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Electrophysiological Investigation Of Amygdaloid Inputs To The Ventral Pallidum Via The Nucleus Accumbens And Their Modulation By Dopamine

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ELECTROPHYSIOLOGICAL INVESTIGATION OF

AMYGDALOID INPUTS TO THE VENTRAL PALLIDUM

VIA THE NUCLEUS ACCUMBENS

AND THEIR MODULATION BY DOPAMINE

by

Conrad Chi Yiu Yim

Submitted in partial fulfillment

of the requirements for the degree of

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ABSTRACT

The nucleus accumbens (NA) receives inputs from limbic structures and projects to the basal ganglia. In addition, it is the target of a heavy dopaminergic projection from the ventral tegmental area (VTA). The purpose of the present study is to investigate using electrophysiological techniques whether or not the NA forms a functional link between the amygdala (AMY) and the ventral pallidum (VP), and whether or not the mesolimbic dopamine projection from the VTA interacts with this pathway.

Electrical stimulation of the basolateral nucleus of the AMY caused an excitation of neurons in the NA of urethane anesthetized rats. The excitation was attenuated by iontophoretically applied dopamine (DA) or electrical stimulation of the VTA at 10 Hz for 1 s (VTA conditioning stimulation) prior to stimulation of the AMY. The attenuating effect of VTA conditioning stimulation was abolished by acute intraperitoneal injection of haloperidol, a DA antagonist, and was not observed in rats in which the mesolimbic DA projection had been lesioned by 6-hydroxydopamine.

Electrical stimulation of the AMY produced predominantly inhibitory responses in the VP. The onset latencies of the inhibitory responses showed a bimodal distribution suggesting that the responses could be elicited via two pathways. Those with long onset latencies (> 12 ms) were likely mediated via the nucleus accumbens since microinjection of procaine HCl or d-amphetamine into the NA abolished these responses. VTA conditioning stimulation also produced an attenuating effect on the long latency inhibitory responses in normal

rats but not in rats with 6-OHDA lesions in the VTA. Inhibitory responses with short onset latencies (<= 12 ms) were not affected by any of these treatments.

These results suggest that the NA forms a connecting link between the AMY and the VP thus allowing output from the AMY to influence activity of neurons in the VP. Activity of the mesolimbic DA projection to the NA modulates the response of NA neurons to AMY input and thus the AMY's influence on the VP. Since the VP projects to motor areas of the brain, it is suggested that the AMY to NA to VP pathway may be a connecting link between the limbic and motor systems. The mesolimbic DA projection to the NA may serve as a "gate" to modulate output from limbic structures to the motor system via this pathway.

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INTRODUCTION

The nucleus accumbens, located ventral and medial to the caudate nucleus, was recognized by anatomists more than a hundred years ago. However, its anatomical connections and functional significance were not investigated until recently when interest in the presence of dopamine in the central nervous system led to the discovery that the nucleus accumbens is the target of a heavy dopaminergic projection from the midbrain. Since then, anatomical studies using newer tracer methods have revealed in some detail the connections of the accumbens and hypotheses concerning its function have been suggested.

Observations from these anatomical studies indicate that the nucleus accumbens is closely associated with the limbic system and very likely with the motor system as well. Major inputs to the nucleus accumbens were found to be derived from limbic structures such as the amygdala, hippocampus and septum. Efferent projections of the nucleus accumbens reach mainly an area ventral to the globus pallidus designated ventral pallidum (see historical review). Although it has not been conclusively shown that the ventral pallidum is related to the motor system, its proximity and similarity in cytoarchitecture to the globus pallidus is a strong indication that it is. Consequently, a number of investigators have proposed that the nucleus accumbens may form an anatomical link between the limbic and the extrapyramidal motor systems (Powell and Leman, 1976, Graybiel and Ragsdale, 1979, Dray, 1980, Mogenson et al., 1980). The hypothesis suggests that limbic structures that project to the nucleus accumbens can influence the extrapyramidal motor system via the accumbens' connection with the

basal ganglia.

A limbic input to the nucleus accumbens, of particular interest, is the amygdalar projection since the amygdaloid complex has long been known to be involved in the elaboration of emotional responses and motivational behaviors. Recent studies of amygdaloid functions indicate that the amygdala receives sensory inputs of all modalities from association areas of the cerebral cortex (see Ben-Ari, 1982). Integration of these inputs by the amygdala presumably generates emotional responses and motivational behaviors appropriate to the animal's adaptation to the external environment (see historical review). Visceral changes characteristic of most types of emotional responses are mediated via the amygdala's extensive connections with the hypothalamus. On the other hand, behavioral responses that involve locomotion or other motor functions presumably involve pathway(s) from the amygdala to the motor system. Accordingly, the amygdala to accumbens to ventral pallidum connection is possibly one of such pathways that subserve behavioral response initiation (Fig. 1).

As indicated earlier, attention was drawn to the nucleus accumbens initially because of the discovery of a major dopaminergic projection from the midbrain to the accumbens. It is not surprising, therefore, that the nucleus accumbens has also been the subject of behavioral studies concerned with the investigation of dopaminergic function in the central nervous system. The dopamine projection from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens, designated mesolimbic dopamine projection (Ungerstedt, 1971), has been shown in behavioral pharmacological experiments to be

FIGURE 1

A schematic diagram to illustrate the connections of the nucleus accumbens with the amygdala and ventral pallidum in relation to a tentative hypothesis that the accumbens may form a link between the limbic and motor systems. The nucleus accumbens receives afferents from limbic structures, such as the amygdala as illustrated in this diagram, and projects to the ventral pallidum. The ventral pallidum is considered to be associated with the motor system as it projects to the dorsomedial nucleus of the thalamus and the mesencephalic locomotor region.

The nucleus accumbens is contiguous with the caudate nucleus and is indeed designated by Heimer and Wilson (1975) as the ventral striatum. The ventral pallidum, on the other hand, is a ventral and rostral extension of the globus pallidus. The pathway from the accumbens to the ventral pallidum is considered a ventral analogue of the better known striatal-pallidal pathway (Heimer and Wilson, 1975), depicted here in thicker lines to illustrate its heavier projections.

Both the nucleus accumbens and the caudate nucleus receive dopamine projections from the midbrain. It was shown in the present study that the mesolimbic dopamine projection from the VTA to the nucleus accumbens modulates or "gates" the amygdala's output to the ventral pallidum via the nucleus accumbens.

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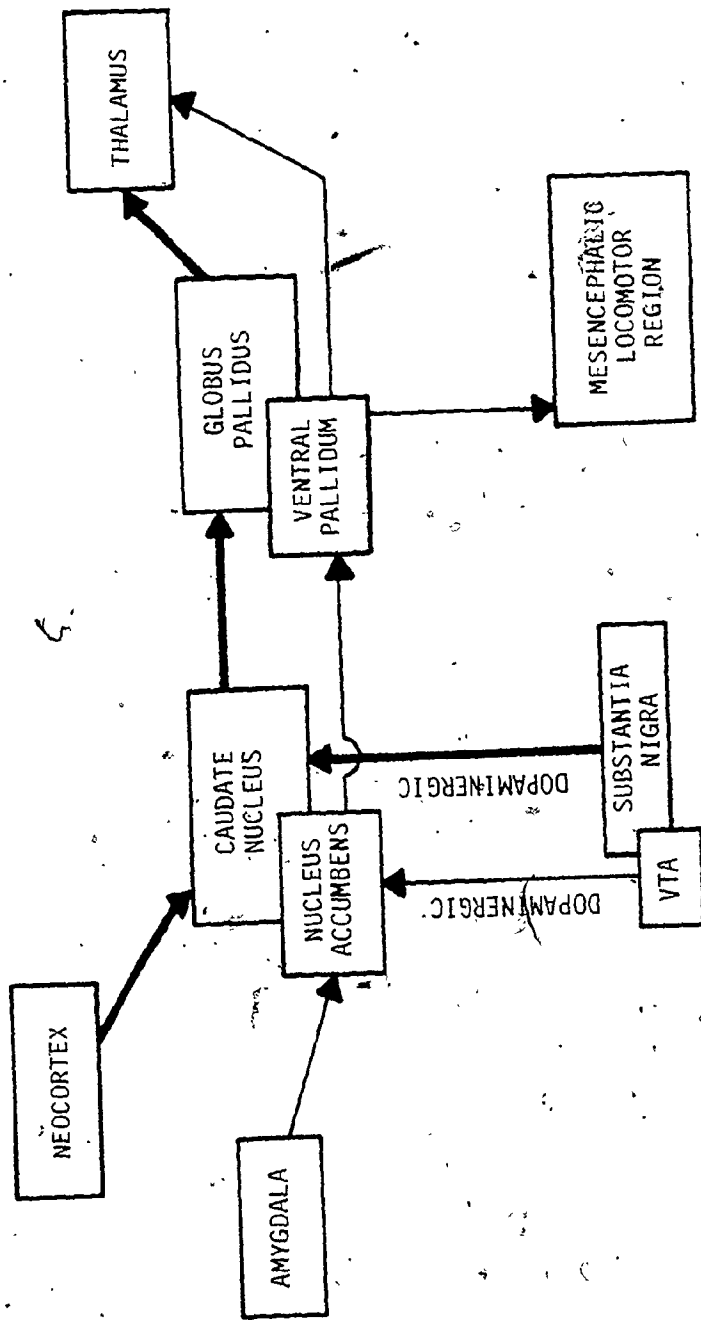
concerned with the initiation of locomotion, self-stimulation reinforcement and ingestive behaviors. The antipsychotic action of major neuroleptics has also been thought to exert their action by blocking dopamine receptors in the nucleus accumbens in addition to those in the frontal cortex.

Although the nucleus accumbens has been suggested as a possible anatomical link between the limbic and extrapyramidal motor systems, the hypothesis has not been investigated in functional studies. Behavioral experiments involving the nucleus accumbens have been concerned primarily with dopamine function and results have not been considered in relation to limbic-motor integration. This neglect is probably in part due to limited information on the effect of dopamine on neurons in the nucleus accumbens and the interaction between various inputs to this area.

It is the objective of this thesis to investigate, using electrophysiological techniques, the functional relationship between the amygdala, nucleus accumbens and ventral pallidum, as well as the interaction of these projections with the mesolimbic dopamine projection to the accumbens. Single unit recordings were obtained from the nucleus accumbens and the ventral pallidum respectively (see Fig. 1). The effects of electrical stimulation of the amygdala on the discharge rate of neurons in these nuclei were investigated. Procaine hydrochloride was injected into the nucleus accumbens while recording from the ventral pallidum to determine if output from the amygdala reaches the ventral pallidum via the nucleus accumbens. The effect of dopamine, either administered directly into the accumbens or released by stimulation of VTA, on the responses of nucleus accumbens and

ventral pallidal neurons to input from the amygdala was also investigated. Findings from these experiments are consistent with the tentative hypothesis that the accumbens provides a link between the amygdala and the ventral pallidum. Dopamine appears to modulate the influence that the amygdala has on the ventral pallidum. Based on these observations, an integrated view of the role of the nucleus accumbens as a limbic-motor interface and the functional significance of the mesolimbic dopamine projection to the accumbens is suggested.
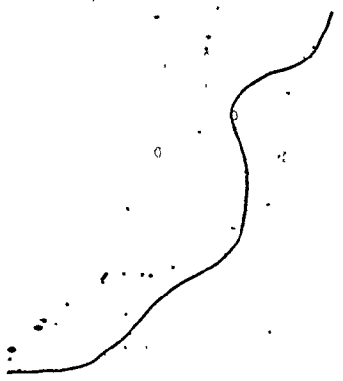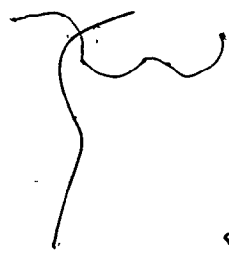
HISTORICAL REVIEW

As indicated in the "Introduction", the hypothesis that the nucleus accumbens forms an interface between the limbic and motor systems is derived from anatomical observations that the nucleus accumbens receives afferents from limbic structures and in turn projects to the basal ganglia. This thesis presents results from electrophysiological experiments that were designed to investigate the functional connections between the amygdala, nucleus accumbens and ventral pallidum in relation to this hypothesis. To provide a background for discussion of the results in relation to limbic-motor integration, a brief review of the anatomy and biological functions related to the amygdala, the nucleus accumbens and the ventral pallidum will be presented in this section.

Since the nucleus accumbens is also the target of a heavy dopaminergic projection from the midbrain, a second objective of the thesis is to investigate the functional role of dopamine in the accumbens and possible interaction with the amygdala to accumbens to ventral pallidum connection. To provide background for the discussion, a review of the current understanding of dopaminergic function in the central nervous system will also be included in this section.

1.0 The Amygdala

The amygdala has long been known as a subcortical limbic structure concerned with various autonomic, endocrine and motivational

functions (see Gloor, 1960). But because of the multitude of behavioral processes that the amygdala has been shown to be involved with, it has been difficult to describe its function precisely. Nevertheless, recent studies have provided additional information to allow a better conceptual understanding of amygdaloid function. It has become apparent that the amygdala receives highly integrated sensory inputs of every modality from association areas of the cerebral cortex. Presumably by processing these highly integrated sensory inputs, the amygdala can in turn elicit appropriate emotional responses and motivational behaviors that are of adaptive significance to the animal (see Ben-Ari, 1982). The amygdala has extensive reciprocal connections with the hypothalamus which undoubtedly account for its ability to produce viseral changes characteristic of emotional responses. On the other hand, the amygdala's projection to the ventral striatum, which is the subject of investigation in this thesis, may provide access to the motor system to subserve the initiation of motivational behaviors. In this section, a concise account of the anatomy and behavioral functions of the amygdala relevant to the thesis is presented. For an extensive description of detailed anatomical connections and behavioral effects of stimulation and ablation of the amygdala, readers are referred to excellent reviews in the literature (see Gloor, 1960, Eleftheriou, 1972, Ben-Ari, 1982).

1.1 Anatomical Connections

The amygdaloid nuclear complex is found in the dorsomedial

portion of the temporal lobes. The position of the amygdala varies slightly in different animals but in most mammals, the nuclei lie anterior to the inferior horn of the lateral ventricles and are continuous caudally with the uncus of the parahippocampal gyrus. The corpus amygdala can be divided into cortical, medial, basal, central and lateral nuclear groups although the definition of the boundaries of these subdivisions has not been consistent among anatomists. However, the borders suggested by Brodal (1947) for the rat and by Fox (1940) for the cat have been widely adopted.

The amygdaloid complex receives multiple inputs from the lower brain stem, the thalamus, the hypothalamus and the cerebral cortex (see Ottersen, 1981a for a comprehensive review). Among these brain areas, the hypothalamus has one of the most extensive reciprocal connections with the amygdala (Cowan et al., 1965, Veening, 1978). In general, most of the hypothalamic-amygdaloid fibers originate in the rostral part of the hypothalamus and terminate in the medial part of amygdaloid complex. Ottersen (1980), using horseradish peroxidase (HRP) retrograde tracing technique, showed more specifically that the ventromedial and arcuate nuclei of the hypothalamus project to the medial nucleus of the amygdala. Some of these fibers, however, extend to the central nucleus and the basolateral nucleus as well. The lateral hypothalamic area has dense projections to the central nucleus and the dorsal hypothalamic area has restricted projections to the central and basolateral nuclei.

Besides afferents from the hypothalamus, the amygdala receives extensive sensory inputs of every modality. The olfactory fibers projecting to the amygdala have been thought to be the best

established sensory afferents. Nearly all parts of the amygdaloid complex receive either direct or indirect olfactory inputs. The olfactory bulb projects via the lateral olfactory tract to terminate in the cortico-medial group. The dorsal subdivision of the lateral olfactory tract projects to the basolateral nucleus as well as to the basomedial and cortical nuclei (Ottersen, 1981b). The ventral subdivision, on the other hand, projects to the central nucleus (Ottersen, 1981b). In addition to direct projections from the olfactory bulb, the basolateral nucleus also receives an indirect olfactory input via relays in the prepyriform cortex.

Although the amygdala receives strong olfactory inputs especially in animals that rely heavily on the olfactory sense for adaptation, it has become evident that the amygdala also receives sensory inputs of other modalities. The olfactory input is unique among others in that it is the only direct sensory input to the amygdala, others are relayed from the diencephalon and neocortical areas (Lammers, 1972).

Gustatory inputs are relayed to the amygdala in the thalamus and the brain stem. Several thalamic areas project extensively to the amygdala (Ottersen and Ben-Ari, 1979, Nauta, 1962). The paraventricular and parataenial nuclei were found to send fibers to the entire amygdaloid complex. The medial geniculate complex and the basal nucleus of the ventromedial complex of the thalamus project to the centromedial part of the amygdala (Ottersen, 1980). Since the ventromedial complex of the thalamus receives projections from the pontine taste area (Norgren, 1974), its connection with the amygdala probably relays gustatory input to the amygdala. In addition to inputs relayed in the thalamus, the amygdala receives projections from

the parabrachial nucleus and the nucleus of the solitary tract. These nuclei likely relay gustatory and visceral inputs to the amygdala as well (Norgren, 1974, Ottersen, 1981b).

Previous anatomical studies have noted cortical projections to the amygdala from the transitional cortical areas including the anterior cingulate gyrus, the orbitofrontal cortex, the inferior temporal cortex and the piriform cortex (Cowan et al., 1965, Lammers, 1972). Recent studies, however, revealed a far more widespread interconnection between the cortex and the amygdala (Turner et al., 1980, Turner, 1982, Lohman and Russhcen, 1982). In brief, cortical projections to the amygdala seem to arise from a circumscribed region of the cortex, namely the anterior part of the temporal lobe, the ventral and periallocortical areas of the insula. None of the primary sensory areas project to the amygdala, but as Turner and others (1980) as well as Lohman and Russchen (1982) pointed out, those areas that project to the amygdala are parts of cortical relays that ultimately arise from one of auditory, visual or somatosensory areas. These projections terminate in almost all parts of the amygdala, but the lateral and basolateral nuclei receive the densest projection.

Apart from connections with the hypothalamus, thalamus and the cortex, the amygdaloid complex receives fibers from monoaminergic cell groups in the lower brain stem. The central nucleus of the amygdala receives dopaminergic projections from the substantia nigra pars compacta and the VTA (Fallon and Moore, 1978, Beckstead et al., 1979, Ottersen, 1981b) and noradrenergic fibers from the locus coeruleus (Jones and Moore, 1977, McBride and Sutin, 1976, Ottersen, 1981b). The median and dorsal raphe nuclei project upon the central nucleus,

the projections presumably are serotonergic fibers (Azmitia and Segal, 1978, Moore et al., 1978, Ottersen, 1981). The function of these projections is largely unknown.

The efferent projections of the amygdala can be distinguished into two major components: those that are collected in the stria terminalis and those that form the diffuse ventral amygdalofugal projections.

Fibers of the stria terminalis arise mainly from the corticomedial and basal nuclei of the amygdaloid complex (Cowan et al., 1965, DeOlmos, 1972, Lammers, 1972). The stria terminalis arches along the medial border of the caudate nucleus and terminates massively in the bed nucleus of the stria terminalis (Heimer and Nauta, 1969). Part of the fibers of the stria terminalis continue caudally and terminate in various nuclei of the hypothalamus including the anterior hypothalamic area, medial preoptic area and the ventromedial hypothalamic nucleus.

The ventral amygdalofugal pathways have a much wider distribution than the stria terminalis. Fibers originate from the basal, lateral and central amygdaloid nuclei and spread medially and forward to form direct connections with the cortex, thalamus, hypothalamus, mesencephalon, pons and the medulla.

The hypothalamus receives projections from the amygdaloid complex via the stria terminalis as well as the ventral amygdalofugal pathways. As mentioned above, the anterior hypothalamus and preoptic area receive efferent fibers of the stria terminalis. Taking the ventral route, fibers from the basomedial nucleus of the amygdala terminate in the ventral medial hypothalamus and the premamillary

nucleus (McBride and Sutin, 1977). Fibers from the central nucleus, on the other hand, project primarily to the lateral hypothalamus.

Of particular interest in this thesis is the amygdala's projection to the striatum. The basolateral nucleus projects strongly to the ventral part of the striatum, namely the nucleus accumbens and the olfactory tubercle (Krettek and Price, 1978a). This amygdalostriatal projection has recently been shown to extend beyond the ventral part of the striatum to terminate in some areas of the caudate nucleus as well (Kelley et al., 1982). Sparse projection from the basomedial nucleus to the nucleus accumbens has also been observed.

Other fibers derived from the basolateral nucleus are seen in the frontal cortex and the dorsal agranular insular area (Krettek and Price, 1977a). Projections to the hippocampal formation terminate primarily in the entorhinal cortex and the ventral subiculum (Krettek and Price, 1977b). In addition to the projections to the cortex and the striatum, the basal amygdaloid nuclei also have prominent projections to the dorsomedial thalamus (Nauta, 1961, Cowan et al., 1965).

The central nucleus projects to a large number of structures in the mesencephalon and the lower brain stem. The fibers from the central nucleus terminate in and around catecholamine and serotonergic cell groups. Thus the ventral tegmental area, substantia nigra pars compacta and the dorsal raphe nuclei are all targets of the central nucleus (Krettek and Price, 1978a). More caudally, the central nucleus projections terminate heavily in the dorsal nucleus of the vagus and the nucleus of the solitary tract (Krettek and Price,

1978a).

1.2 Functional Significance

The functions of the amygdala have been extensively investigated using a variety of experimental approaches. From stimulation and lesioning experiments, the amygdala has been implicated in various autonomic, endocrine and motivational functions (see Gloor, 1960).

Since the amygdala has reciprocal associations with the hypothalamus and visceral centers of the lower brain stem, it is not surprising that electrical stimulation of the amygdala produces changes in respiration, arterial pressure and gastrointestinal motility. In addition, presumably because of the influences that the hypothalamus has on the endocrine system, stimulation of the amygdala has been shown to produce uterine contraction and ovulation (Gloor, 1960) in the rabbit. Electrical stimulation of the lateral and medial amygdaloid nuclei produces general arousal and an orienting reaction. The animal looks around with glancing or searching movements (Ursin and Kaada, 1960). According to the investigators, the orienting responses resemble the initial phase of the flight or fight response (Kaada, 1972).

Although stimulation of the amygdala produces a variety of visceral responses, bilateral ablation of the amygdala did not produce significant deficits in homeostasis. Changes in respiration and arterial pressure were observed but the effects were transient. In contrast to the subtlety of the visceral disturbances, however, bilateral amygdalectomy in animals produces dramatic alterations in

integrated behaviors. The range of behaviors affected by the lesion varies among species and appears to depend on the species' normal behavioral repetoire in its natural habitat.

One of the prominent aspects of bilateral ablation of the amygdala is the disruption of social interactions in animals. Such lesions produce placidity, loss of fear and rage in monkeys (Dicks et al., 1969, Weiskrantz, 1956), in cats (Schreiner and Kling, 1953) and in rats (Anand and Brobeck, 1952, Galef, 1970). Dominance in primates is lost (Kling, 1972). In human, amygdalectomy has also been shown to reduce aggressiveness in patients (Scoville, 1954, Green et al., 1951). Hypersexuality was observed in cats and monkeys following bilateral lesion of the amygdala (Schreiner and Kling, 1953, Kluver and Bucy, 1937) but similar lesions produced no change in sexual behavior in human patients (Green et al., 1951). Many investigators also reported "oral compulsive behavior" in animals that received bilateral amygdalectomy. Those animals had strong tendencies to examine objects by mouth, whether they are innocuous or obnoxious (Brady et al., 1954, Kluver and Bucy, 1937).

The amygdala, therefore, appears to be involved in a multitude of functions that are integral components of the behavior of the animal. An interesting observation, however, is that most of the functions with which the amygdala appears to be involved are represented in the hypothalamus as well (Gloor, 1972). Consequently, it has been difficult to determine the precise role of the amygdala in behaviors. However, results from more recent anatomical and behavioral studies have provided a more integrated view of the functions of the amygdala.

As indicated earlier, anatomical studies have recently revealed

more extensive cortical inputs to the amygdala than previosuly observed (Turner et al., 1980, Lohman and Russchen, 1982). These studies showed that the amygdala receives inputs from almost all sensory modalities. Furthermore, except for the olfactory system, all sensory inputs to the amygdala are derived from modality-specific association areas of the cortex rather than from the primary sensory areas. In this regard, the amygdala is in a position to integrate extensive processed sensory information. Through its output to the basal ganglia and the hypothalamus, the amygdala is capable of translating these integrated sensory inputs into appropriate emotional states or motivational behaviors in adaptation to changes in the environment.

Behavioral experiments are in accord with these suggestions. Most disabilities produced by amygdalar lesions are failures of the animal to react appropriately to changes in the external environment (Kaada, 1972, Vergnes, 1982). The amygdala can be considered as having an inventory of the visceral changes for different emotional states and motivations stored, perhaps in various specific nuclei in view of the localization of behavioral functions as shown in ablation studies (Kaada, 1972). Integration of highly processed sensory and cognitive (in higher animals) information releases or activates specific patterns of emotional response that are elaborated through the amygdala's output to the hypothalamus and the basal ganglia. Such emotional arousal in response to changes in the environment is of obvious adaptive significance.

2.0 Nucleus Accumbens

The nucleus accumbens was first described by Ziehen (cited in Chronister and DeFrance, 1981) in 1901 as a distinct structure located in the ventromedial part of the striatum, but it remained relatively unknown until the 1960's when mapping of the dopaminergic pathways in the central nervous system showed that the nucleus accumbens is the target of a heavy dopaminergic projection from the midbrain. (Anden et al., 1966, Ungerstedt, 1971a). Subsequent anatomical studies showed that the accumbens receives afferents from limbic structures and in turn projects to the basal ganglia. These observations have led investigators to consider the accumbens as a link between the limbic and motor systems (see Mogenson and Yim, 1981). In the following sections, a review of the anatomical connections of the accumbens leading to the hypothesis is presented. In addition, a concise account of putative neurotransmitter candidates found in the accumbens as well as a description of some possible behavioral functions of the nucleus accumbens in relation to its dopaminergic afferents are presented.

2.1 Anatomical connections

The nucleus accumbens is located ventral and medial to the caudate nucleus. It surrounds the anterior commissure and part of the anterior horn of the lateral ventricle, and is lateral to the septal area and dorsal to the olfactory tubercle. Although the accumbens can be identified as a distinct nucleus, the demarcation of its borders

with adjacent structures, with the exception of the septum, are rather difficult to define. The border with the septum is relatively clear and is marked by ascending and descending fibers of the septum. By contrast, the ventral border with the olfactory tubercle and the dorsal border with the caudate are rather obscure. The border with the olfactory tubercle is coarsely marked by fiber layers of "olfactory radiations" (see Domesick, 1981), but there are "cell bridges" that perforate these fibers which make the nucleus accumbens continuous with the olfactory tubercle. On the dorsal side, the nucleus accumbens virtually forms a continuum with the caudate nucleus as well. A distinct border is impossible to draw, but several anatomical and cytoarchitectural features can be used to distinguish the two areas. In both primates (White, 1981) and rodents (Domesick, 1981), the nucleus accumbens is distinguishable from the rest of the striatum by the lack of perforating fascicles of the internal capsule and a higher density of cells.

The proximity of the nucleus accumbens to the caudate nucleus and the difficulty in defining the border between these two nuclei has led anatomists to consider the accumbens to be merely a ventral extension of the neostriatum (Gurdjian, 1928, Lauer, 1945). However, in examining the connections of the accumbens with other areas of the brain, a distinction between the accumbens and the rest of the striatum becomes apparent.

a. Afferent connections

Before discussing the afferent connections of the nucleus

accumbens that sets it apart from the caudate, it is necessary to point out that no area of the striatum, including the nucleus accumbens, can be defined by a unique afferent projection. Most of the projections are relatively diffuse and there is a large degree of overlap. Sub-areas within the striatum such as the accumbens can only be identified on the basis of the relative density of afferents from different areas of the cortex and the mesencephalon.

The nucleus accumbens receives its major inputs from the telencephalon and the mesencephalon with minor afferents from the thalamus. Telencephalic projections to the nucleus accumbens arise from both the neocortex and the allocortex, as well as from the amygdala and other forebrain subcortical structures. The projections from the neocortex to the nucleus accumbens in the primate (Whitlock and Nauta, 1956) and the rodent (Newman and Winans, 1980, Beckstead, 1979), however, are relatively minor. The strongest telencephalic inputs to the accumbens arise from structures classically known as the limbic areas. In contrast, almost the entire neocortex projects to the caudate putamen in a topographical manner (Carman et al., 1963, Webster, 1961).

As indicated in the last section, the amygdala projects strongly to the nucleus accumbens. This amygdalo-accumbens projection has been demonstrated in the rat (Krettek and Price, 1978a, Domesick, 1981, Swanson and Cowan, 1975), the cat (Groenewegen et al., 1980, Groenewegen et al., 1981), the golden hamster (Newman and Winans, 1980), the rabbit (Chronister et al., 1981) and the monkey (Hemphill et al., 1981). Sources of the projection vary slightly between species but are all derived mainly from the basolateral

nucleus of the amygdala. Other nuclei of the amygdaloid complex that give rise to afferents to the nucleus accumbens include the basomedial (in the cat and monkey), the accessory basal nucleus (in the monkey) and the cortical nucleus in the monkey and the rabbit. There is some topographical organization in the cat and the hamster, the anterior part of the basolateral nucleus projects to the ventral and lateral part of the accumbens and the posterior part of the basolateral nucleus projects to the medial nucleus accumbens.

The hippocampal formation projects to the nucleus accumbens in the rat (Swanson and Cowan, 1975, Carman et al., 1963, Raisman et al., 1966, Siegel et al., 1974, Domesick, 1981), the cat (Fox, 1943, Groenewegen et al., 1981, Siegel and Tassoni, 1971, Siegel et al., 1974), the golden hamster (Newman and Winans, 1980), the rabbit (Siegel et al., 1974, Chronister et al., 1981, Cragg and Hamlyn, 1960) and the monkey (Rosene and Van Hoesen, 1977, Hemphill et al., 1981, Siegel et al., 1975). The projection arises from the subiculum (exclusively in the cat) and to a lesser extent from CA1 cellular field in the rat. The projection distributes predominately to the most medial part of the nucleus accumbens with only sparse terminations in the more lateral part. There is some topographical organization of the hippocampal-nucleus accumbens projection. The most medial part of the nucleus accumbens receives afferents from the ventral temporal pole of the hippocampus via the fimbria and the more lateral part receives afferents from the dorsal septal pole of the hippocampus via the fornix.

Other limbic structures that have been shown to have relatively minor projections to the nucleus accumbens include the entorhinal and

perirhinal cortices, as well as the cingulate gyrus (Krayniak et al., 1981, Groenewegen et al., 1981, Newman and Winans, 1980). Fibers originating from the entorhinal cortex reach the nucleus accumbens by way of the external capsule rather than the fornix.

The nucleus accumbens receives a heavy dopaminergic projection from the midbrain. The projection was first demonstrated in histofluorescence studies of central monoaminergic neurons in the central nervous system (Fuxe, 1965, Anden et al., 1966, Ungerstedt, 1971a). These studies indicate that a highly topographically organized pathway of dopamine containing neurons connects the midbrain with the entire striatum. The nucleus accumbens receives projections mainly from the ventral tegmental area (VTA) (designated cell group A10 by Dahlstrom and Fuxe, (1964)). The caudate nucleus on the other hand, receives projections primarily from the more laterally located substantia nigra pars compacta (designated cell group A9).

These dopaminergic projections have been confirmed by investigators using other anatomical techniques (Nauta et al., 1978, Domesick, 1981, Swanson and Cowan, 1975, Groenewegen et al., 1981, Newman and Winans, 1980, Chronister et al., 1981, Hemphill et al., 1981, Phillipson, 1979). It is now clear that the dopaminergic projections from the VTA and the substantia nigra to the forebrain are not entirely separate. Although the nucleus accumbens receives dopaminergic afferents mainly from the VTA, some fibers from the substantia nigra also reach the nucleus accumbens.

In addition to the dopamine projection from the midbrain, the nucleus accumbens also receives a relatively minor serotonin projection from the dorsal raphei nuclei. Scattered labelled cells in

the reticular formation, parabrachial nucleus and the locus coeruleus were also observed following injection of horse radish peroxidase into the nucleus accumbens (Groenewegen et al., 1981).

The striatum as a whole receives diffuse inputs from non-specific nuclei of the thalamus. Whereas the more dorsal caudate nucleus receives inputs from the intralaminar nuclei, projections to the nucleus accumbens arise predominantly from the midline nonspecific thalamic nuclei including the parafascicular region, nucleus reuniens, parataenial and paraventricular areas (Groenewegen et al., 1980, Newman and Winans, 1980, Chronister et al., 1981, Hemphill et al., 1981).

b. **Efferent connections**

The efferent projections of the nucleus accumbens have been investigated in a number of species of animals including the rat, cat, rabbit, hamster and the monkey. Although there are minor differences in the observations of the various investigators, the general picture suggests that the nucleus accumbens projects to a wide range of targets related to the limbic and extrapyramidal systems.

The majority of the nucleus accumbens projections are desecending fibers to the diencephalon and mesencephalon. The only ascending efferents observed were those to the cingulate gyrus in the rat (Williams et al., 1977) and in the squirrel monkey (Powell and Leman, 1976).

The first major target of descending fibers from the nucleus accumbens is the ventral medial portion of the globus pallidus

(Swanson and Cowan, 1975; Newman and Winans, 1980, Williams et al., 1977, Nauta et al., 1978, Chronister et al., 1981, Conrad and Pfaff, 1976), an area considered by Heimer and Wilson (1975) to be a ventral extension of the pallidum and termed ventral pallidum (see below). The rest of the descending fibers follow the course of the medial forebrain bundle. Some of these fibers terminate diffusely in the medial and lateral preoptic area. A few projections end in other areas of the hypothalamus, the lateral habenula nucleus and the zona incerta (Conrad and Pfaff, 1976, Williams et al., 1977, Nauta et al., 1978). Most of the descending fibers terminate in the substantia nigra, mainly in the most dorsal zone of the pars reticulata and the adjacent pars compacta. Some of the fibers also terminate diffusely in the more medial VTA (Nauta et al., 1978, Phillipson, 1979). Another branch of the descending projection terminates in the thalamus, including the paratanenial and periventricular nuclei (Conrad and Pfaff, 1976, Williams et al., 1977).

2.2 Transmitter candidates in the nucleus accumbens

a. Acetylcholine

Using histochemical and biochemical techniques, it has been shown that the nucleus accumbens contains high levels of the acetylcholine synthesizing enzyme, choline acetyltransferase and the acetylcholine metabolizing enzyme, acetylchloinesterase (Fonnum et al., 1977, Palkovits et al., 1974) as well as acetylcholine itself (Costa et al., 1975, Koslow et al., 1974). Walaas and Fonnum (1979a, 1979b) showed

that hemitransection of the rat brain at the level of the globus pallidus did not alter the activity of choline acetyltransferase in the accumbens. Following the injection of kainic acid, a neurotoxin that specifically destroys nerve cell bodies, into the nucleus accumbens, choline acetyltransferase fell 75% and acetylcholinesterase activity was reduced by 35%. These data confirmed the presence of intrinsic cholinergic neurons within the nucleus accumbens.

b. Monoamines

Using histofluoresence technique, Anden et al. (1966) first identified the presence of dopamine nerve terminals in the nucleus accumbens. This was later confirmed by a more detailed mapping of the catecholamine pathways by Ungerstedt (1971a). More recent studies have found that the nucleus accumbens contains a high concentration of dopamine which is exceeded only by dopamine concentration in the caudate (Horn et al., 1974, Koslow et al., 1974). The nucleus accumbens also contains a comparatively high level of norepinephrine (Versteeg et al., 1976). Biochemical and immuoenzymatic measurements of the enzymes tyrosine hydroxylase and DOPA decarboxylase showed levels consistent with high levels of catecholamines in the accumbens (Fonnum et al., 1977, Gilad and Reis, 1978, Walaas and Fonnum, 1979b, Holkfelt et al., 1977, Cuello, 1978).

The nucleus accumbens also receives serotonin containing nerve endings (Koslow, et at., 1974, Saavedra et al.; 1974) originating from the doral raphe nucleus (Azmitia and Segal, 1978, Bobillier et al., 1976). However, the density of innervation is relatively low

(Saavedra et al., 1974).

c. Gamma Amino Butyric Acid (GABA)

The levels of GABA and its synthesizing enzyme, glutamic acid decarboxylase in the nucleus accumbens are relatively high (Fonnum and Walaas, 1981). Similar to cholinergic structures in the accumbens, kainic acid lesion of the accumbens caused a 70% reduction in glutamic acid decarboxylase whereas hemitransection at the level of the globus pallidus did not produce a similar reduction (Fonnum et al., 1977, Walaas and Fonnum, 1979b). These results indicate an intrinsic system of GABAergic neurons within the nucleus accumbens. From measurements of glutamic acid decarboxylase levels in other brain areas following electrocoagulation of the nucleus accumbens, these investigators also concluded that GABA neurons project from the nucleus accumbens to the substantia nigra, ventral pallidum and the VTA (Fonnum et al., 1977, Walaas and Fonnum, 1979b).

d. Glutamate

Using high affinity glutamate uptake as a marker for glutaminergic structures in the brain, it has been shown that the nucleus accumbens contains a significant density of glutaminergic structures (Fonnum et al., 1979). Since transection of the fornix or the fimbria reduced glutamate uptake in the nucleus accumbens, and since the level of glutamic acid in the accumbens was reduced following degeneration of the allocortical fibers, it has been

concluded that the projection from the subiculum of the hippocampus to the nucleus accumbens is glutaminergic (Fonnum and Walaas, 1981, Walaas and Fonnum, 1979b).

e. Peptides

A large number of peptides has been found in the nucleus accumbens using immunohistochemical techniques. These include substance P, thyrotropin releasing hormone, somatostatin, enkephalin, vasoactive intestinal polypeptide, gastrin, neurotensin and angiotensin (see Johansson and Hokfelt, 1981 for review). The origins and functions of these peptide containing neurons are largely unknown although at least one of them, substance P, has been postulated as a neurotransmitter (Henry, 1980).

2.3 Functional Significance

Behavioral studies involving manipulation of the nucleus accumbens are relatively few in number. Indications of the biological function of the accumbens come mostly from studies of catecholaminergic function in the central nervous system. Since Carlsson and Lindqvist (1963) proposed that action of the major neuroleptics were due to their blockade of dopamine receptors, interest has been directed to the possibility that alteration of the activity of the mesolimbic dopamine pathway is a factor contributing to the schizophrenic process. The nucleus accumbens, being a target of the mesolimbic dopamine projection, has thus been investigated in

most behavioral studies in relation to dopaminergic function.

The dopamine projection to the nucleus accumbens has been shown consistently to have a strong enhancement effect on locomotor activity in the rat. Dopamine or its agonist, apomorphine, produces hyperactivity when injected into the nucleus accumbens of the rat (Pijnenburg et al., 1975). Lesioning of the nucleus accumbens with 6-hydroxydopamine abolishes increased locomotor activity following systemic injection of amphetamine (Kelly et al., 1975). Injection of picrotoxin into the VTA which presumably activates dopamine neurons by blocking the inhibitory effect of GABA on these neurons also produces hyperactivity (Mogenson et al., 1979b). The effect could be blocked by injection of spiroperidol, a dopamine receptor blocker into the nucleus accumbens.

Some investigators showed that in addition to hyperactivity, dopamine injected into the nucleus accumbens also produces stereotypy, a behavior that is more consistently observed if dopamine is injected into the caudate nucleus (Costall and Naylor, 1975, Pijnenburg et al., 1975). Other investigators, however, showed that 6-hydroxydopamine lesion of the accumbens did not reduce stereotypy induced by systemic injection of amphetamine (Kelly et al., 1975). Two possibilities may account for the discrepancy between these experiments: first, spreading of dopamine from the nucleus accumbens to the caudate nucleus in Costall and Naylor as well as in Pijnenburg's experiments might have caused the stereotypy observed, or alternatively, the nucleus accumbens may indeed make a minor contribution to stereotypy.

Electrical self-stimulation experiments suggest that the nucleus accumbens may have a role in behavioral reinforcement

(Van Rossum et al., 1977). Amphetamine injected into the nucleus accumbens enhanced rate of self-stimulation of the lateral hypothalamus or the VTA (Broekkamp et al., 1975). By contrast, spiroperidol, a dopamine antagonist injected into the nucleus accumbens reduced the rate of self-stimulation of the VTA (Mogenson et al., 1979a).

More recent studies by Mogenson and others (see Mogenson and Yim, 1981) showed that the nucleus accumbens may contribute to the initiation of goal directed behaviors such as feeding and drinking. Spiroperidol injected into the nucleus accumbens significantly attenuates feeding elicited by electrical stimulation of the lateral hypothalamus (Mogenson, 1982) and drinking induced by injection of angiotensin into the cerebral ventricles (Jones and Mogenson, 1982). The attenuation of the ingestive behaviors was shown not to be due to nonspecific motor deficits but, according to the investigators, was likely due to an interference with the "appetitive phase" of the behavior.

In summary, it appears that a clear definition of the biological function of the nucleus accumbens is not possible at the present time. However, based on the anatomical observations discussed above, a number of investigators have suggested that the nucleus accumbens may serve as an "interface" or "bridge" between the limbic and motor systems (Graybiel and Ragsdale, 1979, Dray, 1980, Powell and Leman, 1976, Nauta, 1981, Heimer and Wilson, 1975, Mogenson et al., 1980). The hypothesis suggests that limbic structures such as the amygdala and the hippocampus may be able to influence the extrapyramidal motor system through this pathway. A further elaboration of this hypothesis

is presented in the "Discussion" section.

3.0 The Ventral Pallidum

The striatum of the basal ganglia receives afferents from large areas of the neocortex and projects strongly to the globus pallidus. The globus pallidus, the major output nucleus of the basal ganglia, in turn projects mainly to the ventroanterior and ventrolateral nuclei of the thalamus. The projection from the neocortex to the striatum and then to the globus pallidus forms the well known neocortico-strio-pallidal pathway that forms part of the cortico-basal ganglia-thalamo-cortico loop (Cowan and Powell, 1966, Kemp and Powell, 1971).

A number of investigators (Swanson and Cowan, 1975, Powell and Leman, 1976) have pointed out that the nucleus accumbens, as well as the olfactory tubercle, share similarities with the caudate nucleus in cytoarchitecture and afferent connections. While the caudate nucleus receives projections from the neocortex (Kemp and Powell, 1970, Webster, 1961) and the substantia nigra (Ungerstedt, 1971a), the nucleus accumbens and the olfactory tubercle receive projections from the allocortex (hippocampus and piriform cortex) and the VTA, medial to the substantia nigra pars compacta. Heimer and Wilson (1975), in referring to these similarities, considered the nucleus accumbens and the olfactory tubercle to be a ventral extension of the neostriatum and referred to these two structures collectively as the ventral striatum. They also suggested that the pathway from the hippocampus and piriform cortex to the ventral striatum probably forms a part of

the allocortical parallel of the neocortico-strio-pallidal projection (Cowan and Powell, 1966, Kemp and Powell, 1970). The concept is further supported by examination of the efferent projection of the nucleus accumbens and the olfactory tubercle. The two nuclei project to a ventral part of the globus pallidus (Swanson and Cowan, 1975, Heimer and Wilson, 1975) and an area ventromedial to the striatum underneath the temporal limb of the anterior commissure. The latter area has previously been considered by anatomists to be part of the lateral preoptic area or the substantia innominata (Konig and Klippel, 1953, Mizuno et al., 1969). Heimer and Wilson (1975) noticed, however, that cytoarchitecture as well as ultrastructural characteristics of neurons in these areas as revealed by the light microscope and the electron microscope respectively are remarkably similar to that of the globus pallidus. Consequently, they considered it a ventral extension of the pallidum and introduced the term ventral pallidum to describe this area.

Thus, according to Heimer and Wilson (1975) and Heimer et al (1982), the ventral pallidum is an area rostral and ventral to the globus pallidus defined by its afferents from the ventral striatum, i.e. the nucleus accumbens and the olfactory tubercle. Little else is known of the afferent connections of the ventral pallidum. In addition to input from the nucleus accumbens and olfactory tubercle, previous anatomical and electrophysiological studies have shown that the substantia innominata receives input from the ventromedial nucleus of the hypothalamus (Saper et al., 1975), the pontine taste area (Norgren, 1974) and the piriform cortex (Nauta, 1961). It is not known, however, if the area described as substantia innominata in

these papers corresponds to the present definition of the ventral pallidum.

Recent interest in whether or not output from the nucleus accumbens reaches the motor system has led to a few anatomical studies on the efferent projections of the ventral pallidum. Evidence obtained in these studies suggest that the ventral pallidum may be related to the motor system in the same way that the dorsal pallidum (globus pallidus) is. Heimer et al. (1982) showed that the ventral pallidum projects to the dorsomedial nucleus of the thalamus which in turn projects to the anterior cingulate gyrus that may have connections with the motor cortex and the supplementary motor cortex. Swanson et al. (1982), on the other hand, showed that the ventral pallidum projects directly to the dorsal parts of the midbrain reticular formation including the pedunculo-pontine and cuneiform nuclei. The same areas in the cat correspond to the "mesencephalic locomotor region" of Grillner and Shik (1973) who showed that electrical stimulation of this area produces locomotion.

4.0 The Dopaminergic System

Carlsson et al. (1958) first demonstrated that dopamine is normally present in the brain using a sensitive fluorimetric dopamine assay (Carlsson and Waldeck, 1958). With the subsequent development of the formaldehyde histofluoresence technique (Falck et al., 1962), the presence of dopamine in nerve cell bodies and terminals could be visualized (Carlsson et al., 1962, Dahlstrom and Fuxe, 1964, Fuxe, 1965) and the dopaminergic pathways were later mapped out

(Anden et al., 1966, Ungerstedt, 1971a). Following the description of
the dopaminergic pathways, extensive studies have been conducted to
investigate the behavioral function of dopamine in the central nervous
system, particularly after it was demonstrated that Parkinson's
disease and possibly schizophrenic psychosis are due to an imbalance
of dopaminergic function. Much has also been done to elucidate the
action of dopamine at the cellular level, but a correlation between
the behavioral function and cellular effect of dopamine has not been
suggested. An objective of this thesis is to attempt such a synthesis
by investiging the cellular action of dopamine in the nucleus
accumbens in relation to the accumbens' possible role as a
limbic-motor interface.

In this section, a review of the anatomy of the major
dopaminergic pathways in the brain is presented. This is followed by
a brief account of the cellular action of dopamine and its influences
on behaviors.

4.1 Divisions

Cell bodies of the dopamine containing neurons are located
primarily in the midbrain, mainly in the substantia nigra pars
compacta and the more medially located ventral tegmental area (VTA).
Dahlstrom and Fuxe (1964) adopted a systematic nomenclature of these
cell groups in relation to their location. The dopamine cell group of
the substantia nigra pars compacta was designated A9 (with a more
caudal cell group designated A8) and those in the VTA was designated
A10. The A8 and A9 cell groups project primarily to the caudate

nucleus (with minor projections to the nucleus accumbens) and the A10 cell group projects to the nucleus accumbens and a number of limbic structures including the olfactory tubercle, the amygdaloid complex and the septum. Both A9 and A10 cell groups project sparsely to parts of the suprarhinal cortex, entorhinal cortex and medial frontal cortex. , The substantia nigra to caudate projection has commonly been known as the nigro-striatal projection. The projection from the VTA to the nucleus accumbens and other limbic structures, on the other hand, is commonly referred to as the mesolimbic projection (Ungerstedt, 1971a).

Some investigators have recently adopted a different system of classification of this midbrain to forebrain dopamine projection. Noting the continuity of the cell groups A9 and A10, Moore and Bloom (1978) as well as Lindvall (1979) suggested that the entire meso-telencephalic projection should be reclassified into two divisions according to their terminal fields: the meso-striatal projection and the meso-cortical projection. The meso-striatal projection refers to the projection from the substantia nigra and the VTA to the striatum. The meso-cortical projection refers to the projection from the same areas to the amygdala, septum, olfactory tubercle and the cortical areas. This system of classification has not been widely adopted in the literature possibly because of two reasons. First, there is an inconsistency in the classification of the ventral tegmental projection to the nucleus accumbens among these investigators. Moore and Bloom (1978) consider this projection to be part of the mesocortical system whereas Lindvall (1979) consider it part of the mesostriatal system. Secondly, confusion arises in the

inclusion of projections to subcortical structures such as the olfactory tubercle, septum and amygdala in the "mesocortical" system. Moreover, functionally there is a clear distinction between the nigral projection to the dorsal striatum (caudate nucleus) and the ventral tegmental projection to the ventral striatum (nucleus accumbens). To consider the two as a single mesostriatal projection would overlook their functional difference. Hence, in this thesis, the term mesolimbic dopamine projection will be used to refer to the dopamine pathway between the VTA and the nucleus accumbens.

In addition to the main midbrain to forebrain projection, intrinsic dopamine circuits with limited distribution are found in the brain. These include pathways in the hypothalamus, the retina, the olfactory bulb and the medulla. A summary of the different dopamine pathways in the brain is shown in Table 1.

4.2 Dopaminergic Functions

a. Cellular Effects

There is abundant evidence to suggest that dopamine acts as a neurotransmitter (for review, see Hornykiewicz, 1966, Kostowski, 1972). For example, dopamine has been shown to be concentrated in nerve terminals (Anden et al., 1964) and is released from terminals of nigral pathway by stimulation of the substantia nigra (Portig et al., 1968, McLennan, 1964). Dopamine released in the superior cervical ganglion of the rabbit was shown to cause a slow inhibitory postsynaptic potential in the ganglion cells (Libet and Tosaka, 1970).

Table 1

Summary of dopamine neuron systems in the mammalian brain

	Origin of Cell Bodies	Terminal Fields
Nigral·Striatal	Substantia nigra pars compacta (A8,A9)	caudate putamen
Mesolimbic	Ventral tegmental area (A10)	Nucleus accumbens, septal area, amygdala, olfactory tubercle, entorhinal cortex, frontal cortex
Retinal	Interplexiform cells of retina	Inner and outer plexiform layers of retina
Tubero-·hypophysial	Arcuate and periventricular nuclei of hypothalamus	median eminence intermediate lobe of pituitary
Incerto-hypothalamic	Zona incerta posterior hypothalamus	dorsal hypothalamic area, septum
Periventricular	Mesencephalic peri-aqueductal gray and periventricular gray	Periaqueductal gray, medial thalamus and hypothalamus
Olfactory·Bulb	periglomerular cells of olfactory bulb	Glomeruli (mitral cells)

Nevertheless, other investigators still consider the status of
dopamine as a neurotransmitter to be hypothetical (Krnjevic, 1981b).
One of the problems is that the precise cellular action of dopamine
released in the brain remains unclear.

The electrophysiological effects of dopamine on the postsynaptic
neuron have been studied in the caudate nucleus and in the nucleus
accumbens using electrophysiological techniques. The major action of
dopamine, either applied iontophoretically or released by stimulation
of the midbrain dopamine cell groups, has been observed in most
studies to cause a depression in the firing rates (Connor, 1970,
McLennan and York, 1967, McCarthy et al., 1977). Some investigators,
on the other hand, found that dopamine has a predominantly excitatory
effect (Bevan et al., 1975, Spencer and Havlicek, 1974). Kitai et al
(1976) using intracellular recording techniques showed that very short
iontophoretic application of dopamine depolarizes caudate neurons
which show excitatory postsynaptic potentials to stimulation of
substantia nigra. He suggested that dopamine may indeed be an
excitatory neurotransmitter and that the inhibitory response observed
previously was due to the diffusion and activation of an inhibitory
interneuron by dopamine. The view is shared by a few other
investigators (York, 1979, Assaf and Miller, 1977) but difficulties in
interpreting the results from such brief pulses of dopamine
application have also been raised (Moore and Bloom, 1978). Thus the
issue on the postsynaptic influence of dopamine in the central nervous
system remains controversial.

Whether or not the postsynaptic effect of dopamine is excitatory
or inhibitory, there is evidence that the effect may be associated

with adenyl cyclase. Kebabian and Greengard (1971) and subsequently other investigators. (Brown and Makman, 1972, Iversen, 1975) demonstrated that dopamine was effective in stimulating the activity of adenylate cyclase and suggested that dopaminergic transmission may be mediated by cyclic adenosine-3',5'-monophosphate (cAMP). However, other studies using dopamine agonist and antagonist radioligand binding techniques revealed that not all dopamine receptors are linked to adenyl cyclase and therefore not all biological responses elicited by dopamine or its agonists are due to the synthesis of cAMP (see Seeman, 1980). Results of these binding studies indicate that there are multiple classes of dopamine receptors in the CNS. The same concept is also suggested by behavioral studies as shown by Cools and Van Rossum (1976) as well as Costall and Naylor (1979). A number of investigators have subsequently proposed systems of classification of the various types of dopamine receptors based either on binding studies (see Seeman, 1980, Creese et al., 1981) or on pharmacological-behavioral studies (Cools and Van Rossum, 1980, Costall and Naylor, 1976). However, a consensus on a system of classification has not been reached.

Recent biochemical evidence has shown that dopamine receptors are present on plasma membrane of dopamine containing neurons. These receptors have been refered to as autoreceptors and presumably form a feedback control mechanism (see Nowycky and Roth, 1978) regulating the synaptic release of dopamine. Thus dopamine receptor blockers (such as neuroleptics) have been shown to enhance the release of dopamine from terminals in neostriatal slices whereas apomorphine, a dopamine agonist, inhibits dopamine release (Farnebo and Hamberger, 1971). The

binding of dopamine or its agonist to autoreceptors on the cell bodies of dopamine neurons in the substantia nigra has also been shown to cause a depression in the activities of the neuron (Aghajanian and Bunney, 1973). In fact, this property has been used as a criterion in identifying dopamine neurons in recordings obtained from the substantia nigra (Guyenet and Aghajanian, 1978).

Dopamine presynaptic receptors were also found in intrinsic as well as non-dopaminergic afferents to the striatum. Binding of dopamine to presynaptic dopamine receptors on glutaminergic neurons has been shown to reduce the rate of axonal transport of glutamate presumably causing a subsequent decrease in the amount of glutamate released by an action potential (Murrin and Robertson, 1980).

b. Behavioral Effects

Indication that dopamine in the central nervous system has an important behavioral function was initially suggested by the following biochemical and pharmacological observations: i) the level of dopamine content in striatum of Parkinson patients was significantly lower than controls and there is always a pronounced cell loss in the substantia nigra of these patients, ii) neuroleptics, effective in treating the symptoms of schizophrenia, are dopamine receptor blockers and amphetamine, which releases dopamine from dopaminergic nerve terminals, produces classical symptoms of schizophrenia when administered to normal patients (see Hornykiewics, 1966). These associations indicate that dopamine may be functionally important in the extrapyramidal motor system as well as in those parts of the brain

involved in cognitive behaviors. Several experimental approaches have since then been used to determine the behavioral influences of dopamine. An extensive catalogue of all behavioral effects associated with dopamine is beyond the scope of this review, only a summary of the major findings will be presented.

i) <u>Ambulatory Effects</u>. Amphetamine causes hyperactivity when given systemically to animals. At high doses, the animal typically exhibits stereotyped behaviors such as continuous sniffing, licking and gnawing (Lyon and Robbins, 1975). These effects are attributed to the ability of amphetamine to release dopamine from dopaminergic terminals in the striatum (Randrup and Munkvad, 1966). More detailed investigations involving differential lesioning of the mesencephalic to telencephalic dopamine pathways (Creese and Iversen, 1972, Kelly <u>et al</u>., 1975) or intracerebral injection of dopamine or its agonists into different sites in the striatum (Fog, 1972; Costall <u>et al</u>., 1974, Pijnenburg and Van Rossum, 1973) revealed that stereotypy and hyperlocomotion can be elicited independently. Typically, dopamine or amphetamine injected into the caudate nucleus causes stereotypy without hyperlocomotion whereas dopamine or amphetamine injected into the nucleus accumbens (ventral striatum) causes hyperlocomotion without stereotypy (see section on Nucleus Accumbens). Some investigators have reported even more specific differentiation of stereotyped behaviors depending on the site of injection and type of dopamine agonist used (Costall and Naylor, 1976). From these findings of differential effects with different agonists, the presence of subtypes of dopamine receptors in the striatum was postulated (Costall and Naylor, 1979). However, although

research in this area has been extensive, a precise description of the functional role of dopamine release in the striatum has not been possible.

ii) Motivational Effects. Apart from influencing the extrapyramidal motor system and thus the ambulatory function of the animal, some investigators have shown that dopamine may be important in the motivational aspects of goal-directed behavior. Bilateral lesioning of the ascending dopamine neurons with 6-hydroxydopamine typically induces severe adipsia and aphagia (Ungerstedt, 1971b). Spiroperidol, a dopamine receptor blocker, when injected into the nucleus accumbens causes attenuation of angiotensin II induced drinking without causing oral motor deficits (Jones and Mogenson, 1982). Such results indicate that dopamine may be important in the motivational phase of ingestive behavior.

A correlation between functional hyperactivity of the mesolimbic dopamine system and schizophrenia has been proposed. This was based on the antipsychotic effects of dopamine blockers and the observation of abnormally high dopamine content in the nucleus accumbens found postmortum in schizophrenic patients (Bird et al., 1977). Although an adequate animal model to study the etiology of schizophrenia in terms of dopamine hyperactivity is not available, the relationship between motivational and cognitive processes and dopamine function seems established.

Another experimental observation that suggests a correlation between dopamine function and motivational processes is the attenuation of intracranial self-stimulation by interfering with brain dopamine pathways (see Crow, 1972, Fibiger and Phillips, 1979).

Dopamine receptor blockers such as haloperidol and spiroperidol decreased the rate of self stimulation of a number of brain sites including the ventral tegmental area and the medial forebrain bundle (Phillips and Fibiger, 1978, Rolls et al., 1974). Lesioning of dopamine pathways with 6-hydroxydopamine produced a similar attenuation (Phillips and Fibiger, 1978). Arguments have been made on the possibility of non-specific motor deficit as a cause of an attenuation of frequency of self stimulation (Figiber, 1978), but nevertheless, that the dopaminergic projections play a role in the mechanism of reinforcement cannot be excluded.

iii) Neuroendocrine Effects. Dopamine is also involved in neuroendocrine processes which might affect the behavior of an animal in a different way (see Lichtensteiger, 1979). The tuberoinfundibular dopamine system originates in the arcuate nucleus and projects to the median eminence as well as the intermediate lobe of the pituitary (Fuxe and Hokfelt, 1966). Dopamine appears to influence the secretion of a number of hormones from the anterior pituitary by its release into the hypothalamic-pituitary portal system. It also influences the secretion of melanocyte stimulating hormone apparently by direct innervation of pars intermedia.

There is good evidence that dopamine acts as a tonic inhibitor of the release of prolactin from the anterior pituitary (Lu et al., 1970, Lu et al., 1971, Lawson and Gala, 1975). Neuroleptics such as chlorpromazine increase prolactin level in female rats whereas L-DOPA inhibits prolactin secretion. Dopamine also appears to alter the secretion of gonadotropins. Neuroleptic administration disrupts oestrous cycle in rodents and mensural cycle in female patients

(Lichtensteiger, 1979). However, the precise role of dopamine in the regulation of leutinizing hormone and follicle stimulating hormone secretion is still unknown.

METHODS

1. Animals and Surgery

Male adult Wistar rats weighing 250-350 g were used for the recording experiments. Animals were anesthetized with urethane at 1.15 - 1.20 g/kg i.p. and received supplementary doses of 50 mg at 2-hour intervals throughout the experiment. The anesthetized animal was mounted in a Kopf stereotaxic apparatus with the incisor bar positioned at 5 mm above the ear bars. Body temperature was monitored by a rectal probe connected to a telethermometer (Model 73 A Yellow Springs Instruments, Yellow Springs, Ohio) and maintained at 36 - 38 C with a radiant lamp controlled by the telethermometer. A midline incision was made in the scalp and the skull was exposed. Burr holes of 2-3 mm diameter were drilled through the skull immediately above the appropriate sites. Recording electrode, stimulating electrode and injection cannula were lowered on stereotaxic carriers through burr holes in the skull to appropriate sites using coordinates modified from those of Pellegrino and Cushman (1967). Coordinates used to approach the different nuclei involved in these experiments are listed in Table 2. The nucleus accumbens, amygdala and ventral pallidum were approached vertically but the VTA was approached at an inclination of 15 degrees to the sagittal plane to avoid injury to the sagittal sinus.

TABLE 2

Stereotaxic Coordinates Used for Placement of Recording and Stimulating Electrodes as well as Injection Cannulae to Various Nuclei in the Rat Brain.

	Anterior/ Posterior of Bregma	Lateral of Sagittal Sinus	Depth from Surface of Cortex
Nucleus Accumbens	A 3.2 - 3.8 mm	1.0 - 1.6 mm	5.5 - 7.2 mm
VTA	P 2.8 - 3.2 mm	0.8 - 1.6 mm	8.4 - 9.0 mm
Amygdala	P 0.6 - 1.2 mm	4.2 - 5.4 mm	8.2 - 9.2 mm
Ventral Pallidum	A 0.6 - 1.4 mm	2.0 - 3.4 mm	7.0 - 8.0 mm

2. Recording from Single Neurons

Glass micropipettes were used to obtain single unit extracellular recordings. The micropipettes were pulled from filament filled borosilicate glass capillary tubes (W-P Instruments, New Haven, CT.) on a Narishige microelectrode puller (Narishige Scientific Instruments Lab., Tokyo, Japan). The tip of the micropipette was broken back to a diameter of 1-2 um under microscopic guidance. The micropipette was then filled with 0.5 M sodium acetate containing 2% Pontamine Sky Blue (Gurr, U.K.). Electrodes had typical impedances of 3-5 megaohms measured with a 1000 Hz sine wave signal.

Recorded signals were fed into a miniature operational amplifier on the electrode holder and then to a differential preamplifier (PBA-1, Frederick Haer). The output from the differential preamplifier was displayed on a Tektronix 565 oscilloscope (Tektronix, Beaverton, Oregon) and on a Tektronix R5103N storage oscilloscope. Photographic records were obtained from the storage oscilloscope with a Tektronix C-12 oscilloscope camera using Polaroid films. Amplified signal was also fed into an audio monitor (Grass AM-7) and a window discriminator (Frederick Haer). Discrete square pulses of fixed amplitude corresponding to individual spikes were generated by the window discriminator. These pulses were sampled online by a PDP-11/44 computer as well as a frequency counter. The frequency counter provided a continuous display of the number of action potentials recorded as well as the number of stimulations delivered by the stimulator. The computer stored the spike frequency for every second and individual interspike intervals with a resolution of 1 msec. The

data were later used to compile various types of histograms for display and analysis.

3. Electrical Stimulation

Stainless steel concentric bipolar electrodes (NE-100, Rhodes Medical, 0.5 mm diameter, 0.5 mm tip separation) were used for delivery of electrical stimulation. Electrical pulses were generated by a Grass S44 stimulator (Grass Instruments, Mass.) coupled to a Grass stimulation isolation unit (SIU 5). Stimulations were monophasic square pulses of 0.1 - 0.3 ms duration, with amplitudes of 6-30 V producing currents of 150-800 uA. Currents were determined by measuring the voltage across a 10 kohm resistor in series in the circuit. In interaction experiments which involved the stimulation of two sites at different times, two S44 stimulators were used. The timing of the pulses was controlled by a digital timer (Digitimer, Devices, Hertfordshire, England) programmed to sequence the stimulus pulses from the two stimulators.

4. Identification of Antidromic Activations

Response of a neuron to electrical stimulation of another area of the brain was considered to be antidromic when the response met the following criteria.

i)   An all-or-none single spike was elicited for each stimulation and the latency of activation was constant.

ii)   The neuron was able to follow stimuli delivered at above
      200 Hz. This criterion was tested by the delivery of twin
      pulses to the stimulating electrode, the interval between the 2
      pulses being 5 ms or less.

iii) The spontaneous spike from the same neuron was able to cancel
      the activated spike. This could be observed occasionally when
      a spontaneous spike occurred just before or shortly after the
      delivery of the stimulus. More often, the test was carried out
      using a Schmitt trigger that allowed the stimulator to be
      triggered by the spontaneous spike. A variable delay was
      introduced between the arrival of the spontaneous spike and the
      delivery of the stimulus. If a delay that was equal to or less
      than the latency of the activation caused cancellation of the
      elicited spike whereas a delay that was greater than the
      latency did not, the response was considered antidromic. The
      Schmitt trigger used for these tests had a flip flop latch that
      prevents feedback oscillation in the circuit.

5. Identification of Significant Orthodromic Responses

      Peristimulus time histograms (PSTH) were computed from the
recorded interspike and inter-stimulation intervals using a
cross-correlation algorithm. The number of stimulus presentations
used to compile the PSTH was dependent on the baseline firing rate and
was determined during the sampling. In most cases, more than 1500
interspike intervals would be collected before sampling was terminated
manually. Since the stimuli were presented at 1 to 1.5 Hz, 1500

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spikes would normally give a PSTH having a baseline mean greater than 1.5 and a standard error of less than 1.0 to allow a reliable detection of significant post stimulus response. Significant changes in activity of neurons following stimulations were identified and quantified by comparing the height of each poststimulus bin of the histogram with the average height of the bins before the stimulus. The average bin height for the period of 100 ms before the stimulus was determined and considered as the baseline activity of the cell. Significant responses to the electrical stimulation were then defined, as the occurrence of a period of time following the stimulation during which the mean height of the PSTH was significantly different from the baseline. The boundaries of possible periods of significant response were defined by the occurrence of consecutive bins of height significantly different from the baseline mean. The beginning of such a period was defined as the time of the first of three consecutive bins with heights that were more than one standard deviation from the baseline mean. The end of the period was similarly defined as the time of the first of three consecutive bins with heights that were within one standard deviation from the baseline mean. With the boundaries defined, the mean height and standard deviation of the bins within the region were compared to the baseline assuming that both samples were normally distributed. The Student's 't' test was used when the region of possible significant response contained less than 20 bins. If the difference had a probability of less than 0.05 occuring by chance, the response was considered significant.

In interaction experiments, comparison of responses before and after drug application or VTA stimulation was based on PSTH compiled

from exactly the same number of presentation of stimulations. The ratio of the mean height of the bins in the period of significant response to that of the baseline was computed for each PSTH. A reduction of more than 25% of this ratio was considered a significant change.

6. Iontophoretic Application of Drugs

Seven-barrel glass micropipettes were used for recording and iontophoretic application of drugs. Electrode blanks were made by binding Kimax 51 borosilicate capillaries (Fisher Scientific) with heat shrinkable tubing and epoxy. Micropipettes were then pulled from blanks on a Narishige microelectrode puller. Tips were broken back to an overall average diameter of 4.5 - 6.0 um. The center barrel was filled with 1 M sodium chloride solution for recording. The peripheral 6 barrels contained one of the following compounds or the vehicle in which the compound was dissolved for control tests: dopamine hydrochloride (1 M solution, with trace of ascorbic acid and pH adjusted with N/10 NaOH to 4.0), picrotoxin (saturated solution in 150 mM saline), L-monosodium glutamate (1 M solution, pH 8.0), GABA (1 M solution, pH 4.0) (all from Sigma, MO.), pontamine sky blue - 5BX (2% in 0.5 M · sodium acetate, Gurr, U.K.), nipecotic acid (0.2 M), trifluoperazine (0.2 M), (nipecotic acid and trifluoperazine were from Smith, Kline and French Laboratories, Philadelphia, PA.) and saline for current balance or current control.

The electrodes were filled and then centrifuged at 4000 x g for 10 min 2-3 h before each experiment. The typical impedance of the

recording barrel was 5-10 M ohm and those of the iontophoretic channels were 8-15 M ohm when measured with 1 kHz sine wave.

Iontophoretic currents were driven by a custom built iontophoresis unit with 6 channels and monitored by a Keithley 179 TRMS digital multimeter connected across a 10 kohm resistor. Except for glutamate and pontamine sky blue, which were ejected as anions, all other compounds were ejected as cations using a positive current. Retaining currents of 5-8 nA were routinely used to prevent diffusion of drugs out of the electrode while they were not ejected. Ejection times ranged from 10 s pulses (e.g. GABA, dopamine) to up to 512 s (e.g. picrotoxin, glutamate) continuous application.

Responses to an iontophoretically applied compound were accepted as genuine only if the following criteria were met: (1) the response was reversible, (2) the response could be reproduced by ejecting the compound at the same current again, (3) the effect of the drug could not be mimicked by passing the same current through saline or the vehicle in which the compound was dissolved. A significant response was arbitrarily defined as a 30% change in activity of the neuron.

7. Intracerebral Microinjection of Drugs

Guide cannulae were made from 23 gauge hypodermic needles. The plastic hub of the needle was removed and the needle cut to a length of 14 mm. At the beginning of the experiment, the cannula was lowered stereotaxically to the appropriate depth of the brain through burr holes in the skull and then secured with cranioplastic acrylic (L. D. Cauk Co., Millford, Ontario) to stainless steel jewellery

screws inserted into the skull beforehand. Injection cannula was made from 30 gauge stainless steel tubing (HTX-30, Small Parts Inc.) which fitted snugly into the 23 gauge guide cannula. The injection cannula was bent to an L shape with one arm grounded to a length of 14.5 mm such that when inserted, the tip protruded 0.5 mm beyond the tip of the guide cannula. Drugs were injected using a Hamilton microsyringe connected to the injection cannula by PE-10 tubing in volumes of 0.5 to 1 μl. Compounds that were injected directly into the brain with this technique were procaine hydrochloride (20% solution in distilled water) and D-amphetamine (0.1% solution in distilled water).

8. Systemic Administration of Haloperidol

Haloperidol was injected intraperitoneally to some animals at a dose of 0.5 mg/kg to block the effect of dopamine released in the central nervous system (Carlsson and Lindquist, 1963). Haloperidol (Haldol, McNeil Laboratories) injectate contained 5 mg haloperidol per ml.

9. 6-Hydroxydopamine Lesion of Mesolimbic Dopamine Neurons

Dopamine containing neurons in the ventral tegmental area were lesioned in some rats with 6-hydroxydopamine, a toxin for catecholamine containing neurons, two days prior to the recording experiment. The animal was first injected with pertofrane (desipramine HCl, Geigy Company, Canada) intraperitoneally at a dose of 25 mg/kg to prevent uptake of 6-hydroxydopamine by noradrenergic

neurons (Roberts et al., 1975). Thirty minutes after injection of pertofrane, the animal was anesthetized with pentobarbital (Nembutal, 60 mg/kg i.p.) and a 30 gauge injection cannula was lowered into the VTA stereotaxically. Six μg of 6-hydroxydopamine was injected in 1 μl unilaterally on the side ipsilateral to the recording site.

10. Histological Procedures

At the end of the experiment, one or two reference sites along the track(s) of the electrode were marked by ejecting potamine sky blue dye from the tip of the recording electrode by passing a negative current of 10 μA for 10 min through the electrode (Hellon, 1971). Actual positions of recording sites were later determined from the location of these marks. Electrical stimulation sites were marked by passing a positive current of 10 μA for 1 min to leave an iron deposit. The animal was then sacrificed with an overdose of urethane and perfused with 50 ml normal saline followed by 50 ml buffered formalin containing 2% potassium ferricyanide. The ferricyanide reacted with the iron deposit to form Prussian Blue which marked the position of the tip of the stimulating electrode. The brain was then removed and fixed in formalin for 24 hours.

Frozen transverse sections of 70 μm were cut on a microtome from the appropriate regions. Sections were mounted on slides and counterstained with thionin for examination.

RESULTS

1.0 Single Unit Recordings from the Nucleus Accumbens

1.1 Spontaneous Activity of Neurons in Nucleus Accumbens

Recordings were made from a total of 206 neurons (42 rats) in the nucleus accumbens with most of the recording sites medial to the anterior commissure (1.0 - 1.4 mm lateral to sagittal sinus, Fig 2). Neurons in this region had slow discharge rates, 90% having spontaneous firing rates of less than 5 spikes/s. Some neurons were quiescent unless excited by iontophoretically applied glutamate. A number of neurons in the nucleus accumbens had a tendency to discharge in bursts of 3-4 spikes so that the interspike interval histogram characteristically shows a sharp peak at 10-20 ms (Fig 3).

Recordings were also made from 41 neurons in the caudate nucleus, dorsal to the accumbens, for comparison. Spontaneous activity of caudate neurons was so similar to that of the nucleus accumbens that the demarcation of the dorsal border of the accumbens was not clear from observation of single unit activities. However, at the ventral border of the nucleus accumbens, a band of fast firing neurons (> 20 spikes/s) was always encountered. They appeared to demarcate the border between the nucleus accumbens and the olfactory tubercle.

FIGURE 2

Photomicrograph of a coronal section of the rat's brain
through the region of the nucleus accumbens. The dye
deposit indicated by the arrow shows a recording site from
which an excitatory response to amygdala stimulation was
observed.

CD   Caudate Nucleus

NA   Nucleus Accumbens

OT   Olfactory Tubercle
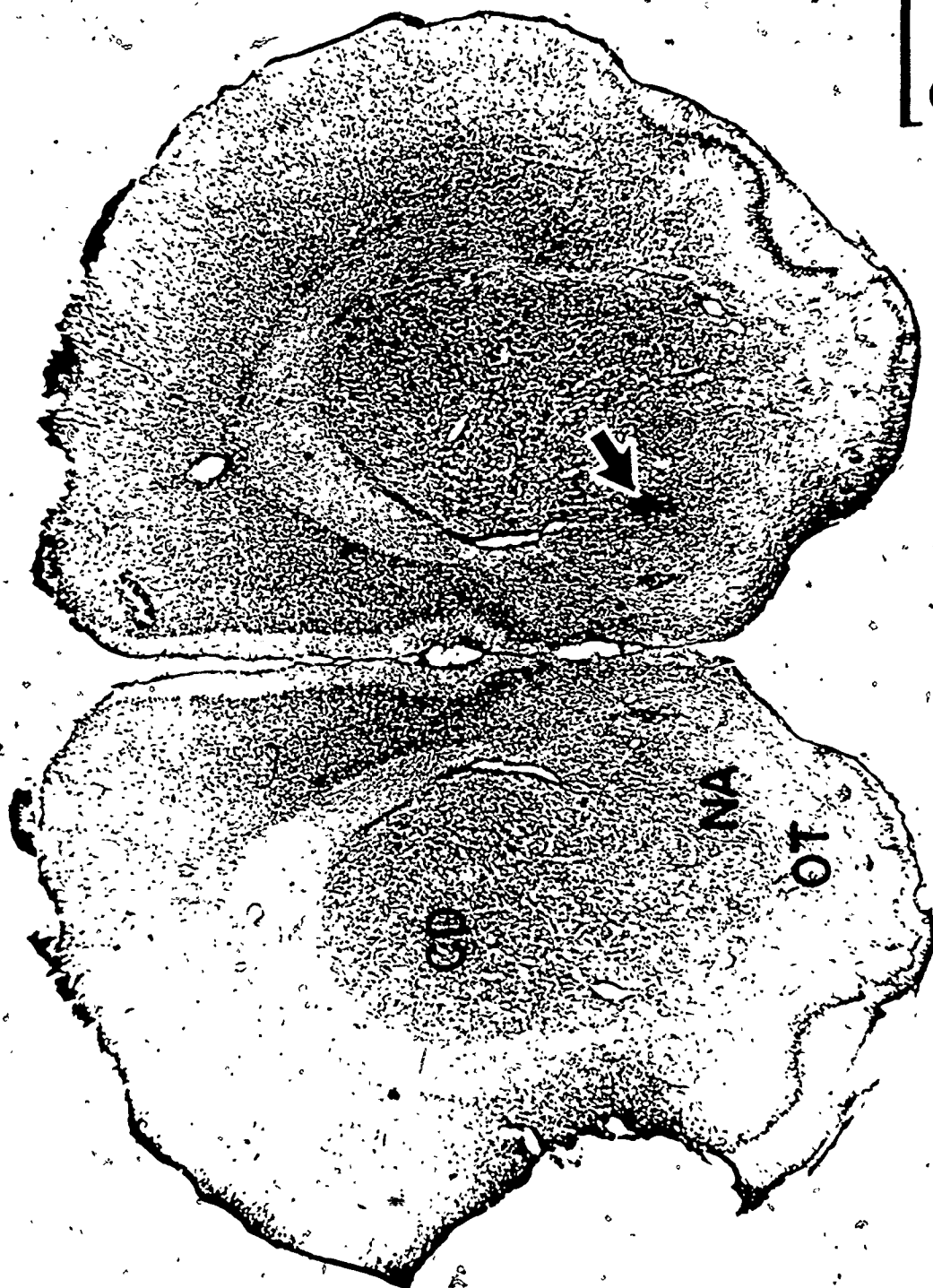
FIGURE 3

Interspike interval histogram of a neuron recorded from the nucleus accumbens. The distribution of interspike intervals of neurons recorded from the nucleus accumbens often shows a prominent peak at 10-20 ms and then levels off as in a Poisson distribution. Occasionally a second peak is discernable at 80-100 ms. This pattern of distribution is characteristic of neurons with a bursting nature. The initial peak corresponds to the interspike intervals within bursts while the remainder of the histogram shows the distribution of the interspike intervals of superimposed non-bursting activity and inter-burst intervals. A second peak can be discerned when the neuron discharges with regular bursts.

Inset shows a reproduction of a typical spike train recorded from a different accumbens neuron. Note bursting pattern of discharge and the slow firing rate.
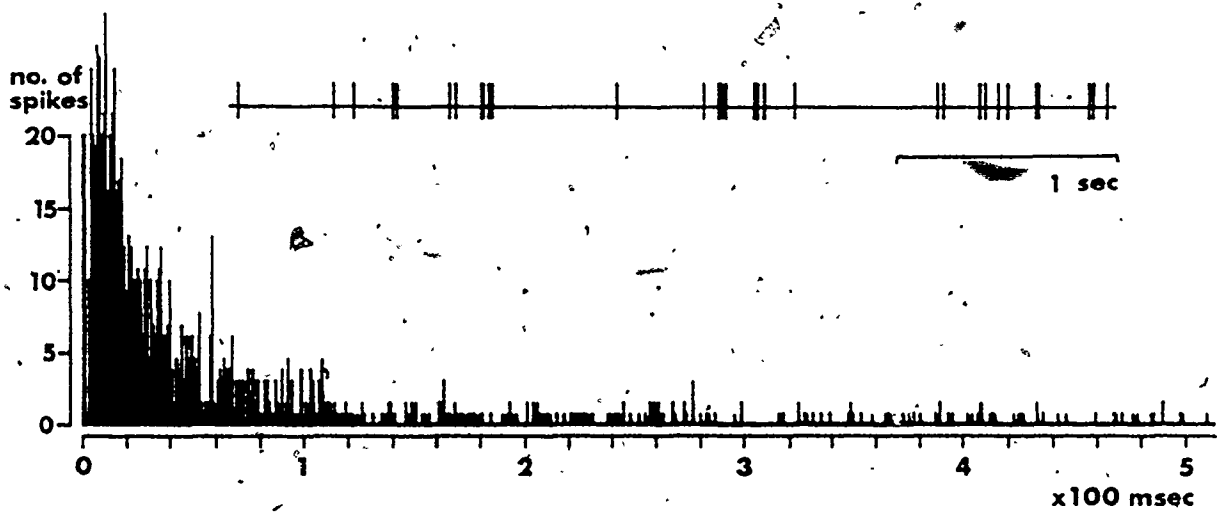
1,2 .Effects of Electrical Stimulation of the Amygdala

on Activity of Neurons in the Nucleus Accumbens

Electrical stimulation of the amygdala caused excitation in 55% (113/206) of the nucleus accumbens neurons tested (Table 3). The mean latency of the excitatory responses was 10.7 ms, 72% of the latencies were in the range of 8 to 24 ms. A single-pulse stimulus usually resulted in the activation of a single spike but occasionally a burst of 2-3 spikes was observed. The variation in the latency of the elicited response was usually small, so that when only one spike was elicited for each stimulation, the response appeared in peristimulus time histograms as a very sharp peak with a short duration (Fig 4A). However, when a burst of spikes was elicited, the response appeared as one with a long duration in the peristimulus time histogram (Fig 4B). Activation was followed in 67 cases by a prolonged period of inhibition. The inhibition sometimes lasted over 100 ms (Figs 4A and 4B).

Inhibition not accompanied by excitation following stimulation of the amygdala was seen in 30 (15%) of the 206 nucleus accumbens neurons tested. The mean latency of these responses (16.2 ms) was longer than that of excitation.

Comparison of the effects of stimulation of different areas of the amygdala showed that electrodes placed at close proximity to the basolateral nucleus elicited the highest percentage of responses in the nucleus accumbens with the lowest threshold (< 200 uA, Table 3). When the stimulating electrode was placed close to the basomedial nucleus, a significantly lower percentage of neurons in the nucleus

TABLE 3

Distribution of Types of Responses of Neurons in the Nucleus Accumbens to Stimulation of Three Different Nuclei of the Amygdala Complex

Stimulating Electrode Placement	Total No. Tested	Number Excited	Number Inhibited	Number Unaffected
Basolateral Nucleus	84	56(67%)	12(14%)	16(19%)
Basomedial Nucleus	91	47(52%)	15(16%)	29(32%)
Central Nucleus	31	10(32%)	3(10%)	18(58%)
Total	206	113(55%)	30(14%)	63(31%)

FIGURE 4

A). Peristimulus time histogram showing a typical response of a neuron in the nucleus accumbens to amygdala stimulation. The stimulus pulse was 500 μA in amplitude, 0.15 ms in duration and was delivered at time indicated by arrow. Note the short latency of the excitatory response (7 ms), the narrow spread of the response (15 ms) and the prolonged inhibition that followed (> 200 ms). Inset shows record from same cell on oscilloscope. Record was obtained from 10 sweeps. Arrow denotes time of stimulation. Calibration bars: 200 μV and 5 ms. Histogram was compiled from 200 sweeps at 1.5 Hz.

B). Peristimulus time histogram which shows the excitatory response of an accumbens neuron to amygdala stimulation. The neuron responded to each stimulation with a burst of 3-4 spikes resulting in a long duration excitation in the histogram. Stimulation was 600 μA, 0.15 ms at 1.5 Hz. Histogram was compiled from 170 sweeps. Arrow indicates time of stimulation.

A

no. of spikes

B

no. of spikes
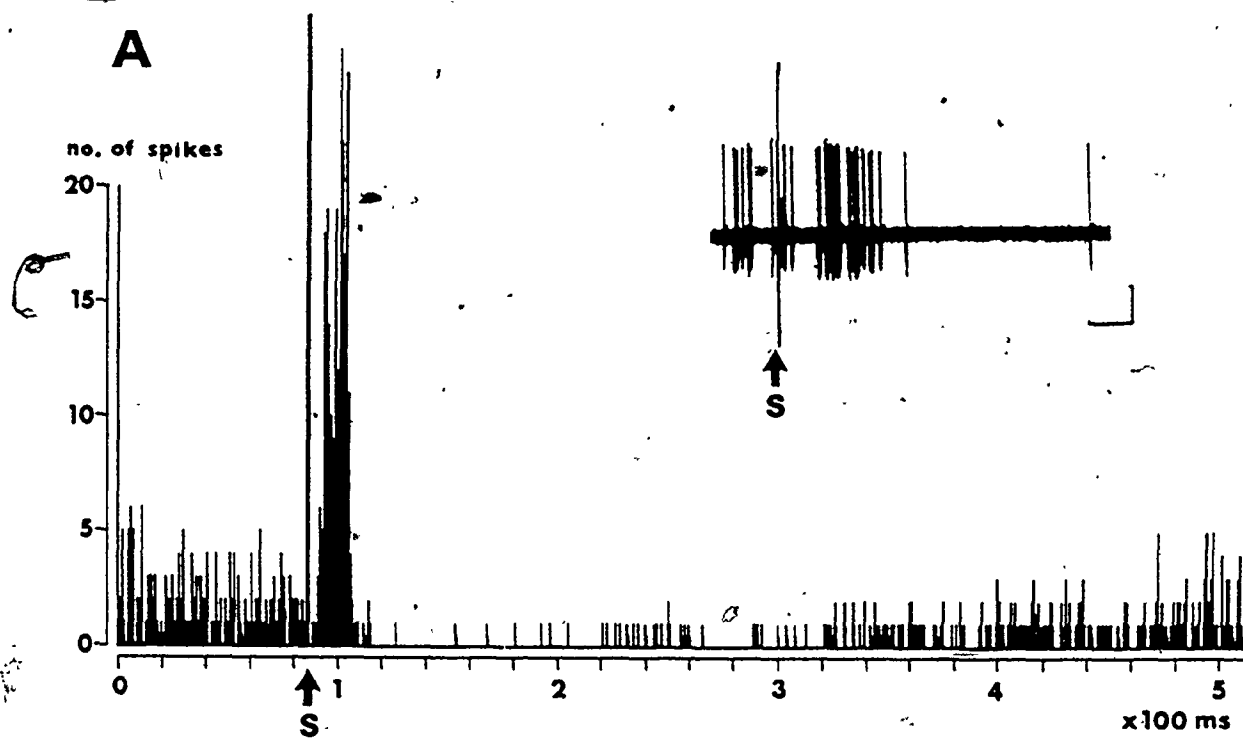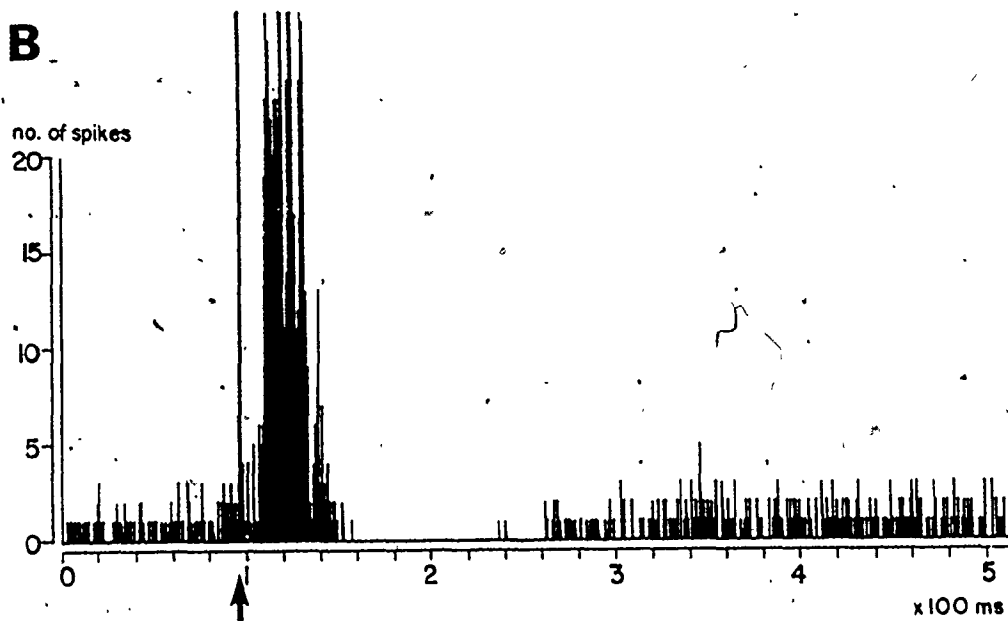
accumbens responded ($\chi^2 = 3.76$, p < 0.06). (Chi square was calculated from a 2 X 2 contingency table with numbers of cells affected by stimulation forming one column and numbers of cells not affected by stimulation forming a second column.) When the stimulating electrode was placed close to the central nucleus, a still lower percentage of neurons responded ($\chi^2 = 16.55$, p < 0.005) and the threshold of excitation was higher (> 350 μA). The proportion of neurons that showed excitation compared to those that showed inhibition following stimulation of the basomedial or central nucleus was not significantly different from that obtained following stimulation of the basolateral nucleus (χ^2 (stimulation of basomedial nucleus) = 0.84, p < 0.6; χ^2(stimulation of central nucleus) = 0.21, p < 0.8).

1.3 Modification of Responses to Amygdala Stimulation
by Iontophoretically Applied Dopamine

Of 39 neurons in the nucleus accumbens tested , all were inhibited by iontophoretically applied dopamine (Fig 5). Since the spontaneous activity of neurons in the accumbens was usually slow, these responses were tested after the spontaneous firing frequencies of the neurons had been increased to 10 to 20 spikes/s by the iontophoretic application of glutamate. The inhibitory response to dopamine was dose-dependent. Of 39 units tested, 11 (28%) were inhibited when dopamine was applied at 5 nA. 32 of 39 (82%) units ceased firing when dopamine was delivered at 20 nA.

Dopamine applied continuously at currents of between 5 and 10 nA markedly attenuated the excitatory effect of amygdala stimulation on

FIGURE 5

Continuous time frequency histogram showing inhibitory response of a nucleus accumbens neuron to iontophoretically applied dopamine. Solid bars above histogram indicate drug applications. Dopamine applied at 20 nA caused cessation of activity of neuron whereas at 10 nA, dopamine caused an approximate 80% reduction in firing rate. The same currents passed through a saline channel did not cause a change in the activity of the neuron. Trifluoperazine, a dopamine antagonist, caused attenuation of the inhibitory effect of dopamine but at the same time produced a non-specific suppression of the spontaneous activity of the cell as well. Bin width of histogram is 1 second.

DA -- dopamine

Na -- current control through saline channel

TFP -- trifluoperazine
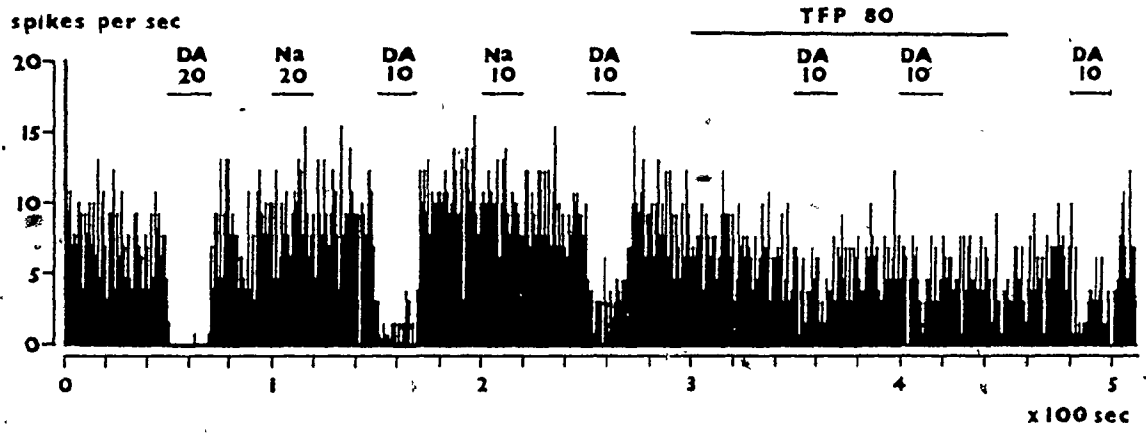
42 of 53 (79%) nucleus accumbens neurons (Fig 6 and 7). The attenuation appeared not to be due merely to a suppression of the spontaneous activity of the cell. Although in most cases the spontaneous firing rate was decreased by dopamine, the attenuation of the excitatory response from amygdala stimulation was proportionally larger. This is shown in Fig 6, in which the excitation was attenuated 63% by dopamine applied at 5 nA but the spontaneous activity of the cell was only depressed by 30%. When dopamine was applied at 10 nA, the excitatory response was further attenuated by 59% whereas the spontaneous activity showed a further 5% suppression only. In all tests, care was taken to ensure that the attenuation observed was not due to a failure of the instruments in discriminating spikes from background noise. Fig 7 is an oscilloscope tracing of a recording from a different neuron, the figure shows that the excitatory response of this neuron was attenuated by dopamine but the spike amplitude was not affected. Inhibition that followed the excitatory response was slightly prolonged in 9 neurons but was not affected in others.

1.4 Modification of Responses to Amygdala Stimulation by stimulation of the Ventral Tegmental Area

Single-pulse stimulation of the VTA produced a variety of responses in neurons of the nucleus accumbens (Fig 8). Responses included pure excitation (12/111(11%), mean latency 12.4 ms), pure inhibition (19/111(17%), mean latency 8.1 ms) and combinations of these responses (22/111(20%)) (Table 4). Twenty-four cells in the

FIGURE 6

Peristimulus time histogram showing the response of a neuron in the nucleus accumbens to amygdala stimulation and its attenuation by ionotphoretically applied dopamine.

A: Response to single pulse stimulation of the amygdala at 600 uA, 0.15 ms. In this example, a single stimulation of the amygdala elicited a burst of 2 to 3 spikes from the accumbens neuron. The response is thus seen as an excitatory response with a long duration in the histogram.

B: Dopamine was applied iontophoretically at .5 nA continuqusly during the sequence of stimulation. The spontaneous activity of the cell was depressed slightly but the elicited excitatory response from amygdala stimulation was markedly attenuated.

C: Iontophoretic application of dopamine at 10 nA further attenuated the elicited excitatory response but the spontaneous activity was affected to a much lesser extent.

Histogram was compiled from 300 sweeps at 1.5 Hz. Arrow indicates time of stimulation.
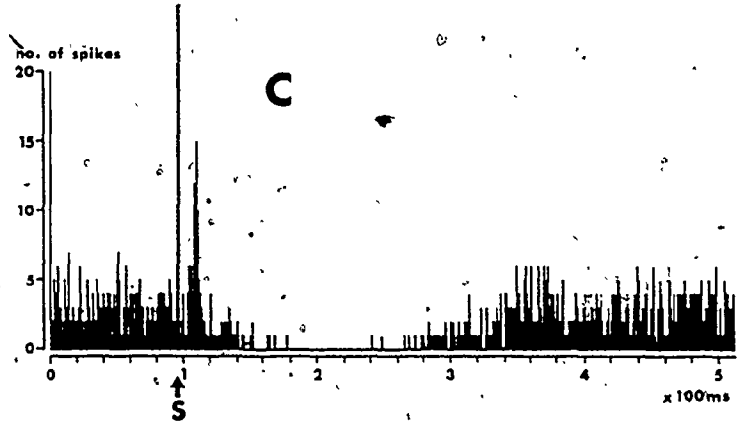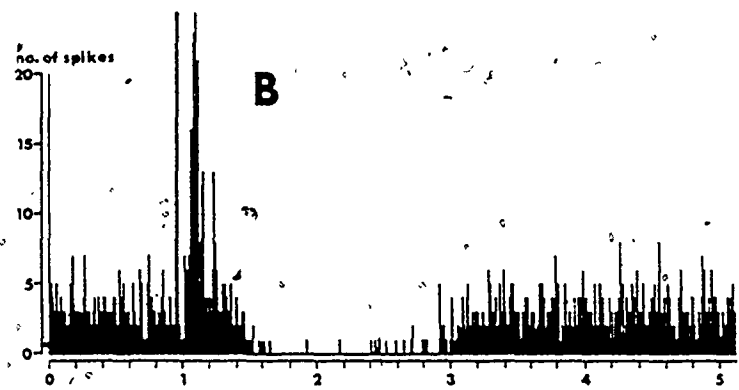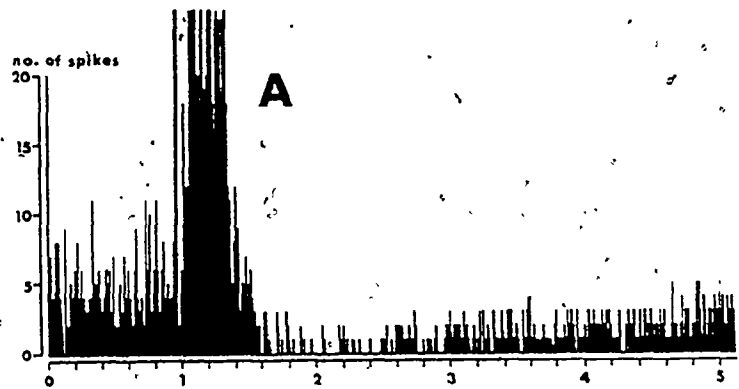
FIGURE 7

Record of oscilloscope tracings to show effect of iontophoretically applied dopamine on response of a nucleus accumbens neuron to amygdala stimulation. Upper tracing shows control response and lower tracing shows response during continuous iontophoretic application of dopamine at 10 nA. Note that spike amplitude was not affected by the iontophretic current. Arrow denotes time of stimulation. Trace was compiled from 10 sweeps. Calibration bar: 200 uV and 5 ms.
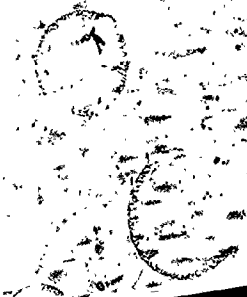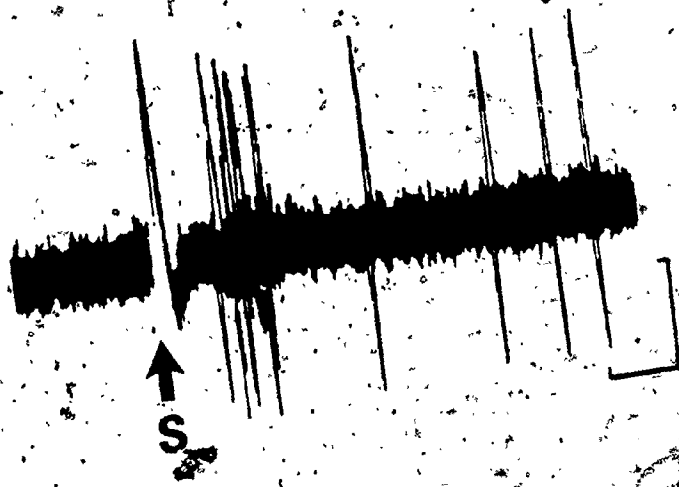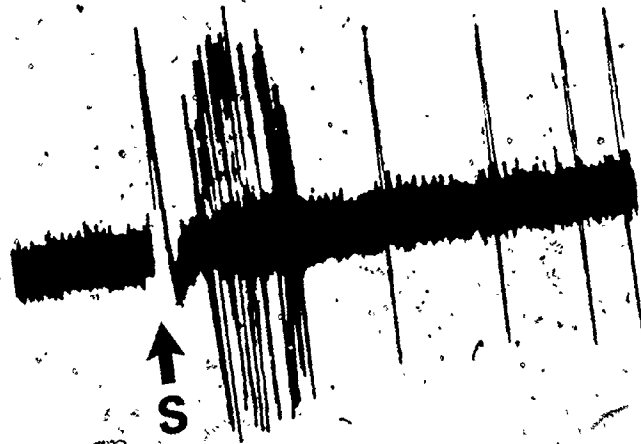
FIGURE 8

Stimulation of the VTA with single pulses elicited in about half of the neurons in nucleus accumbens various patterns of responses. Shown in this figure are peristimulus time histograms illustrating the various patterns of responses. A) Excitatory response. B) Inhibitory response. C) Excitatory response followed by inhibitory response. D) Inhibitory response followed by excitatory response.

Histograms were compiled from 200 sweeps at 1.2 Hz. Arrows indicate times of stimulation.

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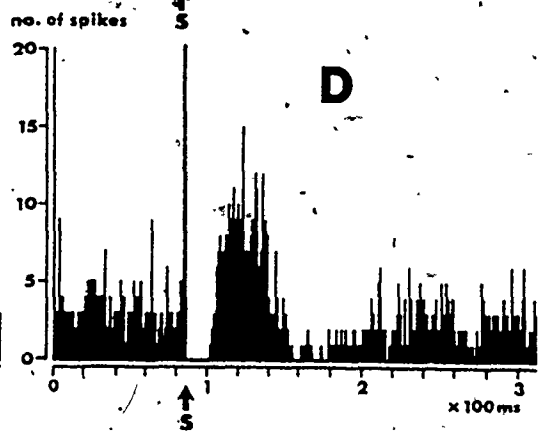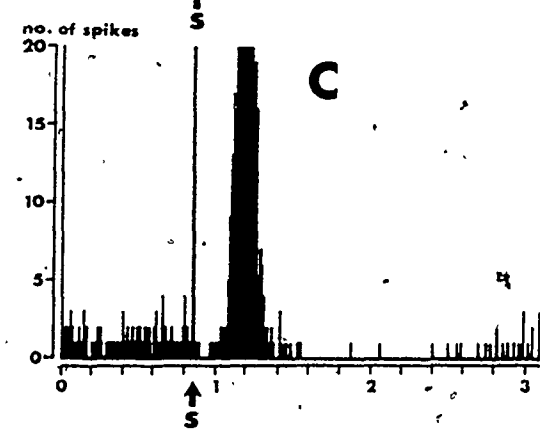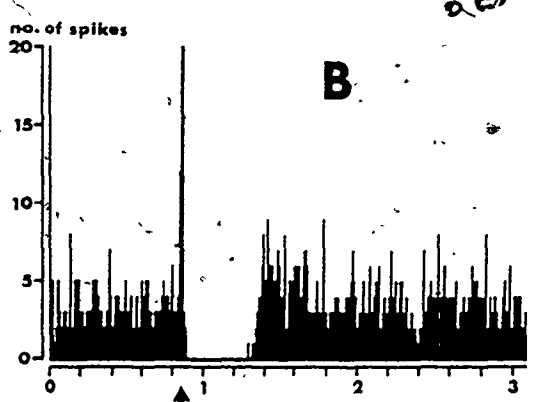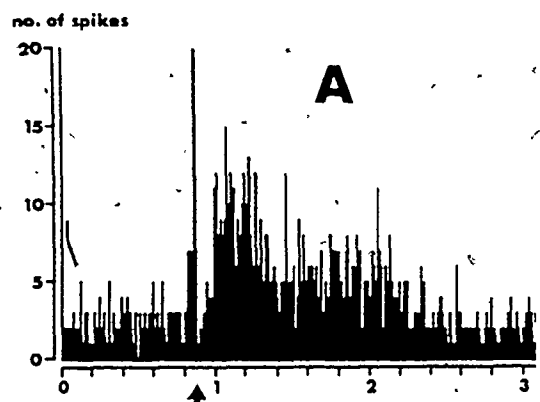
TABLE 4

Distribution of Types of Responses of Nucleus Accumbens Neurons to Single Pulse Stimulation of the Ventral Tegmental Area.

	Number showing this type of response	Mean Latency
Excitation	12 (11%)	12.4 ms
Excitation-Inhibition	7 (6%)	11.8 ms
Inhibition	19 (17%)	8.1 ms
Inhibition-Excitation	15 (14%)	6.3 ms
No Response	58 (52%)	
Total tested	111	

nucleus accumbens received convergent excitatory and inhibitory inputs from the amygdala and the VTA respectively. In the typical example illustrated in Fig 9, the neuron was excited by stimulation of the amygdala and inhibited by stimulation of the VTA. When both areas were stimulated simultaneously, the resulting response was a summation of the two responses.

The excitatory response of nucleus accumbens neurons to amygdala stimulation was attenuated in some cases by stimulating the VTA with a train of pulses prior to single pulse stimulation of the amygdala (Fig 10). The train of 10 pulses (0.15 ms, 200 - 600 μA) was delivered at 10 Hz with the last pulse delivered at 100 ms before the amygdala was stimulated. Of 31 neurons tested with this procedure, the excitatory responses to amygdala stimulation of 22 were attenuated. Of these 22 neurons 9 showed either excitatory or inhibitory responses to individual single pulse stimulation of the VTA as well. This interaction between VTA and amygdala stimulations was observed only when a train of pulses was used to stimulate the VTA. Stimulation of the VTA with a single pulse at 100 ms before stimulation of the amygdala had no effect on the excitatory response. Moreover, if the train of pulses terminated more than 500 ms before amygdala stimulation, little or no attenuation of the excitatory response was seen.

FIGURE 9

Peristimulus time histogram showing convergence of inputs
from the VTA and amygdala on a nucleus accumbens neuron.
VTA was first stimulated by a single pulse at 600 µA,
0.15 ms, followed by a single pulse stimulation of the
amygdala 100 ms later at 400 µA, 0.15 ms. The neuron was
inhibited by the VTA stimulation but excited by the amygdala
stimulation. Histogram was compiled from 250 sweeps at
1.5 Hz. Arrows mark times of stimulation.

SV - stimulation of VTA

SA - stimulation of amygdala
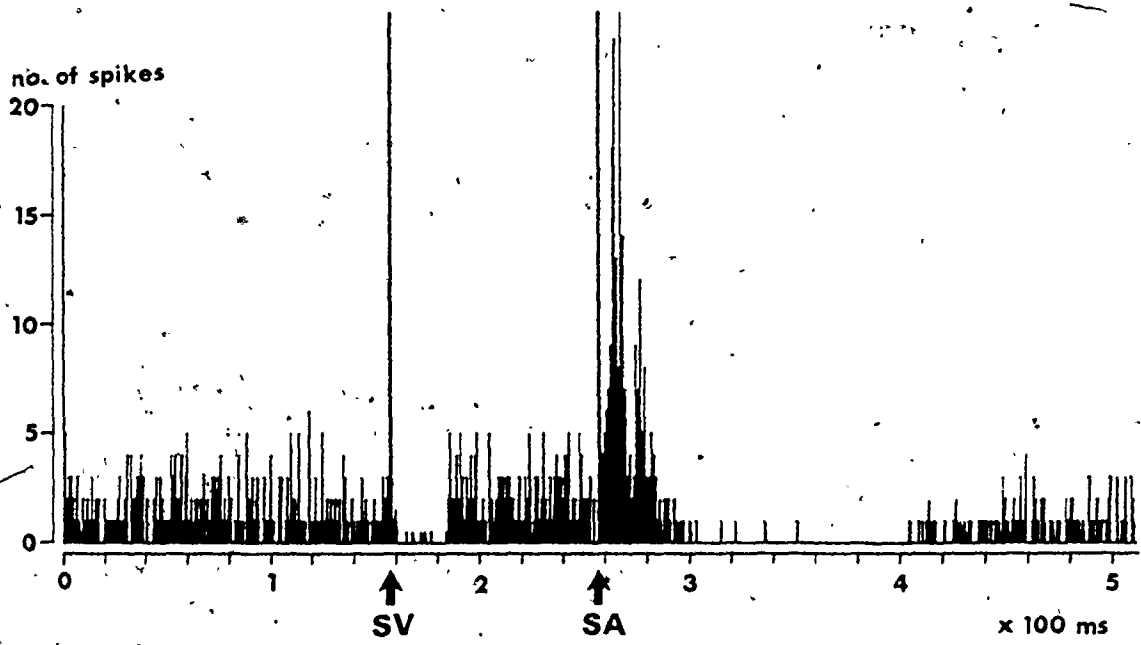
FIGURE 10

Peristimulus time histogram showing the excitatory response
of a neuron in the nucleus accumbens and its attenuation by
electrical stimulation of the VTA.   A) Excitatory response
to single pulse stimulation of the amygdala at 500 uA,
0.15 ms. B) Stimulation of the VTA with a train of 10
pulses (600 uA, 0.15 ms duration) delivered at 10 Hz prior
to stimulation of the amygdala attenuated the excitatory
response of this accumbens neuron to amygala stimulation.
Histograms were compiled from 150 sweeps.   Arrows indicate
times of stimulation.

    SV - stimulation of VTA

    SA - stimulation of amygdala
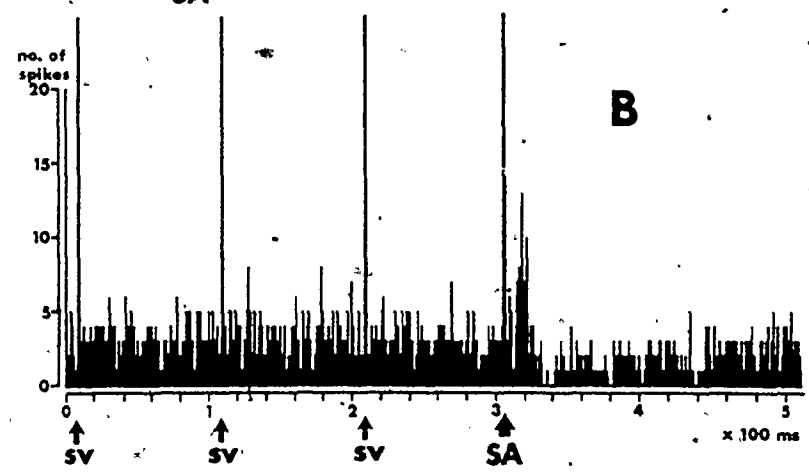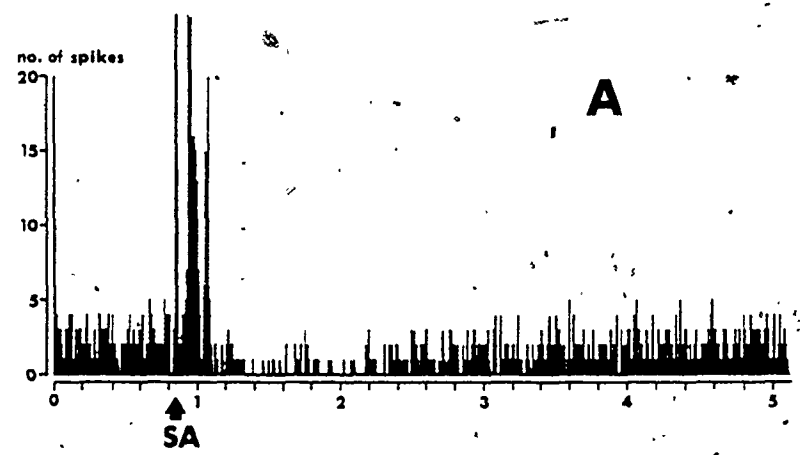
1.5 Effects of 6-hydroxydopamine and Haloperidol Treatments

on Interaction of VTA Stimulation with Responses

to Amygdala Stimulation

In a series of 10 rats, 6-hydroxydopamine was injected into the VTA 2 days prior to the recording sessions to selectively lesion cell bodies of dopaminergic neurons. In 18 accumbens neurons the activation from amygdala stimulation was not attenuated by the presentation of a train of 10 pulses to the VTA (Table 5). However, single-pulse stimulation of the VTA produced both excitatory and inhibitory responses in 5 of these 18 accumbens neurons. Another 16 cells in the same area which were not activated by amygdala stimulation also responded to single pulse stimulation of the VTA.

Another 5 rats were injected with haloperidol intraperitoneally (0.5 mg/kg) 1 h before the recording sessions. Additional injections of haloperidol (0.2 mg/kg) were administered every 2 h throughout the experiment. A total of 14 cells in the nucleus accumbens showed excitatory response to amygdala stimulation. These cells were tested for their responses to VTA stimulation. Single-pulse stimulation of the VTA produced either excitatory or inhibitory responses in 4 of these cells, but stimulation of the VTA with a train of pulses only attenuated the excitatory response of 1 of the 14 cells tested (Table 5).

TABLE 5

Effect of 6-Hydroxydopamine and Haloperidol Treatment on Interaction of VTA Stimulation with Excitatory Responses to Amygdala Stimulation.

	No treatment	From rats with 6-hydroxydopamine lesion	From rats treated with haloperidol
Total number Tested	31	18	14
Number attenuated by VTA conditioning stimulation	22	0	1
Number which responded to single-pulse stimulation of VTA	8	5	4

Shown are number of recordings obtained from the nucleus accumbens which exhibited excitation following stimulation of amygdala.

2.0 Antidromic Activation of Amygdaloid Neurons
from Nucleus Accumbens

Recordings were obtained from 82 neurons in the basolateral nucleus of the amygdala and their responses to electrical stimulation of the nucleus accumbens were tested. These neurons were mostly quiescent, and were observed only when stimulation produced antidromic spikes. Of the 82 neurons tested, 6 showed orthodromic responses (5 excited, mean latency = 8.7 ms, 1 inhibited, latency = 11 ms) to stimulation of the nucleus accumbens and 57 were antidromically activated. Two examples are illustrated in Figure 11. The latencies of the antidromic activations ranged from 5.6 ms to 24.8 ms with a mean of 14.3 ms. Distribution of the latencies is shown in Table 6.

3.0 Electrophysiological Properties of Neurons in the
Ventral Tegmental Area

3.1 Characterization of Units

Reordings were obtained from 222 neurons (31 rats) from histologically verified sites in the ventral tegmental area (VTA) (Fig 12B). Based on spike characteristics, discharge rate and discharge pattern, these neurons were of two types. Ninety-four units, designated type A, had typically long spike durations of > 2.5 ms (Fig 13A), mean discharge rates of 1-6 spikes/s and random discharge patterns. The interspike intervals recorded from this group of cells usually has a wide distribution over 20-40 ms (Fig 14A,B).

FIGURE 11

Photographs of oscilloscope tracings showing the antidromic activation of two neurons in basolateral nucleus of amygdala from the nucleus accumbens.

Upper panel: The amygdala neuron was antidromically activated by stimulation of the nucleus accumbens (at 500 uA, 0.15 ms) as indicated by the constancy of the latency (14.2 ms) and the ability of the response to follow at 200 Hz (stimulus pulses were 5 ms apart). Trace was compiled from 10 sweeps.

Calibration bars: 200 uV and 5 ms.

Lower panel: Antidromic activation of an amygdala neuron by stimulation of the nucleus accumbens as indicated by the collision of the antidromic spike with spontaneous spike. Both the stimulator and oscilloscope were triggered by a spontaneous spike (part of which is visible at beginning of trace). When the delay between the occurrence of the spontaneous spike and the presentation of the stimulus was greater (16.7 ms) than the latency of the antidromic activation, no collision occurred (upper trace). When the delay was equal to the latency of the antidromic activation (7.8 ms), collision between the spontaneous and antidromically activated spikes occurred (lower trace).

Calibration bars: 200 uV and 5 ms.
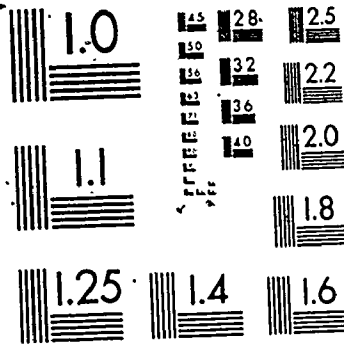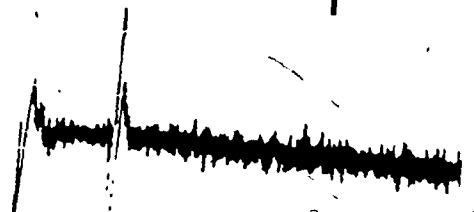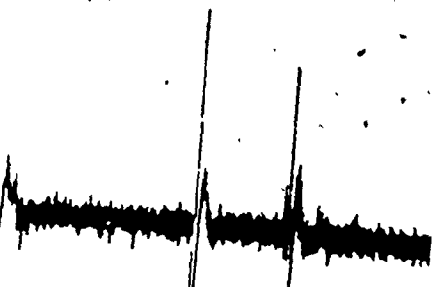
TABLE 6

Distribution of Latencies of Antidromic Activation of Amygdala Neurons from Stimulation of Nucleus Accumbens.

Latency	No. in this range
5.0– 9.9 ms	10
10.0–14.9 ms	21
15.0–19.9 ms	13
20.0–24.9 ms	13

FIGURE 12

A: photomicrograph of a coronal section of the rat brain to show a stimulation site in the nucleus accumbens where antidromic activations were obtained in the VTA on the ipsilateral side.

B: photomicrograph of coronal section of the rat brain showing a recording site in the VTA.

2 mm

FIGURE 13

Antidromic activation of neurons in the VTA by electrical stimulation of the nucleus accumbens.

A: antidromic activation of a type A neuron in the VTA. Lower trace showed cancellation of an antidromic spike by a spontaneous spike 7 ms after the stimulus. Note the relatively long latency and spike duration. Trace was compiled from 4 sweeps.

B: antidromic activation of a group B neuron in the VTA. Note the cancellation of one antidromic spike by a spontaneous spike 2 ms before the stimulus. Trace was compiled from 5 sweeps.

C: high frequency following of antidromic spike. Cell was able to follow twin pulses delivered at > 900 Hz. Note slight attenuation of spike amplitude of second spike on the upper trace and the cancellation of the second antidromic spike when stimulus was delivered at > 1000 Hz.

A   B   C

600µv
5 msec

100µv
2msec
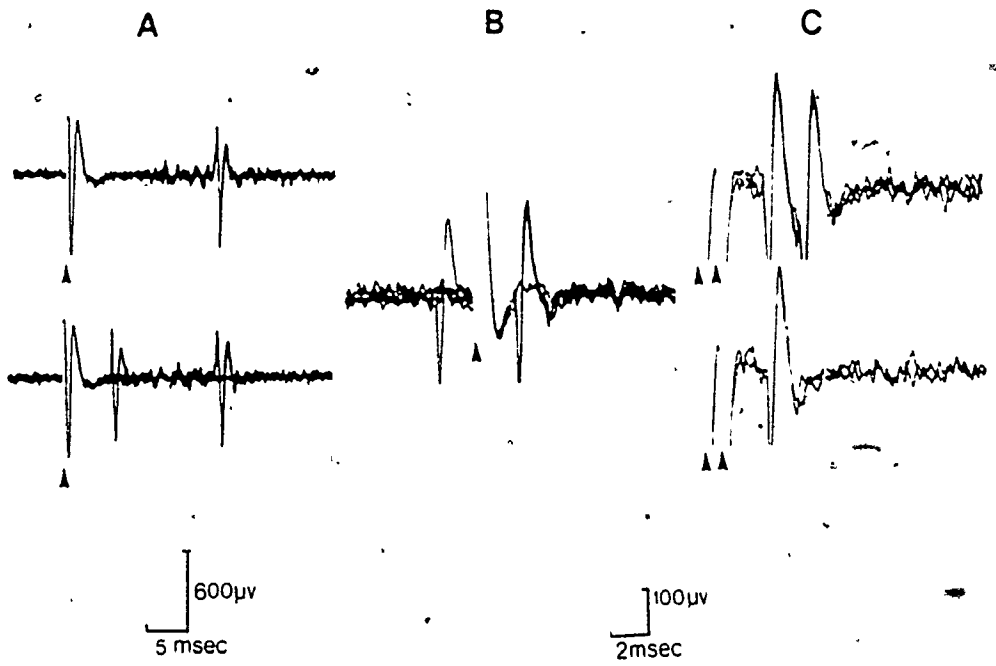
FIGURE 14

First order interspike interval histograms of three spontaneously active neurons in the VTA. Histograms have binwidths of 1 second.

A: The unit was a type A neuron and had a firing rate of 3.7±2.0 spikes/s (mean ± S.D.). The relatively wide distribution of interspike intervals illustrated the random nature of the firing pattern.

B: The unit was a bursting type A neuron and had a firing rate of 19.1±3.1 spikes/s. Note that the histogram showed two peaks: the initial peak at 10 ms (cut off at number of spikes > 25) represented the mean interspike interval within bursts, the second peak at 130 ms represented the mean interspike interval between bursts. Because of the bursting nature, the neuron had a higher firing rate than average.

C: The unit was a type B neuron and had a firing rate of 43.5±2.3 spikes/s. Note the very narrow distribution of the interspike intervals.

A

no. of spikes

Mean firing Rate: 3.7 spikes/sec
St. Dev.: 2.0 spikes/sec

B

no. of spikes

Mean firing Rate: 19.1 spikes/sec
St. Dev.: 3.1 spikes/sec

C

no. of spikes

Mean firing Rate: 43.5 spikes/sec
St. Dev.: 2.3 spikes/sec
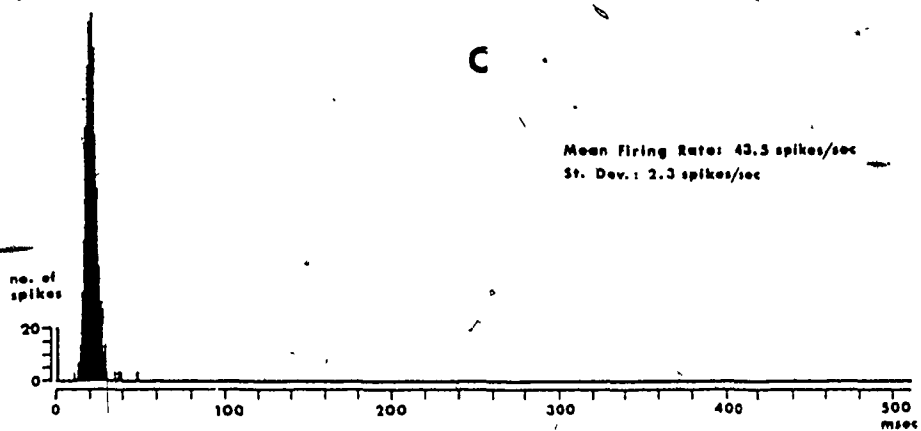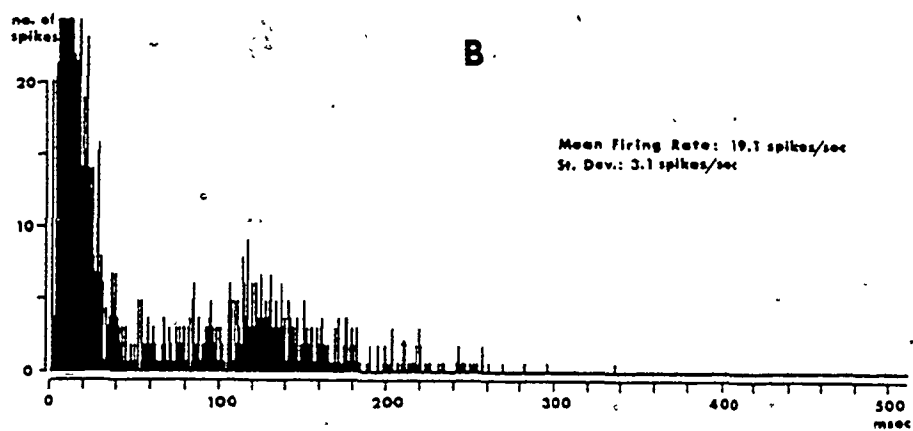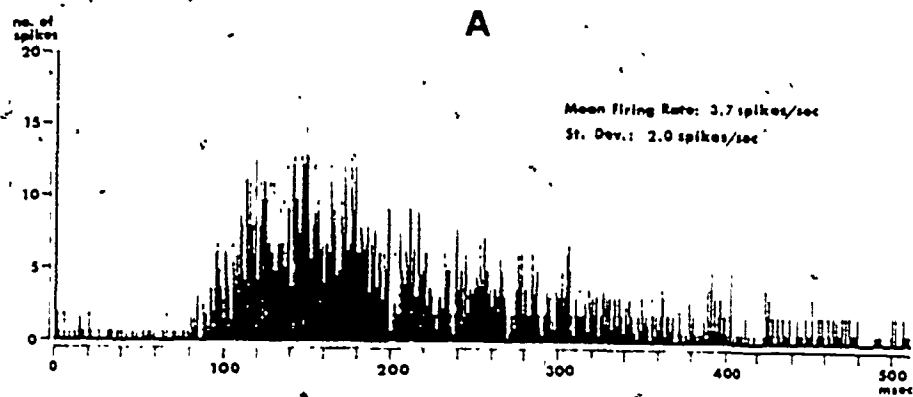
Bursting was observed in some of these slow firing units but it was not found to be a consistent feature of all neurons of this type. The remaining 128 neurons recorded from the VTA, designated type B neurons, had faster mean firing rates of 10 - 50 spikes/s, spike durations of < 2 ms and often showed rhythmical firing patterns (Fig 14C). No bursting was observed for these cells.

Of the series of 222 units, 49 were antidromically activated from the nucleus accumbens. Stimulation sites were confined to a narrow medial region of the nucleus accumbens (Fig 12A) which receives a denser projection from the VTA than the more lateral region. Of the 49 units antidromically activated, 20 were Type A neurons. The mean latency of activation of this group was 18.9 ms, corresponding to an average conduction velocity of 0.46 m/s (Fig 13A). The threshold stimulus was approximately 1 mA at 0.3 ms duration. The remaining 29 neurons that were antidromically activated were neurons of group B (Fig 13B,C). This group of neurons had a faster conduction velocity. The mean latency of activation was much shorter (4.2 ms) and the estimated conduction velocity was 2.2 m/s. The stimulus threshold was lower (approximately 0.3 mA at 0.15 ms duration). Antidromic activations of these units were usually observed only after the discharge rate of the neuron had been slowed down to approximately 5 spikes/sec with GABA (see below), otherwise collision with the frequent spontaneous spikes made it immpossible to observe the antidromic spikes.

3.2 Responses to Iontophoretically Applied Dopamine, GABA and Picrotoxin

Results of the responses of neurons in the ventral tegmental area to dopamine, GABA and picrotoxin are summarized in Table 7.

a. **Responses to Dopamine** – Sixty-four of the Type A neurons were tested for their response to iontophoretically applied dopamine. The discharge rates of 57 (89%) were reduced (Figs 15A and B) whereas the remainder were unaffected. Inhibition was usually clear only after the cell was accelerated by applying glutamate iontophoretically. Iontophoretic current used to eject dopamine was generally in the range of 40 - 60 nA. Control for the possibility of re-routing of glutamate into the dopamine barrel was done by passing the same current through a sodium channel or one that contained the vehicle only. The control currents did not produce a similar inhibition. A considerably lower percentage of Type B neurons (19 of 48, 40%) responded to iontophoretically applied dopamine. Because of their relatively faster firing rate, the inhibition could be observed without the concomitant application of glutamate.

b. **Responses to GABA and Picrotoxin** – The application of GABA reduced the rate of discharge of 141 of 142 neurons in the VTA that were tested (Table 7). Complete cessation of firing was normally observed with an iontophoretic current of 4-8 nA. Specificity of the inhibitory response was confirmed by passing current through control solutions and selective blockade with picrotoxin. In the example

TABLE 7

Characteristics of Neurons in the Ventral Tegmental Area and Their Responses to Iontophoretically Applied Dopamine, GABA and Picrotoxin.

	Type A	Type B
Number recorded	94	128
Mean firing rates	1-6 spikes/s	10-50 spikes/s
Mean conduction velocity	0.46 m/s	2.2 m/s
Inhibited by dopamine	57/64 (89%)	19/48 (40%)
Inhibited by GABA	66/66 (100%)	75/76 (99%)
Activated by picrotoxin	42/60 (70%)	32/95 (34%)

Numerators of fractions represent number of neurons that responded in the manner indicated. Denominators represent number of neurons in that category being tested.

FIGURE 15

Continuous time-frequency histograms to show activity of type A neurons in the VTA and their response to iontophoretically applied compounds.

A: Histogram to show inhibition of a type A neuron in the VTA by GABA and dopamine. GABA and dopamine (DA) were applied in alternate pulses of 10 seconds each. Picrotoxin (PIC) was applied continuously for 2 minute after the second DA pulse. Responses to two subsequent GABA pulses were seen to be attenuated but the inhibitory effect of DA remained relatively unaffected. Inhibitory responses to GABA returned after picrotoxin was shut off. Neuron had a spontaneous firing rate of 2.2 spikes/s and was accelerated to about 20 spikes/s by continuous application of glutamate at 8 nA.

B: Histogram to show activation of a type A neuron in the VTA by picrotoxin and its inhibition by dopamine. Horizontal bars represent application of drugs. Picrotoxin activated the neuron for a duration of 10 minutes in this example. There was a slight attenuation of the firing rate initially, possibly a current artifact. The same neuron was inhibited by dopamine but was not affected by a control current through a sodium channel.

Histograms have binwidths of 1 s.
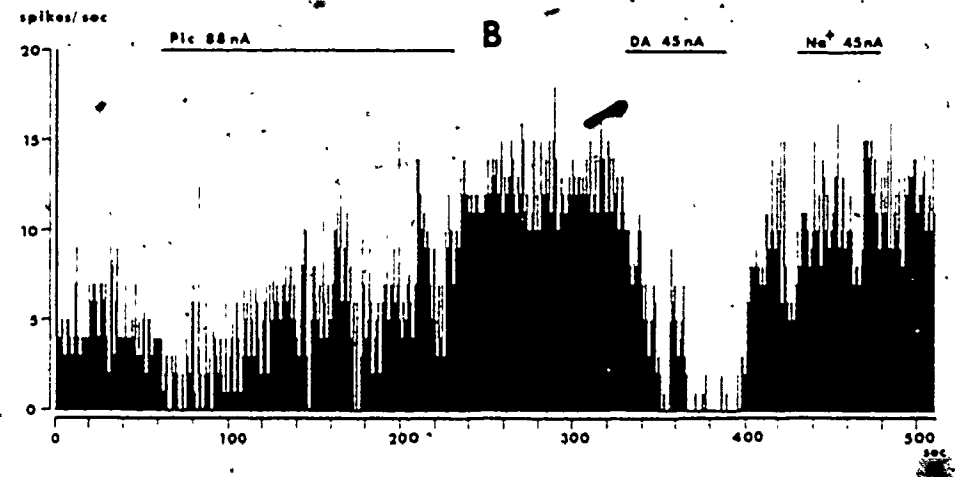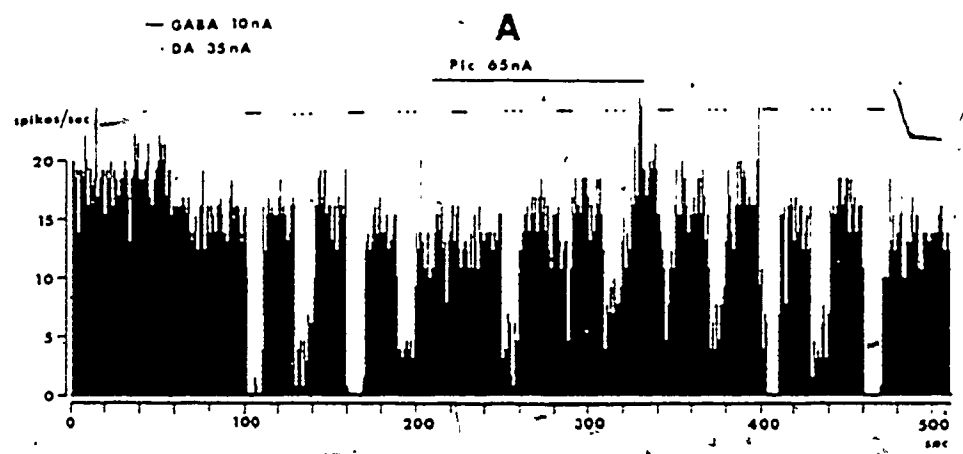
illustrated in Fig 15A, the neuron tested was a Type A neuron. It was inhibited by both dopamine and GABA, but during the application of picrotoxin the inhibition caused by GABA was blocked whereas the response to dopamine was not significantly affected. Blockade of the inhibitory effect of GABA by picrotoxin required a higher iontophoretic current (40-90 nA) compared to the current for GABA, possibly due to a lower transport number of picrotoxin. Picrotoxin was ejected alone in some cases to investigate the possibility of a tonic GABAergic input to neurons in the VTA (Table 7, Fig 15B). 42 of 60 Type A neurons (70%) and 32 of 95 Type B neurons (34%) showed an increased rate of discharge. The remainder were not affected. Responses were normally observed with an ejection current of 50-90 nA. Type B neurons activated by picrotoxin were those that had lower firing rates. Activation usually had an onset latency of 15-70 s and lasted between 1 and 10 min following 1 min application of the drug. In all cases, activation by picrotoxin was not accompanied by changes, either in the duration of individual spikes or in the firing pattern of the neuron.

3.3 Effect of Picrotoxin and Nipecotic Acid on Inhibitory Response of Dopaminergic Neurons in the Ventral Tegmental Area following Stimulation of the Nucleus Accumbens

In a series of 36 experiments, 94 Type A cells were identified from histologically verified recording sites in the VTA. Their orthodromic responses to electrical stimulation of the nucleus accumbens were investigated. It was found that 49% (46/94) of the

Type A cells tested were inhibited (Figs 16A and 17A), 16% (15/94) were excited and the remainder not affected. The threshold stimulation required to elicit these responses was between 0.3 and 0.6 mA. The onset latencies of the inhibitory responses ranged from 3 to 29 ms with a mean of 9.1 ms. The distribution was skewed towards the shorter latencies. Excitation had longer latencies, from 10 to 27 ms with a mean of 16.7 ms. Among the cells inhibited, 4 units were also antidromically activated; the mean latency of the antidromic activation was 15.8 ms. In the example illustrated in Fig 18, the cell was inhibited and excited by stimulation of the nucleus accumbens with a current of 0.6 mA, duration of 0.15 ms. When the stimulus pulse was increased to 1.2 mA, 0.3 ms duration, antidromically activated spikes were observed within the period of inhibition. The activation was shown to be antidromic by its constant latency and cancellation with the spontaneous spike used to trigger the stimulator (Fig 18).

In order to determine if the inhibition resulting from electrical stimulation of the nucleus accumbens was mediated by GABAergic neurons, picrotoxin was applied iontophoretically while recording from neurons in the VTA. The inhibitory response of 16 neurons out of 26 tested was attenuated after 20-30 min application of picrotoxin at 50 nA (Fig 16B). In 75% of the cases, concomitant to the attenuation of the inhibitory response, there was an increase in the base line firing rate, an observation that is consistent with that previously reported. However, when the same cell was activated with iontophoretically applied glutamate to a similar firing rate, the inhibitory response to nucleus accumbens stimulation was not

FIGURE 16

A) Peristimulus time histogram to show the inhibitory response of a type A neuron recorded from the VTA to electrical stimulation of the nucleus accumbens. Stimulus pulse used was at an amplitude of 400 μA, a duration of 0.15 ms. B) The inhibitory response was attenuated after a 20 minute iontophoretic application of picrotoxin. There was a concomitant increase in base line firing rate as well. Histograms were compiled from 250 sweeps at 1.5 Hz and had binwidths of 1 ms.

A

B
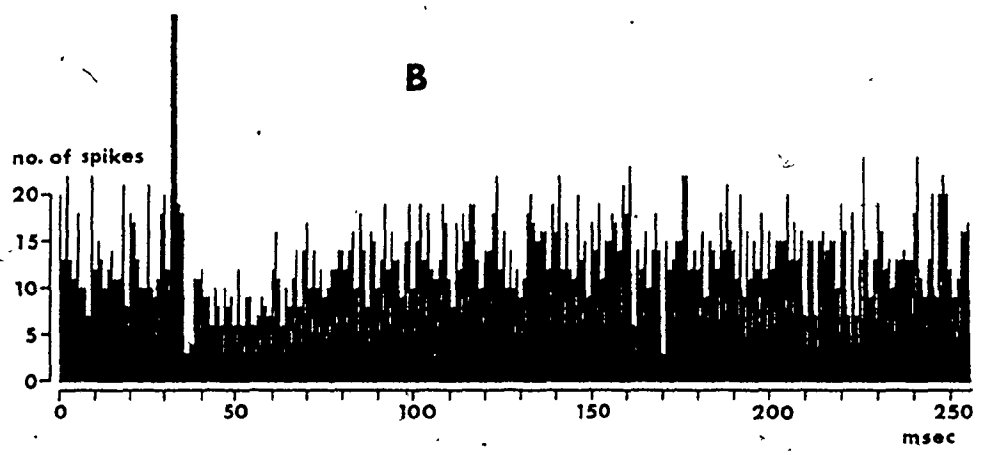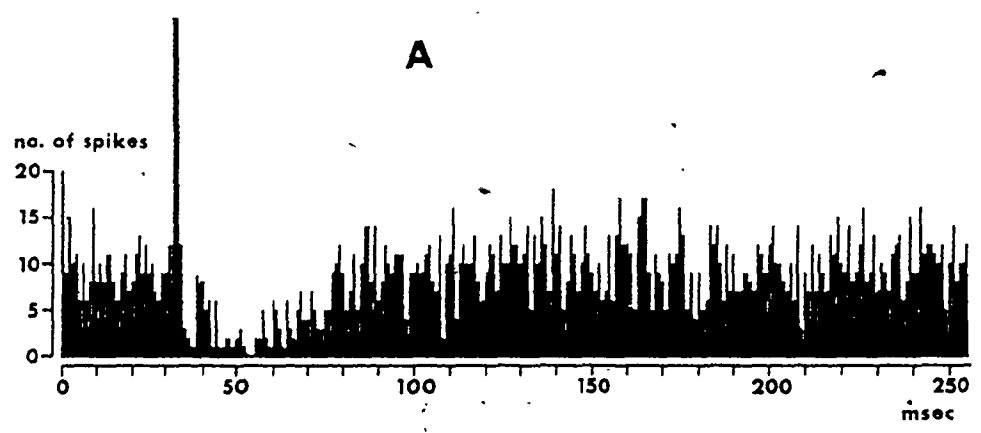
FIGURE 17

A) Peristimulus time histogram to show the inhibition of a neuron in the VTA by electrical stimulation of the nucleus accumbens. B) After 15 min application of nipecotic acid at .45 nA, the duration of inhibition was prolonged from 24 ms to 33 ms. Note that the latency of the inhibitory response has not changed. Concomitant to potentiation of the inhibitory response, there was a decrease in the baseline firing rate. Histograms were compiled from 200 sweeps at 1.5 Hz and had binwidths of 1 ms.
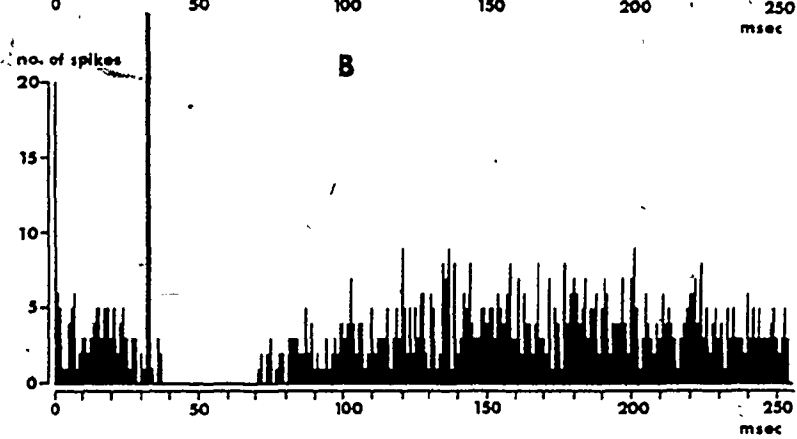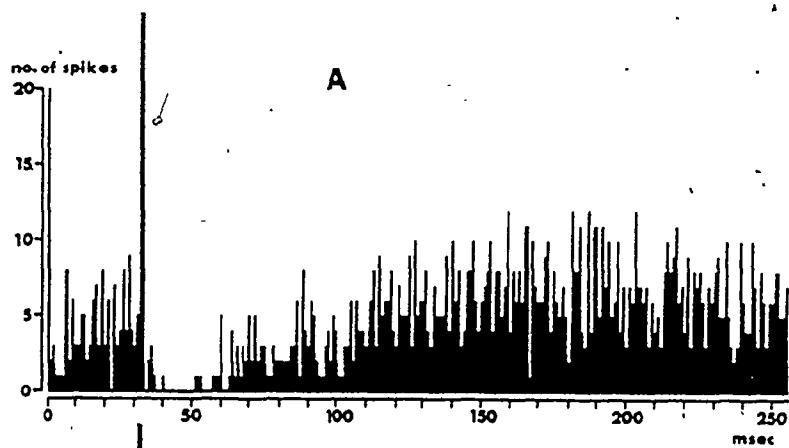
FIGURE 18

A: Peristimulus time histogram to show inhibitory-excitatory response sequence of a neuron in the VTA to electrical stimulation of the nucleus accumbens. Inset shows an oscilloscope tracing of the response compiled from 20 sweeps. Stimulus strength was 600 μA, 0.15 ms duration. Arrow indicates when stimulus was delivered. Calibration bars: 10 ms and 50 μV.

B: Perstimulus time histogram to show antidromic activation of the same neuron in addition to the orthodromic response. Inset shows oscilloscope tracing of the antidromic response. Traces were triggered by a spontaneous spike shown at the beginning of the trace. Upper trace shows antidromic spikes at 17 ms. Lower trace show cancellation of the antidromic spikes when the delay between stimulus pulse and the spontaneous spike used to trigger the pulse was less than the latency of activation. Traces were compiled from 3 sweeps.

Histograms were compiled from 250 sweeps at 1.5 Hz and had binwidths of 1 ms.

A

no. of spikes

20 —

15 —

10 —

5 —

0 —

0   1   2   3   4   5

x 100 msec

B

no. of spikes

20 —

15 —

10 —

5 —

0 —

0   1   2   3   4   5

x 100 msec
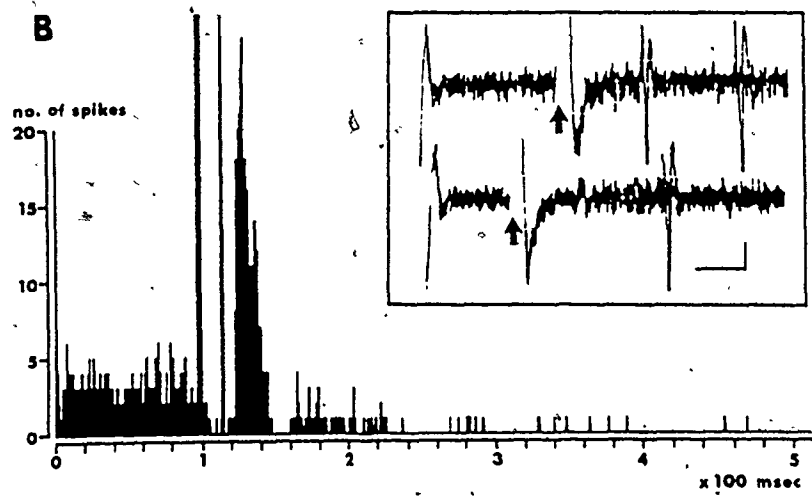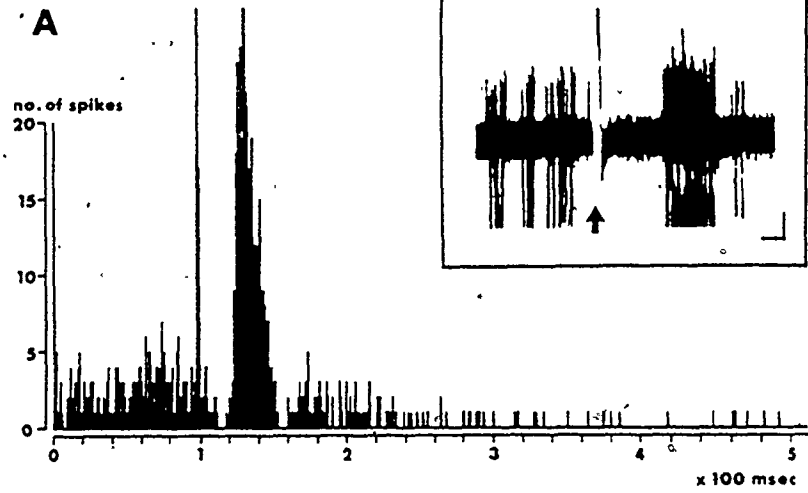
attenuated. This indicates that the attenuation of the inhibitory response by picrotoxin was not due to a non-specific increase in base line firing rate.

To further investigate the involvememt of GABAergic neurons in mediating the inhibitory effect, nipecotic acid, a GABA uptake inhibitor, was iontophoretically applied. In 9 of 14 neurons the inhibitory response from electrical stimulation of the nucleus accumbens was potentiated. As illustrated in Fig 17, a Type A neuron was inhibited by electrical stimulation of the nucleus accumbens and the duration of the inhibitory period was extended by about 30% following 15 min application of nipecotic acid at 45 nA. The latency of the inhibitory response remained at 7 ms. The potentiation was accompanied by a 23% decrease in base line firing rate. However, reducing the firing rate by the same percentage by iontophoretic application of GABA did not potentiate the inhibitory effect.

4.0 Recordings from the Ventral Pallidum

Recordings were obtained from 392 neurons (41 rats) from histologically verified sites in the ventral pallidum (Fig 19). The discharge rates of neurons in these areas were high with mean firing rates of 8 to 50 spikes/s. Activity was rhythmic and no consistent bursting characteristic was observed.

4.1 Response of Ventral Pallidal Neurons to Stimulation of Amygdala

Electrical stimulation of the amygdala produced inhibitory

FIGURE 19

Coronal sections of the rat brain to show recording sites in the ventral pallidum and neighboring areas where inhibitory and excitatory responses to amygdala stimulation were observed. Section A is approximately at 1.6 mm anterior of bregma. Subsequent sections are 0.2 mm apart. Filled circles indicate recording sites from which long -latency inhibitory responses (> 12 ms) and open circles indicate recording sites from which short latency inhibitory responses (< 12 ms) were recorded. Crosses indicate recording sites where neurons were excited. Recordings obtained from sites not within the ventral pallidum were not included in the results.

ac - anterior commissure

CP - caudate putamen

GP - globus pallidus

IC - internal capsule

SI - substantia innominata
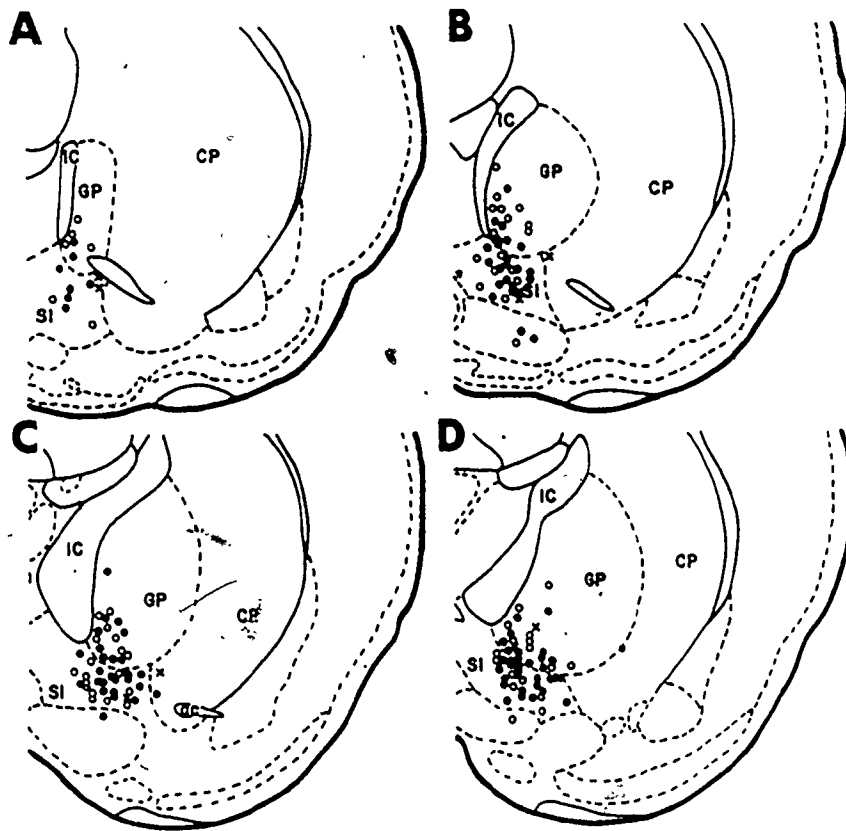
(141/392(36%)) and excitatory (42/392(11%)) responses from the neurons recorded from the ventral pallidum (Fig 20). The two types of responses differed in their mean and range of the onset latencies and the effective sites of stimulation within the amygdaloid complex. The latencies of inhibitory responses ranged from 3 ms to 26 ms. A plot of the distribution of the latencies of the inhibitory responses showed a bimodal distribution with one peak in the range of 4-6 ms and another in the range of 16-18 ms (Fig 21A). The bimodal distribution of the latencies indicated that 2 types of inhibitory responses possibly with different characteristics were present. The inhibitory responses were thus divided into 2 categories according to their onset latencies and were designated short-latency inhibitory responses (latency < 12 ms) and long-latency inhibitory responses (latency > 12 ms).

Long latency inhibitory response was observed in 90 neurons (Fig 20B). Durations of the long latency inhibitory response were from 8 to 42 ms. 21% of these responses were followed by prolonged excitation, the durations of which were often greater than 100 ms (Fig 20B). The threshold stimulus for long latency inhibitory responses ranged from 150 uA to 300 uA. The lowest threshold was obtained when the site of stimulation was within or close to the basolateral nucleus. Long latency inhibitory responses could also be elicited from stimulation sites within the basomedial nucleus but not from sites within the central nucleus of the amygdala.

Short latency inhibitory responses were observed in 51 neurons. The duration of short latency inhibitory response ranged from 11 to 45 ms. For only 4 of these cells did excitation follow the

FIGURE 20

Peristimulus time histograms to show various patterns of responses of ventral pallidal neurons to stimulation of the amygdala.

A: An inhibitory response with a short onset latency of 4 ms. About 16% of ventral pallidal neurons recorded had this type of response.

Histogram was compiled from 100 sweeps at 1.2 Hz. Stimulations were 400 μA pulses of 0.15 ms duration.

B: An inhibitory response with onset latency of 16 ms. About 21% of ventral pallidal neurons recorded had this type of response. Inhibitory responses with relatively long latencies were sometimes followed by prolonged period of excitation as illustrated in this example.

Histogram was compiled from 150 sweeps at 1.2 Hz. Stimulations were 350 μA pulses of 0.15 ms duration.

C: An excitatory response not accompanied by inhibition. A relatively long latency of 16 ms shown here is typical of this type of response. About 11% of ventral pallidal neurons tested showed this type of response.

Histogram was compiled from 100 sweeps at 1.2 Hz. Stimulations were 400 μA pulses of 0.15 ms duration.
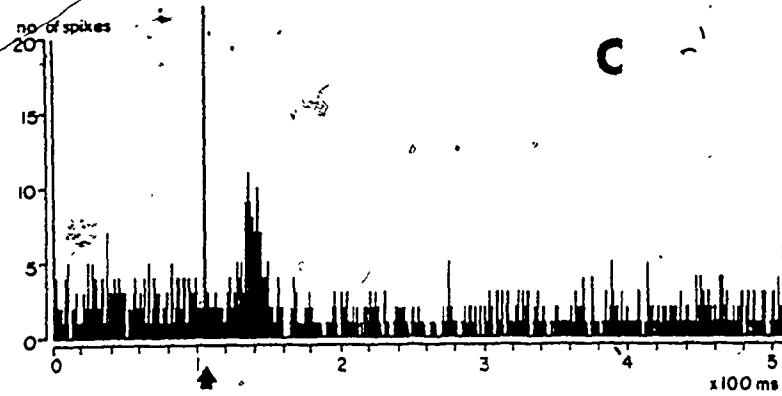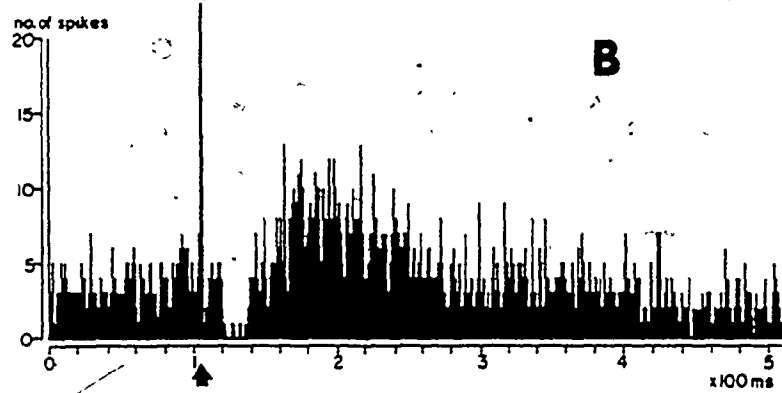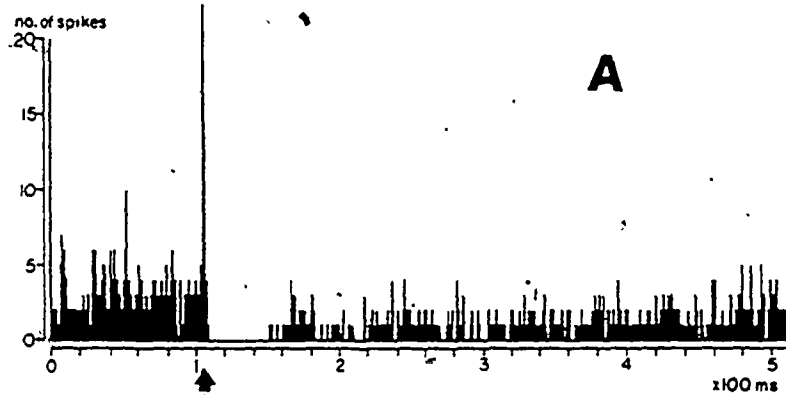
FIGURE 21

A) Histogram to show distribution of onset latencies of
inhibitory responses of ventral pallidal neurons to
stimulation of amygdala. Note the bimodal distribution of
the latencies: the distribution has peaks at 4-6 ms and
16-18 ms ranges. B) Histogram to show distribution of
latency of excitatory responses of ventral pallidal neurons
to stimulation of amygdala.

Figure A: No. of Cells vs. Latency of Inhibitory Response (msec)

Figure B: No. of Cells vs. Latency of Excitatory Response (msec)
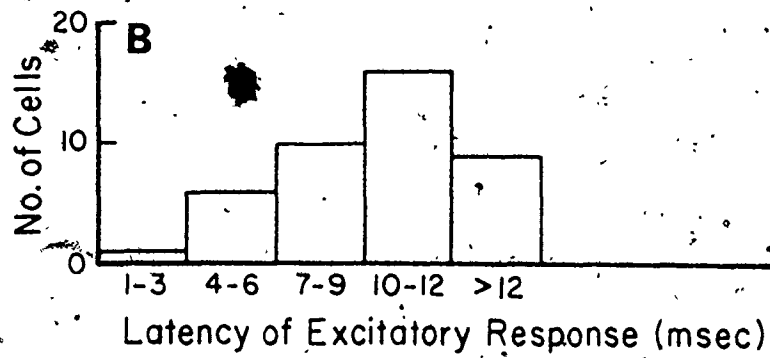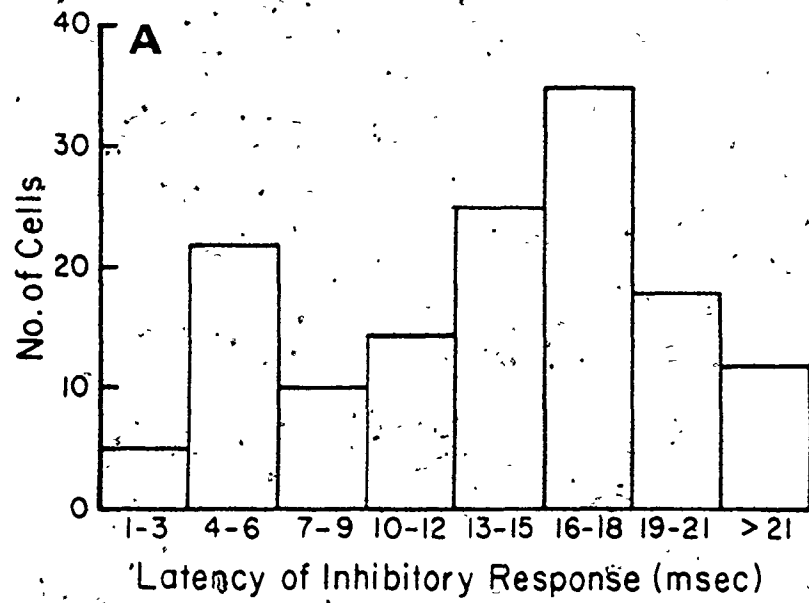
inhibition. Threshold stimuli for short latency inhibitory responses were the same as for long latency inhibitory response. Responses could be elicited from basolateral nucleus, basal medial nucleus and central nucleus.

Excitatory responses were observed in 42 (11%) neurons recorded from ventral pallidum (Fig 20C). The mean latency of excitatory responses was 11 ms and the distribution of the latencies followed that of a normal curve (Fig 21B). Duration of responses ranged from 14 to 82 ms. Threshold stimuli were from 200 to 350 μA and responses could be elicited from basolateral nucleus, basomedial nucleus and central nucleus of the amygdaloid complex.

4.2 Effect of Injection of Procaine HCl into the Nucleus Accumbens on Responses of Ventral Pallidal Neurons to Amygdala Stimulation

In 5 experiments, procaine HCl was injected into the nucleus accumbens to test the effect of blocking conduction of action potential in the nucleus accumbens on response of ventral pallidal neurons to amygdala stimulation. A total of 19 ventral pallidal neurons which responded to amygdala stimulation were tested. Of these 19 neurons, 15 were inhibited and 4 were excited by amygdala stimulation. 11 of the 15 inhibitory responses had long onset latencies and the remaining 4 had short onset latencies. Procaine HCl injected into the nucleus accumbens attenuated the response of 6 of the 11 neurons which showed long latency inhibitory responses. Figure 22 illustrates a ventral pallidal cell that was inhibited by amygdala stimulation with an onset latency of 17 ms. Injection of

FIGURE 22

A) Peristimulus time histogram showing the inhibitory response of a ventral pallidal neuron to electrical stimulation of the amygdala at 300 μA, 0.15 ms duration. B) Response of the same cell to amygdala stimulation 10 minutes after injection of 1.0 μl 20% procaine hydrochloride into the nucleus accumbens. Note attenuation of original inhibitory response. The response recovered 40 minutes after injection. Histograms were compiled from 150 sweeps and had binwidth of 1 ms. Arrows indicate time of stimulation of amygdala (SA).
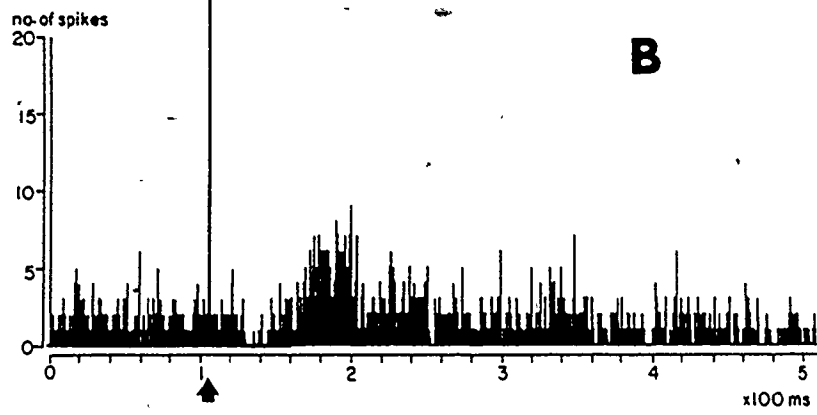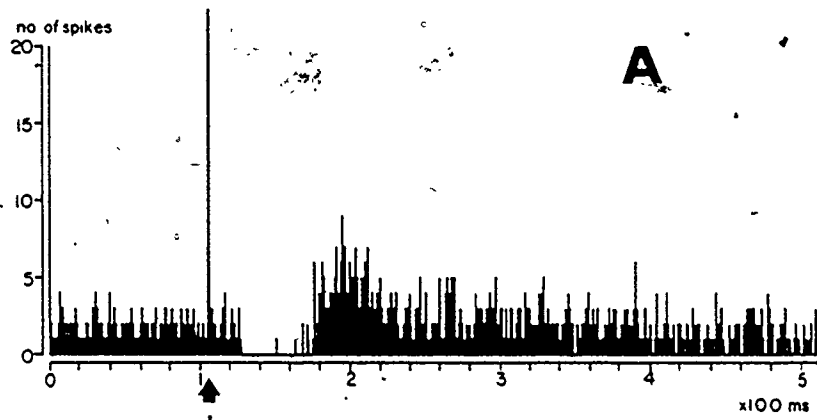
1 ul of 20% procaine HCl markedly attenuated the response (Fig 22B). Similar injections, however, did not affect short latency inhibitory response (4 cells) nor the excitatory response (4 cells).

Procaine HCl injected into the nucleus accumbens did not cause a significant change in the spontaneous activity of any of the ventral pallidal cells. The blocking of the inhibitory response by procaine HCl lasted 30 to 50 min in most cases. Responses reappeared after this period of time.

4.3 Effect of Injection of D-amphetamine into the Nucleus Accumbens on Response of Ventral Pallidal Neurons to Amygdala Stimulation

The injection of D-amphetamine into the nucleus accumbens had an attenuating effect, similar to that of procaine HCl, on the inhibition of ventral pallidal neurons following amygdala stimulation. A total of 26 ventral pallidal neurons which responded to amygdala stimulation were tested. Fifteen of these neurons were inhibited with long onset latency, 6 were inhibited with short onset latency and the remaining 5 were excited. Injection of D-amphetamine into the nucleus accumbens attenuated the long latency inhibitory responses of 8 of 15 cells observed (Fig 23). None of the short latency inhibitory responses was affected and 1 of the 5 excitatory response was attenuated.

The attenuating effect of D-amphetamine on responses of ventral pallidal neurons to amygdala stimulation was not observed in animals in which the mesolimbic dopamine neurons were lesioned with 6-hydroxydopamine. Twenty-one ventral pallidal neurons responsive to amygdala stimulation were examined in 6-hydroxydopamine lesioned rats.

FIGURE 23

A) Peristimulus time histogram to show inhibitory response
of a ventral pallidal neuron to electrical stimulation of
the amygdala at 400 μA, 0.15 ms duration. B) Peristimulus
time histogram to show response of the same neuron to
electrical stimulation of amygdala at 400 μA, 0.15 ms 5
minutes after injection of 1.5 μg of D-amphetamine in 1.5 μl
into the nucleus accumbens. The inhibitory response was
attenuated whereas the excitatory response that followed was
not affected. Histograms were compiled from 200 sweeps at
1.2 Hz, binwidths were 1 ms.
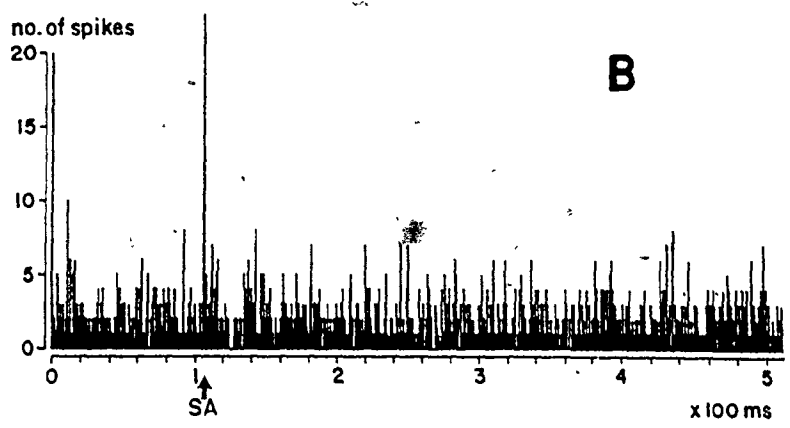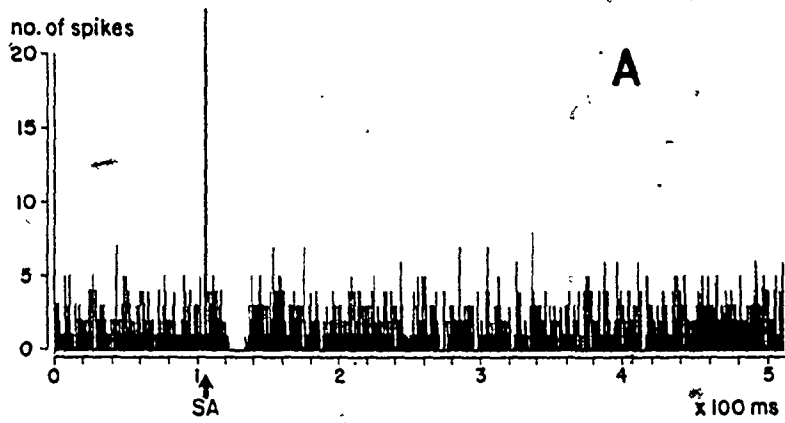
The distribution of these responses is shown in Table 8. D-amphetamine injected into the nucleus accumbens only attenuated the long latency response of 1 cell (9%), in contrast to 53% of cells affected in non-lesioned rats (X^2 = 4.26, p < 0.025). However, injection of procaine HCl into the nucleus accumbens remained effective in attenuating long latency inhibitory responses of ventral pallidal neurons to amygdala stimulation in 6-hydroxydopamine lesioned rats.

4.4 Effect of Conditioning Stimulation of Ventral Tegmental Area on Response of Ventral Pallidal Neurons to Amygdala Stimulation

Inhibitory responses of ventral pallidal neurons to amygdala stimulation were diminished by stimulating the VTA for 1 sec at 10 Hz (VTA conditioning stimulation) 1.1 sec prior to stimulating the amygdala. A total of 78 ventral pallidal neurons which showed an inhibitory response to amygdala stimulation were tested with this procedure. The inhibitory response of 41 of these cells was attenuated and the remaining 37 were not affected. As shown in Table 9, VTA conditioning stimulation had greater attenuating effect on long-latency inhibitory response (X^2 = 23.6, p < 0.001). An example of this interaction is shown in Fig 24. The neuron showed an inhibitory response at 23 ms following stimulation of the amygdala at 350 μA, 0.15 ms (Fig 24A). When the amygdala stimulation was preceded by VTA conditioning stimulation at 400 μA, 0.15 ms delivered at 10 Hz, there was a 55% reduction in the inhibition (Fig 24B).

Prominent characteristics of this interaction were: (i) A train

TABLE 8

Attenuating Effect of Injection of 20% Procaine HCl or 1% D-amphetamine into the Nucleus Accumbens on Responses of Ventral Pallidal Neurons to Amygdala Stimulation.

		Long Latency Inhibition	Short Latency Inhibition	Excitation
	Procaine HCl	6/11 (55%)	0/4 (0%)	0/4 (0%)
	D-amphe-tamine	8/15 (53%)	0/6 (0%)	1/5 (20%)
After 6-OH Dopamine Lesion	Procaine HCl	4/8 (50%)	0/3 (0%)	2/5 (40%)
	D-amphe-tamine	1/11 (9%)	0/7 (0%)	0/3 (0%)

Fractions show the number of ventral pallidal neurons of which the response to amygdala stimulation was attenuated over the number tested.

FIGURE 24

A: Peristimulus time histogram illustrating a long latency inhibitory response of a ventral pallidal neuron to electrical stimulation of the amygdala at 350 uA, 0.15 ms duration.

B: Peristimulus time histogram illustrating the effect of stimulation of the ventral tegmental area with a train of 10 pulses at 400 uA, 0.15 ms duration at 10 Hz prior to stimulation of the amygdala. Response was from the same cell as in A. Note the attenuated inhibitory response to amygdala stimulation.

Large arrows indicate times of stimulation of amygdala, small arrows indicate times of stimulation of VTA.

C: Effects of haloperidol (0.5 mg/kg I.P., 15 min before test) on the effects of VTA stimulation. Response was obtained from the same cell as in A and B. Note that a period of inhibition is discernable following stimulation of the amygdala, indicating that the VTA conditioning stimulation was not as effective in attenuating the inhibitory response as in B.

Histograms were compiled from 200 sweeps at 1.2 Hz.
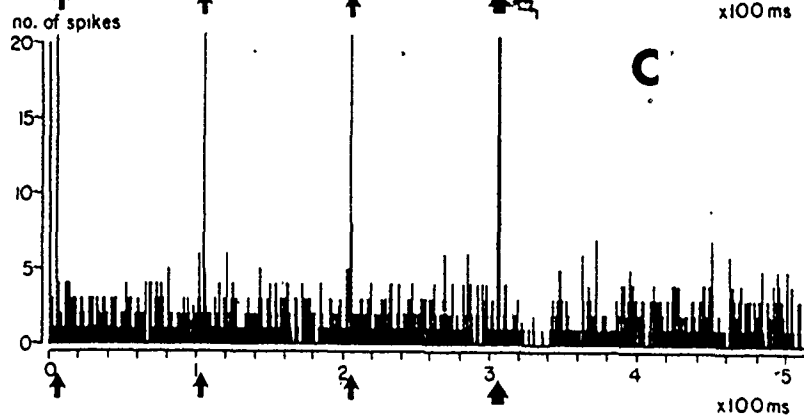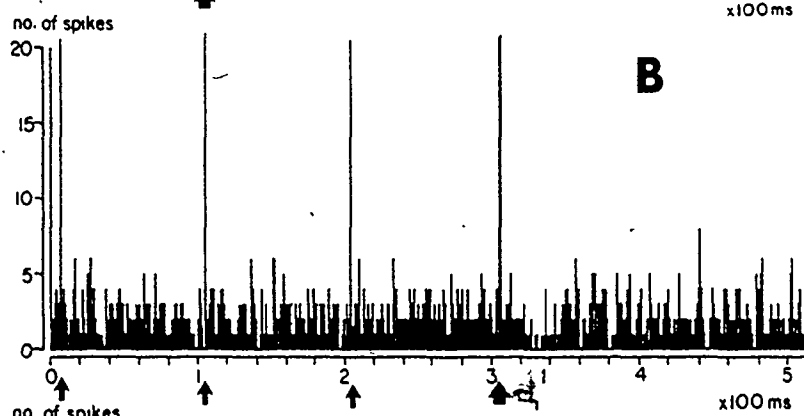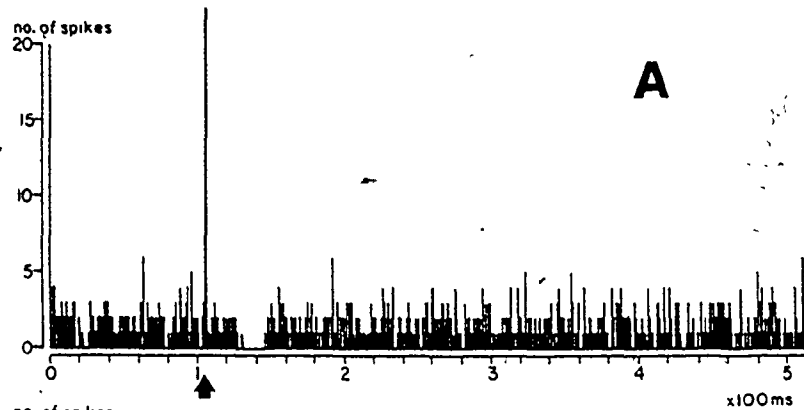
of pulses was necessary. A train of 10 pulses was routinely used in the interaction experiments. However, a train of 4 pulses was also effective in attenuating the inhibitory response in some cases (5 out of 9 cells tested) whereas a train of more than 10 pulses was no more effective than a train of 10 pulses. A single pulse was never found to be effective in attenuating the inhibitory response. (ii) If the delay between the last pulse of the train of stimulations was greater than 500 ms, the train was not effective in attenuating the inhibitory response. (iii) Inhibitory responses with onset latencies of > 12 ms were much more likely to be attenuated by the VTA conditioning stimulation than those with onset latencies of 12 ms or less (Table 9).

4.5 Effect of Haloperidol and 6-hydroxydopamine on Efficacy of Conditioning Stimulation of VTA

The attenuating effect of VTA conditioning stimulation on inhibitory response to amygdala stimulation was reduced by acute intraperitoneal injection of haloperidol (0.5 mg/kg), a dopamine receptor blocker. The attenuation was also observed in significantly fewer neurons in animals that received microinjections of 6-hydroxydopamine into the VTA two days prior to the recording experiment. Haloperidol reduced the attenuating effect of VTA conditioning stimulation in 7 of 12 neurons tested. The remaining 5 were not affected. In the example shown in Fig 24, the ventral pallidal neuron was inhibited by amygdala stimulation and the inhibitory response was attenuated by conditioning stimulation of the

TABLE 9

Effect of VTA Conditioning Stimulation on Inhibitory Response of Ventral Pallidal Neurons to Amygdala Stimulation.

		Long Latency Inhibition	Short Latency Inhibition
	Number of cells tested	51	27
	Number of cells having inhibition attenuated	37 (73%)	4 (15%)
After 6-OH Dopamine Lesion	Number of cells tested	21	3
	Number of cells having inhibition attenuated	3 (14%)	0 (0%)

VTA prior to stimulation of the amygdala. Twenty minutes after an intraperitoneal injection of haloperidol, the neuron continued to show inhibition following amygdala stimulation; but conditioning stimulation of the VTA was no longer effective in attenuating the inhibitory response (Fig 24C). The effect of haloperidol persisted in most cases for over 1 hour.

In a series of 10 rats, 6 µg of 6-hydroxydopamine was injected into VTA of the rats two days prior to the recording experiment. 21 neurons recorded from the ventral pallidum of these animals showed long latency inhibition following amygdala stimulation, but only three cells showed interaction with VTA conditioning stimulation. Three other cells had short latency inhibitory response and none was affected. A comparison of the percentages of cells showing interaction of VTA stimulation with amygdala stimulation in rats with and without 6-hydroxydopamine injection is shown in Table 9. The difference in the proportion of responses attenuated between the 2 groups was statistically significant at 0.001 level (X^2 = 19.6, p < 0.001).

DISCUSSION

Electrical stimulation of the amygdala, especially in the region of the basolateral nucleus, influenced activity of neurons in the nucleus accumbens and the ventral pallidal region. The most prominent response of accumbens neurons was excitation whereas inhibition was the predominant response of ventral pallidal neurons to amygdala stimulation. The onset latencies of the inhibitory responses of ventral pallidal neurons to amygdala stimulation showed a bimodal distribution. This suggests that the responses were elicited via two pathways. Those with relatively long latency were apparently mediated via the nucleus accumbens. Those with short latency were not. The excitatory response of accumbens neurons and the inhibitory response of ventral pallidal neurons were attenuated by stimulation of the VTA for one second at 10 Hz (VTA conditioning stimulation) prior to single pulse stimulation of the amygdala. It was shown that two types of neurons, type A and type B neurons (considered to be dopaminergic and non-dopaminergic respectively as will be discussed below), project from the VTA to the nucleus accumbens. The effect of VTA conditioning stimulation, however, seems to be dopamine mediated since the effect was blocked by haloperidol, a dopamine antagonist.

Findings from these electrophysiological experiments are in line with recent concepts developed from anatomical and behavioral experiments concerned with limbic-motor integration. In order to focus the discussion, results from the present experiments will be discussed in relation to a tenative model that the nucleus accumbens forms an interface between the limbic and motor systems and that this

link is "gated" by the mesolimbic dopamine projection from the VTA (see Fig. 1).

1. Projection from the Amygdala to the Nucleus Accumbens

It was observed in the present experiments that the amygdala has a strong excitatory influence on activity of neurons in the nucleus accumbens of the rat. These observations are consistent with those obtained by other investigators from the rabbit (DeFrance et al., 1980) and the cat (Ito et al., 1974). In studies of evoked potentials, DeFrance et al. (1980) have shown that the pathway from the amygdala to the accumbens is monosynaptic. Since the onset latencies of the excitatory responses observed in these experiments were short and relatively constant (shown by the sharp peak in the peristimulus time histograms), it appears that the pathway from the amygdala to the nucleus accumbens in the rat may be monosynaptic as well. This suggestion is supported also by the observation that amygdala neurons could be antidromically activated from the nucleus accumbens. The distribution of the latencies of the antidromic activation, however, showed a wider range than those observed for the orthodromic responses of the accumbens neurons following stimulation of the amygdala. This is interpreted to indicate that inhibitory responses that often followed the excitation (Fig. 3) were due to the activation of a different population of neurons projecting from the amygdala to the accumbens. The longer onset latency of the inhibitory response is likely due to slower conduction velocities of this group of neurons which would also account for the antidromic activations

with latencies greater than 20 ms.

It appears that the projection from the amygdala to the nucleus accumbens arises mainly from the basolateral and perhaps the basomedial nuclei of the amygdala. This is concluded because the lowest threshold for eliciting a response in accumbens neurons was obtained when the stimulating electrode was placed in close proximity to these nuclei. Anatomical studies have shown heavy projection from the basolateral nucleus to the nucleus accumbens (De Olmos and Ingram, 1972; Krettek and Price, 1978a; Newman and Winnans, 1980), but only sparse projection from the basomedial nucleus has been observed. On the basis of these anatomical observations, it seems likely that responses elicited from stimulation of the basomedial and central nuclei could have been due to current spreading to the basolateral nucleus or to activation of intrinsic neurons (Ottersen, 1982) within the amygdaloid complex that activate neurons of the basolateral nucleus.

The identity of the transmitter released that caused excitation in the accumbens following stimulation of the amygdala has not been determined. Although there is evidence that allocortical and neocortical projections to the accumbens and the adjacent caudate nucleus are glutaminergic (Walaas and Fonnum, 1979b), it remains to be determined if amygdala projection to the nucleus accumbens is glutaminergic as well or not. On the other hand, since there is evidence of intrinsic GABAergic neurons within the nucleus accumbens (Fonnum et al., 1977), the frequent inhibition that follows the excitatory response could be due to activation of these GABAergic interneurons.

2. Dopaminergic Modulation of Accumbens Response to Excitatory

    Amygdala Input

Dopamine applied iontophoretically to neurons in the nucleus accumbens reduced their spontaneous or glutamate-induced activity. The result has been observed previously (Woodruff et al., 1976) and is consistent with the majority of observations in other brain areas (Connor, 1970, McLennan and York, 1967, Stone and Bailey, 1975). Although the effect of iontophoretically applied dopamine or its agonist in the striatum has been consistently reported as inhibitory, the actual postsynaptic effect of dopamine as a transmitter remains controversial. A number of investigators have concluded that dopamine is an excitatory transmitter (Kitai et al., 1976, Assaf and Miller, 1977, York, 1979) but most others consider dopamine to be inhibitory (Moore and Bloom, 1978, Connor, 1970, Woodruff et al., 1976).

It is difficult to explain the discrepancy in these findings although a number of investigators have reviewed the subject in an attempt to resolve the issue (Moore and Bloom, 1978, York, 1979). Results from the present experiments, however, neither support the contention that dopamine is an excitatory transmitter nor that it is inhibitory. Instead, an entirely different mode of action of dopamine was observed. Electrical stimulation of the VTA with single pulses produced a variety of responses in the nucleus accumbens which included both excitation and inhibition. None of these responses, however, was sensitive to haloperidol. Moreover, the responses could be observed in rats in which dopamine neurons of the VTA were destroyed by 6-hydroxydopamine. These results indicate that the

responses of accumbens neurons following single pulse stimulation of the VTA were not due to activation of the AlO dopamine neurons but rather to a group of non-dopaminergic neurons projecting from the VTA. The present data also suggest that dopamine released in the nucleus accumbens by stimulation of the VTA did not cause a significant change in the spontaneous activity of the accumbens neurons but instead produced an attenuating effect on afferent input (see below).

In addition to suppressing the spontaneous firing rates, iontophoretically applied dopamine caused a marked attenuation of the response of accumbens neurons to the excitatory input from amygdala. This elicited excitatory response was much more sensitive to dopamine inhibition than was the spontaneous activity of the same cell. The percent attenuation of the elicited response was always proportionally greater than the precent reduction in the spontaneous firing rate. In addition, when stimulation of the amygdala produced excitation followed by inhibition, only the excitation was attenuated. These observations indicate that the action of dopamine was selective. The mechanism for this selectivity has not been determined but one possibility is the presence of dopamine receptors on presynaptic terminals of the excitatory neurons from the amygdala. Binding of dopamine to these receptors may cause a reduction in the amount of transmitter released thereby attenuating the postsynaptic response. This possibility is plausible since there is evidence of dopamine receptors on glutaminergic neurons projecting from the neocortex to the striatum (Schwarcz et al., 1978) and binding of dopamine to these receptors has been shown to reduce the axonal transport of glutamate

(Murrin and Robertson, 1980).

As mentioned above, single pulse stimulation of the VTA produced a variety of responses in the nucleus accumbens but none of these responses appear to be due to activation of the A10 dopamine neurons. On the other hand, the attenuating effect of VTA conditioning stimulation on the response of accumbens neurons to amygdala stimulation seems to be dopamine-mediated. Evidence from the present experiments support this hypothesis. First, the effects of VTA conditioning stimulation and that of iontophoretic application of dopamine on the excitatory response to amygdala stimulation were similar. Both produced a proportionally greater attenuation of the elicited response than the spontaneous activity. Second, injections of 6-hydroxydopamine, a specific neurotoxin for catecholamine containing neurons, into the VTA two days prior to the recording experiment abolished the attenuating effect of VTA conditioning stimulation in most units. Third, acute intraperitoneal injection of haloperidol, a dopamine receptor blocker, also abolished the attenuating effect (Table II). Thus, in contrast to observations made in the caudate nucleus, dopamine does not seem to serve as a quick "coupling" transmitter in the nucleus accumbens. Instead, dopamine seems to act as a "modulator" that changes the response of the postsynaptic neuron to another input. Such a neuromodulatory role has been described for norepinephrine (Woodward et al., 1979) and acetylcholine (Krnjevic, 1981a) in the central nervous system but has not been reported for dopamine. It must be emphasized, however, that the suggestion that dopamine behaves as a neuromodulator is a tentative one, its confirmation will require more detailed studies.

It is interesting to note that a train of pulses was necessary to produce the attenuating effect; single shock stimulation of the VTA prior to amygdala stimulation had no effect on the excitatory response. The reason for the requirement of stimulus trains to produce the attenuating effect is not known. High frequency trains have been known to be effective in producing long duration inhibitory post-synaptic potentials in ganglion cells (Libet and Kobayashi, 1969) and the technique has been used to investigate caudate response to nigral input (Connor, 1970, Hull et al., 1974). The frequency used in the caudate experiments, however, was up to 400 Hz. The low frequency (10 Hz) effect observed in the present experiments is similar to the effect of locus coeruleus stimulation on response of Purkinje cells to iontophoretically applied GABA and climbing fiber input (Waterhouse and Woodward, 1980; Woodward et al., 1979). But whereas dopamine selectively attenuates an excitatory input, norepinephrine enhances both inhibitory and excitatory responses.

Behavioral studies have shown that dopamine injected into the accumbens causes non-specific hyperactivity in rats (Pijnenburg et al, 1973) and interference with ingestive behaviors (Mogenson and Yim, 1981). It has also been suggested from pharmacological studies that the mesolimbic dopamine projection may be associated with the pathogenesis of schizophrenia (Matthysse, 1981). The correlation between the behavioral and neuromodulatory functions of dopamine has not been determined but a brief discussion will be presented later.

As mentioned above, pharmacological tests indicate that the pathway between the VTA and the nucleus accumbens may consist of both dopaminergic and non-dopaminergic neurons. To further investigate

this possibility, recordings were obtained from the VTA to examine the electrophysiological properties of neurons in this area. In addition, the suggestion from pharmacological tests that dopamine neurons in the VTA are subjected to GABAergic control (Fuxe et al., 1975, Stevens et al., 1974, Mogenson et al., 1979b), which has possible clinical relevance in the treatment of schizophrenia, was also investigated.

3.   Characterization of Neurons in VTA

Analysis of the spike characteristics and firing patterns of recordings made from neurons in the VTA confirmed that two types of neurons project from the VTA to the nucleus accumbens. Type A neurons are considered to be dopaminergic neurons, since the electrophysiological properties of this group of neurons (spike durations of > 2.5 ms, discharge rates of < 10 spikes/s and typical conduction velocity of 0.5 m/s) are remarkably similar to those of dopaminergic neurons in the substantia nigra pars compacta (Groves et al., 1978, Guynet and Aghajanian, 1978). Recordings obtained from neurons in the substantia nigra pars compacta which showed these properties were initially presumed to be made from dopaminergic neurons for the following reasons:

1)   it has been known from histofluoresence experiments that dopaminergic cell bodies are located in the substantia nigra pars compacta (Dahlstrom and Fuxe, 1964),

2)   these neurons could not be detected following injection of 6-hydroxydopamine, a neurotoxin for dopamine containing neurons, into

the substantia nigra (Bunney et al., 1973),

3) neuroleptics accelerated the discharge rate of these neurons whereas apomorphine slowed their discharge rate, an observation that is suggested to be characteristic of dopamine neurons due to the presence of dopamine autoreceptors on these neurons (Bunney et al., 1973),

4) conduction velocity of these neurons ·was consistent with histological data which showed that axons of dopamine neurons are fine and non-myelinated (Hokfelt and Ungerstedt, 1973).

Grace and Bunney (1981) recently confirmed that the electrophysiological properties described above are adequate criteria for identifying recordings made from dopaminergic neurons. They injected L-DOPA intracellularly into neurons in the substantia nigra and showed that only those cells with electrophysiological properties described above displayed intense fluorescence afterwards. Similar observations in the VTA were later reported by Wang (1981). Given that these electrophysiological properties are characteristic of dopamine neurons, it is therefore concluded that Type A neurons were A10 dopaminergic neurons.

The nature of Type B neurons has not been determined. Since their electrophysiological properties (spike duration < 2 ms, discharge rat > 20 Hz, typical conduction velocity 2.2 m/s) are considerably different from those of Type A neurons, they are considered non-dopaminergic neurons. The presence of non-dopaminergic neurons ·in the VTA has recently been reported by a number of investigators as well (Deniau et al., 1980, Maeda and Mogenson, 1981, German et al., 1980, Wang, 1981, Swanson, 1982). As discussed above,

the nucleus accumbens likely receives dopaminergic and non-dopaminergic projections from the VTA. This is confirmed by the observation that both Type A and Type B neurons could be antidromically activated by stimulation of the nucleus accumbens. Indeed, Swanson (1982), using immunoflouresence technique, estimated that about 15% of neurons projecting from the VTA to the nucleus accumbens are non-dopaminergic.

Dopaminergic and non-dopaminergic neurons were found to be homogeneously distributed in the VTA. By contrast, dopaminergic neurons in the substantia nigra are concerntrated in a narrow band in the dorsal region known as the pars compacta. Non-dopaminergic neurons on the other hand, occupy the ventral part or the pars reticulata.

The majority of Type A neurons were inhibited by iontophoretically applied dopamine. This observation is consistent with the suggestion that there are autoreceptors on dopamine neurons (Aghajanian and Bunney, 1977). However, a small percentage of Type B neurons were inhibited by iontophoretically applied dopamine as well. This observation suggests that dopamine receptors may be present on some of these non-dopaminergic neurons. Since there is evidence of dendritic accumulation of dopamine (Bjorklund and Lindvall, 1975) which can be released within the substantia nigra (Geffen et al., 1976), it has been suggested that there is possible dendrodendritic and dendroaxonic (Cuello and Iversen, 1978) interaction between dopaminergic and non-dopaminergic neurons. The presence of dopamine receptors on somas of non-dopaminergic neurons appears to be consistent with these suggestions. This observation also indicates

that suppression of firing rate by dopamine or apomorphine is an not adequate criterion to identify recordings obtained from dopaminergic neurons.

4. GABAergic Inhibition of VTA Neurons

Pharmacological and behavioral (Fuxe et al., 1975, Stevens et ál., 1974, Mogenson et al., 1979b) experiments suggest that dopamine neurons of the VTA have an inhibitory GABA input. Indeed, Fuxe et al. (1975) and Stevens (1975) further suggested that overactivity of mesolimbic dopamine neurons in schizophrenia might be associated with some deficit in GABA input to these neurons. For these reasons, the response of VTA dopaminergic neurons to GABA and its antagonist, picrotoxin, was investigated.

The iontophoretic application of GABA reduced the rate of discharge of 99% of all VTA neurons tested. The sample included Type A and Type B neurons (considered as dopaminergic and non-dopaminergic neurons as discussed above). The inhibition by GABA seems to be specific since iontophoretic administration of' picrotoxin, a specific antagonist of GABA at receptor sites in mammalian tissues (MacDonald and Barker, 1978), reversed the inhibition. These findings therefore suggest that both dopaminergic and non-dopaminergic neurons in the VTA receive an inhibitory GABA input. Furthermore, because picrotoxin administration alone activated the dopaminergic neurons, it is suggested that these neurons receive a tonic GABA input.

5.   Evidence of Nucleus Accumbens to VTA GABAergic Projection

A tonic GABA input to dopamine neurons in the VTA implies that the pronounced effect of dopamine on the response of accumbens neurons to other inputs is under inhibitory control. The source of this GABAergic input is therefore of considerable interest. In particular, a reciprocal pathway from the accumbens back to the VTA constitues a pathway that may provide possible feedback control of the activity of the dopaminergic neurons.

Evidence of a GABAergic projection from striatum to substantia nigra .(Crossman et al., 1973; Dray et al., 1976; Feltz, 1971b; Precht and Yoshida, 1971) has raised the possibility that GABA neurons also project from the nucleus accumbens to the VTA (Fuxe et al., 1975; Stevens et al., 1974). However, biochemical data in the literature are equivocal. Waddington and Cross (1978) observed that glutamic acid decarboxylase (GAD), the GABA synthesizing enzyme, was depleted in the VTA when kainic acid was injected into the nucleus accumbens and considered this as evidence for a GABAergic projection from the nucleus accumbens to the VTA. On the other hand, Fonnum et al. (1977) found no depletion of GAD activity in the VTA after hemisections of the medial forebrain bundle. Walaas and Fonnum (1980) recently reported only a slight decrease in GAD activity in the rostral part of the VTA following electrocoagulation of the nucleus accumbens and concluded that A10 dopamine neurons are not influenced by a GABA projection from the nucleus accumbens.

Results from the present experiments indicate that an inhibitory pathway projects from the accumbens to the VTA and that GABA is likely

the transmitter mediating the inhibition. VTA neurons were inhibited by electrical stimulation of the nucleus accumbens, an observation consistent with those of other investigators (German et al., 1980; Wolf, et al., 1978). That the inhibition from stimulation of the nucleus accumbens is GABA-mediated is suggested by the attenuation of the inhibitory effect by the iontophoretic application of picrotoxin (Fig 16) and the prolongation of the inhibitory effect by the iontophoretic application of nipecotic acid (Fig 17). This observation is in agreement with the findings of Wolf and co-workers who reported that the inhibitory response from stimulation of the nucleus accumbens was attenuated by bicuculline, a GABA antagonist. In addition, Type A neurons in the VTA (considered dopaminergic neurons as discussed above) were inhibited by stimulation of the nucleus accumbens and were also antidromically activated from the same area. Although the number of such units was small, the observations indicate that dopaminergic neurons projecting to the nucleus accumbens may at the same time receive a reciprocal GABA-mediated inhibitory input.

It is not clear from the present results whether the inhibitory innervation is a direct GABAergic projection from the nucleus accumbens or instead involves short GABAergic interneurons within the VTA. The wide distribution of the latencies suggests the presence of both monosynaptic and polysynaptic pathways. The very short latencies of a few milliseconds in most responses suggest that a direct monosynaptic pathway is very likely. Further studies involving intracellular recording techniques will be necessary to clarify the nature of the pathway. In addition to the inhibitory responses, excitation was observed in some cases. The excitatory responses

indicate that a pathway other than the GABAergic one may also project from the nucleus accumbens to the VTA. The nature of the transmitter involved is not yet known.

The nucleus accumbens does not appear to be the only structure that provides a descending GABAergic input to the VTA. Dopamine neurons in the VTA also receive inhibitory input from the preoptic area (Maeda and Mogenson, 1981), amygdala and septum (Maeda and Mogenson, 1980) although it has not been shown that these pathways are GABAergic.

6. The Nucleus Accumbens as an Anatomical Link between the Amygdala and the Ventral Pallidum

Previous anatomical experiments have demonstrated neural connections between the amygdala and the nucleus accumbens (Krettek and Price, 1978a; Groenewegan et al., 1980), between the nucleus accumbens and the ventral pallidum (Swanson and Cowan, 1975; Conrad and Pfaff, 1976; Newman and Winen, 1980; Nauta et al., 1978) as well as possible direct connections between the amygdala and the ventral pallidum (Krettek and Price, 1978a; Leonard and Scott, 1971). In the present study, it was found that ventral pallidal neurons responded to amygdala stimulation and that some of the responses observed were clearly mediated via the nucleus accumbens.

The amygdala was found to influence the ventral pallidum: 47% of ventral pallidal neurons were affected by amygdala stimulation. Although a systematic mapping of the effective stimulation sites within the amygdala was not done, the majority of the responses

observed were elicited from the basolateral nucleus of the amygdala, the same area that was shown to have an excitatory projection to the nucleus accumbens (Table 3; DeFrance et al., 1980). Electrodes occasionally placed in the basomedial or central nuclei of the amygdaloid complex also elicited responses, but a higher threshold stimulus was required and fewer ventral pallidal neurons responded. Anatomical findings are consistent with these observations; degeneration and autoradiographic studies showed that the basolateral nucleus of the amygdala projects primarily to the ventral striatum and the ventral pallidum (Krettek and Price, 1978a; Leonard and Scott, 1971).

The predominant responses of ventral pallidal neurons to amygdala stimulation were inhibitory. The latencies of the inhibitory responses observed in the ventral pallidum following amygdala stimulation showed a bimodal distribution which, together with other evidence discussed below, suggest that there is more than one pathway connecting the amygdala with the ventral pallidum. Since injection of procaine hydrochloride or D-amphetamine into the nucleus accumbens attenuated the response of some ventral pallidal neurons to amygdala stimulation, it is evident that one of the pathways by which output from the amygdala reaches the ventral pallidum is by way of the nucleus accumbens. The possibility of the drugs diffusing to the amygdala or the ventral pallidum, thereby causing the attenuating effects observed was considered. However, because only responses with relatively long latencies were affected, it seems more likely that the attenuating effect was due to the blocking of a pathway that courses through the nucleus accumbens. Procaine hydrochloride is a local

anesthetic and probably exerted its effect in the accumbens by blocking conduction of action potentials. The effect of D-amphetamine, on the other hand, is likely due to the stimulation of the release of dopamine in the accumbens since its attenuating effect was not observed after 6-hydroxydopamine lesioning of the VTA. The dopaminergic modulation of neural transmission in the nucleus accumbens was discussed in an earlier section.

It was shown in the previous section that the projection from the basolateral nucleus of the amygdala to the nucleus accumbens is excitatory. Other investigators have shown that the projection from the nucleus accumbens to the globus pallidus is primarily inhibitory and contains GABAergic fibers (Dray and Oakley, 1978; Jones and Mogenson, 1980a). Results obtained in this study are consistent with the view that stimulation of the amygdala causes excitation of GABAergic output neurons in the nucleus accumbens thereby causing inhibition of ventral pallidal neurons.

Excitatory and inhibitory responses of ventral pallidal neurons following amygdala stimulation which were not affected by procaine hydrochloride or D-amphetamine injected into the nucleus accumbens provide evidence of extra-accumbens pathways from the amygdala to the ventral pallidum. In view of widespread ventro-amygdalofugal projections coursing through the ventral pallidal area (Krettek and Price, 1978a; Leonard and Scott, 1971), the short latency responses indicative of monosynaptic projections from the amygdala to the ventral pallidum were not unexpected. It is not known, however, what pathway mediates the relatively long latency excitatory responses occasionally observed in the ventral pallidum following amygdala

stimulation. These responses were not affected by procaine hydrochloride injected into the nucleus accumbens and could be elicited from nulcei of the amygdala other than the basolateral nucleus.

7. Dopaminergic Modulation of Ventral Pallidal Response to Amygdala Stimulation

The attenuation of the inhibitory responses of ventral pallidal neurons to amygdala stimulation by injection of d-amphetamine into the nucleus accumbens and by VTA conditioning stimulation are evidently dopamine mediated. The effects were similar to the attenuation of the excitatory response of accumbens neurons to amygdala stimulation by iontophretically applied dopamine and VTA conditioning stimulation. The effect of d-amphetamine is likely due to the release of dopamine from dopaminergic terminals (Farnebo, 1971) in the nucleus accumbens since the same injection was not effective in rats in which the mesolimbic dopamine neurons were lesioned by 6-hydroxydopamine. The attenuation of the inhibitory responses by VTA conditioning stimulation has the same characteristics as the attenuation of the excitatory response of accumbens neurons by the same stimulations. The effect was likewise abolished by acute intraperitoneal injection of haloperidol and could not be observed in rats with A10 neurons lesioned by 6-hydroxydopamine. These similarities suggest that the dopaminergic modulation of pallidal response to amygdala stimulation is the result of a modulation of the response of accumbens neurons to amygdala stimulation. In other words, dopamine released in the

nucleus accumbens by d-amphetamine or VTA conditioning stimulation attenuates the excitatory response of accumbens neurons to amygdala stimulation. For those accumbens neurons that project to the ventral pallidum, an attenuation of their excitatory response is reflected as a reduction in their inhibition of neurons in the ventral pallidum.

8. Functional Significance of Pathway from Amygdala to

Ventral Pallidum via Nucleus Accumbens

Following the demonstration that output neurons of the accumbens project to the basal ganglia, there have been speculations that limbic projections to the nucleus accumbens may be functionally significant pathways by which limbic structures can influence the motor system (Graybiel and Ragsdale, 1979; Dray, 1980; Powell and Leman, 1976; Nauta, 1981; Domesick, 1981; Heimer and Wilson, 1975; Mogenson et al., 1980). Results from the present study confirm the presence of a connection from the amygdala to the ventral pallidum via the nucleus accumbens as illustrated in Fig. 1. However, whether or not the functional significance of this route is to form a link up between the limbic and motor systems as suggested by other investigators should remain tentative. Current behavioral and anatomical studies are supportive of the hypothesis to some extent, but there is also evidence that is not supportive. These contrasting interpretations are discussed in this section.

Behavioral studies have demonstrated that the projection from the nucleus accumbens to the ventral pallidum contributes to locomotor activity. In pharmacological-behavioral experiments, it was shown

that picrotoxin, a GABA antagonist, when injected into the ventral pallidum produced ambulatory activity in the rat (Jones and Mogenson, 1980b). In addition, hyperactivity elicited by microinjection of dopamine into the nucleus accumbens was attenuated by GABA injected into the ventral pallidum (Jones and Mogenson, 1980b). These observations provide evidence that a projection from the nucleus accumbens - to the ventral pallidum is involved in the initiation of locomotor activity.

It is unfortunate that little is known of the behavioral significance of the pathway from the amygdala to the nucleus accumbens. Part of the problem in investigating the role of these neural projections in behavior is the difficulty in producing a selective lesion of these pathways because of their diffuse nature. Electrophysiological observations from the present study indicate that the predominant influence the amygdala has on ventral pallidal neurons is inhibitory. According to the behavioral experiments referred to above, inhibition of the ventral pallidum produces an attenuation in ambulatory activity (Jones and Mogenson, 1980b). The amygdala, therefore, seems likely to have an inhibitory effect on ambulatory activity. In this regard, it is interesting to note that electrical stimulation of the amygdala in cats produces arrest of locomotion and general arousal (Kaada, 1972) which is consistent with this hypothesis.

From an anatomical point of view, although the connection from the amygdala to the ventral pallidum via the nucleus accumbens is clearly established in this present study, there is difficulty in defining a clear association of the ventral pallidum with the motor

system to support the contention that the route represents a limbic-motor interface. The difficulty lies mainly in the scarcity of information on the efferent projections of the ventral pallidum.

Heimer and Wilson (1975) concluded from anatomical observations that the ventral pallidum is related to the motor system. These investigators considered the allocortical to nucleus accumbens (ventral striatum) to ventral pallidum pathway to be a ventral analogue of the well known neocortical to caudate (dorsal striatum) to globus pallidus (dorsal pallidum) pathway (see Historical Review). They further inferred from this analogy and indeed recently showed (Heimer et al., 1982) that the ventral pallidum projects to the same efferent targets of the globus pallidus, namely the subthalamic nucleus and the thalamus (dorsomedial nucleus as shown in Heimer et al., 1982). The dorsomedial nucleus was shown in turn to project to the supplementary motor areas which has strong connections with the motor cortex.

An alternative pathway by which the ventral pallidum may be associated with the motor system was pointed out by Graybiel and Ragsdale (1979). They suggested that the ventral pallidum might project to the mesencephalic locomotor region of Grillner and Shik (1973). The mesencephalic locomotor region, which corresponds to the pedunculo-pontine and cuneiform nuclei in the rat, has been shown to produce stepping movements in the cat when the area was stimulated (Grillner and Shik, 1973). Projection from the ventral pallidum to this area would have a possible functional role in the initiation of locomotion. Such a pathway was recently demonstrated in the rat by Swanson et al. (1982) providing support for this hypothesis.

On the other hand, other anatomical considerations are not as supportive. The substantia innominata, of which the ventral pallidum is considered a component, projects to the lateral hypothalamus and lateral habenula nucleus (Barone et al., 1981; Palkovits and Zaborsky, 1979). A projection from the amygdala to these areas would form a limbic-basal ganglia-limbic loop that may not be directly involved in somatic activity. Kemp and Powell (1971) suggested, on anatomical grounds, that the basal ganglia integrates inputs from cortical association areas and transmit these influences back to the motor cortex. Such a view, however, has been challenged. DeLong and Georgopoulos (1981) pointed out that a segregation of the sensorimotor and frontal association projections is maintained throughout the basal ganglia and the thalamus. There is little evidence of convergence of these inputs as suggested by Kemp and Powell (1971). DeLong and Georgopoulos (1981) further suggested that instead of integration of cortical inputs, the basal ganglia performs a uniform operation upon different cortical inputs. A limbic-basal ganglia-limbic loop would be consistent with this view and would also suggest that the ventral pallidum is not a motor structure in the sense that it is directly related to control of movements.

If the accumbens forms a link between the limbic and motor systems, it probably does not represent the only pathway by which limbic structures have access to the motor system. It has recently been shown that the amygdala has a far more extensive projection to the dorsal neostriatum than was previously observed (Kelley et al., 1982). The extensive projection from the amygdala to the dorsal neostriatum, ie. the caudate nucleus, could provide another

significant pathway from this limbic structure to the motor system. Furthermore, results from this study and other anatomical works (see Historical Review) suggest that the amygdala may have direct projections to the ventral pallidum. The relative contribution of these other extra-accumbens pathways in providing limbic influences on somatic activities remains to be clarified in future studies.

The amygdala's connection with the ventral pallidum via the nucleus accumbens is, however, unique in that the mesolimbic dopamine projection interacts with afferents·from the amygdala in the accumbens as shown in this study. The response of ventral pallidal neurons to amygdala input is also modulated by the mesolimbic dopamine pathway from the VTA. The function of the mesolimbic dopamine projection has been known to be related to the pathogenesis of schizophrenia (see Hornykiewicz, 1978), and to ambulatory activity (Pijnenburg et al., 1976; Iversen, 1977; Mogenson et al., 1979b). It has also been suggested from behavioral experiments that dopamine in the accumbens may be important in the initiation of movement (Mogenson et al, 1980a; Mogenson and Yim, 1981). This view is shared by Price and others (1978) who observed that akinesia in patients with Parkinson's disease could be related to depletion of dopamine in the nucleus accumbens. Mogenson and Yim (1981) proposed that this midbrain to telencephalic dopamine projection "gates" signal transmission in the accumbens to modulate the influence which a limbic structure may have on the somatic activities of the motor system. Results from this study support the gating hypothesis, and in addition, showed more specifically that dopamine released in the accumbens gates an attenuating output from the amygdala to the ventral pallidum.

Accordingly, the ambulatory effect of dopamine in the accumbens is likely due to the blockade of inhibitory limbic output to the ventral pallidum. The role of dopamine in behavioral initiation as suggested by other investigators (Mogenson et al., 1980a) should also be interpreted as the removal of a tonic inhibition rather than as an excitatory trigger.

As a concluding remark, this study confirms a functional connection between the amygdala and the ventral pallidum by way of the nucleus accumbens. Although this may not be the only connection between the amygdala and the ventral pallidum, it is unique in that the mesolimbic dopamine projection to the nucleus accumbens gates the inhibitory influence that the amygdala has on ventral pallidal neurons. The functional role of this connection and the gating property of dopamine are likely related to limbic-motor integration as suggested by a number of investigators, but the contention must be considered tentative and remains to be further investigated.

SUMMARY

1.   Anatomical studies indicate that the nucleus accumbens, a ventral medial part of the striatum, receives afferents from a number of limbic structures and in turn sends efferents to the basal ganglia. The first objective of this study was to investigate, using electrophysiological recording techniques, whether or not the nucleus accumbens relays output from the amygdala to the ventral pallidum thereby forming a functional link between this limbic structure and the extrapyramidal motor system as suggested by the anatomical studies.

2.   Since the nucleus accumbens is also the target of a heavy dopaminergic input from the ventral tegemntal area of the midbrain, the second objective of this study was to investigate the effects of dopamine administration on the spontaneous activity of neurons in the nucleus accumbens as well as their response to amygdala input.

3.   In view of the possibility that the nucleus accumbens may form link between the amygdala and the ventral pallidum, the third objective of the study was to investigate if dopamine released in the accumbens from fibers originating in the VTA modifies response of ventral pallidal neurons to amygdala stimulation.

4.   Recordings were obtained from 206 neurons in the nucleus accumbens of urethane anesthetized rats. These neurons had slow spontaneous firing rates of less than 5 spikes/s. Spontaneous

activity of these neurons was indistinguishable from that of the more dorsally situated caudate nucleus.

5.   Electrical stimulation of the amygdala caused excitation in 113 of a sample of 206 (55%) nucleus accumbens neurons recorded. The mean latency of excitation was 10.7 ms. In 67 cases, the excitation was followed by a prolonged period of inhibition some of which lasted over 100 ms. Inhibition not accompanied by excitation following amygdala stimulation was seen in 30 (15%) of the 206 accumbens neurons recorded. The mean latency of this category of response was 16.2 ms.

6.   The most effective site within the amygdaloid complex for eliciting excitatory response in the nucleus accumbens was the basolateral nucleus. The lowest threshold for eliciting response in the accumbens from this nucleus was 200 uA.

7.   Fifty seven neurons recorded from the basolateral nucleus of the amygdala were antidromically activated by electrical stimulation of the nucleus accumbens. Latencies of the antidromic activation ranged from 5.6 ms to 24.8 ms with a mean of 14.3 ms.

8.   Dopamine applied iontophonetically caused suppression of firing rates of all nucleus accumbens neurons tested. In addition, in 42 of 53 accumbens neurons tested, their excitatory response to electrical stimultaion of the amygala was attenuated. The attenuation of the elicited response was dose dependent and was always proportionally greater than the suppression of the spontaneous

activity.

9.   Electrical stimulation of the ventral tegmental area (VTA) produced a variety of responses in neurons of the nucleus accumbens. Responses included excitation (11%), inhibition (17%) and combination of these resposes (20%). Twenty four out of a sample of 111 neurons in the accumbens received convergent excitatory and inhibitory inputs from the amygdala and the VTA.

10.   In 22 of a sample of 31 nucleus accumbens neurons that were excited by stimulation of the amygdala, the excitatory responses were attenuated if the VTA was stimulated for 1 second at 10 Hz (VTA conditioning stimulation) starting 1.1 s prior to stimulation of the amygdala. The attenuation was observed only if a pulse-train was used and the latency between the termination of the pulse-train and stimulation of the amygdala was less than 500 ms.

11.   Destruction of the mesolimbic dopaminergic neurons by injecting 6-hydroxydopamine into the VTA two days before the recording experiment abolished the attenuating effect of the VTA conditioning stimulation. The lesion, however, did not abolish the responses of accumbens neurons to single pulse stimulation of the VTA. Acute intraperitoneal injection of haloperidol during the recording experiment also abolished the effect of VTA conditioning stimulation.

12.   Since lesioning of the VTA with 6-hydroxydopamine did not abolish the responses of accumbens neurons to single pulse stimulation

of the VTA, the possibility of the presence of dopaminergic and non-dopaminergic neurons in the VTA was investigated. Recordings were obtained from 222 neurons in the VTA. Based on spike characteristics, firing rates and firing patterns, two types of neurons could be identified. Ninety four neurons with characteristically long spike durations of > 2.5 ms and slow discharge rates were designated type A neurons. The remaining 128 neurons had spike durations shorter than 2 ms and had faster firing rates of 10-50 spikes/s. These neurons were designated type B neurons.

13.   Forty nine of the 222 neurons in the VTA could be antidromically activated by stimulation of the nucleus accumbens. Of the 49 neurons antidromically activated, 20 were type A neurons and the remaining 29 were type B neurons. From the latencies of antidromic activation, it was determined that axons of type A neurons had an average conduction velocity of 0.46 m/s. By contrast, the average conduction velocity of the axons of type B neurons was found to be 2.2 m/s.

14.   Iontophoretically applied dopamine suppressed the spontaneous activity of 57 (89%) of a sample of 64 type A neurons, the remaining 7 (11%) was not affected. A considerably lower percentage of type B neurons responded to iontophoretically applied dopamine. Out of a sample of 48 tested, 19 (40%) were inhibited, the remaining 29 (60%) were not affected.

15.   Iontophoretically applied GABA reduced the rate of discharge

of 141 of 142 neurons in the VTA. Picrotoxin, a GABA antagonist, applied iontophoretically reversed the inhibition of GABA but not dopamine. In 42 of a sample of 60 type A neurons and in 32 of a sample of 95 type B neuons, picrotoxin ejected alone caused an increase in firing rate of the neurons.

16. Electrical stimulation of the nucleus accumbens inhibited 49% of a sample of 94 type A neurons in the VTA. Four of the 46 VTA neurons that were inhibited were also antidromically activated. The inhibition was attenuated by iontophoretically applied picrotoxin, a GABA antagonist but was enhanced by iontophoretically applied nipecotic acid, a GABA uptake inhibitor.

17. To determine whether or not output from the amygdala is relayed to the ventral pallidum via the nucleus accumbens, the response of ventral pallidal neurons to electrical stimulation of the amygdala was investigated. Recordings were obtained from a total of 392 neurons from the ventral pallidum. These neurons had relatively fast firing rates of between 8 to 50 spikes/s and the firing patterns were usually rhythmic.

18. Electrical stimulation of the amygdala produced inhibitory (141/392=36%) and excitatory (42/392=11%) responses in ventral pallidal neurons. Latencies of the onset of the inhibitory responses ranged from 3 to 26 ms and those of the excitatory responses from 3 to 22 ms. A plot of the distribution of the latencies of the inhibitory responses showed a bimodal distribution with one peak in the range of

4-6 ms and another in the range of 16-18 ms.

19. The inhibitory responses were divided into two categories according to their onset latencies. Those with latencies < 12 ms (51) were designated short-latency inhibitory responses whereas those with latencies > 12 ms (90) were designated long-latency inhibitory responses. It was observed that the two types of inhibitory responses had different properties.

20. Procaine hydrochloride injected into the nucleus accumbens attenuated the long-latency inhibitory responses of 6 of a sample of 11 ventral pallidal neurons to amygdala stimulation. Similar injections did not affect the short-latency inhibitory response or excitatory response.

21. D-amphetamine injected into the nucleus accumbens had a similar attenuating effect as procaine HCl on the long-latency inhibition of 8 ventral pallidal neurons following amygdala stimulation. The effect of amphetamine, however, could not be observed in rats in which the VTA was lesioned by 6-hydroxydopamine.

22. Long-latency inhibitory responses of ventral pallidal neurons to amygdala stimulation could be attenuated by VTA conditioning stimulation (see above). Thirty four of a sample of 47 ventral pallidal neurons which showed long-latency responses to amygdala stimulation were thus attenuated. By contrast, only 2 of a sample of 24 pallidal neurons which showed short-latency responses were

affected.

23.　　Lesioning of the VTA with 6-hydroxydopamine two days prior to the recording experiment abolished the attenuating effect of VTA conditioning stimulation on the inhibitory response of pallidal neurons to amygdala stimulation. Acute intraperitoneal injection of haloperidol also had the same blocking effect.

24.　　In conclusion, result of the experiments indicate that the nucleus accumbens receives a strong excitatory input from the basolateral nucleus of the amygdala. Part of the excitatory input to the accumbens is relayed as an inhibitory output to the ventral pallidum. The nucleus accumbens, therefore, forms a link between the amygdala and the ventral pallidum providing a channel by which the amygdala can influence the basal ganglia in its elaboration of motivational behavior.

25.　　The pathway between the VTA and the nucleus accumbens appears to consist of both dopaminergic and non-dopaminergic neuronal projections. The nature and functional role of the non-dopaminergic projections is not known, but dopamine released in the nucleus accumbens by the dopaminergic neurons modifies the response of accumbens neurons to the excitatory input from the amygdala. The modulation of the response of accumbens neurons to amygdala input is in turn reflected in a change of the response of ventral pallidal neurons to output from the amygdala. It is postulated that the mesolimbic dopamine projection may serve to "gate" limbic influence on

the extrapyramidal motor system via the nucleus accumbens.

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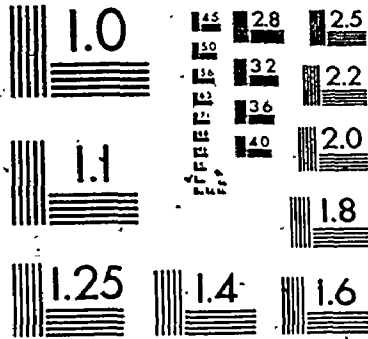
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