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HALLUCINOGEN-INDUCED ROTATIONAL BEHAVIOR IN RATS

by

Lloyd N. Fleisher

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

1977

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

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Abstract

HALLUCINOGEN-INDUCED ROTATIONAL BEHAVIOR IN RATS

by

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Following unilateral lesions of the nigrostriatal pathway, animals will turn in circles, or rotate contralateral to the side of the lesion. Rotation is markedly enhanced by apomorphine or d-amphetamine, which are directly- and indirectly-acting dopaminergic agonists, respectively. The direction of rotation is always contralateral to the striatum with higher dopaminergic activity. Apomorphine or d-amphetamine will also induce rotation in normal animals. Apomorphine-induced rotation has been attributed to a postsynaptic asymmetry in dopamine receptor sensitivity; d-amphetamine-induced rotation has been correlated with a presynaptic asymmetry in striatal dopamine content.

LSD reversibly inhibits the firing of serotonergic midbrain raphe neurons, as does mescaline or 5-methoxy-N,N-dimethyl-tryptamine (MDMT). Recently, LSD has been shown to be a partial dopaminergic agonist in various brain regions, particularly in the striatum. It will stimulate (i.e., increase cyclic AMP production) the striatal dopamine-sensitive adenylate cyclase in the absence of dopamine, but block it in the presence of dopamine. LSD has also been shown to induce contralateral rotation in animals with unilateral lesions of the nigrostratal pathway. This thesis examined rotation induced by hallucinogens in normal rats. In

addition, agents which interact with serotonergic and dopaminergic transmission were examined for their capacity to induce rotation and for possible interactions with LSD-induced rotation. LSD, mescaline and MDMT induced dose-dependent rotation which was consistent in direction from week to week. Individual animals were found to rotate in the same direction when administered LSD, mescaline or MDMT, with one week separating the administration of each hallucinogen. The direction of LSD-induced rotation for individual animals was found to be the same as d-amphetamine-induced rotation, but not the same as apomorphine-induced rotation. Of the three postsynaptic serotonin antagonists (methysergide, cyproheptadine and 2-bromo-LSD) tested, only methysergide induced rotation. Methysergide-induced rotation was consistent in direction from week to week, and was in the same direction as LSD when the two drugs were given one week apart. L-LSD, the non-hallucinogenic enantiomer of d-LSD, induced weak rotation at the highest dose tested. It was approximately six times less potent than d-LSD.

LSD-induced rotation was blocked by pretreatment with a tyrosine hydroxylase inhibitor (α-methyl-p-tyrosine), or a sub-cataleptic dose of a dopamine receptor antagonist (haloperidol). Simultaneous administration of LSD and d-amphetamine induced rotation significantly greater than seen with d-amphetamine alone; a similar effect was observed following the simultaneous administration of LSD and scopolamine. However, the simultaneous administration of apomorphine and LSD induced rotation similar in magnitude to apomorphine alone.

P-chlorophenylalanine pretreatment increased the sensitivity of animals to the rotational effects of LSD. L-tryptophan pre-

treatment had no effect on LSD-induced rotation.

The results of this investigation suggested that the mechanism by which these three hallucinogens induced rotation was consistent with an inhibitory action on the serotonin-containing midbrain raphe neurons. The inhibition of raphe neuronal firing would result in disinhibition of nigrostriatal activity (possibly at the level of the substantia nigra). Methysergide-induced rotation was suggested to result from partial antagonism of postsynaptic serotonin receptors in the substantia nigra or striatum. The dopaminergic properties of LSD and the noradrenergic properties of mescaline were proposed to attenuate rotation resulting from disinhibition of nigrostriatal activity by interacting with presynaptic nigrostriatal dopamine auto-receptors (for LSD) or by interacting with a locus coeruleus to frontal cortex to striatum pathway (for mescaline).

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Sorry to group you together, but I'm running out of things to say. I love you all and hope our friendship continues.

To my family and friends (they know who they are) -- when it seemed there was no way out, they helped me realize there was.

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INTRODUCTION

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Perhaps for as long as man has been aware of his perceptual faculties, various plants and extracts have been used to alter them. In recent years, particularly during the "hippie" phenomenon of the 60s and early 70s, there has been increasing use of such drugs to modify states of consciousness.

This class of drugs has been referred to as psychotomimetic, psychedelic, "mind-expanding," hallucinogenic, etc. They produce, even when taken in minute quantities, altered physiologic and psychic states. The physiologic alterations are generally mydriasis, tachycardia, hyperthermia, hyperreflexia, and increased muscle tone. Various somatic complaints include dizziness, weaknexx, paresthesia, nausea, shaking, drowsiness and visual blurring.

However, the most prominent effects are those of a perceptual and psychic nature often described as psychotomimetic or psychedelic. These perceptual alterations involve distortion of shapes and colors, an increased awareness or discrimination of contrast and sounds, and simple to complex hallucinations. There are usually alterations in mood and affect which are intimately tied to subjects and setting. Various schizophrenia-like symptoms may appear such as distored time sense, dream-like feelings, depersonalization and disordered thinking (Brawley & Duffield, 1972; Hoffer; 1965; Isbell, Belleville, Fraser, Wikler & Logan, 1956; Salvatore & Hyde, 1956; Smythies, Benington & Morim, 1970; Wikler, Rosenberg, Hawthorne & Cassidy, 1965; Wolbach, Minei & Isbell, 1962).

The prototypic psychotomimetic agent is the amine alkaloid d-lysergic acid diethylamide (d-LSD or d-LSD-25) originally obtained from the ergot fungus claviceps purpurea and subsequently synthesized by Stoll & Hofmann in 1938 (see Hofmann, 1963). The unusual psychic properties of the drug were adventitiously discovered by Hofmann and described as follows:

> In the afternoon of 16 April 1943, when I was working on this problem, I was seized by a peculiar sensation of vertigo and restlessness. Objects as well as the shape of my associates in the laboratory, appeared to undergo optical changes. I was unable to concentrate on my work. In a dream-like state, I left for home where an irresistable urge to lie down overcame me. I drew the curtains and immediately fell into a peculiar state similar to a drunkeness, characterized by an exaggerated imagination. With my eyes closed, fantastic pictures of extraordinary plasticity and intensive color seemed to surge toward me. After two hours, this state gradually wore off (Goodman & Gilman, 1963).

This type of perceptual or psychic syndrome can be produced by a myriad of natural and synthetic compounds with varying chemical structures ranging from indoleaklyamine to phenylalkylamine derivatives.

The indoleaklyamine or tryptamine derivatives include N,Ń-dimethyltryptamine (DMT), N,Ń-diethyltryptamine (DET), bufotenine (5-hydroxy-N,Ń-dimethyl tryptamine), 5-methoxy-N,Ń-dimethyl tryptamine (MDMT) and psilocin (4-hydroxy-N,Ń-dimethyl tryptamine). Derivatives of phenylethylamine and phenylisopropylamine (amphetamine) include mescaline (3,4,5-trimethoxy phenylethylamine), 2,5-dimethoxy-4-methyphenylisopropylamine (DOM; STP) and 2,5-dimethoxy-4-ethyl-phenylisopropylamine (DOET).

The biochemical and neurochemical properties of LSD have been investigated with peaks and valleys of intensity since the early

1950's, but as of yet no single theory can adequately explain all the effects of the drug. Nonetheless, two major hypotheses have been advanced to explain the action of LSD; the serotonin or 5-hydroxytryptamine (5-HT) hypothesis (Gaddum, 1957; Wooley & Shaw, 1954) and the sensory system hypothesis (Bradley and Hance, 1957; Bradley and Key, 1958; Bradley and Marley, 1965). According to the serotonin hypothesis, the actions of LSD (and possibly many other hallucinogens) result from effects upon the 5-HT-containing brainstem raphe nuclei or their synapses, while the sensory system hypothesis contends that these actions are due to effects upon sensory systems, particularly upon sensory collaterals to the reticular formation of the brainstem and spinal cord. It seems plausible that these two hypotheses are not mutually exclusive and support of one or the other often is a result of predisposition.

Gaddum (1953, 1957) observed that LSD was the most potent of all ergot alkaloids in antagonizing the contractile effects of 5-HT on the isolated rat uterus and perfused rabbit ear, and these results were replicated by Wooley and Shaw (1954). Gaddum proposed that LSD might produce its central effects by interfering with serotonergic transmission within the central nervous system. Later studies by Costa (1956) on rat uterus and Welsh (1957) on clam heart showed that lower doses of LSD mimicked, rather that antagonized the excitatory effects of 5-HT.

Freedman and Giarman (1962), utilizing a clam heart bioassay found relatively low doses of LSD produced small increases in 5-HT levels of whole rat brain, and Freedman (1963; rat) extended this to include d,l-acetyl-LSD (hallucinogenic), psilocybin and mescaline, but not the 5-HT antagonist 2-bromolysergic acid diethylamide

(2-bromo-LSD). Rosencrans, Lovell and Freedman (1967) and Tonge and Leonard (1969) found that along with a rise in 5-HT there was a fall in 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, indicating that LSD slowed the turnover of 5-HT.

How might LSD decrease the turnover of 5-HT? One possibility is that it affects enzymes controlling the metabolism of 5-HT. However, Tonge and Leonard (1969) found LSD had no effects upon the activities of the aromatic amino acid decarboxylase (synthetic enzyme) or monoamine oxidase (MAO; degradative enzyme). Anden, Corrodi, Fuxe and Hokfelt (1968), using acutely spinalized rats, found that LSD (with or without the MAO inhibitor nialamide) mimicked the athetoid movements, hindlimb hyperextension, forelimb tremor and head movements caused by 5-hydroxytryptophan (5-HTP), the immediate precursor of 5-HT. This effect was not blocked by phenoxybenzamine, haloperidol, chlorpromazine, reserpine or α-propyldopacetamide. α-Propyldopacetamide inhibits tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT from dietary L-tryptophan (Jequier, Lovenberg & Sjoerdsma, 1967). Since LSD decreased the rate of disappearance of 5-HT after pretreatment with α-propyldopacetamide, they suggested that LSD was stimulating 5-HT receptors, thus activating an inhibitory feedback mechanism to presynaptic 5-HT neurons, resulting in decreased presynaptic release of 5-HT. It has been established that ^{3}H-5-HT is actively accumulated into synaptosomes (Aghajanian & Bloom, 1967; Marchbanks, Rosenblat & O'Brien, 1964) and brain slices (Schanberg, 1963) and subsequently localized in nerve endings (Ross & Renyi, 1967). Katz and Kopin

(1969), after loading with ^{3}H-5-HT or ^{3}H-norepinephrine, found superfused LSD antagonized the electrically-induced release of either tritiated compound from rat brain slices. However, mescaline, 1-acetyl-LSD and MDMT decreased the release of ^{3}H-5-HT only.

The effects of LSD, 5-HT and related compounds upon individual serotonergic neurons would be particularly informative since the turnover of a transmitter is intimately related to the level of impulse traffic in the neurons releasing it (Carlsson, Kehr & Lindqvist, 1976). A number of studies have indicated an excitatory role for 5-HT on rates of neuronal firing which can be blocked by LSD, but the nature of the neurotransmitter systems innervating these neurons is undetermined. Roberts and Straughan (1967) found iontophoretic LSD or the 5-HT antagonists methysergide, cinanserin or 2-bromo-LSD blocked the extracellularly recorded excitatory effects of iontophoretic 5-HT on single neurons in the post-sigmoid and suprasylvian gyri of the cat cerebral cortex. These cells were far more sensitive to LSD than the 5-HT antagonists. A small proportion of neurons were inhibited by 5-HT and this was not blocked by LSD or the 5-HT antagonists. Boakes, Bradley, Briggs and Dray (1970; cat) obtained similar results monitoring neurons in the bulbar reticular formation. Low intravenous doses of LSD (12 µg/kg) blocked the extracellulary recorded excitatory effects of iontophoretic 5-HT in approximately fifteen minutes. LSD also antagonized 5-HT excitations of neurons induced to fire by iontophoretic L-glutamate. Couch (1970; cat) electrically stimulated the nucleus paragigantocellularis lateralis of the medulla, the terminals of which innervate pontine and mesencephalic raphe neurons

(Taber, 1961; Bloom, Hoffer, Siggins & Barker, 1972). He recorded excitatory and inhibitory responses extracellularly in neurons of the nucleus raphe pontis. These neurons responded to iontophoresed 5-HT in the same manner as to electrical stimulation of the nucleus paragigantocellularis lateralis. In a subsequent study (Couch, 1976; cat), LSD administered either iontophoretically or intravenously (37-150 µg/kg), blocked the excitatory and mimicked the inhibitory effects of iontophoretic 5-HT. A similar relation between excitatory (but not inhibitory) input from the nucleus paragigantocellularis lateralis and microiontophoretic 5-HT has been established by Bloom, Hoffer, Siggins, Barker and Nicoll (1972; rat).

In a comprehensive series of investigations utilizing extracellular recording techniques, Aghajanian and co-workers found that minute intravenous doses of LSD (approximately 10 µg/kg), DMT or 2-bromo-LSD reversibly suppressed the intrinsic firing of midbrain raphe neurons (usual intrinsic firing rates range from .1-10 Hz) although 2-bromo-LSD rarely produced more than a 50% reduction (Aghajanian, Foote & Sheard, 1968, 1970). It was since shown that neurons of the dorsal and/or median raphe are inhibited by iontophoretic LSD (Aghajanian, 1972; Aghajanian, Haigler & Bloom, 1972). Systemically or iontophoretically administered L-tryptophan (Aghajanian, 1972; Gallagher & Aghajanian, 1976), L-5-HTP, (Gallagher & Aghajanian, 1976; Trulson & Jacobs, 1975) or MAO inhibitors (Aghajanian, 1972) (which, when administered systemically, increase brain 5-HT concentrations and the intensity of histofluorescence of raphe neurons) (Aghaganian & Asher, 1971) also depress raphe firing. Gallagher and Aghajanian (1976) found that following

pretreatment with high doses of the aromatic amino acid decarboxylase inhibitor RO-4-4602, dorsal raphe units were no longer depressed by L-tryptophan (administered systemically or iontophoretically) or L-5-HTP (administered systemically). RO-4-4602 did not block inhibition produced by systemic LSD or iontophoretic 5-HT. On the other hand, pretreatment with PCPA had no effect on dorsal raphe inhibition induced by systemic L-tryptophan. Since PCPA blocks 5-HT synthesis in 5-HT terminals far better than in 5-HT perikarya (Aghajanian, Kuhar & Roth, 1973), Gallagher and Aghajanian suggested that an increase in 5-HT in the vicinity of raphe perikarya is sufficient to depress firing. Aghajanian (1972) noted that the sensitivity of raphe units to systemic L-tryptophan is approximately four to five times greater than for L-5-HTP. Raphe cell fluorescence is not appreciably increased by L-5-HTP unless an MAO inhibitor is administered concurrently (Corrodi, Fuxe & Hokfelt,1967; Dahlstrom & Fuxe, 1964).However, with MAO inhibition, there is an abnormal regional distribution of 5-HT with most of the increased fluorescence occuring in endothelial cells throughout the brain (Moir & Eccleston, 1968). In contrast, L-tryptophan selectively increases raphe cell fluorescence (Aghajanian & Asher, 1971). Most of the brain aromatic amino acid decarboxylase (which catalyzes the conversion of L-5-HTP to 5-HT) is located outside the raphe system, whereas tryptophan hydroxylase is located almost exclusively within it (Kuhar, Roth & Aghajanian, 1971). Thus 5-HT synthesized from L-tryptophan would be localized to the raphe system, whereas that synthesized from L-5-HTP would not.

Many of the recent electrophysiological studies have compared the responses of raphe units to those of postsynaptic cells innervated by that particular raphe nucleus. Haigler and Aghajanian (1974; rat) found both dorsal raphe units and postsynaptic cells in the ventral lateral geniculate, cortical and basolateral amygdaloid nuclei, optic tectum and subiculum were equally depressed by iontophoretic 5-HT. However, neither systemic nor iontophoretic LSD (which totally inhibited dorsal raphe units) produced more than a slight depression of firing in postsynaptic cells. Low intravenous doses of LSD (20 µg/kg) produced a slight acceleration of firing in postsynaptic cells which was not related to antagonism of endogenous 5-HT, since directly applied 5-HT still inhibited postsynaptic cells without need to increase the ejection parameters. The above findings together with the failure of a diencephalic-mesencephalic transection to block the inhibition of dorsal raphe units by intravenous LSD (Haigler & Aghajanian, 1974) argue against the neuronal feedback model suggested by Andén et al. (1968). However, feedback inhibition of raphe cells could be mediated by postsynaptic cells in the midbrain.

Haigler and Aghajanian (1974; rat) utilizing a similar experimental paradigm found neither intravenous nor iontophoretic administration of five 5-HT antagonists (cyproheptadine, cinanserin, methysergide, methiothepin or metergoline) could block the inhibition of postsynaptic cells produced by iontophoretic 5-HT. However, 5-HT induced excitatory responses of unidentified neurons in the midbrain reticular formation were blocked by these antagonists. The 5-HT antagonists were inhibitory in their own respect and

increased the inhibitory effects of 5-HT when adminstered together. However, Segal (1975; rat) found that systemic methysergide or cyproheptadine partially antagonized the inhibition of hippocampal pyramidal cells induced by iontophoretic 5-HT or electrical stimulation of the dorsal and median raphe. PCPA could block the response of pyramidal cells to raphe stimulation and parenteral L-5-HTP could restore it. In a recent report, Aghajanian (1976) reported that LSD and 2-bromo-LSD had weak depressant effects on postsynaptic cells in the ventral lateral geniculate and amygdala. However, although 2-bromo-LSD also had weak depressant effects on dorsal raphe units, LSD was highly effective. He suggested that the difference in psychotogenic potency of these two drugs may result from differential effects on the rostral raphe perikarya.

One of the most pronounced psychic effects of LSD is an alteration of perception; thus it is not surprising that much investigation has centered on the electrophysiological effects of LSD and related compounds on specific and non-specific sensory systems. The visual pathways have received particular attention.

Mouriz-Garcia, Schmidt and Arlazoroff (1969) administered large intravenous doses of LSD (50 µg/kg) to cats and monitored the extracellular response of retinal ganglion and lateral geniculate neurons. Two-thirds of the retinal ganglion cells increased and one-third decreased their firing rates accompanied by increased gross activity of the optic tract. A similar pattern was seen in lateral geniculate cells. Evarts, Landau, Freygang & Marshall (1955; cat) found intra-carotid LSD (10-20 µg), reduced or blocked the extracellularly

recorded postsynaptic response of lateral geniculate neurons to optic nerve stimulation. Higher doses of LSD (50 µg/kg) had no effect on the cortical response to optic radiation stimulation, but reduced the optic tract response to photic stimulation of the retina. Virtually identical results were obtained by Bishop, Field, Hennessy and Smith (1958; cat). Horn and McKay (1973; cat) found intravenous LSD (25-30 µg per animal) depressed the spontaneous activity of lateral geniculate neurons and the responses to light stimuli delivered to the center and surround regions of receptive fields. In a given cell changes in spontaneous activity were not correlated with changes in the response to field center or surround stimulation. 2-Bromo-LSD only weakly reproduced the effects of LSD. It was suggested that LSD interferes with synaptic transmission in the lateral geniculate either presynaptically, possibly by decreasing the release of transmitter, or postsynaptically by competing for receptors. A similar conclusion was reached by Curtis and Davis (1962; cat) and Phillis, Tebecis and York (1967; cat) on the basis of iontophoresis of LSD onto neurons in the dorsal portion of the lateral geniculate nucleus. Iontophoretic LSD, 2-bromo-LSD and 5-HT all depressed the orthodromic excitation of lateral geniculate neurons induced by optic tract stimulation. LSD was unable to antagonize the effects of 5-HT. Antidromic excitation induced by stimulation of the optic radiation was unaffected by these drugs. It should be noted that both groups obtained similar results with iontophoretic dopamine or norepinephrine. Purpura (1956; cat) noted that intravenous LSD (2-30 µg/kg) facilitated the

slow surface-negative component of the cortical response to brief photic stimulation. Etevenon and Boissier (1972; rabbit) examined the effects of intravenous LSD (5 µg/kg) on the signal-to-noise ratio (S/N) and lateralization index ($\frac{\text{left geniculate}}{\text{right geniculate}}$ or $\frac{\text{left visual cortex}}{\text{right visual cortex}}$) in the lateral geniculate nuclei and visual cortices following contralateral or bilateral photic stimulation of the retina. LSD increased the S/N of the right and left geniculate and left visual cortex during contralateral or bilateral stimulation and there was a 50-fold increase in the lateralization index. Interestingly enough, in 80% of the animals the left response was greater than the right after contralateral stimulation; the reverse occurred in the remaining 20%.

The effects of LSD upon the visual pathways have not provided much insight into the hallucinatory properties of the drug, despite the initial excitement surrounding these investigations. Nonetheless, three generalizations can be formulated. LSD increases the firing rate of retinal ganglion cells; LSD impairs synaptic transmission through the lateral geniculate nucleus; and LSD does not affect transmission from the lateral geniculate nucleus to the occipital cortex.

LSD and related drugs have an activating effect on the electroencephalogram (EEG) characterized by a decrease in the amount of slower components and progressive desynchronization (Elkes, Elkes & Bradley, 1954; Shagass, 1967). 2-Bromo-LSD does so only in huge doses (Schweigerdt & Hemwich, 1966). As noted by Bradley and Elkes (1953; cat) both the physiological and EEG effects of LSD are typically seen during states of behavioral arousal. The activating

effects of LSD are intimately related to the level of environmental stimulation such that after intravenous LSD (5 μg/kg), the electrocorticogram of cat in a quiet environment is quite similar to that of a resting animal (Bradley & Key, 1963). A number of human studies indicate that the subjective effects of LSD ingestion increase with increasing environmental stimulation (Cohen & Edwards, 1964; Elkes, Elkes & Bradley, 1954). It has also been substantiated on the basis of transections at various levels of the neuraxis that LSD and related compounds activate the electrocorticogram and induce arousal only if connections between the mesencephalon and medulla are intact (Bradley & Elkes, 1957; Schweigerdt & Himwich, 1966).

Behavioral Studies of LSD and Related Compounds

I. Effects on schedule-bound patterns of responding

Numerous studies suggest that a serotonergic mechanism is involved in behavioral suppression (i.e., decreased rates of responding). Intramuscular 5-HTP produces a dose-dependent decrease in responding in pigeons (Aprison & Ferster, 1960), rats (Aprison & Hingtgen, 1966) and monkeys (Macchitelli, Fischetti & Montanarelli, 1966) working on various schedules of food reinforcement. The decreased rates following 50 mg/kg 5-HTP (i.m.) have been temporally correlated with changes in 5-HT levels in the telencephalon and upper brainstem of pigeons (Aprison, Wolf, Poulos & Folkerth, 1962) and the telencephalon of rats (Aprison & Hingtgen, 1966). Recently, similar results have been obtained with L-tryptophan (300 mg/kg, i.m.) for pigeons working on a multiple fixed-ratio, fixed-interval schedule of food reinforcement (Smith, Hingtgen, Lane & Aprison, 1976). Consequently, it is not surprising that in many of the behavioral studies, it is assumed that manipulation of 5-HT levels will influence how LSD affects a particular behavior.

Freedman, Appel, Hartman and Molliver (1964) administered LSD (130 µg/kg, ip) to rats working on a fixed-ratio schedule of food reinforcement and observed decreased response rates and longer post-reinforcement intervals. Seven daily injections of this dose of LSD produced tolerance and some acute tolerance was observed after just three hourly doses. In a later study, Appel and Freedman (1968; rat) were able to produce tolerance and cross-tolerance to LSD, psilocybin, mescaline and 2-bromo-

LSD in rats working on a fixed-ratio schedule of milk reinforcement. No cross-tolerance was observed with d-amphetamine. Altman and Appel (1975) found LSD (20-320 µg/kg, i.p.) to have similar effects on rats working on a fixed-interval schedule of food reinforcement. LSD increased the low rates in the first half and decreased the high rats in the second half of the interval; the highest doses (160 and 320 µg/kg) depressed overall rates of responding. Kovacic and Domino (1976) observed tolerance and partial cross-tolerance to LSD (100 µg/kg, i.p.) or DMT (3.2 mg/kg, i.p.) in rats responding on a fixed-ratio schedule of milk reinforcement.

Reduction of central 5-HT levels by PCPA (Appel, Lovell & Freedman, 1970) or mesencephalic raphe lesions (Appel, Sheard & Freedman, 1970) enhanced the disrupting effects of low doses of LSD (20-40 µg/kg, i.p.) in rats on fixed-ratio schedules of food reinforcement. Comparable doses of PCPA were also found to potentiate the discriminative stimulus properties of LSD (Cameron & Appel, 1973) or mescaline (Browne & Ho, 1975).

Stoff, Mandel, Gorelick and Bridger (1974; rat) administered LSD acutely (one 100 or 500 µg/kg dose, i.p.) or chronically (five 500 µg/kg doses daily) to pre-trained poor shuttlebox avoiders and observed decreased escape and avoidance latencies during acquisition and saline retest twenty-four hours after acquisition. Bridger and Mandel (1971; rat) obtained similar results with mescaline. PCPA was found to potentiate the facilitatory effects of mescaline on shuttlebox escape and avoidance latencies in rats (Stoff, Wyatt & Gillin, 1976). Lorens and

Yunger (1974) and Srebro and Lorens (1975) found that lesions of the median plus dorsal raphe, but not dorsal or median raphe alone facilitated the acquisition of a two-way avoidance task. Srebro and Lorens (1975) suggested that the mesencephalic raphe nuclei function synergistically in mediating the response to aversive stimuli.

Geller and Blum (1970) suggested an involvement of serotonergic mechanisms in the suppression of conditioned responses by electric shock since PCPA attenuated, and 5-HTP restored the suppressive effect of electric shock on lever pressing for food reinforcement in rats. Utilizing a similar paradigm, Schoenfeld (1976) found LSD, mescaline, cyproheptadine or alpha-propyldopacetamide decreased the suppressive effect of electric shock on licking behavior in rats. DMT, Δ^9-tetrahydrocannabinol or chlorimipramine were ineffective. He suggested that the hallucinogen-induced attentuation of punishment results from decreased activity of serotonergic neurons and the subsequent release from inhibition of those areas innervated by these neurons.

II. Effects on unlearned or spontaneous behaviors

Basically there are four forms of spontaneous behavior that have received the most attention from behavioral pharmacologists interested in the effects of LSD and related compounds: spontaneous and drug-induced locomotor activity, various stereotyped behaviors, behaviors dependent upon electric shock or other "pain" thresholds, and rotational or circling behavior. These behaviors are intimately related to levels of behavioral arousal. The involvement of serotonergic systems is consistent with the speculation

of Brodie and Shore (1957) that behavioral activation mediated by central catecholaminergic pathways may be tonically suppressed by serotonergic systems.

Fibiger and Campbell (1971; rat) observed a significant increase in spontaneous locomotor activity starting 24-48 hours after PCPA and persisting throughout the day-night cycle in animals previously habituated to a stabilimter or running wheel. The onset and duration of this effect was dose-dependent, suppressed by 5-HTP and corresponded to the depletion and repletion of forebrain 5-HT levels. They suggested that 5-HT depletion decreases the threshold for behavioral arousal. Marsden and Curzon (1976; rat), monitoring both gross and medium movements, also found PCPA-induced increases in open-field activity which could be antagonized in a dose-dependent manner by L-tryptophan. L-tryptophan had no effect on the activity of saline controls, and pimozide (a central dopaminergic blocking agent) (Janssen, Niemegers, Schellekens, Dresse, Lenaerto, Pinchard, Schaper, Van Neuten & Verbruggen, 1968) decreased the light-period activities of PCPA-pretreated and control animals.

Mabry and Campbell (1973; rat), utilizing a stabilimter, found PCPA-pretreatment to synergize with d-amphetamine-induced increases in locomotor activity; 5-HTP antagonized d-amphetamine-induced hyperactivity in both PCPA-pretreated and control animals. Segal (1976; rat) obtained similar results, but at higher doses of d-amphetamine (5 mg/kg and higher) there was a marked increase in locomotion during periods usually characterized by intense

stereotypic response patterns in animals not pre-treated with PCPA (e.g. sniffing, gnawing and biting). He proposed that the potentiation of d-amphetamine-induced hyperactivity by PCPA is different from the effects of a high dose of amphetamine. That is, within a hierarchy of competing response tendencies locomotion has the highest priority, but a relatively small response output capacity; whereas stereotypy has lower priority, but higher capacity. With increasing doses of amphetamine (increasing behavioral activation) hyperactivity would gradually give way to stereotypy. Segal suggests that PCPA may elevate the ceilings that limit response output capacity so that hyperactivity would remain the predominant response over a wider range of amphetamine-induced central nervous system activation. Srebro and Lorens (1975; rat), Jacobs and Cohen (1976; rat), Geyer, Puerto, Menkes, Segal and Mandell (1976b, rat) found lesions of the median raphe potentiated spontaneous activity and d-amphetamine-induced hyperactivity. Geyer et al. (1976) found these lesioned animals were hyper-reactive to a novel environment throughout the day-night cycle and displayed augmented startle responses. In contrast, lesions of the dorsal raphe nucleus had no effect upon any of these behavioral parameters.

Hollister, Breese, Kuhn, Cooper and Schanberg (1976; rat) examined the effects of drug-induced alterations in serotonergic activity in normal, food-deprived and L-tryptophan-deprived animals. Both groups of deprived animals showed decreased 5-HT turnover and 5-HTP or L-tryptophan reversed, in a dose-dependent

manner, d-amphetamine-induced hyperactivity. L-tryptophan had no effect on d-amphetamine-induced hyperactivity in control animals, but methysergide or cyproheptadine increased it. They suggested that serotonergic systems were interacting with dopaminergic systems in an inhibitory manner, thus reducing motor output.

Involvement of the hippocampus in drug- or lesion-induced hyperactivity has been suggested by Jacobs, Trimbach, Eubanks and Trulson (1975; rat), since bilateral aspiration of the anterodorsal hippocampus antagonized the hyperactivity accompanying PCPA-pretreatment or median raphe lesions; hippocampal lesions in untreated animals induced hyperactivity.

Gumulka, Kostowski and Czlonkowski (1973; rat) found PCPA or LSD reduced chlorpromazine-or haloperidol-induced catalepsy as did lesions of the midbrain raphe nuclei. These lesions increased the stereotypic response to d-amphetamine, whereas PCPA or LSD reduced it. Weiner, Goetz, Westheimer & Klawans (1973; guinea pig) found 5-HTP decreased and methysergide increased d-amphetamine-induced stereotypy. Baldessarini, Amatruda, Griffith and Gerson (1975; rat) pretreated animals with either methysergide, PCPA, 5-HTP, 5,6- or 5,7-dihydroxytryptamine (plus desmethylimipramine); none of these pretreatments had any effect on apomorphine-induced stereotypy. However, Weiner, Goetz and Klawans (1975, guinea pig) found 5-HTP decreased and methysergide increased apomorphine-induced stereotypy. Thus, although serotonergic systems appear to modulate stereotypic behaviors, the effects are far from clear at the present time.

Serotonergic systems have been implicated in the modulation of various "pain" thresholds. The relative importance of 5-HT as opposed to catecholamines is suggested by a number of drug interaction studies. Lints and Harvey (1969; rat) found lesions of the ventrolateral midbrain tegmentum, which reduced telencephalic norepinephrine, but not 5-HT levels had no effect on jump thresholds, and Yunger, Harvey and Lorens (1973; rat) found no change in hot plate latencies after depletion of central catecholamines with the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine (AMPT) (Spector, Sjoerdsma & Udenfriend, 1965). PCPA treatment usually produces a decrease in jump thresholds (Tenen, 1967; Harvey & Yunger, 1973), but Hole and Lorens (1975; rat) found neither PCPA nor midbrain raphe lesions (either electrolytically or with 5,7-dihydroxytryptamine) affected jump thresholds. Yunger and Harvey (1976; rat) demonstrated that bilateral electrolytic lesions of the MFB decreased flinch jump thresholds and 5-HTP could restore thresholds to control levels in these animals but not in animals receiving MFB lesions plus intraventricular 6-OH-DA. Since rats receiving 6-OH-DA alone exhibited decreased accumulation of 5-HT (as compared to controls) they suggested that catecholaminergic neurons may mediate some of the 5-HTP-induced reversal of the lowered jump threshold possibly by 5-HT functioning as a false transmitter within catecholaminergic neurons.

Jacobs and Cohen (1976; rat) obtained differential behavioral effects with lesions specific to the median or dorsal raphe. Median raphe lesions, in addition to augmenting both d-amphetamine-induced hyperactivity and spontaneous activity, antagonized the

suppression of open-field activity of a foot-shock which followed the previous open-field testing period. Dorsal raphe lesions had no significant effect upon any of the above behavioral parameters, but did increase pain-elicited aggression as determined by the frequency of rearings following a foot-shock. They suggested that median raphe lesioned animals exhibit increased emotionality due to decreased hippocampal 5-HT, whereas dorsal raphe lesions result in increased aggression via reductions in striatal 5-HT.

An interesting behavioral syndrome originally described by Corne, Pickering and Warner (1963; mouse) and later popularized by Graham-Smith (1971a, 1971b, rat) is suggested (Graham-Smith, 1971a, 1971b, Jacobs, 1976) to result from increased stimulation of central 5-HT receptors and consists of resting tremor, rigidity or hypertonus, reciprocal forepaw treading, Straub tail, hindlimb abduction, lateral headweaving, head shaking, hyperreactivity, hyperactivity and salivation. The suggestion that this stereotyped behavioral syndrome is serotonin-mediated was originally based upon its induction by administration of 5-HTP or L-tryptophan to rats or mice pretreated with an MAO inhibitor (Butcher, Engel & Fuxe, 1972; Modigh, 1972), although similar behavioral effects occur with an MAO inhibitor plus loading doses of L-DOPA (Jacobs, 1974). However, the effects of these precursors can be blocked by inhibition of tryptophan hydroxylase (with PCPA) or L-aromatic amino acid decarboxylase (with Ro4-4602) (Graham-Smith, 1971a), but not by inhibition of catecholamine synthesis with AMPT (Jacobs, 1974). The putative

serotonergic agonist MDMT produces the syndrome (Graham-Smith, 1971) as does p-chloroamphetamine or fenfluramine (Jacobs, 1976), and chlorimipramine potentiates the 5-HTP-induced syndrome (Modigh, 1973). Recently, Trulson, Eubanks and Jacobs (1976; rat) demonstrated that the dose of 5-HTP, L-tryptophan or MDMT necessary to elicit the syndrome is significantly reduced in animals whose serotonergic nerve terminals have been destroyed by intraventricular administration of 5,7-dihydroxytryptamine.

Despite the similarities of many of the components of this syndrome to neurological signs associated with the corpus striatum (i.e., tremor, rigidity and chorea), it was unaffected by various cerveau isole transections or total cerebellectomies (Jacobs & Klemfuss, 1975); Jacobs and Klemfuss (1975; rat) suggested that neural mechanisms present in the pons, medulla and/or spinal cord are sufficient for the manifestation of the syndrome.

The final area of behavioral pharmacology, rotational or circling behavior in rodents has been utilized fundamentally as an animal model of central dopaminergic activity and is indirectly related to the pharmacology of LSD and related compounds. Andén, Dahlstrom, Fuxe and Larsson (1966) examined the effects of drug-induced alterations of various central monoamines in rats with unilateral electrolytic lesions of the crus cerebri or aspiration of the corpus striatum. Both lesions produced significant decreases in forebrain dopamine levels ipsilateral to the side of the lesion. Reserpine, haloperidol, chlorpromazine or L-DOPA plus nialamide all induced turning, whereas, 5-HTP, phenoxybenzamine, propranolol, promethazine and barbiturates did not. They suggested that rats with unilateral

lesions of the nigrostriatal system might be used as a model of central dopaminergic activity. Ungerstedt and Arbuthnott (1970) quantified rotational behavior in rats using a hemispherical rotometer. They observed dose-dependent, amphetamine-induced ipsilateral rotation (towards the side of the lesion) in animals with unilateral 6-OH-DA-induced degeneration of the nigrostriatal pathway. The rotation was attributed to the release of dopamine in the intact striatum. Arbuthnott and Crow (1971; rat) found unilateral electrical stimulation of the substantia nigra or nigrostriatal pathway produced turning away from the side of stimulation. Ungerstedt (1971) observed that the intensity of rotation was proportional to the extent of degeneration of the nigrostriatal pathway and that the direction of rotation depended upon the manner in which the drug affected nigrostriatal activity. Following the administration of d,l-amphetamine rats rotated ipsilateral to the lesion; following apomorphine they rotated contralateral (away from) to the lesion. Thus, amphetamine, which facilitates dopaminergic transmission presynaptically (by releasing dopamine and possibly blocking its reuptake) (Carlsson, Fuxe, Hamberger & Lindqvist, 1966; Carr & Moore, 1969; Glowinski & Axelrod, 1965; Randrup & Munkvad, 1966), induced rotation opposite in direction to apomorphine which directly stimulates postsynaptic dopamine receptors (Ernst, 1969). Ungerstedt (1971) has suggested that the dose-dependent contralateral rotation produced by apomorphine or L-DOPA in rats with unilateral 6-OH-DA induced lesions of the nigrostriatal pathway results from the stimulation of supersensitive dopamine receptors in the denervated striatum. Thornburg and Moore (1975), using mice, have verified denervation supersensitivity by

showing that the dose-response relationship for apomorphine-induced contralateral rotation shifted to the left with time (up to thirty days post-lesion). There also was a three-fold increase in the maximal response which occurred between two and ten days post-lesion.

The involvement of dopaminergic mechanisms in rotation has received considerable support from a number of drug-interaction studies. Ungerstedt, Butcher, Butcher, Andén and Fuxe (1969) injected drugs stereotaxically into the striatum of nialamide pretreated rats. Unilateral administration of dopamine, apomorphine or norepinephrine induced contralateral turning, which could be prevented by bilateral intrastriatal chlorpromazine; unilateral administration of chlorpromazine induced ipsilateral turning. Inhibition of tyrosine hydroxylase with AMPT markedly reduced amphetamine-induced rotation (Christie & Crow, 1971; Ungerstedt, 1971; Von Voigtlander & Moore, 1973), but was without effect upon apomorphine-induced rotation (Von Voigtlander & Moore, 1973). Inhibition of dopamine-beta-hydroxylase (which catalyzes the conversion of dopamine to norepinephrine) with FLA-63 (Corrodi, Fuxe, Hamberger & Ljungdahl, 1970) either increased (Ungerstedt, 1971) or had no effect (Christie & Crow, 1971) upon amphetamine-induced rotation. Haloperidol (Ungerstedt, 1971) spiroperidol (Ungerstedt, 1971) or chlorpromazine (Christie & Crow, 1971) blocked amphetamine-induced rotation in sub-cataleptic doses.

What emerges from these studies is the idea that by producing a dopaminergic asymmetry, the subsequent administration of agents that modulate dopaminergic activity will produce circling away from the striatum with greater activity. Recently, it has been demonstrated

that the same agents will induce rotation in animals without lesions of the nigrostriatal pathway (Jerussi & Glick, 1974, 1975), when tested in an automated, spherical rotometer. Amphetamine (Jerussi & Glick, 1974) or apomorphine (Jerussi & Glick, 1975) induced dose-dependent rotation which was consistent for individual animals, in both magnitude and direction from week to week. Drug-interaction studies yielded results similar to those obtained in the lesion studies; AMPT or haloperidol blocked amphetamine-induced rotation, dopamine-beta-hydroxylase inhibition (with diethyldithiocarbamate) had little effect, while haloperidol blocked and AMPT had no effect on apomorphine-induced rotation (Jerussi & Glick, 1976). Jerussi and Glick (1976) have found that an intrinsic bilateral striatal dopamine asymmetry exists such that the dopamine content of left and right striata differed by 10-15% in normal rats and was increased to 25% following d-amphetamine (20 mg/kg i.p.) (Glick, Jerussi, Waters & Green, 1974).

In addition to drugs which affect dopaminergic activity, certain cholinergic agents have also been shown to induce rotation in lesioned and unlesioned animals. Kelly and Miller (1975), using rats with unilateral, 6-OH-DA lesions of the nigrostriatal pathway, demonstrated ipsilateral rotation following scopolamine; the ipsilateral rotation produced by methamphetamine was markedly attentuated by the muscarinic agonist oxotremorine (Bebbington & Brimblecombe, 1965). Mendez, Cotzias, Finn and Dahl (1975), using a similar lesion model, found potentiation of apomorphine- or L-DOPA-induced rotation in atropine-pretreated rats. Using unlesioned rats, Jerussi and Glick (1976) have shown that the direction of rotation induced by scopolamine is

the same as that induced by d-amphetamine; pilocarpine pretreatment antagonized d-amphetamine-induced rotation, whereas scopolamine pretreatment potentiated it.

The induction of rotation by cholinergic agents has been attributed to a dopaminergic-cholinergic interaction within the striatum (Kelly & Miller, 1975). This relationship is reciprocal, so that any procedure that increases striatal dopaminergic activity will decrease intrinsic striatal cholinergic activity. Various neurochemical studies have provided additional support for this hypothesis: the blockade of dopaminergic transmission by certain neuroleptics increased the release of ACh from the caudate nucleus (Stadler, Lloyd, Gadea-Ciria & Bartholini, 1973) and reduced the striatal levels of ACh (Agid, Guyenet, Javoy, Beaujoian & Glowinski, 1974; Sethy & Van Woert, 1974), whereas dopaminergic agonists such as apomorphine or L-DOPA increased striatal levels of ACh (Sethy & Van Woert, 1974).

An as yet unresolved controvery concerns the direction animals with unilateral destruction of the nigrostriatal pathway will rotate following the administration of directly acting dopamine agonists. Following 6-OH-DA-induced degeneration of the nigrostriatal pathway, apomorphine always induces contralateral rotation (Costall, Marsden, Naylor & Pycock, 1975; Ungerstedt, 1971; Von Voigtlander & Moore, 1973), however, although Ungerstedt (1971) observed apomorphine-induced contralateral rotation following electrolytic lesions at the rostral level of the mesencephalic ventral tegmentum, electrolytic lesions made in the substantia nigra resulted in apomorphine-induced ipsilateral rotation (Costall et al., 1975; Iwamto, Loh & Leong Way, 1976). Iwamoto, Loh and Leong Way (1976); rat) have suggested that the 70% reduction

in striatal dopamine resulting from electrolytic nigral lesions is insufficient to produce denervation supersensitivity; dopamine decreases of 80-90% (as seen with 6-OH-DA lesions) are necessary for its appearance. However, in this study the 6-OH-DA lesions produced a 31% decrease in forebrain norepinephrine levels; this was not seen following the electrolytic lesions. Perhaps this partial depletion of forebrain norepinephrine plays some undetermined role in the development of denervation supersensitivity. Costall, Marsden, Naylor and Pycock (1975; rat) have suggested that electrolytic lesions of the substantia nigra may destroy a non-dopaminergic nigrostriatal pathway or a strio-pallidal efferent pathway required for the expression of rotational behavior.

Although the nigrostriatal system appears to be the primary neuroanatomical substrate for rotation, various other systems may play a modulatory role. D-amphetamine-induced contralateral rotation has been reported following unilateral electrolytic lesions of an area corresponding to the claustrum (Fleisher & Glick, 1975). Dray, Fowler, Oakley, Simmonds and Tanner (1975) found amphetamine or apomorphine induced ipsilateral rotation in rats which had ethanolamine-O-sulfate (a GABA-transaminase inhibitor) (Fowler & John, 1972) injected unilaterally into the zona reticulata of the substantia nigra; unilateral administration of the putative GABA antagonist picrotoxin (Precht & Yoshida, 1971) induced contralateral rotation which was abolished in animals pretreated with 6-OH-DA (Tarsy, Pycock, Meldrum & Marsden, 1975) (injected into the substantia nigra homolateral to the picrotoxin injection). Discrete unilateral electrolytic lesions of the zona compacta resulted in apomorphine-induced contralateral

rotation, whereas the same lesions of the zona reticulata resulted in apomorphine-induced ipsilateral rotation (Dray, Fowler & Oakley, 1975). These results have been interpreted in terms of an inhibitory, GABA-mediated strionigral (and/or pallidonigral) pathway impinging (either monosynaptically or via a nigral interneuron) upon the dopaminergic perikarya of the nigrostriatal system (Tarsy et al., 1975). Glick and Greenstein (1973; rat) observed d-amphetamine-induced rotation following unilateral ablation of the frontal cortex; the direction of rotation varied with the post-lesion interval. From 1-7 days post-lesion the animals rotated ipsilateral, but this gradually gave way to contralateral rotation (15-30 days post-lesion). A similar phenomenon was described by Pycock, Donaldson and Marsden (1975; rat) following unilateral electrolytic destruction of the locus coeruleus. However, these animals did not switch to contralateral rotation; they simply stopped rotating after thirty days. Since these lesions produced a 55% decrease in cortical norepinephrine levels ipsilateral to the lesion, and since striatal dopamine levels on the lesioned side were significantly increased five days after surgery (when drug-induced rotation occurred) but returned to normal thirty days after surgery (when rotation disappeared), it was suggested that a facilitatory noradrenergic input to the nigrostriatal pathway was removed by the lesion. However, it could be argued that the locus coeruleus lesion removed inhibitory noradrenergic input to the frontal cortex, resulting in disinhibition of an excitatory fronto-striatal system.

The possible involvement of mesolimbic dopaminergic neurons in rotation has been suggested by Kelly and Moore (1976; rat). 6-OH-DA was used to destroy the nuclei accumbens bilaterally and the

nigrostriatal system unilaterally; this resulted in increased apomorphine-induced contralateral rotation and decreased amphetamine-induced ipsilateral rotation. They attributed these results to the development of supersensitivity of the denervated mesolimbic dopamine receptors, the activity of which facilitated nigrostriatal activity. Thus the animal would be more sensitive to apomorphine, but less sensitive to amphetamine (since the presynaptic terminals were destroyed by 6-OH-DA). However, the nigrostriatal system was lesioned by injecting 6-OH-DA into the striatum which resulted in a further depletion of dopamine in the nucleus accumbens on the same side (i.e., in excess of the depletions produced by the bilateral lesions). Perhaps this is why these animals displayed the above mentioned rotational behavior.

The final modulatory system to be discussed involves the serotonergic median and/or dorsal raphe nuclei. Marsden and Guldberg (1973; rat) electrolytically destroyed the median and dorsal raphe, but observed no rotation upon administration of amphetamine. Unilateral lesions of the mesencephalic reticular formation, however, induced a contralateral position asymmetry which was potentiated into rotation by amphetamine. Costall and Naylor (1974; rat) made asymmetric lesions of the median or dorsal raphe electrolytically; following apomorphine, d-amphetamine or methylphenidate, median raphe-lesioned animals exhibited dose-dependent contralateral rotation which could be decreased by haloperidol or methiothepin, whereas dorsal raphe-lesioned animals exhibited some contralateral head asymmetries but no rotation. They suggested that median raphe lesions may remove

an inhibitory serotonergic input to the nigrostriatal system. However, as described in the section on the raphe nuclear complex, the median raphe projects to the limbic area while the dorsal raphe projects to the striatum. Thus the absence of any rotational effects following asymmetric destruction of the dorsal raphe is somewhat perplexing.

Pieri, Pieri and Haefely (1974; rat) made unilateral lesions of the nigrostriatal pathway by injecting 6-OH-DA (which depletes dopamine and norepinephrine) or 5,6-dihydroxytryptamine (which depletes dopamine and serotonin) into the MFB. Following either lesion methamphetamine induced ipsilateral and apomorphine induced contralateral rotation. In addition, LSD-induced contralateral rotation which was maximal (in terms of the number of rotations per minute) at 100 µg/kg (i.p.). Higher doses (200 and 1500 µg/kg) prolonged the duration of peak rotation but had no effect upon intensity. Haloperidol blocked LSD-induced rotation, whereas AMPT or 2-bromo-LSD had no effect. They suggested that LSD was functioning as a dopamine agonist and was inducing contralateral rotation by stimulating the denervated, supersensitive striatal dopamine receptors. However, Pycock and Anzelark (1975), using a similar 6-OH-DA lesion model in mice have observed weak and inconsistent contralateral rotation followng high doses of LSD (1000 and 1500 µg/kg) which is blocked by haloperidol and unaffected by AMPT. Lower doses of LSD (25-500 µg/kg) produced no behavioral or postural asymmetries and had no effect upon amphetamine or apomorphine-induced rotation.

Thus, although LSD appears to possess some capacity to induce rotation in lesioned animals, its mode of action is far from clear. In addition, the involvement of serotonergic systems in this effect

is even more poorly understood. With this in mind, the research to be presented was undertaken to elucidate the manner in which LSD and related compounds affect rotation in unlesioned rats. In order to discuss this properly, descriptions of the anatomy and electrophysiology of the basal ganglia and the anatomy of the raphe nuclear complex are necessary.

Anatomy, Ultrastructure and Electrophysiology of the Basal Ganglia and Related Structures

The basal ganglia (corpus striatum, amygdaloid nuclear complex and claustrum) are large subcortical nuclear masses derived from the telencephalon (Truex & Carpenter, 1969). The corpus striatum is composed of the striatum (caudate nucleus plus putamen) and globus pallidus. The presence of a striatal afferent system arising in the substantia nigra was initially proposed following observations of apparent retrograde degeneration in the pars compacta of the substantia nigra following destruction of the striatum (Ferraro, 1928; Mettler, 1943). However, the existence of this nigrostriatal pathway was questioned because of the failure to demonstrate anterograde degeneration of axon terminals in the striatum following lesions of the substantia nigra (Afifi & Kaelber, 1965; Carpenter & McMasters, 1964; Cole, Nauta & Mehler, 1964; Faull & Carman, 1968). By use of Falck-Hillarp's histofluoresence method (Falck, Hillarp, Thieme & Thorp, 1962), Andén and co-workers (Andén, Carlsson, Dahlstrom, Fuxe & Hillarp, 1964; Andén, Dahlstrom, Fuxe & Larsson, 1965; Andén, Carlsson, Dahlstrom, Fuxe, Olson & Ungerstedt, 1966) demonstrated the nigrostriatal pathway in rat. Hedreen (1971) and Shimizu and Ohnishi (1973) in rat, and Moore, Bhatnagar and Heller (1971) in cat, have verified the existence of the nigrostriatal pathway utilizing Fink-Heimer's modification of the Nauta technique. Nauta, Pritz and Lasek (1974) and Kuypers, Kievit & Green-Klevant (1974) utilizing the retrograde transport of horseradish

peroxidase have provided a third means of verificiation of the nigrostriatal pathway. In the rat, this pathway arises from medium-sized cells (15-20 μ in diameter) in the pars compacta of the substantia nigra (Gulley & Wood, 1971; Hadju, Hassler & Bak, 1973), passes rostromedially through the ventral tegmental area and Forel's field H, ascends in the lateral hypothalamus, enters the crus cerebri and medial internal capsule, fans out in the globus pallidus and terminates in the striatum (Ungerstedt, 1971).

Carpenter and Peter (1972), using the Wittanen technique and short survival periods, have characterized the nigrostriatal pathway in the monkey. In Forel's field H, this bundle splits into two: a smaller dorsal bundle projects dorsally, parallel to the mammillothalamic tract and enters certain thalamic nuclei while a larger bundle projects dorsal to the subthalamic nucleus, through the internal capsule and into the corpus striatum.

The striatum contains high levels of dopamine (3-hydroxy-tyramine) (Andén, Carlsson, Dahlstrom, Fuxe, Hillarp & Larsson, 1964; Andén, Dahlstrom, Fuxe & Larsson, 1965; Bertler & Rosengren, 1959; Broch & Marsden, 1972) but rather low levels of norepinephrine (10 μg/g dopamine; 0.1 μg/g norepinephrine wet weight; Hornykiewicz, 1966) indicating a role for dopamine other than as a precursor of norepinephrine. Electrical stimulation of the substantia nigra increased the release of dopamine from the caudate (Portig & Vogt, 1969) or putamen (McClennan, 1965), and following intraventricular administration of ^{3}H-dopamine, electrical stimulation of the pars compacta, the caudate nucleus

(Von Voigtlander & Moore, 1971a, 1971b) or the nigrostriatal pathway (Chiueh & Moore, 1973; Von Voigtlander and Moore, 1971a, 1971b) increased the release of ^{3}H-dopamine into cerebral ventricles. Similarly, ^{3}H-dopamine release (both spontaneous and electrically induced) increased following intraventricular (Chiueh & Moore, 1973) or intravenous (Besson, Cheramy, Feltz & Glowinski, 1971), d-amphetamine, a phenylethylamine compound which increases the presynaptic release of catecholamines (Carlsson, Fuxe, Hamberger, & Lindqvist, 1966; Carr & Moore, 1969; Glowinski & Axelrod, 1965; Randrup & Munkvad, 1966). This drug-induced augmentation of ^{3}H-dopamine release is markedly reduced by destruction of the nigrostriatal pathway (Von Voigtlander & Moore, 1973). Following intraventricular administration of ^{14}C-tyrosine, the enhanced release of ^{14}C-dopamine (either by electrical stimulation of the nigrostriatal pathway or intraventricular d-amphetamine) as demonstrated by Chiueh and Moore (1973), provides further evidence that dopamine is the in situ transmitter released by the terminals of the nigrostriatal pathway.

The striking depletions of striatal dopamine seen in Parkinsonism (Hornykiewicz, 1966) (which involves marked degeneration of nigral cells) and after experimental destruction of the substantia nigra (Andén et al., 1964; Poirier & Sourkes, 1965; Poirier, Singh, Bouvier, Olivier & Larochelle, 1967; Bedard, Larochelle, Parent & Poirier, 1969) support the contention that the nigrostriatal pathway is the source of striatal dopamine.

Assuming that dopamine is released by the nigrostriatal pathway, what effect does it have on striatal neurons? This has been investigated by monitoring the response of striatal

neurons to electrical stimulation of some part of the nigrostriatal pathway and/or to iontophoretic administration of dopamine or drugs with dopaminergic properties. Striatal neurons are monitored in two ways: extracellularly measuring frequency of firing of single neurons or alterations in field potentials, or intracellularly measuring firing rates, membrane potentials, or synaptic potentials.

Extracellular studies involving iontophoresis of dopamine on striatal neurons by Bloom, Costa and Salmoiraghi (1965; cat), York (1967; cat) and Herz and Zieglgansberger (1968; rabbit) yielded similar results, i.e., approximately 60% of cells tested showed decreased firing rates while approximately 10% showed increased firing rates. Dopamine decreased rates of firing regardless of whether the striatal neurons were spontaneously active (Bloom et al., 1965; Herz & Zieglgansberger, 1968; York, 1967), induced to fire by iontophoretic L-glutamate (Bloom, et al., 1965; Herz & Zieglgansberger, 1968; York, 1967), or driven by stimulation of the medial or central thalamic nuclei (Herz & Zieglgansberger, 1968). Connor (1970; cat) and Gonzalez-Vegas (1974; rat) observed inhibition of firing rates by nigral stimulation or iontophoretic dopamine, and Connor (1970) could block both types of inhibition with iontophoretic alpha-methyldopamine. It should be noted that in the above investigations involving stimulation of the substantia nigra, despite the small percentage of neurons excited, facilitation of firing always had a shorter latency than depression of firing (12-15 msec vs. 18 msec; Connor, 1970); 15-25 msec vs. 38.7 msec; Gonzalez-Vegas, 1974).

Most of the intracellular and some of the extracellular studies have indicated an excitatory role for dopamine in the striatum. York (1970; cat), recording extracellularly from putamen neurons induced to fire with L-glutamate or D,L-homocysteic acid recorded negative field potentials and increased firing rates after stimulation of the nigra or iontophoretic dopamine; the excitatory effects of dopamine were blocked by iontophoretic phentolamine or chlorpromazine. Frigyesi and Purpura (1967; cat) recorded extracellular negative field potentials which led to a spike from caudate neurons. Hull, Bernardi and Buchwald (1970; cat) recorded EPSP-IPSP sequences intracellularly after stimulation of the nigra or the region immediately dorsal to it. This sequential response was unaffected by lesions of the centromedian-parafascicular (CM-PF) nuclear complex, thus ruling out a thalamic relay from nigra to caudate.

Feltz and Albe-Fessard (1972; cat) monitored two distinct populations of striatal neurons. Within the medial two thirds of the caudate, they found neurons which fired neither spontaneously nor following stimulation of the cortex or thalamus, but which were excited by nigral stimulation with a latency of 18.5 msec (NCE cells). Within the head of the caudate, particularly in the lateral and superficial portions, they found spontaneously active neurons which were inhibited by nigral stimulation (NCI cells). The latency of inhibition was variable (15-50 msec) with many NCI cells often showing short latency excitations (10-20 msec) temporally similar to the response of NCE cells. They suggested that all nigral afferents to the striatum formed excitatory synaptic

contacts with small NCE cells which were intrinsic to the striatum and had extensive inhibitory connections with larger NCI cells.

Kitai and co-workers have recently suggested that caudate neurons which project to the substantia nigra (i.e. strionigral pathway) do not receive monosynaptic connections from nigrostriatal fibers. However, caudate neurons not projecting to the substantia nigra (i.e., neurons which did not respond to antidromic stimulation of the mesencephalic cerebral peduncle or the diencephalic internal capsule) did show EPSP or EPSP-IPSP sequences following stimulation of the substantia nigra (Kitai, Wagner, Precht & Ohno, 1975). Subsequently, Kitai, Sugimori and Kocsis (1976) found that electrical stimulation of the nigrostriatal pathway at the level of the MFB produced monosynaptic EPSP's in certain caudate neurons; EPSP's were also obtained with iontophoretic dopamine. Concurrent iontophoretic dopamine and MFB stimulation increased EPSP amplitudes without affecting latencies, while iontophoretic chlorpromazine blocked MFB-induced EPSP's. Kitai, et al. (1976), using procion dye labeling, have shown that the caudate neurons receiving direct nigral input are medium-sized cells (approximately 13 μ in diameter) similar to those described by Kemp and Powell (1971a, 1971b). Kemp and Powell (1971a, 1971b) observed that after lesions of the nigrostriatal pathway, degenerating terminals were most commonly found in contact with spines and dendritic shafts of the medium spiny cell (Kemp & Powell, 1971a), whereas only intracaudate lesions produced degenerating terminals on initial segments of caudate neurons. Kitai, et al. (1976), suggest that excitatory

nigrostriatal inputs drive medium spiny cells which have extensive inhibitory connections within the striatum. However, in a subsequent report, Kitai, Kocsis, Preston and Sugimori (1976) found that intracellular administration of horseradish peroxidase to medium spiny caudate neurons (identified by excitation following stimulation of the substantia nigra, CM-PF nuclear complex and/or precruciate cortex) illustrated a long axon, extensively branching within the striatum and possibly projecting to the pallidum.

Hull, Levine, Buchwald, Heller and Browning (1974) found that unilateral lesions in and around the nigrostriatal pathway altered the extracellularly recorded firing patterns of neurons in both caudate nuclei; the most common response being a decrease in firing rates in the caudate contralateral to the lesion. However, these alterations in firing pattern were independent of changes in striatal dopamine levels.

It is conceivable that a non-dopaminergic nigrostriatal pathway exists, possibly originating in the pars reticulata and projecting to the striatum as suggested by Rosegay (1944), Andén et al. (1964) and Hedreen (1971). This might explain the findings of Hull et al. (1974) and particularly those of Feltz and DeChamplain (1972a, 1972b) who found that caudate excitations produced by electrical stimulation of the substantia nigra survived 6-OH-DA induced depletion of striatal dopamine (Ungerstedt, 1968).

Two other major afferent systems to the striatum arise from the cerebral cortex (corticostriatal) (Carman, Cowan & Powell, 1963; Domestick, 1969; Dusser de Barrenne, Garol & McCulloch, 1942; Glees, 1944, Webster, 1961) and certain thalamic nuclei (thalamo-

striatal) (Jones & Leavitt, 1974; Kuypers, Kievet & Groen-Klevant, 1974; Nauta, Pritz & Lasek, 1974; Powell & Cowan, 1956; Pritz & Lasek, 1974). All portions of the cortex project to the ipsilateral striatum topographically probably via unmyelinated (or poorly myelinated) collaterals of internal capsule axons. Recently, Blake, Zarzecki and Somjen (1976; cat) have demonstrated by combined electrophysiological and anatomical techniques, that the corticostriatal system is not collaterals of internal capsule axons and is independent of the corticospinal or corticobulbar systems. Primary input is from the anterior half of the cortex, particularly the sensorimotor portions. The thalamostriatal pathway in the rat arises mainly from the intralaminar thalamic nuclei, particularly the CM-PF nuclear complex and innervates the entire striatum. In the monkey, Powell and Cowan (1956) observed projections of the CM-PF complex only to the putamen, whereas the central medial, paracentral and central lateral nuclei projected to the head of the caudate.

Electrophysiological studies of corticostriatal and thalamostriatal pathways indicate that many caudate neurons receive multiple inputs (Buchwald, Price, Vernon & Hull, 1973; Hull, Bernardi, Price & Buchwald, 1973; Kitai et al., 1976; Liles, 1974; Malliani & Purpura, 1967; Purpura & Malliani, 1967). A single caudate neuron can receive inputs from more than one cortical area, from the intralaminar thalamus and from the substantia nigra. McClennan, (1974; cat) found that electrical stimulation of the CM nucleus increased the release of dopamine into the cerebral ventricles. This increased release could be blocked by stimulatior

of the anterior sigmoid gyrus, although direct stimulation of the anterior sigmoid gyrus did not affect the resting release of dopamine. Stimulation of the sigmoid or cingulate gyri (Rocha-Miranda, 1965; cat) usually decreased firing rates of caudate neurons monitored extracellularly. Intracellular studies indicated that stimulation of the medial thalamus produced long-latency (15-20 msec), prolonged (60-100 msec) EPSP's in neurons in the head of the caudate, which increased with repetitive stimulation (Purpura & Malliani, 1967), whereas, the same stimulation elicited 6-10 msec latency EPSP's and some repetitive spike discharges in dorsal putamen cells (Malliani & Purpura, 1967). Buchwald, Price, Vernon and Hull (1973; cat), monitoring intracellular responses of caudate neurons to stimulation of CM-PF nuclear complex, nigrostriatal pathway or precruciate cortex found EPSP-IPSP sequences or pure EPSP's as the most common responses. Liles (1974, cat) recorded extracellularly from caudate units identified as output neurons by their antidromic invasion following stimulation of the substantia nigra or entopeduncular nucleus. Only 6% of these neurons could be excited by stimulation of gyrus proreus (orbitofrontal cortex; area 6) or medial or lateral portions of the anterior sigmoid gyrus (motor cortex; area 4). Because of the long and variable response latencies, and the absence of any alteration in response following destruction of the thalamus, he suggested that the cortical inputs (which conduct slowly themselves) impinge on striatal interneurons which synapse upon the units being monitored. Marco, Copack, Edelson

and Gilman (1973; cat) have demonstrated that impulses conduct slowly within the striatum by directly stimulating chronically isolated caudate preparations. They proposed the existence of well organized, slowly conducting interneuronal pathways which, when activated, produce (at latencies averaging 10 msec, but never less than 7 msec) excitatory or inhibitory effects on neurons over a maximum distance of 1.5 mm. Kitai et al. (1976; rat) recording intracellularly from medium spiny caudate neurons (identified by intracellular horseradish peroxidase) observed monosynapstic EPSP's often followed by prolonged (80 msec) hyperpolarizing potentials after stimulation of the precruciate cortex, CM-PF nuclear complex or substantia nigra. As stated earlier, these inputs often converged on the same caudate neuron.

The striatum also receives extensive 5-hydroxytryptaminergic input from neurons arising in the dorsal raphe nucleus of the mesencephalon. However, a description of this system will be deferred to the section on the raphe system.

Striatal and Pallidal Efferent Systems

Two major output systems arise from the striatum: the striopallidal and the strionigral projections. Hattori, Fibiger and McGeer (1975; rat), Voneida (1960; cat) and Niimi, Ikeda, Kawamura and Inoshita (1970; cat) have demonstrated a striopallidal projection arising from all portions of the striatum and topographically innervating the globus pallidus (pallidum) and entopeduncular nucleus (homologous to the medial pallidal segment in primates). In the monkey, the head of the caudate nucleus projects to dorsal and rostral parts of the pallidum (Cowan & Powell, 1966).

The strionigral projection in cat and monkey has been extensively investigated by Voneida (1960). Following discrete lesions in the head of the caudate nucleus, the anterograde degeneration of striatal axons was observed using a silver impregnation technique. Strionigral fibers descend in the ventrolateral portion of the internal capsule and the basis pedunculi and terminate in the rostal limits of the pars reticulata. Niimi et al. (1970), utilizing a similar technique demonstrated a topographical organization of the strionigral system within the ventromedial portions of the pars reticulata.

Studies utilizing the retrograde transport of horseradish peroxidase or the anterograde transport of labelled amino acids indicate the existence of pallidonigral and stronigral systems. Hattori, Fibiger and McGeer (1975) injected ^{3}H-leucine into the striatum or pallidum of normal rats and of rats depleted of central dopamine by intraventricular 6-OHDA, and observed anterograde transport of the label with light or electron microscopy. Striatal injections resulted in preferential labelling of the pars reticulata, while pallidal injections resulted in heavy labelling of the subthalamic nucleus and the pars compacta. After 6-OH-DA, electron microscopic analysis revealed terminals in the reticulata synapsing on intact dendritic processes, and terminals in the compacta synapsing on degenerating dendritic processes. They suggested that the pallidonigral system terminated on dopaminergic neurons (possibly nigrostriatal) in the pars compacta. Grofova (1975; cat) injected horseradish peroxidase into the substantia

nigra and observed its retrograde transport to medium-sized striatal cells and large cells of the pallidum (but not the entopeduncular nucleus). She suggested that both the strionigral and pallidonigral systems projected to the pars reticulata, but this is somewhat doubtful (particularly for the pallidonigral system) since the injected horseradish peroxidase wasn't restricted to the reticulata. Kanazawa, Marshall & Kelly (1976; rat) utilizing the same horseradish peroxidase technique, concluded that the striatum projects preferentially to the ipsilateral pars reticulata, while the pallidum projects preferentially to the ipsilateral pars compacta. They also observed a homolateral subthalamonigral projection. In a recent study by Bunney and Aghajanian (1976; rat), using horseradish peroxidase injected iontophoretically into the substantia nigra, 30-50% of all striatal cells (except for a medial core) projected to the substantia nigra. A pallidonigral projection was also observed, but injections into the pars reticulata resulted in more horseradish peroxidase-positive cells in the pallidum than injections into the pars compacta. They also found a projection to the nigra from the central amygdaloid nucleus and the habenula. In an earlier investigation, Ungerstedt (1971), presented histofluorescent evidence for a dopaminergic projection from the pars compacta to the central amygdaloid nucleus, which might represent axon collaterals of the nigrostriatal pathway.

The neurotransmitters released by the pallidonigral and/or strionigral systems are as yet undetermined, but acetylcholine (ACh) and gamma-aminobutyric acid (GABA) are the leading candidates.

The argument for ACh is based upon the high levels of acetylcholinesterase (AChE) (ACh metabolizing enzyme) in the substantia nigra (Koelle, 1954; Olivier, Parent, Simard & Poirier, 1970), and of AChE and choline acetyltransferase (CAT; ACh synthesizing enzyme) in the caudate (Andén, Dahlstrom, Fuxe & Larsson, 1966; McGeer, Fibiger & Wickson, 1971). However, McGeer et al. (1971), found no change in striatal CAT or AChE levels after destruction of all the major inputs to the striatum and Fonnum, Grofova, Rinvik, Storm-Mathiesen and Walberg (1974) observed low levels of CAT in the substantia nigra despite high AChE levels (AChE: CAT=1000.:1). Lesions of the globus pallidus or transections between the corpus striatum and the substantia nigra decreased nigral levels of GABA and glutamate decarboxylase (GAD; GABA synthesizing enzyme), but had no effect on nigral or striatal levels of ACh or CAT (Fonnum et al., 1974; McGeer, Fibiger, McGeer & Brooke, 1973). Striatal ACh would appear to be located within neurons which originate and terminate in the striatum (i.e. striatal interneurons) (McGeer et al., 1973).

On the other hand, the putative role of GABA as the transmitter of the strionigral and/or pallidonigral systems has considerable experimental support. The effects of lesions on GAD and GABA were mentioned in the previous paragraph. The highest concentrations of GABA and GAD in the mammalian central nervous system are found in the substantia nigra (Fahn & Cote, 1968; Okada, Nitsch-Hassler, Kim, Bak & Hassler, 1971), particularly in the medial portion of the pars reticulata and the lateral portion of the pars compacta as it merges with the reticulata

(Fonnum et al., 1974). Okada and Hassler (1973) found that electrical stimulation of slices of rat substantia nigra resulted in uptake and release of ^{14}C-GABA. Hattori, McGeer, Fibiger and McGeer (1973; rat) observed the transport of ^{3}H-GABA from the pallidum to the nigra.

Electrophysiological studies have provided further evidence for a GABAergic pathway from the corpus striatum to the substantia nigra. Feltz (1971; rat), recording extracellularly from spontaneously active or amino acid driven nigral cells, found stimulation of the deep medial or lateral caudate inhibited nigral units with a latency of 5-10 msec and a duration of 30-70 msec. These same units were inhibited by iontophoretic GABA, but not ACh or glycine. Yoshida and Precht (1971; cat) stimulated the head of the caudate and recorded monosynaptic IPSP's (mean latency 18.2 msec) in nigral cells, the rising phase of which coincided temporally with extracellularly recorded positive field potentials (approximately 16 msec). In a subsequent report, Precht and Yoshida (1971; cat) showed that intravenous picrotoxin blocked the inhibition of nigral cells and the positive field potentials evoked by caudate stimulation. Crossman, Walker and Woodruff (1973; rat) found that the depressant effect of caudate stimulation or iontophoretic GABA was antagonized by iontophoretic picrotoxin. Thus, a descending, inhibitory GABAergic system originates in the caudate and/or pallidum and terminates in the reticular and/or compact portions of the substantia nigra. Yoshida, Rabin and Anderson (1971; cat) have suggested that the strionigral projection sends axon collaterals to the entopeduncular nucleus, thus explaining the

monosynaptic IPSP's and positive field potentials recorded in the entopeduncular nucleus following stimulation of an area around the substantia nigra which corresponds to the termination points of the strionigral system.

The best understood pallidal efferent system is the pallidothalamic projection, which has been described in the monkey by Nauta and Mehler (1966). The medial pallidal segment gives rise to the ansa lenticularis and lenticular fasciculus which pass through the internal capsule and merge in Forel's field H. Fibers then pass rostrally and laterally in the thalamic fasciculus. Most of the pallidothalamic fibers (contained in the thalamic fasciculus) terminate in the ventral lateral (VL) (pars oralis and medialis) and ventral anterior (VA) (pars principalis) nuclei. They also observed fine fibers which separated from the thalamic fasciculus, traversed parts of the ventral posteromedial thalamic nucleus and terminated in the CM nucleus. These fibers were assumed to be collaterals of the large projection to the ventral tier nuclei. The VL nucleus represents a relay by which corpus striatal output is projected to the motor cortex, whereas the VA nucleus represents a relay to the frontal cortex (Purpura, Frigyesi, McMurty & Scarff, 1966). Desiraju and Purpura (1969; cat) stimulated the ansa lenticularis or the contralateral brachium conjunctivum (which contains cerebellar efferents projecting to the VL nucleus) and recorded intracellularly in VL neurons. Pallidal and cerebellar inputs were found to converge monosynaptically on VL neurons and exhibited short latency EPSP's (.7-.9 msec for ansa lenticularis stimulation; 1.3-1.5 msec for

brachium conjunctivum stimulation). Brachium conjunctivum induced EPSP's were often succeeded by prolonged IPSP's, but this was not seen after ansa lenticularis stimulation.

In addition to pallidothalamic fibers, Nauta and Mehler (1966), also observed projections to the habenula, pedunculopontine nucleus and a small circumscript caudal area of the pars compacta. No pallidotegmental fibers extended caudally beyond the mesencephalon.

Remaining Projections of the Substantia Nigra

The nigrostriatal, strionigral and pallidonigral projections have already been discussed. A serotonergic input to the nigra will be dealt with in the section on the raphe system. The remaining efferent projections of the nigra are nigrothalamic, nigrotectal and nigroreticular.

Afifi and Kaelber (1965), traced the anterograde degeneration of nigral axons followng lesions of the nigra. The greatest outflow was to the ipsilateral midbrain tegmentum and tectum. There were also projections to the ipsilateral red nucleus, subthalamic nucleus, inferior colliculus, nucleus of darkschevitsch, VA and ventral medial (VM) thalamic nuclei. Faull and Carman (1968; rat), utilizing a similar technique observed nigral projections entering the ventrolateral border of the VM nucleus. Since lesions of the superior cerebellar peduncle, red nucleus or prerubral radiation also produced terminal degeneration in the VM nucleus, they suggested that this nucleus is the rat homologue of the VA and VL nuclei in primates. Rinvik (1975; cat) injected horseradish peroxidase into VL and VM nuclei and observed granules

throughout the ipsilateral pars reticulata (particularly in the lateral portion) in large, elongated or spindle-shaped cells. In a subsequent investigation, Rinvik, Grofova and Ottersen (1976; cat) compared the retrograde transport of horseradish peroxidase injected into different parts of the superior colliculus and brainstem reticular formation with the anterograde transport of ^{3}H-leucine or ^{3}H-proline injected into the middle third of the pars reticulata. Deep collicular injections produced labelling in the ipsilateral reticulata while reticular formation injections (particularly in mesencephalon and pontine reticular formation) produced labelling in the reticulata and compacta. Autoradiographic analysis of the labelled amino acids showed radioactivity in the stratum intermedium and profundum of the ipsilateral superior colliculus. Carpenter and Peter (1972; monkey) suggest that the nigrothalamic projection arises exclusively from the pars reticulata since lesions primarily involving the crus cerebri but infringing upon the adjacent reticulata produce degeneration in thalamic nuclei but none in the striatum. In a recent study, Carpenter, Nakano and Kim (1976; monkey) have found nigral projections to the paralaminar part of the dorsomedial thalamic nucleus in addition to projections to VL and VA nuclei.

There have been a number of recent reports indicating the existence of a mesocortical dopamine system. It appears to arise in the dopaminergic A10 nucleus (of Dahlstrom & Fuxe, 1964) of the mesencephalon and projects to the prefrontal cortex (Berger, Tassin, Blanc, Moyne & Thierry, 1974; Berger, Thierry, Tassin & Moyne, 1976; Fuxe, Hokfelt, Johansson, Jonsson, Lidbrink & Ljungdahl

1974; Lindvall, Bjorklund, Moore & Stenevi, 1974). Berger et al., 1976; rat) noted the similar projections of the mesocortical dopamine system and the mediodorsal nucleus of the thalamus (Leonard, 1969). Mora, Sweeney, Rolls and Sanguinetti (1976; rat) found that systemic administration of either apomorphine, amphetamine, or L-DOPA (plus a peripheral aromatic amino acid decarboxylase inhibitor), inhibited the spontaneous activity of extracellularly recorded units in the medial prefrontal cortex. This inhibition could be blocked by pretreatment with spiroperidol, an antagonist at central dopamine receptors (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970).

Anatomy of the Raphe System

The raphe system or complex consists of a group of midline brainstem nuclei beginning slightly above the caudal pole of the medial accessory olive in the caudal medulla and extending to the rostral mesencephalon. According to the nomenclature of Taber, Brodal and Walberg (1960; cat), starting caudally and moving rostrally the raphe nuclei consist of the nucleus raphe obscurus, raphe pallidus, raphe magnus, raphe pontis, centralis superior (median raphe in rat), raphe dorsalis, linearis intermedius and linearis rostralis. Brodal, Taber and Walberg (1960; cat) and Brodal, Walberg and Taber (1960; cat) investigating the efferent and afferent connections of the raphe nuclei utilizing various degeneration techniques have determined that long ascending and to a slightly lesser extent long descending fibers are the major efferents of the raphe nuclei. They noted the marked similarity of the efferent projections to those of the reticular formation. Ascending axons projected to the corpus striatum, anterior thalamus, mesencephalic tegementum and intracerebellar nuclei, while descending axons descended, in part, in the dorsal half of the lateral funiculus and did not appear to pass below the thoracic cord. Raphe afferents ascended in the ventrolateral funiculus and a few arose from levels below thoracic 12. Extensive input came from the cerebral cortex (particularly the sensorimotor region) and the fastigial nucleus of the cerebellum. Ungerstedt (1971; rat), characterized the raphe system by staining its 5-hydroxytryptaminergic projections and noting fluoresence before and after various lesions of the brainstem. He confirmed the existence of long ascending and descending fibers and observed a prominent projection from the

median and dorsal raphe which, after running rostroventrally toward the interpeduncular nucleus, joined the ventral portion of the MFB and split into medial and lateral components. The medial axons ascended in the septum and turned caudally in the cingulum, while the lateral axons infiltrated the hypothalamic area and amygdaloid tract. Due to the weak fluorescence of serotonergic terminals, it was impossible to determine the exact areas of innervation, but some terminals were observed in the globus pallidus, septal area, amygdaloid complex, hypothalamus and cingulate gyrus.

Kuhar, Aghajanian and Roth (1972; rat) correlated decreased serotonergic fluoresence following lesions of the midbrain raphe nuclei with decreased serotonin levels or decreased activity of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin from dietary L-tryptophan (Jequier, Lovenberg & Sjoerdsma, 1967). They found evidence for raphe projections to the cerebral cortex, globus pallidus, pars reticulata, pretectal nucleus, superior colliculus, preoptic area, septal area, cortical and basal amygdaloid nuclei, mammilary bodies, habenula, ventral lateral geniculate, reuniens nuclei, hippocampus, and a sparse projection to the cerebellum. An extensive investigation of the ascending and descending efferent connections of the median and dorsal raphe nuclei in the albino rat by Conrad, Leonard and Pfaff (1974) confirmed and expanded the observations of Ungerstedt. Utilizing reduced silver staining after lesions or ^{3}H-proline, the major ascending projection was seen to sweep ventrally and then rostrally through the ventral tegmentum and join the MFB, while a

smaller, dorsal projection radiated through the mesencephalic reticular formation and central grey, turned ventrally at the posterior thalamic border and entered the subthalamus. Fibers from the MFB branched into the ventral caudate nucleus, nucleus accumbens, hypothalamus, preoptic areas, anterior amygdala, olfactory tubercle, septal nuclei and cingulum bundle, while some fibers entered the fornix or stria terminalis. Fibers in the cingulum bundle projected into the cell-free layers of the pregenual cortex, subiculum and hippocampus. Ascending projections were observed to the mediodorsal, parafascicular and reuniens nuclei of the thalamus and to the habenular nuclei via the fasciculus retroflexus. Descending projections to the dorsal tegmental nucleus, locus coeruleus, pontine reticular formation and caudal central grey were observed with no projections below the level of the facial nerve nucleus. No projections were seen to the cerebellum, caudal raphe nuclei, cranial nerve nuclei, lateral geniculate nucleus, superior colliculus, globus pallidus, suprachiasmatic nucleus of the hypothalamus and most of the neocortex. Geyer, Puerto, Dawsey, Knapp, Bullard and Mandell (1976a, rat) destroyed the median or dorsal raphe nuclei selectively and measured changes in tryptophan hydroxylase activity in various brain regions. Both the median and dorsal raphe nuclei sent overlapping serotonergic projections to the cerebral cortex and certain hypothalamic nuclei, but the median raphe differentially projected to the septal nuclei and hippocampus and the dorsal raphe to the striatum and thalamus. They suggested that the median and dorsal raphe represented two distinct though overlapping serotonergic systems, characterized by mesolimbic (median raphe) and mesostriatal (dorsal raphe) com-

[illegible] Salvert, Touret and Jouvet

(1976) injected ^{14}C-leucine stereotaxically into the median raphe, dorsal raphe, raphe magnus or raphe pontis of the cat and observed its anterograde transport autoradiographically. The median raphe showed unexpectedly dense projections to the mesencephalic reticular formation, interpeduncular nucleus, mammillary bodies, hippocampus and entorhinal cortex; the dorsal raphe sent projections to the central grey, nucleus accumbens, striatum, globus pallidus, amygdala, piriform lobe and olfactory bulb. A projection from the median to dorsal raphe was also seen. The median and dorsal raphe sent overlapping projections to the pars compacta of the substantia nigra, most hypothalamic nuclei, certain thalamic nuclei, preoptic area, diagonal band of Broca, neocortex (particularly the frontal lobes), septal nuclei, stria terminalis and tuberculum olfactorium. The ascending projections of the raphe magnus and pontis were much less dense, terminating preferentially in the superior colliculus, pretctum, nucleus of the posterior commissure, preoculomotor complex and the intralaminar nuclei of the thalamus. Both nuclei sent diffuse projections to the mesencephalic and pontobulbar reticular formations and to the cerebellum.

The contention that the median and dorsal raphe have differential projections has received considerable support from a number of studies, particularly in relation to striatal, hippocampal and nigral inputs. Lorens and Guldberg (1974; rat) observed a 54% decrease in striatal 5-HT following dorsal raphe lesions and a 62% decrease in hippocampal 5-HT following median raphe lesions. Dorsal raphe lesions produced 5-HT decreases in the telencephalon-diencephalon twice as large as median raphe lesions. Neither lesion affected spinal 5-HT levels. Similar findings in rat have recently

been presented by Jacobs and Cohen (1976). Injection of horseradish peroxidase into the rat striatum by Nauta, Pritz and Lasek (1974) resulted in labelling of the dorsal raphe only. Kanazawa, Marshall and Kelly (1976; rat) and Bunney and Aghajanian (1976; rat) demonstrated input to the substantia nigra originating in the dorsal raphe by the retrograde transport of horseradish peroxidase. Kanazawa, Marshall and Kelly suggest that the dorsal raphe projects specifically to the pars compacta of the substantia nigra and might modify nigrostriatal activity. Modification of nigrostriatal activity by serotonergic input from the median raphe to the substantia nigra has been suggested by Dray, Gonye, Oakley and Tanner (1976; rat). Their conclusions are based upon the similar effects of electrical stimulation of the median raphe and the iontophoresis of 5-HT into the substantia nigra (predominantly inhibiton of neuronal firing). They also observed a decrease in nigral serotonin (but not GABA) and a concomitant increase in striatal dopamine levels following destruction of the median raphe.

It seems reasonable to state that the raphe nuclear complex projects to all levels of the neuraxis and exhibits differential mesolimbic and mesostriatal components, probably originating in the median and dorsal raphe nuclei respectively. If this is considered together with the prominent interconnections of the raphe nuclei and the brainstem reticular formation a logical neuroanatomical substrate for the integration and control of both visceral and somatic functions emerges.

The Present Investigation

The observations of Pieri, Pieri and Haefely (1974; rat) that chemically-induced unilateral depletion of nigrostriatal dopamine resulted in LSD-induced contralateral rotation markedly similar to that induced by the directly acting dopamine agonist apomorphine, prompted this investigator to examine the rotational efficacy of LSD in normal rats. Although these investigators attributed the rotation induced by LSD to stimulation of denervated, and thus supersensitive striatal dopamine receptors, the possibility that serotonergic mechanisms were involved could not be excluded. The research to be presented represents an extensive investigation of the effects of manipulation of dopaminergic and serotonergic transmission upon pharmacologically-induced rotation in normal rats.

Once it had been demonstrated that LSD could induce consistent and dose-dependent rotation, two other hallucinogens without putative dopaminergic properties, mescaline and 5-methoxy-N,N-dimethyl tryptamine were examined. L-LSD, the non-hallucinogenic enantiomer of d-LSD was tested to ascertain whether the hallucinogenic properties of LSD could be differentiated from its rotational properties. Methysergide, 2-bromo-LSD a cyproheptadine, peripheral serotonergic antagonists with putative central potency, but virtually no dopaminergic activity, were utilized as probes into the serotonergic involvement in drug-induced rotation.

The drug-interaction studies provided additional ways of examining the relative contributions of serotonergic and dopaminergic mechanisms in LSD-induced rotation and can be divided into three general categories: (1) Those which increase (L-tryptophan) or decrease (p-chloro-phenylalanine) central serotonin levels (2) Those which affect central dopaminergic transmission, such as the dopamine receptor antagonist haloperidol; the dopamine synthesis inhibitor alpha-methyl-p-tyrosine; the indirectly acting dopamine agonist d-amphetamine, the directly acting dopamine agonist apomorphine and (3) The anti-muscarinic scopolamine.

The Methods and Results are divided into three sections: (1) Dose-response relationships (2) Directional consistency of pharmacologically-induced rotation and (3) The effects of pharmacological interactions upon LSD-induced rotation.

BEHAVIORAL METHODS

General

The animals used in all of the experiments were female Sprague-Dawley albino rats approximately three months of age and ranging in weight from 200 to 300 grams.

The animals were tested in an automated rotometer (Greenstein & Glick, 1975) adapted from and originally described by Ungerstedt and Arbuthnott (1970). The apparatus consists of two Plexiglas hemispheres, twelve inches in diameter, which together form a sphere. The animal is placed in the lower hemisphere and harnassed using a stainless wire sheathed in silicone tubing with an alligator clip at one end and a button magnet at the other. The alligator clip is gently slipped around the midsection of the animal and clipped to the wire forming a loop. The button magnet is fastened to an iron washer at the base of a vertical center shaft which projects one inch into the upper hemisphere. On top of, and connected to the center shaft, is a circular plastic disc (the upper disc) such that as the animal rotates the upper disc does likewise. Immediately below the upper disc is a stationary lower disc of equal size which is fastened to the upper hemisphere. Four photocells are mounted 3/4 inch from the center of the lower disc and 90 degrees apart, face flush with the top of the disc. The upper disc has one hole in it, 3/4 inch from the center. A stationary light source is mounted approximately one inch above the upper disc,

such that, as the upper disc revolves 360 degrees, it illuminates the four photocells. With this apparatus both the number and direction of quarter turns (90 degrees) and full turns (four consecutive quarter turns in the same direction) are automatically recorded on a printout counter at five minute intervals.

The experimental procedure consisted of a 15 minute habituation period, immediately followed by intraperitoneal administration of drug or vehicle, and a 60 minute testing period. Net rotations for the pre- and post-injection periods were determined by subtracting rotations in the non-dominant direction from rotations in the dominant direction.

Drugs were usually dissolved in physiological saline (0.9%). The injection volume was 1 milliliter/kilogram (ml/kg). The following drugs were used: d-lysergic acid diethylamide tartrate (LSD); l-lysergic acid diethylamide tartrate (l-LSD); 2-bromo-d-lysergic acid diethylamide tartrate (2-bromo-LSD); mescaline hydrochloride; 5-methoxy-N,N-dimethyltryptamine (MDMT); methysergide bimaleate; cyproheptadine hydrochloride; d-amphetamine sulfate; apomorphine hydrochloride; scopolamine hydrobromide; L-tryptophan; D,L-alpha-methyl-p-tyrosine methyl ester hydrochloride (AMPT):D,L-p-chlorophenylalanine methyl ester hydrochloride (PCPA); haloperidol. Drug doses are expressed as milligrams/kilogram (mg/kg).

Dose-Response Relationships

Dose-response relationships were obtained for three hallucinogenic agents with differing chemical structures: LSD, mescaline and MDMT; the non-hallucinogenic enantiomer of LSD, l-LSD; and

the serotonergic antagonists 2-bromo-LSD, methysergide and cyproheptadine. In addition, a dose-response relationship for LSD before, and after pretreatment with the tryptophan hydroxylase inhibitor PCPA, was also generated.

Each point on a dose-response curve represents the mean net rotations (rotation in the dominant direction minus rotation in the non-dominant direction) for the 60 minute interval immediately following the administration of drug or vehicle. Separate groups of animals were used for each dose on the dose-response curve.

Directional Consistency Between Drugs Which Induce Rotation

Rats were tested twice for rotational preferences (i.e. the dominant direction of rotation) with a one week interval separating the two testing sessions. Previous work has demonstrated that amphetamine- (Jerussi & Glick, 1974) or apomorphine-induced rotation (Jerussi & Glick, 1975) in unlesioned rats is consistent in direction and magnitude from one week to the next. This does not mean that all animals rotate in the same direction with a drug such as amphetamine, but when this drug is administered at the same dose to the same animal, it will induce rotation in the same direction and of comparable magnitude from one week to the next. The importance of directional consistency stems from the possibility that if two different drugs cause the same animal to rotate in the same direction from week to week, the drugs may have a common mechanism of action. Of course, directional consistency by itself, is not sufficient to support a

common mechanism of action. However, when it is combined with other data, such as that obtained from a drug-interaction experiment, a relatively convincing argument can be formulated regarding the mechanism of action.

Pharmacological Interactions: Effects on Rotational Behavior

The objective of the drug-interaction experiments was to elucidate the neurotransmitter systems subserving rotation induced by LSD. For each drug-interaction experiment, the same group of animals was used throughout, so that each animal served as its own control.

NEUROCHEMICAL METHODS

Each rat was killed by decapitation, and the excised brain was dissected into left and right halves. The cerebellum and lower brainstem (i.e., everything caudal to the colliculi) were discarded.

5-Hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid (5-HIAA) were extracted and measured by a modification of the spectrofluorometric method of Curzon and Green (1970). Each half-brain was homogenized in 3.5 ml of cold, acidified n-butanol; an additional 0.5 ml of cold, acidified n-butanol was added to facilitate the removal of the homogenate. After centrifugation at 15,000 RPM for 20 minutes, 3.5 ml aliquots of the supernatant were transferred to 15 ml glass centrifuge tubes. 0.4 ml of 0.1% L-cysteine in 0.1N HCl and 7 ml of n-heptane were added and the mixture was mechanically shaken for 5 minutes, and centrifuged at 3,000 RPM for 5 minutes. 8 ml aliquots of the upper organic phase were transferred to 15 ml glass centrifuge tubes and the remaining organic phase (including the tissue disc at the organic-aqueous interface) was aspirated; these organic aliquots were kept on ice for 5-HIAA determination.

For determination of 5-HT, duplicate 0.1 ml aliquots of the aqueous (acidic) phase were transferred to Kimble borosilicate culture tubes (12 mm x 75 mm), designted as A and B tubes (the B tubes were used to determine how much quenching of fluoresence had occurred). 0.1 ml of 0.1N HCl was added to the A tubes, while 0.5 µg of 5-HT (in 0.1 ml of 0.1N HCl) was added to the B tubes.

0.6 ml of 0.004 % o-phthaldialdehyde (OPT) in 10N HCl was added to all tubes, they were vortexed for 5 seconds, heated in a sand bath at 90°C for 30 minutes and rapidly cooled in cold water. The samples were transferred to J4-8112 Suprasil . quartz micro-cuvettes (6.5 mm round I.D. x 40 mm high; 0.2 ml minimum volume) and read in a Turner 430 spectofluorometer (excitation wavelength= 360 nm; emission wavelength=470 nm).

5-HIAA was determined using the 8 ml aliquots of organic phase referred to earlier. 0.6 ml of 0.5M phosphate buffer (pH=7.0) was added and the mixture was mechanically shaken for 5 minutes and centrifuged at 3,000 RPM for 5 minutes. The organic phase was aspirated and duplicate 0.1 ml aliquots of the aqueous phase were transferred to A and B tubes. 0.1 ml of 0.1N HCl was added to the A tubes, while 0.25 µg of 5-HIAA (in 0.1 ml of 0.1N HCl) was added to the B tubes. 0.1 ml of 0.1% OPT-methanol (w/v), 0.1 ml of 1% L-cysteine in distilled water and 0.4 ml of concentrated HCl were added to each tube and they were vortexed for 5 seconds, heated in a sand bath at 90°C for 30 minutes, rapidly cooled in cold water, transferred to the microcuvettes and read in the manner described for the 5-HT samples.

Except for the initial homogenization and centrifugation an internal standard was subjected to the same extraction procedure as the tissue samples. The internal standard was prepared by adding 0.1 ml of 0.1N HCl (containing 0.5 µg of 5-HT), plus another 0.1 ml of 0.1N HCl (containing 0.25 µg of 5-HIAA) to 3.8 ml of cold, acidified n-butanol and then removing 0.5 ml of the resulting mixture.

In order to determine to what degree quenching was obscuring the fluorescence being measured, the following procedures were followed: The fluorescence of the A tube was subtracted from the fluorescence of the B tube; the difference represents the quenched fluorescence of the 5-HT (or 5-HIAA) added to the B tube. This quenched fluorescence was divided by the unquenched fluorescence of the same amount of 5-HT (or 5-HIAA) determined from an external standard; the resulting quotient represents the quenching factor. The unquenched fluorescence of the A tube was determined by dividing the quenched fluorescence of the A tube by the quenching factor.

An additional methodological problem was encountered during the final extraction of 5-HIAA into the phosphate buffer. Instead of being a clear liquid, the buffer (aqueous) phase had a jelly-like consistency which made it extremely difficult to take the 0.1 ml aliquots necessary for determination of fluorescence. Thus the values for 5-HIAA are incomplete, but are included in the Results section.

BEHAVIORAL RESULTS

Dose-Response Relationships

Since the number of rats used to generate the dose-response relationships varied, the sample size for any particular dose will follow it parenthetically unless otherwise indicated. For the time course of drug-induced rotation, the lowest dose producing peak rotation was used. Negative net rotations in a given 5 minute interval signifies that the net rotations were in the non-dominant direction (as compared to the entire 60 minute testing period). Analysis of variance and two-tailed *t*-tests were used for data analysis.

LSD dose-response

Figure 1 illustrates the dose-response relationship generated after the administration of 0.0 (6), 0.031 (6), 0.062 (6), 0.125 (10), 0.25 (52), 0.5 (8), 1.0 (6) and 2.0 mg/kg (6) of LSD. One-way analysis of variance indicated a significant drug effect ($p<0.001$) and subsequent t-tests indicated that all doses greater than 0.31 mg/k induced significant roation ($p<0.05$ to $p<0.001$) as compared to saline injected controls. Maximum rotation occurred in the 0.25 to 0.5 mg/kg range. The rotation induced by LSD in the dose range of 0.062 to 0.5 mg/kg occurred without any other gross behavioral changes. Within this dose range, the animals rotated by standing on their hind paws and moving along the inner surface of the spherical rotometer with their front paws. However, at the highest doses of LSD (1.0 and 2.0 mg/kg) the animals exhibited a characteristic behavioral syndrome consisting of shaking, piloerection,

Figure 1. Dose-response relationship for d-LSD-induced rotation (mean $\pm$ standard error).

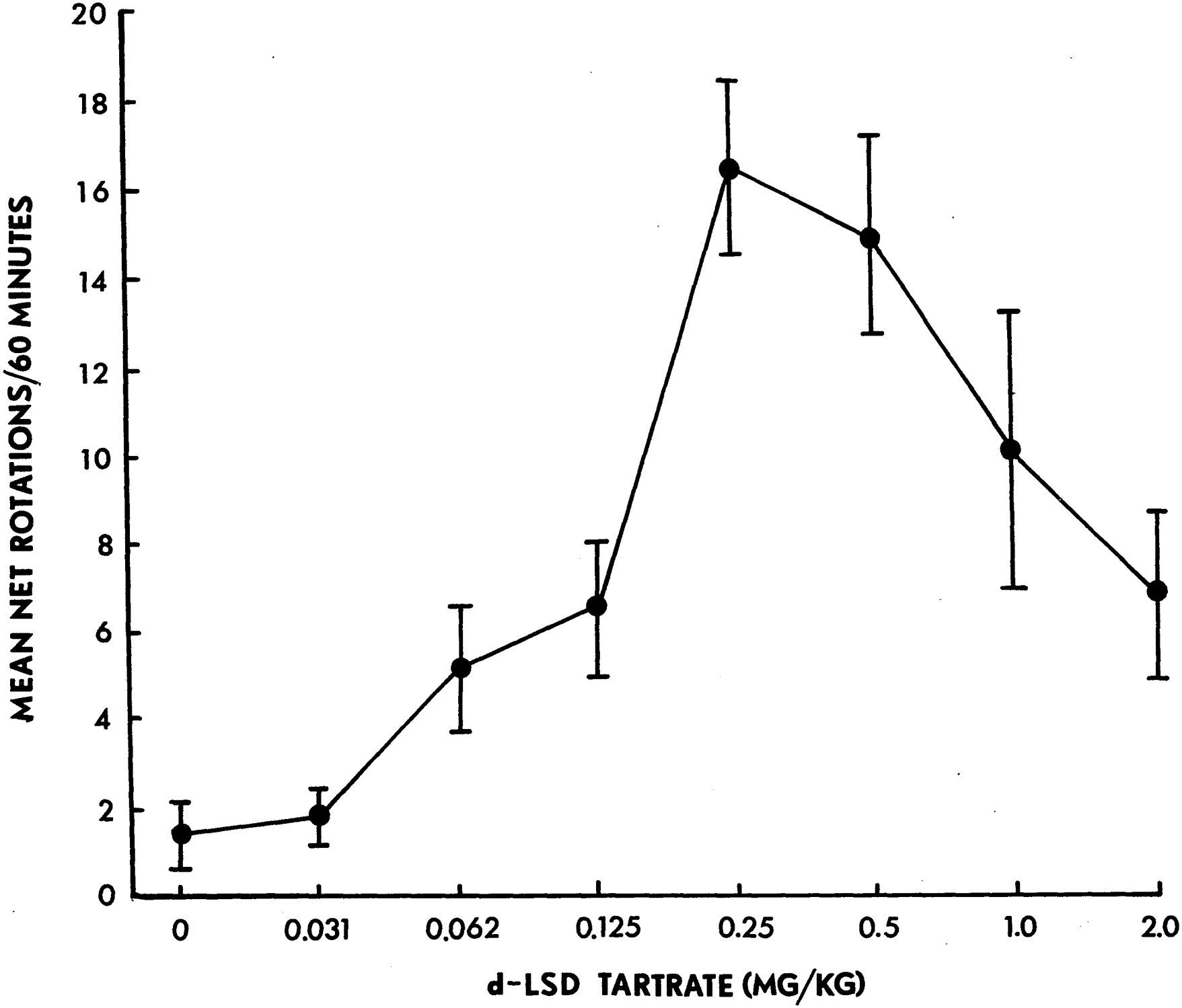
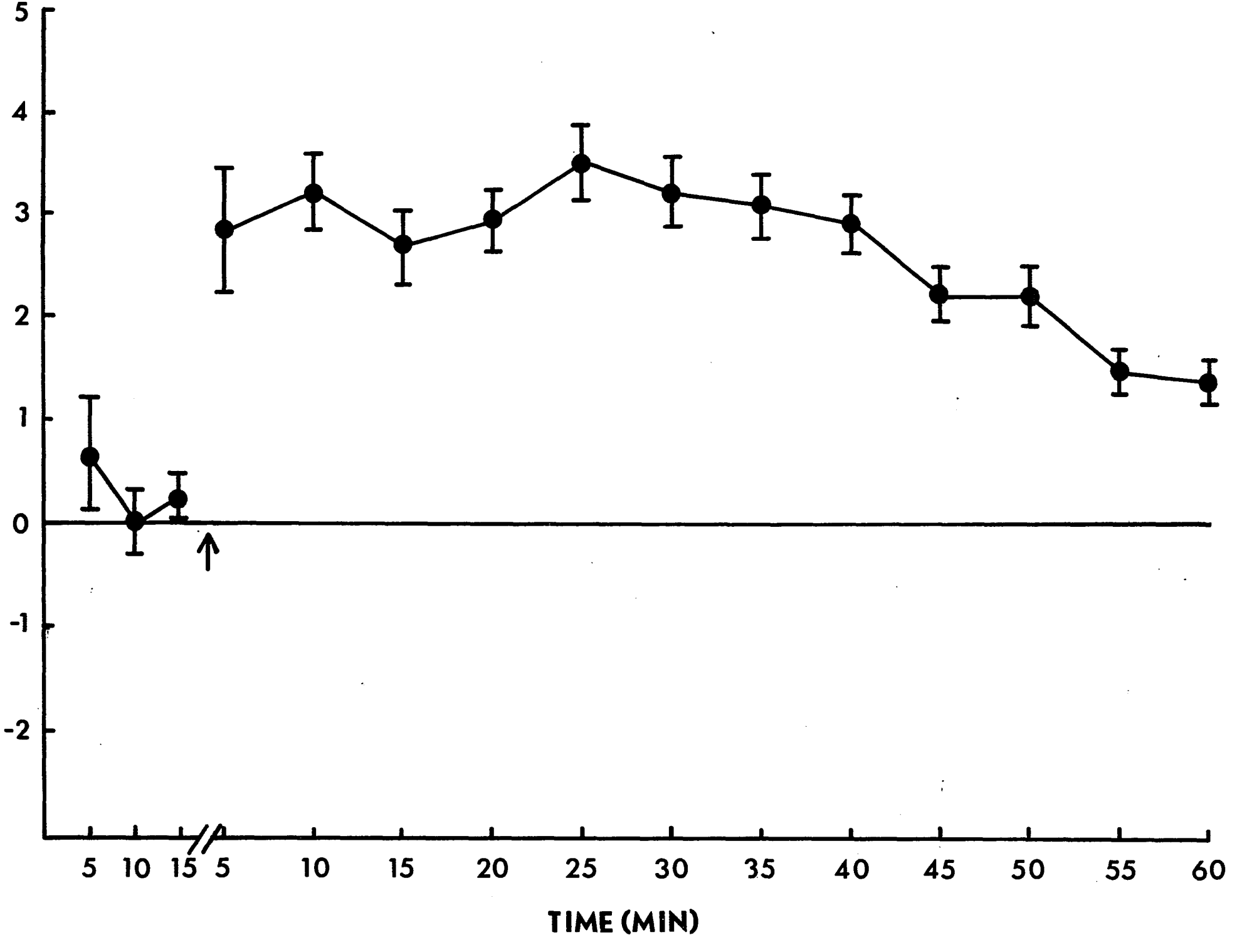

MEAN NET ROTATIONS/60 MINUTES
20
18
16
14
12
10
8
6
4
2
0
0
0.031
0.062
0.125
0.25
0.5
1.0
2.0
d-LSD TARTRATE (MG/KG)

Figure 2. Time course of d-LSD-induced rotation (mean ± standard error) for 0.25 mg/kg preceding and following injection (arrow).


5
4
3
2
1
0
-1
-2
5
10
15
5
10
15
20
25
30
35
40
45
50
55
60
TIME (MIN)

salivation, and marked splaying of the limbs so that they lay flat against the surface of the rotometer. This behavioral repertoire has been called aberrant behavior by Dixon (1968) and is remarkably similar to a syndrome induced by L-tryptophan (plus a monoamine oxidase inhibitor), L-5-HTP (Graham-Smith, 1971a; Jacobs, 1976; Modigh, 1972) or MDMT (Graham-Smith, 1971b). Figure 2 illustrates the time course of LSD-induced rotation following a 0.25 mg/kg (36) dose. Maximum rotational intensity was observed in the first 5 minute interval with a gradual decrease over the last 30 minutes.

Mescaline dose-response

Figure 3 illustrates the dose-response relationship generated after the administration of 0.0, 5.0, 10.0, 20.0 and 40.0 mg/kg of mescaline. Six rats were used for each dose. One-way analysis of variance indicated that there was a significant drug effect ($p<0.025$). The results obtained with t-tests showed that significant rotation was induced by 20.0 and 40.0 mg/kg doses ($p<0.01$ and $p<0.05$ respectively). In Figure 4, the time course of a 20.0 mg/kg (9) dose of mescaline, the induction of rotation is a bit slower than observed after LSD with a gradual increase over the first 15 minutes, a plateau over the next 20 minutes and a second peak during the last 10 minutes.

MDMT dose-response

Figure 5 illustrates the dose-response relationship generated after the administration of 0.0, 0.5, 1.0 and 2.5 mg/kg of MDMT. Six rats were used for each dose. One-way analysis of variance revealed a significant drug effect ($p<0.005$) and subsequent t-tests

Figure 3. Dose-response relationship for mescaline-induced rotation (mean $\pm$ standard error).

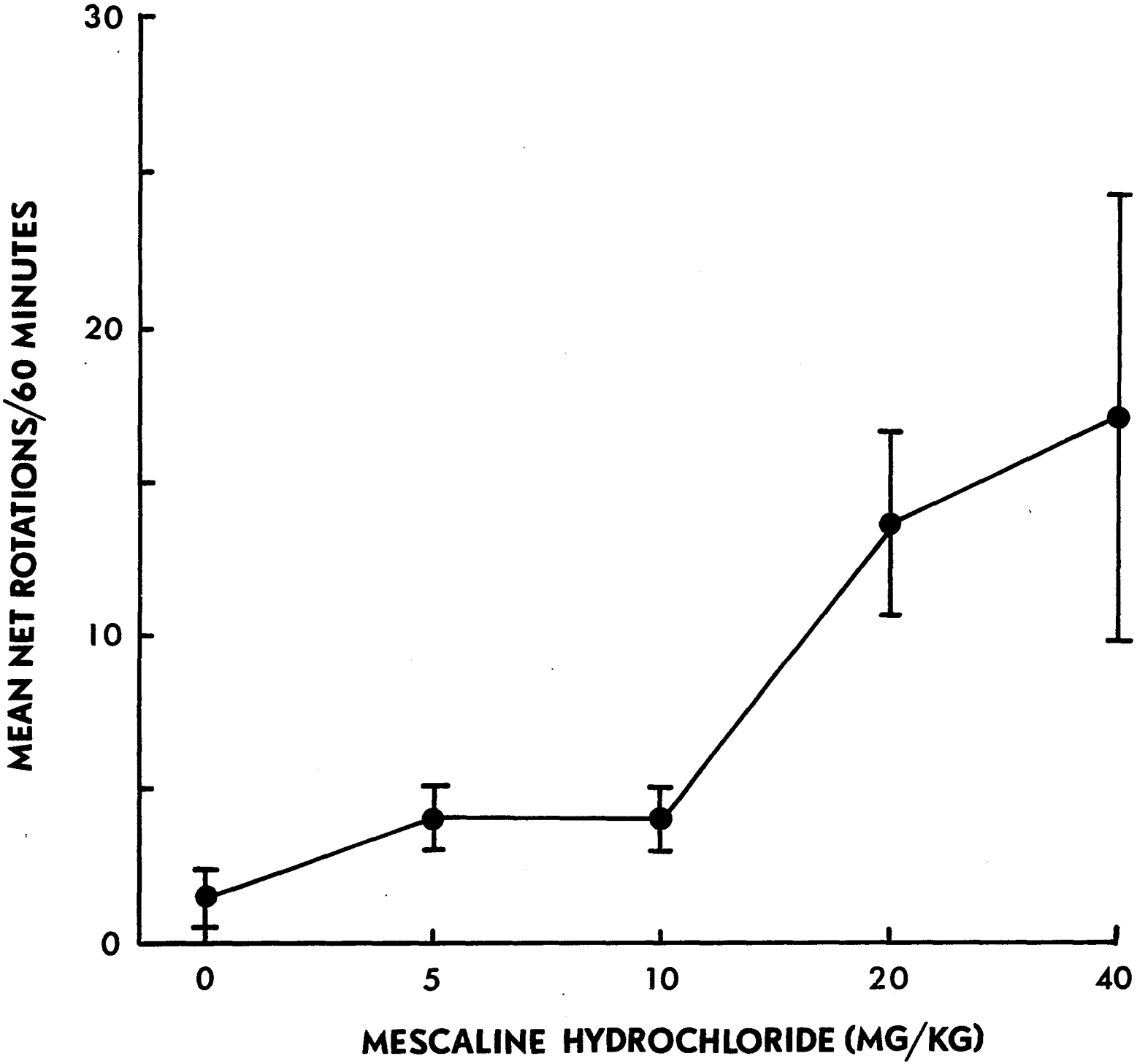

30
20
10
0
MEAN NET ROTATIONS/60 MINUTES
0
5
10
20
40
MESCALINE HYDROCHLORIDE (MG/KG)

Figure 4. Time course of mescaline-induced rotation (mean ± standard error) for 20.0 mg/kg preceding and following injection (arrow).

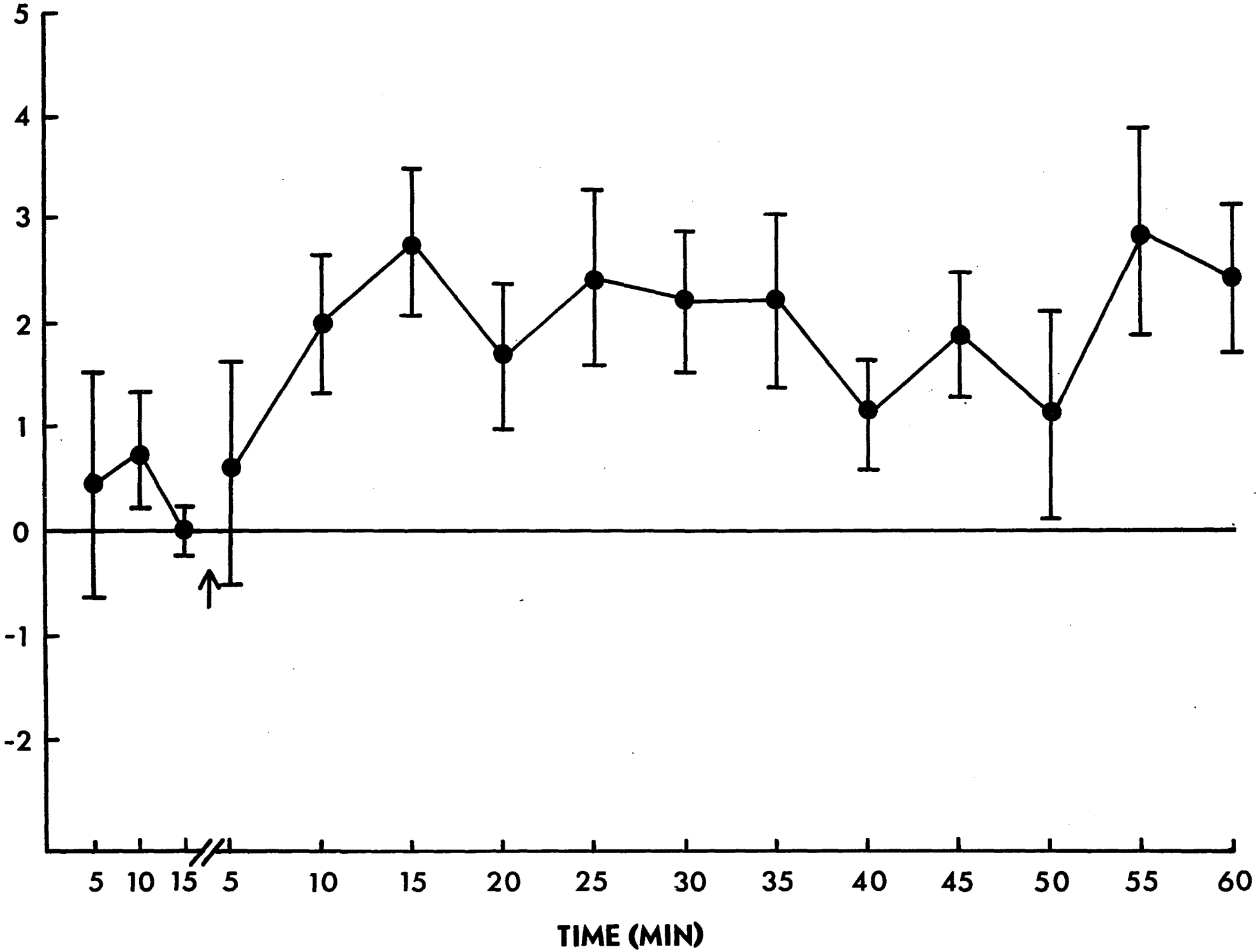
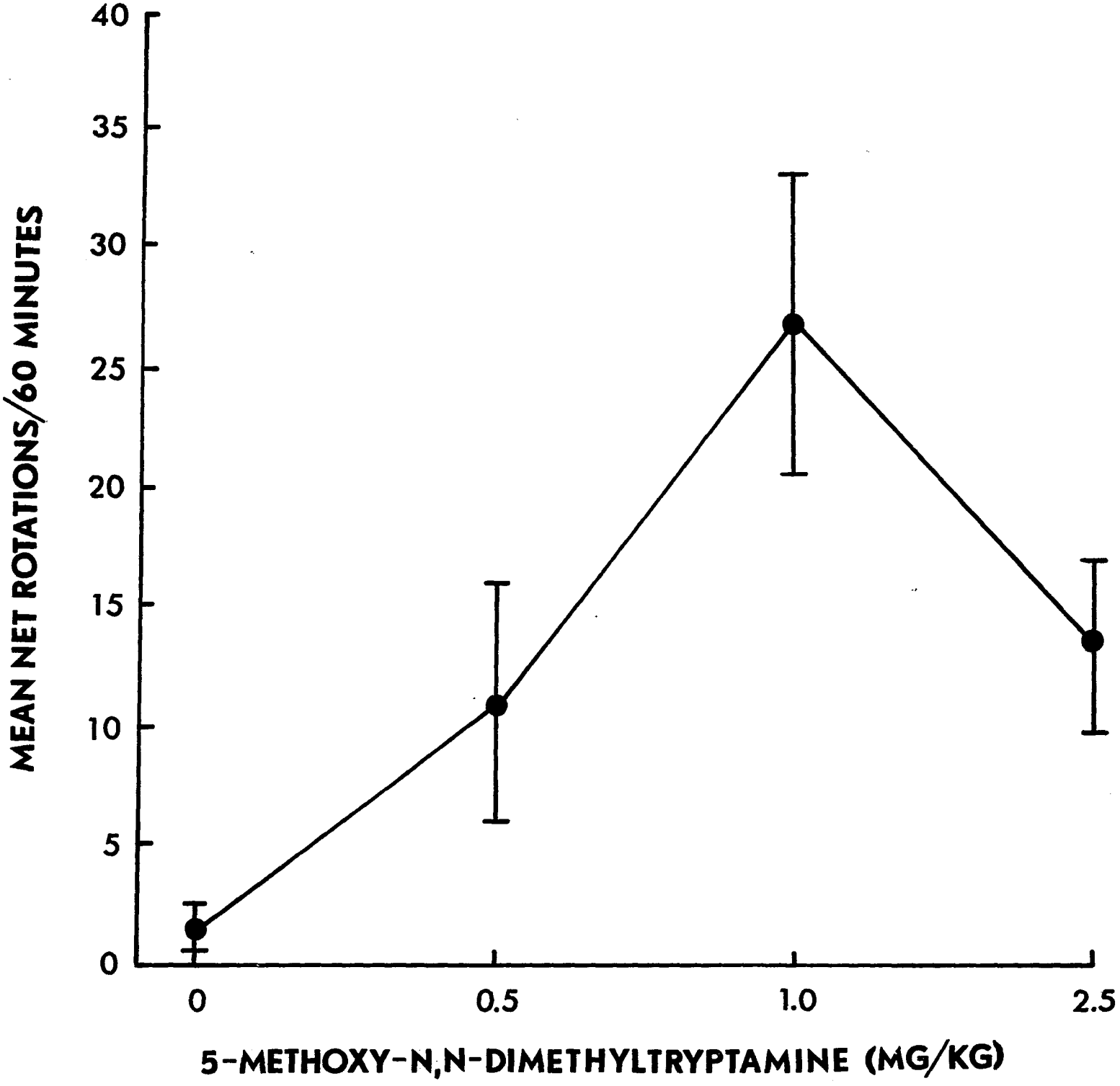

5
4
3
2
1
0
-1
-2
5 10 15 5 10 15 20 25 30 35 40 45 50 55 60
TIME (MIN)

Figure 5. Dose-response relationship for 5-methoxy-N,N-dimethyltryptamine-induced rotation (mean ± standard error).


40
35
30
25
20
15
10
5
0
MEAN NET ROTATIONS/60 MINUTES
0
0.5
1.0
2.5
5-METHOXY-N,N-DIMETHYLTRYPTAMINE (MG/KG)

showed that significant rotation was induced by the 1.0 and 2.5 mg/kg doses ($p<0.005$ and $p<0.01$ respectively). Maximum rotation occurred after the 1.0 mg/kg dose. Following the 2.5 mg/kg dose the animals displayed a high degree of aberrant behavior, similar to that seen after 1.0 or 2.0 mg/kg of LSD. The time course of rotation following a 1.0 mg/kg (10) dose of MDMT is shown in Figure 6. Maximum rotational intensity was observed during the first 5 minutes with an abrupt decline over the next 10 minutes and virtually no rotation during the last 45 minutes.

Methysergide dose-response

Figure 7 illustrates the dose-response relationship generated after the administration of 0.0 (6), 5.0 (5), 10.0 (8) and 20.0 mg/kg (6) of methysergide. One-way analysis of variance revealed no significant drug effect. However, a t-test indicated that rotation induced by the 10.0 mg/kg dose was significantly greater ($p<0.005$) than saline-injected controls. Figure 8 illustrates the time-course of methysergide-induced rotation following a 10.0 mg/kg (13) dose. Maximum rotational intensity was observed during the first 5 minutes and was relatively constant throughout the 60 minute interval.

Cyproheptadine dose-response

Cyproheptadine was administered to rats at the following doses; the numbers in parenthesis are the mean net rotations $\pm$ standard error 0.0 (1.3 $\pm$ 0.80), 5.0 (3.8 $\pm$ 1.14) and 10.0 (9.0 $\pm$ 4.33) mg/kg. Six rats were used for each dose. None of the doses tested induced significant rotation.

2-Bromo-LSD-dose-response

2-Bromo-LSD was administered to rats at the following doses; the numbers in parentheses are the mean net rotations $\pm$ standard

Figure 6. Time course of 5-methoxy-N,N-dimethyltryptamine-induced rotation (mean ± standard error) for 1.0 mg/kg preceding and following injection (arrow).

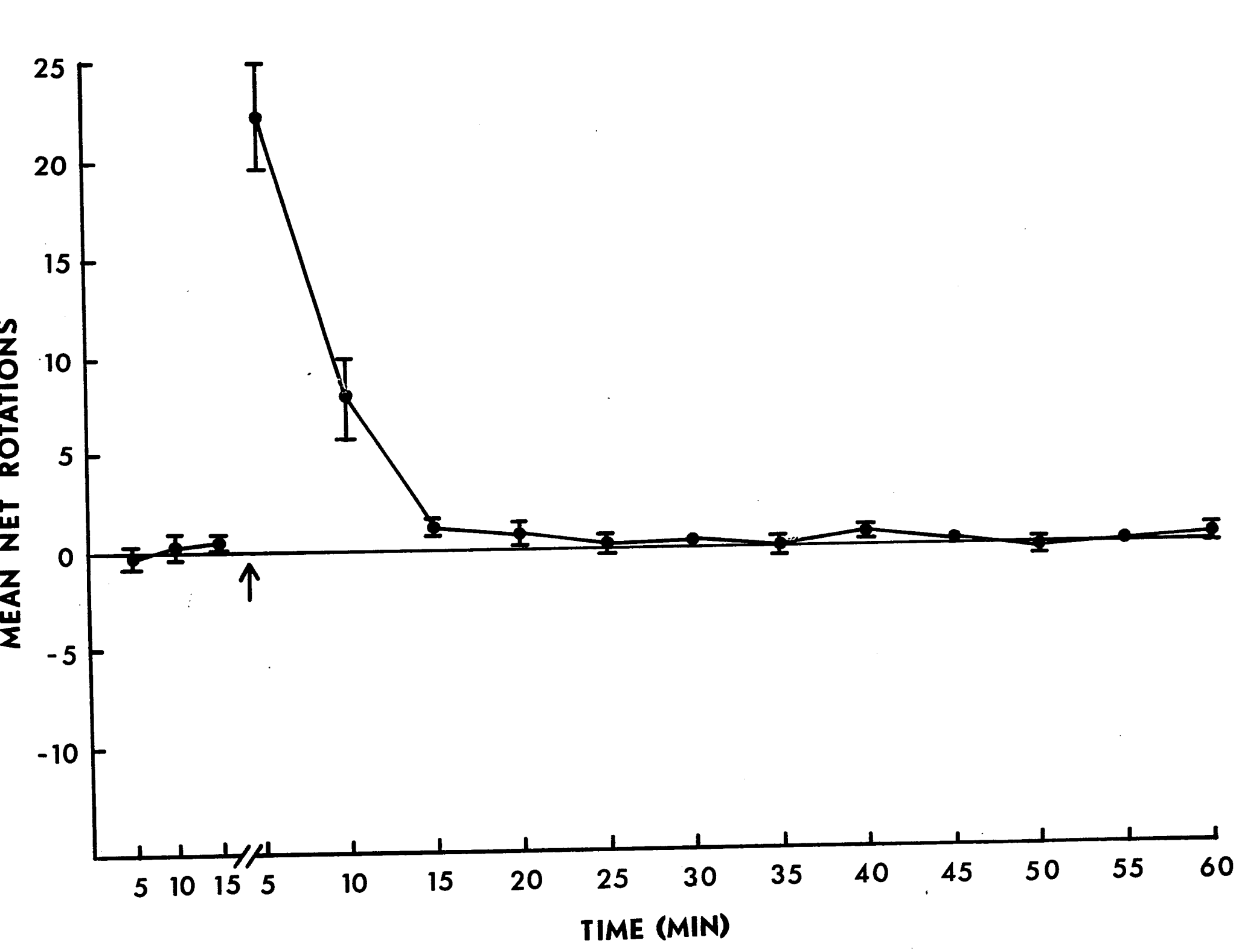

25
20
15
10
5
0
-5
-10
MEAN NET ROTATIONS
5
10
15
5
10
15
20
25
30
35
40
45
50
55
60
TIME (MIN)

Figure 7. Dose-response relationship for methysergide-induced rotation (mean $\pm$ standard error).

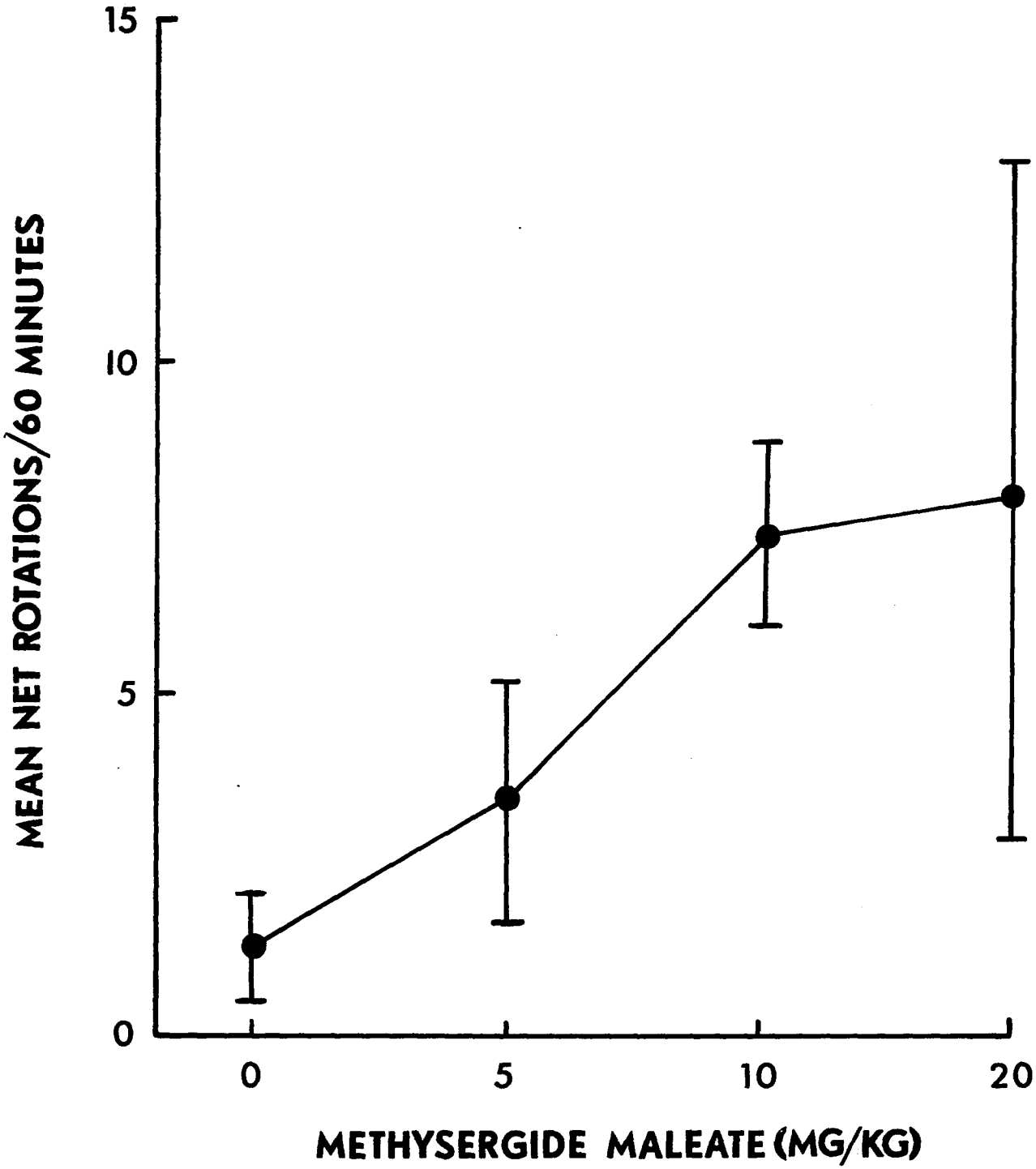
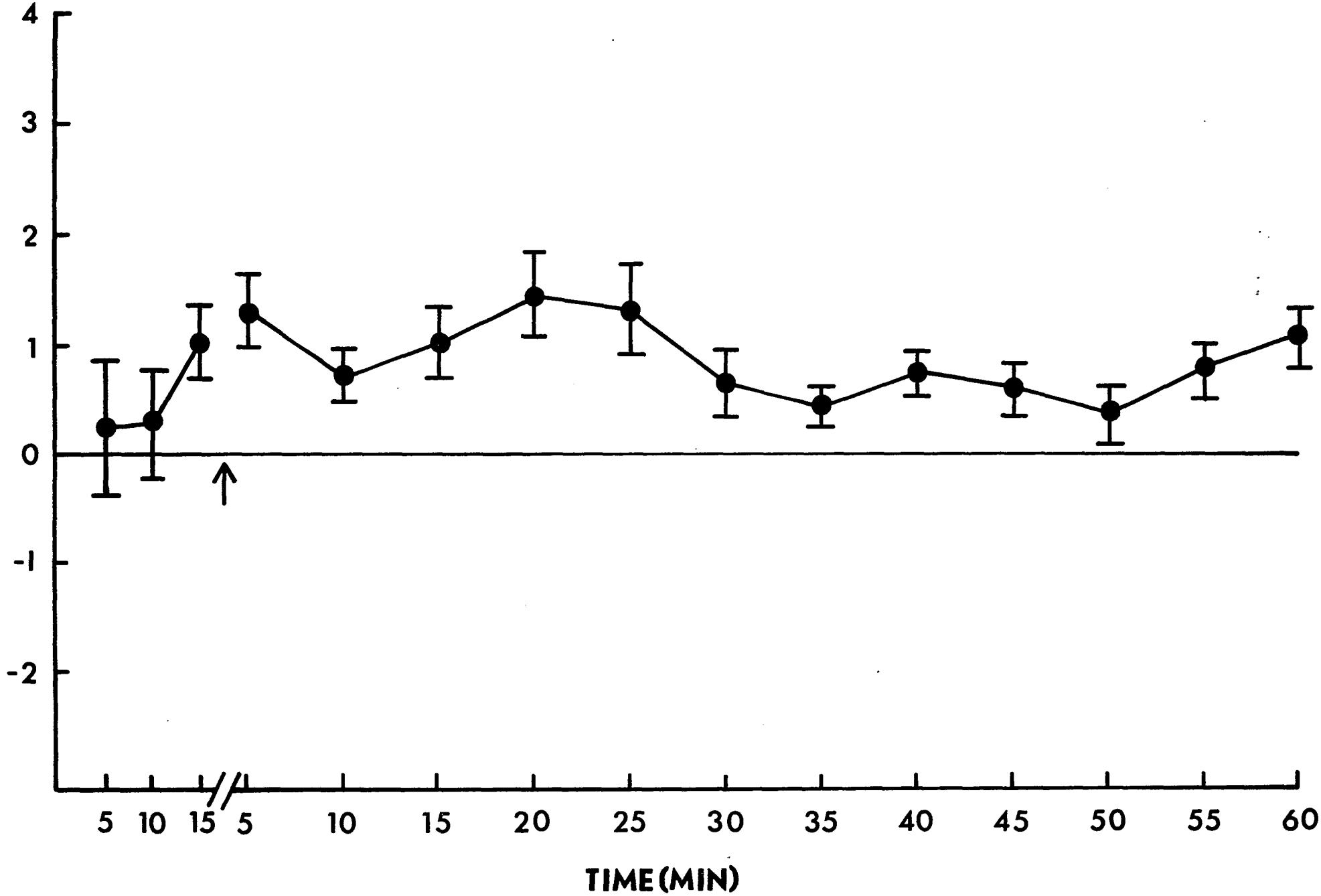

15
10
5
0
MEAN NET ROTATIONS/60 MINUTES
0
5
10
20
METHYSERGIDE MALEATE (MG/KG)

Figure 8. Time course of methysergide-induced rotation (mean ± standard error) for 10.0 mg/kg preceding and following injection (arrow).


4
3
2
1
0
-1
-2
5
10
15
5
10
15
20
25
30
35
40
45
50
55
60
TIME (MIN)

error: 0.0 (1.3 ± 0.80), 0.5 (1.5 ± 0.56), 1.0 (0.83 ± 0.48) and 5.0 (0.83 ± 0.48) mg/kg. Six rats were used for each dose. None of the doses tested induced significant rotation.

1-LSD dose-response

Figure 9 illustrates the dose-response relationship generated after the administration of 0.0, 0.25 and 0.5 mg/kg of 1-LSD. Six rats were used for each dose. One-way analysis of variance revealed a significant drug effect ($p<0.05$) and subsequent *t*-tests indicated that the 0.5 mg/kg dose induced significant rotation ($p<0.02$), although the magnitude was considerably less than after d-LSD.

LSD and PCPA dose-response interactions

In Figure 10, the dose-response relationships for LSD-induced rotation both before (day 1), and after (days 8 and 15) PCPA are plotted as a function of time. Rats were tested on day 1, administered PCPA (300 mg/kg; i.p.) on day 5 and retested on days 8 and 15. The following doses of LSD were used: 0.0 (6), 0.031 (6) 0.062 (5), 0.125 (5), 0.25 (5) and 0.5 mg/kg (4).

Three-way analysis of variance indicated that there was a significant effect of dose ($p<0.01$), a significant effect of time ($p<0.05$), and a significant effect of PCPA treatment ($p<0.05$). In addition, there was a significant interaction between the dose of LSD and the PCPA treatment ($p<0.05$). In other words, the effects of PCPA depended on the dose of LSD administered. There were no significant interactions between dose and time, time and PCPA treatment, and dose, time and PCPA treatment.

Subsequent analysis with t-tests revealed that on day 8, the

Figure 9. Dose-response relationship for l-LSD-induced rotation (mean $\pm$ standard error).

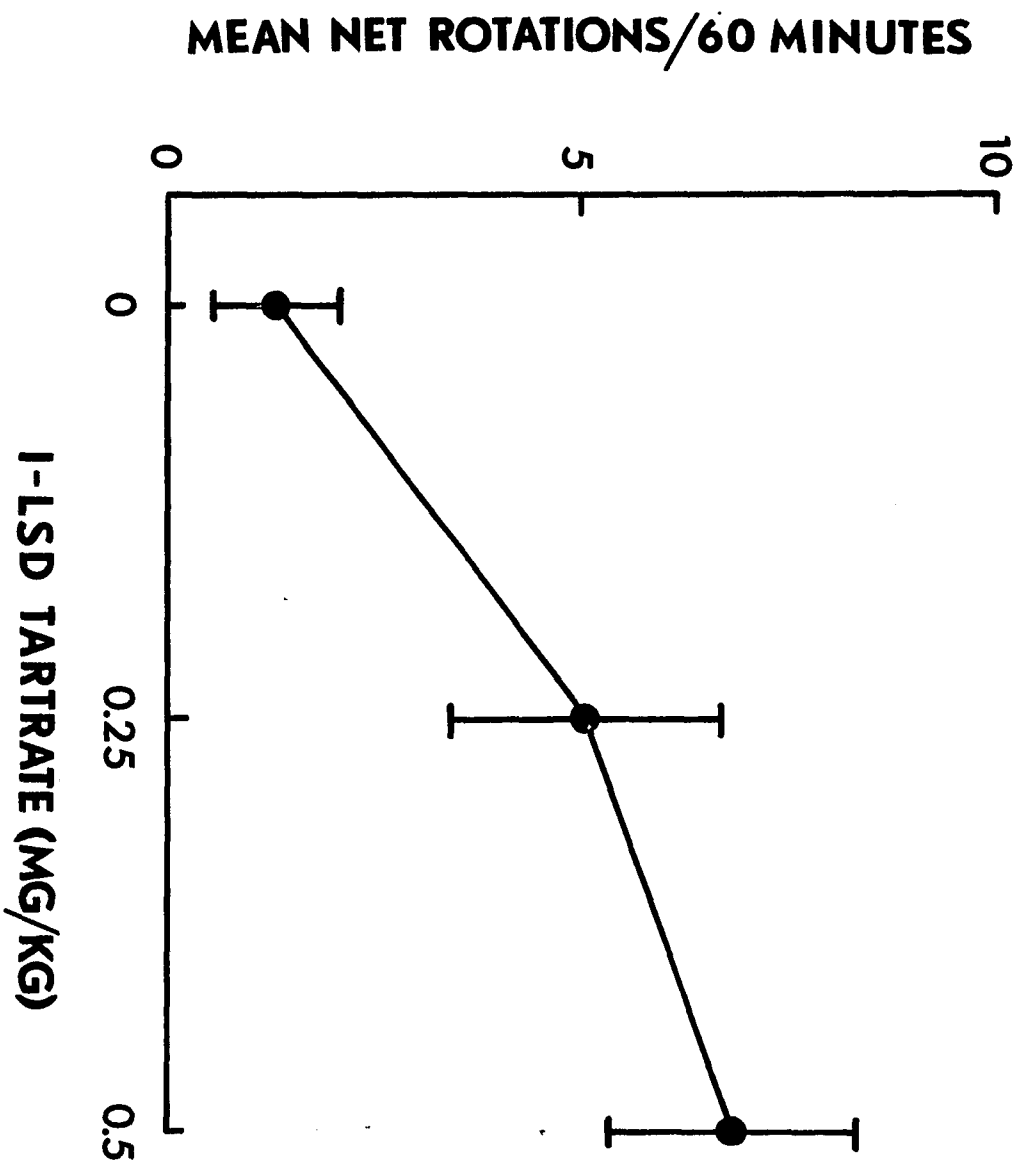
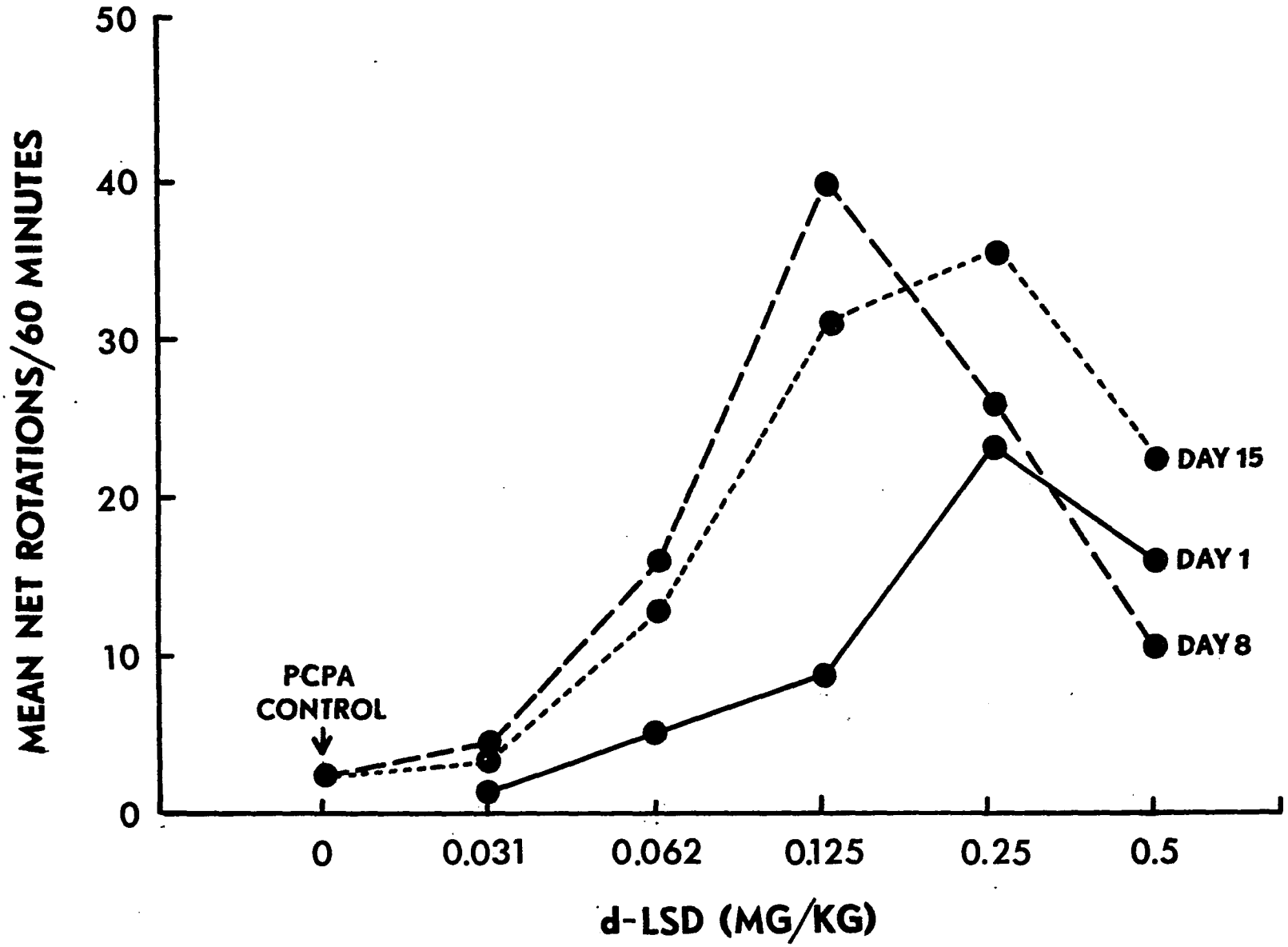

MEAN NET ROTATIONS/60 MINUTES
0
5
10
0
0.25
0.5
I-LSD TARTRATE (MG/KG)

Figure 10. Dose-response relationship for d-LSD-induced rotation, before (day 1) and after (days 8 and 15) treatment with p-chlorophenylalanine (300 mg/kg on day 15).


MEAN NET ROTATIONS/60 MINUTES
50
40
30
20
10
0
PCPA
CONTROL
DAY 15
DAY 1
DAY 8
0
0.031
0.062
0.125
0.25
0.5
d-LSD (MG/KG)

0.125 mg/kg dose of LSD induced rotation significantly greater than the day 1 control ($p<0.05$) receiving a comparable dose of LSD; an identical pattern was observed on day 15, as compared to day 1 controls.

The time course of rotation induced by 0.125 mg/kg of LSD on day 8 showed no outstanding differences from that induced by 0.25 mg/kg of LSD in untreated rats.

Consistency of Pharmacologically-Induced Rotation: Directional and Quantitative Correlations

The directional consistency of drug-induced rotation was determined (using Chi-square analysis) by comparing the direction of net rotations for the same animal given the same or different drugs, with one week separating drug administrations. The doses used for the determination of directional consistency were those inducing peak rotational behavior. Since it is difficult to determine rotational consistency when an animal produces few net rotations, all LSD rotaters exhibiting less than ten net rotations for the 60 minute testing period were not used for the Chi-Square analyses. The magnitude of rotation was analyzed using paired *t*-tests and linear regression analysis.

Tables 1 and 2 summarize the results of the consistency experiments. For all drugs tested twice at the same dose (i.e., LSD, mescaline, MDMT and methysergide), the direction of rotation was consistent from week to week. LSD-induced rotation was also consistent when given at 0.25 mg/kg on one week and 0.5 mg/kg on the other. Since the mean net rotations for these two doses are not significantly different (see Figure 1), these animals were grouped together to see if the magnitude of LSD-induced rotation was significantly correlated. The magnitude of LSD- and mescaline-induced rotation were each significantly correlated from week to week and there were no significant differences between the magnitudes of rotation for either LSD, mescaline, MDMT or methysergide from week to week.

TABLE 1

ROTATIONAL CONSISTENCY FOR THE SAME DRUG

Mean Net Rotations (± Standard Error)			Significance of Linear Regression Analysis
Drug 1	Drug 2	Consistency	(Sample Size)
LSD (0.25 mg/kg) 22.2 ± 2.18	LSD (0.25 mg/kg) 31.2 ± 7.74	p<0.025	not significant (6
LSD (0.25 mg/kg) 33.3 ± 8.16	LSD (0.5 mg/kg) 30.5 ± 1.38	p<0.025	not significant (6
LSD (0.25 mg/kg) 27.4 ± 4.77	LSD (0.25 + 0.5 mg/kg) 31.6 ± 4.01	p<0.001	p<0.05 (12)
Mescaline (20 mg/kg) 15.3 ± 4.13	Mescaline (20 mg/kg) 12.2 ± 2.62	p<0.001	p<0.01 (11)
MDMT (1mg/kg) 26.5 ± 6.43	MDMT(1mg/kg) 35.8 ± 5.46	p<0.025	not significant (6
Methysergide (10 mg/kg) 8.0 ± 1.27	Methysergide (10 mg/kg) 12.7 ± 2.26	p<0.05	not significant (

Consistency of direction was determined using Chi-Square analysis.

Significance of linear regression was determined using a t-test.

Since the direction of rotation was consistent for LSD, mescaline, MDMT and methysergide, directional consistency was examined between these drugs. That is, animals were tested for rotational preference on one week with LSD and then retested with either mescaline, MDMT or methysergide on the other. If these various agents induce rotation by a common mechanism, then they should cause the same animal to rotate in the same direction from week to week. Indeed, the direction of rotation was the same for LSD, mescaline, MDMT and methysergide. However, the magnitude of rotation was not significantly correlated between drugs.

Amphetamine-induced rotation in unlesioned rats has been correlated with a presynaptic nigrostriatal dopamine asymmetry (Glick et al., 1974; Jerussi & Glick, 1976), while apomorphine-induced rotation in unlesioned rats has been attributed to a postsynaptic asymmetry in striatal dopamine receptor sensitivity (Glick, Jerussi & Zimmerberg, 1977; Jerussi & Glick, 1975). If the direction of LSD-induced rotation was the same as either the indirectly-acting dopamine agonist (i.e., amphetamine) or the directly-acting dopamine agonist (i.e., apomorphine), this might provide some insight into the relationship between LSD-induced rotation and alterations in nigrostriatal activity. As can be seen from Table 2, the direction of rotation induced by LSD was the same as that induced by amphetamine, but not the same as that induced by apomorphine. For LSD and amphetamine, the magnitude of rotation was not significantly correlated, though the effect of amphetamine was significantly greater than that of LSD.

TABLE 2

ROTATIONAL CONSISTENCY BETWEEN DIFFERENT DRUGS

Mean Net Rotations (± Standard Error) Drug 1	Drug 2	Consistency (Sample Size)
LSD (0.25 mg/kg) 21.3 ± 2.21	Mescaline (20 mg/kg) 17.9 ± 4.49	p<0.025 (12)
LSD (0.25 mg/kg) 31.2 ± 6.72	MDMT (1 mg/kg) 34.0 ± 5.89	p<0.05 (5)
LSD (0.25 mg/kg) 23.7 ± 6.50	Methysergide (10 mg/kg) 10.0 ± 2.14	p<0.01 (7)
LSD (0.25 mg/kg) 24.4 ± 2.39	d-Amphetamine (1 mg/kg) 62.2 ± 11.66	p<0.05 (19)
LSD (0.25 mg/kg) 24.4 ± 2.39	Apomorphine (10 mg/kg) 48.0 ± 9.91	not significant (19)

Consistency of direction was determined using Chi-Square analysis.

Pharmacological Interactions: Effects upon Rotational Behavior

The drug interaction experiments were concerned with the elucidation of the neurotransmitter systems underlying LSD-induced rotation in unlesioned animals. The magnitude of LSD-induced rotation was examined before and after treatment with various agents which have fairly specific actions on central neural transmission. Haloperidol was used to determine the influence of blockade of catecholaminergic receptors (particularly dopaminergic receptors) on LSD-induced rotation, while AMPT was used to determine the importance of presynaptic stores of catecholamines on LSD-induced rotation. L-tryptophan, the dietary precursor of 5-HT, was used to increase central 5-HT levels and to see whether it induced rotation by itself or influenced LSD-induced rotation. LSD-induced rotation was then looked at in combination with an indirectly-acting dopamine agonist (amphetamine) and a directly-acting dopamine agonist (apomorphine). Cholinergic influences on LSD-induced rotation were examined using the anti-cholinergic agent scopolamine.

For the LSD-amphetamine, LSD-apomorphine and LSD-scopolamine interaction experiments (see Table 5), the term (B) refers to the mean net rotations induced by the other drug used in that particular interaction experiment (i.e., amphetamine, apomorphine or scopalamine). Combo refers to the mean net rotations induced by the simultaneous administration of 0.25 mg/kg of LSD and either 1.0 mg/kg of amphetamine, 10.0 mg/kg of apomorphine or 1.0 mg/kg of scopolamine. The term (LSD) + (B) refers to the algebraic

sum of the mean net rotations induced by either drug alone, and was computed as follows: If an animal went in the same direction with LSD or (B), then the net rotations were added together (e.g., if the animal made 16 net rotations to the right with LSD and 30 net rotations to the right with amphetamine, then (LSD) + (B) =46). If an animal went in opposite directions with LSD or (B), then the net rotations were subtracted (e.g., if the animal made 16 net rotations to the right with LSD and 30 net rotations to the left with amphetamine, then (LSD) + (B) = 14).

Using the algebraic sum of the net rotations induced by (LSD) + (B) takes into account the directions of rotation induced by (LSD) or (B) when administered alone, since they would be expected to add if in the same direction and subtract if in opposite directions.

The data from all the interaction experiments was analyzed using two-tailed t-tests.

LSD and haloperidol interactions

As can be seen in Table 3, pretreatment with haloperidol, 30 minutes prior to retest with LSD, significantly reduced the magnitude of rotation induced by 0.25 mg/kg of LSD ($p<0.05$; paired t-test). The dose of haloperidol used was 0.5 mg/kg since this has been shown to be sub-cataleptic and ineffective as a rotational agent (Jerussi & Glick, 1976). Six rats were used in this experiment.

LSD and AMPT interactions

As can be seen in Table 3, pretreatment with AMPT significantly reduced the magnitude of rotation induced by 0.25 mg/kg of LSD

TABLE 3

LSD-HALOPERIDOL AND LSD-AMPT INTERACTIONS

Mean Net Rotations (± Standard Error)		
Drug 1	Drug 2	Significance (t-test)
LSD (0.25 mg/kg) 14.8 ± 3.68	Haloperidol pretreatment (0.5 mg/kg) followed by d-LSD (0.25 mg/kg) 2.7 ± 0.95	$p<0.05$
LSD (0.25 mg/kg) 21.0 ± 3.20	AMPT pretreatment (150 mg/kg) followed by d-LSD (0.25 mg/kg) 5.7 ± 2.48	$p<0.005$

($p<0.005$; paired *t*-test). AMPT was administered 135 minutes prior to retest with LSD. The dose of AMPT used was 150.0 mg/kg. Nine rats were used in this experiment.

LSD-L-tryptophan interactions

Experiment 1: Six rats were initially tested with 0.25 mg/kg of LSD. One week later, they were given 200 mg/kg of L-tryptophan, 30 minutes before the 60 minute testing period. Half the animals received 0.25 mg/kg of LSD, while the other half received saline. One week later, the same procedure was followed except that those animals given LSD the previous week received saline, while those given saline the previous week received LSD.

As can be seen in Table 4, pretreatment with L-tryptophan had no effect upon the magnitude of LSD-induced rotation ($p>0.4$; paired *t*-test). In addition, L-tryptophan by itself did not induce rotation as compared to an individual group of saline-injected controls ($p>0.2$; unpaired *t*-test).

Experiment 2: Eleven rats were initially tested with 0.25 mg/kg of LSD. One week later they were given 200 mg/kg of L-tryptophan and 0.25 mg/kg of LSD simultaneously, immediately before the 60 minute testing period.

As can be seen in Table 4, the magnitude of rotation induced by the combination of L-tryptophan and LSD was no different from that induced by LSD alone ($p>0.1$; paired *t*-test).

LSD-amphetamine, LSD-apomorphine and LSD-scopolamine interactions

Table 5 summarizes the results of the LSD interaction experiments with amphetamine, apomorphine and scopolamine. Eight rats were used for the LSD-amphetamine and LSD-scopolamine experiments, while six rats were used for the LSD-apomorphine experiment.

TABLE 4

LSD-L-TRYPTOPHAN INTERACTIONS

Experiment 1	Mean Net Rotations (± Standard Error)	Significance (t-test)
LSD (0.25 mg/kg)	21.2 ± 6.49	
L-Tryptophan (200 mg/kg) 30 min prior to saline	2.2 ± 0.65	p>0.2
L-Tryptophan (200 mg/kg) 30 min prior to LSD (0.25 mg/kg)	26.3 ± 6.73	p>0.4
Experiment 2		
LSD (0.25 mg/kg)	14.1 ± 3.49	
LSD (0.25 mg/kg) plus L-Tryptophan (200 mg/kg)	18.6 ± 3.25	p>0.1

TABLE 5

d-AMPHETAMINE-, APOMORPHINE- AND SCOPOLAMINE-INDUCED ROTATION-INTERACTIONS WITH LSD-INDUCED ROTATION

ug Treatment	d-Amphetamine + LSD	Apomorphine + LSD	Scopolamine +LSD
(LSD) .25 mg/kg)	18.2 ± 5.38	10.2 ± 3.21	8.8 ± 3.06
(B) Amphetamine (1 mg/kg) omorphine (10 mg/kg) opolamine (1 mg/kg)	20.1 ± 9.68	42.3 ± 14.56	38.6 ± 8.78
Combo	110.8 ± 38.17*	64.2 ± 25.76	69.9 ± 6.66***
SD) + (B)	31.1 ± 11.82	43.5 ± 13.10**	44.1 ± 10.19****

*Significantly greater than (LSD), (B), (LSD)+(B) ($p<0.05$)

**Significantly greater than (LSD) ($p<0.05$)

***Significantly greater than (LSD) or (B) ($p<0.001$) and $p<0.05$ respective

****Significantly greater than LSD ($p<0.01$)

Mean net rotations were compared using two-tailed t-tests.

LSD-amphetamine interactions: The mean net rotations induced by the Combo were significantly higher than LSD ($p<0.05$; paired t-test) or amphetamine ($p<0.05$, paired t-test) alone. The Combo was also significantly higher than (LSD) + (amphetamine) ($p<0.05$; paired t-test). However, when (LSD) + (amphetamine) was compared to LSD or amphetamine alone, there were no significant differences ($p>0.2$, $p>0.1$ respectively; paired t-tests).

LSD-apomorphine interactions: Analysis with paired t-tests indicated that the only means that were significantly different were LSD compared to (LSD) + (apomorphine) ($p<0.05$).

LSD-scopolamine interactions: The mean net rotations induced by the Combo were significantly higher than LSD ($p<0.05$; paired t-test) or scopolamine ($p<0.05$; paired t-test) alone. In addition, the mean net rotations induced by (LSD) + (scopolamine) were significantly higher than for LSD ($p<0.01$; paired t-test), but not significantly higher than for scopolamine ($p>0.2$; paired t-test).

NEUROCHEMICAL RESULTS

Table 6 represents the 5-HT and 5-HIAA values before (quenched) and after (unquenched) correcting for quenching. Although the number of animals examined was small, no left-right differences were observed for 5-HT levels based on the quenched ($p>0.6$; unpaired t-test) or unquenched ($p>0.8$; unpaired t-test) fluorescence values. Quenching factors for the 5-HT determinations ranged from 0.323 to 0.532 (0.413 ± 0.0240; mean $\pm$ SEM). In other words, the fluorescence of the 5-HT-OPT fluorophore was attenuated approximately 59%, presumably as a result of quenching due to the presence of small amounts of organic solvents in the aqueous phase.

Table 6 also contains the 5-HIAA levels both before and after correcting for quenching, but they have not been statistically analyzed because of the limited number of animals examined. The quenching factors for the 5-HIAA determinations, ranging from 0.714 to 0.833 (0.761 ± 0.02631; mean $\pm$ SEM), indicated less quenching of the OPT-5-HIAA as compared to the OPT-5-HT fluorophore.

The 5-HT levels measured by this method are slightly higher than most of the values reported in the literature, but the ratio of 5-HT/5-HIAA of approximately 2-3 agrees quite well with most of the published values, particularly those reported by Curzon and Green (1970) for whole rat brain.

The high degree of organic quenching encountered in this investigation made it impossible to look at 5-HT turnover in discrete brain areas. As a result, half-brains had to be used. If

TABLE 6

HALF-BRAIN LEVELS (μg/g) OF 5-HT and 5-HIAA

5-HT

Left Half-Brain		Right Half-Brain	
Quenched	Unquenched	Quenched	Unquenched
1.016	0.976	1.233	1.141
1.002	0.905	0.970	0.617
1.242	0.968	1.139	0.958
1.279	1.108	1.386	1.216
1.135±0.0730	0.989±0.0426	1.182±0.0871	0.983±0.1335

Mean (± Standard Error)

5-HIAA

Left Half-Brain		Right Half-Brain	
Quenched	Unquenched	Quenched	Unquenched
0.505	0.434	--	--
0.611	0.595	0.332	0.310

one is forced to use half-brains, then a change in 5-HT turnover in a localized area of the brain (e.g., in the striatum or the substantia nigra) will be virtually impossible to resolve. Even if only 5-HT levels were measured the use of half-brains would obscure a small alteration in a localized area of the brain. Thus, with the sensitivity of the assay being what it was, any possible asymmetries in 5-HT levels or turnover in localized brain areas could not be monitored. This is why only a small number of animals were included in the results shown in Table 6, and why the problem was not pursued further.

DISCUSSION

As can be seen from the data presented, agents which are considered to be hallucinogenic can induce significant, dose-dependent rotational behavior in normal rats. The magnitude of the rotational response (as well as the direction) varied considerably from animal to animal, but for LSD and mescaline, was quite consistent for individual animals. All of the hallucinogenic agents used in this study have an inhibitory action upon midbrain raphe neurons. The extent to which this contributes to hallucinogen-induced rotation in normal rats will be considered in the following discussion.

LSD-induced rotation: LSD as a postsynpatic dopamine agonist

Perhaps the simplest explanation of LSD-induced rotation involves LSD as an agonist at postsynaptic dopamine receptors in the striatum, with the other actions of LSD, such as inhibition of the firing of midbrain raphe neurons on interaction with postsynaptic serotonin receptors (to be discussed later) having little or no influence.

It has been demonstrated that LSD interacts with two classes of postsynaptic receptors isolated from various brain regions; an LSD receptor and a dopamine receptor. Kebabian, Petzold and Greengard (1972) and Clement-Cormier, Kebabian, Petzold and Greengard (1974) have characterized a catecholamine-sensitive adenylate cyclase in homogenates of rat caudate or limbic region which is activated by relatively low concentrations of dopamine. The dopamine stimulation is blocked by various antipsychotic agents such as chlorpromazine or

haloperidol. This proposed 'dopamine receptor' can be stimulated by apomorphine (Stratten & Aylott, 1974) or L-DOPA (Garelis & Neff, 1973); the L-DOPA-induced stimulation of cyclic 3',5'-adenosine-monophosphate (cAMP) levels can be antagonized with the aromatic amino acid decarboxylase inhibitor Ro-4-4602. Using rat caudate slices, Forn, Kreuger and Greengard (1974) found that dopamine-stimulated increases in cAMP levels within the caudate slices were antagonized by fluphenazine, but not propranolol, whereas the reverse was true for isoproterenol-induced increases. They suggested that there may be two catecholamine receptors in rat caudate capable of increasing cAMP levels: One similar to the dopamine receptor, the other similar to a beta-adrenergic receptor.

In order to avoid any misinterpretations resulting from the terminology being used, what is meant by presynaptic and post-synaptic receptors should be clarified. Postsynaptic receptors are located on the postsynaptic cell membranes of soma and dendrites, interact with transmitter released from axon terminals of presynaptic neurons, and appear to be involved in the regulation of the firing rate of the neuron that it is part of. Presynaptic receptors (or autoreceptors) are located on the axon terminals and are probably involved in the regulation of the activity of tyrosine hydroxylase.

The supposition that the dopamine-sensitive adenylate cyclase is, or is intimately associated with, the postsynaptic dopamine receptor has been studied by examining dopaminergically-induced contralateral rotation in animals with unilateral lesions of the

nigrostriatal pathway and the adenylate cyclase activity of the denervated and intact striata. Satoh, Satoh, Notsu and Honda (1976) found that intraventricular dopamine, norepinephrine, apomorphine or dibutyryl-cAMP induced contralateral rotation. The apomorphine-induced contralateral rotation was accompanied by a bilateral increase in striatal cAMP levels in vivo. Both the rotation and the increase in cAMP levels were potentiated by theophylline and antagonized by haloperidol. The cAMP response to dopamine or norepinephrine in striatal homogenates ipsilateral to the lesion was significantly higher than in striatal homogenates contralateral to the lesion. A similar enhancement of adenylate cyclase activity to dopamine or S584 (the active metabolite of the directly-acting dopaminergic agonist Piribedil) in homogenates of denervated striata has been demonstrated by Mishra, Gardner, Katzman and Makman (1974). Kreuger, Forn, Walters, Roth and Greengard (1976) observed enhanced activity of adenylate cyclase in caudate slices ipsilateral to the lesion. However, the stimulation of adenylate cyclase by dopamine was the same in caudate homogenates ipsilateral or contralateral to the lesion. Von Voigtlander, Boukma and Johnson (1973) were also unable to demonstrate an enhanced dopamine-induced cAMP response in homogenates of denervated mouse striata. Kreuger et al. (1976) have proposed that the enhanced cAMP response to dopamine in denervated striatal slices is due to increased accessibility of postsynaptic receptors, rather than to increased number or sensitivity. However, Satoh et al. (1976) have disputed this. Using unlesioned rats they found that unilateral intrastriatal administration of dopamine or norepinephrine induced

turning away from the side of administration; dopamine was considerably more potent than norepinephrine. However, in homogenates of denervated striata (but not intact striata), the maximum stimulation of cAMP by norepinephrine did not differ from that induced by dopamine. They proposed that dopamine receptors in an intact striatum can discriminate dopamine in favor of norepinephrine. Denervation, in addition to sensitizing the postsynaptic dopamine receptors, also renders them non-selective to either catecholamine.

Mishra et al. (1974) have suggested that the negative results of Von Voigtlander, Boukma and Johnson (1973) may be due to freezing the tissue before assay, thus causing an appreciable loss of activity. However, this would not explain the absence of an enhanced cAMP response in caudate homogenates seen by Kreuger et al. (1976). All of the above-mentioned adenylate cyclase assays were minor modifications of the protein binding assay of Kebabian et al. (1972), so that the general methodology employed was basically the same. One minor exception was that Satoh et al. (1976) performed the dissections and prepared the homogenates in a cold room.

Recently, Von Hungen, Roberts and Hill (1975) have proposed that LSD interacts with the postsynaptic dopamine-sensitive adenylate cyclase. Using particulate preparations of rat corpus striatum, they found that 10 μM LSD completely blocked the cAMP response to 10 μM dopamine, but stimulated the adenylate cyclase when added alone. Activation of adenylate cyclase by either LSD or dopamine was unaffected by propranolol, but was blocked by the anti-psychotic agents trifluperazine, thioridazine, chlorpromazine or haloperidol or the anti-serotonergic agents

2-bromo-LSD or cyproheptadine. Neither 2-bromo-LSD, cyproheptadine, mescaline, DMT, psilocin or bufotenine stimulated the dopamine-sensitive adenylate cyclase when added alone. Burt, Creese and Snyder (1976) observed stereospecific binding of LSD to dopamine binding sites in tissue homogenates of calf caudate or hippocampus. 2-Bromo-LSD was similar in potency to LSD as were certain ergot alkaloids such as ergotamine or ergocornine. The serotonin antagonists methiothepin or methysergide were 10-14% as potent as LSD, while mianserin or cyproheptadine were only 1-3% as potent. Various hallucinogenic agents such as psilocin, DMT, mescaline, DOM or DOET showed little affinity for dopamine binding sites. By comparing the binding of LSD to postsynaptic receptors in the caudate in the presence or absence of 1 μM serotonin, they demonstrated that as much as 40-45% of the high affinity binding of LSD is to postsynaptic dopamine receptors. By contrast, in the hippocampus, which contains virtually no dopamine, LSD apparently binds exclusively to postsynaptic serotonin receptors (to be discussed later).

Since there appears to be an asymmetry in postsynaptic dopamine receptor sensitivity between the two striata of unlesioned rats (Glick, Jerussi & Zimmerberg, 1977; Jerussi & Glick, 1975; Jerussi, Glick & Johnson, in press), LSD could stimulate one striatum to a greater extent than the other, resulting in rotation contralateral to the side of greater stimulation. However, if LSD-induced rotation is solely a function of stimulation of postsynaptic striatal dopamine receptors, then apomorphine, a directly acting dopaminergic agonist, should induce rotation in the same direction as LSD, when administered to the same animal. As can be seen from Table 2, there was no directional consitency between LSD- or apomorphine-induced

rotation. Additionally, the antagonism of LSD-induced rotation by the tyrosine hydroxylase inhibitor AMPT would not be expected if LSD were only stimulating postsynaptic dopamine receptors. In animals with (Von Voigtlander & Moore, 1973b) or without (Jerussi & Glick, 1976) unilateral lesions of the nigrostriatal pathway, pretreatment with AMPT has no effect on the magnitude of apomorphine-induced rotation.

LSD-induced rotation: Amphetamine-like action of LSD

An alternative explanation of the AMPT-induced antagonism of LSD-induced rotation is that LSD possesses an amphetamine-like action resulting in increased presynaptic release of nigrostriatal dopamine. AMPT has been shown to antagonize amphetamine-induced rotation in animals with (Christie & Crow, 1971; Ungerstedt, 1971; Von Voigtlander & Moore, 1973b) or without (Jerussi & Glick, 1976) unilateral lesions of the nigrostriatal pathway. In addition, the directional consistency between LSD- and amphetamine-induced rotation (see Table 2) is consistent with an amphetamine-like action of LSD upon neurons of the nigrostriatal pathway. However, LSD-induced contralateral rotation in animals with unilateral lesions of the nigrostriatal pathway (Pieri, Pieri & Haefely, 1974; Pycock & Anzelark, 1975) does not support this hypothesis.

LSD-induced rotation: LSD as an agonist at nigrostriatal autoreceptor

In unlesioned animals, there is evidence (Persson, 1977) that LSD interacts as a dopamine agonist predominantly with presynaptic autoreceptors apparently involved in the regulation of dopamine synthesis and release (Carlsson, 1975; Carlsson, Kehr & Lindqvist, 1976; Roth, Walters, Murrin & Morgenroth, 1975). Using functionally intact dopaminergic systems, Persson (1977) has shown that LSD or

apomorphine will antagonize the increase in L-DOPA accumulation induced by gamma-butyrolactone. Roth et al. (1975) have previously shown that gamma-butyrolactone blocks impulse flow in the nigrostriatal pathway. Presumably in the absence of activity of this system, any modulation of nigrostriatal tyrosine hydroxylase activity could not result from alterations in nigrostriatal impulse traffic. Thus the only way a dopamine agonist could slow down dopamine synthesis would be to interact directly with autoreceptors on the nigrostriatal neurons.

As has been stated previously, LSD appears to possess mixed agonist-antagonist properties upon striatal dopamine-sensitive adenylate cyclase, so that cAMP levels are only stimulated in the absence of dopamine. In animals with unilateral lesions of the nigrostriatal pathway little or no dopamine would be released in the denervated striatum so that the dopamine agonist properties of LSD on postsynaptic receptors would become prominent and contralateral rotation would ensue. The presynaptic autoreceptors would only be present in the striatum with intact dopaminergic innervation. The interaction of LSD with these autoreceptors would decrease the activity of tyrosine hydroxylase, thus decreasing the release of dopamine. This would add to the stimulation of postsynaptic dopamine receptors in the denervated striatum. Thus, robust contralateral rotation, similar to that observed by Pieri, Pieri and Haefely (1974) would ensue. However, in intact animals the primary action of LSD would be to activate these autoreceptors producing a bilateral decrease in dopamine release. If this did not disturb the intrinsic presynaptic asymmetry in dopamine content between the two striata

(Glick et al., 1974; Jerussi & Glick, 1976), then low magnitude rotational behavior, similar to that observed in the present investigation (see Figure 2) could occur. Thus, by invoking a presynaptic dopaminergic action of LSD on the axon terminals of the nigrostriatal pathway in intact striata, and a postsynaptic dopaminergic action in denervated striata, the apparent discrepancy between the results of Pieri, Pieri and Haefely (1974) and the present investigation can be resolved.

However, the results of the amphetamine-LSD interaction experiment (see Table 5) suggest that LSD-induced rotation in unlesioned animals cannot be explained simply by an action on presynaptic receptors.

LSD-induced rotation: LSD-amphetamine interactions; interactions of LSD with postsynaptic serotonin receptors

The mean net rotations following a combination of amphetamine (1 mg/kg) and LSD (0.25 mg/kg) were significantly greater than that observed with amphetamine alone (1 mg/kg), although the algebraic sum was not. The mean net rotations for the amphetamine-LSD combination (110.8) were higher than any published mean for a 1 mg/kg dose of amphetamine administered to normal rats: 42.3 (Glick, Cox, Jerussi & Greenstein, 1977), 48.2, 46.8 (Glick, Crane, Jerussi, Fleisher & Green, 1975), 59.2, 50.5 (Glick, Jerussi, Cox & Fleisher, 1977), 85.0 (Jerussi & Glick, 1976). Furthermore, when the amphetamine-LSD combination was compared to a large group of rats (N=93) administered 1 mg/kg of amphetamine (mean net rotations = 44.9), the combination exhibited significantly greater ($p<0.001$; unpaired *t*-test) mean net rotations. Since this dose is at the peak of the dose-response relationship for amphetamine-induced rotation in normal

rats (Jerussi & Glick, 1976), the additivity of rotation induced by an amphetamine-LSD combination suggests an interaction with at least two different receptor systems.

LSD has been shown to interact with postsynaptic serotonin receptors (Bennett & Aghajanian, 1974; Bennett & Snyder, 1975; Farrow & Van Vunakis, 1972; 1973) and with serotonin receptors probably located on the soma and dendrites of midbrain raphe neurons (Aghajanian,1972; Aghajanian, 1976; Haigler & Aghajanian, 1974a). The postsynaptic serotonin receptors (which are probably a subgroup of the postsynaptic LSD receptors) will be discussed first.

Farrow and Van Vunakis (1972; 1973), using equilibrium dialysis, were the first to demonstrate saturable high affinity binding of LSD to subcellular fractions from cerebral cortex, but not from other rat brain areas. The bound LSD could be displayed by serotonin and various other hallucinogenic agents such as DOM, MDMT, psilocin or bufotenine. Using a rapid filtration technique, Bennett and Aghajanian (1974) found stereospecific high affinity LSD binding in rat brain homogenates and synaptosomal fractions from subcortical, as well as cortical regions; similar results were obtained by Bennett and Snyder (1975). The binding of either LSD or serotonin appears to be postsynaptic since destruction of the midbrain raphe nuclei had no effect upon the binding of either ligand (Bennett & Aghajanian, 1974; Bennett & Snyder, 1975). Bennett and Snyder (1976) have suggested that this postsynaptic receptor may exist in two states, designated as agonist and antagonist, since serotonin and related 5-HT agonists exhibit 100-fold greater affinity for receptors bound to serotonin, whereas 5-HT antagonists such as

methysergide, cyproheptadine, methiothepin and mianserin, show 4-100 times greater affinity for receptors bound to LSD. LSD itself has equal affinity for either binding state, so that it appears to function as a mixed agonist-antagonist. Assuming that the interconversion of the two binding states is limited by certain energy constraints, ^{3}H-5-HT should label only the agonist states while ^{3}H-LSD should label both agonist and antagonist states. The number of high affinity LSD binding sites should equal the total number of available 5-HT sites (i.e. agonist plus antagonist sites), while the number of antagonist sites should equal the number of high affinity LSD binding sites minus the number of 5-HT binding sites. Bennett and Snyder (1976) compared the apparent dissociation constants and maximal number of binding sites for ^{3}H-5-HT and ^{3}H-LSD in the corpus striatum, hippocampus, cerebral cortex and cerebellum of the rat. The ratio of LSD to 5-HT binding sites was about two.

Bennett and Aghajanian (1976) have recently presented evidence that a physiological response (i.e., inhibition of the firing of dorsal raphe neurons) to a low intravenous dose of LSD (16 μg/kg) occurs in a concentration range corresponding to the high affinity LSD binding site in vitro. They estimated that the concentration of free LSD in the midbrain producing 50% inhibition of dorsal raphe firing was 4.6 nM, while the concentration producing complete inhibition of firing was 9.7 nM. These values agree quite well with their previous in vitro determination (Bennett & Aghajanian, 1974) of 4 nM for the concentration of LSD producing half-maximal saturation of the postsynaptic serotonin receptor. The only problem is that LSD appears to depress the firing of raphe neurons by a presynaptic

mechanism (or at synapses intrinsic to the midbrain raphe nuclei) (Aghajanian, Foote & Sheard, 1970; Aghajanian, Foote & Sheard, 1973; Aghajanian, Haigler & Bloom, 1972; Bramwell & Gonye, 1976; Haigler & Aghajanian,1974b; Mosko & Jacobs, 1977), while the *in vitro* determination of LSD binding was performed on postsynaptic receptors. Of course the apparent agreement between *in vitro* and *in vivo* observations may be spurious, or, as suggested by Haigler and Aghajanian (1974), the depression of midbrain raphe neurons by systemically administered LSD may result from interaction with postsynaptic receptors within the midbrain itself.

LSD has been demonstrated to produce electrophysiological and biochemical changes in serotonergic systems, particularly those originating in the median and dorsal raphe nuclei of the midbrain. The decreased turnover of serotonin following administration of LSD (Andén et al., 1968; Rosencrans, Lovell & Freedman, 1967; Tonge & Leonard, 1969) is considered to be secondary to a decrease in the firing rate of serotonergic neurons (Aghajanian, Foote & Sheard, 1968; 1970; Bramwell & Gonye, 1976). A similar effect upon the firing rate of serotonergic neurons is produced by iontophoretic 5-HT (Haigler & Aghajanian, 1974a) or the systemically administered 5-HT precursors L-tryptophan (Aghajanian, 1972; Gallagher & Aghajanian, 1976) or 5-HTP (Bramwell & Gonye, 1973; Gallagher & Aghajanian, 1976; Trulson & Jacobs, 1975). Iontophoretic studies have shown that although 5-HT is a potent inhibitor of postsynaptic neurons receiving an identified serotonergic input (Haigler & Aghajanian, 1974a; 1974b), LSD produces little (Aghajanian, 1976)

or no change (Haigler & Aghajanian, 1974a, 1974b) in the firing rates of these neurons. Since a complete diencephalic-mesencephalic transection failed to block the inhibition of dorsal raphe neurons by intravenous LSD (Haigler & Aghajanian, 1974a), the inhibition of raphe unit activity by LSD is probably not linked to an interaction with postsynaptic receptors in the forebrain, but occurs on the soma and dendrites of raphe neurons themselves or on some postsynaptic receptor in close proximity to the midbrain raphe neurons.

Electrical stimulation of the median and/or dorsal raphe produces inhibition of firing in various brain regions known to receive prominent serotonergic input from these nuclei. Inhibition has been recorded in hippocampal pyramidal cells (Segal, 1975), the suprachiasmatic nucleus of the hypothalamus (Bloom et al., 1972), the striatum (Miller, Richardson, Fibiger & McLennan, 1975; Olpe & Koella, 1977) and the substantia nigra (Dray et al., 1976). Because the midbrain raphe neurons are tonically active with intrinsic firing rates ranging from 0.1-10 Hz., LSD might be expected to disinhibit those neurons postsynaptic to the raphe terminals. Following low intravenous doses of LSD, Haigler and Aghajanian (1974a) observed increased firing rates in postsynaptic cells receiving an identified serotonergic input (i.e., ventral lateral geniculate and cortical and basal amygdaloid nuclei).

Numerous studies indicate an inhibitory role for serotonin in behavior maintained by dopaminergic and/or noradrenergic mechanisms. Depletion of serotonin with PCPA has been demonstrated to potentiate

spontaneous locmotor activity (Fibiger & Campbell, 1971; Marsden & Curzon, 1976) or amphetamine-induced hyperactivity (Mabry & Campbell, 1973; Segal, 1976); similar results have been obtained following lesions of the median raphe (Geyer et al., 1976b; Jacobs & Cohen, 1976; Srebro & Lorens, 1975). In all of the above-mentioned studies utilizing PCPA, the potentiation of locomotor activity was antagonized in a dose-dependent manner by L-tryptophan or 5-HTP. Baldessarini et al. (1975) found that 5-HTP decreased and PCPA or methysergide increased apomorphine-induced rotation in rats with unilateral electrothermic lesions of the nigrostriatal pathway. However, interpretation of these results is difficult since the lesions (made at the rostral end of the substantia nigra) not only decreased striatal dopamine, but serotonin as well. Milson and Pycock (1976) found that L-tryptophan or 5-HTP decreased and PCPA increased amphetamine- or apomorphine-induced rotation in mice with unilateral 6-OH-DA-induced destruction of striatal dopaminergic terminals. However, methysergide, cyproheptadine, chlorimipramine or LSD produced no consistent effect upon amphetamine- or apomorphine-induced rotation.

The increase in rotation induced by an amphetamine-LSD combination (as compared to LSD or amphetamine alone) could be due to amphetamine-induced increases in the release of nigrostriatal dopamine coupled with LSD-induced increases in the firing rates of nigrostriatal neurons. Indeed, Von Voigtlander and Moore (1973a) have demonstrated that electrical stimulation of the nigrostriatal pathway (which increases the firing rate of nigrostriatal neurons) increased amphetamine- or amantadine-induced release of ^{3}H-dopamine into the cerebral ventricles.

LSD-induced rotation: Neural substrates of LSD-induced disinhibition of nigrostriatal activity.

What neural pathways subserve the 5-HT-induced, and LSD-antagonized inhibition of nigrostriatal activity? Perhaps the most obvious candidate would be the dorsal raphe since it has been shown to selectively innervate the striatum (Bobillier et al., 1976; Conrad, Leonard & Pfaff, 1974; Geyer et al., 1976a; Jacobs & Cohen, 1976). However, the behavioral consequences of lesions to the dorsal raphe are surprisingly inconsequential, with an increase in pain-elicited aggression (Jacobs & Cohen, 1976) or mild contralateral head asymmetries (following asymmetric dorsal raphe lesions) (Costall & Naylor, 1974) being the most pronounced. In contrast to the absence of behavioral effects of dorsal raphe lesions, lesions of the median raphe produce quite striking effects. Both Jacobs and Cohen (1976) and Geyer et al. (1976b) observed potentiation of spontaneous locomotor activity and amphetamine-induced hyperactivity following lesions of the median raphe. Of particular relevance are the observations of Costall & Naylor (1974) that asymmetric lesions of the median raphe resulted in apomorphine-, amphetamine- or methylphenidate-induced contralateral rotation in rats, which could be decreased by haloperidol or methiothepin.

Dray et al. (1976) have demonstrated a median raphe to substantia nigra projection which could be the neural substrate for LSD-induced disinhibition of the nigrostriatal pathway. Following electrical stimulation of the median raphe, they observed a decrease in neuronal firing in the substantia nigra (particularly in the pars compacta), which could be mimicked by iontophoretic serotonin.

In addition, lesions of the median raphe resulted in a decrease in nigral serotonin. Thus LSD, by inhibiting the firing of median raphe neurons, would disinhibit the nigrostriatal pathway at the level of the substantia nigra.

Of the mechanisms that have been proposed to explain LSD-induced rotation in unlesioned rats, disinhibition of nigrostriatal activity appears to be the most likely candidate. This does not mean that an action of LSD on nigrostriatal autoreceptors has no influence on LSD-induced rotation, but that it is probably not of primary importance. Interaction with dopamine autoreceptors could not account for the increase in amphetamine-induced rotation when amphetamine is administered with LSD, since LSD would be expected to decrease the release of nigrostriatal dopamine. Furthermore, in the forthcoming section on MDMT-induced rotation, it will be aruged that the interaction of LSD with dopamine autoreceptors probably attenuates rotation resulting from LSD-induced disinhibition of nigrostriatal activity.

The antagonism of LSD-induced rotation by a sub-cataleptic dose of halperiodol is consistent with LSD-induced disinhibition of the nigrostriatal system, since haloperidol would block the interaction of dopamine with the postsynaptic receptors.

LSD-induced rotation: LSD-PCPA interactions

The enhancement of LSD-induced rotation by pretreatment with the tryptophan hydroxylase inhibitor PCPA is consistent with a large body of experimental evidence suggesting that depletion of central serotonin levels reduces the threshold dose of LSD necessary

to induce the behavioral parameter being measured (Appel, Lovell & Freedman, 1970; Appel, Sheard & Freedman, 1970; Cameron & Appel, 1973).

Both PCPA and LSD decrease the amount of 5-HT released from the terminals of raphe neurons, so it is not surprising that PCPA increased the sensitivity of rats to the rotational effects of LSD. In a state of partial 5-HT depletion, particularly in the raphe terminals, since Aghajanian, Kuhar and Roth (1973) have shown that PCPA blocks 5-HT synthesis in raphe terminals far better than in raphe soma and dendrites, a lower concentration of LSD would be required to reduce 5-HT output to some critical level. Once the 5-HT output of raphe neurons had been reduced to this critical level, the subsequent disinhibition of nigrostriatal activity (and the increased firing rate of nigrostriatal neurons) would be behaviorally manifested as rotation. As can be seen in Figure 9, 0.125 mg/kg of LSD was maximally effective and induced rotation significantly greater than on days 1 and 8. In untreated rats this dose of LSD was submaximal. On day 8, there were no significant increases in LSD-induced rotation following the 0.25 or 0.5 mg/kg doses. In fact, at 0.5 mg/kg of LSD rotation on day 8 was considerably lower than on day 1. It is conceivable that in PCPA-pretreated rats, at the 0.125 mg/kg dose the inhibition of raphe firing together with the already reduced output of 5-HT would be sufficient to produce maximal disinhibition of nigrostriatal activity, without producing significant interactions with nigrostriatal dopamine autoreceptors. Thus, robust rotation ensues. However, as the dose

of LSD is increased, the activation of nigrostriatal dopamine autoreceptors is also increased, resulting in rotation of a lower magnitude even though raphe activity may be completely turned off.

There is some experimental evidence supportive of this line of reasoning. Bennett and Aghajanian (1976) estimated that the concentration of free LSD in the midbrain producing 50% inhibition of dorsal raphe firing was 4.6 nM, while the concentration producing complete inhibition of firing was 9.7 nM. These values were very close to their in vitro determination (Bennett & Aghajanian, 1974) of 4 nM as the concentration of LSD producing half-maximal saturation of postsynaptic serotonin receptors. However, Von Hungen, Roberts and Hill (1975) found that LSD did not significantly stimulate the dopamine-sensitive adenylate cyclase in particulate preparations from rat corpus striatum at concentrations less than 100 nM. Assuming that the interaction of LSD with nigrostriatal dopamine autoreceptors is comparable to the interaction with striatal dopamine-sensitive adenylate cyclase, then the increased sensitivity of PCPA-pretreated rats to low (i.e., 0.125) mg/kg) but not higher (i.e., 0.25 and 0.5 mg/kg) doses of LSD could be the result of differential sensitivities of midbrain LSD receptors and nigrostriatal dopamine autoceptors to LSD.

LSD-induced rotation: LSD-L-tryptophan interactions

Since depletion of serotonin potentiated LSD-induced rotation, it seemed plausible that elevation of serotonin with the 5-HT precursor L-tryptophan might antagonize, or at least decrease this

rotation. It is also possible that L-tryptophan could induce rotation by itself, by virtue of its capacity to inhibit the firing of raphe neurons. However, as shown in Table 4, 200 mg/kg of L-tryptophan neither induced rotation alone, nor decreased LSD-induced rotation. Aghajanian (1972) has shown that systemically administered L-tryptophan inhibits raphe neurons in approximately 15 minutes. Consequently, this amino acid was administered 30 minutes prior to, or simultaneously with LSD, so that the rotational efficacy of LSD could be examined during periods of normal or reduced rates of raphe activity. Neither protocol had any effect on LSD-induced rotation.

L-tryptophan decreases the firing rate of raphe neurons, but does not shut them off completely (Aghajanian, 1972; Gallagher & Aghajanian, 1976). Thus, L-tryptophan-induced decreases in raphe firing rate could be compensated for by increases in 5-HT release from raphe terminals. The net effect would be no change in raphe-induced inhibition of nigrostriatal activity and no rotation. When LSD is administered 30 minutes after L-tryptophan, the raphe neurons would be in this compensated state. The inhibition of raphe firing by LSD, which produces total cessation of firing (Aghajanian, 1972; Bramwell & Gonye, 1976; Haigler & Aghajanian, 1974a) would induce disinhibition of nigrostriatal activity (and rotation) comparable to that seen in untreated animals. When L-tryptophan and LSD are administered simultaneously, the total inhibition of raphe activity by LSD would obviate any effects of L-tryptophan and the resulting rotation would be no different than with LSD alone.

LSD-induced rotation: LSD-scopolamine interactions

The increase in scopolamine-induced rotation as compared to the LSD-scopolamine combination (see Table 5) was not altogether unexpected since anti-cholinergics share some common neuropharmacological and behavioral properties with agents that increase the activation of striatal dopamine receptors; and, LSD had already been demonstrated to increase amphetamine-induced rotation. Apomorphine will decrease the turnover of striatal ACh (Guyenet, Agid, Javoy, Beaujouan, Rossier & Glowinski, 1975), whereas certain neuroleptics will increase it (Sethy & Van Woert, 1974; Stadler et al., 1973). The effects of dopaminergic agonists and antagonists on striatal ACh turnover are through to be secondary to decreases and increases in cholinergic impulse activity, respectively. This is consistent with considerable experimental evidence indicating that iontophoretically applied dopamine (Bloom, Costa & Salmoiraghi, 1965; Connor, 1970; Herz & Zieglgansberger, 1968; York, 1967) or electrical stimulation of the substantia nigra (Connor, 1970; Gonzalez-Vegas, 1974) inhibit the firing rate of many neurons within the striatum. Amphetamine-induced rotation in unlesioned animals (Jerussi & Glick, 1976) is decreased by pilocarpine, but increased by scopolamine. In addition, the directon of scopolamine- and amphetamine-induced rotation is consistent for the same animal (Jerussi & Glick,,1976). Thus, it appears that agents which facilitate striatal dopaminergic transmission (e.g., amphetamine) induce rotation in the same direction as agents which block striatal cholinergic receptors (e.g., scopolamine). Amphetamine-induced increases

in nigrostriatal dopamine release could inhibit the activity of these cholinergic interneurons, while scopolamine would mimick this effect by blocking the output of these interneurons.

LSD-induced rotation: LSD-apomorphine interactions

The failure of LSD to alter the magnitude of apomorphine-induced rotation (see Table 5) may be due to apomorphine-induced inhibition of tyrosine hydroxylase activity through interaction with nigrostriatal dopamine autoreceptors. Apomorphine is a potent inhibitor of the conversion of ^{3}H-tyrosine to dopamine in rat striatal synaptosomal preparations (Iversen, Rogawski & Miller, 1976). In the absence of nigrostriatal impulse activity following HA-966 (1-hydroxy-3-amino-pyrrolidone-2) (Van Zwieten-Boot & Noach, 1975) or gamma-butyrolactone (Persson, 1977), apomorphine has been shown to inhibit tyrosine hydroxylase activity. This presynaptically-induced inhibition of dopamine synthesis could attenuate the effects of LSD-induced disinhibition of the nigrostriatal pathway. Furthermore, whereas amphetamine-induced rotation in normal rats has been correlated with a presynaptic asymmetry in striatal dopamine content (Glick et al., 1974; Jerussi & Glick, 1976), apomorphine-induced rotation has been attributed to a postsynaptic asymmetry in dopamine-receptor sensitivity (Glick, Jerussi & Zimmerberg, 1977; Jerussi & Glick, 1975). Indeed, these two drugs usually induce rotation in opposite directions (Glick et al., 1977). In non-drugged rats, the presynaptic asymmetry appears to be dominant (Zimmerberg, Glick & Jerussi, 1974), so that amphetamine enhances and apomorphine

reverses the normal direction of behavioral laterality (Glick, Jerussi & Zimmerberg, 1977). Since LSD usually induced rotation in the same direction as amphetamine (see Table 2), the proposed LSD-induced disinhibition of the nigrostriatal pathway is more likely to increase rotation induced by a drug acting presynaptically (i.e., amphetamine) than one acting postsynaptically (i.e., apomorphine).

Mescaline-induced rotation

As was true of LSD, mescaline-induced rotation occurred without any other gross behavioral changes, and was directionally consistent from week to week (see Table 1). The time course of mescaline-induced rotation was somewhat similar to LSD's except that rotation was not readily apparent until the second 5 minute interval and seemed to fluctuate more from interval to interval (see Figure 4).

In the previous section, LSD-induced rotation was proposed to be primarily a consequence of disinhibition of nigrostriatal activity. Since the direction of rotation induced by mescaline and LSD was consistent for individual animals (see Table 2), the underlying mechanism may be the same. Mescaline has been shown to inhibit the firing of neurons in the median and dorsal raphe nuclei (Aghajanian, Foote & Sheard, 1970; Foote, Sheard & Aghajanian 1969). However, it does not stimulate the dopamine-sensitive adenylate cyclase from rat striatum (Von Hungen, Roberts & Hill, 1975), nor does it show appreciable binding to postsynaptic dopamine receptors from calf caudate (Burt, Creese & Snyder, 1976).

Furthermore, Mescaline has been demonstrated to interact with central noradrenergic mechanisms. Gonzalez-Vegas (1971) found that iontophoretic mescaline antagonized the depression of firing of brain stem neurons induced by iontophoretic norepinephrine. Bevan, Bradshaw, Roberts and Szabadi (1974) monitoring cortical neurons, found that most cells were excited (159) by iontophoretic mescaline, while some (34) were inhibited. When a neuron responded in opposite directions to iontophoretic norepinephrine and 5-HT, the response to mescaline was invariably in the same direction as the response to norepinephrine. Furthermore, mescaline responses (i.e., either increases or decreases in responses rates) were antagonized by iontophoretic sotalol, a beta-adrenergic antagonist. Using synaptosomes from rat cerebral cortex, Bevan (1975) found that mescaline, in addition to being taken up itself (approximately 10% of norepinephrine uptake), non-competitively inhibited the uptake of norepinephrine.

Since both mescaline and LSD share the capacity to inhibit firing of midbrain raphe neurons, but not partial dopaminergic agonism, the disinhibition of nigrostriatal activity (secondary to the inhibition of midbrain raphe neurons) is the most likely mechanism subserving mescaline-induced rotation. Presumably this would result in a bilateral increase in nigrostriatal activity, thus accentuating an intrinsic, presynaptic striatal dopamine asymmetry. The resulting rotation would be contralateral to the striatum with higher dopaminergic activity.

Based on the available evidence regarding noradrenergic neurons and rotation, the noradrenergic actions of mescaline

would appear to be a minor factor in mescaline-induced rotation. Amphetamine- or apomorphine-induced rotation in rats with unilateral electrolytic lesions of the locus coeruleus (Pycock, Donaldson & Marsden, 1975) or ventral noradrenergic bundle (Donaldson, Dolphin, Jenner, Marsden & Pycock, 1976) and the subsequent alterations in striatal dopamine levels ipsilateral to the lesion suggest that noradrenergic mechanisms play some role in rotational behavior. Pycock, Donaldson and Marsden (1975) cite the observations of Lindvall and Bjorklund (1974), that many of the norepinephrine-containing fibers entering the striatum may terminate there, as evidence that a noradrenergic pathway, originating in the locus coeruleus and coursing in the ventral noradrenergic bundle, produced facilitation of nigrostriatal activity. However, the concentration of norepinephrine in the striatum is very low (Hornykiewicz, 1966) and there are virtually no electrophysiological or histological data to support a monosynaptic input from the locus coeruleus to the substantia nigra or striatum.

As was suggested in the introductory section on the behavioral pharmacology of LSD and related compounds, the drug-induced rotation following unilateral lesions of the locus coeruleus may result from interruption of a noradrenergic pathway which projects to the frontal cortex; the frontal cortex in turn projects to the striatum. A cortical relay would be consistent with the previously mentioned actions of mescaline on cortical neurons (Bevan, 1975; Bevan et al., 1974). It would be interesting to study the effects of mescaline (both systemically- and iontophoretically applied) on cortical neurons exhibiting the same response

to iontophoretic norepinephrine and stimulation of the locus coeruleus, and then stimulate these cortical cells and monitor responses in striatal neurons. This might assist in the elucidation of the role of noradrenergic mechanisms in rotational behavior.

MDMT-induced rotation

The rotation induced by MDMT was directionally consistent from week to week and was directionally consistent when compared to LSD- and mescaline-induced rotation (see Table 1 and 2). Examination of the time-course of MDMT-induced rotation (see Figure 6) reveals that it was very rapid in onset, with maximal rotational intensity in the first two 5 minutes intervals (intensity in the first interval was approximately three times greater than the intensity in the second interval) and virutally no rotation during the remaining 50 minutes. Since MDMT is generally considered to be a directly-acting 5-HT agonist (Fuxe, Holmstedt & Jonsson, 1972; Graham-Smith, 1971a) and tachyphylaxis is a prominent feature of the central action of 5-HT (Johnson, Roberts & Straughan. 1969; Roberts & Straughan, 1967), it is conceivable that the transiency of rotation induced by MDMT was due to tachyphylaxis of central 5-HT receptor response.

What is particular interesting about MDMT-induced rotation is that although it occurred during a short time interval, it was rather intense; the mean net rotations (26.5) were of greater magnitude than for either LSD- or mescaline-induced rotation. Yet, although MDMT seems to depress raphe neurons by a direct

action on the cell bodies or synapses intrinsic to the midbrain raphe nuclei (Aghajanian, Haigler & Bloom, 1972; Mosko & Jacobs, 1977) it does not appear to directly interact with dopaminergic or noradrenergic systems. Thus, MDMT stands out from the other two hallucinogens in that its rotational potency is greatest (albeit brief) and its only known major central action is as a 5-HT agonist.

If MDMT does induce rotation exclusively through blockade of raphe-mediated inhibition of nigrostriatal activity (by inhibiting the firing of raphe neurons), then this may be the primary mechanism by which the three hallucinogens tested induce rotation. The dopaminergic properties of LSD and possibly the noradrenergic properties of mescaline probably attenuate the rotation concomitant with disinhibition of nigrostriatal activity. Of course, it could be argued that the serotonergic agonist properties of MDMT are greater than LSD's, but this is doubtful if one considers the exquisite sensitivity of raphe neurons to intravenously administered LSD; 10 µg/kg (in rats) produced a total but reversible inhibition of firing (Aghajanian, Foote & Sheard, 1968; 1970). Mosko and Jacobs (1977) have observed a similar inhibition of raphe firing in rats with the intravenous infusion of 20 µg/kg of MDMT. Since MDMT was adminstered in the unconjugated form, whereas LSD was administered as the tartrate salt, and LSD has a higher molecular weight than MDMT (323 compared to 202), it would appear that LSD is probably the more potent 5-HT agonist.

Methysergide, 2-bromo-LSD, cyproheptadine and 1-LSD

Of the three 5-HT antagonist tested only methysergide induced significant rotation (see Figure 7). The magnitude of methysergide-induced rotation was low, but the direction was

consistent from week to week, and was consistent with the direction of LSD-, mescaline- and MDMT-induced rotation (see Table 2).

Segal (1975) found that systemically administered methysergide partially antagonized the inhibition of hippocampal pyramidal cells induced by iontophoretic 5-HT or electrical stimulation of the midbrain raphe. Olpe and Koella (1977) found that iontophoretic methysergide antagonized the inhibition of striatal neurons induced by electrical stimulation of the dorsal raphe, although the time-course of methysergide-induced antagonism was slow; it required 2-4 minutes of iontophoresis to produce significant antagonism. Thus, methysergide could induce a mild disinhibition of nigrostriatal activity by partially antagonizing the depressant effects of serotonin on target neurons in the striatum and/or substantia nigra. This would explain the low magnitude of methysergide-induced rotation and its directional consistency with LSD, mescaline- and MDMT-induced rotation.

Cyproheptadine failed to induce rotation at any of the doses tested. Although it possesses potent peripheral anti-serotonergic properties (Stone, Wenger, Ludden, Stavorski & Ross, 1961) and partially antagonizes the inhibition of hippocampal pyramidal cells induced by electrical stimulation of the midbrain raphe nuclei (Segal, 1975), it also has potent anti-histaminic properties (Stone et al., 1961). Perhaps the anti-histamic properties of the drug mask, in some as yet unexplainable manner, rotation resulting from the anti-serotonergic properties. This effect need only be subtle since rotation induced by methysergide, which is devoid of anti-histaminic activity, is of very low magnitude.

It might be fruitful to see if other anti-histaminic agents antagonize methysergide-induced rotation.

2-Bromo-LSD was ineffective as a rotational agent at all doses tested. Although 2-bromo-LSD is generally considered to be a central 5-HT antagonist (Graeff & Schoenfeld, 1970; Vane, Collier, Corne, Marley & Bradly, 1961), Aghajanian (1976) found that iontophoretic 2-bromo-LSD produced a slight decrease in the firing rate of dorsal raphe neurons, and intensified the depressant effects of iontophoretic 5-HT or LSD when administered concurrently. In the same study, the depressant effects of iontophoretic 5-HT on identified, serotonergically-innervated neurons in the ventral lateral geniculate and amygdala were not attenuated by simultaneous iontophoretic administration of 2-bromo-LSD. These data do not support the contention that 2-bromo-LSD is a 5-HT antagonist on dorsal raphe neurons or on neurons receiving serotonergic innervation.

Von Hungen, Roberts and Hill (1975), using particulate preparations from rat striatum, have shown that 2-bromo-LSD blocks dopamime-, norepinephrine- or LSD-induced activation of adenylate cyclase, although it has no effect on the activity of adenylate cyclase by itself. They have proposed that 2-bromo-LSD is a dopamine antagonist. Persson (1977) has recently proposed that 2-bromo-LSD is not only a postsynaptic dopamine antagonist (since it antagonized the apomorphine-induced decrease in L-DOPA accumulation following inhibition of the aromatic amino acid decarboxylase), but a presynaptic antagonist (at dopamine autoreceptors) as well. This is based upon the observation that 2-bromo-LSD or

haloperidol antagonize LSD-induced inhibition of L-DOPA accumulation in animals pretreated with gamma-butyrolactone. In this system, LSD is presumably acting as a presynaptic dopmaine agonist.

Thus, although 2-bromo-LSD is a potent peripheral 5-HT antagonist, its central actions in this respect are at best moderate. Since its pharmacological properties are closer to that of a dopaminergic anatagonist the possibility exists that some dose, perhaps below 0.5 mg/kg, might induce rotational behavior of low magnitude; i.e., similar to that induced by 0.125 mg/kg of haloperidol (Jerussi & Glick, 1976).

The rotation induced by the highest dose of l-LSD tested (see Figure 9), was of very low magnitude and was, to say the least, unexpected. Of all the derivatives of lysergic acid that have been synthesized and assayed for psychotomimetic potency, only the d-isomers are active (Brawley & Duffield, 1972). Thus, l-LSD-induced rotation is probably not related to psychotomimetic potency, although high enough doses might have some subjective effects. Since there are no reports of any pharmacological properties attributed to l-LSD, little more can be said about it, except that in terms of the dose used and the magnitude of rotation induced by it, it was approximately six times less potent than the d-isomer.

SUMMARY AND CONCLUSIONS

LSD, mescaline, MDMT and methysergide were found to induce dose-dependent rotational behavior in normal rats. The direction of rotation was consistent for individual animals when the same drug was administered with an interval of one week separating drug administrations. In addition, the direction of rotation was the same for individual animals when these drugs were compared to each other. L-LSD induced weak rotation at the highest dose tested; it was approximately six times less potent than the d-isomer. The direction of LSD-induced rotation was found to be the same as that of d-amphetamine-induced rotation, but not the same as apomorphine-induced rotation.

The rotation induced by the simultaneous administration of LSD and d-amphetamine or LSD and scopolamine was significantly greater than for d-amphetamine alone, or scopolamine alone, respectively. The simultaneous administration of LSD and apomorphine induced rotation no different than with apomorphine alone.

Pretreatment with the tryptophan hydroxylase inhibitor PCPA, increased the sensitivity of animals to rotation induced by LSD. Pretreatment with the serotonin precursor L-tryptophan, had no effect on LSD-induced rotation. LSD-induced rotation was blocked by pretreatment with a subcataleptic dose of haloperidol, which blocks dopamine receptors. LSD-induced rotation was also blocked by pretreatment with the tyrosine hydroxylase inhibitor AMPT.

The results of this thesis are consistent with an inhibitory action of LSD, mescaline and MDMT on midbrain raphe neurons. The subsequent disinhibition of nigrostriatal activity (possibly at the level of the substantia nigra) would result in rotation. Methysergide

induced rotation could result from a partial blockade of post-synaptic serotonin receptors in the substantia nigra or striatum.

It was also suggested that LSD was interacting with striatal presynaptic autoreceptors, producing an inhibition of tyrosine hydroxylase activity and a subsequent decrease in dopamine release. This effect may partially antagonize rotation resulting from disinhibition of nigrostriatal activity. Similarly, the noradrenergic action of mescaline might partially block rotation resulting from disinhibition of nigrostriatal activity.

Since no single behavioral parameter in animals correlates reliably with hallucinogenic potency in man (Brawley & Duffield, 1972), no testing procedure presently exists capable of predicting hallucinogenic potency. Since all of the hallucinogens used in this study induced dose-dependent rotational behavior, could this behavioral paradigm be utilized as a screening test for hallucinogenic agents ? In terms of the doses necessay to induce maximum rotation, LSD was four times more potent than MDMT and eighty times more potent than mescaline. Thus, the rank order of potency for hallucinogen-induced rotation is the same as the rank order of potency for subjective effects (i.e., psychotomimetic) in humans (Brawley & Duffield, 1972).

Obviously, the induction of rotation by an agent with unknown pharmacological properties is not sufficient to classify it as an hallucinogen, since many non-hallucinogenic drugs such as amphetamine, apomorphine,scopolamine, etc. induce dose-dependent rotation in normal rats. However, if it can be demonstrated that mescaline or MDMT increases amphetamine-induced rotation, and that PCPA-pretreatment increases the sensitivity of rats to mescaline- or MDMT-induced rotation, these drug interactions might be used to

predict hallucinogenic potency. Of course, false positives could still be obtained with non-hallucinogenic agents.

It is doubtful that the dopamine agonist properties of LSD are related to its hallucinogenic properties. Other agents such as MDMT or psilocin have negligible affinities for dopamine receptors (Creese, Burt & Snyder, 1975), but are potent hallucinogens. 2-Bromo-LSD, which is virtually inactive as an hallucinogenic agent, binds the dopamine receptor almost as well as LSD (Creese, Burt & Snyder, 1975).

Thus, it would appear that the inhibitory actions of LSD, mescaline, MDMT and possibly other hallucinogenic agents on midbrain raphe neurons is the basis of their capacity to induce rotation in normal rats and probably of their psychedelic actions.

Finally, it would be particularly interesting to monitor the firing rate of nigrostriatal neurons following systemic administration of LSD, mescaline or MDMT. An increase in the rate of firing would provide evidence that disinhibition of nigrostriatal activity is the mechanism by which LSD, mescaline and MDMT induce rotation in normal rats.

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