

Location of the systems generating REM sleep: Lateral versus medial pons

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Hobson et al. are to be congratulated for their acceptance of the evidence inconsistent with their original hypothesis. This evidence includes findings that:

(1) Neurons in the medial pontine reticular formation do not discharge selectively in REM sleep (McGinty, Harper & Fairbanks 1974; Siegel & McGinty 1977; Siegel, McGinty & Breedlove 1977; Vertes 1977). Although intracellular recordings of these cell groups have produced new data, these do not bear on the selectivity issue unless control recordings are made from other pontine cell groups and the entire profile of the waking-sleep cycle discharge is compared. The original error, which was based on the absence of movement in the head-restrained animal, should not be repeated in the intracellular series.

(2) The best site for cholinergic elicitation of REM sleep is not in the gigantocellular tegmental field (FTG) region of the medial pons.

(3) Total destruction of the medial reticular formation of the pons does not prevent REM sleep (Sastre, Sakai & Jouvet 1981; Drucker-Colin, Bernal-Pedraza, Fernandez-Cancino & Morrison 1983). What is most striking about these two studies is not that REM sleep eventually recovers from the lesions but rather that these gigantic lesions of the medial reticular formation are almost completely without effect on REM sleep. REM sleep was reported to be present in nearly normal amounts within 24 hours after the lesion (Sastre et al. 1981). Hobson et al. argue that there are many examples, such as suprachiasmatic nucleus (SCN) lesions, in which a total function is not lost after the lesion. However, although not all circadian rhythms are lost after SCN lesions, there is a clear discrete deficit, loss of some circadian rhythms, including that of sleep-wakefulness. Analogous arguments can be applied to the other lesions mentioned by Hobson et al., in contrast to the lack of effects of FTG lesions.

Having accepted these data, where do we go from here? The approach taken by Hobson et al. is to hypothesize a distributed system, organized so that destruction of any one of its elements does not disrupt REM sleep. This is a very attractive idea, since it is a truism that few functions are entirely localized to a small group of neurons. In fact, we have ourselves previously proposed theories of distributed generation of REM sleep (Siegel 1979b; McGinty 1985). However, the reciprocal-interaction model would seem to require the existence of selective REM-on neurons. Although a few localized REM-on neurons have been described, these have been implicated only in the atonia of REM, not the generation of REM as a whole. We fail to see the advantage of a distributed system of neurons that do not fit the model.

Nearly all models accept the evidence from pharmacological and unit-recording studies that putative aminergic REM-off neurons modulate REM and that the suppression of aminergic functions may permit transitory increases in REM. Hobson et al. now emphasize that a distributed system of aminergic neurons is an essential component of their reciprocal-interaction

model. A distributed system is required because it is known that destruction of the largest noradrenergic nucleus, the locus coeruleus, does not block REM sleep (Jones, Harper & Halaris 1977), whereas transections behind the dorsal raphe nucleus, the largest collection of serotonergic neurons, do not alter the REM cycle in the pontine preparation (e.g., Serman, McGinty & Iwamura 1974). Thus, the model must be revised to speculate that some additional poorly studied neurons, not yet directly implicated in REM control, can serve the required aminergic function. In addition, it has been 10 years since the presentation of the Lotka-Volterra model of the reciprocal-interaction system. A major problem with this model is that it predicts that aminergic neurons will reach near-highest rates near the end of the REM period - as one would expect, since the theory states that they are excited by REM-on cells. All available data, including those of the Hobson group, fail to fulfill this prediction. The model must be revised.

Finally, recent evidence suggests that further localization of the REM-sleep-generating mechanism is possible. Jouvett first found that structures rostral to the pons were not required for REM sleep. *Although REM sleep was present in brain stem structures after the transection, it was absent from forebrain structures.* More recent studies utilizing transections between the pons and medulla (Siegel, Nienhuis & Tomaszewski 1984) have demonstrated that pontine mechanisms are sufficient to generate REM sleep. *Although REM sleep was present in the pons and forebrain of these preparations, it was entirely absent in the medulla and caudal regions of the neuraxis.* The idea that REM sleep is generated by a distributed network would be strongly supported by evidence that neuronal activity in the forebrain or medulla of such preparation showed the defining signs of REM sleep. However, we could see no evidence of this. Whereas a small piece of the neuraxis containing the pons shows virtually all the local signs of REM sleep, the massive forebrain and medulla-spinal cord, when detached from the pons, show no signs of REM sleep - despite the fact that both these regions contain cells that go off in REM sleep and cells that show the characteristic medial reticular pattern of activation during waking movements and REM sleep. No one would say that the forebrain and medulla make no contribution to REM sleep (in fact, it has been hypothesized that the medulla has a critical role in modulating the REM sleep state (Siegel, Tomaszewski & Nienhuis 1986)); however, it is clear that the pons contains the neurons critical for generating REM sleep.

Having localized the neurons critical to REM sleep in the pons, can we then conclude that the REM-sleep-generating function is distributed throughout the pons? Recent evidence clearly shows that further localization is possible. Massive lesions of the medial pons have little effect on REM sleep (Jones 1985b; Sastre et al. 1981), but relatively small lesions of the dorsal half of the lateral pontine reticular formation can totally and permanently abolish REM sleep throughout the brain. Cholinergic stimulation of the medial pontine reticular formation produces REM sleep only after relatively long latencies, but stimulation of the dorsolateral reticular formation, outside the FTG, produces REM sleep at relatively short latencies. A recent mapping study using very small volumes of carbachol concluded that "sites located in the zone below the level of the ventral margin of PAG [periaqueductal gray] and above the level of the dorsal margin of FTG were significantly more effective in eliciting M4 [the state of complete atonia] than sites in PAG or in the principal nucleus of LC ($p < 0.01$) or in FTG ($p < 0.01$)" (Katayama, DeWitt, Becker & Hayes 1984). In fact, although there are some ChAT-positive neurons in the medial pons, the greatest concentration is in the same dorsolateral area whose stimulation induces REM sleep at short latency (Kimura, McGeer, Peng & McGeer 1981). Recent work on the medial reticular formation has shown that cells with very specific motor correlates are intermixed throughout various subregions of the reticular formation (Siegel & Tomaszewski 1983; Siegel, Toma-

szewski & R. L. Wheeler 1983). Thus, cells, related to tongue movement arc restricted to a relatively small pontine region, although within that region they are intermixed with cells relating to totally different movements. Might there be a similar localization of cells related only to the atonia, EEG desynchrony, or other aspects of REM sleep? Or are the cells that are active during the motor activations of both waking and REM sleep critical for REM sleep generation? Recent evidence indicates that there are in fact cells that are selectively active in REM sleep. These cells discharge during REM sleep but are completely inactive during waking movement (Sakai 1985a). The greatest concentration of such cells is in the lateral pons, the same region that stimulation and lesion studies point to. It seems to us that this concordance of stimulation, lesion, and recording evidence indicates that a further localization of systems critical for REM sleep has been achieved. *The lateral pons is the brain region critical for REM sleep.* Medial pontine regions, including the FTG, are not critical for REM sleep generation. Furthermore, it is clear that, as is the case for reticulomotor functions, the neurons whose interaction is critical for REM sleep constitute only a small percentage of the cells within the lateral pontine region.

As we mentioned above, the fact that certain regions are not required for REM sleep generation does not mean that they make no contribution to REM sleep control. In fact, it is likely that all brain regions make some contribution to REM sleep. However, it is of considerable heuristic value to try to distinguish as precisely as possible those neurons that play critical roles in the REM sleep process from those that play minor or modulatory roles in its control. We can abandon the localizationist approach only when the data will not support the further identification of brain stem areas or cell groups critical for REM sleep.