ABSTRACT

Carl J. Dila, M.D. A midbrain projection to the centre median nucleus of the thalamus. A neurophysiological study. A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science. Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University.

Neuroanatomists, using a variety of techniques, have demonstrated ascending fibers from the medial 2/3 of the brain stem reticular formation (RF). Neurophysiological studies by other investigators have shown that the nucleus gigantocellularis of the medulla is a relay in the spinoreticulothalamic pathway to nucleus centre median (CM).

In the present work the midbrain reticular projection to CM was studied in the cat by means of unit and evoked potential analysis using a computer of average transients. Most CM units which responded to stimulation of the midbrain RF exhibited a pattern of early activation-inhibition and sometimes later activation. Units which were also tested with peripheral stimulation showed a similar response.

The convergence of impulses from peripheral and midbrain stimulation is demonstrated by facilitation and occlusion of the slow wave response evoked in CM. The possible reticular pathways and the functional significance of the reticulothalamic projection are discussed.

RESUME

Carl J. Dila, M.D. Une projection du mesencephale au noyau centre median du thalamus: Etude Neurophysiologique. (A midbrain projection to the centre median nucleus of the thalamus. A neurophysiological study). Une Thèse présentée au Département de Neurologie et Neurochirurgie (Neurophysiologie) de l'Université McGill, Montréal, pour l'obtention de la Maitrise en Sciences.

Les neuroanatomistes, à l'aide de différentes techniques, ont démontré l'existence de fibres ascendantes a partir des deux-tiers internes de la formation réticulée (FR) du tronc cérébral. Des études neurophysiologiques par d'autres chercheurs ont montré que le noyau giganto-cellularis du bulbe constitue un centre de relai sur la voie spinoreticulothalamique vers le noyau centre median (CM).

Au cours du présent travail la projection mésencephalique vers le centre median a été étudiée chez le chat par analyse des potentiels unitaires et évoqués avec l'aide d'un appareil CAT. La plupart des unités du CM qui ont répendu à la stimulation de la FR mésencephalique ont montré un pattern d'activation-inhibition rapide et parfois plustard d'activation. Des unités qui furent aussi investiguées après stimulation péripherique ont donné lieu à une réponse similaire.

La convergence d'influx dans le CM après stimulation péripherique et mésencephalique est demontrée par la facilitation et l'occlusion de la réponse en forme d'onde lente évoquée dans le CM. Les voies réticulaires possiblement impliquées, de même que la signification fonctionelle de la projection reticulo-thalamique sont ensuite discutées.

MIDBRAIN PROJECTION TO THE CENTRE MEDIAN NUCLEUS

Carl J. Dila.

A MIDBRAIN PROJECTION TO THE CENTRE MEDIAN NUCLEUS OF THE THALAMUS. A NEUROPHYSIOLOGICAL STUDY

by

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A Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

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To

Kay

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INTRODUCTION

In recent years the concept of the brain stem reticular formation (RF) has undergone important changes owing to the more detailed knowledge of its intrinsic organization and connections, brought about by more refined neuroanatomical techniques.

The experiments recorded here were undertaken to test the hypothesis that the midbrain RF is the origin of a fiber projection to the nucleus centre median (CM) of the thalamus. Firm anatomical evidence exists for the spinoreticular and ascending reticular pathways as far rostral as the midbrain tegmentum. Anatomical studies have suggested that there is a midbrain reticulothalamic projection which terminates in part in CM, but the evidence for this does not enjoy universal acceptance. The failure to demonstrate this projection by antegrade degeneration methods, because of limitations of the technique, has been particularly troublesome.

In the present study the neuroanatomical and neurophysological background of this problem is reviewed and neurophysiological methods are applied with the aim of introducing new evidence in favor of a projection from the midbrain RF to CM. The relation of this projection to the spinoreticulothalamic system in general is discussed.

BRAIN STEM RETICULAR FORMATION: ANATOMY

The term "reticular formation" was first used in anatomy prior to the turn of the twentieth century (Brodal, 1957). Details which accrued to the concept of the reticular formation during the first half of this century suggested a loosely organized (anatomically) structure performing essentially non-specific functions. In his classic monograph on the subject Brodal (1957) defined the RF as "...those areas of the brain stem which are characterized structurally by being made up of diffuse aggregations of cells of different types and sizes, separated by a wealth of fibres travelling in all directions". This definition obviously excluded "circumscribed groups of cells" such as the cranial nerve nuclei and motor relay nuclei of the brain stem. Cognizant of Olszewski and Baxter's (1954) cytoarchitectonic study with its subdivision of the RF into circumscribed nuclear groups, which implied functional specificity, Brodal (1957) nonetheless resisted the suggestion that the term "reticular" be replaced by a more precise nomenclature, arguing that "... since there are many structural and presumably, therefore, also functional, similarities between the several 'nuclei' of the reticular formation, it may still be useful to group them together in a common term." Seven years later, however, in the light of new experimental evidence, including his own, Brodal (1964) declared,

> "Anatomically the RF of the brain stem is no entity. It can be subdivided into a number of nuclei or cellular groups, which differ architectonically as well

> as with regard to their fibre connections... Admitting that the RF is of importance for the maintenance of, and the level of, consciousness, the anatomical data induce scepticism towards the concept that it works as an entity in this function... It would perhaps help to clarify thoughts if we agreed to delete the word 'reticular' from the concept 'the reticular ascending activating system.' "

In the anatomical essay to follow the RF will be considered in terms of its cytoarchitectonics, fibre connections and intrinsic organization.

CYTOARCHITECTONICS OF THE BRAIN STEM

RETICULAR FORMATION

> "The term cytoarchitectonics is applied to a method of anatomical investigation which is primarily concerned with patterns of arrangement and morphological details of nerve cells as revealed by magnifications within the range of the ordinary light microscope. The staining method almost exclusively used is the Nissl technique or one of its innumerable variants." (Olszewski and Baxter, 1954).

The cytoarchitectonic subdivision of the RF into nuclei was a fundamental and essential development in the process of imposing order on this hitherto uncharted wilderness of brain territory. For clearly it is possible to identify discrete subunits within the RF on the basis of cellular pattern. And if other subunits are less clear and distinct it remains for anatomical techniques using other criteria to prove or disprove their identity. To be sure, the charts of the early sailors showing the continents and isles of the New World are crude, the occasional peninsula being mistaken for an island and the wandering coastline being deficient in

scale. But none can doubt that geography has been enriched immeasurably by these contributions and the more precise charts of modern mariners are but modifications of the original.

In their extensive comparative study Kappers, Huber and Crosby (1936) review and integrate data from cytoarchitectonic studies of the brain stem RF dating back some 50 years. Of particular interest are two cell groups, one located in the medulla at the level of the entrance of the acoustic nerve and the other located in the midbrain. The former described as a poorly circumscribed group of large reticular neurons was termed nucleus reticularis medius. According to these authors this nucleus had previously been subdivided by Jacobsohn (1909) into two nuclear masses which he had called nucleus gigantocellularis formationis reticularis and nucleus motorius dissipatus formationis reticularis. Fibres from the nucleus gigantocellularis reticularis (GCR) were traced to the medial longitudinal fasciculus of the same and the opposite side by Papez (1926). The descending, or reticulospinal contribution of this nucleus was demonstrated early but its ascending connections remained undiscovered for some years.

Within the midbrain the nucleus lateralis profundus mesencephali, is found in a position lateral and dorsolateral to the red nucleus. Made up of scattered, multipolar cells of medium size the nucleus lateralis profundus was considered to be the rostral continuation of the nucleus

reticularis superior of the pons (Gastaldi, 1923). Like those of the nucleus gigantocellularis, its axons seemed to course medially to the medial longitudinal fasciculus. Summarizing these data, Kappers, Huber and Crosby (1936) concluded that,

> "...it is evident that the reticular elements of the medulla oblongata and midbrain constitute an integral part of the effector apparatus of the brain stem... Their neuraxes do not terminate in peripheral end-organs but end in synaptic relation with motor neurons of the brain and spinal cord."

Subsequent cytoarchitectonic studies have confirmed the presence of these more or less discrete cell groups within the RF. Brown (1943) in his paper on the midbrain nuclei of the dog and cat subdivided the nucleus lateralis profundus mesencephalic into a pars dorsalis and a pars lateralis with reference to the red nucleus. He further notes that the nucleus lateralis profundus mesencephali extends rostrally to the diencephalic grey. Taber (1961), conforming to the nomenclature in the atlas of the human brain stem by Olszewski and Baxter (1954), substitutes the terms nucleus cuneiformis and nucleus subcuneiformis for cell groups of the midbrain RF dorsolateral and dorsal, respectively, to the red nucleus in the cat. Further, her observations permit her to subscribe to the general cytoarchitectonic scheme of the brain stem RF articulated earlier by Brodal (1957), to wit,

> "Within the reticular core of the brain stem, three dimensional territories, nuclei, are recognized. These nuclei are organized into two longitudinal zones, a medial magnocellular zone and a lateral parvocellular zone. The raphé nuclei form a third longitudinal column."

The medial magnocellular zone includes the nucleus gigantocellularis of the medulla, the nuclei pontis centralis caudalis and oralis and the nuclei cuneiformis and subcuneiformis. In this paper the nomenclature of Olszewski and Baxter will be used, in accordance with Taber's precedent. Degeneration studies have yielded further clues to the functional significance of the medial magnocellular zone.

FIBER CONNECTIONS OF THE BRAIN STEM RF

If a recognizable population of cell types and distinct cellular pattern are necessary for the designation of a nucleus, another equally important criterion is a distinct system of fibers projecting to and from the cell group so designated. The demonstration of such fiber connections has usually involved methods which employ the selective staining or impregnation of degenerated fibers after a lesion has been made somewhere in the pathway being studied. The origin of fibers has been determined by using the principle of retrograde degeneration, based on changes within the soma following interruption of its axon. A recent refinement of the study of retrograde degeneration using histochemical techniques has been applied to the brain stem RF (Shute and Lewis, 1967). Studies of the antegrade degeneration of myelin sheaths (Marchi method), while being useful in showing the general features of fiber pathways, failed to show adequately the terminations of fiber bundles, and sometimes the technique stained normal as well as degenerating myelin. Various

techniques for the impregnation by silver of degenerating axons and axon terminals were developed in the 1950s, that of Nauta and Gygax (1954) being, perhaps, most widely used. The application of the Golgi technique, in which the nerve cell with all its processes, is impregnated with silver has been of great value in elucidating "short-range" connections of the RF and will be discussed in detail in a separate section.

Brodal (1957) breaks down the long efferent connections of the RF into three general groups, those going to cerebellum, long descending and long ascending connections. The cerebellar projections of the RF are not pertinent to this paper; long descending pathways will be discussed briefly and the ascending fiber systems will be discussed in detail.

THE SPINORETICULAR PATHWAY

It is clear from numerous antegrade degeneration studies that ascending input to the brain stem RF is conveyed by the ventral and lateral funiculi of the spinal cord. Rossi and Brodal (1957) show that the spinoreticular pathway originates in neurons at all levels of the cord. Nauta and Kuypers (1958) show that after a lesion of the ventral and lateral funiculi of the cord, degeneration of lateral discrete bundles containing spinocerebellar and spinothalamic tracts can be distinguished from more centrally located, more diffuse fiber systems. The latter, Bechterew's "ground bundles", show massive terminal degeneration within the lateral reticular

nucleus and the nucleus gigantocellularis of the medulla. This central spinoreticular system, greatly attenuated by its terminations within the medial magnocellular zone of the medulla, ascends through the brain stem giving off terminals to reticular nuclei of the medial magnocellular zone at all levels. At the mesencephalic-diencephalic junction a group of these fibers enter the thalamus, terminating in a variety of thalamic nuclei, (Fig. 1).

Throughout its brain stem course, the spinoreticular tract ascends in parallel to and intermingled with the ascending reticular fibers of brain stem origin, in the tractus fasciculorum of Forel (Nauta and Kuypers, 1958). The term "ascending reticular system" is used here as a synonym for the tractus fasciculorum of Forel; it refers to the brain stem fiber bundle which is composed of axons which originate in several different structures, within the spinal cord and the brain stem itself. It is convenient to consider the "ascending reticular system" as an entity because the fibers of these various spinal and brain stem structures do in fact ascend in a common bundle and their terminals are distributed in common to many other structures. But, it is equally important that the variety of afferent impulses which are mediated by the ascending reticular system not be overlooked. The ascending reticular system is an anatomically heterogeneous system of fibers.

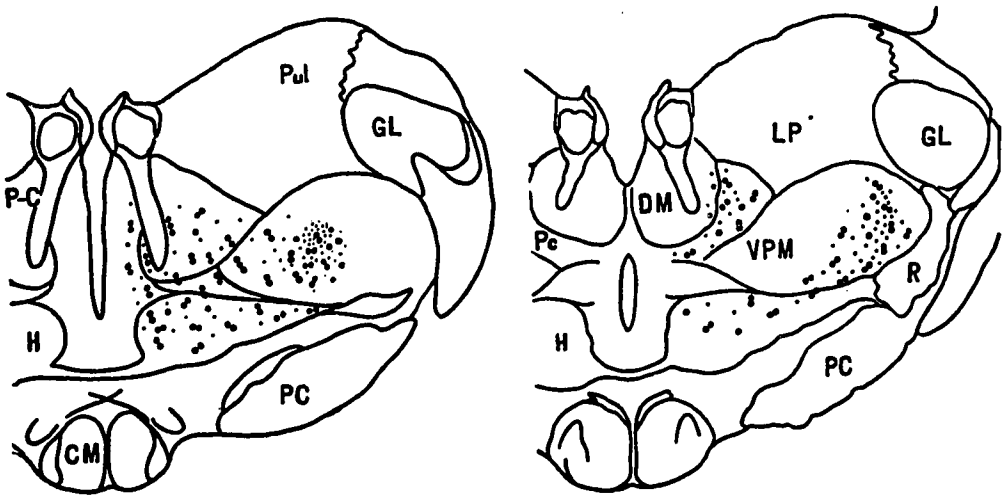


FIGURE 1. Ascending axon degeneration of the spino-reticulothalamic pathway resulting from section of the anterior and lateral funiculi of the spinal cord at C1. Coarse dots indicate fibers of passage; fine stipple, terminal degeneration. (P-C is centre median-parafascicular complex, DM is nucleus medialis dorsalis). (Nauta and Kuypers, 1958).

THE ASCENDING RETICULAR SYSTEM

In the last decade of the nineteenth century Held (1893) described ascending axons from the brain stem RF in Golgi preparations of mammalian brains. Cajal's (1909) magnificent study confirmed this observation, as did the papers of Kohnstamm and his co-workers (1908, 1910). Nauta and Kuypers credit Quensel (1907) with the original formulation of the concept of a multineuronal pathway for pain and temperature sensation passing through the brain stem RF en route to the thalamus. Morin (1953) using the Marchi method to study antegrade degeneration, demonstrated fibers ascending in the medial part of the midbrain tegmentum toward the subthalamus and nucleus centre median following lesions of the lower brain stem. He noted that the area occupied by these fibers at the intercollicular level of the midbrain coincides with the location commonly assigned to the central tegmental tract. Brodal and Rossi (1955) studied the retrograde degeneration changes in the brainstem of the young kitten using the Gudden method in order to ascertain the origin of the ascending fibers of the brain stem RF.

After making a lesion at the midbrain-diencephalic junction they found the changes of retrograde degeneration in cells of the medulla, pons and midbrain. The location of the majority of these altered cells corresponded with the cytoarchitectonic boundaries of the nucleus gigantocellularis, nucleus pontis centralis caudalis and oralis and nucleus

cuneiformis and subcuneiformis. When the lesion was unilateral, the changes were bilateral, but were more marked on the side of the lesion. These nuclei, it will be recalled, compose the medial magnocellular zone of the brain stem RF referred to above. Two further points should be made. Brodal and Rossi state that no changes of retrograde degeneration are to be seen in the giant cells of the nucleus gigantocellularis of the medulla after a lesion has been made rostral to the medulla; only the medium and small cells of this nucleus seem to give rise to ascending fibers. The fact that the axons of the giant cells of this nucleus bifurcate sending branches both rostrally and caudally, may explain the lack of chromatolysis under conditions in which only the rostral branch of the axon was sectioned. Thus, ascending fibers arise from the entire length of the medial magnocellular zone of the brain stem RF. On the other hand, none of the descending fibers of the RF have thus far been found to originate in the midbrain. It is apparent, therefore, that although the origins of the descending and ascending pathways of the brain stem RF overlap to a large extent, a pattern of preferential regions of origin is also discernable.

A study of the ascending projections of the brain stem RF in the cat was undertaken by Nauta and Kuypers (1958) using the Nauta-Gygax method to show antegrade degeneration. After a lesion had been made in the medial 2/3 of the bulbar tegmentum, an ascending pathway could be traced throughout

the length of the brain stem tegmentum. It follows the course of Forel's tractus fasciculorum and is composed of axons of different lengths, being distributed to the central RF of the midbrain tegmentum, the periaqueductal grey matter, superior colliculus and pretectal area, intralaminar thalamic nuclei and subthalamic region (Fig. 2). In contrast to this a lesion of the lateral 1/3 of the bulbar RF indicates that the lateral parvocellular zone contributes fewer fibers to the long ascending RF system. The lateral zone of the bulbar RF is the source of sparse projections to the medial magnocellular zone of the medulla and a more impressive lateral fasciculus, the "ventral collateral plexus" of Thiele and Horsley, which ascends medial to the spinal nucleus of the trigeminal nerve and definitely receives some fibers from the ventral spinocerebellar tract, to terminate in reticular area adjoining the main sensory nucleus of the trigeminus. From this region arises a reticular pathway, Wallenberg's "dorsal trigeminal tract", which joins the more medial tractus fasiculorum of Forel, distributing with it to the midbrain and diencephalon. Throughout the length of the brain stem fibers of the lateral spinothalamic tract are seen to move medially to join the ascending reticular system.

Lesion of the medial midbrain tegmentum just rostral to the isthmus produces degeneration of a fiber bundle which forms the mammillary peduncle, ascending into the lateral hypothalamus and projecting as far rostrally as the preoptic area and the medial septal nucleus. A projection to

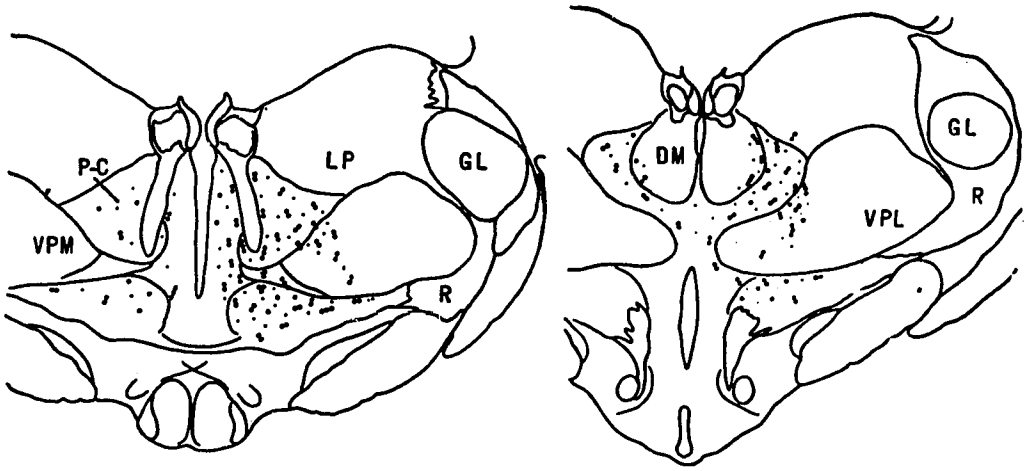


FIGURE 2. Ascending degeneration following lesion of the medial region of the bulbar tegmentum (rostral end of nucleus gigantocellularis). The ascending reticular axons together with the spinoreticulothalamic axons comprise the ascending reticular system which enters the CM-Pf complex (P-C in the diagram) as a component of Papez' intrathalamic fasciculus. Coarse dots indicate fibers of passage; fine stipple, terminal degeneration. Cf. Fig. 1. (Nauta and Kuypers, 1958).

the caudate and lentiform nuclei is demonstrated by a lesion placed in the midbrain RF ventral and medial to the red nucleus. Nauta and Kuypers were unable to provide data concerning the projections of the rostral midbrain RF (dorsolateral to the red nucleus, the nucleus cuneiformis and nucleus subcuneiformis) for a lesion of this area would involve ascending RF fibers which originate in more caudal regions of the brain stem, rendering interpretation of degeneration patterns hazardous at best.

The Golgi studies of Scheibel and Scheibel (1958, 1967a) confirm and add detail to the hodological studies of the brain stem RF. These authors show that most of the giant cells of the bulbar RF have axons which bifurcate into caudad and rostrad running fibers which may reach the spinal cord and mesencephalon or diencephalon, respectively. In sagittal sections of mouse brain the Scheibels show that most of the ascending fibers of the brain stem RF bifurcate in the posterior thalamus, just caudal to the centre median-parafascicular complex. Fibers of the dorsal lamella project to the intralaminar nuclei and the nucleus reticularis thalami, sending collaterals to and terminating in these nuclei. Fibers of the ventral lamella are seen to run through the subthalamus to the lateral hypothalamus, septum, caudate and putamen and even to the orbitofrontal cortex.

Physiological studies have repeatedly postulated lemniscal collaterals to the brain stem reticular core (Moruzzi and Magoun, 1949; Starzl, Taylor and Magoun, 1951b). However,

anatomical studies have failed to confirm this hypothesis. In fact since Quensel's (1907) emphasis on the massive termination of the crossed pain and temperature pathways in Kohnstamm's "centrum receptorium" (nucleus gigantocellularis) neuroanatomists (Brodal, 1957; Nauta and Kuypers, 1958) have consistently pointed out the relationship of the classical lateral spinothalamic tract and the brain stem RF to the exclusion of the lemniscal system. Scheibel and Scheibel (1967a) on the basis of their failure to demonstrate lemniscal collaterals in Golgi studies of more than 4000 brains conclude that the medial lemniscus,

> "...probably contributes no collaterals to the (reticular) core, thus suggesting that information with a high degree of locus and mode specificity is not crucial to the operation of the reticular mosaic."

DESCENDING RETICULOPETAL FIBERS

Tectoreticular fibers, from the superior colliculus to the brain stem RF, have been described by Cajal (1909) and Rasmussen (1936). Wolf and Sutin (1966) demonstrated fibers from the lateral hypothalamic region coursing via the medial forebrain bundle to the midbrain RF (nucleus cuneiformis). The distribution of corticoreticular fibers throughout the brain stem RF was confirmed by Rossi and Brodal (1956). They showed that the majority of these fibers terminated in the medial (magnocellular) zone of the bulbar and pontine RF.

RETICULOSPINAL CONNECTIONS

Nyberg-Hansen (1965) in his study of reticulospinal pathways in the cat points out the weakness of earlier studies of the origin of reticulospinal fibers which used antegrade degeneration techniques. Because any lesion of the brain stem RF will involve fibers of passage as well as reticular neurons, conclusions drawn from subsequent antegrade degeneration will be of limited value. Torvik and Brodal (1957) using the retrograde degeneration method of Gudden in young kittens showed that the reticulospinal fibers originate from neurons of the medial 2/3 of the RF of the medulla and pons. They further concluded that the pontine reticulospinal projection is entirely ipsilateral and occupies the medial part of the ventral funiculus of the cord. The ventral part of the lateral funiculus contains the reticulospinal fibers which originate in the medulla; this projection is mostly, but not entirely, ipsilateral. Most of the reticulospinal fibers originate in the nucleus gigantocellularis of the medulla and the nucleus pontis centralis caudalis; minor contributions to this system are made by the nucleus reticularis ventralis of the medulla and the nucleus pontis centralis oralis. However, Torvik and Brodal (1957) did not study the mesencephalic RF. Nyberg-Hansen (1965) made lesions in various parts of the brainstem in order to study the reticulospinal pathways and terminations. Three cats had lesions of that part of the midbrain RF which corresponds to the nucleus cuneiformis and

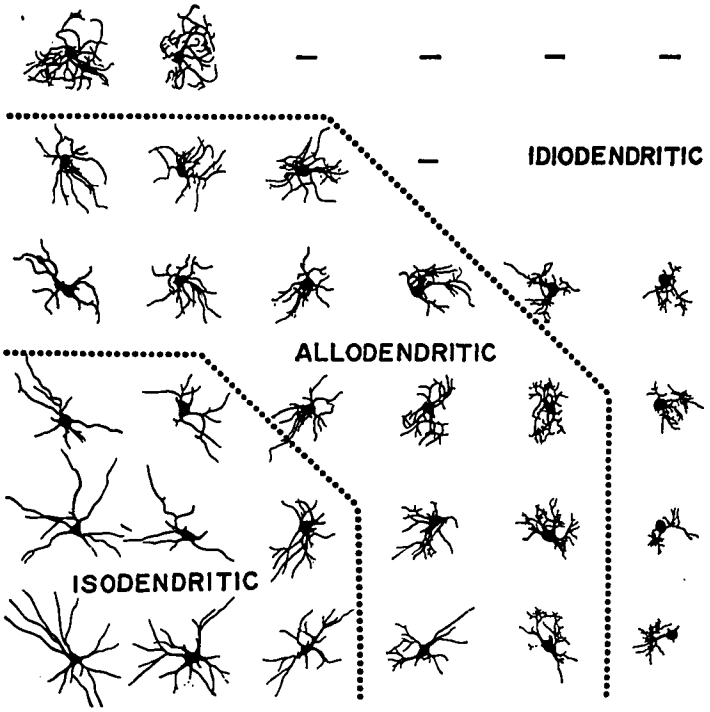
nucleus subcuneiformis; in none of these cats was there evidence of degeneration of nerve fibers anywhere in the spinal cord. These data suggest that the midbrain RF makes no contribution to the reticulospinal pathways, but this opinion must be held with reservations. Nyberg-Hansen's study confirms and refines the observations of Torvik and Brodal and the much earlier, but excellent, Marchi study of Papez (1926) concerning the medullary and pontine reticulospinal pathways. Analysis of the pattern of terminal and preterminal degeneration within the spinal cord after lesions of the brain stem RF enable him to conclude that the reticulospinal pathways end in laminae VII, VIII and IX of the spinal grey matter with reference to the laminar organization of the spinal grey described by Rexed (1952, 1954). Terminal degeneration was seen adjacent to the cell bodies as well as the dendrites of cells of all sizes. An excellent discussion of the functional considerations implicit in these anatomical data is to be found in the paper by Nyberg-Hansen cited above.

INTRINSIC ORGANIZATION OF THE BRAIN STEM RETICULAR FORMATION.

Reference has been made already to the subdivision of the brain stem RF into medial magnocellular and lateral parvocellular zones on the basis of cytoarchitectonic criteria. The origin of long ascending and descending fiber systems from the medial zone, and the supplementary influx to the

medial fiber system from the lateral zone have been demonstrated by conventional degeneration techniques. In recent years a renaissance of the old Golgi technique and its modifications for the impregnation with silver of entire neurons has been particularly enlightening to students of the reticular formation.

There is agreement among recent observers that the reticular neuron conforms to a generalized, if not stereotyped description (Valverde, 1961; Leontovich and Zhukova, 1963; Ramon-Moliner and Nauta, 1966). This neuron, described by Ramon-Moliner and Nauta as the "isodendritic" neuron is seen to have long, rather uniform dendrites "which show little tendency to branch and, when they do branch, the resulting segments are, as a rule, longer than those from which they take origin" (Fig. 3). These authors contrast the simplicity of the dendritic tree of the reticular neuron with other neurons whose dendrites show more branching, "waviness" or "tuftedness". Depending on the degree of departure from the generalized "isodendritic" pattern, these neurons are described as "allodendritic" or "idiodendritic". Reticular neurons vary in size of the perikaryon, and number and extent of the dendrites, but the common dendritic features are distinctive. Two additional characteristics of the isodendritic neuron must be considered. Mannen (1960) found that he was able to distinguish within the brainstem two types of nuclei. The "noyau ouvert" possessed dendrites which intermingle



Varieties of dendritic patterns in the brain stem of the cat. In the lower left corner the generalized or isodendritic patterns are found. The allodendritic neurons represent a step towards specialization. The idiodendritic neurons represent the highest degree of specialization which results in either a pronounced degree of waviness (upper left) or tuftedness (lower right) of their dendrites.

(Ramon-Moliner and Nauta, 1966).

FIGURE 3.

freely with the heavily myelinated fiber bundles passing through the nucleus, whereas the "noyau fermé" shows no such intermingling of dendrites with fibers in transit. He points out that the brain stem RF is "...un vaste 'système ouvert' contenant seulement quelques 'noyaux fermés.' ". The overlapping dendritic fields is yet another feature which has impressed anatomists who have studied the brainstem RF by means of the Golgi method (Ramon-Moliner and Nauta, 1966; Scheibel and Scheibel, 1958, 1967a). The Scheibels (1958) show that the dendritic apparatus of most reticular neurons in the medial (magnocellular) zone is oriented in the transverse plane, and flattened with respect to the long axis of the brain stem. On the basis of a dendritic tree which is 400 micra in diameter and 100 micra in height (along the long axis of the stem) they calculate that a single reticular neuron might overlap with the receptive field of approximately 4000 neighboring neurons. As concerns the output of the brain stem RF the Golgi studies are in agreement with the antegrade degeneration studies discussed above. Scheibel and Scheibel (1958) state that most of the ascending and descending axons arise from neurons in the medial zone, and that many of these neurons give off axons which bifurcate yielding both an ascending and a descending branch. These authors and others (Ramon-Moliner and Nauta, 1966) while failing to find any "Golgi type II" (short axon) neurons in the RF, show that many of the RF neurons give off short axon collaterals which take a perpendicular course to the main axon back into the environment of the parent cell.

STRUCTURAL ORGANIZATION OF THE BRAIN STEM RF: SUMMARY

Firm experimental evidence supports the view of the brain stem RF as an "isodendritic core" divisible in transverse section into a lateral (parvocellular) zone and a medial (magnocellular) zone. The massive termination of spinoreticular fibers in nucleus gigantocellularis of the medulla may reflect some degree of differentiation in RF input and although both ascending and descending RF fibers are known to originate at all levels of the brain stem, there is evidence that most descending fibers originate in the medulla and caudal pontine tegmentum, while the midbrain RF contributes little to the reticulospinal projection. Less dense input to the RF comes through the lateral zone where spinoreticular fibers and fibers of the lateral spinothalamic tract and spinal nucleus of the trigeminus terminate on small reticular neurons and/or proceed medially to join the long ascending reticular system at all levels of the brain stem. Thus, although there are obvious connections between adjacent reticular neurons, there is good evidence for differential input and output with respect to different levels of the brain stem. The physiological and theoretical implications of this arrangement will be discussed in a later section.

NUCLEUS CENTRE MEDIAN OF THE THALAMUS: ANATOMY

Controversy and apparent paradox fill the literature which deals with the intralaminar nuclei of the thalamus in

general and the nucleus centre median (CM) in particular. Most of the contradictory statements have revolved about a single basic issue. Physiological studies suggested that the intralaminar nuclei project diffusely to all areas of the cerebral cortex (Morison and Dempsey, 1942; Jasper, 1949). Neuroanatomical studies have apparently demonstrated the very opposite, that the intralaminar nuclei have no projections or very scanty projections to the cerebral cortex (Walker, 1938; Murray, 1966; Mehler, 1966). And, whereas Rioch (1929) was criticized for omitting the nucleus centre median in his then definitive study of the diencephalon of carnivores, an omission he later corrected, (Rioch, 1931) more recent authors (Jasper and Ajmone-Marsan, 1954) are taken to task for erroneously labelling a number of other posterior intralaminar nuclei as CM (Mehler, 1966; Rinvik, 1968a), (Fig. 4 and 5).

Traditionally, the thalamic nuclei medial to and within the internal medullary lamina have been designated as the intralaminar group. Walker (1938) observed that after hemidecortication virtually no changes of retrograde degeneration could be seen in the intralaminar nuclei; an exception to this was the nucleus centralis lateralis where "slight degeneration" was observed. In the macaque the CM is a large nucleus, comprising, with the nucleus medialis dorsalis the greater part of the intralaminar group, according to Walker. Aside from its location as the most caudal of the intralaminar nuclei, merging imperceptibly into nucleus parafascicularis medially, there was little of substance that could be said about CM. Walker supposed that it received fibers from the

FIGURE 4. Thionin stained section through cat thalamus. The cytoarchitectonic differences between CM and Pf are evident. CM has the shape of a crescent. N.B. The plane of section is frontal oblique, therefore, ventral structures are more rostral than dorsal structures. (Rinvik, 1968a).

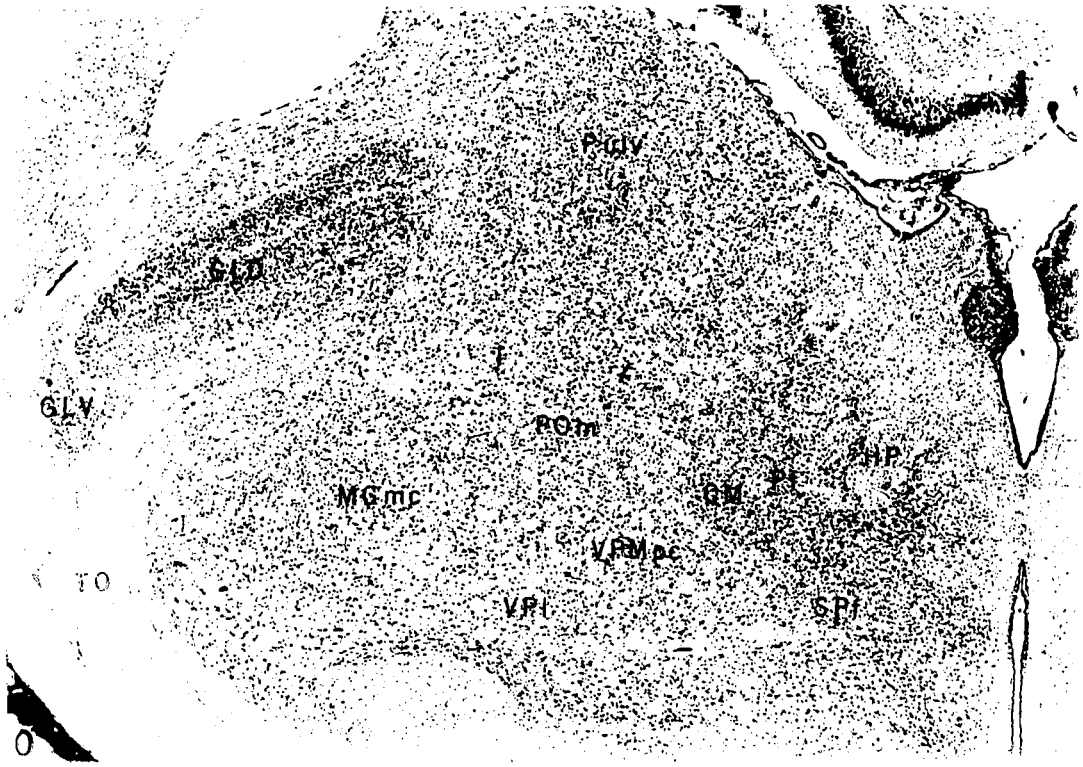


FIGURE 1. Cresyl violet stained section through cat thalamus. The cytoarchitectonic differences between CM and Pf are evident. CM has the shape of a crescent. H.P. The plane of section is frontal oblique, therefore, ventral structures are more rostral than dorsal structures (Nauta, 1958).

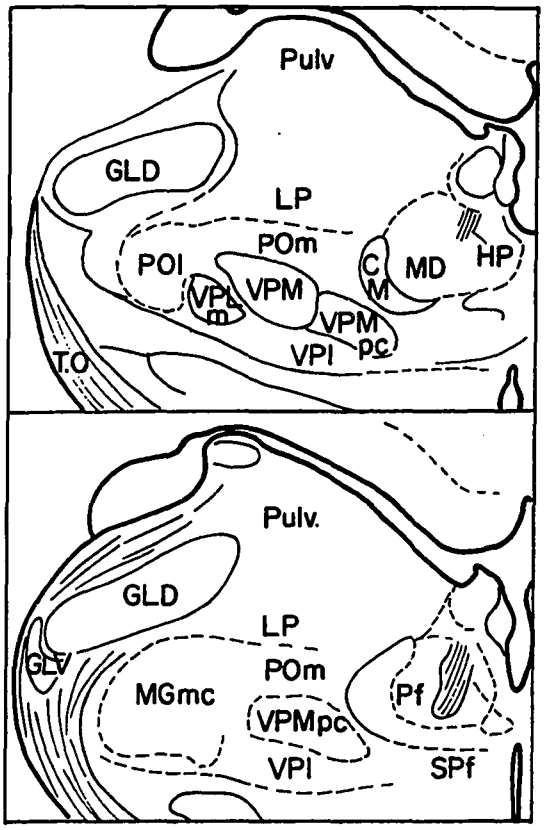


FIGURE 5. Drawings made from thionin stained sections (Fig. 4) show the crescent shaped CM, a large portion of nucleus Pf and MD extending lateral to the habenulointerpeduncular tract (HP). (Rinvik, 1968a).

midbrain and that it projected to the striatum (globus pallidus) but was at a loss to explain the functional significance of these connections.

The CM had been described, originally, by Luys (1865). Rioch (1931) in ammending his earlier paper on the diencephalon (Rioch, 1929) stated that the CM of the dog and cat is smaller and less compact than the CM of the primates. He emphasizes the phylogenetic development seen in the CM which, although it is probably present in all mammals, increases in size from carnivores to primates to man.

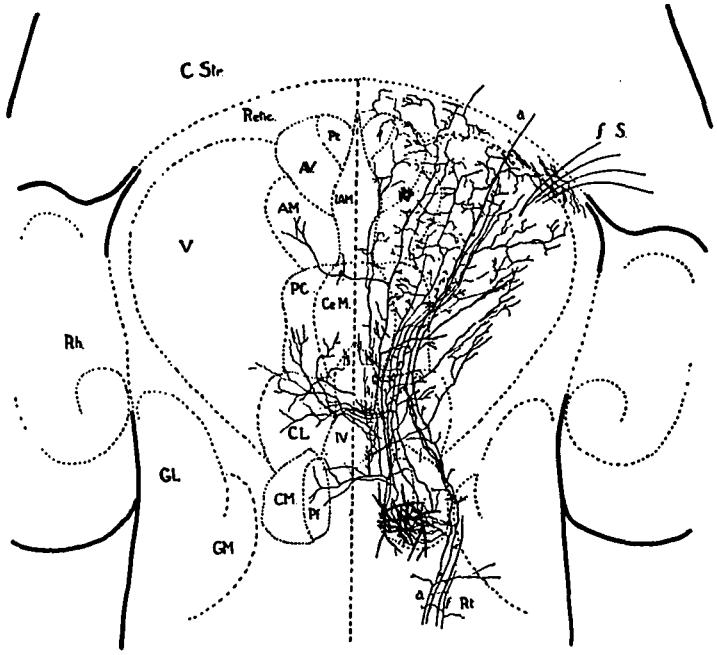
Nauta and Whitlock (1954) were the first to apply silver techniques to the study of antegrade degeneration patterns after lesions of the intralaminar nuclei. In the cat lesions confined to the CM produced fiber degeneration in more rostral intralaminar nuclei, in the ventral nuclei, in the reticular nucleus of the thalamus and in the putamen. No fiber degeneration was traced to the cortex. Nauta and Mehler (1965) and Mehler (1966) provide firm evidence, based on antegrade degeneration studies, that CM of cat and monkey projects to the putamen and receives afferents from motor cortex and the globus pallidus (entopeduncular nucleus in the cat). Rinvik (1968b), using silver impregnation techniques, has also demonstrated projections from the motor cortex to the CM in the cat. Bowsher (1966) is of the opinion that CM may project to cortex by way of collaterals of the putamenal projection but this theory defies anatomical proof. Murray's (1966) recent attempt to clarify the question of cortical

projections from the intralaminar nuclei by studying the changes of retrograde degeneration after massive cortical ablations which included limbic cortex have but confirmed the earlier finding of Walker (1938) and Rose and Woolsey (1943) viz, variable degeneration in nuclei centralis medialis, paracentralis and centralis lateralis. Degeneration was not seen in the CM or in any other intralaminar nuclei.

The neurons of the intralaminar nuclei have been shown by Golgi technique to share many features in common with reticular neurons (Leontovich and Zhukova, 1963; Scheibel and Scheibel 1967b). These include the pattern of long, radiating, poorly ramified dendrites. Intralaminar axons usually bifurcate, sending fibers in both rostrad and caudad directions, and numerous short collateral branches are seen connecting with other nonspecific and specific thalamic nuclei. Scheibel and Scheibel (1967b) point out the conspicuous absence of Golgi type II (short axon) cells within the intralaminar nuclei, another feature shared in common with the brainstem RF. These authors have traced afferent fibers to the intralaminar nuclei from the lateral spinothalamic tract, the dorsal lamella of the brainstem ascending reticular system, tectal and pretectal areas, and orbitofrontal cortex. The demonstration of a considerable projection from the anterior 1/3 of the intralaminar field to the medial part of the nucleus ventralis anterior and the nucleus reticularis when considered together with the fact that well over 90% of the axons of the nucleus reticularis project back on

specific and nonspecific thalamic nuclei (Scheibel and Scheibel, 1966), reaching as far caudally as the CM, leads to far-reaching theoretical conclusions which will be discussed below.

Combining the evidence from several anatomical studies, cited above, it seems safe to conclude that CM receives input from the brain stem RF, the lateral spinothalamic tract, the globus pallidus and the motor cortex. Efferent projections of CM go to more rostral intralaminar nuclei (Fig. 6), specific thalamic nuclei, the nucleus reticularis of the thalamus and the putamen. Bowsher (1961) is of the opinion that most ascending afferents to the intralaminar nuclei terminate in axosomatic boutons in so far as this can be determined using silver impregnation techniques. However, in their electron microscopical study Pappas and his colleagues (1966) state that, "axosomatic synapses are not prevalent in the thalamus". Axodendritic synapses constitute the majority synapses observed by these workers both in the intralaminar thalamus and in the specific thalamic nuclei. These authors also demonstrate axoaxonal synapses in both medial and lateral thalamic nuclei. They raise the theoretical possibility that some of these axoaxonal connections may be involved in the presynaptic inhibition of inhibitory synapses. However, since axosomatic synapses are not prevalent in the thalamus most of the axoaxonal contacts are seen to be related to dendritic postsynaptic membranes.



C.str.: carpus striatum
V.: nucleus ventralis lateralis
Rh.: rhinencephalon
G.L.: lateral geniculate nucleus
G.M.: medial geniculate nucleus
A.V.: nucleus anterioventralis
A.M.: nucleus anteriomedialis
Pt.: nucleus paratenialis inferior
CeM.: nucleus centralis medius
C.L.: nucleus centralis lateralis
C.M.: centromedian nucleus
I.V.: nucleus ventralis inferior
F.S.: thalamocortical fibers
Retic.: reticular nucleus

Horizontal sagittal section through the diencephalon of a 12-day-old mouse, showing the axonal projection from the centromedian–parafascicular nucleus complex running rostrally and supplying collaterals to the intralaminar nuclear groups, ipsilaterally and contralaterally. Collaterals are also given profusely to the ventral nucleus complex. Most fibers appear to terminate no farther rostrally than the reticular nucleus of the thalamus in fairly rich horizontal arbors. Several reticulothalamic fibers (f. Rt.) are also shown entering the area and running parallel to this projection. One of these, marked *a*, is seen to pass through the reticular nucleus of the thalamus and continue into the striatum. Several thalamocortical fibers of the specific sensory relay are also shown (f.S.).
(Scheibel and Scheibel, 1958).

FIGURE 6.

PHYSIOLOGY OF THE ASCENDING RETICULAR SYSTEMS

Rossi and Zanchetti (1957) in their review of the anatomy and physiology of the reticular formation enumerated seven groups of responses that had been obtained from electrical stimulation of the reticular core.

1. Respiratory responses.
2. Vasomotor and other autonomic responses.
3. Effects on postural tonus and phasic movements.
4. Effects on electrical cortical activity.
5. Effects on the electrical activity of subcortical centers.
6. Effects on sensory neurons.
7. Electrical responses of the cerebellum.

This list must, of course, be considered to be a preliminary inventory of the functions of the RF, incomplete and obviously lacking in detail. The discussion contained herein is an essay to review the important physiological studies of the ascending systems of the RF. The author does not pretend to have written a comprehensive review of RF physiology. Rather, the subject will be limited to items 4 and 5 of Rossi and Zanchetti's list; other aspects of RF physiology, to wit, a consideration of the natural and experimental input to the RF on which the "effector" systems depend are included inasmuch as they are necessary for a coherent view of the ascending systems of the RF.

ASCENDING RETICULAR ACTIVATING SYSTEM

The electroencephalographic (EEG) correlates of arousal were known to the early students of the electrical activity of the brain. Berger (1930) reported that the alpha rhythm of the human EEG was abolished by the opening of the eyes and by any other stimulus which alerted the subject. Subsequent investigations showed that in lower mammals as in man low voltage fast activity predominated during the aroused, alert state and high voltage slow waves were seen during sleep, (Rheinberger and Jasper, 1937). Against the background of these earlier investigations, Moruzzi and Magoun (1949) in their classic paper were to refer to the "typical EEG arousal reactions" produced by stimulation of the reticular core of the brain stem.

These authors showed that, "stimulation of the reticular formation of the brainstem evokes changes in the EEG, consisting of abolition of synchronized discharge and introduction of low voltage fast activity in its place...". They found that this effect was produced by stimulation of the medial bulbar RF, the pontine and midbrain tegmentum, the dorsal hypothalamus and the subthalamus. Trains of high frequency stimuli, between 50 and 300 per second, were required. It was also noted that the activation response abolished the cortical recruiting phenomenon produced by low frequency thalamic stimulation. Moruzzi and Magoun concluded that the activating system of the brain stem consists of a series of reticular relays which cause a general desynchronization of

the cortical rhythms, mediated in part at least by the non-specific nuclei of the thalamus.

The relation of the ascending reticular activating system (ARAS) of the brainstem to the "diffuse thalamic projection system" (the intralaminar nuclei) has been the subject of debate and controversy. Starzl et al (1951a) showed that, in addition to the brain stem RF and the subthalamic structures, the ventral parts of the thalamus viz., ventral parts of CM, ventromedial and ventrolateral thalamic nuclei and the internal capsule, were sites from which high frequency stimulation produced EEG activation. These areas of the diencephalon also showed desynchronization when stimulation was applied in the brain stem. However, lesions ablating the entire thalamus, did not abolish the activating effect of midbrain RF stimulation, nor did lesions in the internal capsule. Thus the evidence suggested alternate routes for the ARAS in the diencephalon, one via the nonspecific nuclei of the thalamus and the other through the internal capsule via the subthalamus (Magoun, 1963).

The thalamic structures found by Starzl et al to give rise to cortical activation are the same areas which had previously been found to produce synchronizing effects on the cortical rhythms when stimulated at low frequencies. Dempsey and Morison (1942), stimulating the intralaminar nuclei at low frequencies (around 10 per second), produced a generalized response of the cortex. This response was characterized by a progressive increase of the evoked

cortical waves, the so-called recruiting response. And this same thalamic area has received from Hess (1954) the designation "somnogenic area" after its stimulation was shown to produce behavioral and electrographic sleep. On the basis of this and similar data physiologists have referred to the intralaminar nuclei as the "diffuse thalamic projection system" a term appropriated by Magoun and his colleagues in their studies of the ARAS. Jasper (1958) has referred to this part of the thalamus as the "thalamic reticular system," implying its functional interdependence on the RF of the brain stem. From strictly anatomical data (Scheibel and Scheibel, 1958, 1967a,; Leontovich and Zhukova, 1963) there may be justification for the term "thalamic reticular system", but the term "diffuse thalamic projection system" is speculative, pretentious and perhaps misleading. Reconciliation of the apparently opposite effects attributed to stimulation of the intralaminar thalamus has been a difficult problem, theoretically and experimentally (see discussion between Morison and Magoun in Magoun, (1954)). Indeed it was shown by Akimoto et al (1956) that through an electrode placed in the massa intermedia, synchrony and sleep was produced by low frequency stimulation thus confirming Hess' earlier results, while high frequency stimulation caused arousal and low voltage fast activity on the cortex. This paradox was finally satisfactorily resolved by Schlag and Chaillet (1963) who showed that in cats midbrain transection prevented EEG desynchronization induced by high frequency intralaminar

thalamic stimulation. The same results were obtained by a partial lesion at the level of the midbrain-diencephalic junction, a lesion which spared the midbrain tegmentum. These authors concluded that their lesions had interrupted a thalamoreticular pathway which mediated the cortical low voltage fast activity seen to result from high frequency stimulation of the intralaminar thalamus. Brémer's (1954) observation that the conscious level of the cerveau isolé cat is one of "permanent sleep" supports the conclusion that activation of thalamic origin must be mediated by the reticular core of the brain stem.

PERIPHERAL AFFERENTS TO THE RETICULAR CORE: PHYSIOLOGY

Stimulation of the sciatic nerve and auditory stimulation have been shown to evoke slow wave potentials in the tegmentum of the midbrain and the subthalamus and ventromedial thalamus (Starzl, et al, 1951b). These evoked potentials persisted even after ablation of specific sensory pathways at brain stem and diencephalic levels, leading the authors to postulate a system of afferent collaterals to the reticular core by which the reticular activation of the EEG and arousal were mediated. Morin (1953) showed that the spinal course of these reticular afferents followed ipsilateral and contralateral pathways in the ventral and lateral funiculi of the cord. Collins and O'Leary (1954), analyzing the midbrain potential evoked by stimulation of a

peripheral nerve, cast doubt on the hypothesis that the reticular core receives collaterals from the medial lemniscus. Rather, their data suggested that both the midbrain RF and the CM slow waves evoked by peripheral stimulation were mediated by common small diameter afferent fibers ascending in the ventral and lateral funiculi of the cord.

By studying the EEG and behavioral effects on unrestrained cats of stimulation of pure cutaneous and muscle afferent fibers, Pompeiano and Swett (1962) demonstrated that arousal and EEG activation were produced mainly through the mediation of group III cutaneous and muscle afferent fibers; (their data do not eliminate the possibility that some high threshold group II fibers may also be involved in the arousal reaction). These data, not inconsistent with the findings of Collins and O'Leary (1954), indicate that myelinated afferent fibers of about 1-6 micron diameter are the first link in the spinoreticular chain. Pain and temperature afferent fibers are usually reported to be of group III and muscle pressure-pain receptors also fall into this category (Pompeiano and Swett, 1962). The responses reported by these authors persisted even after cerebellectomy and dorsal column section. Scheibel et al (1955) showed that there is widespread but variable convergence of sensory impulses on reticular units of the medulla and midbrain. They found that reticular units responded to one or more of the following modalities: cerebellar polarization, sciatic nerve

stimulation, strychnine waves on the sensorimotor cortex, tactile stimulation, tendon stretch, electrical stimulation of the sensorimotor cortex and acoustic clicks. These authors conceived of the bulbar and midbrain RF, "...as being composed of groups of functionally distinguishable fractions, each fraction consisting of those cells whose synaptic scale includes terminals from the same afferent modalities".

Amassian and Waller (1958) extended the study of convergence on units of the midbrain RF by showing that the temporal parameters of a particular neuron discharge, i.e. one of repetitive discharge, latency of discharge and interspike intervals, could be altered by changing the spacial parameters of the peripheral stimulation. Thus, although somatotopic organization is not found among reticular neurons, frequency coding may contain information concerning the spacial characteristics of the stimulus. It was seen that more than 50% of the reticular neurons which respond to electrical stimulation of the paw of one limb also respond to electrical stimulation of at least one other limb.

The response of reticular units to graded peripheral nerve stimulation was reported by Pompeiano and Swett (1963). They found that in the decerebrate, cerebellectomized cat reticular units responded (by inhibition or facilitation) to peripheral stimulation only at group II or III intensity-frequency threshold. It is of great interest that of the units they encountered in the medulla and at the ponto-medullary junction, well over half responded to stimulation of group II

fibers, fibers which they had shown (Pompeiano and Swett, (1962) to be associated with EEG synchronization. In the rostral pons and midbrain between 65.3 and 72.5% of the units encountered responded to group III fiber stimulation, previously identified as the fiber mediating EEG activation and arousal. (No reticular unit was found to respond to peripheral stimulation at group I fiber threshold). According to these investigators, units which responded to stimulation of group II fibers were found in the region of the medial lemniscus, nucleus reticularis gigantocellularis and nucleus reticularis paramedianus; group III fiber stimulation was most frequently associated with unit responses in the periaqueductal grey, midbrain RF, and nuclei reticularis pontis oralis and pontis caudalis. It is also of interest that the centre median nucleus of the thalamus is said to receive group III but no group I or II muscle afferent fiber projections (Mallart, 1961). The presence of an afferent projection to the centre median has been demonstrated by Albe-Fessard and her co-workers. Kruger and Albe-Fessard (1960) defined the characteristics of the slow wave evoked in the centre median by natural and electrical stimulation of the limbs in cats anesthetized with chloralose and immobilized with Flaxedil. The large slow wave, which was found throughout the centre median-parafascicular complex (CM-Pf), had a latency about twice as long as that of the somatic afferent evoked potential found in the ventrobasal complex (VB). For hind limb stimulation the CM-Pf slow wave

latency was approximately 16 msec and for forelimb stimulation it was about 12 msec compared to latencies of approximately 9 msec and 5 msec respectively for the somatic afferent evoked potentials in VB. Unit studies in chloralose anesthetized cats of the afferent projection to CM-Pf (Albe-Fessard and Kruger, 1962) showed that one third of the neurons encountered displayed a "short latency" activation (mean for the forepaw: 18.9 msec) and another third were activated only after a very long latency (mean: 605.1 msec). The remainder showed mixed responses. The natural stimulus for eliciting these unit responses was a "sharply applied localized pinprick". Aside from their statement that unit discharge could be elicited from stimulation of the skin, articular capsules, periosteum and cornea, but never from stroking the hair, light touch or muscle stretch, the authors did not precisely define the peripheral receptors involved in the afferent projection to CM-Pf.

Subsequent experiments have shown that a brusque, mechanical stimulus (a sharp tap), not necessarily noxious, is the effective natural stimulus for the activation of the somatic afferent pathway to CM-Pf (Bowsher et al, 1968). These authors demonstrated an important bulbar relay in this pathway. A slow wave evoked by peripheral stimulation was shown to correspond to the cytoarchitectonic limits of nucleus reticularis gigantocellularis of the medulla. Neurons in RGC showed both heterotopic and heterosensory convergence. Almost 95% of the units encountered responded to stimulation

of all four limbs. Auditory stimuli activated 60.5% of the units and 27% were also responsive to light flashes. Stimulation in some of the responsive areas of RGC evoked a slow wave in the CM-Pf complex. The spinoreticular part of this pathway seems to be mainly crossed, while the reticulothalamic part is mainly uncrossed.

There have been no systematic physiological studies of pontine or midbrain reticulothalamic projections comparable to the paper on the bulbar relay by Bowsher et al. Single shocks delivered to the sciatic nerve evoked a negative slow wave and activated neuronal units in the midbrain RF (Machne et al, 1955). Akimoto and Saito (1966) reported that single shocks to the midbrain RF were accompanied by a 10-60 msec inhibition of "non-specific thalamic neurons"; in some cases a 10-40 msec period of facilitation was observed preceding the inhibition. Delivery of a high frequency train (100 Hz) stimulus to the midbrain RF was associated with decrease in firing rate of 16 units and an increase in firing rate of 13 units of the non-specific thalamic nuclei. Purpura and Shofer (1963) placed stimulating electrodes into the CM of encéphale isolé cats and made intracellular recordings from the rostral intralaminar nuclei. At stimulus frequency of 7 Hz the recorded units showed that each shock was associated with an EPSP during which the unit discharged one or several times, followed by a large IPSP which lasted until the next stimulus arrived. This rhythmic oscillation of the membrane potential, with unit discharge at the peak of the

EPSP, has been designated "neuronal recruitment", a usage implying analogy to and perhaps a common mechanism with the recruitment of cortical potentials seen in macroelectrode recordings. When higher frequency trains (25-75 Hz) were delivered the same units would show a single IPSP followed by a high frequency unit discharge. In a specific thalamic nucleus (VL) the typical "recruiting" response to low frequency medial thalamic stimulation was modified by simultaneous high frequency brain stem RF stimulation so that the prominent IPSP of "neuronal recruitment" was attenuated and the rhythmic unit discharge yielded to a random discharge pattern (Purpura et al, 1966a). Although these authors do not specifically analyze the discharge rates of their thalamic units, their illustrations suggest that interspike interval rather than raw rate of discharge is altered by high frequency stimulation. They propose that the high frequency stimulation modifies the unit "recruiting" phenomenon by a disinhibition mechanism.

Since the earliest days of the investigation of the ARAS (Starzl et al, 1951) a number of investigators have used high frequency stimulation of the medial thalamic structures to study local and distant concomitants of "activation" (Jasper and Ajmone-Marsan, 1952; Purpura and Shofer, 1963; Purpura et al, 1966b). Such high frequency stimulation of the medial thalamus has been based on the assumption that it is equivalent to stimulation of the bulbar or midbrain RF. Jasper (1958) discussed some of the difficulties inherent in the concept of the reticular formation as an entity, including brain

stem tegmentum and intralaminar and medial thalamic nuclei, an entity which at a number of different levels possesses dual response capabilities dependent solely on the stimulus frequency. Indeed there are important differences between the activation pattern produced by stimulation at the thalamus and the pattern produced by brain stem stimulation. According to Jasper (1958), thalamic "activation" is short-lived, whereas brain stem "activation" is longer lasting, tonic. The brain stem system is adrenaline-sensitive and can be blocked with chlorpromazine; the thalamic system is not adrenaline-sensitive (Rothballer, 1956, 1957). And yet another objection to the concept which considers the intralaminar and medial thalamic structures to be simply "the cephalic end of the reticular activating or 'waking' system", is to be found in the work of Brémer (1954) who described the cerveau isolé state as one of permanent sleep. Within the context of this controversy the work of Schlag and Chaillet (1963) showing that thalamic activation is abolished by a lesion of the mesencephalic-diencephalic junction assumes particular significance. These investigators suggest that the habenulotegmental tract (Nauta, 1958) and the cortico-tegmental fibers which pass through the caudal diencephalon (Hugelin and Bonvallet, 1957) may carry the thalamoreticular pathway with which they propose to explain the hodology of thalamic "activation". In any case, serious objections to the equivalence of thalamic and midbrain "activation" have been raised, and the interpretation of data related to high frequency stimulation of any thalamic structures must be interpreted with caution.

EXPERIMENTAL SERIES

MATERIALS AND METHODS

Experiments were performed on 16 adult cats of both sexes ranging in weight from 2.5 to 4.5 Kg (median weight: 3.35 Kg). All the experiments were "acute", the longest ones lasting up to 20 hours from the beginning of anesthesia.

In all cats ether inhalation was used for the induction of anesthesia. After local infiltration of the skin with Novocaine 1% (Winthrop) a femoral vein was cannulated for the intravenous infusion of medications and fluids. The trachea was cannulated after infiltration of the skin and soft tissues of the neck with Novocaine 1%. The tracheal canula was a Y-shaped glass tube, one limb of which was attached to a respirator; a short piece of rubber tubing attached to the other limb was partly occluded so as to permit adjustment of the tidal volume delivered by the respirator.

The animal's head was then mounted in a Lab-Tronics stereotaxic frame using only the ear bars, initially. The head was flexed to facilitate surgical exposure of the upper cervical region. The suboccipital and upper cervical skin and muscles were infiltrated with Novocaine 1% and a small incision was carried down to the posterior lip of the foramen magnum and the posterior arch of the first cervical vertebra. The atlanto-occipital ligament, dura and arachnoid were then opened by a mid-line incision. In 8 cats an encéphale isolé preparation was made. Ephedrine hydrochloride 4.5 mgm/Kg and Pitressin 1 pressor unit/Kg were given intravenously 1

minute prior to the severance of the spinal cord at the C1 level. The animals were maintained on artificial respiration from the time of cord section. In some of the experiments it was necessary to give small doses of curare intravenously (Tubocurarine chloride, Squibb; maximum dose: 0.6 mgm/Kg/hour) because of interference with the microelectrode recording procedure produced by spinal cord reflex spasms of the lower extremities. In 8 cats the neural axis remained intact and the animals were anesthetized with intravenous Chloralose 20-80 mgm/Kg after the ether induction and the initial canulation procedures. The chloralose was prepared according to the method described by Kruger and Albe-Fessard (1960) in order to eliminate the epileptogenic fraction from the solution. In all the cats the posterior neck incision was either closed loosely or left open in order to permit constant cisternal drainage of the cerebrospinal fluid. Ether was discontinued at the time of the cervical cord section or the administration of chloralose. No recordings were made for at least 2 hours after the cessation of ether inhalation. All the pressure points on the head were then infiltrated with Novocaine 1% and the head was securely mounted in the stereotaxic frame. A craniectomy was performed to expose the brain from posterior 5 to the anterior 10 frontal planes and the lateral 5 planes bilaterally. The animals which were anesthetized with chloralose were paralyzed with intravenous curare (Tubocurarine chloride, Squibb) 0.6 mgm/Kg/hour or Flaxedil (Gallamine triethiodide, Poulenc) 2 mgm/Kg/hour prior to the start of

the recording. They then remained under respirator control for the duration of the experiment. Rectal temperature was monitored continuously with a tele-thermometer (Yellow Springs Instrument Co., Inc.) and the temperature was maintained at between 38 and 40 degrees Centigrade with a heat lamp. The adequacy of oxygenation and hemodynamics with reference to the brain were indirectly assessed by periodic monitoring of the electrocorticogram (ECoG) in all experiments.

STIMULATION TECHNIQUES

The mesencephalic reticular formation was stimulated through bipolar stainless steel needle electrodes which were insulated with Isonel to within 0.5 mm of the pointed tip. The electrodes had a tip separation of 1 mm and a resistance of 30-40 Kilohms measured in saline. A single electrode of this pair was on occasion used for macroelectrode monopolar recording of slow wave evoked potentials within the midbrain RF. These electrodes were mounted on the Lab-Tronics stereotaxic electrode holder.

Microelectrode, extracellular unit recordings of thalamic neurons were obtained through tungsten microelectrodes (Hubel, 1957) which were electropolished in saturated solution of potassium nitrite to a tip diameter of approximately 1 micron. The microelectrodes were insulated with Isonel and had a resistance of 30-50 Meghoms measured in saline. The microelectrode was mounted on the stereotaxic electrode holder of a hydraulic microdrive system (David Kopf Instruments, Model 1207B).

Electrical stimulation to the midbrain RF was delivered by a constant-current stimulator (Nuclear-Chicago, Model 7150 Series). Usually, symmetrical, rectangular, biphasic pulses of 0.5 msec duration and 0.2-3.0 mamp intensity were used (Lilly, 1961). On occasion monophasic pulses of either positive or negative polarity were used to verify thalamic slow wave evoked potentials.

Electrical stimulation was delivered to the limbs through a pair of #26 hypodermic needles inserted into the footpad of the limb with a separation of 5-10 mm between the needles. A Grass stimulator (Model S4) generated pulses of 0.2 msec duration and 2.0-12.0 volt intensity. The pulses were carried to the needle electrodes through a stimulus isolation unit. Both the central and peripheral stimuli were triggered by a "synch-pulse" (Grass stimulator, Model S4) after a variable delay.

RECORDING

Thalamic units and slow waves were recorded through the same microelectrode through a common high impedance FET preamplifier. The preamplifier output was then taken to separate system amplifiers* so that the units and the evoked potentials could be displayed independently.

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* The custom-made system amplifier was designed by Mr. D. Skuce and employed 4 solid state operational amplifiers (Philbrick Model P85 AU) to provide calibrated gains up to 100,000 and variable upper and lower roll-off frequencies.

For unit recordings a band-pass of 1,000-10,000 Hz was used and for the thalamic slow wave a band-pass of 1-200 Hz was used. Similarly, the potentials of the midbrain RF slow wave were led through an identical, custom-made, system amplifier with a band-pass of 1-200 Hz. The thalamic units required a gain of 5,000-20,000 and the thalamic and RF slow waves were amplified with a gain of 2,500-5,000. Cortical potentials were recorded from silver ball electrodes of 1mm diameter resting on the pial surface and led through a system amplifier with a band-pass of 1-200 Hz and a gain of 5,000.

The signals from the thalamic units and slow wave, the RF slow wave and the cortical potentials were displayed on a Tectronics RM 565 dual beam oscilloscope and a Tectronics Type 564 storage oscilloscope. Photographs from the storage oscilloscope were made with a Tektronix Type C-12 oscilloscope camera (Polaroid). The thalamic units and slow wave, RF slow wave, corticogram and "synch-pulse" were recorded on a Hewlett Packard 3900 Series 7 track magnetic tape recorder for subsequent play-back and analysis. In addition to visual and photographic analysis the thalamic unit recordings were subjected to various statistical analyses by the Mnemotron Computer of Average Transients (CAT) using the Mnemotron Model 605 Amplitude Discriminator and an oscilloscope "beam intensifier". The neuronal unit studies were facilitated by means of an audiomonitor of the unit

signals. Histograms obtain from the CAT were written out on an Esterline Angus Speed Servo inkwriter.

ANATOMIC CONTROLS

At the conclusion of each experiment the animal was killed with an overdose of Nembutal administered intravenously after the stimulating and recording electrode sites had been marked by passage of a direct current through the electrodes. The carotid arteries were then dissected out and used to perfuse the brain with 100 cc of 10% formalin solution. While the brain was still in the skull it was cut stereotaxically so that all electrode tracks could be studied with reference to standard stereotaxic coordinates. The block of brain tissue was kept in 10% formalin solution for 2 weeks before being submitted for final processing. The brains were then imbedded in parafin and sectioned in the frontal plane at 10 micra thickness. One section in 20 of each series was stained with thionin and examined microscopically. All recording sites and most of the stimulation sites were verified anatomically.

STATISTICAL ANALYSIS OF NEURON SPIKE DATA

For analysis by the special purpose computer (CAT), the neuron spike train (unit action potentials) is treated as a stochastic point process. For the spontaneous activity of the neuron it is assumed that the spike train is a stationary, renewal process.

> "In a stationary process, the underlying probability distributions of which the observed (interspike) intervals constitute a sample do not themselves depend on the time of observation... If successive (interspike) intervals in a spike train are drawn independently from a common probability distribution, the process is a renewal process..." (Moore, Perkel and Segundo, 1966).

The statistical analysis of units subjected to single shock stimulation is based, therefore, on the assumption that the spontaneous activity of these units may be described as a stationary, renewal, stochastic point process. The analysis most commonly performed on units subjected to single shock stimulation is the post-stimulus-time histogram (PST histogram), which is essentially a cross-correlation between the train of stimuli and the train of unit spikes. Unit responses to the stimulus are identified by significant departures from the expected constant value of a null cross-correlation histogram. Peaks in the PST histogram represent increased probability of unit firing (excitation or activation) and troughs represent decreased probability of firing (inhibition). In this study the responses of many of the units were clear-cut on inspection of the PST histogram. However, when the significance of a response was in any degree questionable, and in all the cases used for illustration, a null value histogram was constructed for the unit by introducing a fictitious series of stimuli throughout a portion of the record when no actual stimuli were presented. The actual PST histogram was compared with the null value histogram.

The latency of early responses (activation) to stimulation was measured directly from the raw unit data displayed on an oscilloscope screen. During a period of stimulation the time of occurrence of 5 consecutive responses to single shock stimulation was averaged for each unit studied.

Response duration of both activation and inhibition was most easily measured from the PST histograms. Some of the units were subjected to trains (several seconds long) of high frequency stimulation of the midbrain RF. For these units the most elementary level of analysis consisted of observation of change in the firing rate of the neuron after delivery of the stimulus train. This was displayed as a simple histogram of firing frequency and time, showing the "base-line" rate for a period of time prior to the stimulus (spontaneous activity) and the slower or faster frequency after the stimulus train (FT histogram). The response of units to high-frequency stimulus trains was also analyzed by means of interspike-interval histograms (ISI histograms). The interspike-intervals of an equal number of consecutive spikes before (spontaneous activity) and after the stimulus train were compared.

Finally, an attempt was made to show a correlation between unit responses and evoked potentials recorded simultaneously from the same microelectrode. For this purpose the evoked potential was averaged by the CAT and was compared with the PST histogram of the unit using the same analysis time for both (Gerstein, 1961; Fox and O'Brien, 1965; Dreifuss et al, 1968).

EXPERIMENTAL RESULTS

The experiments were designed to test the hypothesis that the midbrain tegmentum projects directly to the nucleus centre median of the thalamus. In view of the established knowledge of multisensory convergence on reticular neurons throughout the brain stem it would follow that the RF of the midbrain is one of several relays along the ascending reticular pathways. Input to the RF of the midbrain from spinal afferent systems was investigated and the convergence of these spinal afferent and midbrain reticulothalamic systems within the CM was demonstrated. The effect of olfactory, trigeminal, visual and auditory input to the brain stem RF was not considered. The CM was explored with a microelectrode within the stereotaxic coordinates (Jasper and Ajmone-Marsan, 1954) frontal 7.0 or 7.5, lateral 2.5 to 3.5 and horizontal +1.0 to -2.0. Adjacent electrode tracks were always 1 mm apart. The aforementioned stereotaxic coordinates were adhered to in order to insure that the electrode was well within the limits of the CM. The stimulating electrodes were located within the RF of the midbrain at the stereotaxic coordinates frontal 3.0, lateral 3.0 and horizontal 0.0 to -2.0.

Only units which were easily discriminated from the background by the use of the CAT Amplitude Discriminator (units whose amplitude was at least 50% above the background level) are included in this report. On a few occasions when two separate and clearly distinguishable units were encountered simultaneously, each was analyzed by subtraction with the CAT.

RESPONSE OF CM UNITS TO SINGLE SHOCK STIMULATION OF THE MIDBRAIN RF

Single shocks were delivered to the midbrain RF at the rate of 1 per second. The threshold intensity for the CM slow potential evoked by single shock stimulation of the midbrain RF was determined to be 0.4 to 0.5 mamp and the intensity of stimulus required for an evoked CM potential of maximum amplitude was 1.5 mamp using a rectangular biphasic pulse of 0.5 msec duration. For CM unit analysis a pulse of 1.5 to 3.0 mamp intensity, 0.5 msec duration was used.

Within the CM 89 units were observed for a period of time long enough to analyze the response to single shock stimulation of the midbrain RF. The spontaneous firing pattern of these units was variable, some having slow to moderately fast sporadic firing patterns and others firing in bursts. Any neuron with a rapid, regular firing pattern was considered to be injured and was excluded from the study. Of the 89 units analyzed 29 showed no significant change in firing pattern after single shock stimulation of the midbrain RF. Most of these units were located at or medial to the lateral 3.0 plane and at or above the horizontal 0.0 plane. By way of contrast most neurons which responded to stimulation of the midbrain RF tended to be located in more lateral and inferior areas of CM, with reference to the atlas of Jasper and Ajmone-Marsan (1954).

Forty-five neurons responded to single shock stimulation of the midbrain RF with early activation. The latency for this response (Fig. 7A) was found to be between 2 and 12 msec (mean latency = 7.2 msec). Among these units later responses were also observed. Inhibition, following the early activation, was seen in 32 units. The duration of the period of inhibition ranged from 10 to 225 msec (mean duration = 69 msec). Further, in a number of units late activation occurred as a secondary event, following the initial activation-inhibition sequence. This late activation often showed a prolonged time course (Fig. 7C).

Late activation as a primary response was seen in 6 units (Fig. 8). Among these units the response latency varied between 18 and 100 msec (mean latency = 35 msec). Duration of late primary activation response was from 20 to 150 msec (mean duration = 66 msec). Primary inhibition following single shock stimulation of the midbrain RF was seen in 9 units (Fig. 9). In these cases the period of inhibition lasted from 20 to 150 msec (mean duration = 65 msec). A period of activation followed the primary inhibition in 6 of 9 units.

RESPONSE OF CM UNITS TO HIGH-FREQUENCY STIMULATION OF THE MIDBRAIN RF

Since the publications of Moruzzi and Magoun (1949) and Starzl et al (1951) EEG desynchronization (low voltage fast activity) and behavioral arousal have been associated with

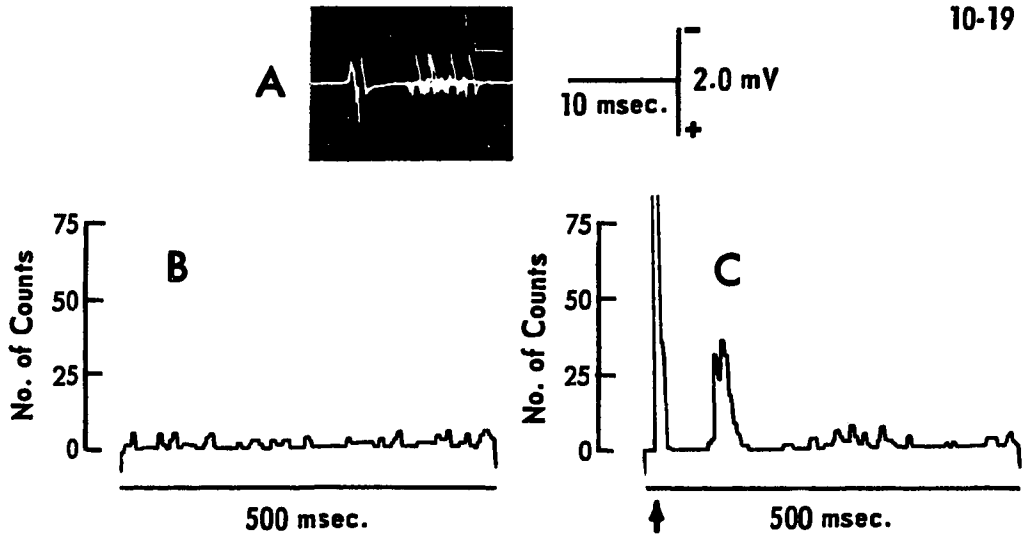


FIGURE 7. Activation-inhibition-activation response of a CM unit to stimulation of the ipsilateral RF. A: Early activation (7 msec); this early response is "lost" in the stimulus artifact in C: PST histogram. B: null histogram; in this and all subsequent illustrations a histogram of the spontaneous unit activity is made using the same time scale and number of sweeps as were used in the PST histogram. Comparison of the PST histogram with the null histogram indicates the statistical significance of the responses. A: 5 sweeps; B,C: 99 sweeps. Arrow in this and subsequent illustrations indicates stimulus artifact.

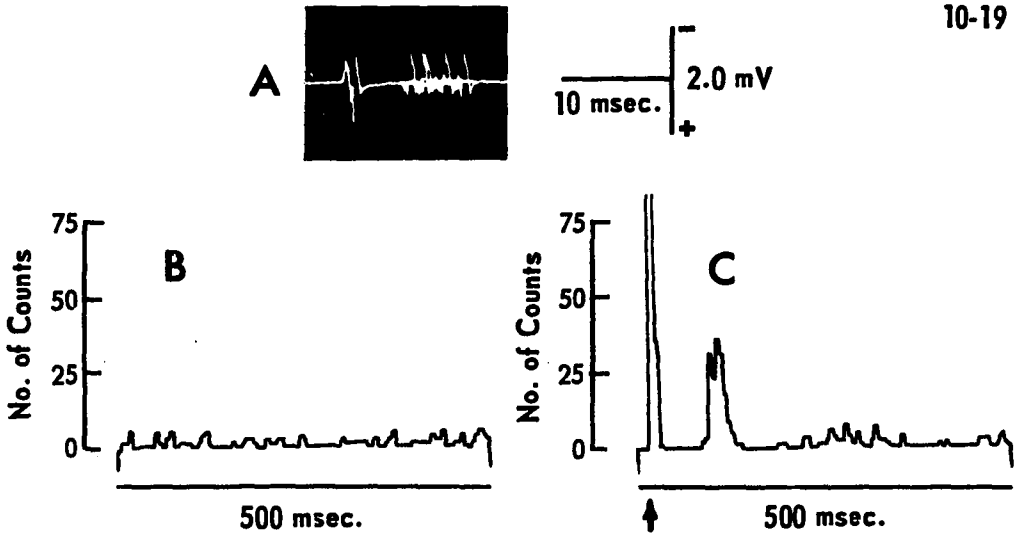


FIGURE 7. Activation-inhibition-activation response of a CM unit to stimulation of the ipsilateral RF. A: Early activation (7 msec); this early response is "lost" in the stimulus artifact in C: PST histogram. B: null histogram; in this and all subsequent illustrations a histogram of the spontaneous unit activity is made using the same time scale and number of sweeps as were used in the PST histogram. Comparison of the PST histogram with the null histogram indicates the statistical significance of the responses. A: 5 sweeps; B,C: 99 sweeps. Arrow in this and subsequent illustrations indicates stimulus artifact.

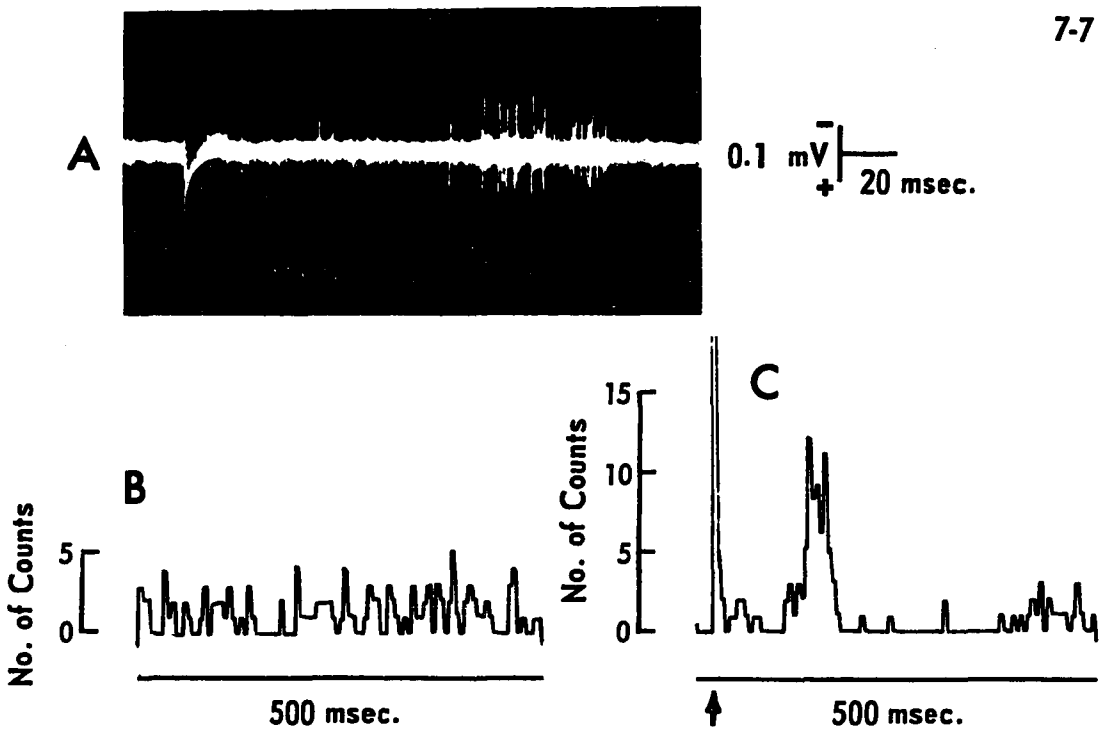


FIGURE 8. Late activation of CM unit in response to stimulation of the ipsilateral RF. A: Oscilloscope display (5 sweeps) showing long latency (approximately 100 msec) response of the larger unit. This unit is discriminated by its amplitude for CAT analysis in B: Null histogram and C: PST histogram. (99 sweeps).

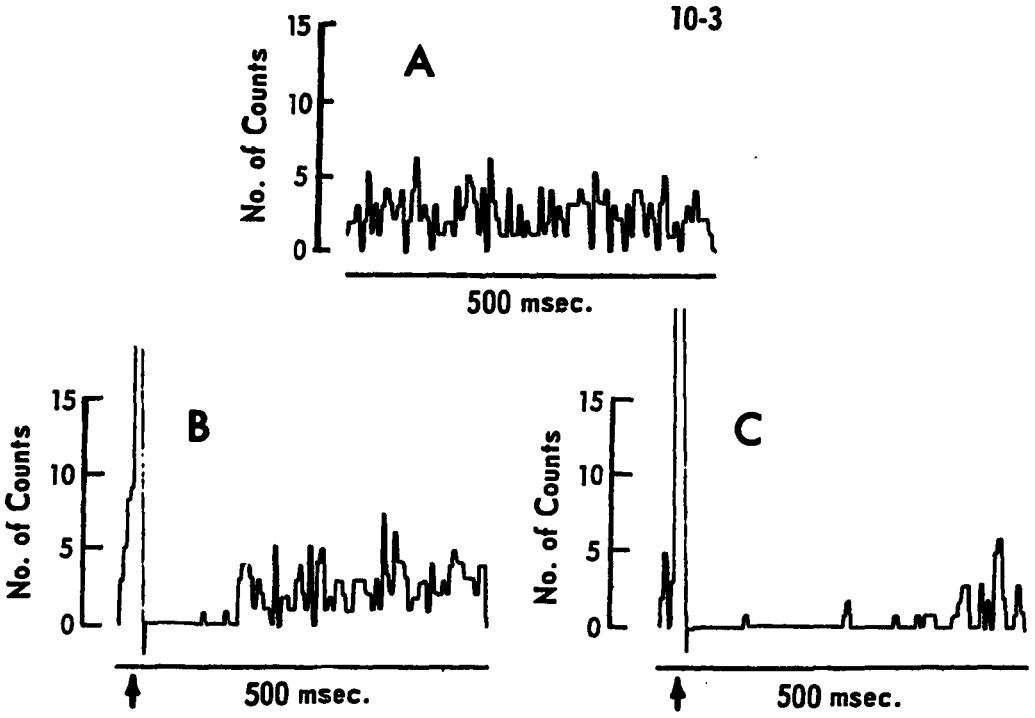


FIGURE 9. Data from CM unit showing primary inhibition after RF stimulation. A: Null histogram. B: PST histogram; the inhibition following stimulation of the ipsilateral RF using single shocks. C: PST histogram shows prolonged inhibition after paired shock stimulation (5 msec interval between shocks). (all 99 sweeps).

high-frequency stimulation of the reticular core of the brainstem. Purpura et al (1966) demonstrated alterations in the membrane potentials of specific thalamic neurons during high-frequency stimulation of either medial thalamic structures or pontine RF. For this reason the firing patterns of CM neurons before and after delivery of a high-frequency train of stimuli to the midbrain RF was studied. Twenty-seven units were so studied. A period of spontaneous activity was observed in order to establish a base-line of mean firing rate and interspike intervals. Then a 1-5 sec train of high-frequency stimuli (200/sec) was delivered to the midbrain RF. The post-stimulus firing pattern was then compared with the spontaneous activity of the same CM unit. Of the 27 units, 16 responded to high-frequency stimulation. For 11 units there was no significant change in firing rate. Seven of the 16 responsive units showed an increase in the mean firing rate (Fig. 10) and 9 showed a decrease (Fig. 11) after RF stimulation. Most of these units showed changes in interspike intervals consistent with the response, viz, shortening of the intervals in units which had increased firing rates and lengthening of the intervals in units which slowed after RF stimulation. In 5 units the change in intervals was "paradoxical", that is, shorter intervals were seen in a unit which showed a decrease in firing rate and vice versa. The explanation for this "paradox" of intervals and firing rate is twofold. In some units the spontaneous firing rate varied over the time of observation, thus violating the assumption that the spike train be a

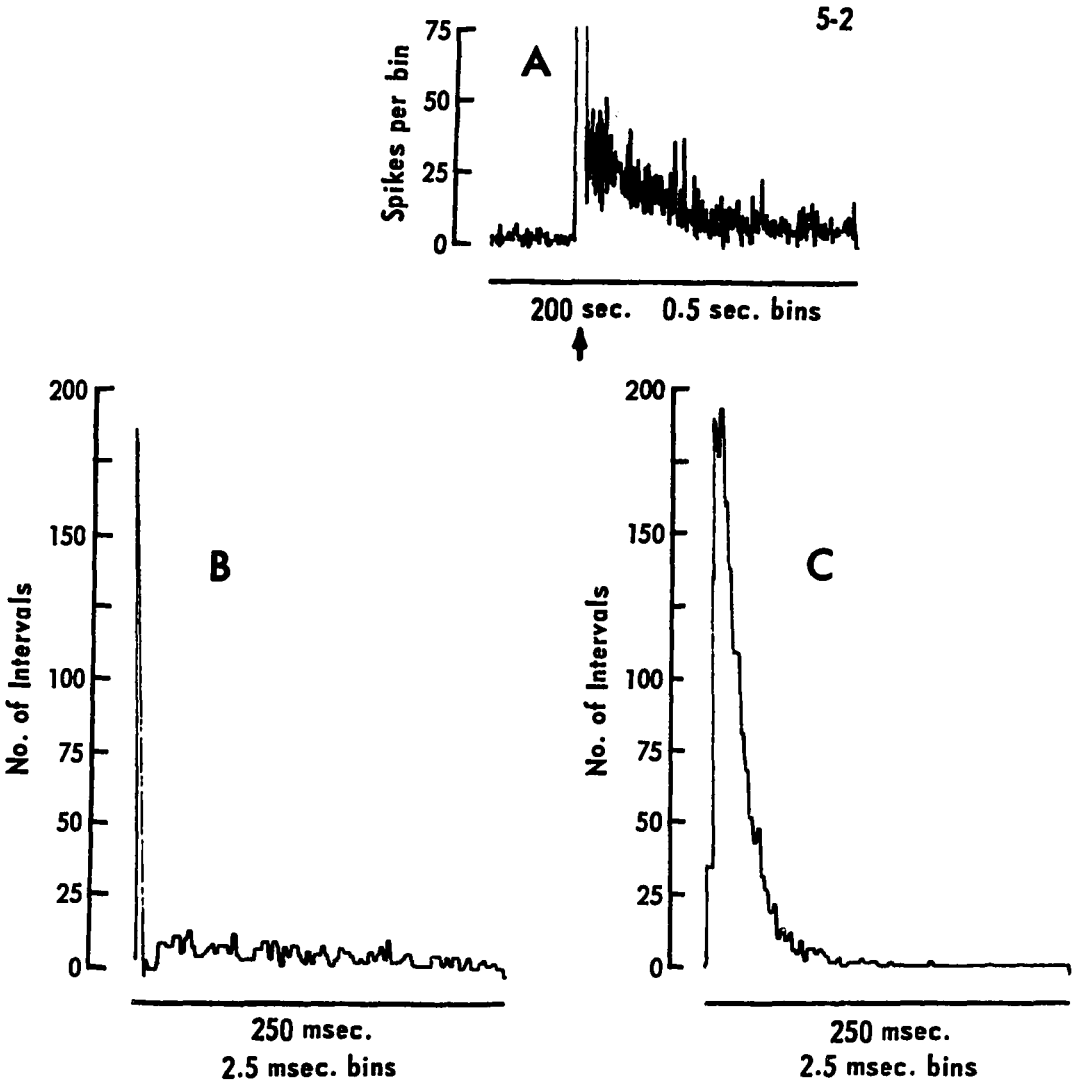


FIGURE 10. Activation of a CM unit after 5 sec train of high frequency (200/sec) stimulation of the midbrain RF. A: Frequency-time histogram shows spontaneous unit activity and marked increase in the firing rate after delivery of the stimulus train. B: Interspike interval (ISI) histogram of the spontaneous unit activity. The first bin represents the number of intervals longer than 250 msec. C: ISI histogram of the unit activity immediately following the stimulus train shows increase in the number of shorter intervals. Single shock stimulation of the RF produced a pattern of primary inhibition followed by activation in this unit.

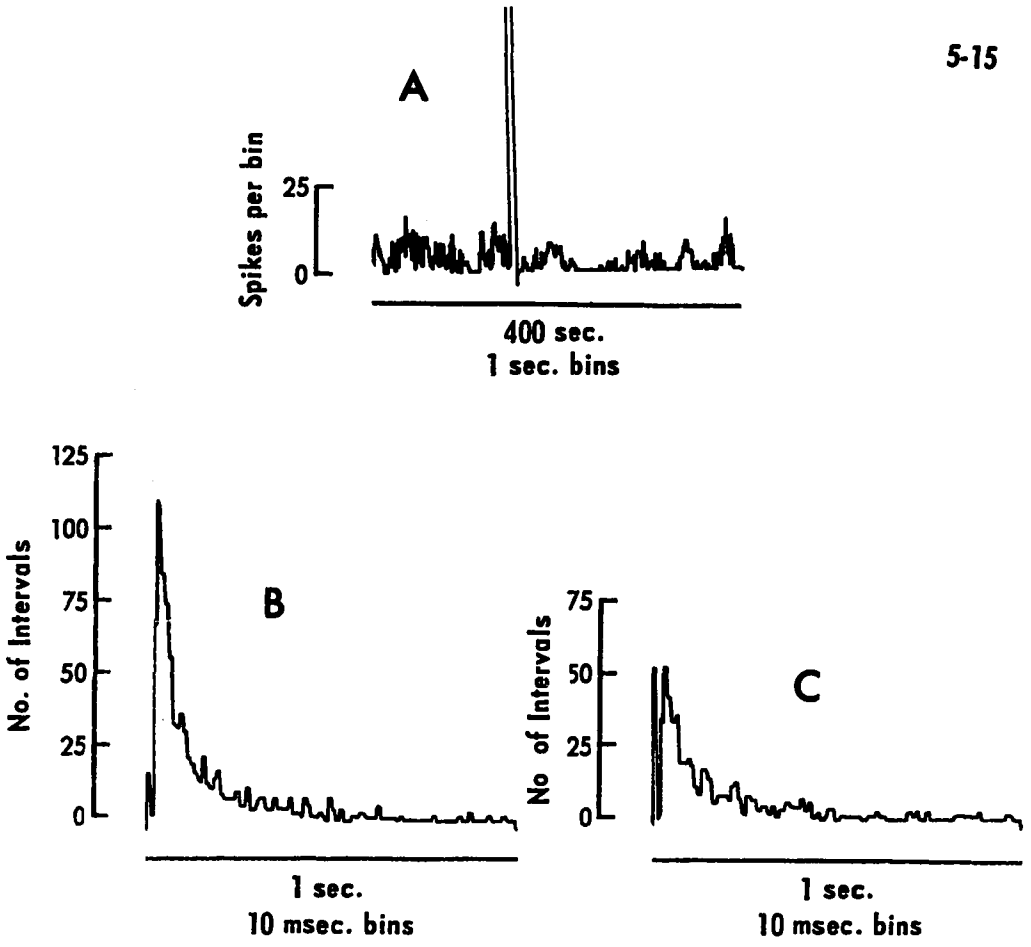


FIGURE 11. CM unit response to 5 sec train of high frequency (200/sec) stimulation of the midbrain RF. A: Frequency-time histogram showing spontaneous firing rate (prestimulus) and slowing of unit firing after delivery of the stimulus train. B: Interspike interval histogram of spontaneous cell firing. C: ISI histogram immediately after the stimulus train shows greater number of longer intervals. B & C each total 300 intervals.

stationary process (see STATISTICAL ANALYSIS above). In other units, high frequency stimulation of the midbrain RF produced high frequency bursts of unit firing so that the response was not analyzable statistically by the CAT, long periods of apparent inhibition being nullified by short periods of high frequency spike discharge. All the units that responded to high-frequency stimulation of the RF also responded to single-shock stimulation. Of the 11 units which showed no change in firing rate after high-frequency stimulation 4 did show a change in interspike intervals and 5 also responded to single-shock stimulation.

RESPONSE OF CM UNITS TO ELECTRICAL STIMULATION OF THE EXTREMITIES

Other investigators have commented on the virtual absence of spontaneous firing of neurons in the CM under conditions of chloralose anesthesia (Albe-Fessard and Kruger, 1962). Thus, while the study of slow transients is facilitated with this agent, the study of unit activity is made more difficult. In order to locate CM units in intact chloralose anesthetized animals (using a standard dose of chloralose: 80 mgm/Kg) it was necessary to apply a constant train of stimuli at low frequency while the exploring microelectrode was being lowered. Electrical stimuli were delivered to the foot pad of the contralateral (to CM) forelimb at a frequency of 1 per 35 sec, in essence a succession of single shocks. With this technique few units were found before they exhibited

obvious injury potentials. Therefore, two animals were anesthetized very lightly with chloralose (20 mgm/Kg) producing a state in which the CM neurons retained spontaneous activity. In these 2 experiments there was no difficulty locating spontaneously firing neurons; indeed, these experiments yielded as many or more analyzable units as comparable experiments in unanesthetized (encephale isolé) cats. All the chloralose anesthetized animals were paralyzed with Flaxedil.

A total of 17 CM units were studied with single shock electrical stimulation of the limbs. Ten of 17 units responded to peripheral stimulation. In 9 of the responsive units a pattern of activation was seen (Fig. 12); one unit exhibited primary inhibition after peripheral stimulation (Fig. 13). All the responsive units were shown to respond to electrical stimulation of more than one limb. Further, all the units which responded with activation to electrical stimulation of the limbs also responded in a similar manner to natural stimulation of two or more limbs. The effective natural stimulus was a pin prick or a brusque tap delivered manually by the investigator using a pencil. The latter stimulus was not felt to be painful when administered by the investigator to himself. None of the responsive units were affected by light touch, stroking the hair or joint movement.

The latency from electrical stimulus (contralateral forelimb) to first spike was between 18 and 40 msec (mean latency = 24.2 msec) for the 10 units which exhibited primary activation. Thirteen of the 17 units studied with peripheral stimulation were also tested with single-shock stimulation of

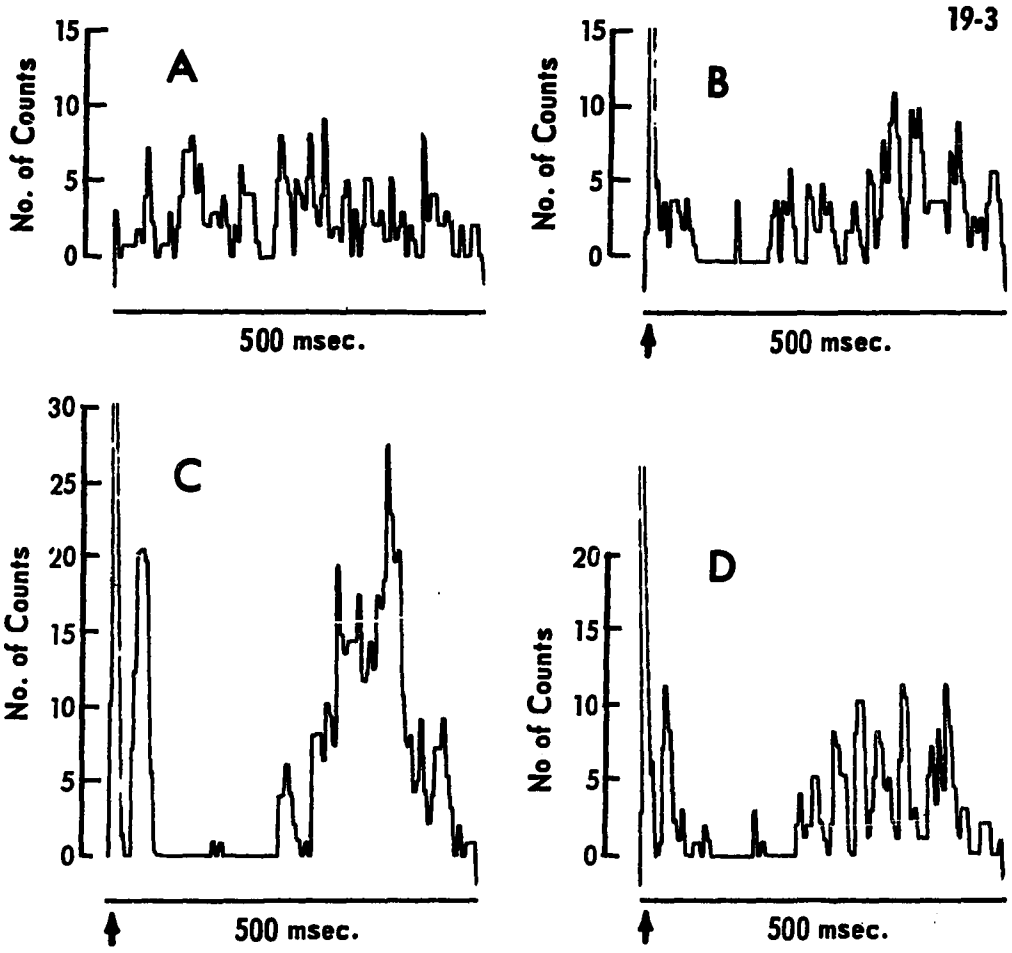


FIGURE 12. Data from CM unit comparing responses to RF and peripheral stimulation. A: null histogram. B: PST histogram showing delayed inhibition after stimulation of the ipsilateral RF. C: PST histogram of activation-inhibition-activation response from stimulation of the contralateral forelimb. D: PST histogram showing much "weaker" response to stimulation of the ipsilateral forelimb. (all 99 sweeps).

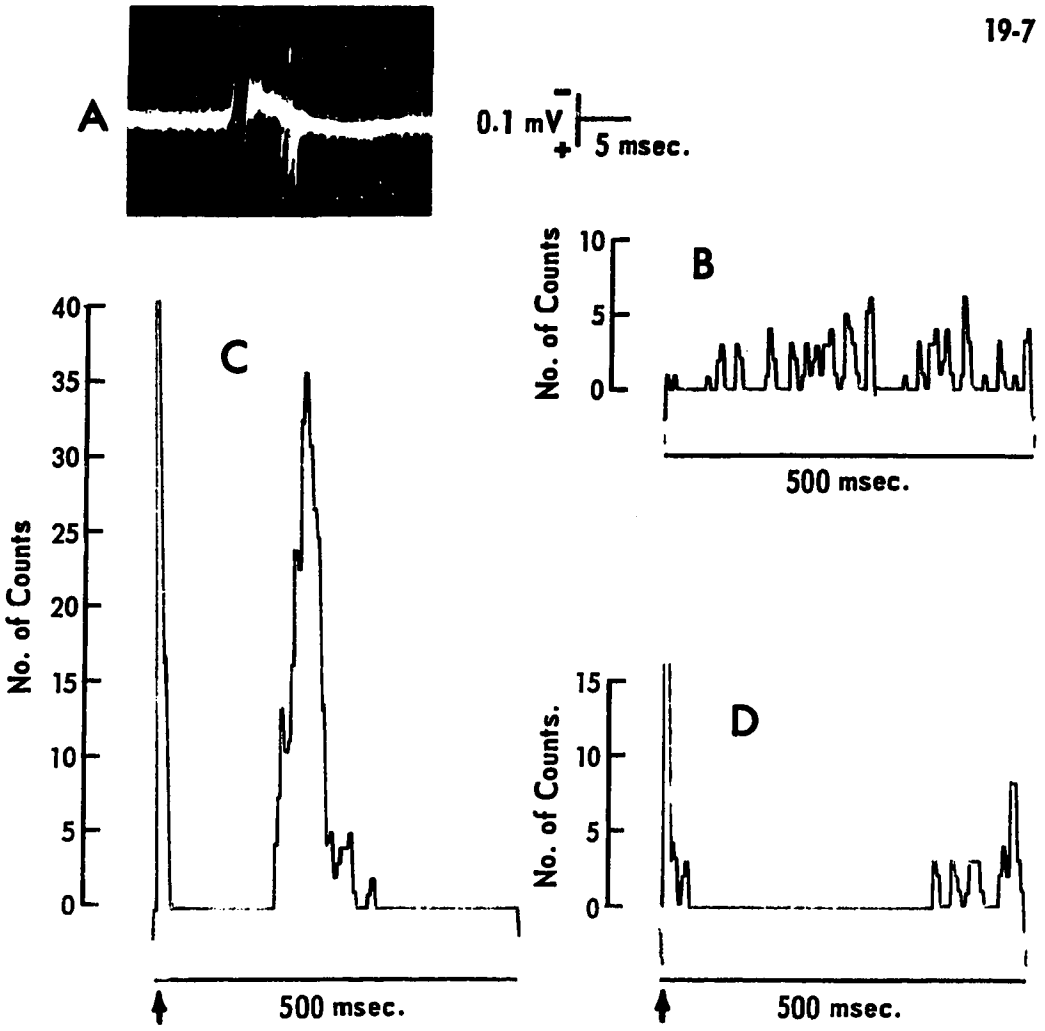


FIGURE 13. A unique response of a CM unit which showed primary inhibition after stimulation of the contralateral forelimb. This unit exhibited an early activation-inhibition-activation response to stimulation of the ipsilateral RF. A: early activation response to reticular stimulation. B: null histogram. C: PST histogram showing response to stimulation of the ipsilateral RF: the early activation is "lost" in the stimulus artifact. D: PST histogram showing response to stimulation of the contralateral forelimb; the spikes in the first few bins following the stimulus artifact are spontaneous activity, reflecting the latency of the inhibition. (A: 5 sweeps; B-D: 99 sweeps).

the midbrain RF. Eight units were affected alike by peripheral and RF stimulation, that is they were either activated (4 units) or they showed no response (4 units) to both peripheral and RF stimulation. Five units were affected differently by the two types of stimulation (Fig. 14), 4 being responsive to one but not to the other and 1 unit being activated by peripheral stimulation but showing primary inhibition with RF stimulation.

SUMMARY OF CM UNIT RESPONSES

From the data in the present study certain generalizations concerning the responses of CM neurons are justified. To both peripheral and midbrain reticular stimulation over half the units observed exhibited a response pattern of activation-inhibition. These observations apply to units with established spontaneous spike activity, in both unanesthetized cats (encéphale isolé) in which responses to RF stimulation were studied, and cats anesthetized with light doses of chloralose in which responses to peripheral stimulation were studied. In summary 31 of 45 units responding to reticular stimulation, and 7 of 10 units responding to peripheral stimulation exhibited a pattern of activation-inhibition. In many of these units later activation was also seen.

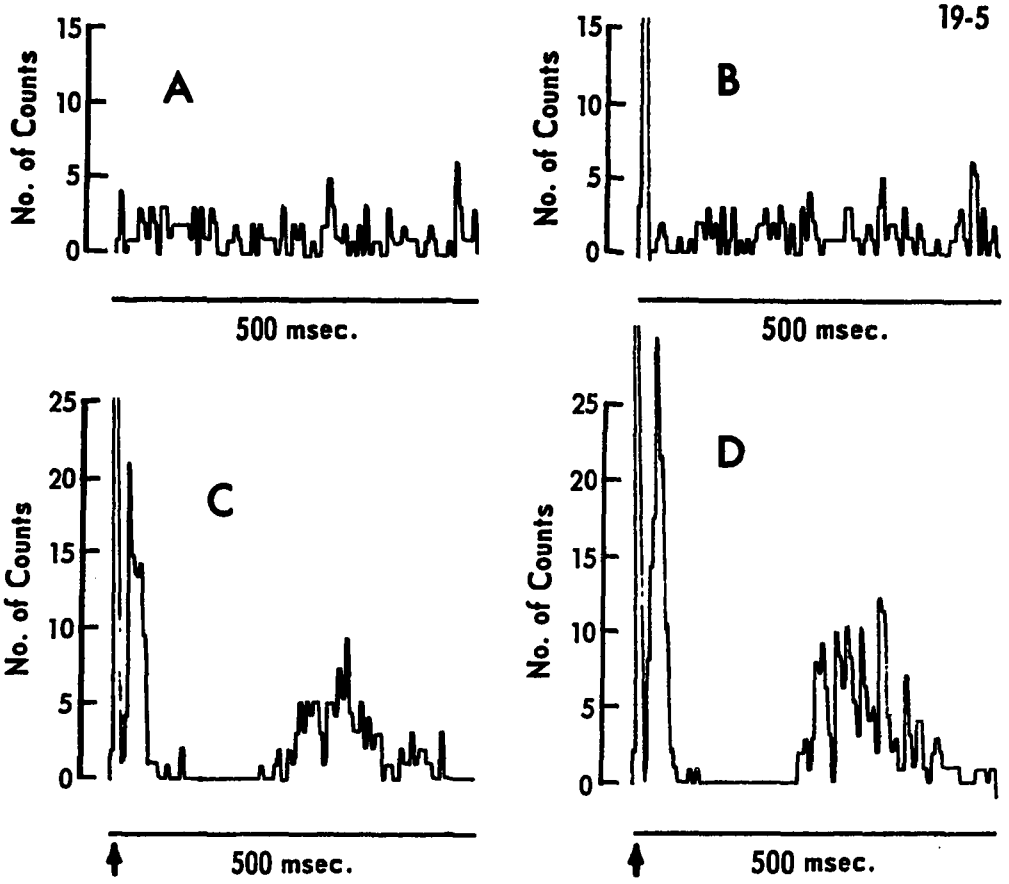


FIGURE 14. Data from CM unit which responds to stimulation of the limbs but not to stimulation of the RF. A: Null histogram. B: Stimulation of the ipsilateral RF produces no response. C: Stimulation of the contralateral forelimb and, D: ipsilateral forelimb both produce a pattern of activation-inhibition-activation. (all 75 sweeps).

EVOKED SLOW POTENTIALS IN THE MIDBRAIN RF AND IN CM

Slow potentials were evoked in the midbrain RF and in CM by electrical stimulation of the limbs and in the CM by electrical stimulation of the midbrain RF. As in the case of the CM units which responded to electrical stimulation of the limbs, the natural stimuli capable of evoking a slow potential in the midbrain RF and the CM were pin-prick and a brusque mechanical tap.

Within the RF a slow potential evoked by peripheral stimulation was found in the medial 2/3 of the midbrain tegmentum at stereotaxic coordinates frontal 3.0, lateral 3.0 between horizontal +1.0 and -3.0 (Jasper and Ajmone-Marsan, 1954), (Fig. 15). This is the region of nucleus cuneiformis and nucleus subcuneiformis described by Taber (1961). The RF slow wave was maximal between the horizontal coordinates 0.0 and -1.5 where it was seen to be an initially positive biphasic wave with a duration of approximately 100 msec. The latency of this slow potential was found to be 10 msec for stimuli delivered to either forelimb, 15 msec for the contralateral hindlimb and 17 msec for the ipsilateral hindlimb.

Within the CM an identical slow wave was evoked by both peripheral and midbrain RF stimulation (Fig. 16). The CM evoked potential was found at the stereotaxic coordinates frontal 7.0 and 7.5 lateral 3.0 and 3.5, horizontal +2 to -1.0 (Jasper and Ajmone-Marsan, 1954). The CM slow wave was usually an initially negative biphasic or triphasic potential with a

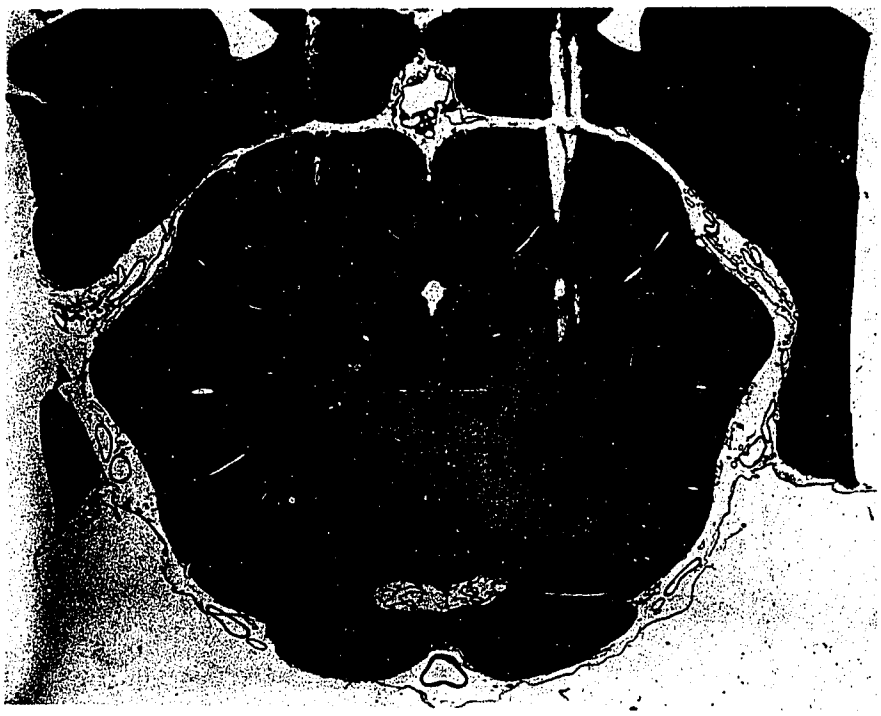


FIGURE 15. Thionin stained section through the midbrain at stereotaxic plane F 3.0, showing bilateral tracks of the stimulating electrodes in the reticular formation dorsal to the red nucleus (nucleus subcuneiformis). The evoked potentials on the opposite page were recorded from the electrode track on the left.

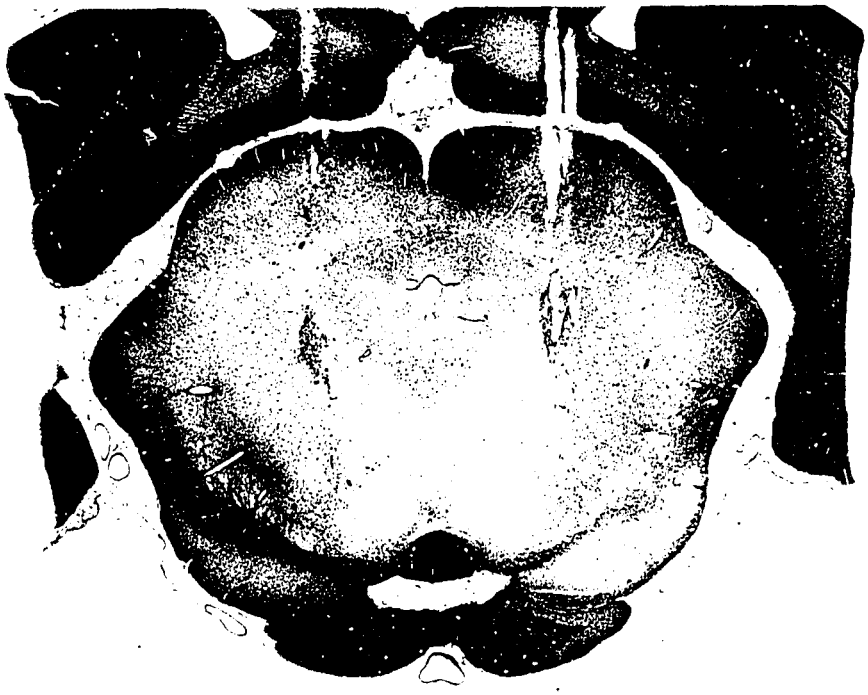


FIGURE 15. Thionin stained section through the midbrain at stereotaxic plane F 3.0, showing bilateral tracks of the stimulating electrodes in the reticular formation dorsal to the red nucleus (nucleus subcuneiformis). The evoked potentials on the opposite page were recorded from the electrode track on the left.

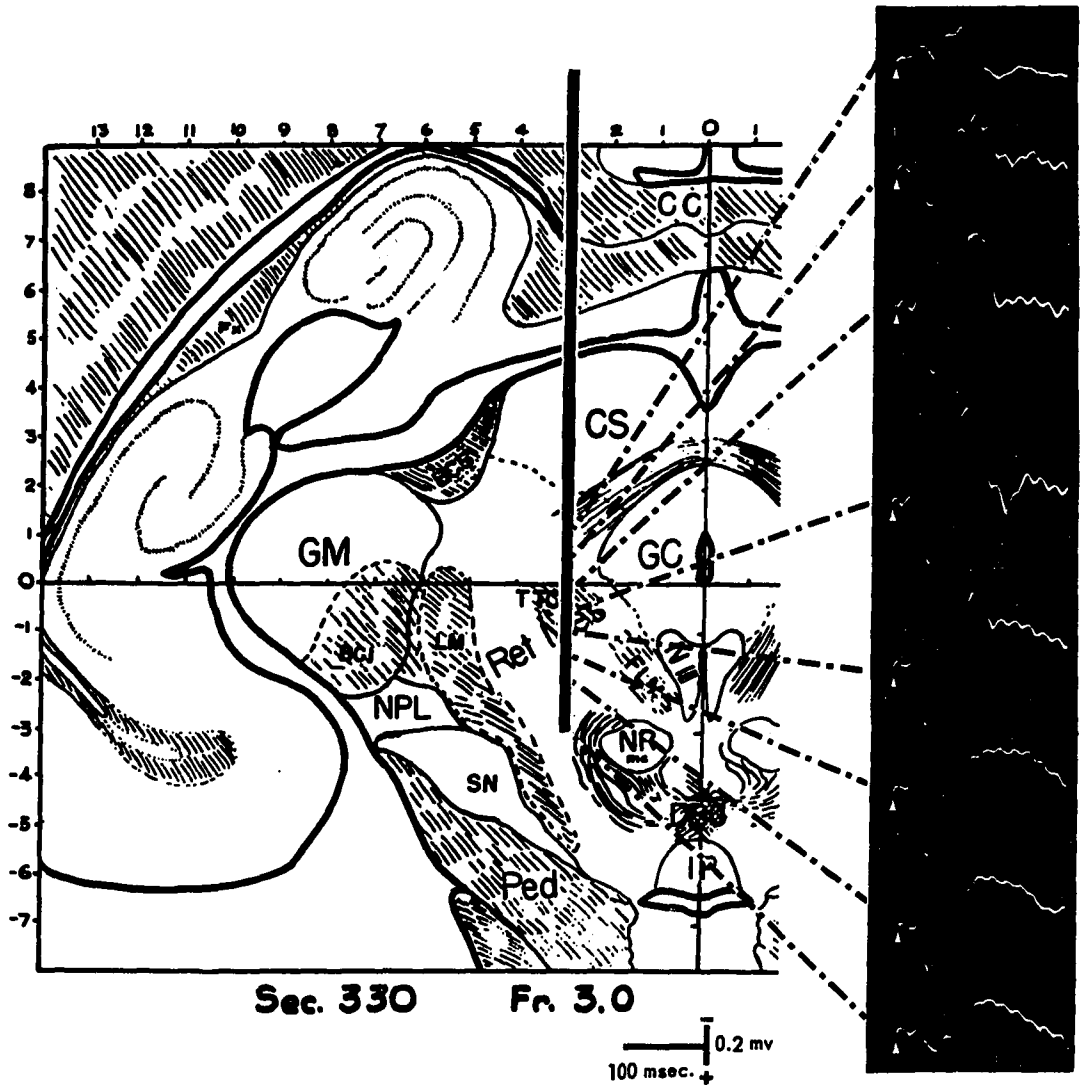


FIGURE 15. The slow potential in the midbrain RF (nucleus subcuneiformis) evoked by electrical stimulation of the contralateral hindlimb. An identical slow wave was evoked by stimulation of all 4 limbs. Stimulus parameters: 8.0 v, 0.2 msec rectangular pulse.

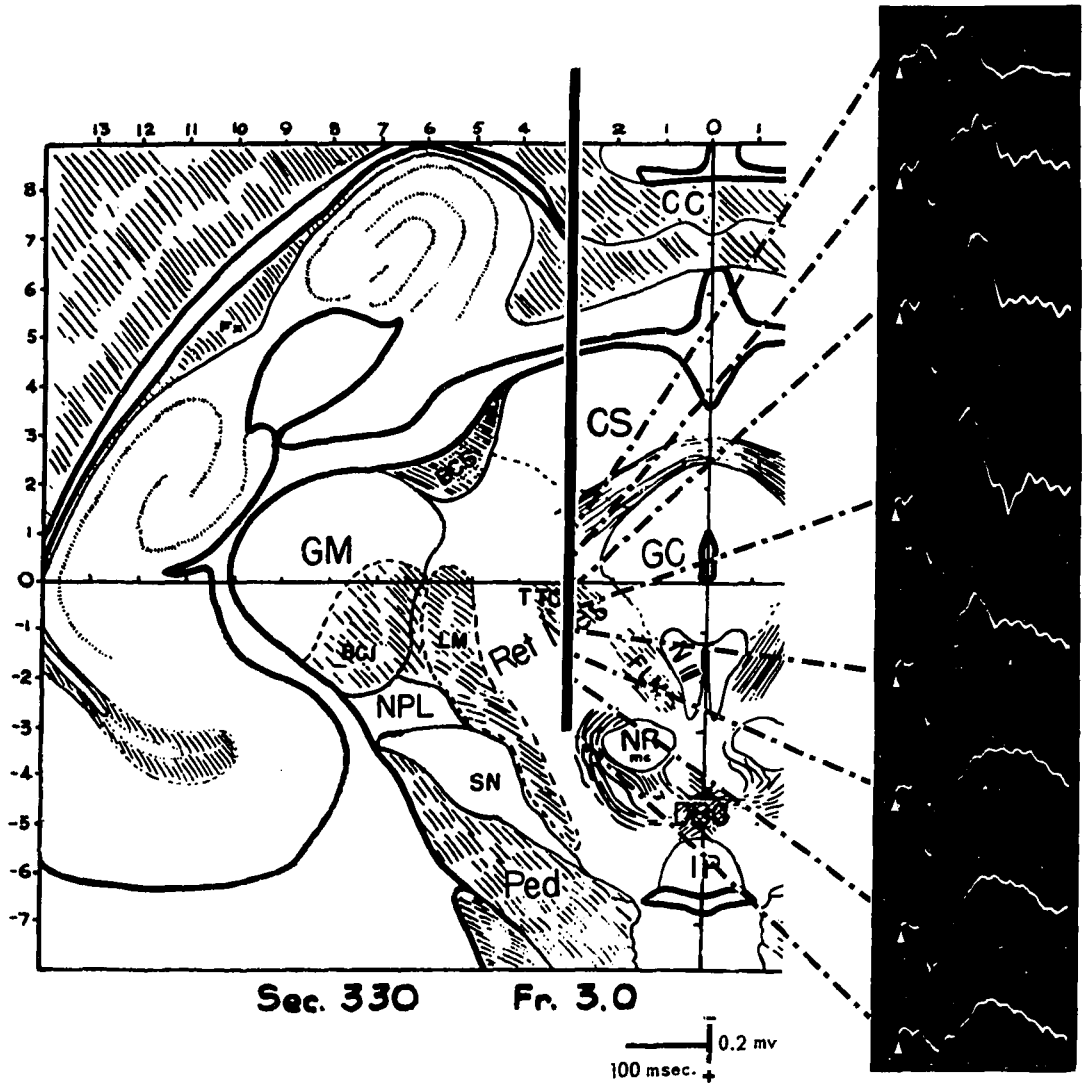


FIGURE 15. The slow potential in the midbrain RF (nucleus subcuneiformis) evoked by electrical stimulation of the contralateral hindlimb. An identical slow wave was evoked by stimulation of all 4 limbs. Stimulus parameters: 8.0 v, 0.2 msec rectangular pulse.

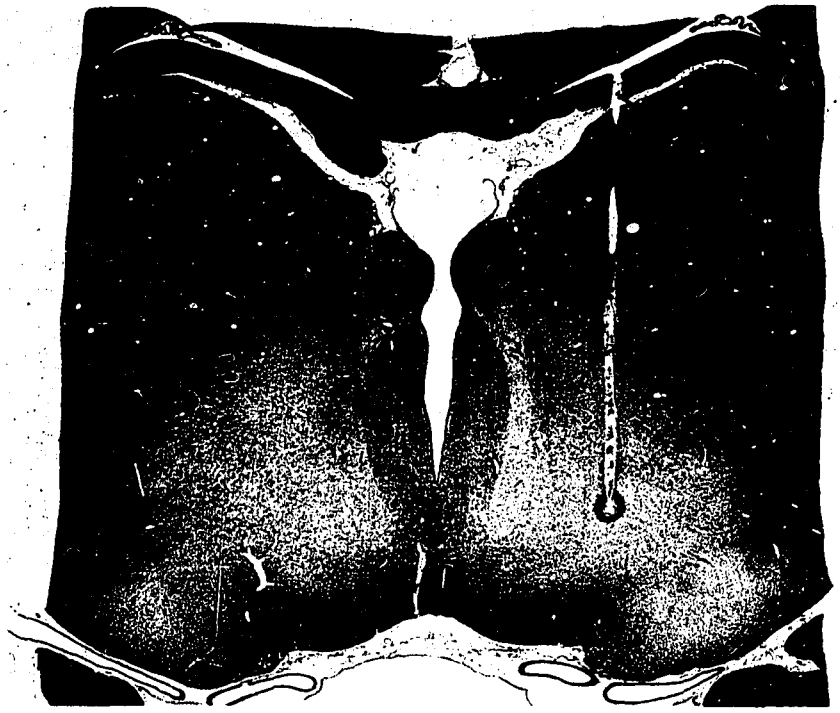


FIGURE 16. Thionin stained section through thalamus at stereotaxic plane F 7.5, showing the track of the microelectrode passing through CM. The evoked potentials shown on the opposite page were recorded from this electrode track. Cf. Fig. 5.

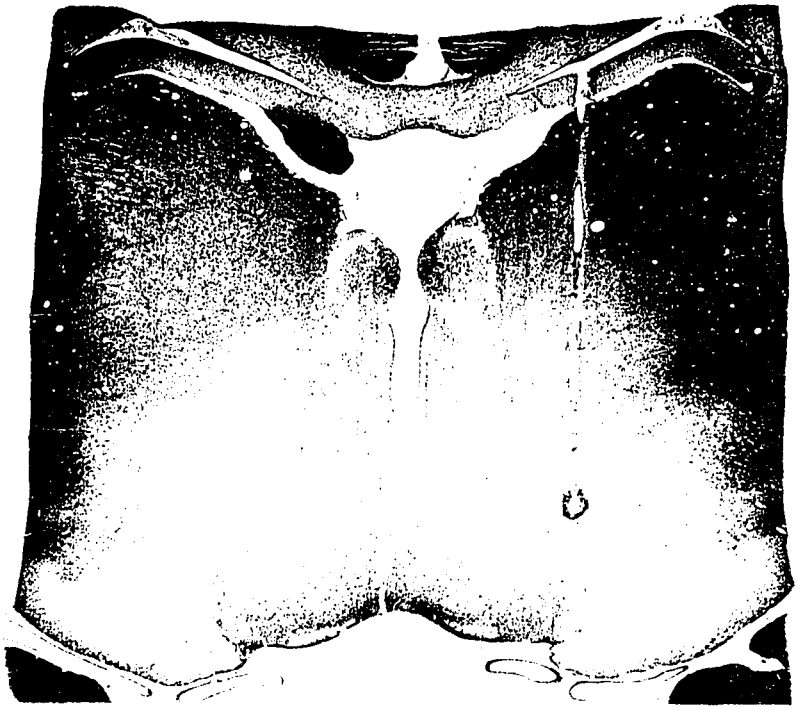


FIGURE 16. Thionin stained section through thalamus at stereotaxic plane P 7.5, showing the track of the microelectrode passing through CM. The evoked potentials shown on the opposite page were recorded from this electrode track. Cf. Fig. 5.

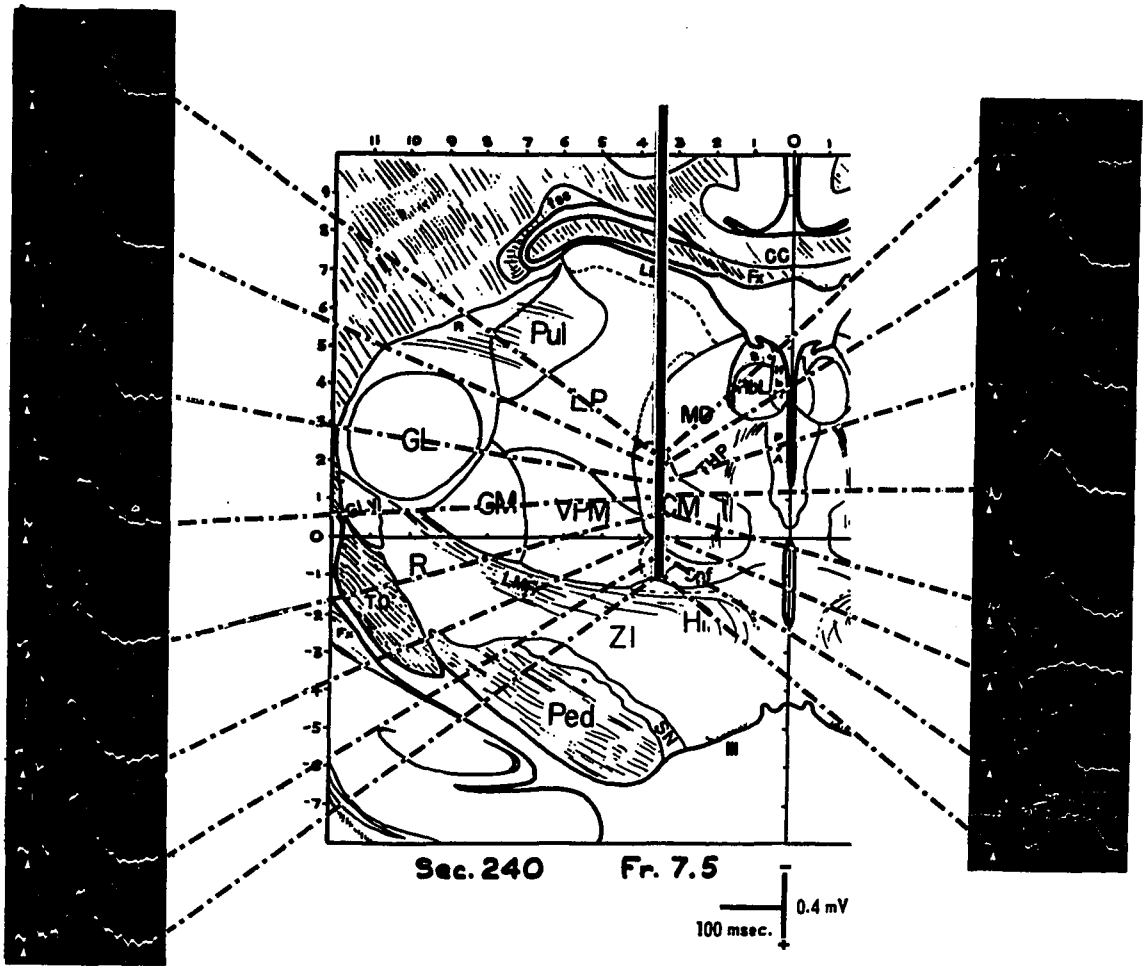


FIGURE 16. The slow potential in the nucleus centre median evoked by electrical stimulation of the ipsilateral midbrain RF (left-hand column) and the contralateral forelimb (right-hand column). The two evoked potentials are very similar in wave form and duration; the large positive component disappears below the inferior border of CM. Stimulus parameters: forelimb; 8.0 v, 0.2 msec rectangular pulse; RF: 1.0 mamp, 0.2 msec biphasic rectangular pulse.

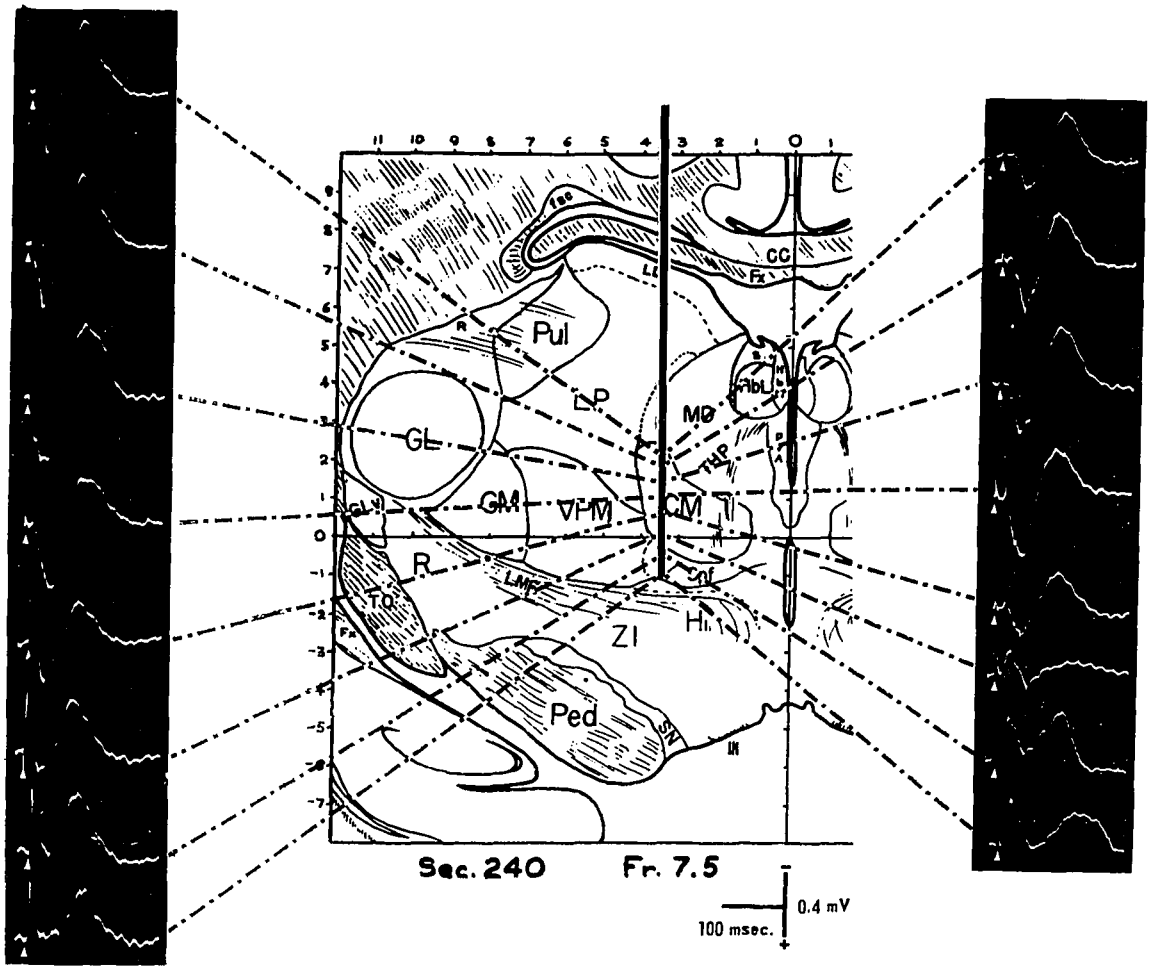


FIGURE 16. The slow potential in the nucleus centre median evoked by electrical stimulation of the ipsilateral midbrain RF (left-hand column) and the contralateral forelimb (right-hand column). The two evoked potentials are very similar in wave form and duration; the large positive component disappears below the inferior border of CM. Stimulus parameters: forelimb; 8.0 v, 0.2 msec rectangular pulse; RF: 1.0 mamp, 0.2 msec biphasic rectangular pulse.

duration of 100-120 msec. The latency of the CM slow wave was 4 msec for stimuli delivered to either side of the midbrain RF. For peripheral stimuli the latencies were contralateral forelimb: 17 msec, ipsilateral forelimb: 22 msec, contralateral hindlimb: 24 msec, ipsilateral hindlimb: 25 msec. The threshold for the slow potentials evoked in the midbrain RF and the CM from electrical stimulation of the limbs was 3.0v (0.2 msec rectangular pulse). Maximum amplitude and duration slow waves required a stimulus intensity 2 to 3 times threshold.

CORRELATION OF CM UNIT ACTIVITY AND SLOW WAVE

The CM unit activity and evoked slow potentials were recorded simultaneously from the tungsten microelectrode (see RECORDING TECHNIQUES above). The unit activity and slow wave were compared by first obtaining a display of superimposed multiple sweeps on the storage oscilloscope screen. Later, the slow wave was averaged by the CAT and compared with the PST histogram of the unit recorded simultaneously. The latter technique permits the storage and summation of much larger quantities of data, thus enhancing the statistical significance of the observations. The results obtained from both techniques, however, were in agreement.

In all cases it was seen that the early negative components of the slow wave, when present, corresponded to periods of neuronal activation and the positive components to neuronal inhibition (Figs. 17 and 18). Frequently, the initial unit

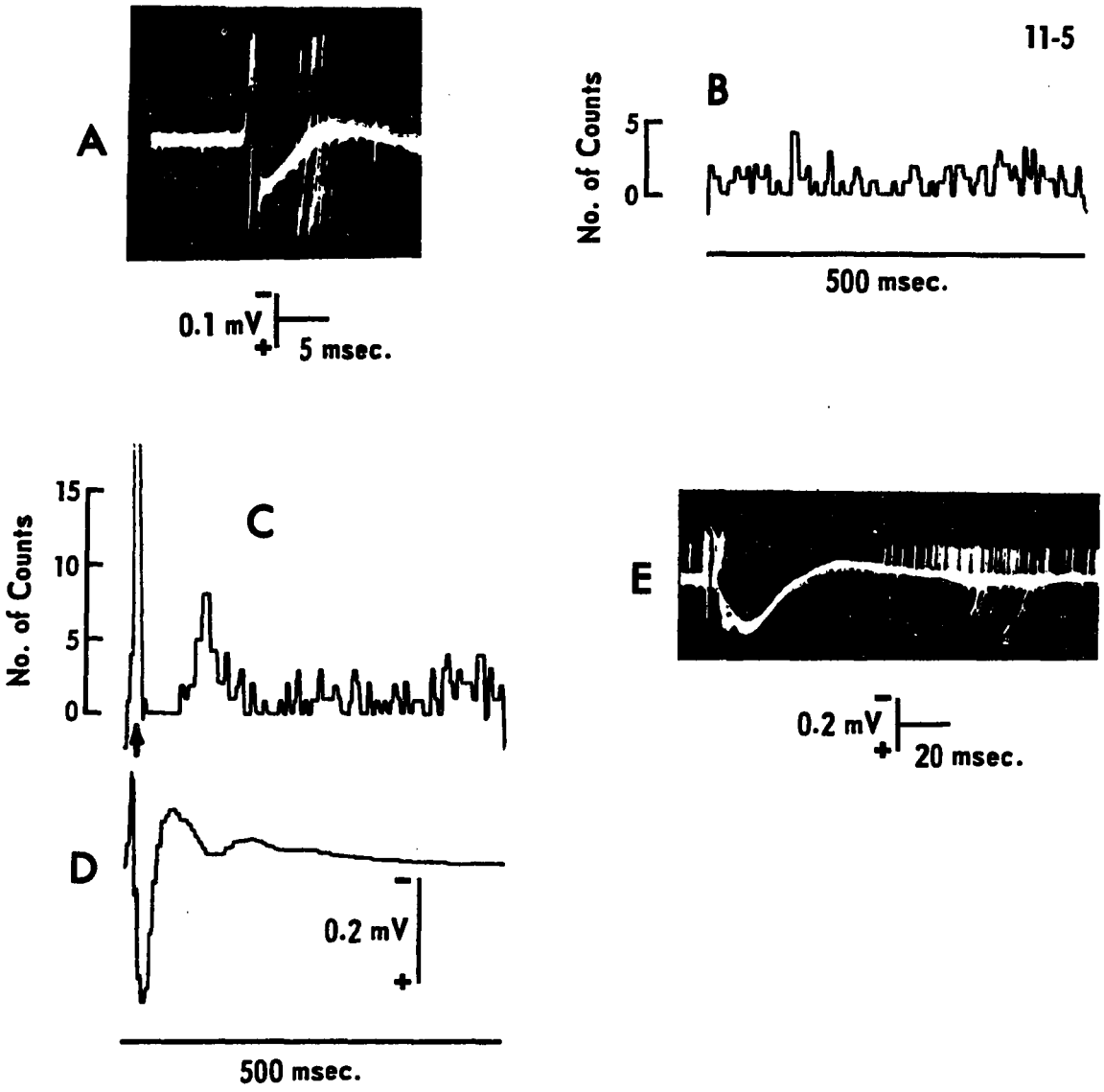


FIGURE 17. Correlation of unit activity with evoked potential recorded simultaneously in CM. A: Short latency response to stimulation of the ipsilateral RF. B: Null histogram. C: PST histogram; the early response is "lost" in the stimulus artifact (arrow) due to the relatively long analysis time. D: CAT averaged evoked potential showing correlation of the initial negative and positive components with unit activation and inhibition, respectively. E: Storage oscilloscope display of superimposed unit activity (99 sweeps) and slow wave (10 sweeps). (A: 5 sweeps; B & C: 99 sweeps; D: 40 sweeps).

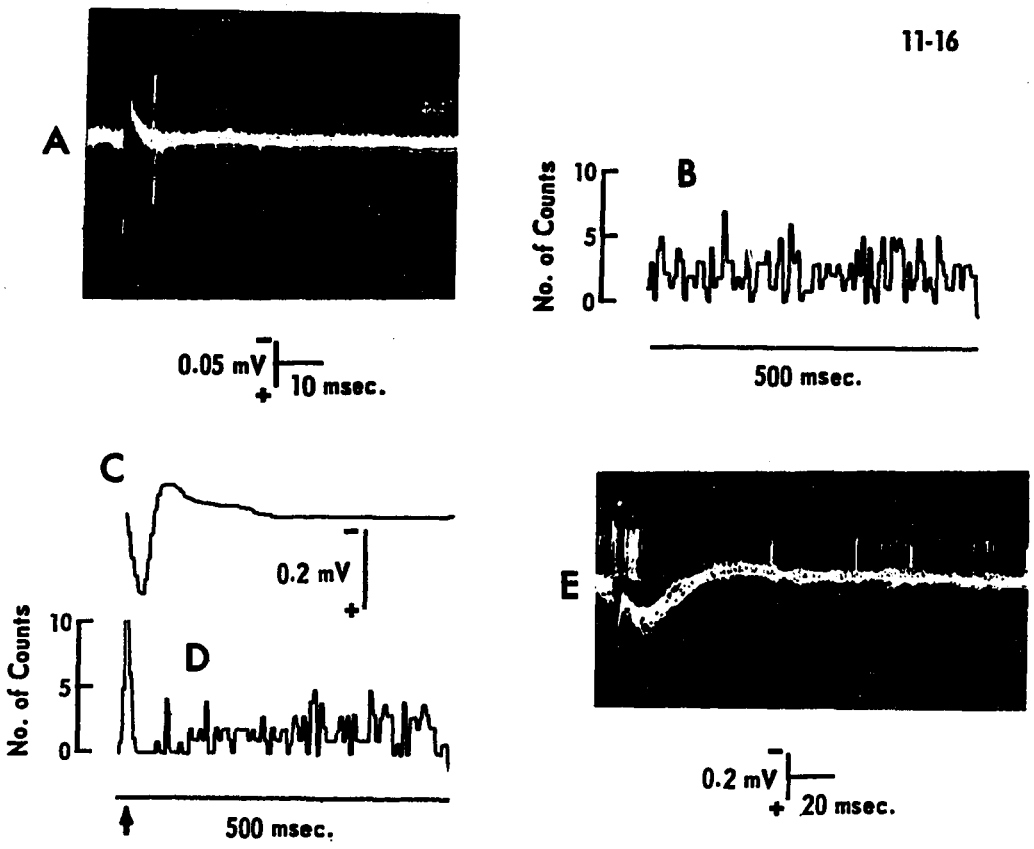


FIGURE 18. Correlation of unit activity with evoked potential recorded simultaneously in CM. A: Short latency response to stimulation of the ipsilateral RF. B: Null histogram. C: CAT averaged evoked potential showing correlation of the positive component with unit inhibition. D: PST histogram; the early response is "lost" in the stimulus artifact (arrow) due to the relatively long analysis time. E: Storage oscilloscope display of superimposed unit activity (99 sweeps) and slow wave (10 sweeps). (A: 5 sweeps; B & D: 99 sweeps; C: 40 sweeps).

activation phase was not associated with a negative deflection of the slow wave response. This may be due to cancellation of the initial negativity by concurrently developed positivity of much greater magnitude. In fact the duration of the inhibition is usually much longer than the duration of the preceding activation (Figs. 18E and 20C). Another possibility to consider is that the early negative component of the slow wave response may be relatively variable in its phase-locking with the stimulus and thus is cancelled in the averaging process. Comparison of the temporal course of the CM slow wave with that of the unit response reveals that although the polarity and relative duration of early components of the slow wave correspond with periods of activation and inhibition of the unit, they are slightly "out of phase". Often, the slow wave component is seen to occur somewhat earlier than the unit response with which it is correlated (Figs. 19, 20). Thus, although the evoked slow wave seems to enable one to predict the relative magnitude, duration and sequence of the activation and inhibition of neuronal activity, the precise temporal parameters of the unit are known only by direct observation.

CONVERGENCE IN CM FROM LIMBS AND MIDBRAIN RF

Using the classic methods of facilitation and occlusion of the evoked potential, convergence of peripheral and midbrain RF stimuli was demonstrated within the CM (Figs. 21, 22). Whereas for monosynaptic pathways the argument rests on measurement of the amplitude of the evoked potentials, the

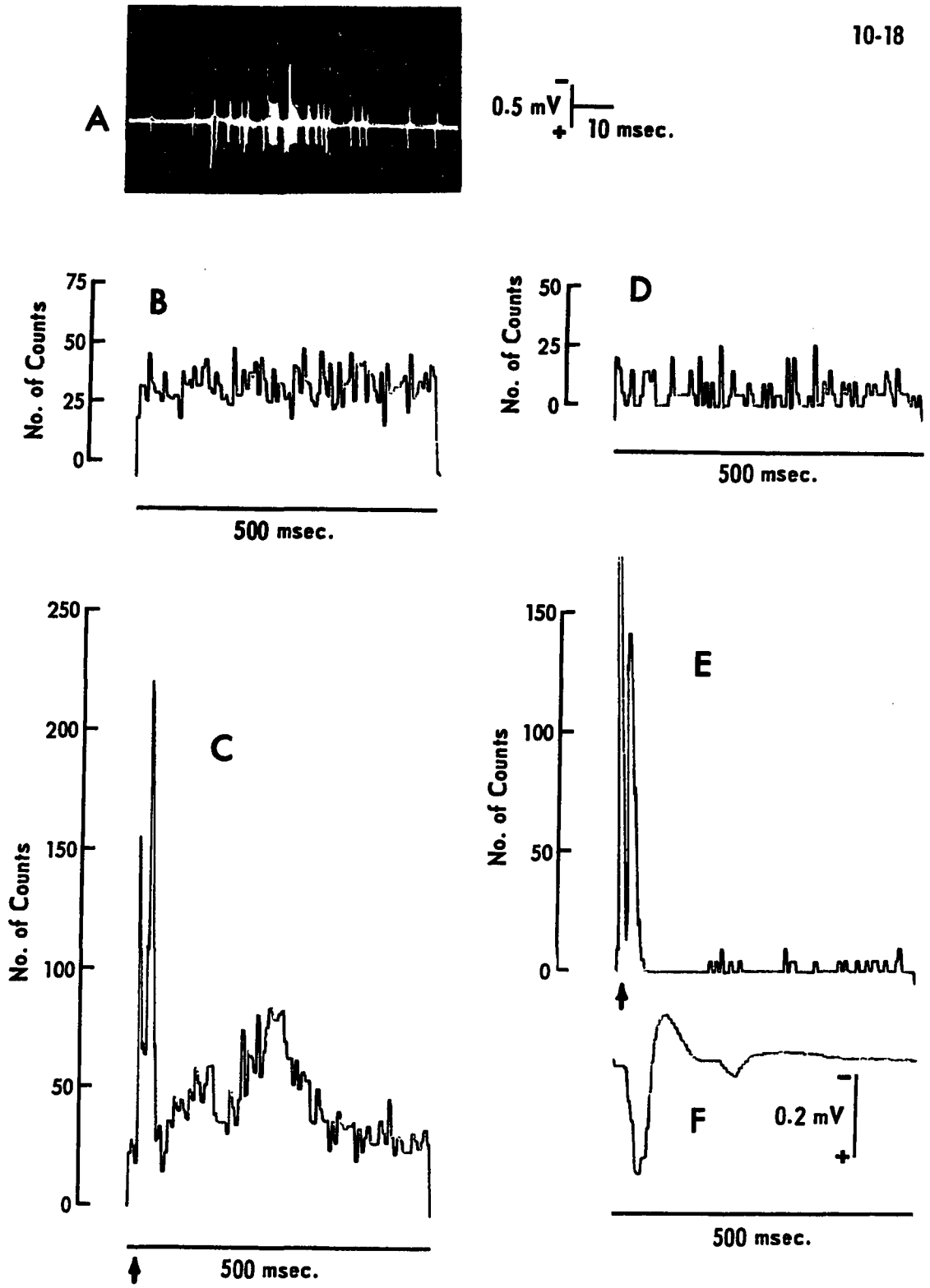


FIGURE 19. Data from two CM units recorded simultaneously, responding to stimulation of the ipsilateral RF. These units were analyzed by means of amplitude discrimination and subtraction with the CAT. A: short latency response of the larger unit (12 msec). B,D: null histograms of the smaller and larger units, respectively. C: PST histogram for the smaller unit showing early and later activation peaks, the second peak corresponding in time with the period of inhibition of the larger unit. E: PST histogram of the larger unit. F: computer averaged slow wave response; factors influencing the correlation of unit and slow wave responses are discussed in the text. (A: 5 sweeps; B-E: 115 sweeps; F: 40 sweeps).

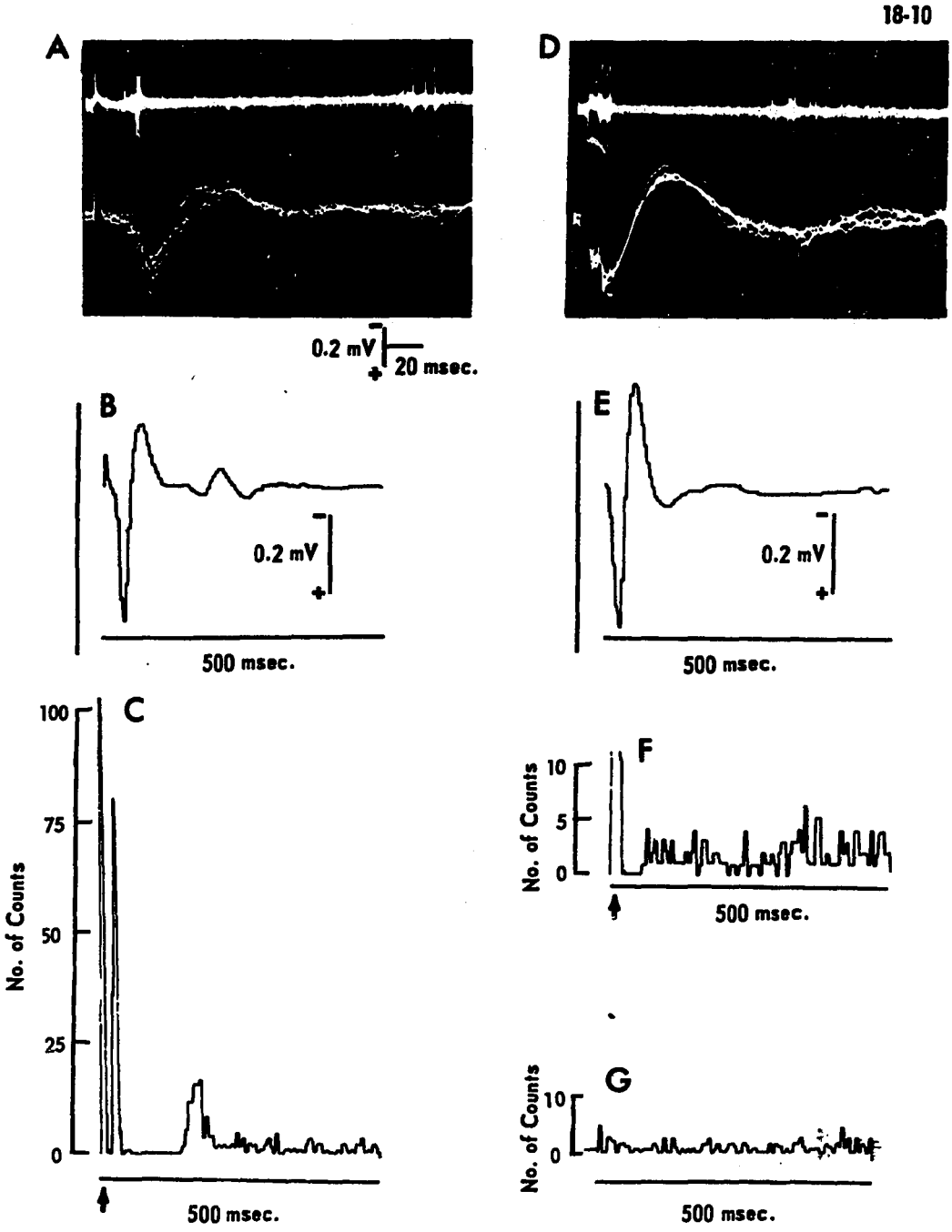


FIGURE 20. Unit-slow wave response correlation. A-C: contralateral forelimb stimulus. D-F: ipsilateral RF stimulus. G: null histogram. A,D: early unit response (upper trace) and simultaneous evoked potential. B,E: averaged evoked potential. C,F: PST histograms of unit activity. (A,D: 5 sweeps; B,E: 50 sweeps; C,F & G: 99 sweeps). See discussion in text.

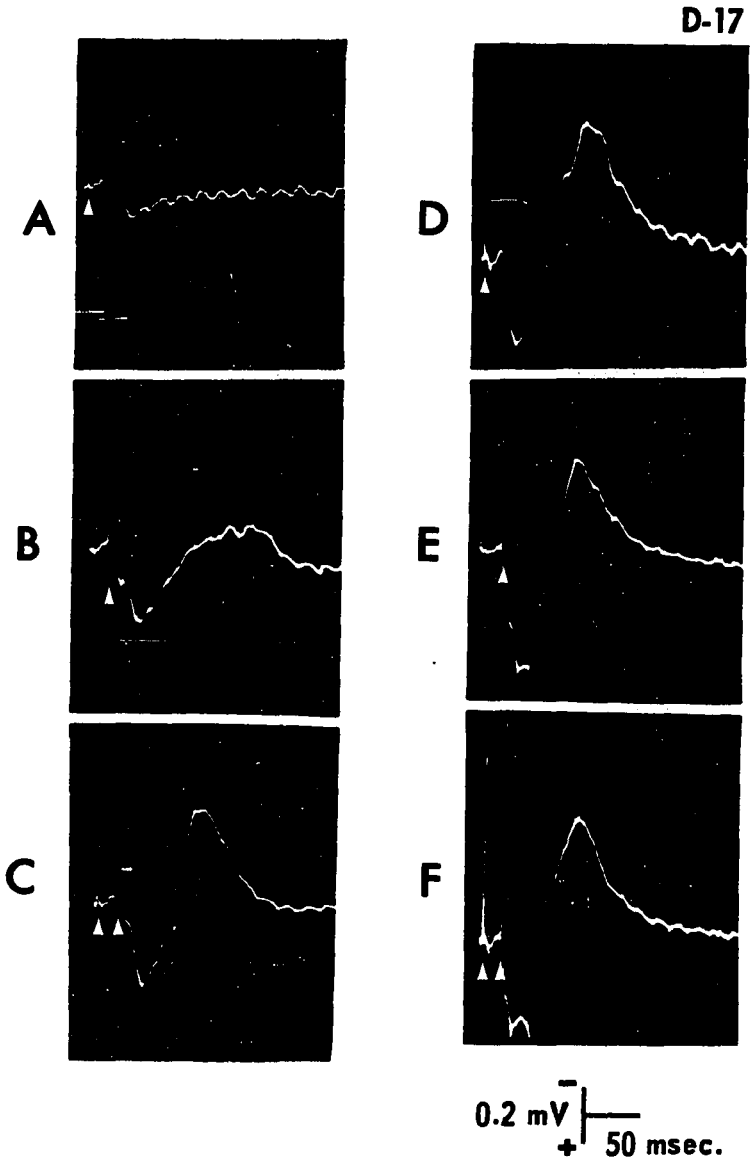
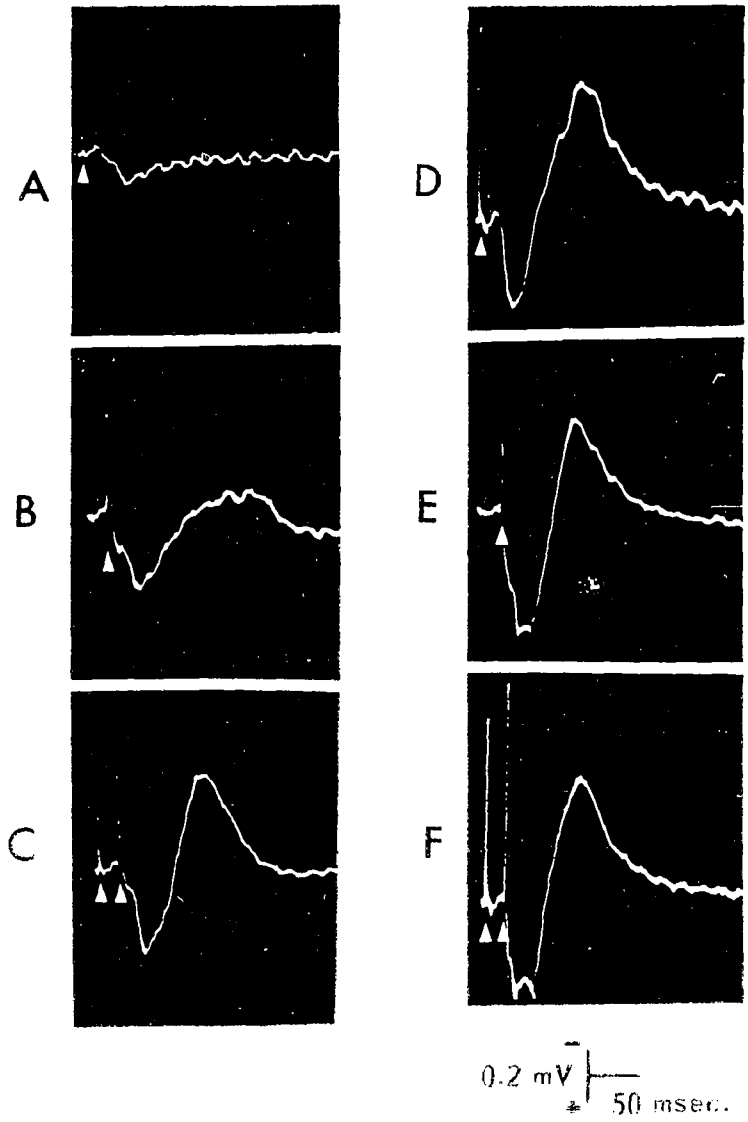


FIGURE 21. Convergence of forelimb spinoreticulothalamic pathway and midbrain RF projection in CM. A-C: facilitation using threshold stimuli; the area under the slow wave in C is greater than the sum of the slow waves in A & B. D-F: occlusion using 3 times threshold stimuli; the area under the slow wave in F is less than the sum of the slow waves in D & E. Stimulus delivered to contralateral forelimb in A & D, to ipsilateral RF in B & E and to both with a 14 msec interval between stimuli in C & F. Arrow indicates stimulus.


A
B
C
D
E
F
0.2 mV
50 msec.

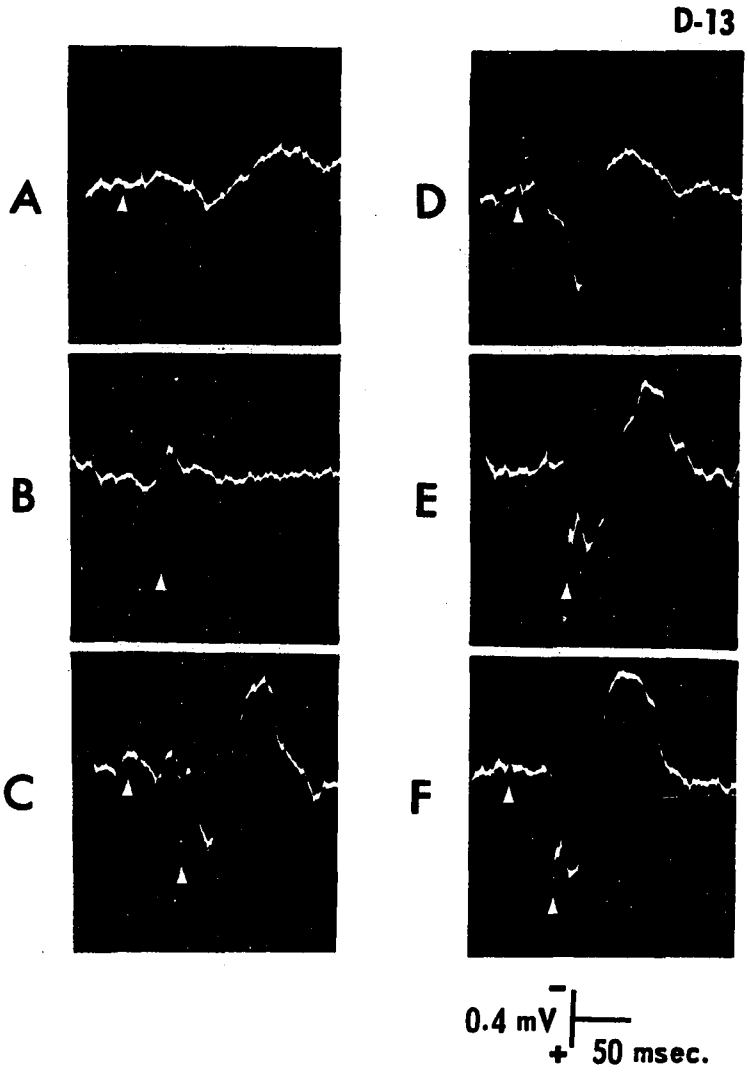
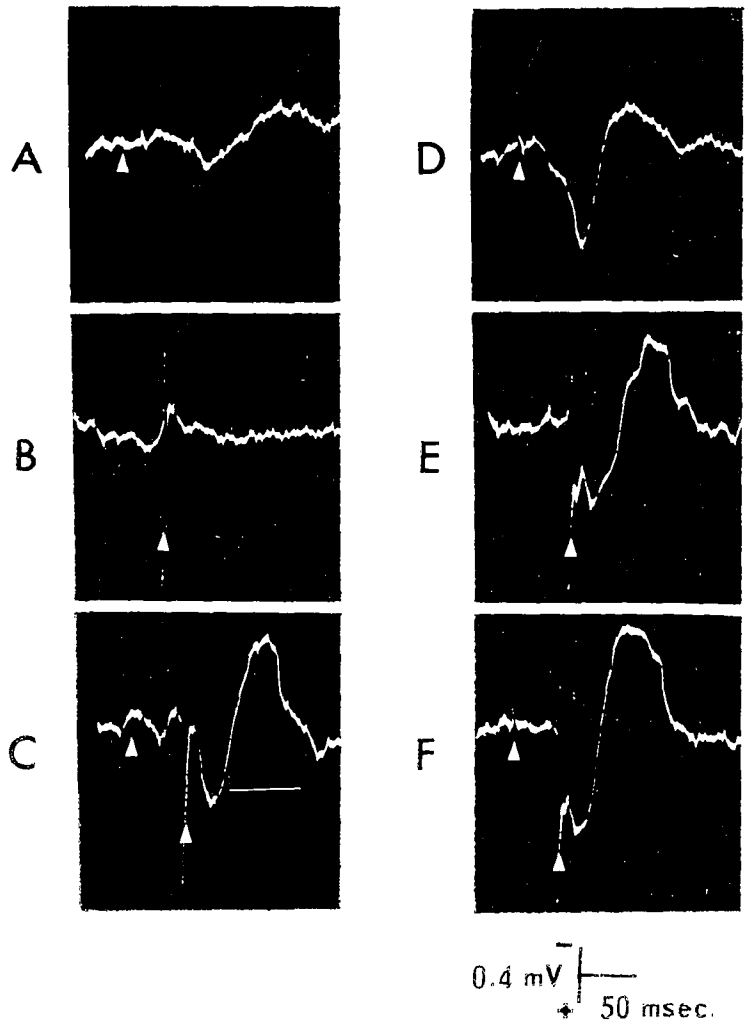


FIGURE 22. Convergence of hindlimb spinoreticulothalamic pathway and midbrain RF projection in CM. A-C: facilitation. D-F: occlusion. Same criteria as in Fig. 21. Stimulus delivered to contralateral hindlimb in A & D, to ipsilateral RF in B & E and to both with 35 msec interval between stimuli in C & F. Arrow indicates stimulus.


A
B
C
D
E
F
0.4 mV
50 msec.

area under the slow wave is the important parameter in the demonstration of facilitation and occlusion in multisynaptic pathways such as the spinoreticular and reticulo-thalamic systems (Ruch, et al, 1965). In the present experiments inspection of the evoked potentials revealed obvious facilitation and occlusion and actual measurements of the areas of the slow waves was unnecessary.

For both facilitation and occlusion the peripheral stimulus was delivered first as the conditioning stimulus, followed at varying intervals by the test stimulus delivered to the midbrain RF. The evoked potentials in CM were recorded by the microelectrode. Threshold stimuli were used to demonstrate facilitation. To demonstrate occlusion stimuli capable of evoking the maximal slow wave response were used, stimuli of 2-3 times threshold intensity. The appropriate interval between conditioning and test stimuli was predicted by subtracting the latency of the RF to CM evoked potential from the latency of the limb to CM evoked potential. In all cases the predicted results agreed well with the empirical data. The interpretation of these data is discussed below (see CONVERGENCE IN NUCLEUS CENTRE MEDIAN).

SPINORETICULOTHALAMIC PATHWAY

Whether the classical spinoreticular pathway, the "ground bundles" of Bechterew, (Nauta and Kuypers, 1958; Mehler et al, 1960) may be further subdivided in the future is at present a matter for speculation. Physiological studies have underscored the apparent overlap of "reticular" and "pain" pathways which, along with spinocerebellar fibers occupy the ventrolateral funiculus of the cord. Cerebellectomy effectively eliminates the spinocerebellar tracts as possible contributors to the reticular evoked potentials, the slow waves and unit responses being found in both the bulbar and midbrain RF after cerebellectomy (Pompeiano and Swett, 1962, 1963). It has been, however, more difficult to distinguish between the contributions of the classical pain pathway, the lateral spinothalamic tract on the one hand and the spinoreticular pathway on the other. Not only are these two systems located in the same fiber bundle of the cord, their impulses are conducted over similar nerve fibers, the smallest myelinated cutaneous and muscle afferents of 1-6 micra diameter (Group III), (Pompeiano and Swett, op cit). Mehler et al (1960) have discussed this question in detail and point out that the surgical procedure of anterolateral cordotomy performed for the relief of intractable pain will cause massive terminal degeneration in the reticular core of the medulla (nucleus gigantocellularis) as well as more rostral structures in the midbrain RF and the thalamus. This point illustrates the difficulty distinguishing between the spinoreticular and the pain pathways on either anatomical or physiological grounds.

DISCUSSION

In the present study the slow wave evoked in the midbrain RF by peripheral stimulation was not studied in great detail. The potential was mapped only in its vertical extent at the frontal 3.0, lateral 3.0 planes. The maximum amplitude of the slow wave was found well within the boundaries of the nucleus subcuneiformis, dorsal to the red nucleus. The threshold and latency of this response are consistent with transmission over a small fiber (Group III) system. The antegrade degeneration studies reviewed above indicate that the lateral spinothalamic tract and the lateral parvocellular relays within the brainstem (Nauta and Kuypers, 1958), sending fibers medially to join the ascending reticular system, conduct the majority of the spinal afferent volley which evoke the midbrain RF slow wave. However, the nature of the intrinsic organization of the reticular core multiplies the occasion for interaction between the spinoreticular and the lateral spinothalamic tracts so that it may be difficult to consider them separately in a physiological context.

Ascending pathways from the brain stem RF to the intralaminar nuclei have been demonstrated by a number of investigators (Nauta and Kuypers, 1958; Scheibel and Scheibel, 1958; Johnson, 1957; and others). In fact these authors have been most impressed by the ascending reticular system which arises in the nucleus gigantocellularis of the medulla, the so-called tractus fasciculorum of Forel.

Unfortunately, the anatomical studies have been inconsistent on this point. Mehler (1966), while emphasizing the lenticulothalamic loop, putamen-globus pallidus-CM-putamen, so

clearly demonstrated by terminal degeneration studies (Nauta and Mehler, 1966), has issued the most serious challenge to the idea of a brain stem reticular projection to CM. He argues that the degenerating fibers seen in CM are passing fibers and that the conclusion that the tractus fasiculorum of Forel contributes terminals to the CM is based upon misinterpretation "...resulting from errors in delimiting CM from adjacent principal and intralaminar nuclei" and upon careless reading of the anatomical texts. Mehler goes on to say, "Nauta and Kuypers (1958) report is frequently misquoted as supporting evidence for the existence of ascending afferent connections with the CM," (emphasis is Mehler's). The work of Nauta and Kuypers will stand on its own merits. As concerns the 1958 report, their description of the tractus fasciculorum of Forel states that,

> "The thalamic fiber group (of the tractus fasciculorum) ...enters the parafascicular-centromedian complex as a component of Papez' intrathalamic fasciculus, with which it continues into the rostrally adjacent nuclei paracentralis and centralis lateralis...Terminal degeneration is evident throughout its intralaminar trajectory." (Nauta and Kuypers, 1958) (Fig. 2).

These authors add that,

> "It appears certain that the midbrain reticular formation also contributes to the ascending pathways in Forel's tractus fasciculorum, but the technique followed in the present study did not lend itself to the reliable demonstration of such ascending midbrain projections."

The reticular projection to CM has been corroborated by other workers using the Golgi technique (Scheibel and Scheibel, 1958, 1967a). Mehler's other objection to the notion of a reticular projection to the CM involves the debate over the precise size and shape of the CM of the cat. This debate is

as yet unresolved, and is obviously of interest to all investigators concerned with the question of reticular efferent projections to the thalamus. The evidence for a projection from the brain stem RF which appears to terminate throughout the CM-Pf complex has been reviewed above. The question where CM leaves off and Pf begins must be regarded as a moot point for the present.

In the present study, estimates of the conduction velocity over the spinoreticulothalamic pathway have been made. The average length of the cat's spinal cord is approximately 250 mm (Albe-Fessard and Kruger, 1962). Considering the midbrain RF slow wave as a hypothetical terminus, the conduction velocity of the impulse mediating this slow wave may be calculated by using the latency difference obtained by subtracting the shortest latency (contralateral fore limb to midbrain RF) from the longest latency (ipsilateral hindlimb to RF). (The hindlimb and the forelimb are assumed to be of equal length). The latency difference, 7 msec, for the midbrain RF evoked potential, thus gives a value of approximately 36 m/sec for the spinal segment of the spinoreticular pathway. Applying the same procedure to the CM potential evoked by limb stimulation (latency difference = 8 msec) yields a conduction velocity of approximately 31 m/sec for the spinal segment of the spinoreticulothalamic pathway. These values are clearly consistent with conduction over a pathway composed of small myelinated fibers (group III) and are well within the values obtained by Pompeiano and Swett (1962) of

15.5-36 m/sec for the conduction velocity in peripheral nerve of the fibers (group III) which transmit the impulses that mediate EEG activation.

The conduction velocity of the reticulothalamic segment (midbrain RF to CM) may be calculated from the latency of the CM potential evoked by midbrain RF stimulation, 4 msec, and the distance between stimulating (midbrain RF) and recording (CM) electrodes, 4 mm. The conduction velocity is thus approximately 1.0 m/sec for the reticulothalamic segment of this ascending pathway. Even by using the shortest latency for the CM unit activation produced by midbrain RF stimulation, 2 msec, a conduction velocity of only about 2 m/sec is calculated.

Giving due consideration to the approximate nature of these calculations it is apparent that conduction over the reticulothalamic segment of the spinoreticulothalamic pathway is much slower than the conduction velocity in the cord. This slowing of the impulse must be accounted for by one or more of the following factors, smaller nerve fibers, different chemical transmitters or polysynaptic transmission. If Eccles' (1964) value of 0.3 msec for synaptic delay does indeed apply to these reticular structures, it would seem that several neurons may in fact participate in a reticulothalamic "chain". A similar difference between the conduction velocities within ascending fiber bundles in the cord and the ascending reticular system of the brain stem has been observed by other workers, whose reports may be compared with the data in the present study.

Albe-Fessard and Kruger (1962) estimated the intraspinal conduction velocity of the afferent impulse to CM to be approximately 50 m/sec basec on forelimb-hindlimb latency difference calculations. However, this value is larger than that obtained from the data of subsequent studies. The mean latencies they report for the response of CM units to peripheral stimulation (forelimbs = 18.9 msec; hindlimbs = 24.3 msec) are remarkably similar to the latencies reported by the same group for the response of units in the bulbar RF, the "bulbar relay to the centre median," (Bowsher et al, 1968) 18.1 msec and 26 msec, respectively. Using the latency difference obtained in the later study a conduction velocity of approximately 31 m/sec for the spinal segment of the spinoreticular pathway is calculated, a value similar to that obtained from the present data. It is also of interest that the study of Bowsher and his colleagues reports a 2 msec latency for the slow wave evoked in CM by stimulation of the bulbar RF; since the distance travelled by this impulse is about 15 mm, the conduction velocity is approximately 7.5 m/sec for the reticulothalamic course of this pathway. This slowing of the afferent impulse within the brainstem although considerable, is not, obviously, of the same magnitude as that reported in the present study.

These reports, along with the present data, support not only the conclusion that the various brain stem structures in the spinoreticulothalamic pathway may receive a common input, but that the "information" is handled differently by various reticular structures, viz., bulbar and midbrain RF,

the differences being reflected in the output of these reticular structures, even when the output being observed is that directed to a common destination, the CM. In figurative language, given a common message (the same stimulus), the bulbar RF (RGC) "tells" the CM one thing while the midbrain RF "tells" the CM something else; this does not imply that bulbar and midbrain RF are "contradicting" each other, but simply that complex reticular input undergoes a degree of refinement in the process of conversion to reticular output. This concept will be elaborated in the discussion of unit responses and convergence of impulses in CM.

UNIT RESPONSES IN THE NUCLEUS CENTRE MEDIAN

Earlier reports concerning the relationship of ascending afferent systems to the intralaminar nuclei and the nature of neuronal mechanisms within these nuclei have yielded much valuable data. However, the recent evolution in the concepts of structure and function in the brain stem reticular core and the "reticular" portions of the thalamus has brought to light several problems which limit the value of these earlier observations. There is, first a tendency to consider the intralaminar nuclei as a group, ignoring important anatomical differences between the individual nuclei. This tendency derives from the now inadequate concept of reticular structures (both brain stem and thalamic) as essentially "non-specific" or "diffusely projecting". As already discussed, CM has important efferent and afferent connections with the lenticular

nuclei, while nucleus centralis lateralis, for example, has no known connections with the basal ganglia. To assume that the data collected from one nucleus may be applied to the intralaminar group in general is no longer acceptable. A second problem which makes these data difficult to interpret is the practice of using high frequency stimulation of intralaminar thalamic nuclei as an equivalent of reticular "activation". Finally, the use of chloralose anesthesia makes impossible the observation of unit responses against a background of normal spontaneous activity.

In the present study chloralose anesthesia has been used primarily to facilitate the study of the slow potentials in CM evoked by peripheral and midbrain stimulation. All the CM units which were studied showed spontaneous activity. Unanesthetized encephale isolé preparations were used for the study of unit responses to midbrain stimulation.

The usual unit response to midbrain RF stimulation was early activation, often followed by a period of inhibition lasting up to 225 msec. The latency of the early activation (mean latency = 7.2 msec) suggests that the ascending fibers are very small or that the pathway is polysynaptic. The pattern of CM unit responses to stimulation of the midbrain RF observed in the present study, shows that inhibition is an important feature of this response. Thirty-one of the 60 units which responded to single shock stimulation of the midbrain RF displayed a pattern of early activation-inhibition; primary inhibition was seen in an additional 9 units. Thus,

some 67% of responsive units were inhibited at some time as a consequence of the stimulus delivered to the midbrain RF.

In their study of CM unit responses to peripheral stimulation Albe-Fessard and Kruger (1962) reported inhibition in only 11 of 181 responsive units. They raise the possibility that some of these units may have been injured, making interpretation of their data on inhibition difficult. Bowsher et al (1968) discussing the results of Albe-Fessard and Kruger (1962) and other investigators, suggests that, "...the proportion of units inhibited by peripheral stimulation decreases rostrally through the reticular formation and centre median." The main objection to this suggestion is that many of the studies cited in its support use data obtained from chloralose anesthetized animals. It has already been stated that a known effect of chloralose, reported by these same authors and observed in the present study as well, is the "silencing" of the spontaneous activity of many CM neurons. Whether intracellular or extracellular recordings are used it is impossible to make generalizations concerning the presence or absence of inhibitory responses in units whose spontaneous activity is markedly reduced or completely abolished by the anesthetic agent. In the present study when very low doses of chloralose were used, so that the spontaneous activity of the CM neurons did not appear to be significantly affected 7 of 10 units responding to peripheral stimulation exhibited a period of inhibition following the primary activation. This datum, although obviously not significant statistically casts serious doubt on the suggestion that inhibition from peripheral stimulation is not seen in more

rostral regions of the RF and the CM.

The significance of inhibition of CM units in response to both peripheral and midbrain RF stimulation is underscored by the correlation of the evoked slow potential with unit activity. The most prominent feature of the CM evoked potential is the positive component (Fig. 16). It is invariably present within the boundaries of CM. The earlier negative component associated with unit activation is variable in its appearance. Current theory explains the relationship of evoked potential to spike discharge in terms of the synaptic genesis of the evoked potential in multipolar dendritic cell populations (Rall, 1964, 1967). The negative component of the evoked potential reflects an excitatory input, a summation of EPSPs within the neuron pool; the positive component arises from summation of inhibitory synaptic potentials. Thus, the slow wave response is useful in predicting the sequence of unit discharge and inhibition.

The activation-inhibition responses observed in the present study are most easily explained in terms of recurrent inhibition through axon collaterals to near-by inhibitory interneurons. Microelectrode recordings within both specific and nonspecific nuclei of the thalamus have suggested that this neuronal mechanism is operative in the development of rhythmic unit discharge associated with EEG recruitment and perhaps other states of EEG rhythmicity such as sleep spindles and barbiturate spindles (Andersen and Eccles, 1962;

Andersen, 1966). Both spontaneously occuring and evoked rhythmic oscillations of the membrane potential were observed by these investigators during periods of rhythmic neuronal spiking. Large IPSPs alternated with EPSPs during which the neuron discharged one or more spikes. These authors invoke the mechanism of recurrent inhibition through interneurons to explain the large IPSPs which seem to be essential for the development of rhythmic spiking in a neuron. A computer model of this system produced the predicted result.

An alternative explanation of this inhibition, worthy of consideration, is that advanced by Scheibel and Scheibel (1966, 1967b). They have shown in Golgi material that axons of the nucleus reticularis of the thalamus project backward upon the specific and nonspecific thalamic nuclei, as far caudalward as the CM-Pf complex. On the other hand, ascending axons of all the thalamic nuclei must traverse the neuropil of the nucleus reticularis. The Scheibels propose that the nucleus reticularis functions as a band pass filter, suppressing high frequency patterns which enter it, essentially a long loop negative feedback mechanism. It has been reported that most of the neurons of the nucleus reticularis adjacent to the lateral geniculate nucleus fire in bursts of (mean) 132 msec duration with a burst frequency of 4.5/sec (Negishi et al, 1962). Other workers (Bowsher et al, 1968) have observed that a single shock delivered anywhere on the body may suppress the CM evoked potential for up to 500 msec

(conditioning-test shock technique), and that CM units will follow peripheral stimuli only up to a frequency of 3-4/sec. These data together with the activation-inhibition pattern observed in the present study of CM units would be quite consistent with the Scheibels' theory. This theory assumes, of course, that the pattern of firing described by Negishi and his co-workers is found throughout the nucleus reticularis; the other assumption is that the reticularis neurons exert an inhibitory effect on other thalamic neurons. To the writer's knowledge neither of these points can be considered proven at the present time.

Anatomical studies are inconclusive as regards the intrinsic organization of the CM. Whereas Bowsher (1966) reported a profusion of axosomatic synapses (thought by some to be inhibitory synapses, (Eccles, 1964))within CM, Pappas et al (1966) report finding few such synapses in an electron microscopic study of intralaminar nuclei; they do report, however, a certain number of axoaxonal synapses in the intralaminar nuclei, including CM. The present data are insufficient to indicate exactly what inhibitory mechanism is operating in CM. It is likely that in the present study a postsynaptic inhibitory mechanism is operative. However, whether this inhibition is mediated by local interneurons or by the long chain negative feedback loop postulated by the Scheibels cannot be ascertained.

CONVERGENCE IN NUCLEUS CENTRE MEDIAN

Convergence of a spinal extralemniscal afferent pathway and an ascending reticular pathway from the midbrain tegmentum, has been demonstrated by facilitation and occlusion of the evoked potential in CM and by the responses of CM units (Figs. 12, 21, 22). Anatomical studies show that there are two pathways for the ascending reticular impulses; these pathways are separated in the lower brain stem but become intermingled as the ascending reticular system, Forel's tractus fasciculorum, reaches midbrain levels. The nucleus gigantocellularis of the medulla has been shown by Bowsher et al (1968) to be an important relay of the spinoreticulothalamic pathway which transmits the impulses responsible for the CM potential evoked by limb stimulation. These investigators have shown that when nucleus gigantocellularis is inactivated by local cooling the CM slow wave evoked by limb stimulation is considerably diminished in amplitude. Anatomical studies are consistent with the view that nucleus gigantocellularis is the major relay in the spinoreticulothalamic pathway; this nucleus has long been recognized as one of the largest of the reticular nuclei (Kohnstamm and Quensel, 1908; Taber, 1961), and its ascending axons form the major part of the ascending reticular system (Nauta and Kuypers, 1958).

The lateral parvocellular regions of the caudal brain stem, the ventral collateral plexus of Thiele and Horsley, is the relay for a smaller group of spinoreticular fibers,

some of which make synapses in the midbrain RF (nucleus subcuneiformis) which in turn contributes axons to the final segment of this spinoreticulothalamic pathway. The lateral spinothalamic tract also contributes axons which join the ascending reticular system throughout the length of the brain stem; some of the lateral spinothalamic tract fibers terminate in nucleus subcuneiformis of the midbrain. Thus a minor component of the ascending reticular system arises from the lateral parvocellular zone and the lateral spinothalamic tract. This minor segment is probably the anatomic substrate of the slow potential evoked in the midbrain RF by limb stimulation.

In spite of the anatomical data pointing to two separable pathways in the ascending reticular system, the physiological data in the present study must be interpreted cautiously. It is recognized that the two pathways so clearly seen in more caudal brain stem structures become intermingled at midbrain levels. Thus a stimulus delivered to the midbrain RF (nucleus subcuneiformis) might be activating passing fibers of the central tegmental tract which originated in the "bulbar relay" to CM, the nucleus gigantocellularis of the medulla, in effect stimulating the same spinoreticulothalamic pathway at a higher level. The definition and criteria for convergence must be considered in this context.

The classical experiments demonstrating convergence by facilitation and occlusion of the evoked potential used spinal cord reflexes, relatively simple, monosynaptic reflexes in homogeneous cell populations. It is reasonable to wonder

whether these principles can be safely applied to a system as complex as the spinoreticulothalamic system. It might be argued that no reticular pathway may be considered a single isolated tract because of the inherent diffuseness and polysynaptic nature of the pathway. If this were true, stimuli delivered to any two loci along the pathway might seem to result in spatial summation, because no single stimulus would be capable of activating the entire reticular pathway. In the present study, occlusion of the CM evoked potential eliminates this possibility. Clearly, a high intensity stimulus (3 times threshold) to any of the limbs was capable of maximally exciting the receptive neuron pool in CM, so that the addition of the midbrain reticular stimulus resulted in occlusion.

The present data do not eliminate the possibility that the facilitation and occlusion of the CM evoked potential might result from temporal summation of stimuli delivered to the same pathway at two different loci. It appears that in fact neurophysiological methods are of limited value in resolving a problem of this kind. An attempt to separate the two pathways physiologically by making a lesion in one of them would fail to yield conclusive data because the size of the required lesion would result in inadvertent destruction of both pathways.

Thus, the evidence of the present data support the interpretation that the converging impulses to CM are mediated by two separate pathways, but this cannot be considered as proven. The evoked potential in nucleus subcuneiformis, the site of the midbrain stimulation, implies a synaptic event

mediated by the minor, lateral ascending reticular pathway of the spinoreticular system (Nauta and Kuypers, 1958). The CM slow potential evoked by stimulation of this region appears to be mediated by the aforementioned post-synaptic elements (neurons of nucleus subcuneiformis) rather than passing fibers from RGC of the medulla for the following reasons. First, several units showed different responses to midbrain stimulation on the one hand and to peripheral stimulation on the other (Figs. 12 and 14). These responses, although different, are within the limits of what might be predicted from analysis of the slow wave response. These unit responses are not easily explained in terms of stimuli delivered to the same pathway at different loci. Second, the difference between the reticulothalamic conduction velocity reported here for the midbrain projection to CM and that calculated from the data of Bowsher and his colleagues (1968) for the bulbar realy to CM, suggest that two separate pathways convey extralemniscal somatosensory impulses to the CM.

FUNCTIONAL CONSIDERATIONS

The significance of the reticular projection to CM must be considered in terms of several apparently inter-related functional systems. The ascending reticular activating system of Moruzzi and Magoun (1949), the pain pathway, overlapping in the brainstem with the spinoreticulothalamic systems, the "extrapyramidal" motor system have each been implicated in the function of either the midbrain RF, CM or both.

The electrophysiological correlates of sleep and arousal have been studied by many investigators over the past 40 years. One aspect of this subject, EEG rhythmicity, was recently reviewed by Needham and Dila (1968). In view of the well known relationship of the brain stem RF with arousal and EEG low voltage fast activity, and the equally well established relationship of the intralaminar nuclei with sleep and high voltage rhythmical cortical activity, it is not unreasonable to wonder whether the reticulothalamic systems which terminate in CM may influence brain rhythms. Indeed, Purpura et al (1962, 1966) have shown that the large IPSPs associated with the rhythmic spiking of specific and intralaminar neurons in the thalamus are attenuated by high frequency stimulation of more caudal intralaminar structures. These authors propose the inhibition of inhibition ("disinhibition") as the thalamic mechanism operative in cortical activation.

Several difficulties are encountered in attempting to compare the results of Purpura and his colleagues with the data in the present study. First, their recordings were made from neurons in more rostral intralaminar nuclei and their data do not necessarily apply to units in the CM. Whether the same neural mechanisms are operative in all the intralaminar nuclei remains to be proven. Second, while their responses are attributed to the reticulocortical activating system, the same may be said of the present study. However, the locus of the stimulus and the stimulus parameters are different in the two studies, Purpura and his group using high frequency stimulation of the caudal intralaminar nuclei (CM-Pf complex) as an equivalent of stimula-

tion of the reticular activating system, and the present study relying on data from single shock stimulation of the midbrain RF. Thus, it is difficult to reconcile the different results obtained in the present study (inhibition of CM units by midbrain RF stimulation) with those obtained by Purpura and his colleagues (disinhibition of intralaminar neurons by high frequency stimulation of the caudal intralaminar nuclei, ostensibly reticulocortical activation). The objections to the use of high frequency stimulation of thalamic structures as an equivalent of reticular stimulation have been discussed above (see PHYSIOLOGY OF THE ASCENDING RETICULAR SYSTEMS). This practice is based on an over-simplification of the differences between the "activating" and "synchronizing" systems of the brain stem, to wit, that they are adequately distinguished in terms of stimulus frequency alone. That thalamic "activation" results from high frequency stimulation of regions which, when stimulated at low frequency produce rhythmic high voltage waves on the cortex, cannot be doubted. However, the differences between thalamic and reticular "activation" reviewed above suggest that high frequency stimulation of the intra-laminar thalamus may in effect be a stimulation of both the synchronizing and the desynchronizing systems, and responses to this kind of stimulation must be interpreted with caution.

Thus, the question whether the reticulothalamic fibers terminating in CM influence brain rhythms is a complex question. It cannot yet be answered satisfactorily. Insofar as the ascending reticular activating system is concerned, the best evidence to date suggests that the impulses which

mediate cortical low voltage fast activity (and presumably arousal) are conveyed over the ventral, subthalamic lamella, rather than the thalamic lamella of the ascending reticular system (reviewed by Scheibel and Scheibel, 1967a).

Fibers of the lateral spinothalamic tract, the classical "pain" pathway have been shown to be intimately related with the brain stem reticular core. These fibers join the ascending reticular system, terminate in the midbrain tegmentum and even reach the CM (Nauta and Kuypers, 1958). A thorough discussion of the physiology of pain will not be undertaken here, but one interesting work will be mentioned. Casey (1966) reported that systematic exploration of the thalamus of the squirrel monkey revealed no units that responded exclusively to noxious stimuli. Some of the thalamic units (including some in the intralaminar nuclei) responded in a different manner to noxious and to innocuous stimuli. This finding is consistent with the difficulties that have plagued investigators who have attempted to "localize" pain in the central nervous system. One must conclude that the perception of pain rests on complex integrations of varied sensory input. The mutual overlap of pain pathways with spinoreticulothalamic systems must imply some degree of functional interdependence.

The amount of attention devoted to the role of the intralaminar nuclei in the mechanisms of sleep, arousal and electro-

graphic brain rhythms has obscured the fact that the CM has important connections with motor systems of the forebrain. The CM receives input from the motor cortex and globus pallidus, and is the origin of a large projection to the putamen (Mehler, 1966; Rinvik, 1968b). The convergence in CM of extralemniscal reticular projections, demonstrated and discussed in the present study, provides a physiological substrate for a complex sensorimotor integrating mechanism.

Over the past few years the need for a broad theory of reticular function has become increasingly urgent. Such a theory would be required to propose the neural mechanisms by which the brain stem RF processes the input fron numerous, sometimes overlapping somatic and special sensory systems, (an input lacking in somatotopic specificity) and converts the input into an ascending and descending output, the most prominent behavioral feature of which is arousal. Differences in the output of different regions of the brain stem RF, given a similar or even an identical input (stimulus) have been reported. Looking only at the criterion of EEG low voltage fast activity, Bonvallet and Newman-Taylor (1967) showed that a high frequency stimulus delivered to the rostral midbrain RF produced a brief period of cortical "activation" but that an identical stimulus delivered to the rostral pontine tegmentum produced a long-lasting period of cortical "activation". The present study show that there are differences in the responses of CM units to stimulation of the midbrain projection on the one hand, and to stimulation

of the spinoreticulothalamic projection to CM on the other.

The application of cybernetic theory to the neural mechanisms operative in the reticular core has recently been attempted (Kilmer et al, 1968). This theory is based on current neuroanatomical and physiological evidence. The fundamental assumption is that the function of the brain stem RF is to put the animal into one of several mutually exclusive "modes" of behavior, for example, eating, drinking, fighting, copulating etc. Kilmer and his colleagues have constructed a schematic model of the reticular formation, based on the intrinsic organization of the RF revealed in Golgi studies (see INTRINSIC ORGANIZATION OF THE BRAIN STEM RETICULAR CORE above). Their model consists of a series of identical, interconnected "modules"; each module, being capable of "looking at" the overall input in general, can at the same time "look at" some specific aspect of the input in detail. In effect the individual modules sample the input and then by a rapid succession of "consultations", derive a single output by consensus. It must be emphasized that this "single output" is in fact a complex of outputs both ascending and descending from the RF, viewed at a single moment in time; the implication is that this complex output is working in concert to place the animal into a single, exclusive behavioral mode.

The application of cybernetic theory to the problem of the function of the brain stem RF is a salutary development in brain research. Without deceiving himself with illusions of facile solutions to hitherto insoluble problems through the

"multidisciplinary" approach, the investigator who has applied the traditional tools of neurophysiological technique to the complex system known as the reticular core soon becomes aware of the limitations of his method. Where the traditional methods answered traditional questions with certainty, the nature of many modern questions determines that the answer be expressed in terms of probability.

The present study has characterized in terms of probability one small fraction of the ascending reticular output, the projection to CM. The relationship of this projection and the spinoreticulothalamic system is suggested on the basis of the present data. The ultimate proof of this relationship depends on the eventual neurophysiological isolation of the various afferent pathways that comprise the reticular input. Although cybernetic theory has provided a unifying concept of reticular function, useful as an inclusive working hypothesis, the elucidation of brain pathways remains a neurophysiological problem of fundamental importance.

CONCLUSIONS

CONCLUSIONS

1. The slow potential in the region of the nucleus subcuneiformis of the midbrain evoked by peripheral stimulation is confirmed. Neuroanatomical studies by other workers indicate that the impulses mediating this potential are conducted over a relatively small portion of the ascending reticular system. Its spinoreticular fibers have synapses in the lateral parvocellular zone of the medulla. Fibers arising in the "ventral collateral plexus" of Thiele and Horsley and the "dorsal trigeminal tract" of Wallenberg are joined by fibers of the lateral spinothalamic tract, the classical "pain" pathway. This heterogeneous pathway ascends in the brain stem parallel to the larger tractus fasciculorum of Forel, and makes synapses in the midbrain tegmentum in the nucleus subcuneiformis.

2. The slow potential which is evoked in CM by peripheral stimulation is mediated by the "bulbar relay" (the tractus fasciculorum of Forel) as shown by Bowsher and his coworkers. The bulbar reticular projection to CM may be considered proven, anatomically.

3. A midbrain projection to the CM arising in the region of the nucleus subcuneiformis is demonstrated by CM unit responses and the CM slow potential evoked by midbrain RF stimulation.

4. Inhibition is a prominent feature of CM unit responses to single shock stimulation of both the midbrain RF and the limbs. Inhibition was seen in 67% of units which responded to stimulation of the midbrain RF. The most common unit response pattern seen was early activation followed by inhibition; the data are insufficient to determine the precise mechanism operating in the neuronal inhibition.

5. Both peripheral and midbrain stimulation evoke an identical slow wave in CM. The natural stimulus which also produces this CM evoked potential is a pin prick or a light, brusque, mechanical tap. Electrical or natural stimulation of any of the limbs evokes the CM slow potential; there is no evidence of somatotopic organization of this response.

6. The spinoreticulothalamic (via the "bulbar relay") pathway and the midbrain reticulothalamic pathway converge upon common neural elements in CM as demonstrated by the facilitation and occlusion of the evoked potential. The evidence supports the conclusion that the converging impulses are mediated by two separate ascending reticular pathways, but the possibility that the convergence may be explained in terms of temporal summation in a single spinoreticulothalamic pathway cannot be excluded.

7. The CM receives input from several extralemniscal sensory systems, generally considered as spinoreticular systems. The CM also receives input from the globus pallidus and projects fibers to the putamen. Within the CM, complex extralemniscal sensory information may be integrated into the operations of major subcortical motor systems.

BIBLIOGRAPHY AND ACKNOWLEDGEMENTS

BIBLIOGRAPHY

Akimoto, H. and Saito, Y.: Synchronizing and desynchronizing influences and their interactions on cortical and thalamic units. In: Progress in Brain Research. 21A. Correlative Neurosciences. Part A: Fundamental Mechanisms, T. Tokizane, and J. Schadé (Eds), Elsevier Publishing Co., Amsterdam, 1966, pp.323-351.

Akimoto, H.; Yamaguchi, N.; Okabe, K.; Nakagawa, T.; Nakamura, I.; Abe, K.; Torri, H. and Masahashi, K.: On the sleep induced through electrical stimulation on dog thalamus. Folia Psychit. Neurol., Japan, 1956, 10:117-146.

Albe-Fessard, D. and Kruger, L.: Duality of unit discharges from cat centrum medianum in response to natural and electrical stimulation. J. Neurophysiol., 1962, 25:3-20.

Amassian, V. and Waller, H.: Spatiotemporal patterns of activity in individual reticular neurons. In: Reticular Formation of the Brain. H. Jasper, L. Proctor, R. Knighton, W. Noshay and R. Costello, (Eds), Little Brown and Co., Boston, 1958, pp.69-110.

Andersen, P.: Rhythmic 10 per sec activity in the thalamus. In: The Thalamus, D. Purpura and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.143-151.

Andersen, P. and Eccles, J.C.: Inhibitory phasing of neuronal discharge, Nature, 1962, 196:645-647.

Andersen, P. and Sears, T.A. The role of inhibition in the phasing of spontaneous thalamo-cortical discharge. J. Physiol. (London), 1964, 173:459-480.

Berger, H. Uber das Electrenkephalogramm des Menschen II. J. Physiol. Neurol., 1930, 40:160-179.

Bonvallet, M. and Newman-Taylor, A.: Neurophysiologic evidence for a differential organization of the mesencephalic reticular formation. Electroenceph. clin. Neurophysiol., 1967, 22:54-73.

Bowsher, D.: The termination of secondary somatosensory neurons within the thalamus of Macaca mulatta: An experimental degeneration study. J. Comp. Neur., 1961, 117-213.

Bowsher, D.: Some afferent and efferent connections of the parafascicular-center median complex. In: The Thalamus, D. Purpura and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.99-108.

Bowsher, D.; Mallart, A.; Petit, D. and Albe-Fessard, D.: A bulbar relay to the centre median. J. Neurophysiol., 1968, 31:288-300.

Bremer, F.: The neurophysiological problem of sleep. In: Brain Mechanisms and Consciousness. A Symposium. J. Delafresnaye, (Ed), Blackwell Scientific Publications, Oxford, 1954, pp.137-162.

Brodal, A.: The Reticular Formation of the Brainstem. Anatomical Aspects and Functional Correlations. Oliver and Boyd, Edinburgh, 1957.

Brodal, A.: Anatomical points of view on the alleged morphological basis of consciousness. Acta Neurochir., 1964, 12:166-186.

Brodal, A. and Rossi, G.: Ascending fibers in brain stem reticular formation of the cat. Arch. Neurol. Psychiat. Chicago, 1955, 74:68-87.

Brown, J.O.: The nuclear pattern of the non-tectal portions of the midbrain and isthmus in the dog and cat. J. Comp-Neurol., 1943, 78:365-406.

Cajal, S. Ramon y.: Histologie du Système Nerveux de l'Homme et des Vertébrés. Maloine, Paris, Tome II, 1911.

Casey, K.L.: Unit analysis of nociceptive mechanisms in the thalamus of the awake squirrel monkey. J. Neurophysiol., 1966, 29:727-750.

Castaldi, L.: Studi sulla struttura e sullo sviluppo del mesencefalo. Ricerche in Cavia cobaya. Parte prima. Arch. Ital. di Anat. e di Embriol., 1923, 20:23.

Clarke, W. and Bowsher, D.: Terminal distribution of primary afferent trigeminal fibers in the rat. Exp. Neurol., 1962, 6:372-383.

Collins, W. and O'Leary, J.: Study of a somatic evoked response and midbrain reticular substance. Electroenceph. clin. Neurophysiol., 1954, 6:619-628.

Collins, W.F. and Randt, C.T.: Evoked central nervous system activity related to peripheral unmyelinated of 'C' fibers in the cat. J. Neurophysiol., 1958, 21:345-352.

Dempsey, E. and Morison, R.: The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. Amer. J. Physiol., 1942, 135:293-300.

Dreifuss, J.J.; Murphy, J.T. and Gloor, P.: Contrasting effects of two identified amygdaloid efferent pathways on single hypothalamic neurons. J. Neurophysiol., 1967, 31: 237-248.

Eccles, J.: Postsynaptic and presynaptic inhibitory action in the spinal cord. In: Progress in Brain Research. Vol. 1, Brain Mechanisms. G. Moruzzi, A. Fessard and H. Jasper, (Eds), Elsevier Publishing Co., N.Y. 1963, pp.1-18.

Eccles, J.C.: The Physiology of Synapses. Academic Press Inc., New York, 1964.

Fox, S.S. and O'Brien, J.H.: Duplication of the evoked potential waveform by curve of probability of firing of a single cell. Science, 1965, 147:888-890.

French, J.; Verzeano, M. and Magoun, H.: An extralemniscal sensory system in the brain. AMA Arch. Neurol. Psychiat., 1953, 69:505-518.

Gerstein, G.L.: Neuron firing patterns and the slow potentials. Electroenceph. clin. Neurophysiol., 1961, 20:68-71.

Gerstein, G.L.: Analysis of firing patterns of the single neurons. Science, 1960, 131:1811-1812.

Held, H.: Beitrage zur feineren anatomie des kleinhirns und des Hirnstammes. Arch. Anat. Physiol., Lpz. (Anat. Abt.) 1893, pp. 435-446. Cited by Brodal, A. The Reticular Formation of the Brain Stem. Anatomical Aspects and Functional Correlations, p.23. Oliver and Boyd, Edinburgh, 1957.

Hess, W.: The diencephalic sleep centre. In: Brain Mechanisms and Consciousness. A Symposium. J. Delafresnaye (Ed). Blackwell Scientific Publications, Oxford, 1954, pp.117-136.

Hubel, D.: Tungsten microelectrodes for recording from single units. Science, 1957, 125:549-550.

Hugelin, A. and Bonvallet, M.: Tonus cortical et contrôle de la facilitation motrice d'origine réticulaire. J. Physiol., (Paris), 1957, 49:1171-1200. Cited by Schlag, J. and Chaillet, F. Thalamic mechanisms involved in cortical desynchronization and recruiting responses. Electroenceph. clin. Neurophysiol., 1963, 15:39-62.

Jacobsohn, L.: Ueber die Kerne des menschlichen Hirnstammes (der Medulla oblongata, des Pons und des Pedunculus). Beurol. Centralbl., Bd. 28, S.674 (1909). Cited by, Kappers, Huber and Crosby, The Comparative Anatomy of the Nervous System of Vertebrates Including Man. The MacMillan Co., N.Y., (Chapter VI, the Coordinating Apparatus), 1936, Vol. 1.

Jasper, H.: Recent advances in our understanding of ascending activities of the reticular system. In: Reticular Formation of the Brain. H. Jasper, L. Proctor, R. Knighton, W. Noshay and R. Costello, (Eds), Little, Brown and Co., Boston, 1958, pp.319-331.

Jasper, H.: Diffuse projection systems: the integrative action of the thalamic reticular system. Electroenceph. clin. Neurophysiol., 1949, 1:405-420.

Jasper, H. and Ajmone-Marsan, C.: A Stereotaxic Atlas of the Diencephalon of the Cat. The National Research Council of Canada, Ottawa, 1954.

Jasper, H. and Ajmone-Marsan, C.: Thalamocortical integrating mechanisms. In: Patterns of Organization of the Central Nervous System. Res. Publ. Ass. Nerv. Ment. Dis., 1952, 30:493-512.

Jasper, H.H.; Ajmone-Marsan, C. and Stoll, J.: Corticofugal projections to the brain stem. Arch. Neurol. Psych., (Chicago), 1952, 67:155-166.

Kappers, C.U.A.; Huber, G.C. and Crosby, E.: The Comparative Anatomy of the Nervous System of Vertebrates Including Man. The MacMillan Co., N.Y., (Chapter VI, The Coordinating Apparatus), 1936, Vol. 1.

Kilmer, W.L.; McCulloch, W.S. and Blum, J.: Towards a theory of the reticular formation. In: The Mind: Biological Approaches to Its Functions. W.C. Corning and M. Balaban, (Eds), Interscience Publishers (John Wiley & Sons), N.Y., 1968, pp.177-232.

Klee, M.: Different effects on the membrane potential of motor cortex units after thalamic and reticular stimulation. In: The Thalamus, D. Purpura and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.287-322.

Kohnstamm, O.: Studien zur physiologischen Anatomie des Hirnstammes. 3. Die tigrolytische Methode nebst Beispielen fur ihre Anwendung. J. Psychol. Neurol., 1910, 17:33. Cited by Brodal, A. The Reticular Formation of the Brainstem. Anatomical Aspects and Functional Correlations. Oliver and Boyd, Edinburgh, 1957.

Kohnstamm, O. and Quensel, F.: Centrum receptorium der Formatio reticularis and gekreutz aufsteigende Bahn. Deutsche Zeitschr. Nervenh. 1908, 36:182. Cited by Brodal, A. The Reticular Formation of the Brainstem. Anatomical Aspects and Functional Correlations. Oliver and Boyd, Edinburgh, 1957.

Kohnstamm, O. and Quensel, F.: Ueber den Kern des hinterent Langsbundels, den roten Haubenkern und den Nucleus intratrigeminalis. Neurol. Centralbl. 1908, 27:242. Cited by Brodal, A. The Reticular Formation of the Brainstem. Anatomical Aspects and Functional Correlations. Oliver and Boyd, Edinburgh, 1957.

Kruger, L. and Albe-Fessard, D.: Distribution of responses to somatic afferent stimuli in the diencephalon of the cat under chloralose anesthesia. Exp. Neurol., 1960, 2: 442-467.

Leontovich, T. and Zhukova, G.: The specificity of the neuronal structure and topography of the reticular formation in the brain and spinal cord of carnivora. J. Comp. Neurol., 1963, 121:347-379.

Lilly, J.C.: Injury and excitation by electric currents. In: Electrical Stimulation of the Brain. D.E. Sheer (Ed) University of Texas Press, Austin, 1961, pp.60-66.

Luys, J.: Recherches sur le système nerveux cérébro-spinal: sa structure, ses fonctions et ses maladies. J.B. Ballière, Paris, 1865, cited by Mehler, W. Further notes on the center median nucleus of Luys. In: The Thalamus. D. Purpura, and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.109-122.

Machne, X.; Calma, I.; Magoun, H.: Unit activity of central cephalic brain stem in EEG arousal. J. Neurophysiol., 1955, 18:547-558.

Magoun, H.: The ascending reticular system and wakefulness. In: Brain Mechanisms and Consciousness. A Symposium. J. Delafresnaye (Ed). Blackwell Scientific Publications, Oxford, 1954, pp.1-22.

Magoun, H.: The Waking Brain. 2nd Edition. Charles C. Thomas, Springfield, 1963.

Mallart, A.: Données sur les types de fibres conduisant les afférences somatiques au noyau centre médian du thalamus. J. Physiologie, 1961, 53:422-423.

Mannen, H.: "Noyau fermé" et "Noyau ouvert". Contribution à l'étude cytoarchitectonique du tronc cérébral envisagée du point de vue du mode d'arborisation dendritique. Arch. Ital. Biol., 1960, 98:333-350.

Mehler, W.: Further notes on the center median nucleus of Luys. In: The Thalamus. D. Purpura and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.109-122.

Mehler, W.R.; Feferman, M.E. and Nauta, W.J.H.: Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. Brain, 1960, 83: 718-750.

Moore, G.P.; Perkel, D.H. and Segundo, J.P.: Statistical analysis and functional interpretation of neuronal spike data. Ann. Rev. Physiol., 1966, 28:493-522.

Morin, F.: Afferent projections to the midbrain tegmentum and their spinal course. Amer. J. Physiol., 1953, 172:483-496.

Morison, R. and Dempsey, E.: A study of thalamocortical relations. Amer. J. Physiol., 1942a, 135:281-292.

Morison, R. and Dempsey, E.: Mechanisms of thalamocortical augmentation and repetition. Amer. J. Physiol., 1942b, 138:297-308.

Morison, R.; Dempsey, E. and Morison, B.: Cortical responses from electrical stimulation of the brain stem. Amer. J. Physiol., 1941, 131:732-742.

Moruzzi, G. and Magoun, H.: Brain stem reticular formation and activation of the EEG. Electroenceph. clin. Neurophysiol., 1949, 1:455-473.

Murphy, J.T. and Renaud, L.P.: Mechanisms of inhibition in the ventromedial nucleus of the hypothalamus. J. Neurophysiol., 1969, 32:85-102.

Murray, M.: Degeneration of some intralaminar thalamic nuclei after cortical removals in the cat. J. Comp. Neur., 1966, 127:341-368.

Nauta, W.J.H.: Hippocampal projections and related neural pathways to the mid-brain in the cat. Brain, 1958, 81: 319-340.

Nauta, W. and Kuypers, H.: Some ascending pathways in the brain stem reticular formation. In: Reticular Formation of the Brain, H. Jasper, L. Proctor, R. Knighton, W. Noshay and R. Costello, (Eds), Little, Brown and Co., Boston, 1958, pp.3-30.

Nauta, W. and Mehler, W.: Projections from the lentiform nuclei in the monkey. Brain Res., 1966, 1:1-38.

Nauta, W. and Whitlock, D.: An anatomical analysis of the nonspecific thalamic projection system. In: Brain Mechanisms and Consciousness. A Symposium. J. Delafresnaye (Ed), Blackwell Scientific Publications, London, 1954.

Needham, C. and Dila, C.: Synchronizing and desynchronizing systems of the old brain. Brain Res., 1968, 11:285-293.

Negishi, K.; Lu, E.S. and Verzeano, M.: Neuronal activity in the lateral geniculate body and the nucleus reticularis of the thalamus. Vision Res., 1962, 1:343-353.

Nyberg-Hansen, R.: Sites and mode of termination of reticulospinal fibers in the cat. An experimental study with silver impregnation methods. J.Comp.Neur., 1965, 124:71-100.

Olszewski, J. and Baxter, D.: Cytoarchitecture of the Human Brain Stem. S. Karger, Basel, 1954.

Papez, J.: Reticulo-spinal tracts in the cat. Marchi method. J. Comp. Neurol., 1926, 41:365-399.

Pappas, G.; Cohen, E. and Purpura, D.: Fine structure of synaptic and nonsynaptic neuronal relations in the thalamus of the cat. In: The Thalamus, D. Purpura, and M. Yahr, (Eds), Columbia University Press, N.Y., 1966, pp.47-76.

Pompeiano, O. and Swett, J.: Identification of cutaneous and muscular afferent fibers producing EEG synchronization or arousal in normal cats. Arch. Ital. Biol., 1962, 100:343-380.

Pompeiano, O. and Swett, J.: Actions of graded cutaneous and muscular afferent volleys on brainstem units in the decerebrate, cerebellectomized cat. Arch. Ital. Biol., 1963, 101:552-583.

Purpura, D.P.; McMurtry, J.G. and Maekawa, K.: Synaptic events in ventrolateral thalamic neurons during suppression of recruiting responses by Brain stem reticular stimulation. Brain Res., 1966a, 1:63-76.

Purpura, D.; Frigyesi, T.; McMurty, J. and Scarff, T.: Synaptic Mechanisms in thalamic regulation of cerebellocortical projection activity. In: The Thalamus. D. Purpura, and M. Yahr, (Eds), Columbia University Press, N.Y., 1966b, pp.153-172.

Purpura, D. and Shofer, R.: Intracellular recording from thalamic neurons during reticulocortical activation. J. Neurophysiol., 1963, 26:494-505.

Quensel, F.: Aktive Zelldegeneration nach Hirnstammverletzung bei Kaninchen. Neurol. Centralbl., 1907, 26:1138, Cited by Nauta, W. and Kuypers, H. Some ascending pathways in the brain stem reticular formation. In: Reticular Formation of the Brain, H. Jasper, L. Proctor, R. Knighton, W. Noshay and R. Costello, (Eds), Little, Brown and Co., Boston, 1958, pp.3-30.

Rall, W.: Theoretical significance of dendritic trees for neuronal input-output relations. In: Neural Theory and Modeling, R.F. Reiss (Ed), Stanford University Press, Stanford, 1964, pp.73-97.

Rall, W.: Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of Synaptic input. J. Neurophysiol., 1967, 30:1138-1168.

Ramon-Moliner, E. and Nauta, W.: The isodendritic core of the brainstem. J. Comp. Neur., 1966, 126:311-336.

Rasmussen, A.: Tractus tecto-spinalis in the cat. J. Comp. Neurol., 1936, 63:501-525.

Rexed, B.: The cytoarchitectonic organization of the spinal cord in the cat. J. Comp. Neur., 1952, 96:415-496.

Rexed, B.: A cytoarchitectonic atlas of the spinal cord of the cat. J. Comp. Neur., 1954, 100:297-380.

Rheinberger, M. and Jasper, H.: Electrical activity of the cerebral cortex in the unanesthetized cat. Am. J. Physiol., 1937, 119:186-196.

Rinvik, E.: A re-evaluation of the cytoarchitecture of the ventral nuclear complex of the cat's thalamus on the basis of corticothalamic connections. Brain Res., 1968a, 8:237-254.

Rinvik, E.: The corticothalamic projection from the pericruciate and coronal gyri in the cat. An experimental study with silver-impregnation methods. Brain Res., 1968b, 10: 79-119.

Rioch, D.: Studies on the diencephalon of carnivora. J. Comp. Neur., 1929, 49:1-153.

Rioch, D.: A note on the centre median nucleus of Luys. J. Anat., 1931, 65:324-327.

Rose, J. and Woolsey, C.: A study of the thalamocortical connections in the rabbit. Bull. Johns Hopkins Hosp., 1943, 73:65-128.

Rossi, G. and Brodal, A.: Corticofugal fibres to the brainstem reticular formation. An experimental study in the cat. J. Anat. (London), 1956, 90:42-62.

Rossi, G. and Zanchetti, A.: The brainstem reticular formation. Anatomy and physiology. Arch. Ital. Biol., 1957, 95:199-435.

Rothballer, A. Studies on the adrenaline-sensitive component of the reticular activating system. Electroenceph. clin. Neurophysiol., 1956, 8:603-621.

Rothballer, A.: EEG activation from microinjection into the brainstem of the cat. Anat. Rec., 1957, 127:359.

Scheibel, M. and Scheibel, A.: Structural substrates for integrative patterns in the brainstem reticular core. In: Reticular Formation of the Brain, H. Jasper, L. Proctor, R. Knighton, W. Noshay and R. Costello, (Eds), Little, Brown and Co., Boston, 1958, pp.31-55.

Scheibel, M. and Scheibel, A.: The organization of the nucleus reticularis thalami. A Golgi study. Brain Res., 1966, 1:43-62.

Scheibel, M. and Scheibel, A.: Anatomical basis of attention mechanisms in vertebrate brains. In: The Neurosciences. A Study Program. The Rockefeller University Press, N.Y., 1967a, pp.577-602.

Scheibel, M. and Scheibel, A.: Structural organization of nonspecific thalamic nuclei and their projection toward cortex. Brain Res., 1967b, 6:60-94.

Scheibel, M.; Scheibel, A.; Mollica, A. and Moruzzi, G.: Convergence and interaction of afferent impulses on single units of reticular formation. J. Neurophysiol., 1955, 18:309-331.

Schlag, J. and Chaillet, F.: Thalamic mechanisms involved in cortical desynchronization and recruiting responses. Electroenceph. clin. Neurophysiol., 1963, 15:39-62.

Shute, C. and Lewis, P.: The ascending cholinergic reticular system: neocortical, olfactory and subcortical projections. Brain, 1967, 90:497-520.

Starzl, T.E. and Magoun, H.W.: Organization of the diffuse thalamic projection system. J. Neurophys., 1951, 14:133-146.

Starzl, T.; Taylor, C. and Magoun, H.: Ascending conduction in the reticular activating system, with special reference to the diencephalon. J. Neurophysiol., 1951a, 14:461-477.

Starzl, T.; Taylor, C. and Magoun, H.: Collateral afferent excitation of reticular formation of the brainstem. J. Neurophys., 1951b, 15:479-496.

Taber, E.: The cytoarchitecture of the brainstem of the cat. J. Comp. Neuro., 1961, 116:27-70.

Torvik, A. and Brodal, A.: The origin of the reticulospinal fibers in the cat. An experimental study. Anat. Rec., 1957, 128:113-138.

Valverde, F.: Reticular formation of the pons and medulla oblongata. A Golgi study. J. Comp. Neurol., 1961, 116:61-100.

Villablanca, J.: The electrocorticogram in the chronic cerveau isolé cat. Electroenceph. clin. Neurophysiol., 1965, 19:576-586.

Walker, A.: The thalamus of the chimpanzee. J. Comp. Neur., 1938, 69:487-506.

Walker, A.E.: Internal structure and afferent-efferent relations of the thalamus. In: Thalamus, D. Purpura and M. Yahr (Eds), Columbia University Press, N.Y., 1966, pp.1-11.

Wolf, G. and Sutin, J.: Fiber degeneration after lateral hypothalamic lesions in the rat. J. Comp. Neurol., 1966, 127:137-156.

Addendum

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