Title
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Editorial overview: Neurobiology of sleep 2017
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Thomas Kilduff directs the Center for Neuroscience at SRI International. He is co-discoverer of the neuropeptide hypocretin (orexin). His research group has identified cortical interneurons that are activated during sleep in proportion to homeostatic sleep drive and also focuses on therapeutics for insomnia and narcolepsy. Tom received his PhD from Stanford University where he held fellowships from the Danforth and National Science Foundations. He is an AAAS Fellow, a SRI Fellow, was a Pfizer Neuroscience Visiting Scholar, and has held multiple elected offices in the Sleep Research Society (SRS). He received the SRS Distinguished Scientist Award in 2017.

Over the past decade, the advent of viral tools for neuroanatomical tracing and cellular targeting, the ability to manipulate neurons using optogenetic and chemogenetic tools, an expanded range of transgenic mouse strains expressing Cre recombinase, and a renaissance of comparative studies afforded by studies in worms, flies, zebrafish and other species has had major impact on system neuroscience generally and sleep research, in particular. This issue of *Current Opinion of Neurobiology* highlights some of the new research insights into sleep/wake control and sleep function afforded by this expanded research armamentarium.

Saper and Fuller provide an overview of wake-sleep circuitry and introduce a revised view that focuses on fast transmission mediated by glutamate and GABA in sleep/wake control, with the biogenic amines playing a modulatory role. A series of papers then focus on specific brain regions. Anaclet and Fuller review early findings indicating that the caudal brainstem contains slow wave sleep (SWS)-promoting circuitry and describe their recent discovery of the SWS-promoting parafacial zone. Yamashita and Yamanaka review the composition of the lateral hypothalamic area (LHA), which contains the hypocretin/orexin neurons and melanin concentrating hormone (MCH) neurons, and discuss the molecular and cellular LHA network that may regulate the switch between wakefulness and sleep. Gomes and colleagues discuss the MCH neurons in detail and their putative role in REM sleep regulation, in particular. Luppi et al. then argue that GABA/glutamate neurons of the hypothalamic supramammillary nucleus and glutamate neurons of the claustrum are important for tonic activation of limbic cortical neurons during REM sleep. The basal forebrain has long been implicated in cortical arousal and Jones and Brown et al. review the diverse cell types therein that contribute to sleep/wake control, cortical activity and reward processing. Nakajima and Halassa discuss evidence that the thalamus regulates functional connectivity within and between cortical regions and that thalamic control of cortical connectivity bridges general arousal to specific processing of categorical content.

Regarding the mechanism underlying the global network dynamics associated with different brain states, Ode et al. remind us that cortical neurons have an intrinsic property to exhibit a firing pattern related to the slow wave oscillation observed in the electroencephalogram of the sleeping brain. Based on theoretical modeling and genetic/pharmacological perturbations, they implicate Ca^{2+}-dependent hyperpolarization mechanisms in cortical neurons whereby Ca^{2+} signaling associated with neuronal excitation evokes kinase cascades and then the activated kinases modify ion channels/pumps to regulate the firing mode of cortical neurons across sleep/wake states.

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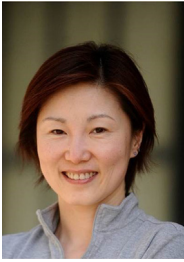
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Akeju and Brown discuss evidence that anesthetic-induced neural oscillations are a primary mechanism of anesthetic action and the differences between anesthesia-induced and sleep states from the perspective of neural oscillations. Siclari and Tononi introduce the concept of local sleep, pointing out that slow waves are not uniformly distributed across the cortex, but can occur locally and asynchronously across brain regions and that the coexistence of local sleep-like and wake-like patterns in different brain areas is characteristic of several sleep disorders.

A major focus within the sleep field is identification of the mechanism(s) underlying sleep homeostasis. As Szymusiak et al. point out, sleep homeostasis is a fundamental property of vigilance state regulation that is highly conserved across species. In flies, a circuit involving the ellipsoid and dorsal fan-shaped bodies has been identified as a candidate for both tracking sleep need during waking and translating it to increased sleep drive and expression. In mammals, the central homeostat is thought to involve A1 receptor-mediated actions of adenosine on wake-promoting neurons in the basal forebrain and hypothalamus, and A2A adenosine receptor-mediated actions on sleep-promoting neurons in the preoptic hypothalamus and nucleus accumbens. Greene and colleagues point out that the neuronal-glial circuit for homeostatic regulation of slow wave activity is primarily under the requisite control of two genes, *Adora1* and *Adk*, which encode the adenosine A1 receptor and the highest affinity enzyme involved in metabolizing adenosine. Haydon then reminds us that astrocytes have been identified as having multiple roles in sleep since they release adenosine, are involved in the glymphatic system and provide energy on demand to neurons through an astrocyte-neuron shuttle. Cirelli introduces the synaptic homeostasis hypothesis, which posits that wakefulness is associated with a net overall increase in synaptic strength in many brain circuits and that the consequent need for renormalization occurs during sleep, and argues that what is being regulated across the sleep/wake cycle is synaptic strength, not firing rate, and that firing rate is not necessarily an adequate proxy for synaptic strength. Timofeev and Chauvette, however, summarize other lines of evidence which indicate that cortical synapses are strengthened, rather than weakened, during SWS. In addition to the homeostatic and circadian drives for sleep, Eban-Rothschild et al. discuss a relatively neglected topic: the effects of motivational processes on sleep/wake behaviors and the possible neuronal mechanisms underlying their control, particularly in the preparation for sleep.

Sleep is thought to play an important role in memory consolidation and neural plasticity. Vyazovskiy et al. suggest a role for sleep in dishabituation which restores attentional capacity and maximizes readiness for learning and goal-directed behavior during subsequent wakefulness. In a related review, Abel focuses on the hippocampus and highlights recent studies that have begun to identify the molecular bases by which sleep deprivation impairs memory consolidation. Boyce and colleagues discuss their work demonstrating that neural activity occurring specifically during REM sleep, in particular the theta rhythm of hippocampal neurons, is required for normal memory consolidation. Feld and Born discuss findings in human memory research and neurophysiological findings from animal studies in an attempt to integrate the effects of sleep on both memory consolidation and forgetting, which together could enhance the abstraction of gist, an important process in high-level human intelligence. Penagos and colleagues propose that recurring nested brain oscillations during sleep may reflect compositional operations that facilitate hierarchical processing of information, which is conducive to general inference, prediction and

insight. Levenstein et al. review studies showing that both the selective plasticity needed to consolidate memory traces and the general plasticity necessary to maintain a well-functioning neural circuit are implemented by the NREM slow oscillation, and they differentially affect neurons based on their intrinsic firing rates. Areal et al. summarize studies on the effects of sleep loss on synaptic functions in both invertebrates (flies) and vertebrates (fish and mice) and provide a lucid discussion regarding why studies in different model organisms appear to yield different results. Frank discusses the role of sleep in experience-dependent plasticity in the visual cortex and what it tells us about the function of sleep.

Sleep and rest occur widely across the animal kingdom. Artiushin and Sehgal summarize the molecular and circuit mechanisms regulating sleep and wakefulness in flies, provide an in-depth comparison of the results obtained by different researchers, and offer insightful analyses of how the different results can be synthesized or reconciled. Barlow and Rihel highlight the advantage of using the larval zebrafish to understand the genetic and neural control of sleep and summarize studies using high throughput monitoring of zebrafish sleep/wake behavior and application of computational tools to large behavioral datasets. Oikonomou and Prober also review pharmacological studies conducted in zebrafish by adding compounds into the water, genetic screening using transient transgenesis, and non-invasive optogenetic manipulations enabled by the use of a transparent organism. Levitas-Djerbi and Appelbaum summarize zebrafish studies that have led to the identification of novel sleep-regulating proteins such as Kcnh4a, Neuromedin U, and QRFP and zebrafish models for various genetic neuropsychiatric disorders. Lyamin et al. cover a fascinating topic—sleep in semiaquatic animals such as fur seals, who not only need sleep strategies for the challenging environment when they are in water, but also have the ability to switch strategies when they move between land and water.

Narcolepsy is a debilitating sleep disorder caused by the loss of hypocretin/orexin signaling in the brain. Pintwala and Peever summarize the use of animal models for identifying the neurobiological basis of narcolepsy, review the normal function of the hypocretin/orexin system in stabilizing the circuits that initiate and sustain normal arousal and motor activity, and discuss how dysfunction of the system causes narcolepsy symptoms. Liu et al. focus on how to modify brain circuits to mitigate cataplexy (which results from orexin neuron degeneration) by reintroducing the orexin gene into various surrogate neurons and determining the efficacy of each strategy to reduce narcolepsy symptoms. Finally, Shi et al. highlight the contribution of human genetics to understanding sleep mechanisms by summarizing recent findings on genetic variations affecting the timing and duration of sleep and EEG patterns, as well as sleep-related neurological disorders and future directions of human genetics in sleep research.

Collectively, the articles in this volume illustrate advances in sleep neurobiology and sleep function that have been enabled by the advent of new systems neuroscience and molecular genetic tools and model systems that have become available in the last decade. We hope the readers will recognize that it is a particularly exciting and fruitful time to be a sleep researcher and that these papers will stimulate others to consider joining this quest.