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Research report

Phylogeny and the function of REM sleep

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Abstract

Phylogenetic studies in placental and marsupial mammals have demonstrated three major correlates of increased REM sleep time across these species. These are high amounts of non-REM sleep time, safe sleep conditions and immaturity at birth. While these variables explain approximately 30% of the variance in REM sleep time across these orders, these relations are violated when animals other than placentals are included. Birds are small, many have safe sleeping situations and are certainly immature at birth, yet they have less REM sleep than the vast majority of mammals. The echidna is immature at birth, has high amounts of non-REM sleep and safe sleeping conditions, yet has been reported to have no REM sleep. Our recent studies in the echidna indicate that REM and non-REM sleep did not evolve sequentially, but rather evolved as a differentiation of a primitive state which held the seeds of both sleep states. The echidna sleeps with an activated brainstem and EEG synchronized forebrain. Future studies of sleep phylogeny need to compare the behavior of key neuronal groups across the sleep cycle, since these results indicate that EEG variables and sleep state durations may give an inadequate picture of the nature of brain activity during sleep.

Key words: Echidna; Monotreme; Evolution; Reticular formation; Unit activity

1. The phylogeny of REM sleep in mammals

While only a small minority of species have been sampled, sleep has been studied in one or more species of most mammalian and avian orders. This has allowed inferences about the correlation of sleep and particularly REM sleep occurrence with physiological, behavioral and genetic characteristics. The following analysis draws on published reviews for their tabulations of REM and non-REM sleep times in various species [1,4,40,41,42].

One important and very surprising observation has been the extensive overlap of REM sleep time across orders. Conversely, closely related species have widely varying REM sleep durations. For example, the amount of REM sleep in marsupials ranges from 1.5–4.0 h, in rodents from 0.8 to 3.4 h, in carnivores from 1.3–3.2 h, in primates from 0.7–1.9 h (1.9 h in man), in edenta (sloth and armadillo) from 3.1–6.1 h, in artiodactyla (cattle, giraffe, pig) from 0.6 to 2.4 h. REM sleep duration does not appear to be strongly related to any of the many characteristics shared by each order. The major determinants of REM sleep time do not seem to be 'order related.'

With regard to REM sleep time, three significant relationships have been described across mammalian orders. One, is that REM sleep time is positively correlated with total sleep time. Animals that have little non-REM sleep have little REM sleep. Non-REM sleep and total sleep time are most highly correlated with body weight. This is a negative correlation, i.e., heavier animals sleep less. This relation may be a factor in the only report of a placental mammal lacking REM sleep. Work by Mukhametov has indicated that the dolphin lacks REM sleep [25]. Other cetaceans have been reported to have small amounts of REM sleepy [27]. Because of their low total sleep time, consistent with their large body mass, low amounts of REM sleep would be expected in cetaceans. However, other variables, most notably the confined recording conditions in which the dolphin observations were made, may have been factors in the total lack of observed REM sleep.

A second major correlate of REM sleep time is maturity at birth. Altricial mammals, that is animals born in a relatively immature state, have high amounts of REM sleep at birth. While these amounts decrease with maturity, even

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after this decrease, the amount of REM sleep in adults of altricial species are considerably greater than in adults of 'precocial' species [20]. Humans have somewhat more REM sleep than other primates. Our 1.9 h/24 is similar to the amount seen in the owl monkey (1.8), the primate with the next highest amount. The relatively high amount of REM sleep in humans correlates with our altriciality.

A third factor that has been found to correlate with REM sleep time is the security of the sleep site. Predators and animals with secure sleep sites have large amounts of REM sleep [1]. For example cats, including lions and tigers as well as *felis domesticus*, have high REM sleep amounts. In contrast, prey animals and those with relatively unprotected sleep sites have short REM sleep periods and low total REM sleep time. For example, cattle and other grazing animals have very low REM sleep amounts.

Attempts have been made to correlate REM sleep time with body temperature, presence of hibernation, lifespan, brain size, brain/body weight ratio and other variables. None of these variables correlates strongly with REM sleep time or REM sleep percent of total sleep [1,41].

To summarize, mammalian phylogenetic data indicate that total sleep time, immaturity at birth and the safety of sleep sites are the variables most highly correlated with REM sleep time. However, these three relationships are all inconsistent with findings in the monotreme mammal, the echidna.

2. Phylogenetic history of the monotremes

Mammals are classified into three taxa, the eutheria (placentals), the metatheria (marsupials) and the prototheria. The monotremes are the only living representatives of the prototheria. DNA hybridization analyses indicate that the monotremes diverged from the other mammalian lines approximately 130 million years ago [21,39]. Thus their divergence was during the early cretaceous period, when theropods such as *allosaurus*, sauropods such as the giant *diplodocus* and ornithischians such as *stegosaurus* flourished. At this time the continents were fused in Gondwanaland. The monotreme divergence occurred at or before the development of the placentals and marsupials. The echidna and platypus lines diverged from each other 60–80 million years ago [38], at the end of the period when *tyrannosaurus, triceratops* and related dinosaurs were dominant. The separation of the platypus and echidna lines coincides with the mass extinctions of the dinosaurs and the major radiations of the eutherian and metatherian lines. It is likely that ancestors of the amphibious platypus were able to occupy vacated niches on land, evolving into echidnas.

3. Sleep in the echidna

The only published study of sleep in monotremes was carried out by Allison and colleagues in 1972 [3]. A major motivation of this study, was to address the issue of whether REM sleep is a phylogenetically old state or whether it evolved relatively recently. The discovery that the pons, a phylogenetically old part of the brain, was critically involved in REM sleep generation and the large amounts of REM sleep early in life, are arguments for the early evolution of this state. The reduction in thermoregulatory responses in REM sleep has some similarity to reptilian thermoregulation and is also consistent with an early evolution of this state. However, the link between REM sleep and dreams in humans, with their rich symbolic content, has been taken to indicate a higher function of REM sleep, consistent with a more recent evolution of this state. Most studies in reptiles and amphibians have not found REM sleep [13,14,17,18,37], also consistent with a relatively recent evolution of this state, although some reports of a REM sleep-like state in reptiles have been presented [5,19].

Allison et al. found that the echidna has periods of EEG synchrony, which are accompanied by elevated arousal thresholds [2]. In contrast with other mammals, the echidna had no EEG spindles during sleep or waking states.

While EEG synchrony was seen, long term recordings from the echidna found that no periods of EEG desynchrony with rapid eye movements occurred while the echidna was quiescent. Since Allison et al. [2] found that they could observe few eye movements in waking in these animals, they sought other possible signs of REM sleep during periods of EEG desynchrony without eye movement. They dubbed these periods 'PS?', to reflect the possibility that they were periods of REM (or paradoxical) sleep. They tested arousal thresholds in PS? and found that unlike REM sleep, which in most species has increased arousal thresholds, PS? had lower thresholds relative to synchronized sleep. Since theta activity is a consistent feature of mammalian REM sleep, they recorded hippocampal activity in the echidna. Theta was present in waking with movement but not in PS?. They looked for cardiac irregularity, a sign of REM sleep in most mammals. This was not present during PS?. They found that brief periods of isoelectric EEG occurred in some, but not all of their echidnas. They found that these brief pauses resulted from apneas rather than having any REM sleep characteristics. They monitored cortical brain temperature and found no abrupt increases characteristic of REM sleep during PS?. Finally they attempted PS? deprivation to see if a PS? rebound akin to REM sleep rebound occurred. They found no evidence of a rebound. Rather the PS?

state *decreased* after the deprivation procedure. Allison et al. interpreted all these findings as consistent with PS? being quiet waking, rather than REM sleep. Hence they concluded that REM sleep did not exist in the echidna. This paper has become a classic in the phylogeny of sleep and forms the starting point for several of the major theories of sleep function and sleep development.

Allison et al. [2] carefully consider the implications of their finding. They first note the desirability of studying sleep in the platypus, the other monotreme. However, "because this species is not available for study" they hypothesize that it too lacks REM sleep. Given their conclusion that monotremes lack REM sleep, what aspect of their biology is responsible for this major difference in state organization and what does this tell us about the evolution of REM sleep? They consider several unusual aspects of monotreme physiology. Monotremes have a low body temperature, though they are homeotherms, so Allison et al. studied the armadillo. They found that it exhibited copious amounts of REM sleep at body temperatures comparable to those seen in the echidna [35]. *Myotis*, a bat that exhibits diurnal torpidity, has REM sleep at temperatures as low as 25 °C [6]. Allison et al., note that the echidna is a hibernator. However hibernators as a group have relatively large amounts of REM sleep [34]. Thus these features of echidna physiology can not explain their lack of REM sleep.

Having rejected body temperature, sleep safety, hibernation and immaturity at birth as explanations for the echidnas lack of REM sleep, Allison et al. [2] conclude that REM sleep is related to the live birth (viviparity) seen in all other mammalian orders. However, while the absence of live birth is a defining feature of monotremes, there is no obvious functional connection between viviparity and REM sleep. Other characteristics found in monotremes but in no other mammals, such as the absence of teats and the electroreceptive sense, could just as well have been linked to the absence of REM sleep.

The findings of no REM sleep in the echidna are inconsistent with the three major predictors of REM sleep time in all other mammalian orders.

1. The echidna, as a relatively small mammal, has the high amount of sleep time expected on the basis of body size. Since REM sleep time is correlated with non-REM sleep time across the mammalian orders, the echidna should have a large amount of REM sleep.

2. The echidna has an extremely safe sleeping situation. It sleeps burrowed into the earth, with only its razor sharp quills protruding. It is quite well camouflaged and extremely difficult to dislodge from its sleeping position even when in a laboratory enclosure. Echidnas typically live for more than 30 years. Ethological observations indicate that they are not preyed upon while they sleep [15]. The safety of its sleeping situation would predict large amounts of REM sleep.

3. The echidna is one of the most immature mammals at birth. Echidnas lay eggs and the newly hatched echidna are helpless, living for extended periods in the mother's pouch before they can function independently. Since altricial animals have relatively high amounts of REM sleep, echidnas should by this criterion be among the mammals with the most REM sleep.

Because of the importance of the echidna findings in formulating theories of REM sleep evolution, we have undertaken a reinvestigation of the issue of the nature of echidna sleep [29]. While the EEG and behavioral characteristics of sleep were thoroughly investigated by Allison et al., the actual neuronal activity was not examined. The epiphenomena of sleep can differ between species. For example, while all other mammals that have been thoroughly examined have REM sleep, the conventional criteria for scoring sleep states can vary considerably. For example animals that are incapable of waking eye movement do not show REM sleep eye movements [4,41]. While the cat and human show complete atonia in REM sleep, the dog shows some tone even in REM sleep [30]. While adult animals always show EEG desynchrony in REM sleep, newborn humans, cats and rats have synchronized EEG during 'active' or REM sleep [16,20]. Therefore the characterization of state in the echidna solely by these variables might be misleading. In order to directly assess the nature of state organization in the echidna, we recorded single unit activity from a wide expanse of the midbrain and pontine reticular formations in the unrestrained echidna. Brainstem activity is responsible for the phenomena of REM sleep [29]. Therefore it should allow a more meaningful characterization of state organization.

In all mammalian species examined, activity of the brainstem reticular formation shows a characteristic change across the sleep cycle. Discharge rate decreases in non-REM sleep relative to quiet waking levels and the interspike interval is regular. In REM sleep, rate increases and interspike intervals become irregular as units fire in a burst pause pattern.

In the echidna we found that neither the REM sleep or non-REM sleep patterns of brainstem unit discharge was present during sleep [29]. Rather, most units reduced discharge rate in sleep (as in non-REM sleep in placental mammals) but increased discharge rate variability (as in REM sleep in placental mammals). The sleep state seen in the echidna has some striking similarities to the sleep states seen in all altricial mammals at birth. Corner and Bour [8] have shown that during active sleep in kittens, unit discharge irregularity is much lower than in adult REM sleep. As pointed out above, 'active sleep' periods

are characterized by a synchronized EEG. Therefore, if echidna sleep represents the evolutionarily 'plesiomorphic' sleep state, this state is to some extent 'recapitulated' early in development.

Our findings in the echidna lead us to a reinterpretation of the conclusions of Allison et al. One should not conclude that REM sleep evolved after non-REM sleep. Rather it appears likely that both states evolved in parallel as a differentiation of a state of decreased discharge rate and increased variability. In this conception we hypothesize advantages of rate reduction in most brain cell groups, including energy conservation and restorative processes that are precluded by synaptic activity. Such processes are maximized by a decrease in discharge rate below that seen in the echidna, as in non-REM sleep. Perhaps this greater decrease could only be sustained if another state (REM sleep) evolved to produce a periodic internal activation of the very neurons that had been inactivated in non-REM sleep. The activation of brain neurons during REM sleep may 'exercise' brainstem synapses, receptors and their coupled intracellular message systems. Some of this 'exercise' may have evolved to compensate for the reduction in discharge rate needed to maximize the energy conservation processes of non-REM sleep. Without such activation, a slow arousal response, as occurs from hibernation, might be required and would put the organism at a selective disadvantage. Other cells groups might be activated in REM sleep to compensate for waking inactivity. Below I discuss a complementary hypothesis of REM sleep function in regulating noradrenergic receptor sensitivity. In the echidna, the primitive sleep state (mixed state of reduced rate and increased discharge variability) would not be expected to produce the same energy savings, nor require a compensatory stimulation of brain circuits to allow rapid arousal.

The novel sleep structure of the echidna constrains sleep theories by showing that non-REM sleep and REM sleep did not evolve sequentially. It also indicates that the primitive sleep state in mammals was not simply non-REM sleep.

4. REM sleep in birds

The presence of REM sleep in birds also violates the laws formulated in mammals for predicting REM sleep time. Most birds are small relative to most mammals. Birds in general are immature at birth. Predator birds are safe during sleep and many other birds have safe sleeping conditions. If the three variables that have been identified in mammals are truly related to underlying REM sleep need, then birds should have larger amounts of REM sleep than most mammals. However, birds typically have very small amounts of REM sleep [4], averaging little more than 30 min per 24 h. Furthermore the largest birds, rather than the smallest, have the largest amounts of REM sleep [7]. Thus those variables that correlate with REM sleep time in mammals do not correlate in birds.

5. Phylogeny and REM sleep function

It therefore appears that phylogenetic relations convey a very confusing message about REM sleep function. REM sleep time is not strongly correlated with phylogenetic order. While studies of placental and marsupial mammals indicate three major predictors of REM sleep duration, these predictors do not explain REM sleep durations in birds nor the nature of sleep in the echidna.

One can argue that REM sleep amount is not indicative of underlying function. It is well known that REM sleep lost during deprivation is not completely compensated for by REM sleep rebound. However, there does appear to be a rebound of REM sleep 'intensity'. This increased intensity can be seen in the longer REM sleep durations and increased frequency of eye movements during recovery REM sleep [9,10,11,22,36]. But this sort of mechanism does not appear to explain the phylogenetic data. In particular, bird REM sleep does not seem to have especially high concentrations of eye movements, twitches or other REM sleep criteria and avian REM sleep durations are shorter than those seen in most mammalian species.

We [31] have presented a theory of REM sleep as a regulator of noradrenergic receptor sensitivity. According to this theory, the cessation of activity of noradrenergic locus coeruleus neurons in REM sleep is a key functional aspect of REM sleep. This cessation of response is hypothesized to modulate receptor sensitivity either by up-regulating receptor number or by changing the coupling of norepinephrine receptors to second messenger systems. Evidence on receptor changes produced by REM sleep deprivation has been mixed [23,24,33]. The one study of postsynaptic response after REM sleep deprivation found decreased postsynaptic norepinephrine response in REM sleep deprived rats [32].

One prediction made in our review was that the echidna like other mammals should have an extended period of complete cessation of locus coeruleus activity in order to fulfill this putative function of REM sleep. In the absence of REM sleep, this should occur in waking or non-REM sleep. This could also be the case in reptiles. The same predictions can also be made for other animal species. Birds may have reduced noradrenergic activity in non-REM sleep or in waking, allowing reduced REM sleep time. If alteration in the activity of monoaminergic cell groups was the underlying 'function' of REM sleep, varia-

tions in activity outside of REM sleep could explain variations in REM sleep duration and intensity. Mammalian evolution might well have led to the loss of a phylogenetically older cessation of activity in monoaminergic cell groups during waking, since the cessation of this discharge in waking might leave animals less alert than would be adaptive in an environment filled with homeotherms able to take advantage of lapses in vigilance. I hypothesize that a cessation of discharge in REM sleep has replaced a cessation in waking in lower mammals and reptiles.

While I am using monoaminergic cell discharge as an example of an underlying functional variable, other cell groups might be of equal or greater importance. Cholinergic, glutamatergic, GABAergic or peptidergic cell populations might be most critical. Neuronal recuperative processes related to decreased or increased activity in neurochemically specific cell populations may be the function of REM and non-REM sleep. However this sort of hypothesis cannot be tested by behavioral observation or by the recording of standard EEG variables.

It is becoming clear that the explanatory power of phylogenetic studies based solely on sleep duration and EEG recording is reaching a point of diminishing returns. Underlying variables must be sought by recording neuronal activity during sleep in a variety of species. When possible, chemical and antidromic identification of cells would be valuable in gaining an insight into the phylogenetic expression of REM sleep processes.

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