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SOME BEHAVIORAL AND PHARMACOLOGICAL CORRELATES OF BRAIN STIMULATION IN RATS

by

Jacques St-Laurent

Thesis presented to the School of Graduate Studies and Research
in partial fulfillment of the requirements
for the degree of Master of Science in Pharmacology.

UNIVERSITY OF OTTAWA
Ottawa, Canada, 1980

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

DEDICATED TO

CAROL

CHANTAL AND SUZANNE

AND

JACQUES

"There are two species of mammals whose behavior has been more intensively studied under conditions of laboratory control than any others. These are rats and men. Since one of these stands near the bottom of the mammalian scale and the other represents the culmination of cortical development, it seems appropriate that our discussion should center about these species... and the problem opened up by the facts available regarding their nervous systems in relation to their behavior patterns".

C. Judson Herrick, 1926*

* From Brain in Rats and Men. University of Chicago Press, 1926.

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TABLES

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FOREWORD

Olds and Milner discovered in 1954 that rats with chronically implanted electrodes in the brain rapidly learned a response to obtain electrical brain stimulation. The electrical stimulation provided reward, in that the rats worked to obtain it. Brain-stimulation reward has been found in all vertebrate species tested, including man, and has been useful in understanding how natural rewards, such as water and food, are processed by the brain, in understanding the neural basis of emotion, motivation and learning, and also in understanding the functioning of the hypothalamus and of limbic and related structures.

Research on brain-stimulation reward has progressed from its discovery to the present time, and now covers the aspects of neuroanatomy; neurophysiology, biochemistry, pharmacology, physiological correlates and psychology. Surprisingly, there are relatively few studies on the behavioral aspects of brain-stimulation reward. The first part of the present investigation will deal with a topographical and quantitative description of the behavioral patterns correlated with brain-stimulation elicited from various brain sites.

It has repeatedly been shown that positive SS loci coincide with known catecholamine fiber trajectories, cell groups, or terminal fields. The view that the catecholamines are critically involved in mediation of intracranial self-stimulation (ICSS) has also been strenghtened by the findings that ICSS is potentiated by drugs that enhance catecholaminergic (CA) neural transmission, whereas it is abolished or attenuated by drugs which impede CA transmission. Initially, noradrenaline was considered to be

the most likely substrate of reward. These speculations on noradrenaline have been greatly influenced by the fact that noradrenergic fibers are found near most ICSS sites and that drugs that interfere with noradrenergic function attenuate ICSS. However, close examination of ICSS sites in the pons and caudal midbrain has shown that these sites are not well correlated with the boundaries or with the relative densities of noradrenergic elements near the electrode tips. In addition, drugs that alter noradrenergic function generally cause a non-selective behavioral debilitation. These and other recent data indicate that it is unlikely that stimulation is rewarding because it activates noradrenergic systems.

In recent years, increasing attention has been paid to the possible involvement of the dopaminergic and serotonergic systems in ICSS. The second part of the present investigation consists of a series of experiments aimed at delineating the chemical mediator or mediators involved in ICSS and ICSS-contingent behavioral patterns.

Mental disorders in man, as well as brain SS in experimental animals, can be influenced by psychotropic drugs. The study of the effects of these drugs on SS might lead to useful implications for neuropsychology and biological psychiatry.

GENERAL INTRODUCTION

Review of the Literature on the Brain Self-Stimulation Model.

I - Introduction

The first major step in experimental studies of the behavioral correlates of the brain occurred in the 1940's when Hess (1944; 1946a; 1946b; 1957) introduced the chronic implantation technique. Electrodes were implanted in the brain of cats. These experiments were based on a qualitative methodology, i.e., the description of various neurovegetative, motor and emotional reactions that can be obtained from electrically stimulating different brain structures.

The next major step occurred in the 1950's, when Miller (1957), Delgado (1955), Hebb (1955) and others began to use the chronic implantation methodology in psychological experimentation oriented towards the quantification of the phenomena being studied.

Using chronic stimulating electrodes in animals, Kaada (1951) and Delgado (1955) observed that the electrical stimulation of the dorsomedial tegmentum (DMT) produced flight behavior. These authors concluded that the intra-cranial stimulation (ICS) served as a punishment and consequently, a neural "aversive" motivational system was postulated. Aversive effects were also obtained from the posterio-medial hypothalamus (PMH) by Olds and Olds (1963). Aversive effects of a lower degree of intensity have also been reported from more anterior areas such as septum (S), by Garner (1969) and hippocampus, by Olds and Olds (1963). Subsequently, St-Laurent and Beaugrand (1972) reported that stimulation of

the ventral part of the reticularis pontis caudalis (RPC) could yield flight reactions of higher intensity when compared to DMT. In a subsequent study from the same laboratory, Leclerc et al. (1973) confirmed this finding and suggested the existence of a gradient of intensity of the aversive effect: the more posterior areas yielded the most intensive aversive effects.

With the observation that stimulation of certain areas of the brain could elicit aversive reactions (Kaada, 1951; Delgado, Roberts and Miller, 1954; Delgado, 1955) and that approach behavior (self-stimulation) could be elicited from other areas (Olds and Milner, 1954), the suggestion was made that these areas could be involved in learning as these stimulations had reinforcing properties.

Finally, it was suggested that the areas responsible for SS could be of importance to the pathophysiology of major affective disorders (Stein, 1962), functional psychoses (Olds and Olds, 1964; Stein and Wise, 1971; St-Laurent and Beaugrand, 1971, 1972; St-Laurent et al., 1973b; 1973c) and some neurotic states (St-Laurent and Beaugrand, 1971; Baum et al., 1973; Leclerc et al., 1973; St-Laurent et al., 1973c).

II - Neuroanatomical Correlates of Self-Stimulation

Self-stimulation behavior was first thought to be mainly related to the olfactory rhinencephalic cortex (e.g., septum). Later studies showed that the main "focus" of the SS phenomenon, as indicated by maxima rates for a minimum stimulus intensity and by lesions studies, lies in a midbrain diencephalic pathway coursing through the posterior lateral hypothalamus and the ventromedial tegmemtum. These studies showed a gradient of SS along

the course of this pathway with the most posterior areas yielding the highest rates. The direction of this gradient, in terms of rates and regularity of the SS phenomena was: a) ventromedial tegmentum which headed the list, b) posterior lateral hypothalamus, c) anterior lateral hypothalamus, and d) septal area (Olds et al., 1960; Olds and Olds, 1963; 1964). In these studies, rats were used but the same regions were implicated in studies with cats (Wilkinson, 1966) and monkeys (Briese and Olds, 1964; Bursten and Delgado, 1958). Minor areas of SS were also found in rhinencephalic areas and thalamus (Olds, 1956), in the tractus olfactorius intermedius (Valenstein, 1966; Valenstein et al., 1968), in the olfactory bulb (Phillips and Morgenson, 1969) and in the mediofrontal cortex (St-Laurent and Beaugrand, 1971; 1972). These findings indicate that SS might be mediated by structures along the medial forebrain bundle (MFB). The SS obtained from the anterior structures were due to their connection with the posterior structures. For Valenstein (1966), the evidence for this interpretation was conflicting. He reported that lesions in the posterior areas failed to abolish SS from anterior areas and while the reciprocal was also true, these results implied that there was no focal or essential area of SS. However, Olds and Olds (1969) restudied the effect of lesions along the MFB and they reported various degrees of SS inhibition. In addition, a correlation was shown between the size of the lesions and the magnitude of the effect. However, lesions in the posterior areas gave greater diminution than comparable lesions in the anterior areas.

Arbuthnott et al., (1970a) reported that SS could be elicited from an even more posterior region, namely from the locus coeruleus. The involvement of the reticular formation in SS has also been studied. O'Donahue and Hagamen (1967) proposed that SS can be obtained from the reticular formation of the brain stem; however, in their mapping study, they did not use SS itself but attention phenomena which they considered as always accompanying SS. However, Glickman (1960) and Sharpless (1958) did obtain SS from the dorsomedial and ventral part of the mesencephalic reticular formation. However, Routtenberg and Malsbury (1969) differentiated SS from the reticular formation and did not obtain SS from this formation. They suggested that the extrapyramidal system might be involved in the brain stem reward system.

German and Bowden (1974) have made an extensive review of the arguments favoring the involvement of the catecholaminergic systems as the neural substrate of SS. According to these authors, "rostral CA lesions would reduce caudal SS by virtue of denervation of terminal structures and some degree of retrograde axonal degeneration beneath the stimulation electrode. The caudal CA lesions, with respect to the SS site, would most severely reduce SS; in addition, all distal CA axons beneath the electrode would have degenerated". Concerning the topographical studies, they express the opinion that both the mesolimbic and the nigrostriatal dopamine (DA) systems arising in nuclei A10 and A9 of Dahlström and Fuxe (1974) and the dorsal norepinephrenic (NE) system arising in nucleus A6 (Locus-coeruleus) would be involved in SS. However, as the cell group

A1, A2 and A5 failed to yield SS (Clavier and Routtenberg, 1974; Anlezark et al., 1974), the ventral NE system would not be involved in SS. German and Bowden (1974) also suggested that the SS system seems to be redundant, in the sense that both DA and NE systems will support SS, and diffuse, in the sense that both DA and NE pathways innervate large brain areas (Maeda and Shimizu, 1972; Understedt, 1971). Hence, stimulating a DA system will produce SS even though a massive MFB lesion destroyed the NE pathway; many lesions have little effect upon SS because they damage only a small percentage of the stimulated NE and DA systems. It is to be noted that, in general, these findings indicated a gradient of intensity of SS along the course of the MFB, the more posterior areas yielding the highest rates.

Later mapping studies of the SS sites in the rat brain stem (Routtenberg, 1970), diencephalon (Huang and Routtenberg, 1971) and forebrain (Routtenberg, 1970), using fine diameter electrodes, reported the following: 1) SS was not elicited from the ventral NA pathway, a finding also confirmed by Anlezark et al. (1974); 2) SS could not be elicited from the substantia nigra (SN), brachium conjunctivum, ventral tegmental decussation and rubrospinal tract, pointing to the involvement of the dorsal NA, the nigro-neostriatal dopaminergic pathways and the extrapyramidal systems in brain stem reward; 3) the higner SS rates were obtained from the anterior mesencephalon rather than from the posterior mesencephalon; 4) SS was not obtained from the serotonergic raphe nuclei, mesencephalic pontine or bulbar reticular nuclei. An extensive mapping of the mesencephalon was carried out by Crow (1972); St-Laurent and Beaugrand (1972);

St-Laurent et al. (1973). These studies pointed to the involvement of the DA system in SS. In reports by Arbuttnott et al. (1970), Crow et al. (1972) and St-Laurent and Beaugrand (1971; 1972), SS was observed from electrode sites clustered within or adjacent to the locus coeruleus (LC); however, St-Laurent and Beaugrand (1971; 1972) reported that in addition to LC, SS could also be elicited from the sub-locus coeruleus (Sub-LC) and dorsal part of the RPC. Finally, St-Laurent et al. (1973a) Simon et al. (1973) and Miliaressis et al. (1975) reported SS from serotonergic median raphe (MR) nuclei. Carter and Phillips (1975) obtained SS from sites in the dorsal medulla oblongata in placements near the nucleus of the solitary tract (NST), or in that portion of the dorsal parvoleccular reticular formation situated ventral to the NST, and mainly in the location ventral to the rostral portions of the NST. Finally, Van der Kvoy and Phillips (1979) obtained SS in a location intra or dorsal to the trigeminal motor system.

III - Neuropharmacological Correlates of Self-Stimulation

Many pharmacological studies have been carried out in order to determine the chemical mediator(s) involved in the SS phenomenon. Drugs that increase SS, such as amphetamine and monoamine oxidase inhibitors, facilitate the release of catecholamines or elevate CA levels in the brain (Stein and Seifter, 1961; Poschel and Ninteman, 1964; Stein, 1964; Margules, 1969; Olds, 1972a; Domino and Olds, 1972). On the other hand, drugs such as reserpine, which deplete CA and 5-HT storage vesicles or which have a blocking effect on NE or DA post-synaptic receptors, such as chlorpromazine and haloperidol, will decrease SS (Olds et al., 1956; Olds and Travis, 1960; Dresse, 1966; Olds, 1972b). Further, the suppressive effects of tetrabenazine (a reserpine-like drug) and chlorpromazine on SS can be reversed by amphetamine (Olds, 1972b). In addition, compounds which decrease CA levels, such as alpha-methyl-paratyrosine (AMPT), an inhibitor of tyrosine hydroxylase (thus limiting the synthesis of CA), suppress SS (Poschel and Ninteman, 1966; Gibson et al., 1970; Black and Cooper, 1970; Stinus et al., 1971; Cooper et al., 1971; Beaugrand and St-Laurent, 1973; St-Laurent et al., 1973d; Yuwiler and Olds, 1973). The suppression of SS by AMPT can be antagonized by amphetamine (Poschel and Ninteman, 1966), and by methylphenidate (Franklin and Herberg, 1974). Reduction of SS rates can also be observed following selective depletion of NE obtained by administration of disulfiram; this reduction is said to be counteracted by DOP, a precursor of NE given ip, (Stinus and Thierry, 1973) and by intraventricular injection of l-NE but not by d-NE or domapine (DA) or serotonin (Wise and Stein, 1969). Poschel and Ninteman

(1963), emphasizing the effects of these drugs on NE, postulated that NE is the chemical mediator involved in SS. The case for the sole involvement of NE in SS is ambiguous. For instance, Rolls (1970) observed that in animals treated with disulfiram, replacement of the rat on the bar was sufficient to induce resumption of SS. Since AMPT affects NE and DA (Spector et al., 1965; Weissman and Koe, 1965), it is not clear which of these two CA is critical for SS. In addition, Gibson et al., (1970) pointed out that with AMPT, NE has to be reduced much further than with reserpine to obtain an equivalent decrease in SS. Moreover, DL-5-bromotryptophan, another tyrosine hydroxylase inhibitor, produced only mild decrease in SS, while para-chlorophenylalanine (PCPA), an inhibitor of tryptophan hydroxylase (hence limiting 5HT synthesis), also produced decrease of SS, although not as pronounced as with AMPT. Margules (1969) obtained SS from the dorsal tegmentum in the vicinity of the dorsal nucleus of the raphe; however, as PCPA did not affect SS at this site, while d-amphetamine increased it, he concluded that SS was due to the stimulation of NE fibers of passage rather than to the stimulation of the serotonergic cell bodies of the dorsal nucleus of the raphe. St-Laurent et al., (1973a) obtained SS from both the dorsal and medial raphe nuclei along with enhanced diffused exploration and dispersed locomotion. The raphe nuclei have a high concentration of 5-HT (Aghajanian and Sheard, 1968); therefore, the hypothesis that serotonin has a role in SS cannot be excluded. Furthermore, it is to be noted that compounds used to manipulate NE or CA levels in general (e.g., reserpine, monoamine oxydase inhibitors) often have an

effect on brain serotonin (Bloom and Nichols, 1968). In addition, the MFB also contains indoleamines. Stark et al. (1964) and Poschel and Ninteman (1968) have suggested that serotonin (5-HT) may indeed play a role in SS.

In a previous study using AMPT, SS could not be reinstated with ip injection of L-DOPA, while this drug was found to reduce SS (Beaugrand and St-Laurent, 1973). However, Stinus and Thierry (1973), using oral administration of L-DOPA, were able to obtain such a reinstatement. However, a reinstatement of PLH and VMT SS was obtained with apomorphine (ip) following depression by AMPT (ip) (St-Laurent et al., 1973e). Previously, Maj et al. (1972) had also reported an increase of motor activity and exploration after administration of apomorphine. Similar phenomena were also observed during SS by Roberts (1958) and St-Laurent and Beaugrand (1972). Increased exploration (St-Laurent and Olds, 1964; Groover, 1966; Christopher and Butter, 1968; St-Laurent and Beaugrand, 1971; 1972; Miliaressis, 1972) was reported to be the most significant behavioral feature correlated with SS from the PLH and VMT. In view of the behavioral excitatory effects of apomorphine, it was felt that this drug could possibly reinstate SS after its suppression by AMPT pretreatment. In addition, apomorphine is believed to be a direct stimulator of DA receptor which would account for the increase in motility (van Rossum and Hurkmans, 1964) and stereotypies often observed in treated rats (Ernst, 1967; Ernst and Smelik, 1966; Anden et al., 1967; Roos, 1969). For these pharmacological reasons, it was thought that SS could be reinstated by apomorphine. The results support the hypothesis of van Rossum and Hurkmans (1964)

that an increase in motility is a result of stimulation of the DA receptors; however, an essential interaction with NE cannot be eliminated in the light of the work of Persson (1970), Persson and Waldeck (1970), Anden et al. (1970), Corrodi et al. (1970) and Svensson and Waldeck (1970), which suggested that the NE neurons are involved in the stimulation of motility. Phillips and Fiberger (1973) have observed that the d-isomer of amphetamine (which is the more potent inhibitor of CA uptake by NE neurons) was more effective in facilitating SS than the l-isomer at the lateral hypothalamic level, a major rostral projection of NE fibers (Understedt, 1971); in contrast, the two isomers were equipotent in facilitating SS at the substantia nigra level where the fibers and cell bodies are almost exclusively dopaminergic (Understedt, 1971). These results suggest that both DA and NE are involved in SS, depending on the site of implantation. However, the involvement of other neuromediators, such as serotonin, cannot be excluded.

For instance, 6-hydroxydopamine (6-OHDA), which selectively destroys CA neurons and reduces SS (hence implying involvement of CA in SS (Stein and Wise, 1971)), has also been shown by Blondaux et al. (1973) to increase 5-HT turnover. In addition, Lippa et al. (1973) have reported that this chemical decreases SS only temporarily; also, further treatment with an alpha-adrenergic receptor blocking agent (Phentolamine) had no additional effect on SS, while haloperidol markedly reduced SS, suggesting an involvement of DA. Furthermore, Briese et al. (1971) have shown that an inhibition of SS can be obtained following administration of pargyline, which potentiates DA but

not NE depletion produced by subsequent 6-OHDA administration. Thus, there seems to be enough pharmacological basis for assuming a relationship between self-stimulation behavior and brain catecholamines and indoleamines. However, there are also objections to the available data. Depletion of catecholamines is accompanied by effects on motor behavior, which in turn could be the cause of reduced SS (Rech et al., 1966). The doses of drugs used to produce depletion are often toxic so that reduction of SS would be non-specific to the SS neural system, (Weissman and Koe, 1965). Furthermore, most compounds which deplete brain catecholamines are not specific to DA or NE; thus it is unclear which of the brain catecholamines, if any, is related to self-stimulation behavior. Indeed, it appears that NE, DA or 5-HT are not the only transmitter substances which modulate SS. For instance, it is possible to depress SS by direct injection of histamine in the brain; this effect is blocked by prior treatment with antihistaminics (Cohn et al., 1973). Also, it is possible to depress or facilitate SS with drug-induced changes of brain acetylcholine levels (Stark and Boyd, 1963; Domino and Olds, 1968; Olds and Domino, 1969; Pradhan and Kamat, 1972; Newman, 1972). Here again, the relationship between brain acetylcholine and histamine on SS is not clear. Finally, diazepam and chlordiazepoxide may have facilitatory effects on SS (Olds, 1972a). The basis of the action of chlordiazepoxide and diazepam, as well as the optimum dosage, is unclear (Olds, 1972a). The effect on SS may be related to the catecholamines or to acetylcholine, or to some other system (for instance, gaba-aminergic mechanisms).

IV - Behavioral Correlates of Self-Stimulation

Roberts (1958) found that the reward produced by stimulation of the hypothalamus seemed to be accompanied by a heightened general activity level, whereas the reward produced by stimulation of a more anterior structure, such as the olfactory cortex, yielded SS often accompanied by more or less complete inhibition of general activity. St-Laurent and Olds (1964), Christopher and Butter (1968), as well as Groover (1966), found that locomotor exploration with approach forward locomotion was the behavior that correlated the best with SS from the lateral hypothalamus. Valenstein et al. (1968) noted that SS at threshold was accompanied by exploration and searching behavior, while at higher current intensities the same regions yielded specific drive behavior (eating, drinking). O'Donahue and Hagamen (1967) proposed that attention phenomena of various types are correlated with SS and they used them in mapping the cat brain for regions producing SS. However, Miliaressis and Le Moal (1976) reported that SS was observed when the intensity of the current reached more than twice the intensity needed to produce exploration. For these authors, the difference in thresholds between exploratory and rewarding activities suggest that MFB stimulation involves two neuronal systems with unequal sensitivities.

St-Laurent and collaborators examined the behavioral patterns associated with SS and flight (St-Laurent and Beaugrand, 1971; 1972; St-Laurent et al., 1973; 1973a, 1973b, 1973c;

Baum et al., 1973; Leclerc et al., 1973). In addition to defining more precisely the behavioral patterns of behaviors accompanying SS, these researchers wanted to verify: a) if a gradient of SS existed; b) if the related behavioral patterns presented some type of organization; c) if the more caudal regions of the reticularis pontis caudalis (RPC) and of the raphe nuclei (R) would yield SS or flight reactions when stimulated.

The existence of a gradient of SS along the MFB was confirmed, the more posterior areas yielding higher rates of SS than the anterior ones.

In addition, as reported by Roberts (1958), St-Laurent and Olds (1964), both motor inhibition and activation were observed to accompany SS from the anterior and posterior structures respectively. As noted by Groover (1966), St-Laurent and Olds (1964), Christopher and Butter (1968), in addition to motor activation, SS from the lateral hypothalamus (ALH; PLH) yielded exploratory phenomena.

Very intense SS by bursts was obtained from the dorsal part of the RPC near the locus coeruleus (LC) which was accompanied by increased motor activity with exploration interrupted by lull periods during which the animal appeared dazed. In addition to the interruptions of the ongoing exploration, an interruption of ongoing motor activity with hypotonia (adynamia) was observed following SS from this area (i.e., dorsal RPC), suggesting a close anatomical relationship between motor and cognitive perceptual phenomena at this reticular level.

SS from the dorsal part of the RPC, in most cases, becomes ambivalent; the animal withdraws immediately after a burst of SS or tries to escape from the box a few seconds after SS, but eventually comes back to press again on the lever.

Finally, immediate and intense withdrawal reactions were elicited from the ventral part of the RPC. These results corroborate the observations of Arbuttnutt et al. (1970) and Ritter and Stein (1975) who obtained SS from the LC, and Jouvet and Mounier (1960) who obtained "a surprising increase of pleasure reactions after lesion of the ventral part of the reticularis pontis oralis and anterior 2/3 of RPC (ventral portion) in cats". After lesion of the dorsal part of the RPC (Jouvet, 1967), the cats showed fear or rage behavior and an apparent "hallucinatory-like" state.

Concurrently, SS has been induced in the raphe nuclei (St-Laurent et al., 1973a) which is known to be involved in sleep phenomena (Jouvet, 1967). The main behavioral characteristics accompanying SS from raphe was diffused exploration and dispersed locomotion.

There appears then to be an organization of exploration observed at SS sites. Indeed, the exploratory behavior seems to be focalized at the ALH and PLH, non-focalized and scattered at the VMT, diffused at the raphe, and non-systematic at the dorsal RPC levels (St-Laurent et al., 1973a).

As noted above, in addition to SS and flight reactions which can be elicited from stimulation of certain brain sites, both approach SS and flight reactions can be obtained from

stimulation of other brain areas. Some workers have applied the term "ambivalent behavior" for this phenomenon (Olds, 1960a; Olds and Olds, 1963; St-Laurent and Beaugrand, 1971; 1972; St-Laurent and Olds, 1964; St-Laurent et al., 1973). In the type of ambivalent behavior described by St-Laurent and Beaugrand (1972) and St-Laurent et al. (1973), simultaneous approach withdrawal reactions were displayed by rats in single-lever operant conditioning boxes. Ambivalence was quantitatively defined as the reaction of withdrawing following SS, approaching the lever again to self-stimulate, retreating again, and so forth. In all of these studies, ambivalence was considered to involve mixed motivational effects (both the positive and negative motivational systems as described by Olds in 1960). It was found that different behavioral patterns, depending on the site of implantation, were involved in ambivalence (St-Laurent et al., 1973). Moreover, the intensity of SS and withdrawal was found to be higher in ambivalent rats implanted in posterior areas than in anterior areas, suggesting the existence of a gradient of ambivalence with the more posterior areas yielding the highest intensity. Ambivalence can be elicited from the septal area, the fornix, the medial hypothalamus, the reticular mesencephalic formation, and the dorsolateral reticular nucleus of the pons. Moreover, the most intense ambivalent behavior was obtained from the RPC where, in addition, hallucinatory-like behavior were at times noted (St-Laurent and Beaugrand, 1972; St-Laurent et al., 1973b; 1973c).

As seen in this review of the literature, there is a scarcity of information on the behavioral correlates of ICSS. As of yet, there is no comprehensive study of the various behavioral correlates of ICSS. For exemple, phenomena, such as sniffing, exploration and various motor activities from ICSS sites at various levels of the CNS have yet to be described. It would be important to determine whether a particular pattern of behavior is always associated with ICSS, independent of the site of stimulation. Such a study may help to elucidate further the nature of the SS system.

OBJECTIVES

The present experimental work was undertaken with four aims. First, the carrying out of an extensive mapping description of the brain sites which yield the self-stimulation (SS) phenomenon. The sites studied extended anterio-posteriorly from the telencephalic to the pontic levels and aimed at completing the existing knowledge on this topic. Second, the study in detail of the behaviors (exploratory and motoric reactions, etc.) associated with intracranial self-stimulation behavior depending on the site stimulated. The question was asked whether a single behavioral pattern is associated with the SS phenomenon or if there are different patterns which vary according to the site stimulated. Two hypothesis motivated this part of the work: 1) The behavioral reactions associated to ICSS are due to the current diffusion towards neighbouring structures and, therefore, are not functionally related to the reinforcement process; 2) some of these behavioral features or reactions (e.g. exploratory reactions) may be due to the activation of the same reinforcing neurons. This second hypothesis, if supported, may provide useful information related to the phylogenetic significance of the reinforcement system. Third, the exploration of the possible existence of flight reactions in the pons and also a mapping and comparative description of the ambivalent reactions elicited from various brain sites. Fourth, a partial and limited study of the neurochemical substrata of the ICSS behavior using pharmacological agents known to act on the monoamine systems.

EXPERIMENTAL PART I

BEHAVIORAL CORRELATES OF BRAIN STIMULATION

I - Material and Methods

A total of 148 male Sprague-Dawley albino rats weighing between 250-300 g at the time of surgery were used for the topography study. For the two subsequent studies (ICSS - associated behavioral patterns and ambivalence), 48 and 32 of these animals were used. Bipolar insulated electrodes (0.25 mm in diameter) were implanted stereotaxically under sodium pentobarbital in the: a) nucleus reticularis pontis caudalis (RPC) and the locus coeruleus (LC) at stereotaxic coordinates -8/1/6 & posterior to Bregma, lateral to the midline and below the skull surface respectively); b) median raphe nucleus (R, nucleus centralis superior) at -6.0 to 7.0/0.0/8.0 to 8.5; c) ventromedial tegmentum area (VMT) at -3.5/1.5/9; d) reticularis mesencephalic formation (RMF) at -3.5/1.5/6; e) posterior lateral hypothalamus (PLH) at -2/1.5/9; f) preoptic area (POA) and anterior lateral hypothalamus area (ALH) at +1.5 to 2.0/1.5/9; g; septal area (S) at+1.5/0.5/5; h) paraolfactory area POlf)at +4/0.5/5; and, i) mediofrontal cortex (MFcx) at +5/1/5. The incisor bar was level with the interaural plane.

Forty-eight animals were used for the first of the quantitative studies, i.e., for the study of the behavioral patterns associated with SS. The POlf and S subjects were pooled with the MFcx. Anatomically, these areas innervated by the MFB are known as the mesocortex (MCx) and are part of the rhinencephalon. Neurophysiologically, they all have a low after-discharge and convulstion threshold. In addition, behaviorally they show similar patterns (Bogacz et al., 1965). Hence, this group will be referred to as mesocortex (MCx) rats.

The number of animals per group was as follows: RPC: n=8; R: n=8; VMT: n=8; PLH: n=8; ALH: n=8; MCx: n=8.

For the ambivalence study, the animals were distributed as follows: RPC: n=8; R: n=8; RMF: n=4; VMT: n=4; and S: n=8.

II - Behavioral Training, Testing and Analysis of Data

Eight days after surgery, rats were trained to self-stimulate five days a week, one hour daily, by pressing a bar in a 30 cm x 20 cm x 40 cm transparent acrylic box. Stimulation was a 250 msec. train of 60 cycles/sec. sine wave current. The current intensity varied between 5 and 70 μA rms and was determined individually for each rat by raising the current intensity by steps of 5 μA during the first days of training until maximal SS behavior was obtained. Training for SS was continued until the arbitrary criterion of at least 600 bar-presses per 60 min. was reached and until relatively constant rates (less than 5% variance) of bar pressing for one hour daily sessions were obtained for 3 consecutive days. Animals not reaching these criteria were discarded.

On the experimental day, animals were allowed to self-stimulate for 30 minutes. All behavioral observations were based on a 3 min. period of film (Beaulieu 3 mm). Each animal was classified as either a "self-stimulator" or as an "ambivalent" subject. The term "self-stimulation" was defined as an action of consecutive bar-pressing, without signs of flight, even at the highest current intensity (70 μA rms). "Ambivalence" was defined as a consistent action of approaching the lever and depressing it, but withdrawing following stimulation at threshold, then approaching the lever again, depressing it, and so forth.

Subsequently, the films of the SS animals were analysed; the behaviors displayed by these animals were classified and scored independently by three raters (inter-rates reliability: 70%). The behaviors were graded on the basis of the following parameters: SS, sniffing, exploration (focalized, scattered and diffused), locomotion (diffused and focalized), lull and idiosyncratic behaviors. The frequency of SS was graded in three categories: high (over 600 responses for 10 min.), moderate (301-600), and low (100-300)). The term "sniffing" was used when the animal was moving his nose and vibrissae. When the animal was sniffing with his nose pointed down towards a restricted area of the lever or an adjacent side in the anterior 1/3 of the box, it was interpreted as "focalized exploration". When the animal showed sniffing with his nose maintained up 1 to 2 inches above the lever, while giving quick inquisitive glances around the lever and its adjacent sides, it was interpreted as "scattered". When the animals showed sniffing in the posterior 2/3 of the box, they were considered as showing "diffused exploration". The term "locomotion" means general body activity and was sub-divided into focalized and diffused; locomotion in the anterior 1/3 of the box, which included the action of pressing the lever, was considered as focalized locomotion, whereas action involving a displacement of body into the posterior 2/3 of the box was considered as diffused locomotion. The term "lull" means an interruption of ongoing body activity which followed SS; "arrest" response means an interruption immediately consecutive to a bar-press; the terms "hébêté,

dazed, withdrawn" indicate a "lull" with the head raised up and the rat apparently "staring blankly into space". When an object, such as the tip of a pencil, was presented to the animal, it would come out of this daze behavior and explore the object, contrary to what would be expected if the animal had been in a "petit mal absence" like state.

Bogacz et al. (1965) have demonstrated that while epileptiform activity usually accompanies SS from anterior areas such as MCx, POA and ALH when using current intensity above SS threshold, this phenomenon was absent during SS from more posterior areas, such as PLH and VMT. This was the case even when current intensities used were eight times higher than SS threshold, producing forced movements such as rotation of head and circling.

The behaviors were considered as "idiosyncratic" when they appeared in less than nine subjects out of 148. For statistical treatment, as shown in Tables 2 and 3, when compared with animals placed in a skinner box, the intensity of the various described behaviors, for SS subjects, were arbitrarily graded as decreased (-1), not present or not changed (0), low (+1), moderate (+2), or high (+3). The idiosyncratic behaviors (Table 1) were considered as present or not present and were not statistically analysed. The Kolmogorov-Smirnov test for small numbers of individuals ($n \leq 40$) (Siegel, 1956) was used in the statistical analysis of the graded behavioral concomitants of SS in the various areas: RPC; R; VMT; PLH; ALH and MCx (Table 2). As well, the scores were correlated and factored (Siegel, 1956) (Table 3). Upon completion of the experiment, the animals

were sacrificed with an overdose of sodium pentobarbital (200 mg/kg, ip). The brains were perfused with 10% formalin, and transverse sections were made for histological verification of electrode positions (Klüver and Barrera technique).

The behaviors of the ambivalent subjects were graded on the basis of the following parameters: approach speed, withdrawal (or flight) speed, interval period, lull period, amount of diffused exploration, amount of focalized exploration, and amount of locomotor activity. Approach speed corresponds to the time involved in approaching and pressing the lever. Withdrawal speed refers to the speed of moving back after bar-pressing, varying from stepping back to jumping back from the lever. By interval period is meant time spent between two bar-presses. A lull consists of stopping after withdrawal or during bar-pressing, varying from a brief pause to freezing (i.e., comparatively long interruption of spontaneous behavior). When the animal showed sniffing in the distal 2/3 of the box away from the lever, the action was classified as diffused exploration. Focalized exploration consisted of the animal sniffing in the proximal 1/3 of the box near the lever. Locomotor activity included such phenomena as pressing of the lever, displacement of the limbs or displacement of the body. The relative intensities of the behaviors for ambivalent subjects were graded on a six point scale with arbitrary weighed values varying between: (0) not present, (+1) low, (+2) low-moderate, (+3) moderate, (+4) moderate high, and (+5) high. This scale is quantitatively described in Table 4. The Kolmogorov-Smirnov test for small numbers of

individuals was used for statistical analysis. Upon completion of the experiment, subjects were sacrificed for histological verification of electrodes positions, using the same techniques as for the other studies on SS subjects.

III - Qualitative Phenomenological Mapping

a) Objectives of the Qualitative Study:

In this first step of the study on the behavioral correlates of ICSS, a qualitative phenomenological mapping description of the various behavioral patterns accompanying SS, flight and ambivalent behaviors obtained from stimulation of various brain sites is presented; to our knowledge, no such comprehensive mapping exists.

b) Qualitative Findings:

Figures 2 to 6 and their respective legend sections from Pellegrino and Cushman (1967), illustrate the various brain areas studied and the behavioral features correlated with SS, with flight and ambivalent behaviors from these areas. A list of anatomical abbreviations is given on pages 46 and 47. Figure 7 (page 49), illustrates schematically most of the major and minor behavioral features observed from the stimulation of various brain implantation sites.

SELF-STIMULATION

1) Meso Cortex (MCx): Medio-Frontal Cortex, Paraolfactory and Septal Area: (Fig. 2, Sections A to E are from Pellegrino and Cushman, 1967, pages 8, 9, 14, 18 and 21 respectively). These anterior structures yield low frequency SS. The major correlated behavioral feature was "arrest" responses. The

other behavioral features were sniffing with the nose of the animal pointing horizontally, along with low focalized and diffused exploration and low motor activity.

2) Pre-Optic Area and Anterior Lateral Hypothalamus: (Fig. 2, Section E to I, pages 21, 24, 26, 30 and 33, Pellegrino and Cushman, 1967). At the level of the POA and ALH, moderate SS frequency was observed, correlated with high intensity of sniffing and focalized exploration (the animal sniffing with its nose pointed downward in a restricted area proximal to the lever). The other features were diffused exploration, moderate but obvious increase of forward-directed motor activity when compared with the MFcx and S animals.

3) Posterior Lateral Hypothalamus: (Fig. 3, Sections A to E, pages 38, 42, 43 and 44, Pellegrino and Cushman, 1967). High SS was noted. Lapping and biting were observed but there were no minor behavioral features, all behaviors being of high intensity. The features observed were high sniffing, high focalized exploration, high increase of motor activity. In certain cases, these behaviors reached excitation, the animal grasping the lever with great force with his hindquarters moving from side to side.

4) Anterior Ventro-Medial Tegmentum: (Fig. 4, Sections A and B, pages 47 and 49 from Pellegrino and Cushman, 1967). Along with high SS, some of the same behavioral features as for the PLH could be observed, that is, high sniffing and high motor activity; however, the main type of exploratory pattern was high "scattered". Focalized and diffused explorations of low intensity were the other features. The focalized type of exploration was obtained from the more medial placements near the

inter-peduncular nucleus, while a different pattern of exploration was obtained from the lateral loci (substantia nigra). In this region, the nose was higher and the animal was giving quick inquisitive looks from side to side; we termed this type of exploration "scattered".

5) Posterior Ventro-Medial Tegmentum and Ventro-Medial Pontine Areas: (Fig. 4, Sections C and E, pages 54 and 57, Pellegrino and Cushman, 1967). One animal (101 D, section C), with its electrode located at the junction between the posterior VMT and anterior medial part of the pons, showed low SS with low sniffing and low focalized exploration as minor features. The major behavioral feature was high intensity of motor activity. A second animal (108 C), with its electrode at the level of the central tegmental nucleus (CT), showed moderate SS along with low diffused exploration and high scattered exploration.

6) Dorsal and Median Raphe Area: (Fig. 4, Section F, page 63; Fig. 5, Section A, page 66, Pellegrino and Cushman, 1967). During SS at low frequency, the main features were sniffing, and diffused exploration (the rat sniffing above the lever, its nose pointing horizontally or in an upward position. In addition, immediately following a few bar-presses, the animal often displayed a "bewildered" or "what is it" reaction, or showed abortive rearing responses near the lever, or explored the whole area of the box. The term "diffused" exploration was used to describe this type of activity. Another main behavioral feature was increased motor activity; the minor features were scattered and focalized exploratory activities.

7) Locus Coeruleus, Sub-Locus Coeruleus and Dorsal Reticularis Pontis Caudalis: (Fig. 5, Sections C and D, pages 69 and 70, Pellegrino and Cushman, 1967). i) Rats with an electrode implanted in the LC were observed to self-stimulate in bursts which were, at times, of very high frequency. However, it took considerable shaping to get the animal to self-stimulate. In addition, bar-pressing was frequently uncoordinated, the animals pressing with both paws and appearing to bounce on the lever with force accompanied by intense motor activity. Between bursts, the animals explored the environment in a non-systematic and fragmented fashion. That is, they displayed exploration of their bodies or the floor, the corners and the walls of the cage in a jerky staccato manner, showed rearing and also lull periods during which they appeared dazed and withdrawn, with blocking of exploration, staring blankly or taking an "hébêté-like" attitude, appearing not to know that to do next, that is, not being able to direct their behavior towards a goal.

ii) Rats with electrodes implanted in the Sub-LC area and dorsal part of the RPC self-stimulated at low rates. Following a few bar-presses, they would often show "adynamia" as defined by Jung and Hassler (1960), suddenly lying down for periods of 5 to 15 seconds. During these periods, the animals showed absence of movements but with conservation of other motor reflexes, such as righting responses. In addition, they might attempt to explore by crawling in various areas of the cage. The return of the tonus occurred suddenly. At times, the subjects interrupted their SS exploration-locomotion

patterns and showed undirected motor activity consisting of rearing on their hind limbs in the middle of the box, looking to left and right sides of the box, and then dropping on "all fours" and pausing before resuming SS. Two rats showed "hallucinatory-like" behavior. After rearing on his hind limbs, the rat batted its paws in mid-air and rolled its head as if it had no control of neck tonus; there also appeared to be a lack of equilibrium as the rat would fall, rather than drop down, on "all fours".

FLIGHT

1) Dorso-Medial Tegmentum: (Fig. 3, Sections A, B, C and D, pages 47, 49, 54 and 59, Pellegrino and Cushman, 1967). At low current intensity, i.e., 10mA above threshold, these animals were either freezing or backing up, and were classified as showing low flight reactions. All of these animals would eventually jump directly out of the box when given higher current intensity (i.e., 10mA above threshold); they were then classified as showing intense flight behavior.

2) Reticularis Pontis and Reticularis Pontis Caudalis: (Fig. 4, Sections A, B, C and D, pages 66, 68, 69 and 70, Pellegrino and Cushman, 1967). All 8 animals implanted in the ventral part of the RPO and RPC showed intense flight behavior, characterized by jumping out of the box.

AMBIVALENCE

1) Lateral Septal Nucleus and Hippocampal Commissure and Fornix: (Fig. 2, Sections A, B and C, pages 21, 26 and 30, Pellegrino and Cushman, 1967). The approach and flight were of low speed.

2) Reticular Mesencephalic Formation: (Fig. 4, Sections C and D, pages 54 and 59, Pellegrino and Cushman, 1967). The RMF animals were observed to approach the lever, press on it, and withdraw from it after each stimulation. This regular pattern was noted from the start, that is, at threshold SS.

3) Reticularis Pontis Oralis: (Fig. 4, Sections A and B, pages 66 and 68, Pellegrino anc Cushman, 1967). RPO subjects displayed violent ipsilateral propulsions of the body, of 45° to 90°. This behavior differed from turning movements, in that it started with the head and progressed to the trunk and the remaincer of the body as observed during SS at high current from the VMT. Another animal with implants in the anterior pons showed rapid stepping-back movements immediately following bar-pressing.

4) Locus Coeruleus, Sub-Locus Coeruleus and Dorsal Part of the Reticularis Pontis Caudalis: (Fig. 5, Sections C and D, pages 69 and 70, Pellegrino and Cushman, 1967). The LC animals did not show ambivalent behavior from the start. After a series of repetitive bursts of high frequency SS, the animals showed obvious aversive behaviors. They withdrew faster and further away from the lever following each burst of SS. Despite the increasingly aversive behavior, the animals drifted back to the lever to press again. In other words, they displayed ambivalent behavior. The ambivalent behavior elicited from the RMF was much more sterio-typed; both the moving away following each bar-press and the return approach to the lever, were fast and well directed. As for the Sub-LC and dorsal part of the RPC, as noted above, the SS was of low frequency. From time to time, after some bar-presses, th

animal displayed adynamia, i.e., sudden loss of tonus and diminution of movements. The return of the tonus occurred suddenly and the animal at times attempted to jump out of the box (as if being afraid of something) but eventually returned to the lever to self-stimulate. Other rats showed what appeared to be a mild type of ambivalence consisting of a slight aversive component usually limited to the pulling away of the paws from the lever. However, in some cases, the aversive component was probably masked by the hypotonia which the animals displayed after self-stimulating.

Figure 1

Histological Findings

The RPC probes were found in the dorsal and anterior portion of this area, in or near the LC or the decussation of the brachium conjunctivum (DBC). The raphe probes were located in the median nucleus of raphe at the level of the pons. The VMT probes were located in an area lateral to the interpeduncular nucleus, either in the area of the Tsai or more laterally in the substantia nigra. The PLH probes were placed in the dorsolateral hypothalamus at the level of or anterior to the mamillary bodies, in or around the medial forebrain bundle (MFB), in or around the rostral portion of the area of Tsai and the field of Forel, or in the substantia nigra or the cerebral peduncles. The ALH probes were located at a point between the lateral preoptic and the anterior amygdaloid areas bordering on the anterior part of the septal area. The POlf probes were located in front of the septal area at the boundary between the hippocampus and the medial part of the corpus callosum and caudate nucleus. The MFcx probes were found slightly anterior compared to the POlf probes.

Figure 1

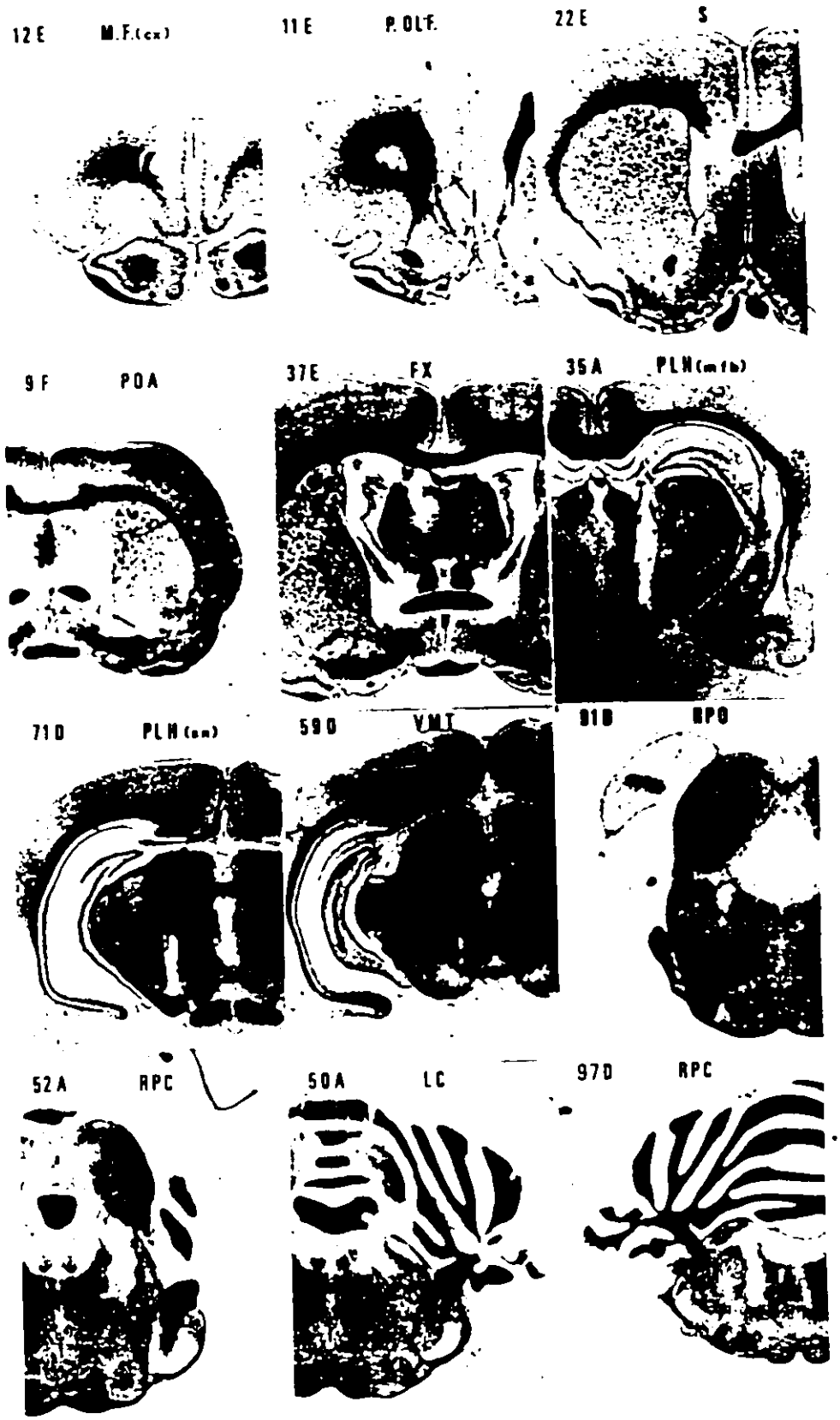

12E M.F.(cx)
11E P.OLF.
22E S
9F POA
37E FX
35A PLH(mfb)
71D PLH(sm)
59D VMT
91B RPO
52A RPC
50A LC
97D RPC

Figure 2

SELF-STIMULATION RATES AND BEHAVIORAL CHARACTERISTICS OF BRAIN STIMULATION

Electrode point and self-stimulation rates are indicated by symbols as follows: ▬ = High (over 601 responses /10 min.). ▲ = moderate (301-600), ● = low (51-300), and ○ = neutral. Intensity of behaviors are indicated as follows: ✦ = High; ✧ = Low. Intensity of ambivalence behaviors are indicated as follows: ✶ = High; ✲ = Low.

Brain sections A to I are from Pellegrino and Cushman (1967: pages 8, 9, 14, 18, 21, 24, 26, 30 and 31 respectively).

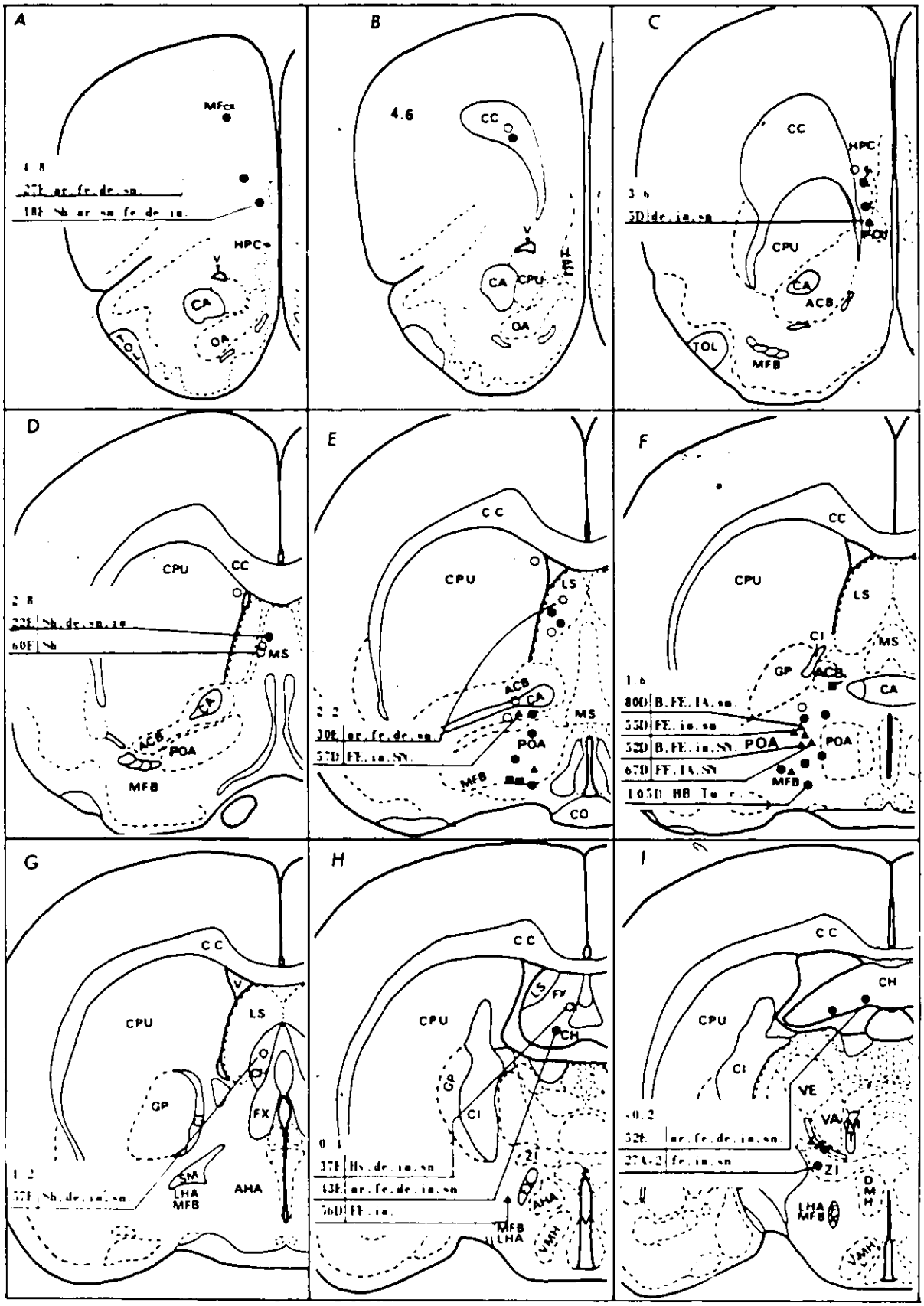
Anatomical abbreviations

ACB:	Lateral paraolfactory area	LS:	Lateral septal nucleus
AHA:	Anterior hypothalamic area	MFB:	Medial forebrain bundle
CA:	Anterior commissure	MFcx:	Medio frontal cortex
CC:	Corpus callosum	POA:	Lateral preoptic area
CH:	Hippocampal commissure	SM:	Stria medullaris thalami
CPU:	Caudate nucleus	V:	Ventricle
DMH:	Dorsomedial nucleus of hypothalamus	VA:	Ventricle nucleus of thalamus, anterior part
FS:	Fornix	VE:	Ventral nucleus of thalamus
GP:	Globus pallidus	VMH:	Ventromedial nucleus of hypothalamus
LHA:	Lateral hypothalamic area		
LM:	Medial lemniscus		

Abbreviations of observed behaviors

ar:	Arrest	Sh:	Shivering
de:	Low diffused exploration	sn:	Low sniffing
fe:	Low focalized exploration	SN:	High sniffing
FE:	High focalized exploration	H B Tu c:	Head and body turning contra
ia:	Low increased motor activity	Hy:	Hypotonia
IA:	High increased motor activity	B:	Biting

Individual rats are identified by numbers on the left hand side (e.g. 27E)


A
MFCx
HPC
V
CA
OA
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4.6
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MFB
VMH

Figure 3

SELF-STIMULATION RATES AND BEHAVIORAL CHARACTERISTICS OF BRAIN STIMULATION

Electrode points, SS rates and intensity of various behaviors are indicated as described in the legend to Fig. 2.

Brain sections A to E are from Pellegrino and Cushman (1967: pages 38, 42, 43, 44 and 46 respectively).

Anatomical abbreviations

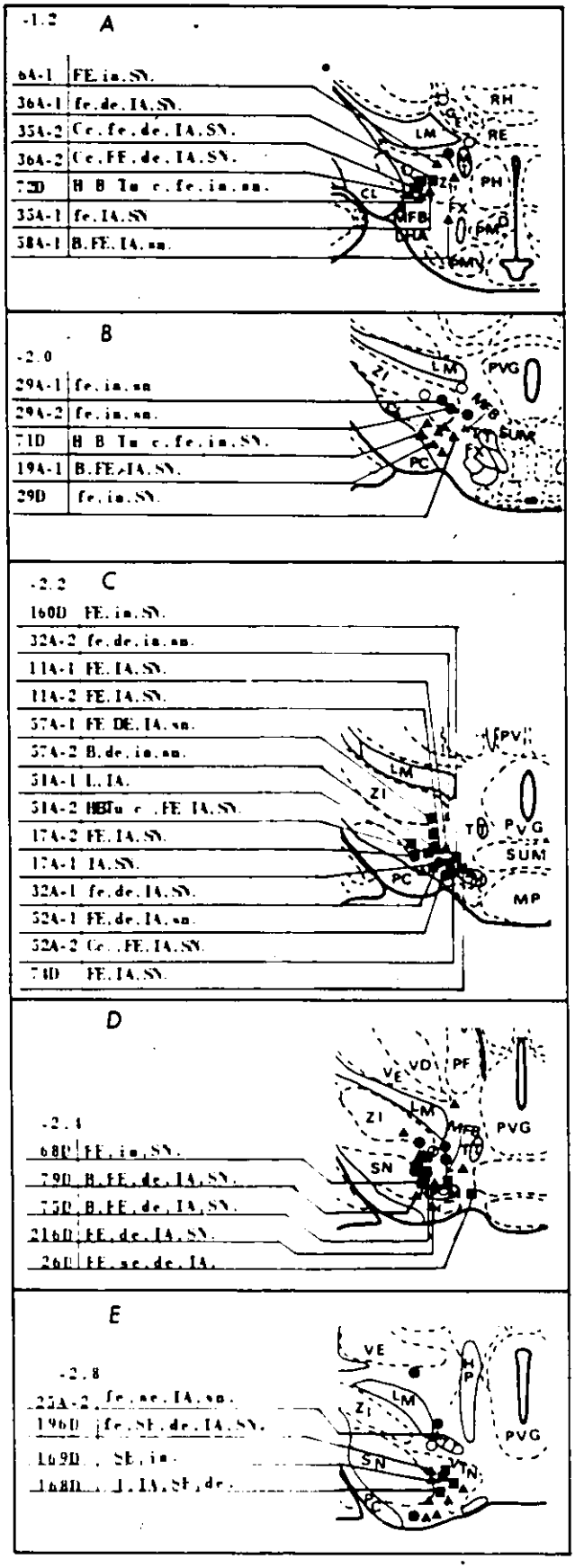
CL: Nucleus of Luys
Fx: Fornix
HP: Tractus bahenulo-interpeduncularis
LM: Medial lemniscus
MM: Medial mamillary nucleus
MP: Posterior mamillary nucleus
PC: Cerebral peduncle
PF: Nucleus parafascicularis thalami
PH: Posterior nucleus of hypothalamus
PMD: Dorsal premamillary nucleus
PMV: Ventral premamillary nucleus
PVG: Central grey substance
RE: Ventral nucleus of thalamus
SN: Substantia nigra
TT: Mamillotegmental tract
VE: Ventral nucleus of thalamus
VTN: Tsai's ventral tegmental nucleus
ZI: Zona incerta

Abbreviations of observed behaviors

de: Low diffused exploration
DE: High diffused exploration
fe: Low focalized exploration
FE: High focalized exploration
H B Tu c: Head and body turning contra
ia: Low increased activity
IA: High increased activity
J: Jaw movements
L: Licking
se: Low scattered exploration
SE: High scattered exploration
sn: Low sniffing
SN: High sniffing

Individual rats are identified by numbers on the left hand side (e.g. 27E).

Figure 3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6A-1 FE.ia.SN.
36A-1 fe.de.IA.SN.
35A-2 Ce.fe.de.IA.SN.
36A-2 Ce.FE.de.IA.SN.
7?D H B Tu c.fe.ia.sn.
35A-1 fe.IA.SN
38A-1 B.FE.IA.sn.
RH
RE
LM
PH
FX
FM
B
-2.0
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29A-2 fe.ia.sn.
71D H B Tu c.fe.ia.SN.
19A-1 B.FE.IA.SN.
29D fe.ia.SN.
ZI
LM
PVG
SUM
PC
C
-2.2
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32A-2 fe.de.ia.sn.
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57A-2 B.de.ia.sn.
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32A-2 FE.de.IA.sn.
32A-2 Ce..FE.IA.SN.
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-2.4
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79D B.FE.de.IA.SN.
75D B.FE.de.IA.SN.
216D FE.de.IA.SN.
26D FE.se.de.IA.
VE
VD
PF
LM
ZI
MFB
PVG
SN
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-2.8
25A-2 fe.se.IA.sn.
196D fe.SE.de.IA.SN.
169D . SE.ia.
168D . J.IA.SE.de.
VE
HP
LM
ZI
PVG
SN
VTN
PC

Figure 4

SELF-STIMULATION RATES AND BEHAVIORAL CHARACTERISTICS OF BRAIN STIMULATION

Electrode points, SS rates and intensity of various behaviors are indicated as described in the legend to Fig.2 and 3.

Brain sections A to F are from Pellegrino and Cushman (1967: pages 47, 49, 54, 56, 59 and 63 respectively).

Anatomical abbreviations

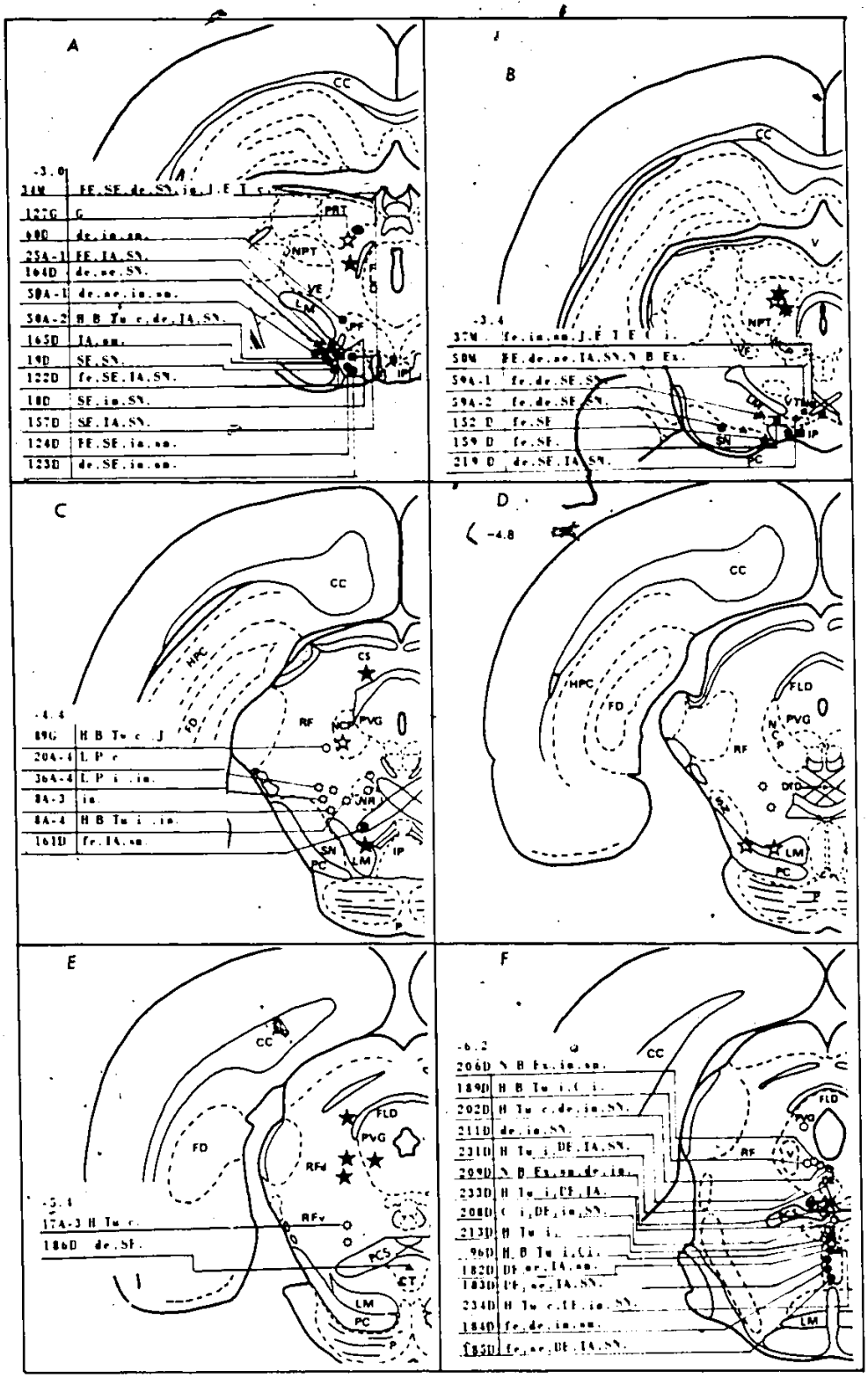
CS: Superior colliculus
DTD: Decussatio tegmenti dorsalis
FDL: Dorsal fasciculus of Schütz
IP: Interpeduncular nucleus
LM: Medial lemniscus
NCP: Nulceus proprius commissure
NPT: Nucleus posterior thalami
NR: Red nucleus
PC: Cerebral peduncle
PCS: Superior cerebellar peduncle
PF: Nucleus parafascicularis thalami
PVG: Central grey substance
RF: Reticular formation of mesencephalon
SN: Substantia nigra
VTN: Tsai's ventral tegmentum nucleus

Abbreviations of behaviors

Ci: Circling ipsi
de: Low diffused exploration
DE: High diffused exploration
fe: Low focalized exploration
FE: High focalized exploration
G: Gnawing
H Tu c: Head turning contra
H Tu i: Head turning ipsi
H B Tu c: Head and body turning contra
H B Tu i: Head and body turning ipsi
H B Tw c: Head and body twisting contra
ia: Low increased motor activity
IA: High increased motor activity
J: Jaw movements
LP i: Lateral body projection ipsi
N B Ex: Neck and body extension
se: Low scattered exploration
SE: High scattered exploration
sn: Low sniffing
SN: High sniffing

Individual rats are identified by numbers on the left hand side (e.g. 27E)

Figure 4


A
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CS
RF
NCP
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DTD
FLD
P
RFd
RFv
PCS
CT
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-3.4
-4.4
-4.8
-5.4
-6.2

Figure 5

SELF-STIMULATION RATES AND BEHAVIORAL CHARACTERISTICS OF BRAIN STIMULATION

Electrode points, SS rates and intensity of various behaviors are indicated as described in the legend to Fig. 2-4.

Brain sections A to F are from Pellegrino and Cushman (1967: pages 66, 68, 69, 70, 71, and 73 respectively).

Anatomical abbreviations

MR: Median Raphe
RPO: Reticularis pontis oralis
RPC: Reticularis pontis caudalis
LC: Locus coeruleus
PCS: Superior cerebellar peduncle
RP: Reticular parvocellularis
RG: Reticular gigantocellularis

Abbreviations of observed behaviors

H Tu i: Head turning ipsi
NF: Neck flexion
Hy: Hypotonia
NBFx: Neck and body extension
J: Jaw movement
ETECi: Ear twitch and eye closure ipsi
HBTw i: Head and body twisting ipsi
HBTu i: Head and body turning ipsi
Sq: Squealing

Individual rats are identified by numbers on the left hand side (e.g., 27E).

Figure 5

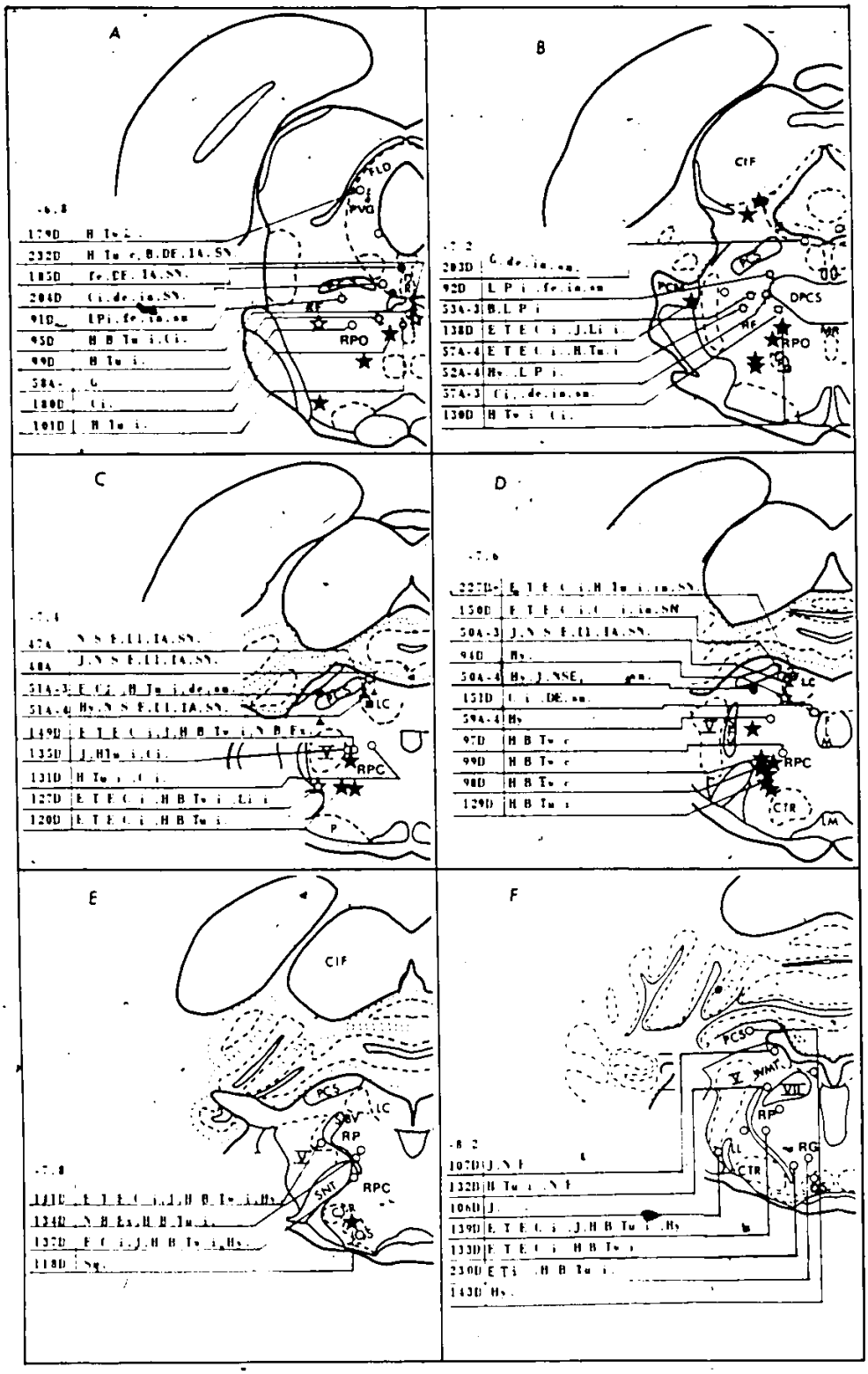

A
FLO
PVO
RPO
B
CIF
PCS
DPCS
RF
MR
RPO
C
LC
RPC
P
D
LC
RPC
CTR
LM
E
CIF
PCS
DBV
LC
RP
SNT
RPC
CTR
F
PCSO
V SNMT
VII
RP
CTR
RG

Figure 6

SELF-STIMULATION RATES AND BEHAVIORAL CHARACTERISTICS OF BRAIN STIMULATION

Electrode points, SS rates and intensity of various behaviors are indicated as described in the legend to Fig. 2-5.

Brain sections A and B are from Pellegrino and Cushman (1967: page 80).

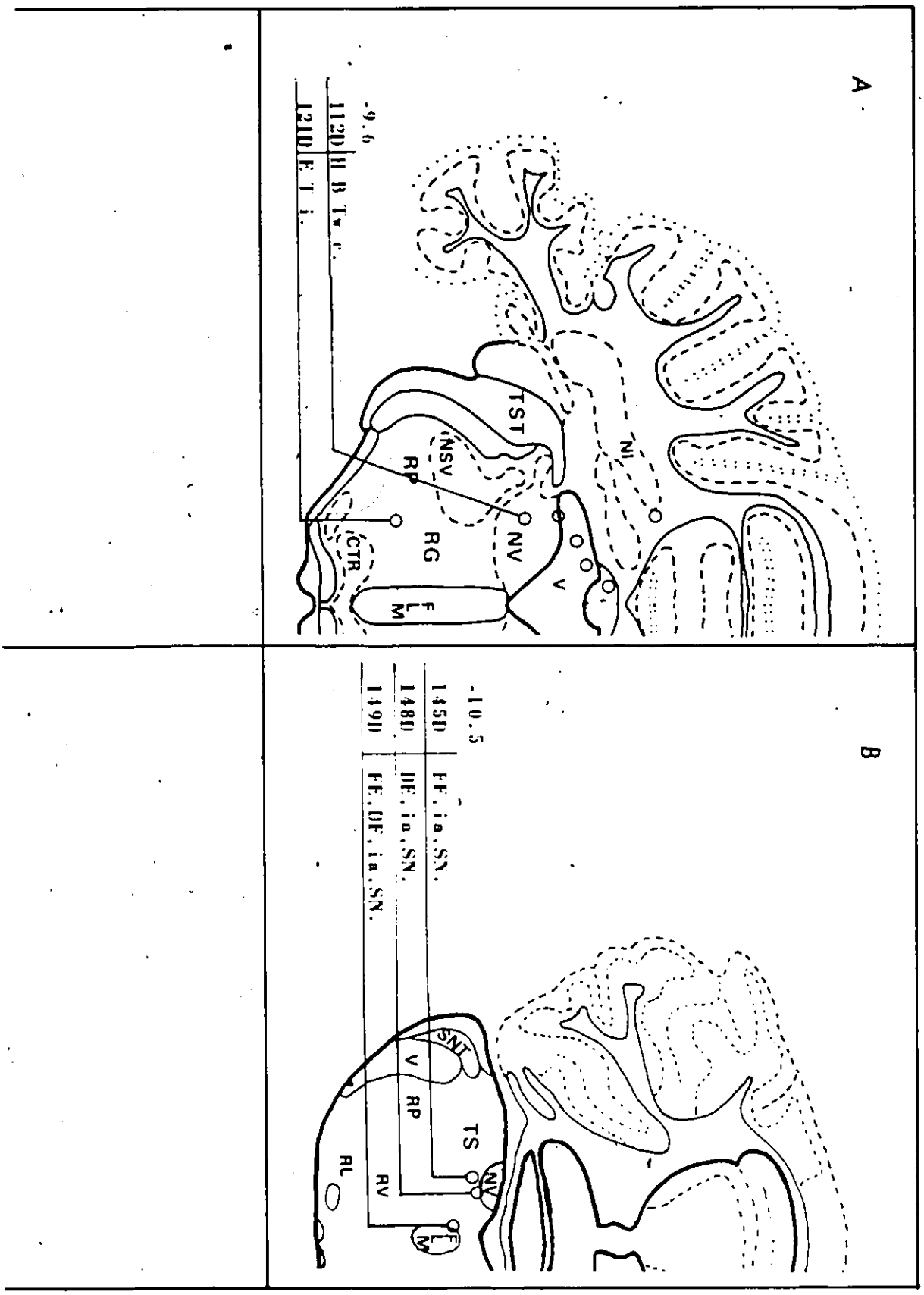
Anatomical abbreviations

CTR: Nucleus corporis trapezoidei
FLM: Medial longitudinal bundle
LL: Lateral lemnicus
NCV: Ventral cochlear nucleus
ND: Nucleus dentatus
NI: Nucleus interpositus
NPV: Medial vestibulary
PCI: Pedunculus cerebellaris inferior
PCS: Pedunculus cerebellaris superior
RG: Nucleus gigantis reticularis
RP: Nucleus parvocellularis
RV: Nucleus reticularis ventralis
SBV: Ventral spinocerebellar tract
TST: Root of spinal tract of trigeminal nerve
V: Spinal nucleus of fifth nerve

Abbreviations of observed behaviors

DE: High diffused exploration
E T i: Ear twitching ipsi
FE: High focalized exploration
ia: Low increased activity
H B Tw c: Head and body twisting contra

Individual rats are identified by numbers on the left hand side (e.g., 27E).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1120
1210
TST
INSV
RP
RG
CTR
NV
NI
V
FLM
B
-10.5
1450
1480
1490
FF, ia, SN.
DF, ia, SN.
FF, DF, ia, SN.
SNT
V
RP
TS
NV
RV
RL
FLM

Figure 6

LIST OF ANATOMICAL ABBREVIATIONS

ACB	Lateral parolfactorial area
CA	Anterior commissure
CH	Hippocampal commissure (Commissura fornicis)
CL	Nucleus of Luys (subthalamicus)
CT	Central tegmental nucleus
CTR	Trapezoid nucleus
DBC	Decussation of brachium conjunctivum
DPCS	Decussation of superior cerebellar peduncles
DR	Dorsal nucleus of raphe
DTD	Decussation of Meynert (tegmenti dorsalis)
DTV	Decussation of Forel (tegmenti ventralis)
FLD	Dorsal fasciculus of Schütz (longitudinal bundle)
FLM	Medial longitudinal bundle
FX	Fornix (Corpus, columna)
HP	Tractus habenulo-interpeduncularis (Fasciculus, retroflexus)
HPC	Hippocampus (Cornu Ammanis)
IP	Interpeduncular nucleus
LC	Locus Coeruleus
LL	Lateral lemniscus
LM	Medial lemniscus
LS	Lateral spetal nucleus
MFB	Medial forebrain bundle
MFcx	Medial frontal cortex
ML	Lateral mamillary nucleus
MR	Medial nucleus of raphe
MS	Medial septal nucleus
NMT	Mesencephalic nucleus of trigeminal nerve
NPV	Medial vestibular nucleus
OS	Superior olivary nucleus
PC	Cerebral peduncle
PCM	Middle cerebellar peduncle
PCS	Superior cerebellar peduncle
PF	Nucleus parafascicularis thalami
PM	Mamillary peduncle

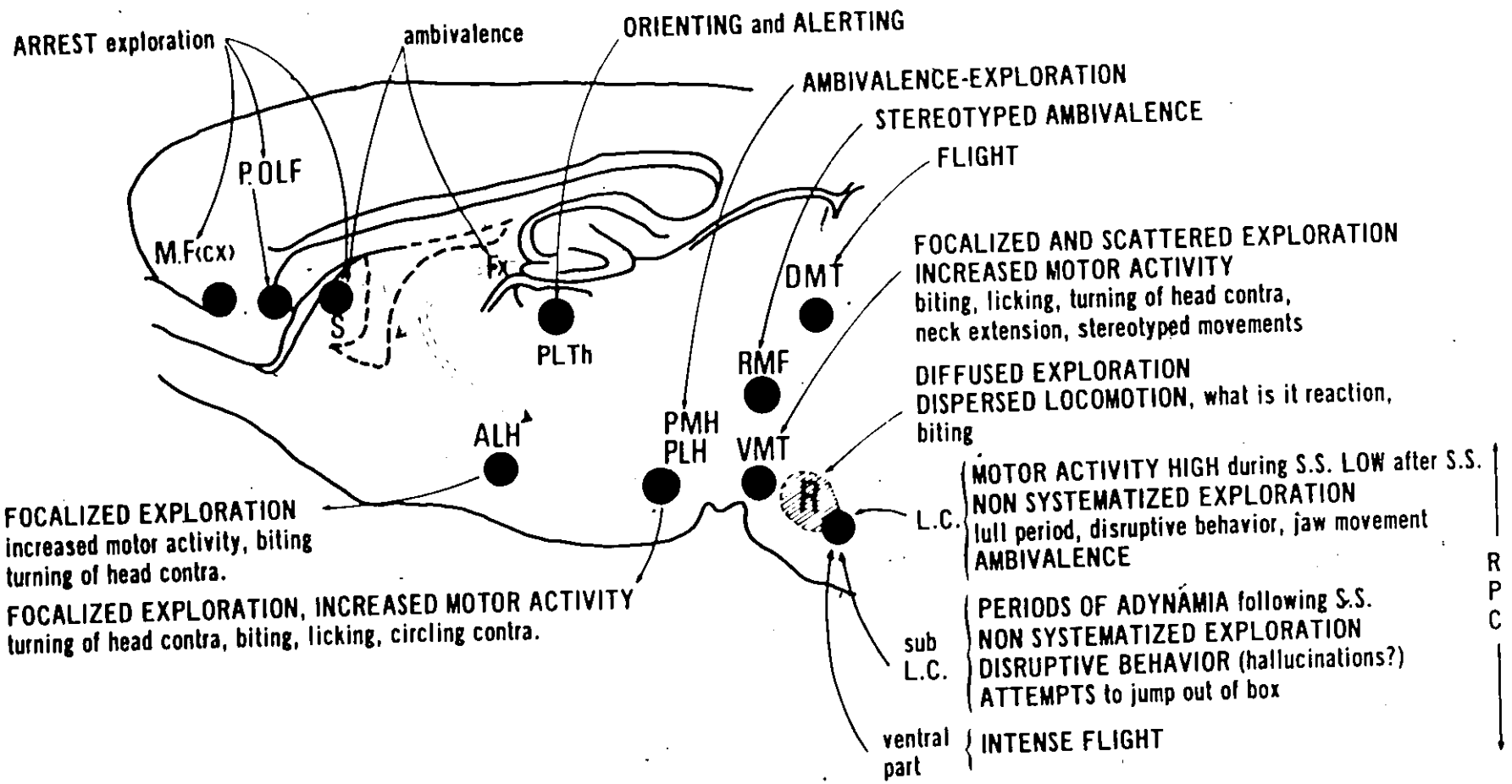
POA	Lateral preoptic area
POlf	Paraolfactory area
PRT	Pretectal area
PVG	Central grey substance
RFd	Reticular formation of mesencephalon (dorsal)
RFv	Reticular formation of mesencephalon (ventral)
RG	Reticularis celluraris giganto
RP	Reticularis cellularis parvo
RPC	Reticularis pontis caudalis
RPO	Reticularis pontis oralis
SBV	Ventral spinocerebellar tract
SN	Substantia nigra
SNT	Nucleus of spinal tract of trigeminal nerve
SUM	Area supramamillaris
TT	Mamillotegmental tract
V	Mesencephalic nucleus of trigeminal nerve
Vll	Facial nerve
VT	Ventral tegmental nucleus
VTN	Tsai's ventral tegmental nucleus
Z	Zona incerta

Figure 7

The major and minor behavioral features observed from the stimulation of various brain areas.

Anatomical abbreviations: RPC: Reticularis pontis caudalis; DMT: Dorsomedial tegmentum; VMT: Ventromedial tegmentum; PMH: Posterior medial hypothalamus; PLH: Posterior lateral hypothalamus; ALH: Anterior lateral hypothalamus; PLTh: Posterior lateral thalamus; S: Septum; POlf: Paraolfactory area; MFcx: Mediofrontal cortex; LC: Locus coeruleus; Sub-LC: Sub-Locus coeruleus; R: Raphe.

Figure 7


ARREST exploration
ambivalence
ORIENTING and ALERTING
AMBIVALENCE-EXPLORATION
STEREOTYPED AMBIVALENCE
FLIGHT
P.OLF
M.F(cx)
S
Fx
PLTh
DMT
RMF
PMH
PLH
VMT
ALH
R
FOCALIZED AND SCATTERED EXPLORATION
INCREASED MOTOR ACTIVITY
biting, licking, turning of head contra,
neck extension, stereotyped movements
DIFFUSED EXPLORATION
DISPERSED LOCOMOTION, what is it reaction,
biting
FOCALIZED EXPLORATION
increased motor activity, biting
turning of head contra.
FOCALIZED EXPLORATION, INCREASED MOTOR ACTIVITY
turning of head contra, biting, licking, circling contra.
L.C.
MOTOR ACTIVITY HIGH during S.S. LOW after S.S.
NON SYSTEMATIZED EXPLORATION
lull period, disruptive behavior, jaw movement
AMBIVALENCE
sub L.C.
PERIODS OF ADYNAMIA following S.S.
NON SYSTEMATIZED EXPLORATION
DISRUPTIVE BEHAVIOR (hallucinations?)
ATTEMPTS to jump out of box
ventral part
INTENSE FLIGHT
R P C

IV - Quantitative Analysis of Stimulation-Induced Behavioral Patterns

SELF-STIMULATION GROUP (The threshold of significance or alpha level for all subsequent statistical treatments is 0.05. See Table 2 for degree of significance).

1) Meso cortex (septum, paraolfactory and mediofrontal areas MCx: The electrodes of these anterior areas elicited significantly lower ($p<0.05$) rates of SS compared to ALH, PLH or VMT. Concerning the behaviors observed with self-stimulation from the S, POlf and MFcx, sniffing was significantly less ($p<0.05$) than for the PLH group, but did not differ from the other groups.

This meso cortex group differed from other groups in that arrest responses were observed in this group exclusively. Arrest was a major feature for this group.

Focalized exploration was noted in all 8 subjects; however, the intensity was lower compared to ALH, PLH or VMT subjects. The rats of the meso cortex group showed significantly more ($p<0.05$) "diffused" exploration than the anterior lateral hypothalamus subjects, but less ($p<0.05$) than the Raphe.

The meso cortex subjects also showed significantly less ($p<0.05$) focalized locomotion compared to ALH, PLH or VMT rats, but had as much diffused locomotion as for these groups and less than the Raphe.

2) Anterior Lateral Hypothalamus: There were no significant differences between ALH and PLH is SS rates. However, the ALH subjects self-stimulated significantly less ($p<0.05$) than the VMT subjects, but significantly more ($p<0.05$) than the MCx and Raphe rats. The ALH subjects did not show more focalized exploration than the PLH, but significantly more

($p<0.05$) than all other groups. There was significantly less ($p<0.05$) diffused exploration in ALH than in other groups (i.e., MCx, VMT, Raphe or RPC). There was no scattered exploration elicited from the ALH.

Concerning focalized locomotion, there was no significant difference between ALH, PLH, Raphe and RPC. There was significantly more ($p<0.05$) focalized locomotion for the ALH group than for the MCx, but less ($p<0.05$) than for the VMT group. Diffused locomotion was found less intense ($p<0.05$) when compared to Raphe.

3) Posterior Lateral Hypothalamus: Self-stimulation rates were significantly higher ($p<0.05$) for the PLH animals than for MCx or Raphe rats. There was significantly more sniffing ($p<0.05$) compared to MCx or RPC animals. There was significantly more ($p<0.05$) "focalized" exploration for PLH than for MCx, Raphe or RPC rats, and significantly less ($p<0.05$) "diffused" exploration than for Raphe and RPC. There was no evidence of scattered exploration. Concerning "focalized" locomotion, there was significantly more ($p<0.05$) than for MCX, Raphe and RPC rats. Diffused locomotion was significantly less ($p<0.05$) in PLH than in Raphe animals. As for ALH, there was no evidence of lull periods.

4) Ventromedial Tegmentum: Self-stimulation rates for VMT were significantly higher ($p<0.05$) than those for MCx, ALH or Raphe, but not significantly different from those of PLH and RPC animals. Focalized exploration in the VMT was significantly more intense ($p<0.05$) compared to the MCx, Raphe or RPC,

but less intense ($p<0.05$) compared to ALH. VMT subjects had significantly more ($p\leq0.05$) diffused exploration than ALH, but less ($p<0.05$) than Raphe. Scattered exploration at the level of the VMT was significantly higher ($p\leq0.05$) compared to MCx and ALH, but not significantly different from the more posterior Raphe and RPC areas. There was significantly less ($p<0.05$) diffused locomotion compared to Raphe subjects; however, except for the PLH group, there was significantly more ($p<0.05$) focalized locomotion than for all the groups: MCx, ALH, Raphe and RPC. Lull periods were not observed following VMT stimulation.

5) Raphe: The rates of Raphe SS were significantly lower ($p<0.05$) compared to ALH, PLH or VMT. There was significantly less ($p<0.05$) "focalized" exploration than for ALH, PLH or VMT subjects. However, scattered exploration was significantly higher ($p<0.05$) for the Raphe than for MCx, ALH or PLH rats. Raphe animals showed significantly higher ($p\leq0.05$) "diffused" exploration than all other groups, i.e., MCx, ALH, PLH, VMT or RPC animals.

There was significantly more diffused locomotion ($p<0.05$) compared to MCx, ALH, PLH or VMT subjects. However, there was significantly less ($p<0.05$) focalized locomotion when compared to PLH or VMT animals.

As for ALH, PLH and VMT, there was no lull observed following Raphe stimulation.

6) Reticularis Pontis Caudalis: Self-stimulation was elicited from the RPC in bursts at a low rate for 5 subjects

and at a high rate for the other 3 rats. There was no significant difference in SS rates compared to all other groups.

Sniffing for the RPC was significantly less ($p<0.05$) than for PLH rats.

Significantly more ($p<0.05$) lull periods were observed following RPC stimulation compared to any other group; lull was significantly higher ($p<0.05$) than for all other groups.

In addition, RPC subjects had significantly higher ($p<0.05$) scattered exploration than MCx, ALH and PLH groups, and significantly higher ($p<0.05$) diffused exploration than ALH and PLH groups. However, focalized exploration for the RPC was significantly less ($p<0.05$) than for ALH, PLH or VMT subjects. Focalized locomotion for RPC was lower than for PLH and VMT. The RPC stimulation also elicited some rather peculiar idiosyncratic behavior, including 8 cases of "hébêté-dazed-withdrawn" like behavior, 2 of which also showed "disruptive" behavior, 8 cases of "non-systematic" exploration, and 4 cases of "adynamia".

To summarize, the data shown in Tables 1 and 2 demonstrate that:

1) <u>The gradient of frequency</u> of SS starting with the areas showing the highest frequency are as follows: VMT, PLH, ALH, RPC, S, PO1f and MCx areas. However, there was no significant difference between VMT and PLH, nor between PLH and ALH SS rates. Nevertheless, the VMT rates were significantly higher ($p<0.05$) than the ALH. The VMT, PLH and ALH rates were

significantly higher ($p<0.05$) compared to those of S, POlf, and MFx areas. Raphe showed no significant difference between one another and no significant difference with the MFx, POlf and S areas.

2) Sniffing intensity between the various brain areas did not differ with exception of the PLH which elicited significantly more sniffing ($p<0.05$) than the MCx and RPC.

3) Exploration:

a) Diffused exploration was significantly higher ($p<0.05$) in the Raphe than in all other brain areas. RPC was significantly different from PLH and ALH, but not different from the remaining areas (i.e., VMT and MCx). VMT and MCx diffused exploration was significantly ($p<0.05$) higher compared to ALH, but not different from PLH. Hence, gradient of diffused exploration would be Raphe, RPC, VMT, MCx, PLH and ALH.

b) Scattered exploration was significantly higher ($p<0.05$) in the posterior areas, i.e., VMT, R and RPC, than in the more anterior, PLH, ALH and MCx regions.

c) Focalized exploration was not higher than for PLH, but it was significantly higher ($p<0.05$) than for all the brain areas studied, i.e., VMT, MCx, R and RPC. The PLH and VMT areas were not significantly higher than one another, but were significantly higher ($p<0.05$) than R, RPC and MCx areas.

4) Locomotor activity:

a) Diffused locomotor activity was significantly higher ($p<0.05$) in the Raphe area than in all other areas, except for the RPC. The RPC itself, however, was not significantly higher than any of the other areas.

b) Focalized locomotor activity in the VMT was not higher compared to the PLH, but was significantly higher than all other areas. In turn, the PLH area was not higher than the ALH, but was higher ($p<0.05$) than all remaining areas. The ALH was significantly higher ($p<0.05$) than MCx, but not significantly different than the remaining areas, i.e., Raphe or RPC. The MCx, R and RPC areas were not different from one another.

5. Lull periods:

The intensity of lull periods was significantly higher ($p<0.05$) in the RPC compared to all other areas. There was no significant difference between all other areas. Therefore, lull can be considered to be a main behavioral feature of the RPC.

For all animals grouped together, the data shown in Table 3 illustrate positive correlations between the following variables: (1) SS rates and focalized motor activity; (2) SS rates and focalized exploration; (3) sniffing and focalized motor activity; (4) sniffing and focalized exploration. Hence, sniffing and SS rates are not correlated; but focalized motor activity and focalized exploration are correlated to SS rates and sniffing. In addition, positive correlations were found between (5) focalized motor activity and focalized exploration; and between (6) diffused locomotion and diffused exploration; (7) lull and hébêté-dazed. Finally, a negative correlation was found between focalized and scattered explorations.

Table 1

RELATIVE INTENSITIES OF SS AND OF CONCOMITANT BEHAVIORAL FEATURES AS ELICITED FROM VARIOUS BRAIN AREAS (N=48)

Brain areas: Meso cortex, MCx; anterior lateral hypothalamus, ALH; posterior lateral hypothalamus, PLH; ventromedial tegmentum, VMT; raphe, R; reticularis pontis caudalis, RPC.

Behaviors observed: Self-stimulation, SS; sniffing, SN; diffused exploration, DE; scattered exploration, SE; focalized exploration, FE; diffused locomotion, DL; focalized locomotion, FL; lull, LL.

Relative intensities of the behaviors: Decreased (-1); not changed (0); low (+1); moderate (+2); high (+3).

Idiosyncratic behavior (IS): Present (P) or not present (NP).

[a]Number of animals in the group showing the particular relative intensity of described behaviors.

N = Number of animals in the group.

Gradation of speeds of SS:
(1) Low (50-300) for 10 min.
(2) Moderate (301-600) for 10 min.
(3) High (600 and over) for 10 min.

Table 1

RELATIVE INTENSITIES OF SS AND OF CONCOMITANT BEHAVIORAL FEATURES AS ELICITED FROM VARIOUS BRAIN AREAS (N=48)

Brain areas	(N=number of subjects) N	Gradation of SS	Rates of bar-pressing SS		SN	DE	SE	FE	DL	FL	LL	Idiosyncratic behavior
MCx	8	1	6[a]	-1	0[a]	0	0	0	2	3	0	(Arrest) P in 5 animals
		2	2	0	2	0	7	0	2	2	5	
		3	0	+1	3	6	1	8	2	1	2	
				+2	3	2	0	0	2	0	1	
				+3	0	0	0	0	0	0	0	
ALH	8	1	1	-1	0	0	0	0	0	0	0	NP
		2	7	0	0	6	8	0	5	0	8	
		3	0	+1	1	1	0	0	3	0	0	
				+2	3	1	0	1	0	4	0	
				+3	4	0	0	6	0	0	0	
PLH	8	1	1	-1	0	0	0	0	0	0	0	(Biting) P in 1 animal
		2	4	0	0	4	8	0	4	0	8	
		3	3	+1	0	4	0	1	4	0	0	
				+2	5	0	0	5	0	0	0	
				+3	3	0	0	2	0	4	0	
VMT	8	1	1	-1	0	0	0	0	0	0	0	(Biting) P in 1 animal
		2	2	0	0	0	4	2	3	0	8	
		3	5	+1	1	7	1	0	4	1	0	
				+2	4	1	3	6	1	2	0	
				+3	3	0	0	0	0	5	0	

Table 1 (Cont'd)

Brain areas	N=number of subjects)	Gradation of SS	Rates of bar-pressing SS		SN	DE	SE	FE	DL	FL	LL	Idiosyncratic behavior
		1	6	-1	0	0	0	0	0	0	0	(Bewildered reaction)
		2	2	0	0	0	2	4	0	4	8	P in
RAPHE	8	3	0	+1	1	0	5	4	1	4	0	8
				+2	6	0	1	0	4	0	0	animals
				+3	1	3	0	0	3	0	0	
		1	5	-1	0	0	0	0	2	1	0	(Dazed-hébêté)
		2	0	-0	1	1	0	4	3	1	1	P in
RPC	8	3	3	+1	4	5	7	3	1	3	1	8 animals
				+2	3	2	1	1	2	3	4	(Non-systematic exploration)
				+3	0	0	0	0	0	0	2	P in 8 animals
												(Adynamia) P in 4 animals
												(Hallucinatory-like) P in 2 animals

Table 2

SUMMARY OF SIGNIFICANT DIFFERENCES IN INTENSITY BETWEEN BEHAVIORS CORRELATED WITH SS FROM VARIOUS BRAIN AREAS ACCORDING TO KOLMOGOROV-SMIRNOV TEST FOR SMALL NUMBERS OF INDIVIDUALS (N=48) OF PAIRED GROUPS

Six brain areas: Meso cortex, MCx; anterior lateral hypothalamus, ALH; posterior lateral hypothalamus, PLH; ventro-medial tegmentum, VMT; raphe, R; reticularis pontis caudalis, RPC.

Behaviors observed: Self-stimulation, SS; sniffing, SN; focalized exploration, FE; scattered exploration, SE; diffused exploration, DE; focalized locomotion, FL; diffused locomotion, DL; and lull, LL.

Relative intensities of the behaviors: Decreased (-1); not changed (0); low (+1); moderate (+2); high (+3).

Gradation of speeds of SS:
(1) Low (50-300) for 10 min.
(2) Moderate (301-600) for 10 min.
(3) High (600 and over) for 10 min.

[a] Intensity significantly greater (>) or lesser (<); $p<0.05$.

See Table for cell distribution.

Table 2

SUMMARY OF ANALYSIS OF DIFFERENCES BETWEEN THE VARIOUS BEHAVIORAL CORRELATES OF SS IN RATS ACCORDING TO KOLMOGOROV-SMIRNOV'S TEST FOR SMALL NUMBERS OF INDIVIDUALS (N=40) OF PAIRED GROUPS

Paired groups	SS	SN	DE	SE	FE	DL	FL	LL
MCx-ALH	MFcx < ALH		MFcx > ALH		MFcx < ALH		MFcx < ALH	
MCx-PLH	MFcx < PLH	FMcx < PLH			MFcx < PLH		MFcx < PLH	
MCx-VMT	MFcx < VMT			MFcx < VMT	MFcx < VMT		MFcx < VMT	
MCx-Raphe			MFcx < RAPHE	MFcx < RAPHE		MFcx < Raphe		
MCx-RPC				MFcx < RPC				MFcx < RPC
ALH-PLH								
ALH-VMT	ALH < VMT		ALH < VMT	ALH < VMT	ALH > VMT		ALH < VMT	
ALH-Raphe	ALH > Raphe		ALH < Raphe	ALH < Raphe	ALH > Raphe	ALH < Raphe		
ALH-RPC			ALH < RPC	ALH < RPC	ALH > RPC			ALH < RPC
PLH-VMT				PLH < VMT				
PLH-Raphe	PLH > Raphe		PLH < Raphe	PLH < Raphe	PLH > Raphe	PLH < Raphe	PLH > Raphe	
PLH-RPC		PLH > RPC	PLH < RPC	PLH < RPC	PLH > RPC		PLH > RPC	PLH < RPC
VMT-Raphe	VMT > Raphe		VMT < Raphe		VMT > Raphe	VMT < Raphe	VMT > Raphe	
VMT-RPC					VMT > RPC		VMT > RPC	VMT < RPC
Raphe-RPC			Raphe > RPC					Raphe < RPC

Table 3

CORRELATION MATRIX INDICATING THE POSITIVE AND NEGATIVE RELATIONSHIP BETWEEN 11 DIFFERENT BEHAVIOR VARIABLES

Current, CR; self-stimulation, SS; sniffing, SN; diffused exploration, DE; scattered exploration, SE; focalized exploration, FE; diffused locomotion, DL; focalized locomotion, FL; arrest, AR; lull, LL; perplexity, P.

The correlation coefficient matrix (Table 8-3, R.A. Fisher and F. Yates, "Statistical Tables for Biological, Agricultural, and Medical Research", Oliver and Boyd Ltd., Edinburg, 1953, by permission of the authors and publishers. Reprinted from G.A. Ferguson, "Statistical Analysis in Psychology and Education", McGraw Hill Book Company, New York, 1971) indicates the critical values of the correlation coefficient. The criterion of significant difference is $p<0.05$, as seen in this table. As indicated previously, the numerical graded responses or weighed values are: decreased (-1); no change (0); low (+1); moderate (+2); and high (+3).

Table 3

VALUES OF CORRELATION COEFFICIENTS OF 11 DIFFERENT SS BEHAVIORAAL VARIABLES (1) (N=48)

MEASURES	(1) CR	(2) SS	(3) SN	(4) DN	(5) SE	(6) FE	(7) DL	(8) FL	(9) AR	(10) LL	(11) P
1) Current	''''	.200	.014	-.172	.112	.010	-.125	.198	-.299	.348	.468
2) Self-stimulation	.200	''''	.408	-.279	-.171	.505	-.337	.604	-.292	.036	-.080
3) Sniffing	.014	.408	''''	-.048	-.163	.530	-.004	.537	-.398	-.360	-.344
4) Diffused exploration	-.172	-.279	-.048	''''	.352	-.438	.891*	-.361	-.005	.122	.050
5) Scattered exploration	.112	-.171	-.163	.352	''''	-.621	.363	-.164	-.085	.235	.327
6) Focalized exploration	.010	.505	.530	-.438	-.621	''''	-.394	.514	-.148	-.309	-.368
7) Diffused locomotion	-.125	-.337	-.004	-.891*	.363	-.394	''''	-.283	-.046	.040	-.014
8) Focalized locomotion	.198	.604	.537	-.361	-.164	.514	-.383	''''	-.260	-.191	-.179
9) Arrest	-.299	-.292	-.398	-.005	-.085	-.148	-.046	-.260	''''	-.009	-.096
10) Lull	.348	.036	-.360	.122	.235	-.309	.040	-.191	-.009	''''	.816*
11) Hébêté-dazed	.468	-.080	-.344	.050	.326	-.368	-.014	-.179	-.096	.816	''''

Note: (1) From brain areas: Mediofrontal cortex, MFcx; anterior lateral hypothalamus, ALH; posterior lateral hypothalamus, PLH; ventromedial tegmentum, VMT; raphe, R; reticularis pontis caudalis, RPC.

* $p < .05$ for two tailed tests (Seigel, 1956)

AMBIVALENCE (APPROACH-FLIGHT REACTION)

1) Histological Findings: The RPC probes were located ventrolateral to the LC, under the superior cerebral peduncle or within the dorsolateral portion of the anterior RPC. The R probes were located dorsolateral to the medial raphe nucleus. The RMF probes were found in the area lateral and ventral to the central grey or at the junction of the mesencephalon and anterior part of the pons. The VMT probes were located in an area lateral to the interpeduncular nucleus, either in the area of Tsai or in the substantia nigra. The PLH probes were found in the dorsolateral hypothalamus at the level of the mamillary bodies around the medial forebrain bundle. The septal probes were placed in the dorsolateral part of the septal area.

2) Behavioral Findings: The relative intensity of self-stimulation and ambivalence is shown in Figure 8. For statistical analysis, the animals were grouped according to their implantation sites and the main behavior elicited: self-stimulating RPC, self-stimulating R, self-stimulating VMT, self-stimulating S, ambivalent RPC, ambivalent R, ambivalent RMF and ambivalent S. Each of the eight groups contained four subjects. As described on page 23, under Behavioral Training, Testing and Analysis of Data, the relative intensity of SS and ambivalence was graded on a six point as follows: (0) not present, (1) low, (2) low-moderate, (3) moderate, (4) moderate-high and (5) high. This scale is quantitatively described in Table 4.

3) Comparisons of ambivalent groups: Ambivalent RPC, R and RMF animals had faster approach speeds than ambivalent S rats, while ambivalent RPC subjects had faster approach speeds

than ambivalent R animals. Withdrawal speeds were faster in ambivalent RPC and R subjects than in ambivalent S animals. Ambivalent S rats had longer interval periods than ambivalent RPC, R or RMF subjects, and longer intervals for RMF than R rats. Lull periods were longer for ambivalent RPC animals than for ambivalent R or RMF rats. Ambivalent R animals showed more diffused exploration than ambivalent RMF or S rats. Ambivalent RMF and S subjects showed more focalized exploration than ambivalent RPC or R animals.

4) Comparisons of self-stimulating groups: Self-stimulating VMT rats had faster approach speeds than self-stimulating RPC or S animals. Locomotor activity was found to a higher degree in self-stimulating VMT rats than in self-stimulating RPC or S animals, and to a higher degree in self-stimulating RPC and R subjects than in self-stimulating S rats.

5) Comparisons of ambivalent and self-stimulating groups: Ambivalent RPC animals were found to have faster approach speeds than self-stimulating RPC subjects; ambivalent S rats had faster approach speeds than self-stimulating S animals. Ambivalent RPC, R, RMF and S subjects had faster withdrawal speeds than their self-stimulating counterparts, RPC, R, VMT and S. Ambivalent RMF and S animals had longer interval periods than self-stimulating VMT and S, respectively, while self-stimulating R rats had longer interval periods than ambivalent R subjects. Lull periods were longer for ambivalent RPC subjects than for self-stimulating RPC rats, while self-stimulating RPC animals showed more focalized exploration than ambivalent RPC subjects. Finally, self-stimulating VMT rats

showed more locomotor activity than ambivalent RMF animals.

If the speed of approach and withdrawal is used as the main criteria for ambivalence, rats with anterior electrodes (i.e., septum) showed less ambivalence than animals stimulated in the reticular mesencephalic formation (RMF), raphe (R) or reticularis pontis caudalis (RPC). In addition, ambivalence was accompanied by site-specific behavioral patterns. For instance, the ambivalent septal group appeared unexcited in comparison with all other groups; interval periods were longer and bar-pressing speed was slower. Ambivalence from the RMF was accompanied by alert and more directed behavior as illustrated by the high bar-pressing speed and withdrawal, and by the low interval and lull periods. Other interesting features indicating RMF-directed ambivalence were the low diffused exploration and the relatively high focalized exploration. Ambivalent Raphe animals bar-pressed at a more predictable rhythm than their self-stimulating counterparts, and showed intense diffused exploration which was less sporadic than for the self-stimulating raphe subjects. Ambivalence obtained by stimulation of the RPC was associated with very fast approach speed (even in comparison with the self-stimulating RPC approach speed) and intense withdrawal. This pattern was accompanied by brief rest interval periods, longer lull periods and occasional incidents of hypotonia. Reticularis pontis caudalis subjects showed a particular type of exploration in addition to focalized, scattered and diffused exploration: the rat would sniff with its nose directed upward, and the explor-

atory activity was occasionally interrupted by lull periods during which the animal would explore its environment in a non-systematic and fragmented fashion, as described in the topography study. Following lull periods, the RPC rat would wander back to the lever in an erratic manner.

All self-stimulating animals were stimulated at high intensities (70 μA rms). Some self-stimulating rats showed forced movements (i.e., head and/or body movements or circling for one VMT subject, seizures for one septal rat, and circling for two RPC animals). However, this pattern was not accompanied by signs of withdrawal or ambivalence and was thus classified as pure self-stimulation. In conclusion, just as behavioral patterns accompanying self-stimulation vary between brain regions, behaviors concomitant with ambivalence vary from one brain area to another, and differ from those accompanying self-stimulation from similar structures.

Table 4

RELATIVE INTENSITIES OF BEHAVIORAL PATTERNS IN AMBIVALENT AND SELF-STIMULATING RATS

Relative intensities of the approach, withdrawal, interval, lull, diffused exploration, focalized exploration and motor activity as observed in self-stimulating and ambivalent animals grouped according to their brain areas implantation sites.

Behaviors were graded on a range from 1 to 5.

Table 4

DESCRIPTION OF RATING OF RELATIVE INTENSITIES OF BEHAVIORAL PATTERNS IN AMBIVALENT AND SELF-STIMULATING RATS

RELATIVE INTENSITIES OF BEHAVIORS	APPROACH	WITHDRAWAL	INTERVAL	LULL	DIFFUSED	FOCALIZED	ACTIVITY
low (1)	1cm or less/ sec.	1cm or less/ sec.	1-3 sec.	1-3 sec.	1-3 sec.	1-3 sec.	1-3 sec
low-moderate (2)	2cm/sec.	2cm/sec.	4-6 sec.	4-6 sec.	4-6 sec.	4-6 sec.	4-6 sec
moderate (3)	3cm/sec.	2cm/sec.	7-9 sec.	7-9 sec.	7-9 sec.	7-9 sec.	7-9 sec
moderate-high (4)	4cm/sec.	4cm/sec.	10-12 sec.	12-10 sec.	10-12 sec.	10-12 sec.	10-12 sec
high (5)	5cm or more/ sec.	4cm or more sec.	13 + sec.	13 + sec.	13 + sec.	13 + sec.	13 + sec.

Table 5

COMPARISON OF RELATIVE INTENSITIES OF THE BEHAVIORS OF PAIRED GROUPS OF ANIMALS ACCORDING TO IMPLANTATION SITES

Self-stimulating RPC, ambivalent R, ambivalent RMF, and ambivalent S. Each of the 8 groups contained four subjects.

Relative intensities (range 0-5) for each behavioral manifestation of each group were used in calculating the different scores. Statistical differences between groups were evaluated by using the Kolmogorov-Smirnov test (Siegel, 1956).

The self-stimulation groups were: (1) - (4).

The ambivalent groups were: (5) - (8).

[a] Intensity significantly greater (>) or lesser (<); $p \leq 0.05$.

----: No significant difference.

Table 5

COMPARISONS OF RELATIVE INTENSITIES OF THE BEHAVIORS OF PAIRED GROUPS OF ANIMALS ACCORDING TO IMPLANTATION SITES

PAIRED GROUPS	APPROACH	WITHDRAWAL	INTERNAL	LULL	DIFFUSED	FOCALIZED	ACTIVITY
(1) RPC - R (2)	1 > 2[a]	----	----	1 > 2	----	----	----
(2) RPC - RMF (3)	----	----	----	1 > 3	----	3 > 1	----
(1) RPC - S (4)	1 > 4	1 > 4	4 > 1	----	----	4 > 1	----
(2) R - RMF (3)	----	----	3 > 2	----	2 > 3	3 > 2	----
(2) R - S (4)	2 > 4	2 > 4	4 > 2	----	2 > 4	4 > 2	----
(3) RMF - S (4)	3 > 4	----	4 > 3	----	----	----	----
(5) RPC - R (6)	----	----	----	----	6 > 5	----	----
(5) RPC - VMT (7)	7 > 5	----	5 > 7	----	----	----	7 > 5
(5) RPC - S (8)	----	----	----	----	5 > 8	----	5 > 8
(6) R - VMT (7)	----	----	6 > 7	----	6 > 7	----	----
(6) R - S (8)	----	----	----	----	6 > 8	----	6 > 8
(7) VMT - S (8)	7 > 8	----	8 > 7	----	----	----	7 > 8
(1) RPC - RPC (5)	1 > 5	1 > 5	----	1 > 5	----	5 > 1	----
(2) R - R (6)	----	2 > 6	6 > 2	----	----	----	----
(3) RMF - VMT (7)	----	3 > 7	3 > 7	----	----	----	7 > 3
(4) S - S (8)	8 > 4	4 > 8	4 > 8	----	----	----	----

Table 6

HISTOGRAM OF RELATIVE INTENSITIES OF BEHAVIORAL MANIFESTATIONS IN SELF-STIMULATING AND AMBIVALENT RATS AS ELICITED FROM VARIOUS BRAIN SITES

Approach speed (approach); withdrawal (withdraw); interval period, lull period, diffused exploration (diffused); focalized exploration (focalized); and locomotor activity (activity).

The mean relative intensities of the behaviors were graded on a six point scale varying between 0 to 5. For statistical analysis, the animals were grouped according to their brain implantation sites and the main behavior elicited was self-stimulation or ambivalence.

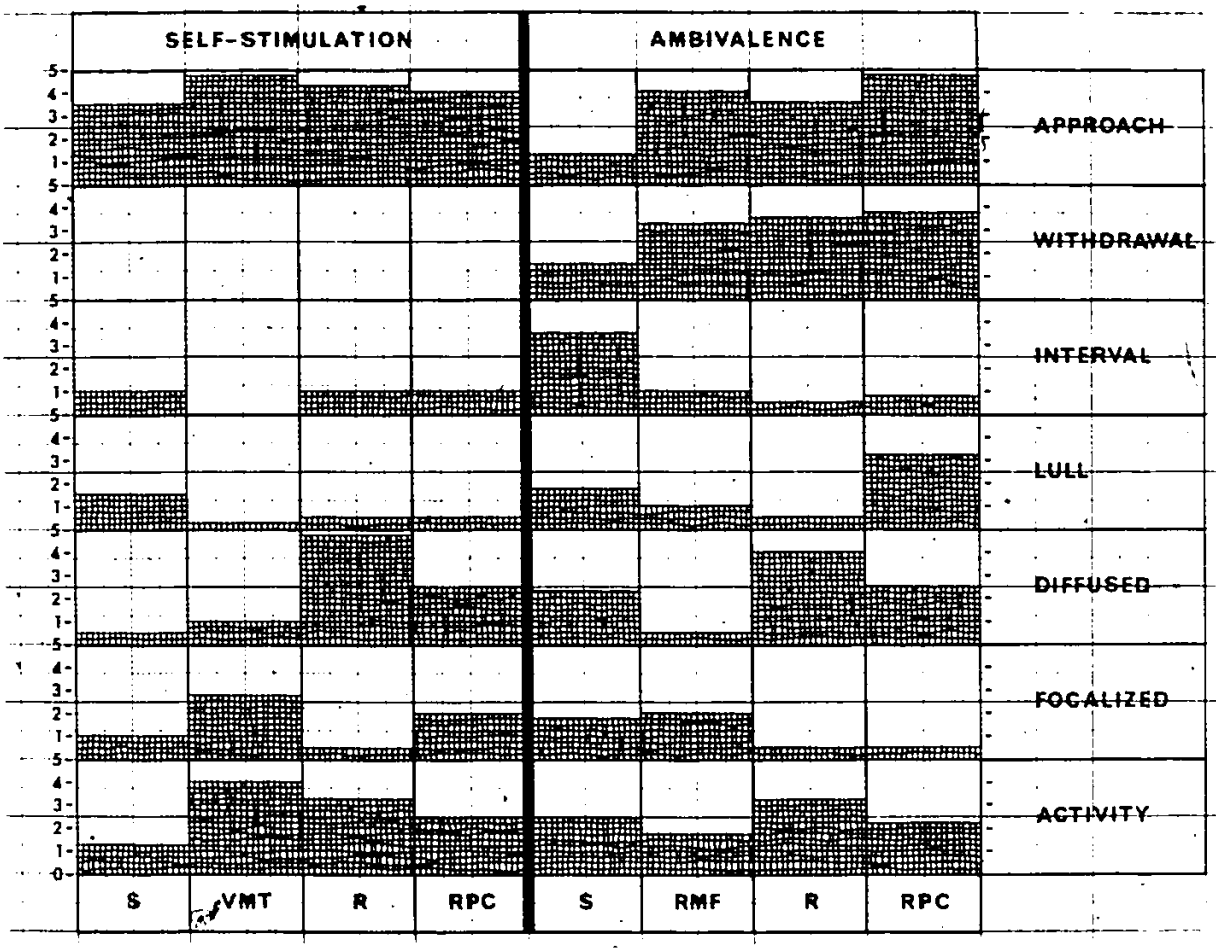
Self-stimulation group: RPC, R, VMT and S.

Ambivalent group: RPC, R, VMT and S.

Each of the 8 groups contained four subjects.

Table 6

HISTOGRAM OF RELATIVE INTENSITIES OF BEHAVIORAL MANIFESTATIONS IN SELF-STIMULATING AND AMBIVALENT RATS AS ELICITED FROM VARIOUS BRAIN SITES



EXPERIMENTAL PART II

PHARMACOLOGICAL CORRELATES

A. Failure to Reinstate Self-Stimulation with Combination of Seryl-Trihydroxibenzil-Hydrazine (RO-4602) and L-Dopa following its Suppression by Alpha-Methyl-Para-Tyrosine

I - Introduction

Alpha-methyl-para-tyrosine (α-MPT) is a potent inhibitor of tyrosine hydroxylase and, as such, limits the synthesis of catecholamines (dopamine, DA and norepinephrine, NE; Nagatsu et al., 1964; Weissman and Koe, 1965; 1966; Levitt et al., 1965). Unlike reserpine, which also affects serotonin, α-MPT causes a selective reduction of brain catecholamines (Spector et al., 1965; Rech et al., 1966).

Appropriate doses of α-MPT produce a deficit in brain catecholamines (CA's) concomitant with a suppression of SS obtained from medial forebrain bundle-innervated regions (Poschel and Ninteman, 1966). In a previous study (Beaugrand and St-Laurent, 1973), α-MPT (100 mg/kg, ip) produced immediate (within the first 30 min. following injection) and long lasting suppressive effects on SS, in spite of the evidence that the central depleting effect on CA's takes place 2-4 hr. after injection (Spector et al., 1965). In the work of Poschel and Ninteman (1966) (in which α-MPT-methyl-ester was used because of its higher solubility), no mention of such an early suppression was made. However, St-Laurent et al. (1973), in a study comparing the effects of α-MPT and α-MPT-methyl-ester, noted that α-MPT had an immediate short lasting depressing effect on SS followed by restitution and subsequent depression of SS after 2½ hr. In contrast, α-MPT-methyl-ester showed no immediate depressing effect. The latter showed a gradual decrease of SS rates with the maximum depress-

ion reached 4 hr. following administration (See Fig. 8).

The present experiment was undertaken in order to determine: 1) whether L-Dopa, after peripheral inhibition of dopa decarboxylase by pretreatment with a low dose of RO 4-4602, could reverse the early suppressive effects on SS induced by α-MPT; 2) the effects of both RO 4-4602 and L-Dopa on rats which were self-stimulating without pretreatment with α-MPT.

II - Material and Methods

a) Animals and Surgery

Subjects were 19 male Sprague-Dawley albino rats weighing 250-300 g at the time of surgery. They were housed in individual cages and maintained on an ad libidum water and food schedule, except during testing.

Surgical procedures used were those described previously. In 10 animals, the electrodes were aimed to place the exposed tip in the posterior lateral hypothalamus (PLH). Coordinates were 5 mm posterior to bregma, 1.5 mm lateral to the saggital suture and 8 mm below the skull surface. The incisor bar was level with the interaural plane. In 9 animals, the more anterior regions of the MFB were aimed for, with the following coordinates: 1.5/1.5/9 and 3/1/5 mm (preoptic area and medio-frontal cortex).

b) Training for Brain Self-stimulation

Following 10 days of post-operative rest, the rats were trained to depress a single metal lever in order to obtain a 0.25 sec train of 60 Hz sine wave. The current intensity

was fixed at 60 μA, (21.4 μA rms) in order to produce optimal response rates. Subjects were given daily 30 min. training sessions during which they could freely self-stimulate. Daily press-rates were recorded and sessions went on for at least 20 days, until performance showed good stability for three consecutive days. Animals were then considered as suitable for the drug experiment on the following day. During this period of shaping and stabilization, each rat worked in a standard session at a fixed time each day and always in the same box.

On the experimental day, subjects were allowed to self-stimulate for 2 periods of 10 min. each. Measures of SS rates were then taken and pooled with the data obtained on the three preceeding days to serve as the baseline for further comparisons. Drugs or their vehicles were administered ip at the end of this 2 x 10 min. session at 0 min. treatment period.

c) Drug Administration

Drugs used were DL-α-methyl-para-tyrosine (α-MPT; Regis Chemical Co., Chicago), RO 4-4602 or N-(DL-seryl) - N' - (2, 3, 4 trihydroxybenzil) hydrazine and L-Dopa (L-Dihydroxy-phenylalanine, Nutritional Biochemical Co., Cleveland). Solutions were prepared by mixing each drug with equivalent amounts of arabic gum and by suspending the mixture in 0.9% NcCl by homogenization. A mixture of arabic gum and 0.9% NaCl served as placebo. Drugs or the vehicle were administered in the following order: 1) α-MPT at 0 min.; 2) RO 4-4602 at 20 min.; 3) L-Dopa at 50 min.

Drugs were injected ip in doses of 100 mg/kg of body weight. The volume of each injection varied from 0.6 to 1.0 ml. Subjects were divided into two groups and a total of four drug conditions were used: Condition A consisted of injections of α-MPT, RO 4-4602 and L-Dopa (α-MPT + RO 4-4602 + L-Dopa); Condition B of placebo, RO 4-4602 and L-Dopa (V + RO 4-4602 + L-Dopa); Condition C of α-MPT and two vehicle injections (α-MPT + V + V); and Condition D of three vehicle injections (V + V + V). Group 1 received treatments described in Conditions A and B; Group 2 underwent Conditions C and D.

Immediately after each injection, the animals were returned to their experimental boxes and allowed to self-stimulate. Ratings of bar-presses were taken every 10 min; a 30 sec. period following each reading was used for verifying if the individual current had remained at the original 60 μA; this involved manually delivering three intracranial shocks to each animal while taking the oscilloscope measurements. There were three readings (and adjustments) following α-MPT injection, two following RO 4-4602, and five following L-Dopa injection. Response rates were calculated for periods of 10 min. throughout experiment. All individual press-rates were linearized by Log 10 (x + 1) transformation (Sokal, 1969). Figure 9 was plotted after this linearization. Results were subjected to statistical analysis using an analysis of variance (mixed schema, repeated measurements on all levels, 2nd factor being random) for difference between conditions, when different conditions were compared using orthogonal tests in order

to localize the differences. Each condition was also subjected to a simple analysis of variance and to Scheffé tests for individual reading comparisons. Comparisons between anterior and posterior electrode placements concerning reactions to different conditions were made using analysis of variance.

Upon completion of experiments, subjects were killed with an overdose of sodium pentobarbital (200 mg/kg ip) and the brains were fixed for at least seven days in formaldehyde (10%). Transverse sections were made (50 μ thick), mounted and stained according to the luxol fast blue technique of Klüver and Barrera (1953), for histological verification of electrode positions.

III - Results

a) Histological Examination

The ten posterior medial forebrain bundle animals had their electrodes located in the dorsolateral hypothalamus, at the level of the mamillary bodies in or around the MFB, in or around the area of Tsai or in the substantia nigra, as illustrated in Fig. 10.

Five out of the 9 probes aimed at the more anterior regions were located in the preoptic area bordering on the anterior part of the MFB. Two probes were found in the paraolfactory area in front of the septal region, at the boundary between the hippocampus and the medial part of the corpus callosum and caudate nucleus. Two mediofrontal cortex probes fell slightly anterior to the paraolfactory probes.

b) Effects of Alpha-methyl-para-tyrosine

After a single dose of 100 mg/kg of α-MPT given ip (Fig. 9, Conditions A and C), 17 out of 19 animals virtually stopped self-stimulating within 10 min. after injection. The other two animals reduced their SS rates to about 50% of their original level immediately after injection; of these two, one subject completely stopped after 60 min. Rats appeared sedated and stopped spontaneous movements completely. α-MPT injections did not appear irritating to the animals as there was absence of vocalization and of retraction of the abdomen. Analysis of variance (ANOVA) of conditions C (α-MPT + V + V) and D (V + V + V) in Group 2 confirmed that the significant difference between the two treatments had to be ascribed to α-MPT effects only ($p<0.05$). ANOVA tests on readings 3 through 10 for both α-MPT + V + V and V + V + V alos revealed that recovery from α-MPT (α-MPT + V + V) was not complete when compared to the controls (V + V + V). In V + V + V group, the slight and gradual decrease in response rates which did not approach significance can be attributed to the accumulation of satiation and/or fatigue.

c) Effects of RO 4-4602

The present experiment was designed to evaluate only those effects of RO 4-4602 which appeared within the first 20 min. following the injection. Inspection of Fig. 4 reveals that injection of 100 mg/kg of RO 4-4602 to animals not pre-treated with α-MPT (V + RO 4-4602 + L-Dopa) did not produce any perceptible effect on SS compared to animals receiving

V + V + V). As for α-MPT pretreated animals (α-MPT + RO 4-4602 + L-Dopa and α-MPT + V + V), the small difference noted between readings 4 and 5 cannot be attributed to RO 4-4602 effects, at least not on a statistical basis. No behavioral differences were noted between subjects that had received RO 4-4602 and their vehicle controls, irrespective of pretreatment (α-MPT or V).

d) Effects of RO 4-4602 and L-Dopa Combined

Within 10 min. after injection of L-Dopa (100 mg/kg ip), the animals showed hyperactivity to sound stimuli (clap of hands) which would elicit a marked startle reaction. They stood on their hind limbs but there was little movement. When picked up at the end of the experiment, they showed escape behavior and attempted to bite. These observations are similar to those noted in our previous study on α-MPT and L-Dopa (200 mg/kg ip) (Beaugrand and St-Laurent, 1973), except for the absence of autonomic effects such as hypersalivation. A reduction of tonus was noted before the injection of L-Dopa had completely disappeared.

ANOVA tests on α-MPT + RO 4-4602 + L-Dopa and V + RO 4-4602 + L-Dopa (Group 1) revealed that the two conditions were significantly different ($p<0.01$), but that some readings were not orthogonal. Tests (error = Conditions x subjects) revealed that the baseline (reading 0) was the same for both conditions and that significant differences were present at readings 1 and 2 ($p<0.01$), 3 and 4 ($p<0.05$) and again at reading 10 ($p<0.01$). Simple ANOVA also revealed that in

α-MPT + RO 4-4602 + L-Dopa and V + RO 4-4602 + L-Dopa groups, the injection of L-Dopa induced a significant lowering of SS performance ($p < 0.01$); this effect lasted for at least 1 hour, as revealed by the Schaffé test ($p < 0.05$). The small recovery observed in V + RO 4-4602 + L-Dopa group (Fig. 9), starting at the 8th reading, was not significant.

Statistical analysis of data was also done in order to determine if there were any differences between anterior and posterior placements of electrodes, and whether these differences were concerned with the possible selective effects of drugs on SS rates. However, no significant differences were found.

Figure 8

Effects of ℓ-MPT and ℓ-MPT-methyl-ester on SS rates.

Median bar-pressing rates were taken each half hour for each group of animals. After a 30 min. pre-test period, the animals were injected with ℓ-MPT (●——●), ℓ-MPT (o- - -o) or (▬▬). Following injections, animals self-stimulated freely for 7 hours.

Figure 8

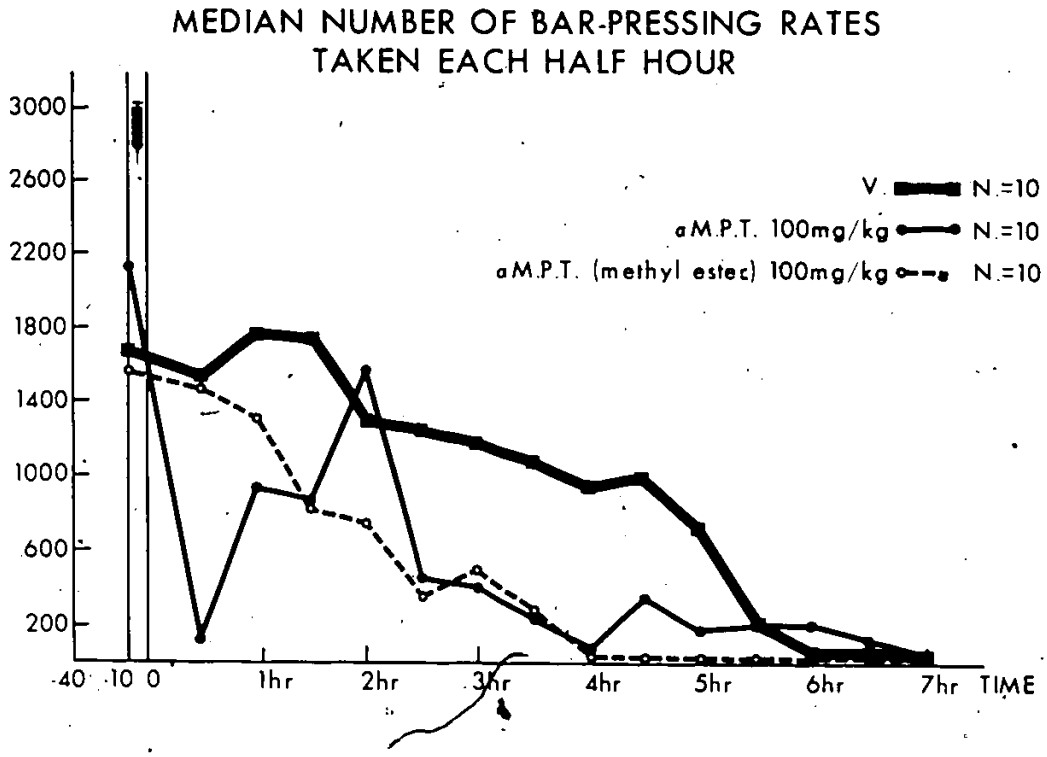

MEDIAN NUMBER OF BAR-PRESSING RATES
TAKEN EACH HALF HOUR
3000
2600
2200
1800
1400
1000
600
200
V. N.=10
aM.P.T. 100mg/kg N.=10
aM.P.T. (methyl estec) 100mg/kg N.=10
-40 -10 0
1hr
2hr
3hr
4hr
5hr
6hr
7hr TIME

Figure 8

Effects of the combination of RO 4-4602 and L-Dopa on self-stimulation in rats with or without pre-treatment with α-MPT. Alpha-methyl-para-tyrosine (α-MPT) or vehicle (V) were administered ip at zero time; RO 4-4602 and L-Dopa or their vehicles at 30 and 54 minutes, respectively. Under Condition A, animals received α-MPT, then RO 4-4602 and L-Dopa. Under Condition B, the same animals, as in A, received the vehicles of α-MPT, then RO 4-4602 and L-Dopa. Under Condition C, other animals received α-MPT followed by vehicles instead of RO 4-4602 and L-Dopa; under Condition D, the same animals, as in C, received only the respective vehicles. Readings of SS rates were taken at 10 min. intervals. There was a significant difference between groups receiving α-MPT and groups receiving its vehicle, at least for the first 52 minutes ($p<0.01$), as well as between controls and animals treated with a combination of RO 4-4602 and L-Dopa from 64 min. on ($p<0.01$). Each point represents the mean of 13 (Conditions A and B) or 6 (Conditions C and D) values previously linearized by the $(X^{\frac{1}{2}} + 1)^{\frac{1}{2}}$ transformation for homogenization of variances (Sokal and Rohlf, 1969).

Figure 9

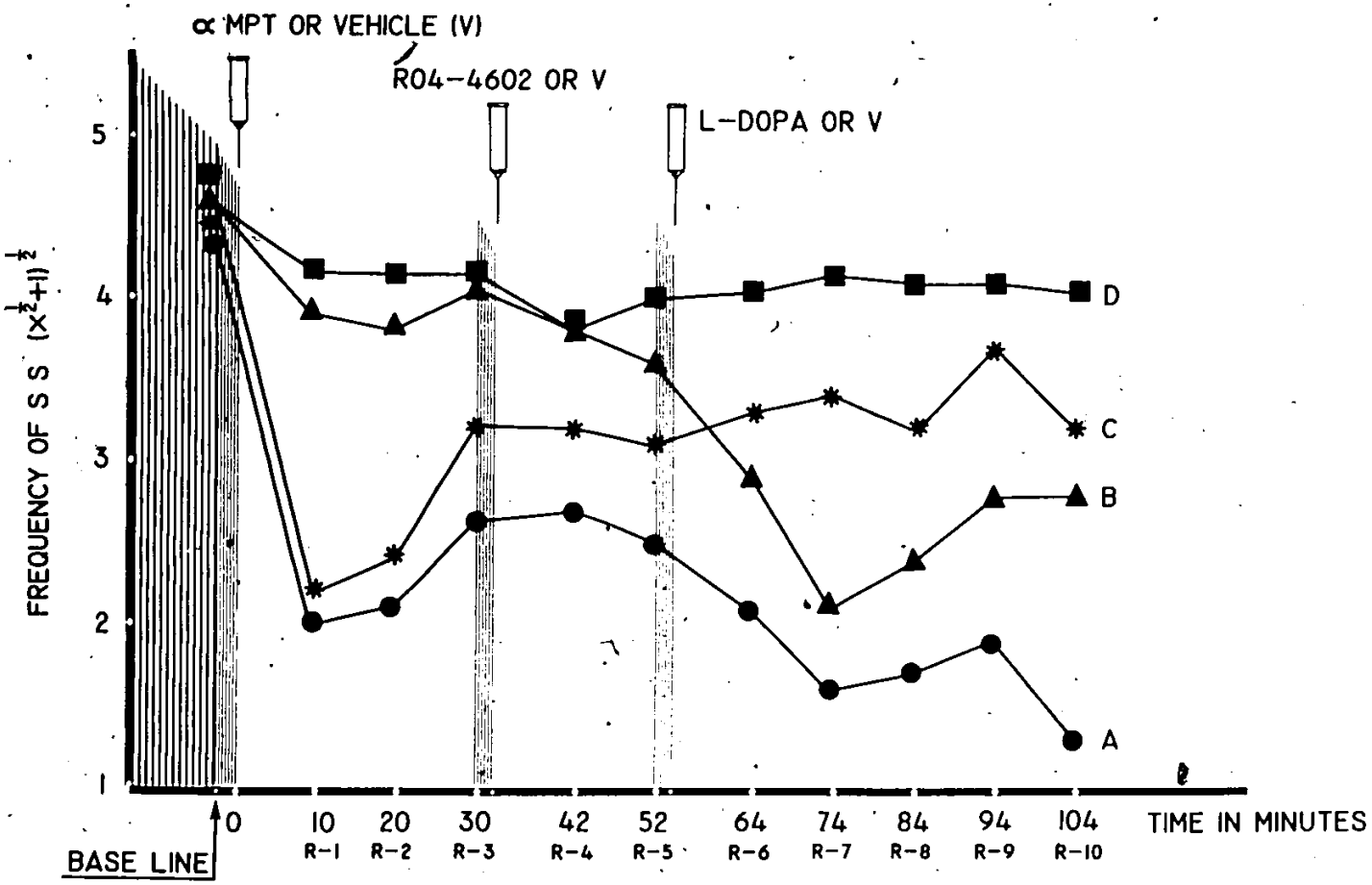
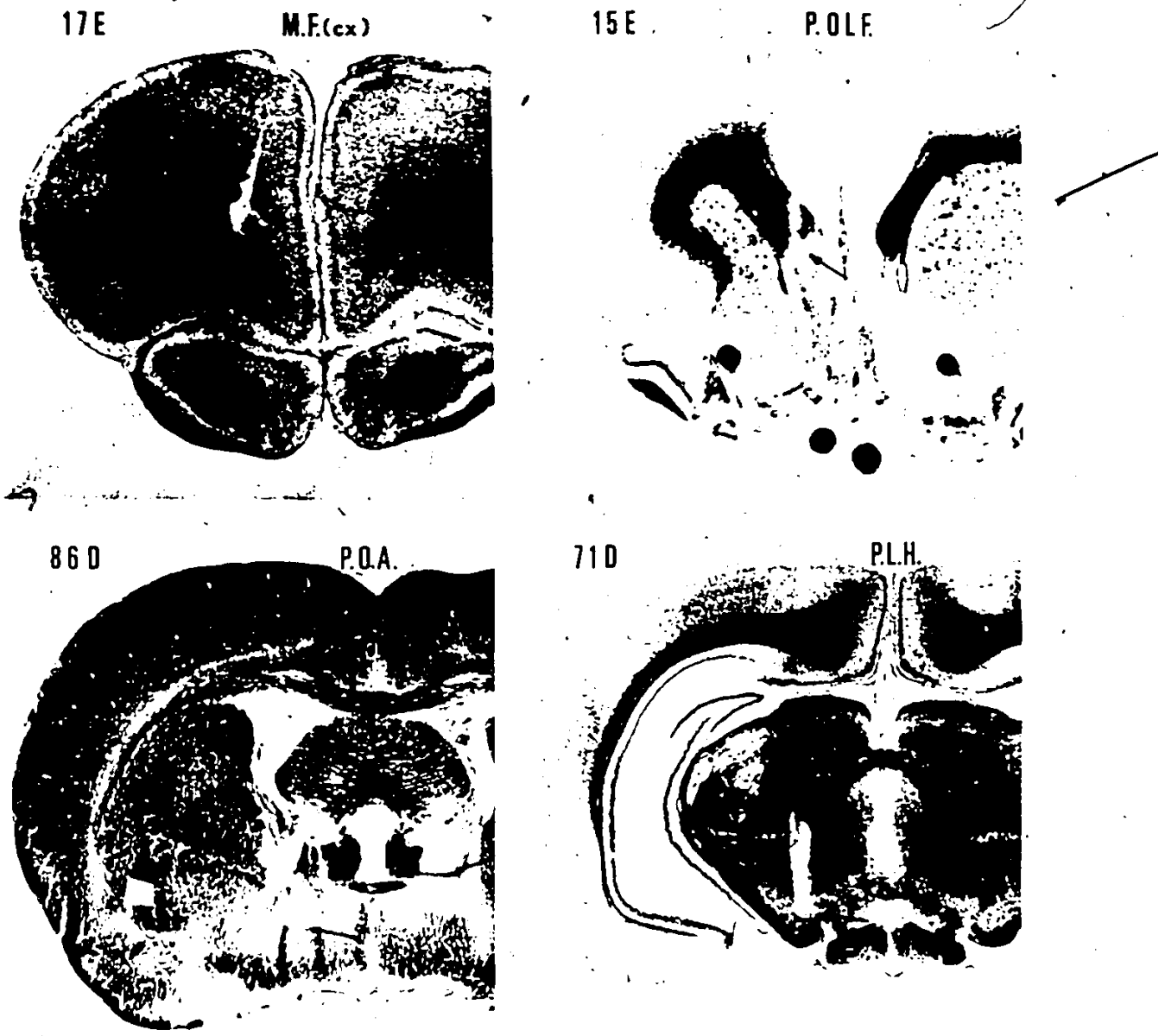

α MPT OR VEHICLE (V)
R04-4602 OR V
L-DOPA OR V
FREQUENCY OF S S $(X^{\frac{1}{2}}+1)^{\frac{1}{2}}$
5
4
3
2
1
D
C
B
A
0
10
R-1
20
R-2
30
R-3
42
R-4
52
R-5
64
R-6
74
R-7
84
R-8
94
R-9
104
R-10
TIME IN MINUTES
BASE LINE
GROUP 1
CONDITION A : α-MPT + R04-4602 + L-DOPA
CONDITION B : V + R04-4602 + L-DOPA
GROUP 2
CONDITION C : α-MPT + V + V
CONDITION D : V + V + V

Figure 10

Representative histological sections of rat brains showing lower extremity of electrode tracks which were aimed at PLH (posterior lateral hypothalamus); POA (preoptic area); POlf (paraolfactory area) and MFcx (medio-frontal cortex).

Figure 10



B. Transitory Reinstatement of Self-Stimulation with Apomorphine Following its Suppression by Alpha-Methyl-Para-Tyrosine

I - Introduction

In a previous study (Beaugrand and St-Laurent, 1973), it was reported that L-Dopa (50 mg and 200 mg/kg ip) could not reinstate SS suppressed by α-MPT (100 mg/kg ip). It was also noted that L-Dopa produced hyperreactivity and a decrease of spontaneous motor activity.

Subsequently, Stinus and Thierry (1973) succeeded in reinstating SS which had been suppressed by α-MPT by administration of catecholamine precursors.

Increase of motor activity and of exploration were obtained by Maj et al. (1972) and Carlsson (1972) after administration of apomorphine (A). Since increases of both motor activity (Roberts, 1958; St-Laurent and Beaugrand, 1972) and exploration (Christopher and Butter, 1968; Groover, 1966; Miliaressis, 1972; St-Laurent and Olds, 1964; St-Laurent and Beaugrand (1972) were reported to be the most significant behavioral features correlated with SS from the posterior lateral hypothalamus (PLH) and ventro-medial tegmentum (VMT), it was felt that apomorphine could possibly reinstate these behaviors and SS after the suppression by α-MPT pretreatment.

Apomorphine is believed to be a direct stimulator of dopaminergic receptors and, therefore, may account for the increase in motility (Anden et al., 1967; van Rossum and Hurkmans, 1964), or for the stereotypies induced in rats (Ernst and Smelik, 1966; Ernst, 1967). Hence, there seems to

be a pharmacological basis for predicting that apomorphine should reinstate SS after its suppression by α-MPT.

In our first study (St-Laurent et al., 1973c), SS from PLH and VMT was suppressed by the ip administration of α-MPT-methyl-ester (100 mg/kg). Subsequently, 3½ hr. after the α-MPT administration, apomorphine (0.25 or 0.5 mg/kg) was injected ip. SS was reinstated to a significant degree 2 hr. after administration of 0.25 mg/kg and 3 hrs. after the 0.50 mg/kg dosage (Fig. 11). The data indicated that apomorphine could reverse the suppressive effects of α-MPT on SS and that the most effective dosage was 0.25 mg/kg.

In the present study, after administration of apomorphine subsequent to saline, the animals showed a transitory suppression of SS (Fig. 11) which started within 10 min. of injection and lasted ½ hr. (0.25 mg/kg) and 1½ hr. (0.5 mg/kg), suggesting that while this dosage of apomorphine induced a more pronounced inhancement sniffing and exploration, it also decreased habituation; hence, apomorphine at a high dose of 0.25 mg/kg gave increase in persistent reactivity to many types of stimuli, making difficult the necessary focus on the SS goal and performance.

It was somewhat surprising that the effect of apomorphine on exploration, when given after saline, was almost immediate. In contrast, it took respectively 2 hr. and 3 hr. after the administration of 0.25 and 0.50 mg/kg of apomorphine to reinstate SS after α-MPT administration. It was hypothesized that a lower dose of apomorphine, e.g., 0.125 mg/kg, could

reinstate SS even more quickly. Hence, the aim of the next study was to determine whether apomorphine at 0.125 would be more effective than at 0.250 mg/kg.

II - Material and Method

a) Animals

The animals were 8 male Sprague-Dawley albino rats weighing between 250-300 g at the time of surgery, housed in individual cages and maintained on an ad lib water and food schedule. Surgery and other standard procedures were identical to those used in previous experiments. The electrodes were aimed stereotaxically to determine the exposed tip in the posterior lateral hypothalamus (PLH) at coordinates 2 mm posterior to bregma, 1.4 mm lateral to the sagittal suture, and 9 mm below the skull surface. The incisor bar was level with the interaural plane. After a 10-day recovery period, animals were trained to self-stimulate for a period of 20 daily sessions (30 min. daily) until SS responding was maintained at relatively constant rates for three consecutive days.

b) Baseline of SS and Drug Administration

On the experimental day, animals were allowed to self-stimulate for a period of 30 min. Following this pretest period, the rats were injected with either saline (Vehicle (V)) or DL-alpha-methyl-para-tyrosine methyl ester (α-MPT) (Regis Chemical Co., Chicago) (100 mg/kg). Alpha-MPT and apomorphine (A) solutions were prepared by dissolving α-MPT or A in 0.9% NaCl. All drugs and vehicles were administered ip at room temperature. A period of 10 min. was allowed for injections.

Following the injection period, animals were permitted to continue SS for the next 30 min. They were to return to their cages for a period of 2½ hr. Subsequently, the rats were returned to their Skinner boxes and another 30 min. reading was taken. They were than injected, at time 4 hr., either with V or with A at dosages of 0.125 mg/kg (A .125) or 0.25 mg/kg (A .25). Eight 30 min. readings were then taken. The 30 min. sessions for all animals commenced with five forced intracranial stimulations in order to verify current intensity which was set at 100 μA (peak-to-peak) for all animals. With the exception of the time alloted for injections and rest period, the animals spent the complete 7 hr. 40 min. experimental time in their Skinner boxes. As can be seen in Fig. 11, there were six combinations of drug treatments. Each of the 8 animals received all six treatments in randomized order. Between each treatment, there was a one week recovery period during which the rats were allowed to self-stimulate; no significant variations of SS rates were observed in subjects during recovery period, when compared to their pretreatment performance. The response rates for each 30 min. session of the same animal were used in calculating the different scores across treatments at a given time reading. The Wilcoxon matched-pairs signed-ranks test (Ferguson, 1971) was used for the purpose of statistical analysis.

Upon completion of the experiment, subjects were killed with an overdose of sodium pentobarbital solution (200 mg/kg). The brains were fixed in formaldehyde (10%); transverse

sections were made and stained according to the luxol fast blue technique of Klüver Barrera (1953) for histological verification of electrode positions.

III - Results

a) Histological Examination

The PLH probes fell either in the posterior lateral hypothalamus at the level of the mamillary bodies or in the ventromedial tegmentum (VMT) in two cases, both in or around the medial forebrain bundle. As the effects of A on VMT animals did not differ from those on PLH animals, their results were grouped together.

The results of the statistical findings on the effects of apomorphine on SS are summarized in Fig. 12. Significant differences were observed at every 30 min. reading from the reading 0:10 (reading 1) to the reading 7:10 (reading 10). The summary of comparisons of paired treatments using the Wilcoxon test (Ferguson 1971) is illustrated in Table 7.

b) Effect of α-MPT on SS

At the time 0:30 following one injection of α-MPT and again at the time 3:30 (readings 2 and 3), there was a definite drop in bar-pressing rates for all α-MPT pre-treatment groups, except α-A.25 which increased somewhat at time 0:30 but then significantly decreased bar-pressing activity by time 3:30. At time 3:30 (reading 3), a significant difference was noted between the V-V treatments (control) and the α-MPT - V treatments; this difference was observed between these two sets of treatments from time 3:30 through 7:10 inclusive (readings 3 to 10).

c) Effect of Apomorphine on SS and Reversal of α-MPT Effect

Regardless of pretreatment (α-MPT or V), a single injection of A.125 or A.25 caused an immediate, but brief suppression of SS behavior. At time 4:10 (reading 4), significant differences in bar-pressing rates were noted between all paired treatments, except α-VA.25, αV-VA.125, α A.25 - VA.25, and VA.25 - VA.125 at time 4:10. At time 4:40 (reading 5), the control group VV made significantly more bar-presses than any other group, except the VA.125 group. At this same time, α-A.25 rats had significantly more bar-presses than αV or αA.125 groups and VA.125 animals had more bar-presses than αV, αA.25, αA.125 or VA.25 subjects.

At time 5:10 (reading 6), VV animals made significantly more bar-presses than αV, αA.25 or αA.125 rats, while αA.25 subjects had higher rates of bar-pressing than αV group. At this same time, VA.125 animals made significantly more bar-presses than αV, αA.25, αA.125 or VA.25 rats, while VA.25 subjects had higher rates of bar-pressing than αA.125 group.

At time 5:40 (reading 7), VV animals made significantly more bar-presses than αV, αA.25, αA.125 or VA.25 subjects. At this same time, VA.25 rats made significantly more bar-presses than αV, αA.25 or αA.125 animals. Finally, at time 5:40 (reading 7), VA.125 rats made significantly more bar-presses than any other group.

At time 6:10 (reading 8), VV rats made significantly more bar-presses than αV, αA.25 or αA.125 subjects. At this same time, αA.25, αA.125, αVA.25 and VA.125 groups made

significantly more bar-presses than αV rats, while VA.25 subjects had more bar-presses than αA.25 animals. Finally, at time 6:10 (reading 8), VA.125 animals had significantly higher bar-pressing rates than αA.25, αA.125 or VA.25 rats.

At time 6:40 (reading 9) VV control group made significantly more bar-presses than αV, αA.25 or αA.125 rats. At this same time, VA.25 animals had significantly higher bar-pressing rates than αV, αA.25 or αA.125 subjects. Finally, at time 6:40 (reading 9), VA.125 animals had significantly more bar-pressing than αV or αA.25 rats.

At time 7:10 (reading 10), VV control group made significantly more bar-presses than αV or αA.25 rats. At this same time, VA.25 subjects had more bar-pressing than αV, αA.25 or αA.125 animals. Finally, at time 7:10 (reading 10), VA.125 rats made significantly more bar-presses than αV, αA.25 or αA.125 animals.

Within 2 to 3 min. after injection of A, it was noted that the rats showed an increase of spontaneous exploration behavior (with sniffing, rearing and other locomotor activities) when compared with V or α-MPT animals.

Table 7

LEVELS OF SIGNIFICANCE IN THE WILKINSON MATCHED-PAIRS SIGNED-RANKS TEST (ONE WAY TEST)

Summary of comparisons of paired treatments using the Wilkinson test.

LEVELS OF SIGNIFICANCE IN THE WILCOXON MATCHED-PAIRS SIGNED-RANKS TEST (ONE WAY TEST)

TIME READINGS	1 -0:10	2 0:30	3 3:30	4 4:10	5 4:40	6 5:10	7 5:40	8 6:10	9 6:40	10 7:10
Paired Treatments										
VV-αV	-----	-----	0.025	0.005	0.005	0.005	0.005	0.005	0.10**	0.05
VV-αA.25	-----	0.05	-----	0.005	0.005	0.025	0.005	0.05**	0.005	0.025
VV-αA.125	0.005	0.005	0.05	0.005	0.005	0.01	0.005	0.05	0.025	-----
VV-VA.25	-----	-----	-----	0.01	0.025	-----	0.025	-----	-----	-----
VV-VA.125	0.025	0.005	0.01	0.025	-----	-----	0.005	-----	-----	-----
αV-αA.25	0.025	0.05	0.05	0.025	0.05	0.025	-----	0.025**	-----	-----
αV-αA.125	0.005	-----	-----	0.005	-----	-----	-----	0.005	-----	-----
αV-VA.25	-----	-----	-----	-----	-----	-----	0.025	0.005	0.025	0.05
αV-VA.125	-----	0.005	0.005	-----	0.005	0.005	0.005	0.005	0.01**	0.025
αA.25-αA.125	0.005	0.005	0.05	0.025**	0.025	-----	-----	-----	-----	-----
αA.25-VA.25	-----	-----	-----	-----	-----	-----	0.025	0.01**	0.01**	0.005
αA.25-VA.125	-----	-----	0.01	0.005	0.005	0.005	0.005	0.005	0.01**	0.01**
αA.125-VA.25	-----	0.01	-----	0.025	-----	0.05	0.01**	-----	0.01	0.05
αA.125-VA.125	0.01	0.005	0.005	0.005	0.005	0.01	0.005	0.025	-----	0.01
VA.25-VA.125	0.005	-----	0.05	-----	0.005	0.01	0.005	0.025	-----	-----

* "p" based on (N=6); ** "p" based on (N=7); all others based on (N=8)

Figure 11

Summary of the effects of α-MPT and Apomorphine (A) on SS rates. Alpha-MPT, 100 mg/kg or saline vehicle (V) were injected ip at time - 0:10 hr. after a control reading of 30 min. Apomorphine, 0.25 mg or 0.5 mg/kg, or V were administered at 3:40 hr. Subsequent readings were taken every 30 min.

Figure 11

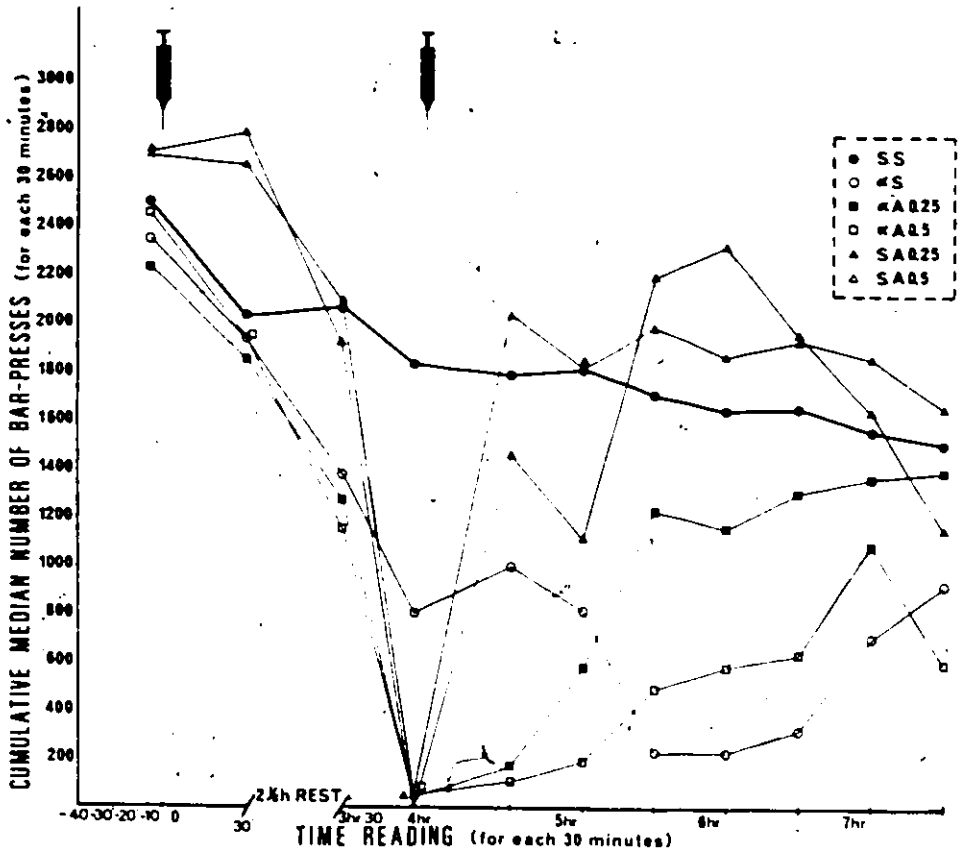
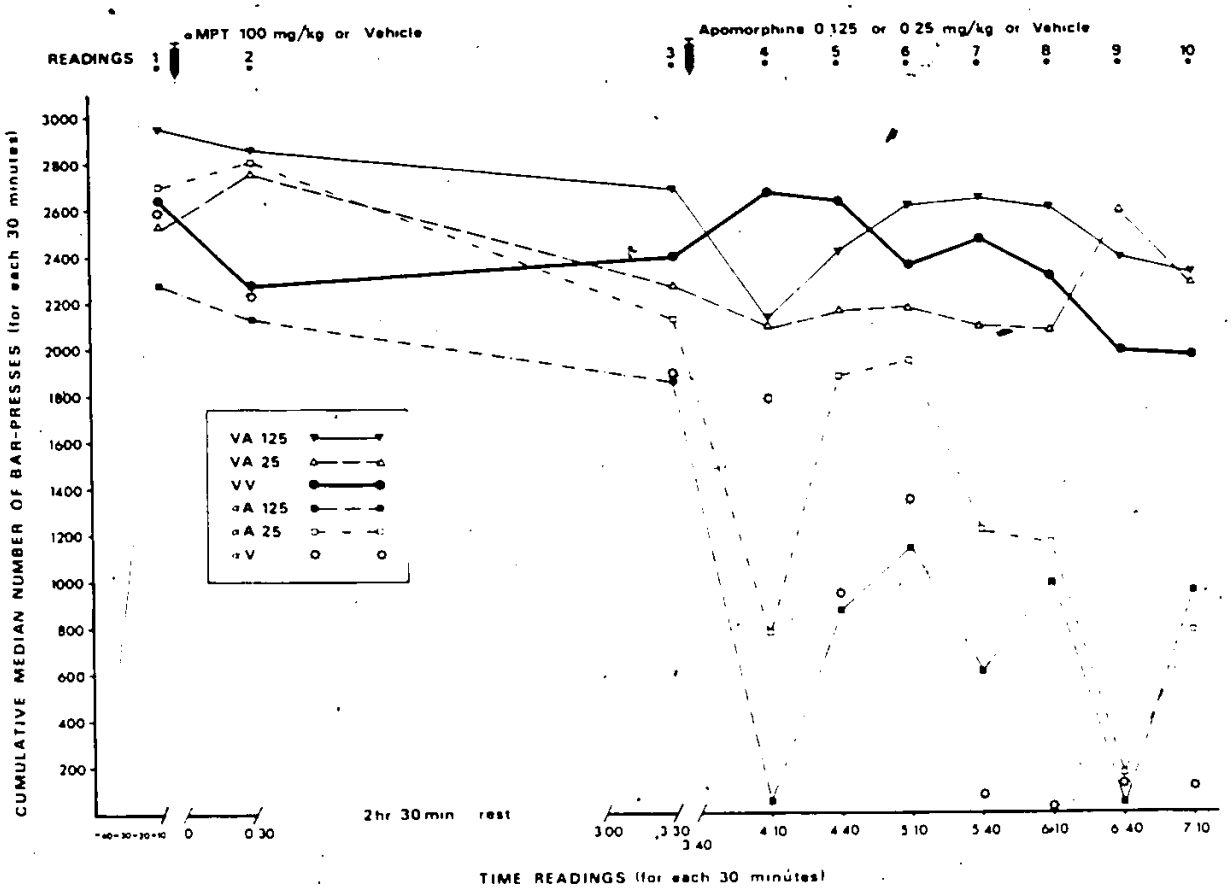

CUMULATIVE MEDIAN NUMBER OF BAR-PRESSES (for each 30 minutes)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
S S
∝S
∝A 0.25
∝A 0.5
S A 0.25
S A 0.5
-40 -30 -20 -10 0
30
2½h REST
3hr 30
4hr
5hr
6hr
7hr
TIME READING (for each 30 minutes)

Figure 12

Summary of the effects of α-MPT and Apomorphine (A) on SS rates. Alpha-MPT, 100 mg/kg or saline vehicle (V) were injected ip at time - 0:10 hr. after a control reading of 30 min. Apomorphine 0.125 mg or 0.25 mg/kg, or V were administered at 3:40 hr. Subsequent readings were taken every 30 min.

Figure 12


αMPT 100 mg/kg or Vehicle
Apomorphine 0.125 or 0.25 mg/kg or Vehicle
READINGS 1 2 3 4 5 6 7 8 9 10
CUMULATIVE MEDIAN NUMBER OF BAR-PRESSES (for each 30 minutes)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
VA 125
VA 25
VV
αA 125
αA 25
αV
2hr 30 min rest
-60 -30 -20 -10 0 0 30 3 00 3 30 3 40 4 10 4 40 5 10 5 40 6 10 6 40 7 10
TIME READINGS (for each 30 minutes)

C. Effects of Parachlorophenylalanine (PCPA) on Self-Stimulation from the Median Raphe Area

I - Introduction

Self-stimulation in the rat is often elicited with electrodes located in brain regions containing mainly catecholaminergic neuronal elements. The consistency between neuroanatomical, biochemical data and the relatively uniform results obtained with drugs known to act on catecholaminergic mechanisms led progressively to a catecholaminergic hypothesis of SS (Liebman and Butcher, 1974).

Investigations of a possible involvement of serotonin (5-HT) in the mediation of SS have led to contradictory conclusions. In a few studies, depletion of central 5-HT by parachlorophenylalanine (PCPA), a serotonin biosynthetic inhibitor, failed to change the intensity of SS (Black and Cooper, 1970; Cooper et al., 1971; Stinus et al., 1970a, 1970b). On the other hand, neurotoxic destruction of serotonin terminals (Poschel et al., 1974) or reduction of brain 5-HT by synthesis inhibitor (Blum and Geller, 1969; Poschel and Ninteman, 1971) was found to facilitate SS.

Contradictory conclusions have also been drawn from studies dealing with anatomical correlates of positive reward. Self-stimulation in the dorsal raphe, which is known to contain the highest amount of brain serotonin, has been attributed to norepinephrine (NE) fibers rather than to serotonergic raphe cell bodies (Margules, 1969). Furthermore, according to Routtenberg and Malsbury's brain stem anatomical map for SS

(Routtenberg and Malsbury, 1969), positive reward was not obtained in the median raphe, while such behavior, though moderate, has been subsequently reported by stimulation of this area (St-Laurent et al., 1973a; Simon et al., 1973; Miliaressis et al., 1975). Failure to consistently and uniformly affect SS by manipulation of serotonin, in addition to the role of this amine in some inhibitory processes, has generally led to an assumption which excludes serotonin as a mediator of SS behavior (Lorens, 1971; Stein, 1971). In contrast to this belief, the present work provides evidence that strong SS behavior can be elicited with electrodes in the median raphe and that this behavior is specifically reduced by the blockage of serotonin synthesis.

II - Material and Methods

a) Animals and Surgery

The experiments were performed on seven male Sprague-Dawley rats (300 g), implanted stereotaxically with bipolar insulated electrodes (0.250 mm. in diameter) in the median raphe (MR) (Nucleus centralis superior) under a sodium pentothal (50 mg/kg ip) anesthesia. With the incisor bar 3 mm. above the interaural line, the median raphe (MR) coordinates were: 6.0 mm. posterior to the bregma, 0.0 mm. lateral to the midline and 8.0 mm. under the surface of the skull.

b) Training for Brain Self-stimulation

Ten days after surgery, rats were trained to self-stimulate in the MR region. Each press delivered a 60 Hz sine current of 250 ms duration. The intensity of the current

was adjusted individually for each rat during the first four days of the training period, in order to elicit optimal SS rates without forced motor movements (mean intensity: 48 ±5.2 μA rms) and was continuously monitored by a cathode ray oscilloscope.

c) Drug Administration

After 10 days of optimal stabilization of SS behavior, the rats were given an ip injection of saline at 6:00 a.m. Twenty-four hours later, the animals were allowed to self-stimulate for 120 minutes; readings of bar-presses were taken every 10 min. in order to obtain a basal level (Basal level day). On the subsequent three days (at 6:00 a.m. of each day), the rats were given three consecutive ip injections of PCPA (150 mg/kg). PCPA was prepared by dissolving 100 mg of PCPA hydrochloride ester in 0.4 ml of propylene glycol, 0.4 ml of H_2O and 0.03 ml of saturated sodium acetate in order to keep the PCPA methyl-ester in solution. Readings were again taken 24 hours, 48 hours and 96 hours after the first injection.

Bar-pressing rates from seven animals were obtained throughout six consecutive days of testing. On each day, 12 successive measures were taken at 10 min. intervals. The first three days constituted a pre-injection period during which the baseline for rate of bar-pressing was established. The first injection of PCPA was given 24 hrs. before the fourth test day and the procedure was repeated for two days. Thus, an injection period was maintained for three days.

III - Results

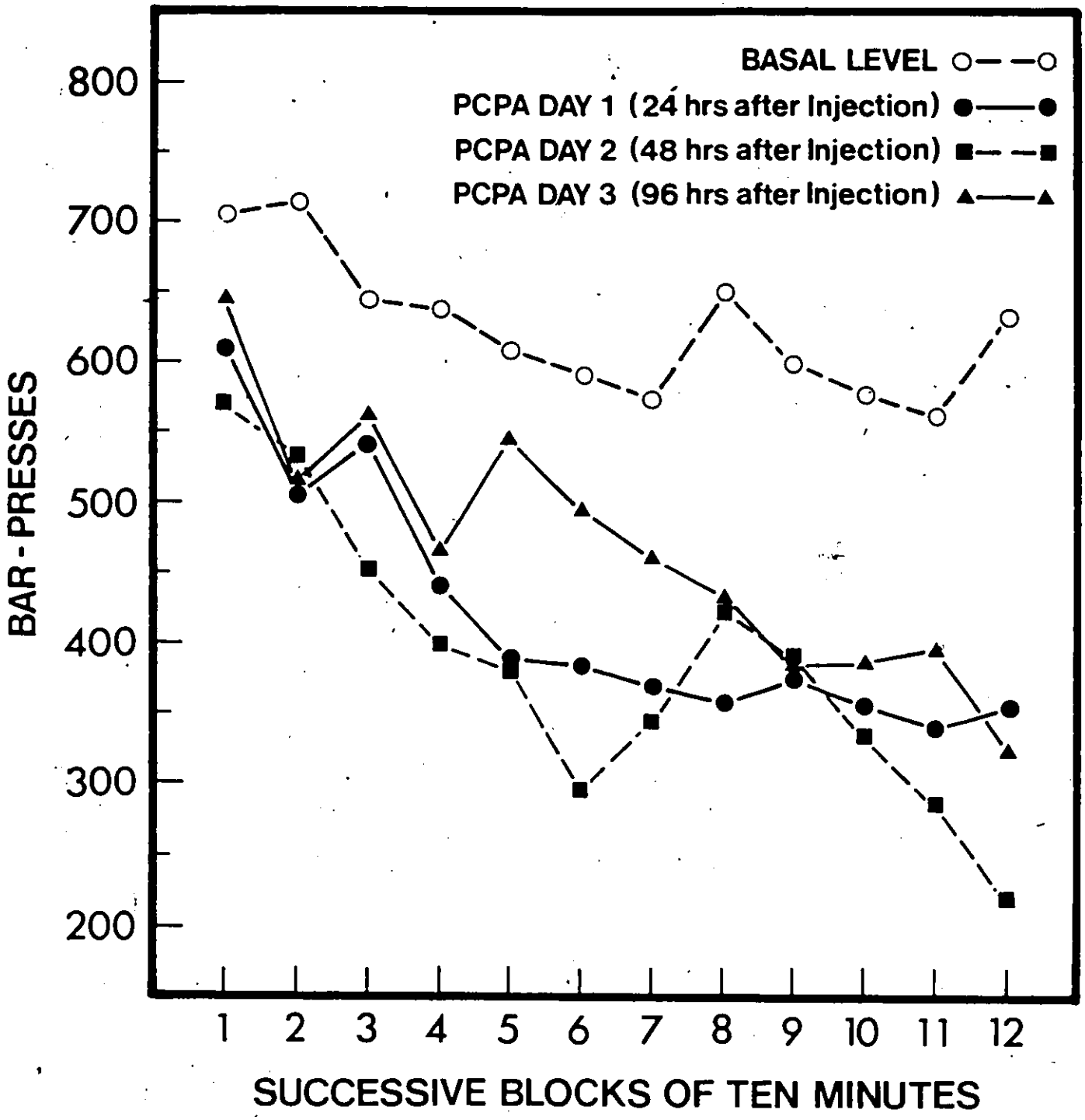
The behavioral data obtained in this experiment are summarized in Fig. 13. They show that the injection of PCPA resulted in a suppression of bar-pressing for SS and that this decrease was more pronounced towards the end of the test sessions.

An ANOVA was performed on each of the first three days, during which time the baseline was established; no significant difference was found ($F2,12) = 4.693$, $p>0.05$). However, the analysis of variance showed a significant effect of time blocks (12 blocks of 10 min.) ($F (11,66) = 2,543$; $p<0.01$) while there was no significant interaction between the days and time-blocks ($F (22,132) = 0.909$; $p>0.05$).

The data obtained on each day during 12 blocks of 10 minutes are shown in Fig. 13. A two-way ANOVA, with repeated measurements over two factors, was performed on these data as follows: An Anova comparing the baseline days with the 3 injections days revealed a significant difference between the baseline and injection days ($F (3,18) = 5,443$; $p<0.01$). A significant difference was also found between the various time-blocks ($F (1,66) = 12,516$; $p<0.001$). Finally, the interaction between these two factors was significant ($F (33,198) = 1,562$; $p<0.05$).

Figure 13

Comparative effects of saline (Basal Level) and of parachlorophenylalanine (PCPA, 150 mg/kg ip) on bar-pressing rates for intracranial self-stimulation in the median raphe (MR) of the rat. Points represent the mean of bar-presses from 7 rats. The animals were allowed to self-stimulate for 120 min; readings were taken every 10 min.


BASAL LEVEL
PCPA DAY 1 (24 hrs after Injection)
PCPA DAY 2 (48 hrs after Injection)
PCPA DAY 3 (96 hrs after Injection)
BAR-PRESSES
800
700
600
500
400
300
200
1 2 3 4 5 6 7 8 9 10 11 12
SUCCESSIVE BLOCKS OF TEN MINUTES

D. Effects of LSD-25 on Self-Stimulation from the Median Raphe of the Rat Brain

I - Introduction

Considerable speculation has been made concerning the mechanism of action of the hallucinogenic drug lysergic acid diethylamide (LSD). Its molecular structure (containing both an indole and a phenylethylamine moiety) suggests the possibility of an interaction with brain monoamines. Neurophysiological and behavioral studies indicated that LSD interact with serotonin and catecholamine receptors in the central nervous system (von Hungen et al., 1974). In addition, speculation has been made concerning the possibility of stimulation of serotonin (5-hydroxytrypamine, 5-HT) receptors by LSD-25 (Anden et al., 1968; Freedman and Giarman, 1962; Haigler and Aghajanian, 1974; Jalfre et al., 1974). However, the earlier hypotheses also postulated a marked anatogonism between LSD-25 and 5-HT in their effects on the receptors of the brain (Aghajanian and Weiss, 1968; Aghajanian et al., 1972). Blocking of the release of 5-HT from nerve endings is another suggested mechanism of action of LSD (Chase et al., 1967; Aghajanian and Weiss, 1968). Other studies indicate that LSD may enhance serotonin binding and decrease its synthesis (Haigler and Aghajanian, 1974), or increase serotonin turnover after chronic administration (Rosecrans et al., 1967). More recent data have shown that LSD depresses the firing of serotonergic neurons in the rat midbrain raphe (Aghajaniah et al., 1968). It is known that electrical self-stimulation can be

obtained from these serotonergic raphe nuclei in the rat (St-Laurent et al., 1973a; Simon et al., 1973; Miliaressis et al., 1975). Assuming that these neurons are involved in the SS phenomenon, one would expect a decrease, and possibly a total inhibition, of SS behavior under LSD. The purpose of the present experiment was to test this hypothesis.

II - Material and Methods

a) Animals and Surgery

The animals were 6 male Sprague-Dawley albino rats, weighing between 250-300 g at the time of surgery, housed in individual cages and maintained on an ad lib food and water schedule. The animals were implanted with indwelling bipolar electrodes in MR, as described on page 102 for PCPA experiments.

b) Training for Brain Self-Stimulation

After a 10 day recovery period, animals were trained for 30 min. daily, for approximately two weeks, until SS behavior was stabilized. Subsequently, rats were allowed to self-stimulate for 120 min. daily. Readings of bar-presses were taken every 10 min.

c) Drug Administration

Once a week, rats were tested successively under the following drug conditions: LSD 60 µg/kg; saline; LSD 30 µg/kg; saline; and LSD 120 µg/kg. The injections (ip) were given immediately after the third reading of each SS period. Solutions were prepared by dissolving LSD-25 in 0.9% NcCl.

Exploratory and motor behavior during SS was also observed and occasionally filmed. Analysis of variance was

done with repeated measurements over two factors (Winer, 1962).

Upon completion of the experiment, subjects were sacrificed and the brains perfused with 10% formalin. Transverse sections were made and stained according to the luxol-fast blue technique of Klüver Barrera (1953) for histological verification of electrode positions.

III - Results

a) Self-Stimulation Performance

Fig. 14 indicates that the SS rates were decreased by administration of LSD. Since the scores of SS did not usually show a normal distribution, the original SS scores were linearized using a logarithmic transformation (log 10 (X+1) (Winer, 1962). The statistical analysis of the data (ANOVA) indicated that global differences existed between the five days (saline and drug days) and between the twelve readings. The second ANOVA on the five days and nine readings following the injections gave similar results. Individual analyses of variances were done in order to compare each drug day with the saline day. Significant difference was found between saline and LSD 30 ug/kg only at reading 7, that is, 40 min. after the injection ($F(1,5) = 7.3446$; $p<0.05$). The same analysis showed a significant difference between saline and LSD 60 µg/kg ($F(1,5) = 7.939$; $p<0.05$) at readings 5 and 6, indicating that the suppressing effect of LSD started 20 min. after the injection and lasted approximately 20 min. Finally, when LSD in a dose of 120 µg/kg was given, significant differences were observed when compared with baseline level

starting at reading 4 ($F(1,5) = 112,420$; $p<0.001$), indicating that the effect of LSD started within 10 min. after injection. Significant differences were also found for readings 5 ($F(1,5) = 23,206$; $p<0.01$) and 6 ($F(1,5) = 50,372$; $p<0.01$). No significant difference was noted at reading 7 ($F(1,5) = 5,115$; $p=0.072$).

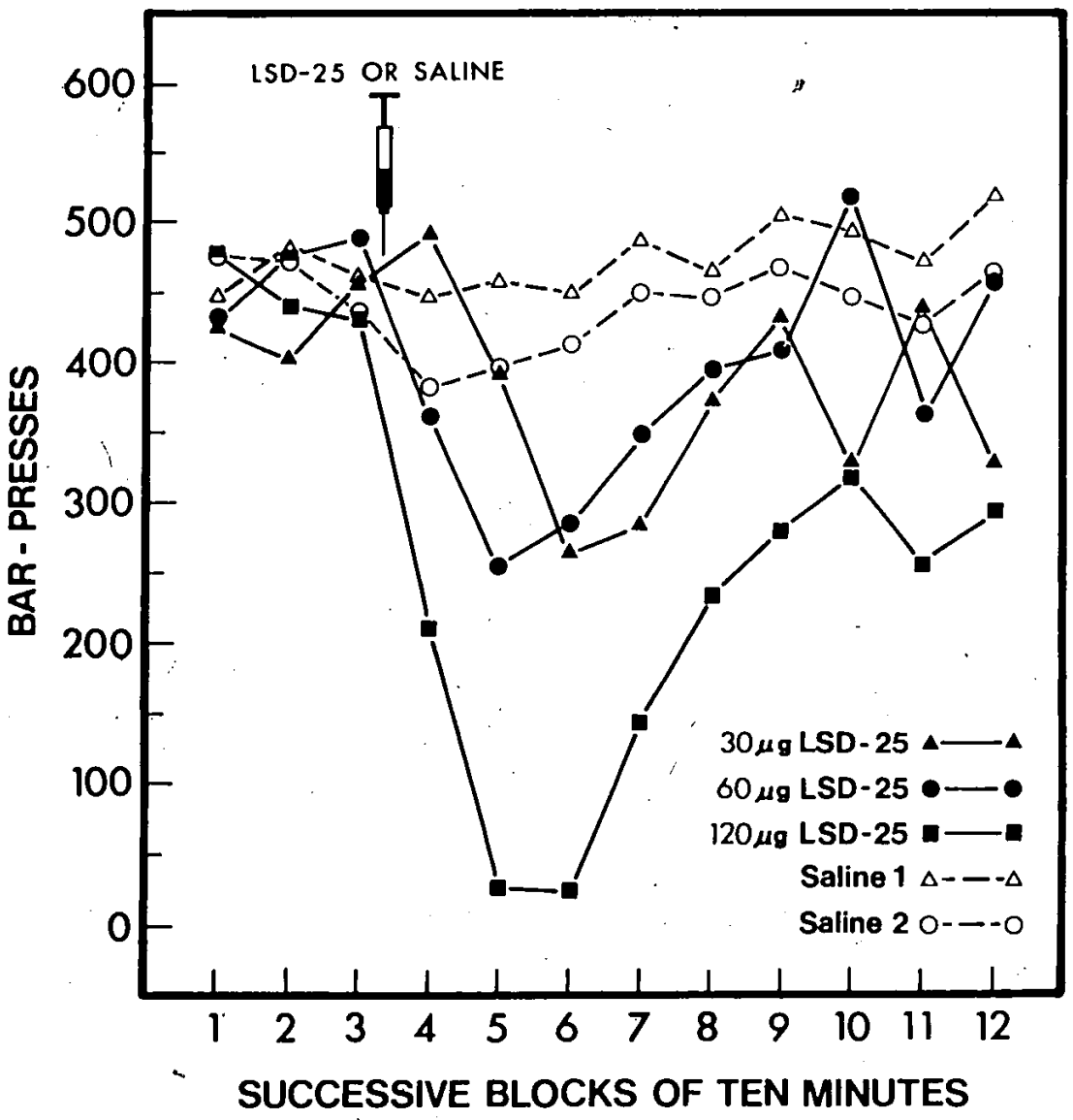
b) Behavior Concomitants of Self-Stimulation after LSD Administration

Twenty minutes after being given 30 µg of LSD, four rats showed crawling and diffused exploration (exploration all over the area of the cage). Only two rats showed these phenomena after 30 min. and only one after 40 min. Of the rats which received 60 µg of LSD, three showed diffused exploration after 10 min., and two others showed crawling accompanied by sagging of the rear trunk. These animals had difficulty crawling from one position to another and had a diminished motor tonus. After 20 min., five animals showed crawling but no exploration. In the group of animals having received 120 µg or LSD, two showed diffused exploration after 10 min., while four others displayed crawling. After 20 min., four displayed diffused exploration and all six were crawling. After 30 min., three showed diffused exploration and all six were still crawling. After 50 min., none of the animals showed crawling or diffused exploration.

Fig. 14 shows the SS performance before and after injection of saline or increasing doses of LSD. Saline or LSD was administered after the 3rd reading was taken.

Figure 14

Comparative effects of LSD-25 at doses of 30, 60 and 120 µg. Readings were taken every 10 minutes. LSD or saline were injected (ip) after the third reading.


LSD-25 OR SALINE
600
500
400
300
200
100
0
BAR-PRESSES
1
2
3
4
5
6
7
8
9
10
11
12
SUCCESSIVE BLOCKS OF TEN MINUTES
30μg LSD-25
60μg LSD-25
120μg LSD-25
Saline 1
Saline 2

DISCUSSION

A - Topographic Organization of Intracranial Self-Stimulation Sites

Low frequency of SS was obtained from the anterior area of MFB or meso-cortex (MCx) (e.g., the mediofrontal cortex, the paraolfactory and septal areas). The SS rates from these mesocortical rhinencephalic structures as a group were then lower than the ones of the ALH, PLH or VMT groups. Self-stimulation rates in the ALH were higher than in the MCx (or anterior MFB) and raphe (R) areas, and not different from the ones in the PLH, but lower compared to the VMT. SS rates for PLH were higher than for the anterior MFB, ALH or Raphe, but not higher than for VMT. SS rates for VMT were higher than those for anterior MFB group, ALH or Raphe animals, but not higher than for PLH. Intracranial stimulation in the Raphe produced SS at lower rates than for MFcx, ALH and PLH. Self-stimulation in the dorsal RPC and Sub-LC was at low rates for 5 subjects, and at high rates for the 3 LC rats.

In the present study, the existence of a gradient of SS along the course of the MFB pathway was confirmed. The gradient was as follows: VMT, PLH, ALH, S, POlf, MFcx, hence, corresponding to the gradient reported previously by Olds et al. (1960), Olds and Olds (1963), and Bogacz et al. (1965). Posterior to the VMT, a gradient of SS is harder to establish (raphe and dorsolateral RPC) as the rates of SS were not stable. For instance, in agreement with some previous studies, (St-Laurent et al., 1973a; Simon et al., 1976), the current investigation reports SS of low frequency from the Raphe, while

Miliaressis et al. (1976) and Miliaressis and Jacobovitz (1976) obtained very high rates of SS. As for the dorsal RPC and LC, varying rates of SS have been reported by different researchers. This could be explained by the fact that the SS rates were observed to fluctuate from day to day, and that a stabilization of ICSS responding was harder to obtain than for more anterior areas. The rates of SS are also influenced by the presence of forced motor movements, such as circling from the median Raphe (Miliaressis, 1981), motor activation (bouncing on the lever), and motor inhibition in the form of adynamia from the LC and dorsal RPC (St-Laurent and Beaugrand, 1972) and motor inhibition in the form of arrest reactions from the septum (St-Laurent and Beaugrand, 1972). It is possible that the rates of responding do not represent an accurate measurement of the strength of reinforcement. Therefore, one has to be prudent in making the proposition that there would exist an hierarchic organization of the ICSS system based on rates of SS. Studies of the threshold of ICSS would have been more appropriate for the establishment of the relative density of neural elements per ICSS site.

B - Behavioral Correlates of Self-Stimulation

a) Non-Specificity of Behavioral Patterns to Self-Stimulation

No single behavioral pattern was found to be specific to SS. There are instead different patterns which vary according to the brain site or area stimulated. However, some of the individual behavioral features which constitute

these patterns are at times common to many brain areas; for instance, in the case of exploration, it is always correlated with SS independent of the site.

Indeed, self-stimulation from the MCx group was accompanied by "arrest" responses and by low locomotor activity. This anterior MFB or MCx group differed from other groups in that arrest responses were observed exclusively in the areas of this group. Previously, Hess (1944), Bursten and Delgado (1958) had also observed "arrest" responses consecutive to stimulation of rhinencephalic areas. For this group of anterior areas, the intensity of the locomotor activity localized around the lever was less marked than in the ALH, PLH or VMT groups. Our findings of SS being correlated with low locomotor activity agrees with earlier observations by Roberts (1958) who reported inhibition of general activity during SS from the anterior areas of the MFB. Roberts' findings were further corroborated by St-Laurent and Olds (1964); St-Laurent and Beaugrand (1971; 1972) and St-Laurent et al. (1973b; 1973c). As reported in this thesis, locomotor activity changed from depression to excitation when the electrodes were moved from the anterior MFB areas to the posterior areas (i.e., ALH, PLH and VMT).

MCx SS was also accompanied by sniffing activity of low intensity, taking place around the lever with the nose pointing horizontally, as previously described by St-Laurent and Beaugrand (1972).

Exploratory behavior of a low intensity, as defined by our criteria, corresponded to the focalized and diffused types. Focalized exploration was seen in all animals of the anterior MFB group, but its intensity was less than for the posterior MFB areas.

To summarize, the behavior patterns accompanying the low SS obtained from the anterior MFB or MCx group were arrest and low locomotor activity, sniffing, focalized and diffused exploration.

The self-stimulating rats from the ALH group showed more focalized exploration than from all other areas, but less diffused exploration than the MCx, VMT, Raphe or RPC groups. There was more localized or focalized locomotion for ALH than for MCx, but less than for VMT and as much as for PLH, Raphe and RPC. There was less diffused locomotion than for Raphe.

Briefly, behavior correlates of high SS in ALH were high focalized exploration and some moderate degree of focalized motor activity.

Self-stimulation from the PLH group elicited a higher degree of sniffing when compared to the anterior MFB or RPC animals. There was no evidence of scattered exploration for PLH subjects. Focalized exploration was higher for PLH and ALH than for anterior MFB, Raphe or RPC rats. There was less "diffused" exploration and locomotion than for Raphe rats. Localized or focalized locomotion was higher in PLH animals than in anterior MFB, Raphe or RPC, but not more than in ALH or VMT rats.

Hence, the behavioral pattern for the PLH area was high sniffing, high focalized exploration and high intensity of localized locomotion.

Self-stimulation from the VMT group yielded focalized exploration which was more intense than for MCx, Raphe or RPC groups, but less than for the ALH group. Subjects from the VMT group showed more diffused exploration than ALH, but less than Raphe. Scattered exploration at the level of the VMT was higher than MCx, ALH and PLH. In addition, diffused or dispersed locomotion was less pronounced compared to Raphe subjects. However, except for the PLH group, there was significantly more localized or focalized locomotion than for all other groups (MFcx, ALH, Raphe and RPC).

Hence, the behavior patterns accompanying the high SS obtained from VMT were high focalized locomotion, high focalized and scattered exploration.

Intracranial stimulation in the Raphe group produced increased sniffing and diffused exploration, that is, sniffing around the cage, the nose pointing horizontally or in a slightly upward position. In addition, consequent to one or two bar-presses, the animal would display "bewildered" (hébêté) reactions, or show abortive or full rearing responses near the lever or around the whole area of the box. There was less Raphe "focalized" exploration compared to ALH, PLH or VMT subjects. However, "scattered" exploration was significantly higher for the R than for the MFcx, ALH or PLH rats, and "diffused" exploration was higher for the R than for MFcx, ALH, PLH or RPC animals. Finally, there was more diffused loco-

motion compared to MFcx, ALH, PLH or VMT subjects.

Therefore, the patterns of behavior observed during Raphe SS was diffused, scattered and dispersed exploration.

The present study confirms that SS can be obtained from the median raphe nuclei, as previously reported (St-Laurent et al., 1973; Simon et al., 1973; Miliaressis et al., 1975). Aghajanian and Sheard (1968) reported that stimulation of the R produced some reduction in directed exploratory behavior. In the present study, it was observed that SS from the Raphe was associated with diffused and scattered exploration, as reported by St-Laurent et al. (1973a).

Self-stimulation was also obtained from the dorsolateral part of the anterior reticularis pontis caudalis (RPC) and from the locus coeruleus (LC) and sub-locus-coeruleus (Sub-LC), that is, an area ventrolateral to the LC under the superior peduncle. We will refer to these self-stimulating rats as being from the LC-RPC groups.

Self-stimulation (SS) from the LC group was performed in bursts and was associated with progressively higher responding frequencies along with intense uncoordinated motor activity, that is, the rat was bouncing with the front paws on the lever and eventually showing transient periods of decreased motor activity. SS from the Sub-LC and adjacent dorsal RPC was slow and followed by transitory periods of diminution of motor activity, and even more often by adynamia, (the animal lying on the floor with hypotonia). These periods of adynamia were sudden, the onset and the ending appearing abruptly.

Following bursts of SS from the LC and Sub-LC, the animal could be seen sniffing and exploring the lever (the head pointing downward), exploring the walls (the head being held horizontally), or showing rearing responses or exploring upward (the head being held vertically). After a few seconds of these fragmentary non-systematized exploratory activities, sudden interruption or "blockage" of the explorating activity would occur, the rat standing still as if "hébêté", fixing in front of him in a daze. At other times, the rat would show "disruptive" phenomena consisting of abrupt, jerky, irregular and repetitive exploration of his body, the lever or the environment.

Self-stimulation elicited from the RPC was in bursts. More lull periods were observed during RPC self-stimulation than for any other group. In addition, RPC subjects had higher diffused and scattered exploration than ALH and PLH groups, but less focalized exploration than for ALH, PLH or VMT subjects. Sniffing was less apparent compared to PLH or VMT rats. The RPC stimulation also elicited some rather peculiar idiosyncratic behavior, including cases of "hébêté-daze-like" behavior, "hallucinatory-like" behavior, "non-systematic" exploration, and cases of "adynamia".

Hence, the pattern of behavior for RPC area was SS in bursts with lull periods, scattered and diffused exploration, along with idiosyncratic behavior (hébêté-daze-like, hallucinatory-like and adynamia). (In addition, flight and ambivalence was obtained from the ventral and dorsal RPC, respectively, as will be discussed below).

Our results on the topography of SS are only partially in agreement with the findings of Arbuthnutt et al. (1970a) and Crow et al. (1972). In these studies, SS was observed only from electrode sites clustered within or adjacent to the LC, while in the present study, SS was observed from the LC and Sub-LC. The present findings are in agreement with previous observations (St-Laurent and Beaugrand, 1971; 1972) showing that SS could be elicited both from the LC and Sub-LC.

Arbuthnott et al. (1970) and Crow et al. (1972) reported that SS and correlated phenomena appeared to be "similar in all respects" to those observed when the electrodes were placed elsewhere, except that the acquisition of SS behavior took longer than in the ventro-medial tegmental areas. There was no mention of marked increase or decrease in locomotor activity, nor of periods of adynamia, disruptive behavior or exploration.

As will be described in section "b", the LC and ventral RPC areas of the pons also yield ambivalence and flight reactions.

In conclusion, the three types of behavior, that is, flight, SS and ambivalence, can be observed during intracranial stimulation in the pons.

The summary of the qualitative data is illustrated in Fig. 7.

The quantitative data shown in Tables 1, 2 and 3 demonstrate that:

1. The gradient of frequency of SS starting with the areas showing the highest frequency is as follows: VMT, PLH, ALH, RPC, S, POlf, and MFcx areas.

2. Sniffing intensity between the various brain areas did not differ; the only exception was between the PLH area which was higher than the MCx and RPC.

3. a) Diffused exploration was higher in the Raphe than in all other brain areas studied. RPC was higher than PLH and ALH, but not any higher than in the remaining areas, that is, VMT and MCx. The VMT and MCx were higher than ALH, but not higher than the PLH, nor than one another. The order of intensity of diffused exploration was Raphe, RPC, VMT, MCx, PLH and ALH.

Hence, apart than in MCx, diffused exploration was higher in the posterior areas.

b) Scattered exploration was higher in the posterior areas, i.e., VMT, R and RPC, than in the more anterior areas such as PLH, ALH and MCx.

c) The gradient of focalized exploration was: ALH, PLH, VMT, MFcx, R and RPC.

4. Motor activity:

a) Diffused locomotor activity was higher in the Raphe area than in all other areas, except for the RPC. The RPC itself, however, was not significantly higher than any of the other areas.

b) Focalized locomotor activity. The VMT was not higher in focalized activity than the PLH, but was higher than all other areas. In turn, the PLH area was not higher than the

ALH, but was higher than all remaining areas. The ALH was higher than MCx, but not different than the remaining areas, i.e., Raphe or RPC. The MCx, R and RPC areas were not different from one another.

5. Lull periods. The intensity of lull periods was higher for RPC than for all other areas. There was no significant difference between all other areas. Therefore, lull can be considered a main behavioral feature for the RPC.

The data shown in Table 3 illustrates a positive correlation between the following variables: (1) Diffused locomotion and exploration; and (2), bewildered dazed-hébêté, withdrawn behavior and lull periods. Additionally, a moderate positive correlation was found between (1) SS rates, focalized motor activity and exploration, and (2), sniffing, focalized and diffused exploration.

b) Specificity of Behavioral Features to Self-Stimulation

In the study of the behavioral correlates of SS, it was observed that behavioral patterns were site specific. However, this was not the case for the individual component features of these patterns. More specifically, exploration was observed from all sites and this behavioral feature can possibly be considered specific to SS.

Exploration:

The correlation between SS and exploratory phenomena, as evidenced in the present study, confirms the results of previous reports. Indeed, Valenstein (1966), St-Laurent and Olds (1964), Groover (1966), Christopher and Butter (1968),

Valenstein et al. (1968), Miliaressis (1972), Rolls and Kelly (1972), St-Laurent and Beaugrand (1972), St-Laurent et al. (1973a), Miliaressis and Le Moal (1976), Rompré and Miliaressis (1980) found that exploration was the main behavior associated with self-stimulation. However, The present study showed that the patterns of exploration is site dependent: fragmented, non-systematized at the level of the dorsal region of the RPC to become diffused at the median-raphe, scattered and focalized at the level of the VMT of the mesencephalon, and focalized at the posterior and anterior lateral hypothalamic sites. These results suggest that as the electrode moves from the caudal parts of the pons to more anterior diencephalic loci, the exploration becomes more goal-oriented. This is in agreement with the views expressed by ST-Laurent and Beaugrand (1972) and St-Laurent et al. (1973a).

Locomotor activity:

The RPC, VMT, PLH, ALH, S, POlf and MFcx areas form an array along the MFB which runs from the pons to the forebrain. Self-stimulation elicited from any of these areas was accompanied by modification of locomotor activity. When stimulation was applied in the LC, SS occured in bursts and was correlated with intense increase of locomotor activity, the animal bouncing on the lever. The increased locomotor activity was of high intensity, hence becoming competitive with SS, and, therefore, diminishing the locus coeruleus SS performance. Self-stimulation in the dorsal RPC was accompanied by gradual hypotonia and progressively longer periods of interruption of SS with adynamia. Self-stimulation in bursts from the Raphe

was interrupted by periods of diffused motor activity, the animal moving from one area to another in the box. When the point of stimulation was changed from VMT, PLH and ALH to septal, POlf and MFcx areas, an orderly change from locomotor excitation to locomotor depression appeared. When stimulation was applied to the VMT, SS was correlated with increased motor activity and some animals were observed to jump and bounce on the lever with force. Stimulation in the PLH caused marked increments in activity. Stimulation in ALH produced moderate increase of motor activity. Stimulation in the septal, POlf and MFcx areas caused arrest responses and, at times, decrements of motor activity, both between periods of SS and after their completion. These "arrest" responses were observed in the areas of the MCx, rhinencephalic group exclusively. Previously, Hess (1944) Bursten and Delgado (1958) had observed arrest responses consequent to stimulation of rhinencephalic areas, while Hunter and Jasper (1949) obtained arrest by stimulation of the intralaminar nuclei.

From these observations, it seems that there is an organization of the motor activity which accompanies self-stimulation. When the point of stimulation was changed from anterior mesocortical (MFcx; POlf and S) areas to more posterior sites (ALH, PLH and VMT), an orderly change from arrest responses and locomotor depression to excitation appeared during SS, while both motor excitation and depression occurred from stimulation of the dorsal RPC and LC.

The anterior MCx areas yielding SS have been shown by Buser (1966) to have inhibitory motor properties. Hernandez Péon and Chavez-Ibarra (1963) reported that the MCx inhibit the reticular activating system of the mesodiencephalon, and Clemente et al. (1963) conceived these MCx areas as being part of a basal forebrain synchronizing inhibitory zone projecting to the lateral hypothalamus and thalamus.

To a certain extent, these findings on the locomotor activity are in agreement with earlier findings of other workers. Kaada (1951), Rosvold and Delgado (1956) reported decreased motor activity following stimulation in septal area. Lesion studies by Brady and Nauta (1953) also suggested an inhibiting effect of the septal area on motor-activity, as lesions in this area were followed by postoperative motor hyperactivity. Poirier et al. (1969) reported hypokinesia in contralateral limbs of monkeys after lesion in the VMT. Hess and Mueller (1946a, 1946b) describe as "adynamia" a syndrome showing both loss of muscle tone and spontaneous activity following coagulation of the posterior hypothalamus, a region that was termed "dynamogenic" zone (Hess, 1944). The PLH area corresponds roughly to the diencephalo-hypothalamic zone which, according to Hess and Mueller (1946a, 1946b) and Hess (1957), has strong dynamogenic properties. Although the more caudal mesencephalo-rhombencephalic areas were not explored by Hess, the results of the present study suggest that the VMT may also be part of the zone giving dynamogenic effects. This "dynamogenic zone" would then extend from the anterior part of PLH to the posterior part of the VMT, and possibly even further back in the pons.

Sniffing:

With R, VMT, PLH and ALH electrodes, sniffing increased during SS and it remained increased after SS bursts. The increase was less pronounced in the RPC and the areas of the MCx. Hese (1944) reported that in cats, stimulation points evoking sniffing and "sniffing at specific objects" were found in a region that included the lateral hypothalamus and lateral pre-optic area (POA). Our findings also support those of Phillips and Morgenson (1969), St-Laurent and Beaugrand (1971; 1972) and Miliaressis (1972), who all suggested a correlation between intensity of SS and intensity of sniffing. The sniffing activity observed from the ALH, PLH and VMT was more intense than from POlf. Possibly, it can be attributed to the direct stimulation of an olfactory system which would be made up not only of olfactory neurons in more anterior areas (olfactory bulb, olfactory peduncles and paraolfactory area), but also of second stage olfactory neurons coursing through the ALH, PLH and VMT areas.

The increase of biogenic amines in a few specific anterior nuclei following SS, such as the VMT (St-Laurent et al., 1975; 1976), indicates a possible anatomical link between posterior areas and the olfactory system.

The brain areas involved in SS and exploration are also involved in locomotor activity, olfaction, biting and approach behavior towards objects which trigger curiosity and their operant acquisition (St-Laurent and Olds, 1964; St-Laurent and Beaugrand, 1972). These SS areas, such as the anterior and

posterior lateral hypothalamus (ALH, PLH), yielding high focalized exploration and other approach behaviors, such as locomotor activation and sniffing, may therefore be part of a common pathway for goal-oriented behavior.

Following the above-mentioned observations, it is suggested that exploration is the behavior which is the most consistently associated with SS. The question therefore arises as to whether the two phenomena are elicited from a single neural system. The arguments for and against this proposition will now be considered.

Many of the factors which influence SS also influence exploration. For example, food (Margules and Olds, 1962) and water (Mendelson, 1967) deprivation increases SS rates and exploration, while satiety decreases both activities. Amphetamine, which induces a dose-dependent exploratory behavior in rats (Randrup and Munkvad, 1967; Schell-Krüger and Randrup, 1967), also facilitates SS (Stein, 1964). Chlorpromazine, which produces an inhibitory effect on SS, also decreases locomotor activity (Olds and Travis, 1960). Furthermore, Fink and Smith (1980) showed that the integrity of the MFB, which is the locus of the highest SS rates, is essential for the maintenance of stimulation-induced exploration. It is also of interest to note that exploration seems to have reinforcing properties. Indeed, it has been observed that an animal learns to press a lever which enables it to visually explore its cage or to turn on a light within its housing environment (Girdner, 1953; Harlow, 1950, 1953; Hurwitz, 1956; Robinson, 1961).

To summarize, it is commonly observed that intracranial self-stimulation (SS) of the medial forebrain bundle (MFB) in the rat is invariably accompanied by active exploration. The correlation is so good that many investigators use this last behavior as a predictor in the initial screening of good self-stimulators. However, despite this correlation, it is not yet known whether these two phenomena are elicited by stimulation of a single neural system or by spread of electrical current to two independent fiber sets intermingled in the MFB. This question is of some theoretical interest since exploratory behavior is usually enhanced during homeostatic imbalance and since natural drives are believed to act via the SS system.

One way to dissociate the above behaviors would be to determine whether their sensitivities to stimulation parameters differ. Indeed, it has been observed that exploration can be induced by current intensities far below those required in order to maintain SS behavior (Christopher and Butter, 1968; Miliaressis and Le Moal, 1976). However, as pointed out by Katz and Roth (1979), a difference in intensity threshold does not guarantee the involvement of independent neural systems.

A more sophisticated procedure would be the use of the double pulse stimulation technique, which allows identification of different populations of neurons by determinating their respective excitability cycles. Rompré and Miliaressis (1980) have used this technique in the study of excitability cycles of hypothalamic neurons stimulated by a single electrode which induced exploration and self-stimulation. It is proposed that this type of approach be carried out on various structures.

C - Behavioral Correlates of Ambivalence and Flight

a) Ambivalence

Animals with electrodes implanted in the septum, the reticular mesencephalic formation and the raphe areas are observed to approach the lever, press on it, withdraw from it, and then approach the lever again and so forth. In the case of the locus coeruleus, the stepping back reaction follows bursts of bar-presses. The animals show conflictual or "mixed motivational behavior" or ambivalence.

The experimental setting in the current study differed from that used by Bower and Miller (1958); Roberts (1958); Olds (1960); Olds and Olds (1963); Poschel (1966); Steiner et al. (1969); Ball (1972), who have also reported mixed motivational phenomena in animals with chronically implanted electrodes. The animals would press a lever to obtain brain stimulation, but, if given continuous stimulation, would learn to press a second lever in order to interrupt the stimulation (escape). In other words, self-stimulation or escape reactions could be elicited from the same point in a brain area. Some investigators (Bower and Miller, 1958) have applied the term "ambivalence" for this mixed motivational phenomenon. In the present study, ambivalence is defined in more qualitative terms as the action of withdrawing following SS, approaching the lever again and so forth. If the approach and withdrawal speed are retained as main criteria for ambivalence, this phenomenon showed a gradient of intensity: rats with anterior electrodes, such as septum,

showed less intense ambivalent behavior than animals stimulated in the reticular mesencephalic formation (RMF), raphe (R), or reticularis pontis caudalis (RPC).

Ambivalence elicited from a given area (i.e., septum, RMF, R or RPC) was accompanied by site specific behavioral patterns. The ambivalent septal group appeared unexcited in comparison with other groups; interval periods were longer and bar-pressing speed was slower. Ambivalence from the RMF was accompanied by alert and more directed behavior, as illustrated by the bar-pressing speed and withdrawal speed, and by the low interval periods. Other interesting features indicating RMF directed ambivalence are the low diffused exploration and the relatively high focalized exploration. Ambivalent Raphe group appeared less sporadic than for the non-ambivalent self-stimulating Raphe subjects. Ambivalence obtained through stimulation of the RPC was associated both with very high approach speed (even in comparison with the self-stimulation RPC approach speed) and with intense withdrawal. Ambivalence was accompanied by brief interval periods, longer lull periods and occasional incidents of hypotonia. In addition, reticularis pontis caudalis (RPC) subjects showed a particular type of focalized and diffused exploration; at times the rat would either sniff with its nose maintained up, 1 to 2 inches above the level of the Skinner box lever, while looking to the left and right, or the rat would sniff in the air with its nose directed upward, perpendicular to the lever. The exploratory activity was occasionally interrupted by lull periods during

which the animal's behavior was very unpredictable. Following lull periods, the RPC rat wandered back to the lever in an erratic manner. For the control group of self-stimulating animals, the electric current was raised from the self-stimulation threshold by steps of 10 μA rms to a maximum of 70 μA rms, in order to verify if ambivalent behavior would appear at these higher intensities. At these intensities, some self-stimulating rats showed forced movements (i.e., head and/or body movements, circling for one VMT subject, seizures for one septal rat, and circling for two RPC animals), but these movements were not accompanied by any signs of withdrawal or flight, and thus were classified as pure self-stimulators.

In conclusion, just as behavioral patterns accompanying SS vary from one stimulated structure to another, behaviors concomitant with ambivalence vary from one brain area to another, and differ from those accompanying SS from similar structures. The existence of specific patterns of ambivalence for specific brain sites suggests the existence of various types of ambivalence. The most plausible explanation of the ambivalent behavior is that the stimulation activated distinct fibers connected respectively with positive and negative motivational systems.

b) Flight

Intracranial stimulation in the dorsomedial tegmentum (DMT) elicited flight reactions. The manifestations of the flight reactions co-varied with current intensity. At threshold or slightly above, the animals would sniff, freeze or back-up; at higher intensity, the animals jumped in the

air or on the walls of the box, or out of it. ICS in a more caudal area, namely in the ventral RPC, also yielded flight reactions. However, the intensity of these reactions was higher, the animals often jumping straight out of the box at threshold or slightly above threshold current intensity. Aversive effects of a low degree of intensity have been elicited from anterior rhinencephalic areas, such as septum (S) (Gardner and Malmo, 1969), amygdala and hippocampus (Olds and Olds (1963). Our observations on flight elicited from the DMT are in agreement with those of Kaada (1951), Delgado (1955) and Olds and Olds (1963). The observations noted in this study, that stimulation of the ventral RPC produces intense flight, is in agreement with those of St-Laurent and Beaugrand (1972) and Leclerc et al (1973), who reported that the ventral part of the RPC yielded flight reactions of higher intensities than those from the DMT. Previously, Abrahams (1960) and Chi and Flynn (1971) had concluded that the regions of the medial hypothalamus, central grey and tegmentum of the mesencephalon, are reflex centres for the flight response of the defence reaction. In addition, Abrahams' study (1960) suggested that the defence reaction could be obtained from points posterior to the mesencephalon, more precisely in the ventral area of the pons. The present report gives support to this suggestion.

D. Neurochemical Mediators

Drugs that facilitate SS, such as amphetamines, release catecholamines from active sites. This facilitation of SS by amphetamine is increased by inhibitors of monoamine oxidase which protect catecholamine from destruction, and also by drugs similar to imipramine which retard the reuptake of catecholamines. Reserpine, which depletes the brain of monoamines, and chlorpromazine, which blocks adrenergic transmission, inhibit SS (Olds and Travis, 1960). Wise and Stein (1969) reported that SS was inhibited by the systemic and intraventricular administration of disulfiram and diethyldithiocarbamate (inhibitors of dopamine-B-hydroxylase, the enzyme involved in the hydroxylation of DA to NE, the final step of norepinephrine (NE) biosynthesis). The suppressed SS was reinstated by intraventricular injections of l-norepinephrine, suggesting the existence of an adrenergic excitatory system.

Domino and Olds (1968) obtained depression of SS in the hypothalamic area utilizing physostigmine, which suggests that depression of SS and other operant behaviors might be due to activation of an inhibitory cholinergic system. These findings complement the adrenergic excitatory system suggested by Poschel and Ninteman (1963) and Wise and Stein (1969). This cholinergic system would overlap the distribution of the medial forebrain bundle which among others contains adrenergic and serotonergic neurons.

Appropriate doses of alpha-methyl-para-tyrosine (α-MPT) produces a deficit in catecholamines associated with the suppression of SS from the brain regions corresponding to the MFB (Poschel and Ninteman, 1963). It is not clear which amine is critical for SS, but, as seen, a good case is made for NE. A possible role for serotonin was explored in this study.

a) Non-Reinstatement of Self-Stimulation with RO 4-4602 and L-Dopa Following Alpha-Methyl-Para-Tyrosine Pre-Treatment

Appropriate doses of α-methyl-para-tyrosine (α-MPT) produce a suppression of the self-stimulation (SS) performance normally obtained from brain regions corresponding to the medial forebrain bundle (MFB) (Poschel and Ninteman, 1966). In a previous study (Beaugrand and St-Laurent, 1973), it was observed that α-MPT (100 mg/kg ip) had a long lasting suppressive effect on SS, which could be explained by the central depleting effect on CA's which takes place 2-4 hr. after injection of α-MPT (Spector et al., 1965). In addition, there is an immediate (within the first 30 min. following injection) suppressive effect for which there is no explanation.

The results of the present experiments showed that α-MPT (100 mg/kg) had significant immediate suppressive effects on SS performance within the first 10 min. following injection; and, that L-Dopa in combination with RO 4-4602 had suppressive effects on SS in animals both pretreated and not pretreated with α-MPT.

The present results were not unexpected and they confirmed the data of earlier studies (Poschel and Ninteman, 1966; Gibson et al., 1970 and Cooper et al., 1971). In all of these reports, the behavioral effects of α-MPT were attributed to the depletion of brain catecholamines. However, in the present study, the reduction of SS took place within 10 min. after the injection and thus preceeded the reduction of catecholamines which presumably takes place much later. The present observations on the overall behavior during SS confirm reports (Sourkes, 1972) claiming that α-MPT can induce sedation and diminish spontaneous locomotor activity. These effects were observed to be maximal within 10 to 15 min. following injection and, although they had largely disappeared 3 hr. later, SS was not re-established. On the basis that the time course of the behavioral deficit following administration of α-MPT does not coincide with the brain catecholamine depletion, Rech et al. (1966), Weissman and Koe (1965), as well as Moore (1966), have suggested that the depressive effects of α-MPT were secondary to the toxicity of ip α-MPT. As we did not observe such signs of toxicity as vocalization, retraction of the abdomen, weight loss or death, it is difficult to attribute these effects to toxicity, although this interpretation still remains a possibility. Thierry et al. (1971) failed to observe an immediate decrease of NA in the cortex of the rat after α-MPT, but DA levels were diminished rapidly; in addition, during the first 20 min., there was a rapid increase of NA/DA ratio which would indicate that part of the DA stored in noradernergic terminals is preferentially utilized for NA formation.

Thierry et al. (1971) have speculated that subsequent to α-MPT injections (200 mg/kg) in rats, an initial significant decrease of DA levels appears within 15 min. following injection, and a second decrease takes place 30 to 180 min. later. These results suggest the existence of a first, "functional", and a second, "main" storage, compartment of DA in nerve endings. The initial decrease of DA in the "functional" pool obtained with α-MPT may explain the initial reduction of SS, while the second reduction would account for the second reduction of SS.

The observation that L-Dopa in combination with RO 4-4602 also had suppressive effects on SS, in animals both pretreated and not pretreated with α-MPT, is worthy of note, as other studies have shown that many behaviors suppressed by pretreatment with α-MPT were restored by L-Dopa administration (Moore, 1966; Bartholini et al., 1967; Butcher and Engel, 1969; Bédard et al., 1970). In these studies, the central effects of L-Dopa seemed to be excitatory, while in the present experiment, L-Dopa appeared to have inhibitory effects on SS performance, as suggested previously by Eiduson (1959). One explanation of the present results may be that the dose of RO 4-4602 used (100 mg/kg) was too high in comparison with 50 mg/kg usually administered in similar studies (Bartholini et al., 1967; Bartholini and Pletscher, 1968; Butcher and Engel, 1969). Another explanation is that after injection of L-Dopa, through a negative feedback mechanism, there was an inhibition of hydroxylase activity which is non-

specific for tyrosine or tryptophan. With reduction of tyrosine hydroxylase and tryptophan hydroxylase, there would be a decrease in the production of NA and serotonin, and consequently, a suppressive effect on SS performance. Finally, in the present study, it was noted that the diminution of motor activity was not accompanied by calmness; on the contrary, the animals appeared alert and hyperreactive. Hence, the decreased motor activity could be due to an exaggerated alertness leading to a "freezing" effect, as suggested by Boissier and Simon (1966).

b) Reinstatement of Self-Stimulation with Apomorphine Following Suppression by Alpha-Methyl-Para-Tyrosine Pre-treatment

In a previous study (St-Laurent et al., 1973e), it was shown that SS from PLH and VMT was suppressed by ip administration of α-MPT-methyl-ester (100 mg/kg). Subsequently, 3½ hr. after the α-MPT administration, apomorphine (0.25 or 0.5 mg/kg) was injected ip. SS was reinstated to a significant degree 2 hr. after administration of 0.25 mg/kg, and 3 hr. after the 0.50 mg/kg dosage (Fig. 11). The results, therefore, indicated that the most effective dosage was 0.25 mg/kg.

After injection of apomorphine subsequent to saline, animals showed a transitory suppression of SS (Fig. 11). The SS suppression started within 10 min. after administration of apomorphine and lasted ½ hr. (0.25 mg/kg of apomorphine) and 1½ hr. (0.5 mg/kg of apomorphine) suggesting that, while this dosage of apomorphine induced a more pronounced enhancement

of sniffing and exploration, it also gave decreased habituation; hence apomorphine at a high dose of 0.25 mg/kg gave increase in persistent reactivity to many types of stimuli, making difficult the necessary focus on the SS goal and performance.

The present results confirmed previous data (St-Laurent et al.,1973e) which showed that apomorphine can reverse the suppressive effects of α-MPT on SS; this reversal was particularly evident with the 0.25 mg/kg dose of apomorphine. However, after an injection of apomorphine subsequent to saline administration, animals showed a transitory suppression of SS which was longer lasting with the higher dose of apomorphine (0.5 mg/kg) (Fig. 11). The animals were then observed to show very intense exploratory activity commencing 2-3 min. after injection. The transitory depressive effects of apomorphine on SS concur with the findings of Butcher and Anden (1969) that apomorphine causes a depressive effect on bar-pressing with a variable-interval schedule or reinforcement. Following injection of apomorphine subsequent to α-MPT administration, SS was further depressed, followed by an increase of bar-pressing rates. The subsequent stimulating effects of apomorphine on SS are in agreement with Butcher's (1968) observation of increased bar-pressing in a free-operant avoidance situation. The depressive effects of apomorphine were thought to be due to intrusion of such phenomena as exaggerated sniffing, while the stimulating action was thought to be related to facilitation of goal-directed behavior (Ernst and Smelik, 1966). However,

Carlsson's study (1972), attributing the suppressive effect of apomorphine to an induction of competing, stereotypical behaviors, might be only partially correct. His data suggested that, while apomorphine induces enhanced sniffing and exploration, it also decreases habituation; hence, apomorphine at a high dose causes an increased and persistent reactivity to many types of stimuli, making the necessary focus on the goal stimulus less probable. On the other hand, at a low dose of 0.125 mg/kg, the increased exploration should have facilitated SS. Surprisingly, although the effect on exploration is almost immediate, the reinstatement of SS after α-MPT injection, in our previous study (St-Laurent et al., 1973e), became significant only after 2 hr. We felt that a lower dose of apomorphine, such as 0.125 mg/kg would reinstate SS more quickly. This study shows that such is not the case; the optimum dose then appears to be 0.25 mg/kg.

The mechanisms of action of apomorphine on SS are possibly dopaminergic, as the suppression of SS induced by α-MPT does not produce a complete blockade at the dopamine receptors; hence, their direct stimulation by apomorphine would reinstate SS. Although our experiment supports the hypothesis of van Rossum and Hurkmans (1964) that an increase in motility is the result of stimulation of dopamine receptors, an essential interaction with noradrenaline cannot be eliminated in the light of the works of many researchers (Anden et al., 1967; Corridi et al., 1970; Persson, 1970; Persson and Waldeck, 1970; which suggest that the noradrenergic neurons are involved in the stimulation of motility.

c) Effects of Parachlorophenylalanine (PCPA) on Self-Stimulation from the Median Raphe Area

Failure to consistently and uniformly affect SS by manipulation of serotonin, in addition to the role of this amine in some inhibitory processes, has generally led to an assumption which excludes serotonin as a mediator of SS behavior (Lorens, 1971; Stein, 1971).

A previous work, St-Laurent et al. (1973a) reported that rats with electrodes in the MR can reach low to moderate high rates of SS. Miliaressis et al. (1975) have found even higher SS rates from the MR (above 6,000 presses/30 min.). These findings, confirmed also by other investigators (Simon et al., 1976), indicate the potential significance of this brain area in reward phenomenon. Miliaressis and Jacobowitz (1976) observed that SS in the MR was accompanied by dramatic hyperthermia. Considering the known role of serotonin in thermoregulation (Myers, 1974), this observation provides additional support to the notion that SS in the MR is elicited by serotonergic stimulation. The specific inhibitoty effect of PCPA on MR SS found in the present experiments thus confirms the findings of previous studies (Miliaressis et al., 1975; Miliaressis, 1977; Katz and Baldrighi, 1979). These results provide evidence for the conclusion that SS in the median raphe region is elicited by stimulation of 5-HT containing neurons. Self-stimulation in the dorsal raphe has been attributed to stimulation of norepinephrine fibers in the vicinity of this area rather than to serotonergic cell bodies (Margules, 1969). A proximity of catecholaminergic fibers

to dorsal raphe cell bodies does exist (Palkovits, 1973). However, the only extensive study on median raphe SS using 87 electrodes (Simon et al., 1973) clearly demonstrated that SS in the median raphe was obtained when electrodes were well-located in the serotonergic nucleus centralis superior, and that sites lateral to this area elicited no, or very low SS. The histological examination of our Raphe rats showed that electrodes were located in the serotonergic nucleus centralis superior. In addition to the classical contribution of histofluorescence techniques, recent biochemical studies performed with a micro-dissection technique (Koe and Weissman, 1966; Palkovits, 1973) have shown that this part of the rat brain and the dorsal raphe contain the highest concentration of 5-HT in the brain (Palkovits et al., 1974). Though this region is generally considered to be purely serotonergic, recent reports suggest that it also contains another unidentified tryptamine and dopamine (Björklund et al., 1971; Ochi and Shimizu, 1978). Also, the existence of a few norepinephrine fibers of passage cannot be excluded. Nevertheless, if these sparse fibers were responsible for the positive reward in this area, one would expect that the resulting SS would be of a low or moderate level. In contrast, electrodes in the median raphe elicit high SS rates which are similar to, or, in some cases, higher than, those obtained in the ventromedian tegmentum (VMT) region (Miliaressis, 1977). In our own studies, we noted some unusual properties of Raphe SS. More particularly, in comparison with catecholamine mediated

SS in CA containing sites (MFB), MR self-stimulation rates were considerably more variable and difficult to maintain.

Katz and Baldrighi (1979) have implanted stimulating electrodes aimed at the MFB or the medial raphe nucleus. The MFB implanted rats self-stimulated at higher stable rates for at least three weeks. Only 1/3 of MR rats self-stimulated and, even in these, the rates were rather variable. Treatment with methysergide, a congener of LSD and a blocker of 5-HT receptors, decreased MR self-stimulation. These results also support a facilitatory role for 5-HT is SS at serotonergic sites.

d) Effects of LSD-25 on Self-Stimulation from the Median Raphe Area of the Rat Brain

The analyses of our results showed that the various doses of LSD (30, 60 and 120 µg/kg) induced a transitory decrease of the SS activity obtained from the raphe nuclei. If LSD produces an inhibition of the serotonergic neurons in this area, as suggested by Aghajanian et al. (1968), it is tempting to use this mechanism to explain the inhibitory action of LSD on SS elicited from the raphe. However, crawling with a partial decrease of muscular tonus has been observed to accompany the decrease of SS in these rats. It is possible that the crawling and the modification of muscular tonus affected the locomotor performance to a point where an ensuing motor deficit was responsible for the transitory fall of SS rates. Von Hungen et al. (1974) have indicated that LSD is capable of blocking the noradrenaline, dopamine and serotonin receptors. The results of this study tend to support the

suggestion that the actions of LSD may indeed be due to the complex agonist and antagonist actions of this drug at central receptors for several neurotransmitter monoamines.

CONCLUSIONS

The results of the present studies cannot be interpreted without taking into consideration the experimental conditions under which they were obtained.

Thus, the mapping study for ICSS seemed to suggest the existence of a gradiant of this behavior along the sagital axis. There are at least two opposing explanations of this finding: a) The gradient of bar-pressing rates reflects the reinforcement value of the stimulation and may depend on the reward-relevant neuronal density below the stimulating electrodes. This interpretation, if true, is of potential interest because it sheds some light on the topographical organization of the reward systems. b) Due to several reasons, bar-pressing rates do not parallel the reinforcement value of the stimulation. In this case, the observed gradient offers only a practical interest (localization of the most efficient ICSS sites), but provides no information on the anatomical organization of brain reward. For instance, higher bar-pressing rates could have been obtained in a given area, had one the possibility to remove from the stimulated field non-relevant neurons, the activation of which interferes with the bar-pressing performance. In view of the behavioral observations in the present work, the last explanation seems the most plausible. Hence, in future studies, the gradient of reinforcement should be examined, using more sophisticated methods, such as the psychophysical procedure that has been recently

proposed by Miliaressis et al. (1982).

The data also showed that the behavioral correlates of ICSS are site-dependant. Again, there are at least two explanations of this finding: a) The ICSS correlates reflect the functional relationship between the reward systems and several other brain functions. b) The ICSS correlates are due to the activation of neuronal elements (for instance, fibers of passage) which lay in close proximity to the reinforcement neurons. With one exception (exploratory activity), the latter represents the most reasonable interpretation. Since the exploratory activity was found to accompany ICSS in all areas, the possibility of a functional link with the reinforcement process can be retained for further investigation. The ambivalent behavior observed in several brain sites can be reasonably attributed to the simultaneous activation of rewarding and punishing neurons lying below the stimulating electrodes.

The pharmacological data may suggest the involvement of both the catecholamine and serotonin neurotransmitters in brain reward. However, the alterations of bar-pressing rates following the various drug treatments cannot be attributed with confidence to a change of the rewarding value of the stimulation. Performance variables could as well account for the observed effects. This problem could have been at least partially circumvented by examination of the drug effects on brain areas that do not contain the neurotransmitter under investigation.

The time contraints and the limited scope of the present studies prevented the application of the large variety of experimental controls which would normally allow one to arrive at more definite conclusions.

It is obvious that the primary merit of the present investigation lays in the fact that the above-mentioned limitations were recognized and properly evaluated. Other merits lay in the localization of several new rewarding areas, especially within the caudal brain. Finally, in spite of its limitations, the measurements of bar-pressing rates, when complemented with the ICSS correlates, have the definite advantage of serving as a guide when electrodes must be implanted in the most efficient and contamination-free ICSS sites.

REFERENCES

Abrahams, V.C., Hilton, S.M. and Sbrozyna, A.: Active muscle vasodilatation produced by stimulation of the brain stem: its significance in the defence reaction. J. Physiol., 154: 491-513, 1960.

Aghajanian, G.K. and Sheard, M.H.: Stimulation of midbrain raphe neurons: behavioral effects of serotonin release. Life Sci., 7: 19-25, 1968.

Aghajanian, G.K., Foote, W.E. and Sheard, M.H.: Lysergic acid diethylamide: sensitive neuronal units in the mid-brain raphe. Science, 161: 706-708, 1968.

Aghajanian, G.K. and Weiss, B.L.: Block by LSD of increase in brain serotonin turnover induced by devated ambient temperature. Nature, 220: 795, 1968.

Aghajanian, G.K., Haigler, H.J. and Bloom, F.E.: Lysergic acid diethylamide and serotonin: direct actions on serotonin containing neurons in rat brain. Life Sci. (Part 1), 11: 615, 1972.

Anden, N.E., Rubenson, A., Fuxe, K. and Hokfelt, B.: Evidence for dopamine receptor stimulation by Apomorphine. J. Pharm. Pharmc., 19: 627, 1967.

Anden, N.E., Corridi, H., Fuxe, K. and Hokfelt, T.: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br. J. Pharmac. Chemother., 34: 1-7, 1968.

Anden, N.E., Corridi, H., Fuxe, K., Hokfelt, B., Rydin, C. and Svensson, T.: Evidence for a central noradrenaline-receptor stimulation by clonidine. Life Sci., 9: 513, 1970.

Anlezard, G.M., Arbuttnott, G.W., Christie, J.E., Crow, T.J. and Spear, P.J.: Electrical self-stimulation in relation to cells of origin of catecholamine-containing neural systems ascending from the brain stem. J. Physiol. (Lond.), 237:31-32, 1974.

Arbuthnott, G.W., Crow, T.J. and Spear, P.J.: Functional role of an aminergic nucleus (locus coeruleus). J. Physiol. (Lond.), 211: 28-29, 1970.

Arbuthnott, G.W., Fuxe, K. and Understedt, U.: Central catecholamine turnover and self-stimulation behavior. Brain Research, 27: 406-413, 1970a.

Ball, G.G.: Self-stimulation in the ventromedial hypothalamus. Science, 178: 72-73, 1972.

Bartholini, G., Bates, H.M., Burkard, W.P. and Pletscher, A.: Increase of cerebral catecholamines by 3 - 4 dihydroxyphenylalanine after inhibition of peripheral decarboxylase. Nature, (London) 215: 852-853, 1967.

Bartholini, G. and Pletscher, A.: Cerebral accumulation and metabolism of C-14-Dopa after selective inhibition of peripheral decarboxylase. J. Pharmacol. Exp. Ther., 161: 14-20, 1968.

Baum, M., Leclerc, R. and St-Laurent, J.: Rewarding vs aversive intracranial stimulation administered during flooding (response prevention) in rats. Psychol. Reports, 32: 551-558, 1973.

Beaugrand, J. and St-Laurent, J.: Effects of alpha-methyl-paratyrosine and L-Dopa on brain self-stimulation and motor activity. Br. J. Pharmacol., 47: 609-612, 1973.

Bedard, P., Larochelle, L., Poirier, L.J. and Sourkes, T.L.: Reversible effect of L-dopa on tremor and catatonia induced by alpha-methyl-para-tyrosine. Can. J. Physiol. Pharmacol., 48: 82-84. 1970.

Björklund, A., Falck, B. and Stenevi, U.: Microspectrofluerimetric characterisation of monoamines in the central nervous system: evidence for a new neuronal monoamine-like compound. In: Histochemistry of Nervous Transmission, Progress in Brain Research (Eranko, O., ed.), 34: 63-73. Elsevier, Amsterdam, 1971.

Black, W.G. and Cooper, B.R.: Reduction of electrically rewarded behavior by interference with monoamine synthesis. Physiol. Behav., 5: 1405-1409, 1970.

Blondaux, C., Jege, A., Sordet, F., Chouvet, G., Jouvet, M. and Pujord, J.F.: Modification du métabolisme de la serotonine (5-HT) cérébrale induite chez le rat par administration de 6-Hydroxydopamine. Brain Res., 50: 101-114, 1973.

Bloom, F.E. and Nichols, N.: Physiologic and pharmacologic considerations of biogeniamines in the nervous system. In: Annual Review of Pharmacology (Elliot, H.W. and Alto, P. ed.) Annual Reviews, Inc., 8: 229-258, 1968.

Blum, K. and Geller, L.: Facilitation of brain stimulation with para-chlorophenylalanine. Fed. Proc., 28: 794, 1969.

Bogacz, J., St-Laurent, J. and Olds, J.: Dissociation of self-stimulation and epileptiform activity. Electroencephalogr. Clin. Neurophysiol., 19: 75-87, 1965.

Boissier, J.R. and Simon, P.: De la potentiation de la dopa par les inhibiteurs de la monoamine oxydase. Phychopharmacol., (Berl.) 8: 428-436; 1966.

Bower, G.H. and Miller, N.E.: Rewarding and punishing effects from stimulating the same place in the rat's brain. J. Comp. Physiol. Psychol., 51: 669, 1958.

Brady, J.V. and Nauta, W.J.: Subcortical mechanisms in emotional behavior: Affective changes following septal forebrain lesions in the albino rat. J. Comp. Physiol. Psychol., 46: 339-346, 1953.

Briese, G.R. and Olds, J.: Reinforcing brain stimulation and memory in monkeys. Exptl. Neurol., 10: 493-508, 1964.

Briese, G.R., Howard, J.L. and Leahy, J.P.: Effect of 6-hydroxydopamine on electrical self-stimulation of the brain. Br. J. Pharmac., 43: 255-257, 1971.

Bursten, B. and Delgado, J.M.R.: Positive reinforcement induced by intracranial stimulation in the monkey. J. Comp. Physiol. Psychol., 51: 6-10, 1958.

Buser, P., Rougeul, A. and Perret, A.: Caudate and thalamic influences on conditioned motor responses in the cat. Bol. Inst. Estud. Med. Biol. Mex., 22: 293-307, 1966.

Butcher, L.L.: Effects of apomorphine on free-operant avoidance behavior in the rat. Eur. J. Pharmac., 3: 163, 1968.

Butcher, L.L. and Anden, N.E.: Effects of apomorphine and amphetamine on schedule-controlled behavior: Reversal of tetrabenazine suppression and dopaminergic correlated. Eur. J. Pharmac., 6: 255-264, 1969.

Butcher, L.L. and Engel, J.: Behavioral and biochemical effects of L-Dopa after peripheral decarboxylase inhibition. Brain Res., 15: 233-242, 1969.

Carlsson, S.G.: Effects of apomorphine in exploration. Physiol. Behav., 9: 127-129, 1972.

Carter, D.A. and Phillips, A.G.: Intracranial self-stimulation at sites in the dorsal medulla oblongate. Brain Res., 94: 155-160, 1975.

Chase, T.N., Briese, G.R. and Kopin, I.J.: Serotonin release from brain slices by electrical stimulation: Regional differences and effects of LSD. Science, 157: 1461, 1967.

Chi, C.C. and Flynn, J.P.: Neural pathways associated with hypothalamically elicited attack behavior in cats. Science, 171: 703-705, 1971.

Christopher, M. and Butter, C.M.: Consummatory behaviors and locomotor exploration evoked from self-stimulation sites in rats. J. Comp. Physiol., 66: 335-339, 1968.

Clavier, R.M. and Routtenberg, A.: Ascending monoamine-containing fiber pathways related to intracranial self-stimulation: Histochemical fluorescence study. Brain Res., 72: 25-40, 1974.

Clemente, C.D. and Sterman, M.B.: Sleep induced by electrical or chemical stimulation of the forebrain. In: The Physiological Basis of Mental Activity (Hernandez Peon, R. ed.), Suppl. 24: 172-178. Electroencephalography and Clinical Neurophysiology, 1963.

Cohn, C.J., Ball, G.G. and Hirsch, J.: Histamine: Effects in self-stimulation. Science, 180: 757-758, 1973.

Cooper, B.R., Black, W.C. and Paolino, R.M.: Decreased septal-forebrain and lateral hypothalamic reward after alpha-methyl-p-tyrosine. Physiol. Behav., 6: 425-429, 1971.

Corrodi, H., Fuxe, A., Ljungdahl, A. and Ogren, S.O.: Studies on the action of some psychoactive drugs on central noradrenaline neuroses after inhibition of dopamine-C-hydroxylase. Brain Res., 24: 451, 1970.

Crow, T.J.: A map of the rat mesencephalon for electrical self-stimulation. Brain Res., 36: 265-273, 1972.

Crow, T.J., Spear, P.J. and Arbuthnott, G.W.: Intracranial self-stimulation with electrodes in the region of the locus coeruleus. Brain Res., 36: 275-287, 1972.

Dalström, A. and Fuxe, K.: Evidence for the existence of monoamines containing neurons in the central nervous system. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand., 62, Suppl. 232: 1-55, 1974.

Delgado, J.M.R., Roberts, W.W. and Miller, N.E.: Learning motivated by electrical stimulation of the brain. Am. J. Physiol., 179: 587-593, 1954.

Delgado, J.M.R.: Cerebral structures involved in transmission and elaboration of noxious stimulation. J. Neurophysiol., 18: 261-275, 1955.

Domino, E.P. and Olds, M.E.: Cholinergic inhibition of self-stimulation behavior. J. Pharmacol. Exp. Ther., 164: 202-211, 1968.

Domino, E.F. and Olds, M.E.: Effects of D-amphetamine, scopolamine, chlodiazepoxide and diphenylhydantoin on self-stimulation behavior and brain acetylcholine. Psychopharmacologia, (Berl.) 23: 1-6, 1972.

Dresse, A.: Importance du système mésencéphalo-télencéphalique noradrénergique comme substriatum anatomique du comportement d'autostimulation. Life Sci., 5: 1003-1014, 1966.

Eiduson, S.: Effects of Dopa, 5-HTP and Iproniazide on self-stimulation of the brain. Fed. Proc., 18: 221-226, 1959.

Ernst, A.M. and Smelik, P.G.: Site of action of dopamine and apomorphine on compulsive gnawing behavior in rats. Experientia, 22: 837-838, 1966.

Ernst, A.: Mode of action of apomorphine and dex-amphetamine on gnawing compulsion in rats. Psychopharmacologia, 10: 317, 1967.

Ferguson, G.A.: A rank test for two correlated samples. In: Statistical Analysis in Psychology and Education. New York: McGraw-Hill Book Co., Chapter 22.6, p. 329, 1971.

Fink, J.S. and Smith, G.P.: Mesolimbic and mesocortical dopaminergic neurons are necessary for normal exploratory behavior in rats. Neurosci. Letters, 17: 61-67, 1980.

Fisher, R.A. and Yates, F.: Statistical tables for biological agricultural and medical research. Oliver and Boyd Ltd., Edinburg, 1953.

Franklin, K.B.J. and Herberg, L.J.: Self-stimulation and catecholamines: Drug-induced mobilization of the "reverse" - pool re-establishes responding in catecholamine-depleted rats. Brain Res. 67: 429-437, 1974.

Freedman, D.X. and Giarman, N.J.: LSD-25 and the status and level of brain serotonin. Am. N.Y. Acad. Sci., 96: 98-106, 1962.

Gadner, L. and Malmo, R.B.: Effect of low-level septal stimulation on escape: Significance for limbic midbrain interaction in pain. J. Comp. Physiol. Psychol., 68: 65-78, 1969.

German, D.C. and Bowden, D.M.: Catecholamines systems as the neural substrate for intracranial self-stimulation: A hypothesis. Brain Res., 73: 381-419, 1974.

Gibson, S., McGeer, E.C. and McGeer, P.I.: Effect of selective inhibitors of tyrosine and tryptophan hydroxylases on self-stimulation in the rat. Expl. Neurol., 27: 283-290, 1970.

Girdner, J.B.: An experimental analysis of the behavioral effects of a perceptual consequence unrelated to organic drive states. Amer. Psychol., 8: 354-355 (abstract), 1953.

Glickman, S.E.: Reinforcing properties of arousal. J. Comp. Physiol. Psychol., 53: 68-71, 1960.

Groover, F.S.: Electrophysiological and behavioral activity accompanying self-stimulation (A comparative study on the hypothalamus and septum). Dissertation Abstracts, 27: 350, 1966.

Haigler, H.J. and Aghajanian, G.K.: LDS and serotonin: A comparison of effects on serotonergic neuron and neurons receiving a serotonergic input. Ther., 188: 688-699, 1974.

Harlow, H.F.: Learning and satiation response in intrinsically motivated complex puzzle performance by monkeys. J. Comp. Physiol. Psychol., 43: 289-294, 1950.

Harlow, H.F.: Motivation as a factor in the acquisition of new responses. In Current theory and research in motivation. Lincoln University of Nebraska Press, 24-49, 1953.

Hebb, D.O.: Drives and conceptual nervous system. Psychol. Rev., 62: 243-254, 1955.

Hernandez Peon, R. and Chavez Ibarra, G.: Sleep induced by electrical or chemical stimulation of the forebrain. (Hernandez Peon, R. ed.) In: The Physiological Basis of Mental Activity. Electroenceph. Clin. Neurophysiol., Suppl. 24: 188-198, 1963.

Hess, W.R.: Das Schlafsyndrom als Folge diencephaler Reizung. Helf. Physiol. Acta, 2: 305-344, 1944.

Hess, W.R. and Mueller, H.R.: Schnuppernbewegungen als zentrale Reizeffekt. Helv. Physiol. Acta, 4: 339-345, 1946a.

Hess, W.R. and Mueller, H.R.: Einflusse des Mittel-und Swischenhirns auf die Atmung. Helv. Physiol. Acta, 4: 347-348, 1946b.

Hess, W.R.: The functional organization of the diencephalon. Grune and Stratton, New York, 1957.

Huang, Y.M. and Routtenberg, A.: Lateral hypothalamic self-stimulation pathways in Rattus norvegicus. Physiol. Behav., 7: 419-432, 1971.

Hunter, J. and Jasper, H.H.: Effects of thalamic stimulation in unanaesthetized animals: arrest reaction and petit-mal-like seizures, activation patterns and generalized convulsions. Electroenceph. Clin. Neurophysiol., 1: 305-324, 1949.

Hurwitz, H.M.B.: Conditioned responses in rats reinforced by light. Brit. J. Animal Behav., 4: 31-33, 1956.

Jalfre, M., Ruch-Monachon, M.A. and Haefely, W.: In: Advances in Biochemical Psychopharmacology 10: 121-134. Raven Press, New York, 1974.

Jouvet, M.: Neurophysiology of the states of sleep. In: Neurosciences (Quarton, G.C., Melnechuk, R. and Schmitt, F.O., eds.): 529-544. The Rockfeller Press, New York, 1967.

Jouvet, M. and Mounier, D.: Effets des lésions de la formation réticulée pontique sur le sommeil du chat. C.R. Soc. Biol., 154: 2301-2305, 1960.

Jung, R. and Hassler, R.: The extrapyramidal motor system. In: Handbook of Physiology, Neurophysiology (Field, J., ed. and Magoun, H.W., Section 1, ed.). Chapter 35: 863-927. American Physiology Society, Washington, D.C., 1960.

Kaada, R.B.: Somatomotor, autonomic and electrocorticographic responses to electrical stimulations of "rhinencephalon" and other structures in primate, cat and dog. Acta Physiol. Scan., 24: 1-285, 1951.

Katz, R.J. and Baldrighi, G.: Serotonergic mediation of reward within the medial raphe nucleus: Some persistant problems in interpretations. Intern. J. Neuroscience 9: 145-148, 1979.

Katz, R.J. and Roth, K.: Open field behavior after chronic self-stimulation. Int. J. Neurosci., 9: 17-19, 1979.

Kluver, H. and Barrera, E.: Method for combined staining of cells and fibers in the nervous system. J. Neuropath. Exp. Neurol.., 12: 400-403, 1953.

Koe, B.K. and Weissman, A.: p-Chlorophenylalanine: A specific depletor of brain serotonin. J. Pharmacol. Exp. Ther., 154: 499-516, 1966.

Leclerc, R., St-Laurent, J. and Baum, M.: Effects of rewarding, aversive and neutral intracranial stimulation administered during flooding (response prevention) in rats. Physiol. Psychol., 1: 24-28, 1973.

Levitt, M. Spector, S., Sjoerdsma, A. and Udenfriend, S.: Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea-pig heart. J. Pharmacol. Exp. Ther., 148: 1-8, 1965.

Liebman, J.M. and Butcher, L.L.: Comparative involvement of dopamine and noradrenaline in rate-free self-stimulation in substantia nigra, lateral hypothalamus and mesencephalic central grey. Arch. Exp. Path. Pharmak., 284: 167-194, 1974.

Lippa, A.S., Antelman, S.M., Fisher, A.E. and Canfield, D.R.: Neurochemical mediation of reward: A significant role for dopamine? Pharmac. Biochem. Behav., 1: 23-28, 1973.

Lorens, S.A.: Effect of lesions in the raphe system on self-stimulation in the rat. Physiol. Behav., 7: 815-818, 1971.

Maeda, T. and Shimizu, N.: Projections ascendantes du locus coeruleus et d'autres neurones aminergiques politiques au niveau du prosencéphale du rat. Brain Res., 36: 19-35, 1972.

Maj. J., Grabowska, M. and Gajda, L.: Effect of apomorphine on mobility in rats. Eur. J. Pharmac., 17: 208-214, 1972.

Margules, D.: Noradrenergic rather than serotonergic bases of reward in the dorsal tegmentum. J. Comp. Physiol. Psychol., 67: 32-35, 1969.

Margules, D.L. and Olds, J.: Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats. Science, 135: 374-375, 1962.

Mendelson, J.: Lateral hypothalamic stimulation in satiated rats. The rewarding effects of self-induced drinking. Science, 157: 1077-1079, 1967.

Miliaressis, T.E.: Rôle du faisceau median télencéphalique dans le comportement d'exploration chez le rat. 40th Congress of ACFAS. Vol. 39, University of Ottawa, Ottawa, p. 128 (abstract), 1972.

Miliaressis, E., Bouchard, A. and Jacobovitz, D.M.: Strong positive reward in median raphe: Specific inhibition by parachlorophenylalanine. Brain Res., 98: 194-201, 1975.

Miliaressis, T.E. and LeMoal, M.: Stimulation of the medial forebrain bundle: Behavioral dissociation of its rewarding and activating effects. Neuroscience Letters, 2: 295-300, 1976.

Miliaressis, E. and Jacobovitz, D.M.: Hyperthemia following self-stimulation in the median raphe of the rat. Pharmac. Biochem. Behav., 4: 477-479, 1976.

Miliaressis, E.: Serotonergic basis of reward in median raphe of the rat. Pharmac. Biochem. Behav., 7: 177-180, 1977.

Miliaressis, T.E.: Refractoriness of neurons subserving circling following stimulation of the median raphe region in the rat. Physiol. Behav., 26: 709-713, 1981.

Miliaressis, T.E., Rompré, P.P. and Durivage, A.: Psychophysical method for mapping behavioral substrates using a moveable electrode. Brain Res. Bull., 8: 693-701, 1982.

Miller, N.E.: Experiments on motivation. Science, 126: 1271-1278, 1957.

Moore, K.E.: Effects of alpha-methyl-tyrosine on brain catecholamines and conditioned behavior in guinea pigs. Life Sci., 5: 55-65, 1966.

Myers, R.D.: Temperature regulation. In: Handbook of Drug and Chemical Stimulation of the Brain (Myers, R.D., ed.): 237-301. Van Nostrand Reinhold, New York, 1974.

Nagatsu, T., Levitt, M. and Underfriend, S.: Tyrosine hydroxylase, the initial step in norepinephrine biosynthesis. J. Biol. Chem., 2910-2917, 1964.

Newman, M.L.: Effects of cholinergic agonists and antagonists on self-stimulation behavior in the rat. J. Comp. Physiol. Psychol., 79: 394-413, 1972.

Ochi, J. and Shimizu, K.: Occurence of dopamine containing neurons in the median raphe nuclei of the rat. Neuroscience Letters, 8(4): 317-321, 1978.

O'Donahue, N.F. and Hagamen, W.D.: A map of the rat brain for regions producing self-stimulation and unilateral attention. Brain Res., 5: 289-305, 1967.

Olds, J. and Milner, P.: Positive reinforcement produced by electrical stimulation of the septal area and other regions of rat brain. J. Comp. Physiol. Psychol., 47: 419-427, 1954.

Olds, J.: A preliminary mapping of electrical reinforcing effects in the rat brain. J. Comp. Physiol. Psychol., 49: 281-285, 1956.

Olds, J., Killam, K.F. and Back-Y-Rita, P.: Self-stimulation of the brain used as a screening method for tranquilizing drugs. Science, 124: 265-266, 1956.

Olds, J.: Differentiation of reward systems in the brain by self-stimulation technique. In: Electrical Studies on the Unanesthetized brain (Ramsey, E.R. and O'Doherty, D.S., eds.) Hoever, New York, 1960.

Olds, J. and Travis, R.P.: Effects of chlorpromazine, meprobamate, pentobarbital and morphine on self-stimulation. J. Pharmacol., 128: 397-404, 1960.

Olds, J., Travis, R.P. and Schwing, R.C.: Topographic organization of hypothalamic self-stimulation functions. J. Comp. Physiol. Psychol., 31: 23-32, 1960.

Olds, M.E. and Olds, J.: Approach avoidance analysis of rat diencephalon. J. Comp. Neurol. 120: 259-295, 1963.

Olds, M.E. and Olds, J.: Pharmacological patterns in subcortical reinforcement behavior. Int. J. Neuropharmacol., 2: 309-325, 1964.

Olds, M.E. and Olds, J.: Effects of lesions in medial forebrain bundle on self-stimulation behavior. Am. J. Physiol., 217: 1253-1264, 1969.

Olds, M.E, and Domino, E.F.: Comparison of muscarinic and nicotinic, cholenergic agonists on self-stimulation behavior. J. Pharmacol. Exp. Ther., 166: 189-204, 1969.

Olds, M.E.: Comparative effect of amphetamine, scopolamine and chlordiazepoxide on self-stimulation. Rev. Can. Biol., 31: 25-47, 1972a.

Olds, M.E.: Alterations by centrally acting drugs of the suppression of self-stimulation behavior in the rat by tetrabenazine, physostigmine, chlorpromazine and pentobarbital. Psychopharmacologia, 25: 299-314, 1972b.

** Palkovits, M., Brownstein, M. and Saavedra, J.M.: Serotonin content of the brain stem nuclei in the rat. Brain Res., 80: 237-249, 1974.

Pellegrino, L.J. and Cushman, A.: Steriotaxic Atlas of the rat brain. Appleton-Century Crosts, New York, 1967.

Persson, I.: Drug induced changes in ^{3}H-catecholamine accumulation after ^{3}H-tyrosine. Acta Pharmac. Tox., 28: 378, 1970.

Persson. I. and Waldeck, B.: Further studies on the possible interaction between dopamine and noradrenaline containing neurons in the brain. Eur. J. Pharmac., 11: 315, 1970.

Phillips, A.G. and Morgenson, G.J.: Self-stimulation of the olfactory bulb. Physiol. Behav., 4: 195-197, 1969.

Phillips, A.G. and Fibiger, H.C.: Dopaminergic and noradrenergic substrate of positive reinforcement: Differential effects of d-and l-amphetamine. Science, 179: 575-577, 1973.

Poirier, L.J., Bouvier, G., Bédard, P., Boucher, R., Larochelle, L., Olivier, A. and Singh, P.: Essai sur les circuits neuronaux impliqués dans le tremblement postural de l'hypokinésie. Rev. Neurol. (Paris), 120: 16-39, 1969.

Poschel, P.B.H. and Ninteman, F.W.: Excitatory (antidepressant) effects of monoamine oxidase inhibitors on the reward system of the brain. Life Sci., 3: 903-910, 1964.

** Palkovits, M.: Isolated removal of hypothalamic or other brain nuclei of rat. Brain Res. 59: 449-450, 1973.

Poschel, B.P.H. and Ninteman, F.W.: Norepinephrine: A possible excitatory neurohormone of the reward system. Life Sci., 2: 782-788, 1963.

Poschel, B.P.H.: Comparison of reinforcing effects yielded by lateral versus medial hypothalamic stimulation. J. Comp. Physiol. Psychol., 61: 346-362, 1966.

Poschel, P.B.H. and Ninteman, F.W.: Hypothalamic self-stimulation: Its suppression by blockade of norepinephrine biosynthesis and reinstatement by methamphetamine. Life Sci., 5: 11-16, 1966.

Poschel, B.P.H. and Ninteman, F.W.: Excitatory effects of 5-HTP on intracranial self-stimulation following MAO blockade. Life Sci., 7: 317-323, 1968.

Poschel, B.P.H. and Ninteman, F.W.: Intracranial reward and the forebrain's serotonergic mechanism: Studies employing parachlorophenylalanine and parachloramphetamine. Physiol. Behav., 7: 39-46, 1971.

Poschel, B.P.H., Ninteman, F.W., McLean, J.R. and Potoczak, D.: Intracranial reward after 5,6-dihydroxytryptamine: Further evidence for serotonin's inhibitory role. Life Sci., 15: 1515-1522, 1974.

Pradhan, S.N. and Kamat, K.A.: Action and interaction of cholinergic agonists and antagonists on self-stimulation. Arch. Int. Pharmacodyn., 196: 321-329, 1972.

Randrup, A. and Munkvad, I.: Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia, (Berl.), 11: 300, 1967.

Rech, R.H., Borys, H.D. and Moore, K.E.: Alterations in behavior and brain catecholamine levels in rats treated with a methyltyrosine. J. Pharmacol. Exp. Ther., 153: 412-419, 1966.

Ritter, S. and Stein, L.: Self-stimulation of the locus coeruleus. Fed. Proc., 31: 820, 1975.

Roberts, W.W.: Both rewarding and punishing effects from stimulation of posterior hypothalamus of cat with same electrode at same intensity. J. Comp. Physiol. Psychol., 51: 400-407, 1958.

Robinson, J.S.: The reinforcing effects of response-contingent light increment and decrement in hooded rats. J. Comp. Physiol. Psychol., 54: 470-473, 1961.

Rolls, E.T.: Neural system involved in intracranial self-stimulation. Brain Res., 24: 538-549, 1970.

Rolls, E.T. and Kelly, P.H.: Neural basis of stimulus-bound locomotor activity in the rat. J. Comp. Physiol. Psychol., 81: 173-182, 1972.

Rompré, P.P. and Miliaressis, T.E.: A comparison of the excitability cycles of the hypothalamic fibers involved in self-stimulation and exploration. Physiol. Behav., 24(5): 995-998, 1980.

Roos, B.: Decrease in homovanillic acid as evidence for dopamine receptor stimulation by apomorphine in the neostriatum of the rat. J. Pharm. Pharmac., 21: 263, 1969.

Rosencrans, J.A., Lovell, R.A. and Freeman, D.X.: Effects of lysergic acid diethylamide on the metabolism of brain 5-hydroxytryptamine. Biochem. Pharmac., 46: 2011-2021, 1967.

Rosvold, H.E. and Delgado, J.M.R.: The effect on delayed alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J. Comp. Physiol. Psychol., 49: 365-372, 1956.

Routtenberg, A. and Malsbury, C.: Brain stem pathways of reward. J. Comp. Physiol. Psychol., 68: 22-30, 1969.

Routtenberg, A.: Forebrain pathways of reward in Rattus norvegius. J. Comp. Physiol. Psychol., 75: 269-276, 1970.

St-Laurent, J. and Olds, J.: Behavior elicited by stimulation in approach and escape structures of the rat's brain. Paper given at Midwestern Psychological Association Meetings in St-Louis, May 30, 1964.

St-Laurent, J. and Beaugrand, J.: Film: "Brain areas of reinforcement and behavior". Vth Congress of Psychiatry in Mexico, November 28, 1971.

St-Laurent, J. and Beaugrand, J.: Brain stimulation, reinforcement and behavior. In: "Contributions of neurosciences to psychopharmacology" and "The Motor System". (St-Laurent, J. ed.). Rev. Can. Biol., 31: 193-213, suppl., 1972.

St-Laurent, J.,Leclerc, R., Beaugrand, J., Mitchell, M. and Paradis, M.: Ambivalence in rats using single-lever Skinner boxes. Can. J. Physiol. Pharmacol., 50: 1104-1107, 1973.

St-Laurent, J., Leclerc, R. and Mitchell, M.: Auto-stimulation et exploration diffuse au niveau des noyaux du Raphé chez le rat. J. Physiol. (Paris), 66: 87-92, 1973a.

St-Laurent, J., Beaugrand, J., Leclerc, R., Mitchell, M. and Paradis, M.: Film: Behaviors electrically induced from brain areas related to sleep and psychotic phenomena. Annual Meeting of the Royal College of Physicians and Surgeons of Canada in Edmonton, January 25, 1973b.

St-Laurent, J. and Beaugrand, J.: Brain stimulation, reinforcement and Behavior. 1st National Conference on Drug Abuse and Alcoholism in Honolulu, May 5 and 6, 1973c.

St-Laurent, J., Leclerc, R., Beaugrand, J.M., Schell, M. and Paradis, M.: Alpha-methyl-para-tyrosine and alpha-methyl-paratyrosine-methyl-ester and self-stimulation in rats. Rev. Can. Biol., 32: 137-141, 1973d.

St-Laurent, J., Leclerc, R., Mitchell, M.E. and Miliaressis, T.E.: Effects of apomorphine on self-stimulation. Pharmacol. Biochem. Behav., 1: 581-585, 1973e.

St-Laurent, J., Roizen, M.F., Beckman, H., Miliaressis, T.E., Goodwin, F.K. and Jacobowitz, D.A.: The effects of self-stimulation on the catecholamine concentration of discrete areas of the brain. Brain Res., 99: 194-200, 1975.

St-Laurent, J., Roizen, M.F. and Jacobovitz, D.A.: Changements neurochimiques au niveau de petites régions spécifiques du cerveau du rat après auto-stimulation dans la région tegmento-ventrale mesencéphalique. Union Med. Can., 105: 944-948, 1976.

Schell-Kruger, J. and Randrup, A.: Stereotyped hyperactive behaviors produced by dopamine in the absence of noradrenaline. Life Sci., 6: 1389, 1967.

Sharpless, S.K.: Designated discussion in reticular formation of the brain.(Jasper, H.H., ed.): 722-723. Little Brown, Boston, 1958.

Seigel, S.: Non-parametric statistics for the behavioral sciences. p. 47-52, McGraw-Hill, New York, 1956.

Simon, H., LeMoal, M. and Cardo, B.: Mise en évidence du comportement d'autostimulation dans le noyau raphé médian du rat. C. R. Acad. Sci., (Paris), 277: 591-593, 1973.

Simon, H., LeMoal, M. and Cardo, B.: Intracranial self-stimulation from the dorsal raphe nucleus of the rat: Effects of the injection of para-chlorophenylalanine and alpha-methyl-para-tyrosine. Behav. Vio., 16: 353-364, 1976.

Sourkes, T.L.: Central actions of dopa and dopamine. In: "Contributions of neurosciences to psychopharmacology" and "The motor system". (St-Laurent, J. ed.). Rev. Can. Biol., 31: 193-213, Spring suppl., 1972.

Sokal, R.R. and Rohlf, R.J.: Geometry, Chapter 13, Freeman Press, San Francisco, 1969.

Spector, S., Sjoerdama, A. and Udenfriend, S.: Blockade of endogeneous norepinephrine synthesis by alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. J. Pharmacol. Exp. Ther., 147: 86-95, 1965.

Stark, P. and Boyd, E.S.: Effects of cholinergic drugs on hypothalamic self-stimulation response rates in dogs. Amer. J. Physiol., 205: 745-748, 1963.

Stark, P., Boyd, E. and Fuller, R.: A possible role of serotonin in hypothalamic self-stimulation in dogs. J. Pharmacol. Exp. Ther., 146: 147-153, 1964.

Stein, L.: Effects and interactions of imipramine, chlorpromazine, reserpine and amphetamine on self-stimulation: Possible neurophysiological basis of depression. Rec. Adv. Biol. Psychiat., 4: 288-308, 1962.

Stein, L.: Amphetamine and neural reward mechanisms. In: Ciba foundation symposium on animal behaviour and drug action (Steinberg, H., de Reuch, A.V.S. and Knight, J., eds.) J. & A. Churchill, London, 1964.

Stein, L.: Neurochemistry of reward and punishment: Some implications for the etiology of schizophrenia. J. Psychiat. Res., 8: 345-361, 1971.

Stein, L. and Seifter, J.: Possible mode of antidepressive action of imipramine. Science, 134: 286-287, 1961.

Stein, L. and Wise, C.D.: Possible etiology of schizophrania: Progressive damage to the noradrenergic reward system by 6-Hydroxydopamine. Science, 171: 1032-1036, 1971.

Steiner, S.S., Beer, B. and Shaffer, M.M.: Escape from self-produced rates of brain stimulation. Science, 163: 90-91, 1969.

Stinus, L., LeMoal, M. and Cardo, B.: Autostimulation et catecholamines. 1. Intervention possible des deux "compartiments" (compartiment fonctionnel et compartiment de réserve). Physiol. Behav., 9: 175-182, 1970a.

Stinus, L., LeMoal, M. and Cardo, B.: Résultats comparatifs d'une étude pharmacologique de l'autostimulation dans les régions hypothalamique et mesencéphalique ventrales. J. Physiol., (Paris), 63: 97-98, 1970b.

Stinus, L., LeMoal, M. and Cardo, B.: Résultats comparatifs d'une étude pharmacologique del'autostimulation dans les régions hypothalamique et mésencéphalique ventrales. J. Physiol., (Paris) 2: 974, 1971.

Stinus, L. and Thierry, A.M.: Self-stimulation and catecholamines. II. Blockade of self-stimulation by alpha-methyl-para-tyrosine treatment and reinstatement by catecholamine precursors adminfstration. Brain Res., 64: 189-198, 1973.

Stinus, L., Thierry, A.M., Blanc, G., Glowinski, J. and Cardo, B.: Self-stimulation and catecholamines. III. Effect of imposed or self-stimulation in the area ventralis tegment in catecholamine utilization in the rat brain. Brain Res., 64: 199-210, 1973.

Svensson, T. and Waldeck, B.: On the role of brain catecholamines in motor activity: Experiments with inhibitors of synthesis and of monoamine oxidase. Psychopharmacologia, 18: 357, 1970.

Thierry, A.M., Javoy, E., Glowinski, J. and Kety, S.S.: Effects of stress on the metabolism of norepinephrine, dopamine and serotonine in the central nervous system of the rat. Modification of turnover. J. Pharmacol. Exp. Ther., 163: 163-169, 1971.

Understedt, U.: Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. , Suppl. 367: 1-48, 1971.

Valenstein, E.S.: The anatomical locus of reinforcement. Progress in Physiological Psychology (Stillar, E. and Sprague, J.M., eds.) 1: 149-150. Academic Press, New York, 1966.

Valenstein, E.S., Verne, C.C. and Kakolewski, J.W.: Modification of motivated behavior elicited by electrical stimulation of the hypothalamus. Science, 159: 1119-1121, 1968.

Van Rossum, J. and Hurkmans, J.: Mechanism of action of psychomotor stimulant drugs. Significance of dopamine in locomotor stimulant action. Int. J. Neuropharmac., 3: 227, 1964.

Van der Kvoy, D. and Phillips, A.G.: Involvement of the trigeminal motor system in brain stem self-stimulation and stimulation-induced behavior. Brain Behav. Evol., 16: 293-314, 1979.

Von Hungen, K., Roberts, S. and Hill, D.F.: LSD as an agonist and antagonist at central dopamine receptors. Nature, 252: 588-589,.1974.

Weissman, A. and Koe, B.K.: Behavioral effects of L-alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. Life Sci., 4: 1037-1048, 1965.

Weissman, A., Kow, B.K. and Tenen, S.S.: Antiamphetamine effects following inhibition or tyrosine hydroxylase. J. Pharmacol. Exp. Ther., 151: 339-352, 1966.

Wilkinson, H.A. and Peele, T.L.: Intracranial self-stimulation in cats. J. Comp. Neurol., 121: 425-440, 1966.

Winer, B.J.: Statistical principles in experimental design. McGraw-Hill, Toronto, 1962.

Wise, D. and Stein, L.: Facilitation of self-stimulation by central administration of norepinephrine. Science, 163: 299-301, 1969.

Yuwiler, A. and Olds, M.E.: Catecholamines and self-stimulation behavior: Effects on brain levels after stimulation, and pre-treatment with DL-α-methyl-p-tyrosine. Brain Res., 50: 331-340, 1973.

RECENT REVIEW OF NEUROPHARMACOLOGICAL LITERATURE AS PERTINENT TO THE FIELD OF BRAIN SELF-STIMULATION

1. INTRODUCTION

The discovery that catecholamine depleters and blockers attenuated self-stimulation whereas catecholamine releasers and reuptake blockers facilitated it (Olds and Travis, 1960; Poschel and Nineteman, 1963, 1964; Stein, 1962; Stein and Ray, 1960) led to the catecholamine hypotheses which guide contemporary research on brain reward mechanisms. There have been extensive reviews of the evidence for the various catecholamine hypotheses (Crow, 1976; Fibiger, 1978; German and Bowden, 1974; Stein, 1969, Wise, 1978).

The first widely circulated catecholamine theory (Stein, 1962, 1969) involved norepinephrine, and while suggested by several investigators (Dresse, 1966; Poschel and Nineteman, 1963; Stein 1962), it has been most widely associated with the work of Stein and his colleagues (Belluzzi et al., 1975; Ritter and Stein, 1973; Stein and Belluzzi, 1976; Stein, 1980; Stein and Wise, 1969). Stein argued that activation of noradrenergic pathways was rewarding on several grounds. First, drugs that inhibited or enhanced noradrenergic function had similar effects on lever-pressing for brain stimulation, second, rewarding stimulation caused norepinephrine release from the terminals of medial forebrain bundle norepinephrine fibers, and, third, positive new sites for brain stimulation reward were found, as hypothesized, along the trajectories of noradrenergic systems.

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Others (Crow, 1972; Lippa et al., 1973) suggested that similar data implicated dopamine systems as well, and German and Bowden (1974) reviewed several hundred papers to come to the conclusion that activation of at least one norepinephrine and two dopamine pathways was rewarding.

Stimulated by the evidence and hypotheses reviewed by German and Bowden (1974), recent studies have probed for finer anatomical and pharmacological data on self-stimulation mechanisms. Often these studies have implicated dopamine but not norepinephrine in reward phenomena.

One of the first report indicating a possible role of dopamine (DA) in SS, was the one of St-Laurent and collaborators (1973). Another study reported in this thesis seems to also indicate this. In these studies, the administration of appropriate dosages of alpha-méthyl-para-tyrosine (MPT) produced a deficit in brain catecholamines (CA's) associated with the suppression of self-stimulation (SS) obtained from posterior lateral hypothalamus (PLH) and ventrotegmental area (VTA). The subsequent injection of apomorphine, a known direct stimulator of the dopaminergic receptors, reinstated the MPT suppressed SS.

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2. PHARMACOLOGICAL STUDIES OF BRAIN STIMULATION REWARD

Critics of the catecholamine-reward hypothesis have suggested that drugs which interfere with noradrenergic function reduce self-stimulation by an action on attention or arousal mechanisms (Roll, 1970; Rolls, Kelly, & Shaw, 1974) and that drugs which attenuate dopaminergic function decrease self-stimulation by interfering with some aspect of motor function such as the ability to initiate and maintain instrumental responding (Fibiger, Carter, & Phillips, 1976) and the ability to organize or execute complex sequences of motor movements (Rolls, Rolls, Kelly, Shaw, Wood, & Dale, 1974). The notion that interference with noradrenergic or dopaminergic neurotransmission reduces the rewarding properties of brain stimulation cannot be seriously entertained until these simple "performance" explanations are ruled out.

2.1 Dopamine

Experiments have suggested that in the case of dopamine receptor blockade, true reward deficits may be involved (Yuke and Wise, 1975). On the other hand, the possibility of a DA-related performance deficit needs special consideration since the nigrostriatal DA system is thought to be involved in motor function, perhaps mediating sensorimotor integration (Marshall, Richardson and Teitebaum, 1974) or the initiation of voluntary motor movements (Fibiger, Zis and Phillips, 1975; Rolls, Rolls, Kelly, Shaw, Wood and Dale, 1974).

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It has been shown in several ways that the doses of neuroleptic which attenuate self-stimulation do not render animals incapable of initiating voluntary movements or organizing complex motor acts.

First, there is disruption of self-stimulation when dopamine blockers are microinjected into the dopamine terminal fields on the side of rewarding stimulation; there is no performance impairment when similar injections are given contralateral to the side of stimulation (Robertson annd Mogenson, 1978). Neuroleptics increase the threshold for self-stimulation, but they do not make the animals incapable of lever-pressing when additional motivational current is given (Liebman and Butcher, 1974; Esposito et al., 1979; Schaefer and Michael, 1980; Zarevics and Setler, 1979).

Analysis of the temporal pattern of normal extinction responding suggests a way to discriminate response cessation due to blocked reward from response cessation due to performance difficulties. When reward is terminated, animals initially respond at normal rates. It is only after several responses fail to produce normal reward feedback that response rates drop (Kimble, 1961). Thus, a drug which attenuates the reward value of stimulation will cause decreased responding only after an early burst of normal responding, where a drug that impairs performance will suppress responding throughout a session.

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Fouriezos and Wise (1976) observed that pimozide produces a pattern of decreased responding which seems to reflect decreased reward value of stimulation, rather than decreased performance capacity of the animal. To the degree that the effects of pimmozide are correctly attributed to a specific action on dopaminergic systems (Anden et al., 1970; Janssen et al., 1968). These data indicate a role for dopamine in central mediation of reward. Further work is required to indicate whether a similar pattern of responding is seen with other agents or in self-stimulation tests involving other electrodes placements (Foubiezos and Wise, 1976).

2.2 Norepinephrine

The effects of the noradrenergic blocker phenoxybenzamine provide an interesting contrast (Fouriezos et al., 1978). Phenoxybenzamine produced response decrements from the very first trial of the very first drug test, and these response decrements do not get stronger either between sessions or within sessions. Performance is no worse on the 10th trial than on the first. Thus phenoxybenzamine, unlike neuroleptics, causes a deficit in performance which is felt before the first earned reinforcement. The fact that it is only after the animal feels the stimulation under neuroleptics that performance begin to deteriorate suggests that the response-sustaining property of the reward is blunted with these drugs; the lack of such deterioration under phenoxybenzamine suggests that the first reward is experienced as normally intense and is not disappointing (Zarevics, Weidley and Setler, 1977).

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It does seems more likely that phenoxybenzamine reduces the animal's capability to respond normally than that it reduced the response-sustaining rewarding impact (the payoff) of stimulation.

Considerable evidence for noradrenergic mediation of self-stimulation has been put forward, though it is not evident which deals very directly with the questions raised above. The major pharmacological leg of the noradrenergic reward hypothesis involves drugs which inhibit norepinephrine but not dopamine synthesis; such inhibition disrupts self-stimulation, and this disruption can be reversed by intraventricular norepinephrine but not dopamine (C. D. Wise and Stein, 1969). This has been viewed as a "reloading" of the reward neuron.

It is not clear whether the norepinephrine-depleted animal is capable of lever-pressing, however, and thus the deficit may well be a performance deficit such as is seen with noradrenergic receptors blockers (phenoxybenzamine, phentolamine and propranolol) (Zarevics, Weidly and Setler, 1977; Fouriezos et al., 1978). Other studies fit with this view. Roll (1970) has argued that the self-stimulation deficits seen with noradrenergic depletion are due to sedation, and studies in which noradrenergic cells are damaged but dopaminergic cells are spared with appropriate 6-hydroxydopamine regimens generally show a sparing of self-stimulation (Cooper et al., 1974; Lippa et al., 1973).

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2.3 Serotonin

Several studies have suggested that serotonergic or 5-hydroxy-tryptamine (5-HT) neurons mediate brain stimulation reward. The hypothesis of a 5-HT basis of reward rests mainly on the fact that high self-stimulation (SS) rates can be obtained with electrodes located in the medial (MR) and dorsal (DR) raphé nuclei as reported by St-Laurent et al., 1973; Simon et al., 1973; Simon et al., 1975 and by ourselves in this thesis.

Furthermore, pharmacological data seem to indicate, although inconsistently, that SS behavior can be either enhanced or inhibited by drugs that alter 5-HT function. The most widely used drug to test 5-HT's role in SS is PCPA. This drug is a potent tryptophan hydroxylase inhibitor and Koe and Weissman (1966) have reported brain 5-HT levels reduction occurring maximally 72 hours after its administration.

The most telling evidence for a positive motivational function for 5-HT was presented by Miliaressis (1975, 1977) and Van der Kooy (1977, 1977). These studies suggest that PCPA specifically suppress DR and MR SS two days after its injection, while SS of either the ventral tegmental area (VTA) (Miliaressis, 1975, 1977) or the lateral hypothalamus (LH) (Van der Kooy, 1977) remain comparatively unaffected by this treatment.

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The differential sensitivity to 5-HT reduction between so called catecholaminergic (VTA, LH) and 5-HT (DR and MR) SS sites led these authors to speculate that 5-HT neurons might also subserve SS behavior.

Although several other studies have obtained midbrain raphé SS suppression after PCPA, 5-HT's involvement in reward was usually dismissed on the basis that maximal SS inhibition did not correlate with the time of maximal 5-HT depletion (Crow and Deakin, 1977; Margules, 1969 and Simmon et al., 1976).

Characteristically, these studies showed moderate to high suppression of SS 12 to 24 hours after PCPA at which time 5-HT levels are only minimally reduced and a partial to complete recovery of SS behavior 2 to 3 days after PCPA when 5-HT levels are at their lowest.

However, even with long SS sessions, the results of Gratton (1983) still showed temporal dissociation between PCPA induced suppression of MR SS and depletion of 5-HT and thus are not in agreement with similar studies which have suggested a 5-HT depletion dependant inhibition of raphé SS (Miliaressis, 1975, Miliaressis 1977, Van der Kooy et al., 1977). In fact, MR SS rates were maximally reduced 24 hours after PCPA when 5-HT levels are only marginally reduced, while SS behavior returned to baseline rates 3 days post-drug, when 5-HT levels are reported to be at their lowest (Koe and Weissman, 1966).

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It may be that recovery from PCPA induced suppression of SS behavior is more directly linked to the return of normal tryptophan hydroxylase activity than to normal 5-HT levels. However, given that tryptophan hydroxylase is the rate limiting step in serotonin production and that its decrease in activity after PCPA follows a time course similar to 5-HT levels, one would expect that the suppression of serotonin synthesis and the changes in SS behavior should still have matching time courses. Nonetheless, being that tryptophan hydroxylase activity after PCPA was not measured in the present study, the possibility that the return of normal SS behavior is dependent on a yet unknown threshold rate of synthesis cannot be dismissed at this time.

Although the time course in PCPA's action on SS does not correspond with its action on 5-HT levels, it is evident that this drug does have inhibitory properties on SS behavior at least 24 hours after its injection. This raises the possibility that PCPA might act on SS behavior through another neurochemical mechanisms. It has already been shown that PCPA causes a slight (10 to 20%) transitory reduction in brain norepinephrine (NE) 6 to 24 hours after its injection (Koe and Weissman, 1966).

Based on this effect several authors have suggested that suppression of SS behavior by PCPA is more directly related to its NE action and in doing so have proposed that SS behavior obtained from the midline central gray region is mediated by fibers of the dorsal NE bundle (DNB) (Margules, 1969; Simon et al., 1976).

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The possibility that small reductions of MF levels might cause a generalized decrease in activity or a greater susceptibility to fatigue cannot be dismissed. Thus it is plausible that because of fatigue, the rats could not sustain the physical effort necessary to maintain high lever pressing rates for long periods of time. The fact that PCPA uniformly suppressed SS in the three structures tested could lead us to speculate that this might be the case.

Finally, overall brain monoamine levels give a fairly good indication of the state of the 5-HT storage pools after PCPA, the observed residual 5-HT may reflect the neuron's ability to synthesize functionally significant amounts of serotonin despite the PCPA treatment. The possibility that newly synthesized 5-HT might be sufficient to maintain SS behavior can not be ruled out.

For Katz and Baldrighi (1979), the studies of Miliaressis (1975; 1977) and of Van der Kooy et al., (1977) showed that serotonin is involved in SS, however they noticed that in comparaison with catecholamine mediated SS from the MFB, MP stimulation was considerably more variable and difficult to maintain. Their results with methysergide support a facilatatory role for 5-HT in SS at a serotonergic site. However, the baseline of SS for MR sites was highly variable, and in fact invariably showed spontaneous cessation of responding, Katz and Baldrighi results with PCPA reversal of spontaneously stopped ICS again suggests that reward from the medial raphé may reflect an anatomical and pharmacological complexity which was greater than anticipated.

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Recent reports suggest this interpretation is in fact likely, since not only 5-HT but also a second tryptamine, and dopamine are present within the nucleus (Bjorklund et al., 1971; Ochi & Shimizu, 1978).

Finally, Deakin (1980) observed that SS from the MR could not be antagonized by four different pharmacological methods of impairing serotonergic neurotransmission. MR SS could not be attenuated by 5-HT receptor blockade with metergoline or cyproheptadine nor by 5-HT depletion induced with parachloroampetamine or by prior destruction of ascending 5-HT pathways with intracerebral microinjections of 5,7-dihydroxy-tryptamine. It therefore seems unlikely that raphé SS is mediated by serotonergic neurons, the rewarding effect would be mediated by a catecholamine system passing through the raphé nuclei.

3. ANATOMICAL MAPPING OF BRAIN STIMULATION REWARD AND THE ROLE OF PSYCHOPHYSICAL PROCEDURES

3.1 Methodologies

The most useful mapping studies have developed recently as direct tests of the catecholamine hypotheses which were advanced in the early 1970s (Crow, 1976; German and Bowden, 1974; Stein, 1971).

The early mapping studies were single electrode mapping studies from which a fuzzy picture of system boundaries could be generated.

Work in which multiple sites are tested in each animal has given stronger resolution to the brain stimulation reward maps. Catecholamine maps were available in reconstruction format without stereotaxic coordinates, based on immature animals (Ungerstedt, 1971); at the present time much more detailed analyses of catecholamine anatomy are available (see Moore and Bloom, 1978, 1979, for extensive reviews). In more recent self-stimulation studies, moreover, catecholamines have been visualized directly in the tissue containing the electrode track, allowing direct observation of catecholamine and self-stimulation anatomy as directly assessed in the same animal.

Finally, more sensitive methods of fluorescence histochemistry have recently been used, allowing visualization of previously unknown catecholamine projections (Lindvall and Björklund, 1974; Lindvall et al., 1974).

3.2 Noradrenergic fibers

As a result of evidence based on these technical developments, it no longer seems likely that noradrenergic systems play a critical role in brain stimulation reward. Lesions of noradrenergic systems fail to disrupt self-stimulation; rather, such lesions, at least in some cases, potentiate self-stimulation (Clavier et al., 1976; Clavier and Routtenberg, 1974, 1976; Corbett et al., 1977; Koob et al., 1976).

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Positive self-stimulation sites near the noradrenergic nucleus locus coeruleus have been found to cluster not around the locus coeruleus itself but rather around the mesencephalic nucleus of the trigeminal or some fiber system anterolateral to locus coeruleus proper (Amaral and Routtenberg, 1974; Corbett and Wise, 1979; Simon et al., 1975).

Self-stimulation in the trajectories of the tegmental dorsal and ventral bundles bears only a chance relation to catecholamine anatomy as determined by fluorescence histochemistry (Corbett and Wise, 1979). Self-stimulation from the region of locus coeruleus survives bilateral destruction of the dorsal noradrenergic fibers from locus coeruleus to the forebrain (Corbett et al., 1977).

3.3 Dopaminergic fibers

It has been shown that Brain Stimulation Reward (BSR) sites in the VTA and in the substantia nigra pars compacta (SNC) are co-extensive with catecholamine fluorescence produced by dopamine (DA)-containing cells of the A9 and A10 regions (Corbett and Wise, 1980; Wise, 1981). Whereas pontine BSR does not correlate anatomically with noradrenaline-containing perikarya (or their efferent fibers) of the locus coeruleus (Amaral and Routtenberg, 1975; Corbett and Wise 1979; Simon, LeMoal and Cardo, 1975).

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However, several recent studies (Gallistel, Schizgal and Yeomans, 1981) suggest that at least a major subset of the directly activated fibers in BSR have refractory periods, conduction velocities and frequency thresholds that differ from electrophysiological characteristics of the monoaminergic fibers which have been the major hypothesized BSR substrate for a decade or more.

Furthermore, the reward-relevant fibers comprising this subset traverse along the MFB in a rostro-caudal direction (Schizgal, Bielajew and Kiss, 1980) whereas catecholamine containing axons project in a caudo-rostral direction. While these data do not rule out the possibility that direct activation of DA fibers makes some contribution to the rewarding effects of MFB stimulation (Gallistel, Schizgal and Yeomans, 1981) they call into question the once-dominant view that catecholamine fibers are the major directly activated substrate of MFB reward.

Reward-relevant fibers may, of course, be making synaptic contacts on ventral tegmental DA cell bodies which then serve as the second stage neurons in the system (Schizgal, Bielajew, Corbett, Skelton and Yeomans, 1980) some such efferent involvement of dopamine elements seems required to explain pharmacological aspects of BSR. The pulse pair studies thus form a complement to the dopamine theory of reward.

The system mapped in the Wise studies appears not to continue through the caudal pole of the dopaminergic cell group; while collision tests indicate that the tegmental sites are connected without synaptic interruption with positive sites in the lateral hypothalamus (Schizgal, Jordan and Bielajew, 1980).

Sites in the more caudal region of the raphé would seem not to be similarly connected. Frequency response and refractory period data suggest that raphé sites, too, might involve myelinated fiber systems as the directly-activated, reward-relevant substrate of self-stimulation (Schizgal, Jordan and Bielajew, 1980) and while dopaminergic blockade also disrupts self-stimulation with these placements, there is currently no evidence relevant to the question of how these more caudal sites are linked to any dopaminergic substrate.

REFERENCES

Amaral, D. G. and Routtenberg, A.: Locus coeruleus and intracranial self-stimulation: A. cautionary note. Behav. Biol. 13: 331-338, 1975.

Andén, N.-E., Corrodi, H., Fuxe, K., Hökfelt, T., Rydin, C. and Svensson, T.: Evidence for a central noradrenaline receptor stimulation by clonidine, Life Sci., 9: 513-523, 1970.

Belluzi, J. D., Ritter, S., Wise, C. D. and Stein, L.: Substantia nigra self-stimulation: Dependence on noradrenergic reward pathways. Behav. Biol. 13: 103-111, 1975.

Bjorklund, A., Falck, B. & Stenevi, U.: Classification of monoamine neurons in the rat mesencephalon: distribution of a new monoamine system. Brain Res. 32: 269-285, 1971.

Clavier, R. M., Fibiger, H. C. and Phillips, A. G.: Evidence that self-stimulation of the region of the locus coeruleus in rats does not depend on noradrenergic projections to telencephalon. Brain Res. 113: 71-81, 1976.

Clavier, R. M. and Routtenberg, A. Ascending monoamine-containing fiber pathways related to intracranial self-stimulation: Histochemical fluorescence study. Brain Res. 72: 25-40, 1974.

Clavier, R. M. and Routtenberg, A. Brainstem self-stimulation attenuated by lesions of medial forebrain bundle but not by lesions of locus coeruleus or the caudal ventral norepinephrine bundle. Brain Res. 101: 251-271, 1976.

Cooper, B. R., Cott, J. M. and Breese, G. R.: Effects of catecholamine-depleting drugs and amphetamine on self-stimulation of brain following various 6-hydroxydopamine treatments. Psychopharmacologia 37: 235-248, 1974.

Corbett, D., Skelton, R. W. and Wise, R. A. Dorsal bundle lesions fail to disrupt self-stimulation from the region of locus coeruleus. Brain Res. 133, 37-44, 1977.

Corbett, D. and Wise, R. A.: Intracranial self-stimulation in relation to the ascending noradrenergic fiber systems of the pontine tegmentum and caudal midbrain: A moveable electrode mapping study. Brain Res. 177: 423-436, 1979.

Corbett, D. and Wise, R. A.: Intracranial self-stimulation in relation to the ascending dopaminergic systems of the midbrain: A moveable electrode mapping study. Brain Res. 185: 1-15, 1980.

Crow, T. J.: Catecholamine-containing neurones and electrical self-stimulation: 1. A review of some data. Psychol. Med. 2: 414-421, 1972.

.../17

Crow, T. J.: Specific monoamine systems as reward pathways: Evidence for the hypothesis that activation of the ventral mesencephalic dopaminergic neurons and noradrenergic neurons of the locus coeruleus complex will support self-stimulation responding. In A. Wauquier and E. T. Rolls (Eds.) Brain Stimulation Reward, Elsevier, New York, pp. 211-238, 1976.

Crow, T. J. And J. F. W. Deakin: Do 5-HT neurones support self-stimulation? Br. J. Pharmac. (Proc.) 60: 320p. 1977.

Deakin, J. F. W.: On the neurochemical basis of self-stimulation with midbrain raphe electrode placements. Pharmacol. Biochem. Behav., 13: 525-530, 1980.

Dresse, A.: Importance du système mésencéphalo-télencéphalique noradrénergique comme substratum anatomique du comportement d'autostimulation. Life Sci. 5: 1003-1004, 1966.

Esposito, R. U., Faulkner, W. and Kornetsky, C.: Specific modulation of brain stimulation reward by haloperidol. Pharmacol. Biochem. Behav., 10: 937-940, 1979.

Fibiger, H. C.: Drugs and reinforcement mechanisms: A critical review of the catecholamine theory. Ann. Rev. Pharmacol. Toxicol. 18: 37-56, 1978.

Fibiger, H. C., Zis, A. P. and Phillips, A. G.: Haloperidol-induced disruption of conditioned avoidance responding: attenuation by prior training or by anticholinergic drugs, Europ. J. Pharmacol.,30: 309-314, 1975.

Fibiger, H. C., Carter, D. A. and Phillips, A. G.: Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than by reduced reward. Psychopharmacology 47: 21-27, 1976.

Fouriezos, G. and Wise, R. A.: Pimozide induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. Brain Res., 103: 377-380, 1976.

Fouriezos, G. Hansson, P. and Wise, R. A.: Neuroleptic-induced attenuation of brain stimulation reward. J. Comp. Physiol. Psychol. 92: 659-669, 1978.

Gallistel, C. R. Shizgal, P. and Yeomans, J.: A portrait of the substrate for self-stimulation Psychol. Rev., 88: 228-273, 1981.

German, D. C. and Bowden, D. M.: Catecholamine systems as the neural substrate for intracranial self-stimulation: A hypothesis. Brain Res., 73: 381-419, 1974.

Gratton, A.: Time course analysis of para-chlorophenylalanine induced suppression of self-stimulation behavior, Pharmac. Biochem. Behav., 17: 1-5, 1982.

.../18

Janssen, P. A., Niemegeers, S., Schellekens, K. H. L., Dresse, A., Lenaerts, F. M., Pinchard, A., Schaper, W. K. A., VanNueten, J. M. and Verbruggen, F. J.: Pimozide, a chemically novel, highly potent and orally long-acting neuroleptic. Part I. The comparative pharmacology of pimozide, haloperidol and chlorpromazine, Arzneimittel-Forsch., 18: 2611-279, 1968.

Katz, R. J. and Baldrighi, G.: Serotonergic mediation of reward within the medial raphe nucleus: some persistent problems in interpretation Intern. J. Neuroscience., 9: 145-148, 1979.

Koe, K. B. and Weissman, A.: p-Chlorophenylalanine: a specific depletor of brain serotonin. J. Pharmac. exp. Ther. 154: 499-516, 1966.

Koob, G. F., Balcom, G. J. and Meyerhoff, J. L.: Increases in intracranial self-stimulation in the posterior hypothalamus following unilateral lesions in the locus coeruleus. Brain Res. 101, 554-560, 1976.

Liebman, J. M. and Butcher, L. L.: Comparative involvement of dopamine and noradrenaline in rate-free self-stimulation in substantia nigra, lateral hypothalamus and mesencephalic central gray. Naunyn-Schmiedeber's Arch. Pharmacol. 284: 167-194, 1974.

Lindvall, O. and Björklund, A.: The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol. Scand. Suppl. 412: 1-48, 1974.

Lindvall, O, Björklund, A., Nobin, A. and Stenevi, U.: The adrenergic innervation of the rat thalamus as revealed by the glyoxylic acid fluorescence method. J. Comp. Neurol. 154: 317-346, 1974.

Lippa, A. S. Antelman, S. M., Fisher, A. E. and Canfield, D. R.: Neurochemical mediation of reward: A significant role for dopamine? Pharmacol. Biochem. Behav. 1: 23-28, 1973.

Margules, D. L.: Noradrenergic rather than serotonnergic basis of reward in the dorsal tegmentum. J. comp. physiol, psychol. 67: 32-35: 1969.

Marshall, J. F., Richardson, J. S., and Teitelbaum, P., Nigrostrital bundle damage and the lateral hypothalamic syndrome, J. comp. physiol. Psychol., 87: 808-830, 1974.

Miliaressis, E., Bouchard, A. and Jaccobowitz, D. M.: Strong positive reward in median raphé: specific inhibition by para-chlorophenylalanine. Brain Res. 98: 194-201. 1975.

Miliaressis, E.: Serotonergic basis of reward in median raphe of the rat. Pharmac. Biochem. Behav. 7: 177-180, 1977.

Moore, R. Y. and Bloom, F. E.: Central catecholamine neuron systems: Anatomy and physiology of the dopamine systems. Ann. Rev. Neurosci. 1: 129-169, 1978.

.../19

Moore, R. Y. and Bloom, F. E.: Central catecholamine neuron systems: Anatomy and physiology of the norepinephrine and epinephrine systems. Ann. Rev. Neurosci., 2: 113-168, 1979.

Ochi, J. & Shimizu, K.: Occurence of dopammine containing neurons in the median raphe nuclei of the rat. Neuroscience Letters, 8: 317-321, 1978.

Olds, J. and Travis, R. P.: Effects of chlorpromazine, meprobamate, pentobarbital and morphine on self-stimulation. J. Pharmacol. Exp. Theran., 128: 397-404, 1960.

Poschel, B. P.H. and Ninteman, F. W.: Norepinephrine: A possible excitatory neurohormone of the reward system. Life Sci., 10: 782-788, 1963, Life Sci., 10: 782-788, 1963.

Poschel, B. P. H. and Ninteman, F. W.: Excitatory (antidepressant?) effects of monoamine oxidase inhibitors on the reward system of the brain. Life Sci. 3: 903-910: 1964.

Ritter, S. and Stein, L.: Self-stimulation of noradrenergic cell group (A6) in locus coeruleus of rats. J. Comp. physiol, Psychol., 85: 443-452, 1973.

Robertson, A. and Mogenson, G. J.: Evidence for a role for dopamine in self-stimulation of the nucleus accumbens of the rat. Can. J. Psychol. 32: 67-76, 1978.

Roll, S. K.: Intracranial self-stimulation annd wakefulnes: Effect of manipulating ambient brain catecholamines. Science, 1968: 1370-1372, 1970.

Rolls, E. T. Rolls, B. J., Kelly, P. H., Shaw, S. G., Wood, R. J. and Dale, R.: The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. Psychopharmacologia, 38: 219-230, 1974.

Saint-Laurent, J., Leclerc, R. and Mitchell, M.: Autostimulation des noyaux du raphé et exploration diffuse. J. Physiol.(Paris) 66: 87-92, 1973.

Schaefer, G. P. and Michael, P. P.: Acute effects of neuroleptics on brain self-stimulation thresholds in rats. Psychopharmacology 67: 9-15, 1980.

Shizgal, P., Bielajew, C. and Kiss, I: Anodal hyperpolarization block technique provides evidence for rostro-caudal conduction of reward related signals in the medial forebrain bundle. Soc. Neurosci. Abst. 6: 422, 1980.

Shizgal, P., Bielajew, C. Corbett, D., Skelton, R. and Yeomans, J.: Behavioral methods for inferring conduction velocity and anatomical linkage: 1. Pathways connecting rewarding brain stimulation sites J. Comp. Physiol, Psychol. 94: 227-237, 1980.

.../20

Simon, H., LeMoal, M. and Cardo, B.: Mise en évidence du comportement d'autostimulation dans le noyau du raphé median du rat. C. r. hebd. Séanc. Acad. Sci., Paris 277: 591-593, 1973.

Simon, H., LeMoal, M., and Cardo, B.: Self-stimulation in the dorsal pontine tegmentum in the rat. Behav. Biol. 13: 339-347, 1975.

Simon, H., M. LeMoal and B. Cardo: Intracranial self-stimulation from the dorsal raphe nucleus of the rat: Fffects of the injection of para-chlorophenylalanine and alpha-methylparatyrosine. Behav. Biol. 16: 353-364, 1976.

Stein, L.: 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, Plenum, New York, pp. 288-308, 1962.

Stein, L.: Chemistry of purposive behavior. In: J. T. Tapp (Ed.) Reinforcement and behavior, Academic Press, New York, pp. 328-355, 1969.

Stein, L.: Neurochemistry of reward and punishment: Some implications for the etiology of schizophrenia. J. Psychiat. Res. 8: 345-361, 1971

Stein L.: The chemistry of reward. In: A. Routtenberg (Ed.) Biology of Reinforcement: Facets of Brain Stimulation Reward, Academic Press, New York, pp. 109-130, 1980.

Stein, L. and Ray, O. S.: Brain stimulation reward 'thresholds' self-determined in rat. Psychopharmacologia 1: 251-256, 1960.

Stein, L. and Wise, C. D.: Release of norepinephrine from hypothalamus and amygdala by rewarding medial forebrain bundle stimulation and amphetamine. J. Comp. Physiol. Psychol., 67: 189-193, 1969.

Stein, L., Belluzzi, J. D. and Wise, C. D.: Norepinephrine self-stimulation pathways: Implications for long-term memory and schizophrenia. In: A. Wauquier and E. T. Rolls (Eds.) Brain Stimulation Reward, Elsevier, New York, pp. 297-331, 1976.

St-Laurent, J., Leclerc, R., Mitchell, M. E. and Miliaressis, T. E.: Effects of apomorphine on self-stimulation. Pharmacol. Biochem. Behav., 1: 581-585, 1973.

Ungerstedt, U.: Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. Suppl. 367: 1-48, 1971.

Van der Kooy, D., H. C.: Fibiger and Phillips, A. G.: Monoamine involvement in hippocampal self-stimulation. Brain Res. 136: 119-130, 1977.

Van der Kooy, D. H. C. : Fibiger and Phillips, A. G.: An analysis of dorsal and median raphe self-stimulation: Effects of para-chlorophenylalanine. Pharmac. Biochem. Behav. 8: 441-445, 1977.

Wise, R. A.: Intracranial self-stimulation: Mapping against the lateral boudaries of the dopaminergic cells of the substantia nigra. Brain Res. 213, 190-194, 1981.

Wise, C. D. and Stein, L.: Facilitation of brain self-stimulation by central administration of norepinephrine. Science 163: 299-301, 1969.

Wise, R. A., Spindler, J., DeWit, H. and Gerber, G. J.: Neuroleptic-induced 'anhedonia' in rats: Pimozide blocks the reward quality of food. Science 201: 262-264, 1978.

Yokel, R. A. and Wise, R. A.: Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. Science 187: 547-549, 1975.

Zarevics, P. and Setler, P. E.: Simultaneous rate-independent and rate-dependent assessment of intracranial self-stimulation: Evidence for the direct involvement of dopamine in brain reinforcement mechanisms. Brain Res. 169: 499-512, 1979.

Zarevics, P., Weidley, E., & Setler, P.: Blockade of intracranial self-stimulation by anti-psychotic drugs: Failure to correlate with central alpha-noradrenergic blockade. Psychopharmacology, 53: 283-288, 1977.