CORTICIFUGAL EXCITATORY AND INHIBITORY INFLUENCES AND THEIR PATHWAYS ON NEURONS OF THE DORSAL COLUMNS IN THE CAT

by

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ABSTRACT

Influences of the motor cortex on the dorsal column nuclei were investigated by analysis of the response discharge of individual cuneate and gracile neurons to peripheral and cortical stimuli. Glass micropipettes 0.5 to 2 micra tip diameter were used to record single unit activity in the dorsal column nuclei of anesthetized cats.

Following electrical stimulation of the footpads with single pulses, the majority of dorsal column neurons responded with a short and slightly variable latency and followed afferent inputs at high rates. These were, therefore, considered to be excited monosynaptically from the periphery. The remaining neurons did not satisfy the above criteria and hence were considered to be excited via the dorsal column relay, or via the recurrent collaterals within the nucleus or by some other mechanism.

Electrical stimulation of the motor cortex altered the excitability of dorsal column neurons in a number of ways: 1) The motor cortex exerted an excitatory influence on 40 per cent of the units isolated in the dorsal column nuclei. This cortical influence appeared to be direct, since most of the units dischargedin response to single cortical shocks with a small and slightly variable latency and faithfully followed repetitive cortical stimulation at rates in excess of 50 per second. 2) The motor cortex exerted a depressive influence on 55 per cent of the units isolated in the dorsal column nuclei. The majority of such units met the criteria of monosynaptic activation by the testing peripheral volley and were considered to be inhibited by the conditioning cortical volley. The remaining units were blocked. The cortical depressive influence appeared to be multisynaptic, since trains of cortical shocks were usually required at conditioning-testing intervals between 50 and 150 msec. In addition, full recovery from

depression was attained at conditioning-testing intervals of 150 to 200 msec. 3) Drastic increases in the intensity or duration of cortical stimulus parameters resulted in a reversal of cortical conditioning influence from depressive to excitatory in five per cent of units isolated in the dorsal column nuclei.

Motor cortical excitatory and depressive influences on the dorsal column nuclei had the following characteristics in common: 1) They could be graded, depending upon the relative strengths of the conditioning and testing volleys. 2) They were demonstrated on the spontaneous discharge, as well as the response discharge of some cuneate units to tapping or maintained pressure on the ipsilateral forepaw. 3) They were more efficacious from the contralateral than from the ipsilateral motor cortex.

In animals with transected brain stems, except for the bulbar pyramids, both excitatory and depressive corticifugal influences on cuneate units could still be demonstrated. In animals with sectioned pyramidal tracts on both sides, corticifugal influences on cuneate units could rarely be demonstrated; when present, these influences were weakly depressive. In animals with a sectioned pyramidal tract on one side, corticifugal influences on cuneate units could rarely be demonstrated if the pyramidal cut and the stimulated motor cortex were contralateral to the cuneate nucleus tapped for unit recording; when present, these were weakly depressive. Corticifugal excitatory and depressive influences were readily demonstrated when the pyramidal cut was contralateral both to the stimulated motor cortex and to the cuneate nucleus tapped for unit recording.

The hypothesis is presented that the anatomically demonstrable direct endings of pyramidal tract fibers on dorsal column neurons provide the necessary anatomical substrate for the corticifugal excitatory pathway.

Furthermore, the anatomically demonstrable direct endings of pyramidal tract fibers on reticular neurons of the lower brain stem provide the first part of the anatomical substrate for the multisynaptic corticifugal inhibitory pathway.

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CHAPTER ONE

HISTORICAL BACKGROUND AND INTRODUCTION

HISTORICAL BACKGROUND

Since 1900 various investigators have suggested, on the basis of anatomical and clinical material, that descending neural systems may terminate in pure sensory nuclei and influence their synaptic transmission (1,23,56,100,105 and 127). In 1911, Head and Holmes (56) argued that contralateral hyperpathia in the so-called thalamic syndrome in man is a cortical release phenomenon and proposed that sensory impulses from the periphery to the cortex are under similar inhibitory influences. Brouwer, in 1933 (23) maintained, from studies of corticifugal projections in the visual system, that, in general, there is a centrifugal side in the process of sensation and that "such a centrifugal influence on sensory centers must be of great significance to physiology" (23, p. 626) and to psychology. Because it is easier to evoke cortical potentials under deep than under light anesthesia, Adrian (1) suggested that deep anesthesia suppresses an inhibitory effect (if that exists at all) on the sensory pathway.

During the last decade there has been an increased interest in the central control of sensory systems. Such controls have been demonstrated at various relay sites for both somatic and special sensory systems. The present dissertation describes corticifugal pathways which exert excitatory and inhibitory influences on the gracile and cuneate neurons in the cat. The present chapter outlines the anatomical and physiological information which formed the background for this study.

SECTION ONE: ANATOMY AND PHYSIOLOGY OF THE DORSAL COLUMN NUCLEI

General considerations

The dorsal column nuclei are the gracile and cuneate nuclei, sometimes referred to as the nuclei of Goll and of Burdach, respectively.* These nuclei are composed of second-order neurons located bilaterally in the dorsal part of the caudal medulla oblongata. Bishop (14) believes the dorsal column nuclei are unique to mammals, but Kappers et. al. (69) state that they are also found in certain lower forms. The two nuclei receive their spinal sensory input through axons which originate in the dorsal root ganglion and then ascend uncrossed as the dorsal columns of the spinal cord. The axons of the dorsal column nuclei decussate shortly after their origin and ascend as the medial lemniscus to terminate on cells of the posterolateral part of ventral nucleus of the thalamus. The latter nucleus projects to the somatosensory cortex. According to Rose and Mountcastle (113), the dorsal column sensory system exhibits several striking organizational features. First, messages from the body surface

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*The external, lateral or accessory cuneate nuclei, bilaterally located in the caudal parts of the medulla, were included as part of the dorsal column nuclei by Ferraro and Barrera (39). In monkeys subjected to cervical and upper thoracic dorsal root sections, degenerated fibers (Marchi technique) have been traced to both the cuneate and external cuneate nuclei (38 and 126). Afferent fibers from the lumbar and sacral segments terminate in the gracile nuclei. Similarly, in cat, degenerating projections (Marchi technique) to both the cuneate and external cuneate nuclei have been noted following section of the first three cervical dorsal roots (36 and 107). The external cuneate nucleus is the brain stem homologue of Clarke's column. The two nuclei are similar in cell morphology, location termination (in the cerebellum) and function as judged by the effect of lesions (38 and 96). Using a silver stain for degenerating fibers, Liu (84) demonstrated in cats that Clarke's nucleus receives afferent input from all body segments except head and upper neck and that the external cuneate nucleus receives input from neck, forelimb and trunk. He suggested that the two nuclei represent a single functional system between the periphery and the cerebellum. The external cuneate nucleus, therefore, probably plays no role in conscious sensation and has not been investigated in the present study.

are projected centrally through the successive relays in a precise topographical arrangement. Secondly, "the system encompasses within a single topographical pattern several submodalities of the general sense of mechanoreception" (113, p. 397). Thirdly, transmission at the various relay stations has a high safety factor.

The functional significance of the dorsal columns may be deduced from the sensory defects which ensue when they are destroyed. Following destruction of the dorsal columns in man, position and movement of the limbs is no longer appreciated, the threshold to tactile stimuli (touch and pressure) is increased and certain perceptual functions (vibration, two-point discrimination, localization, figure writing and stereognosis) are impaired (113 and 115). The sensations served by the dorsal column system are discriminative, gnostic, epicritic or spatial (115). Dorsal column afferents from the viscera have been described but their function is not clear (4,7 and 134).

Neuroanatomical studies

Anatomical tracing of pathways in the central nervous system is accomplished by observing degeneration resulting from surgical or pathological lesions. The staining techniques employed to detect these changes depend on the poorly understood and capricious principle of metallic impregnation of the degenerating fibers (93). The older methods (including the Marchi technique) stained degenerating myelin and hence were of little use in tracing the fine endings which, of course, are unmyelinated. Silver impregnation methods, which stain the axis cylinder (45 and 94), correct this defect and in addition have several other advantages over the Marchi method. The silver-impregnated fragments of degenerating

axons are more readily distinguished from normal tissue than are the droplets of degenerating myelin stained by the Marchi technique. Also, since silver impregnation is applied to sections rather than to whole blocks, alternate sections can be stained by some other method.

However, silver impregnation is capricious and calls for caution in interpretation [for a critical review see Glees and Nauta (48)]. The time allowed for degeneration, duration and type of fixation, variations in purity of reagents and careless staining can lead to significantly different results with the same technique. Glees technique (45) stains normal and degenerating axons equally well but offers the advantage of selectively identifying degenerating terminal rings or boutons. The Nauta-Gygax technique (94) brings out the pathological changes more or less selectivey in the preterminal and pericellular parts of degenerating axons.

The afferent nerve fibers to the dorsal column nuclei have been studied mainly by the Marchi technique following lesions of the dorsal roots and columns in the cat (36,47,49 and 107), the monkey (25,38 and 126) and man (40). By tracing degeneration resulting from lesions placed at various levels, the ascending course of the afferent fibers in the dorsal columns was systematically followed and the approximate area of fiber terminations within the dorsal column nuclei was defined. The results indicated that the dorsal columns and their nuclei possess an orderly topographical arrangement. The tracts are laminated so that afferent fibers from caudal segments terminate in the most medial parts of the gracile nuclei. Successively more rostral segments contribute fibers which terminate in lamellae of cells more laterally situated in the gracile and cuneate nuclei. Thus the cuneate nuclei receive dorsal root fibers from upper thoracic

and cervical segments. The same topographical organization is maintained in the medial lemniscus (37) and, indeed, all the way to the somatosensory cortex. While transverse sections stained by the Marchi technique indicated considerable overlap of the terminals of neighboring dorsal roots, sagittal sections impregnated with silver (47 and 49) showed much less overlap. However, overlap within the terminal area of one root was seen. Each large parent fiber divides into two or three branches immediately before terminating and concomitantly loses its myelin sheath. In turn, each of these branches divides into several branches which end in the form of little brushes on several dorsal column neurons. Since the dendrites of the latter cells were too large and tortuous to follow easily in serial sections, only axo-somatic connections were studied. In the same study (49), it was estimated that about 25 per cent of the fibers entering the cord through the dorsal roots reach the dorsal column nuclei. there is no anatomical evidence that dorsal column nuclei receive an input from cell bodies in the spinal cord.

The axons of the dorsal column nuclei cross entirely at the lower end of the medulla and ascend in the brain stem to end on the posterolateral part of ventral nucleus of the thalamus. Evidence leading to this conclusion was derived from the study of axonal degeneration following lesions of the dorsal column nuclei in the cat (87 and 95), the monkey (17) and in man (110).* The lemniscal fibers appear to terminate only in the ventral nucleus of the thalamus with little or no branching to supply the brain stem reticular formation or the nuclei of the extrapyramidal motor system (17).

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* Physiological evidence purporting to demonstrate ipsilateral conduction in the medial lemniscus is meager and inconclusive (16 and 28).

Electrophysiological studies

Potentials recorded from the surface and from the depth of the cat's cuneate nucleus following electrical stimulation of various forelimb nerves were investigated by Therman (119). A volley entering the "resting" nucleus produced surface potential changes consisting of a triphasic spike (duration one msec.) followed by a notched negative potential (duration five msec.) and a positive potential (duration about 100 msec.). The configuration resembled the spinal cord dorsum potentials described by Hughes and Gasser (64). Analysis of the various components led to the conclusion that the triphasic spike represents the incoming afferent volley and that the final positive potential reflects activity in the underlying reticular formation. The negative potential is more complex; its initial portion represents nuclear activity set up by a direct monosynaptic action. The second elevation of negative potential (beginning three msec. after the beginning of the triphasic spike) indicates delayed nuclear activity initiated by the "dorsal column relay".

The "dorsal column relay" is apparently subserved by the same mechanism as the dorsal root reflex. Toennies (120 and 121) first reported that an afferent volley, whether set up by peripheral nerve stimulation or a tap on the skin or patellar tendon, evokes, after a brief central delay, a centrifugal discharge in the dorsal root fibers. Though regularly present when the spinal cord is at normal temperature, this dorsal root reflex was augmented greatly when the cord was cooled. Hursh (66) showed that the dorsal root reflex is conducted not only over the dorsal root fibers to the periphery, but also along the ascending branches of these dorsal root fibers in the dorsal columns to the gracile and cuneate nuclei.

It is not certain, however, whether the fibers carrying the dorsal root reflex are the same as those which carry the dorsal column relayed discharge. The latency (about 3 msec.), temperature sensitivity and the prolonged discharge of the dorsal root reflex (and its associated dorsal column relay) suggest a synaptic mechanism, but because there is no histological evidence for dorsal root efferents, ephaptic excitation has been invoked as an explanation (54).

Activation of cuneate neurons by the relay mechanism was also noted by Amassian and DeVito (9). Using extracellular microelectrodes to record single unit activity, they distinguished in the cat's cuneate nucleus two functionally distinct groups of neurons. One group responded to forelimb stimulation with a short latency (8 msec. or less from foot pad) high-frequency bursts and faithfully followed frequencies up to 50 to 380 per second. These units were assumed to be activated monosynaptically by the primary dorsal column volley. The second group responded with a much lower frequency burst and with latencies in excess of 8 msec., failed to follow repetitive stimulation at rates exceeding 50 per second and were most frequently encountered in preparations in which the cord temperature was low. The second group, therefore, was believed to be activated through the relay mechanism.

In addition to the primary and relay routes of excitation, Amassian and DeVito (9) found that some cuneate neurons are activated through recurrent collaterals within the nucleus. When precautions were taken to minimize temporal dispersion of the presynaptic volley (stimulating dorsal columns at C2) and to exclude the relay system (cord section below C2), some cuneate neurons discharged with latencies allowing more than one synaptic delay. Also, stimulating the contralateral medial lemniscus

activated such units synaptically (as judged by latency and frequency following) as well as antidromically.

The inputs to the dorsal column nuclei are not all excitatory. Inhibition of evoked single unit activity by stimulation of appropriate nerve trunks or skin areas has been demonstrated in both gracile (50) and cuneate nuclei (9). The occurrence of inhibition and the multiplicity of excitatory mechanisms described above indicate clearly that the dorsal column nuclei are much more complex than might be supposed.

Finally, it may be mentioned that electrophysiological studies confirm the neuroanatomical demonstration of the topographical organization of the dorsal columns and their nuclei (67,74 and 134).

SECTION TWO: MOTOR CORTEX AND ITS DIRECT PROJECTIONS IN THE CAT

The extent of the motor cortex

Since the earliest experiments on the excitable motor cortex by Fritsch and Hitzig (42), a large number of studies have been published on somatic movements resulting from electrical stimulation or the application of drugs to the cortical surface. Responsive cerebral cortical areas have been mapped in various mammals, including man. Although the organization of this motor system (e.g., movement vs. muscle representation) has been vigorously debated (26 and 129), it is generally agreed that somatic activities resulting from cortical stimulation are crude and represent at best only "fragments of skilled movements" (118, p. 799).

In the cat, electrical stimulation of the cerebral cortex (27,44, 88 and 114) has delineated a motor area extending from the sagittal margin of the cortex laterally to include the posterior sigmoid gyrus, most of the anterior sigmoid gyrus and parts of the coronal and diagonal gyri. The

motor area is somatotopically organized with forelimb, hindlimb and head-neck musculature being represented successively in a medial to lateral direction. There is considerable overlap between the somatotopic divisions. Some cortical foci within this area, when stimulated, yield changes in the respiratory (68 and 117) and autonomic (53,63 and 68) systems. The excitable motor cortex hidden within the cruciate, coronal and presylvian sulci occupies an area equal to the exposed motor cortex and follows a pattern of motor representation which is continuous with that of the surface gyri (32 and 33).

Outside this "low threshold" motor area (sometimes referred to as Area I), a few other cortical regions yield somatic movements. The most important of these is Area II, which lies between the anterior suprasylvian and ectosylvian sulci. In this area, forelimb, hindlimb and head-neck representation are in mirror-image orientation to Area I. Stimulation of another area, anteromedial to Area I, causes deviation of head and eyes to the opposite side. Other less consistent and relatively minor somatic motor areas have been described (44).

Most of the cortically elicited motor responses are entirely contralateral. However, an ipsilateral representation of face is found along the middle part and just posterior to the presylvian sulcus (44 and 118). Stimulation of Area II often elicits complex bilateral responses, e.g., movements in the contralateral arm and ipsilateral leg or vice-versa (44). In cat the motor areas are coextensive with the sensory receiving areas as delineated by electrical recording methods (118).

The technique of electrical stimulation in neurophysiological research has limitations. Stimulus parameters, such as pulse form, duration, intensity,

train duration and frequency, all influence the results (2,18,29 and 133). For example, varying these parameters may vary the size of the plotted motor cortex (83). Other variables are the electrode type [mono-vs. bipolar, structure and spacing (118)] and the depth and kind of anesthesia (27).

Efferent projections: general considerations

It is often incorrectly assumed that the movements evoked by stimulating cortex are mediated exclusively by the pyramidal tract.* However, cortical stimulation in bilaterally pyramidotomized cats still elicits movement, indicating that cortically originating extrapyramidal pathways alone are capable of producing movement (123). Furthermore, corticoreticular fibers running with the pyramidal tract are functionally extrapyramidal. For these reasons, and others, the distinction between pyramidal and extrapyramidal systems is artificial and arbitrary (99 and 118).

Origin and termination of the pyramidal tract: neuroanatomical studies

The pyramidal tract is a phylogenetically recent structure, being present only in mammals, and becoming progressively larger in the more advanced forms (81). In monkey, all of the pyramidal tract fibers originate in the cortex (90). They are mainly fine and slowly conducting, only about 61 per cent being myelinated. Of the myelinated fibers only about two per cent are greater than 11 micra in diameter. Because of the predominance of small caliber and unmyelinated fibers, silver stains are most suitable for detecting degeneration following cortical lesions. In cats with

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*The pyramidal tract is composed of those neurons whose descending axons pass longitudinally through the medullary pyramids and excludes the thin transversely coursing external arcuate fibers and other fibers which depart from the main tract at supramedullary levels (99). The direct continuations of the pyramidal fibers into the spinal cord are the corticospinal tracts.

motor cortical lesions, Walberg and Brodal (125) found degenerating fibers (Glees stain) running through the internal capsule, the cerebral peduncle, the longitudinal bundles of the pons and the medullary pyramid to the level of the lumbar segments of the spinal cord. Some fibers crossed the corpus callosum to descend in the contralateral pyramidal tract. Many fibers crossed in the pyramidal decussation to continue as the contralateral lateral corticospinal tract, but the ipsilateral lateral and both ventral corticospinal tracts showed degenerating fibers. Similar but less marked patterns of corticospinal degeneration were found following discrete lesions in the occipital and temporal lobes.

Chambers and Liu (24) argue that the Glees technique stains both normal and degenerating axons; they therefore repeated the above study in cats using the Nauta-Gygax technique and the Marchi stain as control. Their studies indicated that the corticospinal tract originates from cells in the sigmoid, coronal and anterior ectosylvian gyri. They found no evidence for an origin of the pyramidal tract in occipital, temporal or parietal areas. Sections of the bulbar pyramid or ablation of the sigmoid gyrus caused similar patterns of spinal degeneration in a large crossed lateral and a small uncrossed ventral corticospinal tract. Following lesions of the ectosylvian gyrus a few degenerating fibers were seen in the ipsilateral ventral tract and in the contralateral lateral tract, but even in these instances degeneration was most abundant in the crossed lateral and uncrossed ventral tracts. Nauta-Gygax stained sections revealed preterminal degeneration mainly in the dorsal horn but with a sprinkling in the intermediate gray. There was no degeneration in the ventral horn.*

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* These anatomical findings agree with the physiological observations of Lloyd (85) on the spinal connections of the pyramidal tract in the cat.

The distribution of degenerated fibers in the gracile, cuneate and Clark's nuclei will be described in a later section.

In a similar study, Kuypers (75) described direct cortical projections to the pons and lower brain stem in the cat. In addition to fibers ending in sensory nuclei (see below), considerable terminal degeneration was seen in the reticular formation. These fibers were distributed mainly to contralateral lateral reticular nucleus in pons and medulla; others ended diffusely on both sides in the central tegmental region of the medulla oblongata and of the pons. The corticobulbar projections largely explain why the fiber content of the pyramid is significantly less at the caudal than at the rostral end. Fibers from the face area ended predominantly in the spinal trigeminal nucleus (see below) and lateral tegmentum of the medulla. Kuypers considers the latter area as an uninterupted rostral continuation of the area of pyramidal termination in the spinal cord. There were no direct cortical projections to cranial motor nuclei.*

In addition to the well-known descending components of the pyramidal tract, Brodal and Walberg (21) describe an ascending pyramidal system. These authors, using both the Glees and Marchi stains, found in the pyramids of cats subjected to various lesions of spinal cord and dorsal column nuclei, a few degenerating fibers which could be traced all the way to the cortex.** Since the concept of an ascending pyramidal system is

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In monkey, some corticospinal fibers end on ventral horn cells (12,13,77, 99 and 104).

* In contrast, in monkey, chimpanzee (77) and man (76), there are direct cortical connections to cranial motor nuclei; such direct connections in both cord and brain stem appear to be a phylogenetically recent acquisition.

** A purported electrophysiological demonstration of ascending pyramidal

revolutionary, the findings should be checked by other methods. In any case, the number of ascending fibers, if any, is small (only four per cent of the total).

Origin and termination of the pyramidal tract: electrophysiological studies

The pyramid in its bulbar course is readily accessible for either electrical stimulation or recording. However, a frequently ignored pitfall in such procedures comes about from the close proximity of the medial lemniscus which courses just dorsal to the pyramidal tract throughout its bulbar course. So intimately related are the two tracts that they cannot be readily distinguished in normal Weil stained sections although Marchi stained sections, in preparations subjected to cortical ablations or lesions of the dorsal column nuclei, reveal them as separate but contiguous fiber bundles (46). The close relationship between pyramid and lemniscus makes selective stimulation, section or recording from the pyramid difficult. However, careful dissection techniques enable one satisfactorily to separate the two tracts (85,104,122 and 130).

The danger of confusing lemniscal and pyramidal responses is illustrated by studies of the antidromic response of the motor cortex to shocks applied to the surface of the bulbar pyramid. First introduced by Woolsey and Chang (132) and later used by others (79 and 103), this method has been used to map the origin of the pyramidal tract. The basic assumption was that the recorded response was entirely due to antidromic activation of the pyramidal tract. However, when the pyramidal tract is dissected free from the medulla and stimulated in isolation, the resulting pure anti-

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fibers (19) was shown to be erroneous. Afferent activity ascribed to ascending pyramidal fibers was probably recorded from the adjacent medial leminsiscus (80 and 97).

dromic cortical response is far simpler than those induced by indiscriminate surface pyramidal stimulation which invariably spreads to lemniscus and other adjacent systems (122). These findings emphasize the need for cautious interpretation of previous studies which employed surface stimulation.

Another and safer electrophysiological technique for studying the pyramidal tract is to record the pyramidal response to cortical stimulation. Following the pioneering work of Adrian and Moruzzi (3), Patton and Amassian (98) analyzed the pyramidal potentials resulting from cortical stimulation with single short (0.1 msec.) pulses. On the basis of latency, duration, wave form, frequency following, susceptibility to asphyxia, anesthesia and cortical injury, they divided the cortically evoked pyramidal potential complex into an early D wave due to direct activation of pyramidal cells and later repetitive I waves which result from relayed synaptic activation of pyramidal cells through cortical interneurons. Mapping the cortical foci from which stimulation elicits D waves yields a map of the cortical origin of the pyramid (99). In cat, the maps so obtained agree fairly well with those obtained by other methods.

Conduction velocities of pyramidal tract fibers have been estimated by a variety of techniques (15,22,78,85,98,101 and 132). Maximal values appear to be about 60 to 65 meters per second although values up to 164 meters per second have been reported (22). The medullospinal portion of the tract may conduct more slowly than the corticobulbar portion; due to collateral branching along its course in the brain stem, the pyramidal fibers become progressively thinner. According to Lance (78) the compound

action potential of the bulbar pyramid has two separable elevations corresponding to conduction velocities of 70 to 22 meters per second and 22 to 8 meters per second, respectively.

Direct corticifugal projections to somatic sensory nuclei: anatomical studies

As early as 1903, Probst (105) described, in cats subjected to hemisection of the tegmentum, degenerating fibers leaving the pyramidal tract to reach the dorsal column nuclei. He suggested that "...es wäre aber nicht ganz unmöglich, das hier eine Schaltung zwischen sensiblen und motorischen Neuronen stattfände" (105, p. 275). Mettler (89) also described fibers which leave the pyramidal tract rostral to the decussation and pass to the contralateral spinal trigeminal nucleus.

Silver staining techniques, which permit identification of degenerated endings of both myelinated and unmyelinated fibers, provide clearer information. So far, such studies on cortical projections to sensory nuclei have been carried out mainly in the cat (20,24,75 and 124) and to a lesser extent in the monkey (77) and man (76).

Using Glees method, Brodal et. al. (20) described direct bilateral corticifugal projections from all cortical regions to the sensory trigeminal nucleus and to the nucleus of the solitary tract in the cat. Frontoparietal projections to the contralateral side were most abundant. Using the same staining method, Walberg (124) found a similar diffusely originating corticifugal projection to the gracile and cuneate (but not to the external cuneate) nuclei in the cat. The terminal degeneration was bilaterally distributed but was most prominent contralateral to the cortical lesion. The fibers leave the pyramidal tract at the medullary level and either enter the medial lemniscus or go through the reticular formation

to reach the dorsal column nuclei. He found no evidence of somatotopic organization in the projections from the forelimb and hindlimb motor cortex to the cuneate and gracile nuclei, respectively.

Chambers and Liu (24), using the Nauta-Gygax stain, found terminal degeneration in gracile and cuneate nuclei following lesions of the sigmoid, coronal and anterior ectosylvian gyri, but were unable to demonstrate projections from parietal, occipital or temporal lobes. Kuypers (75) traced degenerating recurrent, as well as transverse, fibers from the pyramidal tract to the ventral aspect and to the hilus of the gracile and cuneate nuclei. The projections were almost exclusively contralateral. Other fibers projecting to the medial part of the spinal trigeminal nucleus were bilaterally distributed rostrally; in the caudal part of the nucleus the distribution was almost exclusively contralateral. In contrast to the findings of Brodal et. al. (20), no degeneration was found in either the nucleus of the solitary tract or in the main sensory and substantia gelatinosa parts of the trigeminal nucleus. The cortical projections to the gracile, cuneate and spinal trigeminal nuclei originated from the hindlimb, forelimb and head-neck areas, respectively. There was, however, considerable overlap in the somatotopic organization.

SECTION III. CENTRAL CONTROL OF AFFERENT AND SENSORY SYSTEMS.

Somatic afferent and sensory systems

The demonstration of the regulation of muscle spindles by the gamma efferent cells (52,65, 73 and 82) suggested that perhaps other afferent systems might also be regulated, although probably at some site other than the sense organ. Hagbarth and Kerr (55) were the first to present evidence that higher centers control the transmission of afferent impulses in spinal

cord relays. They found that repetitive electrical stimulation of any one of a number of supraspinal structures depressed the dorsal root reflex and the dorsal column relayed response elicited by dorsal root stimulation without altering the primary afferent spike in the dorsal columns. The significance of this finding is not entirely clear, since the dorsal root reflex and dorsal column relays are presumably ephaptic phenomena and, indeed, may have no functional significance in nature. The contention of Hagbarth and Kerr, that these "relays" are subject to efferent regulation, is therefore surprising and should be reexamined. On the other hand, regulation of the dorsal column-lemniscal system at the synaptic relay sites in the dorsal column nuclei is a plausible possibility. Hagbarth and Kerr also found that supraspinal stimulation diminished ventral column responses to contralateral dorsal root shocks. Assuming that the affected ventral column responses represented synaptically relayed activity in secondary neurons, they postulated a descending pathway which blocks or inhibits transmission in the dorsal horn. They furthermore concluded that these descending pathways exert a tonic inhibitory influence at the cord level, because high spinal transection or deep barbiturate anesthesia (which presumably blocks the components of the descending pathway) increased the amplitude of the evoked ventral column responses.

Evidence has also been adduced for a descending system which regulates transmission through the spinal nucleus of the trigeminal nerve (30,57,59 and 60). Stimulation of sensori-motor cortex or of midbrain reticular substance is said to block relay of impulses through this nucleus. Section of the neuraxis rostral to the recording site or administration of deep barbiturate anesthesia increased the size of the recorded relayed response.

These findings suggest that the descending regulatory system, like that acting on the homologous synapses in the dorsal horn, is tonically active (60).

Several reports suggest a similar regulatory control of the dorsal column nuclei (31,58,62 and 116). Thus brief (0.3 to 3 seconds) trains of electrical shocks to the mesencephalic tegmentum or the sensori-motor cortex in the cat depresses the post-synaptic potential [as defined by Therman's analysis (119)] evoked by single pulse stimulation of either the dorsal columns (62 and 116) or the splanchnic nerves (58). The depressive effect outlasted the stimulus for a variable period of time ranging up to 80 seconds. In rats, Dawson (31) reported that single pulse stimulation of the sensory cortex resulted in a reduction (by as much as 50 per cent) of the evoked cuneate response to single pulse stimulation of the forepaw. The depression persisted for no more than 5 to 10 msec.

Stimulation of the reticular formation is reported also to influence transmission of impulses through the posteroventral thalamic relay nucleus (72). In unanesthetized curarized cats, the response recorded in the internal capsule to the second of two consecutive shocks to the medial lemniscus is facilitated. Following stimulation of the reticular formation this facilitatory interaction is no longer demonstrable. The depressive effect was abolished when barbiturate anesthetics were administered in sufficient dosage to abolish the EEG arousal response which accompanied it. Similar reticular influences upon thalamic potentials evoked by stimulation of the trigeminal nucleus in the cat have also been described (10).

Special sensory systems

Regulation of sensory transmission is not unique to the somatosensory

systems. A variety of studies indicate that the special sensory systems are subject to similar regulation. Although the present study is concerned exclusively with the somatosensory relay in the dorsal column nuclei, regulation of special sensory input is sufficiently pertinent to merit a brief review here.

Centrifugal fibers terminating on secondary neurons have been demonstrated in both the olfactory (5 and 106) and visual (106) systems. In the former, the centrifugal fibers arise from cells in the basal rhinencephalic areas and traverse the anterior limb of the anterior commissure to reach the granule, the mitral and the tufted cells of the olfactory bulb. The axons of the granule cells also terminate on the accessory dendrites of the mitral and tufted cells which are the secondary neurons of the olfactory path. In curarized unanesthetized cats, Kerr and Hagbarth (70) found that electrical stimulation of the anterior commissure or of the basal rhinencephalon depressed both spontaneous and evoked potential activity in the olfactory bulb. The centrifugal fibers appear to be tonically active, for section of the anterior commissure or deep anesthesia caused augmentation of the olfactory responses.

Although efferent fibers entering the retina have been described (102 and 106), little is known about their origin or termination. Efferent fibers in the optic nerve have not yet been convincingly demonstrated by anatomical methods (102), but in rabbits, Dodt(35) recorded late (presumably post-synaptic) spikes in the retina following stimulation of the contralateral optic tract. Granit (51) found that protracted (10 to 30 seconds) repetitive stimulation of tegmental reticular structures was followed by potentiation or, less frequently, by depression of the

spontaneous or evoked discharges of single retinal ganglion cells in the cat. The potentiation was optimally induced by trains of pulses at least two seconds in duration and at frequencies of 200 to 300 per second. Other workers (62) have described similar effects of repetitive reticular stimulation on various components of the evoked potential in the optic tract of the cat. In some instances, reticular stimulation depressed the optic tract potential; more commonly, some of its components were augmented. Augmentation lasted longer than depression; both influences were best seen in unanesthetized preparations. The same authors also reported that stimulation of the mesencephalic tegmentum depressed potentials evoked in the lateral geniculate nucleus and the visual cortex.

In the auditory path, efferent fibers terminate on the primary neuron. Rasmussen (108 and 109) has traced these fibers from the region of the superior olive across the floor of the fourth ventricle and into the eighth nerve whence they are apparently distributed along the entire length of the cochlea. The terminals appear to come into contact with the primary auditory nerve fibers in their course from hair cell to spiral ganglion cells; some may terminate on the hair cells themselves. Electrical stimulation of this olivo-cochlear bundle in its course through the floor of the fourth ventricle depresses the potentials induced in the primary auditory nerve fibers by sound stimuli (43). The input into the olivo-cochlear system may originate partly in the reticular formation; stimulation of the brain stem reticular formation depresses potentials evoked in the cochlea by sound stimuli (61 and 71). However, stimulation of certain diencephalic non-reticular structures (e.g., the area medial to the nucleus geniculatus medialis and dorsolateral to the medial lemniscus)

produces a similar depression (34).

Summary

The experiments reviewed in the preceding section indicate that in a number of somatosensory and special sensory systems, transfer of sensory information is subject to regulation by the central nervous system. The site at which centrifugal fibers condition transmission varies; in some paths (e.g., auditory and muscle spindle), the sensitivity of the receptor is biased by centrifugal influence. In other systems, regulation occurs at synaptic junctions within the nervous system. Also the mode of action of the centrifugal systems varies; some appear to facilitate transmission whereas others suppress the flow of sensory messages. In many instances, available evidence suggests that the centrifugal control systems are tonically active. In some instances, this tonic activity appears to be subject to control by the reticular formation which is also concerned with "arousal" of the cortex. It therefore appears that sensation is not an inevitable consequence of sensory stimulation; even with unvarying stimulation the centripetal flow of impulses which constitutes the functional basis of sensation and perception is governed by the activity of the centrifugal regulatory systems. Variation of tonic activity of the centrifugal systems may underlie such well-known psychological phenomena as sensory inattention and habituation.

INTRODUCTION

Generalizations from studies of evoked potentials in the central nervous system must be regarded with great caution for several reasons: First, evoked potentials are presumably associated with the activity of a large number of neural elements and, therefore, cannot provide information

about the activity of single neural elements. The significance of this becomes apparent when attempts are made to interpret increases or decreases in amplitude or changes in shape of evoked potentials; such factors as the number of evoked discharges per active neural element, the number of active neural elements, occlusion or inhibition are mixed indiscriminately. Second, whatever information can be gained from the size and shape of a synchronized evoked potential, little, if anything, is revealed of the asynchronous background neural activity. Third, since macroelectrodes can record evoked potential activity spreading in volume over rather large distances, the neural elements contributing to the evoked discharge cannot be identified.

In the cuneate nucleus, single unit analysis of the evoked discharge to various stimuli (9) disclosed a pattern of excitation from the periphery more complex than that suggested from multi-unit analysis (119). However, studies of the influence of central nervous structures on the peripherally evoked activity in the cuneate and gracile nuclei have been made only on macroelectrode potential recordings (31,58,62 and 116). It appeared from such studies that central stimuli can only "inhibit" or depress the passage of sensory input.

The present work has been undertaken using a single unit approach to the peripherally evoked activity in the dorsal column nuclei. The technique was thought to allow more definite conclusions concerning processes of excitation and inhibition within the nucleus. Also, the recent neuroanatomical demonstration of direct motor cortical projections (via the pyramidal tracts) to the dorsal column nuclei prompted the search for a physiological correlate of this corticifugal projection system.

CHAPTER TWO

METHODS AND MATERIALS

SECTION ONE: SURGICAL PROCEDURES

Cats anesthetized with either sodium pentobarbital (36 mg. per kg. intraperitoneally) or α-chloralose (35 to 40 mg. per kg. intraperitoneally) were used. The animals were paralyzed with intravenously administered decamethonium bromide and maintained on artificial respiration (21 strokes per minute, stroke volume 35 ml.). Additional doses of the anesthetic and muscle paralyzing agents were given as required during the course of the experiments.

The dorsal column nuclei were exposed by the conventional dorsal approach through the foramen magnum: part of the occipital bone was removed to enlarge the opening and, in some instances, the caudal part of the cerebellar vermis was removed to uncover the underlying dorsal column nuclei. Drying was minimized by covering the exposed brain stem with a polyethylene sheet which was removed only during recording.

The pericruciate cortex was exposed by removing the bone with trephines and rongeurs. After opening and reflecting the dura, the exposed cortex was covered with warm (38°C) mineral oil which was retained by a wall of bone wax built around the bone defect.

As single unit recording requires stabilization of the brain, vascular and respiratory movements are often a problem. The latter were minimized by creating a bilateral open pneumothorax which was maintained by glass tubes inserted into the pleural space between the ribs. This procedure permits expansion of the lungs with little movement of the rib cage (131). Vascular pulsations are more difficult to control but can sometimes be

reduced by varying the position of the head.

In some experiments, the bulbar pyramids were exposed by a parapharyngeal approach and removal of the basiocciput of the sphenoid bone. In some animals, the entire brain stem, with the exception of the pyramidal tracts, was transected at the level of the trapezoid body by suction. This kind of transection under direct vision has some advantages over "blind" transections from the dorsal side (85,104 and 130); in other animals, the medullary pyramid was selectively transected on one or both sides. After the pyramids were isolated or cut, moist cotton patties were placed on the brain stem, and the cut edges of the skin were sutured. At the end of the experiments, the vascular tree was flushed out with saline and perfused with 10 per cent formalin solution. The brain stem was removed, sectioned and stained by Luxol-fast method to determine the exact extent of the lesions (Figs. 20C, 21 and 22).

SECTION TWO: STIMULATION APPARATUS AND PROCEDURES

Stimulation apparatus

Successive stimulus intervals were controlled by a "master unit"--Tektronix 162 waveform generator--which also simultaneously controlled the repetition rate of the triggered sweeps of the dual-beam cathode-ray oscilloscope. Interstimulus interval (reciprocal of repetition rate) could be varied in steps from 10^{-4} to 10 seconds. The "master unit" was connected to a series of Tektronix 162 waveform generators and Tektronix 161 pulse generators, which formed four stimulating channels, such that the pulse intervals between any two channels could be varied over a wide range. Each of the final stage pulse generators was gated

by a pulse-stretching multivibrator, which was triggered by the "master unit", and the Tektronix waveform-pulse generator combination allowed for an independently variable train duration and frequency and individual pulse amplitude and duration from any stimulating channel. Also, the outputs of the pulse generators were connected to a specially designed mixer-isolation apparatus, such that the final pulse output is isolated from ground and has a maximum amplitude of 40 volts. Shielded bipolar leads connected the output of the isolation apparatus to the stimulating electrodes.

Peripheral cutaneous stimulation

One stimulating channel was utilized for peripheral stimulation of the skin. The stimulating electrodes, routinely employed, consisted of a pair of 25-gauge hypodermic needles each soldered 1.5 cm. from its tip to one lead of a shielded bipolar cable connected to the output of the isolation apparatus; the remainder of the needle was cut off and discarded. The bipolar needle electrodes were inserted into the lateral edges of the central foot pads. Depending on whether the recording electrode was in the cuneate or gracile nucleus, the skin of the ipsilateral forepaw or hindpaw, respectively, was stimulated. When a neural element responding to the appropriate peripheral stimulation was isolated, a manually operated electrical switch allowed a separate and independent stimulation of the three other paws, similarly equipped with bipolar needle electrodes and cables to the switch.

Rectangular electrical pulses of 0.1 msec. duration and 40 volts maximum amplitude at the isolation output were used for cutaneous stimulation. Voltage amplitude was adjusted with a linear potentiometer

which was arbitrarily set at 10 for the maximum amplitude. In the search for threshold voltage to cutaneous stimulation, only voltage amplitude was varied.

In some cats, in addition to the electrical stimulation method just cited, a "natural" form of peripheral stimulation was used. For neural elements in the cuneate nucleus which exhibited the property of very rapid adaptation to touch of the paw, a mechanical tapper triggered by a simple relay circuit was used. The force of the tap could be varied by adjusting the amplitude of the driving voltage from the isolation apparatus to the coil of the solenoid. For other units which exhibited little or no adaptation to touch, constant pressure was applied to the paw from the top of a plunger of a surgical syringe connected to a closed air-pressure system.

Cerebral cortical stimulation

One stimulating channel was utilized for each of the motor cortices. The latter were qualified as contralateral or ipsilateral with respect to the position of the recording electrode in the dorsal column nuclei.

Ball-point bipolar silver electrodes (17.5-mills gauge) were connected via a shielded bipolar cable directly to the output of the isolation apparatus. The electrodes were applied gently onto the cortical surface and frequently removed and cleaned during any one experiment. The amplitude and duration of individual pulses, as well as the duration and frequency of train of pulses, was frequently varied. When a train of pulses was used, best results were obtained with a train frequency around 300 per second and train duration not exceeding 25 msec. Individual pulse amplitude was varied between 10 and 4 potentiometric units, and pulse

duration was varied between 0.02 and 2 msec. (rarely exceeding 1 msec.).

SECTION THREE: RECORDING APPARATUS AND PROCEDURES

Recording apparatus

The recording of action potentials of excitable tissues with high impedance microelectrodes presents certain problems to amplification. In order to reduce the distortion of the input signal, a cathode follower was used with a high input and low output impedance, to match the respective microelectrode and preamplifier impedances. A 10-mills gauge platinum electrode connected the KCl-filled glass micropipette to a shielded cable, which constituted the input lead to the cathode follower; the shield of the input lead connected to the cathode, thus reducing input capacitance. A thin (0.25 mm.) and small (20x3 mm.) plate of aluminum inserted under the skin of the cranium served as an indifferent electrode. The output of the cathode follower connected to a push-pull condenser-coupled preamplifier (Grass P5) with a step attenuator and variable time-constants.

One half of the preamplifier output was led to the input of three pieces of monitoring equipment. The first consisted of one or both channels of a dual-beam cathode-ray oscilloscope (Dumont 279). Routinely, the two sweeps were triggered by the same "master unit", which simultaneously triggers the stimulating channels. In initial experiments, one channel was utilized for micropipette recordings, while the other channel was triggered synchronously, used the same sweep speed and displayed timed pulses for calibration from the output of a Tektronix 162 waveform generator. In later experiments, the two channels were utilized for micropipette recording of the same phenomenon but were triggered asynchron-

ously and swept independently in such a manner that the upper channel displayed a slow sweep speed (100 to 300 msec. duration) and allowed observation of the time relationships between conditioning and testing pulses; the lower channel displayed a fast sweep speed (15 to 50 msec. duration) and allowed the observation of small changes in spike latencies following the testing stimuli. In between runs or following changes in sweep speeds, timed pulses for calibration were photographed on both channels (usually 10 msec. on the upper and 1 msec. on the lower channel). The second piece of monitoring equipment consisted of a single-beam cathode-ray oscilloscope (Dumont 304H). The third was an audio-amplifier (Bogan E14) which drove a 12-inch loudspeaker system.

Traces appearing on the dual-beam oscilloscope screen were photographed on 36 mm. film with a special photographic camera (Grass C4D). With triggered sweeps, stationary film was used; however, occasionally movie film (with no sweep) was taken. During photography (and throughout the experiment) signals were monitored visually on an adjacent dual-beam slave scope which had independent controls for focus and intensity of the beam. The single-beam oscilloscope, which was swept recurrently, and the audio amplifier-speaker system allowed continuous visual and auditory monitoring, respectively, of the recorded signals. However, the auditory speaker was disconnected during photography to prevent any possible auditory conditioning of the recorded activity. The further possibility of conditioning effects from the camera shutter noise was precluded by proper timing of the opening and closing of the camera shutter.

Recording electrodes

Micropipettes were drawn from Pyrex capillary tubing (O.D. approximately 1 mm.) with an electrode puller designed by S. Kirk of the Depart-

ment of Physiology and Biophysics, University of Washington. The puller consisted of a pair of clamps (one of which was fixed in position) mounted on a horizontal slide operated by a spring. A 20 cm. piece of glass tube was clamped, the spring was stretched to the required degree and heat from an electrically controlled source was applied to a platinum coil. Although several controllable parameters (shape, size and temperature of the heating coil, the diameter, thickness and composition of the glass tube and the peak magnitude of the pulling force) were available, in practice, only the temperature of the heating coil and the peak magnitude of the pulling force were varied [for a review, see Becker et. al. (11)]. Two very similar micropipette electrodes were drawn from any one glass tube. Micropipette tip diameters best suited for extracellular single unit potentials were found to range from 0.5 to 2 micra.

Soon after a batch of micropipettes was pulled and mounted on a plastic holder in the vertical position, tips downward, they were placed in a cylinder filled with 3M KCl solution and boiled slowly for two hours. After cooling, the micropipettes, thus filled with the KCl solution to both ends and ready to be used, were stored in a refrigerator to minimize evaporation.

Isolation and identification of single neural elements* in the dorsal column nuclei.

Half-amplitude low frequency response of 35 cps and high frequency response of 30 kcps were routinely used at the preamplifier. The micropipette was mounted on a micromanipulator with a 2 mm. range of finely adjusted motion, connected to the recording apparatus and adjusted in posi-

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* Single neural elements will henceforth be referred to as units.

tion perpendicular to the medullary surface at the level of the obex. In any one experiment, explorations of the cuneate or gracile nuclei were started from a surface area not larger than five square mm. in the cuneate tubercle or clava, respectively. In initial experiments on the cuneate nucleus, a 12-mills gauge stainless steel electrode insulated, except at its tip, was inserted for a depth of approximately 1 mm. in the center of the area previously explored with recording micropipettes and connected to the positive terminal of a 9-volt battery for about 15 seconds (the other terminal was connected to the animal's scalp). Then the animals were sacrificed, and the iron deposited from the steel electrode tip was stained blue by Marshall's modification of the Hess method (86). Examination of the resulting sections demonstrated that the cuneate nucleus extended to a depth of 1.5 mm. and that by confining our recordings in depth to the superficial 1.2 mm. we were well within the boundaries of this nucleus (Fig. 1). In the gracile nucleus, units were isolated not deeper than 1.0 mm.

Conventional criteria were used in the identification of units from extracellular micropipette recordings in the dorsal column nuclei (41). However, movement of the brain stem with respiration or the heart beat often proved to be extremely troublesome and some cats (approximately one in four) had to be discarded, because all efforts to reduce brain stem movements were futile. Nevertheless, in the 'average' preparation, units could be isolated for a period of 10 to 15 minutes, and sometimes much longer. Once isolated, responsive units in the dorsal column nuclei were tested as to their ability to follow each shock during repetitive peripheral stimulation and their response to the stimulation of the other three paws;

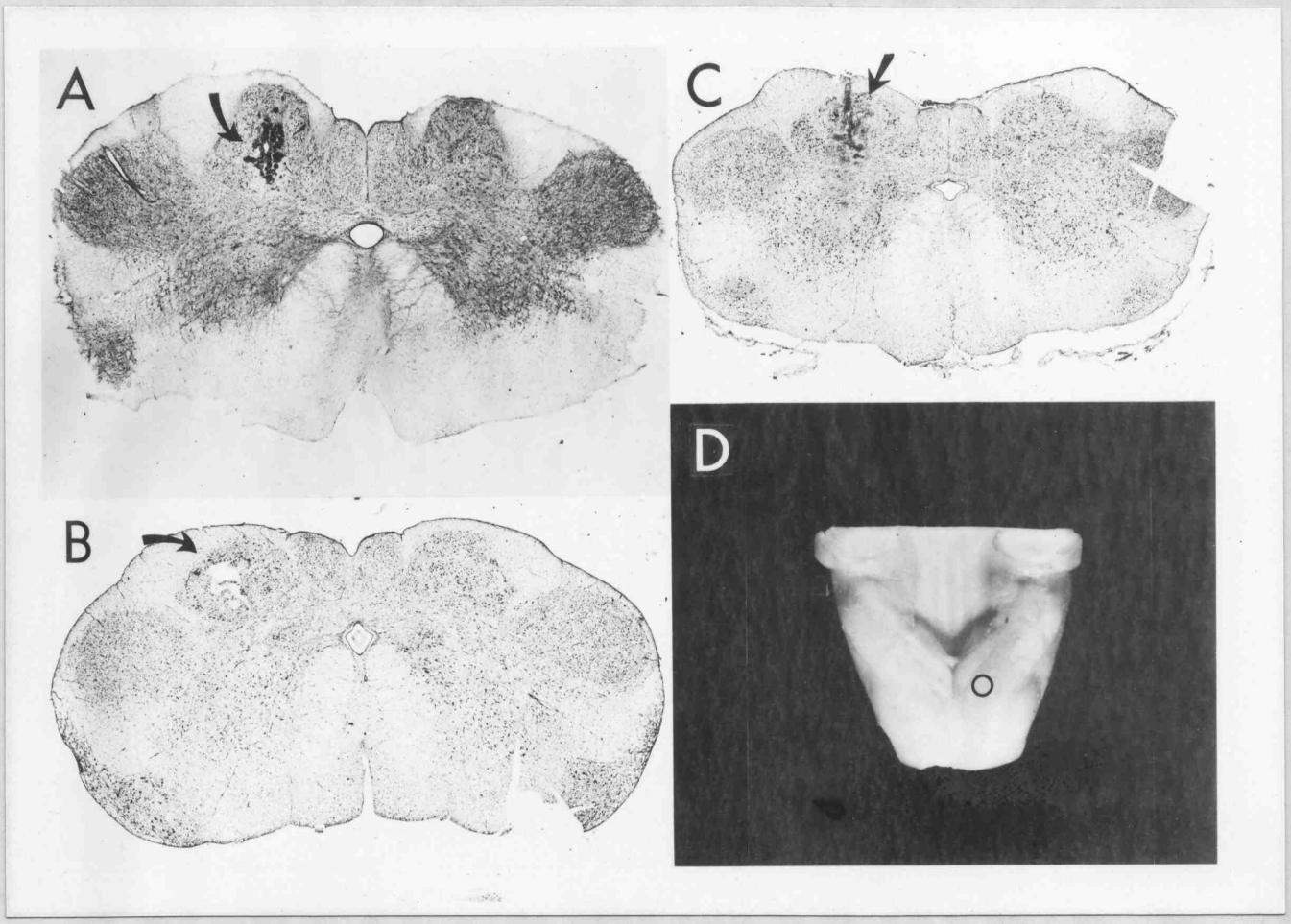

Figure 1. Histological identification of recording field.

A, B and C are Luxol-fast stained sections of brain stems of three different preparations following small electrolytic lesions (indicated by arrows) in the right cuneate nuclei. D is dorsal view of the caudal part of the brain stem. Area within circle represents an approximate extent of the surface of right cuneate tubercle penetrated by recording electrodes before an electrolytic lesion is made.

then the effects of electrical stimulation of the motor cortex on peripherally evoked or spontaneous activity were studied.

Analysis of unit data

At least 10 (sometimes up to 50) observations of unit activity to each stimulus condition were recorded on film. Measurements were made in a film viewer which enlarged the traces approximately seven times.

The mean latencies of the successive spikes and their standard deviations, the mean interspike intervals, the mean number of spikes per discharge and the probability of firing of the first spike to peripheral stimulation were calculated. Similar calculations were made on units receiving an additional excitatory input from the motor cortex. Blocking or inhibitory (see definitions in Chapter Three) motor cortical influence was ascertained from the effects of electrical stimulation of the motor cortex on the response properties of the peripherally evoked units. Although some degree of positive skewness was present in the latency distribution, medians were not used; the arithmetic mean was about as descriptive of distribution as the median. Means were used in the statistical tests employed.

CHAPTER THREE

RESULTS*

SECTION ONE: DISCHARGE PROPERTIES OF DORSAL COLUMN NEURONS TO PERIPHERAL STIMULATION

The activity of 185 single units in the cuneate and gracile nuclei evoked by electrical stimulation of the ipsilateral foot pads was recorded photographically. The activity following tactual stimulation, as well as the spontaneous activity of some of these units, was also recorded photographically. The activity of many more units was visually observed, but was not recorded. Of the total units studied, isolated and recorded, 130 were isolated in the cuneate nucleus and 55 were isolated in the gracile nucleus. The gracile units were similar to cuneate units in their discharge patterns and will be discussed at the end of this section.

Unit potential recording in the cuneate nucleus

In general, the spike forms observed were very similar to extracellular spike forms recorded in the thalamus and the somatosensory cortex with similar recording micropipettes and equipment (6 and 112) and were similar to those shown by Amassian and DeVito (9) from the cuneate nucleus. Unit spikes were either positive-negative, mono-

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* In figure legends, the following abbreviations will be used:
L, mean initial spike latency.
s/d, mean number of spikes per discharge when a discharge occurs.
p, probability of discharge.
ff, maximum ability of a unit to follow each shock during repetitive stimulation.
n, number of observations.
p.d., pulse duration of the cortical stimulus.
C-T, conditioning-testing.

phasically positive or negative in sign. Very few negative-positive spikes were observed. The interpretation of the origin of such spikes in the central nervous system is still uncertain. When the electrode was advanced, negative spikes usually acquired an initially positive phase, which increased continuously, with a gradual decrease in the negative phase; the latter was typically smaller in amplitude and longer in duration than the positive phase. The peak-to-peak spike amplitude ranged from 0.5 to 15 millivolts. Further advance of the recording electrode often led to a rapid increase in peak-to-peak amplitude and transition to a monophasically positive configuration, usually with signs of unit injury. The abrupt appearance of large amplitude positive spikes, without prior indication of unit activity, was commonly observed with micropipettes smaller than 0.5 micron in tip diameter (Figs. 4A and 8 A1). Signs suggestive of unit injury include the appearance of a notch in the spike, abrupt appearance of spontaneous firing or an increase in the spontaneous or evoked firing, often followed by silence of the unit activity. Mountcastle et. al. (92) have suggested that damage to the soma or synapses reduces the unit's responsiveness.

Amassian and DeVito (9) concluded, on the basis of latency measurements of cuneate unit activity evoked by orthodromic or antidromic routes, that initially negative and positive-negative spikes were extracellularly recorded from the soma, or from the basal dendrites or from both. Their conclusions were further supported by the fact that such spikes could not be elicited in pure fiber tracts and were not associated with a resting potential (9). Similar conclusions have been reached by various workers studying unit spikes in the dorsal root ganglia, the gray matter of the spinal cord, the cochlear nuclei, the thalamus, the cerebellum

and the cerebral cortex. A review of the subject is given by Waller (128). However, there is considerable controversy concerning the conditions under which initially negative or positive-negative spikes appear.

In addition to the potential configurations described above, monophasically positive spikes were also recorded from the afferent axons and pre-synaptic arborizations in the cuneate nucleus. These were identified by the following criteria: a)initial spike latency to forepaw stimulation was short and invariant, ranging between 3 and 6 msec.; b)the number of spikes in each discharge rarely exceeded two in number; c)the units followed faithfully trains of stimuli in excess of 400 per second; d)with advance of the micropipette, there was no typical prolonged injury discharge, a finding consistent with the observation that injury to an axon at a distance from the soma does not change cell excitability significantly; e)the spikes were abundant in the superficial 200 micra of the cuneate nucleus; f)they were never influenced, in any manner, by cerebral cortical stimulation. Occasionally, in the superficial layer of the cuneate nucleus, spikes were recorded which had longer latencies than the primary afferent fibers and did not follow high frequency trains of stimuli. These spikes were most commonly observed when the rectal temperature dropped below 35°C and were probably due to the dorsal column relay system (9 and 66).

Distribution in depth of unit activity in the cuneate nucleus

Microelectrode penetrations were confined to the superficial 1.2 mm. of the nuclei, since histological investigation (Chapter Two) suggested that penetration beyond a depth of 1.5 mm. might result in the isolation

of reticular units. A further safeguard against the inclusion of reticular neurons was provided by testing the response of cuneate units to electrical stimulation of the other three paws. Waller (128) showed that a large fraction of reticular units can be fired by electrical stimulation of more than one paw. All of the units in the present study responded only to stimulation of the ipsilateral forepaw. Depth was measured by recording the advancement of the manipulator from the position in which the micropipette tip just touched the pial surface. The errors in such depth measurements usually lead to overestimation of depth (6).

Response characteristics of cuneate units to electrical stimulation of the skin

Almost all of the cuneate units responded* repetitively to single pulse stimulation of the ipsilateral forepaw. For each unit the following measurements were made: the mean number of spikes per discharge, the probability** of firing, mean latency of the first spike and successive mean interspike intervals and the ability of the unit to follow repetitive peripheral stimulation. The following data pertain to discharges evoked by stimulation of the ipsilateral forepaw with the maximal available intensity (40 volts, 0.1 msec.).

(1) The mean number of spikes per discharge. This was calculated for each unit from the total number of evoked spikes divided by the number of stimulus trials in which a discharge occurred. The mean value was 3.86

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* In some units, spontaneous discharge made it difficult to decide whether the unit responded to the stimulus. In such instances, the final decision was based on comparing 10 to 50 traces obtained with stimulation with an equal number of traces obtained without stimulation.

** Probability is defined as the number of times a discharge occurred divided by the number of trials (10 to 50). Probability was 1.00 with maximal intensity stimulation.

spikes per discharge with 2.62 standard deviation.* A train of two to four spikes was most commonly observed. In two units, without any spontaneous discharge, the stimulus regularly elicited a discharge of 16 to 17 spikes in each of many trials extending over a period of 15 minutes (Figs. 4A and 8 A1). Repetitive discharge of units in response to a single peripheral afferent volley has been observed in the spinal cord, the thalamus, the cerebellum and the cerebral cortex (128).

(2) Mean latency of the first spike and mean interspike intervals. Mean latencies to forepaw stimulation ranged between 4 and 18 msec. Units having latencies of less than 8 msec. had less variable latencies than units having longer latencies. Indeed, the variability of the former group (standard deviation of less than 0.1 msec.) was within the range of experimental error of latency measurements. Amassian and DeVito (9) also found that the variability of discharge latency of some cuneate units (as ascertained from the range of maximum to minimum) was so small that it approximated the error (± 20 microseconds) of an electronic pulse interval chronometer.

Mean interspike intervals ranged from 0.6 to 8 msec. Four patterns of repetitive discharge were observed and are listed in order of greatest frequency of occurrence as follows: a)successive intervals increased; b)successive intervals were almost constant except for the last, which was the longest in the train; c)successive intervals decreased; d)a long interspike interval (usually 3 msec. or longer) occurred in the middle of the train simulating two separate bursts of spikes. The last

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* Henceforth, similar computations will be abbreviated as mean of 3.86 ± 2.62 spikes per discharge. In this study, the degree of variability or dispersion was ascertained from standard deviation computations.

pattern was probably due to the dorsal column relay (Figs. 3A and 16A). In all repetitive discharges, the variability in mean spike latencies increased with the successive spikes in a train.

(3) Ability to follow repetitive stimulation. The ability to follow individual stimuli during repetitive peripheral stimulation varied widely. The upper limit of following rates of cuneate units was as low as one per second for one unit to as high as 400 per second for another. Figures 2 and 14 A4 show the responses of typical units to various rates of repetitive stimulation. The ability to follow high frequency (up to 400 per second) afferent bombardment is unique. In the spinal cord, for instance, ventral horn cells monosynaptically excited via the dorsal root do not follow repetitive stimulation in excess of 30 per second (Lloyd, personal communication; Eccles, personal communication).

Activation of cuneate units by monosynaptic and other pathways

Cuneate units do not behave as a homogeneous group. Amassian and DeVito (9) also arrived at this conclusion. About 75 per cent of the cuneate units in the present study had latencies shorter than 8 msec. (mean of 6.02 ± 1.09 msec.) and responded to individual stimuli during repetitive peripheral stimulation at rates of at least 50 per second. Units which had a mean initial response latency less than 8 msec. and a maximum frequency following in excess of 50 per second were considered to be excited monosynaptically (Figs. 3A, 4A, 6A, 8A, 10, 11A, 12, 14, 16-18 and 20 A and B). These units usually had low thresholds, responded repetitively and with high frequency and exhibited a very small variability of initial spike latency. The remaining 25 per cent of the cuneate units

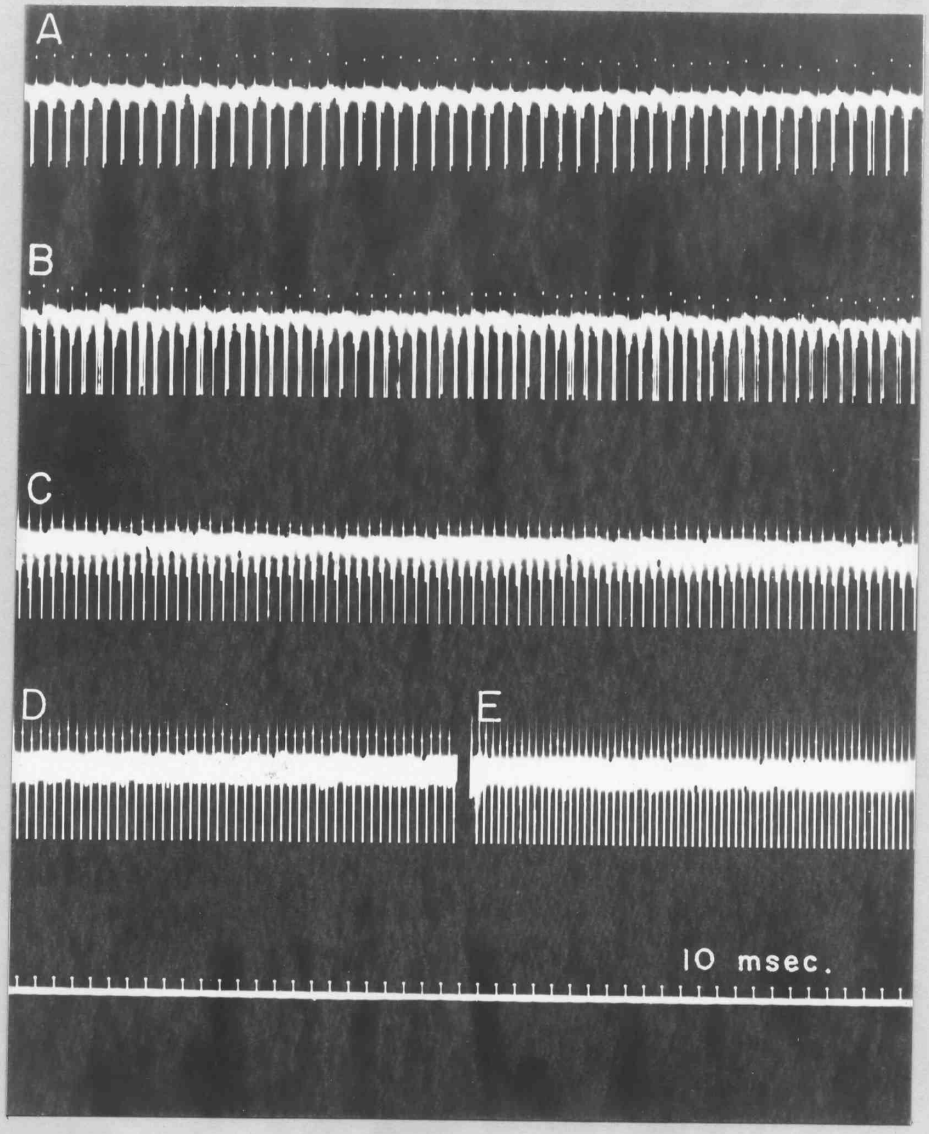

Figure 2. Response of a cuneate unit to electrical stimulation of the ipsilateral forepaw at various frequencies.

A. At frequency of 100 stimuli/second, unit discharges with two spikes.
B. 125/second (one or two spikes per discharge).
C. 160/second (one spike per discharge).
D. 200/second (one spike per discharge).
E. 250/second (one spike per discharge).

Unit failed to discharge to every shock during repetitive peripheral stimulation at rates higher than 250/second.

had latencies greater than 8 msec. (mean of 11.35 ± 3.25 msec.) and responded to individual stimuli during repetitive stimulation only when the rate was less than 50 per second. Cuneate units in this class were considered to be excited via multisynaptic routes (Figs. 7A and 11B). However, it is recognized that the same properties might be displayed by cuneate units fired monosynaptically by stimulation in the periphery of their respective cutaneous receptive fields. Because only peripheral stimuli were employed, it was impossible to distinguish between multisynaptic excitation and excitation via the dorsal column relay (9; see Chapter One).

Effects on cuneate units of altering stimulus intensity above threshold

The data presented above pertain to discharges elicited by stimuli considerably above threshold intensity. However, most of the data on interaction between corticifugal and peripheral inputs was obtained with test (i.e., peripheral) shocks near threshold intensity. Therefore, a description of the effect of changing peripheral stimulus intensity on cuneate unit behavior is in order.

In general, reducing the intensity (voltage amplitude) of the electrical stimulus to the paw resulted in a number of significant changes in evoked cuneate unit activity: a)the mean number of spikes per discharge decreased (Figs. 8A and 14); b)the mean initial spike latency and its variability increased (Fig. 8A); c)mean interspike intervals increased (Fig. 8A); d)the probability of evoking a unit discharge drecreased; e)the ability of a unit to follow individual stimuli during repetitive peripheral stimulation markedly decreased. Similar observations have previously been reported for the cuneate nucleus (9), the

thalamus (112) and the cerebral cortex (6).

If increasing stimulus intensity recruits more excitatory fibers, the changes noted could be explained by an increase in the magnitude and rate of change of pre-synaptic bombardment (91). However, in some units, increasing stimulus intensity elicited the usual changes in discharge characteristics except that the number of spikes per discharge decreased, rather than increased. Such behavior may be due to progressive recruitment of inhibitory fibers. Demonstration of inhibitory post-synaptic potentials in such units might provide the answer to this problem, but unfortunately intracellular recording from cuneate units is difficult.

Spontaneous activity and activity evoked by "natural" stimulation

Although the major portion of this work was devoted to the study of cortical influences on cuneate and gracile unit activity evoked by electrical stimulation of the paw, in some instances, additional observations were made of the effects of cortical stimulation upon the spontaneous activity and upon the activity evoked by "natural" stimulation of the skin.

Less than a fourth of the cuneate units studied showed spontaneous activity. The amount of spontaneous activity, which was estimated roughly by counting from the number of spikes on a slow (150 to 300 msec.) sweep, varied from one spike every fourth or fifth sweep to three to five spikes each sweep.

In 10 instances, the responses of cuneate units to "natural" stimulation of the skin was studied in some detail. Two units responded repetitively to constant pressure on the paw; the discharge showed little

or no adaptation (Fig. 19). The other eight units adapted rapidly to constant pressure and responded with a brief burst to tapping of the paw (Figs. 14 A1 and 16-18). Such a small sample does not allow generalizations concerning the response properties of cuneate units to cutaneous stimulation; however, interesting changes in the properties of these 10 units were produced by conditioning cortical stimulation (see Section Two of this chapter).

Response characteristics of gracile units to electrical stimulation of the skin

Large blood vessels in the vicinity of the gracile nucleus make difficult sustained recording from gracile units. The added disadvantage of smaller surface extent and volume of the gracile nucleus (Fig. 1) made it more convenient to study corticifugal influences on the cuneate nucleus. However data were collected on 55 gracile units.

In most respects, the response properties of the 55 gracile units isolated and studied were similar to those of cuneate units. The differences are partially ascribable to the longer cunduction path for gracile units. The mean latency of the first spike ranged between 11 and 23 msec. and was more variable than that of cuneate units. In contrast to cuneate units, gracile units generally failed to follow repetitive afferent inputs at rates exceeding 250 per second.

SECTION TWO: EFFECT OF STIMULATING THE MOTOR CORTEX ON TRANSMISSION THROUGH THE DORSAL COLUMN NUCLEI

After the response to cutaneous stimulation was determined for each cuneate or gracile unit, the influence of antecedent cortical stimulation

on the responsiveness of the unit was studied. In nearly every instance, electrical stimulation of motor Area I either increased or decreased the excitability of the unit. Some units were discharged by single cortical shocks; other units were rendered less excitable, as measured by their reduced responsiveness to cutaneous stimulation applied at various times following the cortical stimulus. Because the effect of cortical stimulation on gracile units was identical with its effect on cuneate units, the following account lumps the data obtained from the two nuclei.

Excitatory effects following stimulation of the motor cortex

Seventy-five units isolated in the dorsal column nuclei were discharged by electrical stimulation of the contralateral motor cortex. Although occasionally repetitive cortical stimulation was required to activate units in the dorsal column nuclei (Figs 3,6,7,14C,15 B and C and 17C), single electrical pulses were usually sufficient to discharge the unit (Figs. 4,5,13 A2 and 20 B2). Calculations were made of the mean spike latencies (and interspike intervals), the probability of firing and the mean number of spikes per discharge following cortical stimulation. In units discharging spontaneously, the reality of evoked discharge following cortical stimulation was established by criteria similar to those used to verify evoked discharge to peripheral stimuli.

The discharge properties of the cortically driven cuneate and gracile units varied according to the parameters of stimulation (pulse intensity and duration and train frequency and duration). When a train of pulses was required, optimum train frequencies were usually about 300 per second (Figs. 3,6,7,14C,15 B and C and 17C). Figure 6 shows the influence of varying train duration on the response of a cuneate unit. A train of

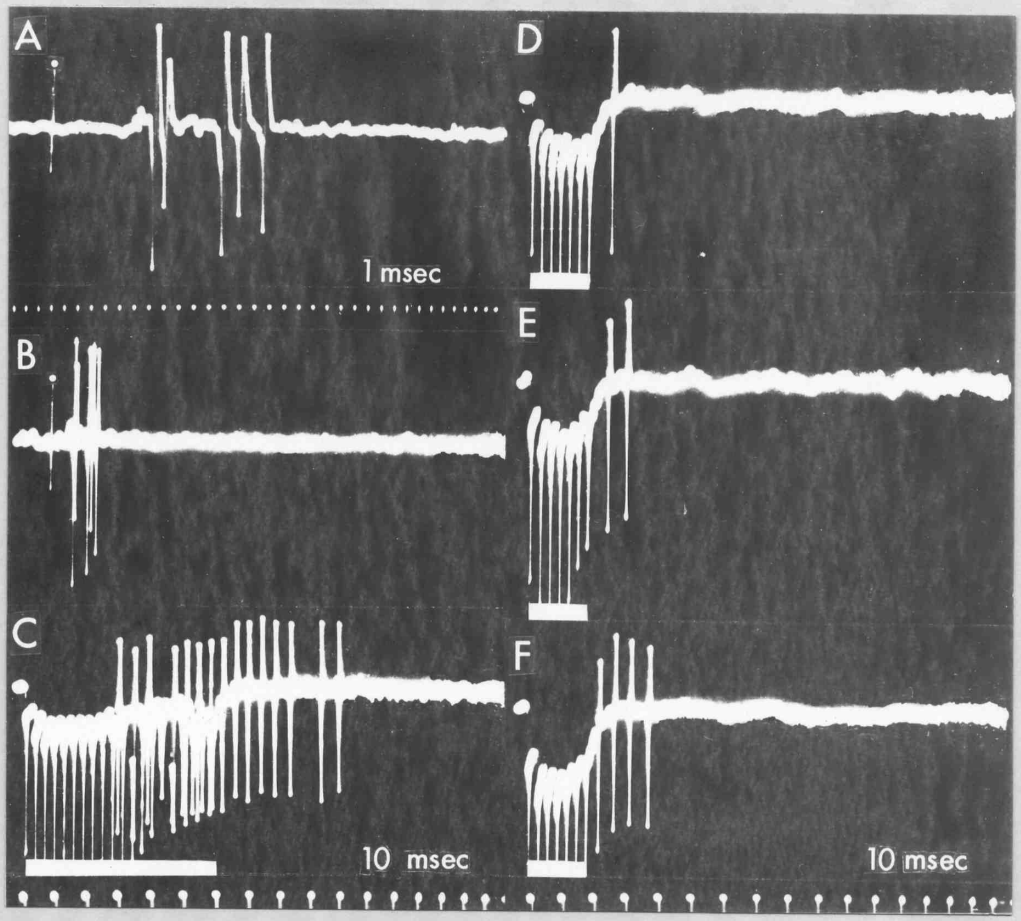

Figure 3. Responses of a cuneate unit to electrical stimulation of the ipsilateral forepaw and of the contralateral motor cortex. Peripheral shock artifacts marked with dot. Durations of cortical trains indicated by horizontal white bars.

A. Response to maximal ipsilateral forepaw stimulation: $\overline{L}$=7.04 msec.; $\overline{s/d}$=4.77; p=1.00; n=35; ff=250/second.
B. Like A on a slower sweep (same sweep speed used in C,D,E and F).
D,E and F. Effect on cuneate unit response of increasing individual pulse duration (pulse intensity and train duration constant) of stimulus train applied to the contralateral motor cortex (7 pulses at 312/second).
D. p.d.=0.4 msec.: $\overline{L}$=26.55 msec. (from beginning of cortical train); $\overline{s/d}$=2.22; p=0.75; n=24.
E. p.d.=0.6 msec.: $\overline{L}$=25.90 msec.; $\overline{s/d}$=2.40; p=1.00; n=10.
F. p.d.=0.8 msec.: $\overline{L}$=22.30 msec.; $\overline{s/d}$=3.20; p=1.00; n=10.
C. Like F, except 20 pulses in stimulus train: $\overline{s/d}$=13.60; n=10.

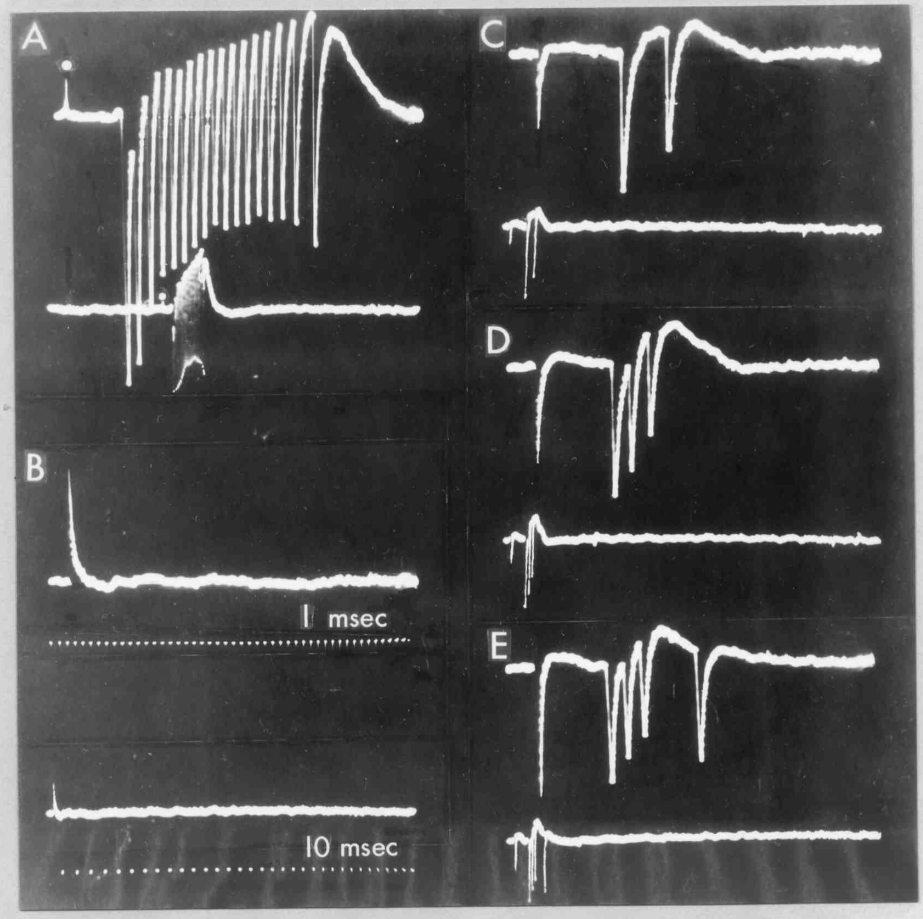

Figure 4. Responses of a cuneate unit to electrical stimulation of the ipsilateral forepaw and of the contralateral motor cortex. Two sweeps show the same event, with upper (fast) sweep showing only the 45 msec. following shock artifacts. Upper and lower sweep speeds are denoted by the 1 and 10 msec. time lines, respectively, in B. Peripheral shock artifacts marked with dot.

A. Response to maximal ipsilateral forepaw stimulation: $\overline{L}$=4.17 msec.; $\overline{s/d}$=16.43; p=1.00; n=10; ff=240/second.
B. Electrical stimulation of the ipsilateral motor cortex (p.d. =0.1 msec.): p=0.
C,D and E. Effect on cuneate unit response of increasing pulse duration (pulse intensity constant) of stimulus applied to the contralateral motor cortex; p (in C,D and E)=1.00.
C. p.d.=0.02 msec.: $\overline{L}$=6.12 msec.; $\overline{s/d}$=2.07; n=14.
D. p.d.=0.04 msec.: $\overline{L}$=5.54 msec.; $\overline{s/d}$=3.69; n=16.
E. p.d.=0.06 msec.: $\overline{L}$=5.22 msec.; $\overline{s/d}$=4.42; n=26.

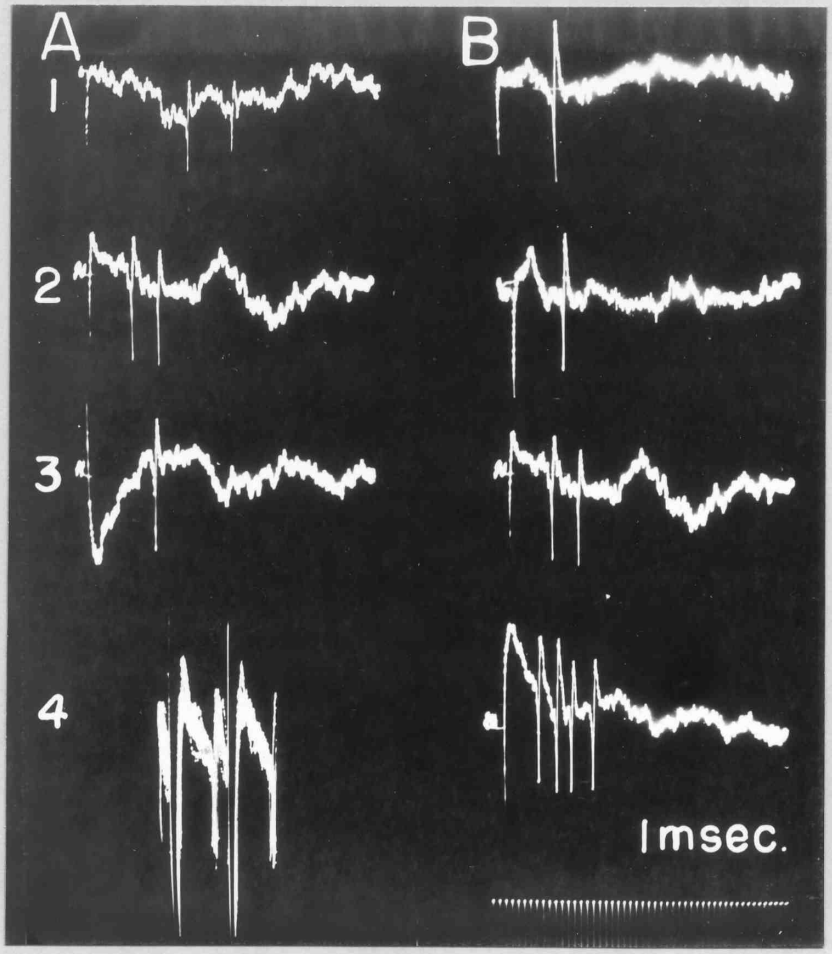

Figure 5. Responses of a gracile unit to electrical stimulation of the ipsilateral hindpaw and of the contralateral and ipsilateral motor cortices. In all responses, p=1.00. 1 msec. time line serves all sweeps except A4.

A1. Response to maximal ipsilateral hindpaw stimulation: $\bar{L}$=16.89 msec.; $\overline{s/d}$=2.00; n=13.

A2. Response to stimulation of the contralateral motor cortex (p.d.=0.2 msec.): $\bar{L}$=7.08 msec.; $\overline{s/d}$=2.09; n=11.

A3. Response to stimulation of the ipsilateral motor crotex (p.d.= 0.2 msec.): $\bar{L}$=11.86 msec.; $\overline{s/d}$=1.12; n=17.

A4. Superimposed sweeps of frequency following (ff) to stimulation of the contralateral motor cortex at 100/second.

B. Effect on gracile unit response of increasing pulse duration (pulse intensity constant) of stimulus applied to the contralateral motor cortex.

B1. p.d.=0.03 msec.: $\bar{L}$=8.51 msec.; $\overline{s/d}$=1.00; n=15.

B2. p.d.=0.06 msec.: $\bar{L}$=7.83 msec.; $\overline{s/d}$=1.30; n=23.

B3. p.d.=0.20 msec.: $\bar{L}$=7.08 msec.; $\overline{s/d}$=2.09; n=11.

B4. p.d.=0.70 msec.: $\bar{L}$=6.84 msec.; $\overline{s/d}$=3.00; n=16.

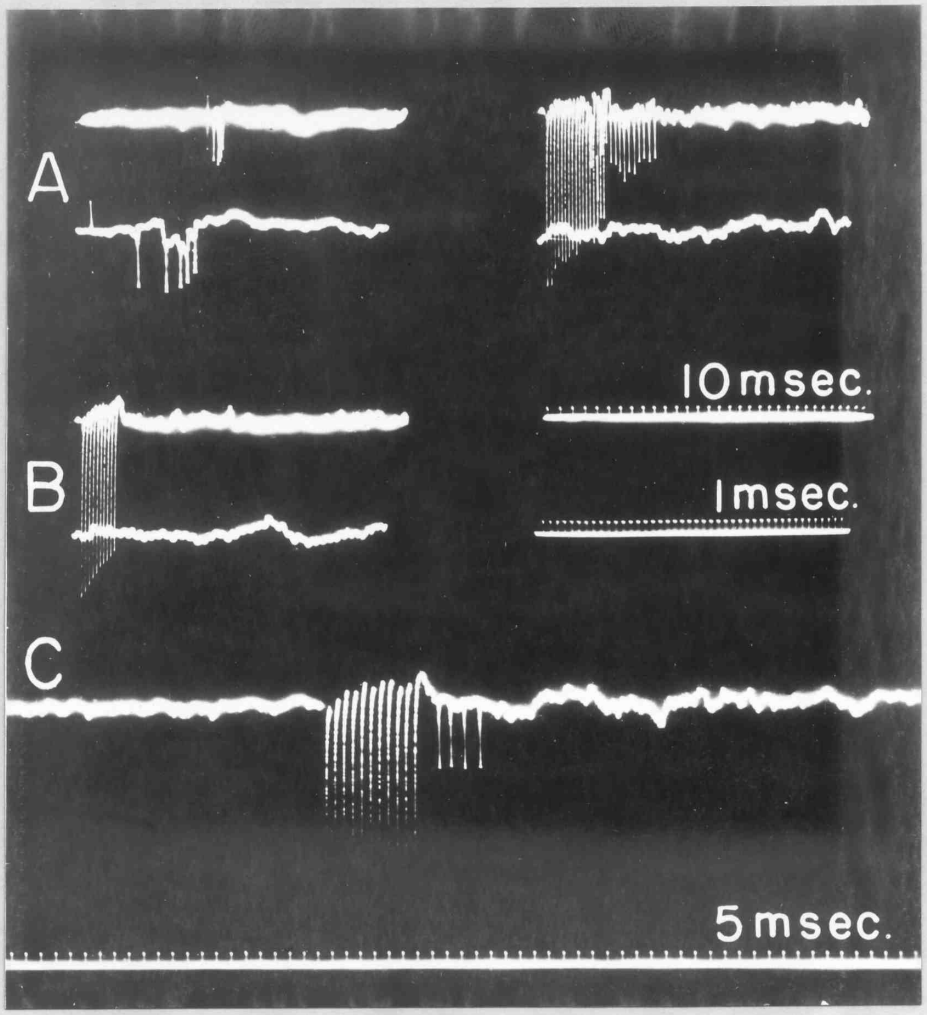

Figure 6. Responses of a cuneate unit to electrical stimulation of the ipsilateral forepaw and of the contralateral motor cortex also showing effect of altering train duration applied to the contralateral motor cortex on the cuneate unit response.

B right. 10 and 1 msec. time lines serve upper and lower sweeps, respectively, of A and B. Lower sweeps in A right and B left not used.

A left. Response to maximal ipsilateral forepaw stimulation: $\overline{L}$=7.81 msec.; $\overline{s/d}$=4.67; p=1.00; n=10; ff=100/second.

B left. Response to electrical stimulation of the contralateral motor cortex (p.d.=0.4 msec.; 10 pulses at 312/second): p=0; n=9.

C. Moving film, showing effect of adding a single pulse to the stimulus train used in B: $\overline{s/d}$=3.95; p=1.00; n=20.

A right. Addition of 7 pulses to the stimulus train in B: $\overline{s/d}$=16.00; p=1.00; n=9.

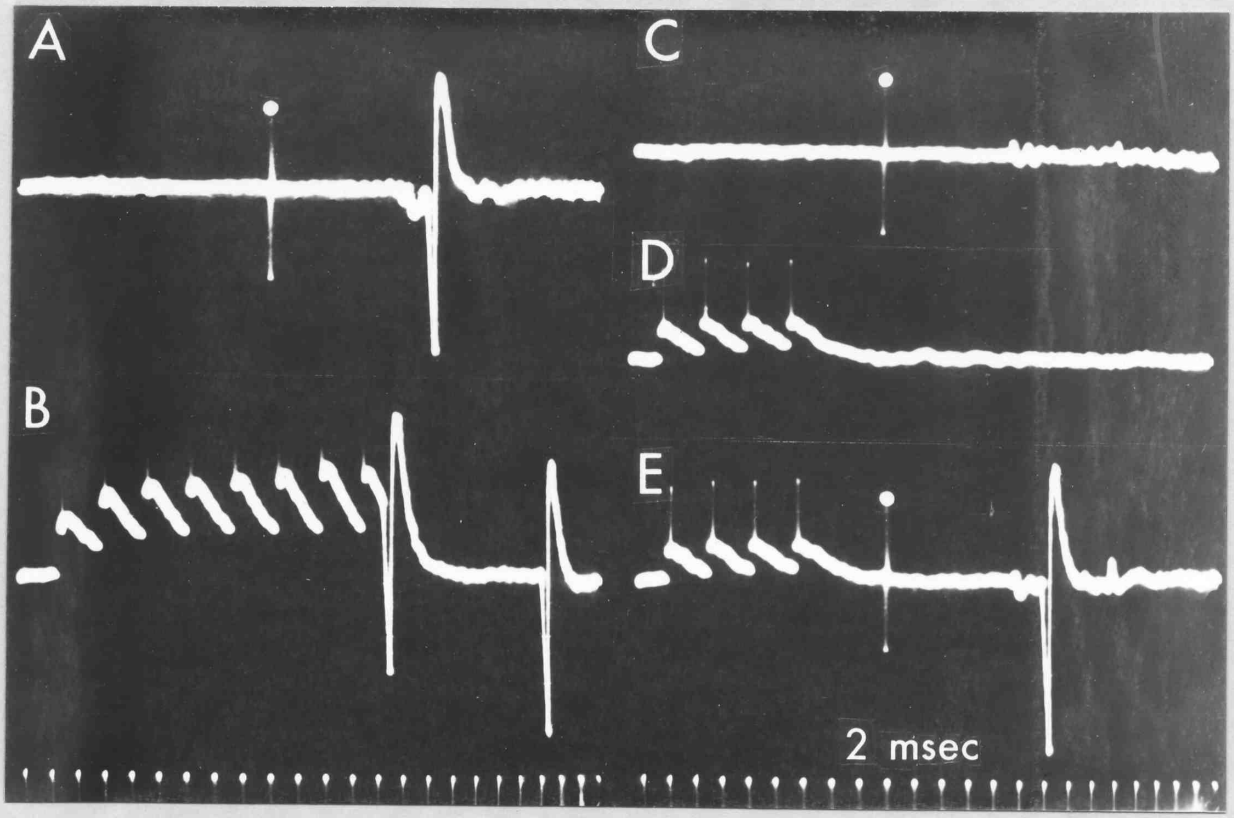

Figure 7. Responses of a cuneate unit to electrical stimulation of the ipsilateral forepaw and of the contralateral motor cortex showing convergence of excitatory inputs from ipsilateral forepaw and contralateral motor cortex on the cuneate unit. Peripheral shock artifacts marked with dot.

A. Response to maximal ipsilateral forepaw stimulation: $\bar{L}$=11.39 msec.; $\overline{s/d}$=2.09; p=1.00; n=11.
B. Response to stimulation of the contralateral motor cortex (p.d.=0.4 msec.; 8 pulses at 312/second): $\bar{L}$ (from beginning of cortical train)=22.72 msec.; $\overline{s/d}$=1.26; p=1.00; n=19.
C. Response to subthreshold stimulation of the ipsilateral forepaw: p=0; n=32.
D. Response to subthreshold stimulation of the contralateral motor cortex (p.d.=0.2 msec.; 4 pulses at 312/second): p=0; n=16.
E. Stimuli in C and D given together: $\bar{L}$ (to ipsilateral forepaw shock artifact)=13.38 msec.; $\overline{s/d}$=1.00; p=0.76; n=17.

11 pulses was just adequate to excite the unit (Fig. 6C), while a train of 10 similar pulses was not (Fig. 6B). Increasing the train beyond the threshold duration produced a prolonged discharge (Fig. 6 A right; see also Figs. 3C and 14C).

Increasing either the pulse intensity or duration applied to the motor cortex (whether single pulses or a train of pulses was used) resulted in a)a decrease in the mean latency of the first spike and in the subsequent interspike intervals. b)an increase in the probability of firing, and c) an increase in the mean number of spikes per discharge. These changes, best illustrated in Figures 3 D,E and F, 4 C,D and E and 5B are similar to the changes in behavior of units of the somatosensory system following increases in the intensity of the peripheral stimulus (see Section One of this chapter).

When single cortical pulses were adequate to activate units in the dorsal column nuclei, mean initial spike latencies were as small as 5 msec. for some units and as large as 28 msec. for others. More than half of such units had latencies less than 8 msec. (mean of 6.71 $\pm$ 0.68 msec.). The variation in latency in individual units was inversly proportional to the latency itself; often the latency dispersion of a cortically driven unit was as small as the latency dispersion of the unit when driven monosynaptically from the periphery. In units which could be driven by single pulse stimulation of either the motor cortex or the forepaw, the latter stimulus usually produced the greater number of spikes per discharge, even when each input was maximally stimulated.

In 15 instances, it was possible to determine the ability of the unit to follow each pulse during repetitive cortical stimulation. In the

majority of the units, such testing was not possible because the effects of the paralytic agent had worn off before the tests were carried out and the cortically evoked movements dislodged the recording electrode. Moreover, it was usually impossible to give supplementary doses of decamethonium bromide, for the muscle twitches produced immediately after an injection resulted in a similar displacement of the recording electrode. Ten of the units successfully tested responded to each pulse in a repetitive cortical train at frequencies in excess of 50 per second; Figure 5 A4 depicts the behavior of one of the three units that followed up to 100 per second. These 10 units had mean latencies of less than 8 msec. following single shock stimulation of the contralateral cortex. The remaining five units followed each pulse in a repetitive cortical train at frequencies greater than 10 per second but less than 50 per second.

When peripheral and cortical excitatory input were interacted, both occlusion or facilitatory convergence could be demonstrated, depending upon the relative stimulus strengths. Occlusion was best demonstrated with a supramaximal peripheral conditioning stimulus and threshold test cortical stimulus; it lasted for about 100 msec. Occlusion could also be demonstrated with strong cortical conditioning stimuli and threshhold peripheral test stimuli. Facilitatory convergence was readily demonstrated when subthreshold cortical and peripheral pulses were interacted, as illustrated in Figure 7.

Comparison between the excitatory inputs from the contralateral and the homologous ipsilateral motor cortex showed the contralateral motor cortex to be more efficacious. Units had longer mean latencies, greater latency dispersions, smaller mean number of spikes per discharge and

smaller probabilities of firing when activated by electrical stimulation of the ipsilateral cortex than by identical stimulation of the homologous point on the contralateral cortex (Fig. 5A). In some units, these comparisons were made at a number of stimulus strengths. In 10 units, the ipsilateral motor cortex had no detectable excitatory input, even with strong cortical stimuli(Fig. 4B).

Inhibitory and blocking influence of the motor cortex on neurons of the dorsal column nuclei

One hundred units isolated in the cuneate and gracile nucleus were rendered less excitable to cutaneous stimulation by prior electrical stimulation of the contralateral motor cortex. The decrease in unit excitability was termed inhibition if the unit was excited monosynaptically from the periphery according to the criteria already described in the preceding section. When the excitatory test pathway could not be clearly established to be monosynaptic, the possibility that the conditioning and test pathways share common elements cannot be excluded. The depression of unit response to the test volley then might be due to post-excitatory depression of the common intercalated element following its discharge by the antecedent conditioning volley. In such instances, the depression is designated by the non-committal term blockade (8). Seventy per cent of the units, rendered less excitable to peripheral stimulation, were inhibited by the motor cortex conditioning stimulus; the rest were blocked.

The decrease in responsiveness to peripheral electrical stimulation was manifested in one or a combination of ways. In some instances, the mean

number of spikes per discharge decreased with (Figs. 10E and 20 A2), or without (Figs. 11 A3 and 12 B2), a significant increase in the initial spike latency. In others, the probability of firing decreased (Figs. 10E, 11 B3 and 13 B2). Response probability reached zero at maximal inhibition or blocking (Figs. 8 A3, 10B and 14 B2).

A short train of cortical pulses was usually required to produce depression of cuneate units. Maximal effects were produced when the conditioning stimulus consisted of at least 10 pulses at a frequency of 300 per second and when the testing stimulus was just above threshold intensity. Maximal interaction occurred at conditioning-testing intervals between 50 and 150 msec., the interval being measured from the beginning of the conditioning cortical train to the test shock artifact. In six units, single conditioning cortical pulses were adequate to reduce the unit's responsiveness to peripheral stimulation. Four of these units were isolated long enough to allow interactions at various conditioning-testing intervals. Two examples, one of inhibition and one of blocking interaction, are plotted in Figure 9. Both processes developed fully within 20 to 70 msec. after the conditioning stimulus and were dissipated within 100 to 200 msec. Plots relating the initial response latency and the mean number of spikes per discharge to conditioning-testing intervals were similar.

Depression of unit response, whether of the blocking or inhibitory type, was graded and could be varied by varying the intensity of the conditioning volley. When the conditioning-testing interval was adjusted to give maximal depression and the intensity of the conditioning shock was gradually increased from zero, the first sign of depression was

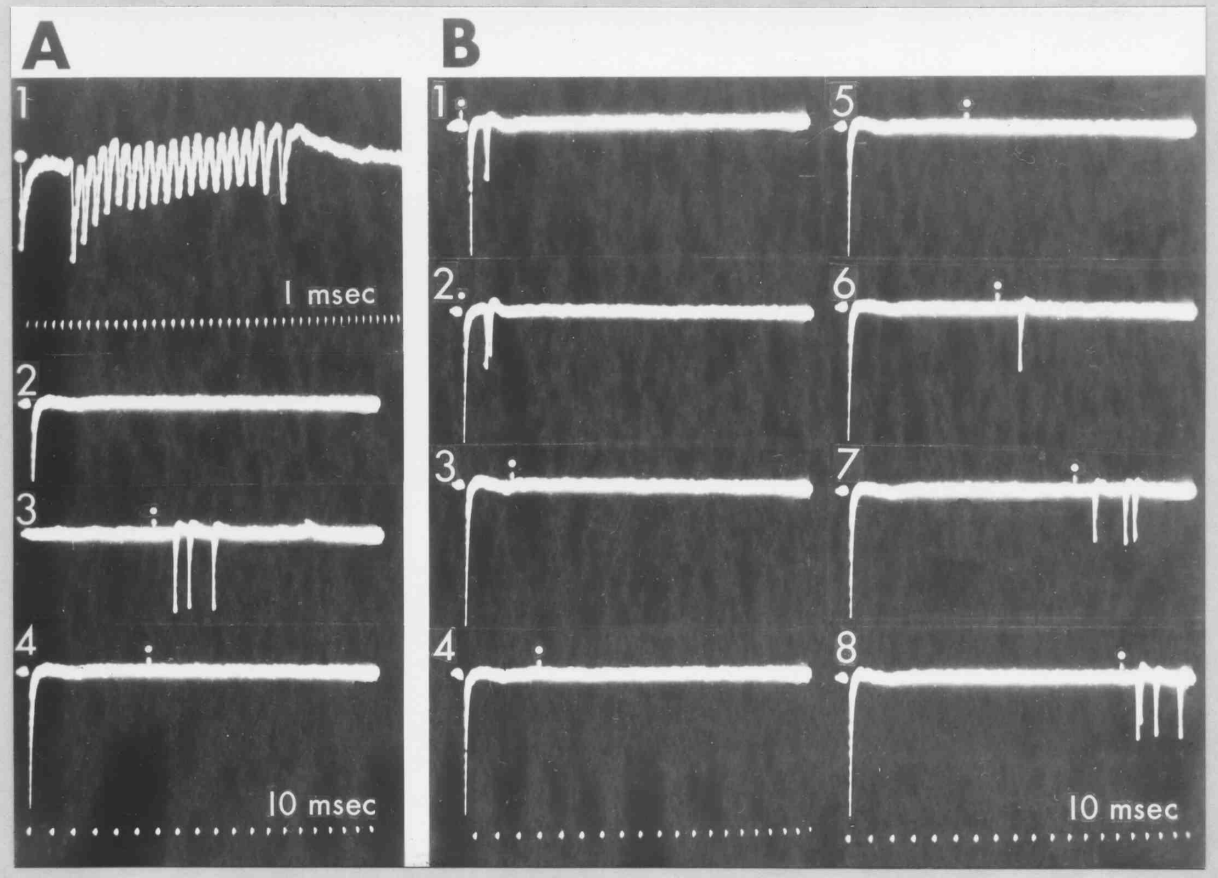

Figure 8. Inhibitory interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to electrical stimulation of the ipsilateral forepaw. Peripheral shock artifacts marked with dot.

A1. Response to maximal ipsilateral forepaw stimulation: $\bar{L}$=6.07 msec.; $\overline{s/d}$=17.00; p=1.00; n=12; ff=250/second.

A2. Conditioning stimulation of the contralateral motor cortex with single pulses (p.d.=0.4 msec.): p=0.

A3. Test stimulation of the ipsilateral forepaw (at near threshold intensity): $\bar{L}$=9.93 msec.; $\overline{s/d}$=2.24; p=1.00; n=204.

A4. Interaction of the conditioning (A2) and testing (A3) stimuli at C-T interval of 57 msec.: p=0; n=10.

B. Inhibitory interaction at various C-T intervals: 1, -3 msec.; 2, 0 msec.; 3, 22 msec.; 4, 37 msec.; 5, 57 msec.; 6, 62 msec.; 7, 116 msec.; 8, 147 msec. Changes in p to peripheral stimulation, as a function of C-T interval, are plotted in Figure 9 (dashed line).

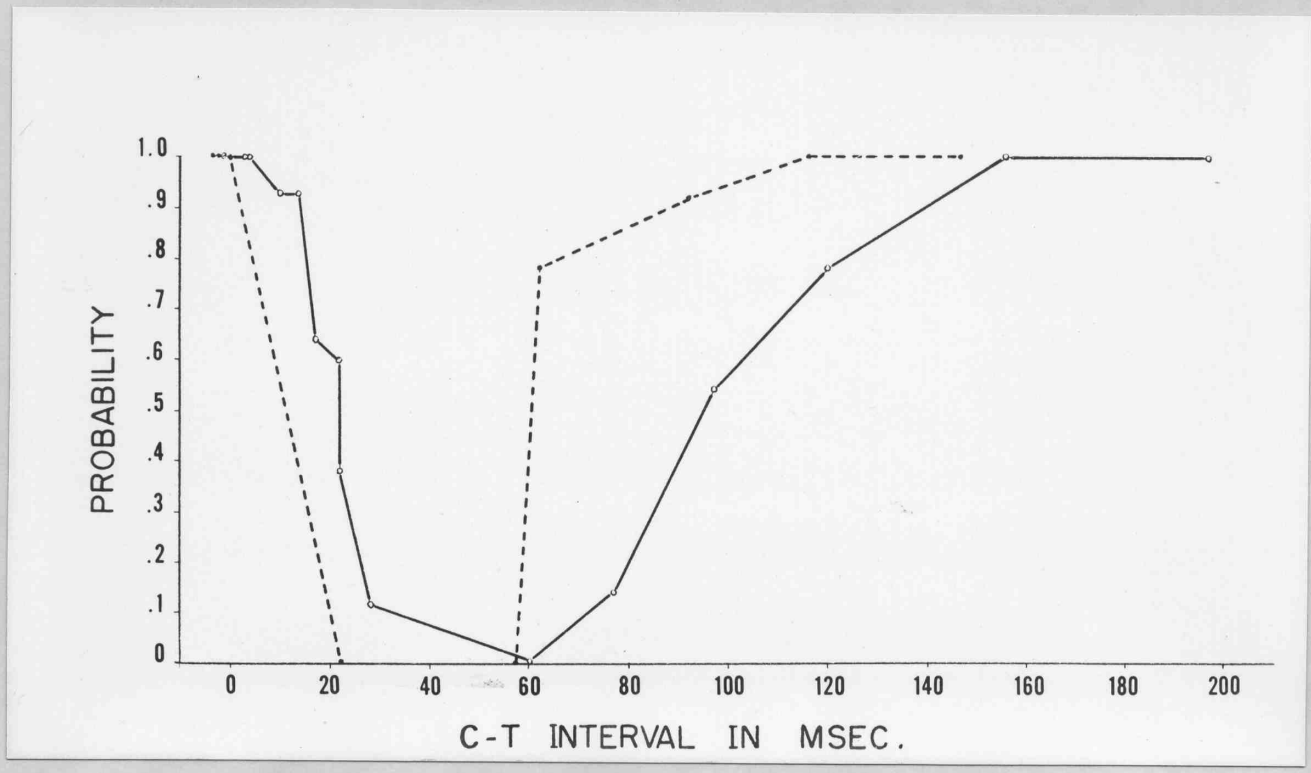

Figure 9. Time course of the inhibitory and depressive interactions (see Fig. 8). Conditioning stimulus was single shock applied to the contralateral motor cortex at various times before the peripheral testing stimulus. The time course is measured as a decrease in probability of discharge of the first spike of the test discharge; other measures yield a similar time course (see text). Dashed line shows inhibitory interaction in a cuneate unit (the same unit shown in Fig. 8). Solid line shows depressive interaction in another cuneate unit.

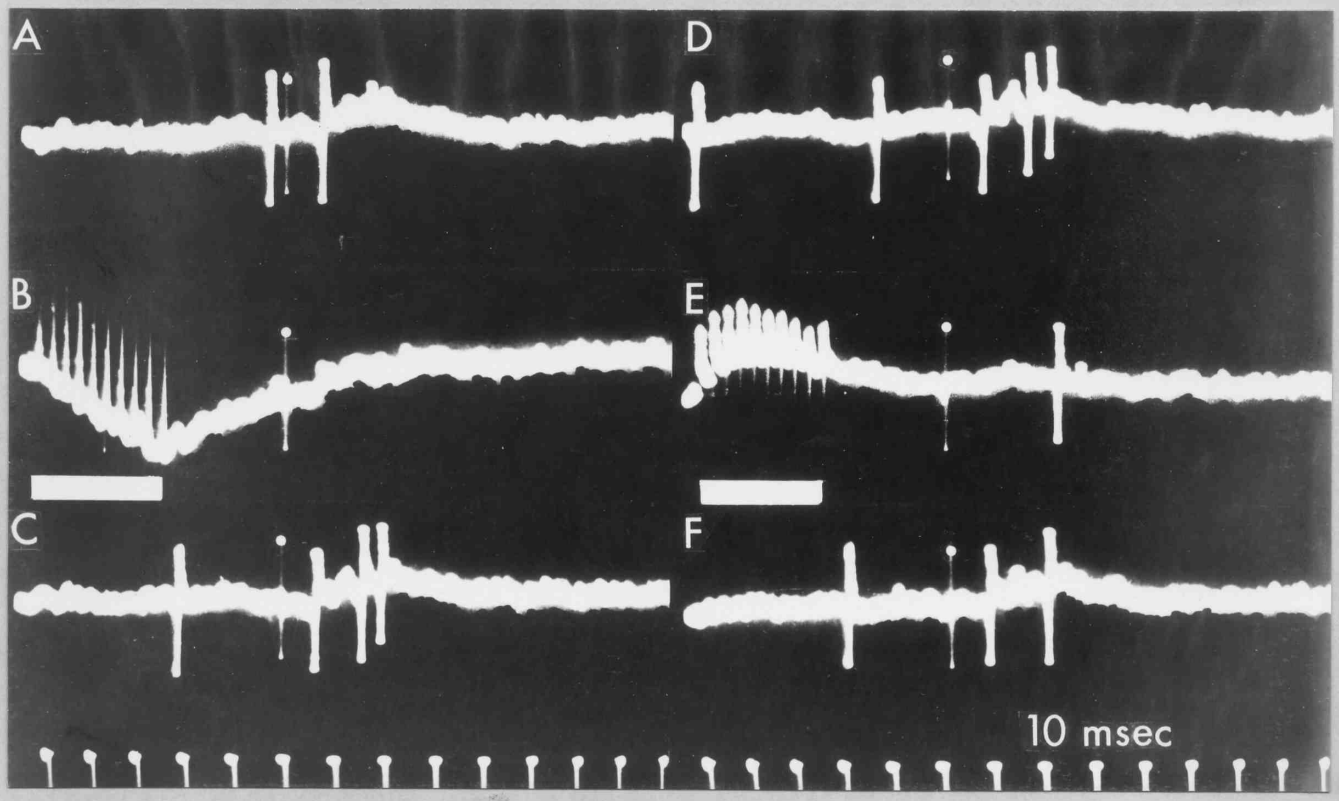

Figure 10. Comparison of efficacy of conditioning electrical stimulation of contralateral and ipsilateral motor cortices in inhibiting the response of a cuneate unit to electrical stimulation of the ipsilateral forepaw.

A, C, D and F. Responses to near threshold ipsilateral forepaw stimulation before (A and D) and after (C and F) conditioning cortical interaction: $\bar{L}$=6.00 msec.; $\overline{s/d}$=1.8; p=1.00; n=39; ff (at maximal peripheral intensity)= 100/second.

B. Response to near threshold ipsilateral forepaw stimulation during conditioning stimulation of the contralateral motor cortex (p.d.=0.4 msec.; 10 pulses at 312/second; C-T interval=53 msec.): p=0; n=10.

E. Response to near threshold ipsilateral forepaw stimulation during conditioning stimulation of the ipsilateral motor cortex (same parameters as in B): $\bar{L}$=20.75 msec. (latency of third spike, when present in unconditioned response, was about 19 msec.); $\overline{s/d}$=1.00; p=0.40; n=10.

In B and E, note depression of spontaneous discharge during and immediately after cortical conditioning.

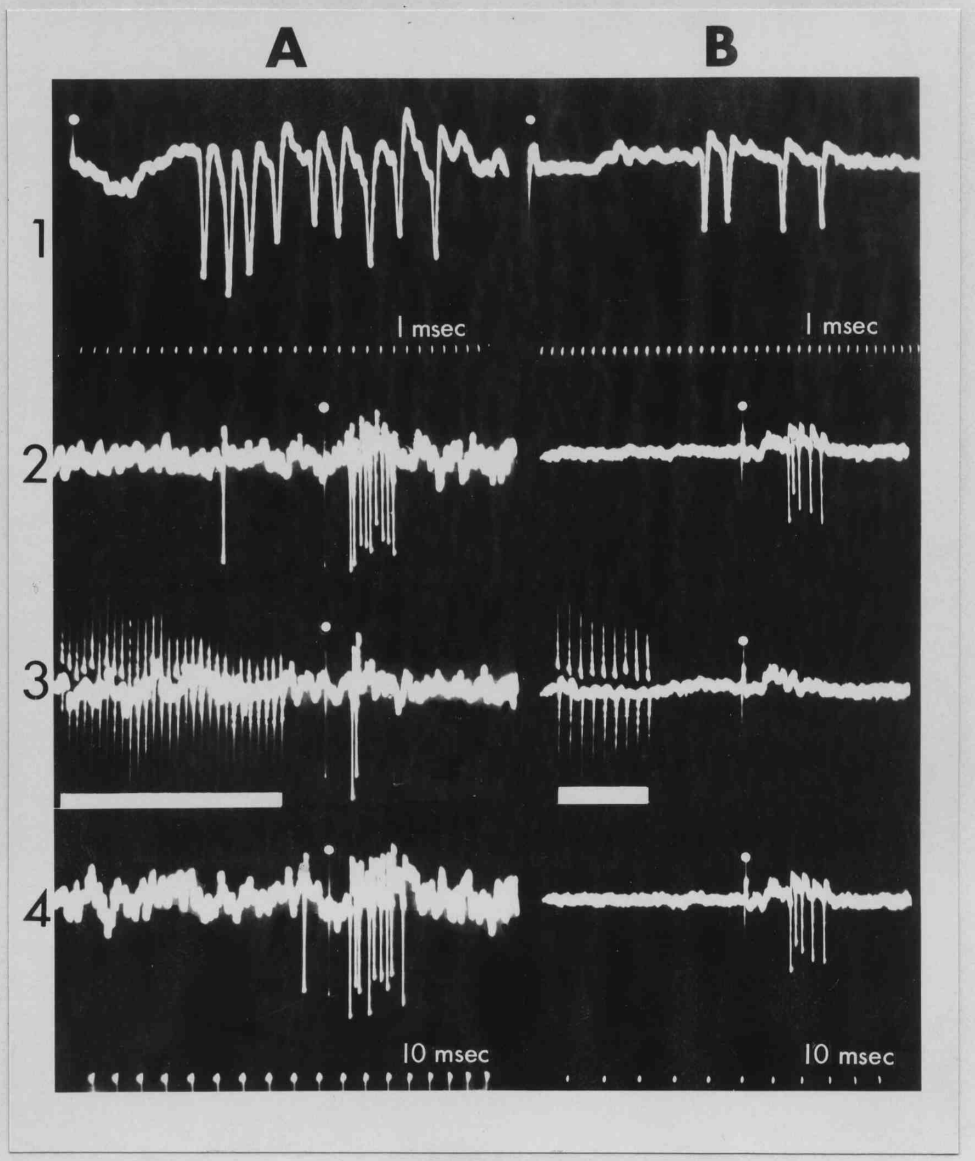

Figure 11.

Figure 11.

A. Inhibitory interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to electrical stimulation of the ipsilateral forepaw. Peripheral shock artifacts marked with dot. Durations of cortical trains indicated by horizontal white bars.

A1. Response to near threshold ipsilateral forepaw stimulation: $\bar{L}$=9.72 msec.; $\overline{s/d}$=8.90; p=1.00; n=44; ff (at maximal peripheral intensity)=125/second.

A2 and 4. Slow sweep recordings of the same phenomena recorded in A1 taken before (A2) and after (A4) conditioning cortical interaction.

A3. Response to near threshold ipsilateral forepaw stimulation during conditioning stimulation of the contralateral motor cortex (p.d.=0.6 msec.; 29 pulses at 312/second; C-T interval=110 msec.): $\bar{L}$=10.18 msec.; $\overline{s/d}$=3.82; p=1.00; n=11. Note depression of spontaneous activity.

B. Depressive interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to electrical stimulation of the ipsilateral forepaw. Peripheral shock artifacts marked with dot. Durations of cortical trains indicated by horizontal white bars.

B1. Response to near threshold ipsilateral forepaw stimulation; $\bar{L}$=17.96 msec.; $\overline{s/d}$=4.63; p=0.97; n=39; ff (at maximal peripheral intensity)=2.5/second.

B2 and 4. Slow sweep recordings of the same phenomena recorded in B1 taken before (B2) and after (B4) conditioning cortical interaction.

B3. Response to near threshold stimulation of the ipsilateral forepaw during conditioning stimulation of the contralateral motor cortex (p.d.=0.6 msec.; 9 pulses at 312/second; C-T interval=54 msec.): $\bar{L}$=17.67 msec.; $\overline{s/d}$=1.33; p=0.20; n=15.

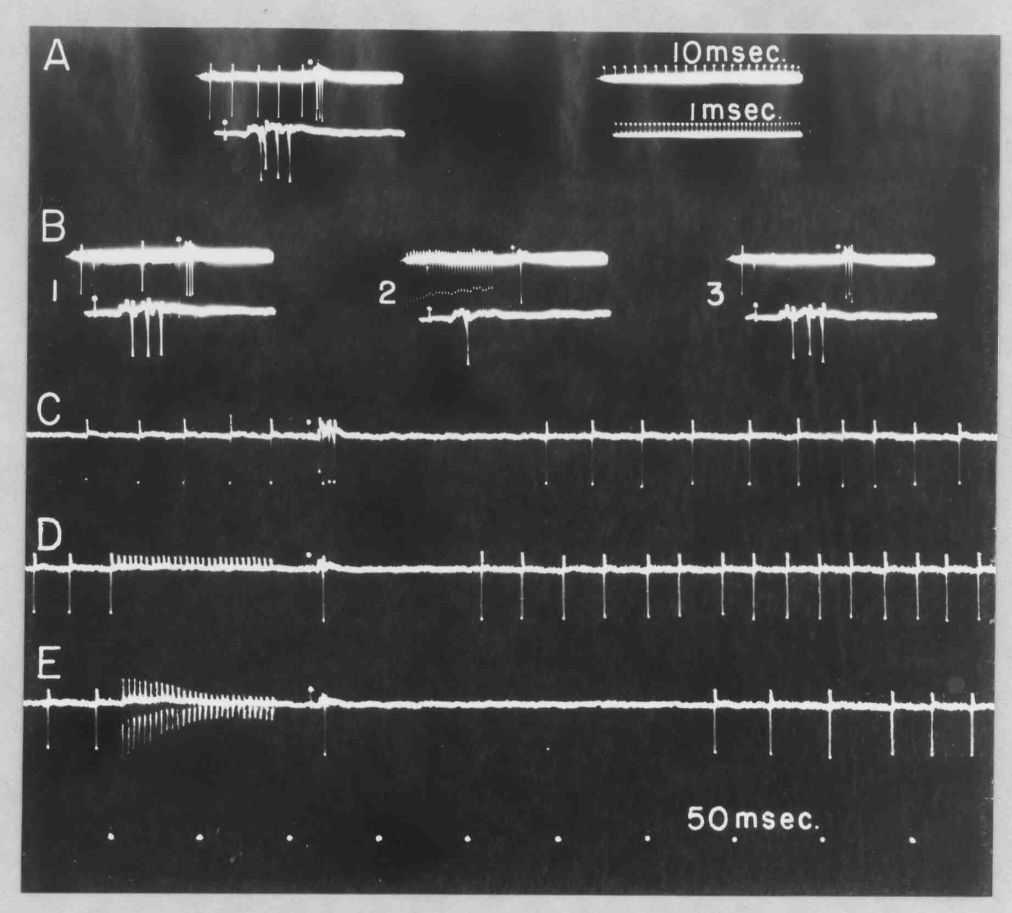

Figure 12. Depressive interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on a cuneate unit's spontaneous discharge and response to electrical stimulation of the ipsilateral forepaw. In A and B, the two sweeps show the same event, with the lower (fast) sweep showing only the 40 msec. following peripheral shock artifacts; the upper and lower sweep speeds are denoted by the 10 and 1 msec. time lines, respectively, in A right. Peripheral shock artifacts marked with dot.

A left. Response to maximal ipsilateral forepaw stimulation: $\bar{L}$=7.48 msec.; $\overline{s/d}$=4.00; p=1.00; n=13; ff=250/second.

B1 and 3. Response to near threshold ipsilateral forepaw stimulation before (B1) and after (B3) conditioning cortical interaction: $\bar{L}$=7.49 msec.; $\overline{s/d}$=2.85; p=1.00; n=27.

B2. Response to near threshold ipsilateral forepaw stimulation during conditioning stimulation of the contralateral motor cortex (p.d.=0.1 msec.; 28 pulses at 312/second; C-T interval =106 msec.): $\bar{L}$=7.47 msec.; $\overline{s/d}$=1.09; p=1.00; n=11.

C and D. Moving film of same phenomena in B2 and B3, showing effect on spontaneous discharge.

E. Conditioning pulse durations increased from 0.1 msec. (used in B2 and D) to 0.5 msec., resulting in longer depression of the spontaneous discharge. Lower tips of spikes in C, D and E are indicated by dots.

usually a shortening of the test response burst, the dropped spikes being those occurring late in the train. Simultaneously, there was an increase in the mean initial spike latency. Some units were found which responded to a peripheral stimulus with a probability of one and with only one spike in each discharge. In such instances, gradual increase in intensity of the conditioning stimulus resulted in small (but significant) decreases in probability before complete failure occurred. Simultaneously, the latency increased significantly (Fig. 13 B2).

As in the case of excitation, cortically induced depression was always more easily demonstrated on cuneate and gracile units contralateral to the stimulated hemisphere (Fig. 10). Indeed, in some instances, ipsilateral cortical stimulation was completely without effect (Fig. 13 C2).

Stimulation of the motor cortex also depressed spontaneous discharge of cuneate and gracile units. The depression was manifested by a decrease of spontaneous discharge frequency or by temporary cessation of the spontaneous discharge. In fact, depression of spontaneous discharge was usually more easily demonstrated than depression of peripherally evoked discharge (Figs. 10E and 12E). The cortical influence on spontaneous activity is illustrated in Figures 10 B and E, 12, 15A and 18C. The duration of the depression of spontaneous discharge increased with increase in the cortical stimulus intensity (Fig. 12E); on several occasions, the decrease in excitability of spontaneous unit activity lasted up to 200 msec. or more, following the end of a conditioning train to the contralateral motor cortex.

Reversal of conditioning influence

Changing the intensity or pulse duration of cortical stimulation resulted in a reversal of cortical influence on 10 units. The evoked activity of these units was depressed by weak conditioning stimulation of the motor cortex. As the conditioning stimulation increased, either by increasing intensity or pulse duration, the effect changed to excitation (Figs. 13 A2 and B, 14 B and C and 15). To produce such reversals it was necessary to increase the strength of the cortical conditioning stimulus drastically. In Figure 15, doubling the duration of the individual pulses in a conditioning cortical train changed the strong inhibitory effect shown in B to the excitatory effect shown in C. In some instances, increasing the conditioning train duration, keeping pulse duration and intensity constant, resulted in a similar reversal.

Cortical influence on cuneate neurons evoked by "natural" peripheral stimulation.

Electrical stimulation of the skin offers distinct advantages over "natural" stimulation. With the former, stimulus intensity and response latency can be measured precisely. However, electrical stimulation is artificial. Therefore, in 10 cuneate units, the test discharge was evoked by "natural" stimulation of the skin. In eight of these, the stimulus was a brief tap delivered to the footpad by a solenoid, and the response was a burst of impulses. In three of these units, antecedent stimulation of the contralateral motor cortex blocked test responses evoked by tapping the paw. An example is shown in Figure 16. The other five units were facilitated by electrical stimulation of the contralateral motor cortex. Figure 18 shows a particularly interesting example of

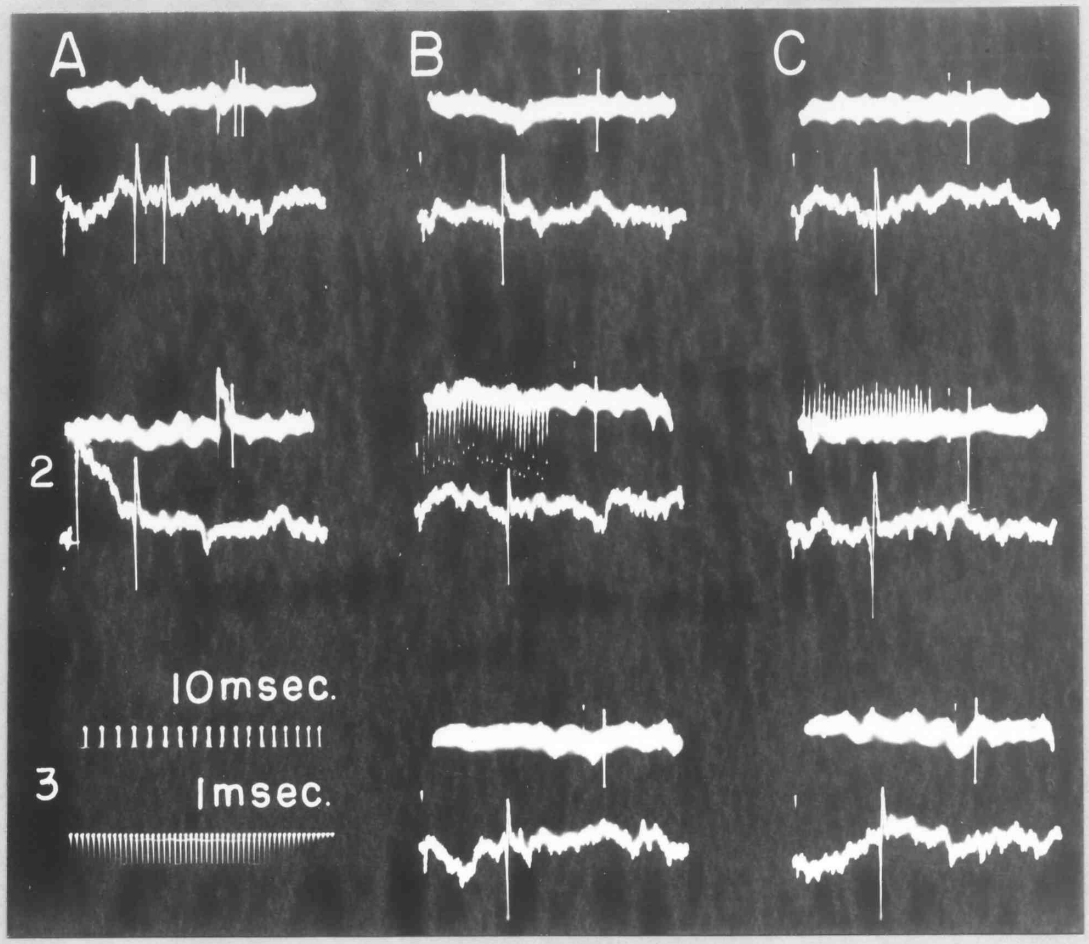

Figure 13. Effect of altering the parameters of conditioning electrical stimulation of the contralateral motor cortex on the responses of a gracile unit. Upper and lower sweeps record the same event, with the lower (fast) sweep showing only the 47 msec. following peripheral shock artifacts.

A1. Response to maximal (electrical) ipsilateral hindpaw stimulation: $\bar{L}$=13.09 msec.; $\overline{s/d}$=1.82; p=1.00; n=11.

A2. Response to stimulation of the contralateral motor cortex (p.d.=0.8 msec.): $\bar{L}$=10.65 msec.; $\overline{s/d}$=1.00; p=0.94; n=18.

B1 and 3. Response to near threshold ipsilateral hindpaw stimulation before (B1) and after (B3) conditioning cortical interaction: $\bar{L}$=14.17 msec.; $\overline{s/d}$=1.04; p=1.00; n=54.

B2. Response to near threshold ipsilateral hindpaw stimulation during conditioning stimulation of the contralateral motor cortex (p.d.=0.02 msec.; 26 pulses at 312/second; C-T intervals =98 msec.): $\bar{L}$=15.71 msec.; $\overline{s/d}$=1.00; p=0.70; n=20.

C1 and 3. Like B1 and 3.

C2. Similar (B2) conditioning train applied to the ipsilateral cortex: $\bar{L}$=15.15 msec.; $\overline{s/d}$=1.00; p=1.00; n=15.

Figure 14. Effect of altering the parameters of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit. In B, upper and lower sweeps record the same event, with the lower (fast) sweep showing only the 20 msec. following the peripheral shock artifacts.

A1. Response to stimulation of the ipsilateral forepaw with a mechanical tapper (controlled by an electrical relay, producing diphasic shock artifact): $\bar{L}$=13.70 msec. (from beginning of artifact); $\overline{s/d}$=3.68; p=1.00; n=22.

A2. Response to maximal (electrical) ipsilateral forepaw stimulation: $\bar{L}$=5.23 msec.; $\overline{s/d}$=3.00; p=1.00; n=12; ff=250/second.

A3. 10 msec. time line serves upper sweeps in B; 1 msec. time line serves lower sweep in B and A2.

A4. Superimposed sweeps of freqnency following at 200 stimuli/second to the ipsilateral forepaw.

B1 and 3. Response to near threshold ipsilateral forepaw stimulation before (B1) and after (B3) conditioning cortical interaction: $\bar{L}$=5.49 msec.; $\overline{s/d}$=1.04; p=1.00; n=25.

B2. Response to near threshold ipsilateral forepaw stimulation during conditioning stimulation of the contralateral motor cortex (p.d.=0.2 msec.; 24 pulses at 312/second; C-T interval=76 msec.): p=0; n=9.

C. Response to stimulation of the contralateral motor cortex (same train used in B2, except p.d.=0.4 msec.); Stimuli and sweeps triggered simultaneously once per second..

C1. Response to first bout of stimulation.

C2. By the fifth bout of stimulation (5 seconds after first bout), the same stimulus train evokes a larger discharge.

C3. By the eighth bout, a long burst of spikes is produced.

C4. Twelve seconds after end of stimulation, the unit is entirely silent (it showed no spontaneous discharge prior to the stimulation period).

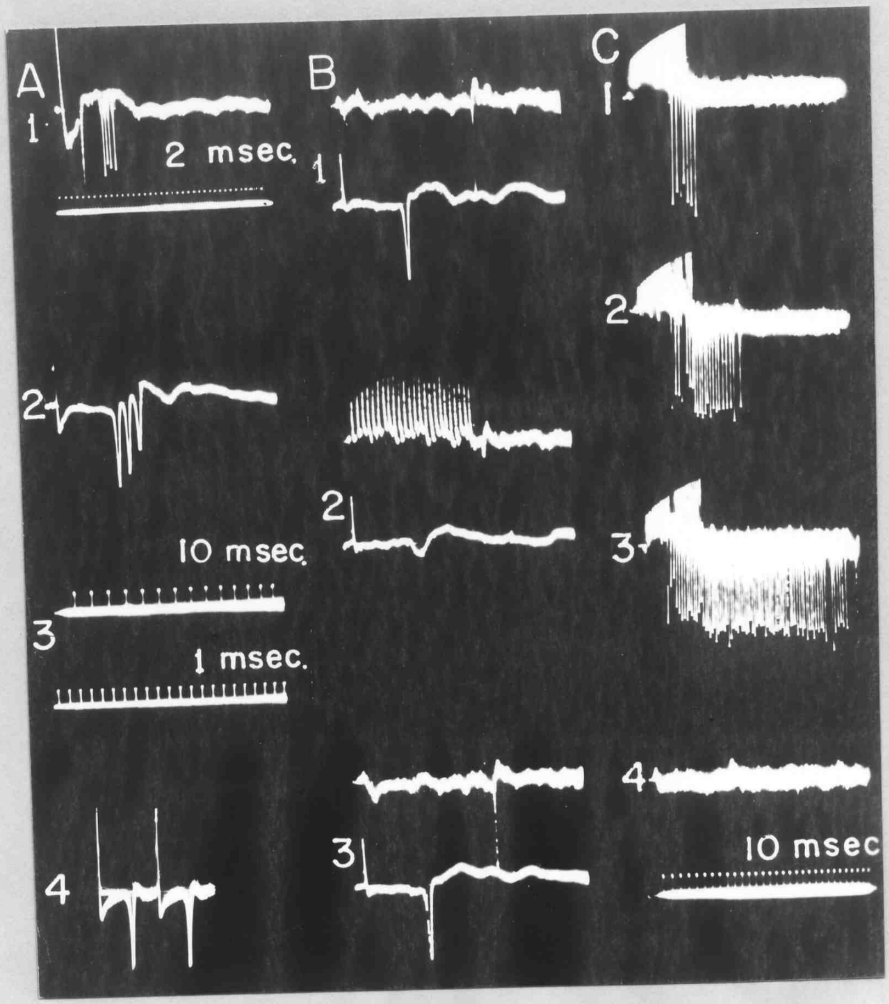

Figure 14.

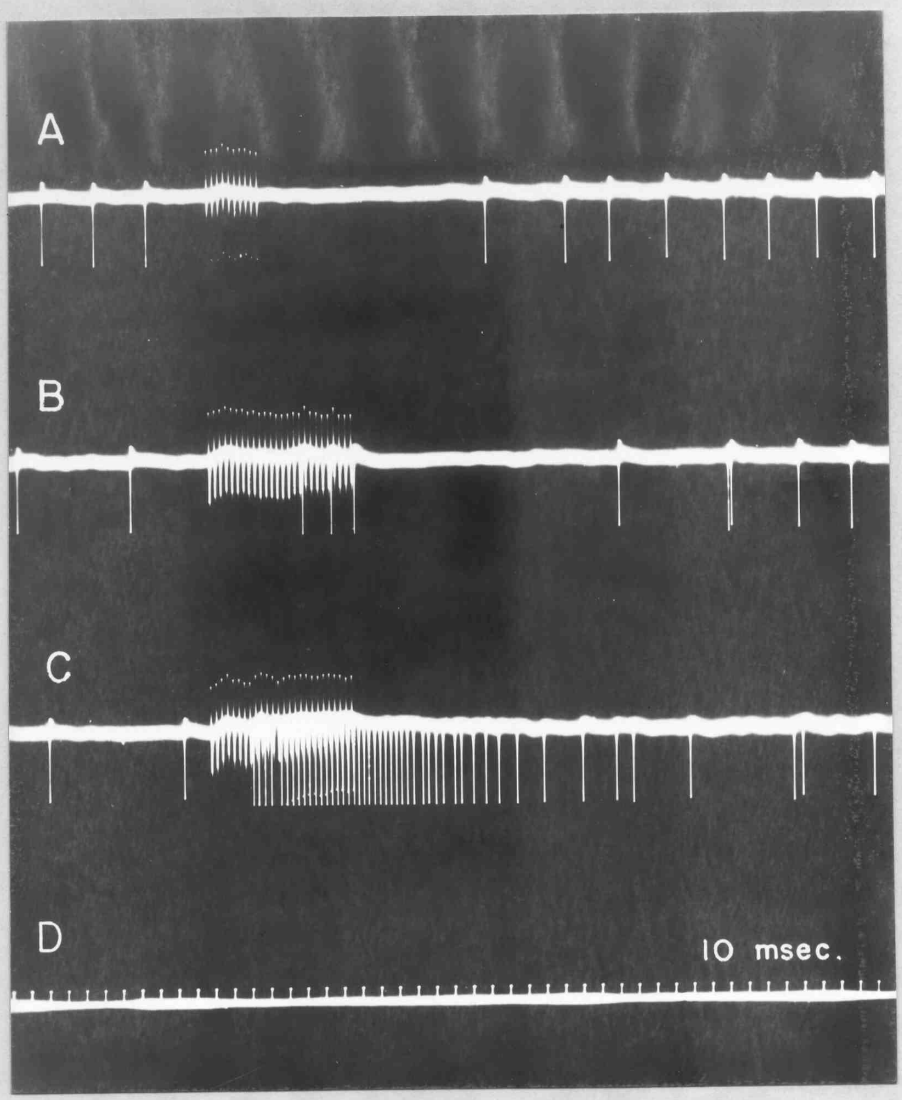

Figure 15. Effects of altering the parameters of conditioning electrical stimulation of the contralateral motor cortex on the spontaneous discharge of a cuneate unit. Unit evoked to peripheral electrical stimulation with a $\bar{L}$ of 4.53 msec. and ff of 100/second.

A. Contralateral motor cortical stimulation (p.d.=0.1 msec.; train of 8 pulses at 312/second). Cortical stimulus regularly depresses the spontaneous discharge.
B. Increasing the train duration to 26 pulses and p.d. to 0.2 msec. from cortical train used in A. Cortical stimulus regularly evokes the unit.
C. Increasing the p.d. to 0.4 msec. from what was used in B. Drastic increase in discharge pattern occurs.

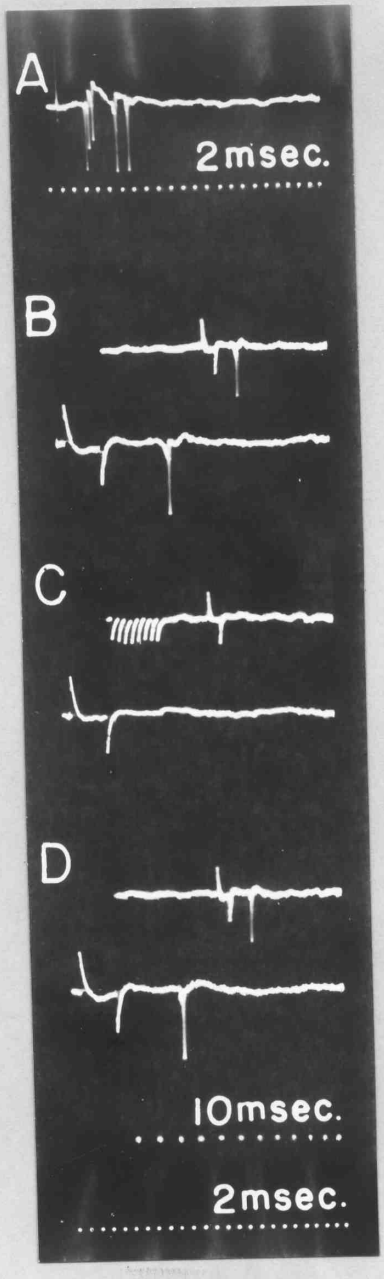

Figure 16. Depressive interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to mechanical tapping of the ipsilateral forepaw. In B,C and D, two sweeps show the same event, with lower (fast) sweep showing only the 46 msec. following peripheral shock artifacts.

A. Response to maximal (electrical) ipsilateral forepaw stimulation: $\overline{L}$=4.60 msec.; $\overline{s/d}$=6.45; p=1.00; n=11; ff=100/second

B and D. Response to mechanical tapping of the ipsilateral forepaw before (B) and after (D) conditioning cortical interaction: $\overline{L}$=17.66 msec. (from beginning of diphasic shock artifact); $\overline{s/d}$=1.55; p=0.87; n=63.

C. Response to mechanical tapping of the ipsilateral forepaw during conditioning stimulation of the contralateral motor cortex (p.d.= 0.3 msec.; 7 pulses at 312/second; C-T interval=47 msec.): p=0; n=21.

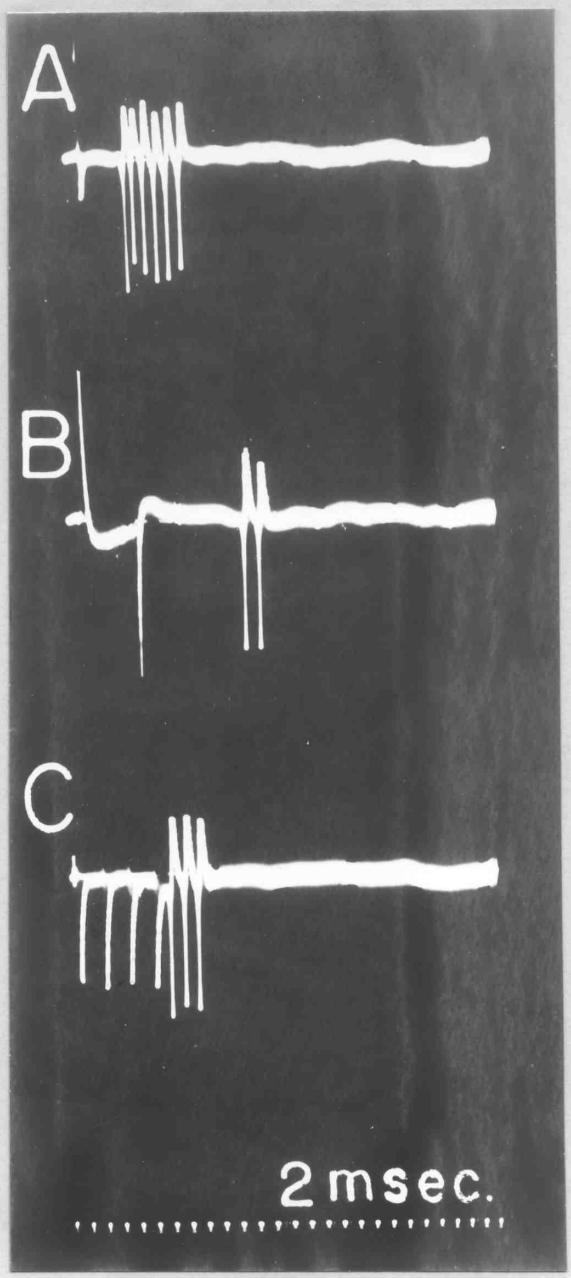

Figure 17. Responses of a cuneate unit to electrical stimulation and mechanical tapping of the ipsilateral forepaw and electrical stimulation of the contralateral motor cortex.

A. Response to maximal (electrical) stimulation of the ipsilateral forepaw: $\bar{L}$=5.13 msec.; $\overline{s/d}$=5.67; p=1.00; n=15.
B. Response to mechanical tapping of the ipsilateral forepaw: $\bar{L}$=18.61 (from beginning of diphasic shock artifact); $\overline{s/d}$=1.64; p=1.00; n=14.
C. Response to electrical stimulation of the contralateral motor cortex:(p.d.=0.05 msec.; 4 pulses at 312/second): $\bar{L}$=11.07 msec.(from beginning of cortical train); $\overline{s/d}$=2.71; p=1.00; n=7.

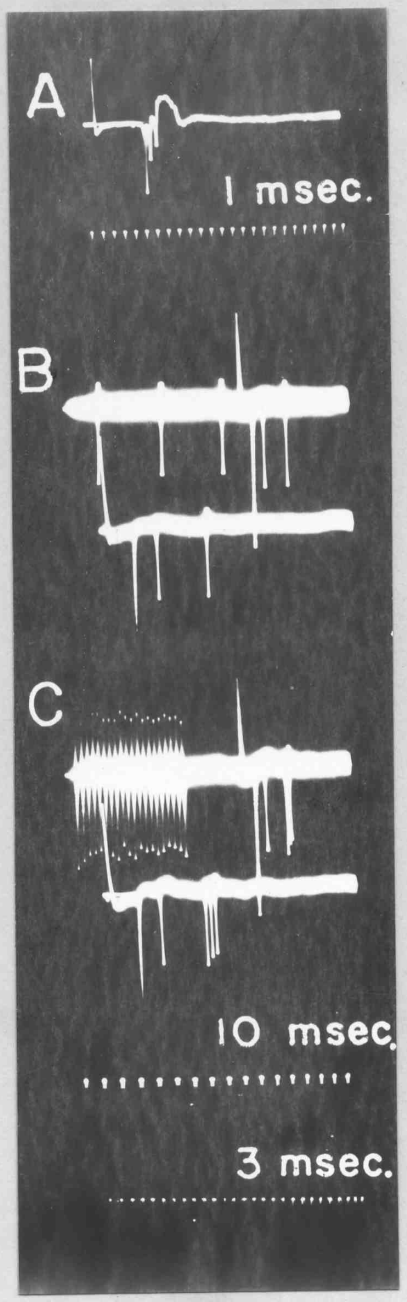

Figure 18.

Figure 18. Facilitatory interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to mechanical tapping of the ipsilateral forepaw. In B and C, two sweeps show the same event, with lower (fast) sweep showing only the 90 msec. following peripheral shock artifacts.

A. Response to maximal (electrical) ipsilateral forepaw stimulation: $\bar{L}$=4.53 msec.; $\overline{s/d}$=3.00; p=1.00: n=9; ff=100/second.

B. Response to mechanical tapping of the ipsilateral forepaw: L=14.48 msec. (from beginning of diphasic shock artifact); p=1.00; $\bar{L}$ (second spike)=29.71 msec.; p (second spike)=1.00: $\bar{L}$ (third spike)=31.18 msec.; p (third spike)=0.83; $\overline{s/d}$=2.94: n=36.

C. Response to mechanical tapping of the ipsilateral forepaw during conditioning stimulation of the contralateral motor cortex (p.d.=0.4 msec.; 20 pulses at 312/second; C-T interval=95 msec.): $\bar{L}$=14.44 msec.; p=1.00: $\bar{L}$ (second spike)=28.38 msec.; p (second spike)=1.00; $\bar{L}$ (third spike)=29.62 msec.: p (third spike)=1.00; $\bar{L}$ (fourth spike)=30.95 msec.; p=1.00; $\overline{s/d}$=4.04; n=24. Note depression of spontaneous discharge during and immediately after cortical conditioning (see text).

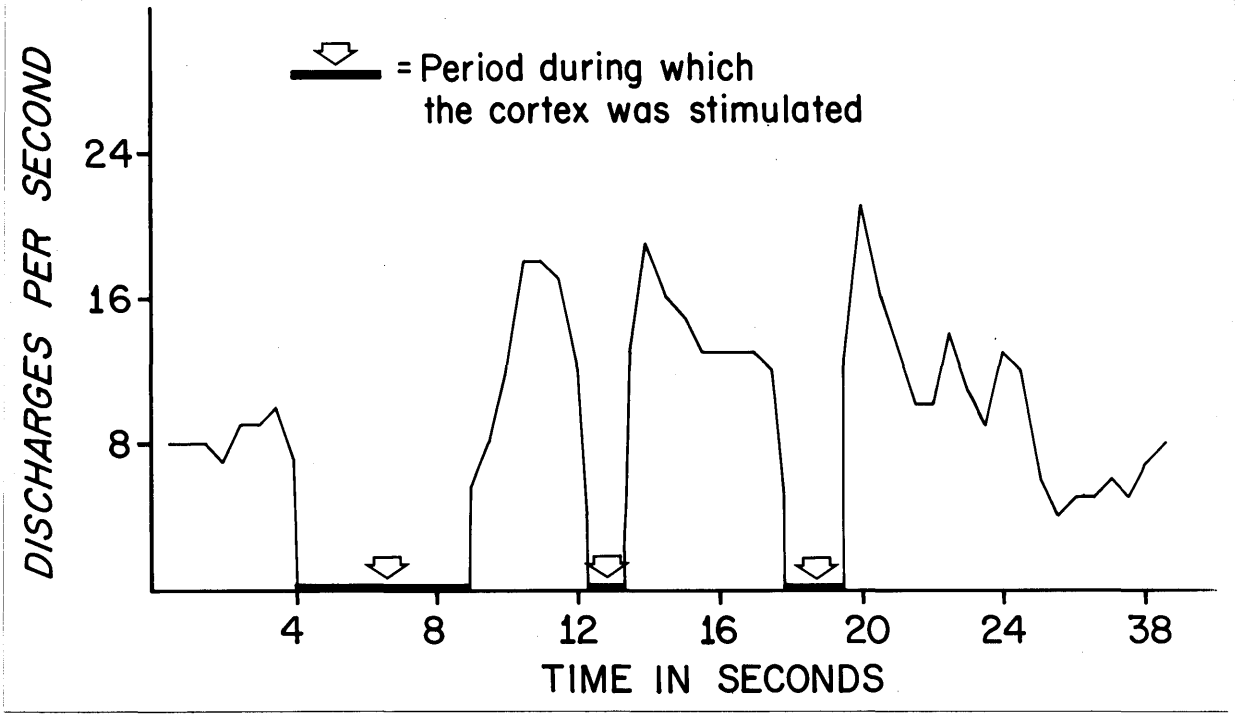

Figure 19. Effect of intermittent electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to maintained pressure on the ipsilateral forepaw. Unit showed no spontaneous discharge. Cortical train parameters: p.d.= 0.4 msec.; 312/second. Not shown in figure: short cortical trains (8 pulses) given at intervals of once every second, regularly (n=20) depressed the response to maintained pressure on the ipsilateral forepaw for at least 200 msec. following end of conditioning train.

excitatory interaction between cortical and "natural" peripheral inputs. The unit illustrated had a high rate of spontaneous discharge. Cortical stimulation blocked the spontaneous discharge but facilitated the test discharge elicited by tapping the foot, the facilitation being evidenced by an increase in the mean number of spikes per discharge from 2.94 to 4.04 and a decrease of the first two interspike intervals from 15.23 and 1.52 msec. to 13.95 and 1.24 msec., respectively.

In two units, sustained discharges, with little or no adaptation, were elicited by pressure on the paw. In one of these, a train of shocks, delivered during a sustained discharge elicited by pressure on the foot, resulted in a temporary but prominent increase in discharge frequency. In the other unit, cortical stimulation depressed the "naturally" evoked discharge; data from this unit are shown graphically in Figure 19.

SECTION THREE: PATHWAYS OF THE CORTICIFUGAL INFLUENCE ON NEURONS OF THE DORSAL COLUMN NUCLEI

In six experiments, 40 cuneate units were isolated in cats in which special surgical procedures were carried out on one or both pyramidal tracts (Chapter Two). In two cats, the brain stem was transected at the level of the trapezoid body, so that only the pyramidal tracts remained intact (Fig. 20C). In two other cats, the brain stem was left intact, but one pyramidal tract was cut (Fig. 22). In two other cats, both pyramidal tracts were transected (Fig. 21).

Pyramidal tract preparations

The influence of motor cortical stimulation was successfully determined on the excitability of 14 cuneate units isolated in animals in which

Figure 20. Motor cortical influences on two cuneate units in a cat with transected brain stem, except for the pyramidal tracts. In A, two sweeps show the same event, with the lower (fast) sweep showing only the 28 msec. following peripheral shock artifacts. Upper and lower sweep speeds in A are denoted by the 10 and 1 msec. time lines, respectively. 1 msec. time line serves sweeps in B.

A. Inhibitory interaction, showing the effect of conditioning electrical stimulation of the contralateral motor cortex on the response of a cuneate unit to electrical stimulation of the ipsilateral forepaw.

A1 and 3. Response to near threshold stimulation of the ipsilateral forepaw before (A1) and after (A3) conditioning cortical interaction: $\bar{L}$=7.64 msec.; s/d=2.00; p=1.00; n=12.

A2. Response to near threshold stimulation of the ipsilateral forepaw during conditioning stimulation of the contralateral motor cortex (p.d.=2 msec.; 8 pulses at 312/second; C-T interval =84 msec.): $\bar{L}$=9.75 msec.; s/d=1.00; p=1.00.

B. Responses of another cuneate unit to electrical stimulation of the ipsilateral forepaw and of the contralateral motor cortex.

B1. Response to maximal ipsilateral forepaw stimulation: $\bar{L}$=5.58 msec.; s/d=2.14; p=1.00; n=14.

B2. Response to stimulation of the contralateral motor cortex (p.d. =2 msec.): $\bar{L}$=11.26 msec.; s/d=1.90; p=1.00; n=20.

C. Luxol-fast stained section showing the amount of tissue remaining after brain stem transection. The overlying medial lemniscus tissue was effectively transected, as revealed by a comparison of sections at various levels through this region.

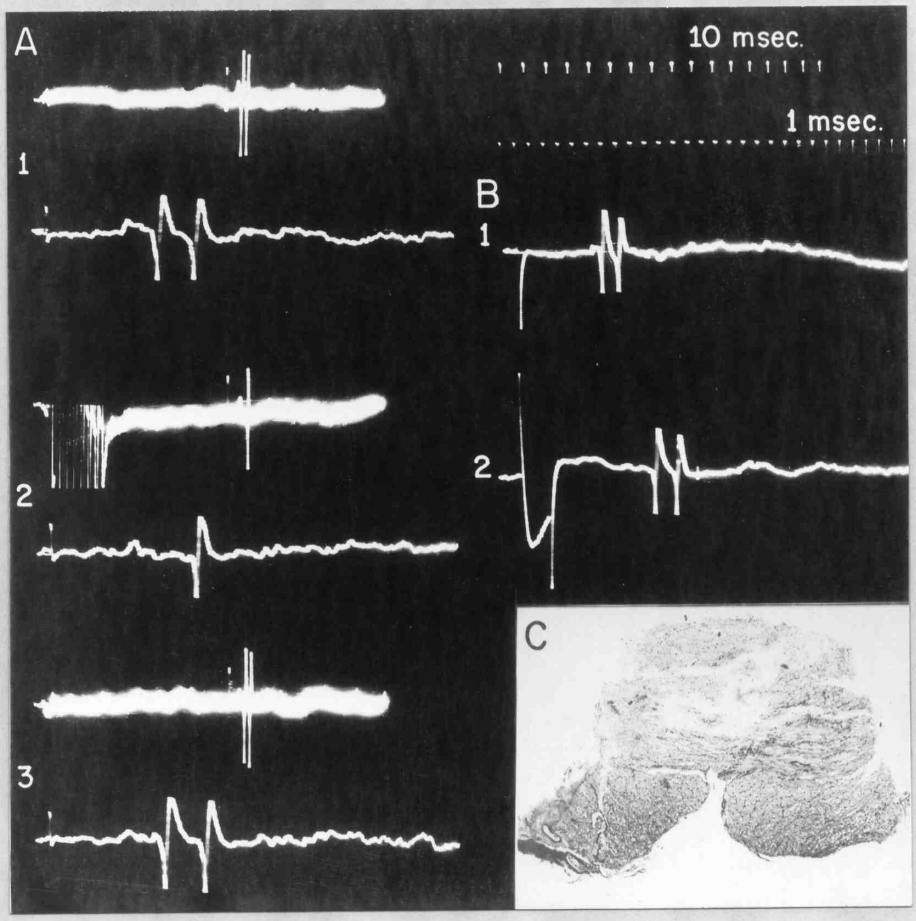

Figure 20.

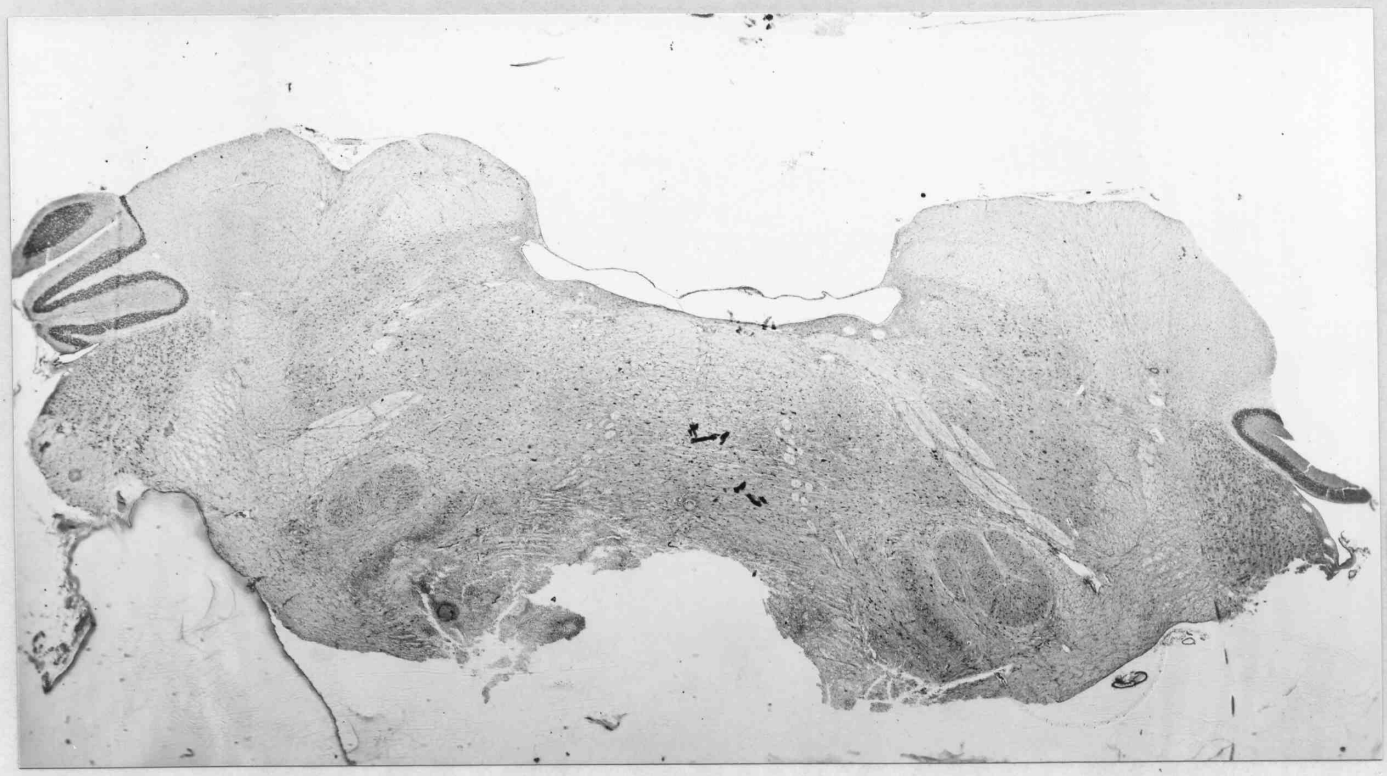

Figure 21. Luxol-fast section through brain stem at level of trapezoid body showing the extent of dissection following transection of both pyramidal tracts.

Figure 22. Luxol-fast section through brain stem at level of trapezoid body showing the extent of dissection following transection of one pyramidal tract.

the pyramidal tracts were the only intact links between cortex and lower bulb. Three of these units were activated by cortical stimulation as well as by peripheral stimulation (Fig. 20B). The excitability of the remaining 11 units was depressed by conditioning electrical stimulation of the contralateral motor cortex (Fig. 20A).

In experiments on isolated pyramidal tract preparation, the strength of the conditioning cortical stimulus required to activate or reduce the responsiveness of the cuneate units was greater than that routinely used. This difference was probably due, at least in part, to the injury sustained by the pyramidal tracts during brain stem section (Fig. 20C).

Pyramidotomized preparations

Twenty-six cuneate units were isolated and studied in animals in which one or both pyramids were sectioned. In bilateral pyramidotomized preparations (Fig. 21), 10 of 14 units were completely uninfluenced by motor cortical stimulation. Of the remaining four units, two were inhibited and two were blocked by conditioning motor cortical stimulation. In only one was induced depression sufficient to reduce the probability of firing to zero, despite the use of a strong conditioning stimulation (at least 15 pulses at 312 per second).

In unilaterally pyramidotomized preparations (Fig. 22) the cortical influence varied according to which of the two cuneate nuclei was tapped for unit recordings. Eight cuneate units were isolated on the side opposite to that of the pyramidal cut. Strong conditioning cortical stimulation produced an inhibition or blockade of the peripherally evoked discharge in all eight units. Furthermore, the units in the cuneate nucleus on the side of the intact pyramid were more easily influenced by stimulating

the ipsilateral motor cortex than by stimulating the contralateral motor cortex. This was in sharp contrast to observations made in intact preparations. On the other hand, four cuneate units, isolated on the same side of the pyramidal cut, were more easily influenced by stimulation of the contralateral motor cortex (inhibitory on two, depressive on one and excitatory on one). In only one of these four units, the ipsilateral motor cortex exerted mild inhibitory effect (changing the probability from 1.00 to 0.78, the mean number of spikes per discharge from 3.67 to 2.29 and the mean initial spike latency from 12.09 to 13.23 msec.); the other three were uninfluenced by stimulation of the ipsilateral motor cortex.

CHAPTER FOUR

DISCUSSION

The present study indicates that stimulation of the motor cortex of the cat can alter the excitability of neurons of the dorsal columns.

On about 40 per cent of the units isolated in the dorsal column nuclei, stimulation of the motor cortex exerted an excitatory influence. This influence could be graded so that a peripheral excitatory input to the same unit was either occluded or facilitated, depending upon the relative intensities of the cortical and peripheral stimuli.

There are several reasons to believe that this cortical excitatory influence on the dorsal column nuclei is monosynaptic. Most of the units in the dorsal column nuclei were discharged in response to single cortical shocks, which suggests a powerful and direct connection. The intensity and duration of the cortical shocks were comparable to the intensity and duration of that cortical shock just adequate to elicit the D and I waves recorded in the pyramidal tract (98). Furthermore, in more than half of the units driven by cortical stimulation, the initial response latency was less than 8 msec. (mean of 6.71 ± 0.68 msec.) and the latency variability was often as small as the variability of the latency of the first spike elicited monosynaptically (see below) from the periphery. Finally, the majority of the units responding to cortical stimulation faithfully followed repetitive cortical stimulation at rates in excess of 50 per second.

Fifty-five per cent of the units isolated in the dorsal column nuclei were depressed by prior conditioning stimulation of the motor cortex. The depression, like the excitation, could be graded by varying the

intensity of the conditioning volley. Two mechanisms for such depressions are possible: a)a direct inhibitory pathway from cortex to dorsal column nuclei; b)an occlusive blocking interaction occuring in neurons shared by the conditioning and testing pathways. Since Amassian and DeVito's (9) experiments indicate that some cuneate neurons act as relays to other cuneate neurons, the latter possibility must be given serious consideration. However, if it can be established that the testing pathway makes direct monosynaptic connections with a cuneate neuron, then depression of that neuron by cortical conditioning cannot be ascribed to neuron sharing and must therefore be due to direct inhibition. The criteria (brief and invariant latency, ability to follow repetitive afferent input at high rates) for monosynaptic activation of cuneate neurons by the testing peripheral volley have been described previously. Units which met these criteria and which were depressed by cortical conditioning stimulation were said to be inhibited. Seventy per cent of the units depressed by cortical stimulation fell within this classification. The remaining 30 per cent did not satisfactorily meet the criteria for monosynaptic activation by the testing volley and no decision could be reached concerning the mechanism of depression. In these instances, the non-committal term blocking interaction was used to describe the depression.

In contrast to the cortical excitatory influence on the dorsal column nuclei, the inhibitory influence seemed to be multisynaptic. Trains of shocks, rather than single shocks, were usually required to produce depression. Optimum conditioning-testing intervals ranged between 50 and 150 msec. On a few occasions, when single cortical conditioning pulses were

adequate to inhibit or block the peripherally evoked activity, full recovery from depression was attained at conditioning-testing intervals of 150 to 200 msec. The long time course of cortical depressive influence suggests that a multisynaptic system connects the cortex to the dorsal column nuclei.

The existence of two cortically originating systems capable of affecting excitability of dorsal column neurons complicates the further analysis of these systems. Whether, for example, each cuneate neuron is subjected in varying degrees to the antagonistic influence of both corticifugal paths or whether the two paths play upon different neurons cannot be stated. Reversal of influence of cortical stimulation with change of cortical stimulus parameters is suggestive of the first possibility, but the non-selective nature of electrical stimulation of the cortex makes any definite decision impossible. Accordingly, an attempt was made to separate the two pathways by making lesions in the brain stem. Attention is first focused upon the pyramidal tract, because branches from this tract to the dorsal column nuclei have been demonstrated anatomically (24,75,76,77 and 124). Furthermore, those projections are predominantly crossed, a finding which is in agreement with the demonstration that cortical stimulation has a more pronounced excitatory influence on the neurons of the contralateral dorsal column nuclei than on those of the ipsilateral nucleus. When the brain stem, except the bulbar pyramids, was transected, at the level of the trapezoid body, both excitatory and inhibitory corticifugal influences on dorsal column nuclei could still be demonstrated. When the pyramids were sectioned at the level of the trapezoid body, corticifugal influences on cuneate neurons

were rarely demonstrated. It is thus evident that the pyramidal tract carries fibers of both systems, but may not be the sole pathway.

It has already been maintained that the excitatory pathway appears to make monosynaptic connections with dorsal column neurons, whereas the inhibitory pathway is probably multisynaptic. The anatomically demonstrable direct endings of pyramidal tract fibers on dorsal column neurons might provide the necessary anatomical substrate for the excitatory pathway. In addition, Kuypers (75) has described numerous collateral or terminal branches from the pyramidal tract which end upon reticular neurons of the lower brain stem. These branches to reticular neurons are predominantly, but not exclusively, crossed. Although there is, at present, no anatomical evidence that these reticular neurons make connections with the dorsal column nuclei, such connections might provide the anatomical substrate for the multisynaptic inhibitory pathway. The significance of such a hypothetical system, in which one element (the pyramidal tract neuron) plays directly upon the sensory relay neuron and at the same time feeds into another neuronal network which exerts an antagonistic action on the sensory relay neuron, is not clear. A similar relation of the pyramidal tract neuron to spinal motoneurons has been suggested (99).

CHAPTER FIVE

SUMMARY AND CONCLUSIONS

The activity of 185 single units in the dorsal column nuclei was studied in cats anesthetized with sodium pentobarbital or α-chloralose. The discharge properties of these units following electrical stimulation of the foot pads were investigated. Following electrical cutaneous stimulation with single pulses, the majority of cuneate and gracile units responded with a short and slightly variable latency, and were able to follow repetitive afferent inputs at high rates. These were considered to be excited monosynaptically from the periphery. The remaining units did not satisfy the above criteria and hence were considered to be excited via the dorsal column relay, or via recurrent collaterals within the nucleus or by some other mechanism. The spontaneous discharge, as well as the response discharge of some cuneate units to tapping or maintained pressure on the ipsilateral forepaw, were also studied.

Electrical stimulation of the motor cortex altered the excitability of dorsal column neurons in a number of ways. These changes in neuronal excitability allow the following interpretations and conclusions:

1. Electrical stimulation of the motor cortex exerted an excitatory influence on 40 per cent of the units isolated in the dorsal column nuclei. This cortical influence appeared to be direct, since most of the units discharged in response to single cortical shocks with a small (less than 8 msec.) and slightly variable initial spike latency and faithfully followed repetitive cortical stimulation at rates in excess of 50 per second.

2. Electrical stimulation of the motor cortex exerted a depressive influence on 55 per cent of the units isolated in the dorsal column nuclei. The majority of such units met the criteria of monosynaptic activation by the testing peripheral volley and were considered to be inhibited by the conditioning cortical volley. The remaining units were blocked. The cortical depressive influence appears to be multisynaptic, since trains of cortical shocks were usually required at conditioning-testing intervals between 50 and 150 msec.; furthermore, full recovery from depression was attained at conditioning-testing intervals of 150 to 200 msec.

3. Drastic increases in the intensity or duration of cortical stimulus parameters resulted in a reversal of cortical conditioning influence from depressive (inhibitory or blocking) to excitatory in five per cent of units isolated in the dorsal column nuclei.

4. Cortical excitatory and depressive influences could be graded, depending upon the relative strengths of the conditioning and testing volleys.

5. Cortical excitatory and depressive influences were demonstrated on the spontaneous discharge, as well as the response discharge of some cuneate units to tapping or maintained pressure on the ipsilateral forepaw.

6. Cortical excitatory and depressive influences on dorsal column nuclei were more efficacious from the contralateral than from the ipsilateral motor cortex.

7. In animals with transected brain stems, except for the bulbar pyramids, both excitatory and inhibitory corticifugal influences on

cuneate units could still be demonstrated.

8. In animals with sectioned pyramidal tracts on both sides, corticifugal influences on cuneate units could rarely be demonstrated; when present, these influences were weakly depressive.

9. In animals with sectioned pyramidal tract on one side, corticifugal influences on cuneate units could rarely be demonstrated if the pyramidal cut and the stimulated motor cortex were contralateral to the cuneate nucleus tapped for unit recording; when present, these influences were weakly depressive. Corticifugal excitatory and inhibitory influences were readily demonstrated when the pyramidal cut was contralateral both to the stimulated motor cortex and to the cuneate nucleus tapped for unit recording.

10. The hypothesis is presented that the anatomically demonstrable direct endings of pyramidal tract fibers on dorsal column neurons provide the necessary anatomical substrate for the corticifugal excitatory pathway. Furthermore, the anatomically demonstrable direct endings of pyramidal tract fibers on reticular neurons of the lower brain stem provide the first part of the anatomical substrate for the multisynaptic corticifugal inhibitory pathway.

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