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MODULATION OF CORTICAL AND PYRAMIDAL TRACT
INDUCED MOTOR RESPONSES BY ELECTRICAL
STIMULATION OF THE BASAL GANGLIA

by

Roberta Ann Newton

B.S., Mary Washington College, 1969

Thesis

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INTRODUCTION

Since the early 1800's, the basal ganglia have been recognized as an extrapyramidal subcortical motor area. Much of the knowledge of basal ganglia involvement in movement has been obtained through clinical symptomology. Consideration of the basal ganglia as a pure inhibitory influence upon motor regulation was a concept generated by early researchers (24,57,58). In spite of the fact that the basal ganglia was considered an inhibitory center, it was known that the basal ganglia produced fore limb flexion or contraversive head turning. At the present, both facilitatory and inhibitory influences upon motor activity have been demonstrated (50). Physiological mechanisms underlying basal ganglia involvement in movement have been difficult to assess due to the fact that: (1) electrical stimulation and discrete surgical lesions within this subcortical area fail to produce as significant a change in locomotor activity as that observed in dysfunction; and (2) the basal ganglia are many synapses removed from sensory input and from lower motoneurons. Various approaches have been utilized to elucidate motor influences of the basal ganglia. These include: (1) ablation of one or more basal ganglia structures; (2) electrical stimulation of basal ganglia structures; (3) modulation of pre-existing motor activity by electrical stimulation of regions within the basal ganglia; (4) more recently, unit

recording in basal ganglia structures in chronic preparations during a task related movement.

Early investigators postulated that the basal ganglia exerted a steady influence upon the pyramidal tract (86). Modulation of the gamma motoneuronal system by subcortical structures pertained to the alteration of background activity on a spinal level. Since some basal ganglia dysfunctions result in the alteration of tone as well as hyperactivity, one would suspect that they modulate the gamma motoneuronal system. Granit and Kaada (26) investigated basal ganglia influences upon gamma activity but did not determine the pathway by which these influences were mediated. They did not investigate basal ganglia modulation of cortically induced increase in gamma discharge. Thus, the question was raised as to whether or not the basal ganglia actually modulated cortically induced increases in gamma activity.

Two general mechanisms based on anatomical studies are possible for the modulation of motor activity by the basal ganglia. These mechanisms are: (1) modulation of the output of cortical neurons that exert motor influences and (2) modulation of subcortical neurons that exert motor influences. The former mechanism would occur via a well defined pathway from basal ganglia structures via the thalamus to the cortex (See Literature Review). Modulation could also occur via basal ganglia projections to subcortical areas which in turn project to the spinal level. Differentiation between

these two mechanisms was accomplished in the present study by two experimental approaches. The first was an investigation of basal ganglia modulation of flexor responses of the anterior tibialis muscle elicited by electrical stimulation of the sensorimotor cortex and pyramidal tract. These investigations were carried out in intact and in decorticate cats. The anterior tibialis muscle is activated during the first phase, the flexion phase of movement (17). Therefore, this muscle was chosen for this study since a characteristic of some basal ganglia dysfunctions involves a slow onset or initiation of movement.

The second approach was an analysis of modulation of cortically induced pyramidal tract responses by conditioning shock trains delivered to various loci within the basal ganglia. Both approaches were designed to determine whether inhibitory and facilitatory motor influences of the basal ganglia occurred at a cortical or subcortical level. A major hypothesis to be tested was whether facilitatory and inhibitory regions existed within the caudate nucleus and more specifically, whether the rostral region of the caudate nucleus was inhibitory and the caudal region facilitatory as proposed by Liles and Davis (50).

REVIEW OF THE LITERATURE

Controversy concerning the functional role of the basal ganglia has evolved since Willis in 1667 postulated the corpus striatum as an integrator between the cortex and medulla oblongata. Not only has the integrator role been disputed, but also whether or not the basal ganglia influenced locomotor activity. Magendie (60) postulated that the corpus striatum controlled backward movement, whereas forward propulsion was under the control of the cerebellum. In 1867, Ferrier (60) described the relation of the corpus striatum with the cortex in terms of motor integration. During this period of time, the corpus striatum was considered a motor organ or a relay center between the cortex and spinal level from which arose fiber tracts that decussated in the medulla oblongata. This concept, then, incorporated the idea that the origin of the pyramidal tract was the corpus striatum.

Wilson (86) through histological techniques and electrical stimulation obtained no positive results regarding the possibility of basal ganglia regulation of cortically induced motor activity. By analyzing the current anatomical and physiological evidence he concluded that: (1) the corpus striatum was not dependent upon the cortex; (2) the caudate nucleus and putamen had connections between themselves; and (3) both had fiber connections with the globus pallidus. The basal ganglia were regarded as a motor center that exerted

a steadying influence upon the pyramidal tract. Major input fibers to this center were derived from the thalamus and the major efferent fibers were channeled in a caudal direction to the spinal level via a rubrospinal projection. Removal of this influence, thereby removing a steadying influence upon the pyramidal tract, would result in tremor.

Wilson's concept was replaced by a proposal of Dusser de Barenne and McCulloch (16) which implicated the basal ganglia in a suppressor circuit: area 4s of the cerebral cortex-caudate nucleus-globus pallidus-thalamus-area 4 of the cerebral cortex. Therefore, the basal ganglia and cerebral cortex were once again considered functionally dependent. Bucy, 1932 (9), organized clinical, anatomical, and physiological research to describe chorea and athetosis, both attributed to dysfunction of the basal ganglia. This pathway, as described below, also considered the basal ganglia and cortex functionally dependent. A postulated pathway independent from the pyramidal tract which principally arose from area 6 was termed the parapyramidal tract. According to Bucy, the parapyramidal tract was composed of those fibers excluding the pyramidal tract fibers that arose in areas 4 and 6 and projected to subcortical structures other than the basal ganglia. These subcortical areas projected to the spinal level. The proposed mechanism for athetosis involved a cortical-cortical loop in which fibers that arose from the suppressor areas 8s and 4s (8s - anterior to area 6;

4s - between areas 4 and 6) projected through a proposed pathway to the caudate nucleus. Fibers from the caudate nucleus passed to the globus pallidus, which in turn projected to areas 4 and 6. This proposed loop, originating in the suppressor areas of the cortex would suppress activity in cortical motor areas 4 and 6. Hence, interruption of the pathway would account for involuntary movements and hyperactivity. Ablation of area 4 disrupted the final pathway from the cortex via subcortical structures to the spinal level and thereby would provide a surgical method to decrease hyperactivity due to basal ganglia dysfunction. A more current analysis of the fiber connections of the basal ganglia will be described below.

During the development of the idea that the basal ganglia was a motor system also evolved the concept of the basal ganglia as an extrapyramidal motor system. The term, extrapyramidal, designated corticospinal projections excluding the pyramidal tract. Wilson employed the term when referring to basal ganglia dysfunctions. As the concept evolved, the terms pyramidal system and voluntary movement became analogous, whereas the extrapyramidal system was concerned with background or steadying influences upon motor activity. Thus pyramidal and extrapyramidal appeared to denote two distinct and separate systems. As a result, the terminology became misleading. Therefore, the term, extrapyramidal, is not employed in the present study.

A. Anatomy of the Basal Ganglia

Located deep within the cerebral hemispheres, the basal ganglia form a conspicuous part of the forebrain. The putamen and caudate nucleus, derived from the telencephalon, are phylogenetically newer than the globus pallidus. Collectively these two structures, putamen and caudate nucleus, are termed striatum, a descriptive term characterizing the myelinated fibers traversing these structures, thereby producing a striated appearance. The putamen and globus pallidus are collectively termed lentiform nucleus. The cytoarchitecture and anatomical connections of these structures will be discussed so that physiological results to be described can be more adequately interpreted. Figure 1 represents major fiber connections of the basal ganglia and related fiber pathways described below.

1. Cytoarchitecture of the Striatum and Globus Pallidus

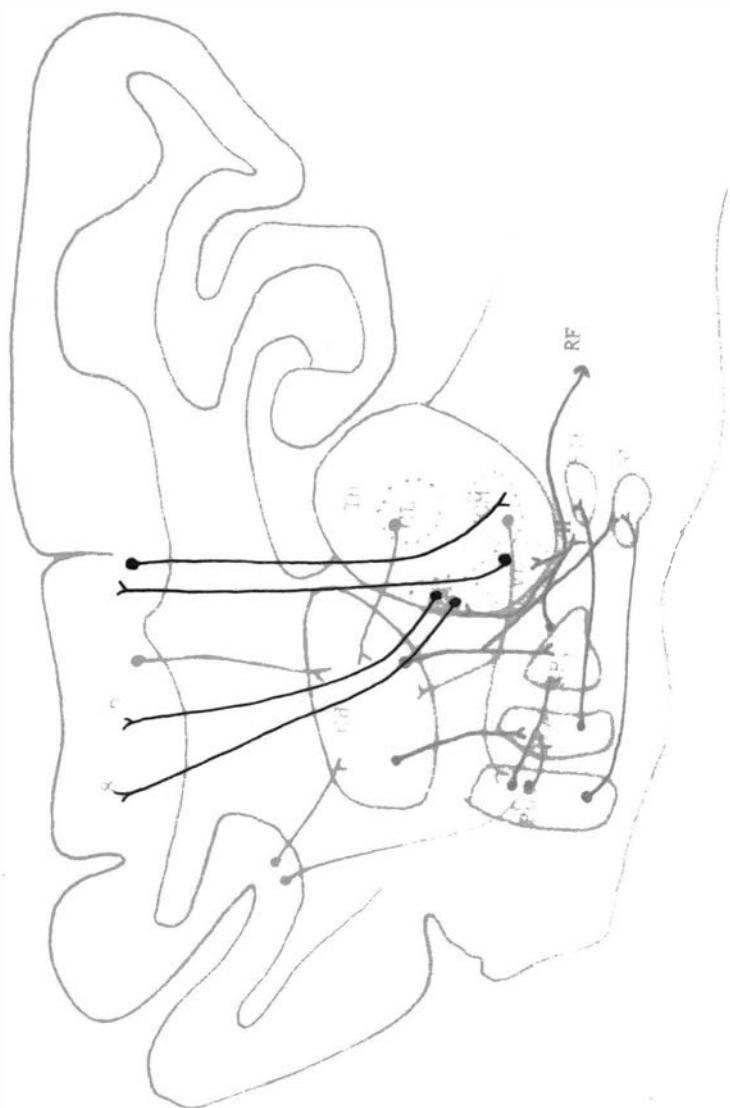
The putamen and caudate nucleus have similar cytoarchitecture. Early anatomical studies employing light microscopy and Nissl stain described the caudate nucleus as a structure containing small, densely packed cells. Extensive light and electron microscopy pertaining to the cytology of the caudate nucleus have been conducted by Kemp and Powell (38). A major characteristic of the caudate nucleus is its homogeneous structure. Approximately ninety-six percent of the cell population is composed of one cell type which is characterized by a soma diameter

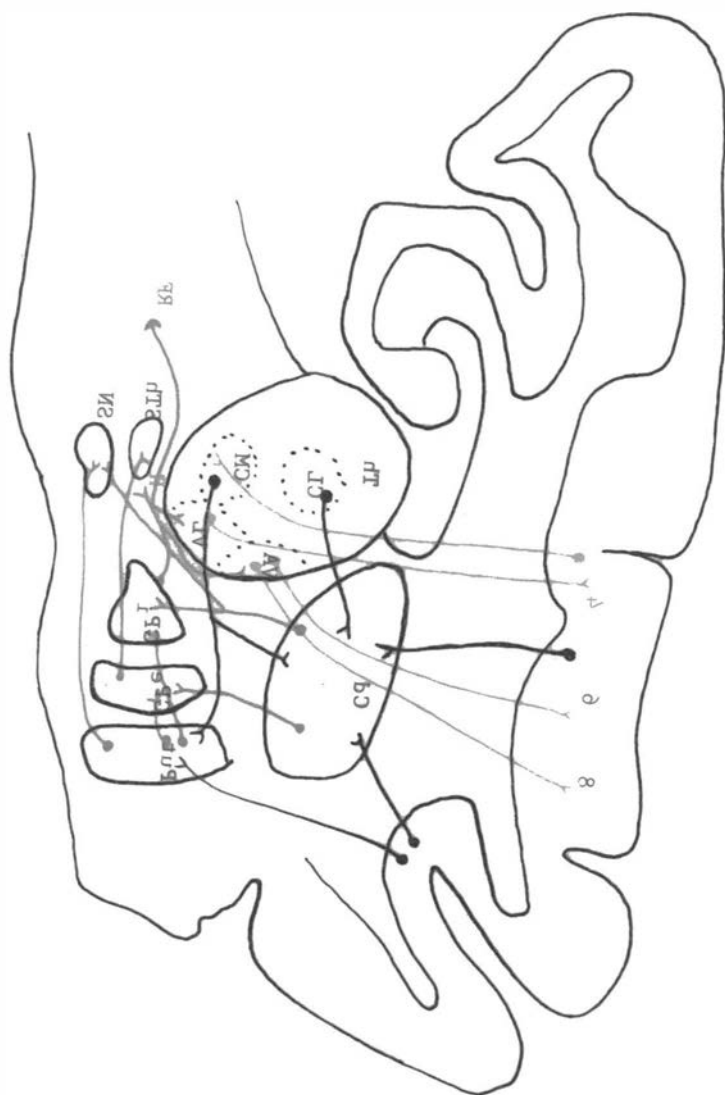
Figure 1 Fiber Projections of the Basal Ganglia and Related Structures

- A. Extrinsic fiber projections to the basal ganglia.
- B. Efferent fiber projections of the basal ganglia.
- C. Related fiber connections.

Abbreviations are as follows:

CL - centralis lateralis
 CM - centrum medianum
 Cd - caudate nucleus
 GP - external segment of the globus pallidus
 GP^e_i - internal segment of the globus pallidus
 H₁ - field of Forel
 Put - putamen
 RF - reticular formation
 SN - substantia nigra
 STh - subthalamie nucleus
 Th - thalamus





between 12 μ m and 18 μ m and a large number of dendritic spines. At locations where the heaviest concentrations of spines occur, they are difficult to differentiate with the aid of light microscopy. Five cell types, differing in soma size and density of dendritic spines, comprise the remaining four per cent of the total cell population. Both myelinated and unmyelinated axons have been described for the striatum. A characteristic of the caudate nucleus is a dense axonal plexus consisting of collaterals from the short axons of the most common cell types as well as extrinsic axons. A striking feature is that axons of the plexus cross dendrites rather than being organized in a parallel arrangement. Many of these axons form en passant contacts with dendrites, a characteristic indicative of widespread influence (42).

In primates the globus pallidus is composed of two segments, the internal segment and the external segment. The volume of the external segment of the globus pallidus represents sixty per cent of the total pallidal volume (29). In carnivores the internal segment of the globus pallidus is represented by the entopenduncular nucleus. Morgan (60) and Nauta and Mehler (62) have confirmed that the ultra-structure and fiber connections of the entopenduncular nucleus in the cat are similar to those of the internal segment of the globus pallidus in the monkey. Cells within the external pallidum are greater in number and smaller in size than those of the internal pallidum. The multipolar

cells of the internal pallidal segment have a fusiform shape and may be as large as 40 to 50 μm in diameter. Axons tend to be more heavily myelinated and larger in diameter than those of the caudate nucleus or putamen.

2. Afferent Fiber Connections of the Striatum

Fiber connections of the basal ganglia have been a subject of much controversy due to limitations in a suitable histological staining procedure for fine degenerating axons and in lesioning a subcortical area without producing secondary necrosis in surrounding tissue. Afferent fiber connections to the striatum arise from two major sources, the cortex and thalamic intralaminar nuclei, and a minor projection originates in the midbrain. An extensive, well organized projection from the entire neocortex projects in an essentially topographical manner to all parts of the caudate nucleus and putamen (85). The heaviest fiber concentration originates in motor and somatosensory cortical regions, areas which receive proprioceptive and somatosensory input. Input to the corpus striatum from the visual cortex is small. Area 5 and the supplementary motor area project bilaterally to the corpus striatum. This bilateral projection tends to be greater in nonprimates. On the other hand, in primates the frontal cortex tends to project to the rostroventral region of the caudate nucleus, whereas, the sensorimotor cortex predominately projects to the putamen, but overlap of fiber projections to both structures

is evident. Although a topographical arrangement is evident, considerable overlap and therefore convergence of afferent fibers from the cortex has been reported. This concept differs from Dusser de Barenne's concept of a non-topographical cortical projection in which suppressor bands project to the caudate nucleus and areas 4 and 6 project to the putamen.

Intralaminar thalamic nuclei, centralis lateralis and parafascicularis project to the caudate nucleus, whereas, the centrum medianum projects predominately to the putamen (4). The centrum medianum also projects to the caudate nucleus. These fiber projections are represented in Figure 1A. These thalamic nuclei, in turn receive projections from cortical areas, thereby forming a complex loop: cerebral cortex-thalamic nuclei-basal ganglia-thalamus-cerebral cortex.

The substantia nigra and a region adjacent to the red nucleus represent the origin of a third trajectory to the striatum. Controversy pertaining to the origin of these axons is due to the fact that electrolytic damage within the nigral area results in vascular damage and therefore secondary necrosis in neighboring areas. Existence for the substantia nigra projection to the caudate nucleus has been substantiated by the Falck and Hillarp (20) histochemical technique for the detection of dopaminergic fibers. Input to the caudate nucleus from the major afferent sources has been further supported by recording intracellular and unit

activity within the caudate nucleus evoked by stimulation of extrinsic sources (See below).

3. Efferent Fiber Projections of the Striatum

Literature pertaining to the fiber connections and even to the polarity of fiber connections of the caudate nucleus represent a confusing picture. Efferent fibers from the corpus striatum, which are more heavily myelinated than the extrinsic afferent axons, terminate in the globus pallidus and in the substantia nigra. Wilson's classic Marchi experiments first described the fine radiating striatal projections. Voneida (83) and Szabo (80) have presented a topographical representation of these efferent fiber connections in the monkey, and cat and monkey, respectively. Efferent fiber projections of the striatum are represented in Figure 1B.

Fibers from the medial aspect of the head of the caudate nucleus project mainly to the internal segment of the globus pallidus. These fibers course in the ventrolateral aspect of the internal capsule and a portion of the bundle terminates in the dorsomedial aspect of the internal pallidal segment. The remainder of the fiber bundle traverses in a ventromedial and caudal direction and terminates in the medial aspect of the substantia nigra. The middle portion of the head of the caudate nucleus gives rise to a fiber trajectory that traverses the ventrolateral portion of the internal capsule and enters the medial aspect of the external pallidal segment

in a fan-like manner. A portion of these fibers project in a diffuse pattern through the external segment to terminate in the internal pallidal segment. The remainder of the fibers, still present in the internal capsule, penetrates the lateral and ventral aspect of the substantia nigra and terminates in the lateral one third of this structure. Fibers from the lateral portion of the head of the caudate nucleus traverse the internal capsule in a ventrolateral and caudal direction and penetrate the laterodorsal pole of the external segment of the globus pallidus. Over half of the bundle terminates in the dorsomedial one half to two thirds of the external pallidal segment. The remainder of the fiber bundle enters the internal pallidal segment and terminates in its dorsomedial aspect. A very few fibers course the internal capsule and terminate in the anterior portion of the substantia nigra. As is evident from the above description, efferent fibers from the head of the caudate nucleus are organized in a mediolateral pattern in both the globus pallidus and substantia nigra.

Szabo also examined efferent fiber projections from the body and tail of the caudate nucleus (78,79). Fibers from the body of the caudate nucleus course in the internal capsule along the medial zone of the globus pallidus and putamen. Some fibers even traverse through the medial region of the putamen. Fiber projections from the lateral and medial region of the body of the caudate nucleus project

predominately to the external and internal segments of the globus pallidus. This topographical arrangement is not strict and overlap from the caudate nucleus to both segments of the globus pallidus occurs. Some fibers remain in the internal capsule, traverse in a ventrolateral direction, course through the cerebral peduncle and terminate predominately in the lateral and ventral regions of the substantia nigra. Efferent fiber projections from the tail of the caudate nucleus course along the ventral border of the globus pallidus toward the cerebral peduncle, then course in a ventromedial-caudal direction and terminate in the pars reticulata of the substantia nigra. These fibers contribute to the "comb system". The "comb system" consists of those fibers that perforate the cerebral peduncle.

Early researchers postulated that the putamen projected only to the globus pallidus. However, fiber projections from the putamen to both the globus pallidus and the substantia nigra have been confirmed (61). Efferent fibers from the putamen project in an organized manner, a dorsoventral and mediolateral arrangement, to the ventrolateral region of both segments of the globus pallidus. Fiber projections of the putamen also terminate in the pars reticulata of the substantia nigra. Topographical organization of fibers from the putamen to the substantia nigra has not been discerned. Nauta and Mehler (61) confirmed an internal loop of the basal ganglia: putamen-globus pallidus-centromedium

nucleus-putamen.

4. Efferent Fiber Projections of the Globus Pallidus

Pallidofugal fibers projecting to the midbrain and thalamus represent the major efferent projection from the basal ganglia. These fiber projections are demonstrated in Figure 1B. Efferent fibers from this region compose von Monakow's ansa lenticularis. As described by von Monakow in 1895, the ansa lenticularis is composed of fibers from the lentiform nucleus which perforate the cerebral peduncle and project to the medial region of the thalamus and to the subthalamic nucleus. Three divisions compose the ansa lenticularis: the dorsal division or fasciculus lenticularis, the middle or subthalamic fasciculus and the ventral or ansa lenticularis. The term, ansa lenticularis, tends to be an ambiguous term since it refers collectively to the three divisions of fibers from the globus pallidus as well as the ventral division of the fiber bundle. Von Monakow postulated that the dorsal and middle divisions originated in the putamen and the ventral division originated from the entire lentiform nucleus. Von Bechterew, 1899, proposed that the ansa lenticularis arose from the globus pallidus.

The dorsal division, fasciculus lenticularis, contains fibers from the dorsum of the internal pallidal segment which traverse the internal capsule and contributes fibers to the field H₂ of Forel. The middle division or subthalamic fasciculus penetrates the cerebral peduncle as

part of the "comb system" in a more caudal and ventral pathway and terminates in the subthalamic nucleus. Nauta and Mehler reconfirmed that this projection which originates in the external pallidal segment (monkey) possibly represents the only source of efferent fiber projection from the external segment of the globus pallidus. Efferent fiber projections of the subthalamic nucleus terminate in the internal pallidal segment, thereby forming a loop: external pallidal segment-subthalamic nucleus-internal pallidal segment. Cells in the more ventral portion of the internal pallidal segment contribute fibers to the ventral division, the ansa lenticularis. These thick fibers from the ventral division project dorsally along the medial edge of the internal capsule to field H_2 of Forel in the subthalamic region. At the subthalamic level, a division occurs in which the majority of fibers reascend forming field H_1 of Forel (Figure 1B). This division projects to the ventral aspect of the thalamus and terminates in the centrum medianum, nucleus ventralis anterior and ventralis lateralis of the thalamus. This latter fiber projection to the thalamus is also termed fasciculus thalamicus. Fiber termination of pallidal axons occurs in the pars principalis of the nucleus ventralis anterior which in turn projects to areas 6 and 8 of the cerebral cortex. Thalamo-cortical fiber projections are represented in Figure 1C. The pallidal fiber projection to the nucleus ventralis lateralis terminates in the pars

oralis, which in turn projects to area 4 of the cerebral cortex. These thalamic nuclei then are related to the motor cortex, thereby forming a cortical-basal ganglia-thalamic-cortical loop.

A second efferent fiber projection from the globus pallidus terminates in prerubral areas and the substantia nigra. At the level of the branching of the fasciculus thalamicus from the ansa occurs a fiber projection from the fasciculus lenticularis which terminates in Forel's field H in the prerubral area and a few fibers terminate in the pars compacta of the substantia nigra. A direct, but sparse, pallidorubral projection in the cat was postulated in the cat. In Nauta and Mehler's extensive studies, no fiber projection from the globus pallidus beyond the mesencephalon was noted.

As is evident from the above discussion, the existence of complex loops provides various pathways for cortical-basal ganglia integration. The centrum medianum, which receives a fiber projection from the motor cortex and the entire neocortex converge upon the caudate nucleus and putamen. The striatum in turn projects to the globus pallidus. The globus pallidus projects to the subthalamic nucleus, nuclei ventralis lateralis and ventralis anterior of the thalamus. In turn, the subthalamic nucleus projects to the internal pallidal segment, and nuclei ventralis lateralis and ventralis anterior project to cortical area 4

and cortical areas 6 and 8, respectively.

B. Ablation Studies Involving the Basal Ganglia

Lesioning within an area may be regarded as a release phenomenon in which expression of the intact systems occur or lesioning may be regarded as a deficit in activity due to the termination of influences from the ablated structure. Ablation techniques employed in the investigation of the caudate nucleus or globus pallidus offer little information unless extensive bilateral lesions are produced. Objections to ablation include: (1) the inability to restrict the lesion to the particular designated structure due to the fact that secondary effects such as disruption of vascular supply which could result in necrosis in areas distant to the lesion or such as removal of the cortex in order to approach the caudate nucleus; and (2) difficulty in interpretation when two complex areas such as the cortex and basal ganglia are ablated. Difficulty arises in attributing dysfunction to a particular structure such as the cortex or basal ganglia due to the complex interactions not only between these structures ablated but also between these and other cortical or subcortical regions.

Mettler and Mettler's (57) investigation of striatal ablation indicated that early detectable signs were not produced with small unilateral striatal lesions; but extensive bilateral lesions produced motor release phenomena characterized by hypertonia and hyperkinesia such as circling.

From ablation studies they suggested that the striatum had an inhibitory influence upon the cortex. Therefore, removal of this area resulted in hyperactivity.

Removal of various regions of the basal ganglia and cerebral cortex was employed by Kennard, 1944 (43), in an attempt to relate physiological research with clinical concepts. Deficits in motor activity due to removal of various cortical areas had been previously described. Therefore additional deficits that occurred following combined cortical-basal ganglia lesions could be partially attributed to basal ganglia dysfunction. Removal of cortical area 6 produced spasticity, transient paresis and deficit in grasp reflex, whereas flaccidity was the major post-operative characteristic of area 4 removal. Ablation of area 8 in the monkey produced a stooped posture and a fixed gaze which was followed by motor hyperactivity. Unilateral or bilateral removal of the caudate nucleus or putamen produced no evident post-operative symptoms in monkeys or chimpanzee. Removal of the caudate nucleus or putamen in conjunction with area 6 of the cerebral cortex produced spasticity slightly greater than that observed with ablation of cortical area 6 alone. A transient paresis and deficit in grasp reflex attributed to cortical area 6 lesion was present as well as tremor attributed to caudate nucleus dysfunction. Tremor was greatest at the onset of movement and diminished towards termination of movement. The tremor described has been

termed activity tremor since no tremor occurred during complete rest. Tremor resulting from combined lesions of cortical area 4 and the caudate nucleus was reduced due to paresis attributed to area 4 ablation. Parkinsonian tremor in man has been diminished or abolished by lesioning in area 4 as well as lesioning within the ventralis lateralis and ventralis anterior of the thalamus. The underlying mechanism in the reduction of tremor was attributed to the resulting hemiparesis. The role of background activity for posture and movement was then attributed to the basal ganglia. Therefore, ablation of this area terminated background activity necessary for voluntary movement and tremor and other locomotor dysfunctions resulted.

Davis, 1958 (10), Villablanca and Marcus, 1973 (82), and Mettler, 1973 (54), ablated the caudate nucleus to observe total locomotor activity as well as to deduce behavioral implications. Monkeys developed locomotor hyperactivity. No forced circling was observed, but forced pacing in confined quarters was evident. Hyperactivity in cats was identified by a tracking phenomenon in which a moving object was followed visually or by locomotion. A decrease in hyperactivity was evident during sleep. As was evident from the above description discrete lesioning within the basal ganglia did not produce dysfunctions as those observed in the clinic. Massive destruction was needed to produce hypertonia, hyperkinesia and circling which are characteristics of basal ganglia

lesioning in animals.

C. Electrical Stimulation of the Basal Ganglia

Electrical stimulation of the caudate nucleus has produced a variety of responses including contraversive head turning, circling, contralateral fore limb and hind limb flexion (23), a "melting" away or inhibition of cortically induced (55,59) or spontaneous movement (25). Electrical stimulation consisted of two types: stimulation within the subcortical area alone, and the conditioning-test technique in which basal ganglia influences upon pre-existing motor activity were observed. Mettler, et al. (56), the first to employ the conditioning (caudate nucleus)-test (cortex) technique in the investigation of the basal ganglia, obtained inhibition of cortically induced fore limb flexion. This technique provided a fruitful method for the investigation of subcortical modulation of pre-existing motor activity. A second type of conditioning-test technique involved basal ganglia influences upon reflex activity. Both facilitatory and inhibitory influences from the caudate nucleus and globus pallidus were observed upon reflex-induced knee jerk and cortically induced fore limb flexion. Facilitation and inhibition of reflex activity occurred from identical regions within the caudate nucleus. Hodes and Peacock (32, 65) postulated the role of the caudate nucleus as an inhibitory area which acted in a unilateral manner through the suppressor cortex and acted in a bilateral manner through

the hypothalamus and medial reticular formation upon the spinal level.

Recent investigation of caudate nucleus modulation of cortically induced hind limb flexion conducted by Liles and Davis (50,51) demonstrated the rostral portion of the caudate nucleus inhibited cortically induced flexion activity, whereas the caudal portion of the caudate nucleus facilitated a cortically induced flexion response (measured indirectly by myogram tension). An increase in stimulation intensity within the rostral area enhanced the cortically induced locomotor activity. This enhancement was attributed to current spread to facilitatory regions of the caudate nucleus.

Responses evoked from the caudate nucleus are not only related to the area stimulated but also to the frequency of stimulation. Responses elicited by the caudate nucleus resulting from various frequencies of stimulation are categorized into three groups: (1) low frequency range, one cycle per five seconds to ten cycles per second during which inhibition occurred; (2) middle frequency range, twenty to thirty cycles per second during which an arrest reaction occurred; and (3) high frequency range, frequency greater than thirty per second to greater than three hundred per second during which desynchronization of cortical activity occurred.

A single shock, up to ninety volts, delivered to the head of the caudate nucleus produced in the precruciate region of the cortex a short latency evoked potential followed by a series of high voltage oscillations termed "caudate-spindles" (29). These spindles having a latency of 200 to 245 msec when recorded in the ipsilateral precruciate cortex may last three seconds. In unanesthetized preparations these spindles occurred at a frequency of ten to twelve cycles per second. The ipsilateral precruciate region was the predominant region for recording "spindles", although "caudate-spindles" were recorded in other cortical sites as well as the thalamus, globus pallidus and contralateral caudate nucleus. Although "caudate-spindles" were independent of background cortical activity, a lower threshold voltage was necessary to elicit "spindles" in an animal which exhibited a synchronyous EEG. Lesioning the ventralis anterior nucleus of the thalamus disrupted spindle production while the evoked potential remained intact, thus demonstrating that the integrity of the thalamus was necessary for spindle production.

The subcortical area that elicited the evoked potential and "caudate-spindle" was disputed among researchers. Due to the approximation of the internal capsule and caudate nucleus, Goldring (25) presented evidence that stimulation of the caudate nucleus resulted in spread of current to the internal capsule. Therefore, activation of caudate-cortical projections within the internal capsule occurred.

On the other hand, Horvath and co-workers (33) demonstrated that threshold values of electrical stimulation for eliciting "caudate-spindles" in the cortex were significantly lower in the caudate nucleus and caudate nucleus-internal capsule border, than in the internal capsule.

Buchwald, and co-workers (2,7,8,30) proposed a "caudate loop", and "inhibitory" loop based upon data obtained from low frequency caudate nucleus stimulation and "caudate-spindle" production. They also attempted to relate the caudate loop to behavioral observations resulting from caudate nucleus stimulation. Low frequency stimulation of one shock per five seconds produced slow wave EEG activity. The cat passed from an alert state into a state of drowsiness or resting which was referred to as an inhibitory state. The proposed "inhibitory" loop from the caudate nucleus to the VA-VL of the thalamus and to the cortex has been postulated to antagonize the arousal system of the reticular formation.

Stimulation within the caudate nucleus at a frequency of twenty to thirty cycles per second produced an arrest reaction as evident by cessation of a task. A slow turning of the neck and trunk to the side as though the animal was looking caudalward could result and prolonged stimulation could maintain this position (30).

High frequency stimulation within the caudate nucleus produced desynchronization of the EEG related to behavioral responses representing alerting or arousal (30). As in the

case of the inhibitory response evoked by caudate nucleus stimulation, the facilitatory responses were also dependent upon the integrity of the ventralis anterior of the thalamus. Therefore, both facilitatory and inhibitory modulation of cortical activity by the caudate nucleus are mediated at least in part via the nucleus ventralis anterior. Chronic preparations, then, provide a technique for the analysis of the basal ganglia in intact, unanesthetized and unrestrained animals.

These behavioral results have also been related to intracellular and unitary cortical responses. A single shock to the caudate nucleus evoked a short depolarizing response followed by a long hyperpolarizing response in cortical cells. The characteristic long hyperpolarizing phase has been interpreted by Hull (36) as a mechanism for the reduction of synaptic noise and enhancement of excitatory inputs. A slow positive DC shift accompanied the long, hyperpolarizing phase which lasted 100 to 200 msec. If the caudate nucleus shock was paired with a shock from an afferent source (visceral or somatic) within a critical time interval, the prolonged inhibitory response (IPSP) observed in the cortical neuron was shortened. A 70 msec time interval was the critical time value during which the shortened IPSP occurred (37). "Disinhibition" was the term describing the decrease in the inhibitory period. Disinhibition was dependent not only upon the time interval between the caudate nucleus

shock and afferent shock, but also upon the number of pairings. Repeated pairings of shocks decreased the disinhibition phenomenon. Pairing two caudate nucleus shocks within a 70 msec interval reset the inhibitory period in which an EPSP and some instances cell firing occurred in response to the second shock delivered to the caudate nucleus, but an increase in the overall inhibitory duration followed. As is evident, repetitive stimulation to the caudate nucleus produces complex facilitatory and inhibitory responses at the cortical level which are consistent with the complex behavioral responses also produced by caudate nucleus stimulation.

D. Intracellular and Unit Activity of the Caudate Nucleus and Lentiform Nucleus

Recording activity within the caudate nucleus has not only aided in the analysis of temporal and spatial interrelations of various structures upon the basal ganglia, but has provided physiological confirmation of striopedal pathways. Kemp and Powell (40,41) have investigated synaptic terminations of striopedal axons. Although distribution of extrinsic axons was throughout the caudate nucleus, axon terminals of both the cortical and intralaminar nuclei projections form clusters or groups within the caudate nucleus. Lesioning studies involving the lateral and medial surfaces of the cerebral cortex demonstrated degeneration of 0.6 to 2.0 μ m diameter, finely myelinated axons which form

synapses with asymmetrical membrane thickenings on dendritic spines. Some extrinsic fibers form en passant connections. Since these thin axons were not detected in Wilson's histological preparations, he postulated that the basal ganglia were independent of the cerebral cortex. Similarly, lesioning within the intralaminar nuclei resulted in degeneration of 0.5 to 2.5 μm diameter, thinly myelinated axons which form synaptic connections with asymmetrical membrane thickenings predominately upon dendritic spines. From the above described lesioning studies and fiber connections, Kemp and Powell postulated that all projections to the caudate nucleus that form synapses with asymmetrical membrane thickenings represented extrinsic axons and therefore the axonal connections with symmetrical membrane thickenings represented intrinsic fibers. The majority of the intrinsic axons terminate on dendritic shafts or upon non-spiny regions of the intracaudate neuron. Furthermore, Kemp and Powell (39) proposed that round vesicles located in boutons with asymmetrical membrane thickenings were associated with excitation or EPSP (excitatory postsynaptic potential) activity, whereas those boutons with flat vesicles and symmetrical membranes were associated with IPSP (inhibitory postsynaptic potential) activity. Their contention was strongly supported by data demonstrating that intracellular responses of the caudate neuron to extrinsic, cortical or thalamic stimulation was an initial EPSP followed

by a long IPSP. This EPSP-IPSP sequence was paralleled by findings that the EPSP would result from direct synaptic connections from extrinsic projections and the IPSP response would result from neighboring intracaudate synaptic effects.

A characteristically low spontaneous activity in the caudate nucleus has been reported by Buchwald, et al. (4), Rocha-Miranda (68), Purpura (67), and Sedgwick and Williams (71), although the latter authors described a regular burst pattern of some units with a 100 to 120 msec burst interval. Intracellular recordings by Hull, et al. (34) also described a low frequency of firing or silent periods of caudate neurons. A comparison of caudate neuronal activity in the unanesthetized versus anesthetized preparations demonstrated that low spontaneous discharge was not a result of anesthesia. Spontaneous activity was similar in both chloralose and nembutal preparations although Segwick and Williams reported more active units with chloralose anesthesia. In deep chloralose anesthesia spontaneous activity was absent, whereas in light chloralose (60-80 mg/kg) or nembutal (35 mg/kg) anesthesia, spontaneous activity was considerably less than in the unanesthetized preparation (1). Terminology characterizing light anesthesia varied among researchers and therefore tended to be ambiguous.

Fluctuations in the resting membrane polarization level have been noted in which depolarizing or hyperpolarizing membrane shifts up to 5 mv occurred and were maintained for

several seconds to several minutes. The length of time the cell was impaled did not correlate with the length of the polarizing membrane shifts. Responses to stimulation also varied during the membrane potential shifts. During a positive depolarizing membrane potential shift, the cell would spontaneously fire, whereas during a negative membrane potential shift electrical stimulation of the cell would not necessarily elicit an action potential.

Three postsynaptic responses characterize caudate neuronal responses to various stimulation sites (6). These responses include: (1) a relatively "pure" EPSP, a response elicited in thirty to forty per cent of the caudate cells in response to centromedial-parafascicularis stimulation; (2) EPSP-IPSP sequence, the most predominant response of caudate cells, and (3) a "pure" IPSP, a relatively rare occurrence. The duration of the EPSP ranges from 5 to 50 msec whereas the IPSP was considerably longer in duration, ranging to 200 to 300 msec (6). One spike was the characteristic response to a single shock rather than a burst of spikes, but more frequently, large amplitude EPSP's without a spike occurred. These responses elicited in the caudate nucleus resulted from stimulation of the three input areas, the cortex, intralaminar nuclei and the substantia nigra. Extracellular responses of caudate units to peripheral stimulation demonstrated that units respond to stimulation

of the four limbs. No units responded to stimulation of the nerve to the hamstrings, which would indicate no proprioceptive input from the periphery. Generally, cortically induced IPSP's were longer in duration than those elicited by the rostral thalamus. The duration of the sequence was longer for cortical stimulation than thalamic stimulation, and response duration to nigral stimulation was the shortest in duration. An increase in stimulus intensity elicited an increase in amplitude of response rather than in duration to the various stimulus sites could not be attributed to stimulus intensity.

Caudate neuronal responses also varied with increasing frequency of stimulation. Caudate cells responded with rhythmic membrane responses when various areas were stimulated at a frequency of one cycle per second to ten cycles per second. At frequencies greater than ten cycles per second long duration hyperpolarizations were evident during the period of stimulation. This response occurred with stimulation to thalamic, cortical and brain stem areas.

Frequencies greater than 100 cycles per second delivered to various areas produced a marked depolarization in which an increase in cell firing was evident. One to two seconds following termination of the stimulus train, a decomposition of spikes occurred with a further depolarization. Thus increasing frequency of electrical stimulation produced more complex membrane potential changes (34) than those observed

with low frequency stimulation.

Pairing of afferent stimuli to the caudate nucleus also produced a variety of responses dependent upon the site of stimulation as well as the time interval of the pairings. Hull, et al. (35) investigated interactions of various stimulation sites, ie, cortex, substantia nigra and thalamus. As stated previously the most common response recorded in the caudate nucleus neurons was an EPSP-IPSP sequence. When the two stimuli were presented simultaneously to a stimulus site, an increase in amplitude of both the EPSP and IPSP with no variation in duration occurred. When the test EPSP coincided with the conditioning EPSP, a decrease in the amplitude of the test EPSP was noted. If the test EPSP coincided with the conditioning IPSP, then an increase in the amplitude of the test EPSP occurred.

Conditioning and test stimuli delivered to different anatomical locations produced similar responses in caudate cells as described above, although cortical stimulation tended to be the predominant influencing factor. If a cortical and subcortical stimulus coincided, the resultant EPSP activity of the caudate nucleus neuron would summate. On the other hand, if a subcortical stimulus was temporally placed so that the EPSP coincided with the cortical IPSP, then the EPSP would be diminished or not evoked. This result indicates a prepotent cortical modulation of subcortical input to neurons of the caudate nucleus.

From the above information a model was formulated whereby integration within the caudate nucleus was based upon organization of the synaptic terminals of extrinsic fibers and the intracaudate neuron (39). Assumptions from Hull, et al. and Kemp and Powell include that: (1) all extrinsic axons are excitatory and terminate mainly upon dendritic spines; (2) cortical and thalamic inputs tend to converge upon common cells; (3) the intracaudate neurons are of an inhibitory nature; and (4) the efferent caudate nucleus projection is mainly inhibitory upon the globus pallidus although some excitatory output to the pallidum is also evident. Information then from the cortex, thalamus, and substantia nigra is excitatory. This input evokes EPSP-IPSP sequences in caudate neurons. The IPSP activity is a result of stimulation of neighboring inhibitory intracaudate neurons. The intracaudate neuron represents ninety-six per cent of the caudate cells and therefore partly accounts for the low spontaneous firing rate of caudate neurons (36). Outflow from the caudate nucleus both excites and inhibits the globus pallidus; the functional consequences of this modulation will be discussed later.

A characteristic difference within the basal ganglia is a high rate of spontaneous activity in the lenticular nucleus cells as compared to low spontaneous activity of caudate nucleus cells. Spontaneous unit discharge varied within the lenticular nucleus and in some instances is

greater than forty pulses per second in the putamen (72). Noda, et al. (63) categorized spontaneous cell firing into high discharge rate, low discharge rate and repetitive bursting. Those units which exhibited a high discharge rate generally demonstrated convergence of afferent input, responding to sensorimotor cortex, midbrain reticular formation and nucleus centrum medianum stimulation. Units which exhibited a low discharge rate generally exhibited a response to only one stimulus site.

Most lenticular neurons respond to both medial thalamic and caudate nucleus stimulation by exhibiting an EPSP-IPSP sequence to repetitive caudate nucleus stimulation (52). A short and often interrupted EPSP usually precedes the 50 to 100 msec duration IPSP which exhibits a latency of 10 to 20 msec. High frequency stimulation delivered to the caudate nucleus produces IPSP summation and therefore sustained membrane polarization in the ventral regions. These cells generally exhibit IPSP responses to medial thalamic stimulation.

In summary, the basal ganglia are involved in a complex circuit in which information from the cortex, thalamus, and substantia nigra are modulated by temporal and spatial interactions within the caudate nucleus. This modulated information impinges upon the globus pallidus mainly evoking IPSP activity within this subcortical structure although some excitation results. The globus pallidus in turn projects

to the thalamus and prerubral areas which influence cortical and spinal level, respectively.

1. Activity of Lenticular Neurons during Movement

The basal ganglia were assumed to be involved in background activity for movement. Mettler, et al. (47), established the first technique for the examination of basal ganglia activity upon cortically induced movement. Evarts, (19) devised a technique to record unit activity in subcortical structures during a movement. This technique provided a method for recording unit activity prior to the onset of movement to the termination of a task related movement. Therefore, the temporal sequences of units in various structures could be analyzed in a chronic preparation during a movement.

DeLong examined the activity of lenticular units in monkeys during a push-pull task (11,12,13). During rest, the putamen exhibited a lower level of spontaneous firing than pallidal neurons which exhibited a high discharge rate. Neurons of the internal pallidal segment were distinguishable from those of the external pallidal segment. The majority of units recorded in the external pallidal segment exhibited two types of activity. Some units exhibited periods of high frequency discharge separated by silence, whereas other units exhibited a low discharge level with a burst pattern. These types of activity were observed by Noda (63) in the anesthetized, but immobilized cat.

One group of monkeys were trained to perform a rapid alternating limb movement, a push-pull task or a side to side movement. Unit activity in both segments of the globus pallidus was recorded. In most units an increase in discharge frequency above the resting discharge rate occurred. Although units responded to both types of movement, they preferentially responded to only one type of movement. No consistent correlation between an increase in cell firing and type of movement was evident during ipsilateral movements. The majority of movement related units were located in both segments of the contralateral globus pallidus. More specifically, the units related to arm or leg movements were located in the lateral portion of both pallidal segments. Only rarely would a unit respond to both arm and leg related movements. This organization of units in the lateral portion of the globus pallidus appeared related to the anatomical organization demonstrated by Kemp and Powell in the monkey. The lateral portion of the caudate nucleus and putamen receive projections from the sensorimotor cortex. These striatal areas project in an essentially topographical manner to both segments of the globus pallidus.

The most distinguishing feature was the temporal relation between the task related movements and unit discharge. Numerous units increased discharge rate prior to movement. During movements, many pallidal neurons responded consistently

throughout movement. Some units discharged predominately during the flexion phase of movement, whereas others discharged predominately during the extension phase of the movement. Change in unit activity was correlated to movement rather than the signal presentation for the initiation of movement. DeLong was not able to demonstrate that the increase in pallidal activity occurred prior to activity in the cerebellum or cerebral cortex. The evidence presented for unit activity prior to the onset of movement could possibly indicate pallidum participation in "voluntary movements".

Putamenal units responded preferentially to slow rather than rapid movements. As in the case of pallidal units, the units in the putamen consistently changed discharge rates in relation to the movements (11). Many of these units responded to slow movements in both directions, but did not respond to rapid movements. This observation can be related to involuntary movements such as chorea, and athetosis (44). Parkinsonian patients have difficulty in the initiation of movement, whereas rapid movements are less impaired (44).

In this survey, the conceptual development of the basal ganglia from participation in background motor activity to participation in the initiation of voluntary movement has been considered. As previously described, the basal ganglia form a complex circuit modulating both cortical and sub-cortical motor activity. The present experiments were designed to further assess the functional roles of these two

modulating circuits.

METHODS

Fifty cats ranging in weight from 2.7 kilograms to 4.2 kilograms were used in the study. Two basic types of experimental preparations were employed. (1) The animal was maintained under light anesthesia (sodium pentobarbital). Modulation of cortical induced and pyramidal tract induced hind limb flexor responses by electrical stimulation of the basal ganglia was investigated. In this preparation the measured parameters were Ia afferent dorsal root activity, myogram and EMG activity of the anterior tibialis muscle. (2) The unanesthetized preparation, ether was administered during the surgical procedure. Following surgery, ether was discontinued, a local anesthetic was applied to wound edges and pressure points. The animal was immobilized with gallamine triethiodide (Flaxedil) and maintained by artificial respiration. Modulation of direct and indirect pyramidal tract responses elicited by a conditioning (caudate nucleus)-test (cortex) technique was recorded in this preparation.

A. Anesthetized Preparation

An intraperitoneal injection of sodium pentobarbital (Nembutal), 30 mg/kg, was used to anesthetize the cat for the duration of the surgical procedure. A cat was considered sufficiently anesthetized when a withdrawal response from a nociceptive stimulus, pinching between the toes, was not evoked. A T-shaped plastic tracheal cannula was inserted

into the trachea and P.E. 190 polyethylene tubing was inserted into the right femoral vein. Cannulation of the vein served as an entry for the administration of sodium thiamylal (Surital) and 5% dextrose in water solution. Periodic injections of dextrose were administered throughout the experiment. EKG and temperature were continuously monitored. Rectal temperature was maintained within a range of 35.5°C to 38°C by a hot water heating system in contact with the ventral surface of the animal. During the course of the experiment the cat was maintained under light anesthesia as evident by a withdrawal response to a nociceptive stimulus. If spontaneous movement occurred, a supplemental dose of 0.4 cc of 2.5% sodium thiamylal was administered intravenously.

1. Surgical Procedures

a. Exposure of the Bulbar Pyramids

The ventral aspect of the cranium was attained by placing the cat in a supine position and ligating and reflecting the sternomastoideus and the sternohyoideus muscles, trachea and esophagus. Rongeurs were used to remove the basoccipital bone, thereby exposing the pyramidal tract rostral to the decussation of these fiber tracts. Frequently, bleeding was encountered from an epidural membrane overlying the basoccipital bone and atlas. Packing this area with gelfoam prevented oozing of blood into the surgical field.

b. Denervation of the Hind Limb and Dissection of the Anterior Tibialis Muscle

The left hind limb was partially denervated by dissecting the nerves from surrounding tissue, identifying, and cutting each nerve. These included nerves to the hamstring muscles, the tibial nerve, the surals, the superficial peroneal nerve, the obturator nerve and the femoral nerve. The common peroneal nerve was traced by following its course on the lateral aspect of the hind limb to the peroneus longus muscle in order to expose the nerve to the anterior tibialis muscle. At this point, the superficial peroneal nerve was located and cut. Other branches of the common peroneal nerve including the nerve to the anterior tibialis muscle were identified and remained intact, thereby eliminating excessive manipulation of the nerve to the anterior tibialis muscle.

The anterior tibialis muscle was then dissected free from surrounding tissue. Skin overlying the ankle joint and anterior tibialis muscle was reflected. Blunt dissection was employed to free the tendon of the muscle and the transverse crural ligament overlying the tendon was cut. A pouch was made by suturing skin over the anterior tibialis muscle. During the experiment the pouch was filled with mineral oil at a temperature of 37°C in order to keep the muscle warm and prevent drying.

c. Framing the Cat

Upon completion of surgery, the cat was removed from the surgical table and placed in a Kopf stereotaxic and spinal apparatus. Ear bars were inserted bilaterally into the external auditory meatus. Clamps were placed on each infra-orbital ridge and upper palate to assure firm head position. A vertebral clamp was attached to a thoracic supraspinous process and six steel pins were placed bilaterally into lumbar vertebrae bodies and then attached to the spinal frame, thereby securing the thoraco-lumbar area. In order to maintain the hind quarters and proximal portion of the left hind limb in a fixed position during the experiment, pins were screwed into the greater trochanter of each femur and a pin was placed in the shaft at its distal end of the left femur. These pins were then attached to the spinal frame.

d. Laminectomy and Preparation of the Dorsal Root

A midsagittal incision through skin, superficial and deep lumbodorsal fascia was made from L_3 to S_1 . Blunt dissection was used to remove the lumbar multifidus, lumbar interspinales, longissimus dorsi and intertransversarii dorsalis muscles overlying the vertebral column from L_3 to S_1 . The dissected muscle was tied and secured to the spinal frame in order to expose the vertebral column and to form a trough for warm mineral oil. Vertebrae overlying

spinal segments L₃ to S₁ were removed. A midsagittal incision was made in the dura mater and the dura mater was then sutured to the muscle. Warm mineral oil (37°C) covered the spinal cord to prevent drying. The pia mater was excised and the sixth lumbar dorsal root identified. A very small filament of this dorsal root was cut centrally and placed over a bipolar, silver recording electrode.

e. Exposure of the Cortex

Skin overlying the cranium was reflected. A hole, drilled in the right side of the dorsal aspect of the cranium, was enlarged with rongeurs to expose the orbital, sigmoid, marginal and suprasylvian gyri. The dura mater was reflected and an agar barrier surrounded the surgical opening in order to contain a mineral oil pool overlying the exposed cortical surface. The warm mineral oil was changed periodically in each pool throughout the experimental day to maintain a temperature of 37°C.

2. Recording Procedure

As previously described, a thin filament of the sixth lumbar dorsal root was placed over a bipolar, silver recording electrode. Action potentials of the filament were amplified with a Tektronix 122 low-level preamplifier and monitored on a Tektronix 502 dual-beam oscilloscope. The signal was further amplified with a Grass P5 preamplifier and stored on magnetic tape on one channel of a four channel Ampex tape recorder. In addition to visual monitoring, an audio system

was employed to hear the frequency of firing of the action potentials recorded from the dorsal root filament. The filament was continually divided with the aid of audio and visual monitoring of the rootlet until a single filament remained containing a Ia afferent fiber from a muscle spindle located in the anterior tibialis muscle. Ia and Ib fibers are difficult to differentiate on the basis of passive stretch and conduction velocity. Therefore, this differentiation was made by electrical stimulation at a frequency of one pulse every two seconds, with a pulse duration of 1.0 msec and a stimulus intensity of sufficient voltage to produce a twitch contraction. Since the Golgi tendon organ lies in series with extrafusal muscle fibers, the Ib afferent fiber from this organ conducts action potentials during the rising phase of the twitch contraction. On the other hand, the muscle spindle, lying in parallel with extrafusal muscle fibers does not elicit action potentials during the rising phase of a twitch contraction. This period during which no action potentials are recorded from a Ia afferent fiber of a muscle spindle is termed the silent period (27,53). An afferent fiber of a muscle spindle was also differentiated from an afferent fiber of a Golgi tendon organ on the basis of response to electrical stimulation of the sensorimotor cortex and pyramidal tract. The gamma motoneuronal system, the motor innervation of the muscle spindle, may be activated by cortical stimulation at stimulus intensities sufficient to

enhance gamma discharge and thus Ia afferent discharge, but not sufficient to activate the alpha motoneuronal system as evident by no change in myogram tension or EMG activity (26). Therefore, those afferent fibers exhibiting a silent period during a twitch contraction and also responding to cortical stimulation were considered Ia afferent fibers from the muscle spindle. Those afferent fibers which did not exhibit both characteristics, ie, silent period during twitch contraction and enhancement of firing in response to cortical stimulation, were not used in the experiment.

Figure 2 demonstrates the location of stimulating and recording electrodes. A bipolar, ball-tipped, stainless steel stimulating electrode was placed on the surface of the contralateral sensorimotor cortex. Location of the hind limb area was obtained by delivering constant current pulses of 1.0 msec pulse duration at a frequency of 60 cycles per second and a current intensity of 0.8 mA to the cortex. The sensorimotor cortex was stimulated at various points until an increase in the rate of the anterior tibialis Ia afferent dorsal root discharge occurred. A stainless steel, bipolar, ball-tipped electrode was placed, under visual control (with a mirror), on the ventral surface of the contralateral pyramidal tract. Location of the electrode was confirmed by observing an increase in dorsal root discharge upon a volley of electrical shocks delivered to this area

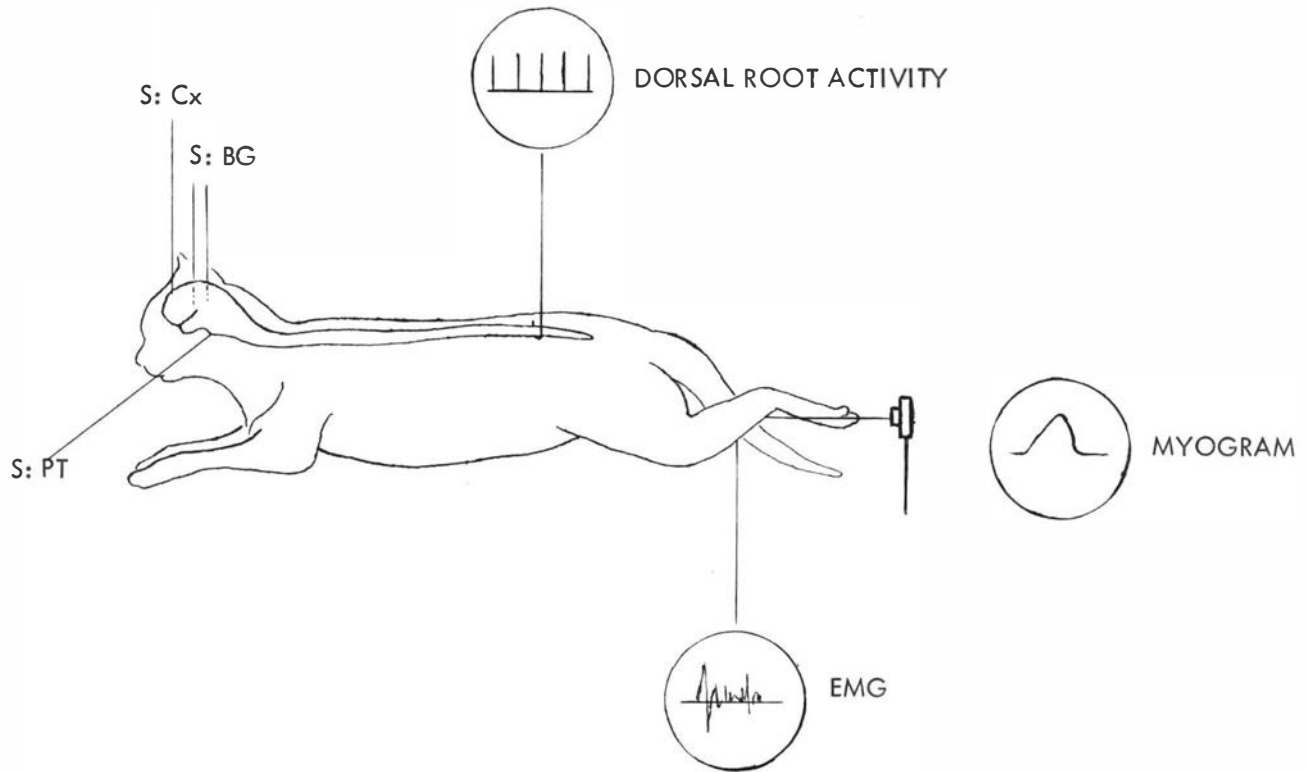
Figure 2 Diagram of the Experimental Arrangement of Stimulating
 and Recording Electrodes in the Anesthetized Preparation
 (explanation in text)

Abbreviations are as follows:

S: BG - caudate nucleus or globus pallidus stimulating
 electrode

S: Cx - cortical stimulating electrode

S: Pt - pyramidal tract stimulating electrode



at a frequency of 60 cycles per second, a pulse duration of 1.0 msec and a current intensity of 0.8 mA. Five type 00 stainless steel insect pins were insulated with Insl-X to within 0.5 millimeters from the tip and were separated at one millimeter intervals into an array or "comb" of electrodes. With the aid of a stereotaxic atlas (Snider and Nieman, 75) this "comb" was stereotaxically placed within either the caudate nucleus or globus pallidus.

The distal end of the tendon of the anterior tibialis muscle was sectioned and tied by means of a thread to a Grass FT 03 force-displacement transducer. A ten gram tension was maintained on the muscle to prevent slack in the system. An EMG needle electrode was placed in the belly of the anterior tibialis muscle. Signals of both the myogram and EMG were amplified, monitored on a Tektronix 502 oscilloscope and stored on magnetic tape.

3. Experimental Format

Flexor responses to shock trains delivered to the pre-cruciate cortex were recorded. A constant current pulse train with a pulse duration of 1.0 msec, a frequency of 60 cycles per second and a train duration of 500 or 1000 msec was delivered to the cortex. The intensity of the stimulus was adjusted until a minimal increase in dorsal root discharge was detected, a response which indicated that only the gamma system was activated. Intensities required to elicit this response ranged from 0.5 mA to 2.0 mA. All

stimulations were made at two minute intervals since it was found that repetitive stimulation of the cortex elicited long term facilitatory effects upon Ia afferent dorsal root discharge. If the cortical responses demonstrated fairly consistent increases in Ia afferent dorsal root discharge, then appropriate tests using trains of shocks delivered simultaneously to the cortex and one locus within either the caudate nucleus or globus pallidus were employed. The train of pulses to the subcortical structures consisted of square wave pulses, a pulse duration of 0.5 msec, a frequency of 100 cycles per second and a duration of 500 or 1000 msec, delivered by a Grass 8S stimulator through a stimulus isolation unit and a constant current unit. Stimulus intensities to the caudate nucleus and globus pallidus were well below that which would by themselves modify Ia afferent discharge. Intensities delivered to these subcortical structures ranged from 20 V to 25 V or 2.0 mA to 2.5 mA.

Flexor responses to cortical stimulation alone and to stimulation of the cortex and one locus in the caudate nucleus were compared. For each electrode pair in the "comb" a minimum of one cortical stimulation and five cortex-caudate nucleus stimulations were performed at regular intervals. Having paired cortical stimulation with each pair of electrodes within the "comb", the experimental format was repeated with paired electrical trains of shocks delivered to the pyramidal

tract and each pair of electrodes within the "comb". Stimulation to the pyramidal tract consisted of a constant current pulse train with a pulse duration of 1.0 msec, a frequency of 60 cycles per second and a duration of 500 or 1000 msec. The intensity of the stimulus required to elicit a minimal increase in dorsal root discharge ranged from 0.5 mA to 1.5 mA. This series of recordings were followed by trains of electrical shocks delivered to each pair of electrodes within the "comb". Upon completion of stimulation through each electrode pair within a horizontal plane, electrolytic lesions were produced by a DC current of 0.05 mA for a ten to fifteen second duration delivered by a Nuclear Chicago constant current stimulator to each electrode within the "comb". The electrode was lowered one millimeter and the experimental format repeated. Mapping of the caudate nucleus and globus pallidus was accomplished in this manner.

A series of experiments employing the recording format described above was used in a decorticate preparation. Recording data previous to and following decortication was not feasible due to a high mortality rate. Cats were unable to survive the trauma of decortication after a ten hour surgical-recording period. Therefore, bilateral surgical ablation of three to four millimeters deep of the entire cortex was completed, and two hours elapsed before the recording began.

4. Data Analysis

The recorded data were filmed on moving Kodak Linagraph paper by a Grass Kymograph camera at a speed of 25 millimeters per second. Latencies from the onset of stimulation to onset of myogram tension and to the onset of EMG activity as well as changes in the Ia afferent activity were measured. Ia afferent activity was analyzed during one second pre-stimulus, stimulus, and post-stimulus periods. Changes in afferent activity attributed to paired stimulation of the cortex and caudate nucleus were compared to the Ia afferent activity elicited by cortical stimulation alone. If a forty percent or more increase in Ia afferent activity due to paired cortical-caudate nucleus stimulation above the control cortical response occurred in a minimum of four of the five test (cortical-caudate nucleus) responses, then a "+" was recorded on the appropriate midsagittal map of the caudate nucleus at the location of the electrode tips. Similarly, if a forty per cent or more decrease in Ia afferent dorsal root activity below the control response was recorded in a minimum of four of the five cortical-caudate nucleus test responses, then a "-" was recorded. These criteria were sufficient to conclude that responses at each "+" and "-" locus were significantly different from control responses ($p < 0.01$, chi square). If changes in Ia afferent activity were less than forty per cent of the cortical-caudate nucleus test responses, then a "0" was placed on the

appropriate caudate nucleus map at the location of the electrode tips to designate the locus as inactive. The term inactive refers to the fact that at the stimulus intensities (20-25 volts, 2.0-2.5 mA) employed only slight changes or no changes upon cortically induced activity were observed. Maps of the caudate nucleus were reproduced from midsagittal histological sections of the brain and represented sections located at 2.5 mm, 3.5 mm, 5.0 mm, and 6.0 mm lateral from the midline.

Similar criteria for assigning "+", "-", and "0" were utilized for the pyramidal tract-caudate nucleus interactions. Pairing of globus pallidus loci with cortical and pyramidal tract stimulation were analyzed and represented in a similar manner on maps reproduced from midsagittal histological sections located 6.0 mm and 8.0 mm from the midline.

B. Unanesthetized Preparation

The animal was placed in a closed box and an ether bottle was introduced in a hole located on the side of the box. When suitably anesthetized, as indicated by the level of ether anesthesia, the animal was placed on a surgical table and a tracheotomy was performed. Throughout the surgical procedure, the cat was maintained by artificial respiration. An ether jar was connected in parallel with the input from the respirator so that the cat was respired with an ether-air mixture. The amount of ether administered was controlled by adjustment of a screw clamp located between the ether jar and input tube

from the respirator. A polyethylene cannula was placed in the right femoral vein. All surgical wounds were infiltrated with 5% lidocaine (Xylocaine) ointment.

1. Surgical Procedure

After exposure of the bulbar pyramids, pins were placed bilaterally in each mastoid process, a part of the mastoid portion of the temporal bone. The lamboidal ridge was palpated and followed in a rostro-ventral course to the mastoid process which is in continuation with the outer aspect of the lamboidal ridge. A hole was drilled in each mastoid process, through the outer wall of the tympanic bulla, and a pin screwed into each hole.

The cat was placed in a Kopf stereotaxic and spinal apparatus. Ear bars were inserted bilaterally and the head secured as previously described. Xylocaine infiltrated all wounds and pressure points. The A-P stereotaxic zero was notched in the cranium. As previously described, the cortex was exposed and covered with warm mineral oil. Ear bars were then removed and the head supported by the pins that were placed in each mastoid process, thereby removing pressure on points exerted by ear bars. Ether was discontinued, gallamine triethiodide was administered to immobilize the cat, and the cat was artificially respired for the remainder of the experiment. Throughout the experiment EKG and body temperature were monitored. Whenever possible the per cent CO_2 of the preparation was monitored and

maintained at 5.2 per cent by proper adjustment of the respirator. Constriction of the pupils and a synchronyous EEG served as criteria to demonstrate lack of stress in this preparation (1). Reapplication of Xylocaine ointment to all pressure points and wound edges was made at regular intervals throughout the experiment.

2. Recording Procedure

The experimental arrangement of electrode placement is demonstrated in Figure 3. A bipolar, ball-tipped, stainless steel stimulating electrode was placed on the surface of the left precruciate gyrus. A recording electrode, similar to the cortical stimulating electrode, was placed on the ventral surface of the ipsilateral pyramidal tract to monitor the direct and indirect (D-I) responses elicited from a single shock delivered to the cortex. An array of "comb" electrodes similar to that used in the anesthetized preparation was stereotaxically placed within the caudate nucleus or globus pallidus.

A single pulse with a 0.1 msec duration was delivered to the sensorimotor cortex and the intensity was adjusted until current levels sufficient to elicit minimal and maximal D-I responses were determined. For the duration of the experiment, a current intensity midway between these two values was employed, so that a change, either an increase or decrease in response, could be detected. Stimulus intensities ranged from 0.5 mA to 2.0 mA. This stimulus was

Figure 3 Diagram of the Experimental Arrangement of Stimulating
 and Recording Electrodes in the Unanesthetized
 Preparation (explanation in text)

Abbreviations are as follows:

Cd - caudate nucleus

D - direct wave

GP - globus pallidus

I - indirect wave

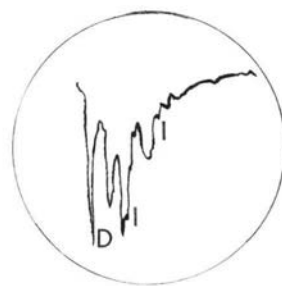
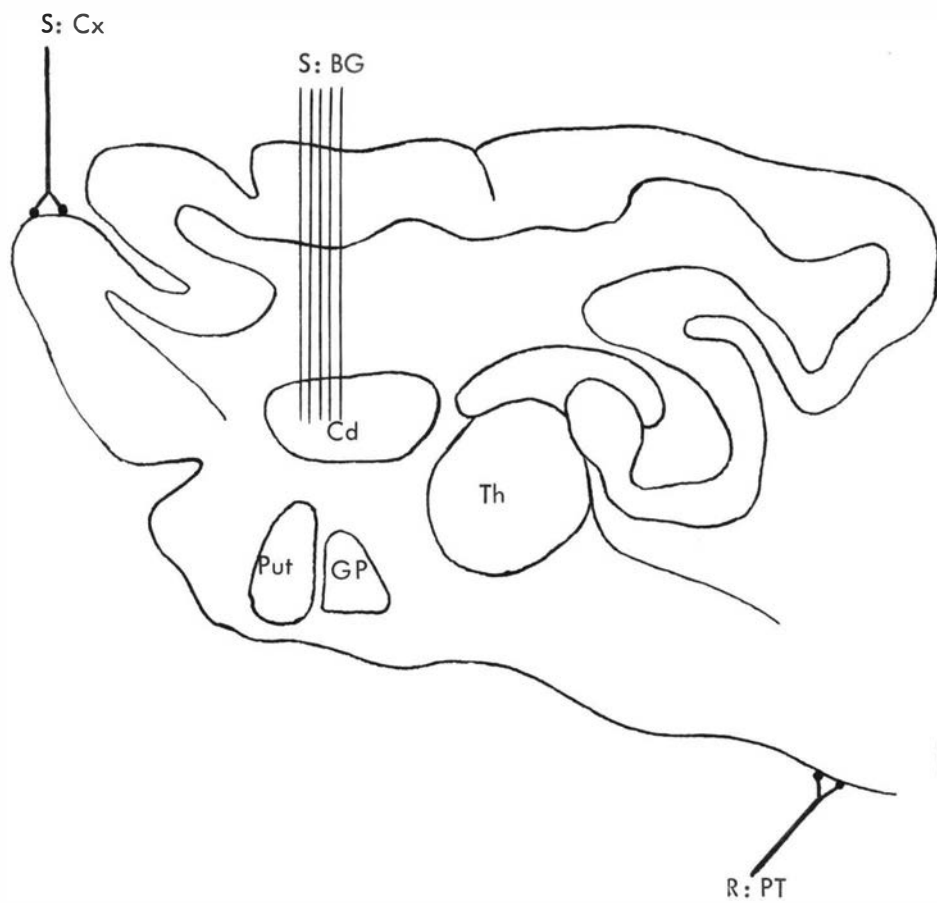
Put - putamen

R: PT - pyramidal tract recording electrode

S: Cx - cortical stimulating electrode

S: BG - caudate nucleus or globus pallidus stimulating
 electrode

Th - thalamus



termed the test stimulus. The conditioning stimulus was a 500 msec train of pulses of 0.5 msec pulse duration with a frequency of 100 cycles per second delivered to a pair of adjacent electrodes within the "comb". Stimulus intensity was 25 V or 2.5 mA. The conditioning stimulus evoked no direct response in the pyramidal tract.

Control test stimulations to the sensorimotor cortex were delivered and the D-I response recorded in the pyramidal tract was amplified, monitored on a Tektronix 5103N storage scope, and stored on magnetic tape. A conditioning-test stimulation sequence followed in which a 500 msec train of pulses delivered to a pair of electrodes within the "comb" followed by a post-stimulus shock to the cortex. For each pair of electrodes within either the caudate nucleus or globus pallidus, a minimum of ten control cortical responses and a minimum of ten responses from the conditioning-test sequence were obtained. A similar format for each pair of electrodes within the "comb" was used. Following recording at a horizontal level within the subcortical structure, electrolytic lesions were produced. The "comb" was lowered one millimeter and the experimental format repeated.

3. Data Analysis

Direct and indirect (D-I) responses recorded from the pyramidal tract were monitored on a Tektronix storage oscilloscope. Representative samples of five consecutive

sweeps from both the cortical stimulation alone and conditioning-test stimulation were photographed on Polaroid black and white Land Pack film type 107 by a Tektronix C-5 camera. All D-I responses recorded from the pyramidal tract were averaged on a Digital PDP Lab 8/E computer. Eight responses elicited by cortical stimulation were averaged and plotted on an X-Y plotter. This procedure was employed for averaging the responses from the conditioning-test sequence for each pair of electrodes within the "comb". Therefore, each conditioning-test sequence response could be compared with the preceeding and following averaged cortical control responses.

Loci were designated as "+", "-", and "0" according to whether the loci respectively facilitated, inhibited or had no effect on cortically induced D-I responses. A locus was designated as "+" if the amplitudes of the direct and indirect responses elicited by the conditioning-test stimulus were at least thirty per cent above the cortical control responses. Similarly, if the amplitudes of the D-I responses elicited by the conditioning-test stimulus were at least thirty per cent less than the cortical control responses, a "-" was employed to designate the locus. For those loci in which the average test response was only thirty per cent different from cortical control response, a further analysis was made in which six of the eight test responses needed to differ from control responses by more than thirty

per cent before the locus was designated either "+" or "-". These criteria were sufficient to conclude that responses at each "+" and "-" locus were significantly different from control responses ($p < 0.01$; Chi Square). Response variability at sites where the conditioning-test responses differed from the cortical control response by more than thirty per cent was similar to the borderline cases and therefore the significance was obvious.

C. Histology

Histological verification of electrode placement within the caudate nucleus and globus pallidus for both types of preparations was made. At the end of an experiment the distal end of each carotid artery was cannulated and the brain perfused with 200 cc of physiological saline followed by 200 cc of 1.0% potassium ferricyanide in 10% formalin solution. The brain was removed and placed in a 10% formalin solution for a minimum of three days. Following infiltration, the brain was sectioned, by means of the frozen section technique, in midsagittal serial sections of 100 micra each and placed in water for mounting. Several representative sections demonstrating electrode placement were photographed. The section, used as the negative, was enlarged in a photographic enlarger and the positive print was made on Kodabromide F-5 paper. Since staining shrinks tissue, the photographic print was used to measure electrode placement (28). All sections were then stained by a modification of

the Nissl stain technique by Fernstrom (22) for further clarification of stimulation points.

RESULTS

A. Anesthetized Preparation1. Ia Afferent Dorsal Root Activity

Spontaneous Ia afferent dorsal root discharge varied among the muscle spindles studied. The resting afferent discharge ranged from zero spikes per second to forty spikes per second. Resting spindle discharge referred to the occurrence of spindle discharge during which a ten gram tension was placed upon the anterior tibialis muscle. Ia afferent dorsal root activity of the anterior tibialis muscle increased when a train of electrical shocks was delivered to the sensorimotor cortex or to the bulbar pyramidal tract. Control cortical and pyramidal tract records demonstrating an increase in Ia afferent activity are shown in Figures 4 and 7, respectively. The small spikes in Figure 4 represent afferent activity of a hip flexor. Muscles, excluding the anterior tibialis muscle, from which afferent fibers were recorded were identified by application of stretch to various areas of the hind limb. Stimulation of the cortex did not elicit an increase in the afferent activity. Lack of responsiveness of hip afferent fiber activity to cortical stimulation was noted in several preparations. However, electrical stimulation of the cortex or pyramidal tract induced changes within the gamma system (indirectly measured by Ia afferent activity) at intensities

lower than that necessary to activate the alpha system (indirectly measured by EMG and myogram) of the anterior tibialis muscle. This indicated a lower threshold of the gamma system to cortical and pyramidal tract stimulation in this preparation. Increase in Ia afferent activity was a function of stimulus intensity, ie, an increase in stimulus intensity elicited an increase in Ia afferent discharge. Therefore, the stimulus intensity level was adjusted in each preparation so a minimal increase in Ia afferent discharge in response to a control cortical stimulation occurred.

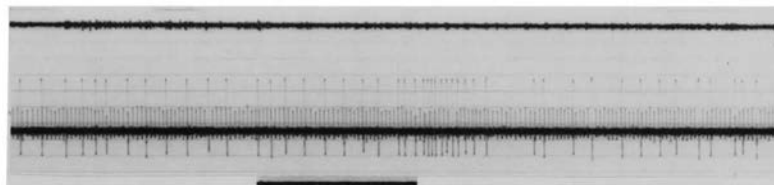
2. Caudate Nucleus Modulation of Cortical and Pyramidal Tract Induced Flexor Activity

Responses elicited from simultaneous stimulation of the cortex and a locus within the caudate nucleus were enhanced, diminished or did not deviate from the control cortical response. Figure 4 demonstrates inhibition of cortically induced hind limb flexor activity. Stimulation of the cortex produced an increase in Ia afferent dorsal root discharge of the anterior tibialis muscle without producing measurable alpha motoneuronal activity. No increase in dorsal root discharge in the hip flexor (small spikes) occurred. Simultaneous pairing of the cortex and caudate nucleus stimulation decreased the cortically induced increase in Ia afferent activity. Electrical stimulation of the caudate nucleus alone produced no effect upon either the Ia afferent

Figure 4 Caudate Nucleus Modulation of a Cortically Induced
Flexor Response: Inhibition

- A. Stimulation of the cortex: an increase in Ia afferent dorsal root activity of the anterior tibialis muscle.
- B. Stimulation of the cortex and caudate nucleus: inhibition of the cortically induced increase in Ia afferent activity.
- C. Stimulation of the caudate nucleus: no increase in Ia afferent activity.

A. Cortex

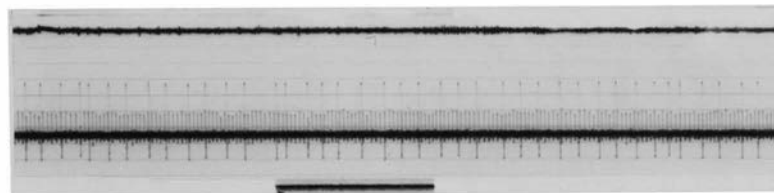


EMG

Dorsal Root

Shock Artifact

B. Cortex and Caudate Nucleus

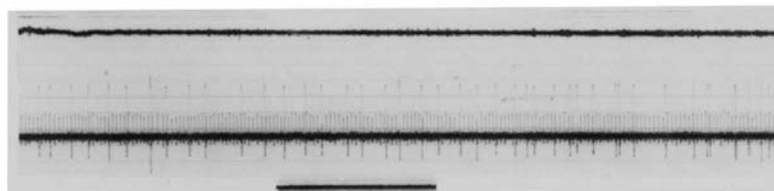


EMG

Dorsal Root

Shock Artifact

C. Caudate Nucleus



EMG

Dorsal Root

Shock Artifact

1.0 sec

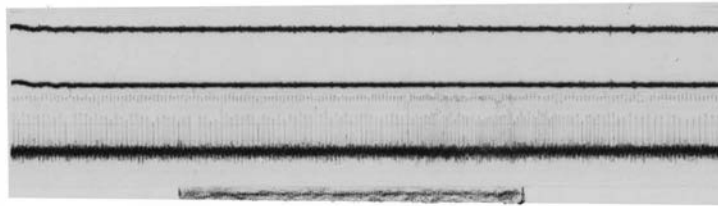
activity of the spindle or the afferent activity of the hip flexor. The decrease or inhibition of the cortically induced increase in Ia afferent activity often occurred with stimulation of loci within the rostral region of the caudate nucleus. Increasing the stimulus intensity of some inhibitory loci enhanced cortically induced activity. The rostral portion of the caudate nucleus tended to be either inhibitory or inactive. Chi square analysis ($p < 0.01$) confirmed the hypothesis that there were significantly more inhibitory loci distributed within the rostral as opposed to the caudal half of the caudate nucleus. However, rostral regions of the caudate nucleus also contained a few facilitatory loci.

When paired trains of electrical shocks were simultaneously delivered to the cortex and to some sites within the caudate nucleus, an increase in firing frequency of the Ia afferent fiber occurred that exceeded the cortical control response. EMG and myogram activity also occurred in some instances as demonstrated in Figure 5 which illustrates caudate nucleus facilitation of cortically induced activity. Stimulation of the caudate nucleus alone produced no effect. Caudal regions of the caudate nucleus tended to facilitate cortically induced hind limb flexor activity. Inactive loci were also found in this region. No inhibitory loci were located in the caudal portion of the caudate nucleus. Increasing the intensity of stimulation to the caudal region of the caudate nucleus increased these facilitatory effects upon gamma activity

Figure 5 Caudate Nucleus Modulation of a Cortically Induced
Flexor Response: Facilitation

- A. Stimulation of the cortex: an increase in
Ia afferent dorsal root activity of the
anterior tibialis muscle.
- B. Stimulation of the cortex and caudate nucleus:
facilitation of Ia afferent activity, increase
in myogram and EMG activity.
- C. Stimulation of the caudate nucleus: no
increase in Ia afferent activity.

A. Cortex

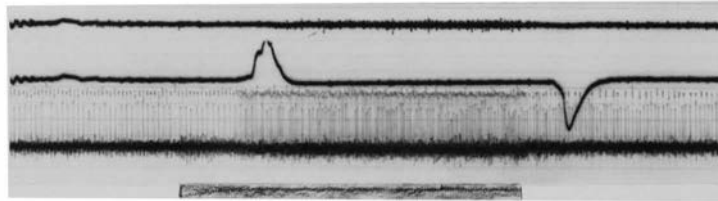


EMG

Myogram
Dorsal Root

Shock Artifact

B. Cortex and Caudate Nucleus

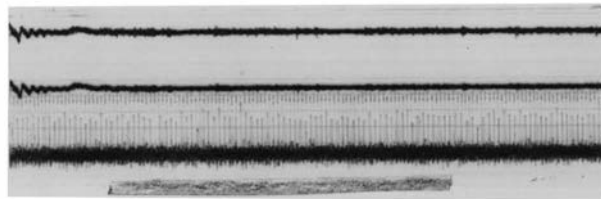


EMG

Myogram
Dorsal Root

Shock Artifact

C. Caudate Nucleus



EMG

Myogram
Dorsal Root

Shock Artifact

1.0 sec

although no alpha activity was recorded.

Figure 6 represents on midsagittal maps the loci within the caudate nucleus that when stimulated enhanced or decreased cortically induced hind limb flexor responses. Loci that did not influence cortically induced hind limb flexor responses are also represented. Whereas facilitatory loci were scattered throughout the caudate nucleus, the inhibitory loci tended to be located in the rostral portion of this structure.

Trains of electrical shocks delivered to the bulbar pyramidal tract elicited an increase in Ia afferent discharge independent of EMG or myogram activity as demonstrated in Figure 7. Paired stimulation of the pyramidal tract and loci within the caudate nucleus produced either facilitation or no effect upon activity induced by pyramidal tract stimulation. Caudate nucleus stimulation alone produced no effects upon hind limb flexor activity. In marked contrast to the inhibitory effects of caudate nucleus stimulation on cortically induced flexor responses, caudate nucleus stimulation did not produce any inhibitory effects upon pyramidal tract induced flexor responses in these same animals. Loci within the caudate nucleus that enhanced or did not influence responses elicited by pyramidal tract stimulation are represented on midsagittal sections in Figure 8.

Figure 6 Loci within the Caudate Nucleus which
Altered Cortically Induced Motor Activity in
the Anesthetized Preparation

Loci indicate areas within the caudate nucleus which when stimulated enhanced (+), decreased (-), or had no effect (0) upon cortically induced hind limb flexor responses. Diagrams A,B,C represent sections 2.5 mm, 3.5 mm, and 5.0 mm from the midline, respectively.

Abbreviations are as follows:

Cd - caudate nucleus
Cx - cortex
IC - internal capsule
Put - putamen
GP - globus pallidus
Th - thalamus

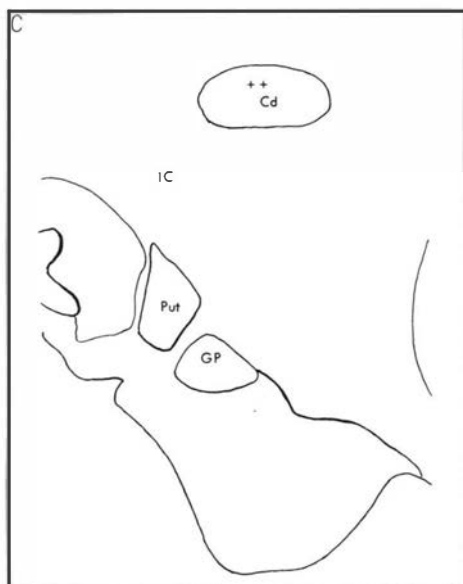
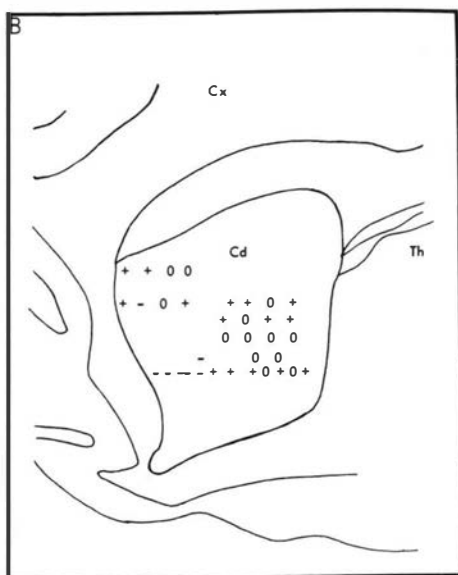
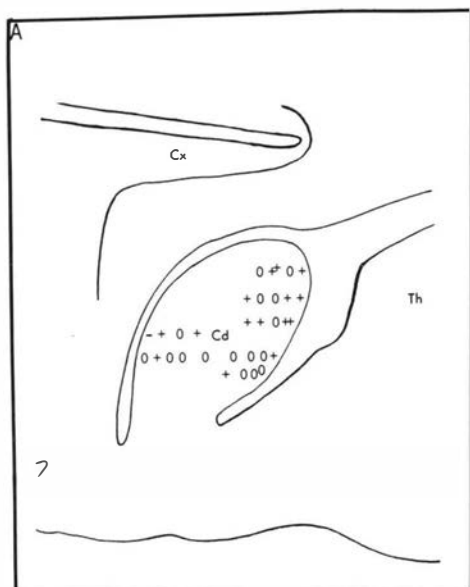
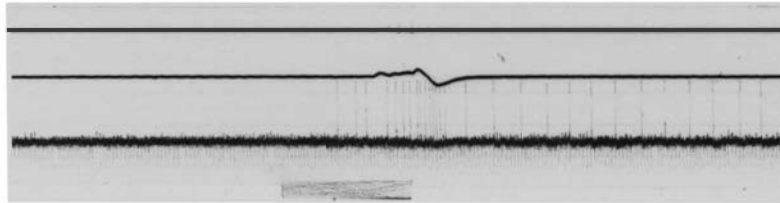


Figure 7 Caudate Nucleus Modulation of a Pyramidal Tract
Induced Flexor Response: Facilitation

- A. Stimulation of the pyramidal tract:
an increase in Ia afferent dorsal root
activity of the anterior tibialis muscle,
myogram and EMG activity.
- B. Stimulation of the pyramidal tract and
caudate nucleus: an enhancement of the
pyramidal tract induced increase in Ia
afferent activity, myogram and EMG activity.
- C. Stimulation of the caudate nucleus: no
increase in Ia afferent activity, no EMG
or myogram activity.

A. Pyramidal Tract



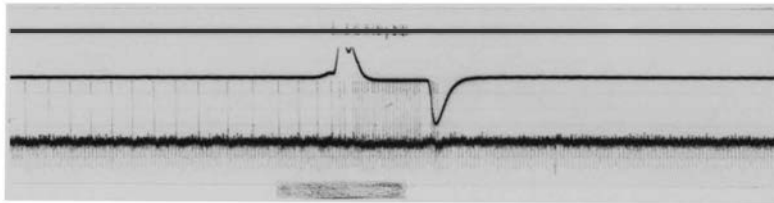
EMG

Myogram

Dorsal Root

Shock Artifact

B. Pyramidal Tract and Caudate Nucleus



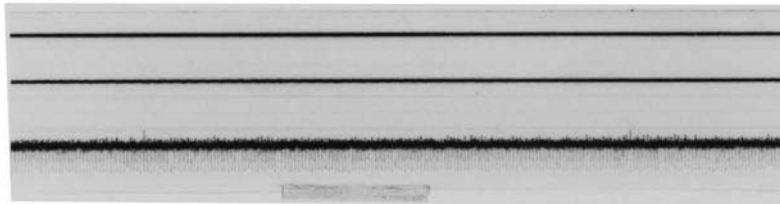
EMG

Myogram

Dorsal Root

Shock Artifact

C. Caudate Nucleus



EMG

Myogram

Dorsal Root

Shock Artifact

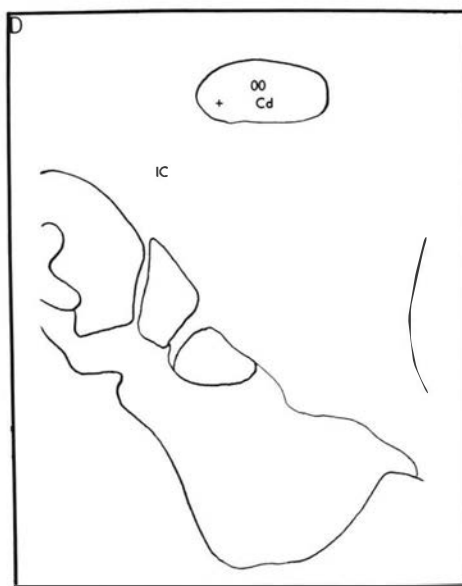
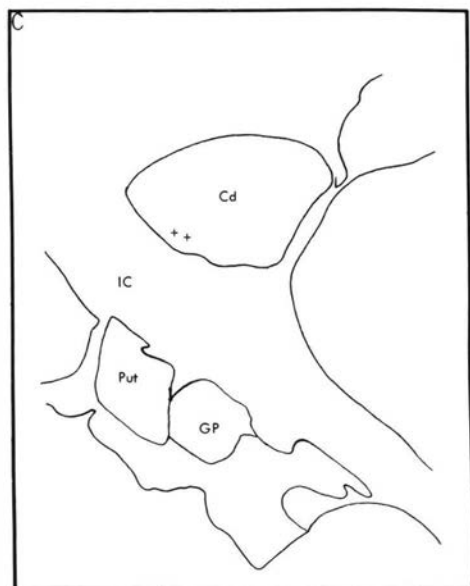
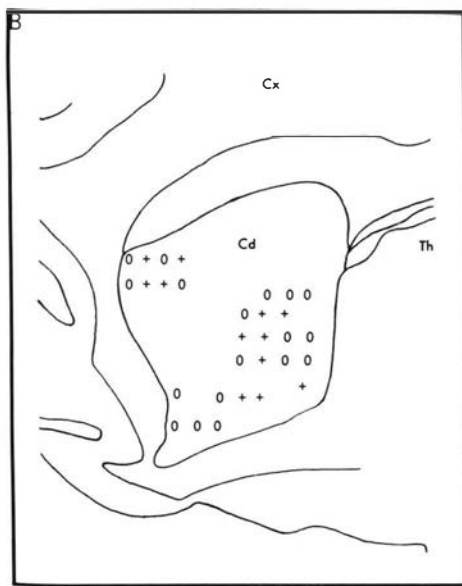
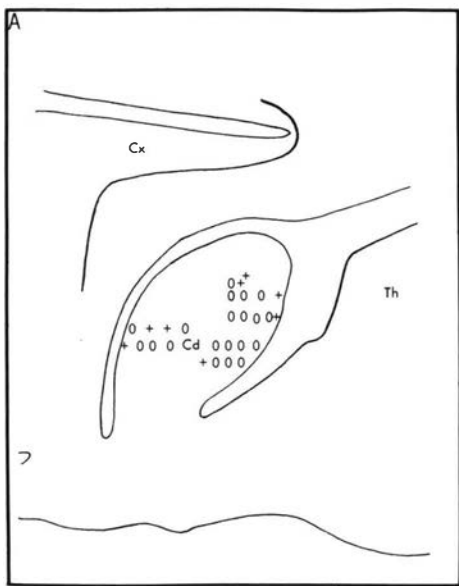
1.0 sec

Figure 8 Loci within the Caudate Nucleus which
Altered Pyramidal Tract Induced Motor Acti-
vity in the Anesthetized Preparation

Loci indicate areas within the caudate nucleus which when stimulated enhanced (+), or had no effect (0) upon pyramidal tract induced hind limb flexor responses. Diagrams A,B,C,D represent sections 2.5 mm, 3.5 mm, 5.0 mm and 6.0 mm from the midline, respectively.

Abbreviations are as follows:

Cd - caudate nucleus
Cx - cortex
IC - internal capsule
Put - putamen
GP - globus pallidus
Th - thalamus



3. Globus Pallidus Modulation of Cortical and Pyramidal Tract Activity

Simultaneous pairing of electrical shocks delivered to the cortex and a locus within the globus pallidus often produced facilitation of the cortically induced hind limb flexor response. Increases in EMG activity were also noted. Similarly, pairing of trains of shocks to the pyramidal tract and globus pallidus produced a facilitation of pyramidal tract induced flexor responses. Figures 9 and 10 demonstrate respectively the facilitation of cortical and pyramidal tract induced Ia afferent activity attributed to pallidal stimulation. Trains of electrical shocks that facilitated cortical or pyramidal tract induced flexor responses when delivered to loci within the globus pallidus did not elicit flexor responses by themselves. The loci within the globus pallidus that facilitated cortically induced or pyramidal tract induced flexor responses are represented on maps of the globus pallidus in Figure 11.

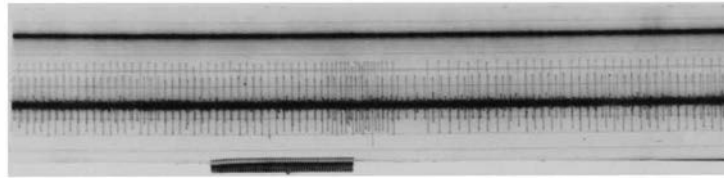
4. Internal Capsule

Influences from the internal capsule upon cortically induced activity served as an indicator for spread of current. Facilitatory influences upon cortically induced Ia afferent activity by internal capsule stimulation occurred as evident by an increase in Ia afferent activity and in some cases an increase in EMG activity and myogram tension. In some instances stimulation of the internal capsule at the same

Figure 9 Globus Pallidus Modulation of a Cortically Induced
Flexor Response

- A. Stimulation of the cortex: an increase in
 Ia afferent dorsal root activity of the anterior
 tibialis muscle.
- B. Stimulation of the cortex and globus pallidus:
 increase in Ia afferent activity, EMG activity.
- C. Stimulation of the globus pallidus: no increase
 in Ia afferent activity.

A. Cortex

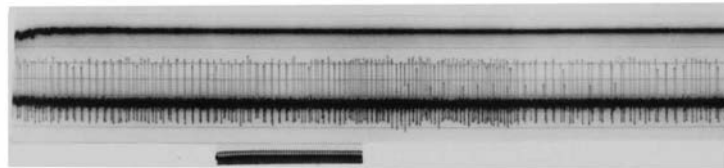


EMG

Dorsal Root

Shock Artifact

B. Cortex and Globus Pallidus

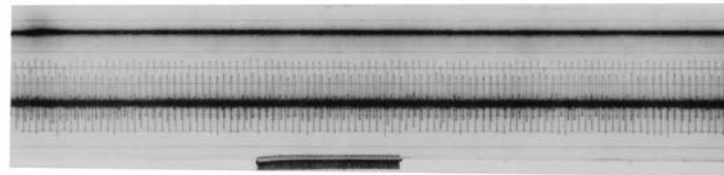


EMG

Dorsal Root

Shock Artifact

C. Globus Pallidus



EMG

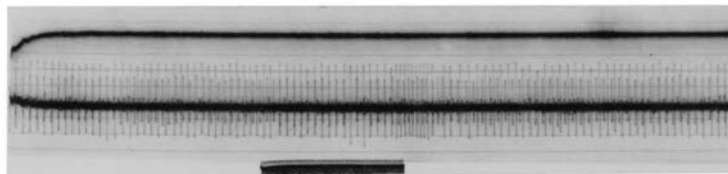
Dorsal Root

Shock Artifact

1.0 sec

- Figure 10 Globus Pallidus Modulation of a Pyramidal Tract
Induced Flexor Response
- A. Stimulation of the pyramidal tract: increase
 in Ia afferent dorsal root activity of the
 anterior tibialis muscle.
 - B. Stimulation of the pyramidal tract and globus
 pallidus: increase in Ia afferent activity.
 - C. Stimulation of the globus pallidus: no increase
 in Ia afferent activity.

A. Pyramidal Tract

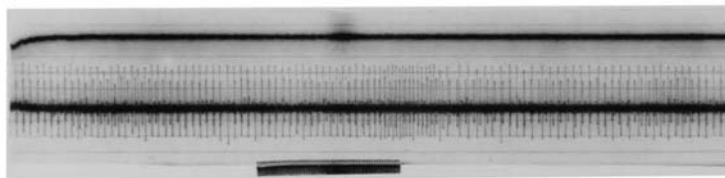


EMG

Dorsal Root

Shock Artifact

B. Pyramidal Tract and Globus Pallidus

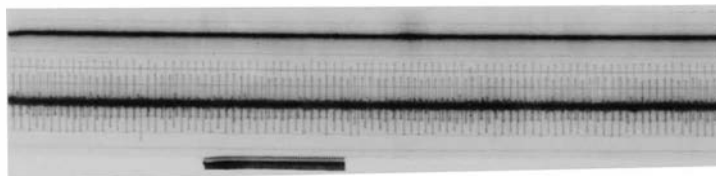


EMG

Dorsal Root

Shock Artifact

C. Globus Pallidus



EMG

Dorsal Root

Shock Artifact

1.0 sec

Figure 11 Loci within the Globus Pallidus which
Altered Cortically Induced and Pyramidal
Tract Induced Motor Responses

- A. Loci indicate areas within the globus pallidus which when stimulated enhanced (+), or had no influence (0) upon cortically induced hind limb flexor response.
- B. Loci indicate areas within the globus pallidus which when stimulated enhanced (+), or had no influence (0) upon cortically induced hind limb flexor response.

Both represent sections 8.0 mm from the midline.

Abbreviations are as follows:

GP - globus pallidus
IC - internal capsule
Put - putamen

intensity as that for the caudate nucleus produced greater facilitatory effects upon cortically induced hind limb flexor responses. When the internal capsule was stimulated alone, an increase in Ia afferent discharge occurred, a result unlike that found for the caudate nucleus or globus pallidus. However, since no further differentiation between effects of the caudate nucleus and internal capsule was evident, loci bordering the caudate nucleus and internal capsule were omitted from the study. In one decorticate preparation, a long latency and prolonged facilitation of pyramidal tract induced afferent activity was observed with paired pyramidal tract-caudate nucleus stimulation, whereas an immediate increase in pyramidal tract induced activity was noted with simultaneous stimulation of the internal capsule and pyramidal tract.

5. Decorticate Preparation

Four cats were decorticated in order to eliminate the caudate nucleus circuit to the cortex via the thalamus. Experimental recordings were made one and one-half hours to two hours following decortication. Purpura (67) confirmed the functional integrity of caudate nucleus cells two hours following cortical ablation rostral to the caudate nucleus. Stimulation of the pyramidal tract resulted in an increase in Ia afferent activity at stimulus intensities that corresponded to those employed in the intact preparation. Simultaneous pairing of pyramidal tract and caudate nucleus stimulation

in three of the four cats resulted in either an increase or prolonged facilitation of Ia afferent activity, thereby indicating the functional integrity of the caudate nucleus. Caudate nucleus stimulation alone produced no changes in Ia afferent activity as demonstrated in Figure 12.

Figure 13 represents on midsagittal sections of the cat brain the distribution of loci stimulated within the caudate nucleus that enhanced or produced no effect upon hind limb flexor responses elicited by stimulation of the pyramidal tract in the decorticate preparation. No inhibition of induced pyramidal tract activity attributed to caudate nucleus stimulation occurred in the rostral portion of the caudate nucleus. Inactive points were recorded throughout the caudate nucleus.

B. Unanesthetized Preparation

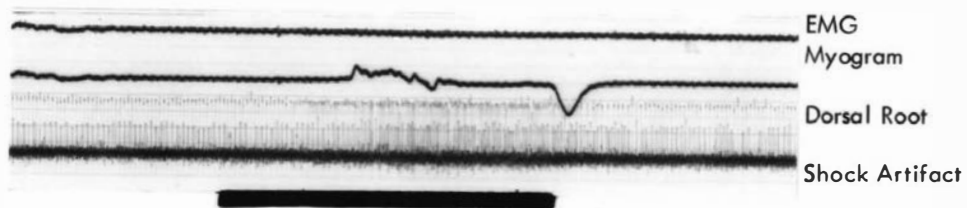
Experiments were performed in an unanesthetized preparation to determine how cortically evoked responses in the bulbar pyramidal tract could be modulated by shock trains delivered to selected sites within the basal ganglia. A single shock delivered to the sensorimotor cortex evoked in the ipsilateral bulbar pyramidal tract a positive deflection with a latency of approximately 0.7 msec. Generally one, but in some cases a series of positive deflections followed the first deflection. Latency for the onset of the second wave was generally 2.0 to 3.0 msec.

- Figure 12 Caudate Nucleus Modulation of a Pyramidal Tract
Induced Flexor Response in the Decorticate Cat
- A. Stimulation of the pyramidal tract: increase in
Ia afferent dorsal root activity of the
anterior tibialis muscle.
 - B. Stimulation of the pyramidal tract and caudate
nucleus: increase in Ia afferent activity.
 - C. Stimulation of the caudate nucleus: no increase
in Ia afferent activity.

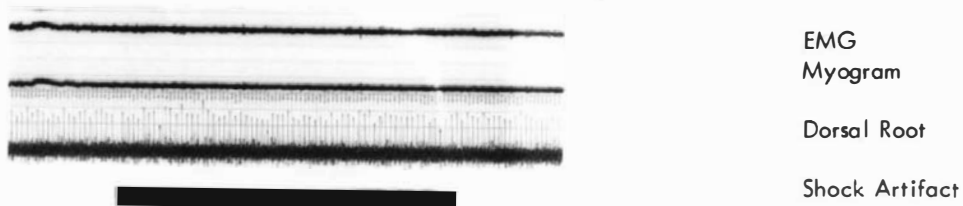
A. Pyramidal Tract



B. Pyramidal Tract and Caudate Nucleus



C. Caudate Nucleus



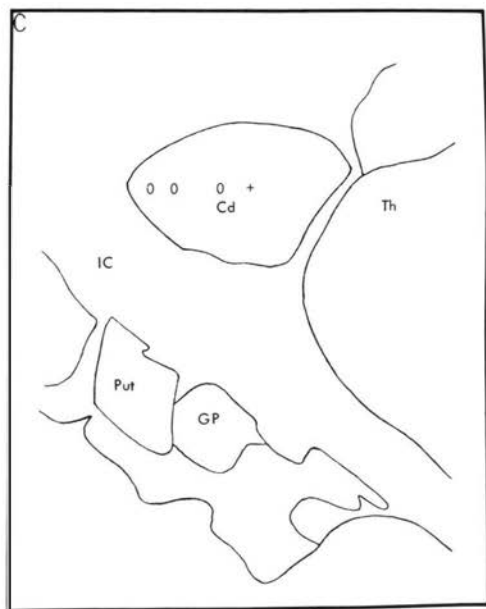
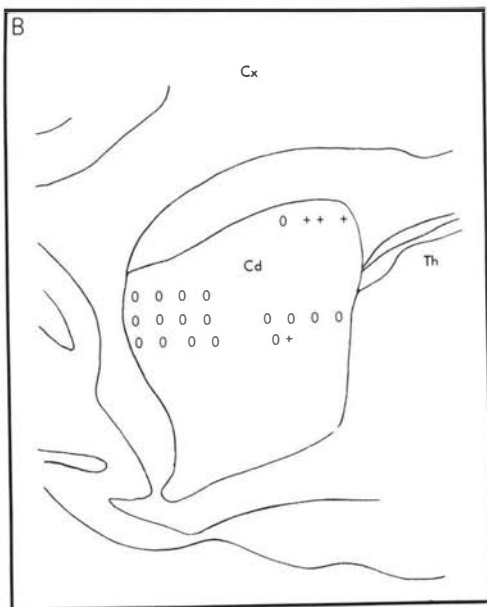
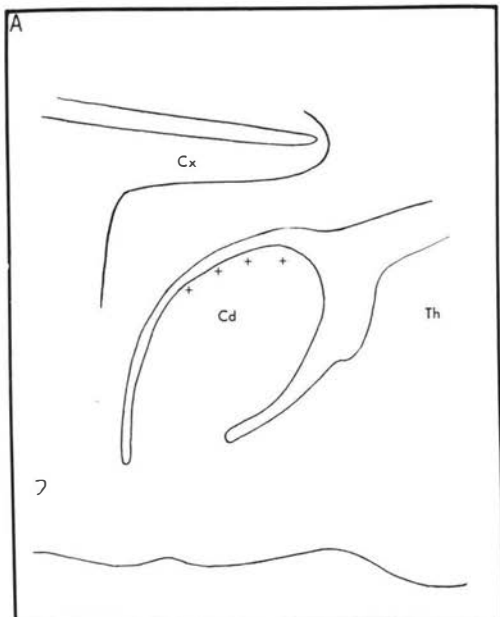
1.0 sec

Figure 13 Loci within the Caudate Nucleus which
Altered Pyramidal Tract Responses in the
Decorticate Preparation

Loci indicate areas within the caudate nucleus which when stimulated enhanced (+), or had no effect (0) upon pyramidal tract induced hind limb flexor responses in the decorticate preparation. Diagrams A, B, C represent sections 2.5 mm, 3.5 mm, and 5.0 mm from the midline, respectively.

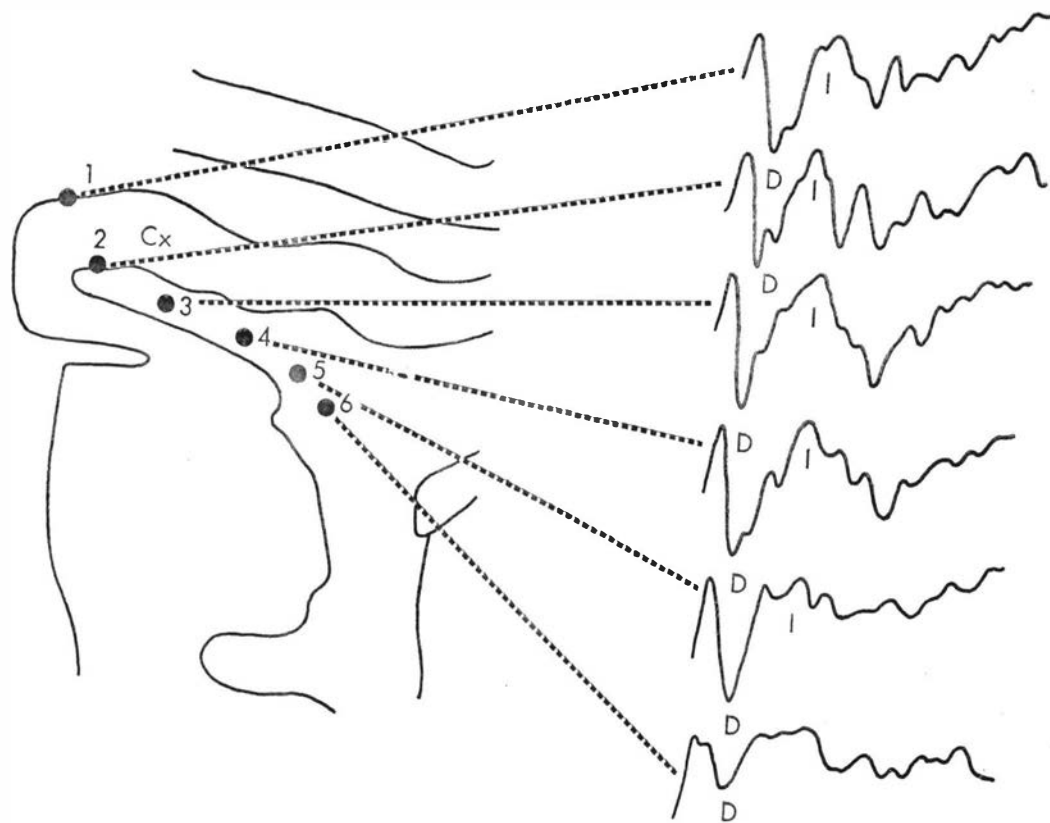
Abbreviations are as follows:

Cd - caudate nucleus
Cx - cortex
GP - globus pallidus
IC - internal capsule
Put - putamen
Th - thalamus



The first positive deflection shall be termed the D or direct wave since it is well established that it results from direct stimulation of pyramidal tract cells (64). The series of positive deflections occurring at 2.0 to 2.5 msec intervals shall be termed indirect responses or I waves which follow the direct response. These indirect waves result from stimulation of pyramidal tract cells via synaptic activation as well as from stimulation of slower conducting pyramidal tract fibers (64). Figure 14 demonstrates the changes in D-I responses at various depths within the cerebral cortex. A single shock of 12.0 volts (1.2 mA) and a pulse duration of 0.1 msec was delivered to the cortex and the evoked D-I responses were recorded in the bulbar pyramidal tract. The I wave reached a maximum amplitude at a depth of approximately 2.0 mm below the cortical surface. As the electrode descended, the I wave decreased until it disappeared at 4.0 mm below the cortical surface at a point at which synaptic activation of cortical cells would be unlikely. The amplitude of the D wave decreased deep within the cortical white matter which indicated the range was exceeded for direct activation of cortical cells. The intensity of cortical stimulation also modified the amplitude of the cortically evoked D-I responses. Various intensities were applied to the sensorimotor cortex in order to elicit the minimum and maximum D-I responses

Figure 14 Changes in Amplitude of the Direct and Indirect
Responses Recorded in the Pyramidal Tract.
Responses Elicited by a Single Shock Delivered
to the Cortex at Various Cortical Depths.



1.0 V
1.0 msec

as indicated in Figure 15.

1. Modulation of Evoked D-I Responses by Stimulation of the Caudate Nucleus

D-I responses recorded in the ipsilateral bulbar pyramidal tract and evoked by conditioning-test stimulation were enhanced, decreased or did not deviate from the control cortical evoked response. Figure 16 demonstrates average cortical control D-I responses and averaged conditioning-test D-I responses in which a decrease in amplitude of the responses occurred as a result of the caudate conditioning train. An enhancement of cortically evoked D-I responses induced by stimulation of another locus in the caudate nucleus is illustrated in Figure 17. Loci within the caudate nucleus which when stimulated decreased the amplitude of the D-I responses were distributed toward the rostral portion of this subcortical structure. Chi square analysis ($p < 0.01$) confirmed the hypothesis that there were significantly more inhibitory loci distributed within the rostral as opposed the caudal half of the caudate nucleus. However, some facilitatory loci as well as inactive points were also located in this region. Loci within the caudal portion of the caudate nucleus either facilitated the cortical responses or had no influence upon the cortical induced activity. In every case, stimulation of the caudate nucleus alone evoked no response in the bulbar pyramidal tract. Loci within the caudate nucleus that were employed in this

Figure 15 Variation in Direct and Indirect Responses Recorded
in the Pyramidal Tract due to Increasing Intensities
of Cortical Stimulation

7.0 V, 0.1 msec



10.0 V, 0.1 msec



15.0 V, 0.1 msec



20.0 V, 0.1 msec

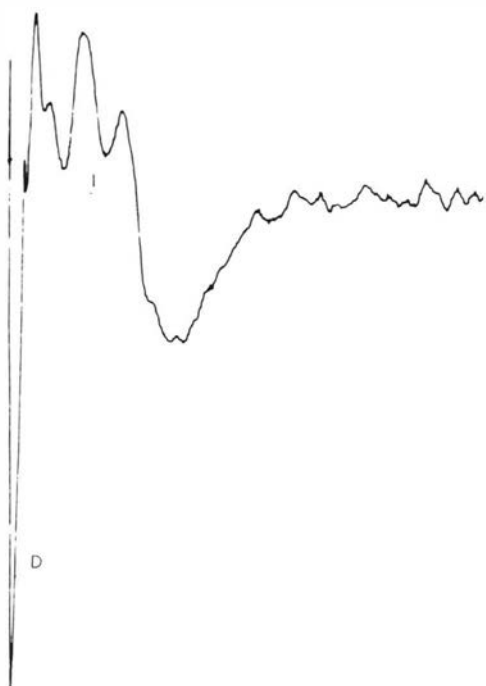


1.0 V
1.0 msec

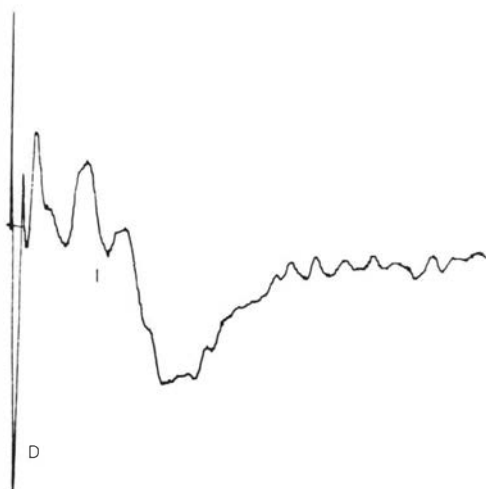
Figure 16 Modulation of Cortically Induced D-I
Responses by Caudate Nucleus Stimulation:
Inhibition

- A. Cortical Control Response:
 D-I responses.
- B. Conditioning-Test Response:
 decrease in D-I responses.
- C. Caudate Nucleus: no response
 recorded in the pyramidal tract.

A.



B.



C.

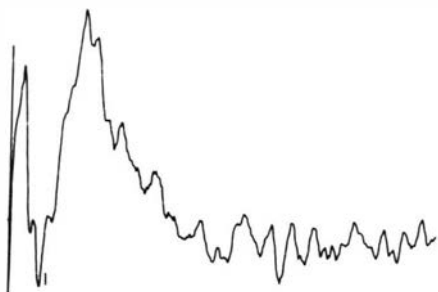


1.0 msec

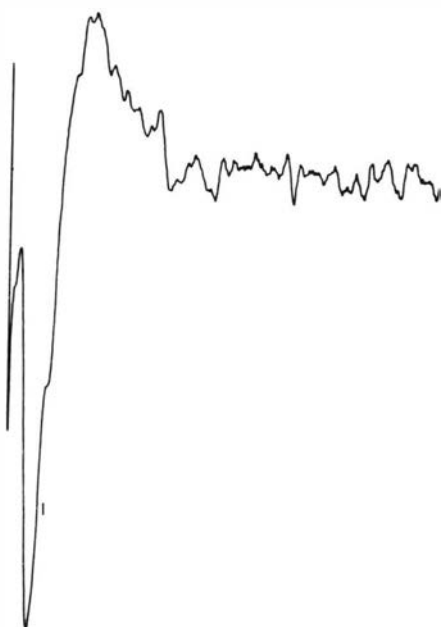
Figure 17 Modulation of Cortically Induced D-I
Responses by Caudate Nucleus
Stimulation: Facilitation

- A. Cortical Control Response:
 D-I responses.
- B. Conditioning-Test Response:
 increase in D-I responses.
- C. Caudate Nucleus: no response
 recorded in pyramidal tract.

A.



B.



C.



1.0 msec

preparation are recorded on midsagittal sections of the cat brain in Figure 18.

2. Globus Pallidus Modulation of D-I Responses

Three loci stimulated within the globus pallidus produced either enhancement (two loci) or no effect (one locus) upon D-I responses elicited by cortical stimulation. Stimulation of loci within this structure did not evoke a response in the pyramidal tract. Structures surrounding the globus pallidus and those loci bordering the internal capsule were omitted from the data.

Figure 18 Loci within the Caudate Nucleus which
Altered Cortical Induced D-I Responses
in the Unanesthetized Preparation

Loci indicate areas within the caudate nucleus which when stimulated enhanced (+), decreased (-), or had no influence (0) upon cortically elicited direct and indirect responses.

Diagrams A,B,C represent sections 2.5 mm, 3.5 mm, and 5.0 mm from the midline, respectively.

Abbreviations are as follows:

Cd - caudate nucleus

GP - globus pallidus

IC - internal capsule

Put - putamen

Th - thalamus

DISCUSSION

The circuitry of the basal ganglia provides a bidirectional mechanism for the modulation of movement and posture. (1) The basal ganglia influence cortical motor systems; and (2) the basal ganglia exert direct influences upon subcortical levels. The ultimate location of the modulatory influences of the basal ganglia occurs at the spinal level where the final integration of motoneuronal output occurs. The present study has attempted to further clarify the contribution of these two mechanisms as to the ultimate control of motoneuronal output. Results from the anesthetized preparation provided evidence for both inhibitory and facilitatory modulation of motor activity by the basal ganglia. The levels at which these modulating effects were exerted were further clarified in an unanesthetized preparation by investigating the influences of basal ganglia stimulation upon cortically induced responses within the pyramidal tract. Results from these two experimental approaches will be discussed and will be related to available literature.

A. Anesthetized Preparation

1. Supraspinal Regulation of Ia Afferent Activity

In the present study, stimulation of central nervous system structures such as the sensorimotor cortex, pyramidal tract and caudate nucleus activated the gamma motoneuronal system (monitored by Ia afferent activity) without simultaneous

activation of the alpha motoneuronal system (monitored by EMG and myogram). In many cases, facilitation of tonic Ia afferent activity due to repetitive stimulation of a cortical structure outlasted the duration of stimulation. The spinal cord internuncial pool with many synaptic connections impinging upon the gamma system could account for prolonged facilitation of the gamma system following termination of stimulation to the central structure. A clear indication that the enhancement of Ia afferent activity was due to central stimulation was the elimination of the silent period during the rising phase of contraction. Normally, a silent period of Ia afferent fibers occurs during a reflex muscle contraction when the spindle is unloaded. However, supraspinal influences impinging upon the spinal level activate gamma motoneurons which result in maintenance in the tension of the muscle spindle. Therefore, during this increase in gamma activity, the silent period exhibited during the rising phase of twitch contraction is absent.

Central influences upon the gamma system were first investigated by Granit and Kaada (26). Spontaneous discharge of Ia afferent fibers could be accelerated or diminished by electrical stimulation of various central structures, including the cerebral cortex, pyramidal tract, reticular formation and rostral portion of the caudate nucleus. Facilitation of Ia afferent activity was more easily elicited

from the reticular formation and the caudate nucleus regions than was elicited from the cortex. These results contrast with those of the present study in which enhancement of tonic Ia afferent activity was more easily elicited by electrical stimulation of the motor cortex and pyramidal tract. The location of the stimulating electrode in the precruciate gyrus and stimulus parameters may account for this difference. For example, Granit and Kaada (26) employed an electrical shock with a 1-2 msec duration and a frequency of 46 cycles per second, whereas a shock of 60 cycles per second and a 1.0 msec duration delivered to the cortex or pyramidal tract was employed in the present study and has been proven a more effective means for activating the gamma system (55). Granit and Kaada simultaneously recorded alpha and gamma discharges and demonstrated that in the anesthetized preparation electrical currents could be selectively employed so that only activation of the gamma motoneurons occurred. The absence of co-activation of the alpha and gamma system may result from anesthetic levels or from lower recruitment thresholds for gamma motoneurons.

Granit and Kaada found that stimulation of rostral and medial regions of the caudate nucleus produced facilitatory effects upon Ia afferent discharge (26). In the present project, the intensity of the trains of electrical shocks delivered to the caudate nucleus was adjusted so that these trains would not alter Ia afferent activity by themselves.

It was noted that a further increase in stimulus intensity to the caudate nucleus or globus pallidus produced an enhancement of Ia afferent activity. This phenomenon was elicited by a number of loci throughout the caudate nucleus, a result similar to that observed by others (50). In the present study, only facilitation, never inhibition, of flexor muscle Ia afferent activity was elicited by electrical stimulation of the sensorimotor cortex, pyramidal tract, or caudate nucleus (at intensities greater than forty volts). When Shimazu, et al. (62), stimulated the caudate nucleus, they often obtained both inhibition of ankle extensor muscle spindle discharge and reciprocal facilitation of flexor muscle spindle discharge. However, variable influences occurred in their preparation in which a moderate amount of anesthetic (nembutal, 15-25 mg/kg) was administered. A weak stimulus intensity (4 volts) facilitated muscle spindle activity of both flexor and extensor muscles of the ankle, whereas a stronger stimulus intensity (6 volts) elicited a reciprocal response, ie, facilitation of flexor muscle spindle discharge and inhibition of extensor muscle spindle discharge. As the depth of anesthesia increased, only reciprocal influences upon Ia afferent activity of these same muscles were elicited with electrical stimulation. These researchers postulated the existence of two descending pathways from the caudate nucleus. The first was considered a tonic, diffuse system which in-

fluenced both extensor and flexor gamma motoneuronal systems in a similar manner and the second system was thought to be a reciprocal system. Thus, the results presented by Shimazu and co-workers do not contradict those of the present study, but rather extend them by demonstrating that reciprocal inhibition of extensor spindle discharge also results from caudate nucleus stimulation.

2. Facilitatory and Inhibitory Modulating Influences of the Basal Ganglia

Evidence was presented above that stimulation of either the caudate nucleus or globus pallidus by themselves activate central mechanisms involved in the regulation of gamma activity. That the basal ganglia are involved in the regulation of motor output of other cortical and subcortical structures was further confirmed in the present study by using a conditioning-test paradigm. Of particular importance in these experiments was the adjustment of the stimulus intensity to the caudate nucleus or globus pallidus so that stimulation of these structures alone produced no flexor responses. Stimulation of the sensorimotor cortex enhanced Ia afferent discharge. Simultaneous stimulation of the cortex and a locus within the caudal portion of the caudate nucleus usually resulted in an enhancement of a cortically induced increase in Ia afferent discharge and in some cases activated the alpha motoneuronal system as was evident by EMG activity and myogram activity. Facilitatory points

were scattered throughout the caudate nucleus, a result different from that of Liles and Davis (50). They presented data that facilitatory effects upon a cortically induced response (measured by myogram tension) were located exclusively in the posterodorsal region of the caudate nucleus.

Stimulation of some rostral sites within the caudate nucleus in conjuncture with cortical stimulation elicited a reduction or cessation of cortically induced gamma activity. In some cases the maximal and minimal stimulus intensity for eliciting inhibition of cortically induced activity by stimulation of the cortex was obtained. For example, the minimal intensity for eliciting a decrease in cortically induced Ia afferent discharge was 12 volts (1.2 mA). As the intensity of the stimulus to the caudate nucleus increased, the decrease in cortically induced activity was more pronounced until a complete inhibition of cortically induced activity occurred at 30 volts (3.0 mA). Stimulus intensities of 40 volts enhanced the cortically induced increase in Ia afferent discharge. Liles and Davis (50) noted similar results and attributed the phenomenon described above as spread of current to facilitatory areas of the caudate nucleus. Inhibitory areas within the caudate nucleus tended to be concentrated in the rostral portion of the caudate nucleus, whereas those loci associated with facilitation were scattered throughout the structure (See figure6). In the present study, the concentration of inhibitory loci

toward the rostral half of the caudate nucleus was statistically significant in both the intact, anesthetized preparation and the unanesthetized preparation, and is similar to the evidence presented by Liles and Davis for caudate nucleus influences upon the alpha motoneuronal system (50).

Simultaneous stimulation of the pyramidal tract and loci within either the anterior or posterior regions of the caudate nucleus often resulted in increases in pyramidal tract induced flexor responses. All caudate nucleus loci that were studied either facilitated pyramidal tract induced responses, or had no effect; no inhibitory loci were observed. Combining these results with those concerning cortically induced responses, one can formulate the following interpretation. With respect to excitatory influences of the pyramidal motor system on flexor responses, the caudate nucleus does not inhibit these influences within the spinal cord itself. On the other hand, caudate nucleus facilitation of pyramidal tract induced flexor responses may partly occur via activation of some brainstem pathway which in turn facilitates spinal cord interneuronal activity. However, since electrical stimulation of the pyramidal tract ipsilateral to the caudate nucleus activates the corticospinal fibers in both orthodromic and antidromic directions, facilitation at the cortical level cannot be excluded. Furthermore, all levels of the pyramidal tract are contaminated with non-pyramidal tract fibers. The bulbar pyramidal tract provides the best level

of study since fiber contamination is not as great as that at other levels of the tract (64). Although only facilitation by the caudate nucleus upon pyramidal tract induced activity was observed, the level at which facilitation occurred could not be precisely defined. Antidromic stimulation of corticospinal and caudatopedal pathways offer alternate mechanisms by which facilitation of pyramidal tract induced activity can occur.

3. Decorticate Preparation

The results of the present study indicate that in the decorticate preparation only enhancement or no influence upon the pyramidal tract induced increase in Ia afferent activity occurred. Facilitatory loci were located throughout the caudate nucleus, but occurred much less frequently as compared to the intact preparation. Simultaneous stimulation of the pyramidal tract and loci within the anterior region of the caudate nucleus did not elicit inhibition of pyramidal tract induced activity, an observation confirmed by Mettler (55). He found that cortical ablation resulted in a deficit of inhibitory influences from the caudate nucleus upon reflex induced activity. Mettler concluded the striatum has a pure inhibitory or steadying influence upon cortically induced activity.

4. Facilitatory Modulation of the Globus Pallidus

Stimulation of some sites with the globus pallidus resulted in facilitation of cortically induced and pyramidal

tract induced flexor responses in the various preparations used in the present project. Substantiating evidence for the existence of facilitatory output from the pallidum is provided by recordings of unit activity during task related movements in the monkey (13). Cells within the globus pallidus associated with the particular types of movement were tonically active and increased their discharge rate prior to the onset of movement. A temporal relationship existed between the increased discharge rate that occurred and the phase of movement. No cessation of discharge rate prior to movement occurred in any of the units studied. That pallidal cells respond prior to the onset of movement further supports the present results that the globus pallidus influences cortically induced flexor responses in a facilitatory manner.

5. Current Spread

The question of current spread was a consideration in the present investigation. One investigator (45,46,48,49) has attributed all cortical or motor responses excluding contraversive head turning and circling to current spread to the internal capsule rather than stimulation of the caudate nucleus. In the present investigation, positive, negative, and inactive loci existed side by side in the caudate nucleus. The systematic localization of these loci were consistent in the various experimental approaches, ie, location of the loci within the caudate nucleus that inhibited cortically

induced responses tended to be localized toward the rostral portion of the caudate nucleus. Such caudate nucleus loci tended to be distributed well within the subcortical structure. In contrast, stimulation of loci within the internal capsule consistently facilitated cortically induced and pyramidal tract induced activity. No inhibitory or inactive loci were located in the internal capsule. Globus pallidus facilitatory sites were surrounded by inactive loci, an observation which would also tend to demonstrate lack of current spread to the internal capsule.

A second consideration involves corticofugal fibers. One could argue that stimulation of the caudate nucleus could result in selective activation of corticopedal fibers and therefore cortical modulation would be attributed to antidromic stimulation of these fibers. The cortico-caudate nucleus projection is composed of very thinly myelinated, fine caliber axons, whereas the efferent fiber projection is composed of more heavily myelinated and larger axons. The stimulus intensity was adjusted such that it was below that necessary to activate C fibers in the periphery, a threshold level that would correspond to the vast majority of caudatopedal axons. Buchwald and co-workers (4) also noted no antidromic cortical response to medial caudate stimulation. Stimulation, then, of the caudate nucleus would more likely result in excitation of intracaudate cells and/or

efferent axons.

B. Proposal of Hypothesis for the Level of Integration of Inhibitory Influences

Anatomical evidence demonstrates two possible circuits for basal ganglia influences: (1) the basal ganglia have fiber trajectories to other subcortical structures which in turn project to the spinal level; and (2) the basal ganglia project to the thalamus which in turn project to cortical areas that are involved in motor functions. In the series of intact, anesthetized preparations, both facilitatory and inhibitory loci occurred with respect to cortically induced flexor responses. In contrast, no inhibitory loci and fewer per cent of facilitatory loci were observed with respect to pyramidal tract induced flexor responses in the decorticate preparation. Also, no inhibition of pyramidal tract induced flexor responses occurred in the intact, anesthetized preparation. These observations in light of known anatomical connections (42, 61) suggest that: (1) inhibitory modulation of the caudate nucleus on cortically induced activity occurs at the cortical level; and (2) that some facilitatory modulation also occurs via the cortex.

C. Unanesthetized Preparation

The above hypothesis proposes that most or all inhibitory and some facilitatory induced activity by the caudate nucleus occurs at the cortical level. A series of unanesthetized, but immobilized cats were employed in order to

to further define the modulation of the basal ganglia upon cortically induced motor activity. The pyramidal tract served as a representative pathway conveying motor influences from the cortex. Direct and indirect waves elicited by electrical stimulation of the cortex were recorded in the pyramidal tract. Zanchetti and Brookhart (87) have provided evidence that evoked discharges recorded in the pyramidal tract could serve as a measure of cortical responsiveness. Furthermore, in the present experiments the placement of the cortical and pyramidal tract electrodes was similar for both the anesthetized and unanesthetized preparations. When used as stimulating electrodes in the anesthetized preparation, both the cortical and pyramidal tract electrodes invariably elicited flexor responses. Therefore, evoked D-I responses in the pyramidal tract in the unanesthetized preparation provides an indication of cortically induced motor activity; these responses can be modulated by stimulation of basal ganglia structures.

Stimulation of some loci in the caudate nucleus in conjuncture with the cortex decreased the cortically induced D-I responses. Inhibitory loci tended to be distributed toward the rostral region of the caudate nucleus and was similar to the distribution anesthetized preparation. The resulting decrease in the amplitude of the direct and indirect waves recorded in the pyramidal tract would reflect a de-

crease in descending influences impinging upon the spinal level. From the present evidence and that of other investigators (55,57), it can be demonstrated that the caudate nucleus exerts some inhibitory influences upon the cortex. Mettler demonstrated that the integrity of the motor cortex was necessary in order for caudate nucleus induced inhibition of pre-existing motor activity to occur. Intracellular cortical studies conducted by Hull and Buchwald (34,35,36) demonstrate that stimulation of the caudate nucleus results in a characteristic membrane hyperpolarization of cortical neurons. Demetrescu and Demetrescu (14) demonstrated the reduction of evoked cortical responses by stimulation of the caudate nucleus. The present investigation extends all of the above observations by demonstrating that stimulation of some caudate nucleus sites inhibits cortical cells whose axons project in the pyramidal tract. Paradoxically, Hodes and Peacock (32,56) excluded the rostral portion of the globus pallidus and most of the striatum as contributing to any significant extent to central facilitation.

In summary, facilitatory and inhibitory influences were elicited by high frequency stimulation of the caudate nucleus in the present study. Both facilitatory and inhibitory loci occurred in the same animal and these loci occurred side by side in the rostral region of this subcortical structure. Facilitatory influences from the caudate nucleus

tended to modulate cortically induced activity both on a subcortical level and a cortical level. Inhibitory influences of the caudate nucleus modulate induced activity on a cortical level. The discrepancy of a greater number of facilitatory influences than inhibitory influences evoked by the caudate nucleus could be partly a result of the frequency utilized in the preparations. Other researchers (4) utilized a low frequency of stimulation to obtain inhibition from the caudate nucleus whereas high frequency stimulation was employed in the present project. During high frequency stimulation, long duration positive membrane potential shifts tend to occur rather than EPSP-IPSP sequences.

D. Synthesis: Regulatory Influences of the Basal Ganglia

From the above description, one can see that the basal ganglia are organized to exert either facilitatory or inhibitory influences on movement during high frequency stimulation of the caudate nucleus. Two possible alternative explanations can be proposed to explain how these influences are manifested at cortical and subcortical levels. One is that there are two separate classes of tonically discharging pallidal cells that are both activated by the caudate nucleus. One group of pallidal cells, when activated by the caudate nucleus, facilitates cortical cells whose axons traverse in the pyramidal tract. This group could also exert facilitation at subcortical levels. The second group of pallidal

cells also activated by the caudate nucleus would inhibit cortical cells whose axons are in the pyramidal tract. Evidence for this model has been provided by unit activity recordings in which pallidal cells increase discharge rate prior to the onset of movement (12,13).

Evidence opposing this mechanism is the fact that the most common response in pallidal cells due to electrical stimulation of the caudate nucleus is a large amplitude IPSP (52). Furthermore, Zelenskeya (74) demonstrated that stimulation of the caudate nucleus elicited EPSP-IPSP responses in the globus pallidus. He noted that stimulation of the caudate nucleus elicited inhibitory influences in the ventral region of the pallidum. Recent evidence of Buchwald and co-workers (84) further substantiates the above proposal by showing that electrical stimulation of the caudate nucleus evokes EPSP, EPSP-IPSP, and IPSP responses in pallidal neurons. Thus, these studies provide evidence for a bidirectional control of the globus pallidus. The present study further substantiates this control by demonstrating that: (1) stimulation of the cortex facilitated Ia afferent activity and evoked D-I responses within the pyramidal tract; (2) the caudate nucleus facilitated or inhibited this cortically induced activity; and (3) the globus pallidus only facilitated cortically induced activity. A more parsimonious explanation of caudate nucleus modulation of cortical motor output then is that

the caudate nucleus has a facilitatory and inhibitory output control of globus pallidus cells but that globus pallidus cells have a predominately or exclusively facilitatory output control upon those cortical cells whose axons project in the pyramidal tract. Pallidal axons would also excite subcortical neurons which in turn facilitate motor output at the spinal level. Cells within the globus pallidus are spontaneously active. The caudate nucleus, then, facilitate and inhibits this activity within the globus pallidus. The latter would in turn modulate cortical activity via the thalamus but only in a facilitatory manner. That a thalamic relay is an intermediate component in this mechanism is supported by anatomical evidence (61,62) as well as electrophysiological data (30,51) that demonstrates that the integrity of the ventralis lateralis is necessary for the production of cortical responses evoked by caudate nucleus stimulation. Figure 19 is a model synthesized from information obtained in the present research and from other studies (8,30,73). According to this model, high frequency stimulation to the caudate nucleus facilitates or inhibits the spontaneous activity of pallidal cells (42). Stimulation of the caudate nucleus would thereby indirectly inhibit or facilitate cortical cells whose axons project in the pyramidal tract. Basal ganglia influences mediated via subcortical levels facilitate cortically induced and pyramidal

Figure 19 Synthesis: Regulatory Influences of the Basal Ganglia

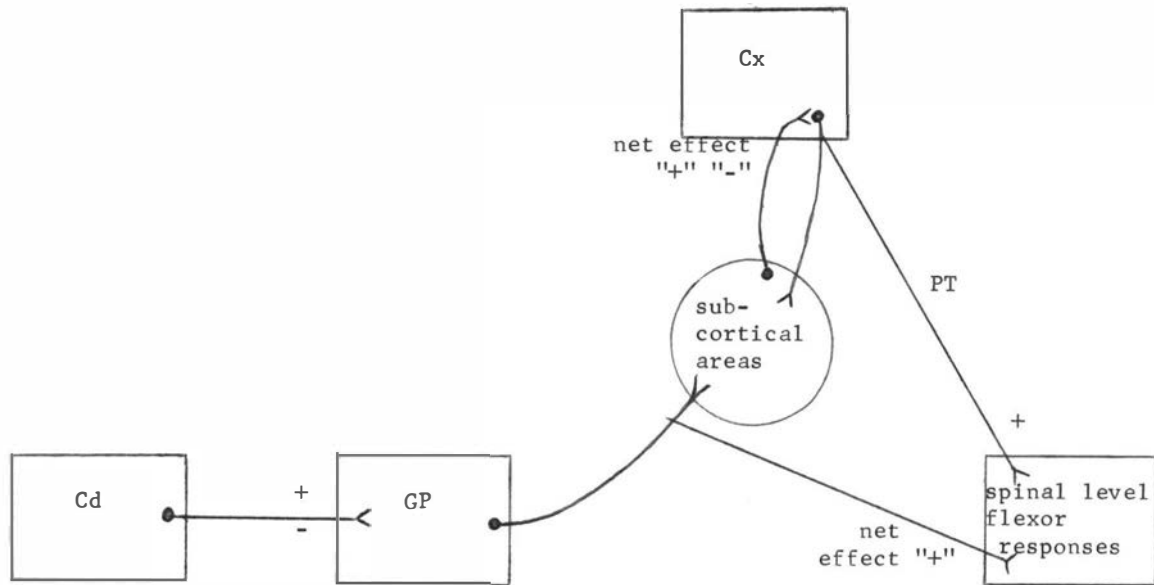
Abbreviations are as follows:

Cd - caudate nucleus

Cx - cortex

GP - globus pallidus

PT - pyramidal tract



tract activity on a spinal level.

E. Central Regulation of Movement

The cortex was once considered to initiate movement via a corticospinal pathway and some fiber pathways which projected to subcortical structures (18). These subcortical structures in turn descend to the spinal level. This concept, then, considered the subcortical structures as the final level in the neuroaxis before the spinal level. Recent proposals developed a hierarchy in which: (1) subcortical structures influence the cortex; and (2) the cortex is considered more closely linked to the spinal level. DeLong (11,12,13) and Thach (81) demonstrated an increase in unit activity in the putamen, globus pallidus and cerebellum prior to the onset of movement. Porter (66) and Evarts (19) obtained an increase in cortical activity prior to the onset of movement. This cortical activity preceded a decrease in extensor motoneuronal activity which in turn preceded an increase in flexor motoneuronal activity. The latter occurred concomitantly with the onset of movement. Therefore, both the cortico-spinal system and the basal ganglia are concurrently involved not only with tension development of movement but also in the temporal relationship of activation, or even the initiation of movement.

Kornhuber (44) hypothesis considers the major function of the basal ganglia as a ramp generator, ie, involved in a

constant velocity of movement. Input to the basal ganglia from joint receptors and the muscle spindle would provide information concerning muscle length and velocity of movement. Dysfunction of the basal ganglia would involve the release of function or deficit of ramp generation. Athetosis, a slow wringing type of movement, is a representative example of basal ganglia deficit, whereas hemiballism, a rapid, involuntary movement generally involving the entire extremity would be a demonstration of release of function. According to Kornhuber, the cerebellum would be more involved in the regulation of ballistic movements. However, DeLong (11) has provided evidence that the basal ganglia not only function as a ramp generator but may also be involved in ballistic movements. His contention was based on a demonstration that units within the putamen respond to fast as well as to slow movements. Movements elicited from the cortex, then would be regulated by both cerebellar and basal ganglia structures. This idea is substantiated by several researchers (11,81) and is consistent with results of the present investigation.

A consideration of basal ganglia influences upon cortical and pyramidal tract evoked activity by itself does not accurately define the role of the basal ganglia in the central regulation of movement, since this function can be expanded as a system interdependent with behavioral dimensions such as feeding behavior. Sorenson (76), and Wang and Akert

(84) studied behavioral organization that occurred with lesions of the striatum in the rat and cat, respectively. Sorenson related the degree of feeding behavior to the extent of the striatal lesion. A striatal preparation is one in the cerebral cortex was removed and in some cases varying degrees of the caudate nucleus were removed. A thalamic animal is one in which the thalamus is the highest remaining structure in the functional organization of the central nervous system. Thus, in the thalamic preparation, the striatum is completely removed. Both researchers observed that striatal animals spontaneously ate and groomed themselves whereas the thalamic preparation did not feed or groom. When food was placed in the mouth of a thalamic preparation, the animal would chew but not swallow, thereby indicating that the organization of feeding behavior following eating was also disrupted in this preparation.

Sorenson postulated that feeding behavior was correlated with the amount of caudate nucleus present. Diencephalic structures have been postulated to be involved in appetitive behavior. The mechanisms facilitated by diencephalic structures involved in feeding behavior include a complex organization of locomotion to find food and the sequence of behavior related to feeding and grooming. These mechanisms are suppressed until the appropriate time for feeding behavior to occur. When feeding behavior is elicited other motivated

activities need to be suppressed. He proposed the hypothesis the thalamic animal lacks the inhibitory influences from the striatum to suppress other behavioral activities in order that feeding behavior be the only active behavioral activity. As the extent of the caudate lesion is decreased, a greater inhibitory influence over non-feeding behavior is exerted. Therefore, activity is channeled to motivational sequences for feeding.

The basal ganglia may also have a functional role in learned tasks. Buchwald (2,7,8,30) attempted to relate the "inhibitory" caudate nucleus loop to behavioral observations resulting from caudate nucleus stimulation. During low frequency stimulation, the cat passed from an aroused state to a state of drowsiness and the accuracy of a bar pressing task decreased during this period, whereas the reaction time for the task increased. A novel stimulus presented to the animal would re-initiate the task. High frequency stimulation within the caudate nucleus did not decrease reaction time nor increase performance level in the task related situation. However, if low frequency stimulation applied to the caudate nucleus resulted in cessation of the task, reapplication of high frequency stimulation resulted in initiation of the task. If both low and high frequency stimulation were applied simultaneously to the caudate nucleus the task continued. As previously described, DeLong

obtained increases in unit discharge prior to the onset of movement and postulated that the basal ganglia may be involved in the initiation of movement. Therefore, in consideration with the above observations of Buchwald, a high frequency stimulus mechanism activating the basal ganglia may be involved in the initiation of movement. The concept for initiation of movement may be further substantiated by a clinical correlation in which the Parkinsonian patient has difficulty in the slow initiation of movement.

The present research demonstrates that the basal ganglia modulate outputs of both cortical and subcortical motor systems. Thus, the basal ganglia not only receive inputs from many central nervous system regions but may exert modulating influences on several efferent systems. Furthermore, the basal ganglia are not only involved in the regulation of movement, but are also involved in the regulation of complex motivated behaviors. Although these two functions may operate independently, it seems more likely that the regulation of motivated behaviors and the modulation of locomotor activity are to an extent subserved by common neural mechanisms within the basal ganglia.

SUMMARY

Physiological mechanisms underlying basal ganglia have been difficult to assess due to: (1) electrical stimulation and discrete surgical lesions within these structures fail to produce as significant a response as that observed in dysfunction; and (2) the basal ganglia are many synapses removed from sensory input and from lower motoneurons. However, two general mechanisms based on anatomical studies are possible for modulation of motor activity by the basal ganglia. These mechanisms are: (1) modulation of the output of cortical neurons that exert motor influences and (2) modulation of subcortical neurons that exert motor influences.

Differentiation between these two mechanisms was accomplished in the present study by two experimental approaches, both of which employed the conditioning-test paradigm. The first approach was an investigation of basal ganglia modulation (conditioning stimulus) of flexor responses of the anterior tibialis muscle elicited by electrical stimulation of the sensorimotor cortex (test stimulus) and pyramidal tract (test stimulus). These investigations were carried out in the intact and in decorticate cats. The anterior tibialis muscle is activated during the first phase of movement and was therefore used in this study since a characteristic of some basal ganglia dysfunctions

involve a show onset or initiation of movement.

The second approach was an analysis of modulation of cortically induced pyramidal tract responses by conditioning shock trains delivered to various loci within the basal ganglia. Both approaches were designed to determine whether inhibitory and facilitatory motor influences of the basal ganglia occurred at a cortical or subcortical level.

Simultaneous pairing of the caudate nucleus and cortex evoked either an enhancement, reduction or no alteration of the cortically induced increase in flexor responses (measured by Ia afferent activity, EMG, myogram) whereas no inhibitory influences occurred from caudate nucleus stimulation upon pyramidal tract induced flexor responses in either the intact or decorticate preparation. Inhibitory loci were distributed toward the rostral portion of the caudate nucleus, whereas facilitatory loci were distributed throughout; and this distribution was statistically significant (Chi Square; $p < 0.01$). Only enhancement or no influence upon cortical induced or pyramidal tract induced responses were obtained by conditioning stimuli to the globus pallidus.

In the unanesthetized, but immobilized cat, trains of shocks delivered to the caudate nucleus enhanced, reduced or had no influence upon the cortically evoked direct and indirect responses recorded in the bulbar pyramidal tract.

Distribution of facilitatory and inhibitory loci were organized in a similar fashion as in the anesthetized preparation. Facilitatory and inhibitory loci existed side by side in the rostral portion of the caudate nucleus and inhibitory loci occurred with significantly greater frequency in rostral as opposed to the caudal half of the caudate nucleus (Chi Square, $p < 0.01$). Facilitatory loci were distributed throughout the structure.

From these observations, a model was proposed in which the output of the caudate nucleus exerts a bidirectional control: the caudate nucleus exerts both facilitatory or inhibitory modulation of the tonically active globus pallidus cells. The latter in turn predominately or exclusively facilitates the pyramidal tract output as well as the output of subcortical structures; both effects facilitate motor responses at the spinal level.

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