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**EFFECTS OF *AD LIBITUM* MIDBRAIN INTRACRANIAL SELF-STIMULATION
ON RAPID EYE MOVEMENT SLEEP IN RATS**

by

Francisco Villegas

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

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

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ABSTRACT**EFFECTS OF *AD LIBITUM* MIDBRAIN INTRACRANIAL SELF-STIMULATION
ON RAPID EYE MOVEMENT SLEEP IN RATS**

By

Francisco Villegas

Adviser: Dr. Steven J. Ellman

This study was performed to examine whether *ad libitum* intracranial self-stimulation (ICSS) elicited from the periaqueductal gray (PAG) significantly reduces REM sleep and prevents the occurrence of subsequent REM rebound in rats. This study evaluates the following: the placement of stimulating electrodes, the occurrence of effects either in the light or dark phase of the circadian cycle, the onset and duration of effects over the 3-day ICSS period, and amount of microcoulomb current delivered to stimulation sites. To assess the specificity of ICSS effects, in REM sleep, SWS, and AWAKE were examined over baseline, *ad libitum* ICSS, and recovery conditions. It was hypothesized that PAG ICSS should significantly reduce REM sleep during the stimulating condition. It was hypothesized that if PAG ICSS reduces REM sleep, it should also prevent an increase in the intensity or duration of subsequent REM time during the recovery period (REM rebound). Two independent groups (9 unilateral and 9 bilateral electrode sites) were tested for effects over a 9-day repeated measures design to assess differences between baseline, *ad libitum* ICSS, and recovery

condition days, in independent 12-h light, 12-h dark cycles, to detect the presence or absence of cyclical effects upon REM sleep, SWS, and AWAKE. Rats were chronically implanted with bipolar stimulating electrodes aimed bilaterally at the PAG and electrodes to record EEG, EMG, and EOG. Animals were shaped to bar-press for ICSS at a variety of current intensities and were stabilized over a 5-day period at an optimal current intensity eliciting peak ICSS rates. The results show that REM and SWS were significantly decreased during the first day in the *ad libitum* ICSS condition in both groups of rats in the dark and light cycles.

Significant decreases in REM and SWS during the first day of stimulation did not reemerge as increases in days 2 and 3 in the *ad libitum* condition. However, REM and SWS reductions were more pronounced during days 2 and 3 in the *ad libitum* condition in lights cycles than in dark cycles. Significant increases in REM sleep and SWS occurred only during the first 12 h dark cycle and were not significant in subsequent recovery cycles. Significant correlations were noted in the absolute number of microcoulombs delivered to each rat during the 3-day stimulation period and resulting REM, SWS, and AWAKE changes. Furthermore, amounts of microcoulombs delivered to unilateral and bilateral electrode sites did not differ significantly from each other for REM sleep differences scores between the baseline and *ad libitum* conditions.

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INTRODUCTION

The purpose of this dissertation was to examine whether *ad libitum* intracranial self-stimulation (ICSS) elicited from the periaqueductal gray (PAG) significantly reduces REM sleep and prevents the occurrence of subsequent REM rebound in rats. This dissertation considers important variables relevant to this phenomenon, including the placement of either unilateral or bilateral stimulating electrodes, the amount of microcoulomb current delivered, the occurrence of effects either in the light or dark phase of the circadian cycle and the onset and duration of effects over a 3-day stimulation period. To assess the specificity of effects, evaluation of alterations in the amount of time spent in waking, SWS and REM sleep stages was examined over baseline, *ad libitum* stimulation and recovery conditions.

The theoretical and empirical impetus for this study was derived from findings (Steiner & Ellman, 1972) that reported a relationship between REM sleep and intracranial self-stimulation behavior elicited from the lateral hypothalamus in rats. These investigators found that REM sleep deprivation significantly lowers the electrical stimulation threshold and increases operant response rates for hypothalamic ICSS. Additionally, access to hypothalamic ICSS during REM deprivation periods significantly reduced the amount of subsequent REM sleep rebound. These data suggest an interchangeability between the rewarding aspects

of hypothalamic ICSS and REM sleep such that REM sleep deprivation lowers the threshold for hypothalamic ICSS and *ad libitum* ICSS elicited from the lateral hypothalamus (LH) significantly reduces subsequent REM sleep rebound. A subsequent study (Spielman, 1979) found that REM sleep deprivation also lowers the threshold for ICSS elicited from the locus coeruleus (LC).

It is not clear whether such REM-ICSS interactions are generalizable to all loci supporting ICSS, or whether they are specific to the LH and LC. The ventro-lateral quadrant of the PAG is implicated in the elicitation of sleep and indirectly in REM sleep (Mouret & Coindet, 1980; Harper et al., 1991). Further, the ventro-lateral PAG is also a site that elicits ICSS in rats (Cooper & Taylor, 1967; Margules, 1969; Liebman et al., 1973; Ellman et al., 1974; Ackermann et al., 1977; Bodnar et al., 1981). Additionally, considerable attention has been focused on the PAG as possible site for the control of autonomic nervous system, modulation of analgesia, sexual behavior, aggression, vocalization and other various appetitive behaviors (see review: Bandler et al., 1991a).

The purpose of this dissertation is to explore whether *ad libitum* exposure to PAG ICSS significantly and selectively reduces REM sleep in rats. It is hypothesized that if ICSS eliminates REM sleep without an increase in the intensity or duration of subsequent REM time (REM rebound)

then the rewarding properties of the ICSS could be acting to "satisfy" the effects of endogenous REM sleep rather than by simply acting to inhibit REM sleep per se. The absence of a REM sleep rebound phenomenon following *ad libitum* ICSS may suggest that the "pressure" for a fixed amount of REM sleep activation has been "satisfied" by the ICSS, and therefore the need to make up lost REM sleep is not necessary.

In order to examine fully the variables affecting the analysis of this dissertation, the following pertinent literature was reviewed: a) neuroanatomy and functional significance of the PAG, b) the neuroanatomical substrates of ICSS, and particularly PAG ICSS, c) the putative neuroanatomy of SWS sleep and the involvement of the PAG, d) the neuroanatomical substrates of REM sleep, and e) a rationale for the present study.

PART ONE: GENERAL BACKGROUND

A. THE NEUROANATOMY OF THE PERIAQUEDUCTAL GRAY

The periaqueductal gray in mammals is not a homogeneous structure, however there has been little agreement as to whether to subdivide the PAG cytoarchitecturally (e.g. Hamilton, 1973; Beitz, 1985; Paxinos & Watson, 1986), or by functional significance (e.g. Mantyh, 1982; Gioia et al., 1984; 1985; Bandler & Carrive, 1988; Bandler et al., 1991b).

1. Anatomy of the Periaqueductal Gray

The periaqueductal gray refers specifically to the portion of the ventricular gray matter (central gray) which surrounds the midbrain aqueduct (Aq). Golgi analyses described the cytoarchitecture of the rat PAG using qualitative and quantitative data on neuronal size, shape, density, and orientation (Beitz, 1985; Beitz & Shepard, 1985). These data are also comparable to the subdivisional scheme proposed by Hamilton (1973; 1974). The PAG is composed of a group of densely-packed and myelin-poor cells which surrounds the mesencephalic Aq. Four major subdivisions of the rat PAG was based on cluster analysis (e.g. cell area, length, width, axial ratio, and orientation) and neuronal density measurements (Beitz, 1985): dorsal, medial, dorso-lateral, and ventro-lateral.

Rostrally, the PAG is continuous with the periventricular gray matter encircling the third ventricle

in the hypothalamus (HYP) and thalamus. Caudally, it is connected with gray matter in the dorsal pons which forms the ventral and ventro-lateral border of the fourth ventricle. Further, the oculomotor and related groups of nuclei (i.e., oculomotor and trochlear nuclei, the Edinger-Westphal nucleus, the nucleus of Darkschewitsch and the interstitial nucleus of Cajal) as well as the dorsal raphe nucleus (DRN), constitute the major part of the gray matter ventral to the midbrain Aq.

i. Location, Size, and Shape of the PAG

The PAG in the rat is formed by small, densely-packed cells surrounding the cerebral Aq. In the adult rat the PAG measures 3,570 μm from its caudal to rostral pole, 2,490 μm at its greatest width, and 2,820 μm at its greatest height. The central gray is partially funnel-shaped with its base located caudally and its apex rostrally. Caudally, the PAG begins at the rostral level of the locus coeruleus at the point where the cerebral Aq opens into the fourth ventricle. The PAG blends into the central gray matter of the pons at the level with no clear boundary separating the two periventricular regions. Rostrally, the PAG extends to the level of the posterior commissure where it merges with periventricular gray matter associated with the third ventricle. Dorsally, and dorso-laterally the PAG borders the rostral and caudal colliculi, while laterally the PAG

borders the mesencephalic nucleus of V and the nucleus cuneiformis. Forming the ventral-most boundary of the central gray is the longitudinal fasciculus, trochlear nucleus, and oculomotor nucleus. The dorsal raphe nucleus, the latero-dorsal and dorsal tegmental nuclei are found embedded in the caudal PAG. At rostral PAG levels, the nucleus of Darkschewitsch is intermingled with the ventral aspect of the PAG (Beitz, 1985).

ii. Periaqueductal Gray Subdivisions

The data from both cluster analysis and neuronal density measurements support the existence of four divisions within the PAG of the rat (Beitz, 1985): medial, dorsal, dorso-lateral, and ventro-lateral. Since the focus of this dissertation centers on the ventro-lateral subdivision as described by Beitz (1985), the following sections will only briefly describe the other subdivisions.

The medial subdivision surrounds the mesencephalic Aq, contains four of the six neuron types and displays the lowest neuronal density per unit volume of tissue. Small bipolar neurons are the most prominent (62.2%) of all the cells in this subdivision. The dendrites of small bipolar neurons are oriented predominantly parallel to the wall of the cerebral Aq, while the axons from these neurons traveled in a lateral or dorso-lateral direction to enter the ventro-lateral or dorso-lateral subdivisions. Small triangular and

small multipolar neurons are the next numerous (39.1%). The dendrites of the small triangular neurons travel parallel to the wall of the mesencephalic Aq, while the small multipolar cells are randomly oriented. Large fusiform multipolar neurons type are mostly found in the dorsal half of the medial subdivision and gives rise to axons that travel dorsally or dorsolateral to enter the dorso-lateral PAG subdivision or the overlying colliculi.

The dorsal subdivision contains all six neuron cell types although the small bipolar, large fusiform, and the small triangular neurons are the most prominent. Dendrites of the small bipolar neurons are aligned in either a dorsal to ventral or a medial to lateral orientation, while the remaining neuron types display dendrites oriented randomly. The axons of these neurons followed laterally into the dorso-lateral PAG subdivision or dorsally toward the overlying colliculi. Axons of large fusiform, small triangular and large triangular neurons travel predominantly dorsally and are observed to enter the overlying colliculi or collicular commissure.

The dorso-lateral subdivision inhibits prominently small triangular and bipolar neurons. The dendrites of these cells are often arranged in a medio-lateral direction so that they display a tangential or radial orientation to the wall of the mesencephalic Aq and, while axons run in a lateral or dorsomedial direction and those of the small

bipolar neurons travel ventrally or ventro-laterally. The large triangular neurons are most prominent in the dorso-lateral subdivision than in the other three. The axons of the large triangular neurons are always directed laterally and its length of the dendritic field are oriented in a medio-lateral direction in most cases but occasionally are directed dorso-ventrally. The axons of the large multipolar neurons also journey laterally into the reticular formation. Axons of some of the large multipolar neurons are directed ventro-medially and occasionally a dorsally directed axon was observed.

The ventro-lateral subdivision contains 52.8% of the small bipolar and triangular neurons. The dendritic trees of most small bipolar neurons are arranged from dorsolateral to ventro-medial, while the long axes of the dendritic fields of the small triangular neurons are commonly oriented in a dorso-medial to ventro-lateral direction. The majority of axons of both the small bipolar and small triangular neurons are directed laterally or ventro-lateral toward the reticular formation. Axons were occasionally found to travel ventro-medially or dorso-medially. The axons of the large fusiform and large multipolar neurons traveled laterally into the reticular formation or traverse the ventro-lateral subdivision to enter the dorso-lateral subdivision. The second subtype of large fusiform neurons with their pyriform shaped soma and few dendritic spines are

the most numerous in this subdivision. These neurons generally have dendritic fields organized in a dorso-lateral to ventro-medial or lateral to medial direction. The axons of the large triangular and small multipolar neurons in the ventro-lateral subdivision follow laterally away from the mesencephalic Aq. The axons of small multipolar neurons can be traced dorsally into the dorso-lateral subdivision. Although the majority of intrinsic studies of the PAG suggest that some overlapping occurs among the subdivisions composing the region, marked quantitative differences in the connections of these subdivision do exist.

iii. Afferent Projections to the PAG

Investigations of the afferent input to the PAG utilizing retrograde tracing techniques in the rat reveal both qualitative and quantitative differences among the four subdivisions (Beitz, 1982; Liu, 1983). Differences in the afferent input to the PAG subdivisions are also visible in anterograde tracing studies. The dorso-lateral subdivision, for instance receives specific inputs from the frontal cortex (Hardy & Leichnetz, 1981a;b) and ventro-medial hypothalamic nucleus, while the ventro-lateral subdivision receives the predominant input from the preoptic area (Krieger et al., 1979), the nucleus reticularis gigantocellularis, the lateral hypothalamus (Hosoya & Matsushita, 1981; Beck & Finkelstein, 1982), the

suprachiasmatic nucleus (Kucera & Favrod, 1979; Stephan et al., 1981), the nucleus accumbens (Nauta et al., 1978), the lateral habenular nucleus (Herkenham & Nauta, 1979) and the central nucleus of the amygdala (Hopkins & Holstege, 1978).

In the rabbit, using both fluorescent dyes (Meller & Dennis, 1983) and horseradish peroxidase as labels (Meller & Dennis, 1986), revealed that over a hundred different regions of the brain were found to provide afferent inputs to the PAG. Discrete placements of labels in the dorsal, lateral, and ventral subdivisions have established that a certain degree of topographical precision exists between these different zones and regions innervating them. Noticeable amongst the regions supplying input to the rabbit's PAG were cortical areas 5, 20, 21, 32 and 40 (Dennis & Meller, 1993).

The medial preoptic area (MPO) has been implicated in a variety of physiological and behavioral functions including thermoregulation, maternal and sexual behaviors, maintenance of water balance, antinociception, autonomic regulation, and sleep (Wang & Randson, 1941; Roberts & Martin, 1977; Swanson et al., 1978; Day et al., 1979; Clemens & Gladue, 1979; Jacobson et al., 1980; Carstens et al., 1982; Swanson & Mogenson, 1981; McGinty & Szymusiak, 1990). Valverde, (1965) in a Golgi study reported that cells in MPO have short axons which extend only short distances. However, subsequent tract tracing studies suggested that PAG was a

target of MPO axons (Enoch & Kerr, 1967; Chi & Flynn, 1971). A number of anterograde tracing studies (Conrad & Pfaff, 1979; Saper et al., 1978; Chiba & Murata, 1985; Simerly & Swanson, 1986) have reported that PAG receives input from MPO. Rizvi et al. (1992), examined systematically the distribution of MPO terminals along the rostrocaudal axis of the PAG.

Rizvi et al. (1992), using anterograde tracing with horseradish peroxidase (HRP) conjugated to wheat germ agglutinin (WGA) and Phaseolus vulgaris-leucoagglutinin (PHA-L) injections demonstrated that the projection from MPO to PAG is very dense and highly organized. Thus, injections in the MPO area resulted in strong anterograde labeling along the entire rostrocaudal axis of the PAG. However, the terminal labeling in PAG from the MPO area was not uniformly distributed throughout the PAG. Instead, this projection formed one or two rostro-caudally oriented longitudinal columns that terminated in different subregions of the PAG along the entire rostrocaudal axis. Rostrally, inputs from the MPO area project heavily to dorso-medial PAG, and at mid-PAG levels, these projection bipartite with two discrete longitudinal terminal columns in dorso-medial and lateral PAG. Caudally, the heaviest labeling was found projecting to the ventro-lateral PAG. The projections also exhibited a central to peripheral (radial) gradient, thus labeled fibers and terminals were heaviest near the Aq and much lower in

the peripheral parts of the PAG. WGA-HRP injections in MPO also produced retrograde of neurons at all rostrocaudal levels of PAG, thus more neurons were labeled in the rostral than in the caudal half of the PAG. The majority of labeled cells were located in dorso-medial and ventral/ventro-lateral parts of the PAG with only a few neurons in the dorsal raphe region appear to project to the MPO.

Van Bockstaele, Pieribone and Aston-Jones (1989) with WGA-HRP, Fluoro-Gold (FG), and PHA-L studied the afferents to the nucleus paragigantocellularis (PAi). Projecting to the PHi were a wide variety of nuclei with autonomic, visceral, and sensory-related functions. The major afferents to the PHi with robust retrograde labeling included the PAG, a preoculomotor nucleus in the ventral PAG, and the supraoculomotor nucleus (SOM).

The trigeminal motor nucleus (TMN) is divided into a dorsolateral part containing the jaw-closers motoneurons and a ventro-medial part containing the jaw-opener motoneurons (Mizuno et al., 1975). To elucidate the afferent connections involved in the trigeminal sensorimotor integration specific to the masseteric muscular atonia (jaw-closer) occurring during the periods of REM sleep Fort et al. (1990), used unconjugated cholera-toxin (CT) restricted into the cat TMN. Fort et al. (1990), found retrogradely labeled neurons in the PAG. A small number of CT-labeled cells (cells were medium-size to small) were seen through-

out the Edinger-Westphal nucleus and the adjacent oculomotor area with some labeled cells scattered within the PAG. Furthermore, a few retrogradely labeled neurons were also observed in the DRN.

iv. Efferent Projections from the PAG

The regions receiving efferent projections from the PAG are as numerous as those providing input to it. Accordingly, the reciprocity of connections was established for most of the regions found to provide afferent connections to the PAG (Meller & Dennis, 1991).

Utilizing anterograde transport labeling techniques, recent studies of the projections from the PAG to the nucleus raphe magnus (NRM) and nucleus reticularis paragigantocellularis, have shown that the ventro-lateral subdivision provides about 70% of the total PAG output to these two nuclei (Beitz & Finkelstein, 1982). The dorsal PAG subdivision projects about 21% of the output to the paragigantocellularis. The medial and dorso-lateral subdivisions contribute 4% of the PAG projections to the NRM and 9% to the nucleus paragigantocellularis. Accordingly, all four subdivisions projects fibers to these lower brainstem nuclei, which accounts for over 90% of these fibers arise in the ventro-lateral and dorsal PAG subdivisions. Recent findings by Herrero et al. (1991) using a retrograde fluorescent tracer, have found evidence

of widespread input from the paleo- and neocortex from region localized to the most ventral part of the PAG.

Herrero et al. (1991), studied in rats the topographical organization of afferent inputs from the PAG to cerebral cortex, with the retrograde fluorescent tracers, Fast blue and Diamidino yellow. The olfactory (including the olfactory bulb), medial frontal areas (prelimbic, infralimbic, and anterior cingulate cortices), lateral frontal (motor), parietal, temporal, occipital and insular cortices were examined with retrograde labeling fluorescent tracers into two different cortical areas.

Herrero et al. (1991), observed that the PAG contained the largest number of neurons retrogradely labeled from the medial frontal cortex sections, followed by the olfactory and lateral cortices. Fewer retrogradely labeled cells were reported after injections in the parietal, temporal occipital and insular cortices. Labeled cells were located exclusively in the medial and latero-ventral divisions of the PAG. Furthermore, along longitudinal extent of the PAG, the labeling in the medial PAG was more extensive than the ventral PAG. The labeled neurons in the medial frontal cortex group extended through most of the PAG, while in the parietal, temporal, occipital, and insular cortices labeling was restricted to the caudal one-third of the PAG. Herrero et al. (1991), data indicates the medial frontal cortex receives most of the direct PAG input, followed by the

lateral frontal cortex. Sensory-related cortical areas (parietal, temporal, occipital, and insular cortices) were reported to receive only minor projections from the PAG, while receiving a substantial projection from the DRN.

The richness of the subcortical connections of both the DRN and PAG (Beitz, 1982) as proposed by Herrero et al. (1991), suggest the possibility of a cortical modulation coming from the subcortical centers, may bypass the thalamic relay, and may be significant for the understanding of cortical function.

Projections from PAG was studied by Rizvi et al. (1992), using multiple WGA-HRP different at rostrocaudal levels of PAG retrogradely labeled large numbers of neurons in the MPO. Labeled were cells primarily located in the medial preoptic nucleus, the median preoptic nucleus, and the region lateral to the medial preoptic nucleus. The distribution of labeled cells shifted medially to laterally along the rostral to caudal axis of the MPO area. Rostrally, selective retrograde labeling was found in the central and lateral divisions of the medial preoptic nucleus, while in the caudal aspect, labeled cells were primarily located only in the lateral subdivision of the medial preoptic nucleus.

Ennis et al. (1991), using retrograde and anterograde labeling and antidromic and orthodromic stimulation techniques examined the projections from PAG to the

dorsolateral tegmentum. Iontophoretic injections of WGA-HRP restricted into the LC produced retrograde labeling of a discrete group of neurons in the caudal half of the PAG and projected to the lateral and ventro-lateral margin of the cerebral Aq. In contrast WGA-HRP injections restricted to the LC proper did not produce retrograde labeling of PAG neurons. Anterograde labeling with PHA-L into sites located in PAG immediately adjacent to the lateral/ventro-lateral wall of the cerebral Aq at the level of the DRN produced labeled fibers that profusely and discretely innervated the ipsilateral rostro-medial pericoerulear area, including Barrington's nucleus. By contrast only a few sparse fibers appeared to enter in the LC proper and the subcoerulear area. Consistent with these results, focal electrical stimulation of LC antidromically activated only a few PAG neurons and all of these cells were located lateral and ventro-lateral to the cerebral Aq.

Ennis et al. (1991), found that the majority of neurons in the rostro-medial pericoerulear area were robustly activated by single pulse stimulation of PAG. In contrast, single pulse electrical stimulation of the lateral PAG produced weak to moderate synaptic activation of some LC neurons. While, stimulation of the ventro-lateral PAG produced predominant inhibition of LC discharge. These results are consistent with the findings of Aston-Jones et al. (1986) using retrograde and anterograde HRP transport

studies of the LC.

Aston-Jones et al. (1986) found that a only few CNS areas are directly afferent to the LC in rats. The only major inputs to the LC were from the PGI and the prepositus hypoglossi (PrH) both in the rostral medulla and also possible minor afferents (weak labeling) from the dorsal cap of the paraventricular hypothalamic nucleus (PVH) and the intermediate gray of the spinal cord (Spc).

The PAG projections to the ventral medulla are circuits that figure prominently in the antinociception and autonomic regulation. Van Bockstaele et al. (1991) demonstrated a high degree of anatomical specificity for projections from subregions of the PAG to the PAi, the ventral nucleus, gigantocellularis and midline brainstem raphe nuclei. Van Bockstaele et al. (1991) with injections of WGA-HRP covering most of the PGI found many retrogradely labeled neurons throughout the rostrocaudal extent of the PAG from the level of the Edinger-Westphal nucleus to the caudal midbrain. The retrogradely labeled neurons were found in the greatest densities in specific subregions of the PAG, as previously reported by Van Bockstaele et al. (1989). Rostrally, at the level of the oculomotor nucleus, labeled neurons were densely collected in the ventro-medial portion of the PAG corresponding to the SOM of the PAG, the lateral and ventro-lateral PAG, and in the medial dorsal central gray. More caudally, retrogradely labeled neurons were found less

numerous in the dorso-medial PAG but were more widely scattered throughout the lateral ventro-lateral parts of the PAG, while only a few retrogradely labeled neurons were found in the ventro-medial parts of the PAG.

In the rat the central nucleus of the amygdala (CNA) forms a prominent area of the caudal amygdaloid complex. Stimulation and ablation studies have demonstrated that the CNA participates in a number of behaviors such as emotional responses, feeding, arousal, avoidance, conditioned fear, the defense reaction, and antinociception (see Price et al. 1987, for review). Common to many of these behaviors are the alteration in heart rate, blood pressure, respiration, and gastrointestinal activity (Kaada, 1972). Many of these same functions are strongly represented in the PAG (Carrive et al., 1987; 1988; 1989a;b; Bandler & Carrive, 1988). Hence, the PAG may be an important structure mediating functions elicited from the CNA. Rizvi et al. (1991) studied the topography and reciprocal connections between the CNA and the PAG, utilized multiple or single localized injections of WGA-HRP into CNA and into several rostrocaudal levels of the PAG.

Discrete injections (Rizvi et al., 1991) of WGA-HRP into several rostro-caudal levels of the PAG retrogradely labeled numerous neurons in the CNA predominantly localized to the medial division of the CNA. Tracer injections into the CNA revealed a high degree of spatial organization to

the PAG. Thus, two discrete longitudinally directed columns were seen in the dorso-medial and lateral/ventro-lateral PAG were strongly labeled by CNA inputs throughout the rostral one-half to two-thirds of the PAG. Beginning at the level of the DRN and continuing caudally, inputs from the central nucleus were seen to terminate more uniformly throughout the ventral half of the PAG. Retrogradely labeled cells from the CNA were also observed to be distributed heterogeneously along the rostro-caudal axis of the PAG. As observed, some of the labeled neurons in the ventro-medial PAG were large and resembled 5-HT-containing dorsal raphe neurons, but many other labeled neurons were well outside of the dorsal raphe. Thus as demonstrated by Rizvi et al. (1991), the PAG receives numerous and highly organized projections from the CNA and in turn, projects efferent reciprocal connections with the central nucleus.

Neurons within the PGI have been implicated in a number of functions including cardiovascular regulation (Ciriello et al., 1986; Dampney et al., 1980; McAllen et al., 1982;), respiratory control (Feldman, 1986), pain and analgesia (Azami et al., 1981; Punnen et al., 1984) and arousal (Aston-Jones et al., 1991). This is consistent with results that show that afferents to the retrofacial portion of the PGI include many brain areas related to autonomic regulation and pain processing (Van Bockstaele et al., 1989). In addition, many brain afferents exhibit topography in the

innervation of various subregions of the PGI, suggesting a possible functional segregation within the PGI (Van Bockstaele et al., 1991).

Restricted iontophoretic injections of WGA-HRP or FG in the retrofacial regions of the PGI showed topography for afferents from the PAG (Van Bockstaele et al., 1991). Injections into the lateral portions of the PGI produced the greatest number of labeled neurons within the rostral ventro-medial PAG. Medially placed injections in the PAI yielded numerous retrogradely labeled neurons in the lateral and ventro-lateral PAG. These labeled neurons were most numerous in the caudal PAG immediately dorsal to the lateral wings of the dorsal raphe along with scattered labeled cells were also found within the dorsal raphe. Injections into the rostral pole of the PGI (medial to the facial nucleus) produced the greatest numbers of retrogradely labeled neurons in the dorsal PAG.

To further examine the pathways of the axons projecting from the PAG neurons to the medulla and to further specify the topography for the terminations of these afferents in the PGI, anterograde tracer PHA-L was iontophoretically deposited into subregions of the PAG that showed retrogradely labeled neurons from the PAG (Van Bockstaele et al., 1991). Distinct afferent fiber pathways were found to the rostral medulla from the dorsal, lateral/ventro-lateral, and ventro-medial parts of the PAG. When injections were

placed in the ventro-lateral PAG labeled fibers were observed at the pontine levels (Aston-Jones et al., 1986). Labeled fibers innervated the dorso-lateral pontine gray near the LC and Barrington's nucleus as well as the subjacent subcoeruleus and supraolivary tegmentum (Ennis et al., 1991). Also noticed were scattered fibers within the LC, especially in its ventral and medial component, and in the lateral division of the parabrachial nucleus. Injections into the rostral ventro-medial PAG near the supraoculomotor nucleus (SOM) produces anterograde labeling immediately ventral to the nucleus ambiguus (Abd) in the ventro-lateral medulla, within the retrofacial portion of the PAi. Injections into the lateral ventro-lateral PAG produced labeled fibers and terminals predominantly in the ventral nucleus gigantocellularis and in the medial retrofacial portion of the PGi. Injections of the dorsal PAG resulted in anterograde labeling predominantly in the nucleus raphe magnus and in the rostral portion of the PGi medial to the facial nucleus.

Van Bockstaele and Aston-Jones (1992), to ascertain whether neurons in the SOM area of the rostral ventro-medial PAG that project to the PGi of the ventral medulla is part of the pre-oculomotor group, used double retrograde transport labeling to determine whether these cells innervate the Abd. The results show that when the PGi was injected with wheat germ agglutinin-conjugated to inactive

horseradish peroxidase coupled to 15-nm gold particles (WGA-apoHRP-Au) and the Abd were deposited with rhodamine-coated latex microspheres in the same animal, retrogradely labeled neurons were seen in the region of the contralateral SOM in the ventro-medial PAG immediately dorsal to the SOM in the ventro-lateral PAG (Lovick, 1988; Maciewicz & Phipps, 1983). The number of labeled cells from the Abd varied with their rostro-caudal location in the SOM area (Maciewicz et al., 1975; May et al., 1987). Caudally, numerous labeled neurons were seen, at the level of the trochlear nucleus. More, rostrally, at the level of the oculomotor nucleus, fewer neurons were retrogradely labeled from the Adb. Neurons in the SOM area retrogradely labeled from the PGi were found to be most numerous rostral to the DRN and end extended throughout the level of the oculomotor nucleus. Comparison of the two labels showed that neurons that project to the Abd were located slightly more ventrally than the PGi-projecting neurons. In addition, neurons in the SOM area were found to also project to the dorsal pontine reticular formation rostral to the Abd.

2. Functional Significance of the PAG

The PAG is an integrative and relay center of the brain that controls animals' reactions to threatening and stressful stimuli (Bandler et al., 1991b). The PAG region is one of several sites in the brain involved in the

modulation of the nociceptive sensory input, through descending inhibitory neuronal processes that project to the spinal cord (Basbaum & Fields, 1984). This pain-inhibitory neuronal system may function as one of the components of an endogenous pain-suppression system, which is activated by factors such as stress, pain and cognitive behaviors (Fields & Heinricher, 1985). The PAG contributes to the analgesic effects of narcotics and opioid peptides (Smith et al., 1992) and integrates defensive behavior patterns like "fight-or-flight" and aversive motivational states (Audi & Graeff, 1984). Additionally, considerable attention has been paid to the PAG as possible sites for the control of autonomic nervous system, modulation of analgesia, sexual behavior, aggression, vocalization and other various appetitive behaviors (Bandler et al., 1991b).

i. Lordosis Behavior and PAG control

Among the numerous innate behavioral repertoires of mammals, lordosis, as a major component of female reproductive behaviors and is one of the best delineated (Ogawa et al., 1991). Lordosis is a stereotyped posture consisting of dorsiflexion of the vertebral column, which causes the elevation of the head and rump, accompanied by hind limb extension (Pfaff & Lewis, 1974). Somatosensory input given by a male partner is essential for every component of naturally occurring lordosis.

Anatomical studies (Krieger et al., 1979; Morrell et al., 1981; Beitz, 1982; Veening et al., 1991) have demonstrated that the dorsal and lateral subdivisions of the rostral and intermediate PAG, which are the most effective stimulation (or lesion) sites for the facilitation (or suppression) of lordosis, receive strong descending input from the ventro-medial nucleus of the hypothalamus (VMH) where the estrogen-containing cells necessary for the behavior are located.

ii. Defense Behavior and PAG control

Defensive behaviors that are part of an animal's behavioral repertoire are designed to ameliorate environmental threats (e.g., a conspecific or a predator). Defensive behaviors are not a singular phenomenon, but rather consist of several well defined sub-categories of defensive reactions. These reactions in the rat include: escape movements, freezing and confrontational behavior (Blanchard & Blanchard, 1981; Fanselow, 1991). Furthermore, defense behaviors are also characterized in the cat by arching of the back, pilo-erections, retraction of the ears, unsheathing of the claws, growling, and hissing which are accompanied by other sympathetic signs such as pupillary dilation, salivation and increase cardiovascular functions (Shaikh et al., 1991).

a. Defense Behavior and Cardiovascular Mediation by PAG

Recent data from the cat suggest that coordinated defensive behavior mediates rapid changes in cardiovascular function by a longitudinally oriented column of cells, lying in the caudal two-thirds of the PAG, lateral to the midbrain Aq. Similarly, neurons mediating different reactions are localized within distinct rostrocaudal sections of this column. In the cat microinjections of excitatory amino acid (EAA) made in the intermediate third of the lateral PAG evokes a threat display, a hypertensive response characterized by increased blood flow to the head and decreased blood flow to the limbs and the viscera. While microinjections of EAA in the caudal third of the lateral PAG evokes a flight response with hypertensive and increase blood flow to the hindlimb but decreased blood flow to the head and viscera (Bandler et al., 1991a; Carrive 1991; Carrive & Bandler, 1991; Carrive et al., 1987; 1989b).

As referred to by Depaulis et al. (1992) the "defensive behavior column" involves neurons that also mediate rapid changes in cardiovascular function. Depaulis et al. (1992) investigated the activation of neurons in the caudal PAG of the rat. When the caudal intermediate third of the PAG is activated with low doses of kainic acid (KA), the PAG evokes the defensive response showing the characteristic reactions displayed by upright postures and backward movements in response to the approach of a non-aggressive partner.

iii. Self-administration of Analgesics to the PAG

Bozarth and Wise (1984) reported that opioids can be rewarding even when they are restricted to brain regions where they do not activate mechanisms involved in physical dependence. Rats trained to press a lever for micromorphine injections into the ventral tegmental area but not into the PAG regions were made physically dependent on morphine by long-term infusions into the PAG but not by infusions restricted to the ventral tegmental areas.

Rats that learned to self-administer 100ng infusions of morphine sulfate into the ventral tegmental area (Bozarth & Wise, 1981a) were challenged with the opiate receptor antagonist naloxone (5 mg/kg, ip) and assessed for the traditional dependent signs (escape from the test box, chattering teeth, and "wet-dog" shakes). The naloxone-challenged rats showed none of the traditional dependent signs. This suggests that the rewarding effect of morphine in these animals was not accompanied by physical dependence. Prolonged morphine infusions into the ventral tegmentum could produce physical dependence (Bläsig et al., 1973). Long-term infusions into the PAG produced clear signs of naloxone-precipitated withdrawal similar to that previously reported for both systemic and centrally administered morphine (Bläsig et al., 1973; Wei, 1981).

iv. Stimulation-produced Analgesia from PAG

Stimulation-produced analgesia (SPA) from the PAG in the restrained and freely moving rats was first reported by Reynolds (1969). Other studies (Mayer et al., 1971; Akil et al., 1972; Giesler & Liebeskind, 1976; Morrow & Casey, 1976; Pert & Walter, 1976; Soper, 1976; Yaksh et al., 1976; Rhodes & Liebeskind, 1978; Dennis et al., 1980; Cannon et al., 1982) further characterized the phenomenon, demonstrating that stimulation at sites throughout the PAG inhibited nociception. Subsequent SPA studies performed in the cat (Guilbaud et al., 1972; Liebeskind et al., 1973; Olivéras et al., 1974; 1978; 1979) and in the rat (Fardin et al., 1981; 1984a;b), have demonstrated that regions producing "pure" analgesia (without other noticeable behavioral changes) is predominantly the DRN located in the ventral part of the PAG. Furthermore, studies showing that brain stimulation could inhibit nociception suggested the presence of an endogenous morphine-like transmitter (Mayer et al., 1971; Mayer & Liebskind, 1974; Akil et al., 1976). Researchers (Millan et al., 1986; Millan et al., 1987) have indicated underlying the SPA elicited from the ventral midbrain PAG is the opioid peptide type β -endorphin and μ -receptor which is the opioid receptor type. In analogy to tolerance which results upon repeated administration of a opioid agonist such as morphine or β -endorphin, tolerance may develop with repeated stimulation of the ventral brainstem PAG.

a. Antinociception by Electrical Stimulation of the PAG

The antinociceptive properties of the PAG stimulation have been widely documented (Reynolds, 1969; Mayer et al., 1971; Baskin et al., 1986). This effect is not limited to the PAG and can be achieved at several loci along a descending pain-inhibiting pathway (Basbaum & Fields, 1978; 1984). Stimulation-produced analgesia can also be achieved from areas of the brain that do not run along the proposed PAG-raphé pain-inhibitory tract, suggesting that more than one pain inhibitory system exists (Cohen & Melzack, 1985; Margalit & Segal, 1979; Moises & Smith, 1985; Seeger & Pert, 1985).

There is additional evidence that more than one antinociceptive system exists within the PAG itself. The finding of Cannon et al. (1982), that the PAG is not equipotent in the potency of analgesia it produces supports this hypothesis. They reported lower analgesic threshold current intensity with ventral PAG stimulation, whereas dorsal stimulation had a longer period of analgesia after stimulation. More recent studies support other dorsal and ventral differences in stimulation-produced analgesia. For example, tolerance to the analgesic effect of ventral stimulation is obtained more rapidly than that of dorsal stimulation (Morgan & Liebeskind, 1987).

The two pain-inhibition pathways within the PAG probably have different neurochemical substrates.

Researchers have reported that naloxone reverses analgesia produced by ventral, but not dorsal, stimulation, suggesting a ventral opiate system and a dorsal non-opiate system (Cannon et al., 1982).

Thorn et al. (1989) using monopolar stimulation, found that the PAG does not have a strong region differentiation in the production of stimulation-produced analgesia. However, they did find a clear distinction between dorsal and ventral stimulation sites in naloxone reversibility. Naloxone reliably reverses analgesia elicited by ventral electrode PAG placement but does not reverse or attenuate analgesia elicited by dorsal placements. The results confirm the findings by Cannon et al. (1982), of differential naloxone reversibility of ventral compared with dorsal PAG sites, but they do not support a regional distinction in the potency of the analgesia induced. Thorn et al. (1989) data also suggest that dorsal PAG sites are involved in a separate, non-opiate pain-inhibitory system and ventral sites are involved in an opiate-mediated system.

B. NEUROANATOMICAL SUBSTRATES OF ICSS

Since the discovery by Olds and Milner, (1954) that rats could be operantly trained to receive trains of electrical stimulation into discrete brain regions, a remarkable amount of research has been conducted to elucidate its substrates and mechanism. The findings by

Olds and Milner (1954) can be briefly summarized: Rats with stimulating electrodes in the septal area, operantly bar-pressed for electrical stimulation of these loci much in the same manner as animals work for conventional primary reinforcers. Such stimulation appeared to be rewarding, in the sense that the rats actively sought the opportunity to produce the electrical stimulation. Subsequently, ICSS delivered to a wide variety of anatomical sites was found to reinforce lever pressing.

1. Anatomical Sites Supporting ICSS

In German and Bowden's (1974) review, sites that support ICSS in the rat were found to be highly correlated with electrodes in 3 of the 4 major catecholamine (CA) systems. With the use of Ungerstedt (1971) stereotaxic mapping of monoamine pathways in the rat brain, German and Bowden (1974) were able to evaluate the extent of overlap between brain areas that support ICSS and the 4 major ascending CA systems: Dorsal and ventral norepinephrine (NE) systems and the mesolimbic and nigrostriatal dopamine (DA) systems. The following is a concise overview of the CA anatomical systems and corresponding sites that support ICSS.

Neurons of the ascending dorsal NE system originate primarily in the locus coeruleus (A6) in the floor of the fourth ventricle. The fibers join with the ventral NE

system briefly, then separate at the level of nucleus pontis to form the dorsal noradrenergic bundle (DNB) which courses rostrally and ventrally to join the medial forebrain bundle (MFB) at the level of the posterior hypothalamus. The DNB continues rostrally through the basal forebrain, curves dorsally around the genu of the corpus callosum, and then caudally as the supracallosal bundle. The major rostral structures of termination include periventricular portions of the hypothalamus, hippocampus, amygdala, and the cortex (Ungerstedt, 1971).

Electrode sites that support ICSS in the ascending dorsal NE system include the nuclei of origin in the LC (Routtenberg & Malsbury, 1969; Routtenberg, 1970; Crow et al., 1972; Ellman et al., 1974), and its pathways, the posterior common noradrenergic bundle (Keene & Casey, 1970; Huang & Routtenberg, 1971; Routtenberg, 1971), DNB (Olds, 1956; Olds et al., 1960; Glickman, 1960; Arbuthnott et al., 1971; Keene & Casey, 1970; Routtenberg, 1971; Wolfle et al., 1971; Crow, 1972), anterior dorsal noradrenergic bundle (Keene & Casey, 1970; Wolfle et al., 1971), posterior medial forebrain bundle (Olds et al., 1960; Routtenberg, 1971; Huang & Routtenberg, 1971; Keene & Casey, 1970), anterior medial forebrain bundle (Olds et al., 1960; Wurtz & Olds, 1963; Routtenberg, 1971; Huang & Routtenberg, 1971), basal forebrain bundle (Olds et al., 1960; Keene & Casey, 1970; Routtenberg, 1971; Routtenberg & Sloan, 1972),

supracallosal bundle (Olds et al., 1960; Keene & Casey, 1970; Routtenberg, 1971; Wurtz & Olds, 1963), and the stria terminalis (Olds et al., 1960; Wurtz & Olds, 1963).

The termination sites supporting ICSS in the ascending dorsal NE system include the medial geniculate body, hypothalamus (HYP), periventricular areas (Olds et al., 1960; Huang & Routtenberg, 1971), frontal pole of the cortex (Wurtz & Olds, 1963; Routtenberg, 1971), dorsal and lateral cortex (Olds et al., 1960; Ursin et al., 1966), pyriform and entorhinal cortex (Wurtz & Olds, 1963; Routtenberg, 1971), hippocampus (Olds et al., 1960; Wurtz & Olds, 1963; Huang & Routtenberg, 1971), amygdala (Wurtz & Olds, 1963), interstitial nucleus of stria terminalis (Olds et al., 1960; Routtenberg, 1971), and the olfactory bulb (Routtenberg, 1971).

Neurons of the ascending ventral NE system arise in areas A1, A2, A5, and A7 and do not appear to support ICSS (Clavier & Routtenberg, 1974). ICSS electrode sites in pathways running from the ascending ventral NE system include the posterior noradrenergic bundle (Routtenberg & Malsbury, 1969; Routtenberg, 1970), the posterior common noradrenergic bundle (Routtenberg & Malsbury, 1969; Routtenberg, 1970; Huang & Routtenberg, 1971), ventral noradrenergic bundle (Routtenberg & Malsbury, 1969; Huang & Routtenberg, 1971; Mayer et al., 1971; Wolfle et al., 1971), anterior ventral noradrenergic bundle (Glickman, 1960; Olds

et al., 1960; Sem-Jacobsen & Torkildsen, 1960; Routtenberg & Malsbury, 1969; Routtenberg, 1970; Arbuthnott et al., 1971; Crow, 1972; Huang & Routtenberg, 1971), common ventral tegmental bundle (Olds et al., 1960; Routtenberg & Malsbury, 1969; Routtenberg, 1970; Arbuthnott et al., 1971; Huang & Routtenberg, 1971; Crow, 1972), posterior medial forebrain bundle (Olds et al., 1960; Huang & Routtenberg, 1971; Keene & Casey, 1970; Routtenberg, 1970), and the anterior medial forebrain bundle (Olds et al., 1960; Wurtz & Olds, 1963; Huang & Routtenberg, 1971; Routtenberg, 1971).

The termination sites reported to supporting ICSS of the ascending ventral NE system include the PAG (Routtenberg, 1970; Mayer et al., 1971; Wolfle et al., 1971), noradrenergic midbrain reticular formation (Routtenberg & Malsbury, 1969; Routtenberg, 1970), HYP, baseo-lateral areas (Olds et al., 1960; Huang & Routtenberg, 1971; Keene & Casey, 1970), and the interstitial nucleus of stria terminalis (Olds et al., 1960; Routtenberg, 1971).

The neurons of the nigrostriatal DA system arise in nucleus zona compacta of the substantia nigra (A9) and probably in the adjacent nucleus A8 (German and Bowden, 1974). Their fibers run rostro-medially to enter the medial forebrain bundle (MFB) and together with the fibers of the mesolimbic system run rostrally in the medial tip of the internal capsule through and fan out to terminate in the caudate putamen.

Neurons within the nigrostriatal DA system are found to support ICSS within A9 (Olds et al., 1960; Routtenberg & Malsbury, 1969; Routtenberg, 1970; Huang & Routtenberg, 1971; Crow, 1972) and A8 (Valenstein & Beer, 1961; Routtenberg & Malsbury, 1969). ICSS electrode sites in pathways arising from the nigrostriatal DA system include the common ventral tegmental bundle (Olds et al., 1960; Routtenberg & Malsbury, 1969; Routtenberg, 1970; Arbuthnott et al., 1971; Crow, 1972; Huang & Routtenberg, 1971), posterior medial forebrain bundle (Olds et al., 1960; Keene & Casey, 1970; Routtenberg, 1970; Huang & Routtenberg, 1971), internal capsule, medial tip (Olds et al., 1960; Routtenberg, 1971), and the transcapsular radiation (Olds et al., 1960; Wurtz & Olds, 1963; Huang & Routtenberg, 1971; Routtenberg, 1971). While, the caudate putamen (Olds et al., 1960; Wurtz & Olds, 1963; Routtenberg, 1970; 1971; Huang & Routtenberg, 1971; Routtenberg & Sloan, 1972), and the amygdala, nucleus centralis (Wurtz & Olds, 1963) are termination points supporting ICSS of the nigrostriatal DA system.

The neurons of the mesolimbic DA system originate in ventral tegmental area (A10) (VTA) in the vicinity of the interpeduncular nucleus. The axons course rostrally in the MFB to a mid-hypothalamic level, where they deviate laterally into the medial tip of the internal capsule, and continue rostrally to terminate in the nucleus accumbens and

olfactory tubercle (German and Bowden, 1974).

The neurons of the mesolimbic DA system also support ICSS within VTA (Routtenberg & Malsbury, 1969; Routtenberg, 1970; Arbuthnott et al., 1971; Huang & Routtenberg, 1971; Wolfle et al., 1971; Crow, 1972; Porrino et al., 1984). ICSS electrode sites in pathways arising from the mesolimbic DA system include the common ventral tegmental bundle (Olds et al., 1960; Routtenberg, 1970; Huang & Routtenberg 1971), posterior medial forebrain bundle (Olds et al., 1960; Keene & Casey, 1970; Routtenberg, 1970; Huang & Routtenberg 1971), medial tip of the internal capsule (Olds et al., 1960; Routtenberg, 1971), and the external medial forebrain bundle (Olds et al., 1960; Routtenberg, 1971). The termination sites reported to support ICSS of the mesolimbic DA system include the olfactory tubercle (Olds et al., 1960; Routtenberg, 1971) and the nucleus accumbens (Olds et al., 1960; Routtenberg, 1970; 1971; Routtenberg & Sloan, 1972; Olds & Fobes, 1981).

Although it is generally agreed that the CA neuronal systems are involved in ICSS behavior, the role and importance of serotonin is still in question. The serotonin system has been implicated in various physiological functions, including sleep, sexual and aggressive behaviors, thermoregulation, locomotion, feeding, pain modulation, learning and memory (Voget, 1982). ICSS behavior has also been reported to single positive electrode located in the

DRN (Saint-Laurent et al., 1973) or from a few electrodes at the limit of this nucleus (Margules, 1969; Liebman et al., 1973; Liebman & Butcher, 1973; Schmitt et al., 1974) and supposedly outside the DRN (Ellman et al., 1974) from the fasciculus longitudinalis/medialis (FLM), while Simon et al. (1976), demonstrated robust ICSS behavior from the ventro-median portion of DRN in the rat.

These author's (Simon et al., 1976) report of ICSS from the DRN support the findings of Margules, (1969); Leibman et al. (1973), Liebman & Butcher (1973), and Scmitt et al. (1974). The ICSS rates were as high as those obtained from the LH or from the ventral mesencephalic tegmentum and higher than those recorded from the median raphe nucleus (Simon et al., 1973). Simon et al. (1976) also report that ICSS was obtain with very low current intensities, lower than the stimulus values used in the Ellman study (1974) for the FLM stimulation.

2. Chemical and Pharmacological Hypotheses of ICSS

Over the last three decades of research on ICSS, three dozen or so distinct reward sites have been studied (German & Bowden, 1974). ICSS has been found to be rewarding at all supra-spinal levels of the CNS, though not in all portions of each level. Thus, a major goal of workers in field has been to find anatomical common denominators for the diverse reward sites that have been identified (Wise, 1978). Olds'

early (1962) theory of the limbic and hypothalamic subsystem has been replaced by the catecholamine theories of Stein (1964) and others (German & Bowden, 1974; Fibiger, 1978; Wise, 1978), and Stein's early (1962), noradrenergic hypothesis has been superseded by the various dopamine hypotheses (Fibiger, 1978; Wise, 1980; Wise & Bozarth, 1981).

The evidence in support of the "catecholamine hypothesis" of ICSS is based on pharmacologic studies in which drugs that facilitate catecholamine neurotransmission increase response rates for brain stimulation, while drugs that interfere with catecholamine neurotransmission depress response rates (German & Bowden, 1974; Wauquier, 1979; Zarevics & Setler, 1979). The "catecholamine hypothesis" was first proposed by Stein (1964), and later elaborated upon by Crow (1972).

Observations that ascending noradrenaline (NA) axons are located within the MFB and that *d*-amphetamine greatly facilitates the rate of responding for ICSS led Stein (1964; 1968) to propose that NA axons within the MFB mediate the reinforcing properties of ICSS. The strongest early support for the NA hypothesis came from the pharmacological investigations. In general, compounds believed to increase central noradrenergic tone such as monoamine oxidase inhibitors (Poschel, 1969), *d*-amphetamine (Stein, 1964), and cocaine (Crow, 1970) increased the rate of the bar pressing

response for ICSS. In contrast, agents such as reserpine (Stein, 1962), chlorpromazine (Stein, 1962), and α -methyl-*p*-tyrosine (α -MT) (Cooper et al., 1971), interfere with central NA mechanisms, and decreased ICSS behavior.

Although these studies were interpreted as evidence for a role of central NA neurons in ICSS, each of these agents also influences DA as well as NA systems. Further, Lippa et al. (1973) observed that injections of FLA-63, a specific dopamine- β -hydroxylase inhibitor, at a dose that had been shown to reduce central NA by 70% and to cause nearly complete inhibition of NA synthesis did not significantly affect ICSS. In the same study, intraventricular injection of the neurotoxin 6-hydroxydopamine (6-OHDA), which reduced telencephalic NA by 90%, produced only transient (5-7 day) decreases in response rates for ICSS. Furthermore, intraventricular injections of phentolamine (α -adrenergic receptor blocker) in control or 6-OHDA-treated rats had no effect on self-stimulation.

The most convincing pharmacological evidence against the NA hypothesis were from Breese and co-workers (Cooper et al., 1974). In the first of these experiments it was found that selective depletion of NA by intracisternal injections of 6-OHDA did not affect ICSS rates in animals with electrodes in the LH. When these animals received intraperitoneal injections of U-14624, (specific dopamine- β -hydroxylase inhibitor) so that whole brain NA was reduced to

8% of control levels, no change in the self-stimulation rate was obtained. In another experiment, self-stimulating rats were pretreated with reserpine 24 h before they received an injection of *d*-amphetamine. One hour before the amphetamine injection the animals were injected with U-14624 or vehicle. In this experiment, treatment failed to block the stimulant effect of *d*-amphetamine on ICSS despite reducing whole brain NA by 99.3%. Stinus et al. (1976), also found that neither U-14624 nor FLA-63 produced any substantial change in responding for ICSS 24 h after reserpine pretreatment, despite reducing NA synthesis to approximately 10% of control levels. However, a problem with these experiments is that they utilized LH or VTA electrodes placements which may have stimulated ascending DA as well as NA axons. Thus, as has been suggested (Crow, 1972), if the DA projections are also involved in ICSS, then the failure to observe effects after disruption of central NA systems may have been due to the heterogeneous nature of the electrode site. Subsequently, Breese and Cooper (1975a) implanted stimulating electrodes in the LC and again, injections of U-14624 reduced brain NA to 27% of control levels without affecting ICSS rate. Furthermore, pretreatment with reserpine and U-14624 as described above failed to influence the stimulant effects of *d*-amphetamine on ICSS obtained from the LC.

Support for the involvement of the mesolimbic DA system

in the mediation of reward functions comes from studies directly examining the rewarding properties of dopaminergic agonist. Several lines of evidence suggest the dopaminergic synapse to be the site of the rewarding actions of the psychomotor stimulants cocaine and amphetamine (Wise, 1984). Amphetamine and cocaine share the ability to increase transmitter concentrations in both the noradrenergic and dopaminergic synapse, cocaine by blocking the reuptake mechanism (which usually terminates catecholamine synaptic action), amphetamine by blocking reuptake and also by directly causing or augmenting synaptic catecholamine release (Axelrod, 1970; Carlson, 1970; Heikkila et al., 1975). The rewarding effects of cocaine and amphetamine are attenuated by nonselective catecholamine synthesis and receptor blockade (Pickens et al., 1968; Wilson & Schuster, 1972), and although selective blockade of noradrenergic synapses alone does not have similar effects, selective blockade of dopaminergic synapses does (Yokel & Wise, 1975; 1976; Risner & Jones, 1976; 1980; deWit & Wise, 1977). When low doses of DA antagonists are given, stimulant self-administration is maintained, but it is maintained at a higher than normal level of hourly intake (Yokel & Wise, 1975; Risner & Jones, 1976; 1980; deWit & Wise, 1977).

Recent evidence supports the involvement of opiate reinforcement action in the dopaminergic mechanism of rewarding action (Wise, 1984; Wise & Bozarth, 1987). Direct

injections of morphine (Phillips & LePiane, 1980; Bozarth & Wise, 1981a; 1982) and other opiates and opioid peptides (van Ree & de Wied, 1980; Phillips & LePiane, 1982) have been shown to be reinforcing when administered in to the region of the dopaminergic cells of the ventral tegmentum. This has been demonstrated in a conditioned place preference paradigm, where rats learn to return to the place where they have experienced opiates in the past (Phillips & LePiane, 1980; 1982; Bozarth & Wise, 1982), and also in a lever-pressing paradigm where responding is reinforced by direct brain injections of morphine (Bozarth & Wise, 1981a) or fentanyl (van Ree & de Wied, 1980). However, injections of opiates to the dorsal (Phillips & LePiane, 1980), anterior or posterior (Bozarth & Wise, 1982) dopaminergic VTA cell groups were found not to be reinforcing. Injections of morphine in other regions particularly in the LH (Stein & Olds, 1977; M. E. Olds, 1979) have also been reported to be reinforcing, but other researchers reported these results as drug injection diffusion and thus, have their reinforcing action in the VTA (Wise & Bozarth, 1981). Furthermore, intravenous heroin reinforcement is not altered by destruction of the cells of the LH, as it would be if there were important reward-relevant opiate receptors in this region (Britt & Wise, 1981), and rats do not learn to lever-press for hypothalamic injections as rapidly or as reliably as they learn to lever-press for VTA injections (Bozarth &

Wise, 1982).

Consequently, ventral tegmental microinjections of opiate antagonists cause compensatory increases at low doses and extinguish responding for intravenous opiates at high doses (Britt & Wise, 1983). Additionally, ventral tegmental microinjections of enkephalinase inhibitor thiorphan produce a reinforcing state, as shown by the place preference test (Glimcher et al., 1983). The evidence that dopamine activation plays a necessary role in opiate reinforcement is confirmed in the conditioned place preference test; if morphine is given during dopaminergic receptor blockade, the animals do not show learning approach to morphine-associated portion of the environment (Bozarth & Wise, 1981b; Spiraki et al., 1983). Thus, the reinforcing action of the opiates seems localized to the region of the DA-containing cells that are implicated in psychomotor stimulant reward (Wise, 1987). The current evidence points to a reward circuit involving a descending myelinated fiber system in the MFB activated directly by ICSS. Thus, the MFB contains axons that communicate with DA cell bodies of the VTA where morphine initiates its reinforcing action, and ultimately resulting in synaptic release of DA at terminals in the nucleus accumbens where the reinforcing effects of psychomotor stimulants are pharmacologically initiated (Wise, 1984). In addition there is evidence that morphine dependence and primary morphine reinforcement are not

causally linked (Wise, 1984).

The evidence that opiate reinforcement and opiate dependence are mediated by anatomically distant neural mechanisms, each with its own population of central opiate receptors was demonstrated by Bozarth and Wise (1983). These investigators found that 72 h of continuous infusion of morphine into an opiate reward site of the VTA failed to produce the opiate dependence syndrome as reflected in naloxone-precipitated withdrawal symptoms. When the same dose was infused into the PAG, on the other hand, strong dependence signs develop (Wei & Loh, 1976; Wei, 1981; Bozarth & Wise, 1983). Drug-naive rats also do not work for injections into the PAG (Bozarth & Wise (1981a), nor do injections in this region produce conditioned place preference (Phillips & LePiane, 1980). Wise (1984) contends that the primary reinforcing effect of opiates may involve a population of opiate receptors that interact with the reward circuitry of the VTA and not on the dependence phenomena, while the dependence-producing effects of opiate involves an anatomically distinct population of opiate receptors that interact with circuitry of the PAG and are not involved in positive reinforcement phenomena.

3. ICSS Interaction among PAG, LC, and LH Sites

Early ICSS studies (Olds and Olds, 1962; Valenstein, 1965) reported that stimulation of the PAG elicited only

escape responding behaviors, implying that PAG stimulation is solely aversive. However, subsequently ICSS was reported from the anterior (Cooper & Taylor, 1967) and from the posterior mid-ventral PAG (Margules, 1969; Liebman et al., 1973; Ellman et al., 1974) electrode placements. Anterior and dorso-lateral PAG sites were also reported as aversive by Liebman et al., (1973). While Keene and Figueroa (1977) demonstrated that all sites eliciting escape but not self-stimulation behavior were located in the dorsal PAG, while sites eliciting ICSS, and not escape behavior, were all found in the ventral areas of the PAG. Other studies (Bower & Miller, 1958; Steiner et al., 1973; Ellman et al., 1975) have demonstrated that both ICSS and escape behaviors can be elicited from the same ICSS electrode, regardless of the location of the ICSS area.

Ackermann et al. (1977), in studies to delineate ICSS elicited from the dorsal and ventral sites found that dorso-lateral areas of the PAG previously reported as predominantly aversive produced consistent and reliable ICSS behavior. Mid-ventral PAG ICSS rates were reported as significantly higher than the dorso-lateral ICSS rates. ICSS behavior from both sites generated regular patterns of behavior producing no seizure activity in any animal and is similar to other brainstem ICSS locations (Mayer & Liebeskind, 1974; Ellman et al., 1975). In contrast with diencephalic and telencephalic ICSS which are marked by

irregular bursts of responding which are highly variable and sometimes accompanied by seizures (Ackermann et al., 1977).

Albino and Lucas (1962), were the first to demonstrate that when two discrete ICSS sites were stimulated simultaneously the response rates were greater than the sum of the ICSS rates elicited by the same current intensities within each site alone. Subsequent, studies have shown that response rates when elicited under simultaneous or near-simultaneous stimulation at two ICSS electrode sites were significantly greater than the sum of the response rates elicited when each of the sites was stimulated separately, suggesting that a behavioral interaction between the two ICSS sites (Ungerleider & Coons, 1970; Coons et al., 1976). Simultaneous or near-simultaneous stimulation interactions have been demonstrated for the following electrode site combinations: LC and HYP, mid-ventral PAG and HYP, dorso-lateral PAG and HYP, substantia nigra (SN) and HYP, and bilateral HYP sites (Ungerleider & Coons, 1970; Ellman et al., 1975; Coons et al., 1976).

Ungerleider and Coons (1970) were able to show interactions by using a more discrete technique which employed monophasic pulse pairs (C-T monophasic pulse pair technique). The C-T technique was first demonstrated by Sherrington (1906) in peripheral nerves, and later by Deutsch (1964) in behavioral preparations. This procedure employs negative going monophasic pulse pairs that are

varied in time to produce alterations in responsiveness.

The first pulse in a pair (C conditioning pulse) parametrically followed in time by a second (T test pulse). This stimulation usually consists of a fixed train length in which pairs of C and T pulses are cycled. The time between the C and T pulse is called the C-T interval. Variations in the duration of this C-T interval will produce a concomitant change in an animal's ICSS responding. An animal will typically emit low rates of responding at short C-T intervals (0.0 - 1.2 msec.) while exhibiting optimally high responding rates at longer intervals (1.5 - 5.0 msec.).

In interaction studies Bodnar et al. (1981), employed monophasic pulse pair C-T technique (Deutsch, 1964) to ascertain whether pairs of ICSS sites interact. In these studies, tested were the interactive properties of ICSS electrode sites in the SN and mid-ventral PAG with hypothalamic ICSS within the MFB or outside the MFB (non-MFB). Bodnar et al. (1981), interpreted the results in terms of behavioral interactions between ICSS sites. The ICSS response rates when pulses of each pulse pair were split between two ICSS sites were significantly higher than the sum of each site stimulated separately with single-pulse trains. Furthermore, all the interactions produced higher rates than pulse pairs delivered to the mesencephalic sites (PAG sites) at an optimal interval, but similar rates to pulse pair stimulation delivered to the diencephalic site

(SN sites). As reported the symmetry of the interactions depended upon electrode location. The PAG/MFB and SN/non-MFB interaction were reported as significantly higher than when the mesencephalic site received the first pulse of each pair. By contrast, the PAG/non-MFB and SN/MFB combinations yield higher ICSS interaction rates than when the diencephalic site was stimulated first than when it was stimulated second.

In an earlier study Bodnar et al. (1979), found similar results for certain LC and hypothalamic ICSS electrode combinations. When the hypothalamic electrode sites was located in the dorsal or far-lateral HYP, C pulses delivered to the LC and the T pulse delivered to the far-lateral HYP were reported to produced significantly higher interactions response rates than C pulse delivered to the dorsal and far-lateral HYP and T pulse to the LC. However, when the HYP electrode sites was localized in either the MFB or the perifornical area, increases in ICSS interaction response rates were similar regardless of which site was stimulated first.

This data (Bodnar et al., 1979) suggested that the LC exerts a modulating influence upon dorsal far-lateral HYP, but not MFB ICSS sites, while SN and mid-ventral PAG exerts a modulating control upon MFB and non-MFB ICSS sites (Bodnar et al., (1981). These finding provide support to the work of Farber et al. (1976) who demonstrated that small

unilateral lesions placed in the LC significantly reduced or abolished LH ICSS behavior. Finally, LH and LC ICSS were found to share very similar pharmacological profiles following amphetamine (*d/l* amphetamine) (Ellman et al., 1975) or opiate pretreatment (Jackler et al., 1979).

Ellman et al. (1975) showed that *d*-amphetamine produced higher ICSS response rates than either *l*-amphetamine or saline at both dorsal brainstem and hypothalamic electrode sites. Similar results were also found with electrodes located in the dorsal noradrenergic bundle (Ellman et al., 1976). Thus, *d*-amphetamine produced higher ICSS response rates than *l*-amphetamine in this site. These results suggested to the authors that noradrenergic dorsal brainstem fibers (or cell bodies) support ICSS. Comparable findings were observed by Jackler et al. (1979) with systemic injections of morphine. In these experiments injections of morphine, produced in dorsal brainstem electrodes more ICSS depressions than the HYP electrode sites. The studies by Ellman et al. (1975; 1976) and Jackler et al. (1979) demonstrate that *d/l* amphetamine and morphine differentially affects ICSS rates elicited at neuroanatomically discrete brain sites.

4. Relationship between ICSS and Sleep

Researchers who have experimented with the role of ICSS in REM sleep have pointed to the interaction of other

rewarding sites with the parameters of REM sleep. Specifically, conclusions drawn from the studies carried out in the lateral hypothalamus by Steiner and Ellman (1972) demonstrated that REM sleep deprivation shifts the entire ICSS rate-intensity curve to the left, showing that animals display lowered thresholds for stimulation, and increases in ICSS response rates. In these experiments, the investigators studied the effects of LH ICSS behavior on REM sleep rebound and demonstrated that 60 to 90 minutes of ICSS per day lowers REM sleep by 50% to 60%. Thus, in the first two experiments, the researchers obtained verification for the notion of the reciprocal relationship between REM sleep and ICSS. In a recent study by Melikov et al. (1990) the water pool method was used (Morden et al., 1967) to deprive 16 rats of REM sleep and found that LH ICSS behavior was significantly increased confirming Steiner and Ellman's (1972) findings. In contrast Marti-Nicolovius et al. (1983) found no significant changes in response rates for LH ICSS after 23 h of REM sleep deprivation using the platform method. The negative finding of Marti-Nicolovius et al. (1983) can be understood since they did not confirm their levels of deprivation in the experimental animals based on EEG sleep-wake activity. Further support for the proposed relationship between REM sleep and ICSS comes from a set of experiments by Spielman, Ellman and Steiner (1973).

Steiner and Ellman (1972) showed that short (60 - 90

min.) exposure to LH ICSS prevented REM sleep rebound in REM-deprived rats. However, Spielman et al. (1973) found that longer (8 h/day) as compared to shorter (2 h/day) exposure to LH ICSS lowers REM sleep rebound in REM-deprived rats.

In this experiment Spielman et al. (1973) used essentially two paradigms, (1) animals were allowed varying amounts of ICSS at fixed times of the day, and (2) animals were allowed free access to ICSS so that both the amounts of time spent in ICSS and the amount of time in sleep were determined by the animal, not by the experimenter. In the first experiment, the investigators used different paradigms that allowed the animals either 2 h of ICSS every 24 h ("2-22" experiment) or 8 h of ICSS every 24 h ("2-4" experiment). In the 2-4 experiment, animals were allowed 2 h of ICSS and after 4 h where not permitted ICSS. In the 2-22 experiment animals were allowed 2 h of ICSS during 24 h. As expected, the 2-4 experimental paradigm allowed more ICSS and reduced REM sleep more then the 2-22 experiment. However, REM rebound was still significant in both the 2-22 and the 2-4 experiments although REM sleep had been reduced significantly. These results did not support the idea of a simple reciprocal relationship between REM sleep and ICSS so that in their second experiment, *ad libitum* ICSS was tried to see if this method could provide a better test of their hypotheses. The results of the *ad*

libitum ICSS study were similar to those of the 2-22 and the 2-4 experiments in that there was a marked reduction in REM sleep on stimulation days. Therefore, by allowing the animals free access in the timing of stimulation, Spielman et al. (1973) has shown that bilateral LC *ad libitum* ICSS affected a suppression of the REM rebound following REM deprivation.

C. NEUROANATOMY OF SWS SLEEP

Sleep is a state of behavioral and physiological quiescence (Jouvet, 1967a). Body temperature, heart rate, respiratory rate, metabolic rate (Abrams et al., 1988; Buchsbaum et al., 1989), resting muscle tone (Jacobson et al., 1964; Gardner & Grossman, 1975), and spontaneous motor activities are decrease when compared with the waking state (Gardner & Grossman, 1975). These changes are accompanied by a diffuse slowing and by synchronization of the electroencephalogram (EEG) (Jouvet, 1967a). In humans, non-REM sleep (NREM) in the stages III and IV exhibits the most slow wave sleep (SWS) or delta sleep. In animals, the entire NREM sleep period is often referred to as SWS.

Jouvet and colleagues (Jouvet & Renault, 1966; Jouvet et al., 1966; Jouvet, 1969) in a series of experiments demonstrated that raphe lesion in the cat, destroying 80-90% of the 5-hydroxytryptamine (5-HT) containing cells in the brainstem raphe produced a complete loss of SWS for 3-4 days

postlesion and only minimal recovery thereafter for the duration of the experiment (10-13 days). A direct relationship was reported between the severity of the insomnia, the extent of the raphe damage, and altered levels of forebrain 5-HT (Jouvet, 1969). Similar results have also been found in the rat (Kostowski et al., 1968).

Pharmacological studies by Jouvet and colleagues provide support for the involvement of brainstem 5-HT system in SWS (Delorme et al., 1966; Jouvet, 1967b: 1969; Mouret et al., 1968; Pujol et al., 1971). Pujol et al. (1971) found that single injections of the potent inhibitor of 5-HT synthesis *p*-chlorophenylalanine (PCPA) in cats produced profound reductions in SWS, beginning approximately 18 h postinjection and continuing for 60 h, followed by a gradual recovery that was not complete until 200 h postinjection. Jouvet (1969) and Pujol et al. (1971) subsequently showed that SWS could be restored in PCPA-treated animals with injections of 5-hydroxytryptophan (5-HTP), which reestablishes 5-HT levels in the brain by bypassing the blocking action of PCPA. As reported by Jouvet (1969), very small doses of 5-HTP given at the height of a PCPA-induced insomnia resulted in a return to normal patterns of sleep within 6-8 h. Mouret et al. (1968) also showed that sleep was essentially altered in cats given balanced daily doses of PCPA and 5-HTP.

Other studies have shown that 5-HT of the DRN inhibits

PGO (pons, lateral geniculate nucleus and occipital cortex) waves and regulates REM sleep. The administration of 5-HT-depleting drugs, such as PCPA and reserpine, release PGO wave into states other than REM sleep (Delorme et al., 1966; Brooks & Gershon., 1971; 1972; Brooks et al., 1972; Jacobs et al., 1972). Reserpine also depletes norepinephrine but its effects on PGO waves is thought to be due to 5-HT depletion because 5-HT precursors block reserpine-induced PGO waves more effectively than do catecholamine precursors (Brooks et al., 1972). Lesions of the DRN and cuts between the DRN and the dorso-lateral pons release PGO waves into wake states (Simon et al., 1973). While, electrical stimulation of the DRN suppresses PGO wave activity during REM sleep (Jacobs et al., 1973).

Spontaneous neuronal activity of DRN have also been reported to correlate to PGO waves and behavior states. Cells (putatively serotonergic) in DRN fire most in AWAKE, less frequently during SWS and generally cease firing during the transition from SWS into REM and REM sleep, when PGO waves are observed (McGinty & Harper, 1976; Trulson & Jacobs, 1979; Cespuglio et al., 1981; Lydic et al., 1987a;b). Furthermore, Lydic et al. (1987a;b) showed that forced locomotor activity, which alters sleep cycle timing, does not abolish the relationship of DRN neuronal firing to the sleep cycle and PGO waves, suggesting the DRN has a role in the regulation of the sleep cycle (Lydic et al.,

1987a;b). Luebke et al. (1992) have found that cholinergic burst neurons in the infant rat latero-dorsal tegmental nuclei (LDT) are inhibited by 5-HT agonist *in vitro* in a manner consistent with hypothesized role DRN in the control of PGO waves. However, neurons with bursting patterns of firing were not found in *in vivo* recordings of LDT in mature rats (Kayama et al., 1992).

D. NEUROANATOMY OF REM SLEEP

Dement and Kleitman (1957) were the first to describe "rapid eye movement" (REM) or dream sleep in humans and in cats. Much of what is known about the mechanisms of REM sleep, is owed to the work of Jouvett (1961; 1967a; 1972; 1973). Jouvett (1973), using chronic pontine and mesencephalic preparations noted a complete muscular atony every 30-40 min, without any external stimulation. These periods were also associated with jerking movements of the whiskers and large neuronal spike discharges in the pontine tegmentum, which later came to be known as the PGO discharges of REM sleep.

Jouvett's (1967b; 1972) now classic monoaminergic theory of sleep cycle control dealt with SWS and REM sleep. Jouvett proposed that SWS is triggered by serotonergic cells of the brainstem raphe nuclei and that the events of REM sleep are controlled by noradrenergic neurons of the LC. Current research findings do not support the notion that the LC

serves any role in REM sleep generation. Although early reports (Jouvet & Delorme, 1965; Roussel et al., 1967; Jones et al., 1969), primarily from the laboratory of Jouvet, indicated that LC destruction altered REM, several subsequent studies have shown that REM remains essentially intact following electrolytic lesions restricted to the LC (Jones et al., 1977) or following pronounced forebrain NA depletion (Panksepp et al., 1973; Lidbrink, 1974). Moreover, the unit discharge profile of LC neurons is inconsistent with a REM-generating function; LC cells are most active in waking, slow in SWS, and are virtually silent in REM sleep (Foote et al., 1980; Aston-Jones & Bloom, 1981).

1. Anatomy of REM Sleep and Phasic Events

Recent studies have shown a common pontine substrate for the generation of eye movement potentials (EMPs) and PGO waves (Laurent & Guerrero, 1975; Sakai et al., 1976; Sakai & Jouvet, 1980; Nelson et al., 1981; 1983). Field potentials (i.e. EMPs) can be recorded from the same structures as PGO waves during the eye movement of waking (Brooks & Gershon, 1971), although EMPs were originally thought to be a related but separate phenomenon from PGO waves (Brooks, 1968). Eye movement potentials and PGO are proposed by Morrison (1979) to function and enhance transmission within the visual system under conditions of alertness which necessitates a

high degree of visual acuity.

i. REM Sleep

Until recent times, sleep was generally regarded as a idling state somewhere near the low end of a continuum of vigilance, or as a state of relative deactivation that has a restorative function. Sleep is now viewed as an active process characterized by a cyclic succession of many different psychophysiological events. Using electroencephalogram (EEG) recording in humans, Aserinsky and Kleitman (1953) reported finding binocularly conjugate rapid eye movements (REMs) that occurred throughout "low voltage, fast", to regularly occur every 90 minutes through sleep, always following a period of sleep without REMs, and was highly correlated with dreaming. Dement and Kleitman (1957) later classified sleep, in human adults, into five stages based upon EEG patterns: stages 1 to 4 are not associated with REMs and are referred to as non-rapid eye movement (NREM) sleep, or slow wave sleep; the fifth stage is stage 1 REM, and is characterized by the occurrence of REMs.

REM sleep is a paradoxical state in which physiological and behavioral activities increase in some parts of the body and decrease in others (Jouvet, 1967a). In many regions of the central nervous system the activity increases dramatically. CNS neuronal firing rates (Evarts et al.,

1962; Jouvet, 1967a; Steriade & Hobson, 1976), blood flow (Reivich et al., 1968; Lenzi et al., 1987; Meyer et al., 1987), metabolism (Abrams et al., 1988; Buchsbaum et al., 1989), and temperature (Kawamura & Sawyer, 1965; Kawamura et al., 1966; Wurtz, 1967; Greenberg, 1980; Parmeggiani et al., 1984) increase, and the EEG exhibits a low voltage, fast activity similar to the which occurs during wakefulness (Jouvet, 1967a; Reivich et al., 1968; Abrams et al., 1988). The structures adjacent to the CNS also increase in activity.

Resting tone in the rectus muscles of the eyes increase (Michel & Rechtschaffen, 1964) and phasic bursts of rapid eye movements occur (Jouvet, 1967a) and respiratory movements becomes rapid and irregular (Jouvet, 1967a; Roffwarg et al., 1966). In newborn animals, the muscles of mastication also becomes active (Roffwarg et al., 1966). Non-shivering thermogenesis appears to switch on in brown adipose tissue adjacent to the spinal cord (Franzini et al., 1986; Wehr, 1992).

Simultaneous, activity in many peripheral structures decreases during REM sleep. Although skeletal muscles exhibit twitches in conjunction with the phasic events of REM sleep, they are paralyzed most of the time, and spinal reflexes are abolished (Gassel et al., 1964; Jouvet, 1967a). The skeletal muscle tone, which decreases at the onset of sleep, remains low during REM sleep (Jacobson et al., 1964).

In addition, tone in head and neck muscles decrease further and is lost during REM sleep (Jacobson et al., 1964). The activities of peripheral thermoregulatory effector mechanisms, such as shivering, panting, and sweating, are largely suspended during REM sleep (Parmeggiani, 1980).

ii. Ponto-Geniculo-Occipital Spikes

In the rat, PGO wave have been reported to originate from the dorso-lateral pontine tegmentum in a region bordering the brachium conjunctivum (BC) (Gottesman, 1969; Farber et al., 1980; Marks et al., 1980; Kaufmen & Morrison, 1981) and in cats (Brooks & Gershon, 1971; Laurent & Guerrero, 1975; Bowker & Morrison, 1976; Sakai et al., 1976). PGO burst neurons have been described in the BC region (Saito et al., 1977; Sakai & Jouvet, 1980; Nelson et al., 1983). Sakai et al. (1981) reports that the majority of the burst neurons appear to be located in the area x, dorso-lateral to the BC, and others have also been found within the rostral part of the lateral parabrachial nucleus and the dorso-lateral tegmental nucleus (Saito et al., 1977; Sakai & Jouvet, 1980). Stimulation of the BC area elicits lateral geniculate nucleus (LGN) and occipital PGO activity (Brooks & Gershon, 1971; Sakai et al., 1976), while cooling (Laurent & Guerrero, 1975) produces reversible PGO behavior and lesioning (Sakai et al., 1976) the BC area eliminates PGO wave activity in an irreversible manner.

2. Unit Activity of DRN in Sleep-Wake-Arousal Cycle

The serotonergic neurons exerts a tonic modulatory influence on its widespread targets. This is expressed primarily in association with the organism's motor activity and is in phase with the sleep-wake-arousal cycle. Thus, 5-HT neurons regulate the expression of neural circuits without being a necessary component of them (Jacobs & Azmitia, 1993).

Serotonergic neuron unit activity in behaving cats (McGinty & Harper, 1976) and rats (McGinty & Harper, 1976; Trulson & Jacobs, 1979) during quiet waking behavior displayed the same slow (1-3 spikes/s) and highly regular activity. This stable pattern of slow and highly regular activity during quiet waking progressively changes across the sleep-waking-arousal cycle (Trulson & Jacobs, 1979). The neuronal activity of the DRN during REM sleep is seen in a resumption of the activity of these neurons signaling the end of a REM sleep epoch. Over 50% of the DRN cells displayed a dramatic increase in neuronal activity as much as 10 s before the end of a REM period (mean lead time was 3.2 s). The level of this resumed activity was about twice that observed during a quiet waking state and was approximately equivalent to that seen during phasic arousal. Corresponding to the decrease in activity that DRN cells display during sleep is an increase in activity is seen as the animal becomes behaviorally activated (Trulson & Jacobs,

1979). Thus, an almost linear positive relationship exists between the level of tonic motor activity and DRN neuron activity. As the animal becomes drowsy and then enters SWS, neuronal activity displays a corresponding decrease in rate and loss of regularity. This culminates during REM sleep, where a complete cessation of DRN neuronal activity is seen.

Results from behaving cats (Trulson et al., 1981) provide support for the existence of a relationship between tonic level of motor activity and DRN unit activity. REM sleep however without muscle atonia are exhibited in cats with bilateral lesions of the pontine tegmentum (Jouvet & Delorme, 1965; Henley & Morrison, 1974). These animals with such lesions have epochs that, by all criteria, appear to be in REM sleep, except that antigravity muscle tonus are present and the animals are therefore capable of moving and even engaging in complex motor acts, including locomotion. When the DRN 5-HT neurons were examined during REM sleep in these animals, it was increased well above that of normal animals in REM sleep (Trulson et al., 1981). Further, the level of neuronal activity was directly related to the degree of restored motor activity during REM sleep. During other phases of the sleep-wake-arousal cycle in these animals, the activity of the DRN 5-HT neurons was similar to that observed in normal animals. In other studies (Steinfels et al., 1983) this reciprocal relationship was demonstrated with cholinomimetic agents. Carbachol was

injected directly into the dorso-medial pontine reticular formation that produced atonia in an otherwise awake cat. Dorsal raphe 5-HT unit activity during this centrally triggered atonia was completely suppressed. While, carbachol injections into nearby areas failed to induced atonia, had no effect on DRN unit activity. These data, suggest that the decrease in raphe unit activity during REM sleep be largely a concomitant of the atonia which characterizes that state (Jacobs & Azmitia, 1993).

3. Respiratory and Cardiovascular-Related Unit Activity of PAG during Sleep-Waking States

In a series of experiments Harper demonstrated that PAG contains neurons that exhibit state-bound cardiac and respiratory patterning relationships of both cycle-by-cycle and breath-by-breath dependencies as well as tonic interactions with the cardiac and respiratory cycles (Harper et al., 1991; Ni, Zhang & Harper, 1990; 1991).

Sleep states significantly influence the cardiovascular system (Mancia et al., 1971; Zanchetti et al., 1982) and greatly modify the spontaneous discharge of neurons in brain sites (Evarts, 1964). Blood pressure and heart rate show a progressive decrease from waking to quiet sleep in the cat. Phasic cardiovascular changes occur with bursts of eye movements and body twitches during REM sleep. During REM sleep, heart rate is very variable, with marked tachycardia

(rapid heartbeat) and bradycardia (slow heartbeat) sequences. A redistribution of blood flow between visceral and muscle beds also occurs during REM sleep (Zanchetti et al., 1982). Although the demands for blood flow are tonically altered from waking to sleep states, the very large phasic changes in heart rate are much greater than the immediate changes in response to movements (which are suppressed by the atonia of REM sleep) or metabolic demand would dictate. Thus, in the absence of major moment-to-moment alterations in demands, both cardiac rate and blood pressure control exhibit major instantaneous changes in REM sleep, and considerable tonic changes during quiet sleep.

A subset of neurons in several brain areas has been found to mediate 'affect' cardiac-related activity. For example, neurons in the anterior cingulate gyrus and the amygdala show a cardiac cycle-by-cycle correlation between unit rate and heart rate. However this relationship is present in certain sleep-waking states and not in others (Frysinger & Harper, 1986; Frysinger et al., 1988). Ni, Zhang and Harper (1990) examined patterns of unit discharge of PAG neurons and cardiovascular activity in freely moving cat to determine the type and frequency of unit discharge correlations with the cardiac cycle across different sleep states.

The PAG discharge patterning relationships to the cardiac cycle produced the most remarkable set of findings;

74% of the neurons showed a discharge timing relationship (cardiac cycle-by-cycle) and/or a tonic correlation with cardiac activity, and nearly all (96%) of these dependencies were state related. The greatest number of phasic discharge timing relationships was found during quiet sleep followed by AWAKE, and then by REM sleep. Ni, Zhang and Harper (1990) concluded from these results that large proportion of neurons showing a state-related cardiac dependency suggests that the PAG may contribute to mediating different cardiac patterns observed in each state.

Stimulation of the PAG was found to result in a variety of respiratory pattern changes, ranging from tachypnea in animals (Baxter & Olszewski, 1955; Nashold et al., 1969) to hyperventilation and apnea in humans (Markgraf et al., 1988). Stimulation of the PAG has been found to inhibit other respiratory-related reflex behavior, such as coughing, swallowing, jaw-opening, and tongue-protrusions reflexes (Sessle et al., 1985). The PAG has an extensive set of neuroanatomical projections to the brainstem motoneurons regulating both upper airway musculature and structures that can modify respiratory patterning in the diaphragm as well. The PAG projects to the nucleus ambiguous-retroambiguous, which, in turn, projects to motoneuronal cell groups supplying muscle activity related to respiration and vocalization (Holstege, 1989), and to the medial nucleus of the solitary tract, which contains neurons mediating

baroreceptor and chemoreceptor afferents (Bandler & Tork, 1987). These connections provide potential pathways through which PAG neurons could modify patterns of respiration associated with the defense reaction, and may have a wider role in mediating affective contributions to activity (Ni, Zhang & Harper, 1989).

Neurons of the central nucleus of the amygdala and the red nucleus of the stria terminalis, which fire in response to aspects of respiratory patterning in a state-dependent manner (Zhang et al., 1986; Frysinger et al., 1988), and cells of the parabrachial nucleus, which have been implicated in respiratory phase switching (Cohen, 1979), project to the PAG (Hopkins & Holstege, 1978; Saper & Loewy, 1980; Holstege et al., 1985). Thus, as was reviewed earlier, a variety of cortical and subcortical structures have the potential to influence respiratory patterning through the PAG via PAG projections to brainstem respiratory regions. Ni, Zhang and Harper (1989), used extracellular single-unit recordings in an attempt to cross-correlate the spontaneous activity from the PAG region in freely moving cats with respiratory patterning.

A substantial portion of recorded PAG cells, nearly a third (28%), of the neurons recorded in the PAG showed a phasic discharged timing (i.e. breath-by-breath) relationship with respiration in at least one sleep-waking state. For 74% of these neurons, the phasic discharge

timing correlations occurred in only one state, while the other 26% of these neurons exhibited discharge timing correlations with respiration across multiple sleep-waking states. These results as stated by Ni, Zhang and Harper (1989), suggest that a subset of PAG cells may play a role in state-related respiratory patterning.

4. Phylogeny, Ontogeny, and Function of REM sleep

i. Phylogeny of REM sleep

Zepelin and Rechtschaffen (1974), using available sleep data from 53 species, correlated these measures with species-specific measures such as metabolic rate gestation period, and brain weight. The researchers found that animals with lower metabolic rates typically sleep less than those with higher metabolic rates, leading to the accession that sleep functions as a method of energy conservation.

In addition, rates of tissue synthesis are higher during rest and sleep than during active behavior (Adam & Oswald, 1977). Measures of available energy, adenosine triphosphate, increases in mouse muscle tissue during sleep and the same is true for measures from the brain (Durie et al., 1978). The growth hormone that promotes anabolic activity is secreted with slow wave sleep (Takahashi et al., 1968), while the corticosteroids that stimulate degradation activity are at their lowest levels at this time (Weitzman et al., 1983). Total body oxygen consumption is lower

during sleep than during wakefulness, suggesting lower catabolism (Brebbia & Altshuler, 1968). This argument was later supported and extended to include the factor of predatory behavior (Allison & Cicchettic, 1976). That is, animals who are relatively safe from predators tend to sleep more than those who are easily preyed upon.

ii. Ontogeny of REM sleep

Total sleep time decreases as organisms develop through childhood to old age, just as metabolic rate decreases (Walker & Berger, 1980). This correlation has been interpreted as support for a energy conservation role of sleep, just as the similar correlation across phyla mentioned above.

The abundance of REM sleep in the infant, as compared to later in life, led to the proposal that REM sleep is instrumental in development of the central nervous system (Roffwarg et al., 1966). Some support for this hypothesis has emerged. For example, Anch and Tepas (1970) have reported that REM sleep acts as an endogenous source of stimulation in the CNS. Recent work continues to suggest that REM sleep plays a role in the development of the brain, at least in terms of the visual system (Oksenberg et al., 1986).

iii. Functions of REM sleep

Over the years since the 'discovery' of REM sleep researchers have proposed a variety of theories about its function. In some cases considerable overlap exists among the types of theories. Some theories deal primarily with REM or NREM sleep, or propose different functions for these two types of sleep. Generally, more proposals have appeared in the literature about the neurophysiological mechanisms in the brain that produce REM sleep than the purpose of REM sleep, or why such mechanisms are there in the first place.

The restorative theory proposes that sleep either allows or promotes physiological processes which rejuvenate the body and brain (Moruzzi, 1972; Oswald, 1974; Adam & Oswald, 1977). The theory postulates the importance of NREM sleep for body tissue restoration and the association of REM sleep with brain tissue restoration. Particularly, sleep is responsible for the restoration of those neurons which are associated with conscious behavior, such as learning.

Indirect support for the role of NREM sleep in body restoration comes from demonstrations of increased SWS following sleep deprivation (Berger & Oswald, 1962), starvation (MacFayden et al., 1973), and during peak development years (Feinberg, 1968) and in athletes (Baekeland & Lasky, 1966; Shapiro et al., 1975). Further support lies in the demonstration of increased growth hormone secretion during NREM Sleep (Takahashi et al.,

1968). Other anabolic hormones also have a sleep dependent rhythm of secretion, such as prolactin (Sassin et al., 1973), testosterone, and luteinizing hormone (Boyar et al., 1975). On the other hand, corticosteroids, which promotes catabolism of protein, sink to lower levels during sleep, particularly during the first few hours in to sleep (Weitzman & Hellman, 1974).

Drucker-Colin (1979) has discussed the supporting evidence that REM sleep is a time of increased brain protein synthesis and may be critical in development of the central nervous system in the young organism and maintenance if higher-level brain activity in the mature organism. Other researchers view sleep as period of enforced rest and energy conservation.

Zepelin and Rechtschaffen's (1974) review of data for many mammalian species have found a high correlation between daily total sleep time and metabolic rate. Generally stated, the enforced immobility of sleep conserves energy. Animals who have high metabolic rate sleep more than do species who use energy more slowly. The fact that animals that self-regulate body temperature (mammals and birds) display SWS, whereas poikilothermic (cold-blooded) animals (amphibians and reptiles) do not show clear SWS patterns, indirectly supports the energy conservation theory. Since mammals and birds use more energy to maintain a constant body temperature in varying environmental temperatures,

perhaps their sleep evolved as a mechanism to conserve energy, since metabolism is at its lowest during SWS (Anch et al., 1988).

Another theory maintains that sleep serves to promote memory consolidation. In animals, the amount of REM sleep have been shown to increase during periods of learning a task, while memory for that task is poor if REM sleep is prevented (Bloch et al., 1977; Dujardin et al., 1989). Furthermore, information learned just after periods of sleep has been shown to be poorly learned (Fishbein, 1971; Ekstrand et al., 1977; Dujardin et al., 1989), possibly indicating that sleep interferes with storage of information. Thus, REM sleep appears to promote storage of information learned previously and inhibits storage of information presented during and immediately after sleep. The finding that hormones and neurotransmitters modulate memory procedures (McGaugh et al., 1975) suggest that the fluctuations of these substances with changes in sleep-waking states may be related to memory processes.

E. RATIONALE FOR THE PRESENT STUDY

Steiner and Ellman (1972) found a relationship between REM sleep and intracranial self-stimulation behavior elicited from the lateral hypothalamus in rats. These investigators found that REM sleep deprivation significantly lowers the threshold and increases operant responding for

hypothalamic ICSS. Additionally, access to hypothalamic ICSS during REM deprivation periods in rats significantly reduced the amount of REM sleep rebound. This suggests an interchangeability between the rewarding aspects of hypothalamic ICSS and REM sleep. While REM sleep deprivation changes the threshold for hypothalamic ICSS, *ad libitum* ICSS elicited from the lateral hypothalamus significantly reduces subsequent REM sleep. Further, the REM sleep reductions elicited by hypothalamic ICSS were not accompanied by a compensatory REM rebound. ICSS elicited from the locus coeruleus also significantly reduced subsequent REM sleep (Spielman, 1979).

It is not clear whether such REM-ICSS interaction are generalizable to all loci supporting ICSS or whether it is a phenomenon localized to specific brain structures like the LH and LC. The latter hypothesis could be quite appealing since the LH and LC ICSS are intimately related. For instance, unilateral lesions placed in the LC significantly decreases LH ICSS (Farber et al., 1976). Further, multiplicative interactions occur for ICSS behavior when rats are given the opportunity to bar press for simultaneous (Ellman et al., 1975) or near-simultaneous (Bodnar et al., 1979) ICSS relative to ICSS elicited from each site alone. Finally, LH and LC ICSS share very similar pharmacological profiles following amphetamine (*d/l* amphetamine) (Ellman et al., 1975) or opiate pretreatment (Jackler et al., 1979)

Nevertheless, there is suggestive evidence that other brain loci supporting ICSS are involved in REM-ICSS interactions. The PAG has been shown to support ICSS and is an integral structure in the modulation of sleep-wake states (Trulson & Jacobs, 1979; Lydic et al., 1987ab; Clement et al., 1991; Portas & McCarley, 1994). The periaqueductal gray is implicated in the elicitation of sleep and indirectly in REM sleep (Mouret & Coindet, 1980; Harper et al., 1991). Further, the ventro-lateral PAG is also a site that elicits ICSS in rats (Cooper & Taylor, 1967; Margules, 1969; Liebman et al., 1973; Ellman et al., 1974; Ackermann et al., 1977; Keene & Figueroa, 1977; Bodnar et al., 1981). Additionally, considerable attention has been paid to the PAG as possible sites for the control of autonomic nervous system, modulation of analgesia, sexual behavior, aggression, vocalization and other various appetitive behaviors (Bandler et al., 1991b).

The purpose of this dissertation is to explore whether *ad libitum* exposure to PAG ICSS significantly and selectively reduces REM sleep in rats. It is hypothesized that PAG ICSS should significantly reduce REM sleep during the stimulating period. Furthermore, it is hypothesized that if PAG ICSS reduces REM sleep, it should also prevent an increase in the intensity or duration of subsequent REM time during the recovery period (REM rebound). This would suggest that the rewarding properties of the PAG ICSS could

be acting in "satisfying" the effects of endogenous REM sleep rather than by simply acting to inhibit REM sleep. The absence of a REM sleep rebound phenomena following *ad Libitum* ICSS may suggest that the "pressure" for a fixed amount of REM sleep activation has been "satisfied" by the ICSS, and therefore the need to make up lost REM sleep is not necessary. To fully examine this issue, a number of variables were explored.

First, this study examined whether the amount of PAG ICSS was crucial in altering REM sleep by studying groups of rats with either one (unilateral) or two (bilateral) electrodes aimed at the PAG. If the amount of stimulation is a crucial determinant, one would expect greater reductions in REM sleep in bilaterally implanted animals relative to unilaterally-implanted animals. However, it is possible that some unilaterally implanted rats might self-stimulate at higher rates and at a higher amperage than some bilaterally-implanted rats and thereby deliver more overall current over the ICSS period. Therefore, an additional analysis tested whether the amount of microcoulomb (μA per unit time) is a critical determinant for REM sleep reductions by correlating microcoulomb stimulation amount and REM sleep alterations in each subject. Given the previous studies (Steiner & Ellman, 1972; Spielman et al., 1973; Spielman, 1979; Melikov et al., 1990), it is hypothesized that *ad libitum* ICSS effects will be most

striking for REM sleep. To examine the specificity of *ad libitum* ICSS effects, alterations in slow wave sleep and waking were evaluated as well.

Second, this study examined whether these effects are sensitive to circadian fluctuations by separately evaluating effects during the light (12-h) and dark (12-h) portions of the light:dark cycle. Under normal conditions, rats display significantly greater amounts of SWS and REM sleep in the light cycle compared with the dark cycle (Fishman & Roffwarg 1972; Zepelin et al., 1972), and alternatively display significantly greater amounts of waking in the dark cycle. Therefore, since there are hypothetically differing amounts of available REM sleep as a function of cycle, this factor may prove to be important either in and of itself, and/or in interaction with other variables.

The last important variable examined was the determination of the onset and duration of any PAG ICSS effects upon REM sleep. Steiner and Ellman (1972) demonstrated that short (60 - 90 min.) exposure to LH ICSS prevented REM sleep rebound in REM-deprived rats. However, Spielman et al. (1973) found that longer (8 h/day) as compared to shorter (2 h/day) exposure to LC ICSS lowers REM sleep rebound in REM-deprived rats. The present study examines this issue of latency and duration by testing rats over a 9-day paradigm with the first 3 days of baseline conditions, 3 days of *ad libitum* PAG ICSS, and the last 3

days of recovery together with dark:light analyses. This paradigm allows for the analysis of latency by determining whether exposure to PAG ICSS will reduce REM sleep in the first (dark) cycle of the first day. This paradigm allows for the analysis of duration by determining whether prolonged exposure to PAG ICSS over the second and third days will result in sensitized REM effects, neutral REM effects or an adaptation to ICSS. Finally, if REM sleep is actually reduced by PAG ICSS, this paradigm allows for the analysis of whether such stimulation substitutes for REM sleep and prevents REM sleep rebound.

Thus, this paradigm entails two independent groups to test unilateral and bilateral ICSS effects over a 9-day repeated measure design to assess differences between baseline, *ad libitum* ICSS, and recovery condition days in independent 12-h light, 12-h dark cycles, and detect the presence or absence of cyclical effects upon waking, SWS and REM sleep.

PART TWO: EXPERIMENTAL RESEARCH

A. EXPERIMENTAL METHODS

1. Subjects and Surgical Procedure

Fifty male, albino Sprague-Dawley rats (280-350 g, Holtzman Company, Madison, WI) were housed individually in a sound-attenuated room in standard laboratory plexiglas cages (18 x 42 x 20 cm) which were equipped with a retractable

lever (Model RC200, Scientific Prototype Mfs. Corp.). The rats were maintained on *ad libitum* rat chow (#5001, Ralsron Purina Company) and water at an ambient room temperature of 20° C. Lighting was set on a reversed 12-h light (2000-0800 h), 12-h dark (0800-2000 h) cycle and controlled automatically.

Each animal was anesthetized using Sodium Pentobarbital (1.3 mg/kg, ip: Veterinary Laboratories Inc.) with supplemental injections (5-10% of initial doses) administered as necessary. Each animal was placed in a stereotaxic instrument (model 1230, David Kopf Instruments) and incisions were made to expose the skull. Each animal was implanted with five electrodes; two electrodes each aimed bilaterally at the PAG and, three electrodes implanted for the recording of electroencephalograph (EEG), electromyograph (EMG), and electrooculogram (EOG).

Bipolar stainless steel electrodes insulated with formvar (MS303/1, Plastic Products Company) were used as stimulation electrodes and consisted of two twisted wires which were completely insulated except at the tips. The diameter of each wire was 0.25 mm and the distance between the tips was about 0.45 mm and cut to 9 cm in length. The electrodes' tips were carefully squared off using a fine sandstone and cleaned with distilled water. Each of the bipolar stimulation electrodes was aligned in a medio-lateral axis perpendicular to the midsagittal plane.

In each rat, the stereotaxic coordinates for bilateral PAG electrodes were: incisor bar: 0, according to DeGroot (1959) and Pellegrino, Pellegrino & Cushman (1981). All the stimulating electrodes were implanted at 20° angle toward the PAG using the following coordinates: 7.0 mm posterior to bregma, 1.0 mm lateral and angled 20° toward the midline and 7.0 mm ventral from the top of the dura. A drilling instrument (Dremal 232-5, Emerson Electric Company) was used to drill holes (1.3 mm diameter) in the skull through which stimulation electrodes were implanted. A hand drill (Model 60, Plastic Products Company) was used to drill holes for the EEG electrodes and anchor screws.

To record EEG behavior bilateral electrodes (MS301/1, Plastic Products Company), stripped of most of their insulation were attached to skull screws. One screw was placed in the skull anterior to bregma and the other screw was placed midway between bregma and lambda approximately 1.0 cm lateral to the midsagittal suture. EMG electrodes (MS303/71, Plastic Products Company) stripped of most their insulation was sewn onto each side of the trapezius muscle. To record EOG activity, electrodes (MS303/3, Plastic Product Company) were stripped of their insulation for approximately 2.0 cm, and the non-insulated portion of the EOG electrodes was turned into a coil placed in the animal's eyelids. Two screws were also placed into the skull as anchoring screws (0-80 X 1/8 0.32 mm long, Plastic Products Company), the

first placed 1.0 cm anterior to bregma and the other about 1.0 cm lateral to the midsagittal suture and 2.0 cm posterior to bregma. The stimulating and recording electrodes were secured in place using dental acrylic (Silverman's, Cold Cure Acrylic).

2. ICSS Stimulating Technique

The pulse pair stimulation technique was used (Deutsch, 1964; Ungerleider & Coons., 1970). Electrical brain stimulation consisted of 700 msec trains of negatively-going, diode-clamped, monophasic rectangular pulse pairs which was delivered to each of the animal's sites. Integrated circuit technology was used to manufacture a constant-current optically-isolated stimulation system which allowed independent control of the current intensity, pulse duration, and the pulse-pulse interval of the stimulation. Using the C-T stimulating technique, the pulse duration was set at 0.1 msec. The first pulse of each pair was designated as the C (conditioning) pulse, while the second pulse was designated as the T (test) pulse. The time between successive C pulses defined the C-C interval and was fixed at 30 msec, and the time between the C and T pulses defined the C-T interval and was fixed at 0.5 msec (Bodnar et al., 1978). The voltage drop across a 10,000-ohm resistor in series with the electrodes was continuously monitored on a cathode ray oscilloscope (Model 1200B,

Hewlett-Packard).

3. Electrical Stimulation Protocol

Seven days after surgery, the electrodes of each rat was attached to a commutator (Model #231, Spalding Medical Products) and connected with insulated wire, which in turn were connected to the stimulator and operant recording equipment in its operant chamber. Each animal was shaped to bar-press for ICSS at a variety of current intensities (50 - 700 μ A) over five to ten daily sessions. The pole of each bipolar electrode which elicited the highest response rates in preliminary testing served as the cathode and the other pole of the same bipolar electrode served as the anode. Utilizing the range of current intensities, electrode sites and current intensities were chosen which yield consistently high response rates of ICSS behavior which surpassed a criterion of 20 responses per min over 1 h. Electrode sites of rats which elicited either no behavior or aversive effects (e.g., vocalization, frantic leaping or disruptive motor reactions) were not used in the study. Eighteen rats (9 unilateral responders, 9 bilateral responders) met this strict criterion.

After the initial operant training sessions and cathode-anode determination procedures, animals were given the opportunity to work for PAG ICSS at nine current intensities (50, 100, 150, 250, 350, 450, 550, 650, 700 μ A)

delivered to each electrode site in separate 6 min periods with a 1 min no-stimulation time-out between each period. The order of intensities was varied in ascending and descending series each day over 5 days. To determine rate-intensity functions of optimal ICSS behavior, the mean of the last 4 min of each 6-min intensity session was used as the ICSS response rates for each current intensity for each day over 5 days for each electrode site. The optimal current intensity was defined as the lowest intensity eliciting peak ICSS rates. The animals were then tested at one intensity over five days, in five, 5-min sessions to observe the stability of ICSS behavior.

4. Recording of EEG EMG/EOG

During the experimental protocol, each rat was continually connected to three channels of a Grass polygraph (model 7D) through a commutator that allowed the animals free movement. All EEG recordings were of the alternating-current variety, and the differential input between recording electrodes was amplified. The polygraphic channels were each calibrated such that a 50 μ V signal resulted in a pen deflection of 1 cm. Reported frequencies were 1-35 Hz at full amplitude for the EEG, 10-75 Hz at full amplitude for EMG channel, and 1-15 Hz at full amplitude for the EOG channel.

5. Wave Form Analysis of EEG Data

The polygraphic data was scored using wave form analysis according to the criteria used by Fishman and Roffwarg (1970) and Steiner and Ellman (1972). Awake behavior was characterized by a low-amplitude, high-frequency EEG with frequently-interspersed theta activity, and a tonic EMG. Slow wave sleep (SWS) was characterized by a high-amplitude, low-frequency EEG, low muscle tonus on the EMG and no eye movements on the EOG. REM sleep was defined by a consistent theta rhythm in the EEG, muscle atonia on the EMG and frequent eye movements on the EOG. All epochs not clearly readable were not scored.

All scoring time thus fell into one of four categories: AWAKE, SWS, REM sleep and unscored sleep time over succeeding 30 sec epochs. If a given sleep-wake category occurred more than 5 s in a 30 s epoch, its duration was noted for that epoch if that category occurred during three of five 6-s category divisions of the 30 s epoch. In those cases in which three periods of a single category did not appear in an epoch, that epoch was scored as "mixed." REM periods were subsequently separated and added to overall REM sleep time. The scorer was uninformed as to the conditions during which the data were collected. The remaining "mixed" time was divided equally between AWAKE and SWS.

6. Experimental Protocol

The animals were given a 3-day no-stimulation period before beginning three days of baseline EEG/EMG/EOG conditions. All recording began on the first day at the onset of the dark cycle and proceeded in 12 h dark:light cycle over 3 days. Immediately thereafter, the PAG ICSS experimental condition commenced, and the animals received three days of *ad libitum* access to ICSS at previously-defined optimal current intensity. The amount PAG ICSS behavior was recorded in three min intervals over the duration of the *ad libitum* condition. EEG, EMG and EOG recordings were monitored simultaneously. Immediately following the PAG ICSS *ad libitum* condition, EEG, EMG and EOG recordings continued for the three recovery condition days.

7. Histology and Electrode Localization

After completion of the experimental procedure, rats were overdosed with sodium pentobarbital and perfused transcardially with 0.9% sodium chloride followed by 10% formalin. Their brains were removed and fixed in 10% formalin for five additional days. Frozen transverse sections (35 μ m were cut using a cryostat microtome (Model 860, AO Instrument Company)), mounted and stained with Luxol fast blue for fibers and cresyl violet for cell bodies Kluver and Barbera (1953). A rater, uninformed of the

experimental conditions determined electrode localization according to the atlas of Paxinos and Watson (1986).

8. Statistical Analysis

As described in detail in the EEG wave form analysis section, three dependent measures were obtained: amount of waking in h over a given 12-h period, amount of SWS in h over a given 12-h period, and amount of REM sleep over a given period. Each of these dependent measures was subject to a split-plot analysis of variance in which two groups of rats receiving either unilateral or bilateral electrical stimulation from the PAG served as the independent measure, and the experimental conditions (baseline, *ad libitum* ICSS day 1, *ad libitum* ICSS day 2, *ad libitum* ICSS day 3, recovery day 1, recovery day 2 and recovery day 3) and the portion of the circadian cycle (12-h light, 12-h dark) served as the repeated measures. Thus, this was a $2 \times 7 \times 2$ analysis of variance design. Additionally, reported are the results of repeated measure analysis of variance of pooled data (number of animals and conditions). Thus, reported are the results of alterations in 18 animals in pooled amounts of REM sleep, SWS, and AWAKE scores during the baseline, *ad libitum* ICSS, and post-ICSS recovery experimental conditions days. One pooled baseline score was utilized since preliminary data failed to find significant differences in either waking, SWS or REM sleep over the

3 baseline days. Once significant was detected and interaction effects were observed, Tukey comparisons ($p < 0.05$) were used to determine whether any of the experimental conditions significantly differed from their corresponding baseline condition for any of the dependent measures in the two groups of rats.

The PAG ICSS behavior as the independent variable (measured microcoulombs) and REM sleep alterations as the dependent measure in the *ad libitum* ICSS condition were analyzed utilizing Pearson product-moment correlation (r) and the modified Bonferroni test for significance. This analysis examined the strength of relationship between the absolute number of microcoulombs received by rats in the *ad libitum* ICSS and post-ICSS recovery conditions and subsequent REM sleep, SWS, and AWAKE alterations.

B. EXPERIMENTAL RESULTS

1. Histological Verification

Eighteen rats successfully completed the experiment, 9 rats with bilateral and 9 rats with unilateral self-stimulating electrodes. Figure 1 provides a schematic representation of electrode placements for the rats that completed the experimental paradigm. Histological verification revealed that electrode placements were localized to the ventro-lateral PAG and either within or adjacent to the DRN.

2. Pooled Effects of PAG ICSS on REM, SWS, and AWAKE

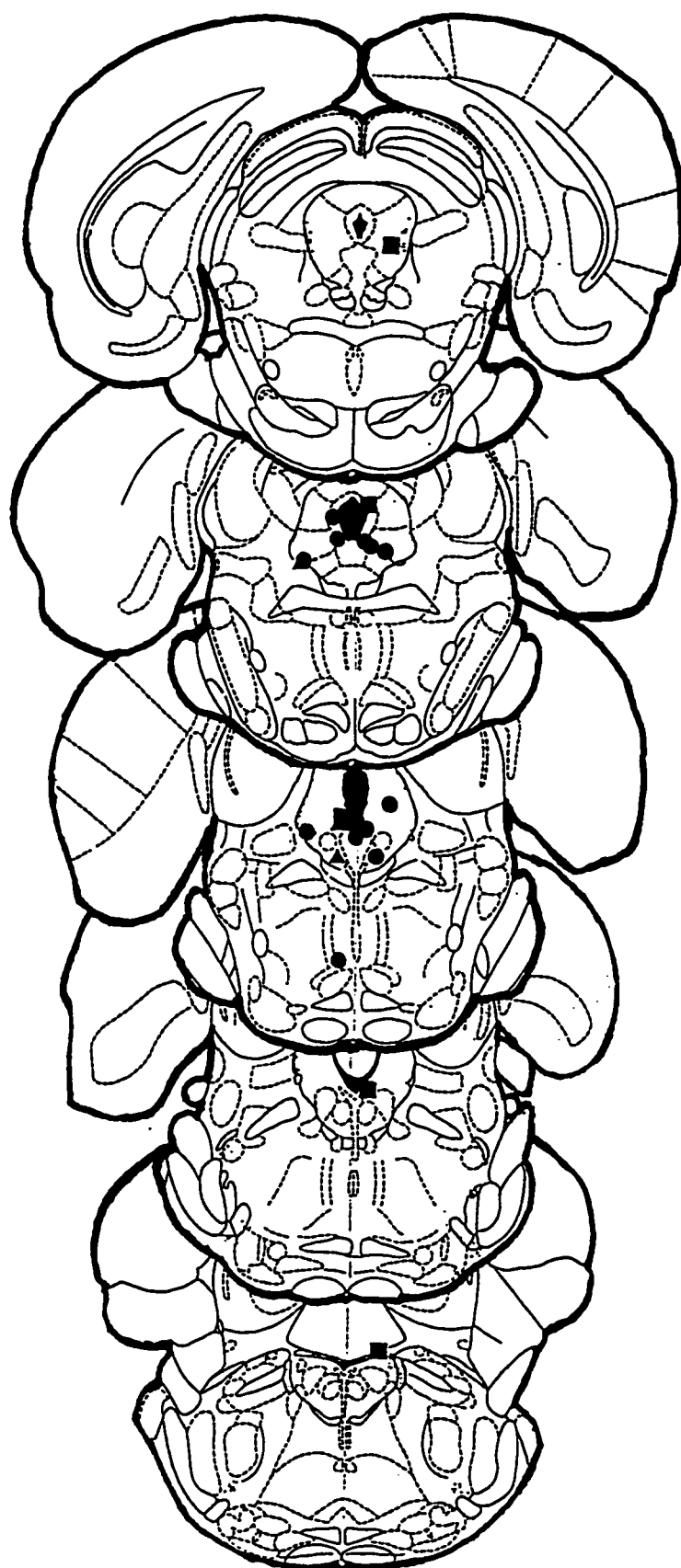
The effects of *ad libitum* PAG ICSS among all rats in pooled amounts of REM sleep, SWS, and AWAKE, are depicted separately in figure 1. Significant differences in REM sleep were observed between baseline, *ad libitum* PAG stimulation and recovery days ($F(6,102) = 18.55, p < .0001$). As expected, REM sleep was significantly reduced during the first ($\bar{x} = 1.4$ h) and second ($\bar{x} = 2.12$ h) days (44% and 15%, Figure 2A) of *ad libitum* PAG ICSS exposure. REM sleep was not significantly reduced during the third ($\bar{x} = 2.26$ h) day (10%, Figure 2A) of PAG ICSS stimulation. In contrast, REM sleep was significantly increased during the first ($\bar{x} = 2.9$ h) post-ICSS recovery day (14%, Figure 2A). However, REM sleep was not significantly affected during the second ($\bar{x} = 2.66$ h) and third ($\bar{x} = 2.66$ h) post-ICSS

recovery days (6% and 6%, Figure 2A).

Significant differences in SWS were observed between baseline, *ad libitum* PAG ICSS stimulation and recovery days ($F(6,102) = 22.48, p < .0001$). SWS was significantly reduced during the first ($\bar{x} = 5.98$ h) and second ($\bar{x} = 8.86$ h) day (41% and 12%, Figure 2B) during *ad libitum* PAG ICSS. SWS sleep was not significantly reduced during the third ($\bar{x} = 9.16$ h) day (9%, Figure 2B) of ICSS stimulation. However, SWS sleep was significantly increased during the first ($\bar{x} = 11.18$ h) post-ICSS recovery day (10%, Figure 2B). SWS sleep was not significantly affected during the second ($\bar{x} = 10.36$ h) and third ($\bar{x} = 10.28$ h) post-ICSS recovery days (3% and 2%, Figure 2B).

Significant differences in AWAKE were observed between baseline, *ad libitum* PAG ICSS stimulation and recovery days ($F(6,102) = 22.12, p < .0001$). AWAKE was significantly increased during the first day ($\bar{x} = 16.62$ h) (29%, Figure 2C) of *ad libitum* PAG ICSS exposure. However, AWAKE sleep was not significantly reduced during the second ($\bar{x} = 12.9$ h) and third ($\bar{x} = 12.24$ h) days of *ad libitum* ICSS exposure (8% and 3%, Figure 2C). AWAKE decreased significantly during the first ($\bar{x} = 9.8$ h) recovery day (17%, Figure 2C). AWAKE was not significantly affected during the second ($\bar{x} = 10.76$ h) and third ($\bar{x} = 10.92$ h) recovery days (9% and 8%, Figure 2C).

Figure 1. Schematic representation for 4 right unilateral (▲), 5 left unilateral (■), and 9 bilateral (●) ICSS electrode placements. The sections were adapted from Paxinos and Watson (1986).



▲ *Right ICSS*

■ *Left ICSS*

● *Bilateral ICSS*

Bregma
-7.30 mm

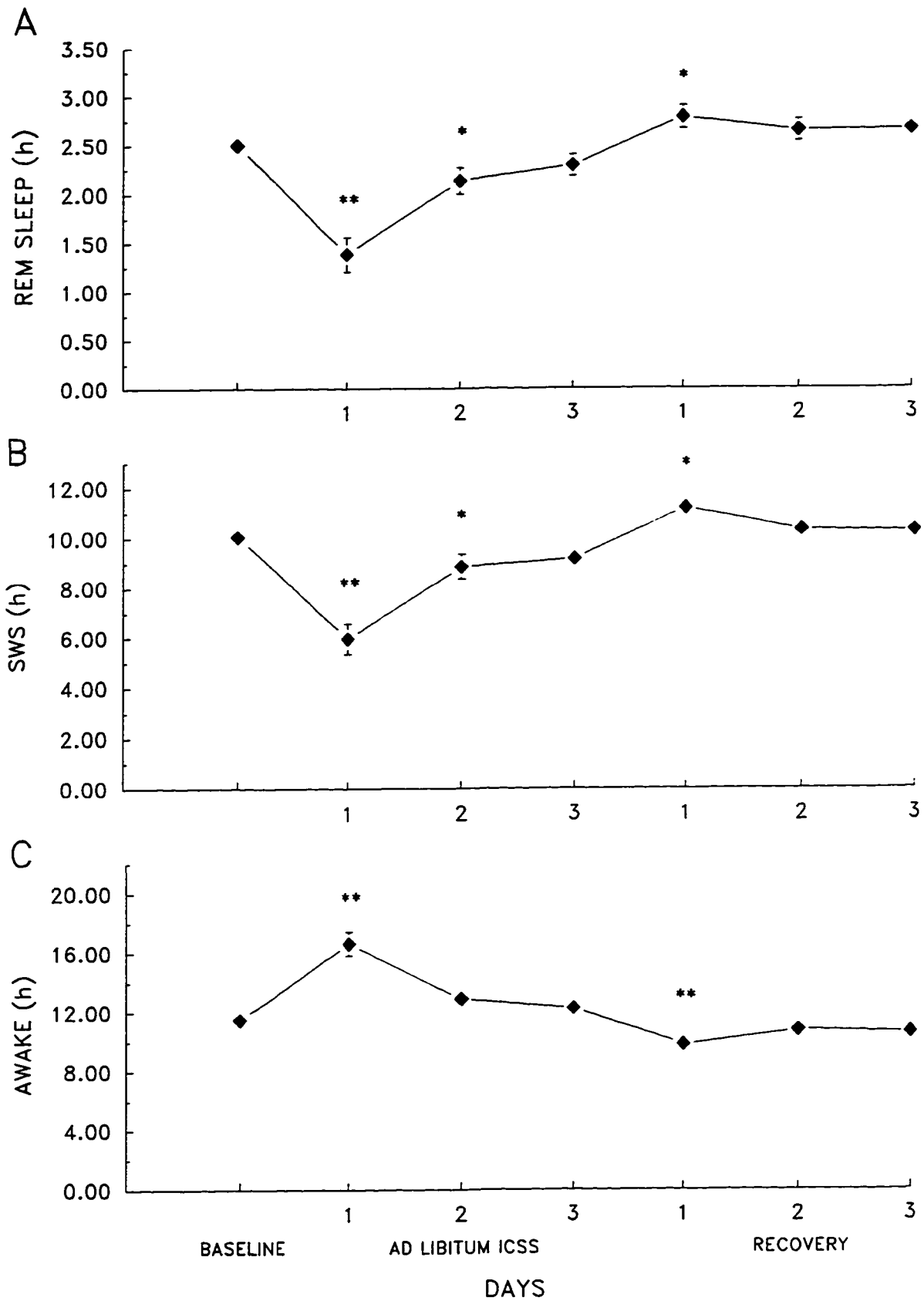
Bregma
-8.00 mm

Bregma
-8.30 mm

Bregma
-8.72 mm

Bregma
-9.16 mm

Figure 2. Alterations in the pooled amounts of rapid eye movement (REM) sleep (Panel A), slow wave sleep (SWS) (Panel B), and waking (AWAKE) (Panel C) ($h \pm SEM$) during baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery conditions in animals with stimulating electrodes aimed at the periaqueductal gray (PAG). * $p < .001$; ** $p < .0001$.



3. PAG ICSS and REM Sleep

Significant differences in REM sleep were observed between rats with unilateral and bilateral stimulating electrodes ($F(1,8) = 6.53$, $p < .034$), among baseline, stimulation and recovery days ($F(6,48) = 23.12$, $p < .0001$), and between the dark and light cycles ($F(1,8) = 399.40$, $p < .0001$). Although the actual difference in overall REM sleep between rats receiving unilateral ($\bar{x} = 1.11$ h) and bilateral ($\bar{x} = 1.24$ h) stimulation was small, Figures 3 and 4 present their respective ICSS effects separately. As expected, the amount of REM sleep during baseline conditions was significantly higher during the light cycle (unilateral group: 1.76 h; bilateral group: 1.73 h) than during the dark cycle (unilateral group: 0.65 h; bilateral group: 0.86 h). Therefore, the effects of PAG ICSS upon REM sleep are depicted separately during the dark (Figure 3) and light (Figure 4) phases. REM sleep was significantly reduced during the dark cycle on the first day of *ad libitum* exposure to PAG ICSS in rats receiving either unilateral (62%, Figure 3A) or bilateral (94%, Figure 3B) stimulation. REM sleep was not significantly affected during the dark cycle on the second and third days of *ad libitum* exposure to PAG ICSS in either group. In contrast, REM sleep was significantly increased during the dark cycle on the first day of recovery after ICSS exposure in rats receiving either unilateral (48%, Figure 3A) or bilateral (38%, Figure 3B)

Figure 3. Alterations in the amount of rapid eye movement (REM) sleep ($h \pm SEM$) during the dark cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.

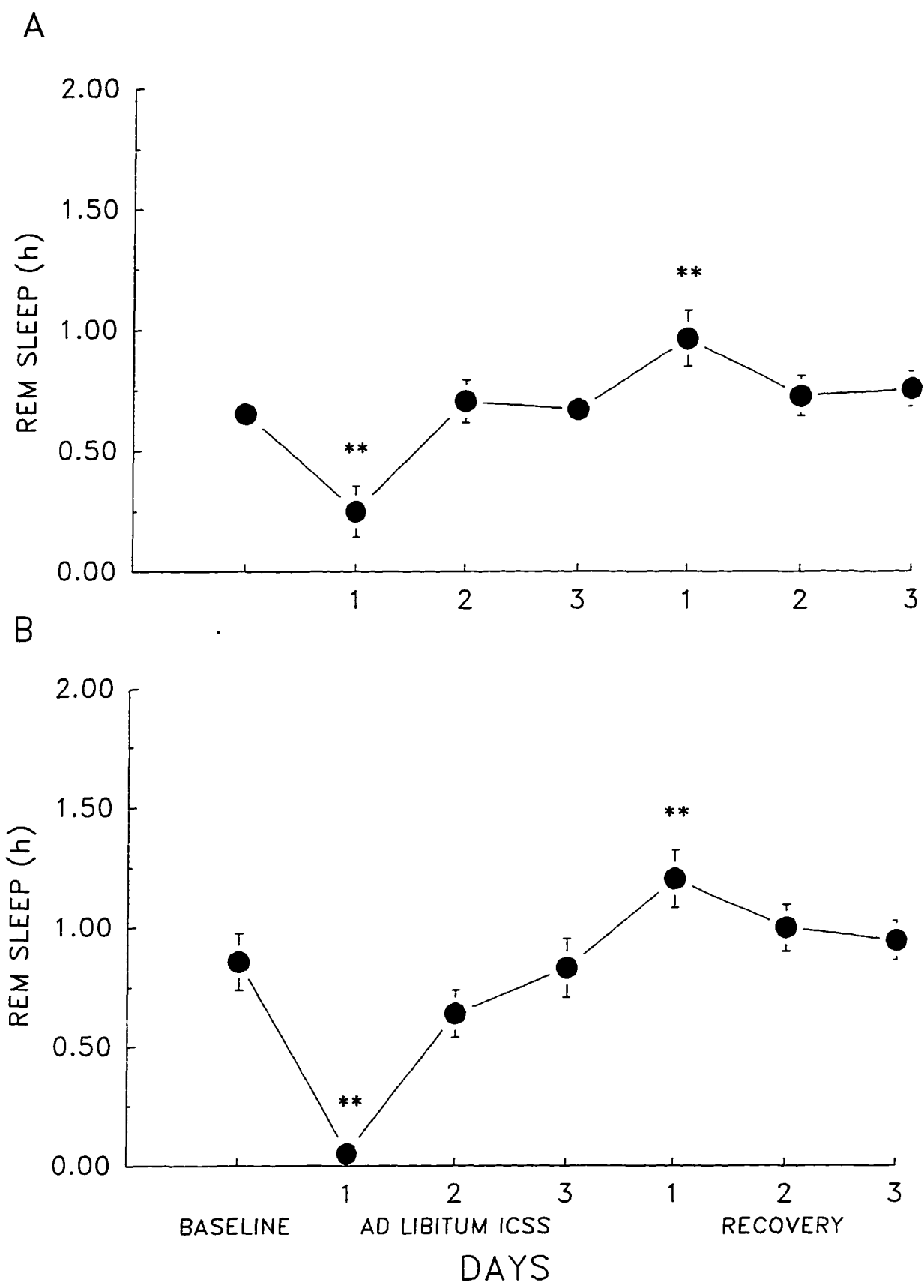
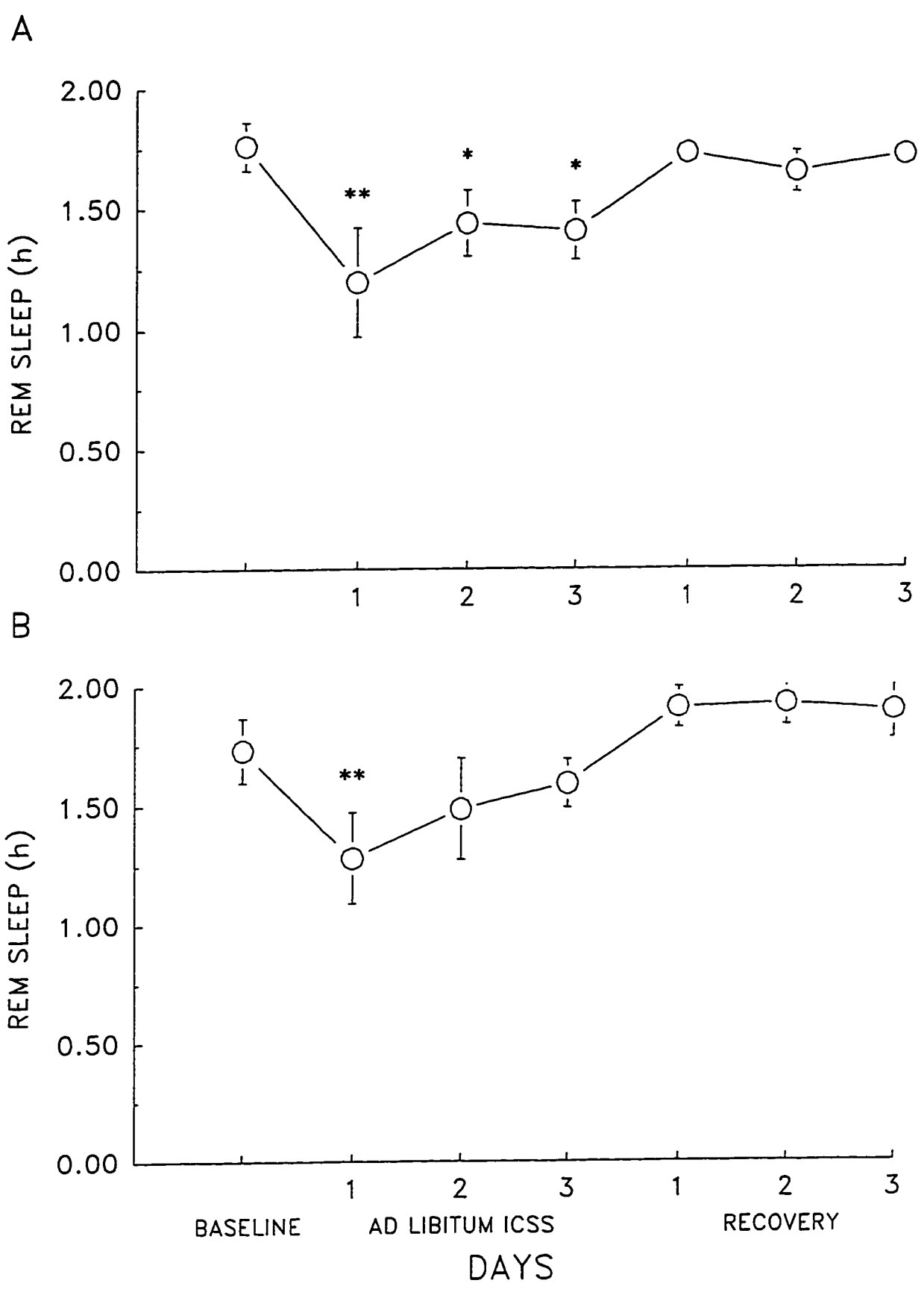


Figure 4. Alterations in the amount of rapid eye movement (REM) sleep ($\bar{h} \pm \text{SEM}$) during the light cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.



stimulation. REM sleep was not significantly affected during the dark cycle on the second and third recovery days.

A more pronounced pattern of effects was observed during the light cycle. REM sleep was significantly reduced during the light cycle throughout the three days of *ad libitum* exposure to PAG ICSS in rats receiving unilateral (32%, 18% and 22%, Figure 4A) stimulation. REM sleep was significantly reduced during the light cycle on the first day of *ad libitum* access to PAG ICSS exposure in the bilateral group (26%, Figure 4B). REM sleep was not significantly affected during the light cycle on the second and third days of *ad libitum* exposure to PAG ICSS in the bilateral group. In addition, REM sleep was not significantly affected during the light cycle of the three recovery days in either group (Figure 4).

4. PAG ICSS and SWS Sleep

Significant differences in SWS were observed between rats with unilateral and bilateral stimulating electrode sites ($F(1, 8) = 7.94, p < .034$), among baseline, stimulation, and recovery days ($F(6, 48) = 30.16, p < .0001$), and between the dark and light cycles ($F(1, 8) = 573.93, p < .0001$). Since a small significant difference in SWS between rats receiving unilateral ($\bar{x} = 4.87$) and bilateral ($\bar{x} = 4.54$) stimulation was observed, their data are presented separately in the upper and lower panels of

Figures 5 and 6. The amount of SWS during baseline conditions was significantly higher during the light cycle (unilateral group: 6.88 h; bilateral group 6.19 h) than during the dark cycle (unilateral group: 3.59 h; bilateral group 3.45 h): SWS was significantly reduced during the dark cycle on the first day of *ad libitum* exposure to PAG ICSS in rats receiving either unilateral (62%, Figure 4A) or bilateral (75%, Figure 4B) stimulation. However, SWS sleep was not significantly affected during the dark cycle on the second and third days of *ad libitum* PAG ICSS in either group. In contract, SWS was significantly increased during the dark cycle on the first recovery day after ICSS exposure in rats with unilateral (21%, Figure 4A) and bilateral (25%, Figure 4B) stimulating electrodes. SWS was not significantly affected during the dark cycle on the second and third recovery days in either group.

Slightly significant SWS reductions were observed during the light cycle on first and third days (27% and 14%, Figure 5A) in the *ad libitum* PAG ICSS exposure in the unilateral group. SWS was significantly reduced during the light cycle on first and second days (24% and 15%, Figure 5A) in *ad libitum* PAG ICSS exposure in the bilateral group. SWS were not significant affected during the light cycle in three recovery days in either group.

Figure 5. Alterations in the amount of slow wave sleep (SWS) ($h \pm SEM$) during the dark cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.

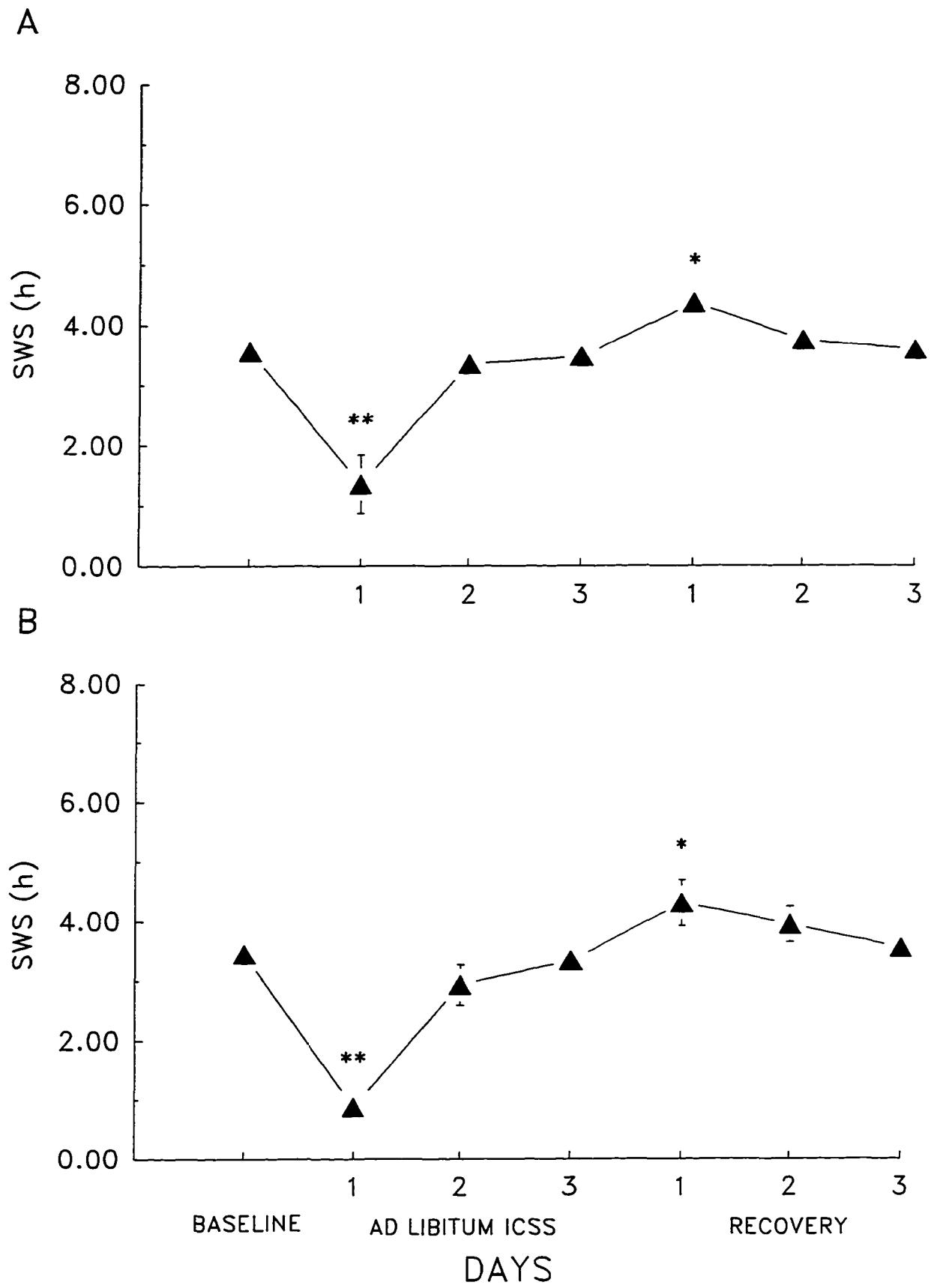
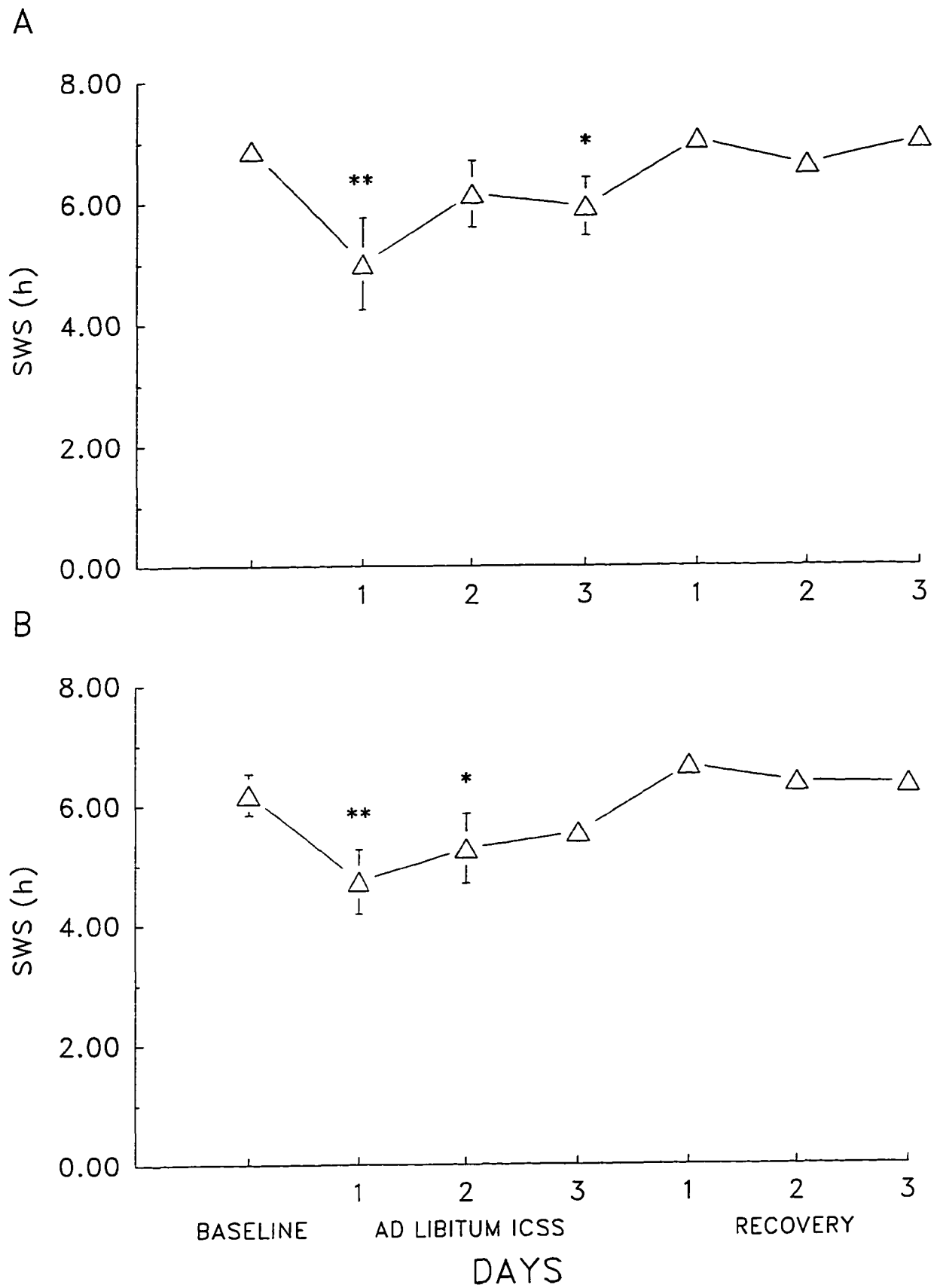


Figure 6. Alterations in the amount of slow wave sleep (SWS) ($h \pm SEM$) during the light cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.



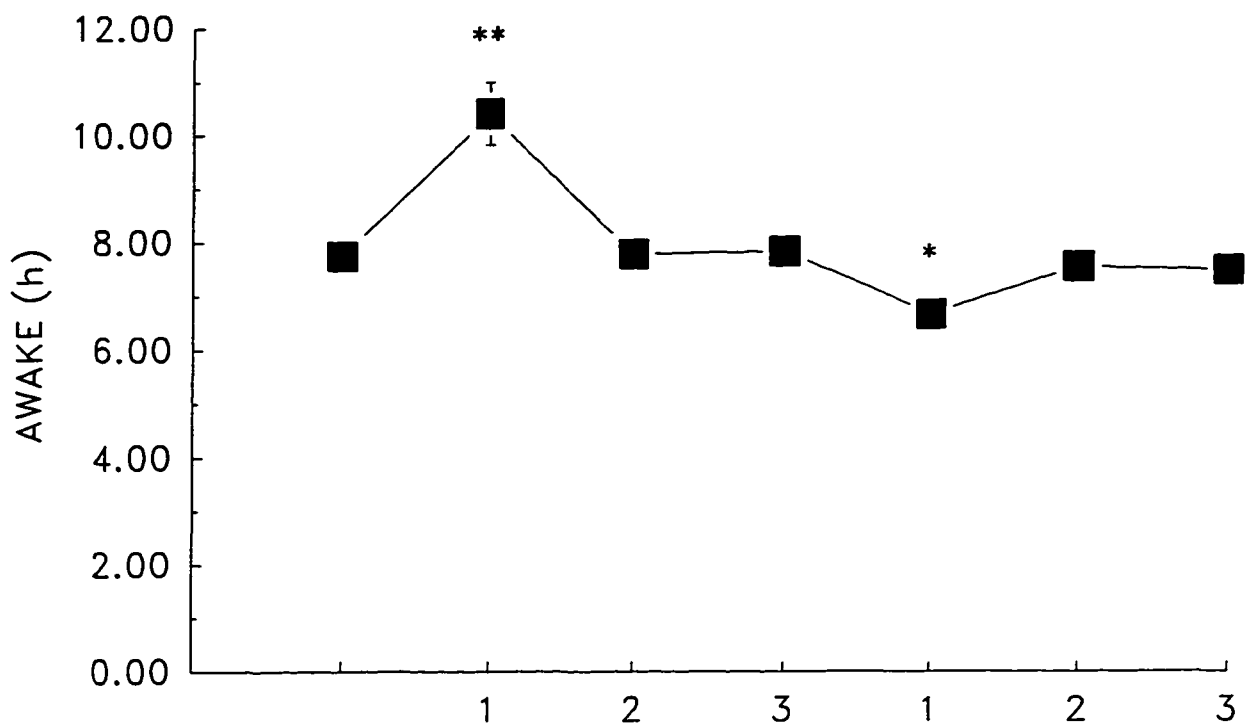
4. PAG ICSS and AWAKE

Significant differences were not observed in AWAKE between rats with unilateral and bilateral stimulating electrode sites ($F(1, 8) = 4.24, p > .073$). Significant differences in AWAKE were observed among baseline, stimulation and recovery days ($F(6, 48) = 31.64, p < .0001$), and between the dark and light cycles ($F(1, 8) = 595.02, p < .0001$). Significant differences in AWAKE were not observed in rats receiving unilateral ($\bar{x} = 5.90$) and bilateral ($\bar{x} = 6.19$), their data are presented separately in the upper and lower panels of Figures 7 and 8. The amount of AWAKE during the baseline conditions was significantly lower during the light (unilateral group: 3.36 h; bilateral group 4.12 h) than during the dark cycle (unilateral group: 7.74 h; bilateral group 7.71 h). AWAKE was significantly increased during the dark cycle on the first day in the *ad libitum* PAG ICSS exposure in rats receiving either unilateral (35%, Figure 7A) or bilateral (43%, Figure 7B) stimulation. However, AWAKE was not significantly affected during the dark cycle in the second and third days in the *ad libitum* PAG ICSS exposure in either groups. AWAKE was slightly significantly reduced during the dark cycle in the first post PAG ICSS recovery day in unilateral (14%, Figure 7A) and bilateral (16%, Figure 7B) groups. However, AWAKE was not significantly affected during the dark cycle of the second and third recovery days in either group.

Figure 7. Alterations in the amount of waking (AWAKE) ($h \pm SEM$) during the dark cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.

A



B

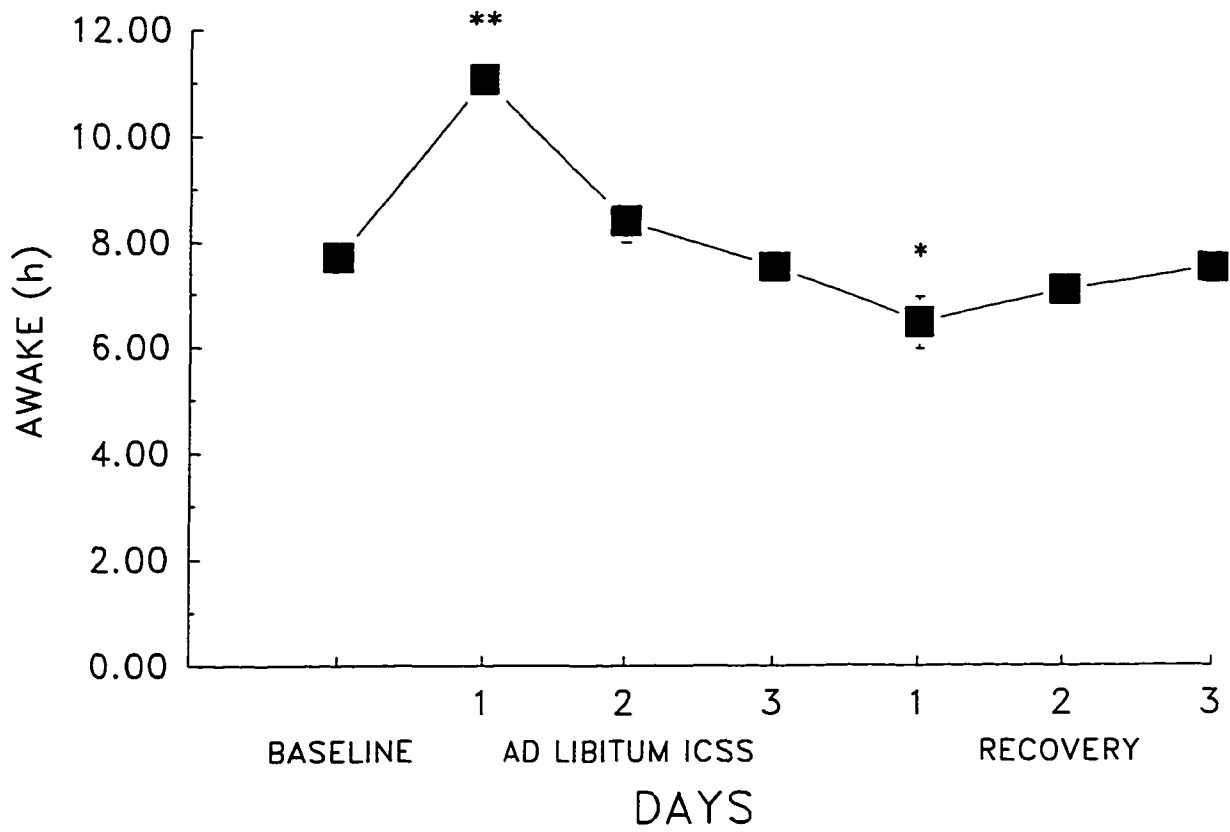
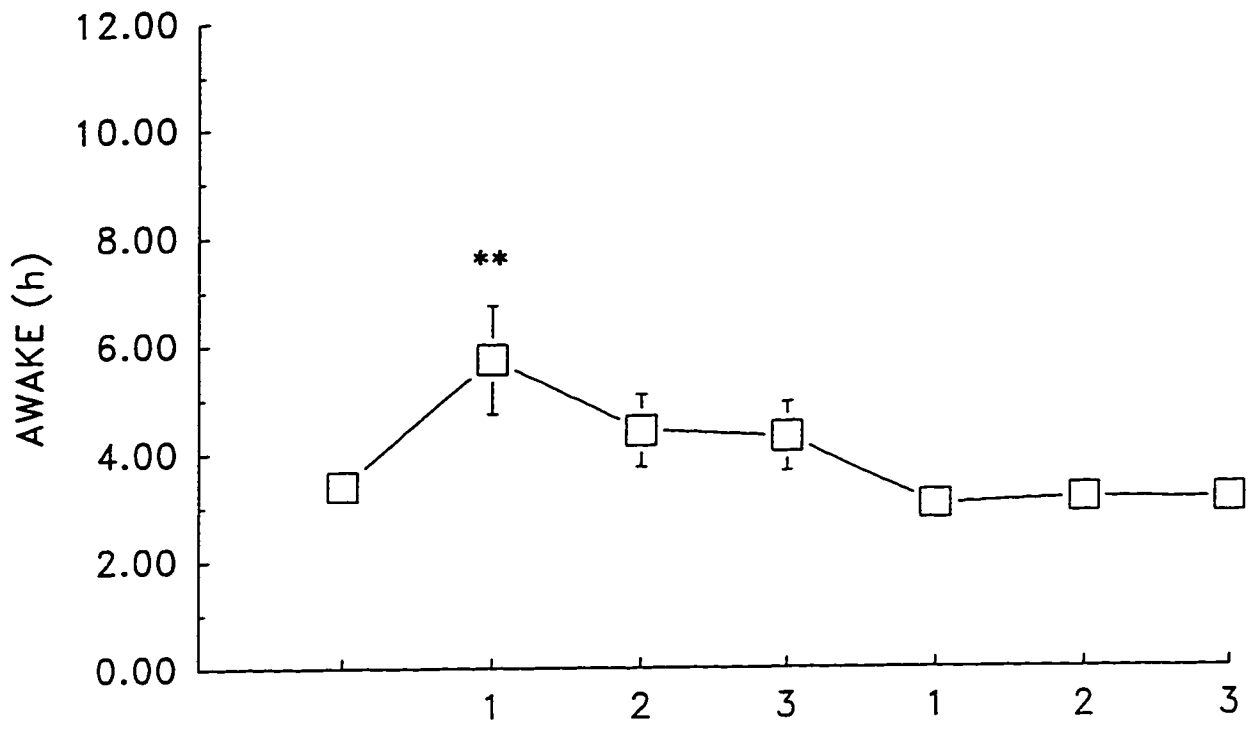


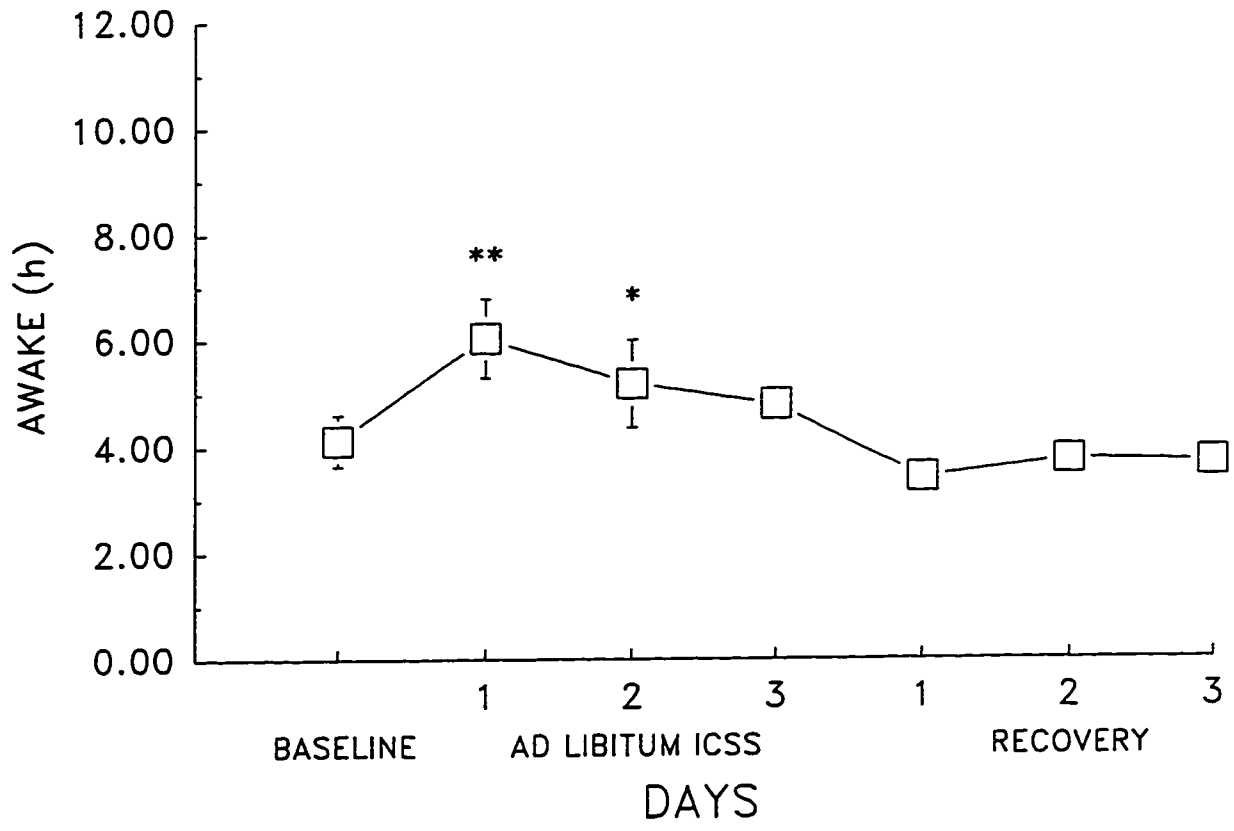
Figure 8. Alterations in the amount of waking (AWAKE) ($h \pm SEM$) during the light cycle as a function of baseline, *ad libitum* intracranial self-stimulation (ICSS) exposure, and post-ICSS recovery in animals with either unilateral (Panel A) or bilateral (Panel B) stimulating electrodes aimed at the periaqueductal gray (PAG).

* $p < .001$; ** $p < .0001$.

A



B



Significant increases in AWAKE were observed during the light cycle in the first day of the *ad libitum* PAG ICSS exposure in rats receiving unilateral (32%, Figure 8A) stimulation. AWAKE was significantly increased during the light cycle on the first and second days of the *ad libitum* exposure to PAG ICSS in rats receiving bilateral (46% and 26%, Figure 8B) stimulation. In contrast, AWAKE were not significant during light cycle in three days during the post PAG ICSS recovery condition days in both groups of rats.

Tables 1 and 2, list the amount of microcoulombs in the dark cycle (12-h) and light cycle (12-h) during the three days in the *ad libitum* ICSS condition in each animal. No significant differences are found between independent means [$t(8) = 0.00$, $p = 0.99$ (two-tailed)], between unilateral and bilateral ICSS sites when assessed with the paired Student *t*-test.

Table 1.

Ad Libitum ICSS Microcoulombs for 12-h Dark and 12-h Light Cycles over Three Days for Rats with Unilateral Electrode Placements Aimed at the Periaqueductal Gray

RAT	DARK 1	LIGHT 1	DARK 2	LIGHT 2	DARK 3	LIGHT 3	TOTAL
4	22,599,014	7,715,951	11,175,598	5,635,403	16,733,995	16,218,758	80,078,720
12	18,982,322	16,501,112	10,073,486	13,523,333	8,016,973	9,733,729	76,830,954
16	5,040,360	295,421	579,641	236,617	196,014	145,610	6,493,664
17	17,853,609	14,245,317	5,865,719	2,241,093	3,745,501	1,017,639	44,968,879
33	8,586,113	1,994,442	3,670,596	954,868	4,086,425	698,183	19,990,628
35	970,026	376,160	706,817	3,584,939	685,582	3,551,570	7,875,096
44	6,390,290	2,040,646	4,765,007	773,555	3,611,091	1,625,283	19,205,872
45	21,079,206	10,257,133	9,669,091	6,884,292	4,168,798	2,885,606	54,944,124
48	12,858,518	184,580	6,559,935	308,722	411,629	129,043	20,452,427
$\bar{x}$	12,706,606	5,956,751	5,896,210	3,793,647	4,628,445	4,000,602	36,760,041

Note. $n = 9$

Table 2.

Ad Libitum ICSS Microcoulombs for 12-h Dark and 12-h Light Cycles over Three Days for Rats with Bilateral Electrode Placements Aimed at the Periaqueductal Gray

RAT	DARK 1	LIGHT 1	DARK 2	LIGHT 2	DARK 3	LIGHT 3	TOTAL
1	11,042,122	2,880,472	3,634,660	1,859,333	4,239,503	1,310,494	24,966,583
11	6,210,844	2,445,508	3,657,061	556,306	2,232,693	2,055,347	17,157,759
19	8,226,988	4,265,638	4,637,131	737,386	3,126,890	1,857,466	22,851,499
22	18,696,002	23,138,986	24,119,056	2,795,533	14,799,057	15,762,793	99,311,427
24	26,187,470	9,898,707	12,058,128	3,420,444	4,292,707	509,636	56,367,093
25	20,758,816	6,575,803	9,824,035	4,809,344	3,523,585	802,724	46,294,307
27	9,666,757	98,007	1,731,457	130,676	780,789	339,758	12,747,444
31	6,331,252	1,205,486	6,294,850	7,710,351	3,692,064	1,884,535	27,118,537
43	11,226,469	4,144,296	5,301,712	5,483,725	6,466,129	4,055,623	36,677,953
$\bar{x}$	13,149,636	6,072,545	7,917,566	3,055,900	4,794,824	3,175,375	38,165,845

Note. $n = 9$

Pearson product-moment correlations were found significant ($p < 0.01$) when the strength of relationship between the absolute amount of microcoulombs the animals received during the *ad libitum* ICSS condition and resulting REM sleep, SWS, and AWAKE differences scores from the baseline condition. The strength of relationship was found high between the absolute number of microcoulombs rats received in the *ad libitum* ICSS condition and subsequent REM sleep reductions difference score ($r = -.81$) from the baseline condition. Additionally, during the same conditions tested the correlations were also high for SWS ($r = -.75$) and AWAKE ($r = +.77$). In comparison, the strength of relationships was smaller between the absolute number of microcoulombs received by animals in the *ad libitum* ICSS condition and subsequent changes in the difference score in REM sleep ($r = +.54$), SWS ($r = +.52$), and AWAKE ($r = -.36$) between the baseline and post-ICSS recovery condition.

C. CONCLUSION

The aim of this dissertation was to examine whether *ad libitum* ICSS elicited from the PAG significantly and selectively reduces REM sleep and prevents the occurrence of subsequent REM rebound in rats. It was hypothesized that PAG ICSS would significantly reduce REM sleep during the stimulating period. Furthermore, it was hypothesized that if PAG ICSS reduces REM sleep, it should also prevent an increase in the intensity or duration of subsequent REM time during the recovery period (REM rebound). This dissertation considered the following important factors about this phenomenon including: (a) the placement of either unilateral or bilateral stimulating electrodes, (b) the occurrence of effects either in the light or dark phase of the circadian cycle, (c) the onset and duration of effects over the 3-day stimulation period, and (d) the amount of microcoulomb current delivered to stimulation sites. To assess the specificity of effects, evaluation of alterations in the amount of REM sleep, SWS and AWAKE was examined over baseline, *ad libitum* ICSS period and recovery conditions.

The results of the present study support the hypotheses that when rats are given the opportunity to self-stimulate freely for electrical stimulation to areas of the ventro-lateral PAG, significant and selective reductions of REM sleep are observed. These significant reductions in REM sleep were demonstrated during the first day in the

ad libitum ICSS condition in both groups of rats (unilateral and bilateral), in the dark and light cycles. The significant decreases seen in REM sleep during the first day of the *ad libitum* condition were not maintained in the subsequent *ad libitum* condition days 2 and 3. Further, the reductions in REM sleep were more pronounced in the light cycle, the time in a 12:12 h dark:light circadian cycle, where rats normally have their highest amount of REM sleep when compared with the dark cycle (Rechtschaffen et al., 1969). Thus, over the *ad libitum* days 2 and 3 ICSS period in the light cycle the duration of REM reductions was either significantly reduced as was demonstrated in the unilateral sites or was not significant but was lower than the baseline condition as was shown in the bilateral sites. Similar effects associated with *ad libitum* ICSS behavior were also observed in SWS in both groups of rats. Accordingly, observed were significant attenuations of SWS during the first day in the *ad libitum* condition in both the dark and light cycle. SWS reductions in the light cycle were either significantly lower during the second and third days in the *ad libitum* ICSS condition. However, SWS behavior never exhibited increases over the baseline condition.

The findings further support's the hypotheses that if PAG *ad libitum* ICSS reduces REM sleep, it should also arrest the increases in the intensity or duration of subsequent REM time during the post-ICSS recovery condition (REM rebound).

Significant increases in REM sleep were only found, in both groups of animals during the first day in the post-ICSS recovery condition when compared with baseline condition in the dark cycle. These same animals in the subsequent recovery days 2 and 3 demonstrated no significant differences from baseline conditions. The best demonstrations of this effect are found in the light cycle data, where no significant increases in REM were seen in all of the three post-ICSS recovery days. Almost identical to the results of those of REM sleep in the post-ICSS recovery conditions are those of SWS.

Significant elevations of SWS were in effect in both groups of rats during the first recovery day with no increases seen in days 2 and 3 in the recovery conditions, in the dark cycle, while in these same animals in the light cycle, no significant changes from baseline were observed in the three days of the post-ICSS recovery conditions. This coincides with the changes in REM and SWS was the concurrent diametric change in the AWAKE variable. Thus, significant reductions in REM and SWS correspond with the significant enhancement of AWAKE as were observed in the first day of the *ad libitum* ICSS condition, and while changes in REM and SWS in the recovery condition coincided with decreases in AWAKE were observed.

The marked differences observed in the REM and SWS data between the dark and light cycles in the ICSS condition days

shows that ICSS behavior is sensitive to circadian fluctuations. Furthermore, the REM and SWS data showed that there are far more significant decreases seen in the light cycle than in the dark cycle and appears to correlate well with a rat's circadian light:dark sleep wake cycles (Rechtschaffen et al., 1969).

The significant increases observed in REM sleep and SWS in the dark cycle during the first recovery condition day appeared less in intensity than the decreases in the *ad libitum* condition when compared with the baseline condition. Additionally, the increases seen in REM and SWS were only seen in the first 12 h in the dark cycle and did not reach duration into the light cycle. The order in which the ICSS experimental condition commenced was in the light cycle can have played an influencing effect on subsequent REM and SWS rebound effects. However, as was indicated earlier rats normally have their highest amount of REM sleep and SWS in the light cycle (Rechtschaffen et al., 1969).

The microcoulombs delivered during the 3-day stimulation condition was a critical predictive factor for REM sleep reductions in rats. The strength of relationship between the absolute number of microcoulombs delivered to each rat in the *ad libitum* ICSS condition and subsequent REM reduction ($r = -.81$), SWS reduction ($r = -.75$), and increases in AWAKE ($r = +.77$) from the baseline condition were highly correlated and significant. However, the

strength of relationships was smaller between the absolute number of microcoulombs received by rats in the *ad libitum* ICSS condition and subsequent changes in the difference score in REM sleep ($r = +.54$), SWS ($r = +.52$), and AWAKE ($r = -.36$) between the baseline and post-ICSS recovery condition. In contrast, the results show that no significant differences exist between the amount of microcoulombs delivered between each group (unilateral and bilateral) and the differences' score found in REM sleep between the baseline and *ad libitum* condition. Thus, differences in the number of microcoulombs delivered to each group were comparable and played no role in determining REM sleep attenuations during the *ad libitum* ICSS condition.

The findings from this study show that in the light circadian cycle of the rat the rewarding properties of self-stimulation in the ventro-lateral PAG may be functioning in "satisfying" or "gratifying" the effects of endogenous REM sleep rather than by functioning to inhibit REM sleep. Furthermore, lack of a REM sleep rebound phenomena (in the light cycle) following PAG *ad libitum* ICSS also showed that the "pressure" or "drive" for a fixed amount of REM sleep activation has been "satisfied" by the PAG ICSS, and therefore the need to make up lost REM sleep is not required. These findings support Ellman's notion of an interchangeability between the rewarding properties of self-

stimulation behavior and REM sleep (Steiner & Ellman, 1972).

The findings in REM reductions during the ventro-lateral PAG ICSS condition and the subsequent lack of a REM rebound (in the light cycle) in the present study are similar to those of Steiner and Ellman (1972), Spielman, Ellman and Steiner (1973), and Melikov et al. (1990) in demonstrating the interchangeability between the rewarding aspects of ICSS behavior and REM sleep. Steiner and Ellman (1972) showed that short periods from 60 to 90 minutes exposures to LH ICSS reduced REM sleep by 50% to 60%. While Melikov et al. (1990), have shown that ICSS behavior significantly increases immediately after 48 h of REM deprivation. In a subsequent study Spielman, Ellman and Steiner (1973), found that allowing animals either 2 h of LH ICSS every 24 h or 8 h of LH ICSS every 24 h found that animals allowed the longer exposure to ICSS had more REM sleep reductions. However, in this experiment REM rebound effect was not observed in these LH ICSS animals. In a second experiment, bilateral LC *ad libitum* ICSS was tested to see if this method could provide a better test of their hypotheses. Thus, by allowing the animals free access in the timing of brain stimulation, Spielman et al. (1973) showed that bilateral LC *ad libitum* ICSS affected a suppression of the REM rebound following REM deprivation. This effect in bilateral LC sites is supported by the present study in bilateral and unilateral ventro-lateral PAG

sites. However, it appears that bilateral stimulation of ventro-lateral PAG sites is not required to attenuate REM sleep and arrest subsequent REM sleep rebound effect since the amount of microcoulombs delivered to unilateral and bilateral sites in the present study were found not to differ from each other.

It has been suggested that 5-HT-containing neurons of the raphe system and NA cells from the LC have common antagonistic regulatory effects upon sleep and waking (Jouvet, 1972). Noradrenergic fibers from the LC and subcoeruleus have been found to project to DRN containing 5-HT cell bodies and the 5-HT projections from the DRN have been found in noradrenergic cell groups such as the LC (Leger & Descarries, 1978; Baraban & Aghajanian, 1981). Further, Immunocytochemical (Pickel et al., 1977) and autoradiographic (Leger & Descarries, 1978) studies have confirmed that the LC receives a dense serotonergic innervation. In brain slices, NE and adrenergic agonist was found to modulate 5-HT release (Göthert et al., 1981) the density and function of 5-HT receptors (Manier et al., 1987). Ennis et al. (1991), using anatomical and physiological techniques showed that the ventro-lateral PAG strongly innervates the ipsilateral rostro-medial pericoerulear area, including Barrington's nucleus. By contrast only a few sparse fibers appeared to enter the LC proper and the subcoerulear area. Consistent with these

results, focal electrical stimulation of LC antidromically activated only a few PAG neurons and all were localized to lateral and ventro-lateral areas of the PAG.

The unit discharge profile of NE neurons (Foote et al., 1980; Aston-Jones & Bloom, 1981) are the only other group of neurons in the CNS (other than α -motoneurons) that display the same pattern of activity across the sleep-wake-arousal cycle as do 5-HT neurons. They are silent in REM sleep, display a low level of activity during SWS, become moderately active during waking, and increase their activity still further during active waking or arousal (Foote et al., 1983; Jacobs, 1986). Spontaneous cellular activity of DRN has also been reported to correlate with PGO waves and behavioral states (Jacobs & Azmitia, 1988). Cells in DRN fire most in AWAKE, less frequently during SWS and generally cease firing during the transition from SWS into REM and REM sleep when PGO waves are observed (McGinty & Harper, 1976; Trulson & Jacobs, 1979; Cespuglio et al., 1981; Lydic et al., 1987a;b). Furthermore, Lydic et al. (1987a;b) showed that forced locomotor activity, which alters sleep cycle timing, does not abolish the relationship of DRN neuronal firing to the sleep cycle and PGO waves, suggesting that the DRN have a role in the regulation of the sleep cycle.

Stimulation of the PAG results in a variety of respiratory pattern changes, ranging from tachypnea in animals (Baxter & Olszewski, 1955; Nashold et al., 1969) to

hyperventilation and apnea in humans (Markgraf et al., 1988). Stimulation of the PAG also inhibits other respiratory-related reflex behavior, such as coughing, swallowing, jaw-opening, and tongue-protrusions reflexes (Sessle et al., 1985). The PAG has an extensive set of neuroanatomical projections to the brainstem motoneurons regulating both upper airway musculature and structures that can modify respiratory patterning in the diaphragm as well. The PAG projects to the nucleus ambiguous-retroambiguous, which, in turn, projects to motoneuronal cell groups supplying muscle activity related to respiration and vocalization (Holstege, 1989), and to the medial nucleus of the solitary tract, which contains neurons mediating baroreceptor and chemoreceptor afferents (Bandler & Tork, 1987).

Neurons of the central nucleus of the amygdala and the red nucleus of the stria terminalis, which fire in response to aspects of respiratory patterning in a state-dependent manner (Zhang et al., 1986; Frysinger et al., 1988), and cells of the parabrachial nucleus, which has been implicated in respiratory phase switching (Cohen, 1979), project to the PAG (Hopkins & Holstege, 1978; Saper & Loewy, 1980; Holstege et al., 1985). Thus, a variety of cortical and subcortical structures have the potential to influence respiratory patterning through the PAG via PAG projections to brainstem respiratory regions.

Ni, Zhang and Harper (1989) found substantial a portion (28%) of neurons recorded in the PAG showed a phasic discharge timing (i.e. breath-by-breath) relationship with respiration in at least one sleep-waking state. For 74% of these neurons, the phasic discharge timing correlations occurred in only one state, while the other 26% of these neurons exhibited discharge timing correlations with respiration across multiple sleep-waking states. Based on these results' Ni, Zhang and Harper (1989), suggest that a subset of PAG cells may play a role in state-related respiratory patterning.

Sleep states have been found to significantly influence the cardiovascular system (Mancia et al., 1971; Zanchetti et al., 1982) and greatly modify the spontaneous discharge of neurons in brain sites (Evarts, 1964). Blood pressure and heart rate show a progressive decrease from waking to quiet sleep in the cat. Phasic cardiovascular changes occur with bursts of eye movements and body twitches during REM sleep. During REM sleep heart rate is very variable, with marked tachycardia and bradycardia sequences. A redistribution of blood flow between visceral and muscle beds also occurs during REM sleep (Zanchetti et al., 1982). Although the demands for blood flow are tonically altered from waking to sleep states, the very large phasic changes in heart rate that are much greater than the immediate changes in response to movements (which are suppressed by the atonia of REM

sleep) or metabolic demand would dictate. Thus, in the absence of major moment-to-moment alterations in demands, both cardiac rate and blood pressure control exhibit immediate changes in REM sleep, and considerable tonic changes during quiet sleep.

A subset of neurons in many brain areas has been found to mediate 'affect' show cardiac-related activity. For example, neurons in the anterior cingulate gyrus and the amygdala show a cardiac cycle-by-cycle correlation between unit rate and heart rate. Although this relationship is present in certain sleep-waking states and not in others (Frysinger & Harper, 1986; Frysinger et al., 1988).

Ni, Zhang and Harper (1990), found that PAG discharge patterning relationships to the cardiac cycle produced the most remarkable set of findings; 74% of the neurons showed a discharge timing relationship (cardiac cycle-by-cycle) and/or a tonic correlation with cardiac activity, and nearly all (96%) of these dependencies was state related. The greatest number of phasic discharge timing relationships was found during quiet sleep followed by AWAKE, and then by REM sleep. Ni, Zhang and Harper (1990), concluded from these results that large proportion of neurons showing a state-related cardiac dependency suggesting that the PAG may contribute to mediating different cardiac patterns observed in each state.

In a study by McRae-Degueurce et al. (1988) neonatal

rats (4 days old) were treated with a single intracisternal injection of the neurotoxin 5,7-dihydroxytryptamine that eliminates selectively 5-HT throughout adulthood as was previously demonstrated by Breese and Cooper, (1975b) and Towle et al. (1984). Sleep recordings in these animals as adult rats (3 months of age) displayed significant reductions in REM sleep. Dissociated fetal 5-HT (16-day-old embryos) suspensions were transplanted in the IVth ventricle of these rats. Rats treated with 5-HT suspension transplants demonstrated restored REM sleep. However, rats treated with fetal neuronal noradrenergic or cholinergic transplants did not have restored REM sleep. Based on the results of this study the authors suggest that the REM sleep can be directly or indirectly mediated through serotonergic mechanisms.

The neuroanatomical and experimental evidence presented in this dissertation support the notion that the DRN of the PAG and/or the lateral-ventral PAG performs a modulating role in the sleep-wake-arousal cycle. The neuroanatomical and electrical physiological (Ennis et al., 1991) results have established the reciprocal interconnections between the PAG and LC. While, noradrenergic fibers from the LC and subcoeruleus have been found to project to DRN containing 5-HT cell bodies and the 5-HT projections from the DRN have been found in LC noradrenergic cell group (Leger & Descarries, 1978; Baraban & Aghajanian, 1981). Further, the

experimental data has demonstrated the DRN innervation of the LC acts to modulate the sleep-wake-arousal cycle (Foote et al., 1983; Jacobs, 1986; Jacobs & Azmitia, 1988). To this end the present study may support this notion, since the effects of *ad libitum* stimulation of the ventro-lateral PAG and DRN showed significant behavioral effects in REM sleep, SWS, and AWAKE though the dark:light circadian cycle.

Significant and selective reductions were caused in REM sleep and SWS during the ventro-lateral PAG/DRN 3-day stimulation period, which were most pronounced in the light cycle. While the occurrence of a REM and SWS rebound was absent in the subsequent recovery periods in the light cycle and only occurring during the first day of the dark cycle. Thus, these results may indicate that rewarding electrical stimulation of the ventro-lateral PAG/DRN may be functioning to replace the endogenous occurrence of REM sleep and SWS by effecting the PAG/DRN modulating sleep-wake-arousal cycle system. The lack of a rebound effect in the recovery condition (in the light cycle), may be indicative of this effect since the "pressure" of a fixed amount of REM sleep and SWS activation has been "satisfied" by the rewarding PAG/DRN ICSS, and therefore the need to make up lost REM sleep and SWS is not required.

1. Suggestion for Future Research

Based on the findings from the present study, the

possible next study would be to investigate some of the same issues in animals receiving passive PAG stimulation. In suggested experiments, rats will be paired; one participant of each subject pair will be required to lever-press to obtain rewarding PAG ICSS, while the other member of each pair will receive its PAG stimulation passively at the same electrical parameters and pattern of stimulation as its ICSS companion (yoked-control) (Stein, 1962; De Witte, 1982; Gallistel et al., 1981; Gallistel & Leon, 1991). The experimental hypothesis to be tested in the suggested experiment is that the active responding ICSS member of each pair will experience a reduced requirement for REM sleep, in contrast to their yoked companions, which will fail to show the reduced-REM effects although they will essentially receive stimulation at the same parameters and temporal patterning as the corresponding ICSS animals. Thus, it is the hypothesis that the behavioral state of the animal is essential in determining whether rewarding PAG stimulation can reduce a rat's "need" for REM sleep.

It would then be predicted that active vs. Passive stimulation animals' REM sleep scores would not differ during baseline, but would differ substantially during the stimulation condition, and would also differ, but in the opposite direction, during the post-stimulation condition because, post-stimulation, yoked-controls, whose REM sleep might have been interrupted by the unrewarding non-

contingent stimulation imposed during the preceding stimulation condition, could be expected to have more REM sleep (REM rebound) than ICSS animals, whose REM-sleep "drive" would have been satisfied by the combination of rewarding stimulation and actual REM-sleep during the preceding condition, and would therefore not be expected to have post-stimulation REM rebound.

2. Summary

REM sleep reductions occurred during the first day in the *ad libitum* ICSS condition were maintained during the subsequent second and third days in the ICSS condition. These reductions were most pronounced in the light cycle in both the unilateral and bilateral groups of rats. Moreover, REM rebound effects were observed during the first 12-h dark cycle in the recovery condition but were not observed during any of the subsequent recovery condition periods.

The strength of relationships was highly correlated in the reductions in REM sleep and SWS seen and in the absolute number of microcoulombs each animal received during the 3 days in the *ad libitum* ICSS and baseline conditions. In contrast, the results show that no significant differences exist between the amount of microcoulombs delivered between each group (unilateral and bilateral) and the differences' score found in REM sleep between the baseline and *ad libitum* condition. Thus, differences in the number of microcoulombs

delivered to each group were similar and played no role in determining REM sleep attenuations during the *ad libitum* ICSS condition.

Hence, rewarding electrical stimulation of the ventro-lateral PAG and/or DRN may be functioning to supersede the endogenous occurrence of REM sleep and SWS by effecting the DRN modulating sleep-wake-arousal cycle system. The absence of a REM rebound in the recovery condition (in the light cycle) may be suggestive of this effect since the "pressure" of a fixed amount of REM sleep and SWS activation have been "satisfied" by the rewarding PAG and/or DRN ICSS, and therefore the need for the animal to make up lost REM sleep and SWS is not required.

D: REFERENCES

- Abrams, R. M., Hutchison, A. A., Jay, T. M., Sokoloff, L. & Kennedy, C. (1988). Local cerebral glucose utilization non-selectivity elevated in rapid eye movement sleep on the fetus. Developmental Brain Research. 40, 65-70.
- Ackermann, R. F., Steiner, S. S., Bodnar, R. J., Jackler, F., Greenblatt, E. & Ellman, S. J. (1977). Characterization of self-stimulation elicited from rat dorsolateral pariaqueductal gray. International Journal of Neuroscience. 7, 235-238.
- Adam, K. & Oswald, I. (1977). Sleep is for tissue restoration. Journal of the Royal College of Physicians. 11, 376-388.
- Akil, H., Madden, J., Patrick, R. L. & Barchas, J. D. (1976). Stress-induced increase in endogenous opiate peptides: concurrent analgesia and its partial reversal by naloxone. In H. W. Kosterlitz (Ed.), Opiate and Endogenous and Opioid Peptides. (pp. 63-70). Amsterdam: Elsevier.
- Akil, H. & Mayer, D. J. (1972). Antagonism of stimulation-produced analgesia by p-CPA, a serotonin synthesis inhibitor. Brain Research. 44, 692-697.
- Albino, R. C. & Lucas, J. W. (1962). Mutual facilitation of self-rewarding regions within the limbic system. Journal of Comparative and Physiological Psychology. 55, 182-185.
- Allison, T. & Cicchetti, D. V. (1976). Sleep in mammals: Ecological and constitutional correlates. Science. 194, 732-734.
- Anch, A. M., Browman, C. P., Mitler, M. M. & Walsh, J. K. (1988). Sleep: A Scientific Perspective. New Jersey: Prentice Hall.
- Anch, A. M. & Tepas, D. I. (1970). Paradoxical sleep in the rat: Comparison of early and late blinding. Psychonomic Science. 19(3), 155-156.
- Arbuthnott, G. W., Fuxe, K. & Ungerstedt, U. (1971). Central catecholamine turnover and self-stimulation behavior. Brain Research. 27, 406-413.
- Aserinsky, E. & Kleitman, N. (1953). Regularly occurring periods of eye mobility and concomitant phenomenon during

- sleep. Science. 118, 273-274.
- Aston-Jones, G. & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. Journal of Neuroscience. 1, 876-886.
- Aston-Jones, G. M., Ennis, V. A., Pieribone, W. T., Nickell, W. T. & Shipley, M. T. (1986). The brain nucleus locus coeruleus: Restricted afferent control of a broad efferent network. Science. 234, 734-737.
- Aston-Jones, G. Shipley, M. T., Chouvet, G., Ennis, M., Van Bockstaele, E. J., Pieribone, V. A., Shiekhata, R., Akaoka, H., Drolet, G., Astier, B., Charlety, P., Valentino, & Williams, J. T. (1991). Afferent regulation of locus coeruleus neurons: Anatomy, physiology and pharmacology. Progress in Brain Research. 88, 44-75.
- Audi, E. A. & Graeff, F. G. (1984). Benzodiazepine receptors in the periaqueductal grey mediate anti-aversive drug action. European Journal of Pharmacology. 103, 279-285.
- Axelrod, J. (1970). Amphetamine: Metabolism physiological disposition and its effects on catecholamine storage. In E. Costa and S. Garattini (Eds.), Amphetamine and Related Compounds. (pp. 207-216). New York: Raven Press.
- Azami, J., Wright, D. M. & Roberts, M. H. T. (1981). Effects of morphine and naloxone on the response to noxious stimulation of neurons in the nucleus reticularis paraventricularis. Neuropharmacology. 20, 869-876.
- Baekeland, F. & Lasky, R. (1966). Exercise and sleep patterns in college athletes. Perceptual and Motor Skills. 23, 1203-1207.
- Bandler, R. & Carrive, P. (1988). Integrated defence reaction elicited by excitatory amino acid injection in the midbrain periaqueductal grey region of the unrestrained cat. Brain Research. 439, 95-106.
- Bandler, R., Carrive, P. & Depaulis, A. (1991b). Introduction: Emerging principles of organization of the midbrain periaqueductal gray matter. In A. Depaulis and R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter Functional, Anatomical, and Neurochemical Organization. (pp. 1-8). New York: Plenum Press.

- Bandler, R., Carrive, P. & Zhang, S. P. (1991a). Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotropic, somatotopic and functional organization. Progress Brain Research. 87, 269-305.
- Bandler, R. & Tork, I. (1987). Midbrain periaqueductal gray region in the cat has afferent and efferent connections with solitary tract nuclei. Neuroscience Letters. 74, 1-6.
- Baraban, J. M. & Aghajanian, G. K. (1981). Noradrenergic innervation of serotonergic neurons of the dorsal raphe: Demonstration by electron microscopic auto-radiography. Brain Research. 204, 1-11.
- Basbaum, A. I. & Fields, H. L. (1978). Endogenous pain control mechanisms: Review and hypothesis. Annals of Neurology. 4, 451-462.
- Basbaum, A. I. & Fields, H. L. (1984). Endogenous pain control systems, brainstem spinal pathways and endorphin circuitry. Annals of Neuroscience. 7, 309-338.
- Baskin, D. S., Mehler, W. R., Hosobuchi, Y., Richardson, D. E., Adams, J. E. & Flitter, M. A. (1986). Autopsy analysis of the safety, efficacy and cartography of electrical stimulation of the central gray in humans. Brain Research. 371, 231-236.
- Baxter, D. W. & Olszewski, J. (1955). Respiratory responses evoked by electrical stimulation of pons and mesencephalon. Journal of Neurophysiology. 18, 276-287.
- Beck, M. L. & Finkelstein, J. A. (1982). Efferent connections of the lateral hypothalamic area of the rat: an autoradiographic investigation. Brain Research Bulletin. 8, 511-526.
- Beitz, A. J. (1982). The organization of afferent Projections to the midbrain periaqueductal gray of the Rat. Neuroscience. 7, 133-159.
- Beitz, A. J. (1985). The midbrain periaqueductal gray in the rat. I. Nuclear volume, cell number, density, orientation, and regional subdivisions. Journal of Comparative Neurology. 237, 445-459.
- Beitz, A. J. & Finkelstein, J. A. (1982). Efferent connections of the lateral hypothalamic area of the rat: An autoradiographic investigation. Brain Research

Bulletin. 8, 511-526.

- Beitz, A. J. & Shepard, R. D. (1985). The midbrain periaqueductal gray in the rat. II. A Golgi analysis. Journal of Comparative Neurology. 237, 460-475.
- Berger, R. & Oswald, I. (1962). Effects of sleep deprivation on behavior, subsequent sleep and dreaming. Journal of Mental Science. 108, 457-465.
- Blanchard, J. R. & Blanchard, D. C. (1981). The organization and modelling of animal aggression. In Brain P. F. & D. Benton (Eds), The biology of aggression. (pp. 529-562). The Netherlands: Sijthoff & Aalphen aan den Rijn.
- Bläsigg, J., Beinhold, K. & Herz, A. (1973). Effects of 6-hydroxydopamine, 5,6-dihydroxytryptamine raphe lesions on the antinociceptive actions of morphine in rats. Psychopharmacologia. 31, 111-119.
- Bloch, V., Hennevin, E. & Leconte, P. (1977). Interaction between post-trial reticular stimulation and subsequent paradoxical sleep in memory consolidation processes. In R. Drucker-Colin and McGaugh (Eds.), Neurobiology of Sleep and Memory. (pp. 255-272). New York: Academic Press.
- Bodnar, R. J., Ellman, S. J., Coons, E. E., Ackermann, & Steiner, S. S. (1979). Differential locus coeruleus and hypothalamic self-stimulation interaction. Physiological Psychology. 7, 269-277.
- Bodnar, R. J., Ellman S. J., Steiner, S. S. Ackermann, R. F. & Coons E. E. (1981). Intracranial self-stimulation: Temporal interaction among mesencephalic and diencephalic sites. Physiology and Behavior. 28, 473-482.
- Bodnar, R. J., Steiner, S. S., Healey, J. M., Halperin, J. & Ellman S. J. (1978). Monophasic pulse pair analysis of Intracranial self-stimulation loci. Physiology and Behavior. 6(2), 170-178.
- Bower, G. H. & Miller, N. E. (1958). Rewarding and punishing effects from stimulating the same place in the rat's brain. Journal of Comparative and Physiological Psychology. 51, 669-674.
- Bowker, R. M. & Morrison, A. R. (1976). The startle reflex and PGO spikes. Brain Research. 102, 185-190.

- Boyar, R. M., Rosenfeld, R. S., Finkelstein, J. W., Kapen, S. Roffwarg, H. P., Weitzman, E. D. & Hellman, L. (1975). Ontogeny of luteinizing hormone and testosterone secretion. Journal of Steroid Biochemistry. 6, 803-808.
- Bozarth, M. A. & Wise, R. A. (1981a). Intracranial self-administration of morphine into the ventral tegmental area in the rat. Life Science. 28, 551-555.
- Bozarth, M. A. & Wise, R. A. (1981b). Heroin reward is dependent on a dopaminergic substrate. Life Science. 29, 1881-1886.
- Bozarth, M. A. & Wise, R. A. (1982). Dissociation of the rewarding and physical dependence-producing properties of morphine. In L. S. Harris (Ed.), Problems of Drug Dependence. National Institutes of Drug Abuse Research Monograph 43. DHEW PUB. No. (ADM) 83-1264. (pp. 171-177). Washington, D.C.: Supplement of Documents, U. S. Government Printing Office.
- Bozarth, M. A. & Wise, R. A. (1983). Neural substrates of opiate reinforcement. Progress in Neuropharmacology and Biological Psychiatry. 7, 569-575.
- Bozarth, M. A. & Wise, R. A. (1984). Anatomically distinct opiate receptor fields mediate reward and physical dependence. Science. 244, 516-517.
- Brebbia, D. R. & Altshuler, K. Z. (1968). Stage-related patterns and nightly trends of energy exchange during sleep. In N. S. Kline and E. Laska (Eds.), Computers and Electronic Devices in Psychiatry. (pp. 319-325). New York: Grune-Stratton.
- Breese, G. R. & Cooper, B. R. (1975a). Relationship of dopamine neural systems to the maintenance of self-stimulation. In (Eds.), E. F. Domino and J. M. Davis, Neurotransmitter Balances Regulating Behavior. (pp. 37-56). Ann Arbor.
- Breese, G. R. & Cooper, B. R. (1975b). Behavioral and biochemical interactions of 5,7-dihydroxytryptamine with various drugs when administered intracisternally to adult and developing rats. Brain Research. 93, 517-527.
- Britt, M. D. & Wise, R. A. (1981). Opiate rewarding action: Independence of the cells of the lateral hypothalamus. Brain Research. 222, 213-217.

- Britt, M. D. & Wise, R. A. (1983). Ventral tegmental site of opiate reward: Antagonism by a hydrophilic opiate receptor blocker. Brain Research. 258, 105-108.
- Brooks, D. C. (1968). Waves associated with eye movement in the awake and sleeping cat. Electroencephalography and Clinical Neurophysiology. 24, 532-541.
- Brooks, D. C. & Gershon, M. D. (1971). Eye movement potentials in the oculomotor and visual systems of the cat: A comparison of reserpine-induced waves with those present during wakefulness and rapid eye movement sleep. Brain Research. 27, 223-239.
- Brooks, D. C. & Gershon, M. D. (1972). An analysis of the effect of reserpine upon ponto-geniculo-occipital wave activity in the cat. Neuropharmacology. 11, 499-510.
- Brooks, D. C., Gershon, M. D. & Simon, R. P. (1972). Brain serotonin depletion and ponto-geniculo-occipital wave activity in the cat treated with reserpine. Neuropharmacology. 11, 511-520.
- Buchsbaum, M. S., Gillin, J. C., Wu, J., Hazlett, E., Sicotte, N., Dupont, R. M. & Bunney, W. E. Jr. (1989). Regional cerebral glucose metabolic rate in human sleep assessed by positron emission topography. Life Science. 45, 1349-1356.
- Cannon J., Prieto G., Lee A. & Liebeskind J. (1982). Evidence for opioid and non-opioid forms of stimulation-produced analgesia in the rat. Brain Research. 243, 315-321.
- Carlson, A. (1970). Amphetamine and brain catecholamine. In E. Costa and S. Garattini (Eds.), Amphetamine and Related Compounds. (pp. 289-300). New York: Raven Press.
- Carrive, P. (1991). Functional organization of PAG neurons controlling regional vascular beds. In A. Depaulis and R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter Functional, Anatomical, and Neurochemical Organization. (pp. 67-100). New York: Plenum Press.
- Carrive, P. & Bandler, R. (1991). Viscerotopic organization of neurones subserving hypotensive reactions within the midbrain periaqueductal grey: A correlative functional and anatomical study. Brain Research. 541, 206-215.

- Carrive, P., Dampney, R. A. L. & Bandler, R. (1987).
Excitation of neurons in a restricted portion of the midbrain periaqueductal gray elicited both behavioral and cardiovascular components of the defense reaction in the unanesthetized decerebrate cat. Neuroscience Letters. 81, 273-278.
- Carrive, P., Dampney, R. A. L. & Bandler, R. (1988).
Anatomical evidence that hypertension associated with the defense reaction in the cat is mediated by a direct projection from a restricted portion of the midbrain periaqueductal gray to the subretrofacial portion of the medulla. Brain Research. 460, 339-345.
- Carrive, P., Dampney, R. A. L. & Bandler, R. (1989a).
Somatic and autonomic integration in the midbrain of the unanesthetized decerebrate cat: A distinctive pattern evoked by excitation of neurons in the subtentorial portion of the midbrain periaqueductal gray. Brain Research. 483, 251-258.
- Carrive, P., Dampney, R. A. L. & Bandler, R. (1989b).
Viscerotopic control of regional vascular beds by discrete groups of neurons within the midbrain periaqueductal gray. Brain Research. 493, 385-390.
- Carstens, C. J. D., MacKinnon, & Guinan, M. J. (1982).
Inhibition of spinal dorsal horn neuronal responses to noxious skin heating by medial preoptic and septal stimulation in the cat. Journal of Neurophysiology. 46, 981-991.
- Cespuglio, R., Faradji, H., Gomez, M. E. & Jouvet, M. (1981).
Single unit recordings in the nuclei raphe dorsalis and magnus during the sleep-waking cycle of semi-chronic prepared cats. Neuroscience Letters. 24, 133-138.
- Chi, C. C. & Flynn, J. P. (1971).
Neuroanatomical projections related to biting attack elicited from hypothalamus in cats. Brain Research. 35, 49-66.
- Chiba, C. & Murata Y. (1985).
Afferent and efferent connections of the medial preoptic area in the rat: A WGA-HRP study. Brain Research Bulletin. 14, 261-272.
- Ciriello, J., Caverson, M. M. & Calaresu, F. R. (1986).
Function of the ventrolateral medulla in the control of circulation. Brain Research. 11, 359-391.

- Clavier, R. M. & Routtenberg, A. (1974). Ascending monoamine-containing fiber pathways related to intracranial self-stimulation: histochemical fluorescence study. Brain Research. 72, 25-40.
- Clemens, L. G. & Gladue, B. A. (1979). Neuroendocrine control of adult sexual behavior. In D. M. Schneider (Ed.), Reviews of Neuroscience 4. (pp. 73-103). New York: Raven Press.
- Clement H. W., Gamsa, D. & Wesemann, W. (1991). Serotonin-norepinephrine interactions: Voltammetric study on the effect of serotonin receptor stimulation followed in the N. raphe dorsalis and locus coeruleus of the rat. Journal of Neural Transmission. 88, 11-23.
- Cohen, M. I. (1979). Neurogenesis of respiratory rhythm in the mammal. Physiological Review. 59, 1105-1173.
- Cohen, S. R. & Melzack, R. (1985). Electrical stimulation of the habenula reduces tonic pain in the formalin test. Neuroscience Abstract. 11, 639.
- Conrad, L. C. A. & Pfaff, D. W. (1976). Effects from medial basal forebrain and hypothalamus in the rat.-1. An autoradiographic study of the medial preoptic area. Journal of Comparative Neurology. 169, 185-220.
- Coons, E. E., Smith, N. & Ungerleider, L. G. (1976). Uses of double pulse stimulation behaviorally to infer refractoriness, summation convergence and transmitter characteristics of hypothalamic reward systems. Journal of Comparative and Physiological Psychology. 90, 317-342.
- Cooper, B. R., Black, W. C. & Paolino, R. M. (1971). Decreased septal-forebrain and lateral hypothalamic reward after alpha methyl-p-tyrosine. Physiology and Behavior. 6, 425-429.
- Cooper, B. R., Cott, J. M. & Breese, G. R. (1974). Effects of catecholamine depleting drugs and amphetamine on self-stimulation of brain following various 6-hydroxydopamine treatments. Psychopharmacologia. 37(3), 235-248.
- Cooper, R. M. & Taylor, L. H. (1967). Thalamic reticular system and central gray: Self-stimulation. Science. 156, 102-103.
- Crow, T. J. (1970). Enhancement by cocaine of intra-cranial self-stimulation in the rat. Life Science. 9, 375-381.

- Crow, T. J. (1972). A map of the rat mesencephalon for electrical self-stimulation. Brain Research. 36, 265-273.
- Crow, T. J., Spear, P. J. & Arbuthnott, G. W. (1972). Intracranial self-stimulation with electrodes in the region of the locus coeruleus. Brain Research. 36, 275-287.
- Dampney, R. A. L. & Moon, E. A. (1980). Role of ventrolateral medulla in vasomotor response to cerebral ischemia. American Journal of Physiology. 239, H349-348.
- Day, T. A., Willoughby, J. O. & Geffen, L. B. (1979). Thermoregulatory effects of preoptic area injections of noradrenaline in restrained and unrestrained rats. Brain Research. 174, 175-179.
- DeGroot, J. (1959). The rat forebrain in stereotaxic coordinates. Verhandelingen der Koninklijke Nederlandse Akademie van Wetenschappen Afdeling Natuurkunde. 2, 1-40.
- Delorme, F., Froment, J. L. & Jouvet, M. (1966). Suppression du sommeil par la parachlorophenylalanine. Comptes Rendus de Sances de la Societe de Biologie (Paris). 160, 2347-2350.
- Dement, W. & Kleitman, N. (1957). Cyclic variation in EEG during sleep and their relation to eye movements, body motility and dreaming. Electroencephalography and Clinical Neurophysiology. 9, 673-690.
- Dement, W. C. & Kleitman, N. (1957). The relation of eye movement during sleep to dream activity: an objective method for the study of dreaming. Journal of Experimental Psychology. 53, 339-346.
- Dennis, B. & Meller, S. (1993). Investigations on the periaqueductal gray (PAG) of the rabbit: With consideration of experimental procedures and functional roles of the PAG. Progress in Neurobiology. 41, 403-434.
- Dennis, S. G., Choinière, M. & Melzack, R. (1980). Stimulation-produced analgesia in rats: Assessment by two pain tests and correlation with self-stimulation. Experimental Neurology. 68, 295-309.
- Depaulis, A., Keay, K. A. & Bandler, R. (1992). Longitudinal neuronal organization of defensive reactions in the midbrain periaqueductal gray region of the rat. Experimental Brain Research. 90, 307-318.

- Deutsch, J. A. (1964). Behavioral measurement of the neural refractory period and its application to intracranial self-stimulation. Journal of Comparative and Psychological Psychology. 58. 1-9.
- deWit, H. & Wise, R. A. (1977). Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide but not with the noradrenergic blockers phentolamine or phenoxybenzamine. Canadian Journal of Psychology. 31, 195-203.
- Drucker-Colin, R. (1979). Protein molecules and the regulation of REM sleep: Possible implications for function. In R. Drucker-Colin, M. Shkurovich and M. B. Stermann (Eds.), The Functions of Sleep. (pp. 99-112). New York: Academic Press.
- Dujardin, K., Guerrien, A. & Leconte, P. (1989). Sleep brain activation and cognition. Physiology and Behavior. 47, 1271-1278.
- Durie, D. J. B., Adam, K., Oswald, I. Flynn, I. W. (1978). Sleep: Cellular energy change and protein synthetic capability. IRCS Medical Science. 6, 351.
- Ekstrand, B. R., Barrett, T. R., West, J. N. & Mair, W. G. (1977). The effects of sleep on human long-term memory. In R. Drucker-Colin and McGaugh (Eds.), Neurobiology of Sleep and Memory. (pp. 419-438). New York: Academic Press.
- Ellman, S. J. Arkermann, R. F., Bodnar, R. J., Jackler, F. & Steiner, S. S. (1975). Comparison of behavior elicited by electrical brain stimulation in dorsal brain-stem and hypothalamus of rats. Journal of Comparative and Physiological Psychology. 88, 816-828.
- Ellman, S. J. Arkermann, R. F., Bodnar, R. J., Jackler, F. & Steiner, S. S. (1976). D- and L-Amphetamine differentially mediates self-stimulation in the rat dorsal midbrain area. Physiology and Behavior. 16, 1-7.
- Ellman, S. J. Arkermann, R. F., Farber, J. Mattiace, L. & Steiner, S. S. (1974). Relationship between dorsal brain stem sleep sites and intracranial self-stimulation. Physiological Psychology. 2, 31-34.
- Ennis, M., Shipley, M. T., Behbehani, E, J., Van Bockstaele, E. & J., Aston-Jones, G. (1991). Projections from the periaqueductal gray to nucleus locus coeruleus and pericoerulear region: Anatomic and physiologic studies. Journal of Comparative Neurology. 306, 480-494.

- Enoch, D. M. & Kerr, F. W. L. (1967). Hypothalamic vasopressor and vesicopressor pathway. II Anatomic study of their course and connections. Achieves of Neurology. 16, 307-320.
- Evarts, E. V. (1962). Activity of neurons in visual cortex of the cat during sleep with low voltage fast EEG activity. Journal Neurophysiology. 25, 812-816.
- Evarts, E. V. (1964). Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey activity. Journal Neurophysiology. 27, 152-171.
- Fanselow, M. (1991). The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety. In A. Depaulis & R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter: Functional, Anatomical and Neurochemical Organization. (pp. 151-174). New York: Plenum Press.
- Farber, J., Ellman, S. J., Mattiace, L. A., Holtzman, I., Ippolito, P., Halperin R. & Steiner, S. S. (1976). Differential effects of unilateral dorsal hindbrain lesions on hypothalamic self-stimulation and sleep in rats. Brain Research. 112, 148-155.
- Farber, J., Marks, G. A. & Roffwarg, H. P. (1980). Rapid eye movement sleep PGO-type waves are present in the dorsal pons of the albino rat. Science. 206, 615-617.
- Fardin, V., Olivéras, J. L. & Besson, J. M. (1981). Effects moteurs et aversifs induits par la stimulation électrique de la substance grise périaqueducule chez le rat. Comptes Rendus de Sances de la Societe de Biologie (Paris). 292, 649-652.
- Fardin, V., Olivéras, J. L. & Besson, J. M. (1984b). A reinvestigation of the analgesic effects induced by stimulation of the periaqueductal gray matter in the rat. II. Differential characteristics of analgesia induced by ventral and dorsal PAG stimulation. Brain Research. 306, 125-139.
- Fardin, V., Olivéras, J. L. & Besson, J. M. (1984a). A reinvestigation of the analgesic effects induced by stimulation of the periaqueductal gray matter in the rat. I. The production of behavioral side effects together with analgesia. Brain Research. 306, 105-123.

- Feldman, J. L. (1986). Neurophysiology of breathing in mammals. In F. E. Bloom (Ed.), Handbook of Physiology, Section I: The nervous System, Vol. 4, Intrinsic Regulatory Systems of the Brain. (pp. 463-524). Bethesda, Md.: American Physiological Society.
- Fibiger, H. C. (1978). Drugs and reinforcement Mechanisms: A critical review of the catecholamine theory. Annual Review of Pharmacology and Toxicology. 18, 37-56.
- Feinberg, I. (1968). The ontogenesis of human sleep and the relationship of sleep variables to intellectual function in the aged. Comprehensive Psychiatry. 9, 138-147.
- Fields, H. L. & Heinricher, M. M. (1985). Anatomy and physiology of a nociceptive modulatory system. Philosophical Transactions of the Royal Society of London Series B, Biological Sciences. 308, 361-381.
- Fishbein, W. (1971). Disruptive effects rapid eye movement sleep deprivation on long-term memory. Physiology and Behavior. 6, 279-282.
- Fishman, R. & Roffwarg, H. P. (1972). REM sleep inhabited by light in the albino rat. Experimental Neurology. 36, 166-178.
- Foote, S. L., Bloom, F. E. & Aston-Jones, G. (1983). Nucleus locus coeruleus: New evidence of anatomical and physiological specificity. Physiological Reviews. 63, 844-914.
- Foote, S. L., Aston-Jones, G. & Bloom, F. E. (1980). Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proceedings of the National Academy of Science USA. 77, 3033-3037.
- Fort, P., Luppi, P.-H., Sakai, K., Salvert, D. & Jouvet, M. (1990). Nuclei of origin of monoaminergic, peptidergic, and cholinergic afferents to the cat trigeminal motor nucleus: A double-labeling study with cholera-toxin as a retrograde tracer. Journal of Comparative Neurology. 301, 262-275.
- Franzini, C., Cianci, T., Lenzi, P., Libert, J. P., Horne, J. A. & Parmeggiani, P. L. (1986). Influence of brown adipose tissue on deep cervical temperature during sleep in the young rabbit. Experientia. 42, 604-606.

- Frysinger, R. C. & Harper, R. M. (1986). Cardiac and respiratory relationships with neural discharge in the anterior cingulate cortex during sleep-waking states. Experimental Neurology. 94, 247-263.
- Frysinger, R. C., Zhang, J. & Harper, R. M. (1988). Cardiovascular and respiratory relationship with neuronal discharge in the central nucleus of the amygdala during sleep-waking states. Sleep. 11, 317-332.
- Gardner, R. Jr., & Grossman, W. I. (1975). Normal motor patterns in sleep in man. In E. D. Weitzman (Ed.), Advances in sleep research. (Vol. 2, pp.67-107). New York: Spectrum Publications.
- Gassel, M. M., Marchiafava, P. L. & Pompeiano, O. (1964). Tonic and phasic inhibition of spinal reflexes during deep, desynchronized sleep in unrestrained cats. Archives of Italian Biology. 102, 471-499.
- German, D. C. & Bowden, D. M. (1974). Catecholamine systems as the neural substrate for intracranial self-stimulation: A hypothesis. Brain Research. 73, 381-419.
- Giesler, G. Jr. & Liebeskind, J. C. (1976). Inhibition of visceral pain by electrical stimulation of the periaqueductal gray matter. Pain. 2, 43-48.
- Gioia, M. Bianchi, R. & Tredict, G. (1984). Cytoarchitecture of the periaqueductal gray matter in the cat: A quantitative Nissl study. Acta Anatomy. 119, 113-117.
- Gioia, M., Tredict, G. & Bianchi, R. (1985). A Golgi study of the periaqueductal gray matter in the cat. neuronal types and their distribution. Experimental Brain Research. 58, 318-332.
- Glickman, S. E. (1960). Reinforcing properties of arousal. Journal of Comparative Physiological Psychology. 53, 68-71.
- Glimcher, P. D., Giovino, A. A. & Hoebel, B. G. (1983). Self-injection of neurotensin into the ventral tegmental area (VTA). Society of Neuroscience Abstract. 9, 120.
- Göthert, M., Huth, H. & Schlicker, E. (1981). Characterization of the receptor subtype involved in alpha-adrenoceptor mediated modulation of serotonin release from rat brain cortex slices. Naunyn-Schmiedeberg's Archive of Pharmacology. 317, 199-203.

- Gottesmann, C. A. (1969). Etude sur les activites elctrophysiologique phasiques chez le rat. Physiology and Behavior. 4, 295-304.
- Greenberg, J. H. (1980). Sleep and the cerebral circulation. In J. Orem, and C. D. Barnes (Eds.), Physiology in sleep (Vol. 3, pp. 57-95). New York: Academic Press.
- Guilbaud, G., Besson, J. M., Liesbeskind, J. C. & Olivèras, J. L. (1972). Analgésie induite par stimulation de la substance grise péraqueducale chez le chat: Données comporte mentales et modifications de l'activité des interneurons de la conre dorsale de la mœlle. Compotes Rendus de Sences de la Societe de Biologie (Paris). 275, 1055-1057.
- Hamilton, B. L. (1973). Cytoarchitectural subdivisions of the periaqueductal gray matter in the cat. Journal of Comparative Neurology. 149, 1-28
- Hamilton, B. L. (1974). Projections of the nuclei of the periaqueductal gray matter in the cat. Journal of Comparative Neurology. 152, 45-48.
- Hardy, S. G. P. & Leichnetz, G. R. (1981a). Cortical projections to the periaqueductal gray in the monkey: a retrograde and orthograde horseradish peroxidase study. Neuroscience Letter. 22, 97-101.
- Hardy, S. G. P. & Leichnetz, G. R. (1981b). Frontal cortical projections to the periaqueductal gray in the rat: a retrograde and orthograde horseradish peroxidase study. Neuroscience Letter. 23, 13-17.
- Harper, R. M., Ni, H. & Zhang, J. (1991). Discharge relationships of periaqueductal gray neurons of cardiac and respiratory patterns during sleep and waking. In A. Depaulis and R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter Functional, Anatomical, and Neurochemical Organization. (pp. 41-55). New York: Plenum Press.
- Heikkila, R. E., Orlansky, H. & Cohen, G. (1975). Studies on the distinction between uptake inhibition and release of (3H) dopamine in rat brain tissue slices. Biochemistry and Pharmacology. 24, 847-852.
- Herkenham, M. & Nauta, W. J. H. (1979). Efferent connections of the habenular nuclei in the rat. Journal of Comparative Neurology. 187, 19-48.

- Herrero, M. T., Insausti, R & Gonzalo, L. M. (1991). Cortically projecting cells in the periaqueductal gray matter of the rat. A retrograde fluorescent tracer study. Brain Research. 543, 201-212.
- Holstege, G. (1989). Anatomical study of the final common pathway for vocalization in the cat. Journal of Comparative Neurology. 284, 242-252.
- Holstege, G., Meiners, L. & Tan, K. (1985). Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat. Experimental Brain Research. 32, 529-547.
- Hopkins, A. & Holstege, G. (1978). Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. Experimental Brain Research. 32, 529-547.
- Hosoya, T. & Matsushita, M. (1981). Brainstem projections from the lateral hypothalamic area in the rat, as studied with autoradiography. Neuroscience Letters. 24(2), 111-116.
- Huang, Y. H. & Routtenberg, A. (1971). Lateral hypothalamus self-stimulation pathways in *Rattus norvegicus*. Physiology and Behavior. 7, 419-432.
- Jackler, F., Steiner, S. S., Bodnar, J. R., Ackermann R. F. & Ellman, S. J. (1979). Morphine and intracranial self-stimulation in the hypothalamus and dorsal hindbrain: differential effects of dose, time and site. International Journal of Neuroscience. 9(1), 21-35.
- Jacobs, B. L. (1986). Single unit activity of locus coeruleus neurons in behaving animals. Progress in Neurobiology. 27, 183-194.
- Jacobs, B. L. & Azmitia, E. C. (1992). Structure and function of the brain serotonin system. Physiological Reviews. 72, 165-229.
- Jacobs, B. L., Asher, R. & Dement, W. C. (1973). Electrophysiological and behavioral effects of electrical stimulation on the raphe nuclei in the cat. Physiology and Behavior. 11, 489-495.
- Jacobs, B. L., Henriksen, S. J. & Dement, W. C. (1972). Neurochemical basis of the PGO wave. Brain Research. 48, 406-411.

- Jacobson, C. S., Terkel, J., Gorski., R. R. & Sawyer, C. H. (1980). Effects of small medial preoptic area lesions on maternal behavior: Retrieval and nest building in the rat. Brain Research. 194, 471-478.
- Jacobson, A., Kales, A., Lehmann, D. & Hoedemaker, F. S. (1964). Muscle tonus in human subjects during sleep and dreaming. Experimental Neurology. 10, 418-424.
- Jones, B., Bobillier, P. & Jouvet, M. (1969). Effects de la destruction des neurones contenant des catecholamines du mesencephale sur le cycle veille-sommeil. Compotes Rendus de Seances de la Societe de Biologie (Paris). 163, 176-180.
- Jones, B. E., Harper, S. T. & Halaris, A. E. (1977). Effects of locus coeruleus lesions upon cerebral monoamine content, sleep wakefulness states and the response to amphetamine in the cat. Brain Research. 124, 473-496.
- Jouvet, M. (1961). Telencephalic and rhombencephalic sleep in the cat. In G. E. W. Wolstenholme and M. O'Connor (Eds.), The nature of sleep (A Ciba Symposium). (pp. 188-208). London: Churchill.
- Jouvet, M. (1967a). Mechanism of the states of sleep: A neuropharmacological approach. In S. S. Kety, E. V. Everts and H. L. Williams (Eds.), Sleep and Altered States of Consciousness. (pp. 86-126). Baltimore: Williams & Williams.
- Jouvet, M. (1967b). Neurophysiology of the states of sleep. Physiological Review. 47, 117-177.
- Jouvet, M. (1969). Biogenic amines and states of sleep. Science. 16, 32-41.
- Jouvet, M. (1972). The role of monoamines and acetylcholine-containing neurons in the regulation of sleep-waking cycle. Ergebnisse der Physiologie. 64, 166-307.
- Jouvet, M. (1973). Telencephalic and rhombencephalic sleep in cats. In W. B. Webb (Eds.), Sleep and Active Process. (pp. 12-32). Glenview, IL.: Scott, Foresmen.
- Jouvet, M. & Delorme, F. (1965). Locus coeruleus et sommeil paradoxal. Compotes Rendus de Seances de la Societe de Biologie. (Paris). 259, 895-899.

- Jouvet, M. & Renault, J. (1966). Insomnie peristante apres lesions des noyaux du raphe chez le chat. Compotes Rendus de Sences de la Societe de Biologie (Paris). 160, 1461-1465.
- Kaada, B. (1972). Stimulation and regional ablation of the amygdaloid complex with reference to functional representations. In B. E. Eleftheriou (Ed.), The Neurobiology of the Amygdala. (pp. 145-204). New York: Plenum Press.
- Kaufman, L. S. & Morrison, A. R. (1981). Spontaneous and elicited PGO spikes in the rat. Brain Research. 214, 61-72.
- Kawamura, H. & Sawyer, C. H. (1965). Elevation in brain temperature during paradoxical sleep. Science. 150, 912.
- Kawamura, H., Whitmeyer, D. I., Sawyer, C. H. (1966). Temperature changes in the rabbit brain during paradoxical sleep. Electroencephalography and Clinical Neurophysiology. 21, 469-477.
- Kayama, Y., Ohta, M. & Jobo, E. (1992). Firing of 'possibly' cholinergic neurons in the rat laterodorsal tegmental nucleus during sleep and wakefulness. Brain Research. 210-220.
- Keene, J. J. & Casey, K. L. (1970). Excitatory connection from lateral hypothalamic self-stimulation sites to escape sites in medullary reticular formation. Experimental Neurology. 28, 155-166.
- Keene, J. J. & Figueroa, A. L. (1977). Motivating, arousing, and analgesic effects of central gray stimulation. Behavioral Biology. 19, 527-533.
- Kluver, H., & Barrera, E. A. (1953). A method for combined staining of cells and fibers in the nervous system. Journal of Neuropathology and Experimental Neurology. 12, 400-403.
- Kostowski, W., Giacalone, E., Garattini, S. & Valzelli, L. (1968). Studies on behavioral and biochemical changes in rats after lesion and midbrain raphe. European Journal Pharmacology. 4, 371-377.
- Krieger, M. S., Conrad, L. C. A., & Pfaff, D. W. (1979). An autoradiographic study of the efferent connections of the ventromedial nucleus of the hypothalamus. Journal of Comparative Neurology. 183, 785-816.

- Kucera, P., Favrod, P. (1979). Suprachiasmatic nucleus projections to mesencephalic grey in the woodmouse (*Apodemus sylvaticus* L.). Neuroscience. 4, 1705-1715.
- Laurent, J. & Guerrero, F. A. (1975). Reversible suppression of ponto-geniculo-occipital waves by localized cooling during paradoxical sleep in cats. Experimental Neurology. 49, 356-349.
- Lenzi, P., Cianci, T., Guidalotti, P. L., Leonardi, G. S., Franzini, C. (1987). Brain circulation during sleep and its relation extracerebral hemodynamics. Brain Research. 415, 14-20.
- Leger, L. & Descarries, L. (1978). Serotonin nerve terminals in the locus coeruleus of the adult rat: A radioautographic study. Brain Research. 145, 1-13.
- Lidbrink, P. (1974). The effects of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Brain Research. 74, 19-40.
- Liebeskind, J. C., Guilbaud, G., Besson, J. M. & Oliv  ras, J. L. (1973). Analgesia from electrical stimulation of the periaqueductal gray matter in the cat: behavioral observations and inhibitory effects on spinal cord interneurons. Brain Research. 50, 441-446.
- Liebman, J. M. & Butcher, L. L. (1973). Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanism. Naunyn-Schmiedeberg's Archives of Pharmacology. 277, 305-318.
- Liebman, J. M., Mayer, D, J. & Liebeskind, J. C. (1973). Self-stimulation loci in the midbrain central gray matter of the rat. Behavioral Biology. 9, 299-306.
- Lippa, A. S., Antelman, S. M., Fisher, A. E. & Canfield, D. Neurochemical mediation of reward: A significant role for dopamine. Pharmacology, Biochemistry and Behavior. 1(1), 23-28.
- Liu, R. P. C. (1983). Laminar origin of spinal projection neurons to the periaqueductal gray of the rat. Brain Research. 264, 118-122.
- Locick, T. A. (1988). Convergent afferent inputs to nucleus paraventricularis lateralis in the cat. Brain Research. 456, 483-487.

- Luebke, J. I., Greene, R. W., Semba, K., Kamondi, A., McCarley, R. W. & Reiner, P. B. (1992). Serotonin hyperpolarizes cholinergic low-threshold burst neurons in the rat laterodorsal tegmental nucleus in vitro. Proceedings of the National Academy of Science. USA. 89(2), 743-747.
- Lydic, R., McCarley, R. W. & Hobson, J. A. (1987a). Serotonin neurons and sleep I. Long-term recording of dorsal raphe discharge frequency and PGO waves. Archive of Italian Biology. 125, 317-343.
- Lydic, R., McCarley, R. W. & Hobson, J. A. (1987b). Serotonin neurons and sleep II. Time course of dorsal raphe discharge PGO waves, and behavioral states. Archive of Italian Biology. 126, 1-28.
- Maciewicz, R. & Phipps, B. S. (1983). The oculomotor internuclear pathway: A double retrograde labeling study. Brain Research. 262, 1-8.
- Maciewicz, R., Kaneko, C. R. S., Highstein, S. M. & Baker, R. (1975). Morphophysiological identification of interneurons in the oculomotor nucleus that project to the abducens nucleus in the cat. Brain Research. 96(1), 60-65.
- MacFayden, U. M., Oswald, I. & Lewis, S. A. (1973). Starvation and human slow-wave sleep. Journal of Applied Physiology. 35, 391-394.
- Mancia, G., Baccelli, G., Adams, D. B. & Zanchetti, A. (1971). Vasomotor regulation during sleep in the cat. American Journal of Physiology. 220, 1086-1093.
- Manier, D. H., Gillespie, D. D., Sanders-Bush, E. & Sulser, F. (1987). The serotonin/norepinephrine-link in brain I. The role of norepinephrine and serotonin in the regulation of density and function of beta adrenoceptors and its alteration by desipramine. Naunyn-Schmiedeberg's Archive of Pharmacology. 335, 109-114.
- Mantyh, P. W. (1982). The midbrain periaqueductal gray in the rat, cat and monkey: A Nissl, Weil and Golgi analysis. Journal of Comparative Neurology. 204, 349-363.
- Margalit, D. & Segal, M. (1979). Pharmacologic study of analgesia produced by stimulation of the nucleus locus coeruleus. Psychopharmacology. 62, 169. (Abstract).

- Margules, D. L. (1969). Noradrenergic rather than serotonergic basis of reward in the dorsal tegmentum. Journal of Comparative and Physiological Psychology. 67, 32-35.
- Markgraf, C. G., Liskowsky, D. R., McCabe, P. M., Winters, R. W. & Schneiderman, N. (1988). Cardiorespiratory, plasma catecholamine and behavioral responses from stimulation of the periaqueductal gray region in the rabbit. Society of Neuroscience Abstract. 14, 446.
- Marks, G., Farber, J. & Roffwarg, H. P. (1980). The demonstration of ponto-geniculo-occipital waves in the albino rat. Experimental Neurology. 69, 667-677.
- Marti-Nicolovius, M., Portell-Cortes, I. & Morgado-Bernal, I. (1983). Intracranial self-stimulation after paradoxical sleep deprivation induced by the platform method in rats. Physiology and Behavior. 33, 165-167.
- May, P. J., Baker, H., Vidal, P.-P., Spencer, R. F. & Baker, R. (1987). Morphology and distribution of serotonergic and oculomotor internuclear neurons in the cat midbrain. Journal of Comparative Neurology. 266, 150-170.
- Mayer, D. & Liebskind, J. C. (1974). Pain relief by focal electrical stimulation of the brain: An anatomical and behavioral analysis. Brain Research. 68, 73-93.
- Mayer, D. J., Wolfle, T. L., Akil, H., Carder, B. & Liebeskind, J. C. (1971). Analgesia from electrical stimulation in the midbrain of the rat. Science. 174, 1351-1354.
- McAllen, R. M., Neil, J. J. & Loewy, A. D. (1982). Effects of kainic acid applied to the ventral surface of the medulla oblongata on vasomotor tone, the baroreceptor reflex and hypothalamic autonomic responses. Brain Research. 238, 65-76.
- McGaugh, J. L. Gold, P. E., Van Buskirk, R. B. & Haycock, J. W. (1975). Modulating influences of hormones and catecholamines on memory storage processes. In W. H. Gispen, T. B. van Wimersma-Greidanus, B. Bohus, and D. de Wied (Eds.), Hormones, Homeostasis and the Brain. (pp. 151-162). Amsterdam: Elsevier.
- McGinty, D. J. & Harper, M. (1976). Dorsal raphe neurons: Depression of firing during sleep in cats. Brain Research. 101, 569-575.

- McGinty, D. & Szymusiak, R. (1990). Keeping cool: A hypothesis about the mechanisms and functions of slow-wave sleep. Physiology and Behavior. 7, 797-805.
- McRae-Degueurce, A., Gandolfo, G., Glin, L., & Gottesmann, C. (1988). Fetal serotonergic transplants in the fourth ventricle of adult rodents reverse sleep disturbances induced by neonatal administration of 5,7-dihydroxytryptamine. Neuroscience Letter. 89, 108-113.
- Melikov, E. M., Movsumov, G. D., Gambararova, R. Kh. & Bagirova, F. B. (1990). Funtional Interconnection between paradoxical sleep and selfstimulation reaction in rats. Journal of Higher Nervous Activity. 40(2), 383-385.
- Meller, S. T. & Dennis, B. J. (1983). Retrograde labelling of periaqueductal gray in the rabbit. In M. Rowe and W. D. Willis, Jr. (Eds.), Development, organization and processing in somatosensory pathways. International Union of Physiological Science XV. Satellite symposium.
- Meller, S. T. & Dennis, B. J. (1986). Afferent projections to the periaqueductal gray in the rabbit. Neuroscience. 19, 927-964.
- Meller, S. T. & Dennis, B. J. (1993). Efferent projections of the periaqueductal gray in the rabbit. Neuroscience. 40, 191-216.
- Meyer, J. S., Ishikawa, Y., Hata, T. & Karacan, I. (1987). Cerebral blood flow in normal and abnormal sleep and dreaming. Brain Cognition. 6, 266-294.
- Michel, F., Rechtschaffen, A. & Vimont-Vicary, P. (1964). activite e'lectrique des muscles oculaires extrinseques au cours du cycle veille-sommeil. Compotes Rendus De Seances de la Societe de Biologie. 164, 106-109.
- Millan, M. H., Czlonkow, A. & Herz, A. (1987). Evidence that μ -opioid receptors mediate midbrain "stimulation-produced analgesia" in the freely moving rat. Neuroscience. 22, 885-896.
- Millan, M. H., Millan, M. J. & Herz, A. (1986). Depletion of central β -endorphin blocks midbrain stimulation-produced analgesia in the rat. Neuroscience. 18, 641-649.
- Mizuno, N., Kanoski, A. & Sato, M. (1975). Localization of masticatory motoneurons in the cat and rat by means of retrograde axonal transport of horseradish peroxidase. Journal of Comparative Neurology. 164, 105-116.

- Moises, H. C. & Smith, C. B. (1985). Changes in central adrenergic receptor function may contribute to opiate dependence. Neuroscience Abstracts. 11, 1070.
- Morden, B. & Dement, M. G. (1967). Selective REM sleep deprivation and compensation phenomena in the rat. Brain Research. 5(3), 339-349.
- Morgan, M. M. & Liebeskind, J. C. (1987). Site specificity in the development of tolerance to stimulation-produced analgesia from the periaqueductal gray matter of the rat. Brain Research. 425, 356-359.
- Morrell, J. I., Greenberger, L. M. & Pfaff, D. W. (1981). Hypothalamic, other diencephalic, and telencephalic neurons that project to the dorsal midbrain. Journal of Comparative Neurology. 201, 589-620.
- Morrison, A. R. (1979). Brain-stem regulation of behavior during sleep and wakefulness. Progress in Neurobiology: Physiological Psychology. 8, 91-131.
- Morrow, T. J. & Casey, K. L. (1976). Analgesia produced by mesencephalic stimulation; effects on bulbo-reticular neurons. In J. J. Bonica and D. Albe-Fessard. (Eds.), Advances in Pain Research and Therapy. Vol. 1. (pp. 503-510). New York: Raven Press.
- Moruzzi, G. (1972). The sleep-waking cycle. Ergebnisse der Physiologie. 64, 1-165.
- Mouret, J., Bobillier, P. & Jouvet, M. (1968). Insomnia following parachlorophenylalanine in the rat. European Journal of Pharmacology. 5, 17-22.
- Mouret, J. & Coindet, J. (1980). Polygraphic evidence against a critical role of the raphe nuclei in sleep in the rat. Brain Research. 186, 273-287.
- Nashold, Jr., B. S., Wilson, W.P. & Slaughter, D. G. (1969). Sensation evoked by stimulation in the midbrain of man. Journal of Neurosurgery. 30, 14-24.
- Nauta, W. J. H., Smith, G. P., Faull, R. M. & Domesick, V. B. (1978). Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience. 3, 385-401.
- Nelson, J. P., McCarley, R. W. & Hobson, J. A. (1981). Cross-correlation of PGO burst cell firing with eye movement potentials of the alert cat. Neuroscience Abstract. 7, 80.

- Nelson, J. P. McCarley, R. W. & Hobson, J. A. (1983). REM sleep burst neurons, PGO waves, and eye movement information. Journal of Neurophysiology. 50, 784-797.
- Ni, H., Zhang, J. & Harper, R. M. (1989). Respiratory-related discharge of periaqueductal gray neurons during sleep-waking states. Brain Research. 511, 319-325.
- Ni, H., Zhang, J. & Harper, R. M. (1990). Cardiovascular-related discharge of periaqueductal gray neurons during sleep-waking states. Brain Research. 532, 242-248.
- Ogawa, S., Kow, L. M., McCarthy, M. M., Pfaff, D. W. & Schwartz-Giblin, S. (1991). Midbrain PAG control of female reproductive behavior. In A. Depaulis and R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter Functional, Anatomical, and Neurochemical Organization. (pp. 211-235). New York: Plenum Press.
- Oksenberg, A., Marks, G., Farber, J., Cobbey, K., Speiale, S., Mihailoff, G. & Roffwarg, H. P. (1986). Effects of REM-sleep deprivation during the critical period of neuroanatomical development of cat visual system. Sleep Research. 15, 53.
- Olds, J. (1956). Runway and maze behavior controlled by basomedial forebrain stimulation in the rat. Journal of Comparative Physiological Psychology. 49, 507-512.
- Olds, J. & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative Neurology. 47, 419-427.
- Olds, J., Travis, R. P. & Schwing, R. C. (1960). Topographic organization of hypothalamic self-stimulation functions. Journal of Comparative Physiological Psychology. 31, 23-32.
- Olds, M. E. & Olds, J. (1962). Approach-escape interactions in rat brain. American Journal of Physiology. 203, 803-810.
- Olds, M. E. (1979). Hypothalamic substrates for the positive reinforcing properties of morphine in the rat. Brain Research. 168, 351-360.
- Olds, M. E. & Fobes, J. L. (1981). The central basis of motivation: Intracranial self-stimulation studies. Annual Review of Psychology. 32, 523-574.

- Olivéras, J. L., Besson, J. M., Guilbaud, G. & Liesbeskind, J. C. (1974). Behavioral and electrophysiological evidence of pain inhibition from midbrain stimulation in the cat. Experimental Brain Research. 20, 32-44.
- Olivéras, J. L., Guilbaud, G. & Besson, J. M. (1979). A map of serotonergic structures involved in stimulation produced analgesia in unrestrained, freely moving cats. Brain Research. 164, 317-322.
- Olivéras, J. L., Hosobuchi, Y., Bruxelle, L., Passot, C. & Besson, J. M. (1978). Analgesic effects induced by electrical stimulation of the nucleus raphé magnus in the rat; interaction with morphine analgesics. Abstracts 7th International Congress of Pharmacology (Paris). 1, 119.
- Oswald, I. (1974). Sleep. Harmondsworth, Middlesex: Penguin.
- Panksepp, J., Jalwicz, J. W., Morgane, P. J., Zolovick, A. J. & Stern, W. C. (1973). Noradrenergic pathways and sleep-waking states in cats. Experimental Neurology. 41, 233-245.
- Parmeggiani, P.-L. (1980). Temperature regulation during sleep: A study in homeostasis. In J. Orem & C. D. (Eds), Physiology in sleep. (pp. 97-143). New York: Academic Press.
- Parmeggiani, P.-L., Zamboni, G., Perez, E. & Lenzi, P. (1984). Hypothalamic temperature during desynchronized sleep. Experimental Brain Research. 54, 315-320.
- Paxinos, G. & Watson, C. (1986). The Rat Brain in Stereotaxic Coordinates. Sydney: Academic Press.
- Pellegrino, L. J., Pellegrino, A. S. & Cushman, A. J. (1981). A Stereotaxic Atlas of the Rat Brain. (2th Ed.). New York: Plenum Press.
- Pert, A. & Walter, M. (1976). Comparison between naloxone reversal of morphine and electrical stimulation-induced analgesia in the rat mesencephalon. Life Science. 19, 1023-1032.
- Pfaff, D. W. & Lewis, C. (1974). Film analyses of lordosis in female rats. Hormones and Behavior. 5, 317-335.
- Phillips, A. G. & LePiane, F. G. (1980). Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacology, Biochemistry and Behavior. 12, 965-968.

- Phillips, A. G. & LePiane, F. G. (1982). Reward produced by microinjection of (d-Ala²), Met⁵-enkephalinamine into the ventral tegmental area. Behavioral Brain Research. 5, 225-229.
- Pickel, V., Joh, T. H. & Reis, D. J. (1977). A serotonergic innervation of noradrenergic neurons in nucleus locus coeruleus: Demonstration by immunocytochemical localization of the transmitter specific enzyme tyrosine and tryptophan hydroxylase. Brain Research. 131, 197-214.
- Pickens, R., Meisch, R. A. & Dougherty, J. A. (1968). Chemical interactions in methamphetamine reinforcement. Psychological Report. 23, 1267-1270.
- Porrino, L. J., Esposito, R. U., Seeger, T. F., Crane, A. M., Pert, A. & Sokoloff, L. (1984). Metabolic mapping of the brain during rewarding self-stimulation. Science. 224, 306-309.
- Portas, C. M. & McCarley, R. W. (1994). Behavioral state-related changes of extracellular serotonin concentration in the dorsal raphe nucleus: A microdialysis study in the freely moving cat. Brain Research. 648, 306-312.
- Poschel, B. P. H. (1969). Mapping of rat brain for self-stimulation under monamine oxidase blockade. Physiology and Behavior. 4, 325-331.
- Price, J. L., Russchen, F. T. & Amarel, D. G. (1987). The limbic region. II. The amygdaloid complex. In A. Bjorklund, T. Hokfelt and L. W. Swanson (Eds.), Handbook of Chemical Neuroanatomy. Vol. 5: Integrated System in the CNS, Part I. Hypothalamus, Hippocampus, Amygdala, and Retina. (pp. 279-388). Amsterdam: North Holland.
- Pujol, J. F., Buguet, A., Froment, J. L., Jones, B. E. & Jouvett, M. (1971). The central metabolism of serotonin in the cat during insomnia. A neurophysiological and biochemical study after administration of p-chlorophenylalanine or destruction of the raphe system. Brain Research, 29, 195-212.
- Punnen, S., Willette, R., Krieger, A. J. & Sapru, H. N. (1984). Cardiovascular response to injections of enkephalin in the pressor area of the ventrolateral medulla. Neuropharmacology. 23, 939-946.
- Rechtschaffen, A., Dates, R., Tobias, M. & Whitehead, W. E. (1969). The effects of lights-off stimulation on the distribution of paradoxical sleep in rats. Communication in Behavioral Biology. 3, 93-99.

- Reivich, M., Isaacs, G., Evarts, E. & Kety, S. (1968). The effects of slow wave sleep and REM sleep on regional cerebral blood flow in cats. Journal of Neurochemistry. 15, 301-306.
- Reynolds, D. V. (1969). Surgery in the rat during electrical analgesia by focal brain stimulation. Science. 164, 444-445.
- Rhodes, D. L. & Liesbeskind, J. C. (1978). Analgesia from rostral brainstem stimulation in the rat. Brain Research. 143, 1978, 521-532.
- Risner, M. E. & Jones, B. E. (1976). Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacology, Biochemistry and Behavior. 5, 477-482.
- Risner, M. E. & Jones, B. E. (1980). Intravenous self-administration of cocaine and norcocaine by dogs. Psychopharmacology. 71, 83-93.
- Rizvi, T. A., Ennis, M., Behbehani, M. M. & Shipley, M. (1991). Connections between the central nucleus of amygdala and midbrain periaqueductal gray: Topography and Reciprocity. Journal of Comparative Neurology. 303, 121-131.
- Rizvi, T. A., Ennis, M. & Shipley, M. (1992). Reciprocal connections between the medial preoptic area and the midbrain periaqueductal gray in rat: A WGA-HRP and PHA-L study. Journal of Comparative Neurology. 315, 1-15.
- Roberts, D. W. & Martin, J. R. (1977). Effects of lesions in central thermosensitive areas in thermoregulation responses in rats. Physiology and Behavior. 19, 503-511.
- Roffwarg, H. P., Muzio, J. & Dement, W. C. (1966). Ontogenetic development of the human sleep-dream cycle. Science. 152. 604-619.
- Roussel, B., Bugeut, A., Bobillier, P. & Jouvet, M. (1967). Locus coeruleus-sommeil paradoxal et noradrenaline cerebrale. Comptes Rendus de Sances de la Societe de Biologie (Paris). 161, 2537-2541.
- Routtenberg, A. (1970). Hippocampal activity and brainstem reward-aversion loci. Journal of Comparative Physiological Psychology. 72, 161-170.

- Routtenberg, A. (1971). Forebrain pathways of reward in *Rattus norvegicus*. Journal of Comparative Physiological Psychology. 75, 269-276.
- Routtenberg, A. & Malsbury, C. (1969). Brainstem pathways of reward. Journal of Comparative Physiological Psychology. 68, 22-30.
- Routtenberg, A. & Sloan, M. (1972). Self-stimulation in the frontal cortex of *Rattus norvegicus*. Behavioral Biology. 7, 567-572.
- Saint-Laurent, J., Leclerc, R. & Mitchell, M. (1973). Autostimulation des noyaux du raphé et exploration diffuse. Journal of Physiology. (Paris). 66, 87-92.
- Saito, H., Sakai, K. & Jouvet, M. (1977). Discharge patterns of the nucleus parabrachialis lateralis neurons of the cat during sleep-waking cycle and their responses to sensory stimuli. Brain Research. 399, 317-326.
- Sakai, K. & Jouvet, M. (1980). Brain stem PGO-on cells projecting directly to the cat dorsal lateral geniculate nucleus. Brain Research. 194, 500-505.
- Sakai, K., Pititjean, F. & Jouvet, M. (1976). Effects of ponto-mesencephalic lesions and electrical stimulation upon PGO waves and EMPs in unanesthetized cats. Electroencephalography and Clinical Neurophysiology. 41, 49-63.
- Sakai, K., Sastre, J-P., Kanamori, N. & Jouvet, M. (1981). State-specific neurons in the ponto-medullary reticular formation with special reference to the postural atonia during paradoxical sleep in the cat. In O. Pompeiano and C. Ajmone-Marsan (Eds.), Brain Mechanisms and Perceptual Awareness. (pp. 405-429). New York: Raven Press.
- Saper, C. B. & Loewy, A. D. (1980). Efferent connections of the parabrachial nucleus in the rat. Brain Research. 197, 291-317.
- Saper, C. B., Swanson, L. W. & Cowan, W. M. (1978). The efferent connections of the anterior hypothalamic area of the rat, cat and monkey. Journal of Comparative Neurology. 182, 575-600.
- Sassin, J. F., Frantz, A. G., Kapen, S. & Weitzman, E. D. (1973). The nocturnal rise of human prolactin is dependent on sleep. Journal of Clinical Endocrinology and Metabolism. 37, 436-440.

- Scmitt, P., Eclancher, F., & Karlit, P. (1974). Etude des systèmes de renforcement négatif et de renforcement positif au niveau de la substance grise centrale chez le rat. Physiology and Behavior. 12, 271-279.
- Seeger, T. F. & Pert, A. (1985). Arcuate nucleus stimulation induction of naloxone-reversible analgesia with concomitant localization of opiate release using in vivo autoradiography. Neuroscience Abstracts. 11, 1068.
- Sem-Jacobsem, C. & Torkildsen, A. (1960). Depth recording and electrical stimulation in the human brain. In E. R. Ramey and D. S. O'Doherty (Eds.), Electrical studies on the Unanesthetized Brain. (pp. 275-290). New York: Hoeber.
- Sessle, B. J., Ball, G. J. & Lucier, G. E. (1981). Suppressive influences from periaqueductal gray and nucleus raphe magnus on respiration and related reflex activities and on solitary tract neurons, and effect of naloxone. Brain Research. 197, 145-161.
- Shaikh, M. B., Lu, C.-L. & Siegel, A. (1991). An enkephalinergic mechanism involved in amygdaloid suppression of affective defence behavior elicited from the midbrain periaqueductal gray in the cat. Brain Research. 559, 109-117.
- Shapiro, C. M., Griesel, R., Bartel, P. & Jooste, P. (1975). Sleep patterns after graded exercise. Journal of Applied Psychology. 39, 187-190.
- Sherrington, C. (1906). The integration action of the nervous system. New Haven: Yale University Press.
- Simerly, R. B. & Swanson, L. W. (1986). The organization of neural inputs to the medial preoptic nucleus of the rat. Journal of Comparative Neurology. 246, 312-341.
- Simon, H., Le Moal, M. & Cardo B. (1973). Mise en évidence du comportement d'autostimulation dans le noyau raphé médian du rat. Comptes Rendus de Seances de la Societe de Biologie. (Paris). 277, 591-593.
- Simon, H., Le Moal, M. & Cardo B. (1976). Intracranial self-stimulation from the dorsal raphe nucleus of the rat: Effects of the injection of para-chlorophenylalanine and alpha-methylparatyrosine. Behavioral Biology. 16, 353-364.

- Simon, R. P., Gershon, M. D. & Brooks, D. C. (1973). The role of raphe nuclei in the regulation of ponto-geniculo-occipital wave activity. Brain Research. 58, 310-330.
- Smith, D. J., Robertson, B., Monroe, P. J., Taylor, D. A., Leedham, J. A. & Cabral, J. D. Y. (1992). Opioid receptors mediating antinociception from β -endorphin and morphine in the periaqueductal gray. Neuropharmacology. 31(11), 1137-1150.
- Soper, W. Y. (1976). Effects of analgesic midbrain stimulation on reflex withdrawal and thermal escape in the rat. Journal of Comparative Neurology. 90, 91-101.
- Spielman, A. J. (1979). The effects of varying the amount and the neuroanatomical locus of intra-cranial self-stimulation on the "normal" sleep cycle of the rat. Physiological Psychology. 6179-B.
- Spielman, A. J., Matiace, L. A., Steiner, S. S. & Ellman, S. J. (1973). The effects of varying the amount and the neuroanatomical locus of intracranial self-stimulation on the "normal" sleep cycle of the rat. Sleep Research. 2, 38.
- Spiraki, C., Fibiger, H. C. & Phillips, A. G. (1983). Attenuation of heroin reward in rat by disruption of the mesolimbic dopamine system. Psychopharmacology. 79, 278-283.
- Stein, E. A. & Olds, J. (1977). Direct intracerebral self-administration of opiates in the rat. Society of Neuroscience Abstract. 3, 302.
- Stein, L. (1962). Effects and interactions of imipramine, chlorpromazine, reserpine and amphetamine on self-stimulation: Possible neurophysiological basis of depression. In J. Wortis (Ed.), Recent Advances in Biological Psychiatry. (pp. 288-308). New York: Plenum Press.
- Stein, L. (1964). Self-stimulation of the brain and the central stimulant action of amphetamine. Federal Proceeding. 23, 836-850.
- Stein, L. (1968). Chemistry of reward and punishment. In D. H. Efron (Ed.), Psychopharmacology. (pp. 105-123). Washington, DC.: U. S. Government Printing Office.

- Steiner, S. S., Bodnar, R. J., Ackermann, R. F. & Ellman, S. J. (1973). Escape from rewarding brain stimulation of dorsal brainstem and hypothalamus. Physiology and Behavior. 11, 589-591.
- Steiner, S. S. & Ellman, S. J. (1972). Relation between REM sleep and intracranial self-stimulation. Science. 177, 1122-1124.
- Stephan, F. K., Berkley, K. J. & Moss, R. L. (1981). Efferent connections of the rat suprachiasmatic nucleus. Neuroscience. 6(12), 2625-2641.
- Steriate, M. & Hobson, J. A. (1976). Neuronal activity during the sleep-waking cycle. Progress in Neurobiology. 6, 155-376.
- Stinus, L., Thierry, A. M. & Cardo. B. (1976). Effects of various inhibitors of tyrosine hydroxylase and dopamine beta-hydroxylase on rat self-stimulation after reserpine treatment. Psychopharmacologia. 45, 287-294.
- Swanson, L. W., Kucharezyk, J. & Mogenson, G. J. (1978). Autoradiographic evidence for pathways from the medial preoptic area to the midbrain involved in the drinking response to angiotensin II. Journal of Comparative Neurology. 178, 645-659.
- Swanson, L. W. & Mongenson, G. J. (1981). Neural mechanisms for the functional coupling of autonomic, endocrine and somatomotor response in adaptive behaviors. Brain Research Review. 3, 1-34.
- Takahashi, Y., Kipnis, D. & Daughaday, W. (1968). Growth hormone secretion during Sleep. Journal of Clinical Investigation. 47, 2079-2090.
- Thorn, B. E., Applegate, L. & Johnson, S. W. (1989). Ability of periaqueductal gray subdivisions and adjacent loci to elicit analgesia and ability of naloxone to reverse analgesia. Behavioral Neuroscience. 103(6), 1335-1339.
- Towle, A., Breese, G., Mueller, R., Coyle, S. & Lauder, J. (1984). Early postnatal administration of 5,7-DHT: Effects on serotonergic neurons and terminals. Brain Research. 310, 67-75.
- Trulson, M. E. & Jacobs, B. L. (1979). Raphe unit activity in freely moving cats: Correlation with level of behavioral arousal. Brain Research. 163(1), 135-150.

- Underleider, L. & Coons, E. E. (1970). A behavioral measure of homosynaptic and heterosynaptic temporal summations in the self-stimulation of rats. Science. 169, 785-787.
- Ungerstedt, U. (1971). Stereotaxic mapping of monoamine pathways in the rat brain. Acta Physiologia Scandinavica 82, Supplementum. 367, 1-48.
- Ursin, R., Ursin, H & olds, J. (1966). Self-stimulation of hippocampus in rats. Journal of Comparative Physiological Psychology. 61, 353-359.
- Valenstein, E. S. (1965). Independence of approach and escape reactions to electrical stimulation of the brain. Journal of Comparative Physiological Psychology. 60, 20-30.
- Valenstein, E. S. & Beer, B. (1961). Unipolar and bipolar electrodes in self-stimulation experiments. American Journal of Physiology. 201, 1181-1186.
- Valverde, F. (1965). Studies on piriform lobe. MA.: Harvard University Press.
- Van Bockstaele, E. J. & Aston-Jones, G. (1992). Distinct population of neurons in ventromedial periaqueductal gray project to the rostral ventral medulla and abducens nucleus. Brain Research. 576, 59-67.
- Van Bockstaele, E. J., Aston-Jones, G., Pieribone, V. A., Ennis, M. & Shipley, M. T. (1991). Subregions of the periaqueductal gray topographically innervate the rostral ventral medulla in the rat. Journal of Comparative Neurology. 309, 305-327.
- Van Bockstaele, E. J., Pieribone, V. A. & Aston-Jones, G. (1989). Diverse afferents converge on the nucleus paragigantocellularis in the rat ventrolateral medulla: Retrograde and anterograde studies. Journal of Comparative Neurology. 290, 561-584.
- van Ree, J. M. & de Wied, D. (1980). Involvement of neurohypophyseal peptides in drug-mediated adaptive responses. Pharmacology, Biochemistry, and Behavior. 11(Suppl. 1), 257-263.

- Veening, J., Buma, P., Ter Horst, G. J., Roeling, T. A. P., Luiten, P. G. M., & Nieuwenhuys R. (1991). Hypothalamic projections to the PAG in the rat: Topographical, immunoelectronmicroscopical and functional aspects. In A. Depaulis and R. Bandler (Eds.), The Midbrain Periaqueductal Gray Matter Functional, Anatomical, and Neurochemical Organization. (pp. 387-415). New York: Plenum Press.
- Vogt, M. (1982). Some functional aspects of central serotonergic neurons. In N. N. Osborne (Ed.), Biology of Serotonergic Transmission. (pp. 299-315). Chichester: Wiley.
- Walker, J. & Berger, R. J. (1980). Sleep as an adaptation for energy conservation functionally related to hibernation and shallow torpor. In P. S. McConnell, G. J. Boer, H. J., Rominjn, N. E. Van de Poll and M. A. Corner (Eds.), Adaptive Capabilities of the Nervous System (Vol. 53). (pp. 255-278). Amsterdam: North Holland.
- Wang, S. & Ranson, S. W. (1941). The role of the hypothalamus and preoptic regions in the regulation of heart rate. American Journal of Physiology. 205, 210.
- Wauquier, A. (1979). The influence of psycholoactive drugs on brain self-stimulation in rats: A review. In A. Wauquier and E. T. Rolls (Eds.), Brain-Stimulation Reward. (pp. 123-170). Amsterdam: Elsevier.
- Weher, T. A. (1992). A Brain-Warming Function for REM Sleep. Neuroscience and Biobehavioral Reviews. 16, 379-397.
- Wei, E. T. (1981). Enkephalin analogs in physical dependence. Journal of Pharmacology and Experimental Therapy. 216, 12-18.
- Wei, E. T. & Loh, H. (1976). Physical dependence on opiate-like peptides. Science. 193, 1262-1263.
- Weitzman, E. & Hellman, L. (1974). Temporal organization of the 24-hour pattern of the hypothalamic-pituitary axis. In M. Ferin, F. Hallberg, R. M. Richart & R. L. Vanderviele (Eds.), Biorhythms and Human Reproductions. (pp. 371-395). New York: John Wiley.
- Weitzman, E., Zimmerman, J., Czeisler, C. & Ronda J. (1983). Cortisol secretion is inhibited during sleep in normal man. Journal of Clinical Endocrinology and Metabolism. 56, 352-358.

- Wilson, M. C. & Schuster, C. R. (1972). The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacologia. 26, 115-126.
- Wise, R. A. (1978). Catecholamine theories of reward: A critical review. Brain Research. 152, 215-247.
- Wise, R. A. (1980). Action of drugs of abuse on brain reward systems. Pharmacology, Biochemistry, and Behavior. 13,(suppl. 1), 213-223.
- Wise, R. A. (1984). Neural mechanism of the reinforcing action of cocaine. In J. Grabowski (Ed.), Cocaine: Pharmacology, Effects, and Treatment of Abuse. NIDA Research Monograph. 50, 19.
- Wise, R. A. & Bozarth, M. A. (1981). Brain substrates for reinforcement and drug-administration. Progress in Neuropsychopharmacology. 5(5-6). 467-474.
- Wise, R. A. & Bozarth, M. A. (1987). Brain Mechanisms of drug reward and euphoria. Psychiatric Medicine. 3(4), 445-460.
- Wolfle, T. L., Mayer, D. J., Carder, B. & Liebeskind, J. C. (1971). Motivational effects of electrical stimulation in dorsal tegmentum of the rat. Physiology and Behavior. 7, 569-574.
- Wurtz, R. H. & Olds, J. (1963), Amygdaloid stimulation and operant reinforcement in the rat. Journal of Comparative Physiological Psychology. 6, 941-949.
- Wurtz, R. H. (1967). Physiological correlates of steady state potential shifts during sleep and wakefulness. II. Brain temperature, blood pressure, and potential changes across the ependyma. Electroencephalography and Clinical Neurophysiology. 22, 43-53.
- Yaksh, T. L., Yeung, J. C. & Rudy, T. A. (1976). An inability to antagonize with naloxone the elevated nociceptive threshold resulting from electrical stimulation of the mesencephalic central gray. Life Science. 18, 1193-1198,
- Yokel, R. A. & Wise, R. A. (1975). Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. Science. 187, 547-549.

- Yokel, R. A. & Wise, R. A. (1976). Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology. 48, 311-318.
- Zanchetti, A., Baccelli, G. & Mancina, G. (1982). Cardiovascular regulation during sleep. Archive of Italian Biology. 120, 120-137.
- Zarevics, P. & Setler, P. E. (1979). Simultaneous rate-independent and rate-dependent assessment of intracranial self-stimulation: evidence for the direct involvement of dopamine in brain reinforcement mechanisms. Brain Research. 169, 499-512.
- Zepelin, H. & Rechtschaffen, A. (1974). Mammalian sleep, longevity and energy metabolism. Brain Behavior Evolution. 10, 425-470.
- Zepelin, H., Whitehead, W. E. & Rechtschaffen, A. (1972). Aging and sleep in the albino rat. Behavioral Biology. 7, 65-74.
- Zhang, J. X., Harper, R. M. & Frysinger, R. C. (1986). Respiratory modulation of neuronal discharge in the central nucleus of the amygdala during sleep and waking states. Experimental Neurology. 91, 193-207.