Is Sleep Beyond Our Control?

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Abstract: Sleep is mysterious. It is ubiquitous and vital, yet its function remains unknown. There are, however, exceptions from the omnipresence of sleep: Birds that exhibit less sleep drive during migration; cetaceans and dolphins that sidestep the need for sleep by sleeping with one hemisphere at a time; frogs that do not seem to sleep at all; and strains of mice and fruit flies that sleep less than their wild-type counterparts. Moreover, new drugs have been discovered that combat the need for sleep in humans without the well known side effects of common stimulants. In the current review, the different ways of evading sleep will be examined. It will be argued that to understand how sleep can be controlled research efforts need to be extended to non-standard laboratory animals that exhibit different methods of evading sleep. Finally, it is argued that emerging clues point to increased membrane excitability as the common neural process used to execute seemingly different forms of sleep-evasion.

Keywords: Sleep, sleep deprivation, unihemispheric sleep, non-sleepers.

INTRODUCTION

In humans, the need for sleep dramatically constrains how individuals can lead their lives and paces the rhythm of society. It is reasonable to assume that the order of society would change radically if sleep needs could be controlled; a change equal to when the gas light allowed humans to colonize the night or when the birth control pill separated sex and conception. Since all of us are familiar with the debilitating effects of sleeplessness, it is easy to imagine that many of us would view sleep as one of the grand constants of life. After all, sleep has persisted in evolution in spite of appearing maladaptive; while sleeping we cannot forage for food, mate, or move out of harm's way. There is, however, a growing number of examples of how sleep can be evaded. These examples have inspired excellent reviews where doubt is cast on the ubiquity of sleep [1] and the function of sleep [2] even though the same examples have also inspired arguments for a central function of sleep [3]. In the current review, the different ways to evade sleep will be examined and, while ignoring the question on the function of sleep, it will be argued that these exceptions provide important clues about the nature of sleep and how it may be controlled. It will be argued, first, that it is necessary to extend studies to non-standard laboratory animals in order to capitalize on what the different methods of sleep-evasion can reveal about sleep itself [4]; and second, that there are neural similarities between what at first may seem different ways to evade sleep.

Definition of Sleep

From Aristotle until the technological advances of the 20th century, sleep, while a complex and multifaceted phenomenon, was defined simply as a reversible state of perceptual disengagement [5]. With the advent of electroencephalography (EEG), sleep became virtually synonymous with a set of electrographic signals seen in the brain [6, 7]. The desire to study sleep at molecular and genetic levels, however, has made it necessary to define and measure sleep in genetically tractable organisms, most of which do not exhibit the defining electrographic signs of sleep. This, at least in part, has resulted in a return to behaviorally based definitions of sleep [8-10]. The hallmark behavioral criteria for sleep include:

Increased Sensory Thresholds

A stronger stimulus is required to generate a response from an organism while sleeping than while awake. (This requirement is, at its core, the same as proposed by Aristotle.)

Homeostatic Control

If sleep deprived, an organism will sleep more if given the chance and/or exhibit greater pressure to enter the sleeping state.

Stable Species Characteristic

Sleep does occur in all species members.

Spontaneity and Reversibility

Sleep emerges spontaneously and is quickly reversible; therefore, sleep is different from a coma.

Typical Posture

Each species adopts a characteristic posture and/or seeks shelter prior to engaging in sleep.

These criteria are used to study sleep at early developmental ages before the onset of differentiated EEG [11] and in genetically tractable organisms such as fruit flies, zebra fish and even nematodes [12-18]. (For discussion on whether electrographic and behaviorally defined sleep represent the same phenomena, please see: [10, 19]). The first two behavioral criteria are the most frequently used criteria to measure

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sleep in the laboratory. Both EEG and behavioral definitions of sleep are, however, phenomenological and offer little insight into the function(s) of sleep states. Specifically, as we will see, none of these defining features, behavioral or electrographic, seem to be *sine qua non* for sleep.

Sleeplessness

A seemingly straightforward way to understand what sleep does is to study the effects of sleep deprivation. In a classic series of studies, Rechtschaffen and co-workers thoroughly described a well defined syndrome that affected sleep deprived rats: debilitated appearance, skin lesions, increased food intake, increased plasma norepinephrine and decreased plasma thyroxone. During the late stages of deprivation body temperature decreased and the rats died [20, 21]. This finding was recently replicated in fruit flies (*Drosophila melanogaster*) [22]. In contrast, sleep deprived humans show none of these symptoms, aside from a mild increase in caloric intake [21]. In humans, the immediate effects of sleep deprivation are largely restricted to cognitive performance [23, 24]. If motivated, humans can stay awake for days without suffering any permanent consequences [25]. Moreover, in a recent study, pigeons (*Columba livia*) were sleep deprived for up to 29 consecutive days, using a deprivation method adapted from the Rechtschaffen group; no evidence was found for the syndrome that affects sleep deprived rats [26]. It cannot be ruled out, however, that the pigeons did engage in brief bouts of unihemispheric slow-wave-sleep (UHSWS) to combat the lack of sleep, and it should also be noted that the sleep deprivation was not as complete as in rats (sleep was reduced to 54 % of baseline levels in the pigeons as compared to 91% in rats). Significant reduction in sleep has also been reported in pigeons subjected to constant light [27]. Thus, it is possible that pigeons simply do not respond to the lack of sleep as either rats or humans. Zebrafish (*Danio rerio*), moreover, seem to respond in different ways to sleeplessness depending on how it is induced: mechanical-stimulation induced sleeplessness is detrimental and introduces homeostatic sleep drive (i.e. rebound) whereas light induced sleeplessness does not [28]. It seems that homeostatic sleep control is not a stable species characteristic exhibited by zebrafish. Investigating how zebrafish side-step sleep need in the presence of ambient light may reveal vital clues on the neural causes of sleep. Importantly, even though most sleep researchers now agree to a common definition of sleep that is applicable across species [8], the effects of sleeplessness seem to differ widely between species. Does this mean that the function of sleep differs across species? Or, that the species have developed different defense mechanisms to counterbalance common detrimental effects due to the lack of sleep? If the answer to either of those questions is yes, learning about sleep in one species could inspire methods of extending wakefulness in another.

Theories on the Function of Sleep

There is no shortage of theories on sleep function, however, most sleep theorists inevitably start off by claiming that the function of sleep remains unknown [29, 30]. Furthermore, many sleep theories contain characteristics that disallow wide acceptance. First, sleep theories tend to be restricted in scope. One may, for example, postulate a role for sleep in development or energy conservation but subsequently lack the power to explain sleep across the lifespan or across species [31, 32]. A second effect of restricted scope is that sleep theories tend to lack parsimony. Freud's theory of dreams is an extreme case in point [33]. A theory of sleep loses its elegance when it only explains a single phenomenon and relies on other theories to explain other sleep phenomena. Third, sleep theories tend to lack consistency. For example, in the ongoing debate about the role of sleep in memory [34, 35] the same neural events have been postulated to hold opposite functions, that is learning and un-learning [36, 37]. Recent theories of sleep are promising, such as the theory of neocortical maintenance (i.e. synaptic downscaling) during sleep that postulates a universal role for sleep applicable throughout development and across species [38]. Similarly, a recent and parsimonious theory of sleep argues for a universal function of sleep [39]. Even with more promising theories in hand, the function of sleep remains debated and it remains to be resolved whether there exists a principle, perhaps at the molecular level, unifying the function of sleep states across development and across species. Alternatively, sleep may hold no function or may fulfill different roles for different species and even, different roles for a given species at different developmental ages. Leaving the question of the function of sleep aside, there do exist ways to sidestep sleep need and we shall consider each of these "sleep-evasions" in turn.

EXCEPTIONS TO THE RULE

Natural Exceptions

Unihemispheric sleep is widespread in the cetacean and avian phyla [40]. During unihemispheric sleep one hemisphere of the brain exhibits low-voltage high-frequency EEG, typical of wakefulness, while the other exhibits high-voltage low-frequency EEG, typical of sleep. Unihemispheric sleep only occurs during slow-wave sleep and unihemispheric slow-wave sleep (UHSWS) defies the traditional definition of sleep; the half of the body ipsilateral to the hemisphere displaying sleep exhibits behavior traditionally associated with wakefulness, e.g. open eyes and movement [40]. Thus, during UHSWS the animal is able to react to the environment, avoid predation, locomote, etc., all the while reaping the benefits of sleep. For example, the pacific white-sided dolphin (*Lagenorhynchus obliquidens*) maintains coordinated group swimming by keeping the "awake eye" toward the group and the "sleeping eye" toward the open ocean [41]. This suggests that the dolphins use visual cues to orient and maintain coordination while engaging in UHSWS. When the dolphin switches from left to right in the group, the sleep state of the hemispheres changes accordingly [41]. Moreover, seals can exhibit UHSWS as well as bihemispheric slow-wave sleep [42]. Here we stress that, marine mammals have evolved or developed mechanisms for UHSWS but not mechanisms to dispense with sleep altogether. This is perhaps due to some cost incurred by total lack of sleep. Furthermore, whatever mechanism results in the ability to utilize UHSWS, it is neurally compatible with the generation of bihemispheric sleep [40].

Bar-tailed godwits (*Limosa Lapponica Baueri*) migrate from their breeding grounds in Alaska to their wintering grounds in New Zealand each fall, seemingly by a non-stop, trans-pacific flight reaching distances up to 11,680 km and a

duration of up to 9,4 days [43]. It is tempting to speculate that Godwits, and other great travelers, such as the Arctic Tern (*Sterna paradisae*) or Eastern curlew (*Numenius madagascariensis*) [43, 44], fly while sleeping or don´t sleep at all [45]. Recent data is consistent with the notion that sleep need is severely depressed during the migratory season [46]. In white-crowned sparrows (*Zonotrichia leucophrys gambelii*) sleep need is reduced by two-thirds during the migratory season and in stark contrast to non-migrating birds sleep reduction does not affect accuracy or responding on repeated-acquisition learning tasks [46]. It cannot be ruled out that flight occurs during unihemispheric slow-wave sleep (UHSWS); after all, motor patterns of flight are under spinal control and do occur even in decerebrated birds [45]. It is, however, improbable that flight is compatible with Rapid Eye Movement (REM)-sleep due to motor inhibition that persists throughout the REM state [47]. Some migrating birds do compensate in part for reduced sleep during migration by increasing the time spent in daytime drowsiness and short napping during the migratory season, as witnessed by recent data obtained from Swanson´s thrush (*Catharus ustulatus)* [48, 49]. Perhaps migrating birds pay some currently unknown price for their lack of sleep. Regardless, these birds have developed methods to reduce sleep – at least postpone or alter it [50] - during the migration season. This pattern of sleep reduction continues to function in captivity, in the absence of whatever external conditions trigger it under natural conditions.

In addition, cetacean mothers and their calves (killer whales, *Orcinus orca*; dolphins, *Tursiops truncatus*) exhibit post-partum wakefulness as witnessed by extended levels of high activity lasting months, without ill effect on either the mother or the developing calf [51]. In these animals normal sleep levels return gradually over the postpartum period but are never exceeded, defying theories of homeostatic sleep control [51]. Similar to the short sleep bouts reported in the Swanson´s thrush, neonates and their mothers may sleep in extremely short bouts while underwater; however, these short bouts still result in a reduced amount of normal adult cetacean sleep [49, 52, 53]. Furthermore, the typical "hanging" behavior exhibited by dolphins which is believed to constitute rest is not exhibited during the post partum period [54, 55]. These observations upend at least two long held dogmas in sleep research. First, it is generally assumed that sleep levels are the greatest in infancy; which in turn has fueled the notion that sleep serves an important role in neural development [31, 56]. This period of sleeplessness in cetaceans, however, co-occurs with a period of massive neural development in the calf [51]. Second, one of the critical elements in the definition of sleep is homeostasis; still cetaceans do not seem to show any rebound after post-partum sleep loss [51]. It cannot be ruled out that there is sleep *in utero* that diminishes at birth and then re-emerges, a similar trend has been documented in fetal sheep [57]. Regardless, perinatal and post-partum sleeplessness suggests that, in mammals, neural development can occur in the absence of sleep and adult mammals can dispense with sleep for weeks without a rebound.

When it comes to lack of sleep the American bullfrog (*Rana catesbeiana*) may be in a category all its own. Only one single study of the sleep state in this remarkable species has been published; the author concluded that the frog never slept [58]. Four clear behavioral states and their electrographic correlates where described: Activity (walking), sitting, reclining (suspended in water), and withdrawal. High-amplitude synchronized EEG accompanied activity and low-amplitude desynchronized EEG accompanied withdrawal; the opposite of what one would expect to find in mammals. During withdrawal the frog closes its eyes and may remain motionless for hours on end, however its sensory thresholds do not increase and it responds vigorously to stimuli even after eight hours of immobility. Frogs were also stimulated intermittently for long periods of time (up to four days). If the reclining or withdrawal states were indeed sleep-like, one would expect that larger stimuli would be needed to elicit a response as the stimulation progressed. In stark contrast to rats and humans this was not found to be the case. Interestingly, the same author studied other related species of frogs and concluded that they did sleep [59]. The bullfrog is the only species of frog, and to my knowledge the only animal, that has been reported not to sleep at all. In terms of neuroanatomy, developmental trajectory or ecology, there are no unique features to the bullfrog that explain why it, but not other frogs, can do without sleep. The bullfrog clearly underscores the importance of studying a broad variety of species. Without these rare and yet highly revealing counterexamples, one would conclude that sleep is ubiquitous and necessary for all frogs and leave it at that. A careful comparison of bullfrogs to closely related species might yield vital clues on the nature of sleep.

Genetic Exceptions

The greatest strides in the molecular dissection of sleep have been made in the fruit fly [18]. Using random mutagenesis, Cirelli *et al*. screened more than 6000 lines of flies for short sleep length [60]. Fifteen of the 6000 lines exhibited less sleep behavior than wild types; one line, termed minisleep (mns), slept 4-5 hrs a day compared to wild-type flies which slept 9-15 hrs a day [60]. The mns line carries a point mutation at a conserved domain of the shaker gene which encodes a voltage-dependent potassium channel. The mns line is homozygous viable, locomotes normally, exhibits normal responses to a handful of behavioral tasks such as geotaxis and has the ability to respond to complex stimuli. Moreover, mns flies do respond homeostatically to sleep loss, albeit less than wild-types, but are not performance impaired from lack of sleep [60]. Thus, in terms of waking performance, mns flies are resistant to the ills of short sleep. One caveat, their lifespan is reduced [60]. A mouse knock-out model of a homologous potassium channel, also shows decreased sleep amounts [61]. Koh *et al*. report that loss of SLEEPLESS protein (a brain-enriched, glycosylphosphatidylinositol-anchored protein) caused a drastic (>80%) reduction in sleep [17]. Molecular analyses revealed that quiver, a mutation that impairs shaker-dependent potassium currents, is an allele of sleepless. And Shaker protein levels were indeed reduced in SLEEPLESS mutants. This is in fact a remarkable story. Two separate forward genetic screens in fruit flies reveal strains that have massively reduced sleep – both strains suffer a mutation that ultimately reduces potassium currents, leading to a widespread increase in membrane excitability. Moreover, a mammalian knock-out of a homologous channel reveals a similar effect.

Pharmaceutical Exceptions

Recently, new drugs have emerged that decrease sleep need in humans, Modafinil™ and CX717. Modafinil™, developed in France, has been available in Europe since the mid 80´s and was recently approved in the USA for treating narcolepsy and other diseases leading to excessive daytime sleepiness (EDS). Modafinil™ restores wakefulness and has become the first line of defense when battling EDS [62]. Human and animal studies have revealed that Modafinil™ does not have the adverse effects that many stimulants do. Specifically, it does not affect blood pressure and has very little effect on neuroendocrine activity [63, 64]; also, repeated use does not seem to induce tolerance or withdrawal [62-64]. Importantly, it does not leave the user in a sleep deficit once use is discontinued [62]; that is, Modafinil™ induces wakefulness and razes sleep homeostasis. Similarly, the ampakine CX717 induces wakefulness and diminishes sleep homeostasis. Furthermore, CX717 may even bring about additional benefits. Using a delayed-match-to-sample task in well trained rhesus monkeys (*Macaca mulatta*), CX717 produced a dose-dependent alleviation of the detrimental effects of 30-36 hrs sleep deprivation; in fact, CX717 brought performance to a level above controls [65, 66]. Neither Modafinil™ nor CX717 induce the detrimental effects of common stimulants and suggest that if achieved through the appropriate mechanisms, sleeplessness is possible.

NEURAL CAUSES

Migratory Birds

The neural control of migratory behavior is not well understood. Migration has been linked with increased hypothalamic-pituitary-adrenocortical-axis (HPA-axis) function on the one hand and reduced circadian amplitude on the other [45, 46]. HPA-axis function has also been implicated in sleep control in mammals: Sleep deprivation leads to increased plasma glucocorticoids [67, 68]. For example, Cushing´s disease causes blood cortisol levels to rise, leading to disrupted sleep [69]. Moreover, sleep can also be severely disrupted by administering HPA-axis controlled steroids and peptides and, finally, decreased HPA-axis activity accompanies sleep disruptions during normal ageing [69].

A study in warblers (*Sylvia borin*) revealed reduced circadian rhythms during migration [70, 71]. It has been suggested that altered pattern of melatonin release leads to a phase-shift in activity resulting in a breakdown of normal sleep-wake rhythms during the migration season [71]. Similarly, the organization of the sleep states in mammals is highly dependent on circadian time, and it is possible that reduced intensity of circadian rhythms not only leads to fractured sleep but also to less total sleep time. In sum, these findings suggest a hypothalamic and neuromodulatory involvement in migration-related sleeplessness. Studying migration-related sleep evasion offers a way for a within-species cellular-level comparison of neural systems during a time when the birds have high (off migration season) versus low (during migration season) sleep need.

Cetaceans

The hypothesis that UHSWS is the mere result of independent control of the hemispheres of the brain is fueled by the notion that cetaceans have relatively small corpus callosi; however, a role for this neuroanatomical modification in unihemispheric sleep is not supported by experimental evidence. For example, following saggital transection, humans invariably sleep bihemispherically [40]. Thus, the corpus callosum does not seem to be necessary for bihemispheric sleep. In the case of UHSWS, it appears that sleep homeostasis is achieved locally, a fact that does not fit well with theories of sleep regulation based on sleep factors that circulate in the blood or cerebrospinal fluid [72, 73]. Indeed, following learning tasks that involve a specific brain region, or following localized transcranial magnetic stimulation, slow-wave amplitude increases locally in the corresponding brain regions [74, 75]. Even though the neural or neurochemical control of UHSWS activation is currently not known, a recent study in northern fur seals (*Callorhinus ursinus*) has demonstrated sleep-related lateralization in acetylcholine (Ach) release [76]. Other sleep-related neurotransmitters may also be released unilaterally. The primary source of cortical Ach, a powerful regulator of cortical arousal, is the nucleus basalis of the forebrain [77]. In rats, unilateral stimulation of the nucleus basalis results in ipsilateral decreases in EEG amplitude and increases in EEG frequency through increased cortical Ach release [76]. Conversely, nucleus basalis lesions result in increased amplitude and decreased frequency of ipsilateral slow-waves [76]. Thus, the release of Ach may be controlled at the level of the nucleus basalis, however, controlling neurotransmitter levels more precisely will involve local mechanisms or signaling [74, 75]. In a detailed anatomical study of the noradrenergic locus coeruleus (LC) of the bottlenose dolphin (*Tursiops truncatus*) Manger *et al*. conclude that the LC of this species is not in any way different, in form or structure, from vertebrates that exhibit bihemispheric sleep [78]. Moreover, the authors speculate that the LC is active with the same general pattern as in other species, that is: most active during active wakefulness, less active during SWS and virtually silent during REM. Accordingly, since REM sleep is all but absent in the dolphin (less than 15 minutes per 24 hours) the LC is active to the same extent [78]. The anatomy of the LC and lateralized levels of acetylcholine, thus, suggest a brainstem-level lateralized control of the sleep states generating UHSWS.

Neonatal Cetaceans

The finding that newborn cetaceans, as well as their mothers, hardly sleep after birth is novel and surprising, and little is known about which neural mechanisms might be at play [51]. Lyamin *et al*. did measure and manipulate cortisol and oxytocin levels; ruling out stress as playing a role in cetacean post-partum sleeplessness [51]. Thus, it is probable that this sleeplessness represents a healthy deviation from normal sleep patterns. It is tempting to speculate that the calves are born without the neural drive for sleep and that only gradually, during development, these systems become active. The surprising lack of sleep early in ontogeny in cetaceans may provide important clues on the mechanisms of sleep later in development in those species. It is important to stress, however, that the aforementioned study does not preclude that there is a healthy amount of sleep in utero during which neural development could occur.

Neonatal cetaceans offer a unique opportunity to study developmental changes in sleep within a species. First, it is

important to validate the finding; preferably using EEG. Assuming that the finding holds up, neonatal cetaceans could be used to test recent theories of synaptic downscaling during sleep [38]. The theory would predict that in the absence of sleep, synaptic downscaling in neonates be reduced and slow waves may be more intense as wakefulness progresses. These predictions could be tested using standard EEG and neuroanatomical methods.

Bullfrogs

As discussed above, details on the neurophysiology of frog sleep are scant; however, a detailed comparison of the sleepless bullfrog to other frog species that have been reported to sleep might yield important clues on sleep and sleep deprivation. To our knowledge the claim that the bullfrog (*rana catesbeina*) does not sleep has not been replicated. However, the author did observe sleep in another species of frogs (genus *Hyla*) [59]. The neurophysiology of these two species should be compared under normal and sleep deprived conditions; e.g. by comparing membrane excitability and levels of as well as sensitivity to extracellular neurotransmitters (i.e., Serotonin, Ach, Histamine, Norepinephrine). Comparative neuroanatomy may also be a good place to start, either by comparing the anatomy of neural systems with known sleep-wake functions, shared with frogs and mammals, or by comparing differences between bullfrogs and other related frogs.

Drosophila and Mice

The short sleeping mns phenotype results from a mutation of the shaker locus that encodes the α-subunit of a tetrameric voltage-dependent potassium channel that controls membrane repolarization and presynaptic transmitter release [60]. In Drosophila shaker channels are expressed mostly in the mushroom bodies and neuropil of the brain [60]; a brain area largely responsible for sleep cycles in drosophila [18]. The mouse equivalent of the shaker gene, Kcna, codes for Kv1.2, a shaker-like voltage-dependent potassium channel that is highly expressed in the thalamocortical system [61]. Similarly, in the SLEEPLESS Drosophila mutant, the mutation also affects a potassium channel [17]. Reduced potassium channel functioning results in increased membrane excitability [79]. Therefore, in sum, the immediate neural cause that leads to reduced sleep in the two strains of flies that have the least amount of sleep (as well as their mammalian homolog) is potassium current mediated increase in membrane excitability.

Modafinil and CX717

Modafinil™ induced wakefulness is likely mediated by norepinepherine (NE) since it is blocked by α1 and β adrenergic receptor antagonists; D1 and D2 dopamine (DA) antagonists, however, do not block the effects of Modafinil™ [63, 64]. The only central neurotransmitter systems that Modafinil™ has been shown to bind to are DA and NE transporters [63, 64]. Modafinil™ use leads to increased extracellular levels of DA, NE, serotonin (5-HT) and histamine (HA) as well as decreased levels of GABA [63, 64]. The effects on 5-HT, HA and GABA may, however, be secondary to those of the DA and NE [63]. The direct effects of Modafinil™ on neurotransmitter levels are largely restricted to the neocortex [63, 64]. However, c-fos immunoreactivity in cats has revealed that Modafinil™ induced wakefulness is associated with activated neurons in the hypothalamus; C-fos studies in rats indicate that, in addition to hypothalamic HA neurons, neurons of the perifornical area and orexin/hypocretin neurons are activated [80]. In contrast to stimulants like amphetamine, Modafinil™ seems to exert its effects by engaging subcortical neural pathways used for normal wakefulness, leading to increased cortical levels of wake-active neurotransmitters.

CX717 administration leads to cognitive enhancement and decreased sleep drive, like Modafinil™, but by utilizing neural pathways "downstream" from the sleep-wake pathways [65]. The ampakine CX717 is a positive allosteric modulator of AMPA receptors that bind to GluR1-4 subunits, increasing amplitude and duration of ion currents through the glutamate-gated channel, which are expressed in nearly every brain region [65]. Therefore, both CX717 and Modafinil™ exert their influence by engaging neural pathways that under natural conditions lead to wakefulness; however, the immediate neural cause of the wakefulness is increased membrane excitability. In a similar manner, increased wakefulness in flies and mammals with altered potassium channel physiology, results from increased membrane excitability [17, 60, 61].

CONCLUSION

We have seen that there exist important exceptions to the rule of ubiquitous sleep. Large groups of animals do not exhibit the differentiated EEG signals that are a prerequisite of an EEG based definition of sleep [10, 11]. Unihemispheric sleep in the cetacean and avian phyla reveals that sleep can be achieved, in neural terms, locally [40]. The american bullfrog exhibits the opposite EEG signals from what one might expect during active and inactive behaviors and does not exhibit increased sensory thresholds when inactive [58]. Migratory birds, neonatal cetaceans, postpartum cetaceans, sleep deprived pigeons and sleep deprived (using light stimuli only) zebrafish do not exhibit sleep homeostasis [26, 28, 46, 51]. And postpartum cetaceans reveal that sleep is, for them, a labile species characteristic [8, 51]. Each of these exceptions holds a little piece of information on how sleep can be controlled. The strains of fruit flies and mice that exhibit less sleep drive as well as the recent drugs that are used to combat sleep further demonstrate that manipulations at the molecular level can alter sleep behavior over short and long timescales [17, 60, 63, 65].

Sleep evasion has at its core a change in membrane excitability that leads to arousal. Sleep evaders, therefore, reveal a trend: regardless of what sleep need represents, it can be evaded locally by UHSWS or globally by pushing membrane dynamics of excitable cells towards depolarization. By sleeping unihemispherically, sleep need is met while maintaining responsiveness in one half of the body. As witnessed by a recent microdialysis study in seals [76], the sleeping side of the brain is depleted, at least, of Ach and likely other excitatory neurotransmitters known to cause low-amplitude fast EEG. Migration is associated with increased HPA-Axis activity which, in turn, leads to decreased sleep [45, 46, 69]. At least in respect to sleep, it is currently unclear how neuropeptide and steroid hormone signals are transmitted in the nervous system, but primary targets of most steroids are in-

tracellular receptors which dimerize into transcription factors after binding and modify gene expression [69]. We hypothesize that neurosteroid-induced changes in gene expression render excitable cells more responsive to wake-inducing neurotransmitters such as, Ach, 5-HT, HA, and NE. Neurosteroids also interact directly with GABAa channels mediating chloride flux [69]. Decreased sleep need could be accomplished *via* HPA-axis induced GABA-mediated inhibition of hypothalamic sleep-active neurons. Point mutation of the shaker gene and the SLEEPLESS mutant in Drosophila and Kcna2 knock-out mice both result in decreased ability of potassium channels to repolarize after action potentials [17, 60, 61, 81]. The net effect is wide-ranging increased neuronal excitability. Similarly, both Modafinil™ and CX717 lead to increased neuronal excitability [64, 65]. Modafinil™ by increasing levels of arousal-inducing neurotransmitters at the level of the cortex by tapping into what seem to be natural wake-circuits and CX717 by increasing glutamatergic tone throughout the brain.

Each of the species discussed in this paper offers a unique way of studying sleep evasion not visible to researchers studying a single species [4]. One might conceive of multiple studies using all the tools in the toolbox of neuroscience; electrophysiology (*in vivo* and *in vitro*), analysis at cellular and molecular levels, as well as gene expression analysis using the following "models" of sleep evasion. The bullfrog offers a between species comparison of closely related species that do or do-not sleep. Whales offer a unique opportunity for studying within-species developmental dependent sleep-evasion. Birds offer a unique opportunity to study within-animal seasonal (during migration) sleep-evasion. Seals and whales offer a way to study within-animal hemispheric control of sleep. Modafinil™ and CX717 offer a way to study how a "natural" wake-on pathway can be exploited in multiple species for extended wakefulness.

Sleep is within our control. Sleep is not ubiquitous throughout ontogeny and phylogeny [1, 3, 39]. What at first might seem to be highly varied methods of evading sleep in the different species presented here may actually be seen as different ways of achieving increased cortical excitability. Importantly, no new methods or insights are needed to study these exceptions from the rule of ubiquitous sleep. Understanding these important exceptions holds the promise of human control over sleep.

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ABBREVIATIONS

EEG = Electroencephalogram

UHSWS = Unihemispheric slow wave sleep

REM = Rapid eye movement

EDS = Excessive daytime sleepiness

HPA-axis = Hypothalamic-pituitary-adrenocortical-axis

Ach = Acetylcholine

LC = Locus coeruleus

DA = Dopamine

NE = Norepinephrine

HA = Histamine

5-HT = Serotonin

GABA = Gamma-aminobutyric acid

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