

- Reich, L., Weiss, B.L., Coble, P., McPartland, R. and Kupfer, D.J. Sleep disturbance in schizophrenia, *Arch. Gen. Psychiatry*, 32 (1985) 51-5.
- Reynolds, C.F., Buysse, D.J., Kupfer, D.J., Hoch, C.C., Houck, R.R., Matzkie, J. and George, C.J. Rapid eye movement sleep deprivation as a probe in elderly subjects. *Arch. Gen. Psychiatry*, 47 (1990) 1128-36.
- Reynolds, C.F., Kupfer, D.J., Taska, L.S., Hoch, C.C., Sewitch DE. and Spiker, D.G. Sleep of Healthy Seniors: A Revisit, *Sleep*, 8 (1985) 20-92.
- Takahashi, K. and Atsumi, Y. Precise Measurement of Individual Rapid Eye Movements in REM Sleep of Humans, *Sleep*, 20 (9) (1997) 743-752.
- Vitiello, M.V., Bokan, J.A., Kukull, W.A., Muniz, R.L., Smallwood, R.G. and Prinz, P.N. Rapid eye movement sleep measures of Alzheimer's-type dementia patients and optimally healthy aged individuals, *Biol. Psychiatry*, 19 (1984) 721-34.
- Zimmermann, J.C., Czeisler, C.A. Weitzman, E.D. REM density is dissociated from REM sleep timing during free-running sleep episodes, *Sleep*, 2 (1980) 409-15.

Rapid Eye Movement Sleep  
B.N. Mallick and S. Inoué (Eds)  
Copyright © 1999, Narosa Publishing House, New Delhi, India

## 27. Why We Believe What We Believe About REM-Sleep Regulation

Joel H. Benington

Department of Biology, Saint Bonaventure University, Saint Bonaventure,  
NY 14778, USA

### Introduction

As described elsewhere in this volume, REM sleep is a highly activated state of the brain, comparable to the most active waking. Yet in this state, the subject lies quiescent and inattentive to the outside world. Its activated brain instead attends to a bizarre progression of dream imagery. To initiate REM sleep, the brain must become intensely activated without the subject's waking up. Specific physiological mechanisms appear to have evolved to make this possible. And even though these mechanisms appear to work well enough, the transition to REM sleep is often interrupted at the very beginning of a REM-sleep episode, making the brain return to nonREM sleep and try again.

The alternation between nonREM sleep and REM sleep is clearly an involved process, and what we already know of the physiological mechanisms underlying it indicates that they are complex and carefully regulated. The existence of such a process in a living thing implies adaptation for some purpose. It is highly unlikely that the vast majority of mammals would express REM sleep in such a characteristic and well regulated manner without some very good reason. And yet it is fair to say that we do not now have any clear idea of what the function of REM sleep is. This is not for want of trying: a number of hypotheses have been advanced over the years, but no hypothesis has been experimentally confirmed with enough authority to cause it to be preferred over all others.

There are two ways one could go about attempting to overcome our current ignorance of the function of REM sleep:

- (1) one could propose a specific, physiologically detailed new hypothesis concerning the function of REM sleep and thereby hope to solve the problem at one stroke, or

- (2) one could proceed more cautiously, considering first what we *do* confidently know about REM sleep and thereby narrow down the range of possible functions that REM sleep *could* serve.

The former approach has its uses. Even though most such hypotheses do not turn out to be right, they stimulate research and seldom fail to advance understanding, often in unexpected ways. If I had such a hypothesis to offer, I would certainly present it for consideration. The latter approach is not as flashy, but in lieu of plausible, specific hypotheses, it is probably our best approach to shedding some light on this difficult subject.

This chapter, re-examines the current thinking about REM sleep, and would argue the following:

- (1) A consensus model of REM-sleep regulation has emerged over the past 40 years.
- (2) This model was not the necessary conclusion of a series of experimental tests, but was instead agreed upon in a surprisingly casual way, presumably because it appeared intuitively obvious.
- (3) The phenomena associated with REM sleep have come to be interpreted in light of this model, causing it to appear to be better substantiated than it is.
- (4) There are in fact a number of robust findings that argue strongly against this model, but the consensus in favor of the currently dominant model of REM-sleep regulation is so strong that they have not had much impact on people's thinking.

### Current View of REM-Sleep Regulation

The following ideas about REM-sleep regulation would be accepted readily by the vast majority of sleep researchers:

#### *(A) REM sleep is homeostatically regulated*

This implies that the amount of REM sleep expressed per day is regulated by mechanisms that increase REM-sleep expression after a period of deprivation. This is often modeled in terms of an increase in the 'need' or 'propensity' for REM sleep over time and the discharge of this need or propensity in REM sleep.

#### *(B) REM sleep is physiologically necessary*

As a rule, inconsequential events and processes are not homeostatically regulated. Temperature, water balance, and ion concentrations are regulated in mammals because physiological performance is reduced if they are not maintained within a narrow range of values. The existence of homeostatic regulation of REM-sleep expression implies that REM sleep is serving some essential function.

#### *(C) The function of REM sleep is somehow related to waking (perhaps to the cognitive activities of waking)*

The majority of hypothesized functions for REM sleep, and in particular the ones that receive the most attention have been waking-related. The idea that REM sleep is necessary for optimal cognitive function in waking is especially favored in the popular literature on sleep and has been the basis of a number of related hypotheses in the scientific literature (e.g., Crick and Mitchison, 1983; Jouvet, 1975). These hypotheses have spawned a great deal of biopsychological research, some of which has been published in prestigious journals quite recently (e.g., Karni et al., 1994).

#### *(D) Homeostatic regulation of REM sleep must occur in relation to waking*

This follows from (A) and (D). If the restorative function of REM relates to the activities of waking, then the need for REM sleep must accumulate in relation to the duration and/or quality of prior waking.

#### *(E) Within sleep, the timing of REM sleep is controlled by an oscillator*

The idea that there is a nonREM/REM sleep cycle is firmly entrenched in the literature. Generally, the implication is that the cycle is controlled by some sort of biological oscillator with an ultradian period, analogous perhaps to the circadian clock in the suprachiasmatic nucleus (SCN) in mammals.

### Evidence for the Current View of REM-Sleep Regulation

These ideas are so well established, and so much research has been based on one or more of them, that many sleep researchers may not have given much thought to the nature of the evidence for them. As these ideas have all been around for more than 30 years, the initial findings that inspired them are buried in the early literature on sleep, in articles that are seldom consulted any longer. Since my research has suggested hypotheses that are at variance with some components of the current view of REM-sleep regulation, I have surveyed the earlier literature to determine how well founded those component ideas are. I have reviewed that literature extensively elsewhere (Benington, 1992; Benington and Heller, 1994a). In this article, I will only highlight the most important points in that development.

Let us take each of the above five ideas in turn and consider their antecedents.

#### *(A) REM sleep is homeostatically regulated*

Evidence for this idea came originally in 1960 with Dement's seminal study of selective REM-sleep deprivation in humans. That study demonstrated two things that have continued to be the basis for this idea ever since: (1) REM-sleep deprivation is followed by a compensatory 'rebound' increase in REM-sleep expression, (2) there is an increase in the frequency of attempts to enter REM sleep as the amount of REM-sleep deprivation increases. These findings

have since been replicated repeatedly in other studies in both animals and humans. No other evidence of homeostatic regulation of REM sleep even approaches the robustness of these findings.

**(B) REM sleep is physiologically necessary**

On one hand, this idea could be seen as following logically from (A), as in the initial statement of this idea above. There have in addition been a number of attempts to demonstrate adverse consequences of REM-sleep deprivation. In Dement's original REM-sleep deprivation study (1960), there are allusions to mild 'behavioral changes', including anxiety, irritability, and difficulty in concentrating. There have since been untold studies purporting to demonstrate definite behavioral consequences of REM-sleep deprivation (for review, see Lewin and Singer, 1991). Most of these studies have been inspired by the general idea that REM sleep is somehow necessary for normal cognitive function. Another sort of evidence that REM sleep is physiologically necessary comes from long-term REM-sleep deprivation studies performed at the University of Chicago, in which rats die after several weeks of 'selective' REM-sleep deprivation (Kushida et al., 1989).

**(C) Function of REM-sleep regulation is waking-related**

This idea is in many ways the most interesting and pivotal element of the widely accepted of REM-sleep regulation, but there is little or no compelling evidence for this idea. At the very least, we can say that this idea was dominant very early, before any of the evidence that may now be advanced in its defense had been collected. It is already implicit in Dement's original REM-sleep deprivation study (1960), at a time when the only evidence at all for it was Dement's anecdotal reports of mild 'behavioral changes' associated with REM-sleep deprivation. It is also striking that no review I have seen of any aspect of REM sleep has bothered to defend this idea against any alternative. It apparently has just been accepted as a given by the sleep research community. This is not so surprising, since REM sleep is after all a sleep state, and one naturally supposes that sleep serves some function in relation to waking. But one does not expect the scientific community to arrive at conclusions in so casual a manner.

**(D) Homeostatic regulation of REM sleep is in relation to waking**

This idea is only reasonable if we accept (A) and (C). Given that homeostatic regulation can be modeled in terms of the accumulation and discharge of a 'need', if the function of REM sleep relates to waking, then the 'need' for REM sleep should accumulate in waking. If, however, the need for REM sleep can be shown to accumulate in nonREM sleep rather than waking, then we should logically conclude that the function of REM sleep concerns some aspect of nonREM sleep rather than waking. I was led to reconsider the

current view of REM-sleep regulation by evidence that REM-sleep expression is homeostatically regulated in relation to nonREM sleep rather than waking.

**(E) Within sleep, the timing of REM sleep is controlled by an oscillator**

Simply put, the evidence for this idea is that REM-sleep episodes occur at fairly regular intervals. The 'rhythmic' occurrence of REM sleep naturally suggests the idea of a 'sleep cycle', which in turn suggested the existence of a biological oscillator, along the lines perhaps of the circadian pacemaker in the SCN. However, an oscillator is only one way to produce a 'cycle', and not necessarily the most likely one. The following considerations suggest that the idea of an oscillator-controlled sleep cycle is worth rethinking.

- (i) Seemingly rhythmic phenomena can be caused by processes that would not usually be described as oscillators. For example, common behaviors such as eating, drinking, and sexual activity will occur at fairly regular intervals in a constant enough environment. Like most biological phenomena that exhibit apparent rhythmicity, these are controlled homeostatically, by an accumulation of a need for gratification. A familiar non-biological example of such a process would be a refrigerator, which turns on at very regular intervals without being controlled by what one would usually call an oscillator. Rather, as long as the need in question accumulates and is discharged at constant rates, the system will 'cycle' between states at fairly regular intervals. A true oscillator such as the circadian clock in the SCN is seldom the mechanism underlying apparently rhythmic behaviors in biological systems.
- (ii) At best, the timing of REM sleep could be said to be 'fairly regular'. It is not rigidly pacemaker-like by any means. Dement and Kleitman's original report on the electrographic manifestation of nonREM sleep vs. REM sleep (1957) illustrates the timing of REM-sleep episodes in a series of nights from a number of human subjects, and there is considerable variation in 'cycle' lengths. Other studies have shown that the standard deviation of sleep cycle length is typically about 1/4 of the mean, the second and third cycles during the night in humans are consistently longer than the first and fourth, and sleep cycle length is even more variable in non-human mammals (for review, see Benington, 1992). As one person has observed, "It seems unreasonable to imply rhythmicity when to account for 95% of the distribution, the range has to be of the order of 50-130 min" (Lewis, 1974)
- (iii) The idea of an oscillator-controlled sleep cycle was personally important to Kleitman as a result of his highly speculative hypothesis of a basic rest-activity cycle (BRAC). According to this hypothesis, which was championed by Kleitman in spite of little or no evidence, the sleep cycle is simply one manifestation of an ultradian rhythm that persists during waking as well (for review, see Benington, 1992). It appears as though Kleitman's enthusiasm for the idea of an ultradian rhythm as

a unifying explanation for the timing of REM sleep as well as other periodic phenomena in both humans and infants may have induced him to stress the idea of an oscillator in the absence of any concrete evidence for one.

- (iv) The idea of an oscillator-controlled sleep cycle was further reinforced when Hobson and McCarley (1975) proposed a neurochemical mechanism for the cycle, involving reciprocal interactions between brainstem cholinergic and monoaminergic neurons. This hypothesis continued to garner attention in the sleep research community for many years, long after the original findings that inspired it had been discredited. The very fact that the most prominent physiological model of REM-sleep regulation was oscillatory in nature was bound to perpetuate the idea of an oscillator-controlled sleep cycle.
- (v) As long as it is thought that REM sleep is homeostatically regulated in relation to waking, then either the sleep cycle is indeed controlled by an oscillator, or there must be two types of REM-sleep need, one that accumulates during waking and manifests itself in a REM-sleep rebound following deprivation, and another that accumulates during nonREM sleep and is responsible for the timing of REM sleep during a period of sleep. If, on the other hand, REM sleep is homeostatically regulated in relation to nonREM sleep, then the situation is vastly simplified, and both the amount and timing of REM sleep are controlled homeostatically by the same accumulation of REM-sleep need.

In brief, the evidence for (A) is quite good, (B) is less well established but seems perfectly reasonable given (A), and (C), (D), and (E) are poorly substantiated, having been established within the sleep research community virtually by fiat. This is not to say that they are not true, but it should encourage us at least to consider alternatives. Logically, the most straightforward alternative is that the function of REM sleep relates to nonREM sleep rather than to waking, that homeostatic regulation of REM-sleep expression is likewise in relation to nonREM sleep, and that the timing of REM sleep is controlled by accumulation of REM-sleep need during nonREM sleep.

### **The Hypothesis that REM Sleep is Functionally Related to NonREM Sleep**

I have presented this hypothesis in detail elsewhere (Benington and Heller, 1994a), and have in that publication cited the other authors that have presented similar hypotheses over the past 30 years. In this chapter, I will give only a summary accounting of the evidence for this view.

First, the states of REM sleep and waking are nearly identical neuro-physiologically, whereas REM sleep and nonREM sleep are quite different. It is difficult to imagine how REM sleep could be physiologically necessary to the optimal expression of another state that is as similar to it as waking is.

Not surprisingly, the functions that have been hypothesized for REM sleep generally involve either: (1) higher-order cognitive functions such as learning and memory which could be manifested quite subtly relative to the basic neurophysiological characteristics of a behavioral state (Crick and Mitchison, 1983; Jouvet, 1975), or (2) one of the few neurophysiological aspects of brain functioning that actually differ between waking and REM sleep, such as the activity of noradrenergic neurons (Siegel and Rogawski, 1988).

Second, the preponderance of evidence suggests that the regularity of the interval between REM-sleep episodes is measured in terms of total nonREM sleep time elapsed rather than total time elapsed (for review, see Benington and Heller, 1994a). Moreover, the 'clock' is not reset by waking. So either there is an oscillator that only runs during nonREM sleep and holds its place during intervening waking, or the timing of REM sleep is determined by accumulation of a need for REM sleep during nonREM sleep. The latter seems the more obvious explanation. Yet so dominant was the idea of an oscillator-controlled cycle that the authors of these studies all referred to their hypothesis in terms of a 'sleep-dependent cycle'.

In my own work, the interval between REM-sleep episodes in the rat has been shown to be punctuated often by one or more abortive attempts to enter REM sleep (Benington and Heller, 1994b). The apparent rhythmicity in REM-sleep timing (when measured according to the occurrence of REM-sleep episodes lasting longer than 30 sec) is underlain by a much less rhythmic occurrence of transitions to REM sleep. Strikingly, there is a very consistent, linear increase in the incidence of these transitions as a function of the time elapsed since the last REM-sleep episode of more than 30 sec. This strongly suggests that a propensity for REM sleep is accumulating progressively between REM-sleep episodes.

In another study that I worked on, drive to enter REM sleep in rats (as measured by the frequency of attempts to enter REM sleep), was found to increase rapidly during just two hours of highly selective REM-sleep deprivation in the rest period (Benington et al., 1994). At the end of the two-hour deprivation period, transitions to REM sleep occurred 44–60 times per hour of nonREM sleep. This suggests that just two hours of rest-period REM-sleep deprivation produces markedly elevated levels of REM-sleep drive, considerably above anything seen under normal sleep/wake conditions. This is consistent with the idea that the need for REM sleep accumulates during nonREM sleep and is normally discharged (in the rat) at circa 11 min intervals. It is difficult to reconcile with the idea that REM-sleep need accumulates over many hours of waking and is discharged over a series of REM-sleep episodes in each sleep period.

Finally, recent analyses of the ontogeny and phylogeny of sleep in mammals have suggested that nonREM sleep and REM sleep emerge in concert from an undifferentiated sleep state that is identical with neither the one nor the other. Marcos Frank and co-workers (1997) have suggested that 'active sleep'

in pre-weanling rats is not REM sleep but that the electrographic characteristics of both slow-wave (nonREM) sleep and REM sleep emerge from a background of relatively undifferentiated EEG waveforms, beginning just before weaning. These findings suggest that nonREM sleep and REM sleep may be functionally interrelated, as opposed to the widespread view that each serves its own independent function in relation to waking.

Jerome Siegel and co-workers have recently published analyses of EEG recordings from two monotremous mammals, the echidna (Siegel et al., 1996) and platypus (Siegel et al., 1997), as well as single-unit recordings from the brainstem of the echidna (Siegel et al., 1996). Although there are differences in the manifestations of sleep states in these two species, Siegel et al. describe echidna sleep as a single state having characteristics of both placental nonREM and REM sleep, while they report that platypus sleep consists predominantly of a strikingly REM sleep-like state, characterized by muscle atonia, phasic EMG activity, and rapid eye movements. The one noteworthy difference between REM sleep in the platypus and placental REM sleep is that the EEG is of moderate to high amplitude in the platypus, "with consistently more power in all of the frequency bands assessed than that during waking states." In this respect, the REM sleep of the platypus is similar to the indeterminate sleep state of the echidna, only with more REM sleep-like motor and oculomotor manifestations. Siegel et al. scored 60% of platypus sleep time as REM sleep, based on EMG, EOG and ECG activity. The state making up the remainder of platypus sleep is not, however, markedly different from platypus REM sleep: EMG, EOG and ECG recordings exhibit some of the same REM sleep-like manifestations as in platypus REM sleep but to a lesser degree, and the EEG remains at moderate to high amplitude (J. Siegel, personal communication).

Thus, both echidna and platypus sleep lack the marked dichotomy between states that is seen in placental nonREM and REM sleep. And the more homogeneous sleep of both echidna and platypus exhibits characteristics typical of both nonREM sleep and REM sleep in placental mammals. It is not unreasonable to suppose that the more homogeneous sleep of monotremous mammals, like neonatal sleep, may represent a primordial condition out of which both nonREM sleep and REM sleep have emerged together. In the more primordial condition, there may be no need for a separate, highly activated state such as placental REM sleep, because the sleep state seen in monotremous mammals and neonates may not be characterized by as marked hyperpolarization and synchronization of neuronal circuits as placental nonREM sleep.

### Conclusion

The hypothesis that the function of REM sleep concerns nonREM sleep rather than waking is a far cry from a concrete physiological hypothesis as to what that function is. However, the sort of function that would cause a need for REM sleep to accumulate during nonREM sleep is very different from one that would cause a need for REM sleep to accumulate during waking. If

we as a community neglect one entire class of potential functions of REM sleep, we may make no progress towards the sort of concrete physiological hypothesis that will tell us in detail what REM sleep is for. I earnestly hope that this chapter will encourage more detailed consideration of what physiological aspects of nonREM sleep could result in a need for expression of the very different state of REM sleep.

### References

- Benington, J.H., REM-sleep homeostasis in the rat. In: *Department of Biological Sciences*, Stanford University, Stanford, California, 1992, pp.160.
- Benington, J.H. and Heller, H.C. Does the function of REM sleep concern non-REM sleep or waking? *Prog. Neurobiol.*, 44 (1994a) 433-449.
- Benington, J.H. and Heller, H.C. REM-sleep timing is controlled homeostatically by accumulation of REM-sleep propensity during non-REM sleep, *Am.J. Physiol.*, 266 (1994b) R1992-R2000.
- Benington, J.H., Woudenberg, M.C. and Heller, H.C. REM-sleep propensity accumulates during two-hour REM-sleep deprivation in the rest period in rats, *Neurosci. Lett.*, 180 (1994) 76-80.
- Crick, F. and Mitchison, G. The function of dream sleep, *Nature*, 304 (1983) 111-113.
- Dement, W., The effect of dream deprivation, *Science*, 131 (1960) 1705-1707.
- Dement, W.C. and Kleitman, N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming, *Electroenceph. Clin. Neurophysiol.*, 9 (1957) 673-690.
- Frank, M.G. and Heller, H.C. Development of REM and slow wave sleep in the rat, *Am. J. Physiol.*, 272 (1997). R1792-9.
- Hobson, J. A. McCarley, R.W. and Wyzinski, P.W. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups, *Science*, 189 (1975) 55-58.
- Jouvet, M. The function of dreaming: a neurophysiologist's point of view. In: *Handbook of psychobiology* (Eds.), M.S. Gazzaniga and C. Blakemore, Academic Press, New York, 1975, pp. 499-527.
- Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J. and Sagi, D. Dependence on REM sleep of overnight improvement of a perceptual skill, *Science*, 265 (1994) 679-682.
- Kushida, C.A., Bergmann, B.M. and Rechtschaffen, A. (1989) Sleep deprivation in the rat: IV. Paradoxical sleep deprivation, *Sleep*, 12 (1989) 22-30.
- Lewin, I. and Singer, J.L. Psychological effects of REM ("dream") deprivation upon waking mentation. In: *The mind in sleep: psychology and psychophysiology*, (Eds.), S.J. Ellman and J.S. Antrobus, John Wiley and Sons, Inc., New York, 1991, pp. 396-412.
- Lewis, S., (1974) The paradoxical sleep cycle revisited. In: *Chronobiology* (Eds.), L.E. Scheving, F. Halberg and J.E. Pauly, Igaku Shoin, Tokyo, 1974, pp. 487-490.
- Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, H.M. and Pettigrew, J.D. The echidna *Tachyglossus aculeatus* combines REM and non-REM aspects in a single sleep state: implications for the evolution of sleep, *J. Neurosci.*, 16 (1996) 3500-6.
- Siegel, J.M., Manger, P.R., Nienhuis, R., Fahringer, H.M. and Pettigrew, J.D. The platypus has REM sleep, *Sleep Res.*, 26 (1997) 177.
- Siegel, J.M. and Rogawski, M.A. A function for REM sleep: regulation of noradrenergic receptor, sensitivity, *Brain Res. Rev.*, 13 (1988) 213-233.