

THE FUNCTIONS OF SLEEP

RETICULAR FORMATION ACTIVITY AND REM SLEEP

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It is unlikely that we will be able to understand the function of REM sleep until we know what brain areas generate and control it. Many groups of investigators have attempted to locate the brain structures responsible for this state. The conclusions of these investigations have been thrown into increasing doubt by recent developments which I will attempt to review.

TRANSECTION AND LESION DATA

General Considerations

The classical approach to analyzing the operation of biological systems has been to remove portions of the system and determine what functions are lost. The limitations of this procedure are often not adequately considered. REM sleep is a fragile state. It is easily disrupted by a variety of non-specific factors. Therefore, the significance of a reduction or loss of REM sleep after destruction of brainstem areas must be carefully assessed.

Studies of sleep utilizing brainstem transections or lesions repeatedly note a variety of problems with the general health of the animal including skin ulcerations, hematuria, hypoglycemia, uremia, hyperkalemia, cardiac arrhythmias, vomiting, hyperthermia, hypothermia, aphagia and adipsia, and absence of spontaneous micturition and defecation (Villablanca, 1966; Hobson, 1965; Bard and

Macht, 1958; Jouvett, 1962; Roussel et al., 1976; Jones et al., 1977). Apneusis and reductions in respiratory rate severe enough to produce EEG disturbances can result from damage in the vicinity of the locus coeruleus (Jones et al., 1977). Most preparations with radical brainstem lesions do not survive the initial surgery, and those which do require constant care to prevent death. In short, most of these preparations are extremely ill and are in an unstable physiological state.

Transections and lesions disrupt blood circulation through adjacent brain areas. The resulting ischemia extends the inactivated region for unknown distances. Discharge in the cut ends of axons, and swelling of tissues adjacent to the lesion will contribute to disruption of remaining tissues.

Lesions of the pontine tegmentum can disrupt the mechanisms which produce motor inhibition in REM sleep. This produces the syndrome of REM sleep without atonia, in which the cat appears to act out a dream (Jouvett and Delorme, 1965). Often this motor behavior arouses the animal from sleep during the SWS-REM sleep transitional state or in the initial seconds of REM sleep (Henley and Morrison, 1974). It has been hypothesized by Henley and Morrison that this motor disturbance may, in its early stages, selectively reduce or eliminate REM sleep. This hypothesis is supported by descriptions of cats without REM sleep after locus coeruleus lesions. These cats typically end a slow wave sleep (SWS) period with an abrupt hyperextension of the neck at the time of arousal (Jouvett and Delorme, 1965).

Neurological shock resulting from the interruption of ascending and descending pathways can lead to a disruption of distant systems. This phenomenon has been most thoroughly studied in the spinal cord (Sherrington, 1947). After section between the cord and medulla, functions which are known to be organized in the cord are lost as a result of the disconnection of higher centers. Some functions recover if animals survive for long enough periods, but many are permanently disturbed. Similar phenomena occur at other levels of the neuraxis (e.g. Sprague, 1966). Thus, the loss of REM sleep after brain transections or lesions cannot be interpreted

as definitive proof that a REM sleep "center" has been destroyed. This is particularly true in light of the short survival time of many critically important preparations (Jouvet, 1962).

Many studies have shown that lesions and transections in infant animals result in far less loss of function than similar procedures in adult animals. Immediately after surgery, behavioral capabilities can be demonstrated in the truncated infant nervous system that were unsuspected in studies on adult animals (Bignall and Schramm, 1974). However, this procedure has not been adequately applied to studies of REM sleep.

Lesions that are slowly created, by successive enlargements in 2 or 3 separate procedures produce far less shock to surrounding tissues than single stage lesions (Rosner, 1970). However, lesion studies of REM sleep mechanisms have typically employed lesions or transections carried out in a single stage. This would tend to underestimate the capabilities of remaining brain structures.

In summary, there are a variety of factors which can account for the loss of neural function after brainstem transections or lesions. It is unlikely that there was ever any strong selective pressure for neural circuitry to evolve to function normally after brainstem transection. When one considers the number of ascending and descending tracts in the brainstem and the infinite anatomical and physiological complexity of this area it is remarkable that any behavioral functions survive extensive brainstem lesions. Therefore, the loss of REM sleep after transection or lesion cannot be viewed as definitive evidence for the localization of a REM sleep center. However, the presence of REM sleep after such lesions does prove that the ablated structures are not essential, although they may of course contribute to normal REM sleep (e.g. Gadea-Ciria, 1976). If, in the evaluation of transection and lesion data, one takes this approach of looking at those lesions which allow REM sleep rather than looking at those which prevent it, one is led to several novel conclusions.

Transection Data

One of the earliest studies of the behavior of chronically maintained decerebrated cats was performed by Bard and Macht (1958) (Fig. 1A). In 1958, before the existence of desynchronized sleep

in cats was generally known, and prior to the discovery that REM sleep was accompanied by loss of motor tone, they pointed out that sleep occurred in cats decerebrated at pontine or ponto-mesencephalic levels and that it was often accompanied by a loss of motor tone. These observations were extended by Jouvét (1962) with the polygraphic recording of EEG and neck muscle tone, and the observation of rapid eye movements and myosis (Fig. 1A and B). Jouvét also established that the cerebellum was not necessary for REM sleep (1962). These observations have been repeatedly confirmed (Hobson, 1965; Villablanca, 1966) and it has been established that these preparations exhibit all of the brainstem components of REM sleep, although in reduced amounts. Furthermore, it has been shown that severing the spinal cord at the C1 level (Fig. 1D) does not prevent REM sleep although, like pontine transections, it reduces REM sleep time (Adey et al., 1968; Puizillout et al., 1974). Certain spinal areas may, however, contribute to the atonia of REM sleep (Morrison and Bowker, 1971).

This evidence demonstrating the survival of REM sleep after transections clearly proves that the brainstem, below the level of the pons and above the spinal cord, is sufficient for the occurrence of the REM sleep state. Jouvét (1962) attempted to further localize the REM sleep center with the use of a retropontine transection (Fig. 1C). Just 2 cats survived this transection and then for a duration of only 7 days. Neither cat showed muscle atonia. This was interpreted as indicating that the REM sleep generating mechanism was above the cut. However, bearing in mind the many explanations of the loss of function after brain transection just discussed and particularly the fact that small pontine lesions can produce a loss of REM sleep atonia without preventing REM sleep (Henley and Morrison, 1974), this negative evidence cannot be regarded as definitive. The loss of REM sleep may have resulted from the behavioral and physiological abnormalities caused by the transection and not by the removal of a REM sleep "center".

Jouvét also identified a "difficult to interpret" state in brain systems anterior to the retropontine transection. This state consisted of cortical desynchrony and myosis, during which no

visual tracking occurred. It was speculated that this state might be a form of REM sleep generated by a pontine center. There are many interpretations of this phenomenon that do not require postulating that this state is a form of REM sleep. For example, this might represent an abnormal waking condition. Indeed, Jouvet does not claim to have demonstrated the identity of this state with REM sleep. Yet this is the crucial piece of positive evidence supporting the hypothesis that the pons contains the generator neurons for REM sleep. Therefore, if one conservatively evaluates the transection data, one is forced to conclude that the system generating REM sleep may be located anywhere between the cervical spinal cord and the anterior pons. It is true, however, that PGO (pontine-geniculate-occipital) spikes, a phenomenon common to REM sleep, waking, (Bowker and Morrison, 1976) and drug induced states, can be generated by the isolated pons (Laurent et al., 1974)

Lesion Data

Several series of lesion studies have been performed in order to further localize the areas responsible for REM sleep. While it has been possible to prevent REM sleep by brainstem lesions, the findings have not been consistent.

Carli and Zanchetti (1965), in an extensive series of studies in 40 cats identified the nucleus reticularis pontis oralis (RPO) as the structure whose destruction was most consistently correlated with REM sleep suppression. They specifically rule out the locus coeruleus and sub coeruleus as essential for REM sleep, since extensive lesions in these areas were not correlated with great reductions in REM sleep time.

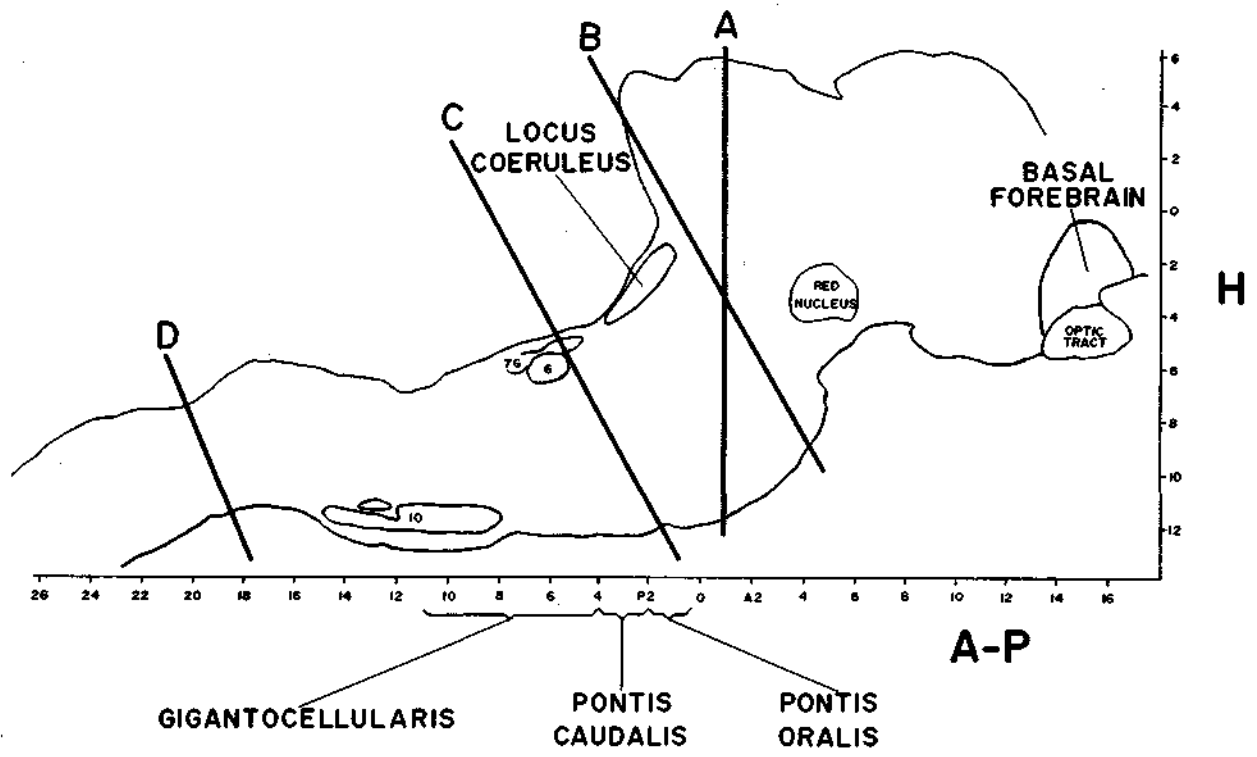
Jouvet in his initial studies (1962) identified the nucleus reticularis pontis caudalis (RPC) as the critical structure for REM sleep. This nucleus, as defined by Jouvet, overlaps somewhat with Carli and Zanchetti's definition of RPO. However, further studies by Jouvet's group pointed to the locus coeruleus not the RPC as the crucial structure (Jouvet, 1972; Roussel et al., 1976). It was also found that lesions restricted to caudal locus coeruleus produced REM sleep without atonia (Jouvet and Delorme, 1965). Recently, Jones et al. (1977) have contended that locus coeruleus lesions

produce only a loss of the atonia of REM sleep. In agreement with Carli and Zanchetti (1965), they conclude that REM sleep remains after destruction of locus coeruleus. Similarly, locus coeruleus lesions in kittens did not disrupt REM sleep (Adrien, 1975).

Henley and Morrison (1974) have demonstrated that locus coeruleus lesions are not even required to produce the syndrome of REM sleep without atonia. They produced REM sleep without atonia with small lesions in the region of RPO. They suggest that Carli and Zanchetti's (1965) finding of a loss of REM sleep after RPO lesions may have resulted from their not detecting REM sleep periods without atonia. However, Carli and Zanchetti were aware of the "hallucinating" episodes previously reported and specifically mention that they did not observe this phenomenon. They also recorded pontine PGO spikes which would have helped locate such episodes.

It is by no means certain that further studies of lesions disrupting REM sleep will clarify the issue of the anatomical location of structures generating it. The principal histological differences between lesions disrupting REM sleep and those sparing it, is the size of the lesions, i.e., Jouvett et al.'s locus coeruleus lesions and Carli and Zanchetti's RPO lesions which eliminated REM sleep signs were larger than the lesions created by Jones et al. (1977) and Henley and Morrison (1974) which did not abolish REM sleep. Carli and Zanchetti (1965) reported that moderate sized lesions of either the medial RPO or the lateral RPO do not abolish REM sleep, while larger lesions destroying both these areas do. This strengthens the argument that nonspecific effects such as trauma, imbalances of neural circuits, or shock in deafferented systems, are the likely explanation of REM sleep loss after these brainstem lesions.

Even if a small, specific region whose destruction eliminated REM sleep could be identified, this would not prove that it was the REM sleep "center." This can be illustrated by the finding of McGinty and Sterman (1968) that lesions of the basal forebrain region (Fig. 1) totally eliminated REM sleep for periods of several weeks; this despite the fact that the basal forebrain is not required for REM sleep, since it is well anterior



to the transections performed by Bard and Macht (1958) and Jouvet (1962) which allowed REM sleep. Lesions of more caudal structures might well produce REM sleep suppressions equal to or greater than those resulting from basal forebrain lesions, even if these areas were not part of the executive mechanisms for REM sleep.

In summary: 1) Transection data clearly localize REM sleep generating mechanisms to the brainstem region lying between the spinal cord and the anterior pons. 2) The main evidence localizing REM sleep generating mechanisms to specific areas within the brainstem is based on the loss of REM sleep after lesions. Nonspecific factors may be responsible for this loss of function. 3) Therefore, on the basis of lesion and transection evidence we cannot confidently localize REM sleep generating mechanisms to any particular nucleus within the brainstem.

UNIT RECORDING DATA

General Considerations

Another method for localizing the cell groups generating REM sleep is the recording of the activity of brainstem units during the sleep cycle. This approach allows observation of the normal functioning of single cells. To the extent that cells in a given cytological area show similar types of activity changes across the sleep cycle, the discharge patterns of large brainstem areas can be determined.

The presence of cell discharge correlated with REM sleep does not prove that a cell group is necessary or even important in REM sleep generation. However, a cell group whose activity is found not to relate closely to REM sleep is unlikely to have an important role in its control.

Most brain neurons show substantial increases in their activity during REM sleep. Therefore, cell discharge must be carefully examined in a variety of behavioral situations to determine whether or not a relationship to REM is an epiphenomenon related to one of the many physiological processes influenced by REM sleep. Before a cell group can be accepted as forming the "executive"

mechanism of REM sleep, it must be shown to relate to the complex of physiological events that identify the REM sleep state. If this requirement is not fulfilled we are forced to accept the simplest plausible explanation of changes in activity, i.e., that the cell group is involved in the regulation of posture, phasic motor activity, eye movement, EEG activation, etc.

It must then be shown that procedures which selectively increase discharge in this cell group (such as electrical or neurochemical stimulation) increase REM sleep duration or intensity (assuming the cells are facilitatory to REM sleep) while procedures that decrease activity in these cell groups (such as lesion or neurochemical inactivation) decrease REM sleep duration or intensity. Nonspecific effects of the procedures used to change cell discharge rates must be experimentally determined.

We have been engaged in studies of units in the medial pontobulbar reticular formation. One motive for studying this region is that it includes the areas that several of the previously discussed lesion studies indicated might be required for REM sleep.

A second motive for studying this region is that it is known to have widespread connections with a variety of brain areas. Regardless of whether it has an executive role in the control of REM sleep, it is hard to imagine any REM sleep generating system that would not employ elements of the medial reticular formation as a pathway to convey physiological changes throughout the central nervous system.

A third reason for studying this structure in relation to sleep is that it has been so thoroughly studied from several other perspectives. Indeed, with the possible exception of the visual cortex, the mammalian reticular formation has probably been more intensively studied than any other brain structure. However, with only a few exceptions, studies of unit discharge in reticular formation cells have been carried out in paralyzed, anesthetized or restrained animals. Thus, an understanding of the functional significance of activity in these cells, based on observations in a variety of behavioral situations, has not been possible. Therefore, we have been recording

activity *in* these cells in unrestrained cats and observing the behavioral correlates of their discharge during both sleep and waking.

Pontine Nucleus Gigantocellularis

The first target of investigation was the pontine nucleus gigantocellularis, or FTG (giganto-cellular tegmental field) in Bermans (1968) terminology. This nucleus occupies a large portion of the brainstem reticular formation. A total of 85 units has been recorded in this area (Siegel et al., 1977).

Three types of gigantocellularis units could be distinguished on the basis of discharge patterns during the sleep-waking cycle. Type one cells had no spontaneous activity during quiet waking, SWS or REM sleep (Fig. 2). They discharged in association with movements and were otherwise silent. These cells are unique in being the only group of brain cells observed which normally show no activity during either REM sleep or SWS. In a quiet, waking animal these cells can be completely silent for periods of up to 40 minutes or more (Siegel and McGinty, 1976). Twenty-eight percent of pontine gigantocellularis cells were of this type.

The second cell type had relatively high levels of tonic activity in both waking and sleep (Fig. 3). Its defining characteristic was a discharge rate greater than 4 spikes/second. These cells showed a relatively small rate increase during the SWS-REM sleep transition. Fifteen percent of gigantocellularis cells were of this type.

The third cell type had an intermediate level of spontaneous discharge in quiet waking and slow wave sleep (Fig. 4). However, it discharged in bursts during both waking movements and REM sleep. Fifty-seven percent of gigantocellularis cells were of this type.

Considering the group of pontine gigantocellularis cells as a whole there was a strong, highly significant positive correlation between a neuron's maximum waking discharge rate and its average or maximum REM sleep rate, i.e., neurons with high REM sleep rates also had high rates during waking. We saw no gigantocellularis cells

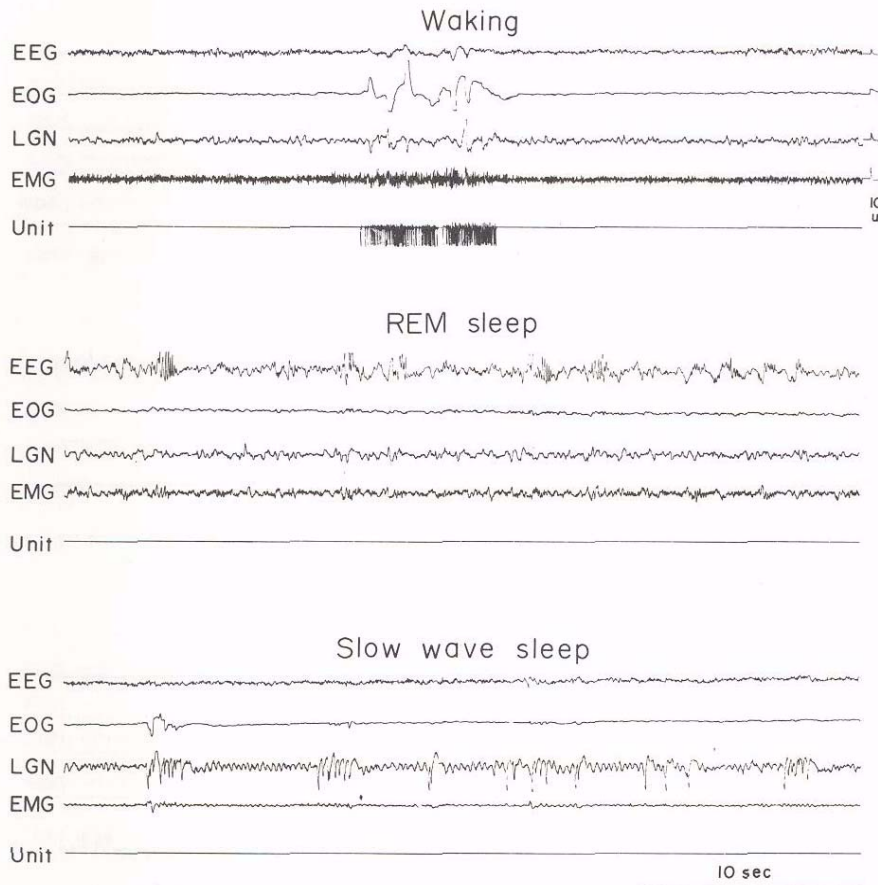


Fig. 2. A type 1 pontine gigantocellularis neuron. Labels for this and succeeding figures: EEG - sensorimotor electroencephalogram; EOG - electrooculogram; LGN - lateral geniculate nucleus; EMG - dorsal neck muscle electromyogram. (From **Experimental Neurology** 56: 553-573, 1977).

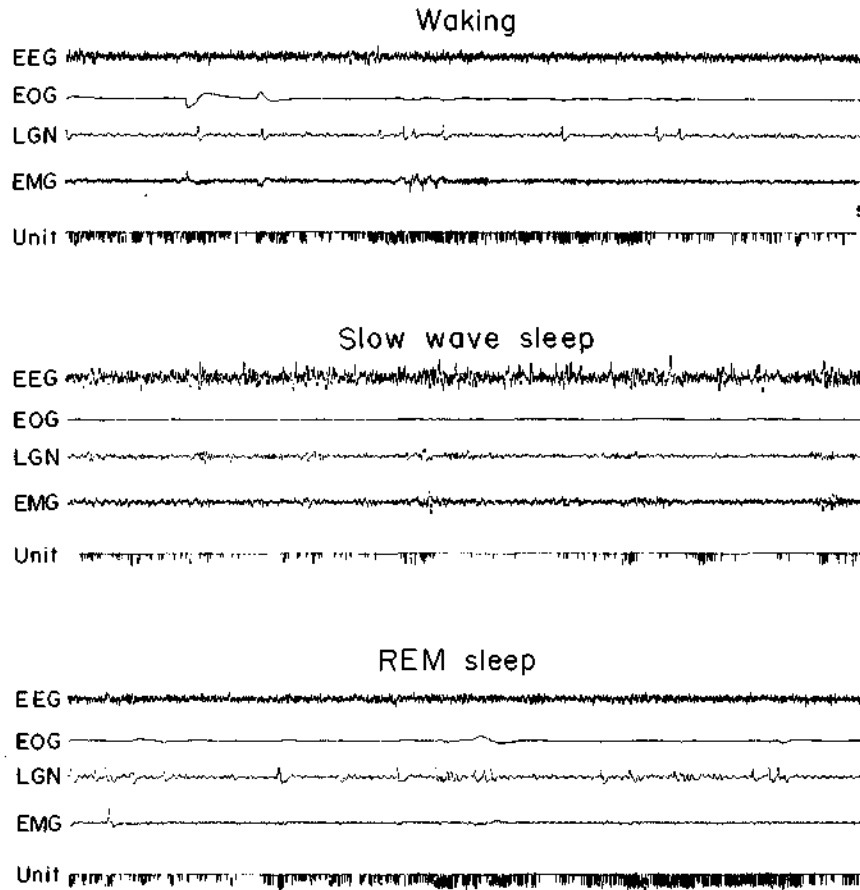


Fig. 3. A type 2 pontine gigantocellularis neuron. (From *Experimental Neurology* 56: 553-573, 1977).

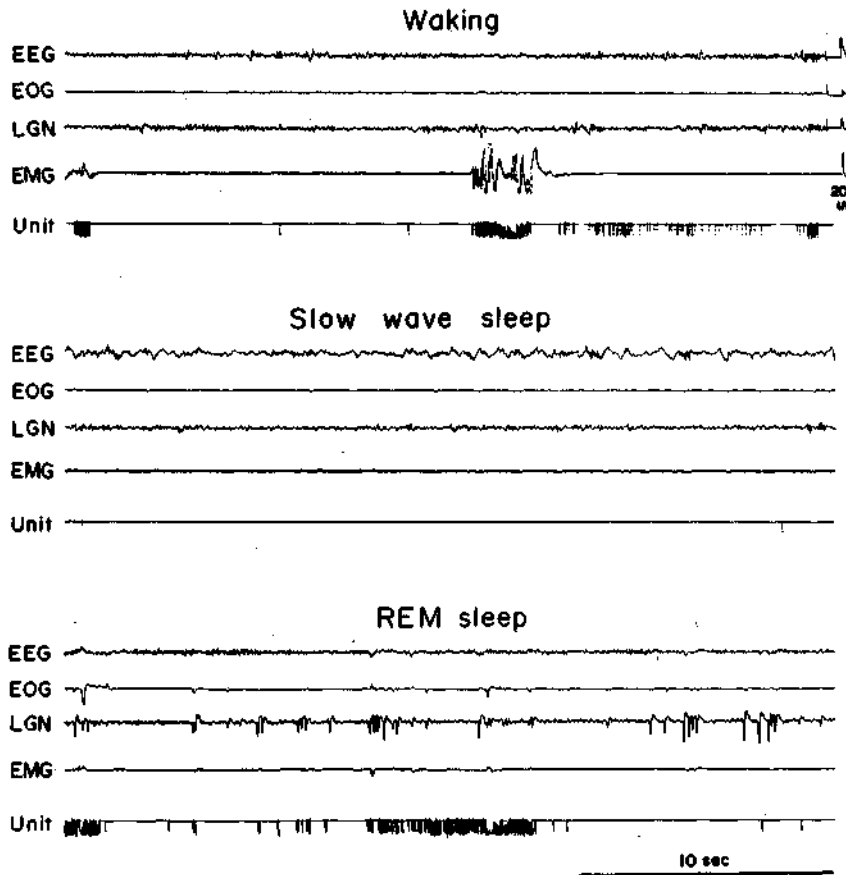


Fig. 4. A type 3 pontine gigantocellularis neuron. (From *Experimental Neurology* 56: 553-573, 1977).

which discharged selectively in REM sleep. All gigantocellularis cells exceeded their mean REM sleep discharge rates during waking movement (Siegel et al. , 1977) .

We have systematically observed the behavioral correlates of waking discharge in these cells (Siegel and McGinty, 1977). Cells were found to relate to specific movements of either the head and neck, ear, forepaw, scapula, or tongue.

Many of these cells also responded to applied sensory stimuli (Fig. 5). However, the responses to applied stimuli were generally brief and habituated rapidly. In this respect, gigantocellularis discharge appears to correlate with the brief motor activity of the startle response. Only when sustained movements were evoked by stimuli did sustained gigantocellularis discharge occur.

In 15 cells the sensory stimuli which were found to evoke unit activity were systematically eliminated or attenuated. Vestibular stimuli, which were the best stimuli for most cells, were eliminated by an atraumatic head restraint system. Somatic stimuli were eliminated by local anesthesia of identified receptive fields. Auditory stimuli were attenuated by occluding the ear canals with cotton impregnated with wax. Visual stimuli were eliminated by placing the cat in a light tight box. In no case did this stimulus reduction procedure greatly reduce or eliminate cell discharge. In most instances unit activity increased. This increase in firing was correlated with phasic bursts of EMG activity (Fig. 6). This experiment demonstrates that gigantocellularis discharge is more closely related to motor output than it is to sensory input.

If restraint continued for more than 3-5 minutes both motor activity and correlated gigantocellularis discharge decreased (Fig. 7). A cat which has previously experienced restraint and is undisturbed will show very little struggling and hence virtually no unit discharge during waking. Therefore, estimates of waking discharge rates in such preparations will greatly underestimate the "average" waking rate. As a consequence, the discharge in these cells will appear to be selective for REM sleep. Previous studies by Hobson and McCarley and their co-workers (McCarley and Hobson, 1971; Hobson et al., 1974) which found that

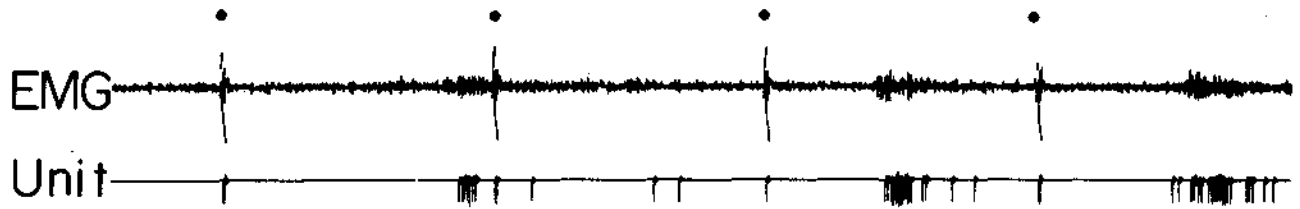


Fig. 5. Response of gigantocellularis neuron to discrete somatic shock stimulus (dots). (From Science 196: 678-680, 1977).

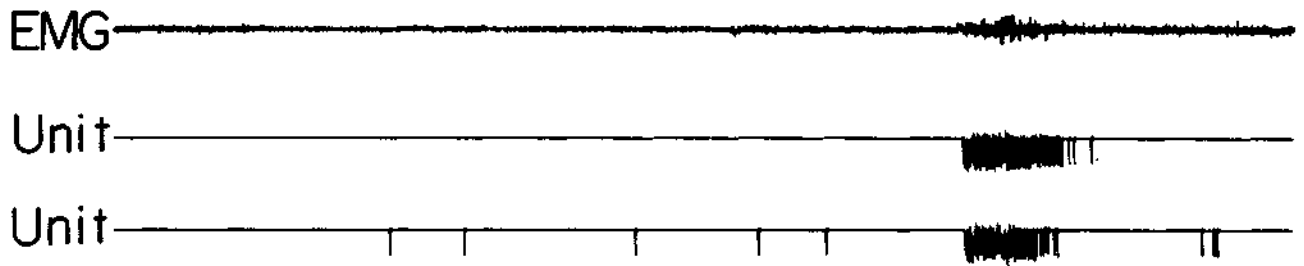


Fig. 6. Gigantocellularis unit firing during stimulus reduction procedure. (From Science 196: 678-680, 1977).

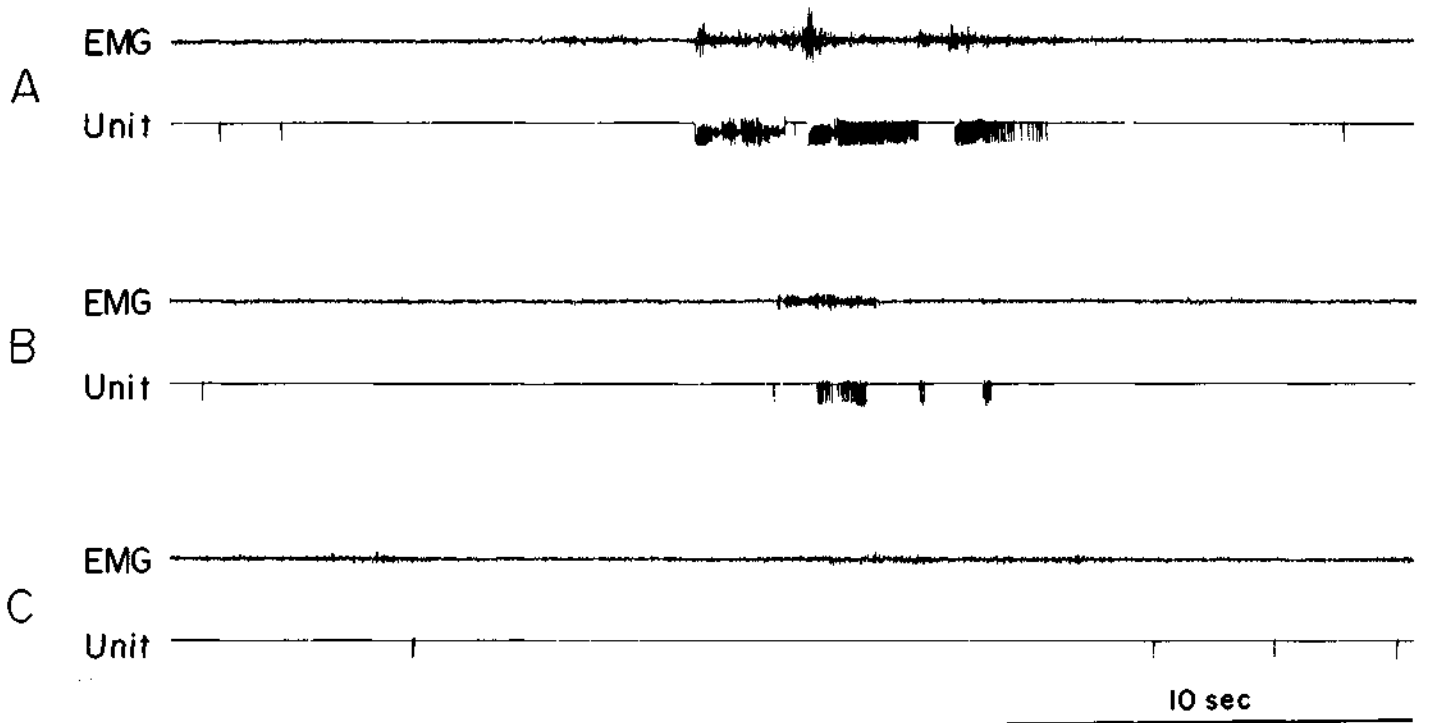


Fig. 7. Gigantocellularis unit firing during restraint. A indicates period immediately after start of restraint. B and C show unit firing after several minutes of undisturbed restraint. (From *Experimental Neurology* 53: 553-573, 1977)

gigantocellularis cells had discharge selective for REM sleep used cats adapted to head restraint. Similarly, studies by Pompeiano and Hoshino (Pompeiano and Hoshino, 1976a; Hoshino and Pompeiano, 1976) which reported that gigantocellularis cells discharge selectively during cataplectic episodes induced by an anticholinesterase, used cats which were immobilized by decerebration.

Most gigantocellularis cells fired rhythmically during some grooming periods (Fig. 8). This illustrates several important points about these cells. 1) It has been reported that these cells habituate to repetitive sensory stimulation (e.g., Scheibel and Scheibel, 1965; Peterson et al., 1976), but during the rhythmic motor activity of grooming no habituation occurs. We also find that units do not habituate to sensory stimuli which repeatedly evoke specific movements. 2) During grooming, reciprocal discharge can be seen in pairs of gigantocellularis cells which are correlated with different movements. This sort of discharge pattern is incompatible with the concept that these cells are related to nonspecific arousal. 3) The high discharge rate during spontaneous behaviors demonstrates that painful stimuli are not required to activate these cells (e.g., Casey, 1969) .



Fig. 8. Gigantocellularis unit discharge during grooming. (From Science 196: 678-680, 1977)

Our behavioral evidence leads to the conclusion that discharge in gigantocellularis cells is a correlate of motor activity. Since movement is a normal accompaniment of a variety of behavioral processes, the motor related activity of pontine gigantocellularis cells can explain many of their previously reported relationships to habituation, arousal processes and painful stimuli (Siegel and McGinty, 1977) . Their discharge in phasic bursts

during REM sleep is also consistent with this view, since REM sleep is a time of intense motor activation. We see no cells in this area whose discharge pattern is consistent with an executive role in REM sleep generation.

Nucleus Reticulus Pontis Oral and Caudalis

The second portion of the medial reticular formation investigated was the area of the nucleus reticularis pontis oral and caudalis. This region lies just anterior to the nucleus gigantocellularis and is the location that Carli and Zanchetti's extensive lesion studies pinpoint as being critical for REM sleep (1965).

Our microdrive bundles were aimed at the center of the region identified by Carli and Zanchetti. We have recorded a total of 22 cells in 3 cats. Their sleep waking discharge patterns do not differ greatly from those observed in the gigantocellularis region. We see the same 3 cell types (Fig. 9). Fourteen percent are type one, 50% type 2 and 36% type 3. Cells with high REM sleep discharge rates tend to have high rates in waking. We see no cells which discharge selectively in REM sleep.

Waking discharge relates to motor activity. However, these cells do not relate primarily to lateral head movements in the way that cells in the gigantocellular nucleus do; instead, they appear to relate to activity in trunk musculature. More of these cells must be investigated before the nature of movement correlations can be clearly understood.

Medullary Gigantocellular Nucleus

The third portion of the medial reticular formation investigated was the medullary portion of the gigantocellular nucleus. This is just caudal to, and continuous with the pontine gigantocellular nucleus. This area overlaps a portion of the Magoun inhibitory region (Magoun, 1944; Magoun and Rhines, 1946). Netick, Orem and Dement (1977) recently described 6 cells found in the medullary gigantocellular region which discharged selectively in REM sleep.

We have explored the portion of this area between P9 and P11 in 3 cats. We see the same

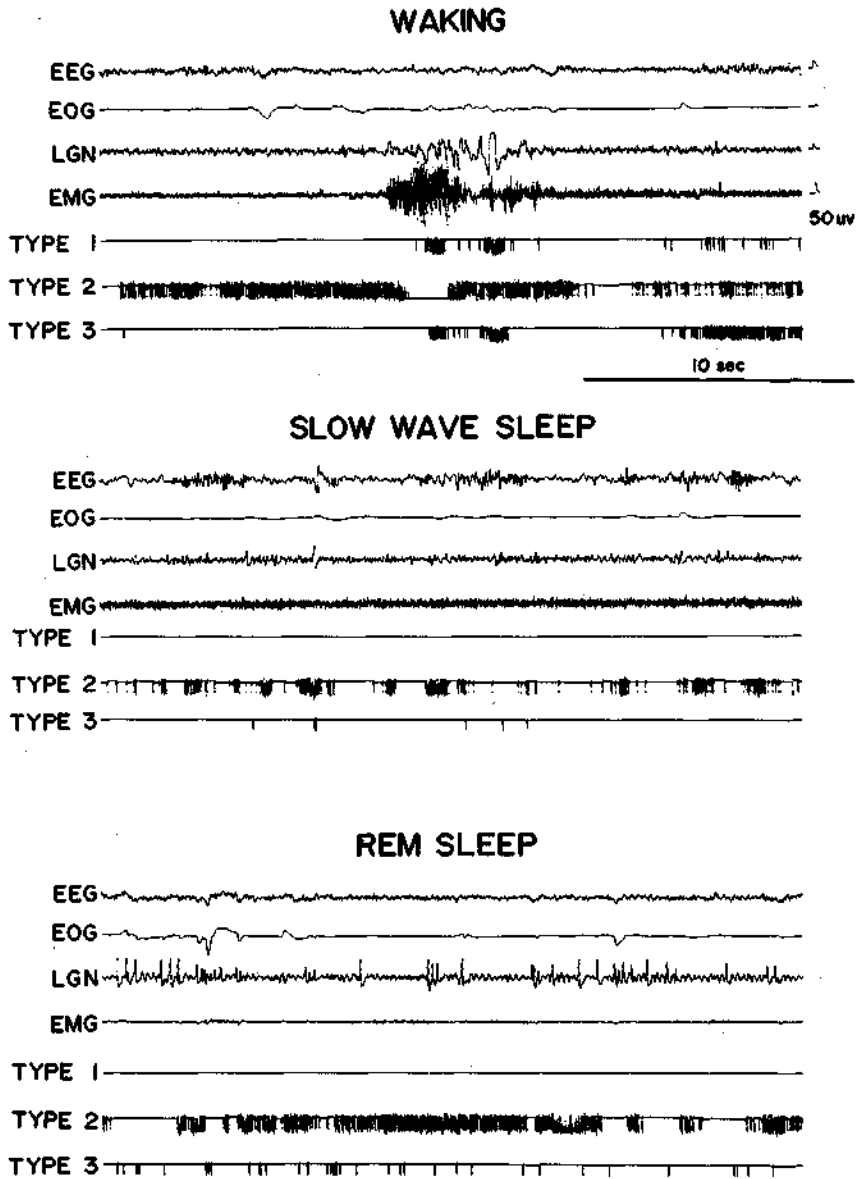


Fig. 9. Simultaneous recording of the three cell types seen in nucleus reticularis pontis caudalis and oralis area.

3 cell types in this area that we found in RPO , RPC and in the pontine gigantocellular area. Of the 29 cells recorded, 28% are type one, 41% type 2 and 31% type 3.

Waking discharge related to motor activity as was the case in the more anterior regions. Several cells in this area discharged at high rates when the cat held particular postures. If the cat shifted into a different position, the discharge rate was greatly reduced.

We saw no cells which discharged selectively in REM sleep, as Netick, Orem and Dement (1977) reported. However, 2 of the posture related cells discharged at a low rate in quiet waking and SWS, showed a tonic rate increase during the SWS-REM sleep transition and maintained this rate throughout REM sleep. Therefore, the sleep and quiet waking behavior of these cells is strikingly similar to that of the cells seen by Netick, Orem and Dement (Fig. 10). Since these workers were recording from cats which were adapted to head restraint, they would not have been able to observe unit activity in a variety of postures. Therefore, it appears likely that the REM sleep selective cells they observed are similar to the posture related cells which we have seen. If this is the case, then the REM sleep related acceleration can be understood as reflecting the motor activation of REM sleep. Just as cells which are phasically active in waking show phasic activity in REM sleep, these cells, which discharge tonically while postures are maintained in waking also show tonic REM sleep activity. It is also conceivable that medullary REM sleep selective cells are rare and were missed by our microelectrodes. Further investigation of this area is required.

In summary: We have explored the medial brainstem reticular formation from H.C. coordinates P2 to P11. We find that cells in this area are related to motor activity in waking. During REM sleep they show discharge patterns which resemble their waking activity. Discharge rates in the two states are positively correlated. These findings suggest a role for these cells in mediating the motor activation of both waking and sleep, but are not consistent with an executive role for these neurons in the generation of REM sleep.

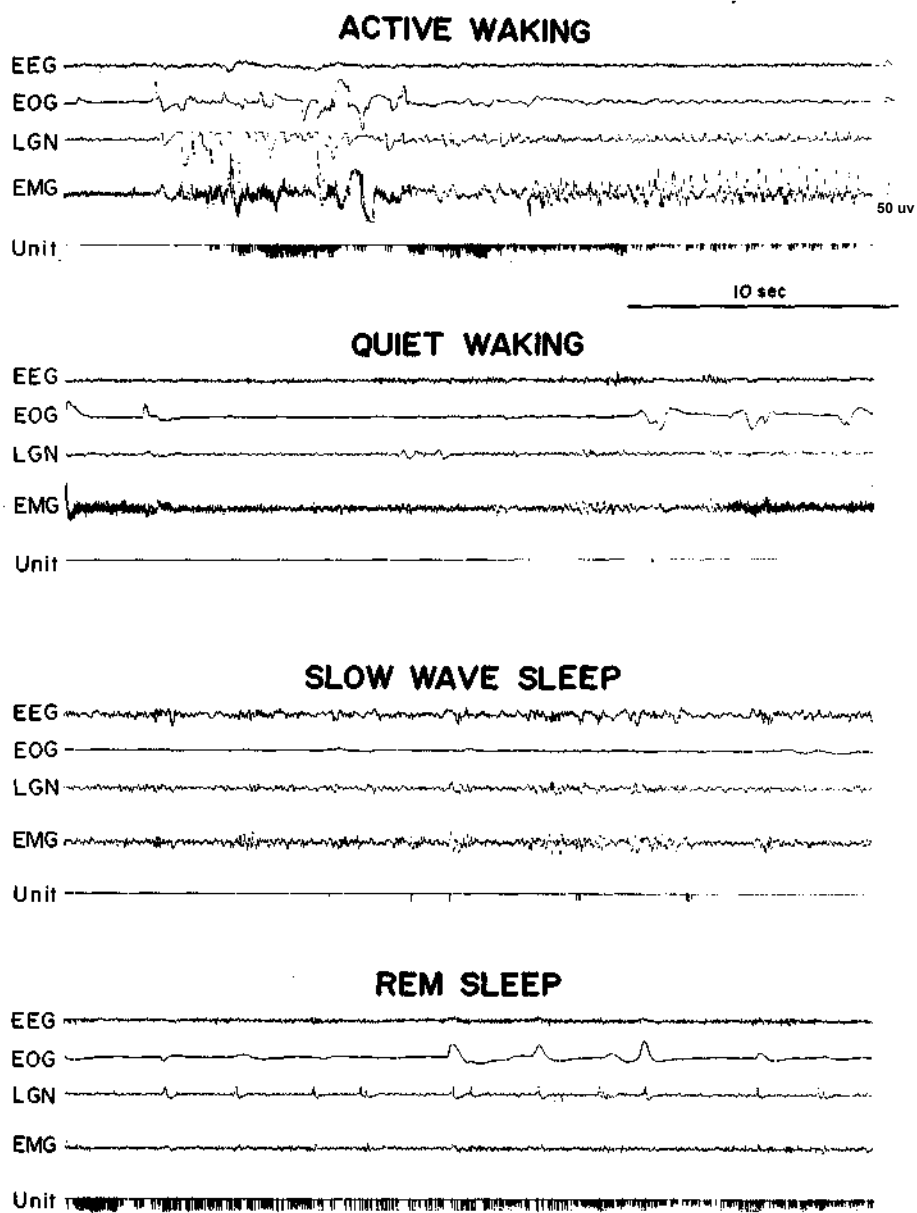


Fig. 10. A medullary gigantocellularis cell which fired in relation to posture.

DISCUSSION

In the first portion of this presentation I reviewed the lesion and transection evidence localizing the brain structures responsible for REM sleep. This evidence demonstrates that the integrity of the pontomedullary brainstem is sufficient for the periodic occurrence of REM sleep. However, lesion evidence does not definitively localize the region crucial for REM sleep.

Unit recording evidence was then presented. These studies reveal a relationship between reticular formation unit activity and movement. They are consistent with the discharge of these cells in REM sleep, whose most obvious behavioral manifestation is motor activation. However, this unit data is essentially negative with respect to the goal of anatomically localizing the neurons responsible for REM sleep. None of the 136 cells studied discharged selectively in REM sleep. None of these neurons appear to be REM sleep "executive" neurons.

There are several possible explanations for our inability to find REM sleep executive neurons in the brainstem.

1) There may be REM sleep executive neurons within the medial reticular area that we have not encountered. We did not record activity at all lateralities and all anteroposterior levels. The fact that medial reticular formation cells from P2 to P11 appear to be fairly homogeneous with respect to their sleep related activity, makes it appear unlikely that there would be a large cluster of undiscovered REM sleep selective cells within this area. However, if REM sleep executive cells are relatively few in number and are not anatomically clustered, they might have escaped detection. The RPO, RPC and medullary gigantocellular nuclei have not been as thoroughly explored as the pontine gigantocellular nucleus, and are therefore promising areas for further study.

2) The REM executive elements may not have been detected because they were too small for our electrodes. While our microwire technique has been shown capable of recording cells as small as 30 μ (McGinty and Harper, 1976), it would not resolve extremely small neurons. However, in general, it has been our experience that cells with small

action potentials were type 2 cells, i.e., they showed less rate increase in REM sleep than most other cells.

A related possibility is that glial elements are responsible for triggering REM sleep. Intracellular studies of glial slow potentials during sleep might shed light on their role.

3) The REM sleep executive neurons may exist in other brainstem areas. The vestibular nuclei appear to have been eliminated on the basis of both lesion and recording studies (Perenin et al., 1972; Bizzi et al., 1964; Morrison and Pompeiano, 1966) although they may affect PGO spike distribution. Similarly the midline raphe nuclei do not appear to be essential for REM sleep, although they may have important roles in the regulation of arousal and of PGO spikes (Simon et al., 1973).

Unit activity in and around the locus coeruleus has been the subject of several studies (Chu and Bloom, 1973; Pompeiano and Hoshino, 1976b; Hobson et al., 1975; Saito et al., 1977). It has been found that many of these cells show a remarkable suppression of discharge apparently specific to REM sleep. Evidence has been presented by Carli and Zanchetti (1965) and more recently by Jones et al. (1977) showing survival of REM sleep after locus coeruleus lesions. This evidence is not consistent with an executive role for these neurons in REM sleep control. If it can be confirmed that complete locus coeruleus lesions are compatible with REM sleep, then the locus coeruleus activity change in REM sleep must be understood primarily in relation to the peripheral variables of REM sleep. A major task of the future will be to establish exactly what behavioral and physiological parameters correlate with activity in these cells. A particularly interesting possibility is that these cells may relate to the control of muscle tone.

A large portion of the lateral brainstem caudal to the locus coeruleus has not been systematically explored. This area might well be important in REM sleep control.

4) It seems likely that one of the first three hypotheses is the correct one. However, we should also consider a fourth hypothesis. Briefly stated, it is that there may be no "executive neurons" for

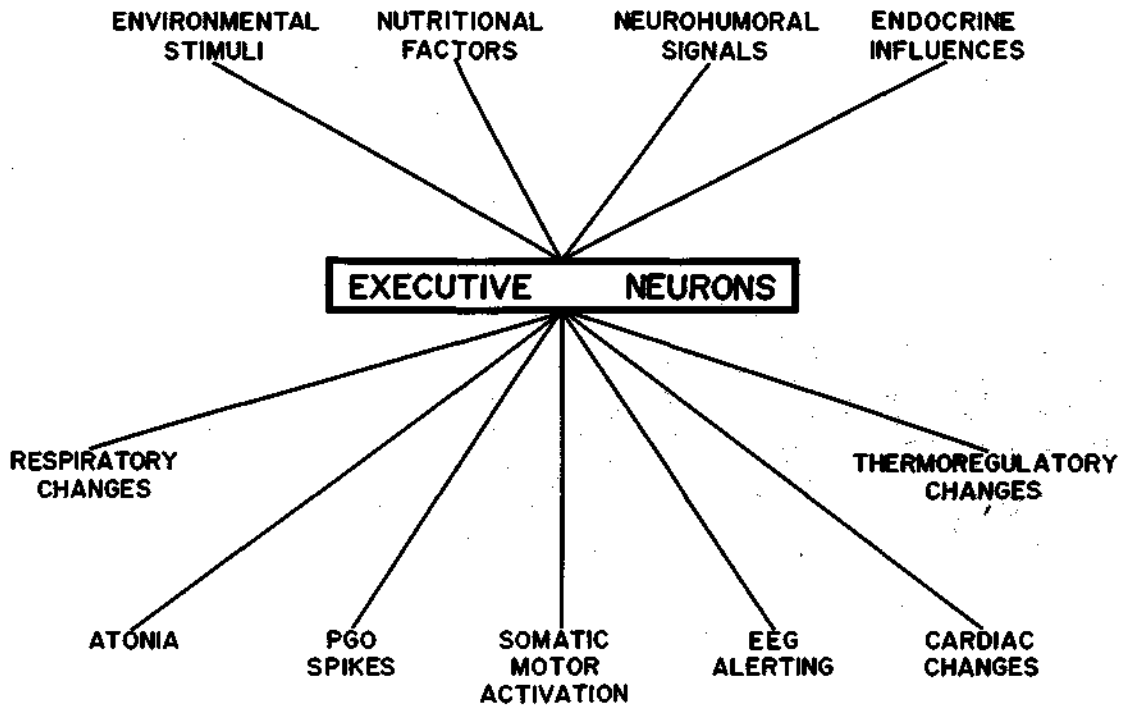


Fig. 11. See text.

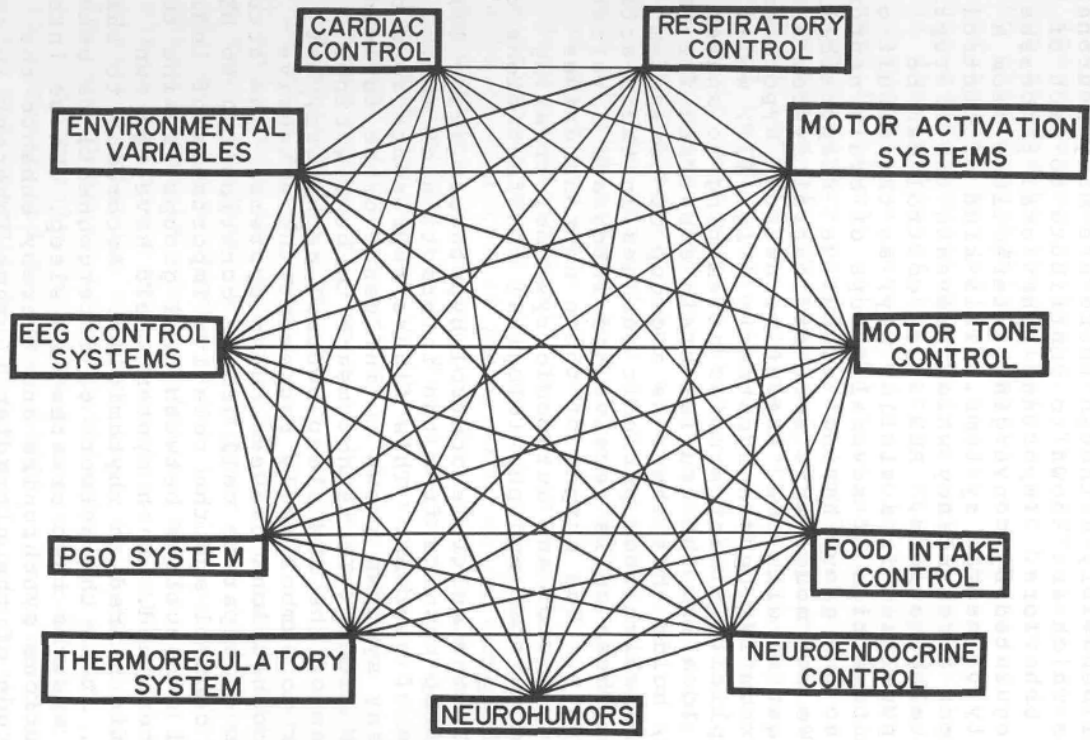


Fig. 12. See text.

REM sleep. In other words, there may be no single group of brain neurons which fulfills the requirements outlined above for "executive neurons." There are, after all, no known "executive neurons" for waking, non-REM sleep, eating, drinking or sexual behavior, although there are many neuronal groups which are known to contribute to each of these behaviors. Important behavioral processes are regulated by converging interactions from a variety of neural systems. This kind of control produces a redundancy which prevents the disruption of vital behaviors. REM sleep control can be conceptualized in a similar way, as the result of the interaction of several groups of brain neurons, with no one group having "executive" responsibility.

We can model this sort of control system and contrast it with the "executive neuron" hypothesis. The executive neuron hypothesis (Fig. 11), which is implicit in many studies attempting to anatomically localize the crucial brain substrate for REM sleep, holds that there is a group of brainstem neurons which show periodic changes in their activity. These cells receive and integrate a variety of inputs. The output of these neurons drives sensory, motor and autonomic systems, creating the behavioral and physiological manifestations of REM sleep.

In the multiple control hypothesis (Fig. 12) REM sleep results from the interaction of many groups of neurons. This figure represents some of the many systems known to influence or be influenced by REM sleep. It is not meant to be a wiring diagram of the REM sleep control mechanism, but rather to symbolically represent the extensive interconnections between these systems. The actual number of separate cell groups contributing to REM sleep control and the relative importance of individual connections between cell groups remains to be determined. Each system would have its own specific ultradian rhythmicity. According to this model, it is the network of interconnections between these systems that creates REM sleep. These interconnections synchronize and thereby enhance the amplitude of the ultradian rhythms inherent in each system. The result is the synchronous occurrence of the cyclical changes which constitute REM sleep. In this model there are no "executive neurons."

This model does not view PGO spikes as the generators of all phasic events (see Baust et al. , 1972; McGinty and Siegel, 1978, Pessah and Roffwarg, 1972).

The regions in which lesions are most effective in disrupting REM sleep are reticular areas filled with intersecting pathways. The REM sleep disruption caused by these lesions can be traced, according to this hypothesis primarily to the destruction of axons, not of cell bodies. The acute effects of destruction of any single system might be the disruption of the entire REM sleep generating network as a result of neurological shock. However, if slowly enlarged lesions, infant animals, and long recovery periods were employed, many of the phenomena of REM sleep might reappear as a result of interactions between the remaining systems above and below the lesion site. It could even be possible in this way to create two independent REM sleep generation networks in the same animal. Forebrain and spinal cord states analogous to REM sleep might be recognized in transected nervous systems if the proper techniques for the measurement of activity were employed.

Many physiological changes that once seemed to be uniquely restricted to REM sleep are now known to be controlled by systems which can operate independently. For example, PGO spikes do not only occur in REM sleep, but also occur in waking (Bowker and Morrison, 1976) and transitional slow wave sleep. Lesions in the vicinity of the vestibular nuclei may prevent PGO spike bursts without abolishing REM sleep. PGO spikes can also be elicited by reserpine (Brooks and Gershon, 1972) and other drugs (McGinty and Krenek, 1974) . Under these conditions they appear and disappear periodically in a rhythm which is independent of REM sleep. Muscle atonia similar to that seen in REM sleep may occur during waking, resulting in cataplectic episodes without loss of consciousness (Mitler and Dement, 1974; Guilleminault et al., 1974). Conversely, REM sleep may occur without atonia (Jouvet and Delorme, 1965) . Pontine transections that permit REM sleep may prevent the EKG irregularities that normally accompany it (Villablanca, 1966). These syndromes can be understood as the result of the partial or complete

disconnection of individual brain circuits from the other systems involved in REM sleep control. The result is a weakened, but independent rhythmic oscillation in the disconnected system. The disconnection of one component should also change the oscillation frequency of the remainder of the system. Lesion procedures which damage systems participating in REM sleep are known to alter the length of the REM sleep cycle (Jouvet, 1962).

During waking the organisms interaction with environmental stimuli would interfere with any synchronous oscillation in these systems. However, during the quiescence of sleep, endogenous rhythmicities would not be disrupted and would synchronize as a result of the network of interconnections. The result would be a strong ultradian rhythm culminating the occurrence of the phenomena of REM sleep.

This model is consistent with findings that stimulation of a variety of structures including cortex (DiPaola et al., 1965) vagal nerve (Puizillout et al., 1974) and visual system (Rechtschaffen et al., 1969) can induce REM sleep, even though none of these structures are required for REM sleep. These stimulations are maximally effective when performed in the deeper phases of slow wave sleep. These effects would be achieved by entraining and intensifying the ultradian increase in unit activity that characterizes REM sleep.

The hypothesis advanced here is that it is the network of interconnections between neural systems that creates REM sleep. A corollary is that understanding of REM sleep can only be achieved by the analysis of the periodicities of each of the physiological systems activated during REM sleep and of the interactions between these systems.

This theory of multiple control sites for REM sleep suggests a subtle change in approach to the question of "What is the function of REM sleep?" If one thinks of a REM sleep system as being guided by an executive neuron or neurons, it is only natural to search for a central "motivation" or function of these "executives." Several hypotheses as to what the function of REM sleep is have been advanced. A multiple control theory

suggests a different approach. Each subsystem contributing to REM sleep would derive different benefits from REM sleep and would exert independent influence on REM sleep parameters. This approach, therefore, emphasizes the multiple functions of REM sleep.

SUMMARY

This paper considers evidence bearing on the question of the anatomical localization of mechanisms generating REM sleep.

1) Studies of sleep states after brainstem transection demonstrate that the area lying rostral to the spinal cord and caudal to the midbrain are sufficient for the occurrence of REM sleep. Investigations further localizing the mechanisms generating REM sleep are confounded by nonspecific effects which could cause loss of REM sleep after lesions.

2) Another technique for localization of REM sleep generating mechanisms is the recording of neuronal activity. Examination of brainstem reticular formation unit activity in unrestrained animals reveals 3 cell types. Type 1 cells discharge only during waking movement periods, being silent in sleep. Type 2 cells discharge at high rates during both waking and sleep, showing a small rate increase in REM sleep and waking movement periods. Type 3 cells discharge at low rates in quiet waking and slow wave sleep, and discharge at high rates during waking movement and REM sleep. All of the cells recorded in the reticularis pontis oralis, reticularis pontis caudalis, pontine gigantocellularis and medullary gigantocellularis nuclei fall into one of these 3 categories. It is suggested that these cells may mediate the motor activation common to both waking and REM sleep. No cells with discharge selective for REM sleep were found.

3) Four hypotheses explaining why no REM sleep "executive neurons" have been observed are presented. Three hypotheses derive from the assumption that technical factors have prevented observation of these cells. The fourth hypothesis considers the possibility that REM sleep "executive" cells may not exist. The implications of this hypothesis are discussed.

REFERENCES

- Adey, W. R., Bors, E. and Porter, R. W. EEG sleep patterns after high cervical lesions in man. Archives of Neurology, 19; 377-383, 1968.
- Adrien, J. Lesions of the locus coeruleus complex and of the raphe nuclei in the newborn kitten. Sleep Research, 4: 69, 1975.
- Bard, P. and Macht, M. B. The behavior of chronically decerebrate cats. In G. E. W. Wolstenholme and L. M. O'Conner (Eds.,) Neurological Basis of Behavior. London, Churchill, 1958, pp. 55-75.
- Baust, W., Holzbach, E. and Zechlin, O. Phasic changes in heart rate and respiration correlated with PGO-Spike activity during REM sleep. Pflugers Archives , 331 ; 113-123, 1972.
- Berman, A. L. The Brain Stem of the Cat. Madison, Wisconsin, University of Wisconsin Press, 1968,
- Bignall, K. E. and Schramm, L. Behavior of chronically decerebrated kittens. Experimental Neurology, 42 : 519-531, 1974.
- Bizzi, E., Pompeiano, O. and Somogyi, I. Spontaneous activity of single vestibular neurons of unrestrained cats during sleep and wake-fulness. Archives italiannes de Biologie, 102: 308-330, 1964.
- Bowker, R. M. and Morrison, A. R. The startle reflex and PGO spikes. Brain Research, 102; 185-190, 1976.
- Brooks, D. C. and Gershon, M. D. An analysis of the effect of reserpine upon ponto-geniculo-occipital wave activity in the cat. Neuropharmacology, 11: 499-510, 1972.
- Carli, G. and Zanchetti, A. A study of pontine lesions suppressing deep sleep in the cat. Archives italiannes de Biologie, 103 ; 751-788, 1965.

- Casey, K. L. Somatic stimuli, spinal pathways, and size of cutaneous fibers influencing unit activity in the medial medullary reticular formation. *Experimental Neurology*, 25: 35-56, 1969.
- Chu, N. and Bloom F. E. Norepinephrine-containing neurons: Changes in spontaneous discharge patterns during sleep and waking. *Science*, 179: 908-910, 1973.
- DiPaola, M., Rossi, G. F. and Zattoni, J. Induction of EEG desynchronized sleep by electrical stimulation of the neocortex. *Archives italiannes de Biologie*, 103 ; 818-831, 1965.
- Gadea-Ciria, M. Tele-encephalic versus cerebellar control upon ponto-geniculo-occipital waves during paradoxical sleep in the cat. *Experientia*, 32; 889-890, 1976.
- Guilleminault, C., Wilson, R. A. and Dement, W.C. A study on cataplexy. *Archives of Neurology*, 31 : 255-261, 1974.
- Henley, K. and Morrison, A. R. A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat. *Acta Neurobiologica Experimental*, 34; 215-232, 1974.
- Hobson, J. A. The effects of chronic brain-stem lesions on cortical and muscular activity during sleep and waking in the cat. *Electro-encephalography and clinical Neurophysiology*, 19: 41-62, 1965.
- Hobson, J. A., McCarley, R. W., Pivik, T. and Freedman, R. Selective firing by cat pontine brain stem neurons in desynchronized sleep. *Journal of Neurophysiology*, 37: 497-511, 1974.
- Hobson, J. A., McCarley, R. W. and Wyzinski, P. W. Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups. *Science*, 189: 55-58, 1975.

- Hoshino, K. and Pompeiano, O. Selective discharge of pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat. Archives italiennes de Biologie, 114; 244-277, 1976.
- Jones, B. E., Harper, S. T. and Halaris, A. E. • Effects of locus coeruleus lesions upon cerebral monoamine content, sleep wakefulness states and the response to amphetamine in the cat. Brain Research, 124: 473-496, 1977.
- Jouvet, M. Recherches sur les structures nerveuses et les mecanismes responsables des different-es phases du sommeil physiologique. Archives italiennes de Biologie, 100 : 125-206, 1962.
- Jouvet, M. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. Ergebnisse der Physiologic, 64: 166-307, 1972.
- Jouvet, M. and Delorme, F. Locus coeruleus et sommeil paradoxal. Comptes Rendus Societe de Biologie, 159: 895-899, 1965.
- Laurent, J. P., Cespuglio, R. and Jouvet, M. De-limitation des voies ascendants de l'activite ponto-geniculo-occipitale chez le chat. Brain Research, 55 ; 29-52, 1974.
- Magoun, H. W., Bulbar inhibition and facilitation of motor activity. Science, 100: 549-550, 1944.
- Magoun, H. W. and Rhines, R. An inhibitory mechanism in the bulbar reticular formation. Journal of Neurophysiology, 9_: 165-171, 1946.
- McCarley, R. W. and Hobson, J. A. Single neuron activity in cat gigantoe ellular tegmental field: Selectivity of discharge in desynchro-nized sleep. Science, 174: 1250-1252, 1971.
- McGinty, D. J. and Harper, R. M. Dorsal raphe neurons: Depression of firing during sleep in cats. Brain Research, 101: 569-575, 1976.

- McGinty, D. J. and Krenck, T. REM phenomena during alpha-chloralose anesthesia in the cat. Sleep Research, 3: 61, 1974.
- McGinty, D. J. and Siegel, J. M. Sleep states. In E. Satinoff and P. Teitelbaum (Eds.), Handbook of Behavioral Neurobiology: Motivation, 1978, in press.
- McGinty, D. J. and Serman, M. B. Sleep suppression after basal forebrain lesions in the cat. Science, 160; 1253-1255, 1968.
- Mitler, M. and Dement, W. Cataplectic-like behavior in cats after micro-injection of carbachol in the pontine reticular formation. Brain Research, 68: 335-343, 1974.
- Morrison, A. R. and Bowker, R. M. A caudal source of cervical and forelimb inhibition during sleep. Experimental Neurology, 33: 684-692, 1971.
- Morrison, A. R. and Pompeiano, O. Vestibular influences during sleep. IV. Functional relations between Vestibular nuclei and lateral geniculate nucleus during desynchronized sleep. Archives italiannes de Biologie, 104 :425-458,1966.
- Netick, A., Orem, J. and Dement, W. Neuronal activity specific to REM sleep and its relationship to breathing. Brain Research, 120: 197-207, 1977.
- Perenin, M. T., Maeda, T. and Jeannerod, M. Are vestibular nuclei responsible for rapid eye movements of paradoxical sleep. Brain Research, 43: 617-621, 1972.
- Pessah, M. A. and Roffwarg, H. P. Spontaneous middle ear muscle activity in man: A rapid eye movement sleep phenomenon. Science, 178; 773-776, 1972.

- Peterson, B. W., Franck, J. I., Pitts, N. G. and Daunton, N. G. Changes in responses of medial pontomedullary reticular neurons during repetitive cutaneous, vestibular, cortical, and tectal stimulation. Journal of Neurophysiology, 39: 564-581, 1976.
- Pompeiano, O. and Hoshino, K. Central control of posture: Reciprocal discharge by two pontine neuronal groups leading to suppression of decerebrate rigidity. Brain Research, 116; 131-138, 1976a.
- Pompeiano, O. and Hoshino, K. Tonic inhibition of dorsal pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat. Archives italiannes de Biologie, 114: 310-340, 1976b.
- Puizillout, J. J. , Ternaux, J. P., Foutz, A. S. and Fernandez, G. Les stades de sommeil de la preparation "encephale isole." I. Declenchement des pointes ponto-geniculo-occipitales et du sommeil phasique a ondes lentes. Role des noyaux du raphe. Electroencephalography and Clinical Neurophysiology, 37: 561-576, 1974.
- Rechtschaffen, A., Dates, R. , Tobias, M. and Whitehead, W. E. The effect of lights-off stimulation on the distribution of paradoxical sleep in the rat. Communications in Behavioral Biology, A3; 93-99, 1969.
- Rosner, B. S. Brain functions. Annual Review of Psychology, 21: 555-594, 1970.
- Roussel, B., Pujol, J. F. and Jouvet, M. Effects des lesions du tegmentum pontique sur les etats de sommeil chez le rat. Archives italiannes de Biologie, 114; 188-209, 1976.
- Saito, H., Sakai, K. and Jouvet, M. Discharge patterns of the nucleus parabrachialis lateralis neurons of the cat during sleep and waking. Brain Research, 1977, in press.

- Scheibel, M. E. and Scheibel, A. B. The response of reticular units to repetitive stimuli. Archives italiannes de Biologie, 103; 279-299, 1965.
- Sherrington, C. S. The integrative action of the nervous system (2nd Edition). New Haven, Connecticut, Yale University Press, 1947.
- Siegel, J. M. and McGinty, D. J. Brainstem neurons without spontaneous unit discharge. Science, 193: 240-242, 1976.
- Siegel, J. M. and McGinty, D. J. Pontine reticular formation neurons: Relationship of discharge to motor activity. Science, 196; 678-680, 1977,
- Siegel, J. M., McGinty, D. J. and Breedlove, S.M. Sleep and waking activity of pontine gigantocellular field neurons. Experimental Neurology, 56; 553-573, 1977.
- Simon, R. P., Gershon, M. D. and Brooks, D. C. The role of the raphe nuclei in the regulation of ponto-geniculo-occipital wave activity. Brain Research, 58: 313-330, 1973.
- Sprague, J. M. Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. Science, 153: 1544-1547, 1966.
- Villablanca, J. Behavioral and polygraphic study of "sleep" and "wakefulness" in chronic decerebrate cats. Electroencephalography and Clinical Neurophysiology, 21 : 562-577, 1966.