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Spotlight

DNA repair as a core function of sleep

John A. Lesku [1,*] and Hannah Elmes[1]

Sleep is widespread across animal species, yet its functions remain enigmatic. In a recent study, Aguillon, Harduf *et al.* characterize sleep in two of the simplest neuron-bearing animals to reveal that DNA, damaged while awake, is repaired during sleep. In doing so, the authors provide evidence for an evolutionarily ancient sleep function.

The typical human will spend approximately one-third of the day, and cumulatively, one-third of their life, asleep. Yet sleep is far from being an idiosyncratic feature of human biology. All animals (seemingly) sleep, including finches and fishes, fruit flies and jumping spiders, roundworms and flatworms, and snails and cephalopods [1]. The aforementioned species are bilaterally symmetric animals with a brain-forming concentration of neurons in the head. But sleep has also been characterized in jellyfish and *Hydra*—members of the phylum Cnidaria—whose neurons are more diffuse across radially symmetric bodies [1]. This suggests that neurons *per se* are a biological target of sleep. The apparent absence of a truly sleepless animal indicates that sleep serves critically important functions that sustain animal biology.

It is therefore not surprising that scientists have uncovered several nonexclusive sleep processes that correct imbalances or repair damage accrued during prior wakefulness. For example, brain activity during wakefulness causes a net increase in synaptic strength, which is renormalized during sleep [2]. Proinflammatory cytokines (e.g., IL-1β and TNF-α) and neuronal waste products, such as amyloid beta (Aβ) and tau proteins, accumulate in the brain while awake and are cleared by the glymphatic system while asleep [3]. Wakefulness progressively pushes neuronal networks away from a computational optimum, which is restored by sleeping [4].

Brain activity during wakefulness also damages the helical structure of neuronal DNA in the form of double-strand breaks (DSBs). These breaks are caused by neuronal activity, extended wakefulness and exploration, transcription, Aβ, chemotherapy medications, and radiation. DSBs can have value in that they facilitate the expression of some early-response genes that are critical for synaptic plasticity (e.g., *Fos* and *Npas4*) [5]. A foundational 2016 study reported the repair of DSBs during sleep in mice and fruit flies [6]. The authors also found that genes involved with DNA repair (*Parp1* and others) are upregulated during sleep in the mouse brain. Subsequent work in zebrafish showed that the reduction of DNA damage during sleep is mediated by *Parp1* and chromosome dynamics [7]. The relationship is bidirectional: sleep repairs DNA damage and DNA damage promotes sleep. These studies raise a fundamental question: from an evolutionary perspective, is sleep-dependent DNA repair a derived sleep process, present in specific species [6,7], or a conserved sleep function?

In a recent study, Aguillon, Harduf *et al.* [8] offer insights into this question from upside-down jellyfish (*Cassiopea andromeda*) and starlet sea anemones (*Nematostella vectensis*). The authors first characterized sleep using a standard battery of behavioral tests to establish reduced sensory responsiveness, the rapid return of responsiveness with sufficient stimulation, and homeostatic regulation to recover lost sleep. In most animals, restfulness is a conspicuous correlate of sleep, yet the round-the-clock pulsing of jellyfish precluded using quiescence as an indicator of sleep. Instead, sleep was characterized by a slower rate of pulsing. Specifically, jellyfish pulsing fewer than 37 times per minute for at least 3 min were slower to respond to a flash of light and thus deemed to be asleep. Using this criterion in the laboratory and in the wild (by monitoring animals in near seashore waters), jellyfish were found to sleep approximately 8 hours per day, mostly at night with a midday nap. A similar approach showed that the sea anemones also slept 8 h per day, mainly in the second half of the night and the first half of the day. Administering melatonin, a hormone that promotes sleep in various species, including humans, zebrafish, and flatworms, was shown to put both cnidarians examined in the study to sleep [8].

In their next set of experiments, Aguillon, Harduf *et al.* [8] sought to address whether sleep-dependent DNA repair occurs in cnidarians. Immunohistochemical assays using an antibody against gamma-H2AX (a biomarker of DNA damage) revealed that the amount of damaged DNA in neuron-rich tissue is high at the end of each species' wakefulness period, higher still with sleep deprivation, and low at the end of their sleep period [8]. Administering melatonin, which promotes sleep, reduced DNA damage. Conversely, exposure to mutagens increased DNA damage and then induced sleep (Figure 1). When viewed alongside studies showing DNA repair in the neurons of sleeping mice, zebrafish, and fruit flies [6,7], a narrative emerges with DNA repair being an early and enduring sleep function.

DNA repair mechanisms have been described in all three domains of life—the Archaea, Bacteria, and Eukarya—suggesting that cnidarians inherited this cellular process to maintain genome stability. It may be that with the evolution of the neuron, it became necessary to coevolve

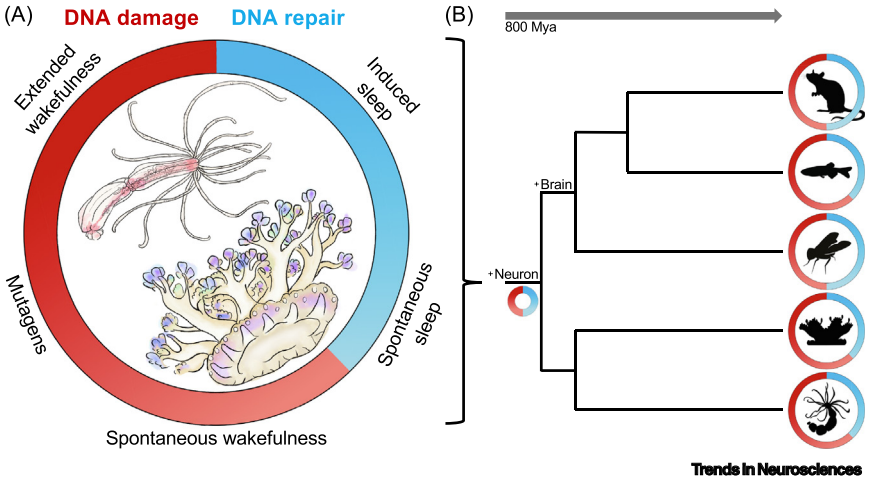

Figure 1. DNA repair as an evolutionarily conserved sleep function. (A) Aguillon, Harduf *et al.* [8] have shown that the upside-down jellyfish and starlet sea anemone, similarly to humans, are awake approximately two-thirds and asleep one-third of the 24-h day. The authors further demonstrated that DNA damage occurs and accrues in neuron-rich tissue across multiple conditions. Such conditions include spontaneous and extended wakefulness, and exposure to mutagens, such as ultraviolet radiation and the chemotherapy medication etoposide (*red*). This damage is then repaired more efficiently during sleep, irrespective of whether sleep is induced using melatonin or occurs spontaneously (*blue*). (B) Their study adds to published data showing sleep-dependent DNA repair in the neurons of mice, zebrafish, and fruit flies. Together, this indicates that maintaining genome stability predates the evolution of the brain and appears to be an early and conserved sleep function. The gray arrow reflects time, expressed as millions of years ago (Mya), which corresponds to the estimated divergence times in the phylogenetic tree. Illustrations by Yifan Pei.

a new, metabolically depressed state, sleep, to support the efficient repair of neuronal DNA. The demonstration of DNA repair as a function of sleep in cnidarians does not preclude, however, other potential sleep functions in these species, such as synaptic downscaling, neuronal waste clearance, and restoring a computational optimum [2–4]. These potential functions remain to be examined in future studies.

Another open question is whether sleep might have evolved before the appearance of cnidarians. Although the identity of the most basal animal remains a topic of debate, sponges are strong candidates, lacking organs, muscles, and neurons. Adult sponges are sessile filter feeders with two notable behaviors. First, they use flagellated cells called choanocytes to drive a flow of seawater and suspended food into and through the animal. Second some sponges 'sneeze' to clear their canals of mucus and debris with slow (hour-long) rhythmical contractions, day and night [9]. Might sponges sleep? The sponge *Tectitethya crypta* decreases exhalant flow at night, likely owing to reduced choanocyte activity. Another sponge, *Tethya wilhelma*, is diurnal to the extent that it sneezes less and contracts ~30% more slowly during the night. Furthermore, the inhibitory neurotransmitter GABA, which promotes sleep in other animals, causes *T. wilhelma* to expand more slowly after contracting. Interestingly, 24 h after irradiation, *T. wilhelma* overexpresses gene transcripts implicated in recognizing and repairing DSBs, some of which have human homologs [10]. Thus, there are intriguing hints of a sleep-like state and DNA repair in sponges. To make a definitive case for sleep in sponges, it would be essential, however, to demonstrate reduced responsiveness and other hallmarks of sleep. Regardless of the outcome of such studies, the findings by Aguillon, Harduf *et al.* [8] broaden current perspectives on the evolution of sleep and its roles by showing DNA repair to be an ancient sleep function whose biological target lies in the nuclei of neurons.

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Declaration of interests

The authors declare no competing interests.

[1]Sleep Ecophysiology Group, School of Agriculture, Biomedicine and Environment, La Trobe University, Melbourne, Victoria 3086, Australia

*Correspondence:
j.lesku@latrobe.edu.au (J.A. Lesku).

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