NEUROBEHAVIORAL CORRELATES OF INTRACRANIAL CHEMICAL STIMULATION OF THE CAT

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CHAPTER I

INTRODUCTION

The first suggestion that neural synaptic transmission was based on the release of neurohumoral substances was made by DuBois-Reymond in 1877 (Grossman, 1967). Subsequently, Otto Loewi (1921) showed that stimulating the vagus nerve resulted in the release of a chemical substance which had an inhibitory effect on cardiac muscle. The vagus substance ("vagusstoff") has been shown to be acetylcholine (Eccles, 1964). Additionally, Loewi found that stimulation of sympathetic fibers resulted in the liberation of a substance which produced an opposite (facilitatory) effect on cardiac muscle. Elliot, in 1904 (Grossman, 1967) pointed out the similarity between sympathetic nerve stimulation and the administration of adrenaline and suggested that peripheral sympathetic nerves released an adrenaline-like substance.

The recent work of Eccles (1964) has contributed greatly to the understanding of neural synaptic transmission in the peripheral nervous system. Transmission of information between neurons appears to involve the diffusion of chemical substances across the synaptic junction. Neurohumoral substances are believed to be held in presynaptic vesicles or tubes in a bound or inactive form. The arrival of an action potential at the end feet of an axon stimulates the liberation of neurohumoral substances in active forms. The neurohumors diffuse across the synaptic gap and interact with specific receptor sites on the postsynaptic

membrane inducing changes in the transmembrane potential of the next neuron (Grossman, 1967). The transmembrane potential of the adjacent neuron may be depolarized (excitatory postsynaptic potential) or hyperpolarized (inhibitory postsynaptic potential). The interaction of excitatory and inhibitory shifts in the membrane potential determine whether an action potential is generated in the postsynaptic neuron. Synaptic release of specific neurohumors can result both in excitatory or inhibitory postsynaptic potentials, depending, in part, on where they are released.

In the peripheral nervous system, acetylcholine-like substances are the neural transmitters at all neuromuscular junctions, at preganglionic junctions in the sympathetic nervous system, and at postganglionic parasympathetic synapses. Norepinephrine-like substances are the neural transmitters at postganglionic sympathetic synaptic junctions. There are some exceptions to such a broad categorization. For example, sweat glands, which are innervated by postganglionic sympathetic fibers, are stimulated by the release of acetylcholine.

In order to simplify classification, when acetylcholine-like substances are the neural transmitters, the synaptic transmission is said to be cholinergic. If norepinephrine-like substances are the neural transmitters, the synaptic transmission is said to be adrenergic.

Adrenergic and cholinergic neural transmission differ in several respects. For example, cholinergic transmission may involve the presynaptic release of an active form of an acetylcholine-like substance, diffusion across the synaptic gap, and the destruction of the transmitter at the postsynaptic level by an antagonist, cholinesterase (Grossman, 1967). Adrenergic neural transmission is not as well understood. It is

currently believed that a norepinephrine-like substance is released from the presynaptic vesicles, is diffused across the synaptic gap, and is only partially destroyed at the postsynaptic level by an antagonist, monoamine oxidase. The remaining transmitter substance is reabsorbed into the presynaptic vesicles (McLennan, 1963; Eccles, 1964). Although acetylcholine and norepinephrine have been found to be nonrandomly distributed in the central nervous system (Shute & Lewis, 1966), information concerning the functional significance of these known peripheral neural transmitters within the central nervous system still remains tenative (Shute & Lewis, 1966; Grossman, 1967). However, pathways have been traced in the brains of rats and cats by various histological staining and biochemical techniques (Shute & Lewis, 1966; Krnjevic, 1969), and attempts are presently being made to unravel the functional significance of these chemical circuits in relation to possible integrative functions based on anatomically specific, chemically coded, neural systems in higher organisms (Myers, 1968).

CHAPTER II

REVIEW OF LITERATURE AND STATEMENT OF THE PROBLEM

The review of the literature is divided into three sections. The first section is concerned with neuroanatomy of the lateral hypothalamus, centre median nucleus of the thalamus and dorsomedial hippocampus; and the emphasis has been placed upon efferent and afferent pathways of the three selected brain areas in cats and rats. The second section is concerned with neurobehavioral correlates of electrically stimulating or lesioning selected brain loci. The final section is devoted to the neurobehavioral correlates of intracranial chemical stimulation.

Anatomy

Lateral Hypothalamus

Based on anatomical information, Nauta (1963) stated that the hypothalamus can be viewed as a structural complex embedded in a major neural circuit extending from the basal and medial walls of the cerebral hemisphere along various thalamic and hypothalamic pathways to a medial region of the mid-brain reticular area. Endocrine and visceral functioning of the hypothalamus reflects the activation or inhibition of neural mechanisms represented in this "limbic system - mid-brain circuit".

The hypothalamus can be divided into medial and lateral regions (Raisman, 1966). The medial region adjoins the third ventricle, is very

cellular, and consists of several distinct nuclei. The lateral region consists of more diffusely arranged cells which are interspersed among fibers of the medial forebrain bundle. The lateral hypothalamus extends rostrally through the preoptic area to the olfactory regions and extends caudally to the mid-brain. It is within the lateral hypothalamus that most of the extrinsic connections of the hypothalamus are made, rather than the medial hypothalamic nuclei.

The major forebrain afferent connections of the hypothalamus arise from the pyriform cortex and the hippocampus which are phylogenetically older areas of the cortex (Raisman, 1966). The septum and amygdala, subcortical nuclear masses which correspond to the hippocampus and pyriform cortex respectively, form a second afferent projection to the hypothalamus. These subcortical nuclei are intimately related to their respective overlying cortical areas by numerous two-way connections. The hypothalamus is reciprocally connected to these afferent forebrain structures, but the efferent fibers originating in the hypothalamus appear to extend only as far as the subcortical nuclei. Neocortical influence on the hypothalamus must apparently be mediated by phylogenetically older cortical structure.

The medial parts of the mid-brain tegmentum and periaqueductal gray matter provide another source of afferent input to the hypothalamus. The hypothalamus is reciprocally connected to these brainstem reticular structures by massive descending efferent projections.

Centre Median Nucleus of the Thalamus

At the mesencephalic level of the brain, the brainstem reticular core branches into dorsal and ventral limbs. The dorsal limb enters the

dorsal thalamus via the centre median nucleus, while the ventral limb extends into the subthalamus and hypothalamus (Jasper, 1961). The ventral projection of the brainstem reticular system has already been discussed in relation to the neural connections of the hypothalamus. The dorsal thalamus, besides including the centre median nucleus, contains several discrete nuclear groupings (Grossman, 1967).

The dorsal thalamus, or thalamus proper, is generally divided into five discrete nuclear masses as follows: the anterior nuclei, the midline nuclei, the lateral nuclei, the ventral nuclei, and the medial nuclei (Grossman, 1967). The anterior nuclei receive afferents from the mammillary bodies and project to the cerebral cortex and cingulate gyrus. Midline nuclei (phylogenetically the oldest thalamic nuclear group) receive fibers from the spinothalamic tracts, trigeminothalamic tracts and the medial leminiscus, and project fibers directly to most cortical areas, basal ganglia, amygdaloid complex, and indirectly to the hypothalamus. The lateral group of nuclei is reciprocally connected with other thalamic nuclei and makes reciprocal connections with various primary projection areas of the cortex including the frontal and temporal cortex. The ventral nuclei receive sensory information from primary tactile, gustatory and visceral receptors and project primarily to the motor cortex. The medial nuclei are of greater importance since the centre median nucleus is within this nuclear mass.

Specific nuclei within the medial grouping of thalamic nuclei include the following: the centre median, dorsomedial, submeduis, paracentral, central lateral, and the parafascicular. The intrathalamic pasciculus, originating largely in the centre median nucleus, connects the medial nuclei to the ventromedial region of the ventral anterior

nucleus (Papez and Rundles, 1937; Nauta and Whitlock, 1954). Collaterals diffuse at points along this pathway to all of the intralaminar nuclei and to the lateral association nuclei, with additional fibers projecting to the reticular nucleus, basal ganglia, hypothalamus, and, possibly to the cortex. The primary source of afferent connections with the medial nuclei comes from secondary sensory and motor pathways (Russell, 1961). The medial nuclei also have indirect reciprocal connections with the hippocampus and septum (Nauta and Whitlock, 1954).

Dorsomedial Hippocampus

The hippocampal formation, a complex archipallial structure, is located in the central portion of the brain hemispheres (Grossman, 1967). It is continuous with the anterior olfactory nucleus via the lamina termenalis. The hippocampal formation is separated from the allocortex and hippocampal gyrus by the hippocampal fissue. The bilateral portions of the formation are connected by the hippocampal commissure.

Areas projecting afferent fibers to the hippocampus are the cingulum, via the presubiculum and the olfactory, via the prepiriform and preamygdaloid area. A third source of afferents from the septum project to the hippocampus, following prior entry into the dentate gyrus. Cortical association fibers and posteromeidal and inferior temporal and the angular gyri provide an additional source of afferent input to the hippocampus (MacLean, 1954).

The fornix provides the only efferent tract from the hippocampus (Grossman, 1967) and projects to the lateral septum, the preoptic region, the diagonal band, and nucleus accumbens (Fox, 1943; Allen, 1944; Simpson, 1952).

On the basis of electrophysiological methods, a distinction has been made between dorsal and ventral portions of the hippocampus (Elul, 1964). The dorsal region projects efferents to the septum; to the specific, association, and intralaminar thalamic nuclei; to the reticular formation; and to both the temporal lobes of the cerebral cortex. The dorsal region of the hippocampus receives afferents from the septum, specific and associational thalamic nuclei, dorsal hypothalamic nuclei, and central gray matter. The ventral portion of the hippocampus recevies afferents from the septum, amygdala, intralaminar and associational thalamic nuclei, preoptic nucleus, caudate and the putamen. The ventral region projects efferents to the amygdala, associational and specific thalamic nuclei, and to the lateral and preoptic hypothalamic nuclei, as well as to the parietal and temporal cortex.

Neurobehavioral Correlates of Electrical Stimulation and Ablation

Lateral Hypothalamus

An extensive review of the effects of lateral hypothalamic stimulation and ablation is beyond the scope of this dissertation. Only an over-view of the directly relevant studies will be considered.

Most studies involving electrical stimulation or ablation of the lateral hypothalamus have been concerned with concurrent changes in food and water intake (Grossman, 1967). Brugger, in 1943, (Grossman, 1967) found that electrical stimulation of the lateral hypothalamus of cats elicited voracious eating, providing an early implication of the lateral hypothalamus as a possible feeding center. Subsequently, Anand and Brobeck (1951) reported that small bilateral lesions made lateral to the ventromeidal nucleus produced complete and permanent aphagia. The fact

that lateral hypothalamic lesions produced both aphagia and adipsia was reported by Teitelbaum and Stellar (1954). They also reported that subjects with mid-lateral lesions could recover from aphagia and adipsia in 6 to 75 days if artificial feeding and watering were introduced; whereas, far-lateral lesioned subjects showed no signs of regaining food and water regulatory functions. These far-lateral lesions produce degeneration in the pallidofugal fiber systems (Teitelbaum and Epstein, 1962) and are believed to reflect a distinct metabolic component. The effects of lesions in the mid-lateral region, however, is interpreted as reflecting a motivational component mediated by the medial forebrain bundle (Grossman, 1967).

Stimulus-bound eating and drinking have been consistently elicited by electrical stimulation of the lateral hypothalamus (Grossman, 1967). In addition, during such stimulation, subjects perform a previously learned bar-press response for food even if the response is infrequently rewarded (Miller, 1957, 1960; Wyrwicka et al., 1960; Morgane, 1961). Further, Olds (1961) reported that electrical stimulation of specific regions in the lateral hypothalamus (medial forebrain bundle) could maintain an operant response that was never rewarded with food or water and could serve as a reinforcer for the acquisition of new responses.

The rewarding effects of electrical brain stimulation have been well documented (Grossman, 1967). Based on behavioral and anatomical observations, it appears that reward effects are mediated by the medial forebrain bundle, which passes through the lateral hypothalamus, and by the projections from this tract (Olds, 1961; Grossman, 1967). The rewarding effects of central stimulation have been shown to interact with primary drives such as hunger, thirst, and sex (Olds, 1958, 1961;

Prescott, 1966), and different brain sites show consistent covariance with specific drives. For example, Wilkinson and Peele (1962), found that food deprivation and feeding only affected bar pressing for central stimulation at lateral hypothalamic electrode placements.

The hypothalamus also appears to be involved in the regulation of emotional behavior. Electrical stimulation of the hypothalamus, particularly the anterior and lateral portions, has been shown to result in rage responses (Hess, 1936, 1949, 1954). Additional emotional responses described as attack, defense, and flight reactions have also been elicited by hypothalamic stimulation (Grossman, 1967). These behavioral effects are accompanied by various emotional responses, such as pilomotor erection, pupil dilation, increased blood pressure, etc.

The effects of hypothalamic lesions on emotional behavior are not as clear as are the results from electrical stimulation. Some studies have shown an opposite behavioral effect from that produced by electrical stimulation, such as decreased emotionality (Ingram et al., 1936; Ranson, 1939; Bard and Mountcastle, 1948). Other studies have reported savage postoperative behavior resulting from various hypothalamic lesions (Kessler, 1941; Wheatley, 1944). It is possible that many of the contradictory results involving lesions are based upon a technical consideration (Donovan, 1966). For example, Donovan (1966) has pointed out that lesions made with steel electrodes often result in a stimulation effect induced by iron deposits being distributed into the neural tissue surrounding the lesion. The more recent use of radio-frequency lesionmakers has corrected this technical problem.

A limited number of studies have attempted to assess the effects of experimental manipulation of the hypothalamus on more complex behavioral

patterns involving acquisition and/or retention of conditioned responses (Grossman, 1967). Impaired acquisition and retention of food-motivated bar pressing response has been reported for rats with bilateral ventromedial hypothalamus lesions (Ingram, 1958; Miller et al., 1950). Acquisition of an instrumental avoidance response by rats was facilitated by lesions in the median eminence (Levine and Soliday, 1960). Knott and Ingram (In: Sheer, 1961) reported both facilitation and inhibition of appetitive bar pressing behavior in cats for several electrically stimulated hypothalamic sites. Grastyan et al. (1956) likewise reported that electrical stimulation of the dorsolateral hypothalamus of cats resulted in facilitation and elicitation of a simple panel pressing appetitive response. In contrast, posteromedial stimulation, including the mesencephalic reticular formation, inhibited the instrumental response. The facilitatory-inhibitory effects were reversed for the two hypothalamic placements when the task consisted of a simple escape-avoidance response. Defensive responses were facilitated with posteromeidal stimulation; whereas, dorsolateral stimulation inhibited defensive responses.

Centre Median Nucleus of the Thalamus

The thalamus has been implicated as an important brain area for acquisition and retention. Brown and Ghiselli (1938) found that acquisition of a complex behavior sequence was unaffected by damage to the anterior nuclei of the thalamus, but damage to other thalamic nuclei resulted in a learning deficit. Lesions in the dorsomedial nucleus of cats resulted in a performance decrement on a preoperatively learned discrimination task (Schreiner et al., 1953). Hypermotionality was also observed in the dorsomedial nuclei lesioned cats and may, in part,

account for the impaired performance. Destruction of the thalamocortical projections of the dorsomedial nucleus resulted in behavioral deficits on a preoperatively learned delayed response and a delayed alternation habit; yet no deficit was reported for acquisition on the same tasks (Peters et al., 1956). Performance decrements have been found on simple lever pressing and single alternation tasks following both medial and dorsomedial thalamic lesions (Rosvald et al., 1958; Schreiner et al., 1953). Likewise, Knott et al. (1960) found performance decrements in a lever pressing task following dorsomedial lesions, but not deficits in bar pressing were found with damage to the centrum medianum nucleus. Thompson and Massopust (1960) found an impairment on a simple discrimination task with dorsomedial lesions that appeared independent of any emotional changes.

Electrical stimulation of various thalamic nuclei results in a variety of emotional and behavioral responses. Stimulation of the medial lemniscus, ventral posterior, and intralaminar nuclei has been shown to potentiate an "alarm" reaction to peripheral pain (Roberts, 1958). Defensive responses are elicited by electrically stimulating the posterior nuclei of cats and monkeys (Delgado, 1955). Roberts (1962) found that stimulating various nonspecific and associational thalamic nuclei resulted in crouching, rage, visual searching, flight, pain and stereotyped motor responses. Endroczi et al. (1959) electrically stimulated the lateral or medial thalamic nuclei of dogs which had been trained on a difficult appetitive discrimination task. Lateral stimulation resulted in inhibition of instrumental responses. Medial stimulation, however, was found to facilitate such responses and often elicit the response independent of the conditioned stimulus.

Motivational changes have also been reported to result from electrical stimulation and lesioning of the thalamus. Lesions in the arcuate nucleus of the thalamus were shown to result in hyperphagia and obesity (Ruch et al., 1941, 1942). Also, electrical stimulation of the anterior thalamus of rats has been shown to result in seizure activity and subsequent ravenous eating (Maire, 1956; Smith, 1967). Miller (1961) found that electrical stimulation of the anterior and paraventricular thalamic nuclei causes satiated rats to begin eating and facilitated bar pressing for food if convulsions did not occur.

Dorsomedial Hippocampus

Studies involving lesioning and electrical stimulation of the hippocampus have shown a variety of emotional, motivational and associative changes in behavior. Increased emotionality was found by MacLean and Delgado (1953) with electrical stimulation of the rostral hippocampus of cats. During electrical stimulation, growling, defensive pawing, and attack behavior was elicited by mildly noxious stimuli. Kaada et al. (1953) and Naquet (1954) likewise found stimulation of the anterior hippocampus resulted in a fully developed rage response in cats, but no rage response was found with electrical stimulation of the posterior hippocampus.

Many studies present conflicting results concerning the effects of electrical stimulation as compared to lesioning of the hippocampus. For example, MacLean (1954) reported that electrical stimulation of the hippocampus of cats resulted in "pleasure" reactions. Bursten and Delgado (1958) found that stimulation of various hippocampal loci in their animals were positively rewarding. However, Mountcastle (1948) also found

enhanced "pleasure" reactions with bilateral ablations of the same or similar hippocampal regions. On the other hand, Rothfield and Harman (1954) found excessive emotionality to normal handling after sectioning of the fornix. Also, Orbach et al. (1960) reported chronic ferocity in monkeys following bilateral hippocampal lesions. In contrast, Fuller et al. (1957) reported a loss of social dominance in dogs following hippocampal damage. Hypersexuality (Kim, 1960) and a reduction in fear of handling (Weisdrahtz, 1956) have also been found with hippocampal damage. Increased food intake and improved instrumental food rewarded behavior were found by Teitelbaum (1960) and by Ehrlich (1963) following damage to similar hippocampal regions in rats. At present, it can only be assumed that there is possibly greater regional differences in the hippocampus than was originally realized.

Hippocampal damage typically has little effect on acquisition and retention of simple conditioned responses. Acquisition on a simple olfactory and visual discrimination task was found to be unaffected by hippocampal lesions (Allen, 1940, 1941; Kimble, 1963). Apparently, hippocampally damaged cats learn a simple conditioned response as readily as do unoperated controls.

In contrast to simple simultaneous discrimination situations, complex behavioral tasks and successive discrimination tasks are selectively affected by hippocampal damage. Thomas and Otis (1958), Kaada et al. (1961), and Kimble (1963) reported poorer performance in complex mazes following rostral and posterior hippocampal lesions. In a simple alternation task, Pribram et al. (1962) observed performance deficits with ventral hippocampal and enthorhinal cortex lesioned monkeys.

Passive avoidance deficits are also consistently reported for

hippocampally damaged animals. Hippocampally lesioned animals appear incapable of withholding a response that is associated with negative reinforcement (Brady and Hunt, 1955; Kimura, 1958; Hunt and Diamond, 1957). For example, Kumura (1958) found that posterior hippocampal lesioned subjects were unable to avoid a food reinforced goal box that had an electrified floor. Kimble (1963) and Teitelbaum and Milner (1963) have reported similar results for rats and cats. Beatty and Schwartzbaum (1968) reported that hippocampally lesioned rats showed deficits on a task which required the suppression of a response. In addition, they reported that the deficits appeared to be independent of motivational changes.

Neurobehavioral Correlates of Intracranial Chemical Stimulation

The following review section is divided into three major categories. First, and by far the most extensively reviewed, are those studies concerned with motivational effects - i.e., food and water behavior - of intracranial chemical injections. The second section is devoted to studies concerned with changes in emotional behavior induced by intracranial chemical stimulation. The final section is concerned with studies which tested the effects of intracranial chemical stimulation on simple and complex behavioral task.

Motivational Effects

In a direct test of the osmometric theory of thirst, Andersson (1952) injected hypertonic salt solutions into the hypothalamus of goats. Within 30 to 90 seconds, the goats began drinking and would consume up to a gallon of water. Andersson stated that the only effective stimulation sites were near the paraventricular nuclei of the medial

diencephalon. In the rat, fibers in the hypothalamus mediating hunger and thirst appear to overlap in the lateral hypothalamus; because, stimulation and ablation of these fibers have been observed to affect both motivational systems (Grossman, 1967). Grossman (1960, 1962a, 1962b) has shown that, at least in the rat, the neural mechanisms underlying hunger and thirst can be biochemically separated by injecting various peripheral neural transmitters and blocking agents directly into the hypothalamus. Injections of cholinergic substances as solutions (Miller et al., 1964) and in crystalline form were shown to elicit vigorous drinking in both satiated and deprived rats. The finding of increased osmolarity and decreased volume of urine with cholinergic stimulation of the lateral hypothalamus of rats provides evidence for cholinergic mediation in the release of antidiuretic hormone, which would be predicted if a cholinergic system normally mediates water regulation in the rat (Miller, 1965).

Further, the cholinergic thirst mechanism is believed to be muscarinic in nature for two reasons. Injections of muscarine, but not nicotine, have been shown to evoke drinking in rats (Stein and Seifter, 1962). Also, atropine, which blocks the muscarinic action of cholinergic substances, has been shown to specifically block cholinergic-induced drinking in the rat (Grossman, 1960, 1962a, 1962b; Stein and Seifter, 1962; Miller, 1965; Levitt and Fisher, 1966). Additional evidence that drinking induced by cholinergic stimulation is mediated by cholinergic synapses comes from the demonstration that injections of eserine into the lateral hypothalamus of rats will result in increased water intake (Miller, 1965). Apparently, esrine inhibits the action of cholinesterase and permits a build up of acetylcholine.

Drinking can also be elicited by cholinergic stimulation of extra-hypothalamic brain areas of the rat. Fisher and Coury (1962, 1964) and Coury (1967) have chemically traced neural pathways mediating thirst in the rat. The cholinergic neural system includes many limbic system structures and their various interconnections. Cholinergic stimulation of the septum (Grossman, 1964b; Greene, 1968), anygdala (Grossman, 1964a; Singer and Montgomery, 1968), hippocampus (Coury, 1967; Macphail, 1968) and the interconnections of these major limbic system structures (Fisher and Coury, 1962) results in increased water intake.

Adrenergic stimulation of the lateral hypothalamus of rats has been shown to elicit eating and result in decreased drinking (Grossman, 1962a; Miller, 1965). Due to the apparent overlap of fibers involved in eating and drinking, hypothalamic sites that show increased eating due to adrenergic stimulation are generally the same anatomical loci that result in cholinergic-induced drinking (Grossman, 1962a, 1962b; Miller, 1965).

Booth (1968) conducted a study that provided additional information about the actual mechanism underlying adrenergic-elicited eating in the rat to the earlier research of Grossman (1962a, 1962b) and Miller (1965). By combining radioactive tracer procedures, pharmacology, biochemical assays, semimicro cannulaes and behavioral measures, Booth reached the following conclusions about the adrenergic mechanism underlying adrenergic-elicited eating in the rat. First, the eating response appears to be molecularly specific in that l-norepinephrine and l-epinephrine give eating responses of similar intensity. Injections of dL-norepinephrine, amphetamine, ephedrine, phenylephrine, histamine and other control substances resulted in negligible food consumption. Dopamine and 5-hydroxytryptamine gave small and delayed effects on eating behavior and

indicate a possible involvement of these catecholamines in adrenergic-induced eating. Phenoxybenzamine and phentolamine, both powerful adrenergic alpha blocking agents, prevented the eating response to norepinephrine stimulation; whereas, propranolol, a beta adrenergic blocking agent, was found ineffective in blocking adrenergic-induced eating. Radioactive labelled norepinephrine was found to be present in sedimentable subcellular fractions by the time rats had begun eating. In conclusion, Booth stated that alpha adrenergic modulation of postsynaptic activity by norepinephrine from nerve endings is involved in the hypothalamic control of feeding in the rat.

However, not all the studies reported in the literature involving chemical stimulation and motivational variables present consonant results with the notion of reciprocally inhibitory chemical systems that regulate food and water behavior. Myers (In: Wayner, 1964), for example, reported that low doses of cholinergic compounds injected into the "drinking center" of rats resulted in eating, sleeping, and a number of motor responses in addition to the usual behavioral response of drinking. Adrenergic stimulation was found to elicit drinking more often than eating. Myers pointed out that his contradictory results may be explainable in terms of regions stimulated, possible differences in strains of rats, or variability of results within a certain species. Besides the possiblity of within species variability, the between species differences have further limited the generalization of neurochemical coding of behavior. For example, Sommer et al. (1966) found that increased eating and drinking was elicited by cholinergic stimulation of the lateral hypothalamus of rabbits. Myers (1968) found that adrenergic stimulation of the lateral hypothalamus of monkeys elicited eating and usually drinking,

but cholinergic stimulation of the same and related regions of the hypothalamus inhibited both eating and drinking behavior. Of the numerous studies involving chemical stimulation of the cat, none have reported any changes in rates of food and water intakes (Hernandez-Peón et al., 1963; Myers, 1964; Macphail and Miller, 1968). As pointed out by Myers (1968), theoretically, the problem of species differences and chemical coding of behavior are most troublesome. If an evolutionary irregularity arises each time a new specie is investigated, a separate volume describing the neurochemistry of each and every Genus will have to be written.

Emotional Behavior

Several studies have reported changes in emotional behavior along with alterations in sleep, arousal and general activity measures resulting from intracranial chemical injections. Hernandez-Peón et al. (1963) reported that cholinergic stimulation of a circumscribed region of the cat brain resulted in light or deep sleep; whereas, adrenergic stimulation of various brain areas resulted in alertness. Alertness and hyperactivity were also found with several cholinergically stimulated sites, but a hypnogenic effect was never found with adrenergic stimulation. In contrast with the findings of Hernandez-Peón et al. (1963), Myers (1964) reported that cholinergic stimulation of the hypothalamus of cats resulted in fear-like responses, withdrawal, growling, and crouching. Higher doses of cholinergic substances resulted in only more exaggerated responses. Pupil dilation, salivation, spitting and attack behavior was also reported with cholenergic stimulation, and no hypnogenic effects from cholinergic stimulation were reported. Adrenergic stimulation, on

the other hand, was found to elicit a hypnogenic type of response. Apparent muscle weakness, drowsiness, ataxia, pupil constriction, and an anaesthetic-like sleep state were induced by adrenergic stimulation of the hypothalamus of cats. Likewise, Macphail and Miller (1968) found only an affective defense reaction with cholinergic stimulation of the cat, and they reported no evidence for sleep or hynogenic-type of behavior. Nashold et al. (1965) found that cholinergic stimulation of selected regions of the brainstem of the cat resulted in various autonomic responses such as defecation, salivation, and urination. With injections of resperine the cats became calm and would set motionless for long periods of time. Cholinergic stimulation of the midbrain reticular formation of rats was shown to result in increased emotionality in an escape and avoidance conditioning situation and in increased locomotor activity (Grossman, 1968). Further, a lowered reactivity to environmental stimuli and a decrease in locomotor activity was found when adrenergic substances were injected into the same regions of the midbrain reticular formation. Cholinergic stimulation of the medial septum of rats was shown to increase locomotor activity in an open field situation (Greene, 1968). Cholinergic stimulation of the hippocampus of unrestrained cats resulted in a pleasure reaction similar to that elicited by electrical stimulation (MacLean, 1957). MacLean (1957), however, suggested that both modes of stimulation may have induced seizures and disrupted normal hippocampal activity. In further support of a "disruption" explanation, Delgado and Kitahata (1967) have observed that local injections of anesthetics into the hippocampus of monkeys resulted in increased tameness and other behavioral signs of hippocampal lesions.

Simple and Complex Behavioral Tasks

Several studies testing the behavioral effects of intracranial chemical injections have utilized acquisition and retention performance on appetitive, avoidance and discrimination tasks. Khavari and Russell (1966), for example, found that for rats, cholinergic-induced drinking and water deprivation were equally effective in motivating acquisition of a runway and a t-maze task. Grossman (1965) reported that cholinergic stimulation of the midline thalamic nuclei of rats retarded acquisition of a shuddle-box avoidance task, but found no effects on asymptotic performance. When the thalamic reticular nuclei were cholinergically stimulated, acquisition and asymptotic performance were depressed. Cholinergic stimulation of both thalamic nuclei reduced exploratory behavior and impaired performance of a previously acquired bar-pressing response. Cholinergic blockage of the thalamic reticular nuclei of rats with atropine resulted in impaired acquisition and asymptotic performance in appetitive and aversive training situations (Grossman and Peters, 1966). It is of interest, however, that cholinergic stimulation and blockage of the thalamic nuclei of rats showed identical behavioral effects. Grossman (1967) stated that "... this pattern of results (similar behavioral effects of chemical stimulation and inhibition) suggests that the reticular nuclei may provide an essential link in the pathways responsible for learning and/or retention." Application of atropine to the thalamic midline nuclei of rats had a facilitory effect on performance in both the appetitive and aversive conditioning situation (Grossman and Peters, 1966) which is opposite from the behavioral effects of cholinergic stimulation of the midline nuclei (Grossman, 1965).

Cholinergic stimulation of the midbrain reticular formation of rats

was found to impair acquisition and retention of appetitively conditioned maze and bar pressing behavior (Grossman and Grossman, 1966). Daily cholinergic injections had a less dramatic effect on behavior than the initial or infrequently repeated stimulations. In a conditioned avoidance task, initial and infrequently administered cholinergic stimulation of the midbrain reticular formation of rats resulted in a performance deficit (Grossman, 1966). The rats failed reliably to respond to the conditioned stimulus and, frequently, would not respond appropriately to a prolonged noxious stimulus. With frequently repeated cholinergic stimulations, the subjects were found to respond faster and more reliably to the conditioned stimulus than the control groups.

Grossman (1968) has recently extended his research on the behavioral effects of adrenergic and cholinergic neurohumors on the midbrain reticular formation of rats. The behavioral effects of adrenergic and cholinergic stimulation and blockage were tested in various appetitive tests (brightness discrimination, 2-lever operant responding) and aversive tests in which the level of shock was varied. In general, Grossman (1968) found that cholinergic stimulation of the midbrain reticular formation resulted in an increased reactivity to environmental stimuli. Both neurohumors were found to interfere with acquisition and performance in the appetitive test situations. In the conditioned avoidance situation, on the other hand, cholinergic stimulation improved conditioning and performance in the low-shock test situation. Adrenergic stimulation, on the other hand, improved performance in the high-shock situation, but lowered responding in the low-shock stiuation. The behavioral effects were explained in terms of differential shifts in the organism's responsiveness to sensory information with the direction of change being

chemically specific.

Chemical manipulation of several limbic system brain areas have resulted in alterations in acquisition and performance of different behavioral tasks. Grossman (1964) found that cholinergic stimulation of the septal region of rats impaired the performance of a previously acquired avoidance response and inhibited the acquisition of a new avoidance response. Cholinergic blockage of the septum with atropine resulted in improved performance of a previously acquired avoidance response. Likewise, adrenergic stimulation of the septum resulted in improved avoidance behavior. In a comparison between cholinergic blockage and lesioning of the septal region of cats, Hamilton et al. (1968) found that cholinergic blockage produced only some, but not all, of the behavioral effects of septal lesions. For example, a deficit in passive avoidance and poorer performance during the extinction of a generalized avoidance response were found with cholinergic septal blockage. However, cholinergic septal blockage had no reliable effects on a position habit reversal or acquisition of a 1-way avoidance task-behavioral tasks which are usually affected by septal lesions. Avery (1969a) found that both adrenergic and cholinergic stimulation of the medial septal region of cats produced a significant decrease in milk-rewarded bar pressing. Margules (1968) found that the behavioral-suppressant effects of punishment were removed by adrenergic stimulation of the amygdala of rats. Injections of atropine into the amygdala produced a decrease of milk-rewarded operant responding. Margules suggested that there are adrenergic inhibitory synapses in the amygdala of rats which attenuate the behavioral-suppressant effects of punishment and cholinergic synapses which increase the behavioral-facilitatory effect of reward.

A reduction in the suppressant effect of punishment on appetitive operant behavior was found with cholinergic blockage of the ventromedial hypothalamus of rats (Margules and Stein, 1969). An increase in spontaneous activity and a reduction in the suppressant effects of food satiation on appetitive operant behavior were also observed. Margules and Stein (1969) suggested that there are cholinergic synapses in the ventromedial hypothalamus and related regions of rats for the suppression of operant behavior by punishment and satiation.

Avery (1969a, 1969b) studied the effects of adrenergic and cholinergic stimulation of the centre median nucleus of the thalamus and dorsomedial hippocampus of cats on fixed ratio five bar pressing and complex visual discrimination tasks. Since the behavioral testing situations and brain areas stimulated by Avery were identical to those in the present study, Avery's results will be presented in detail. In Figure 1, the effects of chemical stimulation and fixed ratio five bar pressing performance are presented (Avery, 1969b). The data are shown in terms of the mean number of reinforcements. The performance on the day of injection (injection day) and 24 hours later (postinjection day) were compared with the control(preinjection) day's performance.

As shown in Figure 1, an intracranial injection of norepinephrine into the centre median nucleus of the thalamus significantly ($p < .01$) increased the amount of FR-5 bar pressing on the day it was injected. Responding remained significantly ($p < .05$) elevated during the postinjection day. Cholinergic stimulation of the centre median nucleus of the thalamus produced a significant ($p < .01$) decrease in FR-5 bar pressing on the day it was injected, but the amount of bar pressing on the postinjection day was nonsignificantly different from the preinjection

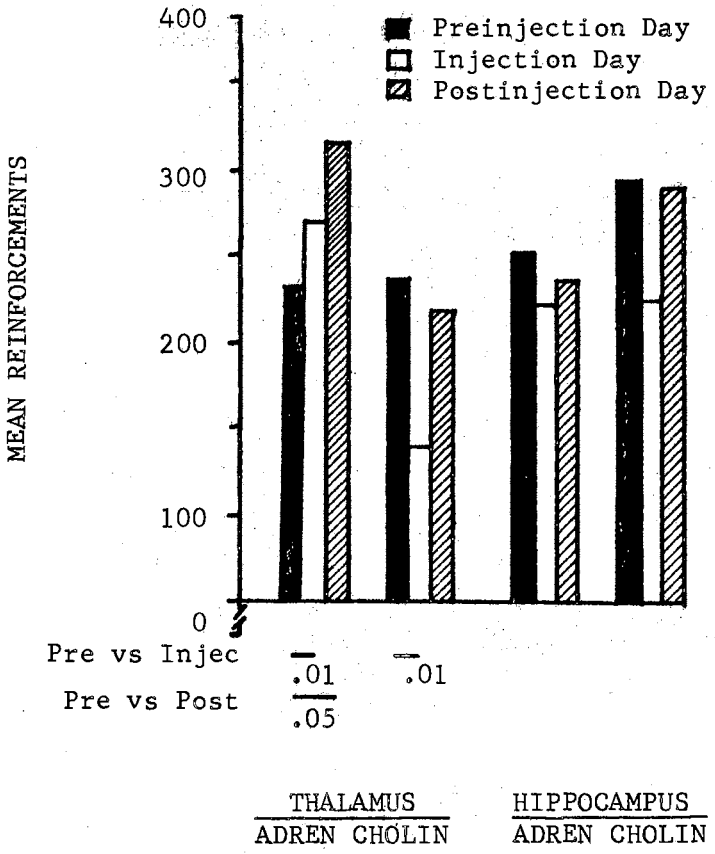

Figure 1. Effects of Adrenergic and Cholinergic Stimulation of the Thalamus and Hippocampus on FR-5 Bar Pressing

day's performance. Although a mean decrease in bar pressing was observed (Figure 1) with both modes of stimulation, adrenergic and cholinergic stimulation of the dorsomedial hippocampus did not reliably affect FR-5 bar pressing performance.

The complex visual discrimination situation was a successive go/no-go discrimination task. Subjects were given milk reinforcement for each bar press during a 10 sec. reinforcement period (S^D) which was signaled by a 7 cycle/sec. flashing light. Each reinforcement period was separated by a variable interval 30 sec. intertrial period in which bar pressing was not reinforced. Each subject had a total of 50 trials a day. The response measures, total responses (TR), intertrial responses (ITR), reinforced responses (S^DR) and discrimination ratio (S^DR/ITR) are presented in Figure 2 and Figure 3 in terms of the percentage mean increase or decrease in responses from the preinjection, baseline day. As shown in Figure 2, cholinergic stimulation of the centre median nucleus of the thalamus produced a significant decrease in the number of reinforced responses, and resulted in significantly ($p < .05$) poorer visual discrimination performance as reflected by the decrease in the S^DR/ITR ratio. Adrenergic stimulation of the centre median nucleus of the thalamus with norepinephrine did not reliably affect any of the response measures.

As shown in Figure 3, Avery (1969a) found that on the go/no-go visual discrimination task, cholinergic stimulation of the dorsomedial hippocampus resulted in a significant ($p < .01$) decrease in the total number of responses and a significant ($p < .05$) decrease in the number of intertrial responses. A trend ($p < .10$) toward a decrease in the number of reinforced responses was observed. Six of the eight subjects

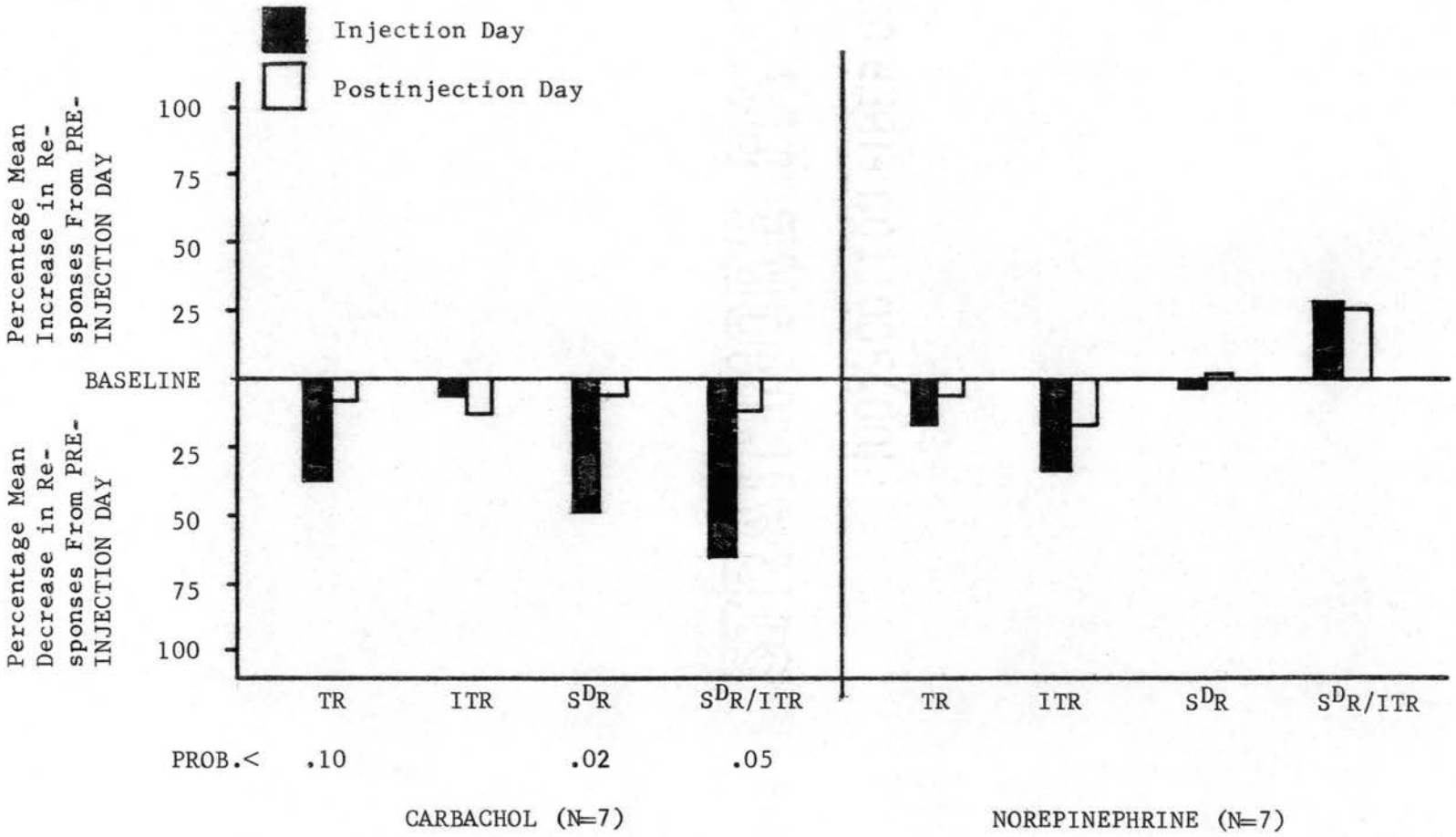

Figure 2. Effects of Adrenergic and Cholinergic Stimulation of the Thalamus on Go/No-Go Visual Discrimination

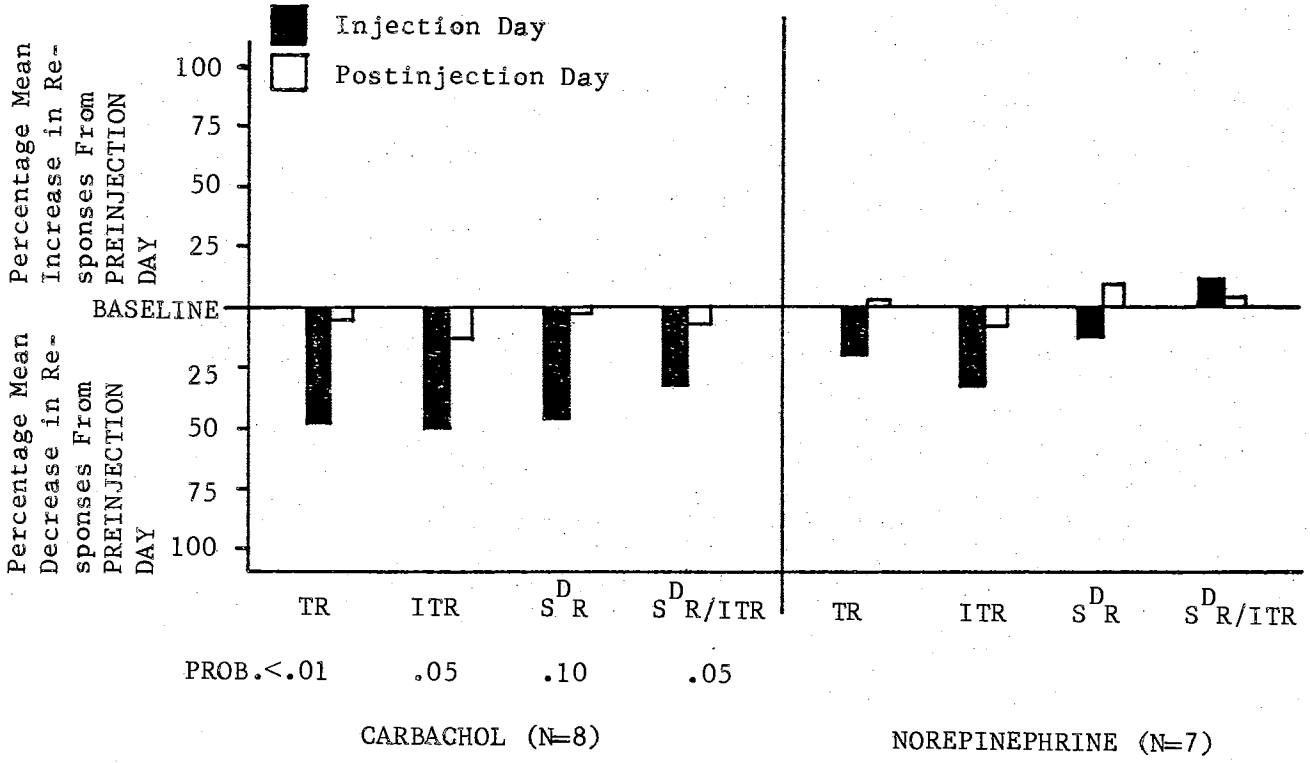

Figure 3. Effects of Adrenergic and Cholinergic Stimulation of the Hippocampus on Go/No-Go Visual Discrimination

showed a decrease in their S^DR/ITR ratio, which is shown graphically as as significantly ($p < .05$) poorer visual discrimination performance. Adrenergic stimulation of the dorsomedial hippocampus had no reliable effects on any of the response measures. Also (Figure 3) better visual discrimination by five of the seven subjects is shown in the increase in the S^DR/ITR ratio.

In conclusion, a variety of motivational and behavioral measures have been found to be sensitive to chemical alterations in specific regions of the mammalian brain. Although of an indirect nature, the studies reviewed indicate adrenergic and cholinergic substances are very likely candidates for central neural transmitters.

Statement of the Problem

Based upon the evidence which indicates adrenergic and cholinergic substances are possible central neural transmitters, the present study was conducted to investigate the behavioral effects of direct chemical stimulation and blockage of the cat's brain with these prospective central transmitters. Two behavioral situations, a fixed ratio five bar pressing task, and a go/no-go visual discrimination task, were used to test the effects of intracranial chemical stimulation of three brain areas of the cat.

Avery (1969a) has previously tested the effects of adrenergic and cholinergic stimulation of the centre median nucleus of the thalamus and dorsomedial hippocampus of cats in identical behavioral situations. The effects of adrenergic and cholinergic blockage of the centre median nucleus of the thalamus and dorsomedial hippocampus were tested in the fixed ratio five and go/no-go visual discrimination situations. Further,

since prior research has not been reported in the literature for cats, the effects of adrenergic and cholinergic stimulation and blockage on the lateral hypothalamus were tested in the fixed ratio five and go/no-go visual discrimination situation.

CHAPTER III

METHODS AND PROCEDURE

Subjects

The subjects were 14 mature, male and female, mongrel cats which weighed between five and ten pounds. The animals were individually housed in stainless steel cages located in the vivarium of the Department of Psychology, University of Houston. Each subject was given pneumonitis vaccine and feline distemper injections two weeks prior to surgery. Subjects were maintained on Purina Dry Cat Food throughout the study.

Cannulae

Double walled stainless steel cannulae were constructed as follows: The external cannula was made from a 2½ in, 20 gauge stainless steel hypodermic syringe needle and the internal brass part of a Harris-type #211 banana plug. A small piece of teflon tubing was glued to one end of a 20 gauge needle with Eastman 910 adhesive. The teflon tubing provided a spacer between the needle and the brass piece. The needle was then glued to the teflon spacer. The external cannula length could be varied by cutting the end of the tubing. An internal injection cannula was made from a 24 gauge stainless steel hypodermic syringe needle, a small brass jeweler's spacer, and a small piece of 20 gauge stainless steel tubing. The jeweler's spacer served as a stop so that the internal injection cannula extended 4 mm beyond the tip of the external cannula.

The small piece of 20 gauge tubing was glued above the spacer to the 24 gauge tubing. This assured a snug fit between the injection cannula and the polyethylene tubing which was attached to a microsyringe.

Surgery

All surgical instruments and stereotaxic components were washed in Phisohex antiseptic soap and placed in a 0.13% solution of Zephiran chloride twelve hours prior to surgery. The anesthetic was a 65% solution of pentobarbitol sodium. One ml per five pounds body weight was injected into the liver or peritoneal cavity of the cat and three to 10 min were required for anesthetization.

Following anesthetization, the scalp was shaved with electrical animal clippers and cleaned with Phisohex and alcohol. A local anesthetic, 2 ml of a 2.5% solution of procaine hydrochloride, was injected subcutaneously. The animal was then positioned in a Johnson cat stereotaxic instrument (Avery, 1969a).

The underlying cranial bone was exposed by making a 40 mm medial-sagittal incision and scrapping the periosteum laterally. Gauze sponges were placed subcutaneously on either side of the exposed cranium to retract the superior temporal musculature. The cranium was cleansed with normal saline and dried.

The stereotaxic placements were marked unilaterally on the left hemisphere. Then, the skull was trephined with a dental burr, and three cannulae were implanted in the left brain hemisphere. The stereotaxic coordinates and brain placements, as determined from an atlas by Reinoso-Suarez (1961), were as follows: lateral hypothalamus, 3.5 mm lateral, 12.0 mm anterior-posterior, 8.0 mm horizontal; centre median nucleus of

the thalamus, 3.5 mm lateral, 6.5 mm anterior-posterior, 11.0 mm horizontal; and dorsomedial hippocampus, 8.0 mm lateral, 2.5 mm anterior, 14.0 mm horizontal. The zero reference point was the interaural canal.

Two additional holes were trephined anterior and posterior to the three cannula placements. The small holes were tapped, and stainless steel anchor bolts were inserted. Nu-Weld dental acrylic, purchased from Pendleton Auto of Houston, Texas, was used in bonding the cannulae to the skull. The incision was finally sutured anteriorly and posteriorly to the dental acrylic. Postoperatively, an injection was given of 300,000 units of veterinary dystricillan, purchased from Pioneer Veterinary Supply of Houston, Texas.

Chemicals

Adrenergic stimulation and blockage were provided by L-norepinephrine bitartrate hydrate and ethobutamoxane, respectively. Cholinergic stimulation and blockage were induced by carbaminocholine (carbachol) and atropine sulfate, respectively. All chemicals were dissolved in a Locke-Ringer buffer suolution (Goodman and Gilman, 1965). The concentration used for each drug was determined on the basis of (1) the solubility characteristics of the various chemicals, (2) results of previous research (Avery, 1969; Halloway, 1966), and (3) by preliminary pilot work. On a weight-volume basis, one gram of solute per 100 ml of solvent equals 1.0%. The concentrations utilized in the experiments were as follows: 4.0% norepinephrine, 1.35% ethobutamoxane, 0.05% carbachol, and 5.0% atropine sulfate. If stated in terms of micrograms of drug per microliter of solution, the various amounts were 40 λg norepinephrine per λL, 13.5 λg ethobutamoxane per λL, 0.5 λg carbachol per λL, and

50 λg atropine sulfate per λL. The ethobutamoxane was provided by Eli Lilly and Co., Indianapolis, Indiana. All other drugs were purchased from K & K Laboratories, Inc., Plainview, New York.

Experimental Apparatus

Microsyringe

A Hamilton 100 microliter syringe #710 was used to inject measured amounts of the various drugs. A vernier calibrated micrometer manipulator and the microsyringe were mounted in a metal stand which allowed measured quantities as small as 1 λL to be injected. A polyethylene tube two feet in length connected the microsyringe and injection cannula.

Testing Chamber

The testing chamber was constructed from white Formica and measured 48x30x30 in. One side was a one-way glass allowing observation of the animal during testing. The chamber was sound resistant and equipped with electrical shielding. Two d-c lights, controlled by a Foringer program board provided illumination. One of the d-c lights was the photic stimulus and was located in a port at one end of the chamber. Located directly below the photic port was a Skinner-type bar and liquid feeder. Located directly above the photic port was an audio speaker.

Liquid Feeder System

A gravity-fed siphon liquid feeder system controlled by a Skinner electric valve allowed measured amounts of liquid reinforcer to be delivered to the feeding cup directly in front of the bar. The value was controlled by a 24 volt d-c microswitch connected to the bar. In

addition, the valve could be operated manually from the Foringer program board or be programmed for various reinforcement schedules or behavioral task. Activation of the solenoid valve caused 0.3 mL of liquid to enter the feeding cup.

Photic Stimulator

A Grass model PS2 photic stimulator, located with the Foringer program board in a room adjacent to the testing chamber, controlled the photic stimulus. The short duration flashes could be varied in intensity and frequency per unit time. A frequency setting of 7 cycle/sec was held constant through-out the experiment.

Control and Recording Apparatus

Foringer and Grayson-Stadler operant behavior equipment controlled all reinforcement contingencies and stimulus inputs into the experimental chamber. A Rheem tape reader, which could read five-, seven-, and eight-channel tape, programmed the reinforcing contingency. The complete series of reinforcing contingencies were contained on perforated tape. Responses during the various trail periods and cumulative total responses were automatically recorded on digital counters.

Experimental Procedure

Preliminary Training - Experiment I

Two days prior to training, subjects were placed on a 23 - ½ hour food and water deprivation schedule. After the initiation of training and throughout both experiments, subjects received free access to food and water for 30 minutes following each daily testing session.

Canned Pet evaporated mild (diluted 1:1 with tap water) served as the liquid reinforcement throughout the study. A small plexiglass shaping box which limited movements and helped orient the subjects to the bar and feeder cup was introduced into the experimental chamber during bar press training. By a process of successive approximations, subjects were gradually shaped to bar press for the milk reinforcement. Until a shaping criterion of two series of 20 consecutive bar presses occurred, a 400 cps tone accompanies delivery of the reinforcer. Upon reaching the shaping criterion, the shaping box was removed, the 400 cps tone was discontinued, the chamber illumination was lowered, and a continuous reinforcement bar press schedule was introduced.

The subjects were then gradually shaped to a FR-5 bar press schedule in the following manner: On Day 1, after they had reached the shaping criterion, the subjects were given 10 min of CR responding and 20 min of a FR-3 reinforcing schedule. Thereafter, on Day 2, the reinforcing schedule was as follows: CR for 10 min, FR-3 for 10 min, and FR-5 for 10 min. On Day 3, the subjects bar pressed for 10 min on a FR-3 and, then, 20 min on a FR-5 reinforcement schedule. On Day 4 and on subsequent days in Experiment I, each subject was given a daily 30 min FR-5 bar press session.

Experiment I

Response measures consisted of the total number of reinforcers the subject received during each daily 30 min testing session and the amount of food and water consumed during the 30 min feeding period following each daily testing session.

Each subject was statistically used as its own control. Given

stabilized bar press performance and stable food and water intakes, the day before an intracranial chemical injection was used as a baseline for testing the effects of chemical stimulation. The chemical stimulation day performance and the post-stimulation day performance were compared with the baseline performance. Before chemical manipulation of various brain structures was begun, subjects had a stabilized response rate on the FR-5 schedule and stabilized food and water intake.

On preinjection, baseline days and on postinjection days, the stainless steel dummy was removed and reinserted into the cannula placement being stimulated on test or chemical injection day. However, on chemical injection days, the procedure was as follows: (1) the internal dummy cannula was removed; (2) the injection cannula was inserted and 2 λL of solution was injected; (3) after approximately one minute, the injection cannula was removed and the dummy cannula was reinserted; (4) the subject was placed in the experimental chamber.

Adrenergic and cholinergic blockage, induced by ethobutamoxane and atropine sulfate, respectively, was tested in the lateral hypothalamus, centre median nucleus of the thalamus and dorsomedial hippocampus. Adrenergic and cholinergic stimulation, induced by norepinephrine bitartrate hydrate and carbachol, respectively, was tested for the lateral hypothalamic placement.

Preliminary Training - Experiment II

During Experiment II, the procedure of 30 minutes of free access to food and water following the daily testing session was continued. Daily food and water intakes were measured daily.

The Rheem tape reader controlled all trials on the go/no-go visual

discrimination task. Trials were separated on a variable interval schedule with a mean intertrial interval of 30 sec, range 27.5 - 33.5 sec. On each trial, a 10 sec reinforcement interval was signaled by a 7 cycle/sec flashing light (S^D trial). During the S^D period, every bar press was reinforced by 0.3 mL of milk. All other bar presses (intertrial) were considered errors and were not reinforced.

Each subject received 50 consecutive daily trials. If as many as 3 errors occurred during the intertrial interval 10 seconds immediately preceeding the S^D period, a reset timer was activated. The subject then had to wait an additional 10 seconds for the reinforcing period.

The following daily response measures were taken: (1) total number of responses, (2) total number of S^D or reinforced responses, (3) total number of intertrial or nonreinforced responses, (4) the discrimination ratio, computed as number of S^D responses divided by the number of intertrial responses, and (5) food and water intake during the 30 min feeding period following the daily test.

Experiment II

The injection and control procedures used were the same as those used in Experiment I. Each subject was allowed to reach a stable level of discrimination, as computed by the discrimination ratio, before intracranial chemical injections were begun. Again, each subject was used as its own control, and the various response measures for the injection day and postinjection day were compared with the preinjection or baseline measures. Daily measures were taken of the following: (1) total responses, (2) S^D responses, (3) intertrial responses, (4) S^DR/ITR ratio, and (5) food and water intakes.

CHAPTER IV

RESULTS

Histological Evaluation

At the conclusion of the experiments a histology was performed on the brains of all 14 subjects. Each subject was perfused through the left ventricle of the heart with saline and 10% formalin. Following decapitation, the heads were immersed in 10% formalin for 24 hours. Each head was then placed in a cat stereotaxic instrument. The top of the skull was removed and blocks of brain tissue were sliced and removed. The blocks of tissue were frozen on a CO_2 freezing microtome stage, and brain sections of approximately 100 microns diameter were made. The brain slices were then floated in water on glass slides, and the anatomical placements of the cannula tips were determined. Brain sections were also stained with hematoxylin stain solution and counter-stained with cresyl violet stain solution to aid in additional evaluation of the cannula placements.

Six subjects were observed to have proper cannula placements in the lateral hypothalamus. Seven subjects had cannula placements in the centre median nucleus of the thalamus, and ten subjects had cannulas in the dorsomedial hippocampus. Subsequently, the behavioral results were appropriately grouped and analyzed according to the anatomical placements; lateral hypothalamus, centre median nucleus of the thalamus and dorsomedial hippocampus.

Behavioral Observations

During pilot research, the concentrations of the various chemicals were adjusted so that no overt behavioral changes occurred during chemical stimulation of the various brain structures. For example, a 2 λL solution of 0.8% carboachol injected into the lateral hypothalamus resulted in affective defense reactions which included growling, hissing, pupil dilation, and piloerection. A 2 λL injection of 0.1% carbachol in the lateral hypothalamus resulted in affective defense reactions approximately 10% of the time. However, a concentration of 0.05% carboachol was found to elicit no overt behavioral changes other than those measured by Experiments I and II. Thus, a 0.05% solution of carbachol was used in Experiment I and Experiment II.

Experiment I

The effects of adrenergic and cholinergic stimulation, blockage of the lateral hypothalamus, and adrenergic and cholinergic blockage of the centre median nucleus of the thalamus and dorsomedial hippocampus on fixed ratio five bar pressing behavior were analyzed by a correlated, 1-tail, t-test (Winer, 1962). The total reinforcements received on the preinjection, baseline day were compared with the total reinforcements subjects received on the injection and on the postinjection days.

Lateral Hypothalamus

Figure 4 presents the effects of adrenergic and cholinergic stimulation and blockage of the lateral hypothalamus on the mean number of reinforcements subjects received during 30 minute periods of FR-5 bar pressing. The mean number of reinforcements the subjects received on

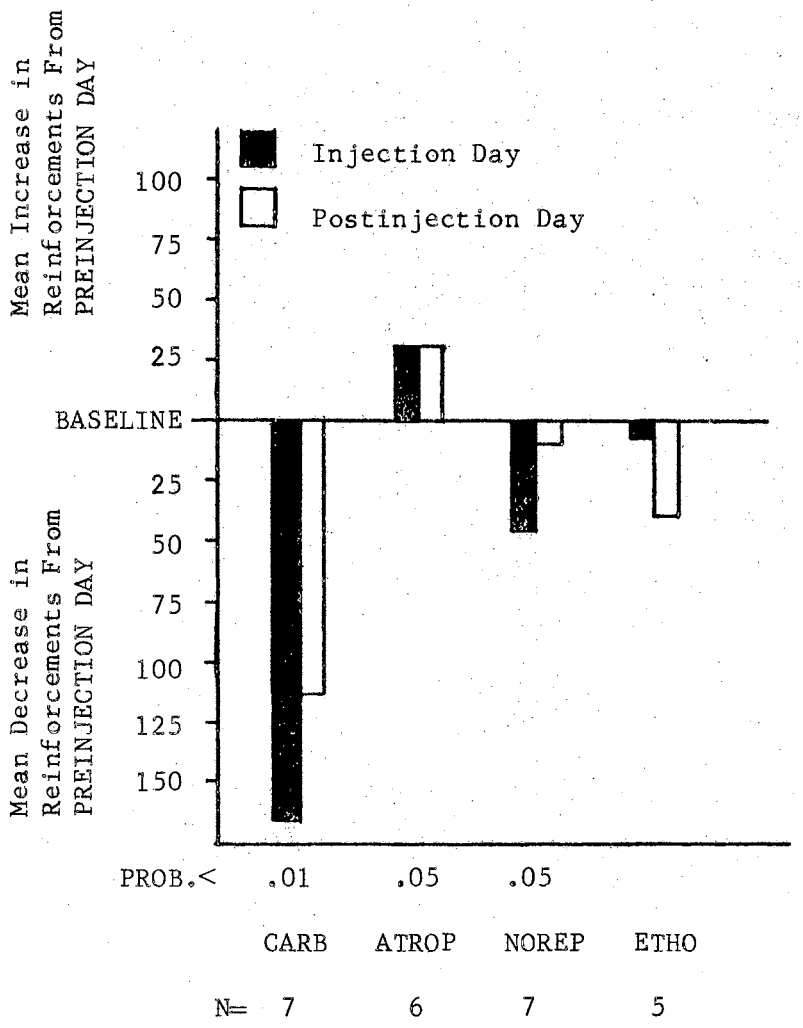

Figure 4. Effects of Adrenergic and Cholinergic Stimulation and Blockage of the Lateral Hypothalamus on FR-5 Bar Pressing

the injection and postinjection days is presented in terms of the mean increase or decrease in reinforcements from the preinjection, baseline day (Figure 4).

As summarized in Figure 4, an injection of two λL of 0.05% carbachol into the lateral hypothalamus resulted in a significant ($t = 3.27$, 6 df; $p < .01$) decrease in FR-5 bar pressing on the day of injection. On the postinjection day, bar pressing was still significantly ($t = 2.26$, 6 df; $p < .05$) lower than on the control, preinjection day.

Atropine, which blocks cholinergic neural transmission, produced a significant ($t = 2.44$, 5df; $p < .05$) increase in the amount of bar pressing on the FR-5 schedule on the injection day when compared with the control (preinjection) day. Bar pressing was also significantly ($t = 2.14$, 5 df; $p < .05$) greater on the postinjection day than on the preinjection day.

An intracranial injection of norepinephrine into the lateral hypothalamus resulted in a significant ($t = 2.09$, 6 df; $p < .05$) drop in the amount of bar pressing on the injection day. On the postinjection day, the amount of bar pressing was not significantly different from the preinjection level.

Although a mean decrease in responding on injection and postinjection days was present, relative to the preinjection day, adrenergic blockage of the lateral hypothalamus by ethobutamoxane resulted in no significant change in the amount of FR-5 bar pressing.

Centre Median Nucleus of the Thalamus

On injection day (Figure 5) cholinergic blockage of the centre median nucleus of the thalamus by atropine resulted in a significant

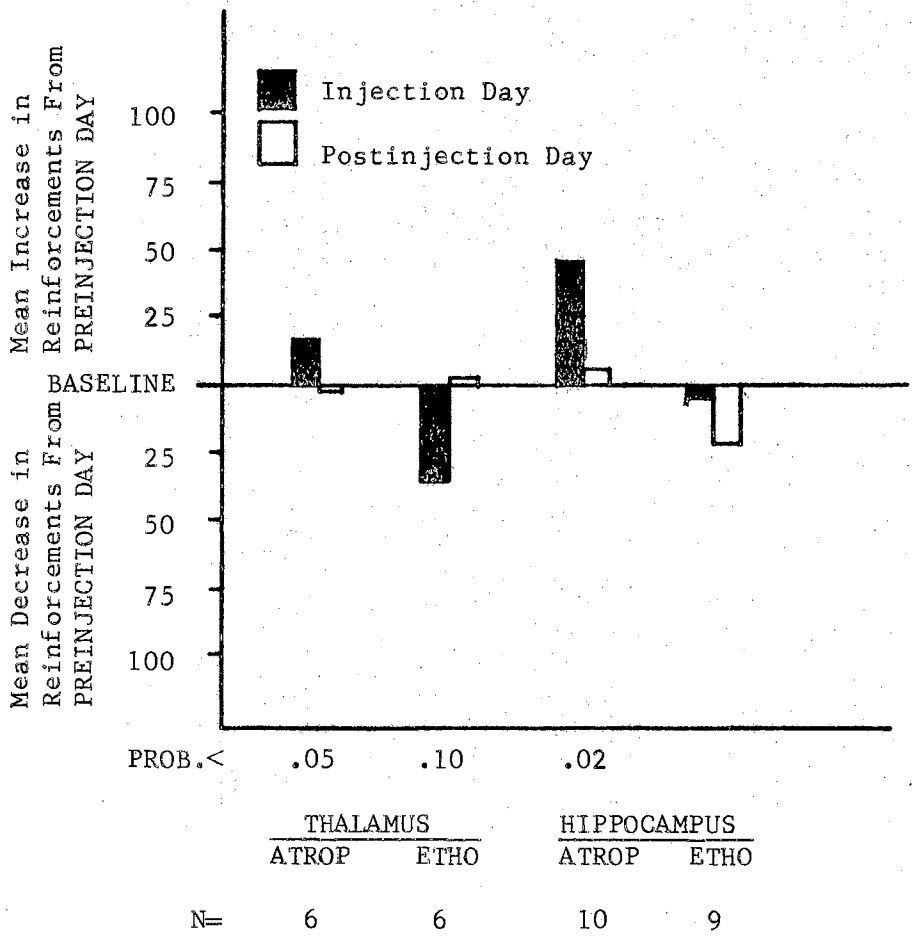

Figure 5. Effects of Adrenergic and Cholinergic Blockage of the Thalamus and Hippocampus on FR-5 Bar Pressing

($t = 1.98$, 5 df; $p < .05$) rise in the amount of FR-5 bar pressing. Atropine had no significant effect on bar pressing on the postinjection day.

Adrenergic blockage of the centre median nucleus of the thalamus with ethobutamoxane did not statistically affect bar pressing behavior.

Dorsomedial Hippocampus

As shown in Figure 5, an injection of atropine resulted in a significant ($t = 2.36$, 9 df; $p < .02$) increase in the amount of FR-5 bar pressing on the injection day. Performance on the postinjection day was not reliably affected by cholinergic blockage. Adrenergic blockage with ethobutamoxane was not observed to have reliable effects on FR-5 bar pressing behavior.

Experiment II

Total responses (TR), intertrial responses (ITR), reinforced responses (S^DR), and response ratio (S^DR/ITR) were independently analyzed using the Friedman Two-Way Analysis of Variance by Ranks (Siegel, 1956). Each of the foregoing response measures is presented graphically in Figures 6-9 in terms of the percentage mean increase or decrease in responses from the preinjection, baseline day.

Lateral Hypothalamus

The percentage mean increase or decrease in the various response measures with cholinergic and adrenergic stimulation of the lateral hypothalamus is shown in Figure 6. Cholinergic stimulation produced a significant ($p < .05$) decrease in the total number of responses and a significant ($p < .05$) decrease in the intertrial responses on the

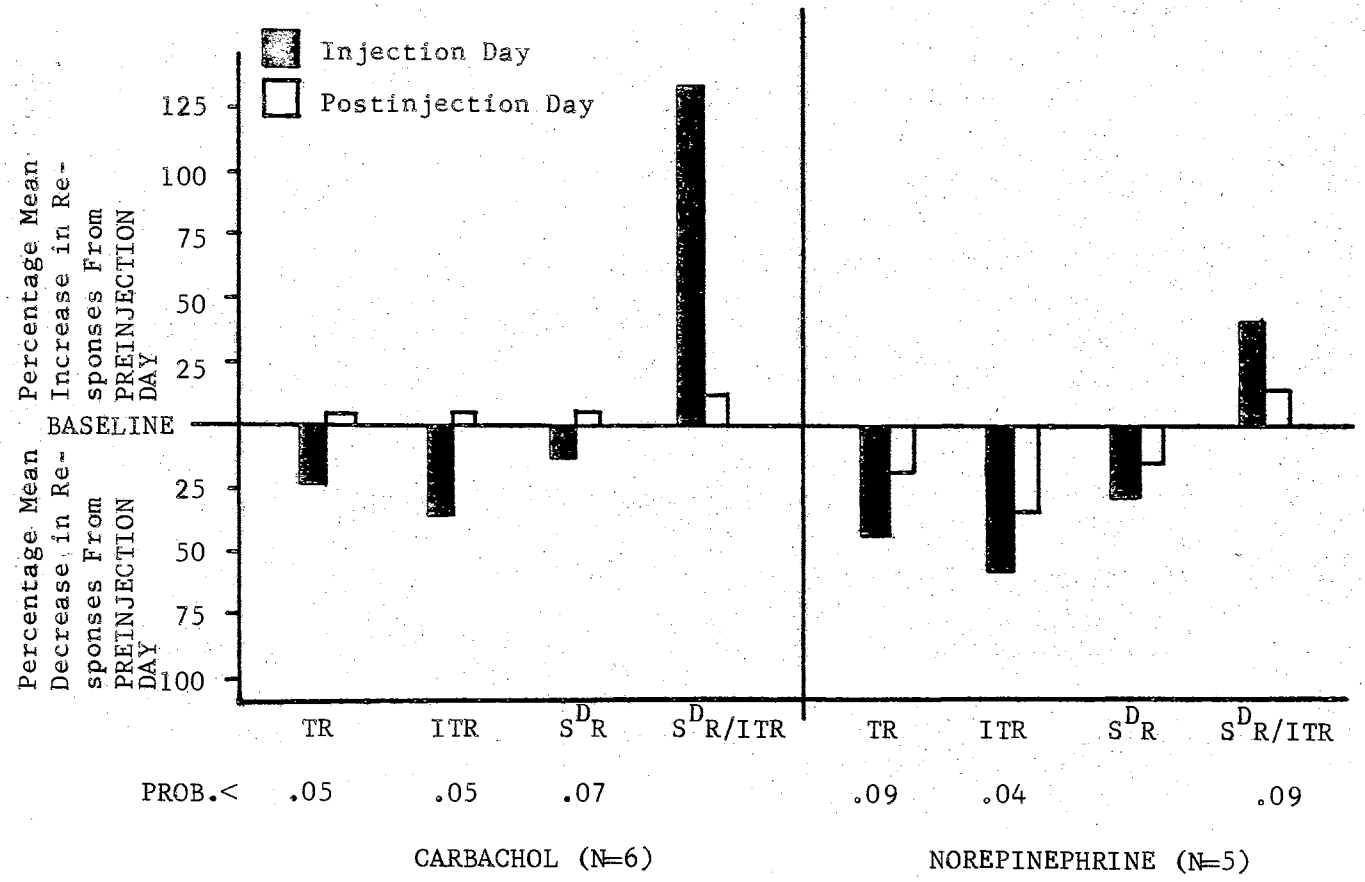

Figure 6. Effects of Adrenergic and Cholinergic Stimulation of the Lateral Hypothalamus on Go/No-Go Visual Discrimination

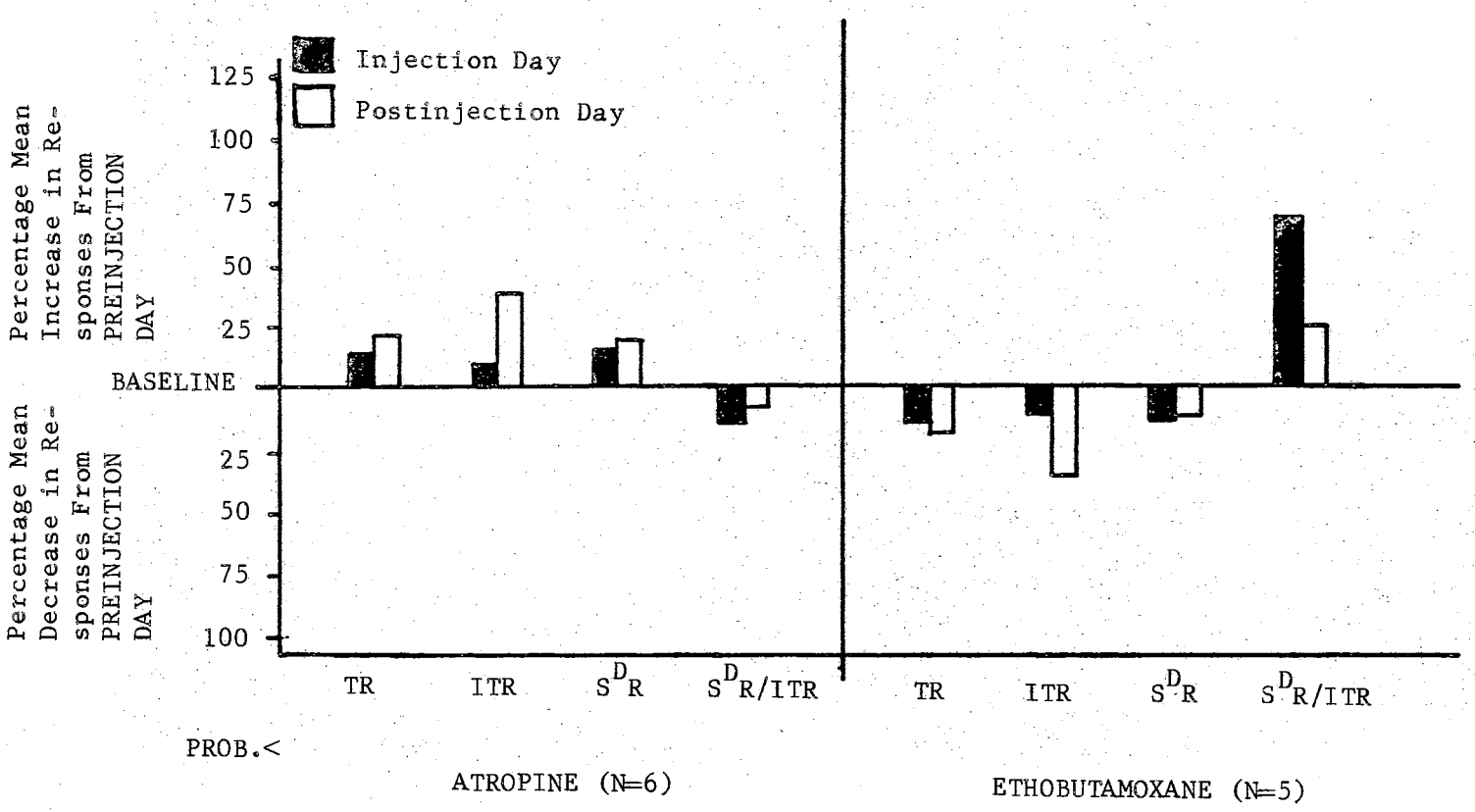

Figure 7. Effects of Adrenergic and Cholinergic Blockage of the Lateral Hypothalamus on Go/No-Go Visual Discrimination

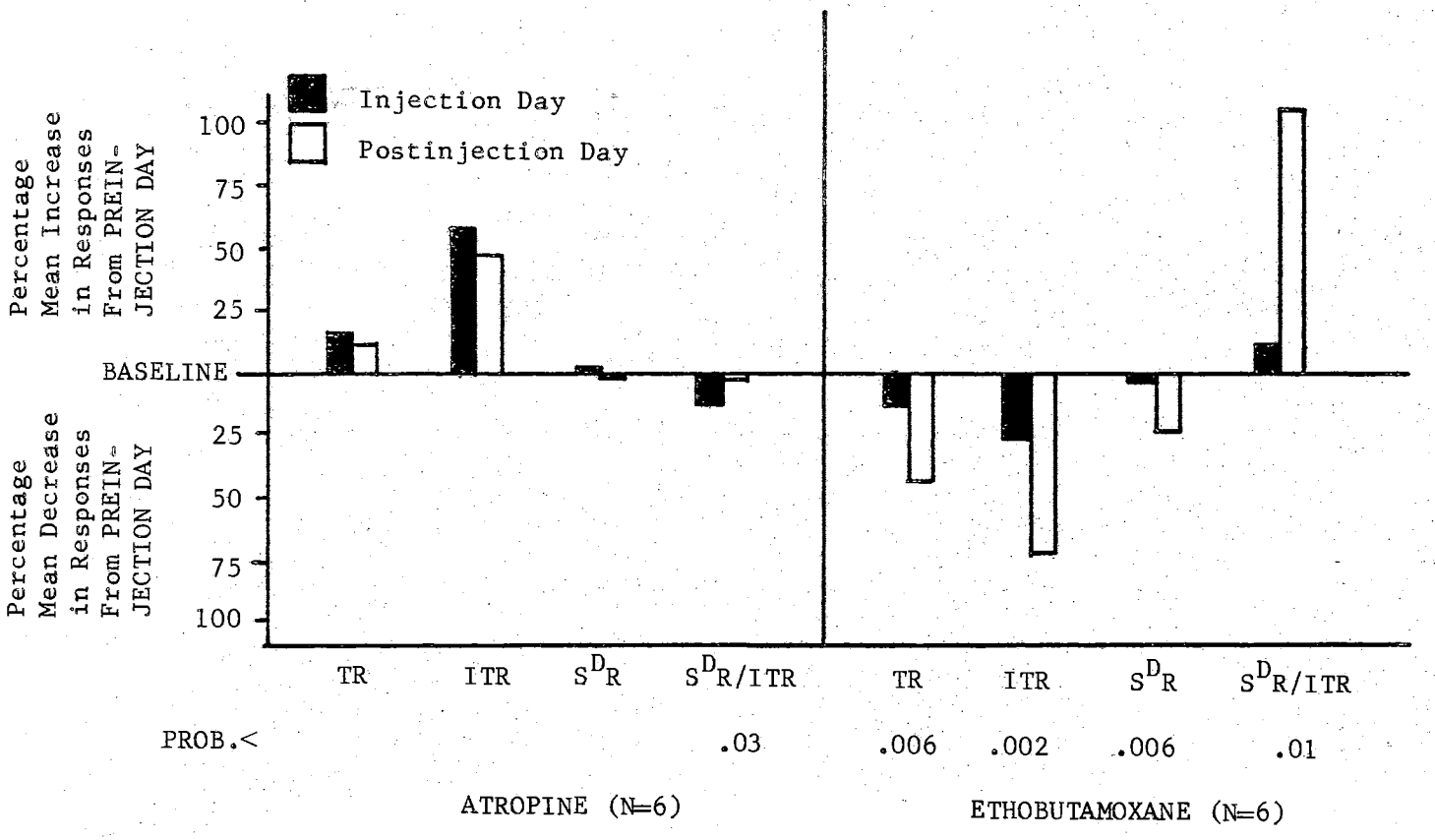

Figure 8. Effects of Adrenergic and Cholinergic Blockage of the Thalamus on Go/No-Go Visual Discrimination

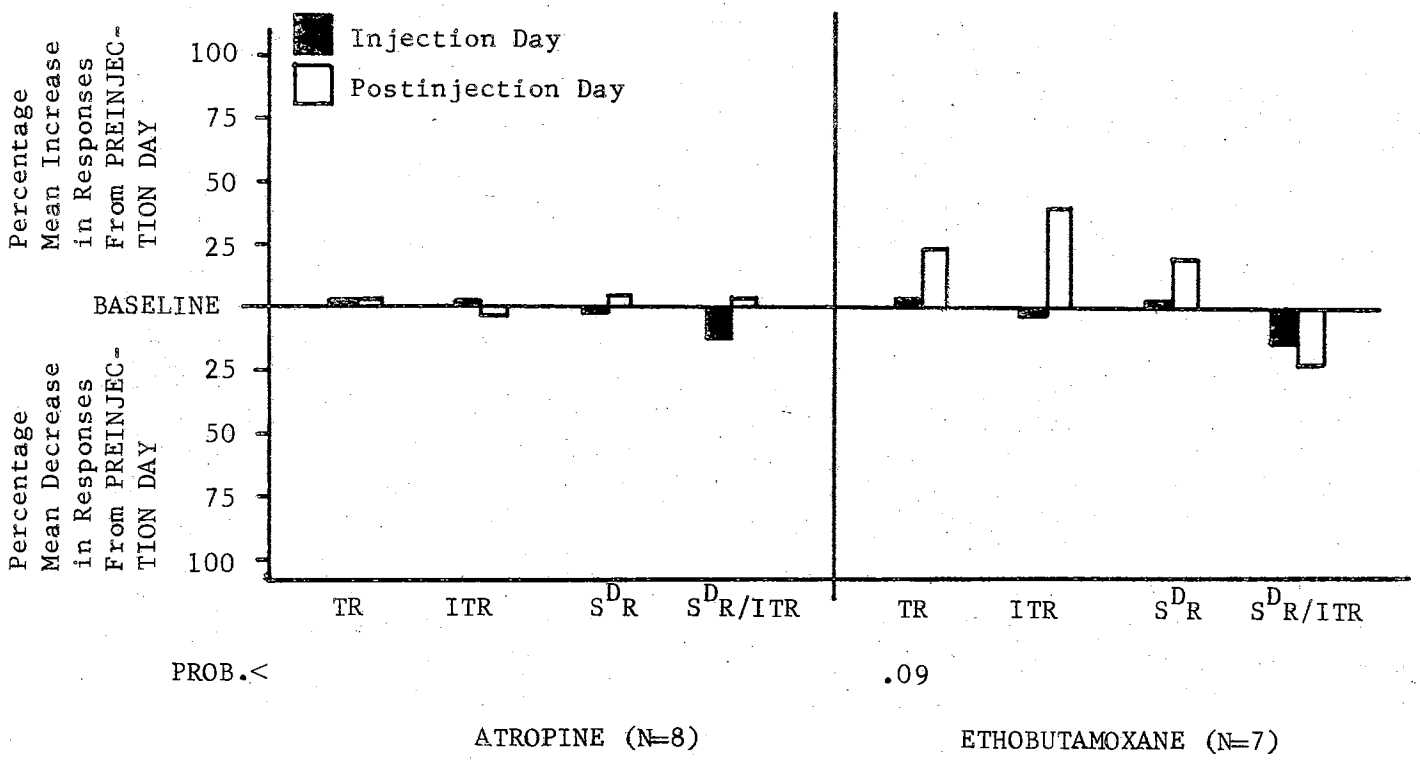

Figure 9. Effects of Adrenergic and Cholinergic Blockage of the Hippocampus on Go/No-Go Visual Discrimination

go/no-go visual discrimination task. Although not statistically reliable, an increase in the discrimination ratio was found for five of the six cats with cholinergic stimulation of the lateral hypothalamus, which indicated better discrimination than on the preinjection day. Adrenergic stimulation of the lateral hypothalamus (Figure 6) resulted in a significant decrease in the number of intertrial responses ($p < .04$) and in a trend for a decrease in total responses ($p < .09$) and in an increase in the discrimination ratio ($p < .09$). Four of the five cats were found to discriminate better with adrenergic stimulation of the lateral hypothalamus.

The effects of cholinergic and adrenergic blockage of the lateral hypothalamus on the go/no-go discrimination task are shown in Figure 7. Cholinergic blockage of the lateral hypothalamus by atropine did not reliably affect any of the response measures. Four of the six cats showed poorer visual discrimination (a decrease in the S^DR/ITR ratio) with cholinergic blockage of the lateral hypothalamus. Further, adrenergic blockage of the lateral hypothalamus (Figure 7) did not reliably affect any of the response measures. However, three of the five subjects showed better visual discrimination with lateral hypothalamic injections of ethobutamoxane.

Centre Median Nucleus of the Thalamus

In Figure 8, the behavioral effects of adrenergic and cholinergic blockage of the centre median nucleus of the thalamus are presented on go/no-go visual discrimination performance. Cholinergic blockage induced by atropine resulted in significantly ($p < .03$) poorer visual discrimination and five of the six animals showed a decrease in the S^DR/ITR

ratio. All other response measures were not reliably affected by cholinergic blockage. As shown in Figure 8, the behavioral effects of adrenergic blockage of the centre median nucleus of the thalamus with ethobutamoxane on visual discrimination performance were pronounced on the postinjection day. Adrenergic blockage resulted in a significant decrease in the number of total responses ($p < .006$), the number of intertrial responses ($p < .002$), and the number of reinforced responses ($p < .006$). All six of the animals tested with ethobutamoxane showed an increase in the S^DR/ITR ratio and resulted in significantly ($p < .01$) better visual discrimination performance.

Dorsomedial Hippocampus

Cholinergic blockage of the dorsomedial hippocampus (Figure 9) did not reliably affect any of the response measures on the go/no-go discrimination task. As shown in Figure 9, blocking adrenergic neural transmission in the hippocampus with ethobutamoxane had its major effect on the postinjection day. A trend ($p < .09$) was present for an increase in the total number of responses. Also of interest was the poorer visual discrimination performance shown by six of the seven subjects on the postinjection day as reflected in the decreased S^DR/ITR ratio. A sign test (Siegel, 1956), showed the probability of such an occurrence is equal to .06.

CHAPTER V

DISCUSSION

Lateral Hypothalamus

Fixed Ratio Five Bar Pressing

The finding of a significant decrease in FR-5 bar pressing with cholinergic stimulation of the lateral hypothalamus is consistent with the suggestion of Margules and Stein (1969) that there are cholinergic synapses in the hypothalamus for the suppression of operant behavior. There are reciprocal connections between the hypothalamus and brainstem reticular formation. Grossman's (1969) finding of decreased bar pressing with cholinergic stimulation of the midbrain reticular formation is also consistent with a possible cholinergically mediated inhibitory chemical circuit in rats and cats. Further evidence for a cholinergic inhibitory circuit is provided by the behavioral effects of cholinergic blockage. Assuming that atropine attenuates or blocks the cholinergic inhibitory synapses, the significant increase in FR-5 bar pressing with injections of atropine into the lateral hypothalamus is to be expected.

The significant drop in FR-5 bar pressing with adrenergic stimulation of the lateral hypothalamus parallels the results of Grossman (1969), who observed that adrenergic stimulation of the midbrain reticular formation of rats produced a decrease in bar pressing behavior. However, the finding of similar behavioral results with adrenergic and

cholinergic stimulation of the hypothalamus is not consistent with the reciprocally inhibitory relationship reported for food and water behavior in rats (Miller, 1965). Yet, Grossman (1969) found that both modes of stimulation in the midbrain reticular formation of rats had identical effects on bar pressing behavior. Likewise, Avery (1969a) found that adrenergic and cholinergic stimulation of the medial septum resulted in a significant reduction in FR-5 bar pressing. It is also possible that the dosages of norepinephrine injected in the present study were too high in concentration and actually induced a functional blockage of adrenergic transmission in the lateral hypothalamus. Although not significant, the effect of adrenergic blockage of the lateral hypothalamus with ethobutamoxane is in a predictable direction if adrenergic and cholinergic systems in the hypothalamus were reciprocally related. Also, a similar drop in FR-5 bar pressing with adrenergic stimulation and blockage makes it impossible to rule out an "over-stimulation" explanation for the decreased responding found with adrenergic stimulation. Obviously, additional concentrations of norepinephrine will have to be tested in the lateral hypothalamus before more conclusive statements can be made about possible adrenergic synapses in the lateral hypothalamus.

Go/No-Go Visual Discrimination

The behavioral effects of cholinergic stimulation (Figure 6) and blockage (Figure 7) of the lateral hypothalamus on go/no-go visual discrimination performance is congruent with the suggestion of Margules and Stein (1969) of cholinergically mediated inhibitory synapses in the hypothalamus. Cholinergic stimulation resulted in a decrease in responding, but, as can be seen in Figure 6, the intertrial responses showed

the largest decrease. The disproportionate drop in intertrial responding (errors) relative to the S^D responding accounted for the rise in the discrimination ratio and resulted in five of the six cats showing better visual discrimination. In order to maximize reinforcement the subjects must learn to inhibit during the intertrial (nonreinforced) period, hence, activation of an inhibitory system would be expected to improve performance. Likewise, blockage of an inhibitory system should result in poorer discrimination in a go/no-go situation. Although not significant, cholinergic blockage of the lateral hypothalamus with atropine (Figure 7) was shown to result in poorer discrimination. Consistent with the notion of the attenuation or blockage of an inhibitory mechanism was the finding of a disproportionate rise in the intertrial responses.

As found in the FR-5 bar pressing situation, adrenergic stimulation and blockage of the lateral hypothalamus had a similar effect on behavior as tested in the go/no-go visual discrimination task. Adrenergic stimulation produced a significant ($p < .04$) drop in the number of intertrial responses which resulted in a trend for better discrimination as shown in Figure 6. The behavioral effects of adrenergic blockage of the lateral hypothalamus with ethobutamoxane were not significant, but all response measures were altered in the direction found with adrenergic stimulation (Figure 7). Thus, as in the FR-5 situation, it is not presently possible to state whether an adrenergic-cholinergic, reciprocally inhibitory (adrenergic "over-stimulation") explanation is feasible.

Centre Median Nucleus of the Thalamus

Fixed Ratio Five Bar Pressing

The finding of a significant increase in FR-5 bar pressing with

cholinergic blockage of the centre median nucleus of the thalamus is predictable from the results of Avery (1969a), who found that cholinergic stimulation significantly reduced FR-5 bar pressing (Figure 1). Likewise, Grossman (1965) found that cholinergic stimulation of the thalamic reticular nucleus of rats produced a decrease in asymptotic performance in a shuttle-box avoidance task. Also, application of atropine to the thalamic midline nuclei of rats was shown to have a facilitory effect on performance in both appetitive and aversive conditioning situations (Grossman and Peters, 1966).

Consistent with the notion of a reciprocally inhibitory relationship between adrenergic and cholinergic neural circuits, Avery (1969a) found that adrenergic stimulation of the centre median nucleus of cats resulted in a significant increase in FR-5 bar pressing (Figure 1). Further evidence for a reciprocally inhibitory relationship between adrenergic and cholinergic neural circuits in the thalamus was found in the present study. As shown in Figure 5, adrenergic blockage of the centre median nucleus of the thalamus resulted in decreased FR-5 bar pressing. Thus, for simple bar pressing behavior, the available evidence indicates a possible reciprocally inhibitory effect for adrenergic and cholinergic stimulation of the thalamus of cats.

Go/No-Go Visual Discrimination

As shown in Figure 2, Avery (1969a) found that cholinergic stimulation of the centre median nucleus of cats resulted in significantly poorer visual discrimination on the go/no-go visual discrimination task. Likewise, cholinergic blockage of the centre median nucleus of the thalamus with atropine was found to produce significantly poorer visual

discrimination performance (Figure 8). Grossman and Peters (1966) reported that cholinergic stimulation and blockage of the thalamic nuclei of rats produced impaired performance in appetitive and aversive conditioning situations. However, by comparing Figure 2 with Figure 8, it is apparent that cholinergic blockage produced poorer visual discrimination by causing a disproportionate rise in intertrial responding (errors). Cholinergic stimulation, however, resulted in poorer visual discrimination because of a disproportionate decrease in the number of reinforced responses.

Avery (1969a) found that adrenergic stimulation of the centre median nucleus of the thalamus had no significant effects on performance in the go/no-go visual discrimination task (Figure 2). However, in the present study adrenergic blockage of the centre median nucleus of the thalamus was found to have a significant effect on go/no-go visual discrimination performance (Figure 8). All response measures were significantly affected by adrenergic blockage of the thalamus, and as can be seen in Figure 8, ethobutamoxane has its major effect on the postinjection day. The significantly better visual discrimination performance found with adrenergic blockage of the thalamus was due to the disproportionate decrease in the number of intertrial responses relative to the drop in reinforced responses. Although not as convincing as the results found on the simple FR-5 bar pressing task, the results of adrenergic and cholinergic stimulation and blockage of the thalamus of cats on visual discrimination performance suggests a possible reciprocally inhibitory relationship between these two neurohumors.

Dorsomedial Hippocampus

Fixed Ratio Five Bar Pressing

Consistent with the notion of the hippocampus as an inhibitory region of the limbic system (Grossman, 1967), Avery (1969b) found that cholinergic stimulation of the dorsomedial hippocampus of cats resulted in a trend for decreased FR-5 bar pressing (Figure 1). Cholinergic blockage of the hippocampus, on the other hand, produced a significant increase in FR-5 bar pressing. Similarly, hippocampal lesions have been shown to result in improved instrumental food rewarded behavior (Teitelbaum, 1960; Ehrlich, 1963).

Neither adrenergic stimulation (Avery, 1969b) nor adrenergic blockage of the dorsomedial hippocampus produced reliable effects on FR-5 bar pressing behavior (Figure 5).

Go/No-Go Visual Discrimination

As in the FR-5 bar pressing task, Avery (1969a) found that cholinergic stimulation of the dorsomedial hippocampus of cats produced a significant decrease in responding in the go/no-go visual discrimination task (Figure 3). The decrease in the number of intertrial responses was not disproportionately larger than the decrease in the number of reinforced responses. Therefore, significantly poorer visual discrimination was found with cholinergic stimulation of the hippocampus. Cholinergic blockage, on the other hand, had no reliable effects on go/no-go visual discrimination performance (Figure 9). However, adrenergic blockage of the hippocampus with ethobuamoxane resulted in a trend for a decrease in the total number of responses (Figure 9). Also, as with adrenergic

blockage of the thalamus, the major effects of ethobutamoxane on the hippocampus appeared on the postinjection day. Six of the seven cats ($p < .06$) showed poorer visual discrimination on the postinjection day with adrenergic blockage of the dorsomedial hippocampus and suggested a possible trend worthy of further research.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Based upon the evidence which indicates adrenergic and cholinergic substances are possible central neural transmitters, the present study was conducted to investigate the behavioral effects of direct chemical stimulation and blockage of the cat's brain with these prospective central transmitters. Two behavioral situations, a fixed ratio five (FR-5) bar pressing task, and a go/no-go visual discrimination task, were used to test the effects of intracranial chemical stimulation of three brain areas of the cat.

Double-walled, stainless steel cannulae were unilaterally chronically implanted in the lateral hypothalamus, centre median nucleus of the thalamus and dorsomedial hippocampus of 14 cats. Carbachol, atropine sulfate, norepinephrine bitartrate hydrate, and ethobutamoxane were each dissolved in Locke-Ringer solution and injected into the selected brain areas via an injection cannula. The effects of adrenergic and cholinergic stimulation and blockage of the three brain areas were determined by comparing the performance on the preinjection (baseline) day with the performance on the day the drugs were injected (injection day) and the postinjection day.

Experiment I consisted of 30 min daily sessions of free operant responding for milk reinforcement on a FR-5 schedule and the total number of reinforcements received were recorded daily. Experiment II was a

complex successive visual discrimination task of a "go/no-go" type. A 10 sec reinforcement period (S^D) in which each bar press was reinforced, was identified by a 7 cycle/sec flashing light. Each S^D period was separated by a variable interval 30 sec intertrial period in which bar pressing was never reinforced. Each animal received 50 trials a day. Daily measures were taken of total responses (TR), reinforced responses (S^DR), intertrial responses (ITR) and the ratio of reinforced to intertrial responses (S^DR/ITR).

The major findings in Experiment I were as follows: (1) Adrenergic and cholinergic stimulation of the lateral hypothalamus significantly decreased FR-5 bar pressing and cholinergic blockage of the lateral hypothalamus significantly increased FR-5 bar pressing: (2) Cholinergic blockage of the centre median nucleus of the thalamus significantly increased FR-5 responding and adrenergic blockage produced a trend for decreased bar pressing; (3) Cholinergic blockage of the dorsomedial hippocampus resulted in a significant rise in FR-5 responding.

Experiment II resulted in the following results: (1) Cholinergic stimulation of the lateral hypothalamus produced a significant decrease in TR, ITR, and a trend for decreased S^DR. Five of the six subjects showed better visual discrimination (rise in S^DR/ITR) with cholinergic stimulation of the lateral hypothalamus; (2) Adrenergic stimulation of the lateral hypothalamus resulted in a significant decrease in ITR, a trend for decrease TR, and a trend for increased S^DR/ITR; (3) Cholinergic blockage of the centre median nucleus of the thalamus resulted in a significant decrease in S^DR/ITR, which indicated poorer visual discrimination performance; (4) Adrenergic blockage of the centre median nucleus of the thalamus produced a significant decrease in TR, ITR, S^DR, and a

significant increase in S^DR/ITR; (5) Adrenergic blockage of the dorsomedial hippocampus produced a trend for increased TR, and on the postinjection day, six of the seven subjects showed poorer visual discrimination (decreased S^DR/ITR).

The results were discussed in terms of a possible reciprocally inhibitory relationship between adrenergic and cholinergic synapses in the central nervous system of the cats. Further, the functional relationship between these suspected central nervous system neural transmitters and overt behavior was discussed in view of possible chemically-specific inhibitory and excitatory neural circuits in the cat.

Although still indirect, the evidence indicates that peripheral adrenergic and cholinergic neural transmitters are very likely candidates for neural transmitters in the central nervous system. The present study has shown that reliable alterations in overt behavior can be elicited by direct application of these neural transmitters to selected regions of the cat brain. However, only by further interdisciplinary efforts and the use of continually more refined techniques, can the full significance of the relationship between brain chemistry and behavior be realized.

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