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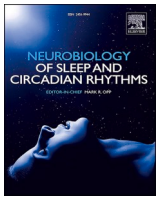

The unified theory of sleep: Eukaryotes endosymbiotic relationship with mitochondria and REM the push-back response for awakening

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ABSTRACT

The Unified Theory suggests that sleep is a process that developed in eukaryotic animals from a relationship with an endosymbiotic bacterium. Over evolutionary time the bacterium evolved into the modern mitochondrion that continues to exert an effect on sleep patterns, e.g. the bacterium *Wolbachia* establishes an endosymbiotic relationship with Drosophila and many other species of insects and is able to change the host's behaviour by making it sleep. The hypothesis is supported by other host-parasite relationships, e.g., *Trypanosoma brucei* which causes day-time sleepiness and night-time insomnia in humans and cattle. For eukaryotes such as Monocercomonoids that don't contain mitochondria we find no evidence of them sleeping.

Mitochondria produce the neurotransmitter gamma aminobutyric acid (GABA), and ornithine a precursor of the neurotransmitter GABA, together with substances such as 3,4dihydroxy phenylalanine (DOPA) a precursor for the neurotransmitter dopamine: These substances have been shown to affect the sleep/wake cycles in animals such as *Drosophilia* and *Hydra.*

Eukaryote animals have traded the very positive side of having mitochondria providing aerobic respiration for them with the negative side of having to sleep. NREM (Quiet sleep) is the process endosymbionts have imposed upon their host eukaryotes and REM (Active sleep) is the push-back adaptation of eukaryotes with brains, returning to wakefulness.

1. Introduction

Sleep is often seen as being a vulnerable state which can be to the detriment of the individual but it occurs in all animals. Historically sleep has been considered to confer some special function because there must have been strong evolutionary pressure to stop this bizarre behaviour, yet sleep has persisted (Siegel 2009; Walker 2021). Here we submit a new unified theory that explains what sleep is, how it came about and why it persists in animals today. We also provide the context to explain what both quiet sleep NREM and active sleep REM are.

Currently there are 6 main theories as to why we need sleep but none as to what sleep is.

(1) The repair and restorative theory is whereby the body needs to repair and replace cellular components that have been used up whilst the body was awake (Adam and Oswald 1977).
(2) Evolutionary or adaptive theory of sleep where the animal requires a period of inactivity especially during a time when wakefulness would be most hazardous. This theory is consistent with evolution in that it favours those individuals that avoid predation and so this strategy is passed on (Siegel 2009). However, it is argued that this theory is not the driver behind the behaviour of sleep.
(3) The energy conservation theory of sleep states that the individual's energy demand and expenditure are reduced during that part of the day/night when it's least efficient for the search of food (Samson et al., 2015). Certainly, this occurs but does not explain why the theory exists.
(4) The brain plasticity theory of sleep, states that a period of sleep is necessary for neurones to repair and reorganise (Frank 2019). Sleep can be seen to play a significant role in the development of infants and children (Jiang 2019). It would seem that by taking away the sensory input of waking it allows the sleeping brain to adjust which may be very important with infants sleeping as much as 14 h/day (Galland et al., 2012). However, if we widen our focus and consider some other mammals this theory starts to

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weaken. Neonate bottle nosed dolphins and killer whales and their mothers have very little or no sleep for the first post-partum month of their lives (Lyamin et al., 2002; Ungurean et al., 2022).

(5) The free radical flux theory of sleep is where free radicals accumulate during wakefulness and are removed during sleep. These free radicals can come from outside the body such as x-rays and ozone or from normal metabolic processes within the animal such as mitochondria, endoplasmic reticulum and peroxisomes. Brain oxidation may be considered to start the process of sleep; however, the available data do not support prolonged wakefulness causing oxidative damage (Gopalakrishnan et al., 2004; Ikeda et al., 2005). Certainly, this theory is valid but it does not explain how sleep behaviour originated nor what it is.

(6) It is a popular theory in science that sleep helps memory and learning. Sleep does this in 2 ways, firstly a sleep refreshed individual is able to adequately focus on the new stimulus and secondly sleep itself consolidates the memory. This theory has been largely explored with laboratory animals and humans and has had a narrow focus, its significance reduces when the behaviour of other animals in their natural habitats are considered (Adams 2022b).

2. Hypothesis

Sleep is an endosymbiont occurrence caused by mitochondria. Awake is the normal state of being for prokaryotes however for eukaryotes with endosymbiont mitochondria, Quiet sleep (NREM), Active sleep (REM) and waking cycles are normal, with REM being the hosts' transition stage back to being Awake.

2.1. Evidence from the wolbachia/Drosophila model

The modern-day evidence for sleep being an endosymbiotic occurrence is firstly, the endosymbiont *Wolbachia* an intracellular bacteria belonging to the alpha-proteobacteria, which infects the cells of *Drosophila* flies, other insects and nematodes and establishes an endosymbiotic relationship with the cell. The endosymbiont is capable of changing the sleep behaviour of its host including promoting sleep (Bi et al., 2018).

Wolbachia (the model in Table 1) has strong similarities with the universal eukaryotic subcellular organelle the mitochondria which likewise can also promote sleep (Kempf et al., 2019). Mitochondria arose as an endosymbiotic bacteria within a larger proto-eukaryotic cell (Burki 2016). The host cell provides a stable environment for the bacterium, and the bacterium contributes a very efficient energy generating system of oxidative phosphorylation to the partnership (Roberts 2017). Like *Wolbachia*, mitochondria, have a double cell membrane and a largely independent genome supporting the long-held view that they are both passed down from an archaic prokaryote. The most recent common ancestor of *Wolbachia* and *Drosophila* mitochondrial genomes are about 8000 years ago (Bayesian phylogenetic analysis) (Richardson et al., 2012; Roberts 2017). Our point is, yes modern-day fruit flies *Drosophila,* do already have mitochondria but we are using Wolbachia endosymbiosis as an example of how this process occurred and continues to the present.

2.2. A new look at the role of mitochondria

It is now known that modern mitochondria have been found outside of cells in a whole state and found to be freely functioning in human blood serum (Al Amir Dache et al., 2020). Conversely, it has been found that some eukaryote cells e.g. Monocercomonoids (Table 1) can survive without the presence of mitochondria (Karnkowska et al., 2016). We can find no evidence that Monocercomonoides sleep.

There are considerable benefits to the host eukaryotes from the endosymbiont mitochondria including allowing for a 15-fold increase of energy i.e., aerobic versus anaerobic respiration. Most importantly the endosymbiont mitochondria are provided with safe housing away from the chaotic competition outside of their hosts' cells.

Mitochondria produce neurotransmitters and other substances that affect the sleep patterns of their host. They produce the enzyme ornithine a precursor of the neurotransmitter GABA; DOPA, a precursor for the neurotransmitter dopamine and GABA itself (Ravasz et al., 2017; Ginguay et al., 2017; Segura-Aguilar 2019) and Kramer et al., (2020).

Ornithine (which is converted to GABA) suppressed *Hydra* sleep in a dose dependent manner and it has been shown to have sleep promoting effects in mated female fruit flies *Drosophila* (Ginguay et al., 2017; Kanaya et al., 2020). In addition, when dosed with the inhibitors of GABA-metabolizing transaminase or GABA reuptake transporter, sleep was promoted in *Hydra* (Kanaya et al., 2020).

Conversely, when the neurotransmitter gamma-aminobutyric acid (GABA, a well-established arousal neurotransmitter that suppresses sleep, in higher animals) was given to *Hydra,* surprisingly, it acted in the opposite way and potently increased daily sleep amount and the number of sleep bouts (Kanaya et al., 2020). GABA is known to modulate dopamine release but it's exact role is unclear (Kramer et al., 2020).

Table 1
Prokaryotes and Monocercomonoides being awake then Eukaryotes with mitochondria in Awake/sleep cycles, then animals with brains having Quiet sleep (NREM) and Active sleep (REM) {theoretical}.

TIME LINE	LIFE FORM	AWAKE OR SLEEP
3.5 billion BP (before present)	Prokaryotes e.g. *Wolbachia* (the model) & Cyanobacteria: & freely available neurotransmitters e.g. dopamine	Awake
2.7 billion BP	Monocercomonoides (Eukaryotes with secondary lost mitochondria).	Awake
2.7 billion BP	Eukaryotes + endosymbiosis with mitochondria	Awake/quiet sleep (NREM) {predicted}
500 million BP	brainless e.g.	
13 million BP	*Hydra & Cassiopeia*	Awake/quiet sleep (NREM
150 million BP	Eukaryotes with mitochondria & with 9 brains e.g. Octopus	Awake/Quiet sleep Active sleep (NREM)/ REM
40 million BP	Eukaryotes with endosymbiont mitochondria; with 1 brain e.g. *Drosophila* + secondary endosymbiont *Wolbachia (the model)*	Awake/Quiet sleep (NREM) + additional sleep control from *Wolbachia*
150 million BP	Eukaryotes Basal birds show the flip-flop switch between NREM and Active sleep REM	Awake/Quiet sleep (NREM) + Active sleep (REM)
130 million BP	Eukaryotes with endosymbiont mitochondria e.g. Monotremes e. g. Platypus	Awake/Quiet sleep (NREM) and REM hard to distinguish
66 million BP (major expansion, first evidence 178 BP)	Mammals Eukaryotes (With endosymbiont mitochondria)	Awake/Quiet sleep (NREM)/Active sleep (REM)

2.3. Other species of infections prokaryotes change the sleep behaviour of their host cell

The notion that prokaryotes living as endosymbionts, change the behaviour of their 'hosts' is further supported by how extracellular parasites change the behaviour of their hosts. For example, *Trypanosoma brucei* causes daytime sleepiness and night-time insomnia in humans and cattle and may cause their hosts to have less sleep overall. In human's the changes are believed to be as a result of inflammation of the brain and are not seen as a benefit to either host or parasite (Magalhães et al., 2022; Rijo-Ferreira and Takahashi 2020).

Interestingly with *Trypanosoma brucei* we see the hosts sleep

behaviour change as unusual but we don't see sleep itself as unusual or different when it occurs in eukaryotes perhaps because it is so familiar.

2.4. Do prokaryotes sleep?

Additionally, as a response to other infectious diseases sleep can be considerably altered (Bentivoglio et al., 1994; Krueger and Opp 2016; Matovu et al., 2001). Many prokaryotes have inactive, unresponsive stages. These "persisters" can cause major problems in the treatment of diseases as they have to be 'woken up' before being responsive to antibiotics (Liu et al., 2021; Wilmaerts et al., 2019). We believe that prokaryote persister (spores) stages are more akin to hibernation in mammals and don't represent sleep *per se*.

2.5. Sleep evolved before the brain

The studies of sleep in the freshwater invertebrate cnidarian *Hydra vulgaris* and the Upside-down jelly fish *Cassiopeia* (Table 1) most significantly show that sleep evolved before brains (Kanaya et al., 2020; Nath et al., 2017). Neurotransmitters for the sleep/wake cycle, serotonin and dopamine both predate the evolution of nervous systems (Kanaya et al., 2020; Moroz 2015; Peroutka 1995). Also *Hydra* which has no brain has an endosymbiotic relationship with mitochondria and has only Quiet (NREM) sleep as does the brainless jellyfish *Cassiopeia* (Kanaya et al., 2020; Nath et al., 2017). Octopus with nine brains have both Quiet sleep and also Active sleep ('REM') (Medeiros et al., 2021; Nath et al., 2017).

Monotremes (Table 1) have Quiet sleep (NREM) and Active Sleep (REM) but it's hard to distinguish the 2 states (Siegel et al., 1999). Basal birds show the flip-flop switch between Quiet sleep (NREM) and Active sleep (REM).

Sleep walking in humans, dogs and sleep state changing in the octopus questions the rigid paradigm of Awake, Quiet sleep (NREM), Active sleep (REM) (Adams 2022b; Bakin 1970; Oudiette et al., 2009; Singh et al., 2018).

Revelations about the sleep behaviour of dolphins, dogs, ducks, elephants and the pontine brain injury in humans point towards Active sleep (REM) being a transitional state between Quiet sleep (NREM) and wakefulness (Adams and Johnson 1993, 1994; Lyamin et al., 2002; Mascetti 2016).

2.6. The biological function of REM within the unified theory of sleep

REM was discovered some 70 years ago and it was heralded as an amazing phenomenon (Aserinsky 1996). Since then there has been much debate as to what its function is. Is it a more superior type of sleep than NREM, is it better for learning to occur, is dreaming more intense, does REM have special properties? (Blumberg et al., 2020). We can readily divide NREM into 4 different stages but if we do divide REM at all, it is only into 2 stages i.e. phasic (bursts of rapid eye movement) and tonic (without) (Ermis et al., 2010) Naturally most of the research into REM has been from a human perspective and the focus has been quite introspective. Now, Blumberg et al. (2020) encourages us to see REM within a wider biological context, as do we. It was initially surprising to find that neither REM nor NREM had an effect on the memory of dogs when they were trained to recognise scents of evolutionary significance and research into the sleep of cetaceans have upended our understanding of the significance of REM for neonates (Adams 2022b; Lyamin et al., 2002; Ungurean et al., 2022). Human babies need more REM for their development, yet with neonate bottle nosed dolphins and killer whales and their mothers have very little or no sleep for the first post-partum month of their lives (Klemm 2011; Lyamin et al., 2002; Ungurean et al., 2022).

The more biologists look at REM the less important its individual function in humans becomes in the wider context. It is necessary to broaden our field of view and see how REM sleep fits into the Unified Theory of Sleep. Many organisms, e.g., the prokaryotes, don't sleep. However, eukaryotes (with mitochondria) do sleep. Many eukaryotes are highly adapted to avoid or delay sleep but one way or another eukaryotes sleep. We see simple organisms with no brains (*Hydra vulgaris* and the upside-down jelly fish *Cassiopeia*) just having NREM sleep (Kanaya et al., 2020; Nath et al., 2017), There are newly emerging animals like the platypus showing primitive REM but essentially all eukaryotes that have a brain (even octopus with its 9 brains) have a form of REM (Lesku et al., 2011; Medeiros et al., 2021). So what is REM, what is its' overall function? We agree with Klemm (2011) and contend that even though it has functions that happen when it occurs in humans, by default REM in its' major biological context, is most likely to be the occurrence where an animal with a brain is getting out of the sleeping state to become awake.

3. Discussion

Evolution stumbles about selecting for mutations or by moving into new domains caused by chromosomal amplifications and the passage of genes through viral vectors; however, over the past billion years, probably on a few occasions, endosymbiosis produced massive bursts of gene transfers leading to modern day plants, fungi and animals (Youle 2019).

It is important to realize that wakefulness is the norm for prokaryotes and alternating wakefulness and sleep is the norm for eukaryotes. Eukaryotes with some few exceptions have endosymbionts and from the animals we have been able to study, they sleep.

We say that mitochondria are the only organelle in animals that is firmly established to be of prokaryote origin and it is most likely that they promote sleep in eukaryotes. The ability of mitochondria being able to function outside of eukaryotic cells (Al Amir Dache et al., 2020) and eukaryotic cells being able to function without mitochondria (Karnkowska et al., 2016) gives further weight to the idea that the association between eukaryote cells and mitochondria is something which can no longer be considered a rigid paradigm.

With mitochondria passing their genome mainly by the female ovum they have not been excluded by the same natural selection upon their 'host' DNA. In this way (despite the mitochondrial genome decreasing over time since becoming an endosymbiont) their asexual reproduction would still have favoured the continuance of uniformity to sleep. So mitochondria have remained part of modern animal cells, and so too, the behaviour of sleep has passed to successive generations.

It is proposed that it was an endosymbiont mitochondria, like Wolbachia, which provided the original command for their 'host' to sleep and that now endosymbiosis continues that same instruction.

Mitochondria still continue with their instruction to sleep, because sleep deprivation causes mitochondrial reactive oxygen to elevate in those neurones promoting sleep which trigger this rise with the assistance of a redox-sensitive channel (Ikeda et al., 2005; Melhuish Beaupre et al., 2022). This change in electrical excitability closes a molecular feedback loop and starts the induction of sleep (Melhuish Beaupre et al., 2022; Rodrigues et al., 2018). Mitochondria provide energy to the cell by oxidative phosphorylation and are known for their importance in cell death and ageing (Kempf et al., 2019; Scheffler 2001).

In humans, mitochondria are most concentrated in heart cells and their study is revealing a new perspective into heart failure and our increased vulnerability during sleep (Chen and Knowlton 2010). However, currently there has been more research into *Drosophila* which has provided further insight into how the mitochondria with their cellular effect, transfer within neurones and hence affect the behaviour of sleep. Sleep promotion occurs at the dorsal part of the fan shaped body (neural bundle) in the brain of *Drosophila* and this is where the switch is to either promote or inhibit sleep; and Monoaminergic signalling transmits the message for the sleep-wake cycles (Liu et al., 2012; Pimentel et al., 2016).

It is likely that archaic endosymbionts promoted a simple form of

slowed behaviour resulting in sleep which was the proto type of Quiet sleep (later to be Slow Wave SWS, or NREM).

Looking back 500 million years ago to the late pre-Cambrian we see the emergence of free-living jellyfish. Sleep in *Cassiopeia* jellyfish (without an organised brain) is Quiet sleep and apart from their endosymbiont mitochondria, their other symbiotic relationship is with photosynthetic dinoflagellates living in their tentacles. *Cassiopeia's* other algal symbionts also change their 'hosts' behaviour and make them float upside down near the bottom, so the dinoflagellates can better photosynthesize (Nath et al., 2017). It is likely that multi cellular eukaryotic organisms, adapted to this slowed behaviour by developing Active (REM) sleep, as a response to promote reactivation of the brain and subsequent waking from sleep. If we move closer to the present day to some 150 million years ago and we can examine the octopus which have highly organised brains (500 million neurones roughly equivalent to a dog). They have a central brain and 8 regional brains all capable of making decisions, so measuring REM is completely inappropriate. However, we can still measure their Quiet and Active sleep (Medeiros et al., 2021; Nath et al., 2017).

Then diverging and continuing up the evolutionary 'ladder' to 150 million years ago to the monotremes (considered to be primitive mammals because of their egg laying), we also see REM occurring but there are times when REM and NREM are indistinguishable (Siegel et al., 1999). In the most basal bird the ostrich, their forebrain flips between REM and NREM and we have now seen this process the flip flop switch occurring in humans (Lesku et al., 2011; Lu et al., 2006). When REM sleep is considered as a function viewed looking outside from the laboratory to the wild, it was realised that it was less like a recovery process (which is better suited to SWS/NREM) and more like a preparation for wakefulness (Horne 2013).

The order for sleep wake cycles in most animals including humans is; Awake, NREM sleep, REM sleep, then Awake. It is most unusual but still possible for this standard cycle to differ. With sleep-walking in humans and dogs the cycle can be Awake, NREM, Awake, whereby a REM cycle is missed and the individual goes straight to wakefulness (Adams 2022a, 2022b; Bakin 1970; Oudiette et al., 2009; Singh et al., 2018). Perhaps this is because the brain is sufficiently reactivated and REM is unnecessary. Sleep walking in NREM may act as *de facto* REM but without tonic immobility. The sleep behaviour of octopus provides further evidence. They are members of a completely different phylum, namely the Mollusca, yet as previously mentioned, these intelligent animals have both Quiet sleep (NREM) and Active sleep (REM). Yet as is the case in sleep walking in humans and dogs, it is also possible for octopus (although rare) to transit directly from Quiet sleep to being not only awake but active (Medeiros et al., 2021). These rare occurrences of REM being skipped indicate that the inclusion of REM has not always been present or necessary. When we consider basal birds and monotremes together e.g. ostriches and platypus which both show signs of REM but there are times where it is incomplete or indistinguishable from NREM.

Additionally, animals such as elephants have adapted to having very little sleep at all. Elephants only need to have NREM sleep for 2 h/day and only experience a brief session of REM every few days. It could be that with these animals we see sleep as becoming vestigial rather like the human appendix now is. Dolphins and ducks avoid the problem of sleep making them vulnerable by sleeping unihemispherically, and as half of their brain is always awake the requirement of REM for reactivating the brain is negated (Lyamin et al., 2002; Mascetti 2016). Effectively dolphins and some birds not so much sleep unihemisperically as remain awake. They have not overcome the need to sleep but rather they have managed it. Other animals such as dogs, have adopted the behavioural strategy of polyphasic sleep wake cycles. Frequently waking 23 times a night, means that they can be less vulnerable when they are asleep and when this behaviour is coupled with their sleep episodes occurring ayncronously with other pack members they counter the dangers of sleep (Adams and Johnson 1993). There was no difference to the response of auditory stimuli in dogs when they were in NREM or REM sleep; instead it was the significance of the sound which woke the dogs (Adams and Johnson 1994).

Like dolphins, dogs have not been able to shake off the endosymbiont requirement to sleep but evolution has provided strategies to increase their survival. In humans we used to believe that REM sleep was necessary for survival. However, in the case where a man suffered a pontine brain injury (caused by shrapnel) he successfully coped with life without REM sleep for decades (Lavie et al., 1984; Magidov et al., 2018). REM is an occurrence but is not always a requirement. We can look closely as to what happens during REM but we say to understand what is REM actually is, it's necessary to travel back in time to see how Quiet sleep came about and realize prokaryotes (currently 4–6 x 10^{30}: 13% of total biomass, plants 80%) are largely awake and eukaryote celled animals for a billion years have likely alternated between waking and Quiet sleep which was probably caused by endosymbiosis. If we have this powerful and prevailing behaviour of Quiet sleep/NREM and we see REM in context, it's reasonable to postulate that it is the animals' evolutionary response to free itself from the costly behaviour of sleep so it can wake. We can only speculate how many times previously the attempt to be rid of sleep has occurred and if it was successful. Eukaryote animals have traded the very positive side of having mitochondria providing aerobic respiration for them with the negative side of having to sleep. Evolutionarily, if a system is favourable, regardless of its imperfections and costs it will be continued. Recent evidence shown in rodents and humans reveals that the toxins caused by mitochondria may be removed from the brain during sleep by glia cells via cerebral spinal fluid (Frank 2019; Xie et al., 2013). As our mitochondria continue to produce free radicals which are toxic to our cells, Quiet/SWS/NREM sleep will be continued. NREM sleep seems to be an endosymbiont occurrence and REM sleep is an evolutionary response to rid us of the bizarre behaviour in order to restore wakefulness. Mitochondria are extremely important to eukaryote celled animals but their price is sleep and the cost is high.

CRediT authorship contribution statement

Graham Joseph Adams: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, writing, drafting, reviewing and editing. **Philip A. O'Brien:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, writing, drafting, reviewing and editing.

Declaration of competing interest

Neither authors received any financial inducements nor have any competing interests.

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