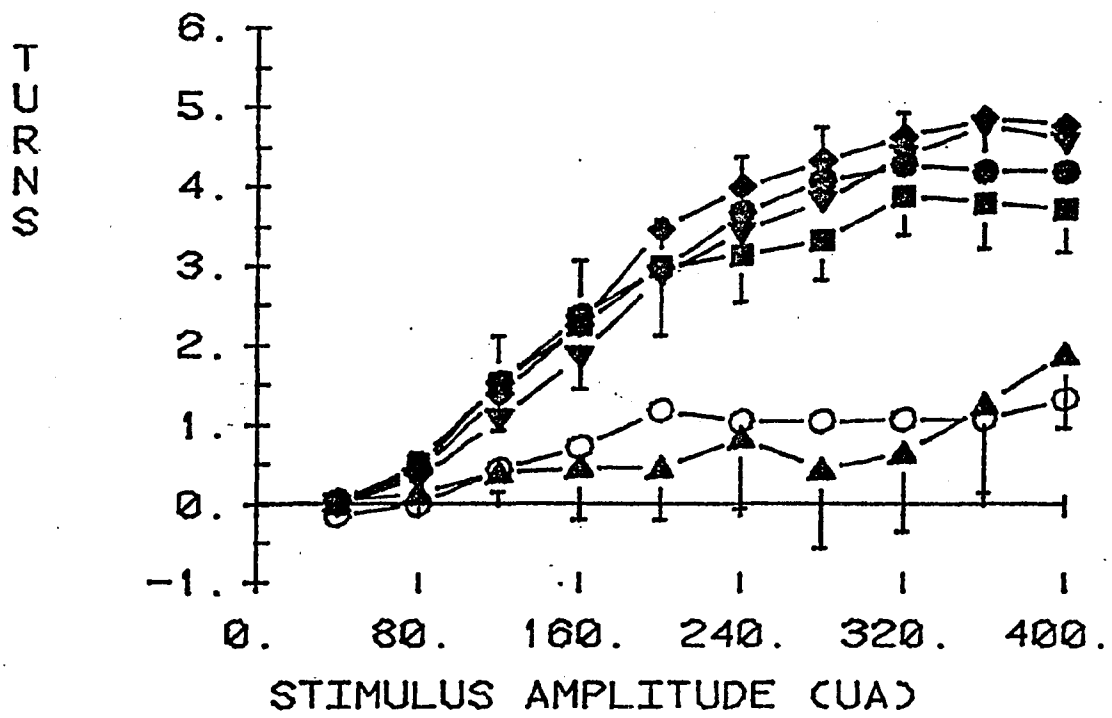


Figure 30

A representative coronal 40 μ section through the caudate-putamen at the level of the visible glial reaction around the area lesioned by ibotenic acid 10 μ g in 0.5 μ l. The section was stained for cell bodies and glia cells by neutral red.

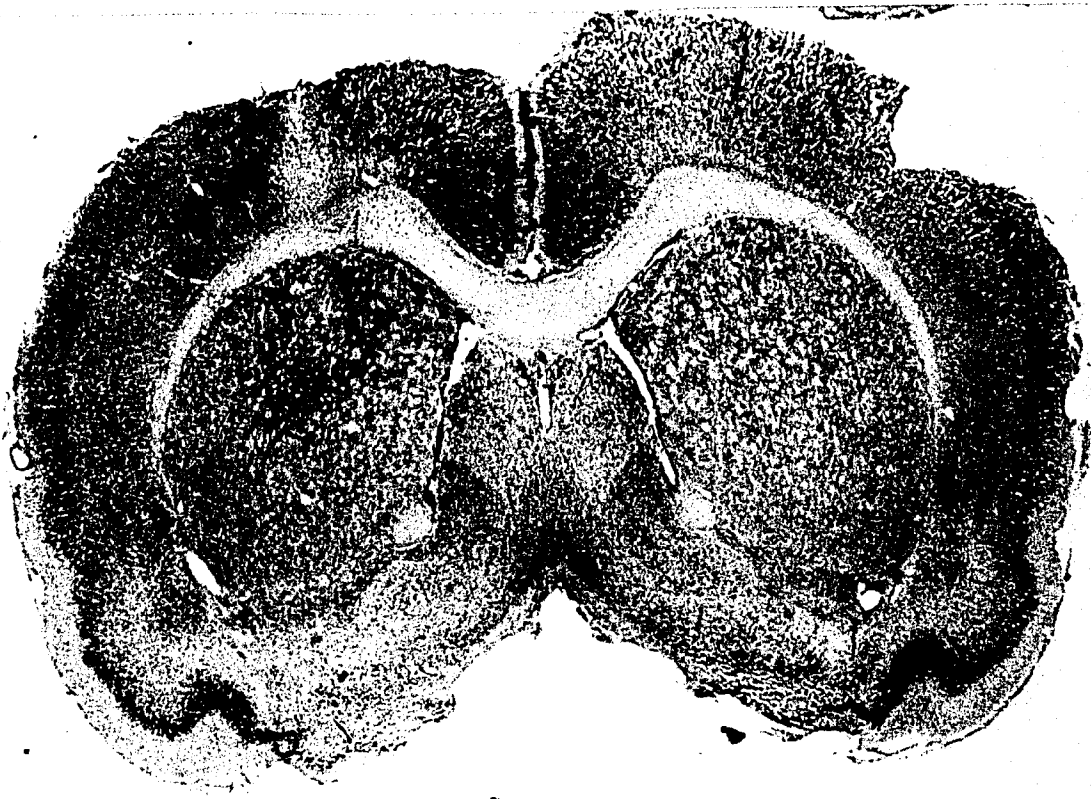
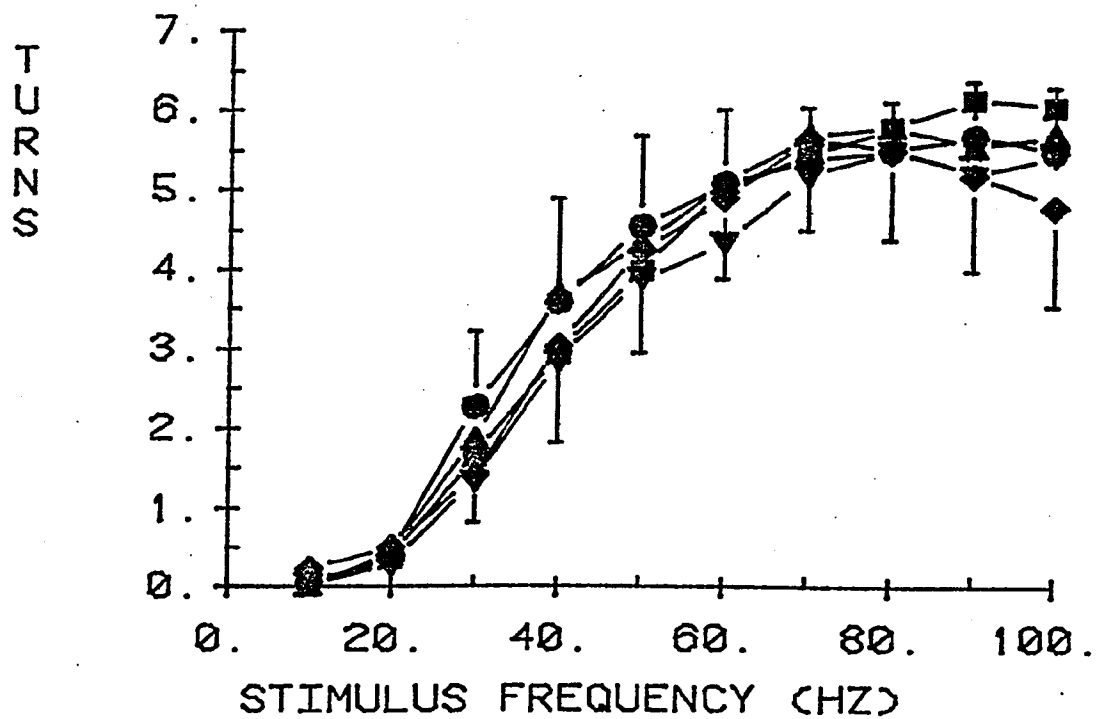
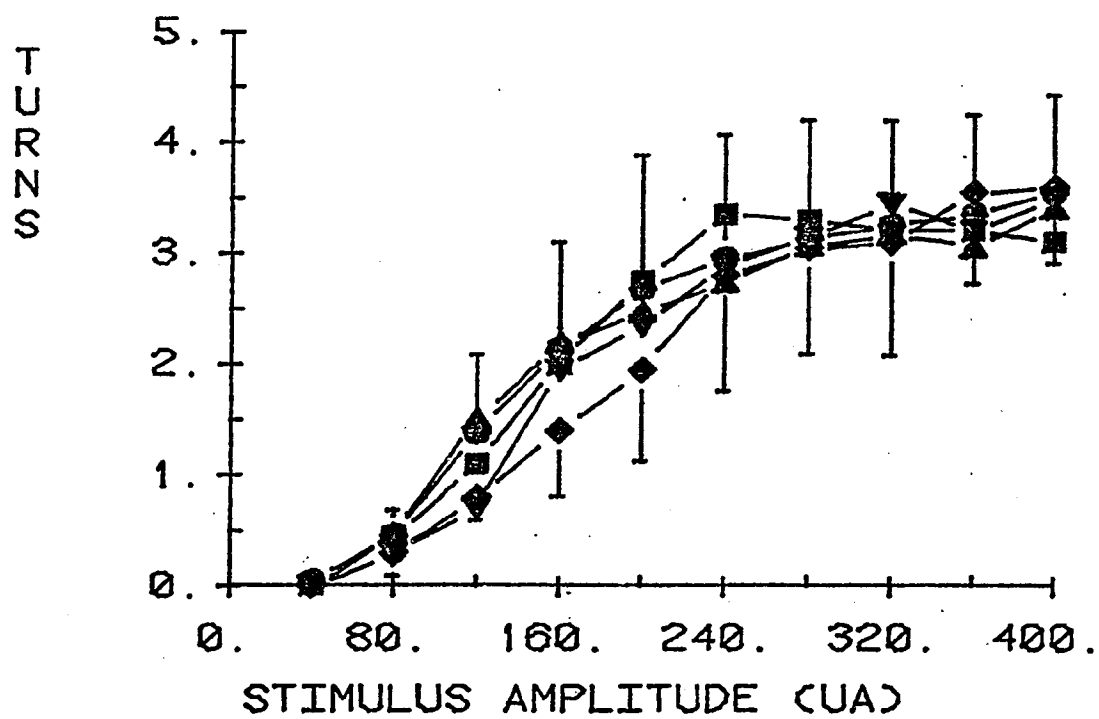


Figure 31

Nigral-evoked contralateral rotation before (●) and after (▲, 2 - 3 hours; ■, 3 days; ▼, 7 days; ◆, 14 days) intrastriatal injections of 0.5 or 1.0 ul of phosphate buffered saline pH 7.4. Each point represents the mean rotation from 5 rats, error bars represent SEM. There was no significant change in the rotation (ANOVA, $F = 0.36$, A-R and 0.57 , F-R, $P > 0.25$). Electrode placements are diagrammed in Figure 25.



stimulus amplitudes of 40 to 200 uA on day 1 postlesion. There was no observable stimulus bound ipsilateral rotation in the remaining 4 rats. These animals had relatively low thresholds for 1 full contralateral turn during control tests. As with GP lesioned rats, F-R tests resulted in contralateral rotation if the rats rotated in that direction at the selected amplitude, and mixed rotation if the rats rotated ipsilaterally. In statistical analysis, ipsilateral rotation was assigned as negative and the net rotation was used when the rats responded in both directions.

All rats had severe spontaneous body torsion with contralateral body roll over (as described by Schwarcz et al., 1979) and contralateral front paw tremor during the 2 to 3 hour postlesion tests. Some rats had mild and short duration tonic-clonic convulsions. They appeared normal during 1 day postlesion test.

Diagrams of electrode placements are shown in Fig. 25B. Histological examination of the serial sections through the CP revealed that area of the degenerated cell bodies was at the middle part of the CP (Fig. 30) and extended to the dorsal and lateral portions in some rats. In none of the ibotenic acid lesioned rats did the lesions hit the GP. The volume of the CP lesioned by ibotenic acid was not determined since the marginal zone of the lesions was not clearly visualized for planimetric measurement. To compare the lesion extent with that of the effective CP electrolytic lesions, the entire rostrocaudal extent of the ibotenic acid lesions as represented by the numbers of serial 40 u sections with visible glial reactions [$\bar{x} \pm \text{SEM} = 1.164 \pm 0.144$ mm, $n = 6$, (the lesion in one rat was not quantitated due to damage of the sections)] was compared with

the rostrocaudal extent of the effective electrolytic lesion of the CP (2.364 ± 0.180 mm, $n = 11$). The rostrocaudal extent of the ibotenic acid lesions at the CP was significantly less than that of effective electrolytic lesions (t-test, $P < 0.001$).

There was no significant change in NER in 5 rats microinjected with the ibotenic acid vehicle, 0.5 or 1.0 μ l of phosphate buffered saline pH 7.4, tested at 2 hours to 14 days after the microinjections (ANOVA, $F = 0.36$ and 0.57 for A-R and F-R curves respectively, $P > 0.25$) (Fig. 31).

Effects of electrolytic lesions of nuclei receiving nigral and/or mesocortical efferents on NER

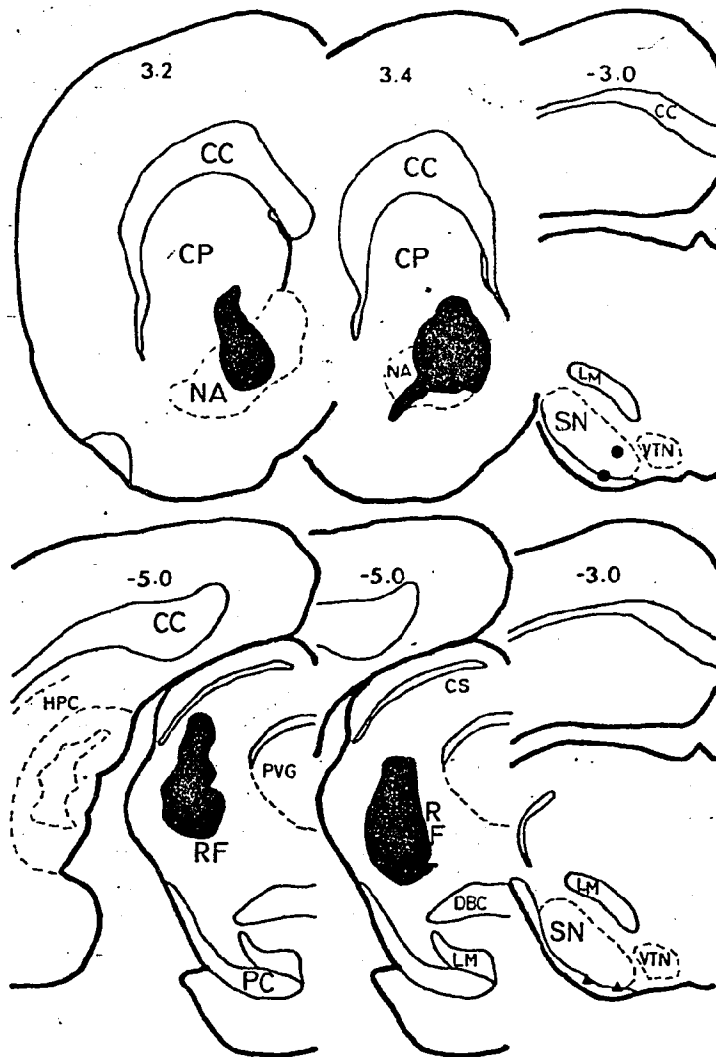
Ipsilateral electrolytic lesions of the nucleus accumbens (2 mA DC, 20 sec) in 2 rats, the ventral anterior thalamic nucleus (2 mA DC, 15 sec) in 2 rats, the ventromedial thalamic nucleus (2 mA DC, 20 sec) in 2 rats, the dorsomedial thalamic nucleus (2 mA DC, 25 sec) in 2 rats, the olfactory tubercle (2 mA DC, 30 sec) in 2 rats, the central amygdala (2 mA DC, 20 sec) in 1 rat, the lateral amygdala (2 mA DC, 25 sec) in 1 rat, the piriform cortex (2 mA DC, 30 sec) in 1 rat, and the periventricular gray matter (2 mA DC, 20 sec) in 1 rat did not change NER tested at 2 hours, 3, 7 and 14 days postlesion. Two rats with ipsilateral mesencephalic reticular formation lesions (2 mA DC, 20 sec) as diagrammed in Fig. 32; one showed partial reduction of NER at 2 hours, 3 and 14 days but not at 7 days postlesion; one showed a complete reduction of NER at 2 hours but an increase in NER at 3, 7, 14 and up to 22 days postlesion. One rat with ipsilateral

Figure 32

A. Extent of ipsilateral accumbens electrolytic lesions (2 mA DC, 20 sec) at the anterior-posterior plane with the largest lesion size in each of 2 rats.

B. Extent of ipsilateral reticular formation electrolytic lesions (2 mA DC, 20 sec) at the anterior-posterior plane with the largest lesion size in each of 2 rats.

Placements of stimulating electrodes in these lesioned rats are shown in the right diagrams. The numbers represent mm. anterior or posterior (-) to bregma. Abbreviations: CC, corpus callosum; CP, caudate putamen; CS, superior colliculus; DBC, decussation of brachium conjunctivum; HPC, hippocampus; LM, medial lemniscus; NA, nucleus accumbens; PC, cerebral peduncle; PVG, central gray substance; RF, reticular formation; SN, substantia nigra; VTN, ventral tegmental nucleus.

**A****B**

parafascicular thalamic nucleus lesion (2 mA DC, 15 sec) showed an increase in NER at 3 to 14 days postlesion.

Stereotaxic coordinates of these nuclei are shown in Table I. The lesions included most of the target area but usually also extended into adjacent structures.

Effects of AMPT and DDTC on NER

AMPT 150 mg/kg i.p. as well as DDTC 200 mg/kg i.p. significantly reduced NER in 8 rats (ANOVA, $F = 14.67$ and 15.29 respectively for A-R curves, $F = 17.28$ and 15.98 respectively for F-R curves, $P < 0.005$) (Fig. 33, 34). Saline i.p. was without effect ($F = 1.15$ and 0.01 for A-R and F-R curves respectively, $P > 0.25$) (Fig. 35). The three pre-injection curves did not differ significantly ($F = 0.34$ and 0.21 for A-R and F-R curves respectively, $P > 0.25$), nor did NER after AMPT differ from NER after DDTC ($F = 0.23$, $P > 0.25$ and $F = 1.71$, $P > 0.10$ for A-R and F-R curves respectively).

Figure 33

Nigral-evoked contralateral rotation before (●) and 4 - 5 hours after (▲) AMPT 150 mg/kg i.p. See methods for schedule of drug administration. Each point represents the mean rotation from 8 rats, error bars represent SEM. There was a significant reduction of the rotation following AMPT (ANOVA, $F = 14.67$, A-R and 17.28, F-R, $P < 0.005$).

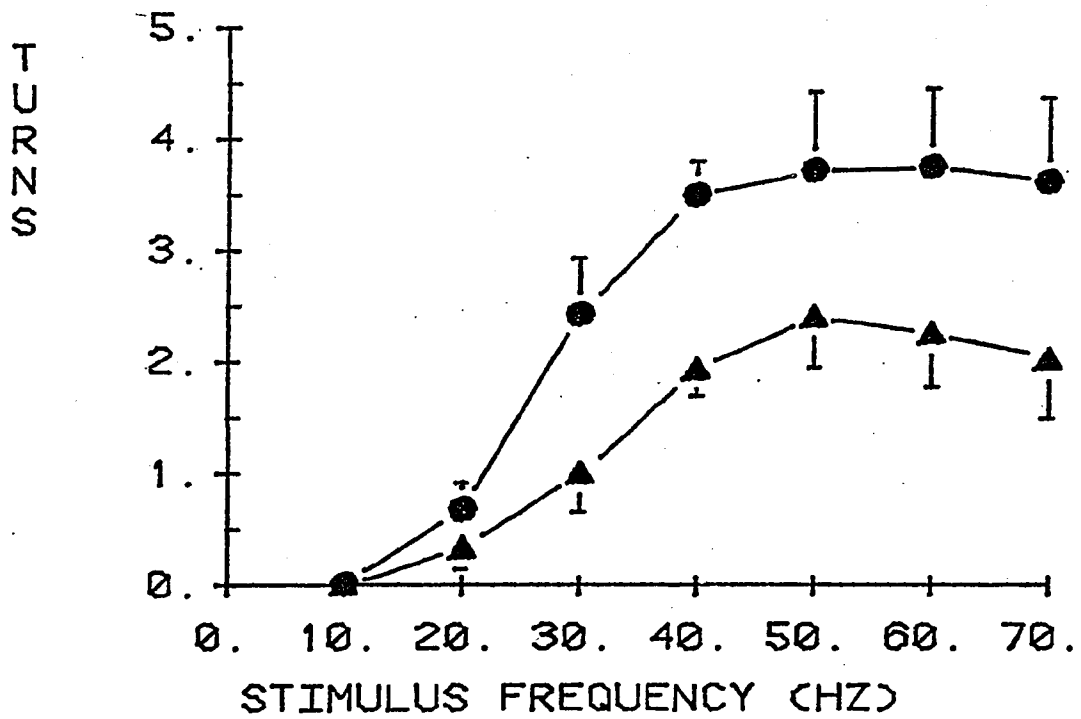
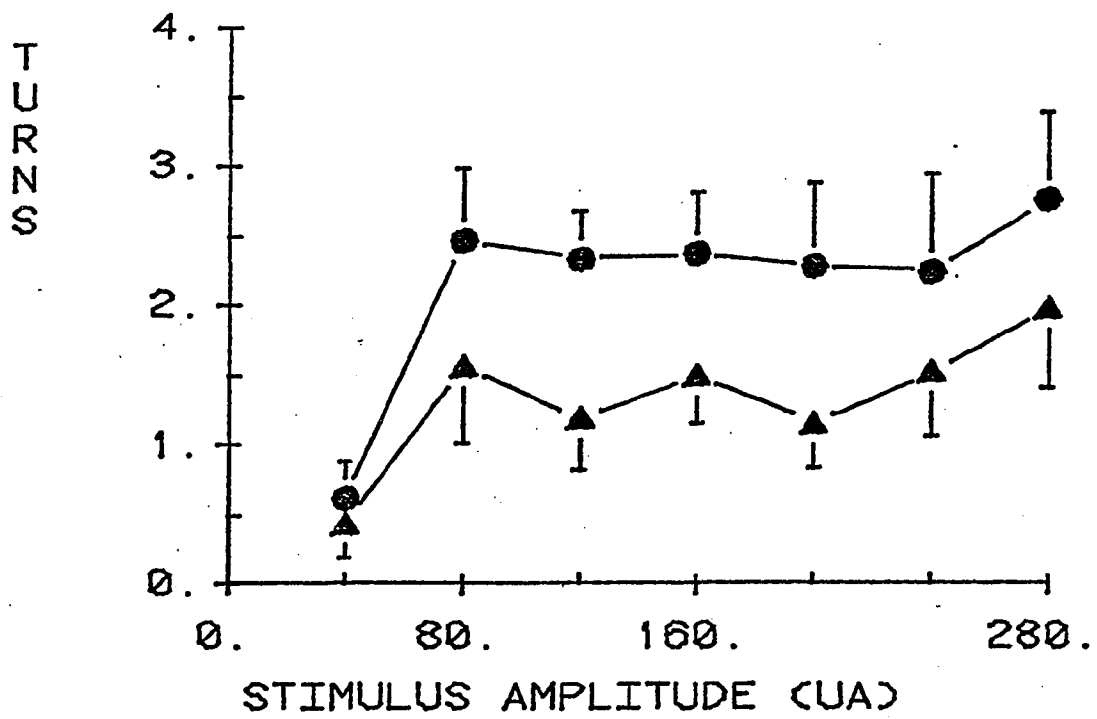


Figure 34

Nigral-evoked contralateral rotation before (●) and 1 - 3 hours after (▲) DDTC 200 mg/kg i.p. Each point represents the mean rotation from 8 rats, error bars represent SEM. There was a significant reduction of the rotation following DDTC (ANOVA, $F = 15.29$, A-R and 15.98 , F-R, $P < 0.005$).

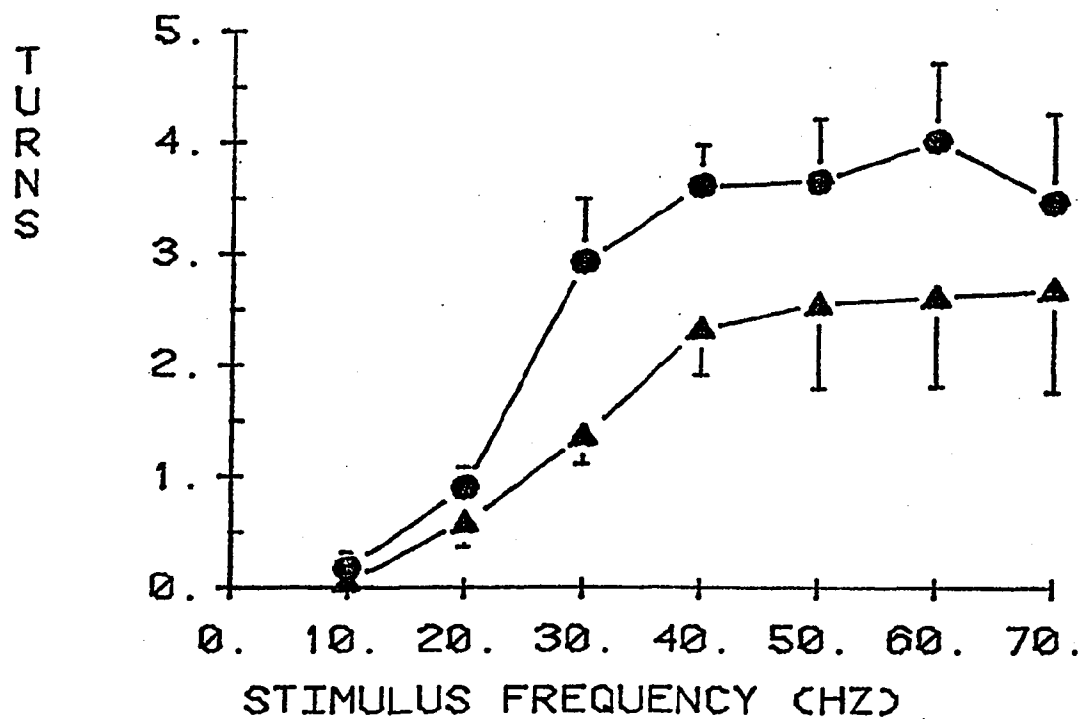
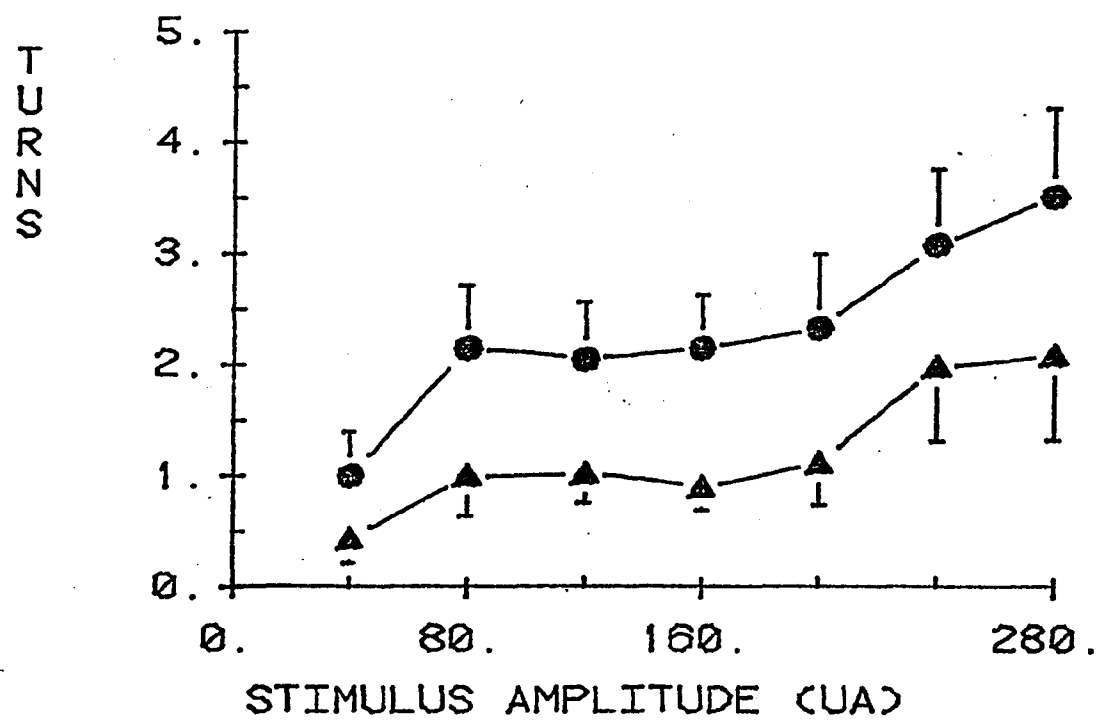
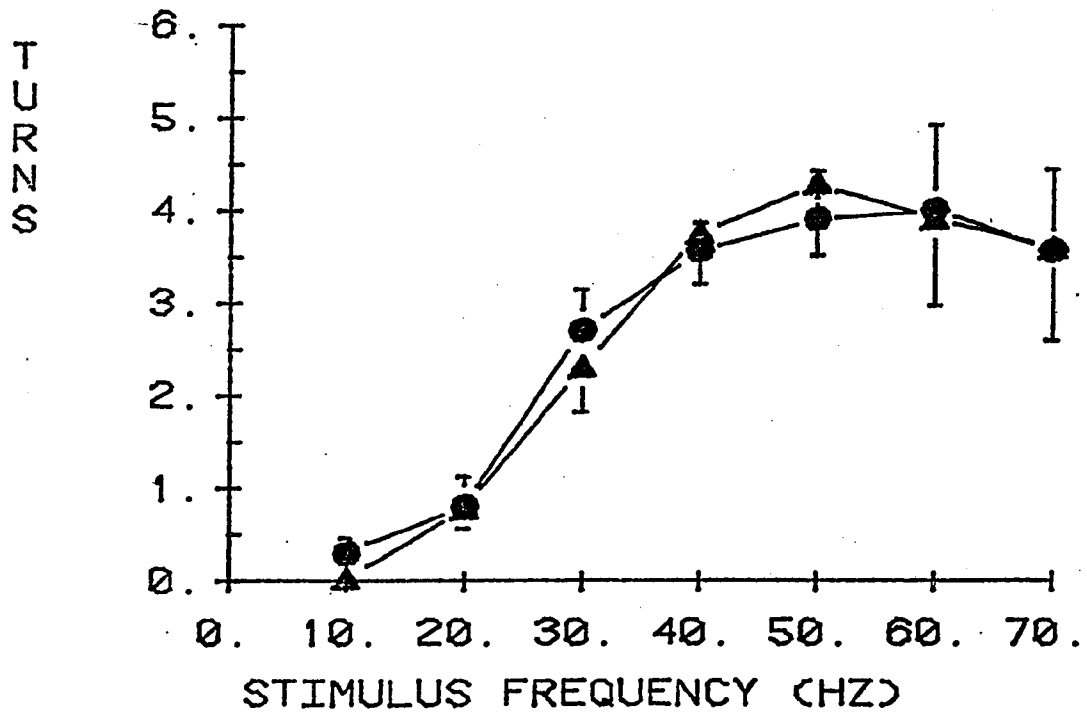
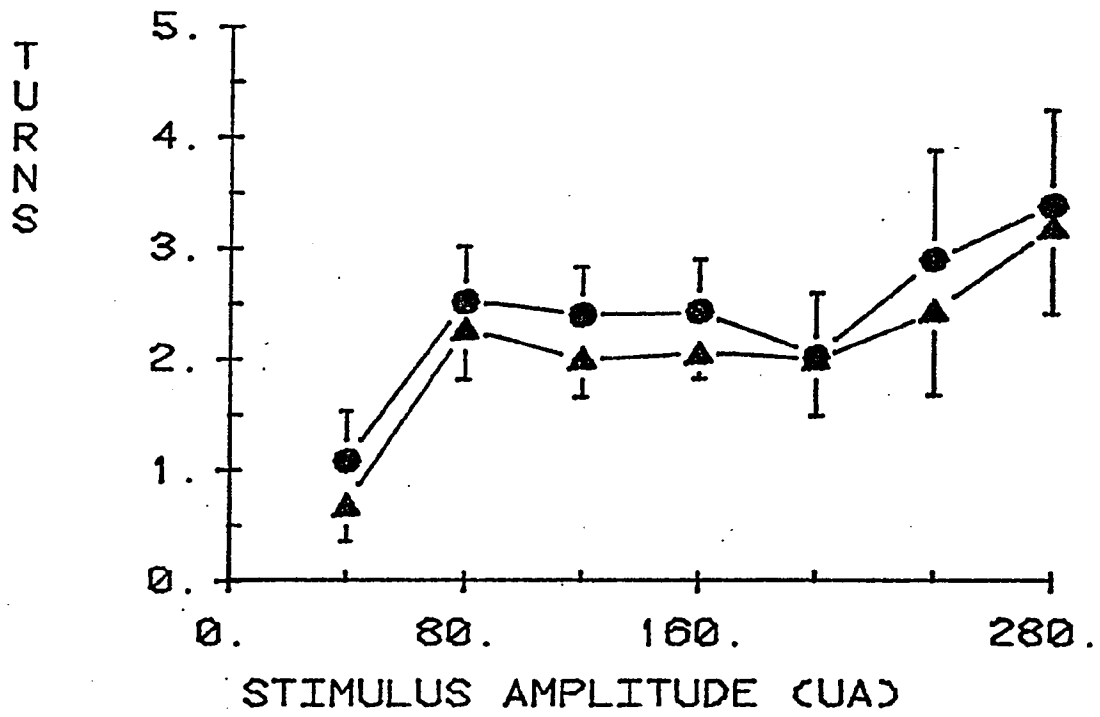


Figure 35

Nigral-evoked contralateral rotation before (●) and 2 - 5 hours after (▲) saline i.p. Each point represents the mean rotation from 8 rats, error bars represent SEM. There was no significant change in the rotation following saline (ANOVA, $F = 1.15$, A-R and 0.01, F-R, $P > 0.25$).



DISCUSSION

Contralateral rotation was reproducibly generated by electrical stimulation of the SN. The rotation reflects stimulation of axons or somata in the SN rather than adjacent structures since there was a good correlation between electrode placement in the SN and contralateral rotation. Also, among rotating rats those with electrode placements well within the SN had lower thresholds for rotation than those with electrodes on the periphery. Stimulus-response relationships were generated using 10 second trains of 1 msec monophasic square pulses and either varying amplitudes at 30 Hz or varying frequency at amplitudes producing 50 to 67 % of maximum rotation. The shape of the stimulus-response curve in individual rats was often an inverted U whether pulse frequency within the train was held constant and amplitude varied, or amplitude held constant and frequency varied.

Increasing pulse amplitude increases the number of neurons activated by the stimulus, by increasing the effective volume of tissue stimulated. In doing so, it also decreases the specificity of the stimulus, since spread to structures adjacent to the SN increases as amplitude increases. This would account for the contralateral front paw tremor and the body torsion at high stimulus amplitudes associated with the descending part of the stimulus response curve. The closer the electrodes were to the cerebral peduncle, the lower the stimulus intensity that would evoke these behaviors. Some rats with electrode tips in the dorsal half of the SN yielded sigmoidal

stimulus response curves as amplitude was increased to 400 uA.

Increasing pulse frequency would increase response primarily by temporal rather than spatial summation. The volume of brain stimulated would remain constant, the same elements being activated at minimum and maximum response. This does not mean, however, that behaviors not seen at low frequency stimulation would also be absent at higher frequencies. If stimulus amplitudes were chosen such that there was insufficient spread to corticospinal axons to induce tremor and torsion at 30 Hz, these might appear at higher frequencies since the postsynaptic temporal summation could compensate for the spatial summation. In fact, such behaviors did occur in some animals at high frequencies (80 to 100 Hz). Most of the stimulus response curves generated by increasing frequency were also inverted U. However, the descending part was not always associated with contralateral front paw tremor and body torsion. These behaviors appeared later than the beginning of descending limb or did not appear up to 100 Hz. That the inverted U was not necessarily accompanied by tremor and torsion, and that the frequency-response curve was an inverted U in rats with sigmoidal amplitude-response curve, supports the notion that the decline in rotation at high frequencies was not solely due to stimulation of extranigral structures.

Two other factors could explain inverted U curves aside from spread of stimulus outside the SN. One is presynaptic autoreceptors at the terminals of the stimulated neurons which decrease transmitter output. The net transmitter released could be less at higher than

at moderate frequencies (Langer, 1974, 1977; Starke et al., 1978; Von Voigtlander and Moore, 1971a, 1971b). The optimum frequency for increasing release of DA following SN or nigrostriatal tract stimulation was 30 Hz (Von Voigtlander and Moore, 1971a, 1971b). Actions of presynaptic autoreceptors are a less likely explanation for decreased response at high amplitudes of stimulation unless there were sufficient convergence and diffusion of transmitter to enable the transmitter released by one terminal to reduce the output from neighboring terminals. A second possibility is that an increase in stimulus amplitude or frequency might favor stimulating nigral neurons whose activation would lead to ipsilateral rotation (DiChiara et al., 1979c; Olanas et al., 1978a, 1978b). Although stimulus-induced ipsilateral rotation was not observed in nonlesioned rats, it was observed in some rats following electrolytic lesions of the GP and ibotenic acid injections in the CP. the ipsilateral rotation was revealed only in rats with high thresholds for contralateral rotation (> 160 μ A) many of which had stimulating electrodes in the caudal SN. When it did occur, stimulus evoked ipsilateral rotation was present at lower stimulus amplitudes or frequencies, and contralateral rotation appeared as amplitude or frequency was increased. Thus suggesting that if activation of neurons mediating ipsilateral rotation affected the shape of stimulus response curves, the effect was more likely to be on the initial rising phase rather than on the descending portion of an inverted U.

Without explicit knowledge of what factors were responsible for the shapes of stimulus-response curves and more seriously, what nigral

elements were predominantly activated by electrical stimulation we could not a priori choose a single set of stimulus parameters for studying effects of lesions and drugs. Instead we used complete stimulus-response curves. Initially, only amplitude-response relationships were studied, in later experiments both amplitude and frequency were varied. In general, the changes in NER following drugs or lesions were independent of whether amplitude or frequency was varied. Frequency-rotation curves were tested at the same amplitude pre and post -lesion. The amplitude selected was one that produced 50 to 67 % of the maximum prelesion response. Since amplitude-response curves were altered by lesions, the amplitudes used in the frequency tests might well have represented a different point on the stimulus-response curve. Changing the test amplitude in the frequency curves on postlesion days to match the criterion of 50 to 67 % of maximum might be one approach to solving this problem. Practical considerations of time and reproducibility made it impossible to test all frequencies at all amplitudes and vice versa. If this had been done at 40 to 280 uA and 10 to 70 Hz (a range that includes the entire ascending part of the curves from most rats), it would have taken 98 minutes to test one rat on each postlesion day. The primary value of varying stimulus frequency to alter rotation is in measurement of drug effects on stimulus-induced rotation since the pool of neurons activated remains constant. Short of complete amplitude/frequency data, altering stimulus amplitude is probably the more appropriate measurement for studying lesion effects, since it obviates some of the problems caused by independent variance in placement of stimulating electrodes and extent of lesions.

Previous workers who have studied contralateral rotation evoked by electrical stimulation of the SN, LH or MFB have concluded that the rotation resulted from activation of nigrostriatal DA neurons (Arbuthnott and Crow, 1971; Arbuthnott and Ungerstedt, 1975; Barghon and Costentin, 1980; Roffman et al., 1978). This conclusion was based on two group of findings: first, anodal electrolytic lesions through the stimulating electrode (which was in a plane 1 mm. rostral to the most anterior point of the SN), that eliminated the ability to obtain stimulus-evoked rotation, were accompanied by a decrease in DA fluorescence in the ipsilateral striatum, and the emergence of amphetamine-induced rotation ipsilateral to the lesion (Arbuthnott and Crow, 1971); second, pharmacological evidence, that rotation evoked by electrical stimulation of the posterior lateral hypothalamus was reduced by haloperidol, pimozide, tetrabenazine and fluphenazine, and enhanced by amphetamine 0.5 mg/kg (Arbuthnott and Ungerstedt, 1975), rotation evoked by stimulation of the SN or the VTA was reduced by haloperidol and clozapine (Roffman et al., 1978), and rotation evoked by stimulation of the MFB was reduced by haloperidol (Barghon and Costentin, 1980). While there is little doubt that electrodes in the vicinity of the SN or its projections can stimulate nigrostriatal DA neurons, or that dopaminergic drugs which act either presynaptically or postsynaptically can induce rotation in the presence of nigrostriatal asymmetry, it has not been shown that the rotation induced by electrical stimulation of the SN was due to the release of DA in the striatum. While pharmacological data suggested that the activation of the nigrostriatal DA neurons might be responsible for NER, the lower sensitivity of NER to haloperidol (48 - 73 % deficit at 1 mg/kg,

Roffman et al., 1978) compared to other stimulus-induced or drug-induced rotation (90 % block of posterior-lateral hypothalamus-evoked rotation in rats at 0.5 mg/kg, Arbuthnott and Ungerstedt, 1975; complete inhibition of MFB-evoked rotation at 0.05 mg/kg, Barghon and Costentin, 1980; 50 % inhibition of amphetamine-induced rotation in rats at 0.05 mg/kg, Stawarz et al., 1975; in mice at 0.11 mg/kg, Pycock et al., 1975b; 50 % inhibition of apomorphine-induced rotation in 6-OHDA lesioned mice at 0.10 mg/kg, Pycock et al., 1975b) casts some doubt on the assumption that turning evoked by electrical stimulation of the SN itself can be accounted for entirely by activation of the nigrostriatal dopaminergic neurons.

When the present experiments were begun, the initial objective was not to question the role of DA in stimulus evoked rotation, but to use the technique to differentiate the role of DA released in the CP from that released in the SN. Electrolytic lesions were made in the LH. If rotation required release of DA in the CP, maximum depression of rotation following the lesion should be immediate, since the pathway was acutely interrupted. If, however, rotation was mediated via DA released in the SN, there should have been minimal immediate effects of the lesion and a progressive decline in rotation as retrograde degeneration of the cells progressed. Reis et al., (1978) demonstrated progressive retrograde degeneration in nigra from 4 to 14 days following electrolytic lesions of the LH. Therefore, within the two weeks in which the rats were tested in the present study one would have expected a decline in DA released in nigra from test day 3 to day 14. In actuality, the maximum depression

of rotation was at 2 hours postlesion and there were no differences in the amplitude-response curves generated at 3, 7 and 14 days postlesion. The decrease in NER at two hours was unlikely to be a simple depressant effect of the methohexital used to anesthetize the rats during the lesion. Sham rats were similarly treated and showed no decrease in NER at the two hour test. It is conceivable that the depression represents a methohexital-electrolytic lesion interaction. This possibility was not further explored. This study, therefore, did not support the hypothesis that DA released in the SN accounted for stimulus-induced rotation. Consonant with this result, unilateral intranigral injections of amphetamine, or apomorphine did not cause rotation in rats (Glick and Crane, 1978; Kelly and Moore, 1978).

Subsequent experiments with 6-OHDA lesions of the LH supported this view. Microinjections of 4 and 1 ug 6-OHDA did not reduce NER, and a dose of 8 ug in 4 ul which depleted DA in the striatum by 93 % (to undetectable levels in 3 rats) increased rotation from 3 to 24 days postlesion. Although nigral DA was not measured, 6-OHDA at LH has been shown to cause disappearance of fluorescent DA cell bodies at 8 - 9 days postlesion, and there was a good correlation between number of remaining nigral DA cells and remaining striatal DA (Ranje and Ungerstedt, 1977). The failure to see a reduction in rotation following 6-OHDA injections was not due to the confounding effects of the probable simultaneous lesion of ascending noradrenergic neurons. Equivalent depletion of striatal DA in rats pretreated with DMI 30 mg/kg did not result in reduced rotation. DMI at this dose has been shown to protect noradrenergic neurons against 6-OHDA (Breese

et al., 1975; Breese and Traylor, 1971).

Although there was severe reduction in striatal DA, one might argue that development of DA supersensitivity was sufficient to not only compensate for the loss of neurons but to produce an increase in NER. The absence of any increase in NER in rats pretreated with DMI prior to 6-OHDA, despite DA depletions equivalent to those in unprotected animals, suggests that the DA depletion alone cannot account for the increase. Of all sham lesion and vehicle control groups, there was only one group in which there was any significant increase in rotation, the rats with sham GP lesions. In 6-OHDA lesioned rats, maximal rotation increased approximately 50 % from 4 to 6 turns, while NER in the sham GP rats increased less than 20 % from 4 to 4.75 turns at the same stimulus amplitude. Thus the possibility that the 6-OHDA result occurred by chance is exceedingly slight. The possibility that DA supersensitivity could compensate for the loss in DA fibers remains. It should be noted, however, that supersensitivity following such a lesion does not compensate for the neuronal loss when indirectly acting amines such as amphetamine are administered. The latter drug routinely produces ipsilateral rotation following 6-OHDA lesions of the ascending DA pathway.

The results from 6-OHDA lesions not only makes it unlikely that DA release in the SN is necessary, but raises serious questions about whether rotation evoked by electrical stimulation of the SN requires activation of the nigrostriatal dopaminergic neurons. Consonant with the possibility that NER is not due to DA release, there was no corre-

lation between reduction of NER and ipsilateral striatal DA depletion in electrolytic lesioned rats. In addition, reducing the amount of 6-OHDA injected to the LH lowered the percent DA depletion to levels equivalent to those obtained with electrolytic lesions. These rats exhibited neither a decrease nor an increase in NER. The differential effects of the lesions, therefore, could not be ascribed to differences in extent of DA depletion -- a partial DA lesion produced electrolytically that reduced NER without concomitant development of supersensitivity, and an extensive 6-OHDA lesion that resulted in DA supersensitivity sufficient to overcompensate for the neuronal loss.

Dopaminergic agonists that induce rotation can be considered in two major groups: directly acting agonists where the preponderant action is on DA receptors postsynaptic to the DA neurons, and indirectly acting agonists that increase release of endogenous DA where the integrity of the presynaptic DA neurons is required. Amphetamine produces ipsilateral rotation after either unilateral electrolytic or 6-OHDA lesions of the SN, apomorphine produces ipsilateral rotation following electrolytic lesions but contralateral rotation following 6-OHDA lesions (Costall et al., 1975, 1976; Iwamoto et al., 1976; Watanabe and Watanabe, 1979). Drug-induced rotation in animals with nigrostriatal asymmetry reflects the net effect of bilateral drug activity. Amphetamine-induced rotation in naive rats was consistently away from the side with higher DA content (Glick et al., 1974; Jerussi and Glick, 1974, 1976). Unilateral interruption of the nigrostriatal-striatonigral circuit modifies drug-induced rotation. In rats with

6-OHDA lesions of SN, contralateral electrolytic lesions of SN increased apomorphine-induced rotation contraversive to the 6-OHDA lesion and decreased amphetamine-induced ipsiversive rotation (Watanabe and Watanabe, 1979).

In contrast, stimulus-induced rotation appears to be a unilateral phenomenon. If the magnitude of NER depended on the spontaneous activity contralateral to the stimulating electrode, unilateral lesions of the LH should have increased rotation evoked by stimulation of contralateral nigra. On the other hand, if activity of the remaining intact neurons ipsilateral to the lesion increased or postsynaptic supersensitivity developed, stimulation of the contralateral SN might have caused less rotation after the lesion. Neither electrolytic lesions which depleted striatal DA by 42 % nor 6-OHDA lesions which depleted striatal DA by 92 % changed rotation induced by stimulation of the contralateral SN. Although NER appears to be a unilateral phenomenon, interaction of the nigrostriatal dopaminergic systems on both sides has been demonstrated electrophysiologically and biochemically. In cats, unilateral electrolytic lesions of the MFB or the SN significantly decreased firing of caudate neurons on both sides (Garcia-Rill et al., 1980). While the firing of ipsilateral caudate neurons returned to control by 7 days postlesion, the firing of contralateral caudate neurons slowed progressively with time after the lesion (Garcia-Rill et al., 1980) and remained slow until 5 weeks postlesion (Hull et al., 1974). Unilateral intranigral injections of glycine or diazepam reduced ^3H -DA release from both caudates, while unilateral intranigral injections of muscimol increased ^3H -DA release

from both caudates (Chéramy et al., 1978a; 1978b). Reciprocal regulation between the two nigrostriatal dopaminergic pathways has also been shown. Unilateral DA depleting lesions decreased ^3H -DA release in the ipsilateral caudate and increased it in the contralateral one (Nieoullon et al., 1977c). Unilateral intranigral injections of DA, d-amphetamine, and benztropine reduced ^3H -DA release in the ipsilateral caudate nucleus but increased the release in the contralateral one (Chéramy et al., 1978a; Nieoullon et al., 1977c). Intranigral injections of haloperidol, thioproperazine, AMPT produced opposite results (Chéramy et al., 1978a). These interactions need not be caused by the alterations in DA turnover per se since unilateral intranigral substance P increased ^3H -DA release in the ipsilateral caudate and decreased it in the ipsilateral SN with no concomitant contralateral effects (Michelot et al., 1979). The absence of substantial change in NER in the present experiments following contralateral lesions implies that the spontaneous activity on the opposite side was insignificant compared to the evoked activity. In addition, the result excludes the possible influence of spontaneous bilateral asymmetry of the nigrostriatal dopaminergic system on NER, and renders the initial determination of rotation direction prior to testing unnecessary.

It should be noted that in nonlesioned rats tested for both amplitude-rotation and frequency-rotation curves, striatal DA on both sides ($\bar{x} \pm \text{SEM} = 14.4 \pm 0.5 \text{ ug/g}$, $n = 10$) was slightly higher than that in rats tested for amplitude-rotation curves only ($\bar{x} \pm \text{SEM} = 12.3 \pm 0.6 \text{ ug/g}$, $n = 10$) (t-test, $P < 0.025$). There was no

significant difference in DA levels ipsilateral and contralateral to the stimulating electrodes (t-test, $P > 0.05$). The increase in DA did not require stimulation of DA cells since rats given 6-OHDA prior to any brain stimulation (the serial lesion experiment) still showed increased DA levels in the contralateral striatum ($\bar{x} \pm \text{SEM} = 14.1 \pm 0.4 \text{ ug/g}$, $n = 8$). The time course of the increase in DA in these rats is unknown, and may have occurred in whole or in part between the final day of testing and the day the rats were killed. Measured DA levels, then, in rats tested for both amplitude and frequency stimulus-response curves may not bear the same relationship to DA levels on test days that held for rats given only amplitude rotation tests. DA depletion was calculated as a percentage of the intact side in these animals. The observation that the increase in DA level was independent of lesions, suggests that this calculation was not subject to additional error.

Since NER reflects only unilateral stimulation, a decrease in NER following a lesion would be equivalent to drug induced ipsiversive rotation; an increase in NER would be equivalent to drug induced contraversive rotation. The results of the present experiments suggest that rotation evoked by stimulation of the SN resembles apomorphine-induced rotation rather than amphetamine-induced rotation. Apomorphine effects are believed to primarily reflect direct postsynaptic dopaminergic effects (Andén et al., 1967; Ernst, 1967; Ungerstedt, 1971c), although presynaptic effects of apomorphine on stereotyped behavior (Costall and Naylor, 1973), on regulation of DA synthesis and storage (Goldstein et al., 1970; Walters and Roth, 1974), and on rota-

tion in normal rats (Glick et al., 1977) have been proposed. Amphetamine effects are indirect, requiring release of DA from the nigrostriatal fibers (Carlsson et al., 1966a; Fuxe and Ungerstedt, 1968; Glowinski and Axelrod, 1965; Ungerstedt, 1971b; Von Voigtlander and Moore, 1973). One would, a priori, have expected that if rotation following nigral stimulation were due to activation of the nigrostriatal dopaminergic fibers, it would resemble amphetamine rather than apomorphine. If, on the other hand, the stimulated cells include those which fire consequent to activation of striatal DA receptors, NER might parallel apomorphine-induced rotation in lesioned rodents. The anatomical data reviewed in the introduction suggest two groups of neurons postsynaptic to the dopamine neurons that could be stimulated: first, nondopaminergic neurons with cell bodies in nigra that could be orthodromically activated, second, nigral afferents which also synapse in other structures that could be antidromically activated. If we are bypassing the DA neurons, how then can one explain the increase in NER following 6-OHDA lesions? The increase could reflect 'supersensitivity' at synapses beyond the one denervated. It has been shown that nigral GABA receptors become supersensitive following 6-OHDA lesions of the nigrostriatal dopaminergic pathway that deplete striatal DA by 85 % (Gale and Bernstein, 1980), or after chronic administration of chlorpromazine or haloperidol (Gale, 1980). An increase in contralateral rotation induced by intranigral injections of muscimol following ipsilateral nigrostriatal 6-OHDA lesions has been shown (Arnt and Scheel-Krüger, 1979b). On the other hand, the increase could reflect a lower threshold for stimulation of nigral elements normally hyperpolarized by DA.

One obvious pathway that might mediate NER would be the nigral afferents from the corpus striatum which appear necessary for the expression of apomorphine-induced rotation (Garcia-Munoz et al., 1977; Marshall and Ungerstedt, 1977a, 1977b; Ungerstedt and Marshall, 1975). Antidromic activation of synapses in striatum or pallidum would be reduced immediately upon lesion of these fibers in the LH. This is consistent with the effects of such lesions on NER. The critical neurons destroyed by these lesions were clearly nondopaminergic in that NER was reduced equivalently by electrolytic lesions at the LH 10 to 14 days after either vehicle or 8 ug 6-OHDA.

There was one difference between rats with sequential lesions and those with only electrolytic lesions, and that was in recovery of NER with time after lesion. Rats with electrolytic lesions only or with electrolytic lesions following microinjections of vehicle to the LH retained their NER deficit for up to 14 days. In rats with sequential 6-OHDA and electrolytic lesions NER at 14 days after the electrolytic lesion was no longer significantly lower than prelesion when NER was quantified as a function of stimulus amplitude. It is conceivable that an initial nonspecific lesion by 6-OHDA (Agid et al., 1973; Sotelo et al., 1973) enhanced recovery of function from the subsequent electrolytic lesion in a manner analogous to functional recovery underlying serial lesion phenomena (Finger et al., 1973). However, the recovery back to control did not occur when NER was quantified as a function of stimulus frequency. This might be due to the fact that increasing stimulus frequency, unlike increasing amplitude, does not recruit additional neurons into the population

being stimulated.

Antidromic activation of nigral afferents from corpus striatum is virtually assured by the electrode placements in the present experiments. Most electrodes were in the PR, the region of termination of the striatonigral fibers (Bunney and Aghajanian, 1976c; Hattori et al., 1975; Tulloch et al., 1978). In addition, the stimulus parameters used in our experiments (1 msec square waves, 40 - 400 uA) exceeded the requirements for antidromic activation of striatonigral fibers from rat SN (0.1 msec, 100 - 400 uA) (Richardson et al., 1977). The collaterals of striatonigral cells are most extensive within the caudate itself (Park et al., 1980; Richardson et al., 1977). Although there is evidence for a separation of striatonigral and striatopallidal efferents (Bunney and Aghajanian, 1976c; Nagy et al., 1978; Richardson et al., 1977) there is also an indication of collaterals of striatonigral neurons in pallidum (Fox and Rafols 1975; Preston et al., 1980; Yoshida et al., 1972a, 1972b). In an attempt to differentiate the cells stimulated, lesions were made in the CP and GP and the effects on NER examined. Small lesions in the CP had no effect on NER. While most of these lesions were in the central core of the caudate which contains predominantly striatopallidal cells (Bunney and Aghajanian, 1976c; Nagy et al., 1978; Richardson et al., 1977) in a number of rats the lesions extended to the region that would be expected to contain nigral afferents (Fig. 23). Large lesions of the CP had no immediate effects at two hours but NER was maximally reduced at 3 days after the lesions (Fig. 21). A second series of CP lesioned animals was done in order to study the time course of

the lesions. In this group the lesions were somewhat more anterior and impinged on cortex anterior to the head of the caudate (Fig. 25). The volume of caudate lesioned was comparable to the original lesions and subsequent experiments in this laboratory (personal communication) did not reveal changes in NER following an attempt to replicate the cortical part of the lesions alone. The time course of caudate lesion effects were studied in this group and NER slowly declined from 6 hours to 3 days (Fig. 24).

In contrast to the delayed effects of large caudate lesions, lesions of the GP had an immediate effect, and NER was severely depressed at 2 hours after the lesions. In accord with these data, one model explaining the results is that NER requires activation of pallidal synapses of axon collaterals of striatonigral neurons. The delay in the effects of caudate lesions reflects the time for anterograde degeneration of the axons from the lesion site to the branch point. The lack of an immediate decrease in NER after large caudate lesions argues against a critical role of intracaudate synapses.

It has been reported that electrolytic lesions at the CP or the LH in rats exhibited an optimum lesion volume at 1 to 7 days (Wolf and DiCara, 1969). The necrotic zone, a direct secondary change induced by the lesion, was optimum at 1 to 7 days and was reduced at 14 days postlesion (Schoenfeld and Hamilton, 1977). Mapping in the present study was done at 14 to 30 days after electrolytic lesions. The extent of the lesions, therefore, might be underestimated especially in rats with long postlesion survival times (e.g. the rats with large

caudate lesions were killed 30 days following the lesions). Although the time course of functional deficit following large electrolytic lesions of the CP fall within the time course of the reported changes in lesion size, this phenomenon does not appear to offer an adequate explanation for the delayed effects of CP lesions. If it were the cause, a similar phenomenon might be expected following GP or LH lesions, where the deficit in NER was immediate. In the latter case the reduction in NER was clearly partial and should have been recorded if the effective lesion size increased.

Immediate depression of NER would also follow GP lesions if rotation resulted from antidromic activation of pallidal neurons rather than striatal cells. To explain the effects of CP lesions, however, we would then have to revert to the argument of delayed effective increase in lesion size with ischemic damage to pallidal cells. In addition to the argument against it above, the present results showing an equivalent time course of reduction in NER with lesions in anterior CP and with more posterior lesions also makes this an unlikely occurrence.

An alternative is that the pallidal lesions are interrupting fibers of passage which may or may not synapse in the GP. If a cell had some collaterals in pallidum with its major axonal arborization in caudate then large CP lesions which destroyed supporting collaterals would result in a delayed loss of transmission at GP as retrograde degeneration progressed. Although our results lead us to question role of DA in NER, it is worth noting at this point that colla-

terals to the GP of the ascending nigrostriatal dopaminergic fibers have been described (Lindvall and Björklund, 1979). Finally, consonant with the postulation of the GP as a critical area for synapses underlying NER, stimulation of GP also produced stimulus-related contralateral rotation (Fig. 28) which was similar to NER obtained from rats with stimulating electrodes close to cerebral peduncle i.e. the descending part of the amplitude-rotation curve was associated with paw tremor and body torsion at relatively low stimulus amplitudes suggesting spread of current to the adjacent internal capsule. This rotation, of course, could reflect stimulation of striatal afferents that course through the pallidum.

The present experiments are not the first to report DA independent contralateral rotation. It has been reported following unilateral microinjections of GABA (Kelly and Moore, 1978; Olpe et al., 1977; Scheel-Krüger et al., 1977), muscimol (Arnt and Scheel-Krüger, 1979a, 1979b; Arnt et al., 1979; Oberlander et al., 1977; Olanas et al., 1978b; Reavill et al., 1979; Scheel-Krüger et al., 1977; Waddington, 1978a, 1978b), baclofen (Kelly and Moore, 1978; Olpe et al., 1977; Scheel-Krüger et al., 1977; Waddington, 1977a, 1978a, 1978b; Waddington and Cross, 1979), flurazepam (Waddington, 1978b), and ethanolamine-O-sulfate (Koob et al., 1976; Tanner, 1978) to the caudal SN. This rotation was enhanced (Arnt and Scheel-Krüger, 1979b; Waddington 1978b) or unchanged (Olanas et al., 1978b) by prior ipsilateral nigrostriatal pathway lesions with 6-OHDA, and was resistant to haloperidol (Arnt and Scheel-Krüger, 1979a, 1979b; Oberlander et al., 1977; Olpe et al., 1977; Reavill et al., 1979; Waddington, 1978a,

1978b). The most likely explanation for these effects is that GABA inhibits non DA neurons in the PR which mediate ipsilateral rotation. This interpretation is supported by the finding that unilateral kainic acid lesions of the PR produced DA-independent contralateral rotation (DiChiara et al., 1977; Olanas et al., 1978a). Electrical stimulation of the SN might mimic the effects of intranigral GABA or GABA mimetic drugs if GABA-containing afferents were preferentially activated. However, one would then expect that as stimulus amplitude increased and the nigral output neurons mediating ipsilateral rotation were directly activated, the direction of rotation would reverse. Although we often noted some decrease in contralateral rotation at high stimulus intensities, in none of the 222 rats used in this study did the direction of rotation reverse at any stimulus intensity in control tests. In fact when ipsilateral rotation did occur in the present study following lesions of GP it was evoked by low amplitude rather than high amplitude stimuli. In addition, if the source of the inhibition of the nigral neurons mediating ipsilateral rotation were activation of the descending nigral efferents, there should have been a delayed effect not an immediate effect of lesions rostral to the SN. If the source of the inhibition were local, these lesions should have had no effect. There is evidence that contralateral rotation induced by intranigral muscimol was not affected by ipsilateral hemitransection rostral to the SN (Gale and Iadora, 1980; Reavill et al., 1981). In the present study contralateral rotation evoked by electrical stimulation of the SN was significantly reduced by electrolytic lesions of the ipsilateral LH. For all these reasons, despite a superficial resemblance, it appears unlikely that the

contralateral rotation we evoke is analogous to that occurring upon intranigral injection of GABA agonists.

While none of the rats in this study showed ipsilateral rotation during control tests, following GP lesions it did occur. It is unclear as to whether the lesions revealed ipsilateral turning as a consequence of the severe reduction in contralateral rotation, or whether the lesions facilitated the stimulation of SN neurons mediating ipsilateral rotation. The present results are paralleled by experiments on head turning where GP lesions increased the time for 90° head turning and in some cases reversed the direction of head turning evoked by electrical stimulation of rat striatum (Lee et al., 1980; Slater et al., 1980).

Ipsilateral NER after GP lesions was unlikely to be due to spread of current to non-nigral elements since it always appeared at stimulus amplitudes lower than those caused contralateral NER. Although we did not see it in controls, ipsilateral rotation following electrical stimulation of the SN (15 sec trains of 0.2 msec symmetrical biphasic pulses at 50 Hz, 40 - 400 uA) has apparently been observed. Cobbin and Atrens (1976) described 36 electrode placements in rat mesencephalon which yielded ipsilateral rotation. Although not identified as such in their text, 7 of these sites were in caudal SN and 6 of these 7 sites were at dorsal part of the SN.

The present data is only suggestive since a prospective study was not done and there was some overlap in electrode location. It

is noteworthy, however, that the three GP lesioned rats showing the most marked ipsilateral rotation were the ones with the most caudal placement of the SN electrodes. Turning evoked by 'rostral' SN injections of muscimol, a GABA uptake inhibitor (ACHC), picrotoxin or tetanus toxin appears DA dependent and the direction of rotation reflects the reciprocity of the DA-GABA relationship; while that resulting from 'caudal' SN injections appears DA independent and the direction of rotation is opposite to that predicted from the known DA-GABA interaction (Straughan and James, 1978; Reavill et al., 1979). The 'rostral' and 'caudal' SN which generated DA-dependent and DA-independent rotation upon intranigral injection of GABA-related drugs appeared to be approximately 0.5 - 0.9 mm. apart (James and Collingridge, 1979; James and Starr, 1978; Reavill et al., 1979; Scheel-Krüger et al., 1977; Straughan and James, 1978). Kozlowski and Marshall (1980) note that injections of GABAergic drugs to the PC induced DA-dependent rotation and injections to the PR induced DA-independent rotation. The concept of a rostro-caudal division of SN, however, is not universally accepted, and there is evidence favoring the view that the actual regions involved in the different responses may be pars compacta and pars reticulata. Kilpatrick and Starr (1981) indicated that DA-dependent ipsilateral rotation was obtained following injection of muscimol to the rostral PC. They noted, however, that it was particularly difficult to confine muscimol injections to the PC when injections were made in the caudal SN, offering a possible explanation for the apparent rostro-caudal functional division. Rostral injections reflecting primarily pars compacta actions, and caudal pars reticulata. The former being dopamine dependent.

Since dendrites of pars compacta neurons extend into the PR, however, one might expect DA dependent drug effects in PR as well as PC. This might explain the dual actions reported for muscimol injections to the PR by Kilpatrick and Starr (1981). DA-independent contralateral rotation followed injection of muscimol to the lateral and ventral longitudinal bands of the PR, a result similar to that previously reported by Arnt and Scheel-Krüger (1979a, 1979b), Arnt et al. (1979), Olanas et al. (1978b), Reavill et al. (1979), Scheel-Krüger et al. (1977), Waddington (1978a, 1978b). DA-dependent contralateral rotation followed injection of muscimol to the central longitudinal band of the PR, a result similar to that previously reported by Martin and Haubrich (1978) and Martin et al. (1978). It is difficult in Kilpatrick and Starr's (1981) experiments, however, to be sure that the two injection sites had intrinsic functional differences. It would appear equally likely that drugs injected in central longitudinal band of the PR had easier access to the adjacent PC than drugs injected more laterally and ventrally.

Opposite directions of rotation by injections of substance P or DA to different loci in the SN have been reported. Substance P induced contralateral rotation following caudal injection and ipsilateral rotation following rostral injection to the SN (Arnt and Scheel-Krüger, 1979b), both seemed DA-dependent (James and Starr, 1979). DA and DA agonists had originally been described as ineffective in evoking rotation upon nigral injection (Glick and Crane, 1978; Kelly and Moore, 1978). A more recent preliminary report by McDevitt and Setler (1980), however, suggests that rostral injections

of DA cause contralateral rotation and caudal injections ipsilateral rotation, with no rotation observed when injections made in central SN. The substrate upon which DA acts in these experiments is not known, but obviously systemic DA antagonists cannot be used to elucidate the role of DA pathways. The report that the DA induced contralateral rotation was enhanced by prior 6-OHDA lesions (McDevitt and Setler, 1980) suggests that this effect is independent of ascending DA neurons.

As a group the GP lesioned rats in the present experiments exhibited relatively little contralateral rotation prelesion at stimulus amplitudes of 40 to 160 uA. This might reflect stimulus conditions favorable for activating ipsiversive neurons. Interestingly, GP lesioned rats that showed no reversal of rotation had the lowest thresholds for evoking 1 full turn. This observation could explain the absence of postlesion ipsilateral rotation in rats with large caudate lesions. The prelesion amplitude rotation curve for the latter group (Fig. 24) showed a much steeper initial slope than that for the GP lesioned rats. Mean prelesion rotation in this group was 3 and 4 turns at 80 and 120 uA respectively.

The results of the present experiments support the hypothesis that there exists in the SN, at least one group of cells whose activation leads to ipsilateral rotation. Electrical stimulation at the SN preferentially activates the contraversive component but when this component was suddenly removed the ipsiversive component was revealed if the stimulating electrodes were appropriately placed.

An attempt was made to distinguish between antidromic activation of the striatonigral pathway and orthodromic activation of the nigrostriatal pathway by using a neurotoxin that would selectively destroy CP cells. Ibotenic acid selectively and irreversibly destroys cell bodies and intrinsic neurons but spares axon terminals and fibers of passage. Intrastriatal ibotenic acid (10 or 20 ug in 1 ul) causes a loss of neuronal cell bodies but not the myelinated bundles, a disappearance of met-enkephalin immunoreactive fibers and cells but not the tyrosine hydroxylase immunoreactive fibers, and a reduction of striatal glutamic acid decarboxylase and choline acetyltransferase but not striatal DA, at 10 days after injection (Schwarcz et al., 1979). Ibotenic acid was chosen instead of kainic acid because the former had been shown to have restricted diffusion and less nonspecific damage compared to the latter (Köhler et al., 1979; Schwarcz et al., 1979). If NER is mediated by antidromic activation of the striatonigral neurons, it should be irreversibly decreased by intrastriatal ibotenic acid. There was a transient reduction of NER 2 hours and 1 day postlesion, and during these times there was stimulus bound ipsilateral rotation similar to that observed in GP lesioned rats. The three animals who had the highest threshold for contralateral turning in the prelesion trials rotated ipsilaterally after ibotenic acid. However, the NER returned to control levels after 1 day postlesion and remained stable until 14 days postlesion, the last day tested. The immediate reduction of NER might reflect pharmacological actions of ibotenic acid. Both excitatory effects (Hall et al., 1979) and excitations followed by prolonged inhibitions (Curtis et al., 1979; MacDonald and Nistri,

1978) have been reported. It has been suggested that ibotenic acid is metabolized in vivo to muscimol (Johnston et al., 1968) by alpha-decarboxylation thus transforming an excitant acid to an inhibitory one. Structure-activity relationships for amino acids established by Curtis and Watkins (1965) indicate excitation from dicarboxylic and inhibition from monocarboxylic acids. The injection volume of ibotenic acid in the present experiments was restricted to 0.5 ul to prevent spread of the acid to the GP. Although the volume of the ibotenic acid lesions could not be accurately determined, it was clear that the rostrocaudal extent of CP lesions following ibotenic acid was less than that of the effective electrolytic lesions. The absence of prolonged reduction in NER following the ibotenic acid lesion might simply reflect the small lesion size. In order to reach any definitive conclusions, it would be necessary to increase the extent of the ibotenic acid lesions in CP without destroying pallidal cells. This might be accomplished with two injections of small volume separated by 1 to 1.5 mm. rostrocaudally in the CP. The absence, in rats with large caudate lesions, of any correlation between the extent of the lesion and percent reduction of NER at 3, 7 and 14 days postlesion suggests that although there may be a critical minimum lesion size for reducing NER, the heterogeneity of the CP has to be considered in determining the location of effective lesions and also in interpreting the results.

The present study includes only limited pilot data exploring the possibility that nondopaminergic nigral efferents such as nigro-thalamic (e.g. Clavier et al., 1976), nigrotectal (e.g. Beckstead et

al., 1981), and nigrotegmental (e.g. Wright and Arbuthnott, 1980) pathways are involved in NER. None of the lesions other than CP or GP resulted in any consistent immediate or delayed reduction of NER. Although tectal lesions were attempted, only the dorsal part of the superior colliculus was lesioned. Since it has been shown by anatomical and electrophysiological experiments that the nigrotectal fibers in rats terminate in the deeper layers of the superior colliculus (Beckstead et al., 1979; Bentivoglio et al., 1979; Chevalier et al., 1981; Deniau et al., 1977), and that only the lesions which extended ventral to the level of the sulcus limitans into the subcollicular tegmentum caused compulsive ipsilateral circling in cats (Winterkorn and Meikle Jr., 1980), the data from attempted tectal lesions was not included. The negative results from lesions of the thalamus and reticular formation did not exclude the possibility of activation of crossed projections, bilateral projections or branching projections from the SN, since in all animals lesions were done only ipsilaterally to the stimulating electrodes. A nondopaminergic nigrostriatal projection with collateral branches to both the VM thalamic nucleus and the superior colliculus has been electrophysiologically described in rats (Deniau et al., 1978b). If the CP innervation by these neurons could be considered supporting collaterals, this would be consonant with the delayed loss of NER following large caudate lesions. However, there was no change following electrolytic lesions of the thalamus. In addition, it has been suggested that striatal branching of the nigrothalamic neurons arises in the MFB (Deniau et al., 1978b), and axons bypass the GP. Thus making it difficult to explain the immediate effects of pallidal lesions.

Some of the data presented and discussed above led us to question the role of DA neurons in NER. The issue of the degree of DA involvement, however, is far from settled, the data being somewhat equivocal. NER was decreased by haloperidol 0.1 and 0.5 mg/kg i.p. in a dose related manner. The sensitivity to haloperidol appeared to be the same among control, electrolytic lesioned and 6-OHDA lesioned rats. The percentage reduction in NER by haloperidol (50 % inhibition at 0.5 mg/kg i.p.) was comparable to that reported by Roffman et al. (1978) (48 - 73 % inhibition at 1 mg/kg i.p.) in similar experiments. In both instances, haloperidol sensitivity was lower than that reported in studies of rotation induced by electrical stimulation at sites other than SN or by systemic amphetamine and apomorphine in rats with unilateral 6-OHDA lesions reviewed above (page 188). ED₅₀'s of haloperidol for increasing DOPAC and HVA in rat striatum were 0.16 and 0.15 mg/kg i.p. respectively (Wilk et al., 1975). Haloperidol doses higher than 0.5 mg/kg were not used in the present study because of catalepsy which might indirectly interfere with the rotation. A reproducible cataleptic response has been reported following haloperidol 0.5 (Kostowski et al., 1977) and 1.0 (Carter and Pycock, 1979) mg/kg i.p. Coupled with the relatively high doses of haloperidol required is the demonstrated multiplicity of action of this drug. Haloperidol has been shown to bind to alpha-noradrenergic receptors (Peroutka et al., 1977), to opiate receptors (Clay and Brougham, 1975; Creese et al., 1976) and to serotonin receptors (Leysen et al., 1978). It has also been reported to inhibit uptake of tritiated GABA into rat brain synaptosomes (Enna et al., 1976; Fjalland, 1978), and to block impulse conduction

in peripheral nerves (Seeman et al., 1974). A subsequent study in this laboratory has shown that (+)-butaclamol (0.25 - 0.5 mg/kg) reduced NER while (-)-butaclamol was ineffective (personal communication). The (+)isomer has the higher affinity in binding studies (Enna et al., 1976). This suggests that the reduction of NER by neuroleptics is likely to be due to a specific action on receptors rather than to nonspecific membrane stabilizing effects. While DA receptors are possible sites of action for both drugs, there is insufficient evidence to conclude that the reduction in NER is via DA antagonism.

Both the nigrostriatal and the mesolimbic dopaminergic systems have been implicated in rotational behavior (Kelly and Moore, 1976, 1977; Pycock and Marsden, 1978). Even if the neurons stimulated were nigral afferents or efferents postsynaptic to the dopaminergic nigrostriatal neurons, bilateral blockade of DA receptors in the nucleus accumbens by systemic haloperidol or (+)-butaclamol might reduce NER by blocking the locomotor component of rotational behavior. Such an action would be comparable to the finding that bilateral intra-accumbens injections of haloperidol (Kelly and Moore, 1977) or bilateral electrolytic lesions of the accumbens (Pycock and Marsden, 1978) reduced amphetamine and apomorphine -induced rotation in rats with unilateral 6-OHDA nigrostriatal lesions. The magnitude of the rotation occurring with NER (generally 12 to 30 turns per minutes) is comparable to that induced by drugs in lesioned animals. Since 'mesolimbic' DA neurons in the VTA could be activated by electrode placements in many rats, this would superimpose stimulation of the

DA input to the ipsilateral accumbens on normal activity and might contribute directly to NER. Electrolytic lesions of accumbens ipsilateral to the stimulating electrodes in two rats did not change NER, arguing against electrical stimulation of accumbens afferents contributing to the response. These unilateral lesions would not necessarily be expected to decrease rotation induced by activation of other neurons since unilateral accumbens lesions were ineffective in decreasing drug induced rotation (Kelly, 1975). It should be remembered in the latter case, however, that systemic DA drugs can activate the nonlesioned accumbens whereas in the present experiments the effect of stimulation would have minimal activating effects on contralateral systems.

If NER had a substantial dopaminergic component and the increase in rotation after 6-OHDA 8 ug at the LH resulted from supersensitivity of the DA receptors, one would have expected no effect of DMI pretreatment on 6-OHDA lesion effects. However, rats pretreated with DMI that had ipsilateral striatal DA depletion equivalent to nonpretreated 6-OHDA lesioned rats, did not show an increase in NER at 3, 7 and 14 days postlesion. Ascending dopaminergic and noradrenergic fibers in rats intermingle in the mesodiencephalic region (Lindvall and Björklund, 1974). The large volume of 6-OHDA used in the present experiments probably destroyed both DA and NE containing neurons. Agid et al. (1973), assuming a spherical distribution, estimated that a 4 ul injection of ^3H -DA at a rate of 1 ul/min to the SN distributed rostrocaudally and mediolaterally in a volume of radius 2.3 mm. Waddington and Crow (1979) reported that 6-OHDA 8 ug in 4 ul at the MFB in rats

resulted in an 85 % depletion of cortical NE and an 80 % depletion of striatal DA. Costall et al. (1976c) reported 37 % depletion of cortical NE and 82 % depletion of striatal DA following the same dose of 6-OHDA at the LH in rats. The reduction of forebrain NE was prevented by pretreatment with 30 mg/kg DMI (Breese et al., 1975; Breese and Traylor, 1971). There was no change in the reduction in striatal or forebrain DA. The ascending noradrenergic fibers in rats course through and adjacent to the SN (Lindvall and Björklund, 1974), and could conceivably be activated by nigral stimulation. Although NE was not measured in the present experiments, the dose of DMI used was sufficient to insure protection of noradrenergic fibers. The data suggest that the increase in NER following 6-OHDA lesions may require the loss of noradrenergic fibers. The prevention of the increase in post 6-OHDA (8 ug) NER following DMI pretreatment are paralleled by a report by Kelly and Moore (1977). In their study both amphetamine and apomorphine-induced rotation were lower in animals given DMI prior to 6-OHDA lesions of caudate than to animals given 6-OHDA alone. Note, however, that the noradrenergic fibers likely to be lesioned by the caudate injections are only a small fraction of those that would be destroyed by 6-OHDA injections into the LH.

DMI itself acutely reduced NER in both lesioned and nonlesioned rats tested 2.5 and 3.5 hours after injections. The mechanism of this effect is not easily discerned. DMI by blocking uptake of NE and 5-HT (Javaid et al., 1979) could increase the concentration of transmitters in the synaptic cleft and enhance the effects of stimulation of nor-

adrenergic or serotonergic fibers. On the other hand, facilitation of synaptic transmission by uptake blockers is not always evident, and might vary with frequency depending on the degree to which the action potential-releasable pool of transmitter is dependent on reuptake. As an example, the decline of excitatory junctional potentials in mouse vas deferens upon electrical stimulation at 10 Hz was more rapid in the presence of DMI than in its absence (Bennett, 1973). Thus uptake blockade in this preparation depressed synaptic transmission. The inability to ascertain in the present experiments whether DMI facilitated or reduced the synaptic effectiveness of any aminergic fibers that might have been activated by nigral stimulation makes it impossible to rationalize its acute vs. chronic effects. Compounding the difficulty are other reported actions of DMI such as inhibition of DA sensitive adenylate cyclase in rat striatum (Karo-bath, 1975) and of histamine sensitive adenylate cyclase in rabbit cerebral cortex (Palmer et al., 1977).

The difference in results of 6-OHDA lesions with and without DMI prompted further attempts to use pharmacological tools to demonstrate the possible role of NE in NER. The catecholamine synthesis inhibitors, AMPT and DDTC, were used to separate DA and NE systems. AMPT, an inhibitor of tyrosine hydroxylase (Spector, 1966), would deplete both DA and NE, while DDTC, an inhibitor of DA beta-hydroxylase (Carlsson et al., 1966b) would deplete only NE. In the present experiments, AMPT 150 mg/kg i.p. 4 hours before testing significantly reduced NER, supporting a role for catecholamines in NER. If DA were the only catecholamine involved, administration of a DA beta-hydroxy-

lase inhibitor should not decrease NER. In fact, there are data indicating that inhibition of DA beta-hydroxylase might increase behaviors mediated by DA. A potent inhibitor, FLA-63, has been shown to increase striatal DA (Nyback, 1971) and enhance striatal DA release (Anden, et al., 1973) in rats. Ungerstedt (1971b) reported that FLA-63 increased amphetamine-induced rotation in rats with 6-OHDA lesions, and there are also reports of facilitation of amphetamine-induced stereotypy by FLA-63 and DDTC (Corrodi et al., 1970; Randrup and Scheel-Kruger, 1966). In the present experiments, however, DDTC reduced NER, in apparent conflict with the interpretation of the 6-OHDA lesion experiments wherein it would be expected that removal of NE fibers potentiated NER.

Clearly DA beta-hydroxylase inhibitors have effects on other enzyme systems. The inhibitors disulfuram and FLA-63 have been reported to increase turnover of brain 5-HT in rats (Johnson and Kim, 1973). Since 5-HT neurons from the median raphe seem to tonically inhibit the dopaminergic nigrostriatal neurons as suggested by electrophysiological, neurochemical and rotational behavior results (see Introduction), the reduction of NER by DDTC might reflect an increase in 5-HT transmission. Copper-containing enzymes e.g. aldehyde dehydrogenase which is required in converting aldehyde to acid in metabolic pathway of many compounds including brain amines, can also be inhibited by DDTC (Albert, 1961).

Even assuming that DDTC is acting via depletion of NE, however, there are two alternatives that could account for the apparent dis-

crepancy in the present experiments. First that whereas 6-OHDA in the LH will block transmission in ascending noradrenergic systems, DDTC should deplete NE in both ascending and descending neurons. If the descending systems were ultimately required for motor expression, this would resolve the discrepancy. A second possibility is that NE supersensitivity developed following the 6-OHDA lesion. The net effect of the lesion on stimulus evoked behavior will depend on the balance between the reduction in transmitter release consequent to the reduced number of fibers and the extent of supersensitivity. Estimates from the literature on the effectiveness of LH 6-OHDA in reducing forebrain NA range from 37 to 85 %, and this reduction was prevented by DMI.

Summary and conclusions

Contralateral rotation was reproducibly generated by electrical stimulation of the SN. Electrode placements in both the pars compacta and the pars reticulata were effective. The rotation appeared to be due to activation of intranigral elements. The functional relationship between the magnitude of contralateral rotation and the stimulus was often an inverted U-shape when either stimulus amplitude or frequency was varied. Contralateral front paw tremor and body torsion were observed in rats with stimulating electrodes near or in the cerebral peduncle. These behaviors were always associated with the

decrease in rotation with increasing amplitude and less so with increasing frequency. Thus the former was due to spread of current, the latter to the intrinsic characteristics of the neural pathways mediating rotation.

Electrolytic lesions of the ipsilateral LH which depleted striatal DA by 58 % significantly reduced NER at 2 hours to 14 days postlesion. Maximum reduction was at 2 hours, NER did not change from 3 to 14 days postlesion. Thus, these lesions were located between the stimulation site and subsequent synapse in the pathway mediating rotation. There was no correlation between percent DA depletion and percent reduction of NER at any time tested.

6-OHDA lesions of the ipsilateral LH which depleted striatal DA by 93 % (undetectable in 3 rats) significantly increased NER at 3 to 24 days postlesion. The immediate reduction of NER following electrolytic lesions and the increase in NER up to 24 days after 6-OHDA lesions argue against a critical role for DA release in NER. Furthermore, the opposite direction of the change in NER following electrolytic and 6-OHDA lesions, analogous to similar differential effects on apomorphine induced rotation, suggests that NER is due to activation of neuronal elements postsynaptic to the dopaminergic nigrostriatal neurons.

The lack of effect on NER of contralateral electrolytic or 6-OHDA lesions indicates that unlike rotation induced by systemic drugs, NER is a unilateral phenomenon and is not modified by activity

on the nonstimulated side.

Low doses of 6-OHDA at the LH which caused depletion of striatal DA equivalent to that produced by electrolytic lesions did not change NER. Electrolytic lesions of the LH preinjected with 6-OHDA 8 ug reduced NER to the same extent as electrolytic lesions in nonpreinjected or vehicle preinjected rats. The results strongly suggest that electrolytic lesions of the LH reduce NER by destruction of non DA neurons.

Nondopaminergic neurons that could be activated by electrical stimulation of the SN include both nigral efferents and afferents, the former orthodromically, the latter antidromically. The delayed reduction of NER following large electrolytic lesions of the CP and the immediate reduction following electrolytic lesions of the GP suggest that the primary synapses required for NER are not in caudate and might be in the GP. Two models consistent with these lesion results are antidromic activation of the striatonigral fibers which send collaterals to the GP or orthodromic activation of neurons synapsing or traversing pallidum which have supporting collaterals in striatum. An attempt to distinguish between the two models by ibotenic acid lesions of the CP did not provide conclusive evidence since the extent of ibotenic acid lesion of the CP was smaller than the lesion size caused by effective electrolytic lesion.

The degree of involvement of dopaminergic neurons in NER remains unanswered. The retention and even enhancement of NER following se-

vere DA depletion argues against it, however, pharmacological evidence is less convincing. Haloperidol can decrease NER but the sensitivity to haloperidol was apparently similar among nonlesioned, LH electrolytic lesioned or 6-OHDA lesioned rats. In addition, the haloperidol sensitivity of NER is less than that reported for drug-induced rotation in unilateral 6-OHDA lesioned animals. However, catecholamines appear to be involved in NER since it was reduced by AMPT, DMI, and DDTC.

NER and dopamine-independent contralateral rotation produced by intranigral muscimol are not likely to be mediated via the same mechanism. The rotation induced by intranigral muscimol has been postulated to be due to inhibition of nigral ipsiversive neurons allowing nigral contraversive descending output to dominate. This contralateral rotation appears independent of any neurons rostral to the SN. In contrast, contralateral rotation induced by electrical stimulation of the SN does not solely involve descending nigral efferents since it is reduced by electrolytic lesions rostral to nigra. In addition, it is unlikely that electrical stimulation directly inhibits nigral ipsiversive neurons to generate contralateral rotation since ipsiversive rotation does not supercede contraversive rotation as stimulus intensity is increased.

The present experiments also support the notion that there exist neurons in the SN whose activation leads to ipsilateral rotation. In nonlesioned animals, upon electrical stimulation of the SN contraversive rotation predominates. In some rats with pallidal lesions

it was possible to demonstrate ipsiversive rotation upon nigral stimulation. The neuronal pathway responsible for this behavior was not delineated.

Although striatal dopamine asymmetry is well accepted as a causative factor in rotation, there is much evidence that alterations in non-DA neurons can induce rotation without either causing, enhancing, or exploiting DA asymmetry. While unilateral nigrostriatal 6-OHDA lesioned rodents are useful animal models for screening directly and indirectly acting DA agonists, contralateral rotation induced by electrical stimulation of the SN cannot be considered a useful model for investigating effects of drugs on dopaminergic neuron function. It may be useful, however, especially following 6-OHDA lesions, for studying activation of the neuronal elements postsynaptic to the dopaminergic nigrostriatal system and of nigral elements involved in rotation.

BIBLIOGRAPHY

Aghajanian G. K. & Bunney B. S. (1973) Central dopaminergic neurons: neurophysiological identification and responses to drugs. In Frontiers in Catecholamine Research (eds Usdin E. & Snyder S.H.), pp. 643-648. Pergamon Press, New York.

Aghajanian G. K. & Bunney B. S. (1975) Dopaminergic and non-dopaminergic neurons of the substantia nigra: differential response to putative transmitters. In Neuropsychopharmacology (eds Boissier J. R., Hippius H. & Pichot P.), pp. 444-452. Excerpta Medica, Amsterdam and American Elsevier, New York.

Aghajanian G. H. & Bunney B. S. (1977) Dopaminergic 'autoreceptors' pharmacological characterization by microiontophoretic single cell recording studies. *Naunyn-Schmiedeberg's Arch. Pharmac.* 297, 1-7.

Aghajanian G. K. and Wang R. Y. (1977) Habenular and other midbrain raphe afferents demonstrated by a modified retrograde tracing technique. *Brain Res.* 122, 229-242.

Agid Y., Javoy F., Glowinski J., Bouvet D. & Sotelo C. (1973) Injection of 6-hydroxydopamine in the substantia nigra of the rat. II. Diffusion and specificity. *Brain Res.* 58, 291-301.

Albert A. (1961) Design of chelating agents for selected biological activity. *Fedn Proc. Fedn Am. Soc. exp. Biol.* 20, Suppl. 10, 137-147.

Anand B. K. & Dua S. (1955) Stimulation of limbic system of the brain in waking animals. *Science, N. Y.* 122, 1139.

Andén N.-E. (1970) Effects of amphetamine and some other drugs on central catecholamine mechanisms. In Amphetamines and Related Compounds (eds Costa E. & Garattini S.), pp. 447-462. Raven Press, New York.

Andén N.-E., Atack C. V. & Svensson T. H. (1973) Release of dopamine from central noradrenaline and dopamine-B-hydroxylase inhibitor. *J. Neural Transm.* 34, 93-100.

Andén N.-E., Carlsson A., Dahlström A., Fuxe K., Hillarp N.-Å. & Larsson K. (1964) Demonstration and mapping out of nigro-neostriatal dopaminergic neurons. *Life Sci.* 3, 523-530.

Andén N.-E., Dahlström A., Fuxe K. & Larsson K. (1965) Further evidence for the presence of nigro-neostriatal dopamine neurons in the rats. *Am. J. Anat.* 116, 329-334.

Andén N.-E., Dahlström A., Fuxe K. & Larsson K. (1966a) Functional role of the nigro-neostriatal dopamine neurons. *Acta pharmac. tox.* 24, 263-274.

- Andén N.-E., Dahlström A., Fuxe K., Larsson K., Olson L. & Ungerstedt U. (1966b) Ascending monoamine neurons to the telencephalon and diencephalon. *Acta physiol. scand.* 67, 313-326.
- Andén N.-E., Fuxe K., Hamberger B. & Hökfelt T. (1966c) A quantitative study on the nigro-neostriatal dopamine neuron system in the rat. *Acta physiol. scand.* 67, 306-312.
- Andén N.-E., Rubenson A., Fuxe K. & Hökfelt T. (1967) Evidence for dopamine receptor stimulation by apomorphine. *J. Pharm. Pharmac.* 19, 627-629.
- Arbuthnott G. W. & Crow T. J. (1971) Relation of contraversive turning to unilateral release of dopamine from the nigrostriatal pathway in rats. *Expl Neurol.* 30, 484-491.
- Arbuthnott G. W., Crow T. J., Fuxe K., Olson L. & Ungerstedt U. (1970a) Depletion of catecholamines in vivo induced by electrical stimulation of central monoamine pathways. *Brain Res.* 24, 471-483.
- Arbuthnott G. W., Crow T. J., Fuxe K. & Ungerstedt U. (1970b) Behavioral effects of stimulation in the region of the substantia nigra. *J. Physiol., Lond.* 210, 61P-62P.
- Arbuthnott G. W. & Ungerstedt U. (1969) Locomotor behavior after electrical stimulation of dopamine containing neurones. *Acta physiol. scand.* 77, Suppl. 330, 117.
- Arbuthnott G. W. & Ungerstedt U. (1975) Turning behavior induced by electrical stimulation of the nigro-neostriatal system of the rat. *Expl Neurol.* 47, 162-172.
- Arnt J. & Scheel-Krüger J. (1979a) Behavioral differences induced by muscimol selectively injected into pars compacta and pars reticulata of substantia nigra. *Naunyn-Schmiedeberg's Arch. Pharmac.* 310, 43-51.
- Arnt J. & Scheel-Krüger J. (1979b) GABAergic and glycinergic mechanisms within the substantia nigra: pharmacological specificity of dopamine-independent contralateral turning behavior and interactions with other neurotransmitters. *Psychopharmacology, Berl.* 62, 267-277.
- Arnt J., Scheel-Krüger J., Magelund G. & Krogsgaard-Larsen P. (1979) Muscimol and related GABA receptor agonists: the potency of GABAergic drugs in vivo determined after intranigral injection. *J. Pharm. Pharmac.* 31, 306-313.
- Atweh S. F. & Kuhar M. J. (1977) Autoradiographic localization of opiate receptors in rat brain. III. The telencephalon. *Brain Res.* 134, 393-405.
- Azmitia E. C. & Segal M. (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *J. comp. Neurol.* 179, 641-668.

- Baig H. & Reid-Miller M. (1980) Prophet Statistics: A User's Guide to Statistical Analysis on the PROPHET System, NIH Publication No. 80-2169 (July, 1980).
- Bak I. J., Choi W. B., Hassler R., Usunoff K. G. & Wagner A. (1975) Fine structural synaptic organization of the corpus striatum and substantia nigra in rat and cat. In *Advances in Neurology* (eds Calne D. B., Chase T. N. & Barbeau A.), Vol. 9, pp. 25-41. Raven Press, New York.
- Baldessarini R. J., Amatrudda III T. T., Griffith F. F. & Gerson S. (1975) Differential effects of serotonin on turning and stereotypy induced by apomorphine. *Brain Res.* 93, 158-163.
- Barghon R. & Costentin J. H. (1980) Rotational behavior induced by unilateral electrical stimulation of nigro-striatal dopamine neurons: modification by low doses of apomorphine. *Eur. J. Pharmac.* 64, 39-46.
- Barnett A. & Goldstien J. (1975) Head-turning induced by electrical stimulation of the caudate nucleus and its antagonism by anti-parkinson drugs. *J. Pharmac. exp. Ther.* 194, 296-302.
- Beckstead R. M., Domesick V. B. & Nauta W. J. H. (1979) Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res.* 175, 191-217.
- Beckstead R. M., Edwards S. B. & Frankfurter A. (1981) A comparison of the intranigral distribution of nigrotectal neurons labeled with horseradish peroxidase in the monkey, cat, and rat. *J. Neuroscience* 1, 121-125.
- Bennet M. R. (1973) An electrophysiological analysis of the uptake of noradrenalin at sympathetic nerve terminals. *J. Physiol., Lond.* 229, 533-546.
- Bentivoglio M., Van Der Kooy D. & Kuypers H. G. J. M. (1979) The organization of the efferent projections of the substantia nigra in the rat. A retrograde fluorescent double labeling study. *Brain Res.* 174, 1-17.
- Biggio G., Casu M., Corda M. G., DiBello C. & Gessa G. L. (1978). Stimulation of dopamine synthesis in caudate nucleus by intrastriatal enkephalins and antagonism by naloxone. *Science, N. Y.* 200, 552-554.
- Björklund A. & Lindvall O. (1975) Dopamine in dendrites of substantia nigra neurons: suggestions for a role in dendritic terminals. *Brain Res.* 83, 531-537.
- Blackburn T. P., Foster G. A., Heapy C. G. & Kemp J. D. (1979) Differential rotational behaviour after unilateral 5,7-dihydroxytryptamine induced lesions of the dorsal raphe nucleus. *Br. J. Pharmac.* 67, 431P-432P.

Bobillier P., Seguin S., Petitjean F., Salvert D., Touret M. & Jouvett M. (1976) The raphe nuclei of the cat brain stem: a topographical atlas of their efferent projections as revealed by autoradiography. *Brain Res.* 113, 449-486.

Breese G. R., Smith R. D., Cooper B. R., Hollister A. S., Kraemer G. & McKinney W. T. (1975) Use of neurocytotoxic compounds in neuropsychopharmacology. In Chemical Tools in Catecholamine Research (eds Jonsson G., Malmfors T. & Sachs Ch.), Vol. 1, pp. 335-342. North-Holland, Amsterdam and American Elsevier, New York.

Breese G. R. & Traylor T. D. (1971) Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine. *Br. J. Pharmac.* 42, 88-99.

Brownstein M. J., Mroz E. A., Tappaz M. L. & Leeman S. E. (1977) On the origin of substance P and glutamic acid decarboxylase (GAD) in the substantia nigra. *Brain Res.* 135, 315-323.

Buchwald N. A. & Ervin F. R. (1957) Evoked potentials and behavior. A study of responses to subcortical stimulation in the awake, unrestrained animal. *Electroenceph. clin. Neurophysiol.* 9, 477-496.

Bunney B. S. & Aghajanian G. K. (1973) Electrophysiological effects of amphetamine on dopaminergic neurons. In Frontiers in Catecholamine Research (eds Usdin E. & Snyder S. H.), pp. 957-962. Pergamon Press, New York.

Bunney B. S. & Aghajanian G. K. (1976a) d-Amphetamine-induced inhibition of central dopaminergic neurons: mediation by a striato-nigral feedback pathway. *Science*, N. Y. 192, 391-393.

Bunney B. S. & Aghajanian G. K. (1976b) Dopaminergic influence in the basal ganglia: evidence for striatonigral feedback regulation. In The Basal Ganglia (ed Yarh M. D.), pp. 249-267. Raven Press, New York.

Bunney B. S. & Aghajanian G. K. (1976c) The precise localization of nigral afferents in the rat as determined by a retrograde tracing technique. *Brain Res.* 117, 423-435.

Bunney B. S. & Aghajanian G. K. (1978) d-Amphetamine-induced depression of central dopamine neurons: evidence for mediation by both autoreceptors and a striato-nigral feedback pathway. *Naunyn-Schmiedeberg's Arch. Pharmac.* 304, 255-261.

Bunney B. S., Walters J. R., Roth R. H. & Aghajanian G. K. (1973) Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmac. exp. Ther.* 185, 560-571.

Butcher L. L., Talbot K. & Bilezikjian L. (1975) Acetylcholinesterase neurons in dopamine-containing regions of the brain. *J. Neural Transm.* 37, 127-153.

Carlsson A., Fuxe K., Hamburger B. & Lindqvist M. (1966a) Biochemical and histochemical studies on the effects of imipramine-like drugs and (+)-amphetamine on central and peripheral catecholamine neurons. *Acta physiol. scand.* 67, 481-497.

Carlsson A., Lindqvist M., Fuxe K. & Hökfelt T. (1966b) Histochemical and biochemical effects of diethyldithiocarbamate on tissue catecholamines. *J. Pharm. Pharmac.* 18, 60-62.

Carter D. A. & Fibiger H. C. (1978) The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. *J. Comp. Neurol.* 117, 113-124.

Carter C. J. & Pycock C. J. (1979) Potentiation of haloperidol-induced catalepsy by dopamine agonists: possible involvement of central 5-hydroxytryptamine. *Pharmac. Biochem. Behav.* 10, 475-480.

Celsen B. & Kuschinsky K. (1974) Effects of morphine on kinetics of ^{14}C -dopamine in rat striatal slices. *Naunyn-Schmiedeberg's Arch. Pharmac.* 284, 159-165.

Chan-Palay V. (1977) Cerebellar Dentate Nucleus: Organization, Cytology and Transmitters, pp. 179-211. Springer, Berlin.

Chéramy A., Leviel V., Nieoullon A. & Glowinsky J. (1978a) Role of various nigral afferences on the activity of the nigrostriatal dopaminergic pathways. In Advances in Pharmacology and Therapeutics (ed Simon P.), Vol. 2, pp. 109-119. Pergamon Press, Oxford.

Chéramy A., Nieoullon A. & Glowinski J. (1978b) Inhibition of dopamine release in the cat caudate nucleus by nigral application of glycine. *Eur. J. Pharmac.* 47, 141-147.

Chéramy A., Nieoullon A. & Glowinski J. (1978c) GABAergic processes involved in the control of dopamine release from nigrostriatal dopaminergic neurons in the cat. *Eur. J. Pharmac.* 48, 281-295.

Chevalier G., Thierry A. M., Shibasaki T. & Féger J. (1981) Evidence for a GABAergic inhibitory nigrotectal pathway in the rat. *Neuroscience Letters* 21, 67-70.

Chiueh C. C. & Moore K. E. (1973) Release of endogenously synthesized catechols from the caudate nucleus by stimulation of the nigro-striatal pathway and by the administration of d-amphetamine. *Brain Res.* 50, 221-225.

Christie J. E. & Crow T. J. (1971) Turning behavior as an index of the action of amphetamines and ephedrine on central dopamine-containing neurones. *Br. J. Pharmac.* 43, 658-667.

Christie J. E., Ljungberg T. & Ungerstedt U. (1973) Dopamine neurones and electrical self-stimulation in the lateral hypothalamus. *J. Physiol., Lond.* 234, 80P-81P.

- Clavier R. M., Atmadja S. & Fibiger H. G. (1976) Nigrothalamic projections in the rat as demonstrated by orthograde and retrograde tracing techniques. *Brain Res. Bulletin* 1, 379-384.
- Clay G. A. & Brougham L. R. (1975) Haloperidol binding to an opiate receptor site. *Biochem. Pharmac.* 24, 1363-1367.
- Cobbin D. M. & Atrens D. M. (1976) Ipsiversive rotation elicited by electrical stimulation of the mesencephalon in the rat: anatomical, physiological, and pharmacological considerations. *Expl Neurol.* 52, 100-109.
- Collingridge G. L., James T. A. & MacLeod N. K. (1979) Neurochemical and electrophysiological evidence for a projection from the locus coeruleus to the substantia nigra. *J. Physiol., Lond.* 290, 44P.
- Commissiong J. W., Gentleman S. & Neff N. H. (1979) Spinal cord dopaminergic neurons: evidence for an uncrossed nigrospinal pathway. *Neuropharmacology* 18, 565-568.
- Connor J. D. (1968) Caudate unit responses to nigral stimuli: evidence for a possible nigro-neostriatal pathway. *Science, N. Y.* 160, 899-900.
- Connor J. D. (1970) Caudate nucleus neurones: correlation of the effects of substantia nigra stimulation with iontophoretic dopamine. *J. Physiol., Lond.* 208, 691-703.
- Conrad L. C. A., Leonard C. M. & Pfaff D. W. (1974) Connections of the median and dorsal raphe nuclei in the rat: an autoradiographic and degeneration study. *J. Comp. Neurol.* 156, 179-206.
- Conrad L. C. A. & Pfaff D. W. (1976) Autoradiographic tracing of nucleus accumbens efferents in the rat. *Brain Res.* 113, 589-596.
- Cools A. R. (1973) Chemical and electrical stimulation of the caudate nucleus in freely moving cats: the role of dopamine. *Brain Res.* 58, 437-451.
- Cools A. R. & Van Rossum J. M. (1976) Excitation-mediating and inhibition-mediating dopamine receptors: a new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. *Psychopharmacologia, Berl.* 45, 243-254.
- Cools A. R. & Van Rossum J. M. (1980) Multiple receptors for brain dopamine in behavior regulation: concept of dopamine-E and dopamine-I receptors. *Life Sci.* 27, 1237-1253.
- Corrodi H., Fuxe K., Ljungdahl, Å. & Ögren S. O. (1970) Studies on the action of some psychoactive drugs on central noradrenaline neurones after inhibition of dopamine-B-hydroxylase. *Brain Res.* 24, 451-470.

Costall B., Marsden C. D., Naylor R. J. & Pycock C. J. (1976a) The relationship between striatal and mesolimbic dopamine dysfunction and the nature of circling responses following 6-hydroxydopamine and electrolytic lesions of the ascending dopamine systems of rat brain. *Brain Res.* 118, 83-113.

Costall B., Naylor R. J. & Olley J. E. (1972) Catalepsy and circling behaviour after intracerebral injections of neuroleptic, cholinergic and anticholinergic agents into the caudate-putamen, globus pallidus and substantia nigra of rat brain. *Neuropharmacology* 11, 645-663.

Costall B. & Naylor R. J. (1974a) Stereotyped and circling behaviour induced by dopaminergic agonists after lesions of the midbrain raphe nuclei. *Eur. J. Pharmac.* 29, 206-222.

Costall B. & Naylor R. J. (1974b) Specific asymmetric behaviour induced by the direct chemical stimulation of neostriatal dopaminergic mechanisms. *Naunyn-Schmiedeberg's Arch. Pharmac.* 285, 83-98.

Costall B. & Naylor R. J. (1975) A comparison of circling models for the detection by antiparkinson activity. *Psychopharmacologia, Berl.* 41, 57-64.

Costall B. & Naylor R. J. (1973) On the mode of action of apomorphine *Eur. J. Pharmac.* 21, 350-361.

Costall B., Naylor R. J., Marsden C. D. & Pycock C. J. (1976b) Circling behaviour produced by asymmetric medial raphe nuclei lesions in rats. *J. Pharm. Pharmac.* 28, 248-249.

Costall B., Naylor R. J. & Olley J. E. (1972) Catalepsy and circling behaviour after intracerebral injections of neuroleptic, cholinergic and anticholinergic agents into the caudate-putamen, globus pallidus and substantia nigra of rat brain. *Neuropharmacology* 11, 645-663.

Costall B., Naylor R. J. & Pycock C. (1976c) Non-specific supersensitivity of striatal dopamine receptors after 6-hydroxydopamine lesion of the nigrostriatal pathway. *Eur. J. Pharmac.* 35, 275-283.

Crane L. A. & Glick S. D. (1979) Simple cannula for repeated intracerebral drug administration in rats. *Pharmac. Biochem. Behav.* 10, 779-800.

Creese I., Feinberg A. P. & Snyder S. H. (1976) Butyrophenone influences on the opiate receptor. *Eur. J. Pharmac.* 36, 231-235.

Crossman A. R., Lee L. A. & Slater P. (1977) Effects of manipulating pallidal and nigral GABA on striatally-mediated head-turning in the rat. *Br. J. Pharmac.* 61, 483P.

Crossman A. R., Walker R. J. & Woodruff G. N. (1973) Picrotoxin antagonism of γ -aminobutyric acid inhibitory responses and synaptic inhibition in the rat substantia nigra. *Br. J. Pharmac.* 49, 696-698.

- Crow T. J. (1971) The relationship between lesion site, dopamine neurons, and turning behavior in rat. *Expl Neurol.* 32, 247-255.
- Crow T. J. & Waddington J. L. (1977) Rotational responses to the putative serotonin agonist 5MeODMT following unilateral 5,6-DHT lesions of the median forebrain bundle: a possible role for 5-HT in the control of rotational behaviour. *Br. J. Pharmac.* 60, 265P-266P.
- Curtis D. R., Lodge D. & McLennan H. (1979) The excitation and depression of spinal neurones by ibotenic acid. *J. Physiol., Lond.* 291, 19-28.
- Curtis D. R. & Watkins J. C. (1965) The pharmacology of amino acids related to gamma-aminobutyric acid. *Pharmac. Rev.* 17, 347-391.
- Dafny N. (1975) Electrophysiological properties of caudate neurons following substantia nigra, motor cortex, and amygdaloid nuclear complex stimulation of the rat. *Appl. Neurophysiol.* 38, 259-272.
- Dahlström A. & Fuxe K. (1964) Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta physiol. scand.* 62, Suppl. 232, 1-80.
- Dalsass M. & Krauthamer G. M. (1981) Intracellular responses in the centrum medianum-parafascicular complex of the cat following medial and lateral caudate, substantia nigra and peripheral stimulation. *Neuroscience Letters* 21, 171-176.
- Dankova J., Boucher R. & Poirier L. J. (1975) Role of the strio-pallidal system and motor cortex in induced circus movements in rats and cats. *Expl Neurol.* 47, 135-149.
- Davies J. & Dray A. (1976) Substance P in the substantia nigra. *Brain Res.* 107, 623-627.
- Davies J. & Tongroach P. (1978) Neuropharmacological studies on the nigro-striatal and raphe-striatal system in the rat. *Eur. J. Pharmac.* 51, 91-100.
- Delgado J. M. R. (1965) Sequential behavior induced repeatedly by stimulation of the red nucleus in free monkeys. *Science, N. Y.* 148, 1361-1363.
- Delgado J. M. R., Delgado-García J. M., Amérigo J. A. & Grau, C. (1975) Behavioral inhibition induced by pallidal stimulation in monkeys. *Expl Neurol.* 49, 580-591.
- Delini-Stula A. & Vassout A. (1979) Modulation of dopamine-mediated behavioural responses by antidepressants: effects of single and repeated treatment. *Eur. J. Pharmac.* 58, 443-451.

De Montis G. M., Olianias M. C., Serra G., Tagliamonte A. & Scheel-Krüger J. (1979) Evidence that a nigral GABAergic-cholinergic balance controls posture. *Eur. J. Pharmac.* 53, 181-190.

Deniau J. M., Chevalier G. & Feger J. (1978a) Electrophysiological study of the nigro-tectal pathway in the rat. *Neuroscience Letters* 10, 215-220.

Deniau J. M., Hammond C., Risz A. & Feger J. (1978b) Electrophysiological properties of identified output neurons of the rat substantia nigra (pars compacta and pars reticulata): evidences for the existence of branched neurons. *Expl Brain Res.* 32, 409-422.

Deniau J. M., Hammond-Le Guyader C., Feger J. & McKenzie J. S. (1977) Bilateral projection of nigro-collocular neurons: an electrophysiological analysis in the rat. *Neuroscience Letters* 5, 45-50.

Deniau J. M., Lackner D. & Feger J. (1978c) Effect of substantia nigra stimulation on identified neurons in the VL-VA thalamic complex: comparison between intact and chronically decorticated cats. *Brain Res.* 145, 27-35.

DiChiara G., Morelli M., Porceddu M. L. & Gessa G. L. (1979a) Role of thalamic -aminobutyrate in motor functions: catalepsy and ipsiversive turning after intrathalamic muscimol. *Neuroscience* 4, 1453-1465.

DiChiara G., Morelli M., Porceddu M. L., Mulas M. & Del Fiocco M. (1980) Effect of discrete kainic acid-induced lesions of corpus caudatus and globus pallidus on glutamic acid decarboxylase of rat substantia nigra. *Brain Res.* 189, 193-208.

DiChiara G., Olianias M., Del Fiocco M., Spano P. F. & Tagliamonte A. (1977) Intranigral kainic acid is evidence that nigral non-dopaminergic neurones control posture. *Nature, Lond.* 268, 743-745.

DiChiara G., Porceddu M. L., Morelli M., Mulas M. L. & Gessa G. L. (1979b) Evidence for a GABAergic projection from the substantia nigra to the ventromedial thalamus and to superior colliculus of the rat. *Brain Res.* 176, 273-384.

DiChiara G., Porceddu M. L., Morelli M., Mulas M. L. & Gessa G. L. (1979c) Substantia nigra as an out-put station for striatal dopaminergic responses: role of a GABA-mediated inhibition of pars reticulata neurons. *Naunyn-Schmiedeberg's Arch. Pharmac.* 306, 153-159.

Donaldson I. McG., Dolphin A., Jenner P., Marsden C. D. & Pycock C. (1976a) The roles of noradrenaline and dopamine in contraversive circling behaviour seen after unilateral electrolytic lesions of the locus coeruleus. *Eur. J. Pharmac.* 39, 179-191.

Donaldson I. MacG., Dolphin A., Jenner P., Marsden C. D. & Pycock C. (1976b) The involvement of noradrenaline in motor activity as shown by rotational behaviour after unilateral lesions of the locus coeruleus. *Brain* 99, 427-446.

Donaldson I. MacG., Dolphin A., Jenner P., Marsden C. D. & Pycock C. (1976c) Contraversive circling behaviour produced by unilateral electrolytic lesions of the ventral noradrenergic bundle mimicking the changes seen with unilateral electrolytic lesions of the locus coeruleus. *J. Pharm. Pharmac.* 28, 329-331.

Donaldson I. MacG., Dolphin A. C., Jenner P., Pycock C. & Marsden C. D. (1978) Rotational behaviour produced in rats by unilateral electrolytic lesions of the ascending noradrenergic bundles. *Brain Res.* 138, 487-509.

Dray A. (1979) The striatum and substantia nigra: a commentary on their relationships. *Neuroscience* 4, 1407-1439.

Dray A., Davies J., Oakley N. R., Tongroach P. & Vellucci S. (1978) the dorsal and medial raphe projections to the substantia nigra in the rat: electrophysiological, biochemical and behavioral observations. *Brain Res.* 151, 431-442.

Dray A., Fowler L. J., Oakley N. R., Simmonds M. A. & Tanner T. (1977) Regulation of nigrostriatal dopaminergic neurotransmission in the rat. *Neuropharmacology* 16, 511-518.

Dray A. & Gonye T. J. (1975) Effects of caudate stimulation and micro-iontophoretically applied substances on neurones in the rat substantia nigra. *J. Physiol., Lond.* 246, 88P-89P.

Dray A., Gonye T. J. & Oakley N. R. (1976a) Effects of α -flupenthixol on dopamine and 5-hydroxytryptamine responses of substantia nigra neurones. *Neuropharmacology* 15, 793-796.

Dray A., Gonye T. J., Oakley N. R. & Tanner T. (1976b) Evidence for the existence of a raphe projection to the substantia nigra of the rat. *Brain Res.* 113, 45-57.

Dray A., Gonye T. J., Oakley N. R. & Tanner T. (1976c) A raphe-substantia nigra projection in the rat. *J. Physiol., Lond.* 257, 29P-30P.

Dray A. & Oakley N. R. (1977) Methiothepin and a 5-HT pathway to rat substantia nigra. *Experientia* 33, 1198-1200.

Dray A. & Straughan D. W. (1976) Synaptic mechanisms in the substantia nigra. *J. Pharm. Pharmac.* 28, 400-405.

Enna S. J., Bennett Jr. J. P., Burt D. R., Creese I. & Snyder S. H. (1976) Stereospecificity of interaction of neuroleptic drugs with neurotransmitters and correlation with clinical potency. *Nature, Lond.* 263, 338-341.

Ernst A. M. (1967) Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. *Psychopharmacologia, Berl.* 10, 316-323.

Fallon J. H., Koziell D. A. & Moore R. Y. (1978a) Catecholamine innervation of the basal forebrain II. Amygdala, suprarhinal cortex and entorhinal cortex. *J. Comp. Neurol.* 180, 509-532.

Fallon J. H., Riley J. N. & Moore R. Y. (1978b) Substantia nigra dopamine neurons: separate populations project to neostriatum and allocortex. *Neuroscience Letters* 7, 157-162.

Fallon J. H. & Moore R. Y. (1978a) Catecholamine innervation of the basal forebrain III. Olfactory bulb, anterior olfactory nuclei, olfactory tubercle and piriform cortex. *J. Comp. Neurol.* 180, 533-544.

Fallon J. H. & Moore R. Y. (1978b) Catecholamine innervation of the basal forebrain IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. Comp. Neurol.* 180, 545-580.

Faull R. L. M. & Carman J. B. (1968) Ascending projections of the substantia nigra in the rat. *J. Comp. Neurol.* 132, 73-92.

Faull R. L. M. & Mehler W. R. (1978) The cells of origin of nigro-tectal, nigrothalamic and nigrostriatal projections in the rat. *Neuroscience* 3, 989-1002.

Feltz P. & De Champlain J. (1972) Persistence of caudate unitary responses to nigral stimulation after destruction and functional impairment of the striatal dopaminergic terminals. *Brain Res.* 43, 595-600.

Feltz P. & MacKenzie J. S. (1969) Properties of caudate unitary responses to repetitive nigral stimulation. *Brain Res.* 13, 612-614.

Ferrier D. (1873) Experimental researches in cerebral physiology and pathology. West Riding Lunatic Asylum Med. Rep. (ed. Crichton Browne J.), Vol. III pp. 30-96.

Fibiger H. C. & Miller J. J. (1977) An anatomical and electrophysiological investigation of the serotonergic projection from the dorsal raphe nucleus to the substantia nigra in the rat. *Neuroscience* 2, 975-987.

Fibiger H. C., Pudritz R. E., McGeer P. L. & McGeer E. G. (1972) Axonal transport in nigro-striatal and nigro-thalamic neurons: effects of medial forebrain bundle lesions and 6-hydroxydopamine. *J. Neurochem.* 19, 1697-1708.

Finger S., Walbran B. & Stein D. G. (1973) Brain damage and behavioral recovery: serial lesion phenomena. *Brain Res.* 63, 1-18.

Fjalland B. (1978) Inhibition by neuroleptics of uptake of ³H-GABA into rat brain synaptosomes. *Acta pharmac. tox.* 42, 73-76.

Fleisher L. N. & Glick S. D. (1979) Hallucinogen-induced rotational behavior in rats. *Psychopharmacology, Berl.* 62, 193-200.

Fonnum F. (1975) A rapid radiochemical method for the determination of choline acetyltransferase. *J. Neurochem.* 24, 407-409.

Fonnum F., Gottesfeld Z. & Grofova I. (1978) Distribution of glutamate decarboxylase, choline acetyl-transferase and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatoentopeduncular and striatonigral GABAergic fibres. *Brain Res.* 143, 125-138.

Forman D. & Ward J. W. (1957) Responses to electrical stimulation of caudate nucleus in cats in chronic experiments. *J. Neurophysiol.* 20, 230-243.

Fox C. A. & Rafols J. A. (1975) The radial fibers in the globus pallidus. *J. Comp. Neurol.* 159, 177-200.

Fuller D. R. G., Hull C. D. & Buchwald N. A. (1975) Intracellular responses of caudate output neurones to orthodromic stimulation. *Brain Res.* 96, 337-341.

Fuxe K. (1965) The distribution of monoamine terminals in the central nervous system. *Acta physiol. scand.* 64, Suppl. 249, 37-85.

Fuxe K., Hökfelt T., Olson L. & Ungerstedt U. (1977) Central monoaminergic pathways with emphasis on their relation to the so called 'extrapyramidal motor system'. *Pharmac. Ther. B.* 3, 169-210.

Fuxe K. & Ungerstedt U. (1968) Histochemical studies on the effect of (+)-amphetamine, drugs of the imipramine group and tryptamine on central catecholamine and 5-hydroxytryptamine neurons after intraventricular injection of catecholamines and 5-hydroxytryptamine. *Eur. J. Pharmac.* 4, 135-144.

Gale K. (1980) Chronic blockade of dopamine receptors by antischizophrenic drugs enhances GABA binding in substantia nigra. *Nature*, Lond. 283, 569-570.

Gale K. & Bernstein H. (1980) Development of supersensitive GABA receptors in substantia nigra after either chronic blockade of dopamine receptors or destruction of nigrostriatal dopamine neurons. *Soc. Neurosci. Abstr.* 6, 343.

Gale K., Guidotti A. & Costa E. (1977a) Dopamine-sensitive adenylate cyclase: location in substantia nigra. *Science*, N. Y. 195, 503-505.

Gale K., Hong J.-S. & Guidotti A. (1977b) Presence of substance P and GABA in separate striatonigral neurons. *Brain Res.* 136, 371-375.

Gale K. & Iadarola M. J. (1980) GABAergic denervation of rat substantia nigra: functional and pharmacological properties. *Brain Res.* 183, 217-223.

Garau L., Govoni S., Stefanini E., Trabucchi M. & Spano P. F. (1978) Dopamine receptors: pharmacological and anatomical evidences indicate

that two distinct dopamine receptor populations are present in rat striatum. *Life Sci.* 23, 1745-1750.

Garcia-Munoz M., Nicolaou N. M., Tulloch I. F., Wright A. K. & Arbuthnott G. W. (1977) Feedback loop or output pathway in striato-nigral fibers? *Nature*, Lond. 265, 363-365.

Garcia-Rill E., Hull C. D., Cherubini E., Levine M. S. & Buchwald N. A. (1980) The spontaneous firing patterns of forebrain neurons V. Time course of changes in caudate unit activity following dopamine-depleting lesions. *Brain Res.* 190, 415-424.

Geffen L. B., Jessell T. M., Cuello A. C. & Iversen L. L. (1976) Release of dopamine from dendrites in rat substantia nigra. *Nature*, Lond. 260, 258-260.

Giambalvo C. T. & Snodgrass S. R. (1978a) Effect of p-chloroamphetamine and 5,7-dihydroxytryptamine on rotation and dopamine turnover. *Brain Res.* 149, 453-467

Giambalvo C. T. & Snodgrass S. R. (1978b) Biochemical and behavioral effects of serotonin neurotoxins on the nigrostriatal dopamine system: comparison of injection sites. *Brain Res.* 152, 555-566.

Glick S. D. & Cox R. D. (1978) Nocturnal rotation in normal rats: correlation with amphetamine-induced rotation and effects of nigrostriatal lesions. *Brain Res.* 150, 149-161.

Glick S. D. & Crane L. A. (1978) Function of nigral dopamine receptors? *Brain Res.* 156, 380-381.

Glick S. D., Jerussi T. P., Cox R. D. & Fleisher L. N. (1977) Pre- and post-synaptic actions of apomorphine: differentiation by rotatory effects in normal rats. *Arch. int. Pharmacodyn.* 225, 303-307.

Glick S. D., Jerussi T. P. & Fleisher L. N. (1976) Turning in circles: the neuropharmacology of rotation. *Life Sci.* 18, 889-896.

Glick S. D., Jerussi T. P., Waters D. H. & Green J. P. (1974) Amphetamine-induced changes in striatal dopamine and acetylcholine levels and relationship to rotation (circling behavior) in rats. *Biochem. Pharmac.* 23, 3223-3225.

Gloor P. (1960) Amygdala. In Handbook of Physiology, Vol. 11, pp. 1395-1420. Amer. Physiol. Soc., Washington, D. C.

Glowinski J. & Axelrod J. (1965) Effect of drugs on the uptake, release, and metabolism of ³H-norepinephrine in the rat brain. *J. Pharmac. exp. Ther.* 149, 43-49.

Glowinski J., Nieoullon A. & Chéramy A. (1978) Regulations of the activity of the nigrostriatal dopaminergic pathways by cortical, cerebellar, and sensory neuronal afferences. In *Advances in Biochemical Psychopharmacology* (eds Roberts P. J., Woodruff G. N. & Iversen L.

L.), Vol. 19, pp. 75-87. Raven Press, New York.

Goldstein M., Freedman L. S. & Backstrom T. (1970) The inhibition of catecholamine biosynthesis by apomorphine. *J. Pharm. Pharmac.* 22, 715-717.

González-Vegas J. A. (1981) Nigro-reticular pathway in the rat: an intracellular study. *Brain Res.* 207, 170-173.

González-vegas J. A. & Pardey B. (1979) A presynaptic action of dopamine on globus pallidus afferents to substantia nigra in the rat. *Neuroscience Letters* 14, 77-80.

Goswell M. J. and Sedgwick E. M. (1973) Is there a cortico-nigral tract? Some neurophysiological observations. *Brain Res.* 50, 437-440.

Groves P. M., Wilson C. J., Young S. J. & Rebec G. V. (1975) Self-inhibition by dopaminergic neurons. An alternative to the "neuronal feedback loop" hypothesis for the mode of action of certain psychotic drugs. *Science, N. Y.* 190, 522-529.

Gulley R. L. & Wood R. L. (1971) The fine structure of the neurons in the rat substantia nigra. *Tissue and Cell* 3, 675-690.

Guyenet P. G. & Aghajanian G. K. (1978) Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra. *Brain Res.* 150, 69-84.

Hajdu F., Hassler R. & Bak I. J. (1973) Electron microscopic study of the substantia nigra and the strio-nigral projection in the rat. *Z. Zellforsch.* 146, 207-221.

Hall J. G., Hicks T. P., McLennan H., Richardson T. L. & Wheal H. V. (1979) The excitation of mammalian central neurones by amino acids. *J. Physiol., Lond.* 286, 29-39.

Hammond C., Deniau J. M., Rizk A. & Feger J. (1978) Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. *Brain Res.* 151, 235-244.

Hassler, R. (1979) Striatal regulation of adverting and attention directing induced by pallidal stimulation. *Appl. Neurophysiol.* 42, 98-102.

Hassler R. & Dieckmann G. (1968) Locomotor movements in opposite directions induced by stimulation of pallidum or of putamen. *J. neurol. Sci.* 8, 189-195.

Hattori T., Fibiger H. C., McGeer P. L. & Maler L. (1973) Analysis of the fine structure of the dopaminergic nigrostriatal projection by electron microscopic autoradiography. *Expl Neurol.* 41, 599-611.

Hattori T., Fibiger H. C. & McGeer P. L. (1975) Demonstration of a pallido-nigral projection innervating dopaminergic neurons. *J. comp.*

Neurol. 162, 487-504.

Hattori T., McGeer P. L. & McGeer E. G. (1979) Dendro axonic neurotransmission. II. Morphological sites for the synthesis, binding and release of neurotransmitters in dopaminergic dendrites in the substantia nigra and cholinergic dendrites in the neostriatum. Brain Res. 170, 71-83.

Hedreen J. C. (1971) Separate demonstration of dopaminergic and non-dopaminergic projections of substantia nigra in the rat. Anat. Rec. 169, 338.

Hedreen J. (1978) Brainstem projections of rat substantia nigra. Anat. Rec. 190, 417.

Hedreen J. C. & Chalmers J. P. (1972) Neuronal degeneration in rat brain induced by 6-hydroxydopamine: a histological and biochemical study. Brain Res. 47, 1-36.

Herkenham M. (1979) The afferent and efferent connections of the ventromedial thalamic nucleus in the rat. J. comp. Neurol. 183, 487-517.

Hodge G. K. & Butcher L. L. (1979) Role of pars compacta of the substantia nigra in circling behavior. Pharmac. Biochem. Behav. 10, 695-709.

Hökfelt T., Kellerth J. O., Nilsson G. & Pernow B. (1975) Substance P: localization in the central nervous system and in some primary sensory neurons. Science, N. Y. 190, 889-890.

Hökfelt T., Phillipson O. & Goldstein M. (1979) Evidence for a dopaminergic pathway in the rat descending from the A11 cell group to the spinal cord. Acta physiol. Scand. 107, 393-395.

Hökfelt T. & Ungerstedt U. (1969) Electron and fluorescence microscopical studies on the nucleus caudatus putamen of the rat after unilateral lesions of ascending nigro-neostriatal dopamine neurons. Acta physiol. scand. 76, 415-426.

Hong J. S., Yang H.-Y. L., Fratta W. & Costa E. (1977a) Determination of methionine enkephalin in discrete regions of rat brain. Brain Res. 134, 383-386.

Hong J. S., Yang H.-Y. T., Racagni G. & Costa E. (1977b) Projections of substance P containing neurons from neostriatum to substantia nigra. Brain Res 122, 541-544.

Hopkins D. A. & Niessen L. W. (1976) Substantia nigra projections to the reticular formation, superior colliculus and central gray in the rat, cat and monkey. Neuroscience Letters 2, 253-259.

Hull C. D., Bernardi G. & Buchwald N. A. (1970) Intracellular responses of caudate neurons to brain stem stimulation. Brain Res. 22,

163-179.

Hull C. D., Levine M. S., Buchwald N. A., Heller, A. & Browning R. A. (1974) The spontaneous firing pattern of forebrain neurons. I. The effects of dopamine and non-dopamine depleting lesions on caudate unit firing patterns. *Brain Res.* 73, 241-262.

Hunter J. & Jasper H. H. (1949) Effects of thalamic stimulation in unanesthetized animals. *Electroenceph. clin. Neurophysiol.* 1, 305-324.

Hyde J. E. (1965) Effects of simultaneous application of opposing stimuli for head turning in cats. *Expl Neurol.* 11, 230-244.

Iwamoto E. T., Loh H. H. & Way E. L. (1976a) Circling behavior in rats with 6-hydroxydopamine or electrolytic nigral lesions. *Eur. J. Pharmac.* 37, 339-356.

Iwamoto E. T., Loh H. H. & Way E. L. (1976b) Circling behavior after narcotic drugs and during naloxone-precipitated abstinence in rats with unilateral nigral lesions. *J. Pharmac. exp. Ther.* 197, 503-516.

Iwamoto E. T. & Way E. L. (1977) Circling behavior and stereotypy induced by intranigral opiate microinjections. *J. Pharmac. exp. Ther.* 203, 347-359.

Iwatsubo K. & Clouet D. H. (1975) Dopamine-sensitive adenylate cyclase of the caudate nucleus of rats treated with morphine or haloperidol. *Biochem. Pharmac.* 24, 1499-1503.

Iwatsubo K. & Clouet D. H. (1977) Effects of morphine and haloperidol on the electrical activity of rat nigrostriatal neurons. *J. Pharmac. exp. Ther.* 202, 429-436.

Jacobs B. L., Simon S. M., Ruimy D. D. & Trulson M. E. (1977) A quantitative rotational model for studying serotonergic function in the rat. *Brain Res.* 124, 271-281.

Jacobwitz D. M. & Goldberg A. M. (1977) Determination of acetylcholine in discrete regions of the rat brain. *Brain Res.* 122, 575-577.

Jacquet Y. S., Carol M. & Russell I. S. (1976) Morphine-induced rotation in naive, nonlesioned rats. *Science*, N. Y. 192, 261-263.

James T. A. & Collingridge G. L. (1979) Rapid behavioural and biochemical effects of tetanus toxin microinjected into the substantia nigra: a dual role for GABA? *Neuroscience Letters* 11, 205-208.

James T. A. & Massey S. (1978) Evidence for a possible dopaminergic link in the action of acetylcholine in the rat substantia nigra. *Neuropharmacology* 17, 687-690.

James T. A. & Starr M. S. (1977) Behavioural and biochemical effects of substantia nigra of the rat. *J. Pharm. Pharmac.* 29, 181-182.

- James T. A & Starr M. S. (1978) The role of GABA in the substantia nigra. *Nature*, Lond. 275, 229-230.
- James T. A. & Starr M. S. (1979) Effects of substance P injected into the substantia nigra. *Br. J. Pharmac.* 65, 423-429.
- Javaid J. I., Perel J. M. & Davis J. M. (1979) Inhibition of biogenic amines uptake by imipramine, desipramine, 2 OH-imipramine and 2 OH-desipramine in rat brain. *Life Sci.* 24, 21-28.
- Jenner P., Marsden C. D., Pycock C. & Reavill, C. (1977) Lack of serotonergic involvement in turning behaviour induced by a unilateral lesion of the locus coeruleus in rats. *Br. J. Pharmac.* 61, 482P.
- Jerussi T. P. & Glick S. D. (1974) Amphetamine-induced rotation in rats without lesions. *Neuropharmacology* 13, 283-286.
- Jerussi T. P. & Glick S. D. (1976) Drug-induced rotation in rats without lesions: behavioral and neurochemical indices of a normal asymmetry in nigro-striatal function. *Psychopharmacology*, Berl. 47, 249-260.
- Jessell T. M., Emson P. C., Paxinos G. & Cuello A. C. (1978) Topographic projections of substance P and GABA pathways in the striato- and pallido-nigral system: a biochemical and immunohistochemical study. *Brain Res.* 152, 487-498.
- Johnson G. A. & Kim E. G. (1973) Increase of brain levels of tryptophan induced by inhibition of dopamine β -hydroxylase. *J. Neurochem.* 20, 1761-1764.
- Johnston G. A. R., Curtis D. R., De Groat W. C. & Duggan A. W. (1968) Central actions of ibotenic acid and muscimol. *Biochem. Pharmac.* 17, 2488-2489.
- Juraska J. M., Wilson C. J. & Groves P. M. (1977) The substantia nigra of the rat: a Golgi study. *J. comp. Neurol.* 172, 585-600.
- Kaada B. R., Jansen Jr. J. & Andersen P. (1953) Stimulation of the hippocampus and medial cortical areas in unanesthetized cats. *Neurology* 3, 844-857.
- Kanazawa I., Emson P. C. & Cuello A. C. (1977) Evidence for the existence of substance P-containing fibres in striato-nigral and pallido-nigral pathways in rat brain. *Brain Res.* 119, 447-453.
- Kanazawa I. & Jessell T. M. (1976) Post mortem changes and regional distribution of substance P in rat and mouse nervous system. *Brain Res.* 117, 362-367.
- Kanazawa I., Marshall G. R. & Kelly J. S. (1976) Afferents to the rat substantia nigra studied with horseradish peroxidase with special reference to fibres from the subthalamic nucleus. *Brain Res.* 115, 485

-491.

Karobath M. E. (1975) Tricyclic antidepressive drugs and dopamine-sensitive adenylate cyclase from rat brain striatum. *Eur. J. Pharmac.* 30, 159-163.

Kebabian J. W. & Calne D. M. (1979) Multiple receptors for dopamine. *Nature, Lond.* 277, 93-96.

Kebabian J. W. & Saavedra J. M. (1976) Dopamine-sensitive adenylate cyclase occurs in a region of substantia nigra containing dopaminergic dendrites. *Science, N. Y.* 193, 683-685.

Kelly P. H. (1975) Unilateral 6-hydroxydopamine lesions of nigrostriatal or mesolimbic dopamine-containing terminals and the drug-induced rotation of rats. *Brain Res.* 100, 163-169.

Kelly P. H. & Miller R. J. (1975) The interaction of neuroleptic and muscarinic agents with central dopaminergic systems. *Br. J. Pharmac.* 54, 115-121.

Kelly P. H. & Moore K. E. (1976) Mesolimbic dopaminergic neurones in the rotational model of nigrostriatal function. *Nature, Lond.* 263, 695-696.

Kelly P. H. & Moore K. E. (1977) Mesolimbic dopamine neurons: effects of 6-hydroxydopamine-induced destruction and receptor blockade on drug-induced rotation of rats. *Psychopharmacology, Berl.* 55, 35-41.

Kelly P. H. & Moore K. E. (1978) Dopamine concentrations in the rat brain following injections into the substantia nigra of baclofen, γ -aminobutyric acid, γ -hydroxybutyric acid, apomorphine and amphetamine. *Neuropharmacology* 17, 169-174.

Kilpatrick I. C. & Starr M. S. (1981) Involvement of dopamine in circling responses to muscimol depends on intranigral site of injection. *Eur. J. Pharmac.* 69, 407-419.

Kilpatrick I. C., Starr M. S., Fletcher A., James T. A. & MacLeod N. K. (1980) Evidence for a GABAergic nigrothalamic pathway in the rat. I. Behavioural and biochemical studies. *Expl Brain Res.* 40, 45-54.

Kitai S. T., Wagner A., Precht W. & Ohno T. (1975) Nigro-caudate and caudato-nigral relationship: an electrophysiological study. *Brain Res.* 85, 44-48.

Kitai S. T., Kocsis J. D., Preston R. J. & Sugimori M. (1976a) Mono-synaptic inputs to caudate neurons identified by intracellular injection of horseradish peroxidase. *Brain Res.* 109, 601-606.

Kitai S. T., Sugimori M. & Kocsis J. D. (1976b) Excitatory nature of dopamine in the nigro-caudate pathway. *Expl Brain Res.* 24, 351-363.

- Kizer J. S., Palkovits M. & Brownstein M. J. (1976) The projections of the A8, A9 and A10 dopaminergic cell bodies: evidence for a nigral-hypothalamic-median eminence dopaminergic pathway. *Brain Res.* 108, 363-370.
- Kocsis J. D. & Kitai S. T. (1977) Dual excitatory inputs to caudate spiny neurons from substantia nigra stimulation. *Brain Res.* 138, 271-283.
- Kökler C., Schwarcz R. & Fuxe K. (1979) Hippocampal lesions indicate differences between the excitotoxic properties of acidic amino acids. *Brain Res.* 175, 366-371.
- Koob G., Del Fiacco M. & Iversen S. D. (1976) The behavioural effects of EOS-induced changes in substantia nigra GABA levels. *Br. J. Pharmac.* 58, 454P.
- Korf J., Grasdijk L. & Westerink B. H. C. (1976a) Effects of electrical stimulation of the nigrostriatal pathway of the rat on dopamine metabolism. *J. Neurochem.* 26, 579-584.
- Korf J., Zielesman M. & Westerink B. H. C. (1976b) Dopamine release in substantia nigra? *Nature, Lond.* 260, 257-258.
- Korf J., Zielesman M. & Westerink B. H. C. (1977) Metabolism of dopamine in the substantia nigra after antidromic activation. *Brain Res.* 120, 184-187.
- Kostowski W., Jerlicz, M., Bidzinski A. & Hauptmann M. (1977) Behavioral effects of neuroleptics, apomorphine and amphetamine after bilateral lesion of the locus coeruleus in rats. *Pharmac. Biochem. Behav.* 7, 289-293.
- Kozlowski M. R. & Marshall J. F. (1980) Rotation induced by intranigral injections of GABA agonists and antagonists: zone-specific effects. *Pharmac. Biochem. Behav.* 13, 561-567.
- Kuhar M. J., Pert C. B. & Snyder, S. H. (1973) Regional distribution of opiate receptor binding in monkey and human brain. *Nature, Lond.* 245, 447-450.
- Langer S. Z. (1974) Presynaptic regulation of catecholamine release. *Biochem. Pharmac.* 23, 1793-1800.
- Langer S. Z. (1977) Presynaptic receptors and their role in the regulation of transmitter release. *Br. J. Pharmac.* 60, 481-497.
- Laursen A. M. (1962) Movements evoked from the region of the caudate nucleus in cats. *Acta physiol. scand.* 54, 175-184.
- Lee L. A., Crossman A. R. & Slater P. (1980) The neurological basis of striatally induced head-turning in the rat: the effects of lesions in putative output pathways. *Neuroscience* 5, 73-79.

- Lehmann J., Fibiger H. C. & Butcher L. L. (1979) The localization of acetylcholinesterase in the corpus striatum and substantia nigra of the rat following kainic acid lesion of the corpus striatum: a biochemical and histochemical study. *Neuroscience* 4, 217-225.
- Leysen J. E., Niemegeers C. J. E., Tollenaere J. P. & Laduron P. M. (1978) Serotonergic component of neuroleptic receptors. *Nature*, Lond. 272, 168-171.
- Lindvall O. & Björklund A. (1974) The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta physiol. scand. Suppl* 412, 1-48.
- Lindvall O. & Björklund A. (1979) Dopaminergic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. *Brain Res.* 172, 169-173.
- Ljungdahl Å., Hökfelt T., Goldstein M. & Park D. (1975) Retrograde peroxidase tracing of neurons combined with transmitter histochemistry. *Brain Res.* 84, 313-319.
- Ljungdahl Å., Hökfelt T., Nilsson G. & Goldstein M. (1978) Distribution of substance P-like immunoreactivity in the central nervous system of the rat - II. Light microscopic localization in relation to catecholamine-containing neurons. *Neuroscience* 3, 945-976.
- Loh H. H., Brase D. A., Sampath-Khanna S., Mar J. B. & Way E. L. (1976) β -endorphin in vitro inhibition of striatal dopamine release. *Nature*, Lond. 264, 567-568.
- Lorens S. A. & Gulberg H. C. (1974) Regional 5-hydroxytryptamine following selective midbrain raphe lesions in the rat. *Brain Res.* 78, 45-56.
- Luscombe G., Clow A., Jenner P. & Marsden C. D. (1975) Antagonism by propranolol of central dopamine receptor stimulation is not related to β -adrenergic blockade. *J. Pharm. Pharmac.* 31, 355-356.
- MacDonald J. F. & Nistri A. (1978) A comparison of the action of glutamate, ibotenate and other related amino acids on feline spinal interneurons. *J. Physiol. Lond.* 275, 449-465.
- MacLean P. D. (1955) The limbic system ("visceral brain") and emotion behavior. *Archs Neurol. Psychiat.*, Chicago 73, 130-134.
- MacLean P. D. (1957) Chemical and electrical stimulation of hippocampus in unrestrained animals. *Archs Neurol. Psychiat.*, Chicago 78, 128-142.
- MacLeod N. K., James T. A., Kilpatrick I. C. & Starr M. S. (1980) Evidence for a GABAergic nigrothalamic pathway in the rat. *Expl Brain Res.* 40, 55-61.

- Marshall J. F. & Ungerstedt U. (1977a) Supersensitivity to apomorphine following destruction of the ascending dopamine neurons: quantification using the rotational model. *Eur. J. Pharmac.* 41, 361-367.
- Marshall J. F. & Ungerstedt U. (1977b) Striatal efferents fibers play a role in maintaining rotational behavior in the rat. *Science*, N. Y. 198, 62-64.
- Martin G. E. & Haubrich D. R. (1978) Striatal dopamine release and contraversive rotation elicited by intranigrally applied muscimol. *Nature*, Lond. 275, 230-231.
- Martin G. E., Papp N. L. & Bacino C. B. (1978) Contralateral turning evoked by the intranigral microinjection of muscimol and other GABA agonists. *Brain Res.* 155, 297-312.
- Matsuda Y. & Jinnai K. (1980) Afferent inputs to caudate output neurons as monitored by antidromic spike invasion of the cell soma. *Brain Res.* 188, 560-565.
- McCarthy P. S., Walker R. J. & Woodruff G. N. (1977) On the depressant action of dopamine in rat caudate nucleus and nucleus accumbens. *Br. J. Pharmacol.* 59, 469P.
- McDevitt J. T. & Setler P. E. (1980) Production of contralateral rotation by injection of dopamine into the pars reticulata of the substantia nigra. *Soc. Neurosci. Abstr.* 6, 722.
- McGeer P. L., McGeer E. G., Fibiger H. C. & Wickson V. (1971) Neostriatal choline acetylase and cholinesterase following selective brain lesions. *Brain Res.* 35, 308-314.
- McGeer P. L., McGeer E. G. & Innanen V. T. (1979) Dendro axonic transmission. I. Evidence from receptor binding of dopaminergic and cholinergic agents. *Brain Res.* 169, 433-441.
- McKenzie G. M., Gordon R. J. & Viik K. (1972) Some biochemical and behavioral correlates of a possible animal model of human hyperkinetic syndromes. *Brain Res.* 47, 439-456.
- McLennan H., Emmons P. R. & Plummer P. M. (1964) Some behavioral effects of stimulation of the caudate nucleus in unrestrained cats. *Can. J. Physiol. Pharmacol.* 42, 329-339.
- McLennan H. & York D. H. (1966) Cholinergic mechanisms in the caudate nucleus. *J. Physiol.*, Lond. 187, 163-175.
- McLennan H. & York D. H. (1967) The action of dopamine on neurones of the caudate nucleus. *J. Physiol*, Lond. 189, 393-402.
- Mettler F. A., Ades H. W., Lipman E. & Culler, E. A. (1939) The extrapyramidal system. An experimental demonstration of function. *Archs Neurol. Psychiat.*, Chicago 41, 984-995.

- Michelot R., Leviel V., Giorguieff-Chesselet M. F., Chéramy A. & Glowinski J. (1979) Effects of the unilateral nigral modulation of substance P transmission on the activity of the two nigro-striatal dopaminergic pathways. *Life Sci.* 24, 715-724.
- Miliaressis E. & Rompré P.-P. (1980) Self-stimulation and circling: differentiation of the neural substrata by behavioral measurement with the use of the double pulse technique. *Physiol. Behav.* 25, 939-943.
- Milson J. A. & Pycock C. J. (1976) Effects of drugs acting on cerebral 5-hydroxytryptamine mechanisms on dopamine-dependent turning behaviour in mice. *Br. J. Pharmac.* 56, 77-85.
- Montanelli R. P. & Hassler R. (1964) Motor effects elicited by stimulation of the pallido-thalamic system in the cat. In Lectures on the diencephalon (eds Bargmann W. & Shadé J. P.), pp. 56-66. Elsevier, Amsterdam.
- Moore R. Y., Halaris A. E. & Jones B. E. (1978) Serotonin neurons of the midbrain raphe: ascending projections. *J. comp. Neurol.* 180, 417-438.
- Moore R. Y. & Bloom F. E. (1978) Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. *A. Rev. Neurosci.* 1, 129-169.
- Motamedi F. & York D. H. (1980) Effects of a nigral descending pathway on cervical spinal cord afferent fibers and interneurons. *Expl Neurol.* 68, 258-268.
- Mroz E. A., Brownstein M. J. & Leeman S. E. (1977) Evidence for substance P in the striato-nigral tract. *Brain Res.* 125, 305-311.
- Murrin L. C. & Roth H. R. (1976) Dopaminergic neurons: Effects of electrical stimulation on dopamine biosynthesis. *Molec. Pharmac.* 12, 463-475.
- Mussen A. T. (1934) Cerebellum and red nucleus. *Archs Neurol. Psychiat.*, Chicago 31, 110-126.
- Nagy J. I., Carter D. A. & Fibiger H. C. (1978) Anterior striatal projections to the globus pallidus, entopeduncular nucleus and substantia nigra in the rat: the GABA connection. *Brain Res.* 158, 15-29.
- Nagy J. I. & Fibiger H. C. (1980) A striatal source of glutamic acid decarboxylase activity in the substantia nigra. *Brain Res.* 187, 237-242.
- Nauta W. J. H., Smith G. P., Faull R. L. M. & Domesick V. B. (1978) Efferent connections and nigral afferents to the nucleus accumbens septi in the rat. *Neuroscience* 3, 385-401.

- Nicolaou N. M., Garcia-Munoz M., Arbuthnott G. W. & Eccleston D. (1979) Interaction between serotonergic and dopaminergic systems in rat brain demonstrated by small unilateral lesions of the raphe nuclei. *Eur. J. Pharmac.* 57, 295-305.
- Nieoullon A., Cheramy A. & Glowinski J. (1977a) An adaptation of the push-pull cannula method to study the in vivo release of [^3H] dopamine synthesized from [^3H] tyrosine in the cat caudate nucleus: effects of various physical and pharmacological treatments. *J. Neurochem.* 28, 819-828.
- Nieoullon A., Cheramy A. & Glowinski J. (1977b) Release of dopamine in vivo from cat substantia nigra. *Nature* 266, 375-377.
- Nieoullon A., Cheramy A. & Glowinski J. (1977c) Interdependence of the nigrostriatal dopaminergic systems on the two sides of the brain in the cat. *Science*, N. Y. 198, 416-418.
- Norcross K. & Spehlmann R. (1977) Selective blockade of excitatory caudate responses to nigral stimulation by microinjection of dopamine antagonists. *Neuroscience Letters* 6, 323-328.
- Nyback H. (1971) Regional disappearance of catecholamines formed from ^{14}C -tyrosine in rat brain: effect of synthesis inhibitors and of chlorpromazine. *Acta Pharmac. Toxicol.* 30, 372-384.
- Oberlander C., Dumont C. & Boissier J. R. (1977) Rotational behaviour after unilateral intranigral injection of muscimol in rats. *Eur. J. Pharmac.* 43, 389-390.
- Oberlander C., Dumont C. & Boissier J. R. (1980) Time course of apomorphine-induced circling behaviour after striatal dopamine receptor denervation. *Eur. J. Pharmac.* 62, 107-110.
- Oke A., Keller R., Mefford I. & Adams R. N. (1978) Lateralization of norepinephrine in human thalamus. *Science*, N. Y. 200, 1411-1413.
- Oke A., Lewis R. & Adams R. N. (1980) Hemispheric asymmetry of norepinephrine distribution in rat thalamus. *Brain Res.* 188, 269-272.
- Olianas M. C., De Montis M., Concu A., Tagliamonte A. & DiChiara G. (1978a) Intranigral kainic acid: evidence for nigral non-dopaminergic neurons controlling posture and behavior in a manner opposite to the dopaminergic ones. *Eur. J. Pharmac.* 49, 223-232.
- Olianas M. C., De Montis G. M., Mulas G. & Tagliamonte A. (1978b) The striatal dopaminergic function is mediated by the inhibition of a nigral, non-dopaminergic neuronal system via a strio-nigral gabaergic pathway. *Eur. J. Pharmac.* 49, 233-241.
- Olpe H.-R. & Koella W. P. (1977a) The release of striatal cells upon stimulation of the dorsal and median raphe nuclei. *Brain Res.* 122, 357-360.

Olpe H.-R. & Koella W. P. (1977b) Rotatory behavior in rats by intranigral application of substance P and an eledoisin fragment. *Brain Res.* 126, 576-579.

Olpe H.-R. & Koella W. P. (1978) The effect of some neuroleptics on the interaction of cortically and nigraly evoked potentials in the rat striatum. *Naunyn-Schmiedeberg's Arch. Pharmac.* 303, 165-170.

Olpe H.-R., Schellenberg H. & Koella W. P. (1977) Rotational behavior induced in rats by intranigral application of GABA-related drugs and gaba antagonists. *Eur. J. Pharmac.* 45, 291-294.

Palacios J. M. & Kuhar M. J. (1980) Beta-adrenergic receptor localization by light microscopic autoradiography. *Science*, N. Y. 208, 1378-1380.

Palmer G. C., Wagner H. R., Palmer S. J. & Manian A. A. (1977) Histamine-stimulated adenylate cyclase: blockade by imipramine and its analogues. *Comm. Psychopharmac.* 1, 61-69.

Papadopoulos G., Nef B. & Huston J. P. (1980) Behavioral effects of kainic acid injection into substantia nigra after ablation of the telencephalon. *Behav. Brain Res.* 1, 331-337.

Papadopoulos G. & Huston J. P. (1980) Removal of the telencephalon spares turning induced by injection of GABA agonists and antagonists into the substantia nigra. *Behav. Brain Res.* 1, 25-38.

Papeschi R., Theiss P. & Herz A. (1975) Effects of morphine on the turnover of brain catecholamines and serotonin in rats - acute morphine administration. *Eur. J. Pharmac.* 34, 253-261.

Parizek J., Hassler R. & Bak I. J. (1971) Light and electron microscopic autoradiography of substantia nigra of rat after intraventricular administration of tritium labelled norepinephrine, dopamine, serotonin and the precursors. *Z. Zellforsch.* 115, 137-148.

Park M. R., Lighthall J. W. & Kitai S. T. (1980) Recurrent inhibition in the rat neostriatum. *Brain Res.* 194, 359-369.

Pasquier D. A., Kemper T. L., Forbes W. B. & Morgane P. J. (1977) Dorsal raphe, substantia nigra and locus coeruleus: interconnections with each other and the neostriatum. *Brain Res. Bulletin* 2, 323-339.

Pellegrino L. J. & Cushman A. J. (1967) A Stereotaxic Atlas of the Rat Brain, Appleton-Century-Crofts, New York.

Perkins M. N. & Stone T. W. (1980) Subthalamic projections to the globus pallidus: an electrophysiological study in the rat. *Expl Neurol.* 68, 500-511.

Peroutka S. J., U'Prichard D. C., Greenberg D. A. & Snyder S. H. (1977) Neuroleptic drug interactions with norepinephrine alpha receptor binding sites in rat brain. *Neuropharmacology* 16, 549-556.

- Pert C. B., Kuhar M. J. & Snyder S. H. (1976) Opiate receptor: autoradiographic localization in rat brain. *Proc. Natn. Acad. Sci.* 73, 3729-3733.
- Phillipson O. T., Emson P. C., Horn A. S. & Jessell T. (1977) Evidence concerning the anatomical location of the dopamine stimulated adenylate cyclase in the substantia nigra. *Brain Res.* 136, 45-58.
- Phillipson O. T. & Horn A. S. (1976) Substantia nigra of the rat contains a dopamine sensitive adenylate cyclase. *Nature, Lond.* 261, 418-420.
- Pieri M., Pieri L., Saner A., Da Prada M. & Haefely W. (1975) A comparison of drug-induced rotation in rats lesioned in the medial fore-brain bundle with 5,6-dihydroxytryptamine or 6-hydroxydopamine. *Arch. int. Pharmacodyn.* 217, 118-130.
- Pinnock R. D., Turnbull M. J. & Woodruff G. N. (1979) Effects of peptides on neurons in the substantia nigra and nucleus accumbens. *Br. J. Pharmac.* 67, 429P-430P.
- Porceddu M. L., Morelli M., Del Fiacco M. & DiChiara G. (1980) Origin of GABA-ergic strio-nigral neurons as studied by kainate-induced lesions. *Pharmac. Res. Comm.* 12, 695-698.
- Powell E. W. & Leman R. B. (1976) Connections of the nucleus accumbens. *Brain Res.* 105, 389-403.
- Preston R. J., Bishop G. A. & Kitai S. T. (1980) Medium spiny neuron projection from the rat striatum: an intracellular horseradish peroxidase study. *Brain Res.* 183, 253-263.
- Pycock C. J., Donaldson, I. MacG. & Marsden C. D. (1975a) Circling behaviour produced by unilateral lesions in the region of the locus coeruleus in rats. *Brain Res.* 97, 317-329.
- Pycock C. J., Jenner, P. G. & Marsden C. D. (1977) The interaction of clonidine with dopamine-dependent behaviour in rodents. *Naunyn-Schmiedeberg's Arch. Pharmac.* 297, 133-141.
- Pycock C. J. & Marsden C. D. (1978) The rotating rodent: a two component system? *Eur. J. Pharmac.* 47, 167-175.
- Pycock C., Milson J., Tarsy D. & Marsden C. D. (1978) The effect of manipulation of cholinergic mechanisms on turning behaviour in mice with unilateral destruction of the nigro-neostriatal dopaminergic system. *Neuropharmacology* 17, 175-183.
- Pycock C., Tarsy D. & Marsden C. D. (1975b) Inhibition of circling behavior by neuroleptic drugs in mice with unilateral 6-hydroxydopamine lesions of the striatum. *Psychopharmacologia, Berl.* 45, 211-219.
- Pycock C., Milson J. A., Tarsy D. & Marsden C. D. (1976) The effects of blocking catecholamine uptake on amphetamine-induced circling beha-

viour in mice with unilateral destruction of striatal dopaminergic nerve terminals. *J. Pharm. Pharmac.* 28, 530-532.

Racagni G., Bruno F., Cattabeni F., Maggi A., DiGiulio A. M., Parenti M. & Groppetti A. (1977) Functional interaction between rat substantia nigra and striatum: GABA and dopamine interrelation. *Brain Res.* 134, 353-358.

Randrup A. & Scheel-Krüger J. (1966) Diethyldithiocarbamate and amphetamine stereotype behaviour. *J. Pharm. Pharmac.* 18, 752.

Ranje C. & Ungerstedt U. (1977) High correlations between number of dopamine cells, dopamine levels and motor performance. *Brain Res.* 134, 83-93.

Reavill C., Jenner P., Leigh N. & Marsden C. D. (1979) Turning behaviour induced by injection of muscimol or picrotoxin into the substantia nigra demonstrates dual GABA components. *Neuroscience Letters* 12, 323-328.

Reavill C., Jenner P., Leigh N. & Marsden C. D. (1981) The role of nigral projections to the thalamus in drug-induced circling behaviour in the rat. *Life Sci.* 28, 1457-1466.

Reis D. J., Gilad G., Pickel V. M. & Joh T. H. (1978) Reversible changes in the activities and amounts of tyrosine hydroxylase in dopamine neurons of the substantia nigra in response to axonal injury as studied by immunochemical and immunocytochemical methods. *Brain Res.* 144, 325-342.

Reubi J.-C. & Emson P. C. (1978) Release and distribution of endogenous 5-HT in rat substantia nigra. *Brain Res.* 139, 164-168.

Reubi J.-C., Iversen L. L. & Jessell T. M. (1977) Dopamine selectively increases ^3H -GABA release from slices of rat substantia nigra in vitro. *Nature* 268, 652-654.

Richardson T. L., Miller J. J. & McLennan H. (1977) Mechanisms of excitation and inhibition in the nigrostriatal system. *Brain Res.* 127, 219-234.

Rinvik E. (1966) The cortico-nigral projection in the cat - an experimental study with silver impregnation methods. *J. comp. Neurol.* 126, 241-254.

Rinvik E. & Walberg F. (1969) Is there a cortico-nigral tract? A comment based on experimental electron microscopic observations in the cat. *Brain Res.* 14, 742-744.

Roffman M., Bernard P. S., Dawson K. M., Sobiski R. E. & Saelen J. K. (1978). The effects of haloperidol and clozapine on circling induced by electrical stimulation of the substantia nigra and the ventromedial tegmentum. *Neuropharmacology* 17, 943-946.

- Roth R. H., Murrin L. C. & Walters J. R. (1976) Central dopaminergic neurons: effects of alterations in impulse flow on the accumulation of dihydroxyphenylacetic acid. *Eur. J. Pharmac.* 36, 163-171.
- Rowlands G. J. & Roberts P. J. (1980) Activation of dopamine receptors inhibits calcium-dependent glutamate release from cortico-striatal terminals in vitro. *Eur. J. Pharmac.* 62, 241-242.
- Ruffieux A. & Schultz W. (1980) Dopaminergic activation of reticular neurons in the substantia nigra. *Nature, Lond.* 285, 240-241.
- Sakai K., Touret M., Salvert D., Leger L. & Jouvet M. (1977) Afferent projections to the cat locus coeruleus as visualized by the horse-radish peroxidase technique. *Brain Res.* 119, 21-41.
- Satoh H., Satoh Y., Notsu Y. & Honda F. (1976) Adenosine 3',5'-cyclic monophosphate as a possible mediator of rotational behaviour induced by dopaminergic receptor stimulation in rats lesioned unilaterally in the substantia nigra. *Eur. J. Pharmac.* 39, 365-377.
- Scatton B., Simon H., Le Moal M. & Bischoff S. (1980) Origin of dopaminergic innervation of the rat hippocampal formation. *Neuroscience Letters* 18, 125-131.
- Scheel-Krüger J., Arnt J. & Magelund G. (1977) Behavioural stimulation induced by muscimol and other GABA agonists injected into the substantia nigra. *Neuroscience Letters* 4, 351-356.
- Schoenfeld T. A. & Hamilton, L. W. (1977) Secondary brain changes following lesions: a new paradigm for lesion experimentation. *Physiol. Behav.* 18, 951-967.
- Schwarcz R., Creese I., Coyle J. T. & Snyder, S. H. (1978) Dopamine receptors localised on cerebral cortical afferents to rat corpus striatum. *Nature, Lond.* 271, 766-768.
- Schwarcz R., Hökfelt T., Fuxe K., Jonsson G., Goldstein M. & Tereinius L. (1979) Ibotenic acid-induced neuronal degeneration: a morphological and neurochemical study. *Expl Brain Res.* 37, 199-216.
- Seeman P., Staiman A. & Chau-Wong, M. (1974) The nerve impulse-blocking actions of tranquilizers and the binding of neuroleptics to synaptosome membranes. *J. Pharmac. exp. Ther.* 190, 123-130.
- Setler P. E., Malesky M., McDevitt J. & Turner K. (1978) Rotation produced by administration of dopamine and related substances directly into the supersensitive caudate nucleus. *Life Sci.* 23, 1277-1284.
- Setler P., Sarau H. & McKenzie G. (1976) Differential attenuation of some effects of haloperidol in rats given scopolamine. *Eur. J. Pharmac.* 39, 117-126.
- Simon H. & Le Moal M. (1977) Demonstration by the Fink-Heimer impregnating method of a ventral mesencephalic-locus coeruleus projection in

the rat. *Experientia* 33, 614-616.

Simon H., Le Moal M., Stinus L. & Calas A. (1979) Anatomical relationships between the ventral mesencephalic tegmentum-A10 region and the locus coeruleus as demonstrated by anterograde and retrograde tracing techniques. *J. Neural Transm.* 44, 77-86.

Skultety F. M. (1962) Circus movements in cats following midbrain stimulation through chronically implanted electrodes. *J. Neurophysiol.* 25, 152-164.

Slater P., Blundell C. & Crossman A. R. (1980) The effects of narcotic analgesics on the turning behaviour of rats with 6-hydroxydopamine-induced unilateral nigrostriatal lesions. *Neuropharmacology* 19, 187-193.

Slater P., Lee L. A., Longman D. A. & Crossman A. R. (1980) An in vivo method for testing putative GABA-like compounds. *J. Pharmac. Methods* 3, 39-49.

Slater P. & Blundell C. (1979) Effects of morphine on amphetamine-induced circling and striatal cyclic AMP in rats and mice. *Neuropharmacology* 18, 705-708.

Sotelo C., Javoy F., Agid Y. & Glowinski J. (1973) Injection of 6-hydroxydopamine in the substantia nigra of the rat. I. Morphological study. *Brain Research* 58, 269-290.

Spano P. F., DiChiara G., Tanon G. C. & Trabucchi M. (1976) A dopamine-stimulated adenylate cyclase in rat substantia nigra. *J. Neurochem.* 27, 1565-1568.

Spano P. F., Trabucchi M. & DiChiara G. (1977) Localization of nigral dopamine-sensitive adenylate cyclase on neurons originating from the corpus striatum. *Science* 196, 1343-1345.

Spector S. (1966) Inhibitors of endogenous catecholamine biosynthesis. *Pharmac. Rev.* 18, 599-609.

Staines Wm. A., Nagy J. I., Vincent S. R. & Fibiger H. C. (1980) Neurotransmitters contained in the efferents of the striatum. *Brain Res.* 194, 391-402.

Starke K., Reimann W., Zumstein A. & Hertting G. (1978) Effect of dopamine receptor agonists and antagonists on release of dopamine in the rabbit caudate nucleus in vitro. *Naunyn-Schmiedeberg's Arch. Pharmac.* 305, 27-36.

Starr M. S. & Kilpatrick I. C. (1981) Nigral-derived muscimol circling - ipsiversive, contraversive or controversial? *Nature, Lond.* 290, 610.

Stawarz R. J., Hill H., Robinson S. E., Setler P., Dingell J. V. & Sulser F. (1975) On the significance of the increase in homovanillic

acid (HVA) caused by antipsychotic drugs in corpus striatum and limbic forebrain. *Psychopharmacologia*, Berl. 43, 125-130.

Stern W. C., Johnson A., Bronzino J. D. & Morgane P. J. (1979) Influence of electrical stimulation of the substantia nigra on spontaneous activity of raphe neurons in the anesthetized rat. *Brain Res. Bulletin* 4, 561-565.

Stevens J. R., Kim C. & MacLean P. D. (1961) Stimulation of caudate nucleus: behavioral effects of chemical and electrical excitation. *Arch. Neurol.* 4, 47-54.

Straughan D. W. & James T. A. (1978) Microphysiological and pharmacological studies on transmitters in the substantia nigra. In Advances in Pharmacology and Therapeutics (ed. Simon P.), Vol. 2, pp. 87-96. Pergamon Press, Oxford.

Streit P., Knecht E. & Cuenod M. (1979) Transmitter-specific retrograde labeling in the striato-nigral and raphe-nigral pathways. *Science*, N. Y. 205, 306-308.

Swanson L. W. & Cowan W. M. (1975) A note on the connections and development of the nucleus accumbens. *Brain Res.* 92, 324-330.

Tanner T. (1978) Circling behaviour in the rat following unilateral injections of p-chlorophenylalanine and ethanolamine-O-sulfate into the substantia nigra. *J. Pharm. Pharmac.* 30, 158-161.

Tarsy D., Pycock C., Meldrum B. & Marsden C. D. (1975) Rotational behavior induced in rats by intranigral picrotoxin. *Brain Res.* 89, 160-165.

Tassin J. P., Cheramy A., Blanc G., Thierry A. M. & Glowinski J. (1976) Topographical distribution of dopaminergic innervation and of dopaminergic receptors in the rat striatum. I. Microestimation of [³H] dopamine uptake and dopamine content in microdiscs. *Brain Res.* 107, 291-301.

Traficante L. J., Friedman E., Oleshansky M. A. & Gershon S. (1976) Dopamine-sensitive adenylate cyclase and cAMP phosphodiesterase in substantia nigra and corpus striatum of rat brain. *Life Sci.* 19, 1061-1066.

Tulloch I. F., Arbuthnott G. W. & Wright A. K. (1978) Topographical organization of the striatonigral pathway revealed by anterograde and retrograde neuroanatomical tracing techniques. *J. Anat.* 127, 425-441.

Ueki A., Uno M., Anderson M. & Yoshida M. (1977) Monosynaptic inhibition of thalamic neurons produced by stimulation of the substantia nigra. *Experientia* 33, 1480-1482.

Ungerstedt U. (1971a) Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta physiol. scand.* 82, Suppl. 367, 1-48.

Ungerstedt U. (1971b) Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. *Acta physiol. scand.* 82, Suppl. 367, 49-68.

Ungerstedt U. (1971c) Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta physiol. scand.* 82, Suppl. 367, 69-93.

Ungerstedt U., Butcher L. L., Butcher S. G., Andén N.-E. & Fuxe K. (1969) Direct chemical stimulation of dopaminergic mechanisms in the neostriatum of the rat. *Brain Res.* 14, 461-471.

Ungerstedt U. & Arbuthnott G. W. (1970) Quantitative recording of rotational behavior in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. *Brain Res.* 24, 485-493.

Ungerstedt U., Avemo A., Ljungberg T. & Ranje C. (1973) Animals models of parkinsonism. *Adv. Neurol.* 3, 257-271.

Ungerstedt U. & Marshall J. (1975) Nerve degeneration in functional studies: experiments illustrating the problem of lesion specificity and compensatory supersensitivity. In Chemical Tools in Catecholamine Research (eds Jonsson G., Malmfors T. & Sachs Ch.) Vol. 1, pp. 311-318.

Vierck Jr. C. J., Brooks R. H. & Goodman D. C. (1968) Forced movement resulting from midbrain stimulation in the rat. *Brain Behav. Evol.* 1, 519-528.

Von Voigtlander P. F. & Moore K. E. (1971a) Nigro-striatal pathway: stimulation-evoked release of [³H] dopamine from caudate nucleus. *Brain Res.* 35, 580-583.

Von Voigtlander P. F. & Moore K. E. (1971b) The release of H³-dopamine from cat brain following electrical stimulation of the substantia nigra and caudate nucleus. *Neuropharmacology* 10, 733-741.

Von Voigtlander P. F. & Moore K. E. (1973) Involvement of nigro-striatal neurons in the in vivo release of dopamine by amphetamine, amantadine, and tyramine. *J. Pharmac. exp. Ther.* 184, 542-522.

Waddington J. L. (1977a) Specificity of monoamine neurotoxins: rotational responses to dopaminergic agonists after unilateral 6-OHDA and 5,6-DHT lesions of the median forebrain bundle. *Br. J. Pharmac.* 59, 465P-466P.

Waddington J. L. (1977b) Induction of rotational behaviour by intranigral baclofen suggests possible GABA-agonist activity. *Experientia*, Basel 33, 1345-1346.

Waddington J. L. (1978a) Rotational behaviour and striatal dopamine metabolism following unilateral activation of nigral GABA mechanisms: GABA-like modulation of dopaminergic and non-dopaminergic neurons in rat substantia nigra. *Br. J. Pharmac.* 63, 384P.

Waddington J. L. (1978b) Behavioural evidence for GABAergic activity of the benzodiazepine flurazepam. *Eur. J. Pharmac.* 51, 417-422.

Waddington J. L. (1980) GABAergic mechanisms in the substantia nigra. *Nature, Lond.* 283, 696-697.

Waddington J. L. & Cross A. L. (1979) Pharmacology of (+)- and (-)-Baclofen: GABA-dependent rotational behaviour and [³H]GABA receptor binding studies. *Neuroscience Letters.* 14, 123-127.

Waddington J. L. & Crow T. J. (1979) Rotational responses to serotonergic and dopaminergic agonists after unilateral dihydroxytryptamine lesions of the medial forebrain bundle: Co-operative interactions of serotonin and dopamine in neostriatum. *Life Sci.* 25, 1307-1314.

Walker R. J., Kemp J. A., Yajima H., Kitagawa K. & Woodruff G. N. (1976) The action of substance P on mesencephalic reticular and substantia nigra neurones of the rat. *Experientia, Basel* 32, 214-215.

Walker J. R. & Roth R. H. (1974) Dopaminergic neurons: drug-induced antagonism of the increase in tyrosine hydroxylase activity produced by cessation of impulse flow. *J. Pharmac. exp. Ther.* 191, 82-91.

Watanabe H. & Watanabe K. (1979) Enhancement of apomorphine-induced rotational behavior in rats following the combination of 6-hydroxydopamine and electrolytic lesions in the substantia nigra. *Japan. J. Pharmac.* 29, 93-104.

Wheeler H. (1980) Effect of intrapallidal injection of GABA drugs on head-turning induced by electrical stimulation of the striatum in rats - in vivo evidence for different GABA receptors in the CNS? *Br. J. Pharmac.* 70, 150P.

White R. P. & Himwich H. E. (1957) Circus movements and excitation of striatal and mesodiencephalic centers in rabbits. *J. Neurophysiol.* 20, 81-90.

Wilk S. & Stanley M. (1977) Perlapine and dopamine metabolism: prediction of antipsychotic efficacy. *Eur. J. Pharmac.* 41, 65-72.

Wilk S., Watson E. & Stanley M. E. (1975) Differential sensitivity of two dopaminergic structures in rat brain to haloperidol and to clozapine. *J. Pharmac. exp. Ther.* 195, 265-270.

Williams D. J., Crossman A. R. & Slater P. (1977) The efferent projections of the nucleus accumbens in the rat. *Brain Res.* 130, 217-227.

Wilson C. J., Groves P. M. & Fifkova E. (1977) Monoaminergic synapses, including dendro-dendritic synapses in the rat substantia nigra. *Expl Brain Res.* 30, 161-174.

- Winterkorn J. M. S. & Meikle Jr. T. H. (1980) Lesions of the tecto-spinal tract of the cat do not produce compulsive circling. *Brain Res.* 190, 597-600.
- Wolf G. & DiCara L. V. (1969) Progressive morphologic changes in electrolytic lesions. *Expl Neurol.* 23, 529-536.
- Wright A. K. & Arbuthnott G. W. (1980) Non-dopamine containing efferents of substantia nigra: the pathway to the lower brain stem. *J. Neural Transm.* 47, 221-226.
- York D. K. (1970) Possible dopaminergic pathway from substantia nigra to putamen. *Brain Res.* 20, 233-249.
- York D. H. (1973) Motor responses induced by stimulation of the substantia nigra. *Expl Neurol.* 41, 323-330.
- York D. H. (1976) Electrophysiology of the nigro-putamen dopamine pathway. *Pharmac. Ther. B.* 2, 1-7.
- York D. H. & Faber J. E. (1977) An electrophysiological study of nigro-tectal relationships: a possible role in turning behavior. *Brain Res.* 130, 383-386.
- Yoshida M., Rabin A. & Anderson M. (1971) Two types of monosynaptic inhibition of pallidal neurons produced by stimulation of the diencephalon and substantia nigra. *Brain Res.* 30, 235-239.
- Yoshida M., Rabin A. & Anderson M. (1972a) Monosynaptic inhibition of pallidal neurons by axon collaterals of caudato-nigral fibers. *Expl Brain Res.* 15, 333-347.
- Yoshida M., Rabin A. & Anderson M. (1972b) Monosynaptic inhibition of pallidal neurons by axon collaterals of caudato-nigral fibers. *Expl Brain Res.* 15, 333-347.
- Zeman W. & Innes J. R. M. (1963) Mesencephalon (Midbrain). Craigie's Neuroanatomy of the Rat, Chapter VI, pp. 103-114. Academic Press, New York.
- Zimmerberg B. & Glick S. D. (1974) Rotation and stereotypy during electrical stimulation of the caudate nucleus. *Res. Comm. Chem. Pathol. Pharmac.* 8, 195-196.