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Modulatory Influences Of The Septum On Hypothalamic Functions: An Electrophysiological And Behavioral Analysis

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MODULATORY INFLUENCES OF THE SEPTUM ON HYPOTHALAMIC

FUNCTIONS: AN ELECTROPHYSIOLOGICAL AND BEHAVIORAL ANALYSIS

by

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ABSTRACT

The effects of electrical stimulation of the septal area on the spontaneous discharge rate of lateral hypothalamic neurons were investigated by extracellular recording in rats under urethane anaesthesia. Septal stimulation exerted both facilitatory and inhibitory effects on the lateral hypothalamus, a finding contrary to the view of previous behavioral and physiological studies suggesting that the septum has predominantly inhibitory effects on hypothalamic functions. The direction and magnitude of these effects were shown to be a function of the spontaneous discharge rate of the lateral hypothalamic neuron. These modulatory effects of septal stimulation were also present in the case of lateral hypothalamic units whose discharge rate was altered by olfactory bulb stimulation.

A similar relationship was observed with the effects of septal stimulation on lateral hypothalamic self-stimulation in rats. Chronic electrodes were implanted in these two regions using electrophysiological control procedures. Animals were tested for lateral hypothalamic self-stimulation at two current levels,

threshold and suprathreshold, and the effect of preceding each lateral hypothalamic pulse with a septal pulse at 5 and 15 msec intervals was investigated. At threshold current levels, when the neural activity was low, septal stimulation facilitated the self-stimulation rate; whereas at suprathreshold levels, when the neural activity was high, either inhibition or no effect was produced. These data provide further support for the concept that the direction of effect exerted by the septal area is determined by the level of neural activity in the lateral hypothalamus.

Evoked potentials recorded in the lateral hypothalamus to stimulation of the septum provide a neuroanatomical framework for the modulatory influences of the septum on hypothalamic mechanisms. Stimulation of the septum evoked one or more individual responses having peak latencies of 3-6, 10-14 or 18-23 msec which were elicited from different regions of the septum. The 3-6 and 10-14 msec responses arose from dorsal and midline regions corresponding to the projection field of the precommissural fornix from the hippocampus; and the 18-23 msec response arose from a ventro-lateral region corresponding to projections of the stria terminalis. Stimulation of the hippocampus and stria terminalis evoked responses in the lateral hypothalamus of similar configuration but with latencies longer than the 10-14 and 18-23 msec components respectively. Lesions in the dorso-midline and ventro-lateral septum attenuated these responses, suggesting that the precommissural fornix and stria terminalis are the pathways mediating the septal evoked

components.

The effects of stimulation of these regions of the septum on lateral hypothalamic neurons suggest that the influences mediated by these pathways are functionally distinct. Stimulation of the mid-line precommissural fornix region resulted in activation of lateral hypothalamic neurons, the latency of which correlated with the 10-14 msec component; while stimulation of the ventro-lateral region resulted in an inhibition, the latency of which correlated with the 18-23 msec component. In some cases inhibition occurred immediately following stimulation, appearing to correlate with the onset of the 3-6 msec component. These short latency effects are attributed to stimulation of direct "fibers of passage" projecting from the hippocampal region through the septum to the lateral hypothalamus.

These results are discussed in the light of behavioral and physiological data demonstrating the variable effects which limbic structures, and more specifically the septum, exert on homeostatic integrative functions mediated by the hypothalamus.

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Since Broca's original anatomical description of the limbic
system in 1878 a number of investigators have attempted to assess
its functional role in a variety of physiological and behavioral
responses. Cajal (1911) proposed that because of its close ana-
tomical association with the rhinencephalon it was concerned main-
ly with olfaction, a concept which pervaded much of the early li-
terature. It was not until the classical study of Kluver and Bucy
(1937) that the limbic system was implicated in functions other
than olfaction. They demonstrated that bilateral temporal lobec-
tomy, which interfered with certain components of the limbic system,
resulted in a disruption of affective behavior. At the same time,
Papez (1937) proposed that this region constituted "a harmonious
mechanism which may elaborate the functions of central emotion as
well as participate in emotional expression". These studies re-
presented a critical turning point in the experimental analysis of
the limbic system and formed the basis for many studies leading to
our present concepts of its functional significance.

By means of stimulation and lesioning techniques, the compo-
nents of the limbic system have been implicated in many autonomic,

1

somatomotor, endocrine and behavioral responses (Fulton, 1951; Gastaut, 1952; Gloor, 1960; Hess, 1957; Kaada, 1951, 1960; MacLean, 1949, 1952, 1954; Ranson and Magoun, 1939). The extent to which the various components of this system are involved with the control of these responses remains unclear. Hess (1957) demonstrated that stimulation of discrete anatomical sites in the caudal regions of the limbic system and especially the hypothalamus, produced specific and often separate effects on many of these responses. In contrast, rostral forebrain components, including the amygdala, hippocampus and septum, produce both facilitatory and inhibitory effects on the limbic responses when the same or overlapping sites are stimulated (Gloor, 1960; Kaada, 1951, 1960). These observations suggested the absence of any topographical representation of functions within the limbic forebrain structures. Furthermore, since lesions of the latter structures have little or no effect on many of the same responses which stimulation is known to influence, it appears that they are unessential for the production of the many physiological and behavioral responses for which the hypothalamus is of critical importance. In view of these findings Gloor (1960) proposed that the role of the limbic forebrain is to exert "regulatory" or "modulatory" influences on responses known to be integrated at the level of the hypothalamus.

Although this proposal was inferred initially from physiological and behavioral data, some of the strongest support for it comes from recent electrophysiological experiments concerned with

limbic forebrain influences on hypothalamic unit activity (Dafny and Feldman, 1969; Dreifuss, Murphy and Gloor, 1968; Egger, 1967; Murphy, Dreifuss and Gloor, 1968b; Sutin, 1963). These studies have demonstrated that structures of the rostral forebrain exert both facilitatory and inhibitory effects on hypothalamic mechanisms and have also raised the possibility that these effects may be more specific than was previously recognized. For the amygdala in particular, it has been shown that there are separate discrete anatomical areas which exert opposite effects on the same hypothalamic site, suggesting some topographical differences in function within this structure (Dreifuss, et al., 1968). Whether this applies to other components of the limbic system is as yet unclear and indicates the necessity for further investigation of the mechanisms underlying limbic modulatory function.

The present study was undertaken to investigate the influences which the septal area exerts on the lateral hypothalamus (LH) using both electrophysiological and behavioral techniques. The initial purpose was to determine the nature of the effects of electrical stimulation of the septum on LH neural activity and self-stimulation behavior, and then, to study the conditions under which these effects are produced and the pathways by which they are mediated.

HISTORICAL REVIEW

I   The Limbic System

Since the earlier studies of Broca (1878) and Cajal (1911) there
have been many reports describing the anatomical connections of the
limbic system between its forebrain, hypothalamic and midbrain re-
gions. The complexity of these interconnecting pathways makes it
difficult to associate physiological or behavioral functions with any
one individual structure. In most cases investigators have stimu-
lated or made lesions in a single structure and attempted to make in-
ferences about its function without recognizing sufficiently that
the functions attributed to one component of the limbic system are
intimately related to the role of other structures of the system.
For this reason, although the present investigation is concerned
with the relationship between the septum and lateral hypothalamus,
it is necessary to consider the limbic system as a whole and how
these two components are anatomically and functionally related with
the remainder of the system. Therefore, this review will begin with
the anatomy of the limbic system and go on to a consideration of its
functions in regard to limbic modulation of the hypothalamic area.

This will be followed by a review of the literature on the anatomy and functions of the septum.

1. Anatomical Overview of the Limbic System

Although there is no precise anatomical definition of the limbic system it is usually considered to include the limbic lobe of Broca (entorhinal, cingulate and pyriform cortex), the hippocampus, amygdala, septum, hypothalamus and midbrain regions, as well as the fiber connections linking these components. In the present review these structures are organized according to the phylogenetic distinction described by Herrick (1933) into two parts consisting of paleo- and archicortical formations. The archipallium, the oldest cortical derivative, is represented by the hippocampal complex, and the entorhinal and cingulate cortex. On the other hand, the paleopallium is represented by the primitive olfactory lobe which Valverde (1965) has indicated includes the olfactory tubercle, pyriform cortex, and amygdaloid complex. The anatomical projections of the two divisions of the limbic system are shown schematically in Fig. 1.

The archicortical division and its interconnections served as the basis upon which Papez (1937) proposed the substrates for emotional expression. He based his hypothesis on the then available evidence of a projection to the cingulate cortex from the anterior thalamic nuclei and upon Cajal's (1911) description of a cingulo-hippocampal pathway. Many later studies (Adey and Meyer, 1952; Krieg, 1947; Raisman, Cowan and Powell, 1965; Rose and Woolsey,

Figure 1   A representation of the anatomical structures

and pathways of the limbic system.
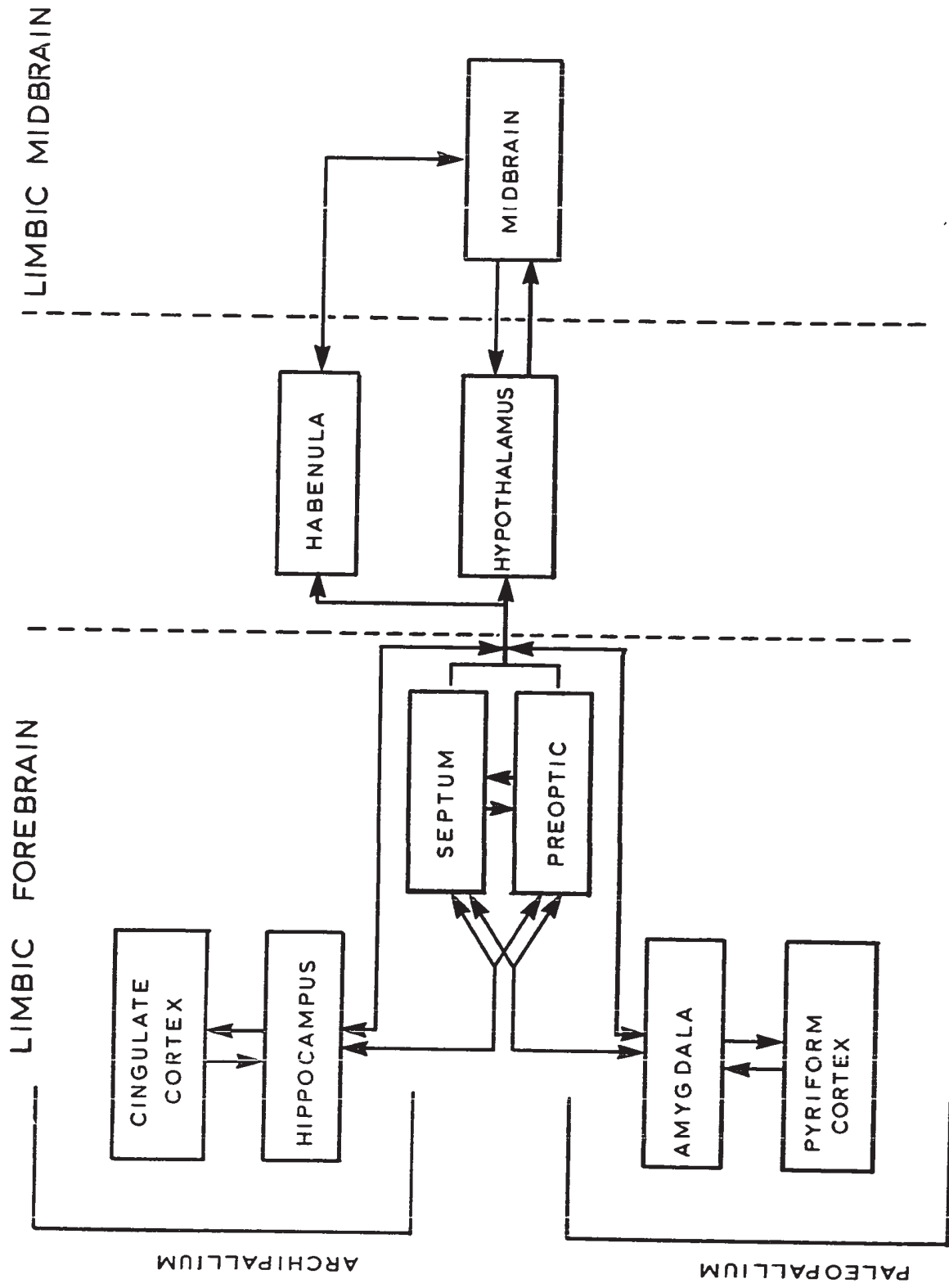
1948) have confirmed the connections of the Papez circuit: the
cingulate cortex - hippocampus - mammillary body - anterior thala-
mic nuclei - cingulate cortex loop. The afferent pathways to the
hippocampus from the cingulate and entorhinal areas course via the
temporo-ammonic pathways described by Cajal (1911) and Lorente de
No (1934). The major efferent pathway of the hippocampus is the
fornix system, through which Papez suggested information was re-
layed from the hippocampus to the mammillary bodies. The complex
fornix system divides into two major fiber bundles upon entering
the septal area: the compact fornix column or postcommissural for-
nix, and the diffuse precommissural component. The latter projects
to the septal area and medial forebrain bundle from which they con-
tinue into the preoptic area, whereas the postcommissural component
distributes further caudally into the anterior thalamic nucleus,
mammillary bodies, anterior and lateral hypothalamic areas, and
midbrain regions.

The structures of the paleocortical division are derived main-
ly from the pyriform cortex. This region has major projections in-
to the amygdaloid complex (Ban and Omukai, 1959; Cajal, 1911;
Cowan, Raisman and Powell, 1965; Valverde, 1965), and also some
projections which pass through the amygdala to relay in the septum,
the preoptic area, and the entire extent of the hypothalamus (Lund-
berg, 1962a; Powell, Cowan and Raisman, 1963, 1965). The amygdala
itself projects over two principal pathways: a diffuse one referred
to as the longitudinal association bundle (Johnston, 1923) or the
ventro-amygdalofugal pathway, and a compact fiber bundle -- the stria

terminalis. The latter is the best known pathway with distribution to the septum, preoptic and hypothalamic areas (Gloor, 1960; Heimer and Nauta, 1969; Valverde, 1965). Although the precise description of the detailed pattern of its termination in the hypothalamic nuclei is somewhat contradictory it would appear that the anterior, lateral and ventromedial regions are the principal terminal sites of strial fibers. The ventro-amygdalofugal projections are more diffuse, with fibers terminating in septal regions and within the medial forebrain bundle and the hypothalamus (Heimer and Nauta, 1969; Leonard and Scott, 1971).

Many of the fibers from both paleocortical and archicortical divisions converge on the septum and preoptic areas. In turn, fiber pathways from these areas serve as secondary projections to hypothalamic and midbrain regions. Two major routes spread caudally from the septum and preoptic areas: fibers which follow the stria medullaris to the habenular nuclei, and, via the medial forebrain bundle, into the hypothalamus (Millhouse, 1969; Nauta, 1958; Powell, 1963; Raisman, 1966). This latter pathway is the more complex of the two projections, consisting of numerous multisynaptic and direct links between the rostral forebrain and all of the hypothalamic nuclei, especially the lateral hypothalamic area which forms the bed nucleus of the medial forebrain bundle.

These subcortical stations in the hypothalamus or habenula nucleus are the source of origin for two further pathways which project into the midbrain region (Nauta, 1960). The habenula projects via the fasciculus retroflexus, and the hypothalamus via the midbrain

extension of the medial forebrain bundle. These pathways are distributed to two distinctive regions of the midbrain: some of their fibers terminate in central and lateral regions of the tegmentum; the remainder distribute to the ventral region of the central gray and ventral tegmentum.

In addition to the descending fiber pathways of the limbic system there are a number of ascending projections which arise in the midbrain region. These fibers serve to complete what Nauta (1963) refers to as "the limbic forebrain - limbic midbrain circuit". Two major systems are present: the dorsal longitudinal fasciculus of Schutz, which originates throughout the length of the central gray substance; and the mammillary peduncle which arises from both the dorsal and ventral tegmental nuclei (Guillery, 1956; Ingram, 1940; Nauta and Kuypers, 1958). The ascending dorsal longitudinal fasciculus projects to the intralaminar thalamic and dorsal and medial hypothalamic nuclei. The mammillary peduncle projection connects with the mammillary body, and some fibers spread rostrally along the medial forebrain bundle to lateral hypothalamic, preoptic and septal regions. In its passage through the lateral hypothalamus this pathway is augmented by additional fibers of local origin (Guillery, 1957; Wolf and Sutin, 1966). In turn, the septal and preoptic regions project to the amygdala and hippocampus over two-way circuits with the latter two structures serving as transit points for projections to pyriform, cingulate and higher cortical regions.

In summary the limbic system is composed of a number of inter-related structures and pathways which are positioned between neo-cortical regions on the one hand and brainstem regions on the other. In addition, the septal and preoptic areas appear to be important junctional points for many of the ascending and descending pathways of this system.

2.   Functional Overview of the Limbic System

As indicated earlier, the classic studies of Kluver and Bucy (1937) and Papez (1937) led to a new interpretation of the functions of limbic forebrain structures. The behavioral syndrome following bilateral temporal lobectomy in monkeys clearly demonstrated that limbic structures are involved in affective behavior and not merely in olfaction (Kluver and Bucy, 1937). The Papez theory suggested an anatomical substrate for this function and stimulated many investigators to study the mechanisms subserving other possible physiological and behavioral functions of the limbic system. The results of some of these studies are reviewed in this section, in particular, those demonstrating its involvement in autonomic, somatomotor, endocrine and behavioral functions. When the effects exerted by limbic forebrain structures are compared to those obtained from the hypothalamic area, it will be apparent that these forebrain structures exert modulatory influences on the hypothalamus.

(1) Autonomic and Somatomotor Effects: Electrical stimulation of

limbic forebrain structures produces a variety of autonomic responses, both sympathetic and parasympathetic. Heart rate and blood pressure have been observed to be increased and decreased and the sites of stimulation that produce these effects have been shown to overlap (Anand and Dua, 1956a; Andy, Bonn, Chinn and Allen, 1959; Andy and Mukawa, 1961; Covian, 1967; Gastaut, 1952; Hilton and Zbrozyna, 1963; Hockman, Telesnick and Livingston, 1969; Kaada, 1951; Koikegami, 1964; MacLean and Delgado, 1953; MacLean, 1952; Malmo, 1964; Naquet, 1954; Ursin and Kaada, 1960). The effect of electrical stimulation has been shown in some cases to depend on the general condition of the animal, the frequency of stimulation, or upon stimulus strength (Gastaut, 1952; Gloor, 1956; Hess, Akert and McDonald, 1951; Kaada, 1951, 1960; Sachs, Brendler and Fulton, 1949; Speakman and Babkin, 1949).

Stimulation of limbic forebrain structures has been shown to both facilitate and inhibit gastrointestinal motility and secretions (Anand and Dua, 1956b; Bailey and Sweet, 1940; Eliasson, 1952; 1960; Gloor, 1960; Hoffman and Rasmussen, 1953; Kaada, 1951; Sen and Anand, 1957; Shealy and Peele, 1957). Similar changes in respiration, pupillary responses, salivation, defecation, micturition, uterine tonus and contraction and piloerection have also been observed (Green, 1964; Kabat, Magoun and Ranson, 1935, 1936; Parmeggiani, 1967). This extensive involvement of the limbic system in autonomic responses prompted MacLean (1958) to call this area the "visceral brain", since it is concerned with visceral responses dealing with

preservation of the self and preservation of the species.

Unfortunately, the term "visceral brain" is a misleading one
because various somatomotor responses are also readily elicited
from limbic forebrain structures. These responses differ from
the discrete, spatially organized motor responses obtained from
the neocortex. The same limbic area, when stimulated, can pro-
duce inhibition, facilitation or a combination of the two.
Changes in spontaneous movements such as shivering can also be
observed (Gastaut, 1952; Hemingway, 1963; Kaada, 1951; MacLean
and Delgado, 1953). Similarly, inhibitory and excitatory influen-
ces on cortically induced movements and spinal reflexes have been
described (Emmers, 1961; Hodes, Peacock and Heath, 1951; Kaada,
1951; Peacock and Hodes, 1951). Overt motor responses may also
be elicited from limbic components, including movements of the
limbs, trunk and neck, mastication, swallowing, licking and vo-
calization (Anand and Dua, 1956c; Baldwin, Frost and Wood, 1954;
Feindl and Penfield, 1954; Gastaut, 1952; Green, 1964; Kaada,
1951; Kaada, Andersen and Jansen, 1954; Votaw, 1959, 1960). Fa-
cilitatory or inhibitory effects have, in all these investigations,
been shown to depend in part upon the levels of experimental anaes-
thesia. Kaada (1951) and Gastaut (1952) have shown that spontaneous
movements and muscle tone are inhibited in lightly anaesthetized
preparations whereas in unanaesthetized preparations the opposite is
true. Similarly, the facilitatory responses of limbic stimulation
on cortically induced movements or spinal reflexes may be converted

to inhibitory responses by increasing the level of anaesthesia (Kaada, 1951).

Although it might be expected that lesions of limbic structures would result in effects opposite to those produced by stimulation, this does not appear to be the case. Lesions do not obviously or grossly interfere with the basic autonomic or somatomotor responses previously described, although stimulation of these sites has strong effects on these responses (Gloor, 1956, 1960). At most, there are occasional transient effects such as minor increases in blood pressure, decreases in respiration and heart rate, and increases in salivation; however, these soon disappear (Anand, Chhina and Dua, 1959; Kaada, 1960).

(2) **Endocrine and Behavioral Effects**:   The role of the limbic system in endocrine responses has not received as much attention as other functional aspects of this system. Increased and decreased secretion of adrenocorticotrophic hormone and plasma 17-hydroxy-corticosteroids have been demonstrated following stimulation and lesions of various limbic components (Endröczi and Lissak, 1960, 1962, 1963; Endröczi, Schreiberg and Lissak, 1963; Harris, 1960; Knigge, 1961; Knigge and Hays, 1963; Mandell, Chapman, Rand and Walter, 1963; Mangili, Motta and Martini, 1966; Mason, 1958, 1959). Limbic function is also implicated in the control of gonadotrophin release (Elwers and Critchlow, 1960, 1961, 1966; Hayward, Hilliard and Sawyer, 1964; Kawakami, Seto, Terasawa and Yoshida, 1967; Koikegami,

1954, 1964; Lundberg, 1962b), and in the release of oxytocin and vasopressin (Cross, 1961; Hayward and Smith, 1963, 1964; Holland, Aulsebrook and Woods, 1963). Once again limbic structures do not appear to be critical for the control of these endocrine responses, since complete removal of forebrain limbic regions does not appear to interfere with their regulation (Woods and Bard, 1960; Woods, Bard and Bleir, 1966).

To include a description of the behavioral functions associated with the limbic system is beyond the scope of this study. Excellent reviews of this literature have been made by Gloor (1960), Kaada (1951, 1960), McCleary (1966) and Goddard (1964) in which the role of the limbic system in arousal, sleep, sexual behavior, temperature regulation, feeding and drinking behavior, self-stimulation, and affective behavior is discussed. The most important conclusion which may be drawn from the extensive literature on this topic is that each component of the limbic system, although involved in some manner in complex behavioral responses, is not by itself essential for their production. For example, lesions of the amygdala may result in either placidity, rage, or no change in the affective behavior of an animal (Adey, 1958; Kling, Orbach, Schwarz and Towne, 1960; Schreiner and Kling, 1953). Similarly stimulation of components of this system have been shown to produce both increases and decreases in feeding and drinking behavior and on approach-avoidance reactions to self-stimulation (Bursten and Delgado, 1958; Doty, 1961; Fonberg and Delgado, 1961; Olds and Milner, 1954; Robinson

and Mishkin, 1962, 1968; Sheer, 1961; Sibole, 1971).

(3) <u>The Hypothalamus</u>:   The hypothalamic region, composed of a number of discrete anatomical nuclei, is centrally positioned in the limbic system between "limbic forebrain" structures, such as the pyriform lobe, cingulate gyrus, hippocampus, amygdala and septum, and the caudally situated "limbic midbrain" area. Some investigators consider the hypothalamus to be an anterior extension of the midbrain reticular formation, since there are neither clear anatomic boundaries nor great differences in general structure between them. Nevertheless it is evident that the hypothalamus, especially its lateral region, is a nodal point between two reciprocally connected circuits of the limbic forebrain and midbrain (Nauta, 1961). Viewed in this manner, it seems logical to assume that the functional state of the hypothalamus is continuously influenced by the prevailing activity patterns in either of these two regions. It is therefore in an ideal location for dealing with "integrative mechanisms" concerned with complex autonomic, somatomotor, endocrine and behavioral response patterns.

The special significance of the hypothalamus as a central regulator of these response patterns has become increasingly evident since Karplus and Kreidl (1909) observed that electrical stimulation of the ventral diencephalon caused sweating, salivation, urination and pupillary dilatation in the cat. Numerous investigators, notably

Ranson and Magoun (1939), Hess (1957), Ingram (1960) and Haymaker, Anderson and Nauta (1969), have demonstrated the functional importance of the hypothalamus in the control of many of the responses produced from forebrain structures of the limbic system. The major distinguishing feature which sets the hypothalamus apart from the remainder of this system rests in its apparent topographical organization. Within this region there are well defined areas which are involved in the production of specific types of responses and which carry specific directional qualities when stimulated or lesioned. This is in direct contrast to the lack of specificity previously described for forebrain limbic structures.

The classical work of Hess (1957) demonstrated two rather distinct areas in the hypothalamus which subserved functionally opposing response mechanisms. Stimulation of an "ergotropic zone", which comprises the posterior hypothalamic region, produces such responses as pupillary dilatation, increased blood pressure and heart rate, activation of respiration, increase in heat production and motor excitability, and general excitement of the animal. In the anterior hypothalamic and preoptic regions, referred to as the "trophotropic zone", stimulation results in similarly directed responses but with functionally opposite activities, such that there is a general "restitution and economy of energies" (Hess, 1957).

These autonomic and somatic functions of the hypothalamus appear to be closely linked with highly integrated behavioral response patterns which may also be produced from this region, some

of which include temperature regulation (Myers, 1969), food and water intake (Stevenson, 1969) and emotional behavior (MacLean, 1969). One might assume that these complex responses are associated closely with the ergotropic and trophotropic zones outlined by Hess (1957), and have a similar dual opposing representation. This suggestion is substantiated by the fact that bilateral lesions in the region of the lateral hypothalamus result in aphagia, whereas bilateral destruction of the ventromedial region results in hyperphagia (Anand and Brobeck, 1951; Heatherington and Ranson, 1940). Also, with electrical stimulation of these areas the opposite response occurs (Anand and Dua, 1955; Delgado and Anand, 1953). Similar observations have been made with regard to the elicitation of "fight or flight" behavior with lesions in the region of the anteromedial portion, and emotionally unreactive behavior from lesions in the lateral extent of the hypothalamus (MacLean, 1969).

Taken together, the physiological and behavioral data demonstrate that the hypothalamus may be considered as a control site for autonomic, somatic and endocrine functions which act synergistically to produce well-coordinated and integrative actions. Although each component of the limbic system has been shown to affect these same responses, their influence is certainly not of an integrative nature since lesions of limbic components do not interfere with the various response patterns. Secondly, because of the lack of topographical localization, responses elicited by stimulation are very seldom in a predetermined direction nor are the behavioral

responses complete in the sense of being purposeful acts (i.e., sham rage) like those produced from the hypothalamus.

The highly coordinated character or responses elicited from the hypothalamus suggest that this region must be dependent upon receiving information from the periphery and from other central structures such as the limbic and cortical regions. Presumably it is these inputs which set the central hypothalamic integrative mechanism in action.

Electrophysiological recordings of evoked potential and unit activity in hypothalamic areas indicates that it does receive and is influenced by a number of peripheral sensory inputs. Cross and Silver (1966), Rudomin, Malliani and Zanchetti (1965), and Stuart, Porter, Adey and Kamikawa (1964) have demonstrated that hypothalamic unit activity may be facilitated or inhibited by a variety of visceral and somatic stimuli. Generally speaking, these responses do not appear to be specific to any region within the hypothalamus (although a greater concentration is located in the anterior or posterior regions), nor does there appear to be a specific response to the modalities stimulated. Similar results have been obtained from other studies in which visual, auditory, olfactory and endocrine inputs were used (Dafny, Bental and Feldman, 1965; Feldman and Dafny, 1968; Lincoln and Cross, 1967; Pfaff and Pfaffman, 1969; Scott and Pfaffman, 1967; Takaori, Masashi and Fukuda, 1968). The only unit responses which have a degree of response specificity are those located in the anterior supraoptic and preoptic regions which respond

to variations in temperature (Birzis and Hemingway, 1957; Nakayama, Hammel, Hardy and Eisenman, 1963) and osmotic stimuli (Brooks, Ishikawa, Koizumi and Lu, 1966; Cross and Green, 1959).

In addition to the peripheral sensory information reaching the hypothalamus, there is also a great deal of afferent input from the surrounding components of the limbic system and possibly from the neocortex, although the latter appears to be mediated by limbic structures (Lundberg, 1960). Hypothalamic evoked responses produced by stimulation of various limbic components confirms the passage of information along many of the described anatomical pathways coursing between these two regions (Gloor, 1955; Sutin, 1963). Single unit recordings in the hypothalamus demonstrate that limbic stimulation produces both facilitatory and inhibitory effects on this region (Dafny et al., 1969; Dreifuss and Murphy, 1968; Egger, 1967; Murphy et al., 1968b; Oomura, Ooyama, Yamamoto, Naka, Kobayashi and Ono, 1967; Stuart, Porter and Adey, 1964). As might be expected, the direction of these effects does not appear to be associated with any one limbic component, although there is some conflicting evidence suggesting that certain areas within a single component structure may exert differential effects on the same focus in the hypothalamus (Dreifuss et al., 1968).

(4) <u>Summary of Limbic Forebrain - Hypothalamic Relationships</u>: It is apparent from the foregoing anatomical and electrophysiological evidence that the hypothalamus is a focal point between limbic

forebrain and midbrain regions. Electrical stimulation or lesions of this area elicit or interfere with the production of highly co-ordinated physiological and behavioral response patterns. The hypothalamus is therefore of critical importance for the integration of afferent information which it receives from central and peripheral structures. The question is then raised as to the precise roles the limbic forebrain structures play in relation to these hypothalamic integrative mechanisms.

In comparing limbic forebrain and hypothalamic characteristics there are definite differences to be observed. Stimulation of limbic forebrain structures has been shown to have an influence on many of the same functions as does the hypothalamus, although a single limbic component is not capable of producing equally complex response patterns. Similarly, lesions fail to produce deficits in many of these same functions, unlike the effects of lesions in hypothalamic areas. This indicates that single limbic forebrain structures do not appear to be essential for the integration of physiological or behavioral functions, whereas the hypothalamic area is necessary. The lack of any topographical localization within the limbic forebrain, and the fact that both facilitatory and inhibitory effects may be exerted on many of these functions from the same locus of stimulation further emphasizes these differences. It is suggested therefore, that the limbic forebrain components play a secondary role in influencing mechanisms primarily under hypothalamic control, and in this regard might serve

in a "modulatory" capacity (Gloor, 1960).

II   Anatomy of the Septum

1.   Developmental Aspects of the Septum

The septum is a region of gray and white matter located in the medial portion of the cerebral hemisphere, bounded by the descending columns of the fornix caudally and the frontal cortex and anterior olfactory nucleus rostrally. It is limited dorsally by the corpus callosum, laterally by the lateral ventricles and ventrally by the olfactory tubercle and preoptic region (Andy and Stephan, 1965; Kappers, Huber and Crosby, 1936).

This region of the telencephalon is first distinguished embryologically as the area epithelialis, located in the medial wall of each cerebral hemisphere and bordering on the lamina terminalis. The ventral part of this area is termed the septum ependymale, which eventually thickens and differentiates into the medial and lateral septal nuclei (Hines, 1922; Smith, 1910). The primordial hippocampus, which lies adjacent to the septum ependymale, is the first cortical structure to differentiate. It develops along the medial wall of the hemisphere in a shallow groove, the fissura hippocampi, which extends from the region of the olfactory bulb to the tip of the temporal pole. The main body of the hippocampus later passes over the interventricular foramen and caudally into the temporal horn. The rostral portion of the hippocampus remains

intimately in contact with the septal region until the neopallium and its commissure, the corpus callosum, begin to differentiate and assume their characteristic configurations. It is the expansion of the developing callosum, both rostrally and caudally, that encroaches on the hippocampus causing it to roll caudad, separating it from the septal region. A remnant of the hippocampus, the induseum griseum, is left along either side of the corpus callosum and it terminates in the rostrally located para-olfactory area (Johnson, 1913).

The embryological development of the septum parallels the phylogenetic evolution of this region (Kappers, Huber and Crosby, 1936). It is present in rudimentary form in lower vertebrates as a relatively undifferentiated mass of gray matter closely associated with the olfactory and primordial hippocampal and striatal regions. In sub-mammalian species a differentiation of medial and lateral septal nuclei are demonstrable but variously developed. In the ascending mammalian evolutionary scale this differentiation becomes more distinct, with secondary subdivisions of these basic nuclei taking place. Contrary to the commonly accepted impression that the septum shows a marked reduction in higher mammals simultaneously with the decreased need for olfaction, Andy and Stephan (1959, 1961, 1965) have shown that it undergoes a progressive enlargement in primate evolution retaining the characteristic features of size, shape and density of cells and fibers which identify this region.

2.   Morphology of the Septum

Since Cajal (1911) described the septal region, in a number of
mammalian species, as consisting of two principal nuclei (medial and
lateral, each containing a homogeneous population of cells), many
studies have been concerned with subdividing this structure on the
basis of its cellular characteristics and its afferent or efferent
projections. Fox (1940), Young (1936) and Lauer (1945), divided
the septum rostro-caudally into medial and lateral lines extending
from the anterior olfactory nucleus caudally to the descending for-
nical columns. The "medial line" of the septum occupies the most
medial portion and consists of the following structures:

(1) Vestigial remnants of the hippocampus include the anterior con-
tinuation of the hippocampus and the nucleus septo-hippocampalis.
The former structure, which is the forward extension of the induseum
griseum, has its rostral termination in the anterior olfactory nu-
cleus. From here it passes caudally under the frontal cortex and
dorsally through the most rostral point of the midline septum to a
position beneath the genu of the corpus callosum. At this point it
branches, with one part continuing over the genu and proceeding cau-
dally on the dorsal surface of the corpus callosum. The other branch,
the nucleus septo-hippocampalis, extends caudally along the ventral
surface of the corpus callosum to the nucleus triangularis. This
latter component is the equivalent of the primordium hippocampi
(Johnston, 1913) and the dorsal septal nucleus as described by Loo
(1931).

(2) <u>The medial septal nucleus</u> lies immediately behind the anterior continuation of the hippocampus. It enlarges towards the midline, becoming continuous with the nucleus of the opposite side, and extends dorsally along the medial border of the nucleus accumbens to blend with the ventral aspect of the lateral septal nucleus. It continues caudally along the medial aspect of the lateral nucleus, above the anterior commissure as far as the fimbrial and triangular nuclei. Ventrocaudally it is continuous with the horizontal limb of the diagonal band of Broca. The anterior portion of the medial septal nucleus is composed of small cells which are similar to those of the anterior continuation of the hippocampus. In its posterior region the cells are relatively large, resembling those of the diagonal band nucleus (Fox, 1940; Lauer, 1945; Loo, 1931).

(3) <u>The nucleus of the diagonal band of Broca</u> is located in the midline region extending from the middle portion of the medial septal nucleus caudally to the anterior commissure. The greater part of the diagonal band extends ventrally and caudally behind the olfactory tubercle. In its dorsal aspect, between the bilateral elements of the medial septal nucleus, are located large cells, while its ventral extent contains relatively smaller cells.

(4) <u>The triangular nucleus</u> is located posteriorly between the two descending columns of the fornix and on the dorsal surface of the anterior commissure.

The "lateral line" of the septum follows the same rostrocaudal extent of the septum as does the previously described components of the "medial lobe". It consists of the following structures:

(1) <u>The lateral septal nucleus</u>, which is the largest component of the septum, is located medial to the lateral ventricle and dorsal to the nucleus accumbens. The nuclei of the two sides form an arch over the top of the two medial septal nuclei. Andy and Stephan (1964) differentiate this arch from the lateral septum and describe it as the dorsal nucleus of the septum, occupying the dorsolateral aspect of the septum just beneath the corpus callosum. Anteriorly the lateral septal nucleus appears dorsolateral to the anterior continuation of the hippocampus and continues caudally to the region of the descending fornix. At the level of the anterior commissure this nucleus is greatly reduced and becomes continuous with the bed nucleus of the anterior commissure and stria terminalis.

(2) <u>The nucleus accumbens</u> is an intermediate region between the striatum and septum, and some authors do not include it as a component of the septum (Andy and Stephan, 1964). It is, however, intimately connected with the lateral septal nucleus. It is bounded ventrally by the olfactory tubercle and laterally by the medial and lateral septal nuclei. It extends from the anterior olfactory nucleus to the bed nuclei of the anterior commissure and stria terminalis with which it is continuous.

(3) <u>The nucleus fimbrialis</u> is a caudal extension of the lateral
septal nucleus which lies ventral and lateral to the descending
columns of the fornix. It is distinguished as a separate compo-
nent from the lateral septal nucleus because fibers from it course
to the habenular nucleus (Loo, 1931).

(4) <u>The bed nuclei of the anterior commissure and stria terminalis</u>
are two nuclei which are located dorsally and ventrally along the
surface of the anterior commissure. They are closely in contact
with the nucleus triangularis, medial septal nucleus, lateral sep-
tal nucleus, fimbrial nucleus and nucleus accumbens (Raisman, 1969;
Valverde, 1965).

3. Intraseptal Connections

There has been little investigation of the intraseptal connec-
tions between the various nuclei outlined above. Since many of these
nuclei blend almost imperceptibly with the adjoining regions it would
appear that they are intimately interconnected with one another via
short internal fibers. Cajal (1955), Raisman (1969) and Tombol and
Petsche (1969) describe many cell types of the septum having axon
collaterals which branch profusely throughout its extent making con-
tacts with other cells. Knook (1965), Raisman (1966) and Valverde
(1963) also describe fibers which interconnect the medial septal,
diagonal band and lateral septal regions. These data suggest a
highly interconnected structure.

4.   Afferent Connections of the Septum

The septum has often been referred to as a subcortical "way station" between the telencephalic structures and the diencephalon since it develops from the junction of these two regions (Fox, 1960; Hines, 1922). It receives its major fiber inputs from the hippocampus, pyriform cortex, amygdala and olfactory tubercle in the telencephalon, and from the hypothalamic regions in the diencephalon.

(1) Afferent connections from the hippocampus

(i)   The commissural fornix system consists of two components: (a) the precommissural fornix which projects to the septal region and has been shown by Powell, Guillery and Cowan (1957) to mediate at least half of the efferent fibers of the hippocampus, and (b) the postcommissural fornix which projects to the anteroventral and anteromedial thalamus and the mammillary bodies (Guillery, 1956; Raisman et al., 1966). Degeneration in the precommissural fornix component to the medial septum, septal fimbrial nucleus, diagonal band and medioventral part of the lateral septal nucleus has been demonstrated by a number of investigators following hippocampal lesions (Fox, 1943; Guillery, 1956; Nauta, 1956; Simpson, 1952; Sprague and Meyer, 1950). More recently Raisman et al. (1966) have demonstrated that degeneration in these areas is produced when lesions are placed in the posterior part of field CA1 of the hippocampus. Lesions in fields CA3 and CA4 result in degeneration which is distributed to the dorsal and lateral parts of the lateral septal

nucleus, the nucleus accumbens and the diagonal band.

(ii)   Dorsal fornix (fornix longus, superior). Fox (1940)
and Sprague and Meyer (1950) have demonstrated that this fiber path-
way, which runs through the anterocaudal extent of the dorsal septum
after perforating the corpus callosum, gives off projections to the
medial septal nucleus and medial portion of the lateral septal nu-
cleus. Evidence by Raisman et al. (1966) has shown that the dorsal
fornix fibers originate in the anterior hippocampal field CA1 which,
when lesioned, results in degeneration in the medial parts of the
fimbrial and triangular nuclei of the septum as well as the medial
septal nucleus. The major projection, however, of these hippocam-
pal fibers is through the postcommissural fornix to the anterior
thalamus and mammillary nuclei.

(2) Afferent connections from the amygdala

(i)   The stria terminalis is a compact fiber pathway pro-
jecting to the septum, preoptic and hypothalamic areas (Fox, 1940,
1943; Heimer and Nauta, 1969; Nauta, 1961; Valverde, 1965). Al-
though Cajal (1911) suggested that this bundle arises in the pyri-
form cortex, more recent evidence has established that it originates
from the caudal extent of the corticomedial amygdaloid nucleus
(Gloor, 1955; Hall, 1963; Lauer, 1945; Leonard and Scott, 1971;
Nauta, 1961; Young, 1936). The fiber projections of the stria ter-
minalis to the septum have been described in detail by Johnston
(1923), Van der Sprenkel (1926), Valverde (1965) and Cowan et al.,

(1965) and Leonard and Scott (1971). At the level of the anterior commissure they are observed to divide into pre- and postcommissural components. The former give collateral or terminal fibers to the bed nucleus of the stria terminalis and nucleus accumbens. The postcommissural component, on the other hand, proceeds ventrally and caudally into the preoptic and hypothalamic regions.

(ii)   The ventral amygdalofugal pathway, or longitudinal association bundle, is a diffuse fiber tract originating mainly in the anterior basolateral amygdaloid nuclei (Fox, 1940; Johnston, 1923). It projects to the diagonal band of Broca, nucleus accumbens of the septum, and to the preoptic and hypothalamic regions along the lateral side of the medial forebrain bundle (Cowan et al., 1965; Fox, 1940, 1943; Johnston, 1923; Leonard and Scott, 1971; Nauta, 1961; Valverde, 1965). In addition to the basolateral amygdaloid contribution to the ventral amygdalofugal pathway, Powell et al. (1965) have shown that efferent fibers of the pyriform cortex are also mediated by this fiber tract after passing through the basolateral amygdala. Lesions in the pyriform cortex produced degeneration which was observed to have an identical distribution to that produced by the basolateral amygdala region. This suggests that much of what has been attributed to an amygdaloid pathway is in fact a projection system of the pyriform cortex.

(3)   Afferent connections from the olfactory tubercle

These pathways have been shown to pass caudally over the medial

surface of the nucleus accumbens to disperse amongst the septal nuclei -- especially the medial septal nucleus (Young, 1936). Similar findings were obtained by Johnson (1959), showing degeneration into the medial septal nucleus following lesions of the olfactory tubercle. There is however some question as to whether these contributions to the septum originate in the tubercle, since lesions in this area may also involve portions of the pyriform cortex and rostral extension of the medial forebrain bundle -- both of which have been shown to have a considerable input into the septum.

(4) Afferent connections from cortical areas

Projections from cortical areas to the septum have been demonstrated, although there is considerable disagreement as to the regions from which these fibers originate and the pathways involved. Young (1936) and Fox (1940) demonstrated an input from the cingulate gyrus to the medial septum and parts of the lateral septal nucleus. On the other hand, a number of investigators have failed to obtain any degeneration in the septum following lesions of the cingulate region (Cragg and Hamlyn, 1959; Domesick, 1969; Raisman et al., 1965). Further contributions from cortical areas 4-5, 6, 9, 11, 13 and 24 have been shown (Kaada, 1951; Mettler, 1935, 1947; Ward, 1948).

(5) The medial forebrain bundle

The medial forebrain bundle is the major afferent projection

pathway to the septum from hypothalamic and midbrain regions. Cajal (1955) described two ascending components of this pathway which reach the septum from the region of the cerebral peduncle: a coarse-fibered tract to the medial septal, diagonal band and dorsal fornix regions; and a fine-fibered tract to the lateral septal region and nucleus accumbens. The fine component was termed the hypothalamo-septal group of fibers by Guillery (1957), because it originates in the lateral hypothalamus; and the coarse component the mesencephalo-septal group, since it originates in the dorsal and ventral tegmen-tal regions of the midbrain (Morest, 1961; Nauta and Kuypers, 1958). Similar results were obtained by Wolf and Sutin (1966) following le-sions of the lateral hypothalamus, although they reported less dege-neration in the lateral septal regions. Most of the coarse ascending degeneration ends in the medial septal nucleus, but some fibers con-tinue into the hippocampus and cingulate regions (Ban, 1964; Guil-lery, 1957; Wolf and Sutin, 1966).

5.   Efferent Projections of the Septum

Fibers from the septum to telencephalic and diencephalic struc-tures appear to be more extensive than septal afferents. The major efferent projections are to the hippocampus, hypothalamus, epithala-mus or habenula, thalamic nuclei and midbrain regions.

(1) Efferent projections to the hippocampus

(i)   Fimbrial fornix fibers from the septum to the hippocampus have been described by Young (1936). Retrograde cell degeneration,

following lesions in the hippocampus and fimbria, have confirmed the presence of such fibers and have shown that they originate mainly in the medial septal nucleus and the diagonal band of Broca (Daitz and Powell, 1954; McLardy, 1955; Mettler, 1943; Rose and Woolsey, 1943). Lesions of the septum, especially the medial septal nucleus, produce degeneration in the fimbria and hippocampus (Ban and Zyo, 1962; Cragg, 1961; DeVito and White, 1967; Morin, 1950; Powell, 1963; Votaw, 1960; Votaw and Lauer, 1963).

(ii) <u>Dorsal fornix</u> projections from the diagonal band region of the septum to the hippocampus have been demonstrated by Sprague and Myer (1950). However, these fibers may not originate in the septum since lesions in the preoptic area or further posterior in the hypothalamus result in the same amount of degeneration in the hippocampal regions (Guillery, 1957; Raisman et al., 1965). Further support for the conclusion that the septum does not contribute to the dorsal fornix was provided by Daitz and Powell (1954). They demonstrated that the retrograde degeneration in the septum was no greater with lesions of both the fimbria and dorsal fornix than with lesions of the fimbria alone.

(2) Efferent projections to the diencephalon

The diencephalic outflow of septal fibers is mediated along a dorsal route via the stria medullaris to the habenular nucleus, and a ventral route via the medial forebrain bundle to the hypothalamus and midbrain regions.

(i)   Septal-habenular projections have been described by a number of investigators (Humphrey, 1936; Lauer, 1945; Loo, 1931; Young, 1936) as arising in the septal fimbrial nucleus and joining the stria medullaris pathway. Lesions of the caudal septum, including portions of the triangular nucleus and lateral septum supports these early descriptions by demonstrating degeneration in this pathway and the habenular nucleus (Cragg, 1961; Nauta, 1956; Raisman, 1966; Valenstein and Nauta, 1959).

(ii)   Septal-hypothalamic projections via the medial forebrain bundle comprise the main efferent pathway from the septum. Nauta (1956, 1958), Powell (1963, 1966) and Raisman (1966) have shown that lesions in the medial and lateral septal nuclei and diagonal band cause extensive degeneration in the lateral preoptic and lateral hypothalamic regions.

(iii)   Septal-thalamic projections have been described by Guillery (1959) to originate in the anterior end of the medial forebrain bundle, diagonal band and nucleus accumbens, and to project to the dorsomedial and ventromedial thalamic nucleus. Similar results were obtained by Cragg (1961) with lesions in the dorsal portions of the caudal septum and in the diagonal band. Alternatively, Raisman (1966) and Trembly and Sutin (1961) have been unable to demonstrate any degeneration in thalamic nuclei following lesions of the septum. They have instead attributed the previously reported thalamic projections to damage of adjacent fiber systems from the pyriform cortex and midbrain

regions.

(iv)   Septal-midbrain projections have been shown, by dege-
neration studies, to originate in the septum and extend along the
medial forebrain bundle into the ventral tegmental areas of the
midbrain. Nauta (1956, 1958) indicates that these projections are
not the result of interrupting hippocampal fibers of passage since
lesions of the hippocampus do not result in degeneration beyond the
lateral hypothalamus and anterior extreme of the midbrain-central
gray region. Similar results were reported by Powell (1963, 1966)
who traced degeneration from the septum to the midbrain tegmentum.
He suggested a difference in the topographical distribution of
hippocampal and septal fibers to the midbrain -- the former pro-
jecting to an anterior and dorsal location in the central gray,
while the latter projects to a more ventral position in the teg-
mentum and which extends further caudally into the midbrain and
pons. As contrary evidence, Raisman (1966) considers these mid-
brain projections from the septum to be hippocampal fibers, and
that the septum does not project further caudally than the hypo-
thalamus.

III Functions of the Septum

The septal area has received considerably less attention than
have many other components of the limbic system such as the amygdala,
hippocampus or hypothalamus -- yet it is considered to be a major

"way station" between these structures. The anatomical evidence reviewed earlier indicates that amygdaloid projections (via the ventro-amygdalofugal and stria terminalis pathways) and hippocampal projections (via the fornix system) converge on the septal area. From the septum, in turn, originates a major part of the medial forebrain bundle -- the principal efferent pathway of the limbic system which passes caudally into the hypothalamus and midbrain regions. In the following sections a brief survey of the physiological and behavioral functions of the septum will be presented. The separation into physiological and behavioral aspects is one of convenience only: the term behavioral being used in the present context to indicate overt response patterns. Since the septum is an integral part of the limbic system it is not surprising that it is involved in many of the same functions as other components of the system.

1. Physiological Functions

(1) <u>Autonomic Effects</u>: A number of investigators have implicated the septum in the control of heart rate and blood pressure. Early studies demonstrated that electrical stimulation of this area produced a decrease in blood pressure which was often accompanied by a decrease in heart rate (Hodes and Magoun, 1942; Kabat, Magoun and Ranson, 1935; Ranson, Kabat and Magoun, 1935). Malmo (1961) reported similar changes in heart rate from rats trained to lever press for intracranial self-stimulation of the septum; while Myers,

Valenstein and Lacey (1963), using the same technique, observed that septal stimulation produced an increase in heart rate or an increase followed by a decrease. In an attempt to account for the contradictory results Malmo (1964) suggested that the histological location of the stimulating electrodes was critical, with the medial septum producing increases and the lateral septum decreases. However, Stuart, Kawamura and Hemingway (1961) reported that both effects could be elicited from the same site of stimulation. Covian, Antunes-Rodrigues and O'Flaherty (1964) and Covian, Lico and Antunes-Rodrigues (1966), in a detailed examination of the effects of septal stimulation on blood pressure and respiration, reported both increases and decreases in these responses, the latter being the most frequent. Although no clear histological differences in stimulation sites were observed in these studies, it has been suggested that there are two antagonistic systems in the septum, and that when stimulated the inhibitory system usually predominates (Covian, 1967).

The septum has also been implicated in other autonomic responses such as changes in pupil size, piloerection, micturition, defecation and salivation (Gastaut, 1952; Hess, 1957; Hodes and Magoun, 1942; Kaada, 1951; Kabat, Magoun and Ranson, 1936).

(2) Somatomotor Effects: Septal stimulation has been reported to both facilitate and inhibit spinal reflexes and cortically-induced movements (Hodes et al., 1951; Peacock and Hodes, 1951). These authors suggested that facilitation and inhibition are related

to two cell types which are intermingled, so that the two responses are frequently produced from the same site of stimulation. Austin and Jasper (1950) and Kaada (1951) reported similar effects of septal stimulation on somatomotor responses although inhibition of movement was observed most frequently. Since no detailed analysis of the histological placements of the stimulating electrodes was made in these studies, it is difficult to ascertain the reasons for these discrepancies in the direction of effects. Many of the placements producing inhibition, however, were located in the extreme anterior or posterior and ventrolateral region of the septum.

Studies have also demonstrated that septal stimulation can produce motor movements such as gross muscle movements of the face, head and upper extremities (Hess, 1957; Votaw, 1960). When lesions were made in these areas, nevertheless, no differences were noted between the preoperative or postoperative behavioral patterns.

In studies of temperature regulation, Akert and Kesselring (1951) and Andersson (1957) have reported that septal stimulation produces shivering and piloerection; whereas lesions of this area have no effect (Stuart, Kawamura, Hemingway and Price, 1962). Similar observations were made by Stuart et al. (1961) in a study comparing the effects of septal and hypothalamic stimulation on shivering and muscle tone. They observed that septal stimulation not only facilitated shivering and increased muscle tone, but also stimulation of some sites often suppressed these responses. These studies provide further support for the view that there are two

overlapping systems within the septum. Stuart et al. (1961) have suggested that these systems differentially activate posterior and anterior hypothalamic regions, which, in turn, respectively suppress or produce the shivering response.

(3) Endocrine Effects: The influence of the septum on endocrine responses is relatively unknown, although a few studies have implicated this region. Endroczi, Schreiberg and Lissak (1963) have demonstrated that stimulation of the septal area has an inhibitory effect on adrenocortical function; while Usher, Kasper and Birmingham (1967) reported that lesions of this area caused an increase in ACTH secretion. A possible role 'n the control of antidiuretic hormone has been suggested by Hayward and Smith (1963) who demonstrated an increased secretion of this hormone following stimulation of the diagonal band and medial septal region. Indirect support for septal involvement in endocrine function was obtained by Lincoln and Cross (1967) who observed that single neurons of this area were responsive to injections of progesterone and estrogen.

In summary, it appears that the septum is involved in many of the same autonomic, somatomotor and endocrine responses which have been related to other limbic structures and which are thought to be regulated by the hypothalamus. Since lesions of the septum do not interfere with most of these responses, it is likely that this area has a modulatory role on hypothalamic integrative mechanisms. Although a number of investigators (Covian, 1967; Kaada, 1951) have

suggested that this modulation is primarily inhibitory, the overall evidence indicates the facilitatory effects are frequently observed also. Often both inhibition and facilitation have arisen from the same site of stimulation.

2. Behavioral Functions

(1) <u>Emotional Behavior</u>:   The septal area was first shown to be associated with changes in emotional behavior by Fulton and Ingraham (1929) and Speigel, Miller and Oppenheimer (1940). They demonstrated that lesions which included this area resulted in a state of chronic rage. Brady and Nauta (1953), in a systematic analysis of behavioral responses following septal lesions, observed similar emotional changes characterized by a state of hyperirritability and vicious attack behavior which they called the "septal syndrome". Many investigators have since confirmed that hyperemotionality occurs following septal lesions (Brady and Nauta, 1955; Harrison and Lyon, 1957; King, 1958; McCleary, 1966; Yutzey, Meyer and Meyer, 1967). It has been suggested that the septum has an inhibitory role in the control of affective behavior and that lesions remove the inhibition resulting in the septal syndrome. Nevertheless, there are a number of studies in which septal lesions failed to produce hyperemotionality (Bond, Randt, Bidder and Rowland, 1957; Buddington, King and Roberts, 1967; Clody and Carlton, 1969; Harrison and Lyon, 1957; Kriekhaus, Simmons, Thomas and Kenyon, 1964; McCleary, 1966; Moore, 1964; Thomas, Moore, Harvey and

Hunt, 1959; Votaw, 1960). Attempts to determine the anatomical regions within the septum which must be destroyed in order to produce the syndrome have usually failed to show a consistent relationship with either site or size of the septal lesions (Harrison and Lyon, 1957; Thomas et al., 1959). More recent studies by Clody and Carlton (1969) and Turner (1970) have reported that lesions confined to the medial septum result in placidity, whereas lesions in the bed nucleus of the stria terminalis and the tracts themselves result in the rage syndrome.

There have been few studies of the effects of electrical stimulation of the septum on affective behavior. Siegel and Skog (1970) reported increases, decreases or no change in the mean latency to attack and in escape behavior. Rubinstein and Delgado (1963) demonstrated that stimulation inhibits aggressiveness, while Votaw (1960) observed no effects from similar sites within the septum.

The conflicting effects which the septum exerts on affective behavior make it difficult to draw any conclusions regarding its influence beyond a general suggestion that it is in some manner involved in the production of these responses. The more recent evidence showing some localization of effects within the septum (Clody and Carlton, 1969; Turner, 1970), raises the possibility that there may be a medial facilitatory region and a more lateral inhibitory region.

(2) <u>Learning Behavior</u>:   Lesions of the septum have been demonstrated, on the one hand, to improve performance in conditioned active avoidance tasks (CAR) (Fox, Kimble and Lickey, 1964; Kenyon and Kriekhaus, 1965a; King, 1958; Kriekhaus <u>et al</u>., 1964; Zucker, 1965).   Other investigators have reported deficits in active avoidance behavior following septal lesions (Kenyon and Kriekhaus, 1965b; Moore, 1964; Nielson, McIver and Boswell, 1965; Rich and Thompson, 1965).   Although suggestions have been put forward to explain these discrepancies in terms of procedures and localization of lesions (McCleary, 1966) no conclusions may be reached on these apparent contradictions.

Similar discrepanices are observed with acquisition of the conditioned emotional response (CER).   Brady and Nauta (1953) demonstrated that following septal lesions there was a decrease in the "freezing" response normally associated with the conditioned shock stimulus.   Similar decreases in the CER have been observed by Harvey, Lints, Jacobson and Hunt (1965) and Sheer (1961) in rats with septal lesions.   However, electrical stimulation of the septum has also been observed to markedly attenuate the CER (Brady and Conrad, 1960) a finding which is difficult to reconcile with the effects of lesions.

Those studies showing a decrease in CER and an increase in CAR attribute these results to the degree of activity which is exhibited by the septal lesioned animals as compared to normals.   In accordance with the inhibitory hypothesis of septal function, it was suggested

that lesions of this area would result in a concomitant increase in spontaneous activity and thus the increase in CAR and decrease in CER. Although a number of studies have demonstrated this to be the case (Brady and Nauta, 1953, 1955; Kaada, Rasmussen and Kviem, 1962; McCleary, 1961; Thomas et al., 1959) conflicting results showing decreases or no changes in activity levels have also been observed (Clody and Carlton, 1969; Douglas and Raphelson, 1966; Kenyon and Kriekhaus, 1965a; Nielson, McIver and Boswell, 1965; Schwartzbaum and Gay, 1966). Electrical stimulation of the septum also indicates contradictory results since both increases (Brady and Conrad, 1960; Kasper, 1964) and decreases in activity levels have been shown (Kaada, 1951; Rubinstein and Delgado, 1963).

In passive avoidance experiments, where the animal is required to withhold or suppress a previously learned response, McCleary (1961) and Kaada et al. (1962) have demonstrated that septal-lesioned animals take longer to inhibit the response. However, Kenyon and Kriekhaus (1965a) and Fried (1969) have shown no such deficits in passive avoidance tasks. In spite of these contradictory results McCleary (1966) has suggested that the inability to suppress previous responses, termed "response perseveration" is once again support for the inhibitory hypothesis of septal functions.

(3) Consummatory Behavior: An increase in daily water intake has been reported following bilateral lesions of the septum (Carey,

1967;   Harvey and Hunt, 1965;   Wolfe, Lubar and Ison, 1967).   The hyperdipsia is primary and, according to some authors (Blass and Hanson, 1970;   Lubar, Boyce, Schaefer and Wells, 1968;   Wishart and Mogenson, 1970), is due to the removal of a satiety mechanism. However, the polydipsia following septal lesions has also been attributed to polyuria secondary to an interference with the neural mechanism controlling antidiuretic hormone secretion (Lubar, Schaefer and Wells, 1969), response perseverations (Gittleson and Donovick, 1968), enhanced sensitivity to taste (Beatty and Schwartz-baum, 1967), and increased sensitivity to deprivation of either food or water (Donovick and Burright, 1968;   Singh and Meyer, 1968;   Wishart and Mogenson, 1970).   Furthermore, lesions of the septum do not always result in hyperdipsia (Gotsick, 1969;   Grace, 1968), and critical areas which produce this effect have yet to be determined (Besch and Van Dyne, 1969;   Carey, 1967;   Lubar et al., 1968;   Pizzi and Lorens, 1967).

Electrical stimulation of the septum has been reported to result in a decrease in water intake (Mabry and Peeler, 1968) and in lapping for water (Asdourian, 1962).   These observations were confirmed by Wishart and Mogenson (1970), who suggested that the septum activates an inhibitory or satiety mechanism which influences the drinking system in the lateral hypothalamus.   Kasper (1965), however, found that continuous low level stimulation of the septum produced no change in the level of water intake.

The septal area has also been shown to be involved in the control

of food intake, although once again the direction of the influence

is non-conclusive. Reynolds (1962) has demonstrated increases,

decreases or no changes in food intake following septal lesions.

Singh and Meyer (1968) have shown transient increases in food in-

take, while Beatty and Schwartzbaum (1968) and Pizzi and Lorens

(1967) report that septal-lesioned animals are lighter in weight

than normal animals. Electrical stimulation of the septum has been

shown to reduce feeding (Fonberg and Delgado, 1961; Rubinstein and

Delgado, 1963); while chemical stimulation with norepinephrine in-

jections into the septum results in feeding in satiated animals

(Booth, 1967) or no effect (Grossman, 1964).

(4) Self-Stimulation: Olds and Milner (1954) first reported

that rats would press a lever to obtain septal stimulation, and

later demonstrated that this area, especially the diagonal band

region, was the anterior extent of a widely distributed "positive

reinforcement" system (Olds, 1958). Stein and Ray (1959), in a

test situation in which the animal could regulate the preferred

current level for reward, observed that septal self-stimulation

was poorly regulated since the animals would raise the current

until convulsions would occur. This finding, they suggested, in-

dicated that the septum did not contain any overlapping "negative

reinforcement" system, which if present would have been indicated

by a regulation of the current level. However, some studies have

demonstrated neutral or negatively reinforcing points within the

septum which overlap with those producing positive effects (Bursten and Delgado, 1958; Doty, 1961; Newman, 1961). It would appear therefore that the septum contains both reward and punishment areas.

(5) Arousal: The septal area, especially the medial and diagonal band regions, has been implicated in arousal patterns of the hippocampus and neocortex. Green and Arduini (1954) demonstrated that lesions in the septum eliminated the characteristic slow wave responses of the hippocampus which normally follow high frequency stimulation of peripheral inputs or activation of the midbrain reticular formation. Arousal or desynchronization of neocortical activity is invariably associated with the appearance of these hippocampal slow waves known as theta rhythm. Conversely, Stumpf, Petsche and Gogolak (1962) demonstrated that stimulation of the septum resulted in the theta rhythm and that the cellular discharge of the diagonal band region correlated with the slow wave activity (Petsche, Stumpf and Gogolak, 1962). These data suggest that the septum functions as a pacemaker in the production of theta rhythm and arousal.

3.   Postulated Roles of the Septum in the Control of Physiological and Behavioral Functions

The experimental findings clearly demonstrate that the septal area is involved in autonomic, somatomotor, endocrine and behavioral functions, but the precise role it plays in the control of such

responses remains unclear. A number of possibilities are suggested from the data, the foremost of which describes the septum as exerting an inhibitory influence. The supportive evidence for such a role relies heavily upon the stimulation work reported by Kaada (1951), and upon lesioning data implicating it in affective behavior (McCleary, 1966). There is sufficient contradictory evidence, nevertheless, to show that stimulation does not always result in inhibition nor lesions in a release of inhibition. These differences raise serious questions concerning the acceptability of an all inclusive "response inhibitory" role for the septal area.

An alternative explanation, which would account for observations of both facilitatory and inhibitory effects produced by either stimulation or lesions, is that there is a degree of topographical specificity within the septum. Relatively few investigations have considered this possibility. Most workers have been primarily interested in demonstrating that the septum, per se, influences a certain response pattern with little regard to the area of stimulation or lesion. Consequently, if there is some differentiation between areas producing facilitation or inhibition, then the lesioned or stimulated sites may encroach on one or both of these areas resulting in conflicting results. Further support for this suggestion is that the septal area anatomically consists of a complexity of many differentiated nuclei, and these could, as was suggested by Andy and Stephan (1965), Clody and Carlton (1969) and Malmo (1964) be functionally distinct. Once again the results of a

number of studies do not support such a view (Harrison and Lyon, 1957; Hodes et al., 1951; McCleary, 1966; Siegel and Skog, 1970; Stuart et al., 1961). These demonstrate that at one point in time stimulation or lesions of one site may elicit a facilitatory effect, whereas at another time they can produce the opposite or no effect. We are therefore left with the possibility that there is no topographical specificity within the septum and that it consists of a homogeneous mixture of both inhibitory and facilitatory neurons which are extensively intermingled.

Another important factor which has frequently been overlooked by a number of investigators is that the septum is not an isolated structure but is interconnected with other limbic components, especially the hypothalamus. As described previously, many of the functions associated with the septum are presumably integrated at the level of the hypothalamus, and the septum, although involved, is not of critical importance. The effects which the septum exerts may not be to alter response patterns directly, but to modulate hypothalamic control mechanisms which are the primary focus for such functions. By examining the manner in which the septum interacts with hypothalamic response patterns, rather than observing its effects in isolation, it may be possible to obtain a better means of interpreting its functional role. Such studies are uncommon. Siegel and Skog (1970) have reported that hypothalamically-elicited attack behavior is inhibited or unchanged by stimulation of the septum, while hissing and escape responses tended to be facilitated.

No clear differentiation of regions within the septum producing
these different effects was described. The authors concluded
that these data make it unlikely that the septum exerts an in-
hibitory role on motor responses, but they suggest that the sep-
tum modulates by acting directly on hypothalamically elicited
aggressive behavior.

Further support for the suggestion that the septum influen-
ces hypothalamic mechanisms is drawn from electrophysiological
studies. Sutin (1963) and Sutin, Van Orden and Tsubokawa (1963),
in an attempt to determine factors which influence the satiety
mechanism of feeding behavior, have examined the excitability
properties of some of the afferent pathways to the ventromedial
hypothalamic nucleus. They reported that evoked responses re-
corded in the ventromedial region following septal stimulation
were increased by norepinephrine injections directly into the hy-
pothalamic nucleus and into the carotid arteries. The interpre-
tation was that the septum projects into this area of the hypo-
thalamus and further that factors influencing the ventromedial re-
gion may result in an alteration in the response which the septum
exerts on it.

Electrophysiological studies of unit recordings from anterior,
posterior, and ventromedial nucleus provide further evidence that
the septal area influences hypothalamic mechanisms. Dafny and Feld-
man (1969), in a study of extrahypothalamic stimulation effects on
posterior hypothalamic units in the cat, demonstrated that the septum

produced mainly an inhibitory effect -- although some units were fa-
cilitated and many remained unchanged. Murphy et al. (1968b),
Oomura et al. (1967) and Tsubokawa and Sutin (1963) have reported
that septal stimulation exerts a predominant facilitatory effect on
ventromedial hypothalamic unit activity: while the few lateral hy-
pothalamic neurons from which they recorded exhibited both an in-
creased and, particularly, a decreased activity. These studies
support the response-modulatory hypothesis concerning limbic in-
fluences on hypothalamic mechanisms. Since their primary concern
was to demonstrate that the septum influences the hypothalamus
little attention has been paid to the areas of stimulation within
this region; only one of the above papers (Murphy et al., 1968b)
presents data indicating where in the septum stimulation was made.

THE PRESENT STUDY

On the basis of the evidence reviewed thus far, the septum has been described as an integral component of the limbic system, located between rostral forebrain structures (amygdala, hippocampus) and the hypothalamus caudally. In this respect it is in an ideal location to receive information from these forebrain structures and to exert a response "modulatory" or "regulatory" influence on behavioral and physiological responses which are under primary hypothalamic control. Little is known about the effects which this area exerts on the hypothalamus. A number of alternative suggestions have been made:

(1)   the septum is part of a forebrain inhibitory system which directly influences hypothalamic mechanisms;

(2)   the septum has topographically distinct regions which exert either inhibitory or facilitatory influences on hypothalamic mechanisms;

(3)   the septum has extensively overlapping regions which exert both inhibitory and facilitatory influences on hypothalamic mechanisms.

The present investigation is an attempt to demonstrate septal

modulation of the hypothalamus, and to determine which of the above alternatives might best describe it. The first of three experiments involved the use of the single unit recording technique in order to determine whether electrical stimulation of the septum influences the lateral hypothalamus. The major conclusion of this study was that the direction and magnitude of the effects (either facilitatory or inhibitory) produced by septal stimulation were, in part, dependent upon the spontaneous activity level of neurons in the lateral hypothalamus. On the basis of these data it was postulated that a similar relationship could be demonstrated between septal effects and the level of neural activity using a behavioral response pattern. The second experiment was therefore designed to test this proposal by: (1) observing the effects of electrical stimulation of the septum on the rate of self-stimulation of the lateral hypothalamus when electrodes were implanted in these areas under electrophysiological control and (2) to determine whether the direction and magnitude of these effects are related to the level of neural activity at the site of the hypothalamic electrode. By assuming that low rates of self-stimulation were an indices of relatively low levels of neural activity and higher rates a higher level of activity, as suggested by Olds (1962, 1968), it was demonstrated that septal stimulation exerted a facilitatory influence on lateral hypothalamic self-stimulation when the rates were low and an inhibitory effect when the rates were high. Evoked potentials recorded in the lateral hypothalamus with septal stimulation suggested the possibility that

different pathways may mediate the described facilitatory and inhi-
bitory effects exerted on the lateral hypothalamic self-stimulation
rates. Thus the third experiment was an attempt to describe the
specific nuclei or regions within the septum which are most effec-
tive in eliciting characteristic evoked responses in the lateral
hypothalamus, and to determine the direction of effect which these
regions exert on lateral hypothalamic unit activity.

METHODS

A total of one hundred and ninety-two male Wistar rats weighing between 250-400 g were used in the three segments of this study: 170 in acute experiments (92 for microelectrode recording and 78 for macroelectrode recording) and the remaining 22 in chronic experiments. In microelectrode recording experiments the animals were anaesthetized with ethyl carbamate (1.0 - 1.5 g/kg i.p.), while animals used for macroelectrode recording were anaesthetized with either sodium pentobarbital (30-40 mg/kg i.p.) or ethyl carbamate. Surgery was performed on animals to be used in chronic experiments under sodium pentobarbital anaesthesia. Supplemental doses to produce a steady state of light anaesthesia were given as necessary throughout the experiments. Body temperature was monitored by a rectal thermistor probe and maintained between 36° to 37°C using a heat lamp regulated by a temperature controller (Model 73, Yellow Springs Instruments) or by the use of a hot water bottle.

1. Surgical Procedures

(1) <u>Acute Preparations</u>: The animals were placed in a Kopf

stereotaxic frame (Model 500) with the head rigidly fixed by the incisor bar at 1.5 mm below zero. A midline incision approximately 20 mm in length was made through the scalp, the flaps of which were then retracted laterally and held with mosquito forceps. The surface of the skull was then scraped and dried. A 6 x 6 mm piece of bone was removed and the dura incised, so that the underlying cortical tissue was exposed over an area roughly corresponding to boundaries 2.5 mm anterior to the bregma, 3.5 mm posterior to the bregma and 3 mm on either side of the saggital suture. Special care was taken not to damage the superior saggital sinus when removing the bone. The exposed cortex was covered with warm mineral oil or saline to keep the area moist throughout the experiment. Additional bone was removed from the skull overlying the olfactory bulb so that visual placements of electrodes could be made in experiments involved with stimulation of this area. In preparations involving sciatic nerve stimulation, the nerve was exposed through an incision over the lateral inter-muscular septum of the thigh for approximately 10 mm in the leg contralateral to the recording electrode placement. The distal end of the nerve was cut and the remainder was covered in mineral oil.

Electrodes were stereotaxically implanted into the septum, lateral hypothalamus, olfactory bulb, hippocampus and stria terminalis using Kopf electrode holders. For microelectrode recording a Kopf hydraulic micromanipulator (Model 1207B) was used to lower the

electrode into the lateral hypothalamus. The anterior-posterior (AP) stereotaxic zero for all electrode placements was measured from the junction of the sagittal suture and bregma while the lateral coordinate (L) was taken from the midline position of the superior sagittal sinus. Vertical coordinates (V) were all measured from the surface of the cortex. Electrodes were positioned in the septum at AP, 0.5-2.0 mm anterior to bregma; L, 0.1-1.3 mm; V, 3.5-5.5 mm below surface of the cortex (BSC); the lateral hypothalamus at AP, 1.5-3.0 mm posterior to bregma; L, 1.0-1.8 mm; V, 6.5-9.0 mm, BSC; the hippocampus at AP, 1.0-3.0 mm posterior to bregma; L, 1.0-2.0 mm; V, 3.0-4.5 mm, BSC; and the stria terminalis at AP, 2.5-3.5 mm posterior to bregma; L, 3.0-4.0 mm; V, 4.5-5.5 mm, BSC. The ipsilateral olfactory bulb electrode placement was usually made visually at coordinates which corresponded to 7.0 mm anterior to bregma; L, 1.0 mm; V, 1.5-2.0 mm, BSC. The vertical positions for all of these electrode placements were adopted from the Konig and Klippel (1963) atlas for the rat.

(2) <u>Chronic Preparations</u>: Similar surgical procedures and coordinates were used for the chronic implantation of electrodes into the septum and lateral hypothalamus, except that the electrodes were inserted through small holes in the calvarium (1.0-1.5 mm in diameter). A needle was used to puncture the dura and the electrode was then lowered to the desired depth. Cranioplastic cement anchored to small jewellers screws placed in the adjacent bone was

then applied to secure the electrode in position.

2.   Stimulation and Recording Procedures

(1) Acute Preparations: Twenty-six gauge concentric bipolar electrodes (SNE 100, Rhodes Instruments, Calif.), having a tip separation of 0.3-0.5 mm and a DC resistance in normal saline of 30-70 kΩ, were positioned according to the previously described coordinates in the septum, hippocampus, stria terminalis and olfactory bulb.   Bipolar stainless steel electrodes (3 mm tip separation) were used to stimulate the exposed contralateral sciatic nerve. Single and repetitive biphasic rectangular pulse stimulation (1-100 Hz) of the central and peripheral sites were delivered by Grass S4K stimulators through isolation units (Grass SIU 4678) and the pulse parameters were 0.1-0.5 msec in duration and .05-.4 mA in current intensity (1-15 V).   The stimulators were controlled either manually in the case of single pulse stimulation or by a programmer (Devices Digitimer, Mk. IV) coupled to a relay unit (Devices Model 255).   The latter produced stimulus trains of desired length and also double pulse stimulations so that interactions between two areas could be determined.

Macroelectrode recordings were made using the same type of concentric bipolar electrode as those used for stimulation.   Recordings of extracellular unit activity were made with stainless steel, tungsten and glass microelectrodes.   The stainless steel electrodes were prepared from insect pins (size 00) according to the method of Green

(1958). The tungsten electrodes were prepared by inserting a 5 mil

tungsten wire (Sylvania Electric Products, Tonawanda, N.Y.) into a

25 gauge hypodermic needle, and this was then electroetched according

to the method of Hubel (1957). Both of these types of electrodes

were insulated in a lacquer (E-33-N, Insl-X Company Inc., Ossining,

N.Y.) and allowed to dry for 24 hrs. These electrodes had tip dia-

meters of 1-3μ and shaft diameters of 150-300μ which gradually ta-

pered to the tip. The exposed tip was 100-150μ in length and the DC

resistance in normal saline, measured on a vacuum tube voltmeter,

was between 1-10 mΩ. The electrical isolation of the electrode

shaft was tested under a dissecting microscope by passing a low

voltage DC current while the electrode was immersed in saline.

Glass microelectrodes were prepared from Corning 7740 Pyrex capil-

lary tubing (outside diameter 1.5 mm) which were pulled in a Kopf

micropipette puller (Model 700B). The electrodes were filled indi-

vidually under a dissecting microscope with 3M NaCl which had been

previously filtered through 0.45μ millipore paper (Millipore Corp.).

The electrolyte was first injected into the shaft of the electrode

using a long 31 gauge hypodermic needle and then a pyrex probe with

long fine tip (15-20μ) was pushed as far down the shaft of the elec-

trode as possible, moving the solution with it. Once the solution

reached a certain point in the shaft, capillary action would draw

it to the tip of the electrode. The electrodes prepared in this way

had tip diameters of less than 1μ and a DC resistance in saline from

5-20 mΩ. For recording purposes an internal micropipette of Ag/AgCl/

Pt. Black (MPI-Hybrid, Rhodes Instruments) was inserted into the shaft of the electrode to establish contact between the electrolyte and amplification system.

The microelectrode or the inner core of the bipolar macro-electrode was coupled to grid 1 of a Grass differential AC pre-amplifier (Model P14). The reference electrode for the monopolar microelectrode, a stainless steel jewellers screw inserted into the skull, and the outer core of the bipolar electrode were coupled to grid 2 of the preamplifier. Extracellular unit activity was filtered using a 30 Hz - 50 KHz bandpass, while evoked potential recordings were filtered using a .3-300 Hz bandpass. The recorded electrical activity was led through a Tektronix 2A61 preamplifier into a Tektronix 565 oscilloscope or through a Tektronix 3A72 dual trace amplifier into a Tektronix 564 storage oscilloscope. In some cases both unit activity and evoked potentials were recorded simultaneously on two beams of the oscilloscope. Amplifier outputs were also connected to an audiomonitor (Grass AM4), and to a Philips (Analog-7) magnetic tape recorder which was used to store data for later analysis. Photographs of the neural responses were made using a Tektronix Polaroid camera (Model C-12), or with a Nihon-Khoden continuous recording camera (Model PC-1B) using Kodak paper film (Kind 1732). Figure 2 is a schematic illustration of the stimulation and recording apparatus.

(2) <u>Chronic Preparations</u>:   Twisted bipolar electrodes (Plastic

Figure 2   Schematic illustration of the stimulation and

                recording apparatus used in the electrophysio-

                logical experiments. Abbreviations: CRO =

                cathode ray oscilloscope; PREAMP = preampli-

                fier; SIU = stimulus isolation unit; STIM =

                stimulator; BIOMAC = BIOMATION 1000 COMPUTER;

                PREP = preparation.

RADIO-FREQUENCY SHIELDED ROOM
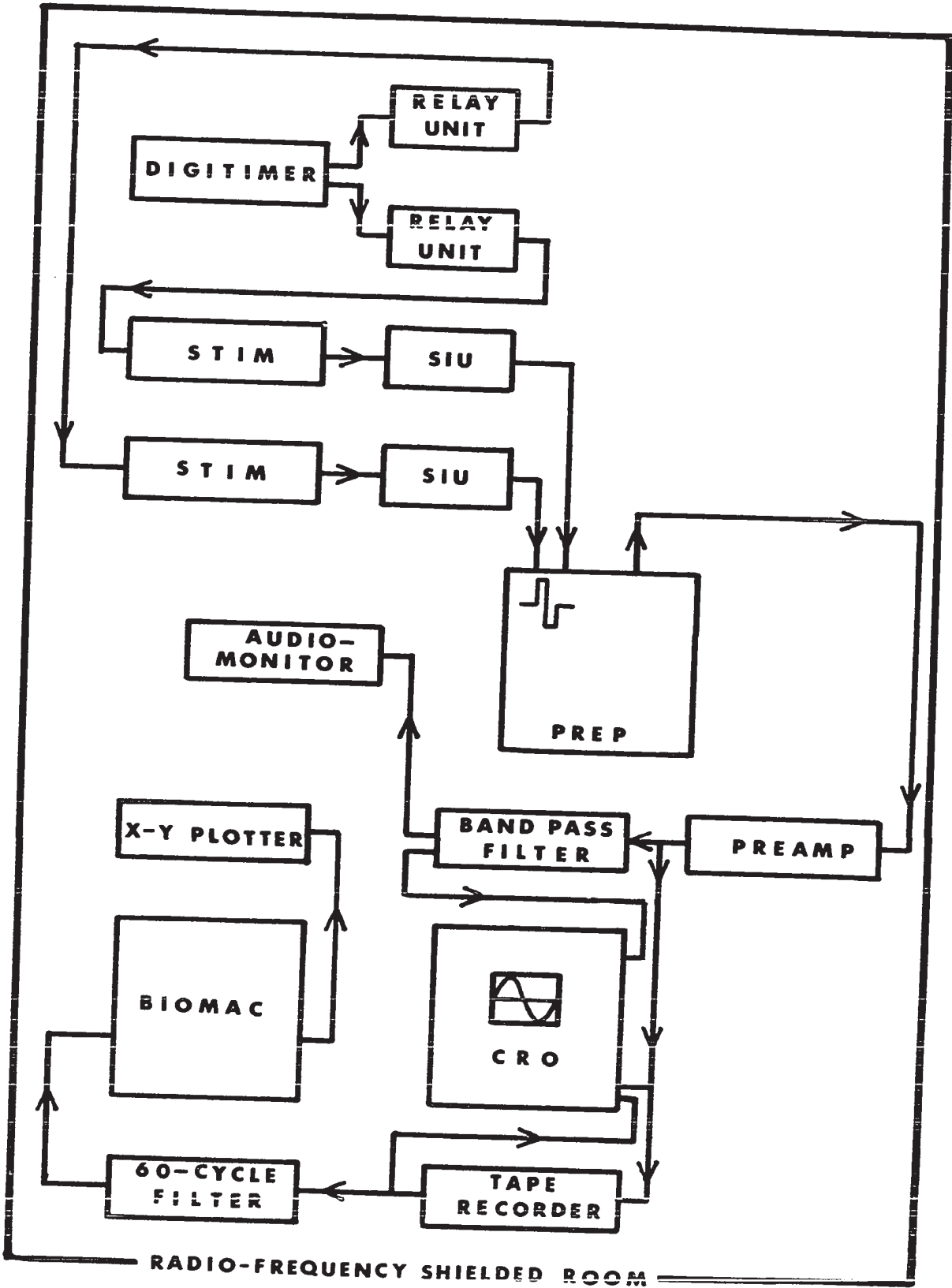
Products MS 303-.018) with a tip separation of 0.1 - 0.2 mm and a
DC resistance of 70-75 kΩ in normal saline were used. Following
surgery, evoked potentials were monitored in the lateral hypo-
thalamus in response to stimulation of the septum using the same
procedures as those described for acute preparations. During
chronic testing electrical stimulation was delivered from two
Grass S4K stimulators coupled to stimulus isolation units (Grass
SIU 4678).

The self-stimulation experiments employed 0.5 sec trains of
50 Hz rectangular pulses of 0.5 msec duration and 50-500μA current
intensity. The current level was constantly monitored on a Tel-
equipment (Type 43B) oscilloscope and measured by the voltage drop
across a 10 kΩ resistor in series with the electrode. The stimulus
train durations of 0.5 sec were controlled by Hunter Timers (Model
111-C).

3.   Testing Procedures and Data Analysis

(1) Microelectrode Recording: Optimal effects produced by sti-
mulation of the septum on lateral hypothalamic unit activity were
observed to occur with repetitive pulses of 20 Hz, 0.5 msec dura-
tion and 10-15 V. Lower frequencies (1-10 Hz) with the same pulse
parameters were used for olfactory bulb and sciatic nerve stimula-
tion. These parameters are also known to minimize A-delta and C-
fiber activation of the midbrain reticular formation by sciatic
nerve stimulation (Lindsley and Adey, 1961).

Various criteria were used to determine whether a unit was influenced by stimulation of one or more of the following sites: the septum, olfactory bulb or sciatic nerve. Changes in the rate of discharge were analyzed using the McNemar test (Siegel, 1956). In this analysis, A is equal to the number of times there is a decrease in the total number of spikes firing in the 1 sec period following stimulation as compared to the 1 sec period before stimulation, and D is equal to the number of times there is an increase in the total number of spikes following stimulation.

$$x^2 = \frac{(A-D)^2}{A+D}$$

The critical ratio test, a variation of the McNemar test, was also used to analyze changes in the discharge rate (Dafny and Feldman, 1967). In this test A stands for the total number of spikes in the 1 sec period following stimulation, and B is the total number of spikes in the 1 sec period before stimulation.

$$C.R. = \frac{A-B}{A+B}$$

Lateral hypothalamic units were also analyzed for a correlation between the spontaneous discharge rate and the discharge rate produced by septal stimulation, using a Spearman rank correlation (Siegel, 1956). The data were analyzed on an I.B.M. 7040 computer programmed with the computational formula:

$$r = 1 - \frac{6\sum\limits_{i=1}^{N} di^2}{N^3 - N}$$

where r equals the correlation coefficient, di^2 equals the square of the differences in ranks between the firing rate before and after stimulation and N equals the number of observations. An "a posteriori" test of significance for the correlation coefficients was made using the formula:

$$t = r \sqrt{\frac{N-2}{1-r^2}}$$

In each of the above tests a probability level of less than 5% due to chance ($p < 0.05$) was used. A minimum of 10 trials of stimulation was carried out on each unit, each trial consisting of 3 sec: 1 sec before stimulation, 1 sec of stimulation, and 1 sec following stimulation. In the case of olfactory bulb and sciatic nerve stimulation trains of stimuli of 1 sec or 3 sec were used on each trial. Inter-trial intervals were at least 6 sec in order to avoid any possible cumulative effects of stimulation.

Each lateral hypothalamic unit analyzed for the effects of combined stimulation of the septum and olfactory bulb was first

shown to be altered by stimulation of one or both of these areas.
This was followed by an equivalent number of stimulation trials in
which the train of pulses to the olfactory bulb lasted for 3 sec,
the last sec overlapping with that of the 1 sec of septal stimu-
lation. This procedure permitted a comparison of the effects of
septal stimulation under two conditions of discharge rates, one
the "normal" or spontaneous discharge rate and the other the rate
produced by olfactory bulb stimulation.

In addition to the analysis of changes in the rate of firing
of lateral hypothalamic units, their spontaneous discharge was al-
so analyzed by interval, frequency and post-stimulus time histo-
grams. Such procedures were only conducted on units from which
sufficient data could be obtained over a relatively long period
of time. Histograms were made from either a Biomation 1000 (Data-
Laboratories) multi-purpose computer or manually from photographed
records and directly from the storage oscilloscope.

(2) Macroelectrode Recording: Evoked potentials were recorded
in the lateral hypothalamus following stimulation of the septum,
hippocampus and stria terminalis, and photographed from either the
storage oscilloscope or from the Biomation 1000 when response
averaging was used. Responses with the largest amplitude or those
exhibiting phase reversal were selected to represent the central
focus of projection from the stimulated site. Latencies were
measured from the beginning of the stimulus artifact to the peak

of the response wave (peak latency, P.L.) and/or to the onset of the response wave (onset latency, O.L.). No attempt was made to analyze the polarity of the evoked responses since bipolar recordings were made.

In order to determine the pathways mediating the evoked responses recorded in the lateral hypothalamus, electrolytic lesions (2 ma, 20 sec; using a Stoelting DC lesion maker, Model no. 58040) were made in regions of the septum and the effect which these had on the amplitudes of lateral hypothalamic evoked responses produced with hippocampal or stria terminalis stimulation were observed. The alterations in the evoked responses were expressed as a percentage difference from the control amplitudes. The evoked responses following lesions were observed for up to two hr in order to determine whether the alteration in amplitude was a result of general depression or from the lesion.

(3) <u>Chronic Self-Stimulation</u>:   Following a 5-7 day post-operative recovery period, 14 animals were tested for lateral hypothalamic self-stimulation using the previously described parameters of stimulation (50 Hz, 0.5 msec duration, 50-500µA intensity, 0.5 sec train duration). Once the animals were identified as self-stimulators (>20 lever presses in 3 min) two current levels were used: a low level which was threshold for self-stimulation and a high level (1.5 - 2.5 x threshold). The animals were then tested once daily for five to ten, 3 min periods, to obtain baseline rates

of self-stimulation at each of these two current levels.

The interaction of septal and lateral hypothalamic stimulation was produced by preceding each hypothalamic stimulation pulse with a septal pulse at intervals of 5 and 15 msec. Septal stimulation parameters were the same as those used for lateral hypothalamic stimulation except that the range of current levels was lower (50-100μA). These current levels were determined by initially setting them equal to the threshold lateral hypothalamic level; or, if this produced any indication of motor deficit, behavioral arrest or seizure activity, the level was then set at one-half the lateral hypothalamic threshold current.

Once the baseline rates of self-stimulation at each of the two lateral hypothalamic current levels were obtained and a current level for septal stimulation was determined, the animals were then tested to observe the effect of septal stimulation on the rate of lateral hypothalamic self-stimulation. Each animal was tested for a 24 min session daily for 6 days. Table I shows how these sessions were divided for the experiment. Each session consisted of two parts, one in which the rate of self-stimulation was measured using threshold and the other at suprathreshold current levels. Each of these parts was subdivided into four 3 min periods: (a) control LH self-stimulation rate; (b) septal-LH interaction rate, 5 msec inter-pulse interval; (c) septal-LH interaction rate, 15 msec inter-pulse interval; (d) LH self-stimulation repeated. Each animal was also given a 1 min "warm-up" period of LH stimulation prior to the testing

TABLE 1

SUMMARY OF TESTING PROCEDURE*

	Threshold Current				Suprathreshold Current			
Warm-up	Control	S-LH$_{(5)}$	After	S-LH$_{(15)}$	Control	S-LH$_{(5)}$	After	S-LH$_{(15)}$

*Following a 1 min "warm-up", each session was divided into eight 3 min periods consisting of control, S-LH interaction of 5 msec, S-LH interaction of 5 msec, S-LH interaction of 15 msec, and after period, for both threshold and suprathreshold currents. Abbreviation: S-LH, septal-lateral hypothalamic interaction.

procedure in each session. The sequence of testing was alter-
nated to control for any cumulative effects. In addition, the
animals were tested on two occasions with eight sequential 3 min
tests with LH stimulation alone. The rates of lever pressing re-
mained constant throughout each of these test periods indicating
that fatigue or time in the test situation did not influence the
self-stimulation rates.

Following these testing procedures comparisons were made
between the rates of self-stimulation in the control period with
those of septal-LH interactions at 5 and 15 msec and with the
after period rates of self-stimulation using a "t" test for re-
lated samples.

4.   Histological Analysis

In those experiments in which stainless steel microelectrodes
were used the recording sites were marked by small DC anodal le-
sions (6 μA, 10 sec; with the reference electrode placement at
the wound edge) producing iron deposits at the electrode tips. In
preparations using tungsten electrodes, lesions at the tip were
made with anodal DC currents of 10-20μA for 20 sec; with glass
microelectrodes, lesions were produced following 5 mA current
applied for 2 min. In most cases the marked sites were the most
ventrally located in a specific penetration and the locations from
which other units were recorded were determined by reference to
this point.

The most ventral stimulation and recording sites of the macro-electrodes were marked by passing a DC anodal current of 6-10μA for 10-15 sec through the inner core of the concentric bipolar electrode with reference to the outer core.

The animals were then given an overdose of the anaesthetic agent and perfused with 0.9% NaCl solution followed by a potassium-ferrocyanide-formalin (1 gm %) solution. Histological verification of the electrode sites was made by cutting 50μ frozen sections and staining them with either cresyl violet or thionin. This fixation and staining procedure has been shown to result in minimal ($<$ .5 - 8%) shrinkage of the tissue so that the locations of the electrode placements in the histological sections are relatively accurate indications of the actual sites of stimulation and recording (Barraclough and Cross, 1963; De Groot, 1959; Konig and Klippel, 1963).

RESULTS

The results of this study are presented in three separate
parts following the chronological order in which they were obtained.
The first part describes the effects of repetitive septal stimula-
tion on lateral hypothalamic unit activity, while the second de-
scribes the effects of septal stimulation on lateral hypothalamic
self-stimulation. The last part describes: 1) the different areas
of the septum from which stimulation produces characteristic evoked
potentials in the lateral hypothalamus; and, 2) the effects which
these areas exert on single unit activity in the lateral hypothala-
mus.

I   Effects of Septal Stimulation on Lateral Hypothalamic Unit
     Activity

Extracellular recordings were obtained from a total of 432
lateral hypothalamic (LH) neurons in these experiments. The spon-
taneous discharge rates of 160 of these neurons are shown in Fig.
3. The mean discharge rate was 8.9/sec with a range from 1/sec
to 50/sec. These discharge rates are similar to those reported

Figure 3   Distribution of spontaneous discharge rates for

160 lateral hypothalamic neurons. Mean dis-

charge rate ($\bar{x}$) = 8.9/sec. These discharge

rates were calculated from twenty random 1 sec

intervals over a period of two minutes.
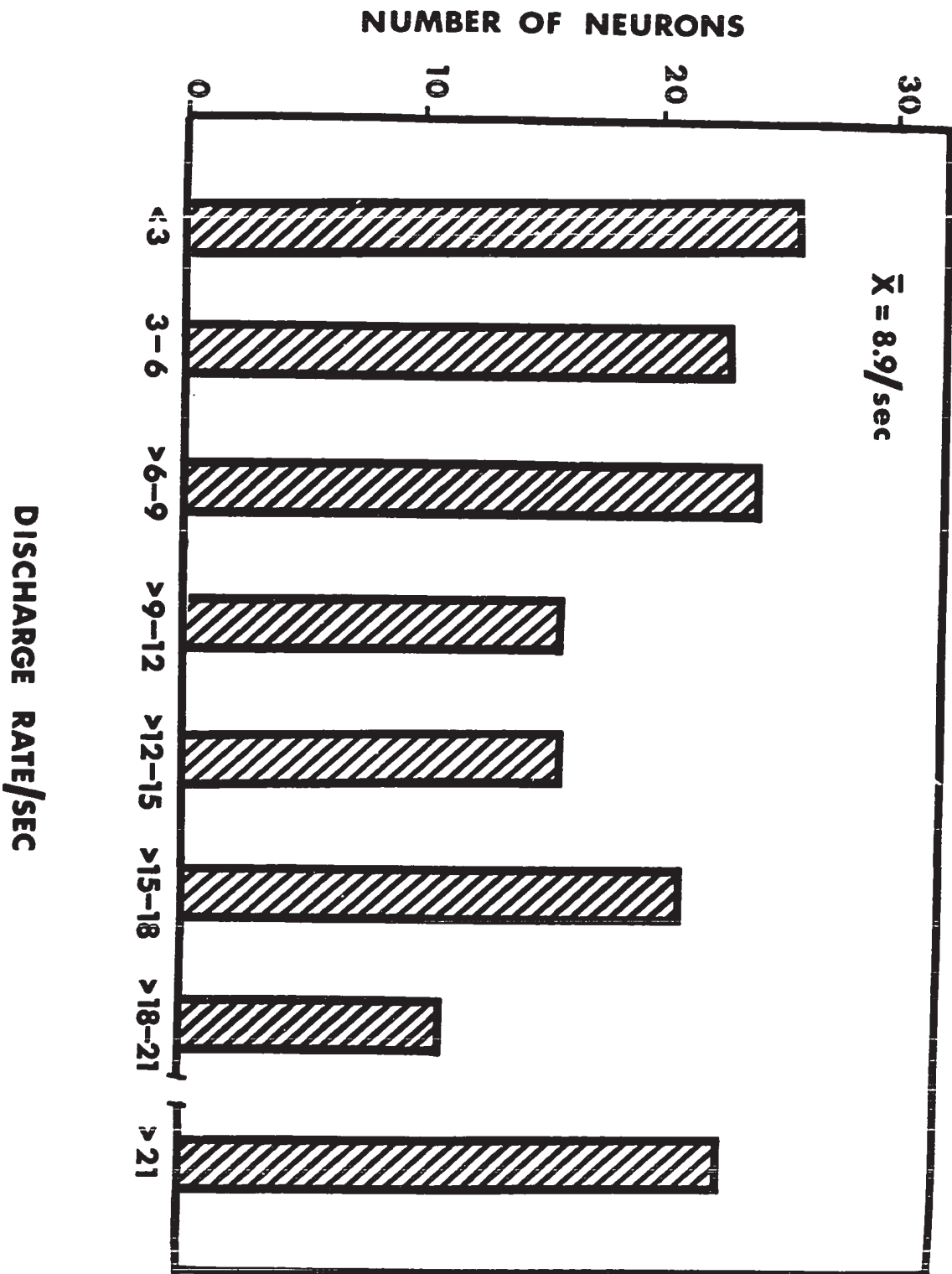
in other investigations (Barraclough and Cross, 1963; Cross and Silver, 1966; Lincoln, 1967) and are considered characteristic of lateral hypothalamic neurons in the rat. Recordings could be made for periods in excess of 2 hrs with little alteration in the mean discharge rates of the neurons indicating relatively stable rates over time. Supplemental doses of urethane anaesthesia were not observed to influence the LH neurons, confirming earlier studies (Cross and Dyer, 1970; Cross and Silver, 1966; Lincoln, 1967). Neurons which could be held for only short periods (2-3 minutes) and whose spontaneous rates were abnormally high, presumably due to mechanical injury of the neuron by the microelectrode, were excluded from the analysis. Interspike interval histograms of the LH neurons demonstrated a unimodal and assymetrical distribution, similar to those reported by Cross and Silver (1966), Murphy et al. (1968b) and Oomura et al. (1967).

The recordings made from LH neurons were distinctly different from those of the overlying thalamus which was traversed by the microelectrode before reaching the hypothalamic area. In advancing the electrode from the ventral portion of the thalamus into the dorsal region of the LH there was a marked decrease both in the number of neurons encountered and in their spontaneous discharge rates. The discharge pattern typically changed from bursting activity or rhythmical firing, characteristic of thalamic neurons, to relatively uniform patterns for LH neurons. These differences provided a clear indication of when the electrode reached the LH region.

The recorded action potentials were usually biphasic waves of initial negativity with amplitudes of 50-700μV and spike durations of 2-3 msec (Fig. 4). In a few cases positive-negative waveforms were observed. These waveforms are indicative of potentials recorded from or in close proximity to cell bodies (Bishop, Burke and Davis, 1962; Fussey, Kidd and Whitwam, 1970; Mountcastle, Davies and Berman, 1957; Rosenthal, 1967; Tasaki, Polley and Orrego, 1954). In addition, these neurons could be injured, as exhibited by a rapid increase in discharge rate, with slight movements of the electrode tip suggesting that the potentials originated from cell somas rather than axons or fiber tracts. Monophasic potentials having relatively low amplitudes and short durations ($<$ 1 msec) were also recorded and, unlike the biphasic potentials, they were not altered in shape or amplitude with movements of the recording electrode tip. Apparently these potentials originated from fiber tracts and they were not included in the analysis.

Histological verification of the recording sites within the LH were found to be dispersed throughout the whole of this region (Fig. 5). No differences in the rate or pattern of spontaneous discharge, or in the waveforms were observed from the different placements. Fig. 6 illustrates histological sections of electrode placements in the LH area.

Figure 4   Action potentials recorded from two spontaneously

discharging lateral hypothalamic neurons. The

monophasic response in the upper photograph is a

recording from a fiber tract. Negativity is in-

dicated by downward deflection.
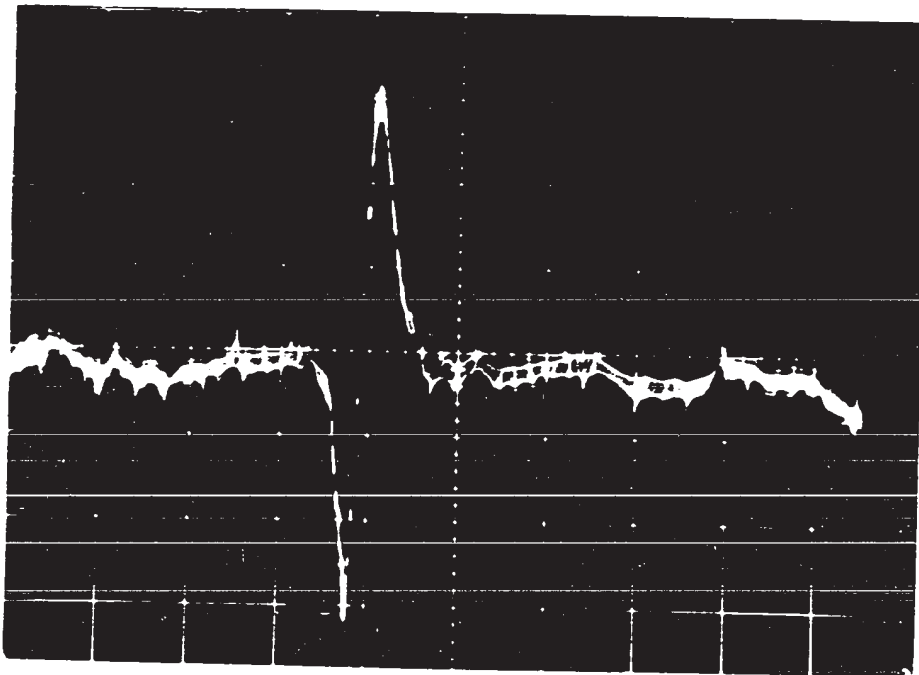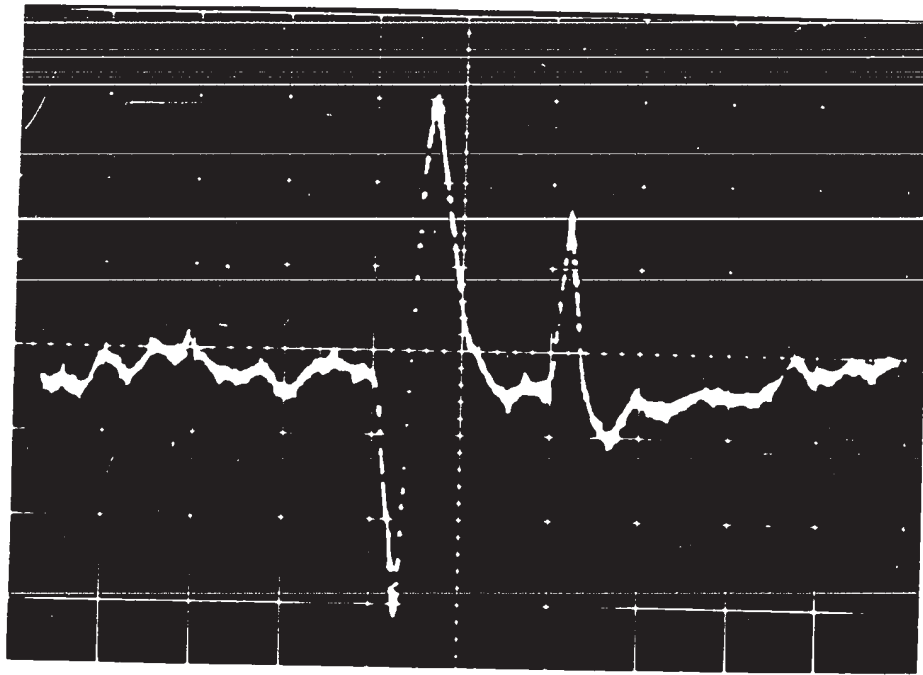
100uv

2msec.

Figure 5   Solid black dots represent the locations of 120

spontaneously active neurons recorded in the

lateral hypothalamus extending from AP 6.2-4.6

according to the De Groot atlas. Electrode place-

ments were transposed from actual histological

sections to each of these transverse sections of

the brain. Abbreviations: AHA = anterior hypo-

thalamus; DMH = dorsomedial hypothalamus; FX =

fornix; LHA = lateral hypothalamus; LM = medial

lemniscus; MFB = medial forebrain bundle; MT =

mammillothalamic tract; OT = optic tract; PH =

posterior hypothalamus; PMV = ventral pre-

mammillary nucleus; VMH = ventromedial hypotha-

lamus; ZI = zona incerta.
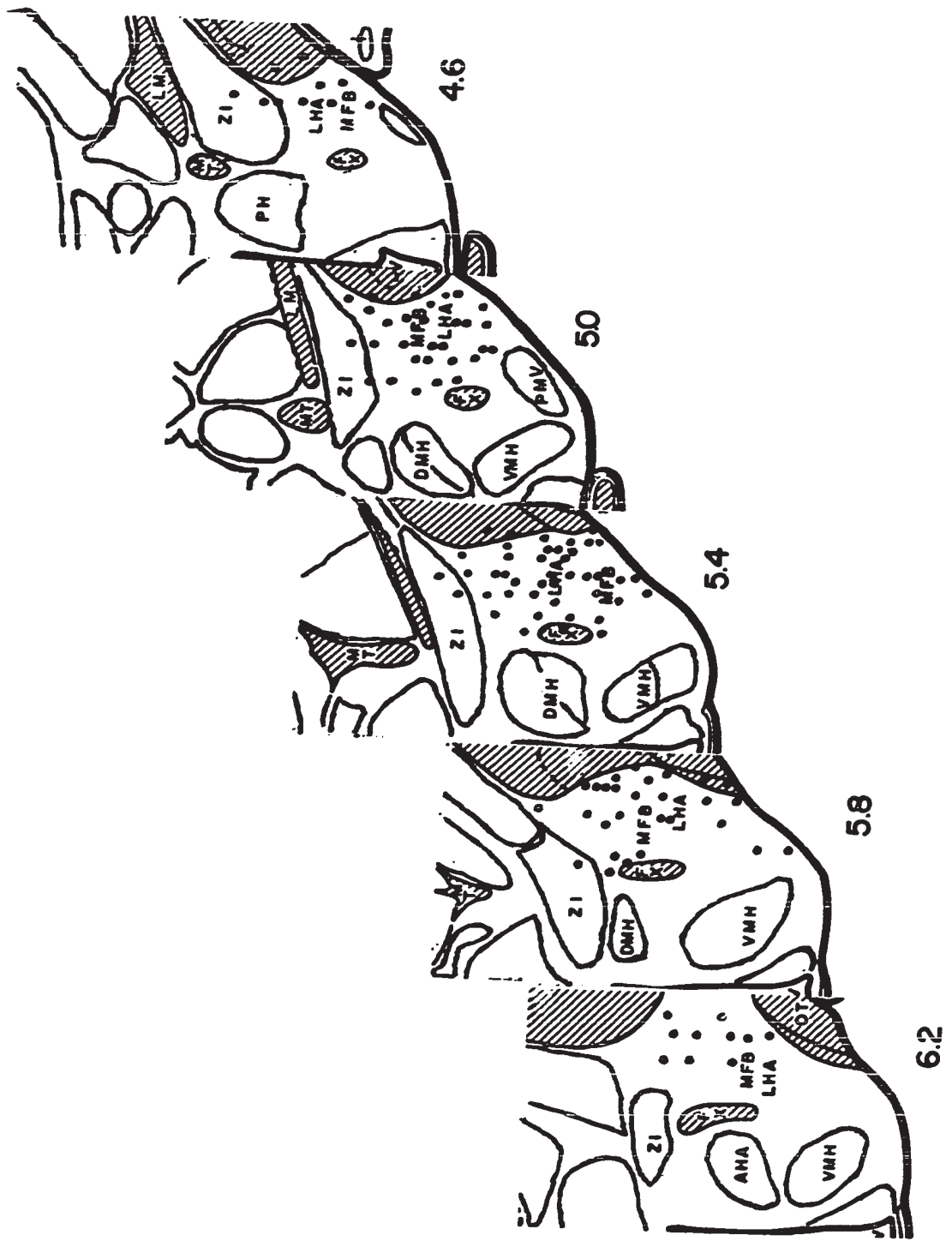
Figure 6   Typical photomicrographs showing the locus of recording microelectrodes in the lateral hypothalamus. Top, glass micropippette; bottom, stainless steel electrode. Magnification, X25.

1. Effects of Septal, Olfactory Bulb and Sciatic Nerve Stimulation

The influences of electrical stimulation of the ipsilateral septum, olfactory bulb and/or contralateral sciatic nerve on three hundred and forty-six spontaneously active LH units were investigated. These results are summarized in Table 2. Septal stimulation influenced 79% of the LH units, 37% being facilitated and 42% being inhibited. Olfactory bulb stimulation influenced 66% of the LH units, 27% being facilitated and 39% being inhibited. Of the LH units sampled with sciatic nerve stimulation, 87% were observed to be influenced, all of them being facilitated.

Septal stimulation sites were shown to be localized in the medial septum, diagonal band of Broca and parts of the lateral septum, nucleus accumbens and bed nucleus of the stria terminalis (Fig. 7). These areas exerted both facilitatory and inhibitory effects on the LH units with the medial septal-diagonal band area being the most effective. The discharge rates before and after stimulation of these areas are shown for different LH neurons in Fig. 8.

Repetitive stimulation of the septum was more effective in producing facilitation or inhibition of the LH neurons than was single pulse stimulation. This is illustrated in Fig. 9, which shows the increasing effectiveness as the frequency of stimulation was raised from 1-20 Hz. The duration of the stimulus pulse train was 1 sec under the standard conditions; longer durations produced a greater degree of facilitation or inhibition while shorter

TABLE 2

TOTAL NUMBER OF LH NEURONS EXAMINED WITH SEPTAL, OLFACTORY BULB,
AND SCIATIC NERVE STIMULATION AND THE EFFECTS PRODUCED BY EACH

	Facilitation	Inhibition	No Effect	Total
Septum	69	78	38	185
Olfactory Bulb	36	51	44	131
Sciatic	26	0	4	30

Figure 7   Location of stimulating electrode placements in

the medial septal-diagonal band region is shown

on the left by the stippled area. On the right

a typical photomicrograph showing the locus of

a stimulating electrode in the medial septum.

Abbreviations: CC = corpus callosum; CO =

optic chiasm; ca = anterior commissure; LS =

lateral septum; MS = medial septum. Magnifi-

cation, X15.
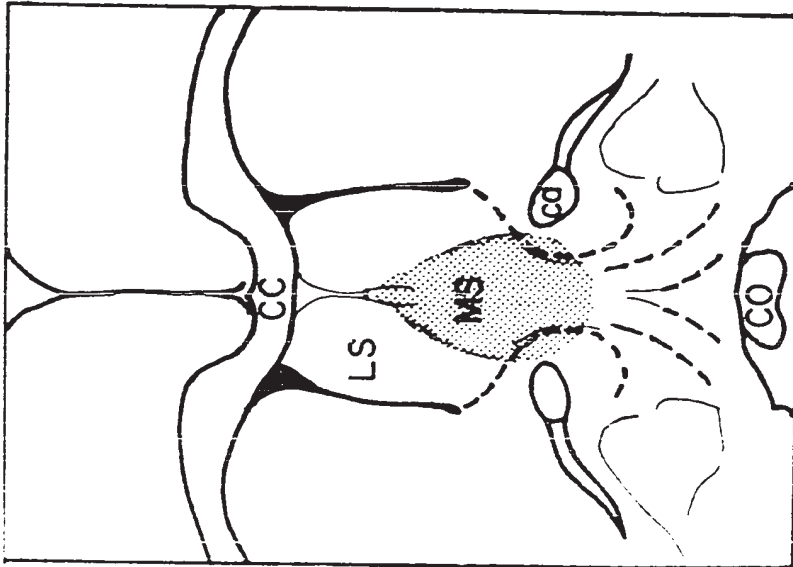
Figure 8   The effects of repetitive septal stimulation

(20 Hz, 1 sec duration) on lateral hypothala-

mic neurons: (A)   facilitation in three dif-

ferent neurons;   (B)   inhibition in three

different neurons. $\bar{x}_b$, mean discharge rate/

sec in one second period before stimulation;

$\bar{x}_a$, mean discharge rate/sec in one second

period following stimulation. Arrows mark

the termination of stimulation.

A

$\bar{x}_b = 4.3$

$\bar{x}_b = 5.8$

$\bar{x}_b = 3.1$

$\bar{x}_a = 10.7$

$\bar{x}_a = 16.2$

$\bar{x}_a = 15.4$

200 μV

250 msec

B

$\bar{x}_b = 11.8$

$\bar{x}_b = 6.6$

$\bar{x}_b = 8.2$

$\bar{x}_a = 5.0$

$\bar{x}_a = 2.4$

$\bar{x}_a = 4.7$

200 μV

250 msec

Figure 9   Frequency histogram showing the spontaneous dis-

charge rate, or baseline, and the increasing dis-

charge rate for one LH neuron in the 1 sec period

following 1, 5, 10, 20 Hz stimulation of the

septum. N = number of trials of stimulation at

each frequency. $\bar{x}$ = mean spontaneous discharge

rate for the LH neuron. The ordinate represents

the total number of impulses over 15 stimulation

trials in each 100 msec address of the histogram.
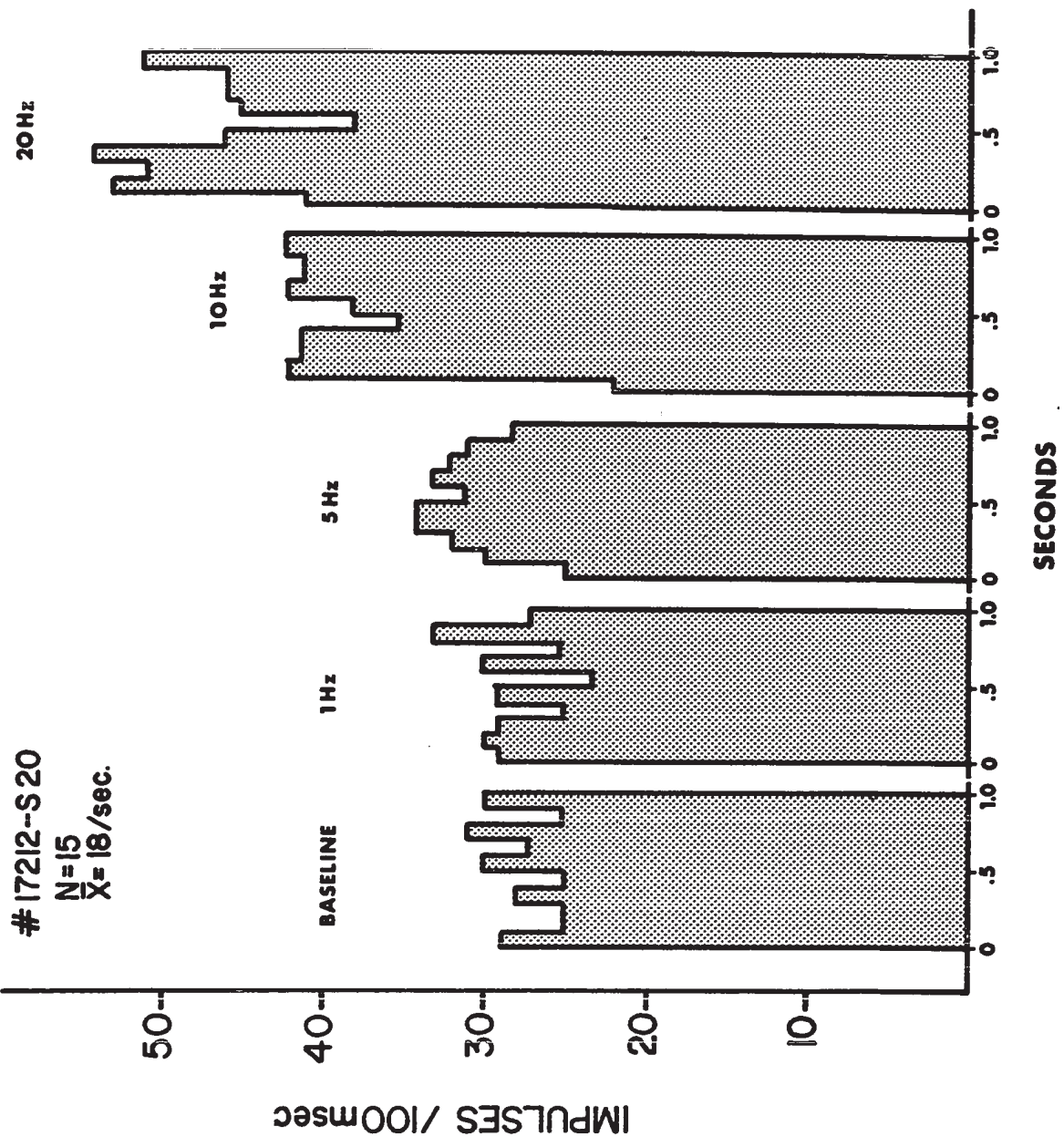
durations were less effective. These changes in either frequency or duration did not alter the direction of effect (i.e. from inhibitory to facilitatory or vice versa).

Although similar findings were observed on most LH neurons with increasing frequency and duration of stimulation to the olfactory bulb or sciatic nerve, 6 LH units did display a reversal effect as a result of increasing the frequency of olfactory bulb stimulation. At lower frequencies (1-10 Hz) stimulation resulted in a facilitation whereas at higher frequencies (10-20 Hz) this effect became inhibitory.

Following cessation of stimulation the duration of the facilitatory and inhibitory effects were shown to be variable in length. Typical recordings of inhibitory and facilitatory effects on LH units produced by septal stimulation are illustrated in Fig. 10. The frequency histograms represent the total number of impulses/100 msec obtained following 10-15 stimulation trials. The inhibitory effect was either a brief pause in spontaneous activity, or a long lasting tonic slowing or complete cessation of the discharge rates for periods of 0-1000 msec. On 16 LH units the inhibitory effects lasted longer than 1000 msec following the cessation of stimulation. Facilitatory effects produced by septal stimulation exhibited similar time characteristics, with either brief increases in the spontaneous activity or long periods of tonic facilitation.

The effects of sciatic nerve and olfactory bulb stimulation on LH units are shown in Fig. 11. As indicated previously (Table 2)

Figure 10   Frequency histograms showing the effects of 20 Hz

septal stimulation on six LH neurons. The plain

area indicates the spontaneous discharge rate and

the stippled area indicates the effect following

stimulation. The top row shows facilitatory ef-

fects of stimulation, the lower, inhibitory ef-

fects. The histogram of unit No. 18183 repre-

sents the number of impulses/200 msec and demon-

strates the long duration of effects observed on

some LH units. N = number of stimulation trials.

The ordinate represents the total number of im-

pulses over N stimulation trials in each 100 msec

address of the histogram.

#17260—S22
N=15

#17280—S23
N=10

#18860—S27
N=15

#13425—S5
N=15

#13424—S5
N=15

#18183—S:27
N=15

SEPTAL STIMULATION (20Hz)

IMPULSES /100 msec.

msec.

msec.

msec.

Figure 11   Frequency histograms showing the effects of 20 Hz

sciatic and olfactory bulb (OB) stimulation on 4

LH neurons. The plain area indicates the spon-

taneous discharge rate and the stippled area in-

dicates the effect following stimulation. In

both instances the effects are of long duration

lasting for periods greater than 1 sec. N =

number of stimulation trials. The ordinate re-

presents the total number of impulses over N

stimulation trials in each 100 msec address of

the histogram.

#20424-24
N=15
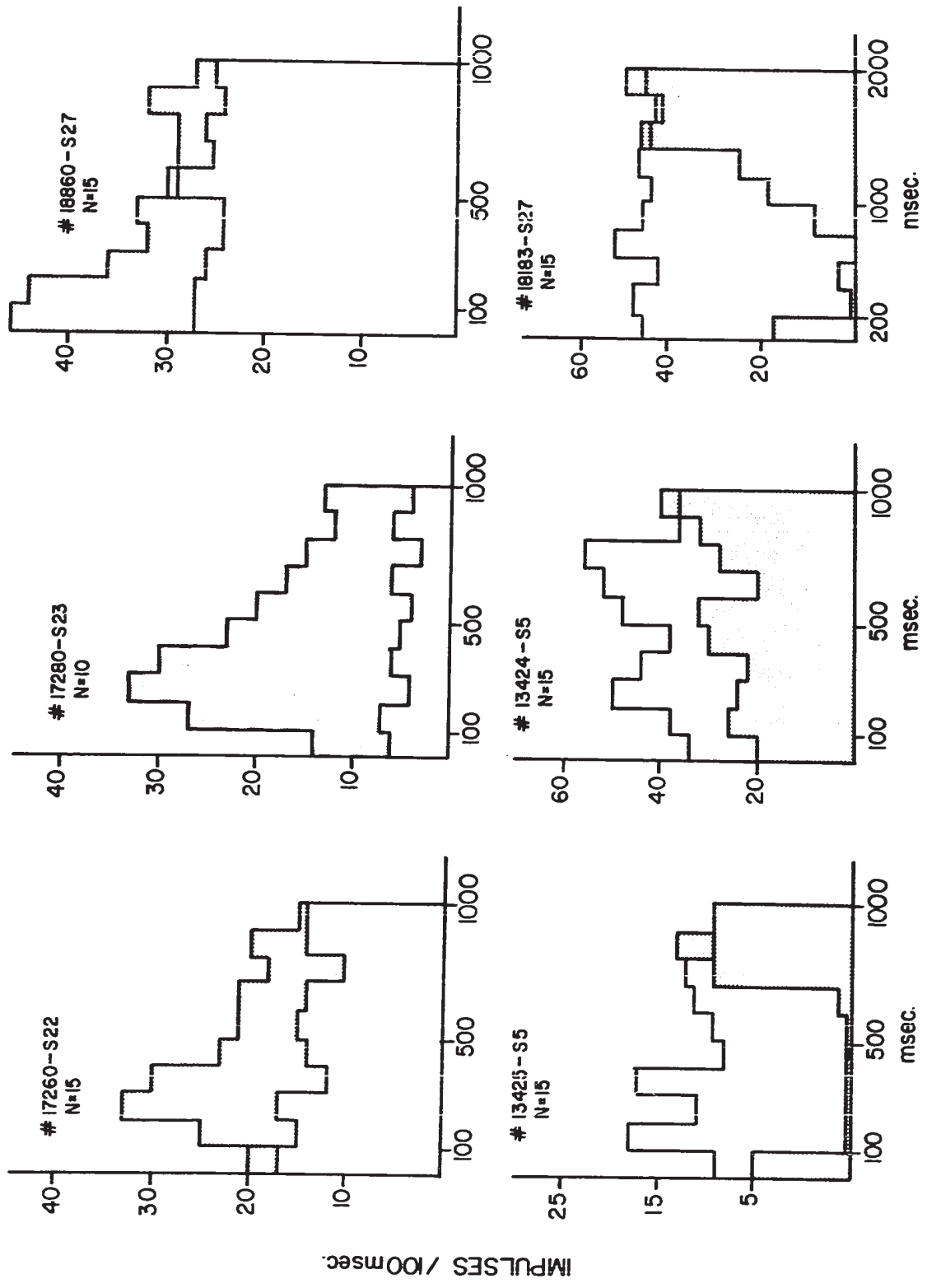
#13348-3
N=10

IMPULSES /100msec.

SCIATIC STIMULATION
(20 Hz)

#16560-56
N=15

#20423-24
N=15

msec.

msec.

OB STIMULATION
(20 Hz)
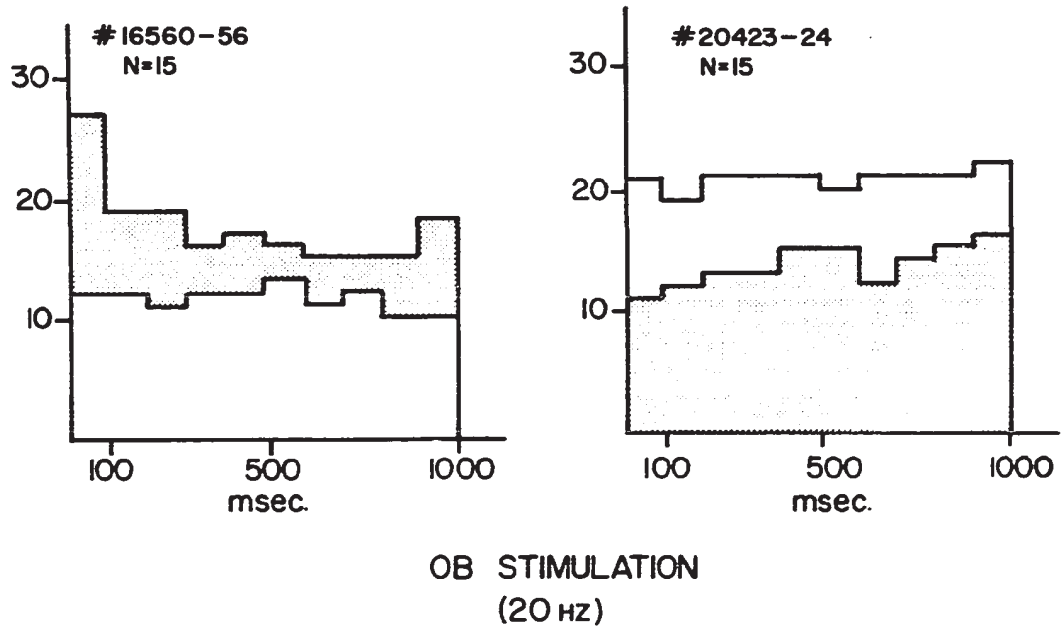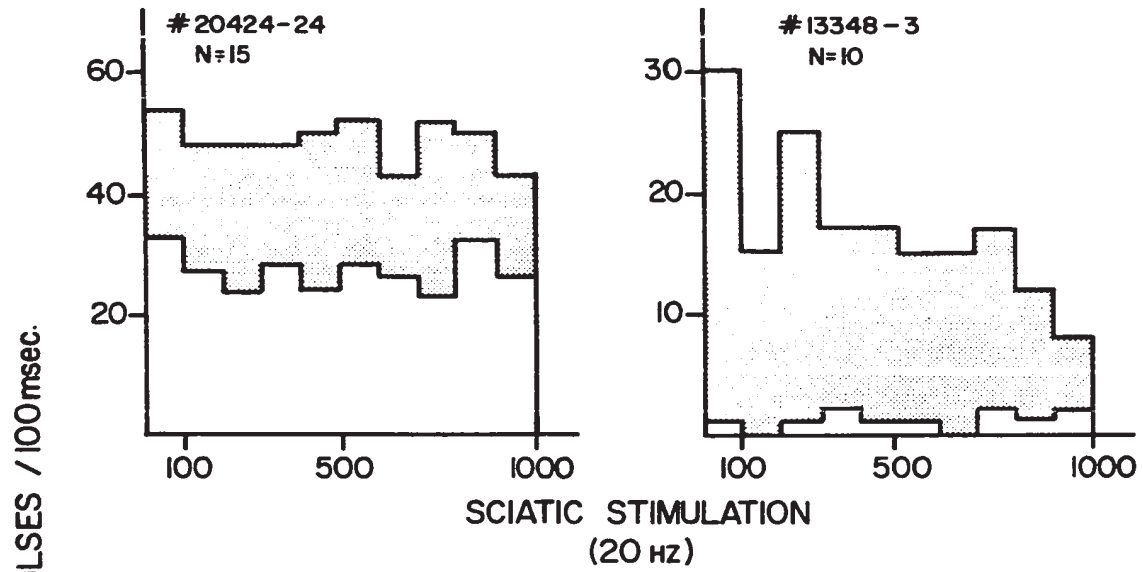
all units influenced by the sciatic nerve were facilitated, and in
5 instances stimulation was observed to initiate unit activity. On
the other hand, neither septal nor olfactory bulb stimulation was
found to initiate the firing of LH units. For both sciatic and
olfactory bulb stimulation the durations of effects were mainly
tonic increases or decreases in discharge rate, lasting for periods
of 500-2000 msec.

As indicated in Methods, the analysis of LH unit data consis-
ted of a comparison between the discharge rate 1 sec before and 1
sec following stimulation. A similar comparison was made between
the discharge rate during and after stimulation on 47 units in-
fluenced by the septum and 22 units influenced by the olfactory
bulb when the stimulus artifacts created by stimulating these areas
were minimal. For the majority of cases (61 units) the direction
of effect produced during stimulation was the same as that following
stimulation, while 8 units (5 influenced by the septum and 3 by the
olfactory bulb) displayed opposite effects, suggesting the possi-
bility of a rebound phenomenon.

2. Convergence of Central and Peripheral Effects

Neurons of the LH whose discharge rates were influenced by
either the septum, olfactory bulb or sciatic nerve were investi-
gated to see whether they could be influenced by both central and
peripheral sites. In the present study the olfactory bulb and
sciatic nerve were the sites of peripheral input to the hypothalamus.

The effects of olfactory bulb and septal stimulation were investigated on 105 units. Both of these exhibited convergence in 61 units while 44 were influenced by one only (Table 3). In 31 of the units showing convergence (51%) a similar effect from both stimulation sites was observed; 11 (18%) were facilitated by stimulation of the olfactory bulb and septum, whereas 20 (33%) were inhibited. In 30 of the units showing convergence (49%) opposite effects were observed with the two stimuli; stimulation of the olfactory bulb facilitated and stimulation of the septum inhibited the firing of 14 (23%), whereas olfactory bulb stimulation inhibited and septal stimulation facilitated 16 LH units (26%).

For another test group of 23 hypothalamic units there was convergence of sciatic nerve and septal stimulation on 19 (83%). Sciatic nerve stimulation had a facilitatory effect in every case, whereas 11 of the 19 units (58%) were inhibited and 8 (42%) facilitated by septal stimulation.

3. Correlation Between Spontaneous Discharge Rate and Effect of Septal Stimulation

The recordings from a sample of 86 LH neurons were analyzed to determine whether there was a correlation between the variation in spontaneous discharge rate and the rate of discharge produced following electrical stimulation of the septum. The results are shown in Table 4. Four patterns were observed: facilitation (type I

TABLE 3

CONVERGENCE OF OLFACTORY BULB OR SCIATIC NERVE STIMULATION
ON LH UNITS WHICH RESPOND TO SEPTAL STIMULATION

	Olfactory Bulb			Sciatic		
	Facilitation	Inhibition	No Effect	Facilitation	Inhibition	No Effect
Septum						
Facilitation	11	16	14	8	0	0
Inhibition	14	20	19	11	0	0
No Effect	5	6	4	4	0	0

TABLE 4

RESPONSES OF 86 LH NEURONS TO SEPTAL STIMULATION

Type 1	Type 2	Type 3	Type 4	Unaffected
Facilitation	Inhibition	Facilitation and Inhibition Spontaneous Discharge Rate	Facilitation or Inhibition Related to Spontaneous Discharge Rate	
12*	14*	23*	17*	20

* $P < 0.05$

Type 3 responses were related to the spontaneous discharge rate and showed facilitation when this rate was low and inhibition when the discharge rate was high. Type 4 responses were either facilitated or inhibited with the degree of facilitation or inhibition being proportional to the spontaneous discharge rate.

response) occurred in 12 LH units; and inhibition (type 2 response) occurred in 14 LH units. For a number of units, the occurrence of facilitation or inhibition from septal stimulation was observed to be dependent on the spontaneous discharge rate. When this spontaneous rate was low, septal stimulation increased the level of neural activity and conversely when the spontaneous rate was high, septal stimulation reduced the level of neural activity (type 3 response). Type 3 responses were recorded in 23 units following septal stimulation. The different effects of septal stimulation on a LH unit classified as having this type of response is shown in Fig. 12. In 14 units following septal stimulation there was an inhibition only, with the degree of inhibition being proportional to the spontaneous discharge rate (type 4 response). This type of response, therefore, displayed characteristics of both type 2 and type 3 responses. In 3 units following septal stimulation there was a decrease in the degree of facilitation as the spontaneous discharge increased. These units demonstrated characteristics of type 1 and type 3 responses.

The four response types are presented in Fig. 13. The change in discharge rate per second is plotted against the spontaneous discharge rate.

4.   Interaction of Central and Peripheral Effects

As indicated previously, the effect of septal stimulation was

Figure 12   Example of a type 3 LH neuron which is both faci-

litated and inhibited by septal stimulation de-

pending on the discharge rate. Top: the changes

in discharge rate/sec following septal stimulation

(20 Hz, 1 sec duration) are plotted against the

spontaneous discharge rate (DR) before stimulation.

Bottom: (A) slow discharge rate; (B) facilitation;

(C) fast discharge rate; (D) inhibition.

CHANGE IN DISCHARGE RATE/SEC

r = 0.85
(P<.01)

DR
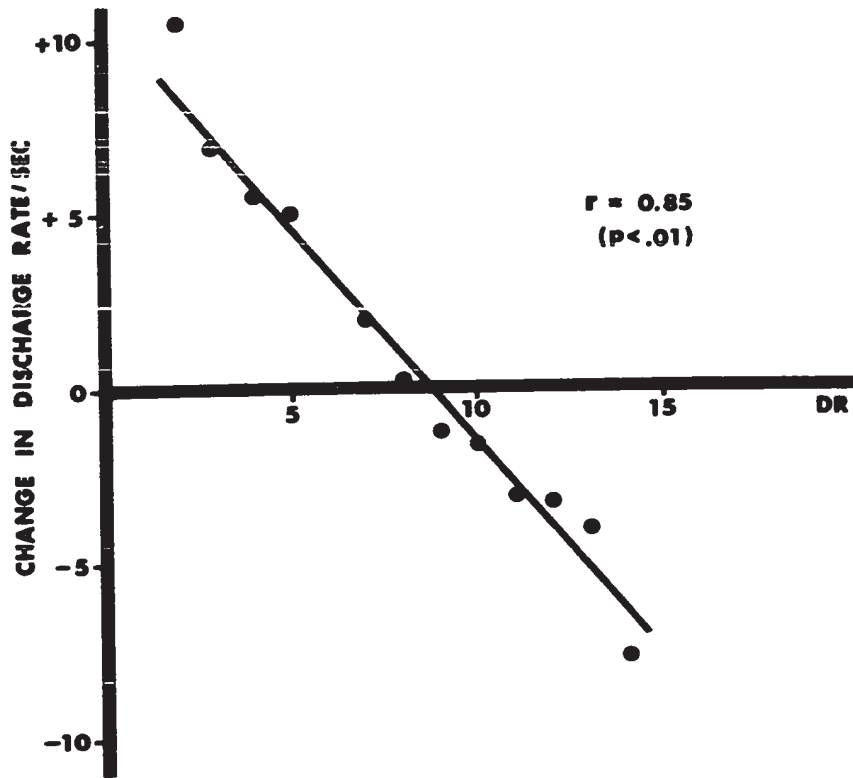
200 μV

500 msec

Figure 13   Examples of LH response types. The change in

discharge rate/sec following septal stimulation

is plotted against the spontaneous discharge

rate (DR) before stimulation: type 1 - facili-

tated; type 2 - inhibited; type 3 - correlated

to DR; type 4 - two units correlated to and

showing proportional relationship with DR.

RESPONSE TYPES TO SEPTAL STIMULATION

TYPE 1

TYPE 2

TYPE 3

r = -0.82
(p<.02)

TYPE 4

r = -0.87
(p<.05)

r = +0.75
(p<.05)

MEAN CHANGE IN DISCHARGE RATE/SEC

D.R.
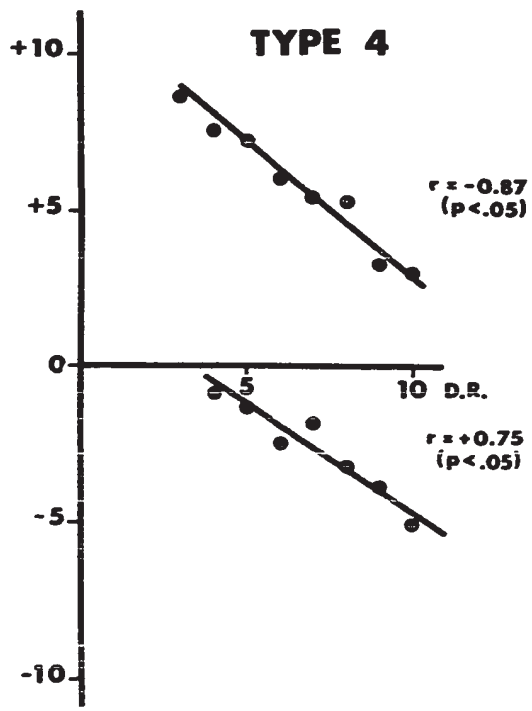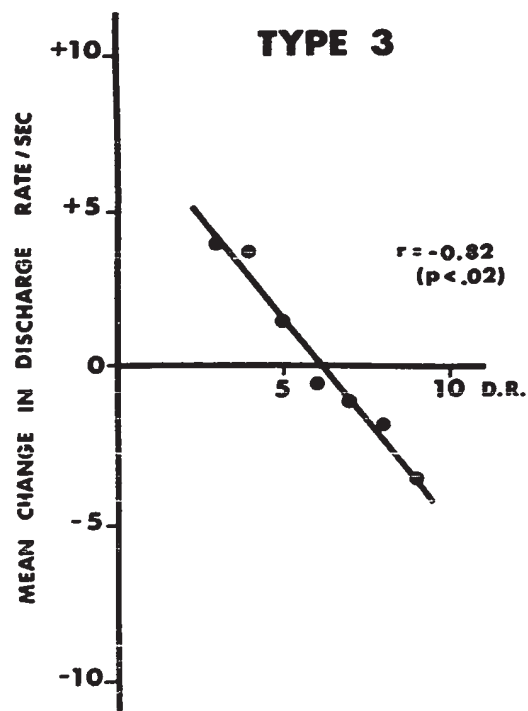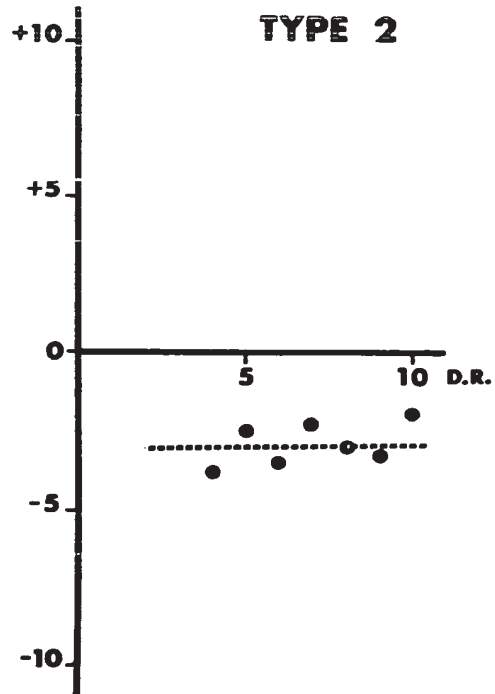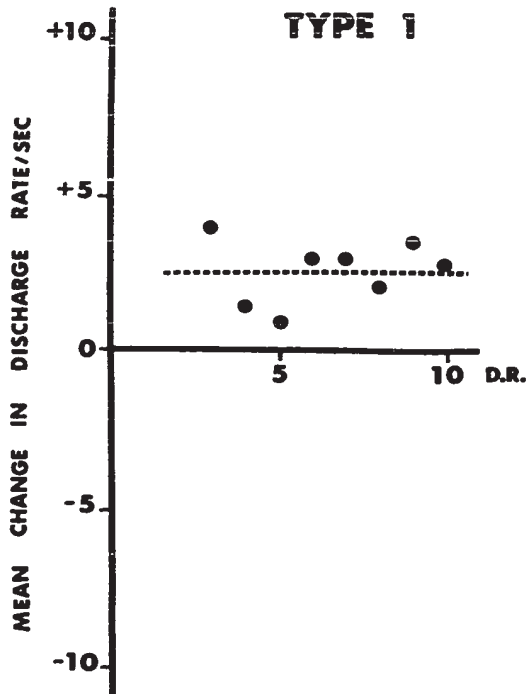
observed in some cases to depend upon the discharge rate of the LH neurons. Since there was a considerable degree of convergence from septal and peripheral stimulation on LH units it was decided to investigate the effect of septal stimulation on their activity under two conditions: (a) when the discharge rate was "normal" (spontaneous discharge rate) and (b) when the discharge rate was altered experimentally by a known peripheral input. Of the two peripheral inputs employed, stimulation of the olfactory bulb was used rather than stimulation of the sciatic nerve. This was done because the former was observed to produce both facilitatory and inhibitory effects on LH unit activity, whereas the sciatic nerve exerted only facilitatory effects (Table 3).

Seventy-four LH units were studied using the combined stimulation periods outlined in the Methods. Septal stimulation alone produced facilitation in 33 (45%) of these units and inhibition in 34 (46%) while 7 units (9%) were unaffected. Stimulation of the olfactory bulb produced facilitation in 30 units (41%) and inhibition in 31 units (42%). In Table 5 the units are grouped by number and direction of effect produced by olfactory bulb and septal stimulation alone and following combined stimulation of the two sites.

The effects of septal stimulation on 12 LH units discharging at a "normal" spontaneous rate and when this rate was increased by olfactory bulb stimulation are shown in Fig. 14. The septum produced a facilitatory effect on all of the units when firing at the "normal" level and inhibition when this rate was increased. In 16

TABLE 5

SEVENTY-FOUR LH NEURONS GROUPED ACCORDING TO THE DIRECTION OF EFFECT
PRODUCED BY SEPTAL AND OLFACTORY BULB STIMULATION ALONE AND COMBINED

Olfactory Bulb	Septum		
	Facilitation	Inhibition	No Effect
Facilitation	12↓ 5↑	8↓	5↑
Inhibition	9↑	16↑ 4↓	2↓
No Effect	7↑	6↓	

The arrows represent the direction of effect produced following combined
stimulation of the two sites; ↑ = facilitation, ↓ = inhibition.

Figure 14   The percentage change in discharge rate produced

by septal stimulation on 12 LH neurons: open

bars, facilitation when the discharge rate was

spontaneous;   closed bars, inhibition when the

discharge rate was altered (increased) by ol-

factory bulb stimulation.

LH NEURONS

PERCENT CHANGE
IN DISCHARGE RATE/SEC

+130
+100
+50
0
-50
-100
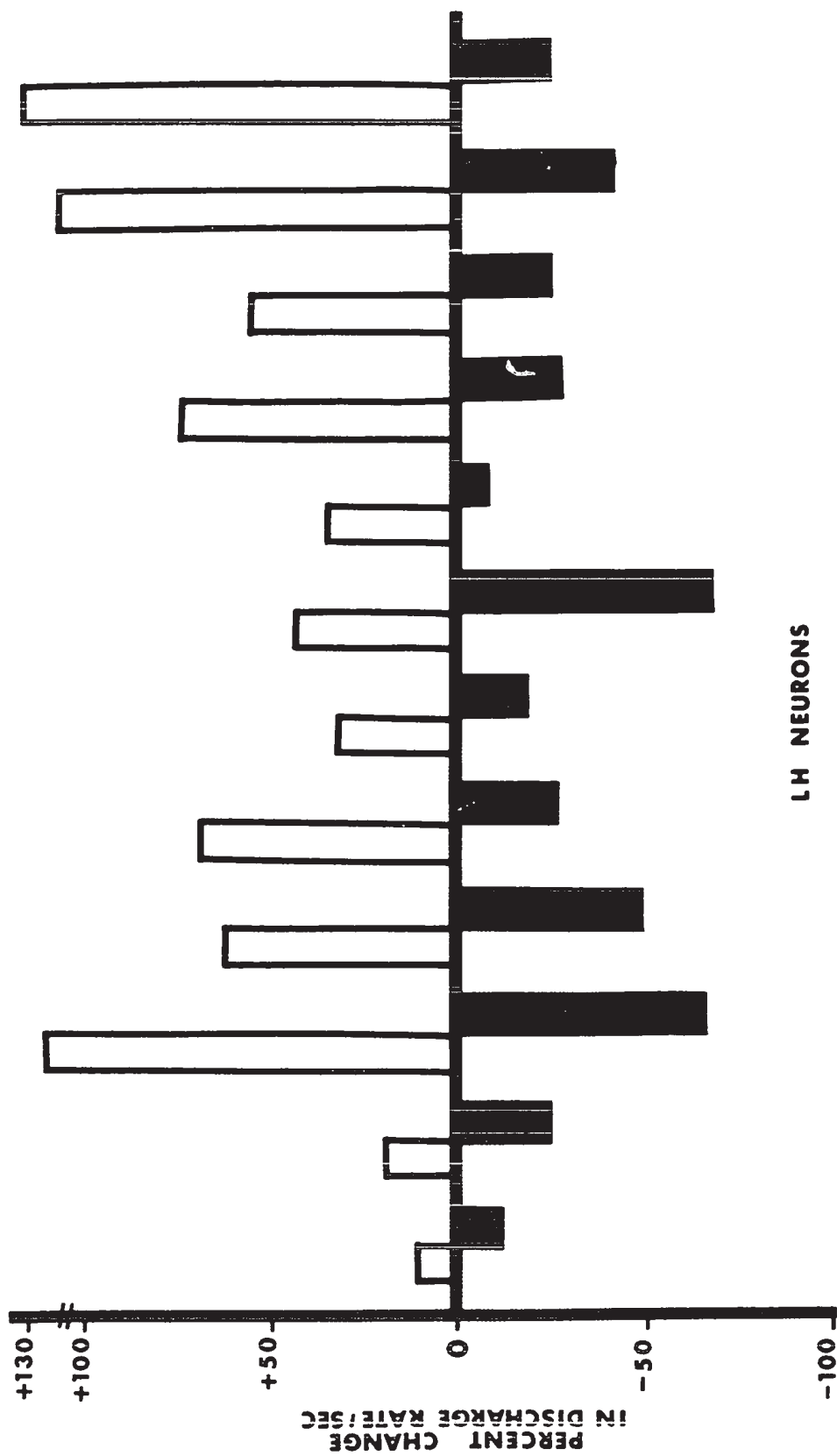
LH units which were initially inhibited by septal stimulation, the opposite effects were observed (facilitation) when their "normal" discharge rate was decreased by olfactory bulb stimulation (Fig. 15). These reversal effects are similar to the type 3 response reported earlier in which septal stimulation produces an inhibitory effect when the discharge level was high and a facilitatory effect when this level was low. In 9 of the LH units, (5 which were facilitated by both septal and olfactory bulb stimulation and 4 which were inhibited by both), there was no difference between the effects of septal stimulation at the "normal" level and that following olfactory bulb stimulation (Fig. 16). These responses do not show any relationship between the direction of effect produced by septal stimulation and the spontaneous discharge level and are therefore considered to be similar to type 1 or 2 responses (Fig. 13).

Seventeen LH units were influenced differently by the septum and olfactory bulb; 9 of these units were facilitated and inhibited respectively while 8 units displayed opposite effects. It was observed that when the discharge level was "normal" the septum initially facilitated the LH unit, and when this level was decreased by olfactory bulb stimulation the septum produced a greater degree of facilitation (Fig. 17A). Similarly when the septum initially inhibited the LH units it was observed that by increasing the discharge level the degree of inhibition increased in 4 of the 8 units (Fig. 17B). These effects are similar to the

Figure 15   The percentage change in discharge rate produced

by septal stimulation on 16 LH neurons: open bars,

inhibition when the discharge rate was spontaneous;

closed bars, facilitation when the discharge rate

was altered (decreased) by olfactory bulb stimula-

tion.

LH NEURONS

PERCENT CHANGE
IN DISCHARGE RATE/SEC
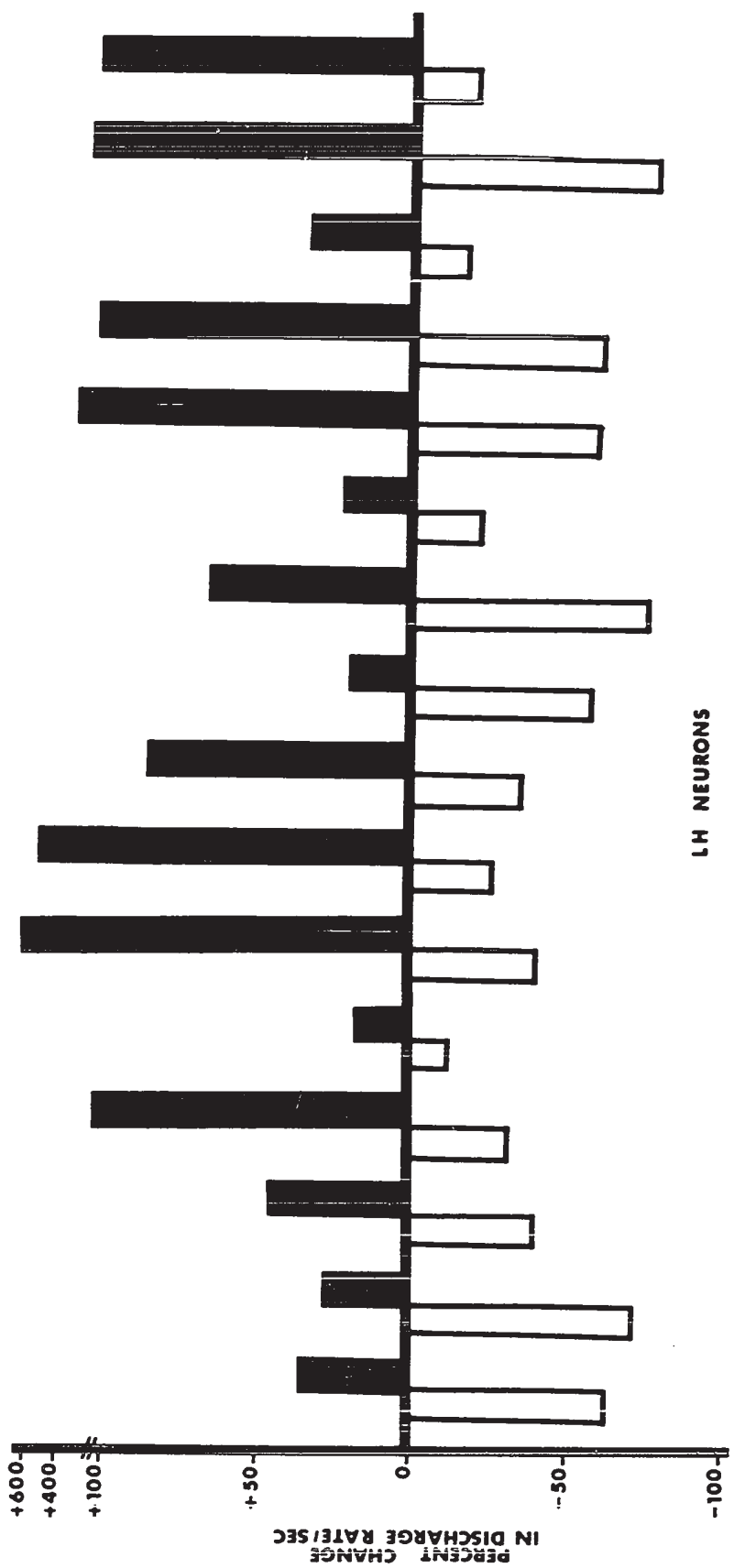
Figure 16   The percentage change in discharge rate produced

by septal stimulation: (A) open bars, inhibition

when the discharge rate was spontaneous; closed

bars, inhibition when the discharge rate was al-

tered (decreased) by olfactory bulb stimulation.

$N = 4$ LH neurons. (B) open bars, facilitation

when the discharge rate was spontaneous; closed

bars, facilitation when the discharge rate was

altered (increased) by olfactory bulb stimula-

tion. $N = 5$ LH neurons.

PERCENT CHANGE
IN DISCHARGE RATE/SEC
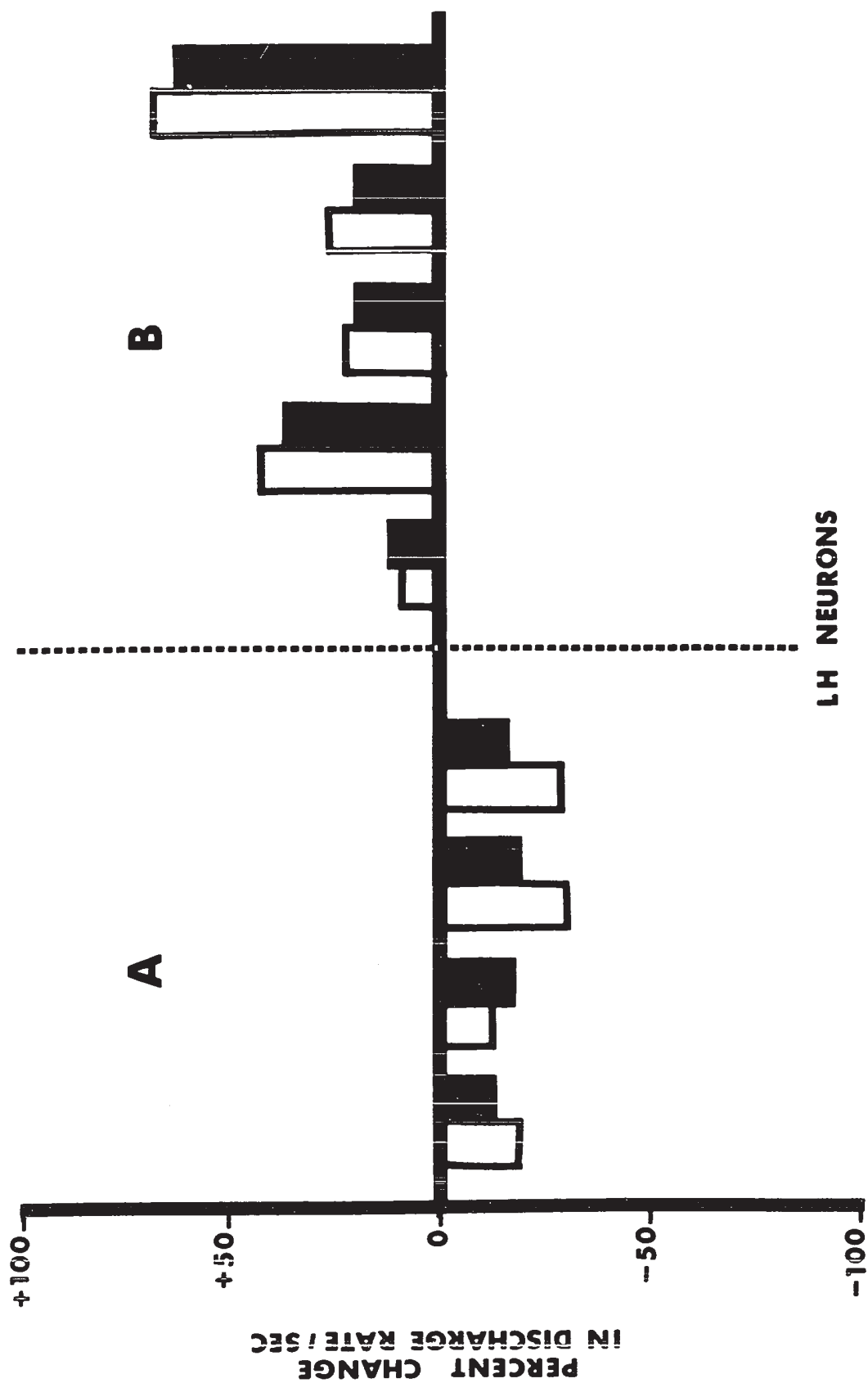
Figure 17   The percentage change in discharge rate produced

by septal stimulation.   (A) open bars, facilita-

tion when the discharge rate was spontaneous;

closed bars, facilitation when the discharge

rate was altered (decreased) by olfactory bulb

stimulation.   N = 9 LH neurons.   (B) open bars,

inhibition when the discharge rate was spon-

taneous;   closed bars, inhibition when the dis-

charge rate was altered (increased) by olfactory

bulb stimulation.   N = 8 LH neurons.

LH NEURONS

PERCENT CHANGE
IN DISCHARGE RATE/SEC

PERCENT CHANGE
IN DISCHARGE RATE/SEC

LH NEURONS
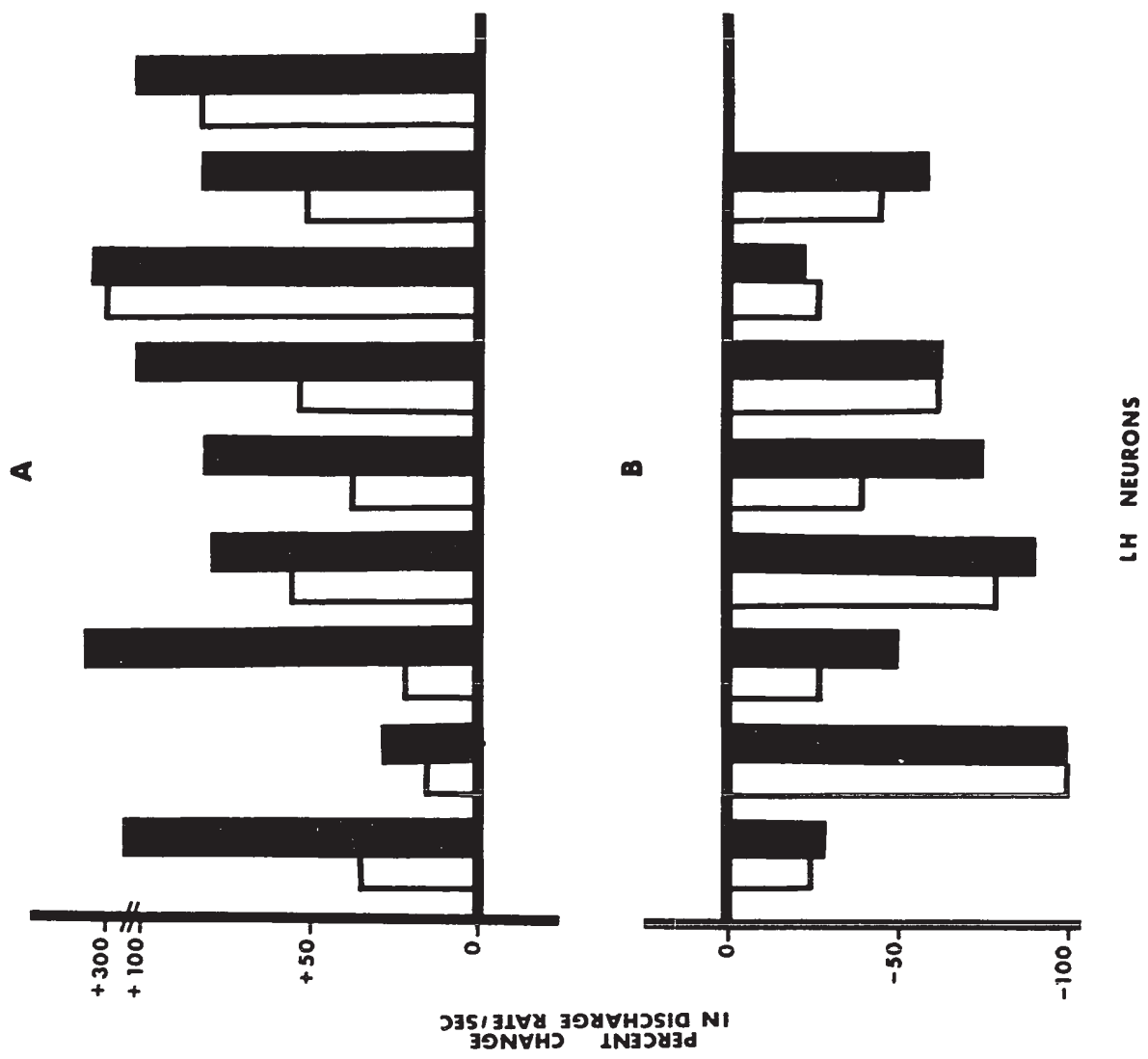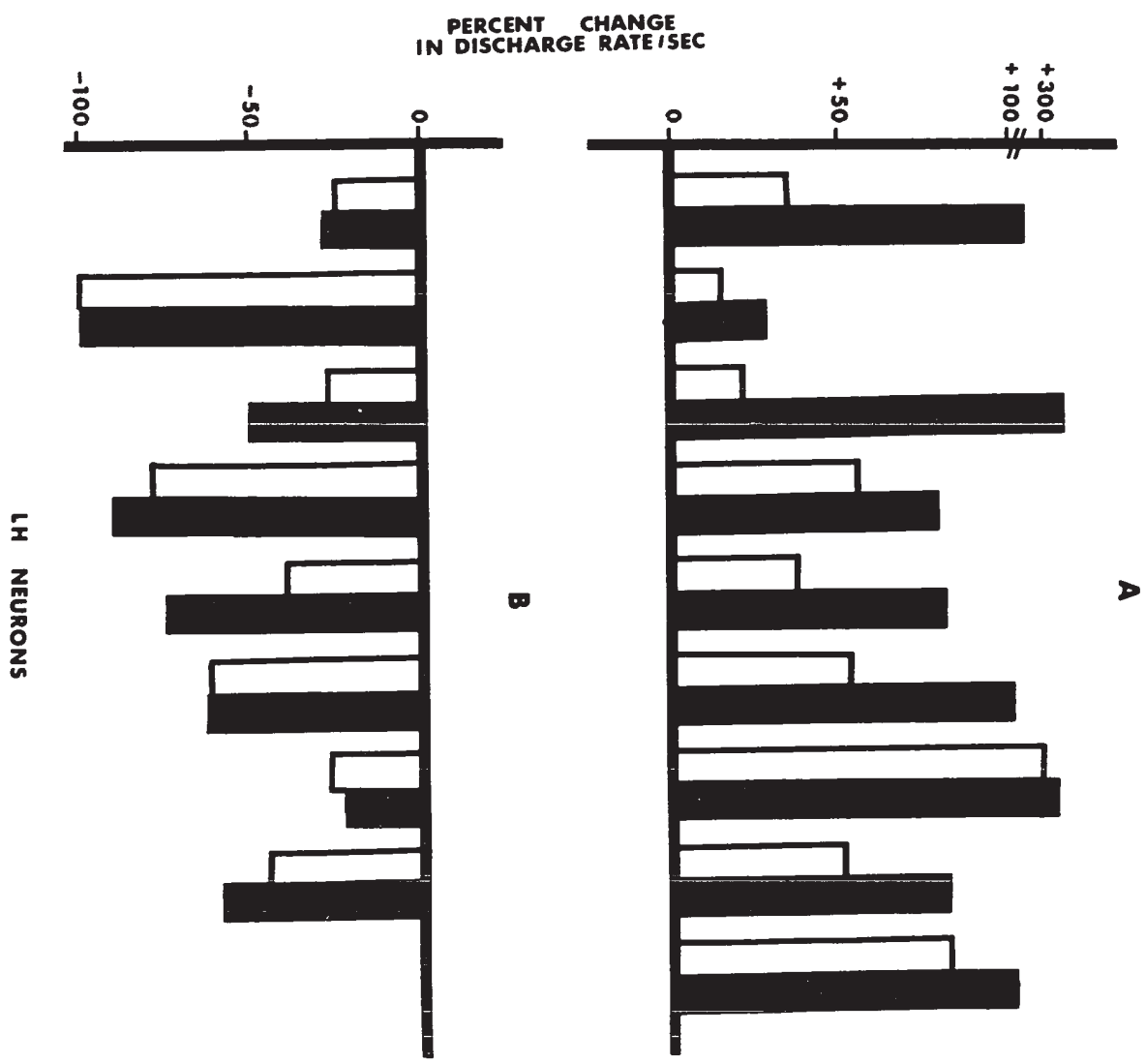
type 4 responses described previously (Fig. 13).

In the 13 units which were unaffected by olfactory bulb stimulation but were influenced by the septum, the effect of combining the two stimuli resulted in a discharge rate which was the same as that produced by the septum alone. With the 7 units which were unaffected by septal stimulation the effects of combining the two stimuli were the same as that produced by olfactory bulb stimulation alone.

II   The Modulatory Influence of the Septum on Lateral Hypothalamic Self-Stimulation

Septal stimulation evoked responses in the lateral hypothalamus of 22 animals indicating that the electrodes were in regions connected anatomically. Components of these potentials, analysed by measuring the time in msec from the stimulus artifact to the peak of the response wave, had latencies of 3-6 msec, 10-14 msec and 18-23 msec. These responses are shown in Fig. 18 along with the sites of stimulation and recording. The polarities of the evoked responses were not considered since monopolar recordings were not made.

The short latency component was observed in only 12 animals and was smaller in amplitude than the longer latency and more consistently evoked 10-14 and 18-23 msec components. Both major components (10-14, 18-23 msec) were present in most of the recordings, but one was usually more prominent depending on the site of stimula-

Figure 18   The location of the septal stimulating and la-
            teral hypothalamic recording sites are shown
            together with examples of evoked responses from
            four of these sites (6, 9, 5, 35). Sections
            extend from AP 8620 to 7190 for the septum and
            from AP 5150 to 4110 for the hypothalamus.
            Calibration 10 msec, 50μV. Abbreviations:
            A = nucleus accumbens; AC = anterior commissure;
            CC = corpus callosum; DBB = diagonal band of
            Broca; DM = dorsomedial hypothalamus; F = for-
            nix; LS = lateral septum; MS = medial septum;
            MFB = medial forebrain bundle; M = mammillo-
            thalamic tract; OT = optic tract; POA = pre-
            optic area; ST = stria terminalis; Z = zona
            incerta.
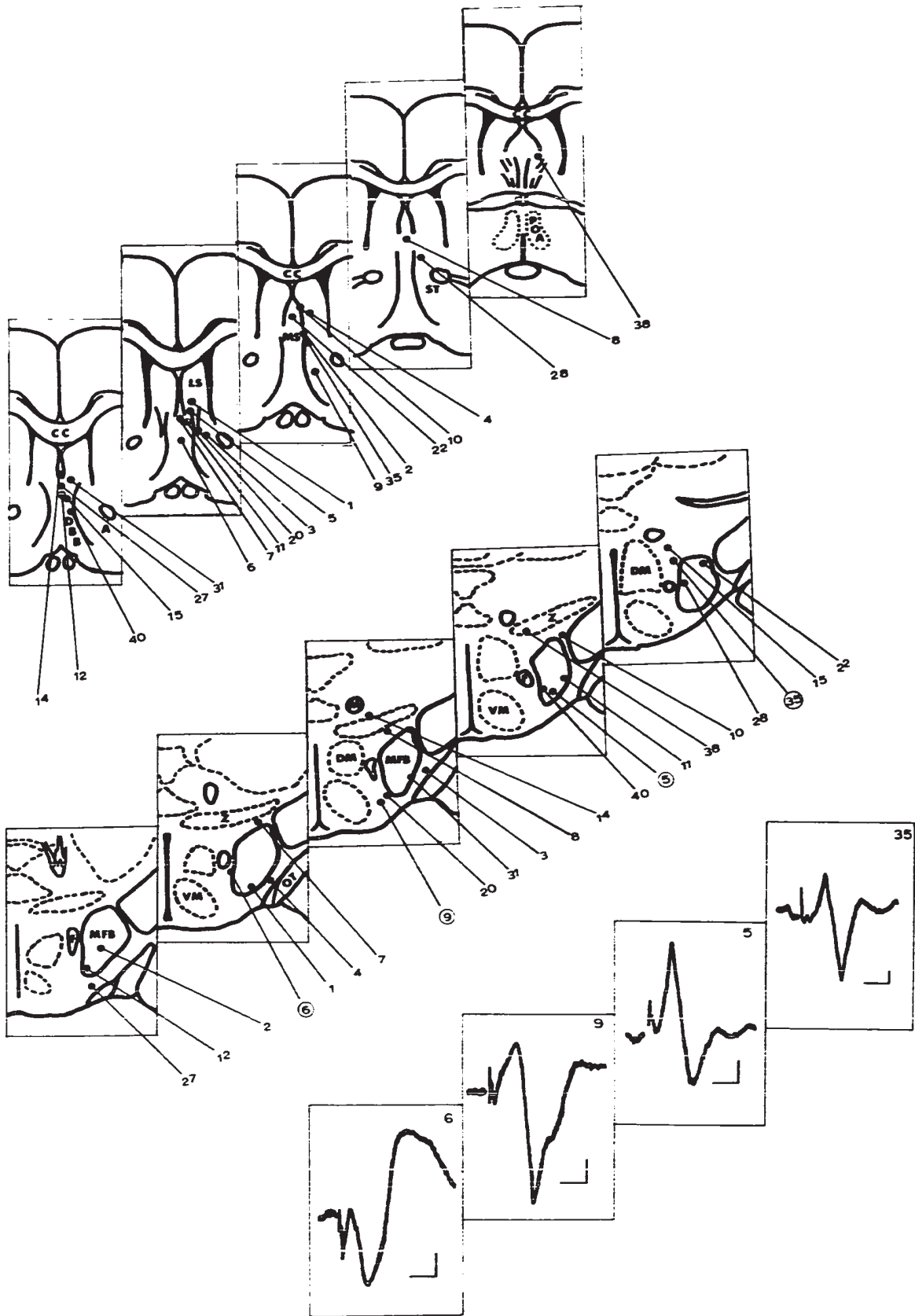
tion in the septum (Table 6). Stimulation of the anterior septum
in the dorsal and narrow medial region which extends into the dia-
gonal band of Broca and medial septum elicited mainly the 10-14
msec response (no 5, 7, 22). On the other hand, when the stimu-
lating electrodes were located more lateral and ventral in the
anterior septum the evoked response consisted mainly of the 18-23
msec component (no 3, 9, 35). The responses recorded from one LH
site while stimulating at each of these two septal regions are
shown in Fig. 19. The 10-14 msec component was elicited from a
more dorsal region while the 18-23 msec component was observed
with stimulation of more ventral sites. On the basis of the his-
tological placements of the recording electrodes there did not
appear to be any localization of these different responses in the
LH area.

In six animals the short latency component had a threshold
between 2-4V, the 10-14 msec component between 7-8V and the 18-23
msec response from 8-12V. The three components differed in their
sensitivity to repetitive stimulation with the long latency (18-23
msec) component following relatively lower rates of repetitive sti-
mulation (20-30 Hz) before disappearing. The short latency com-
ponent, when present, was the most resistant and could follow
pulses up to 100 Hz. In some cases recruitment with progressively
higher frequencies of stimulation was observed, especially for the
18-23 msec component, resulting in a marked increase in its ampli-
tude.

TABLE 6

LATENCIES OF LH EVOKED RESPONSES
PRODUCED WITH SEPTAL STIMULATION[a]

	Latency (msec)			
No.	1	2		3
1c		10	=	18
2	5	10	=	22
3c	3	10		18*
4		12*		18
5c	3	12*		20
6c	6	12*		23
7c	3	12*		
8c	6	10	=	18
9c	3	10		18*
10c				18*
11c	6	14*		22
12c		10	=	18
14		12*		20
15	6			18*
20c	4	10		20*
22		10*		20
27c		12*		
28	4	10		18*
31c		12		20*
35	4	12		18*
38		12		18*
40c		14		22*

[a]Symbols = *predominant response; = equal amplitude
responses; c animals tested for self-stimulation

Figure 19   Evoked responses recorded from one site in the

                 lateral hypothalamus while stimulating at dif-

                 ferent positions in the septum. The dorsal

                 stimulating positions, (A, B) elicit mainly

                 the 10-14 msec component while more ventrally

                 the 18-23 component is produced (C, D). Cali-

                 bration 10 msec, 75 μV. Abbreviations: ac =

                 anterior commissure; CC = corpus callosum;

                 LS = lateral septum; MS = medial septum.
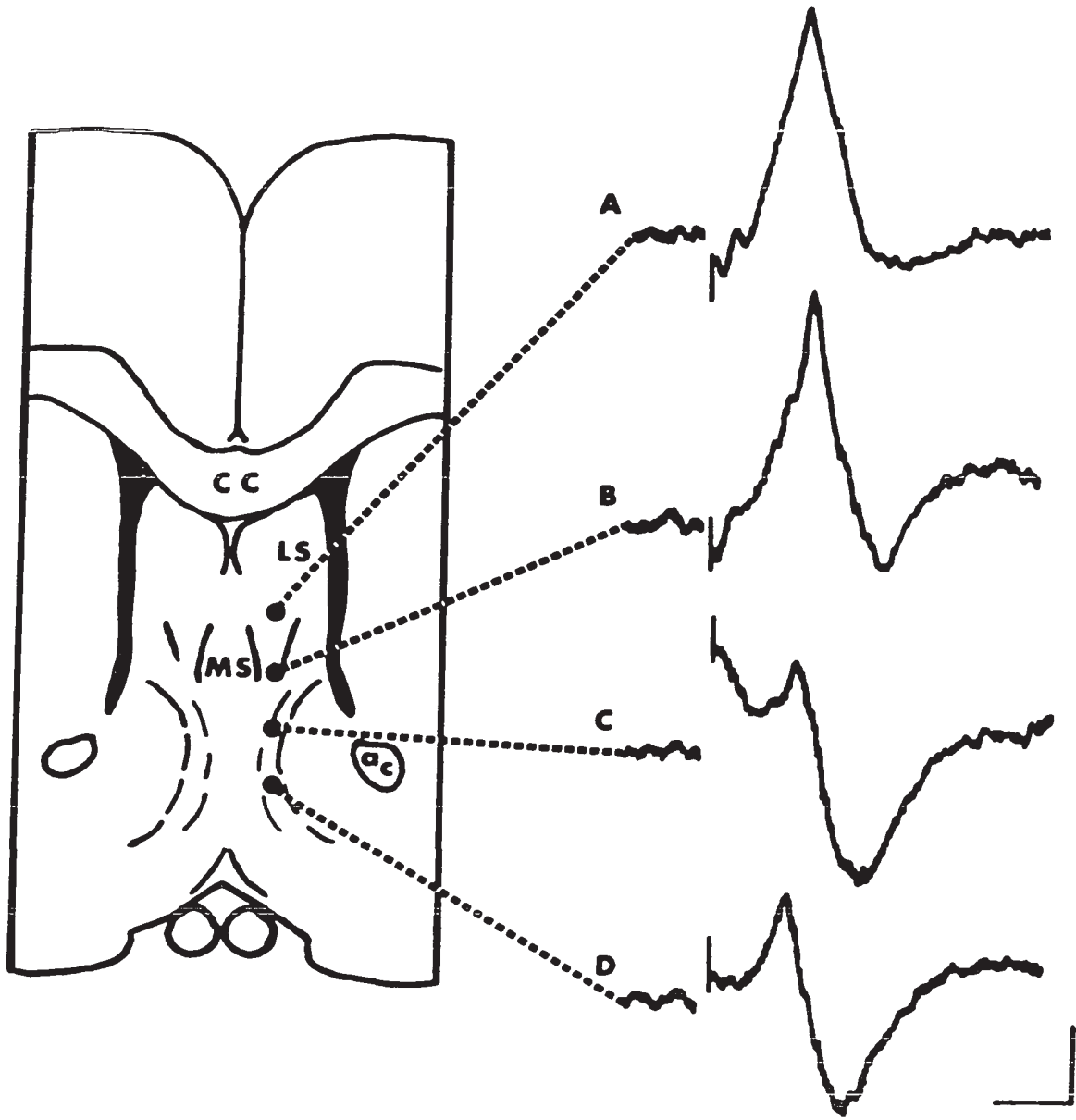
Evoked responses in the septal area produced by LH stimulation in seven animals were not consistent. In some cases no responses were observed (3 animals) whereas in others, responses of variable latency (4-32 msec) were recorded.

2. Chronic Self-Stimulation

Of the 14 animals tested for LH self-stimulation, only 12 reached the criterion of lever pressing, ($>$ 20 per 3 min period); in the other two the stimulation appeared to be aversive. The mean number of lever presses in 3 min test periods for each of the experimental conditions at low (threshold) and high (supra-threshold) levels of hypothalamic stimulation are shown in Table 7. For two of the animals (no 27, 31) there was no difference in self-stimulation rate when the current was raised from the low level to the high level. In the two animals in which the LH stimulation was aversive (no 3, 9) the procedure was reversed so that the self-stimulation rates were obtained from the septal electrode rather than the LH.

(1) Effects of Septal Stimulation on LH Self-Stimulation with Threshold Currents: As shown in Table 7, when septal pulses preceded the LH pulses the self-stimulation rates were increased when the hypothalamic stimulation was at threshold level. Two examples are shown in Fig. 20. The facilitation of self-stimulation occurred for both inter-pulse intervals (5 and 15 msec) and was significant

TABLE 7

EFFECTS OF SEPTAL STIMULATION ON LH SELF-STIMULATION RATES[a]

No.	Low current				High current			
	Control	5 msec	15 msec	After	Control	5 msec	15 msec	After
1	30± 3.9	124± 4.4*	104± 8.7*	29± 5.0	177± 6.6	158± 8.8	171± 5.2	175± 9.1
5	37± 5.5	60± 3.8*	46± 5.5*	33± 5.3	143± 2.9	130± 2.9*	101± 4.0*	115± 2.0*
6	25± 3.0	96± 4.6*	86± 1.0*	37± 9.6*	190± 6.0	117± 4.3*	105± 6.5*	149± 6.0*
7	73±14.9	104± 9.8	97± 8.3	134± 7.0*	159± 4.2	155± 3.0	150± 3.6	157± 3.1
8	49± 7.7	74±12.3*	65±10.9*	58±11.3	201± 2.7	210± 7.2	212± 7.0	218± 8.7
10	97±16.3	129±15.2*	109±17.8	124± 8.5	198± 2.2	185± 9.1	190± 6.5	200± 2.3
11	64±20.3	101±15.0*	94±16.8*	63±18.9	176± 8.8	155± 8.3*	145±14.0*	141±19.9
12	59± 7.4	93± 4.7*	88± 2.8*	110± 2.5*	117± 4.8	92± 2.5*	72± 7.5*	127± 5.1
20	79± 3.4	137± 6.2*	105± 4.5*	65± 4.3	130± 3.6	72± 4.3*	60± 5.5*	122± 7.3
27	25± 3.3	98± 3.8*	72± 5.4*	12± 2.4*	---	---	---	---
31	27± 4.5	81±21.9*	60±16.0*	27± 6.2	---	---	---	---
40	76± 2.7	116± 3.2*	110± 3.8*	80± 3.0	138± 5.2	130± 3.1	132± 4.3	143± 6.1
3	66± 6.3	33± 4.7*	26± 4.8*	51±10.4	84±13.2	54± 4.2*	42± 5.7*	68± 4.6
9	45± 6.3	144±11.6*	142± 4.8*	30± 1.5*	118± 6.8	146± 5.3*	140±14.0*	98± 9.8

[a]Mean lever presses (x ± SD) for 3-min test periods: *p < .05. Animals no. 3 and 9 show the effects of LH stimulation on septal self-stimulation rates. Group analysis of changes in rates of self-stimulation were significantly different from control rates at both low and high current levels using the Wilcoxon Signed-Ranks Test (p < .01).

Figure 20   Two examples (no 5, 6) showing the effect of

septal stimulation on lateral hypothalamic self-

stimulation under conditions of low (threshold)

and high (suprathreshold) current levels. The

difference in self-stimulation rates is ex-

pressed as percentage change from baseline for

each period (5 msec, 15 msec and after).
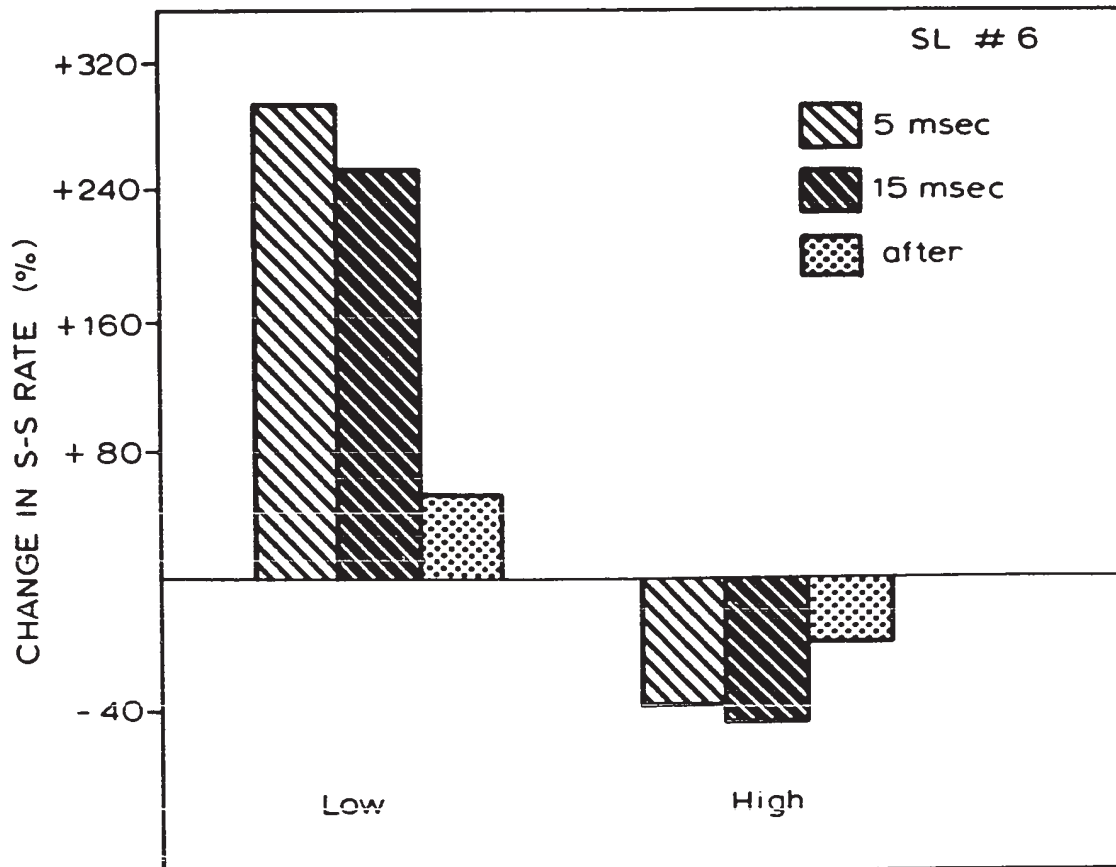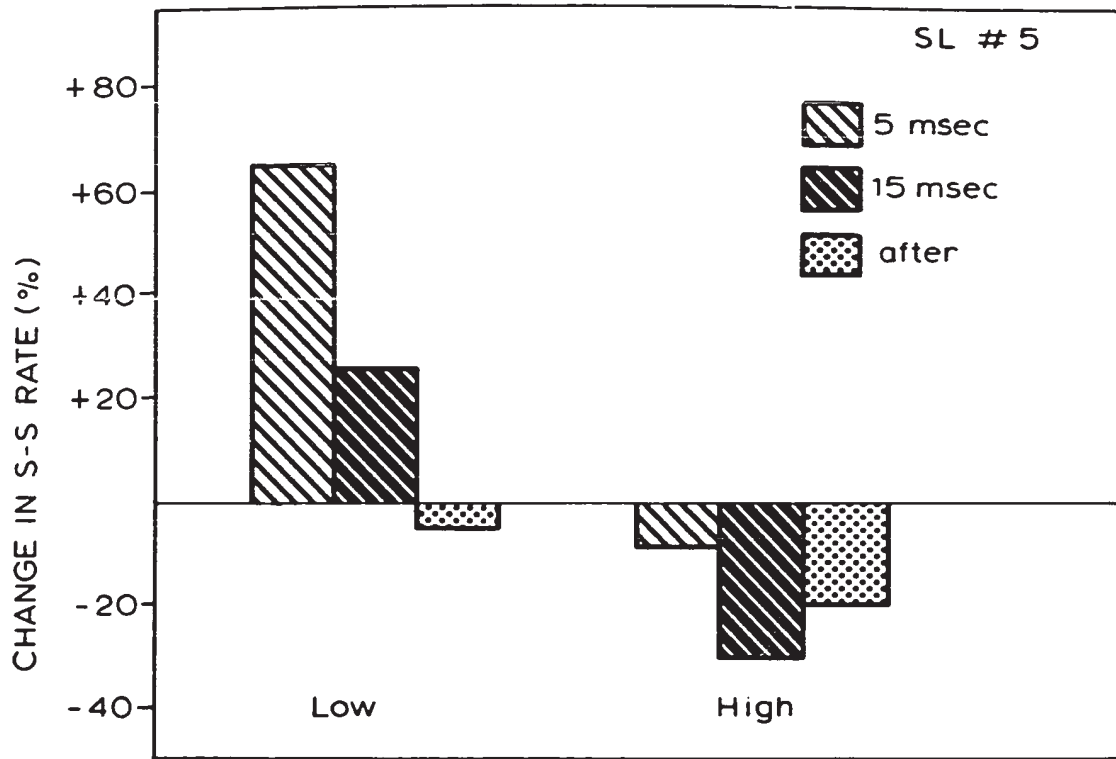
for 11 out of 12 of the animals (p < 0.05), even though there was
considerable variability in the self-stimulation rates under all
conditions when using the threshold current level. In every case
the 5 msec inter-pulse interval appeared to be the most effective
in producing facilitation of LH self-stimulation although this
difference was significant in only 6 of the animals (no 1, 5, 6,
7, 20, 27). In the 3 min test period after septal stimulation
there were also some differences in the self-stimulation rates as
compared to control levels. Three animals exhibited a significant
facilitation compared to both the control period and period of
septal stimulation. One animal (no 27) exhibited a significant
decrease in the rate of self-stimulation following septal stimula-
tion.

(2) Effects of Septal Stimulation on LH Self-Stimulation with
Suprathreshold Currents: In five of the ten animals tested
using suprathreshold stimulation of the LH there was a significant
decrease in the rate of self-stimulation, as compared to the con-
trol level, for both the 5 msec and 15 msec inter-pulse intervals
(Fig. 20). Of the five in which there was a decrease, the 15 msec
interaction period appeared to be the most effective although only
two of these were significantly different from the 5 msec inter-
action period (no 5, 12). In the remaining five animals relatively
little change in LH self-stimulation rate was produced by septal
stimulation.

(3) <u>Effects of LH Stimulation on Septal Self-Stimulation</u>:   In
the two animals in which LH stimulation was aversive the effects of
LH pulses preceding the septal pulses were observed using threshold
and suprathreshold current levels of septal stimulation. The re-
sults are shown at the bottom of Table 7. LH stimulation produced
a significant increase in self-stimulation in one animal, (no 9),
and a decrease in the other, (no 3), with both inter-pulse periods
and at both current levels. There did not appear to be any dif-
ference between the 5 msec or 15 msec periods in the magnitude of
effect produced at each.

(4) <u>Control Procedures</u>:   In addition to the testing sequence out-
lined previously (see Methods), each animal was tested for three
sessions to determine whether it would demonstrate septal self-
stimulation. All animals were observed to self-stimulate imme-
diately with the same current levels received during the inter-
action tests. When these rates of self-stimulation were added to
those obtained using only LH stimulation and compared to the fa-
cilitated rates observed with threshold LH current levels, it was
observed that the effect produced by septal stimulation was not
simply additive.

III   Projections of the Septum to the Lateral Hypothalamus

     The results of this experiment provide systematic information

concerning (a) the specific nuclei or regions within the septum
which are most effective in eliciting characteristic evoked poten-
tials in the lateral hypothalamus and (b) the direction of effect
which these regions exert on lateral hypothalamic unit activity.

1.   Lateral Hypothalamic Evoked Responses

Evoked responses recorded from the LH following single pulse
stimulation of the septum had peak latencies of 3-6, 10-14 and
18-23 msec with onset latencies of .5-2.0, 5.0-8.0 and 12.0-16.5
msec respectively. The modal distribution of peak latencies and
the range of onset latencies for the three components are shown in
Fig. 21.

Responses with the largest amplitude or those exhibiting phase
reversal with small vertical movements of the recording electrode
were selected to represent the central focus of projection from the
stimulated site. The responses were consistently reproducible in
all preparations and displayed characteristic latencies and confi-
gurations. Latencies were measured from the beginning of the sti-
mulus artifact to the peak of the response wave (peak latency, PL),
and/or to the onset of the response wave (onset latency, OL). No
attempt was made to analyze the polarity of the evoked responses
since bipolar recordings were made.

The 3-6 msec component had a threshold of 2.0-4.5V and followed
stimulation of 100 Hz with little or no attenuation. This short
latency response was observed when recording from the dorsal aspect

Figure 21   Distribution of peak latencies (3-6 msec, 10-14
            msec, 18-23 msec) and range of onset latencies
            (horizontal bars) for lateral hypothalamic (LH)
            evoked responses elicited by septal stimulation.
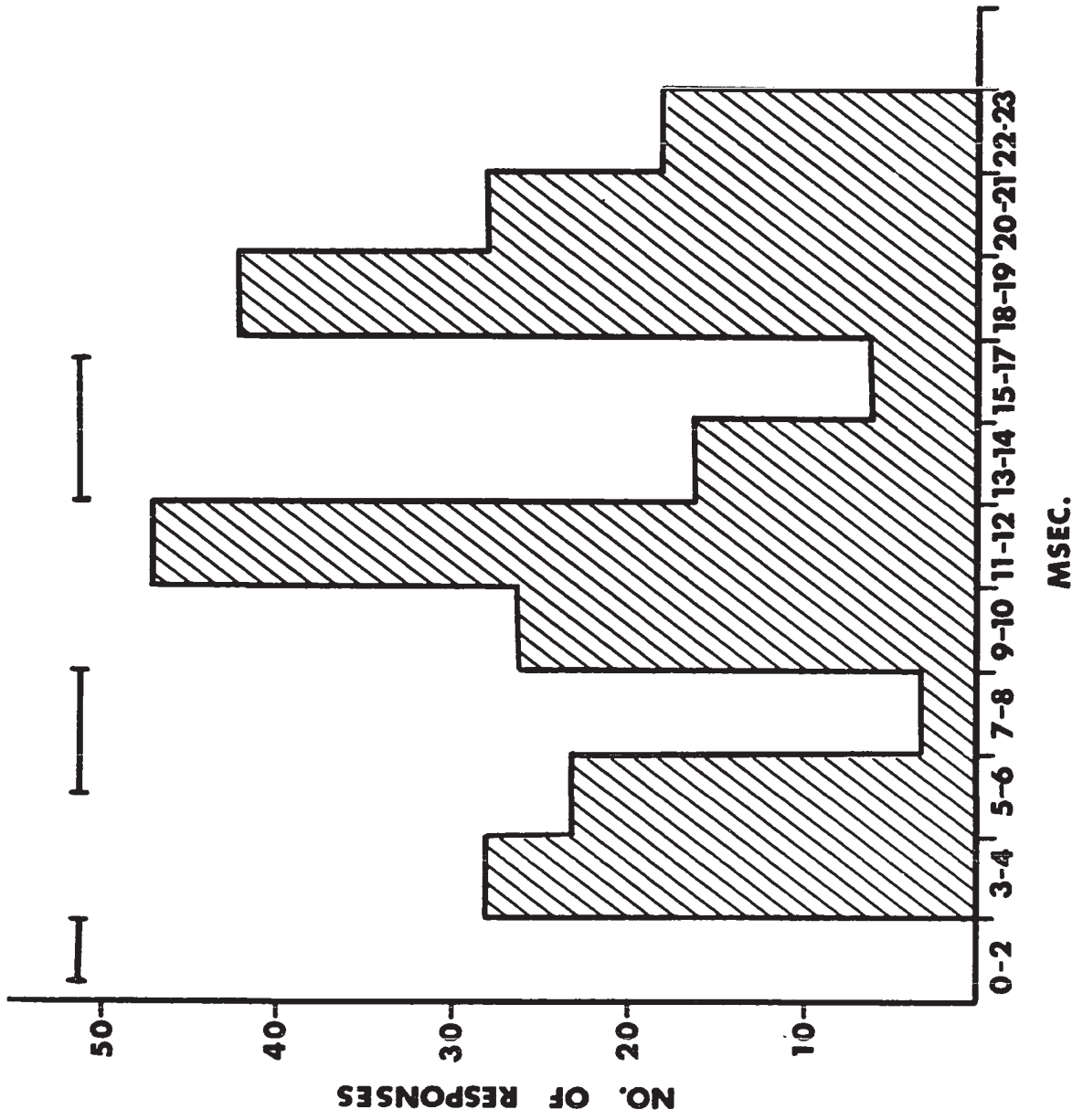
of the LH and was considerably smaller in amplitude than the two later components and not recorded as consistently (see Fig. 21). The response was most prominent with stimulation in the dorso-lateral septum (3.5-4.0 mm, BSC) and phase reversal occurred when the LH electrode reached a region 7.0 mm, BSC (Fig. 22). With deeper penetrations of the recording electrode the response decreased in amplitude and was usually masked by the larger 10-14 msec component which was also elicited from a similar region of the septum.

The two major response components (with latencies of 10-14 msec and 18-23 msec) were also observed to be evoked from different regions of the septum as is shown in Fig. 23. The 10-14 msec response was elicited mainly from the dorso-medial and mid-line septum (Fig. 23 (1) (2)) and had its lowest threshold (4.0V) in these areas. The longer latency, 18-23 msec component was elicited mainly from the region of the bed nucleus of the stria terminalis (Fig. 23 (3) (4)) where it had the lowest threshold (7.0V). Some variability in this response was observed when the septal stimulating electrode was moved in the anterior-posterior plane at the level of the bed nucleus. Stimulation in the descending column of stria terminalis fibers evoked the same response but with a larger amplitude (25-30%). More anteriorly located stimulation sites, in the region of the nucleus accumbens, elicited a response of lower amplitude (10-20%) and a peak latency 1-3 msec longer.

Figure 22   Location of a stimulating electrode site (top)

in the dorso-lateral septum and LH recording

sites (1, 2, 3) from which phase reversals in

the 3-6 msec component were observed. Cali-

bration 10 msec, 10μV. Abbreviations: A =

nucleus accumbens; CC = corpus callosum;

DBB = diagonal band of Broca; DM = dorso-

medial hypothalamus; F = fornix; LS = la-

teral septum; M = mammillothalamic tract;

VM = ventromedial hypothalamus; Z = zona in-

certa.
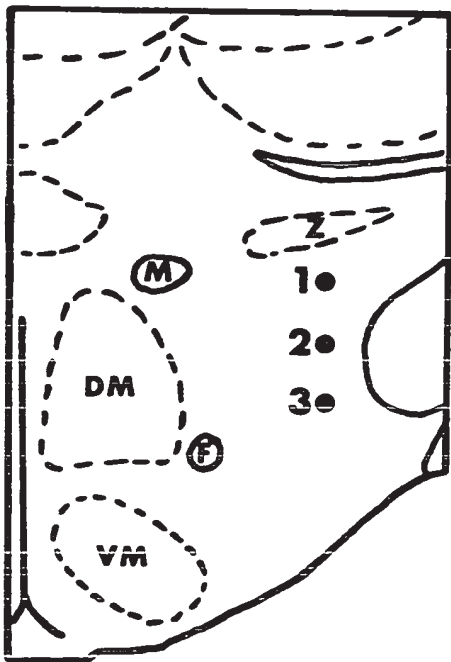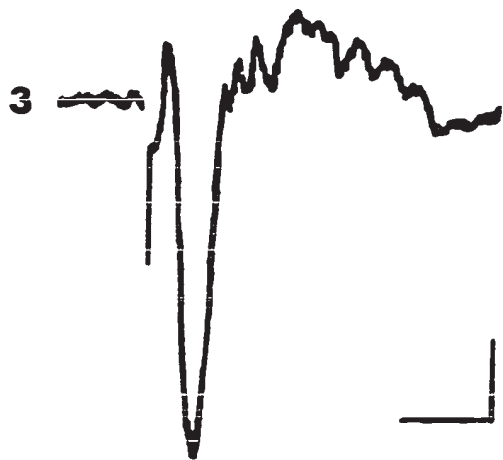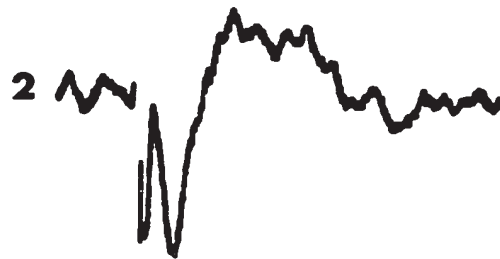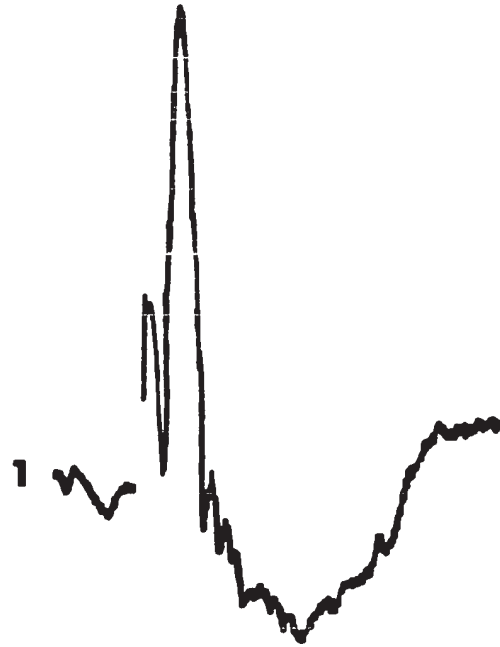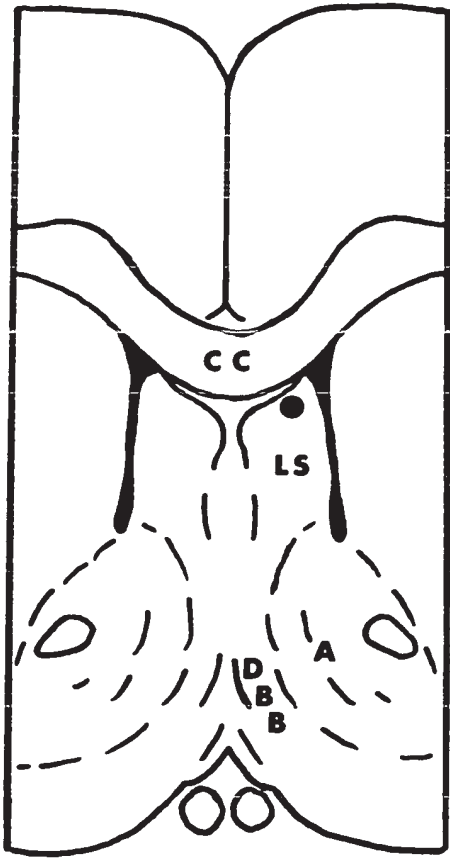
Figure 23   Lateral hypothalamic (LH) evoked responses pro-

duced by stimulation of the dorso-medial (1)

and midline region (2) and the ventro-lateral

region (3, 4) of the septum; (1) and (2) gave

a pronounced 10-14 msec component, and (3) and

(4) and 18-23 msec component. Calibration 10

msec, 50μV. Abbreviations: ac = anterior

commissure; CC = corpus callosum; LS = la-

teral septum; MS = medial septum; ST = stria

terminalis.
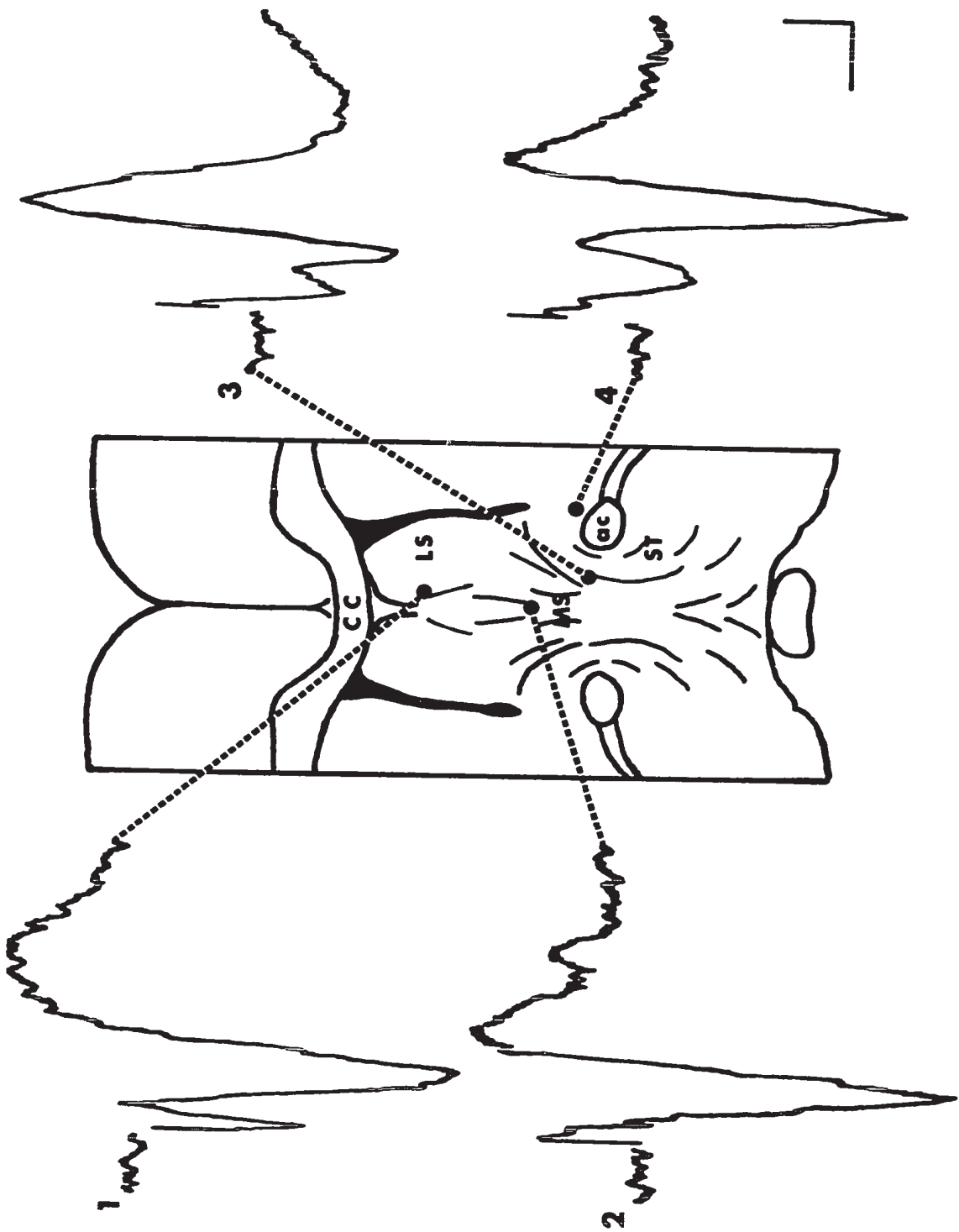
Repetitive stimulation produced either no change in the amplitudes of the 10-14 or 18-23 msec components or increases ranging from 25-150% of the control amplitude. These increases were most evident in the 18-23 msec component with frequencies between 1-20 Hz whereas the 10-14 msec component exhibited an enhancement up to 40 Hz. Higher frequencies resulted in gradual attenuation of the components and eventually their eliminiation. The responses also showed post-tetanic potentiation following 5-10 sec of repetitive stimulation with increases in amplitude of 80-220%, the 18-23 msec component being the most sensitive. In three cases post-tetanic depression was observed for periods of up to 15 sec following stimulation.

The position of the recording electrode within the LH indicated differences in the projection of the fibers mediating the 10-14 and 18-23 msec components. The earlier response exhibited either an amplitude maximum or a phase reversal at a level of 7.5 mm BSC, whereas for the 18-23 msec component reversal occurred more ventrally between 8.0-8.5 mm BSC. Fig. 24 illustrates phase reversals for the two components elicited from the dorso-medial septum and from the region of the bed nucleus of the stria terminalis. In many cases a considerable overlap in the projection of the responses was observed. Fig. 25 illustrates this overlap as the LH electrode was moved ventrally in 0.5 mm increments while stimulating the septum in an area bordering on the two regions from which the characteristic responses were elicited. With the

Figure 24   Recording sites within the lateral hypothalamus

(LH) from which phase reversals in the (A),

10-14 msec component and (B), 18-23 msec com-

ponent were obtained. Calibration 10 msec, 75

μV. Abbreviations: DM = dorsomedial hypothala-

mus; F = fornix; M = mammillothalamic tract;

VM = ventromedial hypothalamus; Z = zona incerta.

A

B

N

M

DM

VM
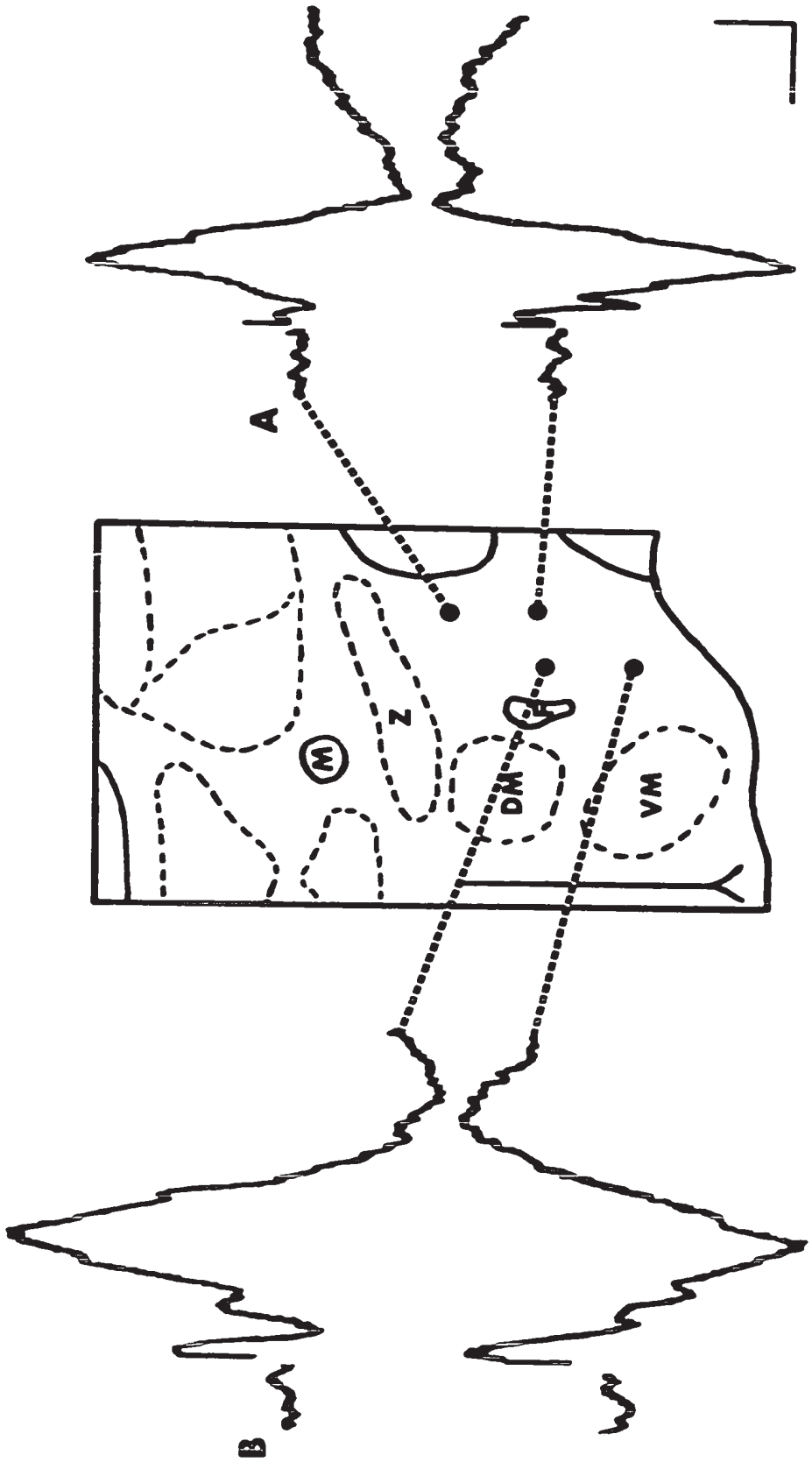
Figure 25   Evoked responses recorded at different levels of

the LH with stimulation of the septum in regions

(A, B) producing both 10-14 and 18-23 msec com-

ponents. The more dorsal recording positions,

(1, 2) show mainly the 10-14 msec component while

the ventral positions (3, 4) show a transition to

the 18-23 msec component. Calibration 10 msec,

50μV. Abbreviations: ac = anterior commissure;

CC = corpus callosum; DM = dorsomedial hypo-

thalamus; F = fornix; M = mammillothalamic

tract; MS = medial septum; VM = ventromedial

hypothalamus; Z = zona incerta.
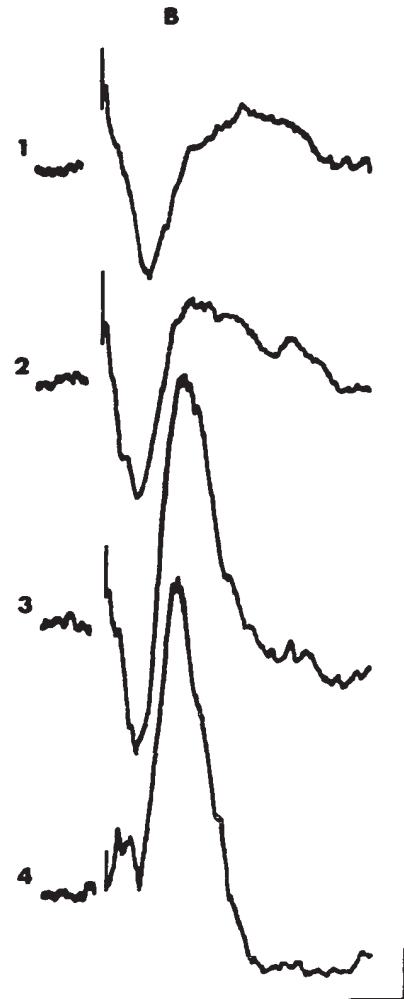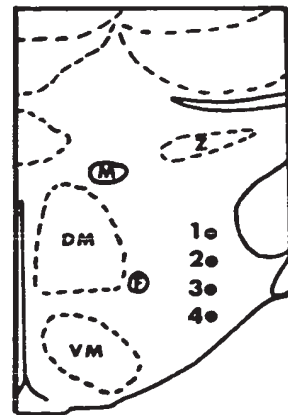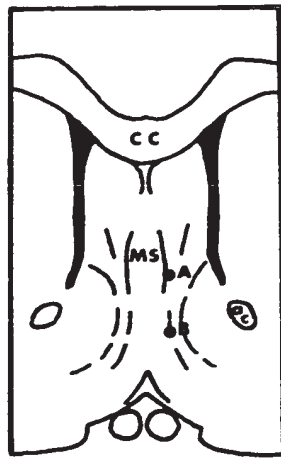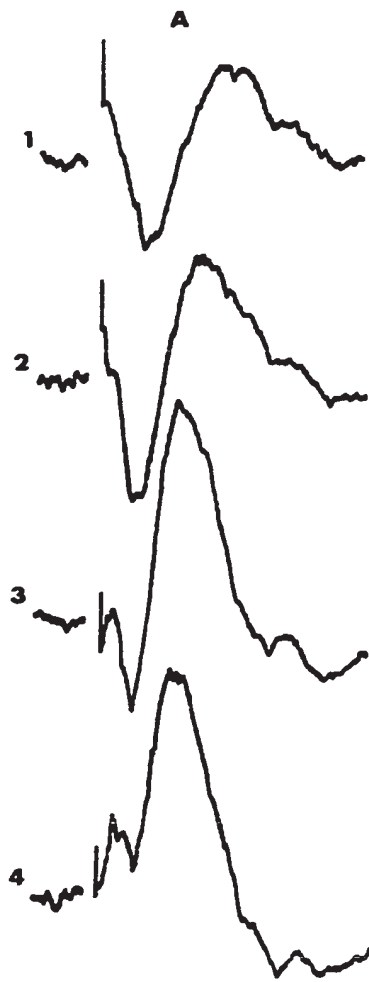
more dorsally located recording sites the 10-14 msec component is prominent whereas more ventrally the 18-23 msec component reaches its maximal amplitude. Interaction of these two components while stimulating the midline region and ventro-lateral septum at various time intervals further demonstrates the overlap of these components in the LH area. When the 18-23 msec component precedes the 10-14 msec component the latter is decreased in amplitude (peak to base-line) throughout the duration of the conditioned response and for a considerable period following. Fig. 26 illustrates this inter-action showing that inhibition lasts from 10-80 msec before re-turning to the control amplitude. When the 10-14 msec component precedes the 18-23 msec component at various time intervals a si-milar inhibitory interaction is observed which lasts from 5-85 msec before returning to the control amplitude (Fig. 27).

2.   Identification of Pathways

The localization of regions within the septum which evoke the characteristic response components in the LH area suggests that two major fiber systems are involved. The region from which the 3-6 and 10-14 msec components are elicited is either part of the pre-commissural fornix system originating in the septum or fibers of passage of this system from the hippocampus. The region from which the 18-23 msec component is elicited in part of the stria termina-lis pathway. Since it was not considered possible to section se-parately each of these pathways between the septum and LH area

Figure 26   Interaction between the 10-14 and 18-23 msec com-

ponents produced by stimulation of the midline

(precommissural fornix - PCF) and ventro-lateral

septal region (bed nucleus of stria terminalis -

ST) respectively. The top record shows the

changes in amplitude of the PCF component when

it is preceded by ST stimulation at different

intervals. Below, the graph represents the

peak to baseline changes in amplitude at the

different time intervals expressed as a per cent

of the control amplitude. Calibration 10 msec,

75μV.

CONTROL   10msec   15msec   20msec   30msec   40msec   60msec

75uv
10msec

PERCENT OF CONTROL PCF

100

50

0   20   40   60   80   100

MSEC INTERVAL
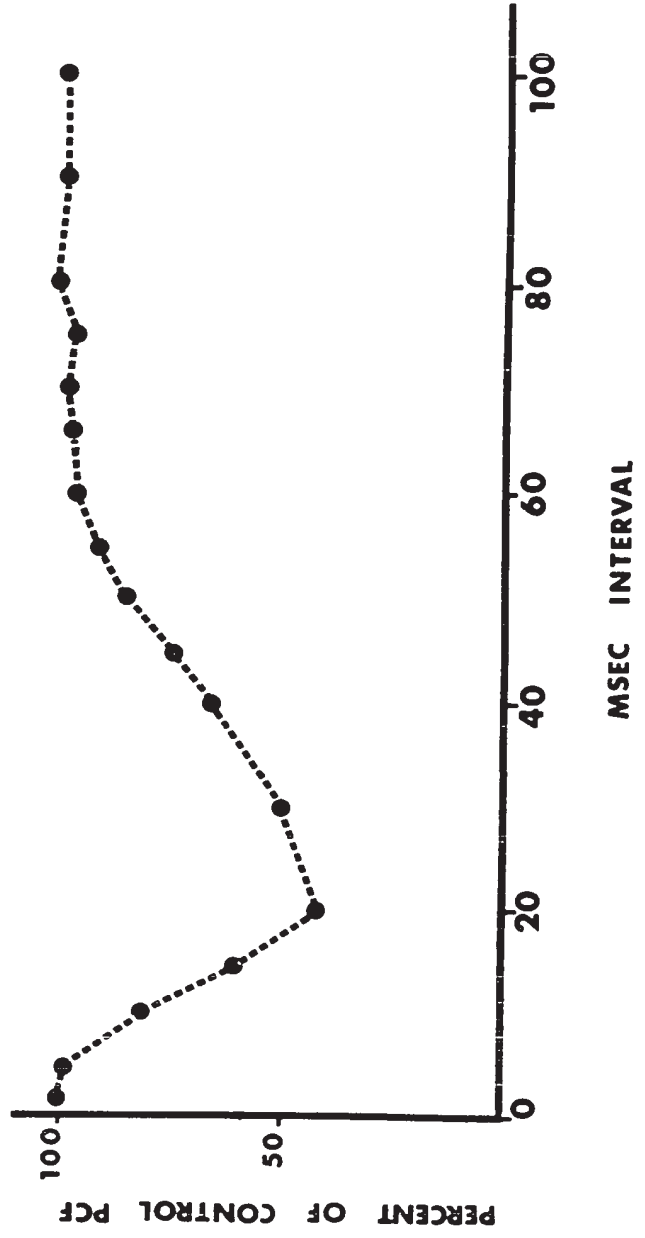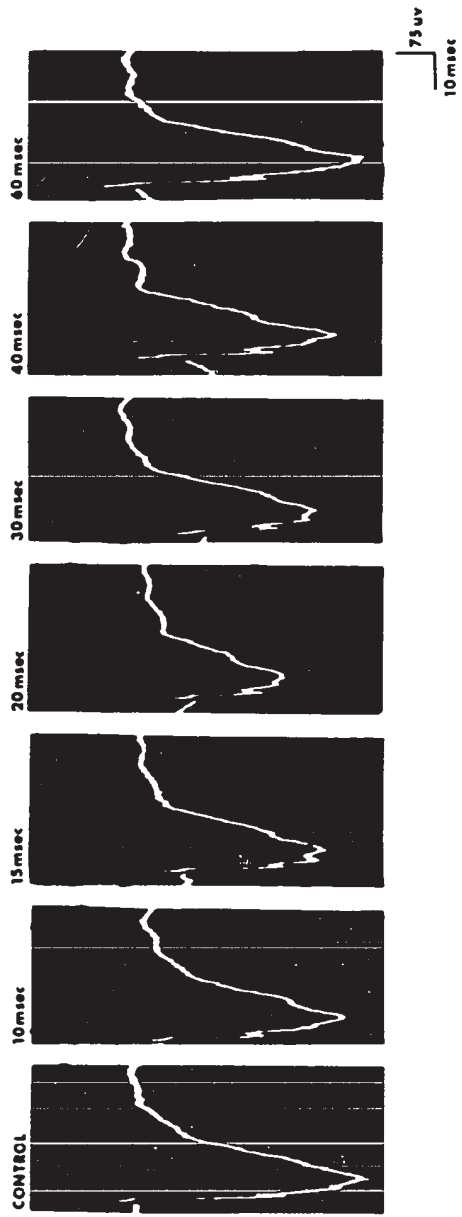
Figure 27   Interaction between the 10-14 and 18-23 msec

components produced by stimulation of the mid-

line (precommissural fornix - PCF) and ventro-

lateral region (bed nucleus of stria terminalis -

ST) respectively. The top record shows the

changes in amplitude of the ST component when

it is preceded by PCF stimulation at different

intervals. Below, the graph represents the

peak to baseline changes in amplitude at the

different intervals expressed as a per cent of

the control amplitude. Calibration 20 msec,

50µV.

CONTROL   10 msec   20 msec   30 msec   40 msec   60 msec   80 msec

50 uv
20 msec

MSEC INTERVAL

PERCENT OF CONTROL ST
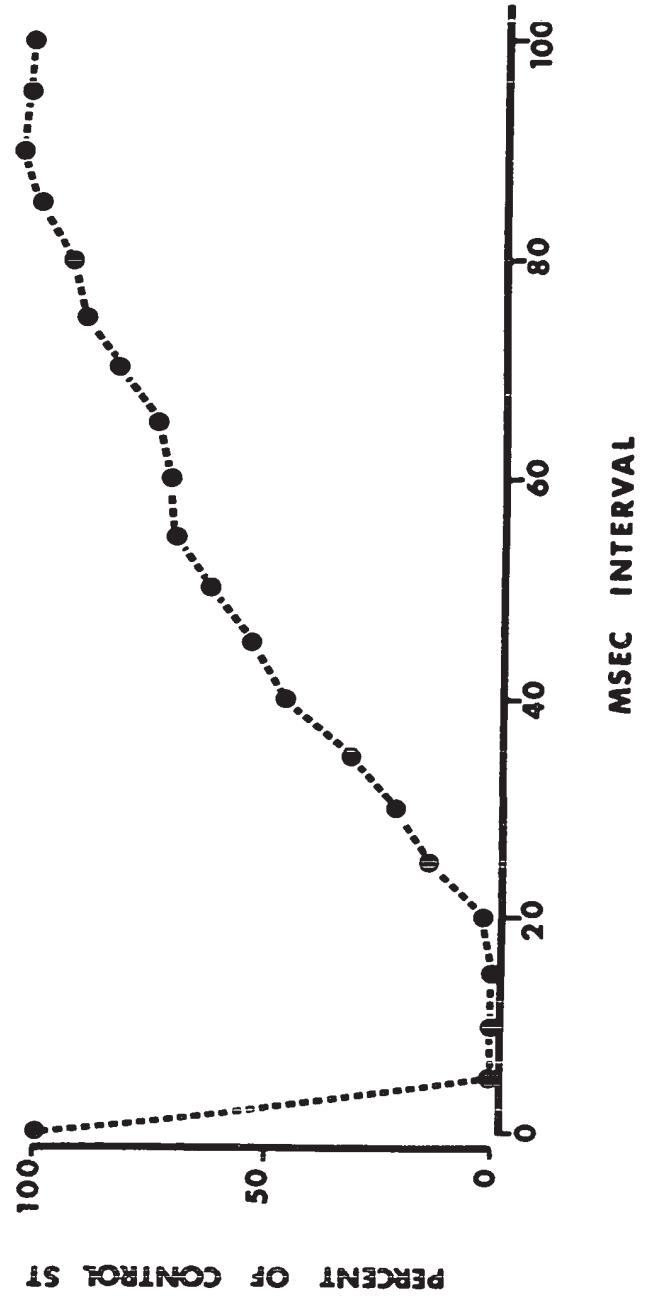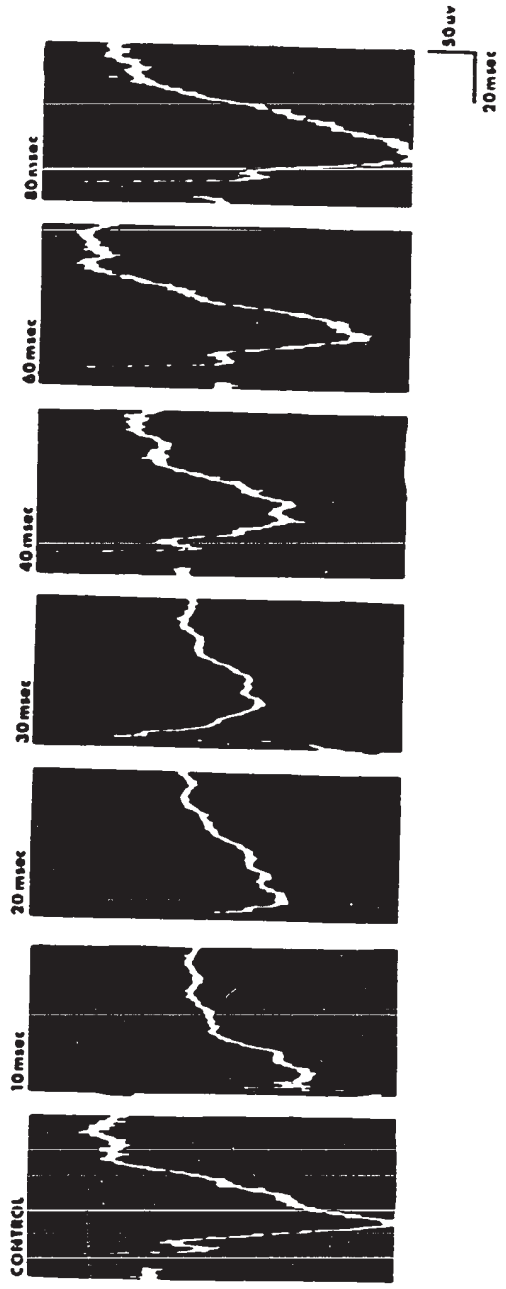
because of their inaccessibility and diffuse nature, stimulating electrodes were positioned in the hippocampal region from which the fornix system originates and in the stria terminalis between the amygdala and septum. Lesions were then made in the regions of the septum which elicited the characteristic evoked potentials in the LH area and the effects of these lesions on hippocampal and stria terminalis elicited responses were observed.

The evoked responses recorded in the dorsal LH area to hippocampal stimulation were observed to have two components; 4-8 msec (2.5-4.0 msec, OL) and 11-17 msec (5.0-8.0 msec, OL). These components could be elicited from stimulation sites either in the anterior or middle one-third of the hippocampus (Fig. 28). In four animals lesions were made in the septum in regions which elicited the 10-14 msec component in the LH. Anterior septal lesions had relatively little effect on the two evoked components whereas lesions in the middle one-third of the septum produced slight decreases in the amplitude of the long latency component (12-23%), but did not alter the amplitude of the short latency component. Similar lesions in the posterior portion of the middle one-third of the septum attenuated the 11-17 msec component by 52-60% and the 4-8 msec component by 28-36% (Fig. 28). With more posterior lesions at the level where the anterior commissure crosses the midline and in the region of the descending postcommissural fornix columns, the 11-17 msec component was reduced in amplitude by 68-74% and the short latency component by 45-53%.

Figure 28   Evoked responses recorded in the dorsal LH to

stimulation of the hippocampus at points A and

B as illustrated in the upper diagram; (A 2,

3) shows the LH component (11-17 msec), eli-

cited from the ventral hippocampal site before

and after lesions of the dorsal and midline

regions of the septum (1); (B 2, 3) shows the

LH component (4-8 msec), elicited from the

dorsal hippocampal site before and after le-

sions more posteriorly in the septum (1).

Calibration 2.5 msec, 50μV. Abbreviations:

ac = anterior commissure; CC = corpus callosum;

FH = fimbrial hippocampus; H = hippocampus;

LS = lateral septum; MS = medial septum; ST =
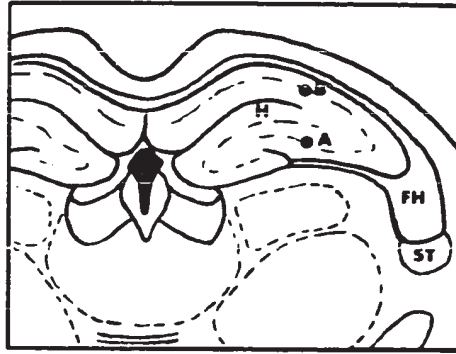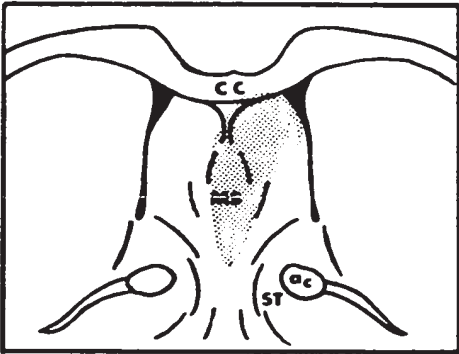
stria terminalis.

A   B
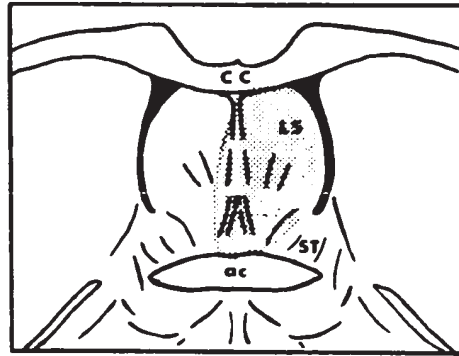
1
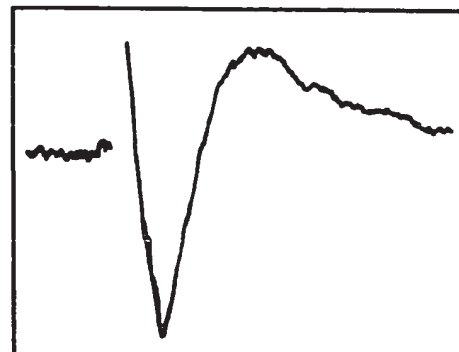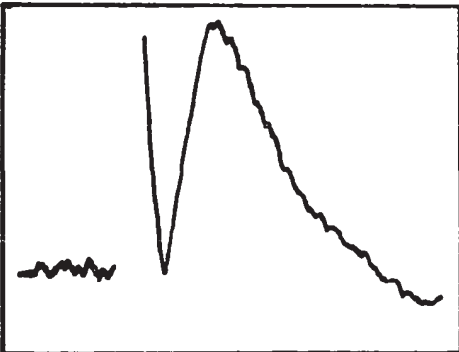
2
BEFORE
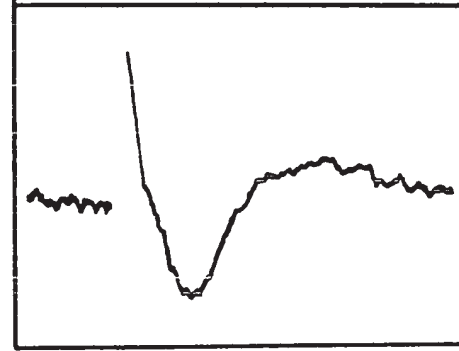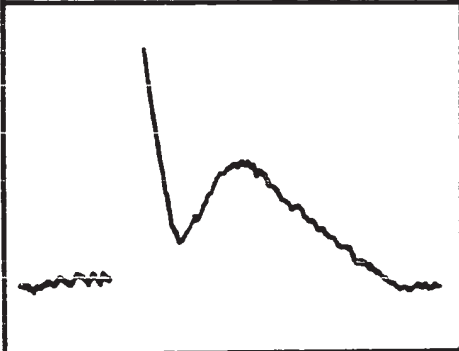
3
AFTER

When recording from the ventral LH area (8.0-8.5 mm BSC, the same region from which the maximal 18-23 msec component was recorded to stimulation of the ventro-lateral septum), stimulation of the stria terminalis, between the thalamus and tail of the caudate nucleus, elicited an evoked response of 32-38 msec (26.5-27.5 msec, OL). Lesions beginning in the middle one-third of the septum and progressing posteriorly into the descending column of the postcommissural stria terminalis were observed to attenuate the evoked response in three animals. With lesions in the ventro-lateral regions of the septum the 32-38 msec response was eliminated and a new component appeared, opposite in polarity to the original one and having a latency of 26-30 msec (Fig. 29). Lesions more posterior and slightly lateral, so as to include the post-commissural stria fibers reduced this component by 48-55%. Further attenuation of 62-68% occurred when lesions were made directly in the column of the stria terminalis.

3. Effects of Stimulation of the Precommissural Septum and Bed Nucleus of the Stria Terminalis on Lateral Hypothalamic Unit Activity

Extracellular recordings of 107 lateral hypothalamic neurons displayed the same characteristics of waveform, discharge pattern and frequency as those reported previously.

Single pulse stimulation of the precommissural fornix (PCF) region throughout the dorsal and ventral extent of the midline septum was studied in 71 LH units with 48 (68%) being influenced

Figure 29   Evoked responses recorded in the ventral LH to

stimulation of the stria terminalis. (A),

control response elicited from stimulation site

in the stria terminalis (B); (C), response

following lesion in the septum (D); (E), re-

sponse following lesion more posteriorly within

the septum (F). Calibration 10 msec, 50µV.

Abbreviations: ac = anterior commissure; CC =

corpus callosum; F = fornix; FH = fimbrial

hippocampus; H = hippocampus; LS = lateral

septum; MS = medial septum; ST = stria ter-

minalis.

A

B

C

D

E

F
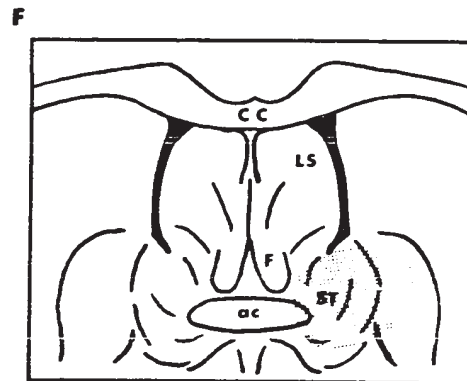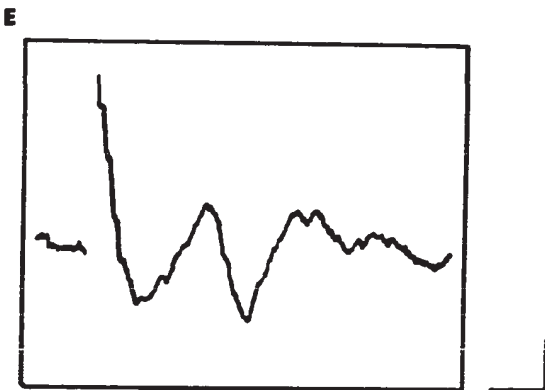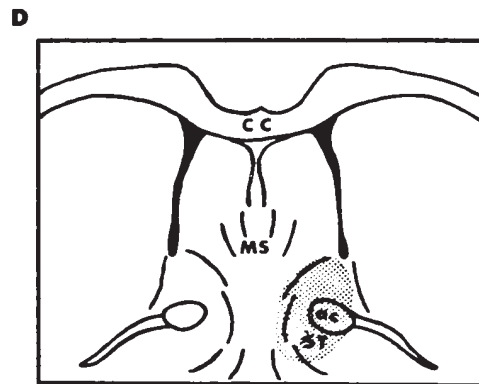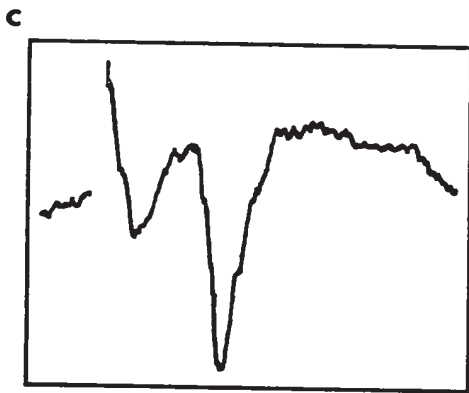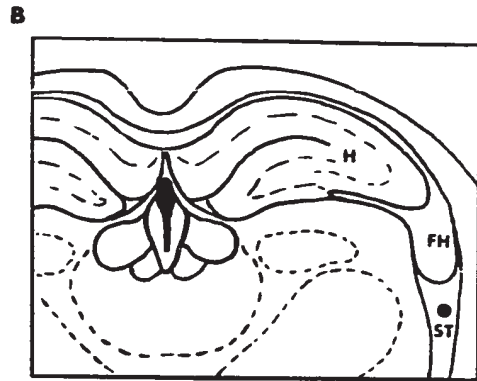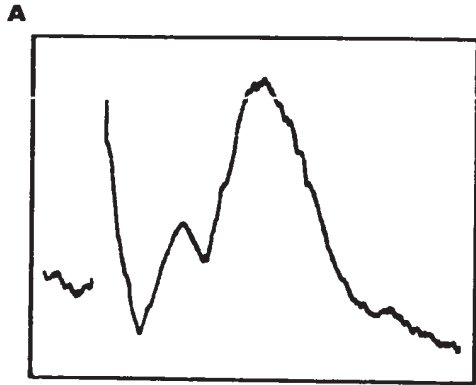
while 23 (32%) units remained unaffected. Stimulation more lateral-
ly and ventrally in the bed nucleus region of the stria terminalis
(ST) and nucleus accumbens influenced 40 LH units (71%) while 16
(29%) were unaffected. The effect of stimulation of both of these
septal regions was examined in 30 units with 21 of these (70%) being
influenced by both, while 9 units (30%) were influenced by only one
region (Table 8).

PCF stimulation activated 15 (31%) of the LH units while 4
units (10%) were activated by ST stimulation. Examples of two
units activated by PCF stimulation are shown in Fig. 30 with their
respective post-stimulus time histograms. The latency to activa-
tion produced with PCF stimulation ranged from 5.0-14.0 msec ($\bar{x}$ =
10.2 ± 1.7 msec) while that for ST stimulation ranged from 20.0-24.0
msec ($\bar{x}$ = 22.5 ± 2.3 msec). The population histograms in Fig. 31
demonstrate that the majority of units activated occur within the
duration of the evoked responses which can be elicited in the LH
area from the septum. PCF stimulation evokes a response of 10-14
msec while ST stimulation evokes the characteristic 18-23 msec com-
ponent.

Many of the LH units influenced by septal stimulation exhibited
an activation-inhibition sequence. Twenty-four units (50%) showed
this response with PCF stimulation while 15 units (37%) were in-
fluenced with ST stimulation. Six of these exhibited the activation-
inhibition sequence from both sites of stimulation (Table 8). No
differences in latency to activation were observed between the two

TABLE 8

NUMBER OF LH NEURONS SHOWING ACTIVATION, ACTIVATION-INHIBITION, INHIBITION OR NO EFFECT FOLLOWING SINGLE PULSE STIMULATION OF THE PRECOMMISSURAL FORNIX (PCF) AND BED NUCLEUS OF THE STRIA TERMINALIS (ST) REGIONS

	Activation	Activation-Inhibition	Inhibition	No Effect
PCF	15	18	5	23
PCF and ST	--	6	4	--
ST	4	9	17	16

100uv

50msec

18127 PCF
N = 60
$\bar{X}$ = 11.3msec.

5196 PCF
N = 50
$\bar{X}$ = 8.21msec.
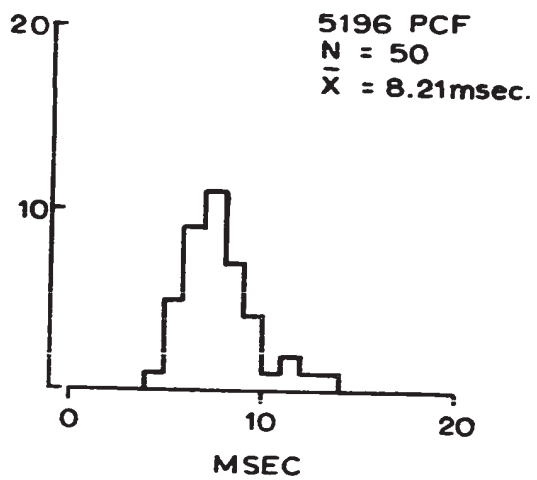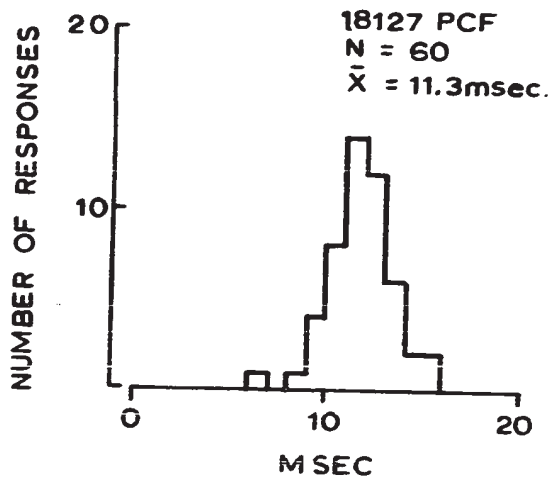
Figure 31   (A) Population histogram of LH neurons activated

by PCF stimulation with an example of an evoked

component recorded from the same site in the

LH. Note the relationship between the increased

discharge rate and the 10-14 msec component. N =

15 LH neurons. (B) Population histogram of LH

neurons activated by ST stimulation with an

example of an evoked component recorded from the

same site in the LH. Note relationship between

activation and the 18-23 msec component. N =

4 LH neurons. $\bar{x}$ = mean latency to activation ±

standard deviation.

A

NUMBER OF UNITS ACTIVATED

PCF
$\bar{X} = 10.2 \pm 1.7 \, msec$

LATENCY
(msec)

B

NUMBER OF UNITS ACTIVATED

ST
$\bar{X} = 22.5 \pm 2.3 \, msec$
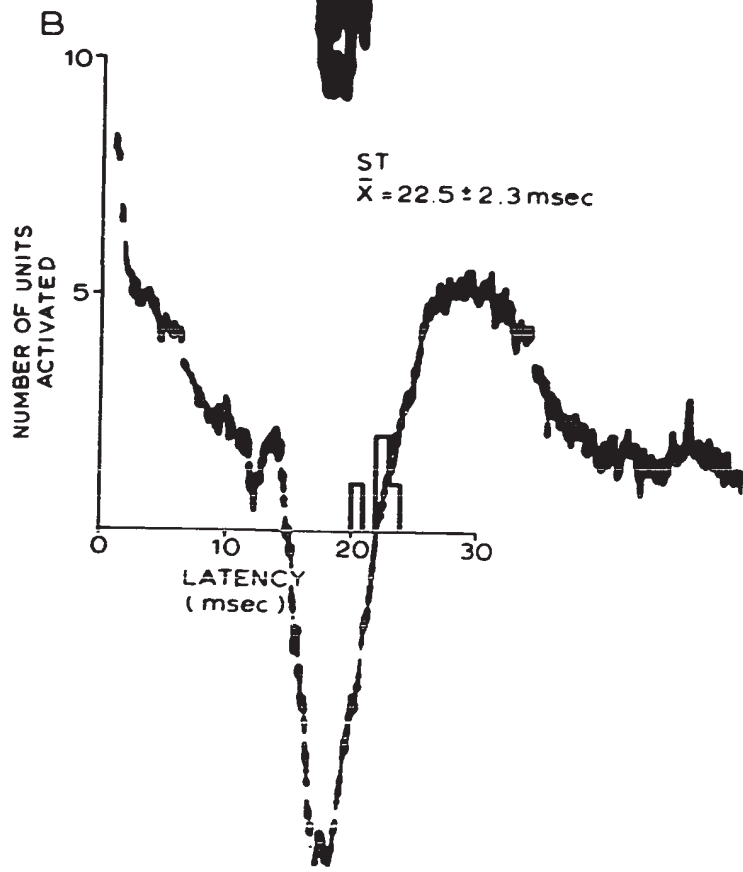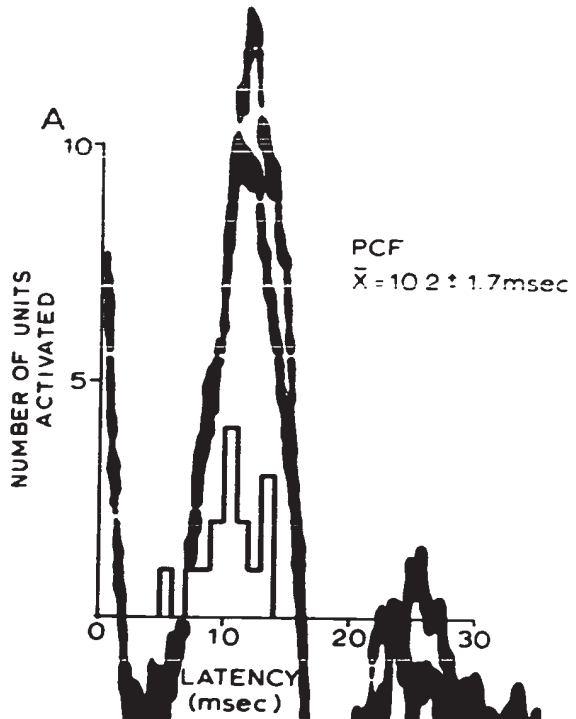
LATENCY
(msec)

regions. These latencies ranged from 5.0-16.0 msec ($\bar{x}$ = 11.1 ± 2.1 msec). The onset of inhibition, measured as the time in msec from the stimulation artifact to the last unit discharge following the activation, ranged from 11.0-24.0 msec ($\bar{x}$ = 18.3 ± 3.1 msec) for PCF stimulation and from 11.0-21.0 msec ($\bar{x}$ = 16.5 ± 3.1 msec) for ST stimulation. The duration of the inhibitory component lasted from 12.0-240. msec ($\bar{x}$ = 78.9 ± 61.4 msec) for PCF stimulation while that produced by ST stimulation lasted longer, from 19.0-385. msec ($\bar{x}$ = 123.9 ± 107.2 msec). The activation-inhibition sequence produced with both PCF and ST stimulation are shown for two LH neurons with their respective post-stimulus time histograms in Fig. 32. The evoked response recorded from this region with either stimulation site is superimposed on the population histogram of the influenced units from both regions and demonstrates the close correlation between the 10-14 msec component showing activation and the 18-23 msec component showing inhibition (Fig. 33).

Nine (19%) LH units were inhibited by single pulse stimulation of the PCF region while 21 (51%) units were inhibited by the ST region (Table 7). Four of these units were influenced in a similar manner by both regions. The onset of inhibition ranged from 0-20 msec for ST stimulation ($\bar{x}$ = 6.4 ± 6.8 msec) and from 0-16 msec for PCF stimulation ($\bar{x}$ = 9.1 ± 5.8 msec). The duration of inhibition ranged from 22.0-280. msec with stimulation of the ST region ($\bar{x}$ = 79.8 ± 71.9 msec) and from 18-290. msec ($\bar{x}$ = 99.7 ± 90.6 msec) for the PCF region. Examples of these responses with their

Figure 32   (A) Recordings of discharge rates of LH neurons

with their corresponding post-stimulus time

histogram showing activation-inhibition se-

quence following single pulse stimulation of

PCF region.   (B) Recording from a different LH

neuron following stimulation of the ST region.

Dotted lines indicate the control discharge

rate per address in the histogram.   N = number

of stimulation trials; $\bar{x}_r$ = mean spontaneous

discharge rate; $\bar{x}_a$ = mean latency to activation.

200uv
100msec

25880 PCF
N = 60
$\bar{X}_R$ = 13.3 /sec.
$\bar{X}_A$ = 8.3 msec.

NUMBER OF RESPONSES

40

20

0   200   400
MSEC

100uv
100msec

17633 ST
N = 100
$\bar{X}_R$ = 5.0 /sec.
$\bar{X}_A$ = 12.2 msec.

NUMBER OF RESPONSES

30

20

10
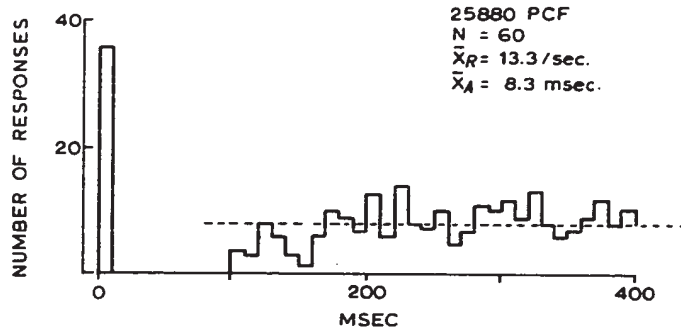
0   200   400
MSEC
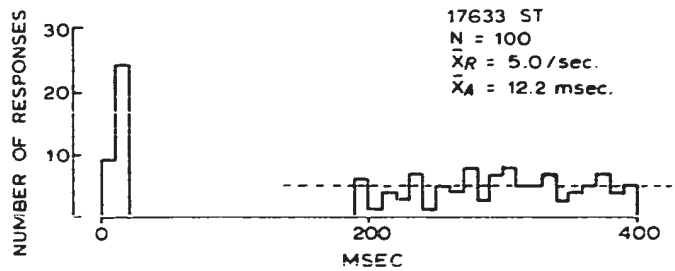
Figure 33   Population histogram of 27 LH neurons showing

the activation-inhibition sequence following

stimulation between the PCF and ST regions of

the septum. The superimposed evoked response

demonstrates the relationship between this ef-

fect and the presence of the 10-14 and 18-23

msec components.

NUMBER OF UNITS

(ACTIVATION)

(INHIBITION)

10

5

5

10

2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

MSEC
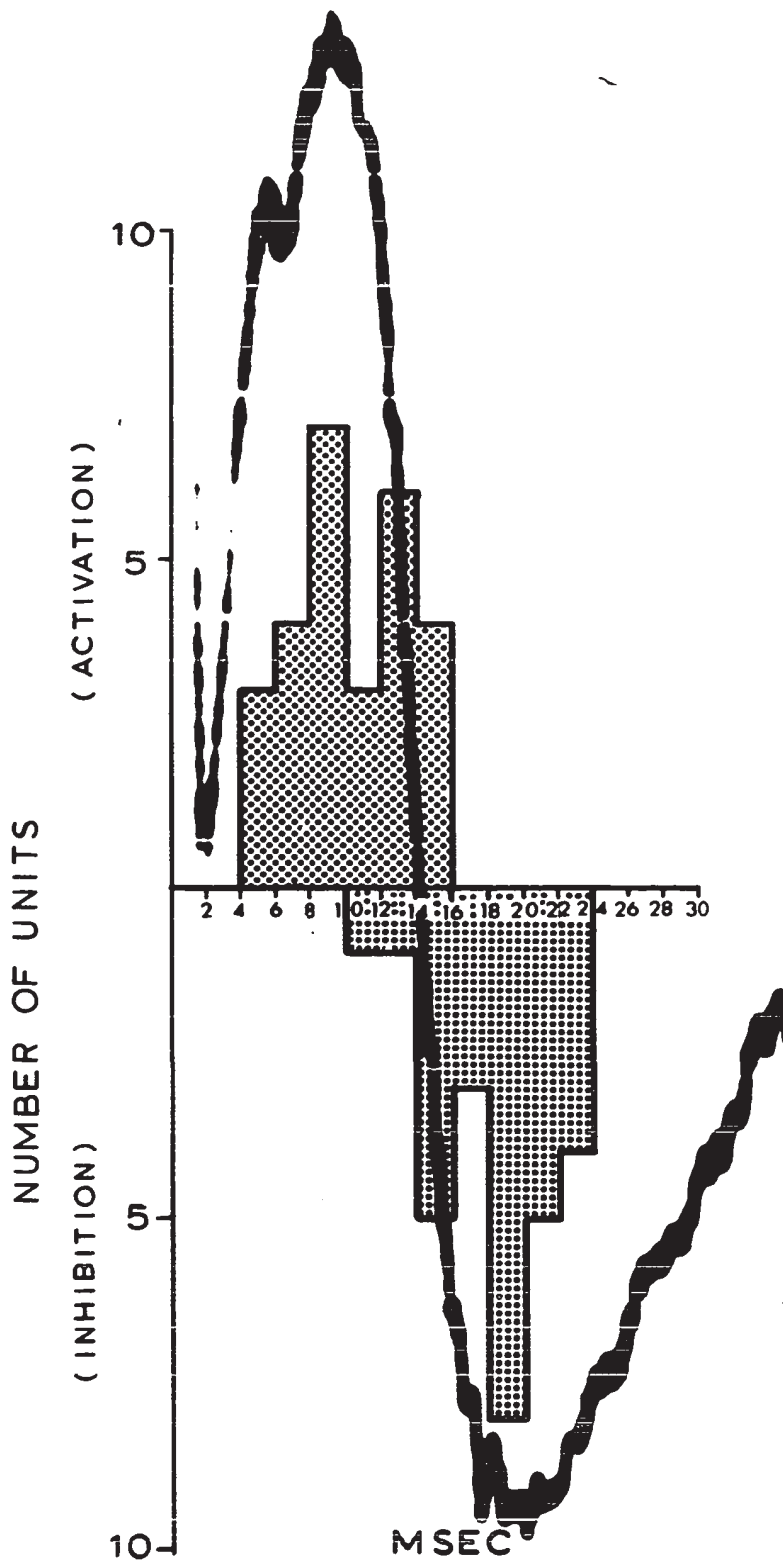
respective post-stimulus time histograms are shown in Fig. 34. The population histogram for all units inhibited by both the PCF and ST regions are shown in Fig. 35. The evoked response elicited from the ST region which produced most of the inhibitory effects is also shown. Eleven units inhibited by this region correlated with the 18-23 msec component while the 10 which were inhibited immediately following stimulation correlated with the 3-6 msec component. Of the 9 units inhibited by PCF stimulation 5 occurred between 7-16 msec and 4 immediately following stimulation.

Of the 30 LH units which responded to both PCF and ST stimulation, 21 showed convergence from the two regions. Ten units were influenced in the same manner (4 inhibited, 6 activated-inhibited) while 11 units which were inhibited by the ST region demonstrated an activation-inhibition sequence following PCF stimulation. Of the remaining 9 units, 5 were observed to have the activation-inhibition sequence with PCF stimulation but were unaffected by the ST region, and 4 were affected in the opposite way.

Histological examination of the stimulating electrode sites demonstrated that the placements which produced activation following PCF stimulation were located along the midline region of the septum while those producing the activation-inhibition sequence were located slightly lateral to the midline. In the case of ST electrode placements those which were confined to the bed nucleus region produced inhibition only, while those more medial produced the activation-inhibition sequence. The stimulating

Figure 34   Recordings of discharge rates obtained from four

LH neurons with their corresponding post-stimulus

time histograms showing inhibition. The onset

of inhibition in the lower two neurons was 12

msec for PCF stimulation (left) and 16 msec for

ST stimulation (right). The dotted line indi-

cates the control discharge rate per address in

the histogram. N = number of stimulation trials;

$\bar{x}$ = mean spontaneous discharge rate.

4766 PCF
N = 50
X̄ = 6.5/sec.

NUMBER OF RESPONSES

20

10

0   200   400

MSEC

4123 ST
N = 60
X̄ = 12.5/sec.

40

20

0   200   400

MSEC

100 uv
100 msec

4672 PCF
N = 128
X̄ = 2.0/sec.

NUMBER OF RESPONES

40

20

0   250   500

MSEC

41A ST
N = 60
X̄ = 13.0/sec.

40

20

0   250   500

MSEC

100 uv
100 msec
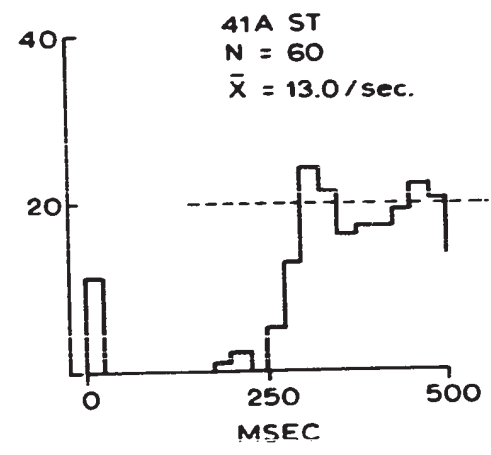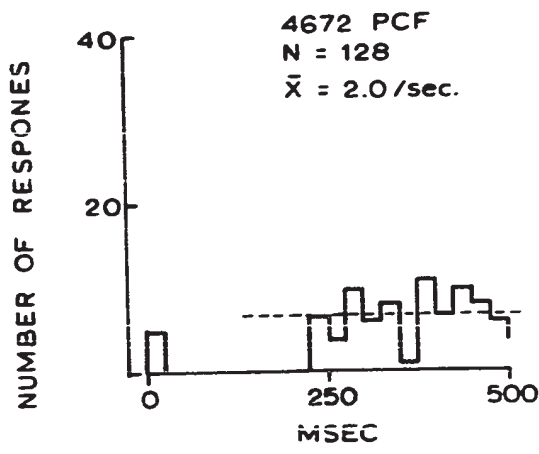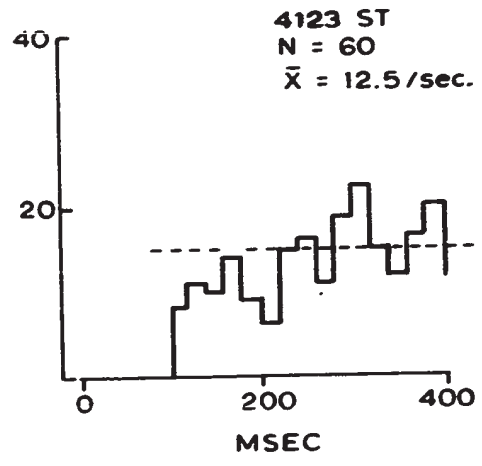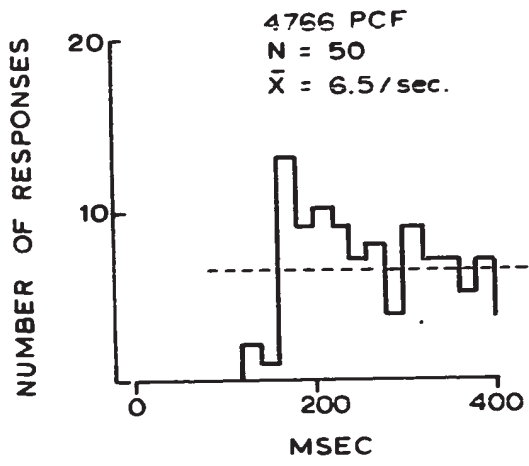
Figure 35   Population histogram of 30 LH neurons showing in-

hibition following stimulation of the PCF and ST

regions of the septum. The superimposed evoked

response demonstrates the relationship between

the inhibitory effect and the 18-23 msec compo-

nent and the short latency 3-6 msec component.
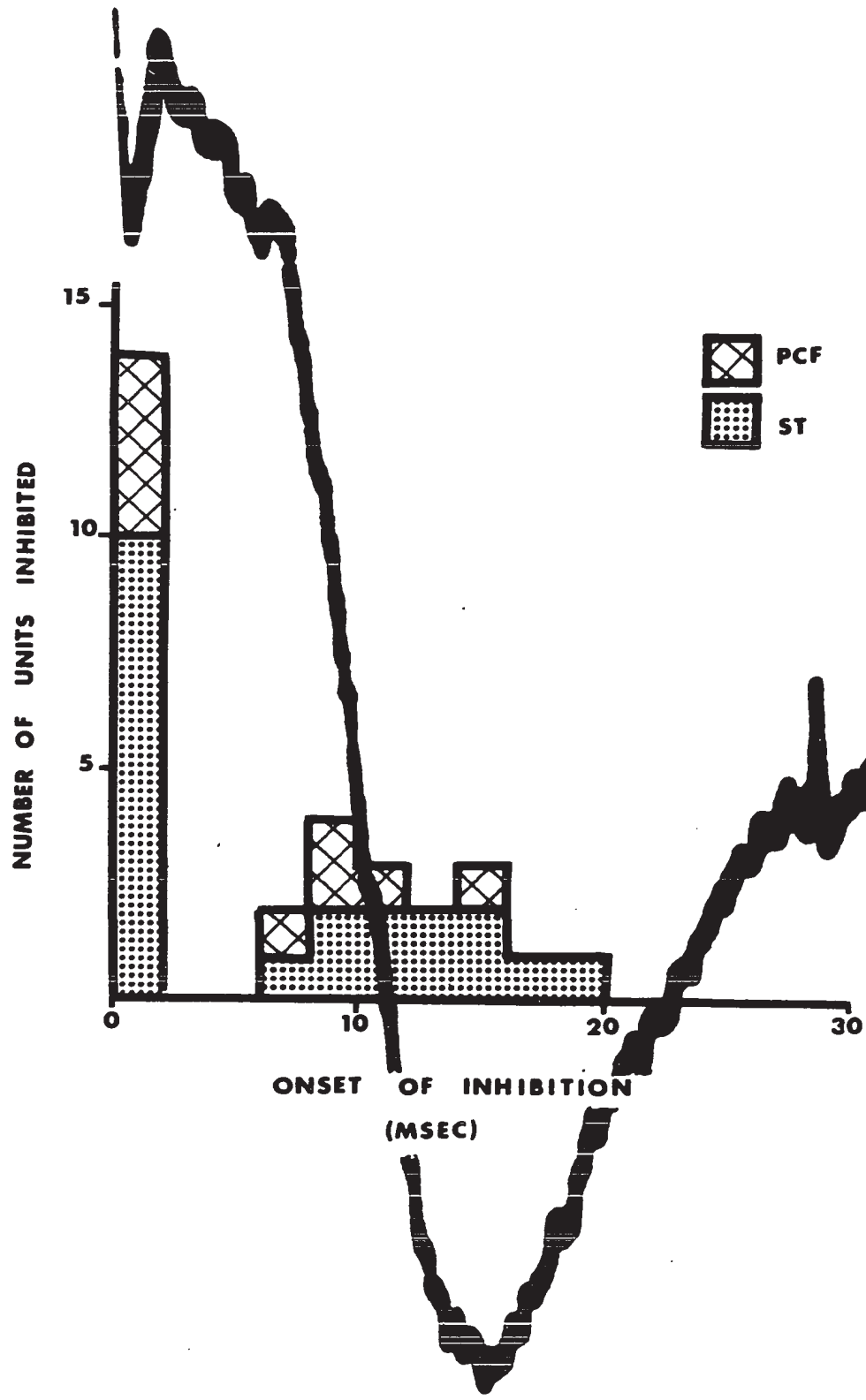
electrode sites and direction of effect produced by each are shown in Fig. 36. No clear differentiation was observed in the LH region between the effect produced and the location of the recording electrodes, although PCF stimulation produced activation of a number of units which were dorsally positioned in the LH (7.0-7.5 mm BSC). Also the 5 units inhibited with PCF stimulation were located ventrally between 8.0-8.5 mm BSC.

Figure 36   Location of stimulation sites in the septal area

producing activation (↑), activation-inhibition

(↕), or inhibition (↓) on LH neurons. A dot

above the arrow indicates two neurons were in-

fluenced from the same site. Note the midline

location of activation in the PCF region and the

gradual transition laterally to activation-

inhibition and then inhibition in the ST region.

Circled arrows are sites which inhibited neurons

following PCF stimulation; squares around arrows

indicate sites which activated neurons following

ST stimulation. Sections extend from AP 8.6 to

7.0. Abbreviations: A = nucleus accumbens;

ac = anterior commissure; CC = corpus callosum;

DBB = diagonal band of Broca; LS = lateral septum;

MS = medial septum; ST = bed nucleus of stria

terminalis.
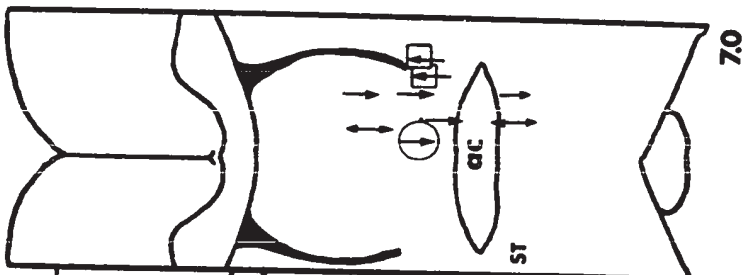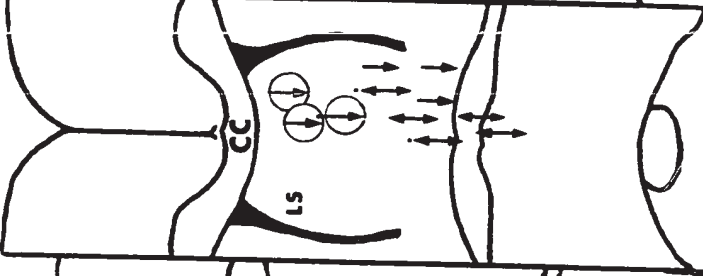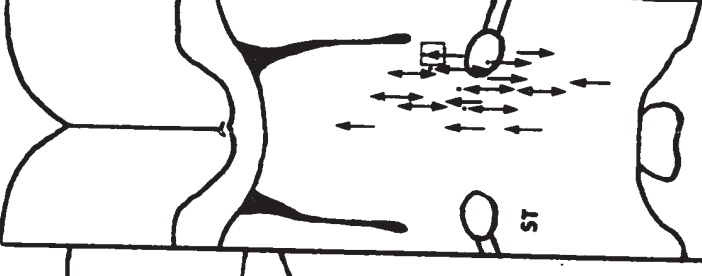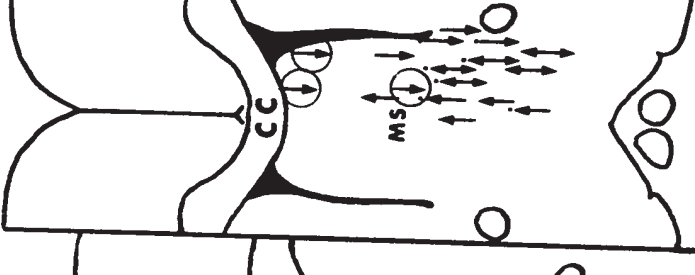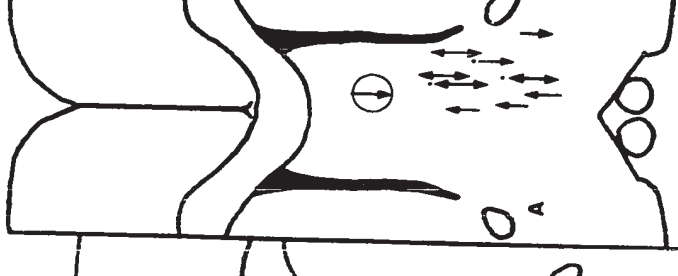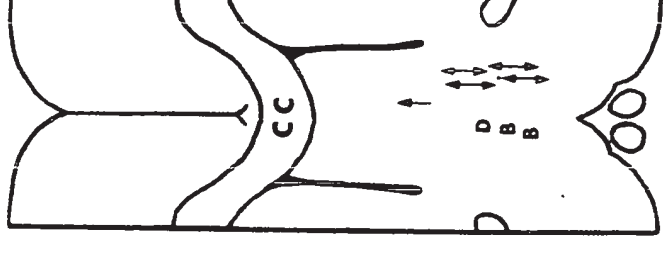
DISCUSSION

Previous investigations in which the septum was stimulated or
lesioned have demonstrated that this region is involved in, but not
of critical importance for, the control of many of the same physio-
logical and behavioral responses integrated at the level of the hy-
pothalamus (Andersson, 1957; Covian, 1967; Gastaut, 1952; Sibole,
Miller and Mogenson, 1971; Siegel and Skog, 1970). These obser-
vations have suggested that the role of the septum is not to control
these responses directly but rather to exert modulatory influences
on hypothalamic control mechanisms (Gloor, 1956; McCleary, 1966).
The results of the present study provide direct evidence for this
role by showing that electrical stimulation of the septal area in-
fluences single unit activity and self-stimulation of the lateral
hypothalamus of the rat. Furthermore, these modulatory influences
appear to be either facilitatory or inhibitory depending upon; (1)
the level of neural activity present in the lateral hypothalamus
and, (2) the locus of stimulation within the septum.

1.   Levels of Neural Activity as a Determinant of the Effects
     Exerted by the Septum on the Lateral Hypothalamus

     The effects produced by septal stimulation on lateral

171

hypothalamic unit activity and self-stimulation clearly indicate
that this region of the limbic forebrain exerts, with almost equal
frequency, both facilitatory and inhibitory influences. These re-
sults differ from those of previous studies which have emphasized
the inhibitory influence of this region on physiological and be-
havioral responses (Carey, 1968; Kaada, 1960; McCleary, 1966;
Rubinstein and Delgado, 1963; Siegel and Skog, 1970; Wishart and
Mogenson, 1970) as well as on the discharge rate of hypothalamic
neurons (Dafny and Feldman, 1968; Dreifuss and Murphy, 1968;
Oomura et al., 1967).

These dual effects of septal stimulation were shown to depend,
in part, upon the rate of discharge of neurons in the lateral hypo-
thalamus. When the neuron was firing slowly septal stimulation
facilitated the discharge rate and when it was firing rapidly sti-
mulation suppressed the discharge rate. Similarly, when an animal
was self-stimulating the lateral hypothalamus at a slow rate, with
a low intensity of hypothalamic stimulation, septal stimulation fa-
cilitated the rate of self-stimulation whereas when the current
level was increased so that the self-stimulation rate was high,
septal stimulation reduced this rate.

The direction of effect produced by the septum on other lateral
hypothalamic neurons did not appear to be related to the level of
activity. In these cases either facilitation or inhibition was ob-
tained regardless of whether the prestimulatory activity was rela-
tively high or low. While it may be premature to suggest that these

neurons are involved in different functions to those which show a relationship to the level of activity, this possibility cannot be excluded.

Repetitive stimulation of the septum with progressively higher frequencies and longer durations was also observed to alter the neuronal discharge rates recorded in the lateral hypothalamus. Since these changes in the rate of discharge were only in the magnitude rather than the direction of the effect produced by the septum, it seems unlikely that the parameters of stimulation are important determinants of whether facilitation or inhibition will occur. These data do show however, that neuronal populations within the septum must undergo temporal summation before reaching maximum effectiveness in modulating the lateral hypothalamic area. These results are in accord with previous studies which have demonstrated that the effects of septal stimulation on blood pressure (Covian and Timo-Iaria, 1966) and shivering (Stuart et al., 1961) occur in one direction, with the magnitude of effect increasing with increasing frequencies and duration up to an optimal level of stimulation. However, the possibility of bidirectional effects being produced by different parameters of stimulation cannot be completely overlooked. Murphy, Dreifuss and Gloor (1968a) demonstrated that in some cases of stimulation of the amygdaloid region both facilitatory and inhibitory effects on ventromedial hypothalamic neurons depend on the frequency of stimulation. Similar effects have been observed on respiration following stimulation of the orbital cortex (Delgado

and Livingston, 1948), and on blood pressure following stimulation of the insular cortex (Kaada, 1951). Since the septal area has not as yet been shown to produce these bidirectional effects with different frequencies of stimulation, it would appear to be quite distinct in this respect from some other limbic structures.

The observation that both facilitation and inhibition may be produced by stimulation of the septum implies that within this region there are two neuronal systems which mediate opposing influences on the lateral hypothalamus. Whether one of these systems predominates over the other does not appear to be predetermined in a rigid manner, but appears more likely to be relatively flexible with the direction and magnitude of effect being determined by the level of neural activity within the lateral hypothalamic region or even within the septal area itself. Since stimulation of the olfactory bulb and sciatic nerve were demonstrated to influence the discharge rate of lateral hypothalamic neurons, as well as was central septal stimulation, it seems that the changing level of neural activity in this region is a function of these peripheral and central inputs. This confirms the findings of previous investigators which have shown evoked potentials and effects on unit activity in the lateral hypothalamus following stimulation of the midbrain reticular formation, thalamus, amygdala and hippocampus (Dafny and Feldman, 1969; Dreifuss and Murphy, 1968; Egger, 1967; Gloor, 1955; Oomura et al., 1967; Stuart, Porter and Adey, 1964; Sutin, 1963; Tsubokawa and Sutin, 1963), as well as from olfactory, gustatory, visual,

auditory, endocrine, visceral and somatic stimulation (Barraclough and Cross, 1963; Cross and Green, 1959; Dafny and Feldman, 1970; Norgren, 1970; Pfaff and Pfaffman, 1969; Rudomin et al., 1965; Scott and Pfaffman, 1967; Stuart et al., 1964; Takaori et al., 1968). These data suggest that the lateral hypothalamus monitors ongoing activity and therefore may, in part, function as a "sensory analyzer" processing both intero and exteroceptive information pertaining to the state of the organism at any one time. Depending upon the afferent bias influencing this region, specific integrative mechanisms are activated leading to the production of appropriate physiological or behavioral responses which serve to restore the organism to a relative "steady-state" (Hess, 1957). Similar central (Cragg and Hamlyn, 1957; Gloor, 1955; Petsche et al., 1965, 1966; Powell, Clark and Mukawa, 1968) and peripheral (Lincoln, 1967; Lincoln and Cross, 1967; Pfaff and Pfaffman, 1969) inputs have been shown to influence the activity level within the septum, suggesting that it too is involved in the processing of sensory information. In this case, however, the afferent bias presumably triggers the appropriate neural system which results in either a facilitation or suppression of the response initiated in the lateral hypothalamic region.

The convergence of the septum, olfactory bulb and sciatic nerve on the same LH neurons is of considerable interest, although there is no indication of whether the actual anatomical convergence

occurred at the level of the LH or at some other location. This
convergence may provide the basis for the modulatory influence of
the septum on physiological and behavioral responses associated
with the lateral hypothalamus and which, as was previously stated,
are activated by peripheral sensory stimuli. These results are
similar to the previous findings of Dafny and Feldman (1969)
showing a convergence on neurons in the posterior hypothalamic
region between the septum and auditory, visual and sciatic nerve
stimulation. However, in contrast to the observations of the pre-
sent study, the septum only exerted inhibitory effects on pos-
terior hypothalamic and some LH units. When combined with the
various peripheral inputs, stimulation produced a summation of
the two resulting in a greater effect than either one had alone,
whether it was facilitation or inhibition. In some cases however,
they reported similar results to our present findings. When the
septal and peripheral inputs were paired, and the latter exhibited
an excitatory effect, there resulted a greater degree of inhibition
than was obtained from the septal stimulation alone. These re-
sults are similar to what have been described as type 4 responses -
those in which the degree of inhibition is increased as the level
of activity is increased.

As most previous investigations have overlooked the possibility
that this "afferent bias" may be an important determinant for the
direction and magnitude of effect exerted by a particular site
within the limbic system, and have therefore not reported the

prestimulatory level of activity, it is difficult to make any comparisons with many of these studies. However, the data of Murphy et al. (1968b) and Oomura et al. (1967) provide some indirect support for the observations of the present study. They demonstrated that leteral hypothalamic neurons usually have relatively high spontaneous discharge rates ($\bar{x} > 6$/sec) as compared to most ventromedial hypothalamic neurons ($\bar{x} < 2$/sec), and that stimulation of the amygdala or septum, as a rule, produced facilitatory effects on neurons in the ventromedial region while it resulted in inhibitory effects on neurons in the lateral region. Similar observations have been incidentally reported to occur on posterior hypothalamic neurons following midbrain reticular stimulation (Dafny and Feldman, 1969), and on bulbar reticular units following stimulation of the motor cortex (Baumgarten, Moruzzi and Magoun, 1953, 1954). In each of these latter cases stimulation produced facilitation on neurons exhibiting a low spontaneous discharge rate and inhibition on neurons with relatively high spontaneous discharge rates. Although, as Murphy et al. (1968b) point out, these differences may be due to difficulties in detecting inhibition in neurons with low spontaneous rates, they do indicate the same general relationship between the level of neural activity and the direction of effect shown in the present study.

As mentioned previously the bidirectional effects exerted by the septum on the lateral hypothalamus appear to result from an activation of one of two neuronal systems within the septum, and which of these systems predominates is dependent upon the level of neural

activity or "afferent bias". Although the mechanism underlying these modulatory influences is not fully understood, the evoked potential data provides some indication of the neuroanatomical framework upon which it might be considered.

2.   Locus of Stimulation as a Determinant of the Effects Exerted by the Septum on the Lateral Hypothalamus

Electrical stimulation of the septum elicited three characteristic evoked responses in the lateral hypothalamus which were related to the anatomical locus of stimulation. The regions of the septum from which the largest amplitude of each of these responses were evoked are shown in Fig. 37.

The two major components, having latencies of 10-14 and 18-23 msec, were elicited by stimulation of the dorsal-midline and ventro-lateral regions of the septum respectively. This anatomical differentiation, together with the differences in peak latencies, thresholds and responses to repetitive stimulation for the two components, suggests that they are mediated by different multisynaptic fiber systems. The regions from which the 10-14 msec component could be elicited included the medial septal area and portions of the diagonal band of Broca, both of which are known to contribute substantially to the precommissural and dorsal fornix pathways which pass through the septum and project to the preoptic, anterior and lateral hypothalamic areas and mammillary bodies (Cragg and Hamlyn, 1959; Nauta, 1956, 1958; Raisman, 1966; Raisman et al.,

Figure 37   Representation of the three areas in the septum

from which the 3-6 msec, 10-14 msec and 18-23

msec components were elicited.

CC

3-6 msec

10-14 msec

18-23 msec
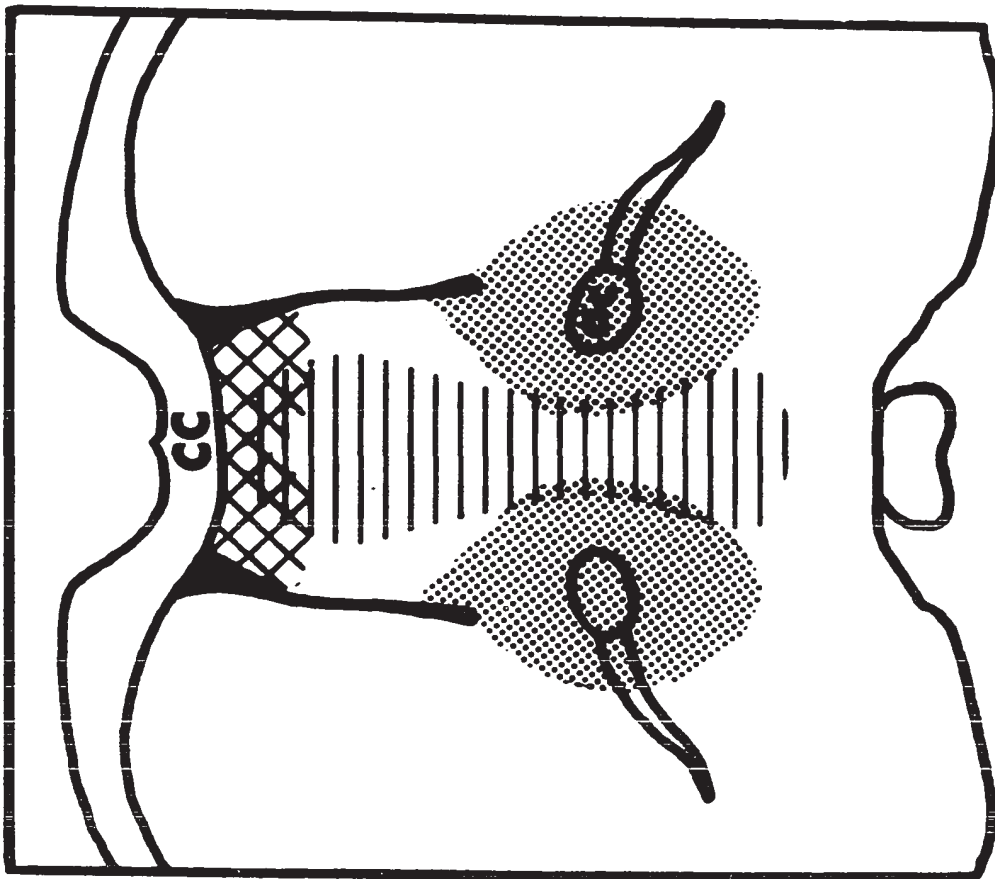
1966; Siegel and Tassoni, 1971). Since lesions in these regions
of the septum attenuated the LH evoked response produced from the
hippocampus it appears that the 10-14 msec component is mediated
via part of the precommissural fornix system. On the other hand,
lesions more ventral and lateral in the septum, which included
regions of the bed nucleus of the stria terminalis, lateral sep-
tum and nucleus accumbens, attenuated the LH evoked response pro-
duced by stimulation of the stria terminalis. Since the fibers of
this pathway, originating in the corticomedial region of the amyg-
dala, have been shown to relay through these regions of the septum
in their passage to anterior, lateral and ventromedial hypothala-
mic areas (Cowan et al., 1965; Heimer and Nauta, 1969; Johnson,
1965; Leonard and Scott, 1971; Valverde, 1963, 1965), it is
suggested that the 18-23 msec component is mediated via septal
contributions to this pathway.

Since both the 10-14 msec and 18-23 msec components could be
elicited in some cases from the same sites within the septum it
appears that the anatomical loci eliciting these components have
a considerable degree of overlap. Similarly, the projections of
the pathways mediating these components were also observed to
overlap in the lateral hypothalamus. These results are consis-
tent with the anatomical findings of Heimer and Nauta (1969),
Powell (1963, 1966), Raisman (1966) and Valverde (1963, 1965)
showing that both the precommissural fornix fibers and those of the
stria terminalis have a considerable overlap in similar regions of

the lateral hypothalamus as those reported in the present study.

As with any evoked potential study there is some question as to whether the various components are localized to the region from which the recordings are made, or, whether they originate at some distance and are conveyed to the recording site by electrical spread. The results demonstrate that phase reversals occur in each of the evoked components and at consistent levels within the lateral hypothalamic region. These findings may be interpreted as indicating the local origin of each of these components, based on the criterion adopted by Trembly and Sutin (1961) which designates that phase reversals are an indication of the anatomical localization of a population of neurons influenced by a particular stimulation site. In addition, the observed association between the activity of single lateral hypothalamic neurons and the 10-14 msec and 18-23 msec components provides further support for the suggestion that these components are of local origin (Dreifuss et al., 1968; Rudomin et al., 1965).

Interaction of the 10-14 msec and 18-23 msec components at different time intervals demonstrated that these two neural systems exerted reciprocal inhibitory effects on one another, so that activation of one produces inhibition of the other and vice versa. These results raise the possibility of some functional differences between the two anatomically distinct regions of the septum eliciting these components. The apparent correlation between the neural activity and both the 10-14 msec and 18-23 msec components

provides some indication that this might in fact be the case. Stimulation in the medial septal-diagonal band region, which elicited the 10-14 msec component, was associated with activation of lateral hypothalamic neurons; while stimulation in the ventro-lateral region, eliciting the 18-23 msec component, was associated with inhibition. The activation-inhibition sequences, observed when both components were recorded, are attributed to stimulation in the region of overlap of the two systems within the septum and on the convergence of their respective pathways in the lateral hypothalamus.

Little may be said about the underlying neural processes which accompany the activation and inhibition effects on the lateral hypothalamus since no intracellular recordings have been made from the relatively small neurons of this region. However, it might be inferred from the extracellular recordings that these effects are a result of post-synaptic membrane changes which presumably take the form of excitatory post-synaptic potentials in the case of activated neurons and inhibitory post-synaptic potentials in the case of inhibited neurons. It might also be suggested that the inhibitory effects of ventro-lateral septal stimulation are mediated via inhibitory interneurons in much the same manner as outlined by Murphy and Renaud (1969) for fibers of the stria terminalis influencing ventromedial hypothalamic neurons.

Several lateral hypothalamic neurons were inhibited from stimulation of the dorso-medial and dorso-lateral septal regions. Since these effects were elicited from similar regions as was the 10-14

msec component there would appear to be a contradiction in the inter-
pretation that this region mediates facilitatory effects on the la-
teral hypothalamus. However, there is the possibility that the fi-
bers mediating these inhibitory effects are not of septal origin but
are actually a result of stimulation of fibers of passage through
the septum from other structures such as the hippocampus (Nauta,
1956, 1958; Raisman, 1966). A similar explanation may account for
the lateral hypothalamic neurons which were observed to be activated
by stimulation of the ventro-lateral region. Not all fibers of the
stria terminalis pathway synapse in this region of the septum, some
continue on to the preoptic and anterior hypothalamic region before
terminating (Fox, 1943; Heimer and Nauta, 1969; Leonard and Scott,
1971; Valverde, 1965). It is quite possible therefore, that these
fibers mediate different effects to those which synapse in the sep-
tal region.

Although particular attention has been given to the two major
evoked components, the properties of the less frequently observed
and relatively small amplitude 3-6 msec component should be con-
sidered. This component was observed to follow high frequency
stimulation (100 Hz) without any attenuation in its amplitude and
displayed a similar response when the stimulation and recording
sites were reversed, suggesting that it is mediated via direct
fiber pathways. Even though this component was demonstrated to
be elicited mainly from the dorsal margin of the septum (Fig. 37),
it is possible that it may be produced from a larger area since it

was frequently masked by the 10-14 msec component. This is consistent with the observations of Nauta (1956, 1958), Powell (1963, 1966) and Raisman (1966) that lesions of either the dorsal region of the medial or lateral septum result in fiber degeneration which passes ventrally through the septum and caudally along the median forebrain bundle into the lateral hypothalamic area. Since lesions of the septum invariably involve fibers of passage from the hippocampal and cingulate regions to the hypothalamus it is difficult to determine whether these direct fibers are of septal origin (Guillery, 1956; Nauta, 1956, 1958; Raisman, 1966; Wolf and Sutin, 1966). Regardless of the site of origin of these direct fibers it was observed that stimulation in the dorsal region of the septum frequently resulted in an immediate inhibitory effect on some lateral hypothalamic neurons, the time course of which correlates with the 3-6 msec component. It is suggested, therefore, that this fiber system may be involved in mediating direct inhibitory influences on the lateral hypothalamus; its role, however, is not fully understood.

3. Functional Implications

Many previous investigators have considered the septal area as a functional unit exerting mainly inhibitory influences on responses traditionally assigned to hypothalamic control mechanisms (Carey, 1968; Kaada, 1960; McCleary, 1966; Oomura et al., 1967; Rubinstein and Delgado, 1963; Wishart and Mogenson, 1970).

Consequently, little attention has been given to the regions of stimulation or lesions within this structure and the possibility that they may exert different influences on these hypothalamic mechanisms. In order to account for the varying and often contradictory effects which stimulation or lesions of the septum exert on autonomic (Covian, 1967; Gastaut, 1952), somatomotor (Enmers, 1961; Hodes et al., 1951; Kaada, 1951; Peacock and Hodes, 1951; Stuart et al., 1961), endocrine (Hayward and Smith, 1963; Sawyer, 1967; Usher et al., 1967), behavioral (Harrison and Lyon, 1957; McCleary, 1966; Siegel and Skog, 1970) and single neuron (Dafny and Feldman, 1969; Murphy et al., 1968b; Oomura et al., 1967) responses, it has been necessary to postulate that the observed facilitation or inhibition results from activation of two functionally different types of neurons which are intermixed with one another (Covian, 1967; Enmers, 1961; Stuart et al., 1961). However, in view of the present data, this does not seem to be the case, since the neurons of the septum have been shown to be organized into topographically distinct regions; the medial septal-diagonal band region exerting mainly facilitatory effects while the ventro-lateral region of the nucleus accumbens and bed nucleus of the stria terminalis exert mainly inhibitory effects on lateral hypothalamic unit activity.

These data provide electrophysiological support for the few studies which have suggested a functional localization within the septum on physiological and behavioral responses. Hodes et al.

(1951) and Peacock and Hodes (1951) demonstrated that stimulation of the dorsal and medial region of the septum usually produced a facilitation of cortically induced movements whereas stimulation more lateral and ventral usually resulted in inhibition of these movements. Similar differences between medial and lateral regions were described by Malmo (1964), who showed that medial septal stimulation resulted in an increase in heart rate while stimulation of the lateral septum produced a decrease. More recently, Sibole (1971) and Sibole et al. (1971) have reported facilitatory effects on lateral hypothalamic induced drinking and feeding when stimulating the medial septal-diagonal band region, and inhibitory effects from the regions of the nucleus accumbens and bed nucleus of the stria terminalis. Although comparisons have not been made between the effects produced by stimulation and those by lesions of these regions of the septum on these same responses, Clody and Carlton (1969) have shown that lesions of the medial septum result in hyporeactivity, while Turner (1970) demonstrated that lesions of the ventro-lateral septum produced hyperreactivity. These studies suggest that the same functional localization within the septum applies to emotional responses.

The presence of a topographical organization within the septum may account for the results of previous studies concerned with the effects produced by this area on LH activity (Dafny and Feldman, 1969; Murphy et al., 1968b; Oomura et al., 1967). These investigators demonstrated a predominance of inhibitory effects

following stimulation of lateral and posterior septal placements which correspond to the region, shown in the present study, to mediate inhibitory influences. In the present study, as well, many of the stimulating placements were located in a more medial and anterior zone of the septum which produced a greater number of facilitatory effects than previously reported.

The findings that both facilitatory and inhibitory effects could be elicited from the same or closely related septal placements following repetitive stimulation, regardless of their location within this structure, suggests that there is an intricate neural mechanism relating the two topographically distinct and opposing regions of the septum. It was suggested previously that the effects mediated by the septum at any one time are dependent, in part, upon the level of neural activity influencing the septum and lateral hypothalamus. The bidirectional effects produced by any one site are therefore presumably a result of a preferential activation of one or the other of these two opposing regions. When one is predominant the other is suppressed, suggesting that they are reciprocally inhibitory. For example, when the activity level is low, stimulation of the septum produces a facilitatory effect, which has been shown to be mediated by the medial septal-diagonal band region. At the same time, the inhibitory influence mediated by the ventro-lateral septal region would be suppressed resulting in an even greater degree of facilitation. On the other hand, when the activity level is high the inhibitory region is

activated and the facilitatory region is suppressed, resulting in an inhibition of lateral hypothalamic mechanisms. This interpretation suggests that not only are the two regions of the septum reciprocally related but further that they exhibit some differential sensitivity to the level of afferent bias which they are capable of monitoring. There is some evidence which makes these possibilities quite plausible.

In the present study it was demonstrated that stimulation of the medial septal region inhibits evoked responses elicited from the ventro-lateral region of the septum, and similarly when the ventro-lateral region was stimulated, the response elicited from the medial septum was inhibited. These data provide support for the view that there is a reciprocal inhibitory mechanism between the two regions. An intrinsic fiber system which establishes contact between neurons of the medial septal-diagonal band region with those of the ventro-lateral septum has also been demonstrated (Knook, 1965; Powell, 1966; Raisman, 1966; Valverde, 1963). Interposed between the diffusely branching axon collaterals of these two regions are small ovoid cells which Tombõl and Petsche (1969) have suggested function as inhibitory interneurons. These anatomical connections may be considered as the neural substrate for the proposed reciprocal inhibitory circuit between the two functionally opposing systems in the septum.

There are a number of considerations which lead one to assume that the two regions of the septum are responsive to different

levels of afferent input. Previous investigators have shown that single cells within the septum respond differently to various levels of midbrain reticular or peripheral sensory excitation (Gogolak, Petsche, Sterc and Stumpf, 1967; Petsche et al., 1962, 1965, 1966). Their results indicated that the cells in the medial septal-diagonal band region, referred to as "active cells", were the most excitable to low levels of reticular inflow and displayed a characteristic bursting activity the rate of which increased with increasing input. It was proposed that this activity was maintained by small closed circuits of self-sustaining re-excitation within this region. As the level of afferent inflow increased, less excitable "passive" or "facultative" cells, located in the lateral regions of the septum, were influenced and their discharge rates changed from random to bursting activity.

Direct stimulation of the two septal regions also indicates that their respective neuronal populations exhibit different excitability levels. Olds (1958) demonstrated that self-stimulation rates were highest in the medial septal-diagonal band region suggesting that the neurons in this region are more excitable in comparison to those of the lateral septum which required higher current intensities to produce self-stimulation. Low intensity stimulation in the medial region has also been shown to result in a variety of motor movements (Votaw, 1960), whereas stimulation more laterally and at higher intensities has been observed to produce behavioral arrest of "freezing" behavior (Mogenson, 1967; Rubinstein and

Delgado, 1963). These data may be interpreted as indicating that different populations of neurons are activated by different levels of either direct or indirect peripheral input. Furthermore the medial region is responsive to low levels of this input while the lateral region is activated at higher levels.

On the basis of the suggested reciprocal inhibitory process between the two functionally opposing systems of the septum and the data which support the view that these systems are activated by different levels of neural input, it is possible to account for much of the previous evidence concerned with septal modulatory influences. If one assumes that under normal conditions the two neural systems within the septum counterbalance one another then there would, in this situation, be no net effect exerted on lateral hypothalamic mechanisms. However, stimulation of the septum, either directly or indirectly via afferent inputs, will interrupt this balance producing a predominance of either facilitation or inhibition depending on the level of the afferent bias. For example, when the level of neural activity is relatively low, stimulation of the medial septal region will produce facilitation. However, if this activity level is gradually increased, the degree of facilitation becomes progressively less with stimulation of this medial region until at some point a critical level is reached. When this occurs stimulation no longer produces a facilitation but may result in either no effect or slight decreases. As the level of activity becomes progressively higher, then stimulation will result in

progressively greater degrees of inhibition, since now the medial facilitatory region is inactivated by the ventro-lateral inhibitory system. This interpretation may account for the observed bidirectional effects produced by single sites of septal stimulation on lateral hypothalamic unit activity and self-stimulation as well as those situations in which no effects were observed.

Lesions of the septal area have been demonstrated to produce relatively little or only transient effects on many of the same responses which stimulation of this area is known to influence (Covian, 1967; Harrison and Lyon, 1957; Reynolds, 1962; Singh and Meyer, 1968; Stuart et al., 1962; Votaw, 1960; Wishart and Mogenson, 1970). In the context of the present proposal it is suggested that the effects resulting from the production of lesions will depend upon the population distribution of cells in these two systems which remain functional. If it happened that a greater proportion of the facilitatory system was damaged, inhibition would develop. Facilitation would be exhibited if a larger percentage of the inhibitory system was destroyed. If fairly equal proportions of the two systems were damaged then the balance between these systems would not be interfered with and no apparent change would be effected.

In the present study the functional properties of different regions of the septum and their effects on lateral hypothalamic mechanisms have been emphasized without taking into consideration the relationship of this system with other limbic forebrain and

cortical regions. As was shown previously, (see Introduction), the septum is positioned between the rostrally located forebrain and higher cortical regions and the caudally located hypothalamic and midbrain regions. In this respect the septal region may be described as an anatomical funnel through which these rostral regions mediate information to integrative mechanisms associated with the hypothalamus and midbrain. It becomes difficult therefore to determine whether the influences exerted by stimulation or lesions of the septum on various physiological or behavioral responses may be attributed solely to that structure or whether these influences result from activation of or interference with "fibers of passage" which are mediated through this region. However, studies comparing degeneration patterns resulting from septal lesions to those from other rostral components have demonstrated that the septum is an important sub-cortical way station in the anatomical pathways projecting to the hypothalamus (Ban and Zyo, 1962; Fox, 1940, 1943; Heimer and Nauta, 1969; Knook, 1965; Lundberg, 1962; Raisman, 1966; Siegel and Tassoni, 1971). Although these studies do not exclude the possibility that stimulation or lesions of the septum influence some "fibers of passage", and in fact in some instances of the present study this was suggested to be the case, they do indicate that it is a nodal region in limbic-cortical projections to the hypothalamus and midbrain reticular formation.

Thus the septal region represents an area which receives,

either directly or indirectly through other central structures, a wide variety of sensory information pertaining to the internal and external environment. In the context of the findings of the present study it would appear to correlate or compare these inputs with those impinging on the hypothalamus, and in turn, result in either facilitatory or inhibitory modulatory influences on homeostatic integrative functions mediated by the hypothalamus.

While it is felt that the specific characterization of the proposed septal modulatory mechanism is wanting in several respects, the preceding implications make it clear that it is a useful one. Whether this proposal finds support in future investigations remains to be seen. Nevertheless, the results of the present study do emphasize the importance of determining the level of neural activity in a system, or the "state of the organism", before attempting to associate any particular site with specific directional effects; and, secondly, that considerations of the functions of the septal area should take into account the possibility of a topographical organization within this structure. In this sense the data are reminiscent of the "Law of Initial Values" proposed by Wilder (1957), and support the conclusion reached by Buchwald and Ervin (1957) that "the response to any stimulus is dependent not only on the specific neural site of stimulation, but more important, on the stimulation parameters and instantaneous organization of the brain as determined by its metabolic rate, its recent history and the background sensory input".

ADDENDUM

1.   It is recognized that the varying levels of anaesthesia in
      preparations used in this study may influence the direction
      of effect produced by septal stimulation. This variable is
      however taken into consideration since it is one contributing
      factor to the "level of neural activity", which was shown to
      be an important determinant of whether electrical stimula-
      tion of the septum exerted either facilitation or inhibition
      on lateral hypothalamic neurons.

2.   The author is aware that the method of electrical stimula-
      tion, although a useful technique in neurophysiological
      investigations, is not equivalent to normal physiological
      conditions. This limitation must be kept in mind in any
      functional interpretation of the results of the present
      study.

SUMMARY

Experiments were carried out to investigate the relationship between the septal area and lateral hypothalamic region in rats by observing: (i) the effects of repetitive stimulation of the septum on lateral hypothalamic unit activity; (ii) the effects of septal stimulation on lateral hypothalamic self-stimulation in chronic preparations when macroelectrodes were implanted in these regions under electrophysiological control; (iii) the different areas of the septum which are most effective in eliciting characteristic evoked responses in the lateral hypothalamus, and, the effects which these areas exert on lateral hypothalamic unit activity.

1.   Extracellular unit activity recorded in the lateral hypo- thalamus was shown to be both facilitated and inhibited, with al- most equal frequency, following repetitive stimulation of the septal area in rats anaesthetized with ethyl carbamate (1.0 - 1.5 g/kg i.p.).

2.   Lateral hypothalamic neurons were classified into four

response types according to the direction of effect produced by septal stimulation: Type 1, neurons which were facilitated; Type 2, neurons which were inhibited; Type 3, neurons which were both facilitated and inhibited, the direction of which was dependent upon the prestimulatory level of spontaneous activity of the lateral hypothalamic neurons such that when the level of neural activity was low, septal stimulation produced facilitation and when the activity level was high, stimulation produced inhibition; Type 4, neurons which were either facilitated or inhibited, the magnitude of which was proportional to the spontaneous level of neural activity.

3. Repetitive stimulation of the septum with progressively higher frequencies and longer durations was also observed to alter the neuronal discharge rates recorded in the lateral hypothalamus. These changes in the rate of discharge were only in magnitude rather than the direction of effect produced by the septum, indicating that the parameters of stimulation are not critical determinants of whether facilitation or inhibition will occur.

4. Lateral hypothalamic neurons were also shown to be influenced by electrical stimulation of the olfactory bulb and sciatic nerve: the olfactory bulb producing both facilitation and inhibition, the sciatic nerve producing only facilitation.

5. Since these peripheral inputs were shown to converge on the same lateral hypothalamic neurons influenced by septal stimulation, it was possible to study the effects of septal stimulation on the "normal" spontaneous discharge rate and on the "altered" discharge rate produced by the olfactory bulb.

6. Lateral hypothalamic neurons, whose spontaneous discharge rate was inhibited by septal stimulation, were facilitated when the "altered" discharge rate was decreased, and neurons whose spontaneous discharge rate was facilitated by septal stimulation, were inhibited when the "altered" discharge rate was increased.

7. In chronic preparations lateral hypothalamic self-stimulation rates were shown to be both facilitated and inhibited following electrical stimulation of the septum. The direction of the effect was shown to be related to the level of neural activity present in the lateral hypothalamus: when an animal was self-stimulating the lateral hypothalamus at a slow rate, with a low intensity of hypothalamic stimulation, septal stimulation facilitated the rate of self-stimulation, whereas when the current level was increased so that the self-stimulation rate was high, septal stimulation exerted either inhibition or no effect.

8. Evoked potentials recorded in the lateral hypothalamus following

stimulation of the septum, in preparations anaesthetized with sodium pentobarbital (30-40 mg/kg i.p.), were observed to have response components of 3-6, 10-14 and 18-23 msec peak latencies. These components were elicited from different regions of the septum; the 3-6 and 10-14 msec components from dorsal and midline regions in the medial septal-diagonal band area corresponding to the projection field of the precommissural fornix from the hippocampus; the 18-23 msec component from a ventro-lateral region, including the bed nucleus of the stria terminalis, nucleus accumbens, and lateral septum, which correspond to the projection field of the stria terminalis.

9. Stimulation of the hippocampus and stria terminalis evoked responses in the lateral hypothalamus of similar configuration but with latencies longer than the 10-14 and 18-23 msec components respectively. Electrolytic lesions in the dorso-midline and ventro-lateral septum attenuated these responses suggesting that parts of the precommissural fornix and stria terminalis are the pathways mediating the septal evoked components.

10. Interaction of the 10-14 and 18-23 msec components at different time intervals demonstrated that the neural systems mediating these response exert reciprocal inhibitory effects on one another so that activation of one produces inhibition of the other

and vice versa.

11. Single pulse stimulation in the medial septal-diagonal band region, which elicited the 10-14 msec component, resulted in activation of lateral hypothalamic neurons with a similar latency. Stimulation in the ventro-lateral region, which elicited the 18-23 msec component, resulted in an inhibition of lateral hypothalamic neural activity, the onset of which corresponds to the latency of this evoked response. The activation-inhibition sequences, observed when both components were recorded, are attributed to stimulation in the region of overlap of the two neural systems in the septum and on the convergence of their respective pathways in the lateral hypothalamus.

12. These data suggest there are two topographical and functionally opposing regions within the septum; a medial facilitatory region and a ventro-lateral inhibitory region. Furthermore, the modulatory effect exerted by the septum on hypothalamic integrative mechanisms is considered to be dependent upon the balance between these two regions and their respective responsiveness to different levels of neural activity.

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