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Review

Neuronal Mechanisms for Sleep/Wake Regulation and Modulatory Drive

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Humans have been fascinated by sleep for millennia. After almost a century of scientific interrogation, significant progress has been made in understanding the neuronal regulation and functions of sleep. The application of new methods in neuroscience that enable the analysis of genetically defined neuronal circuits with unprecedented specificity and precision has been paramount in this endeavor. In this review, we first discuss electrophysiological and behavioral features of sleep/wake states and the principal neuronal populations involved in their regulation. Next, we describe the main modulatory drives of sleep and wakefulness, including homeostatic, circadian, and motivational processes. Finally, we describe a revised integrative model for sleep/wake regulation.
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INTRODUCTION

Sleep is a complex biological state characterized by behavioral, physiological, and electrophysiological parameters. All animals studied thus far show characteristic signs of sleep, including mammals, birds, fish, insects, roundworms, and jellyfish (Cirelli and Tononi, 2008; Eban-Rothschild and Bloch, 2008; Hendricks *et al*, 2000; Kaiser, 1988; Nath *et al*, 2017; Prober *et al*, 2006; Raizen *et al*, 2008; Ramon *et al*, 2004; Shaw *et al*, 2000; Shein-Idelson *et al*, 2016; Vorster *et al*, 2014; Yokogawa *et al*, 2007). The transition between wakefulness and sleep involves profound changes in motor control, cognition, brain activity, and consciousness (McGinley *et al*, 2015). In mammals and birds, sleep and wake states are typically determined using electroencephalogram (EEG) and electromyogram (EMG) recordings, which measure global cortical and muscular activity, respectively. The awake state is heterogeneous, characterized by desynchronized EEG oscillations of low amplitude and mixed frequencies, and a variable amount of muscle activity. Active or motivated wakefulness is rich in theta (4–9 Hz) and gamma (40–300 Hz) EEG frequency ranges, whereas quiet wakefulness is characterized by slower EEG frequencies, including alpha (7–15 Hz) and beta (8–30 Hz). Using EEG and EMG recordings it is possible to recognize two distinct sleep states: non-rapid eye movement (NREM), and rapid eye movement (REM) sleep—that alternate cyclically across sleep. NREM sleep is characterized by high amplitude low-frequency delta oscillations (0.5–4 Hz) and spindles (bursts of 7–15 Hz oscillations) in the EEG, and low postural muscle tone. The EEG during REM sleep is dominated by theta and gamma oscillations, with a complete loss of muscle tone in axial posture muscles (REM muscle atonia). The sleep/wake states also differ in various physiological parameters, such as thermoregulation, cardiac activity, metabolism, and respiration (Brown *et al*, 2012; Saper *et al*, 2010). The characteristic EEG patterns are biomarkers of the different arousal states, and although most non-mammalian species lack the brain structures producing these EEG oscillations, they nonetheless show behavioral and physiological criteria for sleep (Allada and Siegel, 2008; Cirelli and Tononi, 2008; Zimmerman *et al*, 2008). Behaviorally, sleep is defined as a period of quiescence, with a species-specific body posture and/or sleeping site, and an elevated arousal threshold (Campbell and Tobler, 1984). Sleep is also defined by its homeostatic regulation, which is manifested by an increase in sleep need following extended wakefulness. Non-mammalian model organisms, such as the fruit fly (*Drosophila melanogaster*), the nematode worm (*Caenorhabditis elegans*), and zebrafish (*Danio rerio*) are extremely useful for screening novel sleep mutants and investigations on the organizational principles and genetic control of sleep (Chakravarti *et al*, 2017; Levitas-Djerbi and Appelbaum, 2017; Trojanowski and Raizen, 2016). In addition, various non-model organisms, such as the pectoral sandpiper (*Calidris melanotos*), the northern fur seal (*Callorhinus ursinus*), the cavefish (*Astyanax mexicanus*), and the honey bee (*Apis mellifera*), can serve as excellent systems to study the adaptive values of sleep, plasticity during sleep, and the effects of social and environmental cues on sleep (Aulsebrook *et al*, 2016; Duboue *et al*, 2011;

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Eban-Rothschild and Bloch, 2012,2015; Lesku *et al*, 2012; Lyamin *et al*, 2008a; Lyamin *et al*, 2017).

DISSECTING THE NEURONAL MECHANISMS THAT REGULATE SLEEP/WAKE STATES

von Economo, Ranson, and Moruzzi and Magoun (von Economo, 1930; Moruzzi and Magoun, 1949; Ranson, 1939) were among the first to examine a neuronal mechanism for sleep/wake regulation in mammals and many subsequent studies have contributed to the characterizing of the principal regions and neuronal modulators of sleep/wake states. Over several decades, researchers have used various experimental techniques including lesions, pharmacological and genetic manipulations, electrical stimulations, and electrophysiological recordings, to establish a solid base for our current understanding of sleep/wake circuitry. Nonetheless, brain nuclei regulating sleep/wake states are typically heterogeneous and contain intermingled neuronal populations that frequently support different arousal states. Moreover, traditional techniques typically lack temporal resolution and/or can involve compensatory mechanisms in the sleep/wake circuitry. With the application of novel methods to manipulate specific cell types in restricted brain regions *in vivo* with high temporal precision (Kim *et al*, 2017; Lin and Schnitzer, 2016; Roth, 2016), it is now possible to reveal the activity patterns and functionally interrogate the roles of genetically defined neuronal populations involved in sleep/wake regulation. A better understanding of brain mechanisms controlling sleep/wake states would allow us to gain new insights on the functions of sleep and improve the capacity to treat sleep disorders.

Mammalian Neuronal Circuitry of Sleep/Wake States

How does the mammalian brain control sleep and wakefulness? It is currently understood that complex interactions between subcortical neuromodulatory neurons in the brainstem, midbrain, hypothalamus, and basal forebrain (BF), the thalamus, and the cortex drive behavioral, physiological, and electrocortical sleep/wake states. Wake-promoting populations project to various structures through a dorsal and a ventral pathway. The dorsal pathway innervates the thalamus —which facilitates transmission of sensory information to the cortex. The ventral pathway innervates the hypothalamus, BF, and other forebrain structures—which together excite the cortex. It is thought that wakefulness is achieved when both the dorsal and the ventral pathways are activated. In this review, we will mainly focus on wake-promoting neuronal circuits, as excellent recent reviews have covered the neuronal mechanisms underlying NREM and REM sleep (Arrigoni *et al*, 2016; Luppi *et al*, 2017; Peever and Fuller, 2017; Scammell *et al*, 2017; Weber and Dan, 2016).

Historically, monoaminergic and cholinergic producing neurons were assigned as key players in the regulation of arousal states (Jouvet, 1972), yet recent findings reveal important roles for fast gamma-Aminobutyric acid (GABA) and glutamate neurotransmission in sleep/wake regulation (Saper and Fuller, 2017). Among the wake-promoting monoaminergic and cholinergic populations are the noradrenergic locus coeruleus (LC), dopaminergic ventral tegmental area (VTA), dopaminergic and serotonergic (5HT) dorsal raphe nucleus (DRN), histaminergic tuberomammillary nucleus (TMN), and cholinergic pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) and BF neurons (Jones, 2003; Scammell *et al*, 2017) (Figure 1). Importantly, monoaminergic and cholinergic neurons are essential for learning, motivation, attention, reward, mood, and locomotor behaviors in addition to sleep/wake regulation (Lorincz and Adamantidis, 2017).

Hypocretin Neurons

Two decades ago, hypocretin/orexin (Hcrt) neurons of the lateral hypothalamus (LH) emerged as essential orchestrators of sleep and wakefulness. The hypocretins are two alternatively spliced neuropeptides, Hcrt-1 and Hcrt-2, produced from a single-precursor gene (de Lecea *et al*, 1998; Sakurai *et al*, 1998). Hcrt neurons show high discharge rates during active waking and goal-oriented behaviors, decrease their activity during quiet wakefulness, and are silent during sleep (Hassani *et al*, 2009b; Lee *et al*, 2005b; Mileykovskiy *et al*, 2005; Takahashi *et al*, 2008). Hcrt neurons strongly project to various wake-promoting populations in the brain, including cholinergic neurons of the BF and brainstem, noradrenergic

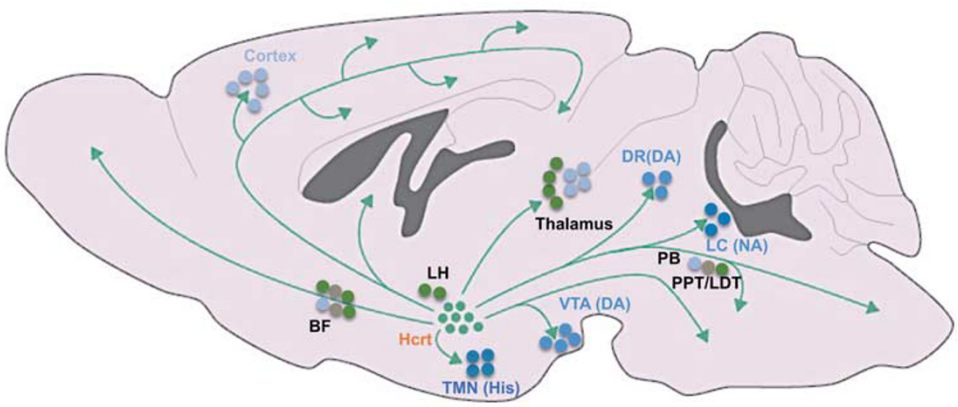

Figure 1 Schematic of neuronal wake-promoting populations. BF, basal forebrain; DA, dopamine; DR, dorsal raphe; Hcrt, hypocretin; His, histamine; LC, locus coeruleus; LH, lateral hypothalamus; NA, noradrenaline; PB, parabrachial area; PPT/LDT, pedunculopontine and laterodorsal tegmental nuclei; TMN, tuberomammillary nucleus; VTA, ventral tegmental area.

neurons of the LC, and dopaminergic neurons of the VTA. The first *in vivo* application of optogenetics was performed by the de Lecea group to reveal that photostimulation of Hcrt neurons increases the probability of sleep-to-wake transitions and promotes wakefulness (Adamantidis *et al*, 2007). Loss of Hcrt-producing neurons or their receptors in humans, dogs and rodents causes narcolepsy with cataplexy—a neurological disorder characterized by an inability to control the boundaries between sleep–wake states (Chemelli *et al*, 1999; Lin *et al*, 1999; Peyron *et al*, 2000; Thannickal *et al*, 2000). In narcoleptics with cataplexy, periods of wakefulness are interrupted by unexpected sleep episodes, and REM-like episodes co-exist with conscious wakefulness (de Lecea, 2015). Nonetheless, Hcrt neurons are not essential for sleep or wake generation—as narcoleptic patients and transgenic mice lacking Hcrt neurons or Hcrt receptor-2 display normal daily amounts of sleep (Branch *et al*, 2016; Chemelli *et al*, 1999; de Lecea and Sutcliffe, 2005). Rather, the coordination between sleep/wake states and the stability of arousal appears to be localized in Hcrt neurons.

The Locus Coeruleus

The LC is the main source of noradrenergic transmission to the cortex. LC neurons fire tonically at 1–3 Hz during wakefulness, reduce their activity during NREM sleep and are nearly silent during REM sleep (Aston-Jones and Bloom, 1981a; Hobson *et al*, 1975). In response to salient stimuli, LC neurons transition to phasic burst firing at 8–10 Hz (Aston-Jones and Bloom, 1981b). The release of noradrenaline in the cortex increases firing rates of pyramidal neurons and electrocortical arousal, while blockade of noradrenergic pathways induces synaptic quiescence during wakefulness (Constantinople and Bruno, 2011). Administration of noradrenaline directly to the ventricles or forebrain promotes wakefulness (Flicker and Geyer, 1982; Segal and Mandell, 1970), while pharmacological inhibition of noradrenergic neurons increases NREM sleep (Berridge and Espana, 2000; De Sarro *et al*, 1987). Nonetheless, neuronal lesions of the LC fail to produce a consistent effect on cortical EEG (Blanco-Centurion *et al*, 2007; Lidbrink, 1974; Tononi *et al*, 1991). Optogenetic interrogations revealed that activity in noradrenergic tyrosine hydroxylase (Th) positive LC neurons is sufficient to induce wakefulness at physiologically relevant frequencies (Carter *et al*, 2010). Moreover, LC activity seems to be essential for Hcrt-induced awakenings, as optogenetic inhibition of Th+ LC neurons during photostimulation of Hcrt neurons prevents Hcrt-mediated sleep-to-wake transitions (Carter *et al*, 2012). Reciprocally, increasing the excitability of Th+ LC neurons dramatically reduces the latency of Hcrt-mediated awakenings (Carter *et al*, 2012). These results strongly support the premise that LC is a major output effector of Hcrt neurons in regard to arousal regulation (Carter *et al*, 2013).

The Basal Forebrain

The BF contains three major cell groups: cholinergic, GABAergic, and glutamatergic neurons. This brain structure has been traditionally regarded as a wake-promoting region, as its activation induce wakefulness and its lesion results in slow oscillations in the EEG and a coma-like state (Buzsaki *et al*, 1988; Fuller *et al*, 2011). Nonetheless, the BF is functionally and anatomically heterogeneous and contains intermingled neurons maximally active during different arousal states (Jones, 2017). Cholinergic neurons of the BF are strongly activated during wakefulness and REM sleep (Boucetta *et al*, 2014; Lee *et al*, 2005a; Xu *et al*, 2015), and their optogenetic stimulation induces cortical activation and transitions from NREM sleep to wakefulness (Han *et al*, 2014; Irmak and de Lecea, 2014; Xu *et al*, 2015). Nonetheless, chemogenetic activation of BF cholinergic neurons mainly reduces delta activity during NREM sleep, rather than substantially increasing wakefulness (Anaclet *et al*, 2015; Chen *et al*, 2016a). The activity pattern of GABAergic neurons of the BF is highly heterogeneous—a subset of neurons are maximally active during wakefulness and REM sleep, another subset during NREM sleep, and a minority are maximally active during REM sleep (Duque *et al*, 2000; Hassani *et al*, 2009a; Jones, 2017). Chemogenetic activation of the entire BF GABAergic population strongly promotes wakefulness and high-frequency cortical EEG, whereas their inhibition increases NREM sleep and slow-frequency oscillations (Anaclet *et al*, 2015). BF parvalbumin (PV) positive GABAergic neurons are wake-active and their optogenetic stimulation induces wakefulness, whereas somatostatin-positive BF GABAergic neurons are functionally heterogeneous and may facilitate NREM sleep (Xu *et al*, 2015). Cortically projecting PV+ BF neurons were also demonstrated to promote cortical arousal, specifically in the gamma band (Kim *et al*, 2015). The neurochemical identity of BF GABAergic neurons maximally active during REM sleep remains to be elucidated. The activity of BF glutamatergic neurons is also heterogeneous (Jones, 2017), and while their optogenetic stimulation induces sleep-to-wake transitions (Xu *et al*, 2015), their chemogenetic activation does not modify sleep/wake architecture (Anaclet *et al*, 2015). Future studies using projection-specific and/or additional neurochemical markers for subpopulations of BF neurons would provide important insights onto the complex roles of this structure in sleep/wake regulation.

The Ventral Tegmental Area

The VTA is a key structure in the regulation of motivational processes, and contains dopaminergic, GABAergic, and glutamatergic neurons (Morales and Margolis, 2017). Although the roles of GABAergic and glutamatergic VTA neurons in sleep/wake regulation remain to be elucidated, much progress has been made in recent years in delineating the roles of the dopaminergic population. It has long been known that stimulants that enhance dopaminergic tone are potent wake-promoting substances (Boutrel and Koob, 2004), and their arousing effects are abolished in mice deficient in dopamine signaling (Qu *et al*, 2008; Wisor *et al*, 2001). Nonetheless, dopaminergic neurons have been considered for several decades as the only monoamine group not involved in sleep/wake regulation (Espana and Scammell, 2011; Saper *et al*, 2010), mainly since early electrophysiological findings suggested that VTA and substantia nigra pars compacta dopaminergic neurons do not change their mean firing rates across sleep–wake states (Miller *et al*, 1983; Steinfels *et al*, 1983; Trulson and Preussler, 1984; Trulson *et al*, 1981). Moreover, lesions to

the VTA and substantia nigra pars compacta were not found to modify the time spent in electrocortical wakefulness (Jones *et al*, 1973). Recently, this view has been changed as we and others have provided compelling evidence that VTA dopaminergic neurons are key modulators of sleep and wakefulness (Dahan *et al*, 2007; Eban-Rothschild *et al*, 2016; Oishi *et al*, 2017a; Taylor *et al*, 2016).

During wakefulness, VTA dopaminergic neurons are strongly activated by various salient stimuli, including sensory cues, social cues, and rewards (Brischoux *et al*, 2009; Cohen *et al*, 2012; Gunaydin *et al*, 2014; Lammel *et al*, 2012). Using unit recording in head restrained rats, Dahan *et al*. revealed a robust increase in bursting activity of VTA dopaminergic neurons during REM sleep, compared to both quiet wakefulness and NREM sleep (Dahan *et al*, 2007). The activity pattern of VTA dopaminergic neurons during REM sleep was found to be similar to that measured during the consumption of palatable food (Dahan *et al*, 2007). Recently using simultaneous calcium-dependent fiber-photometry and EEG/EMG recordings we further demonstrated that VTA dopaminergic neurons reduce their activity during NREM sleep compared to both wakefulness and REM sleep (Eban-Rothschild *et al*, 2016). Using optogenetic and chemogenetic interrogations a causal role for VTA dopaminergic neurons in sleep/wake regulation has been demonstrated. Activation of VTA dopaminergic neurons was found to induce and maintain wakefulness during a period of high sleep pressure (Eban-Rothschild *et al*, 2016; Oishi *et al*, 2017a) and even during 0.8–0.9% isoflurane anesthesia (Taylor *et al*, 2016). We also demonstrated that chemogenetic inhibition of VTA dopaminergic neurons during the dark/active phase promotes sleep—strongly suggesting that activity in these neurons is necessary for wakefulness (Eban-Rothschild *et al*, 2016). Inhibition of VTA dopaminergic neurons promoted sleep even in the presence of various salient stimuli, including a potential mate, predator odor, and palatable food—suggesting a prominent role in salience-induced arousal (Eban-Rothschild *et al*, 2016). We further characterized the contribution of different output pathways of VTA dopaminergic neurons in the regulation of arousal. By employing projection-specific optogenetic manipulations, we demonstrated that stimulation of nucleus accumbens (NAc), central amygdala (CeA), and dorsolateral striatum (DLS), but not medial prefrontal cortex (mPFC) projections promoted a transition from NREM sleep to wakefulness. In addition, stimulation of mPFC and CeA projections promoted a transition from REM sleep to wakefulness (Eban-Rothschild *et al*, 2016). Nonetheless, only the NAc projection was found to have a role in wake maintenance and its stimulation suppressed sleep (Eban-Rothschild *et al*, 2016)—further supporting a role for the NAc in sleep/wake regulation (Lazarus *et al*, 2013; Oishi *et al*, 2017b; Qiu *et al*, 2012). These findings reveal a complex circuitry for VTA dopaminergic regulation of arousal, and highlight the importance of using cell type and projection-specific *in vivo* tools for functional interrogations of circuits participating in sleep/wake regulation.

Most monoaminergic neurons involved in sleep/wake regulation share similar firing patterns—with high rates of firing during wakefulness, slow firing during NREM sleep, and a virtual cessation of firing during REM sleep (Jones, 2003; Scammell *et al*, 2017). In contrast, VTA dopaminergic neurons show strong activation during REM sleep (Dahan *et al*, 2007; Eban-Rothschild *et al*, 2016), as do cholinergic BF neurons (Boucetta *et al*, 2014; Lee *et al*, 2005a; Xu *et al*, 2015). Activation of cholinergic BF neurons has been implicated in cortical arousal (Goard and Dan, 2009; Pinto *et al*, 2013), yet the precise role of dopaminergic activity during REM sleep remains to be elucidated.

The Dorsal Raphe Nucleus/Ventral Periaqueductal Gray

The DRN is a heterogeneous brainstem nucleus that innervates many brain regions implicated in sleep/wake regulation. DRN neurons express various neurotransmitters, including serotonin and dopamine. DRN serotonin neurons were initially hypothesized to play an important role in the initiation and maintenance of NREM sleep, as lesions to the DRN in rats and cats resulted in insomnia (Jouvet, 1972). Nonetheless, further examinations of the activity pattern of serotonergic DRN neurons across arousal states revealed that they are wake-active and predominantly silent during NREM and REM sleep (McGinty and Harper, 1976; Trulson and Jacobs, 1979). Later work suggested that serotonergic DRN neurons facilitate quiet wakefulness and inhibit REM sleep (Jacobs and Fornal, 1993). Further cell type, receptor- and projection-specific functional interrogations of serotonergic DRN circuitry are required to reveal the casual role(s) of this population in sleep/wake regulation.

The DRN or ventral periaqueductal gray (vPAG) contains an additional neuronal population implicated in sleep/wake regulation: the dopaminergic neurons. vPAG dopaminergic neurons show c-Fos immunoreactivity during wakefulness and not during sleep, and their lesion reduces wakefulness and increases sleep (Lu *et al*, 2006). Recently, arousal-state-dependent alterations in population activity of vPAG/DR dopaminergic neurons have been demonstrated and a causal role in sleep/wake regulation (Cho *et al*, 2017). DRN dopaminergic neurons where shown to be wake-active and their optogenetic activation induces wakefulness from sleep (Cho *et al*, 2017). In contrast, chemogenetic inhibition of DRN dopaminergic neurons promotes NREM sleep, even in the presence of various salient stimuli (Cho *et al*, 2017). Interestingly, optogenetic inhibition of DRN dopaminergic neurons during NREM sleep decreases the probability of auditory cues to induce wakefulness (Cho *et al*, 2017)—suggesting a role for these neurons in the arousal response to sensory stimuli.

It is important to note that not all dopaminergic populations promote wakefulness, as SNc dopaminergic neurons projecting to the dorsal striatum have been suggested to promote NREM sleep (Qiu *et al*, 2016b). It would be of interest for future studies to determine the functional role of additional dopaminergic populations, including the caudal hypothalamic A11, arcuate nucleus A12 and the zona incerta A13 groups. In addition, it would be useful to determine whether dopaminergic neurons act in concert or independently to generate, regulate, and/or maintain sleep and wake states.

The Tuberomammillary Nucleus

The TMN of the hypothalamus is the sole source of histamine in the brain (Haas *et al*, 2008). Histaminergic TMN neurons send widespread, yet diffused, projections to various sleep/wake regulatory regions, including to the

ventrolateral preoptic nucleus and the basal forebrain (Haas *et al*, 2008). Histaminergic TMN neurons show arousal-state depended alterations in activity. They fire most rapidly during attentive wakefulness, reduce their activity during quiet wakefulness and are silent during NREM and REM sleep (Steininger *et al*, 1999; Takahashi *et al*, 2006). Histamine has long been implicated in wake maintenance, as antihistamines (histamine H1 receptor antagonists) promote sleep and slow-wave activity (Haas *et al*, 2008; Ikeda-Sagara *et al*, 2012). Mice lacking histamine H1 receptor show reduced wakefulness in the beginning of the active/dark phase, and a reduced arousal response in a novel environment (ie, shorter latency to enter NREM sleep) (Parmentier *et al*, 2016). Nonetheless, ablation of histaminergic TMN neurons produce only a modest effect on sleep/wake patterns (Anaclet *et al*, 2009; Parmentier *et al*, 2002). Recently, activity in TMN histaminergic neurons has been casually demonstrated to be necessary for wakefulness—as their optogenetic inhibition promotes NREM sleep (Fujita *et al*, 2017). Interestingly, mice lacking GABA receptors only in histaminergic neurons show an increased arousal response in a novel environment (ie, longer latency to enter NREM sleep) (Zecharia *et al*, 2012). Histaminergic TMN neurons express GABA, GAD67, and VGAT (Airaksinen *et al*, 1992; Takeda *et al*, 1984). These neurons may also co-release GABA which has been suggested to synergistically promote cortical activation and wakefulness (Yu *et al*, 2015)—yet additional evidence is needed to further support this finding. Future studies should further elucidate the importance of neurotransmitter co-transmission for sleep/wake regulation, in the TMN and additional sleep/wake regulatory populations. Moreover, it remains to be resolved which aspects of arousal histaminergic TMN neurons are contributing.

Glutamatergic Neurons

Glutamate is the principle excitatory neurotransmitter in the brain, and global modulation of glutamatergic signaling pathways dose-dependently modulates sleep/wake states (Maclver *et al*, 1996; Yamamura *et al*, 1990). Glutamate levels in the posterior hypothalamus and cortex rise progressively during wakefulness, decline during NREM sleep and increase rapidly at the onset of REM sleep (John *et al*, 2008; Naylor *et al*, 2012). There are several glutamatergic populations implicated in promoting arousal, including the parabrachial (PB), PPT, and supramammillary nuclei neurons (Pedersen *et al*, 2017; Saper and Fuller, 2017). For example, PB glutamatergic neurons send strong projections to the BF, LH, and cortex (Bernard *et al*, 1991; Fuller *et al*, 2011; Fulwiler and Saper, 1984; Hur and Zaborszky, 2005; Saper and Loewy, 1980). Partial or complete lesions to the PB cause either a reduction in wakefulness or a coma-like state with permanent slow EEG oscillations, respectively (Fuller *et al*, 2011). Genetically driven disruption of glutamate transmission in PB neurons also results in a significant reduction in total wakefulness and an increase in delta oscillations in the waking EEG (Kaur *et al*, 2013). Chemogenetic activation of PB neurons (both glutamatergic and non-glutamatergic) in rats increases wakefulness and decreases both NREM and REM sleep during the light/inactive phase (Qiu *et al*, 2016a). Furthermore, the LH and preoptic-BF area, but not the thalamus, where shown to be the principle output pathways in PB modulation of wakefulness (Qiu *et al*, 2016a). Recently, chemogenetic activation of glutamatergic PPT (and possibly also PB neurons) has been demonstrated to induce prolonged cortical activation and behavioral wakefulness, whereas their chemogenetic inhibition reduces wakefulness and increases NREM sleep (Kroeger *et al*, 2017). As different neuromodulatory populations also release glutamate (and/or GABA), future studies should determine the precise role neuromodulators and fast neurotransmitters play in sleep/wake regulation independently.

GABAergic Neurons

GABA has been traditionally viewed as a sleep-promoting neurotransmitter. Most sleep-promoting populations are GABAergic, including those in the preoptic area (Sherin *et al*, 1996) and parafacial zone (Anaclet *et al*, 2014). Sleep-promoting medications typically target and enhance GABAergic signaling (Luppi *et al*, 2017; Schulz and Macdonald, 1981). Nonetheless, recent studies have identified several GABAergic populations in the LH (Herrera *et al*, 2016; Venner *et al*, 2016) and BF (Anaclet *et al*, 2015; Xu *et al*, 2015) that promote wakefulness and cortical activation. LH GABAergic neurons projecting to the thalamic reticular nucleus (TRN) where shown to increase wakefulness by inhibiting TRN GABAergic neurons (Herrera *et al*, 2016). Optogenetic stimulation of either LH GABAergic cell bodies or their projections to the TRN induces transitions to wakefulness from NREM sleep, while their optogenetic inhibition increases NREM sleep and delta oscillations in the EEG (Herrera *et al*, 2016). In addition, recent chemogenetic interrogations revealed that GABAergic neurons of the ventral LH promote wakefulness, and their inhibition increases NREM sleep, possibly via projections to the ventrolateral preoptic nucleus (Venner *et al*, 2016).

In summary, much progress has been made in recent years in identifying the roles of distinct neuronal populations in sleep/wake regulation. Nonetheless, it is still unclear by which pre- and post-synaptic actions sleep/wake regulatory neuromodulators regulate arousal and what role co-transmission plays in sleep/wake regulation. In addition, a major question that remains to be resolved is how information from the diverse sleep/wake regulatory populations is integrated to result in a coherent arousal state.

Neuronal Mechanisms Regulating Sleep/Wake States Across Species

All animals studied thus far, across six different phyla, sleep. The neuronal, cellular, and molecular pathways associated with sleep are highly conserved across species—suggesting an early and common origin for sleep (Allada and Siegel, 2008; Joiner, 2016; Nall and Sehgal, 2014). In zebrafish, the neurotransmitters and neuromodulators controlling sleep/wake states are located in parallel structures to mammals (Levitas-Djerbi and Appelbaum, 2017; Oikonomou and Prober, 2017; Sundvik and Panula, 2015). For example, in both mammals and zebrafish, Hcrt and histamine neurons are located in the hypothalamus (Appelbaum *et al*, 2009; Sundvik *et al*, 2011) and noradrenaline in the LC (Singh *et al*, 2015). Genetic and pharmacological manipulations of GABAergic, glutamatergic, monoaminergic, and neuropeptidergic

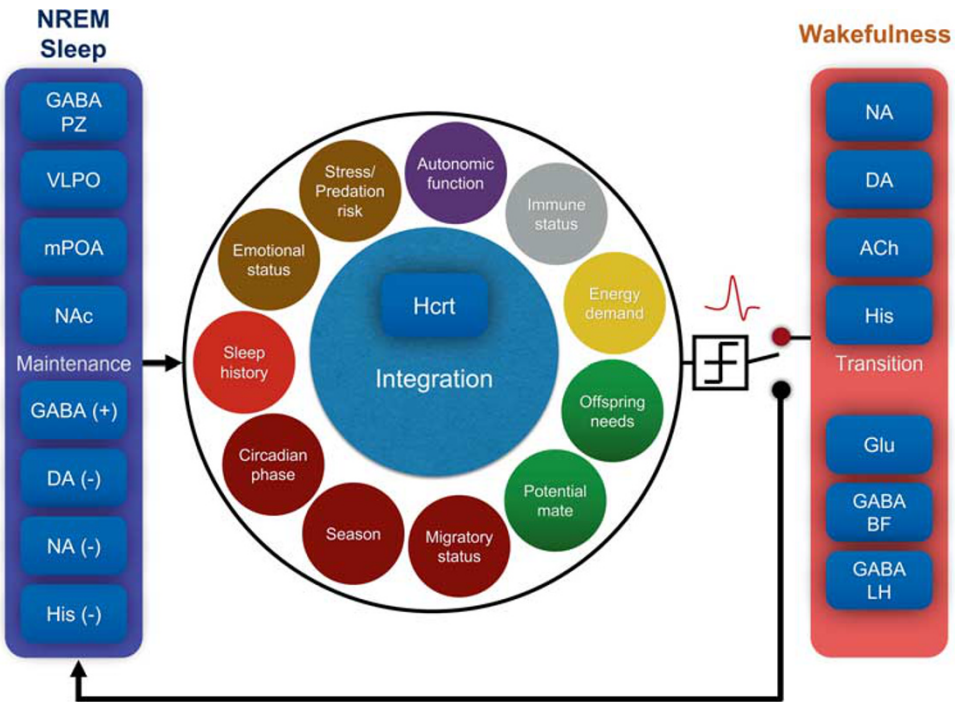

Figure 2 Schematic of the integrative model of sleep/wake regulation. An 'integrator' Hcrt neuron continuously integrates information from multiple and often conflicting variables, and makes the decision whether to fire and wake up the animal, or stay silent and facilitate sleep. The probability of a sleep-to-wake transition depends on (i) the functional connectivity between different sleep/wake regulatory populations, including the GABAergic neurons of the PZ, mPOA, and VLPO and dopaminergic neurons of the VTA, and (ii) internal and external factors, including sleep history, circadian phase, and predation risk. ACh, acetylcholine; BF, basal forebrain; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; Hcrt, hypocretin; His, histamine; LH, lateral hypothalamus; mPOA, medial preoptic area; NAc, nucleus accumbens; NA, noradrenaline; PZ, parafacial zone; VLPO, ventral lateral preoptic area.

neurons in zebrafish result in similar modifications to sleep and wakefulness as in mammals (Barlow and Rihel, 2017; Levitas-Djerbi and Appelbaum, 2017; Rihel *et al*, 2010). In zebrafish, as in mammals, Hcrt neurons send widespread projections throughout the brain and consolidate wakefulness (Elbaz *et al*, 2017; Faraco *et al*, 2006; Prober *et al*, 2006; Yelin-Bekerman *et al*, 2015; Yokogawa *et al*, 2007), whereas ablation of Hcrt neurons fragments sleep/wake states (Chen *et al*, 2016b; Elbaz *et al*, 2012). Mammals and insects also share similar functions in the neurotransmitters and neuromodulators controlling sleep/wake states. For example, as in mammals, dopamine is a major regulator of sleep/wake states in *Drosophila*, and enhancement of dopaminergic neurotransmission dramatically reduces sleep and arousal threshold, and increases locomotor activity (Andretic *et al*, 2005; Hendricks *et al*, 2003; Kume *et al*, 2005; Pimentel *et al*, 2016; Wu *et al*, 2008). In addition, noradrenergic and histaminergic activity promotes wakefulness in *Drosophila*, whereas GABAergic and serotonergic neurotransmission promotes sleep (Michel and Lyons, 2014; Nall and Sehgal, 2014). These similarities, as well as the ease of completing large unbiased screens in simple model systems and the numerous forward and reverse genetic approaches available, have placed these species as prominent models in sleep research. Their study provides important insights into the regulatory processes and functions of sleep.

PROCESSES MODULATING THE PROPENSITY TO STAY AWAKE OR FALL ASLEEP

Most behaviors, such as foraging, courting and predator defense, are incompatible with sleep, and animals need to carefully coordinate the timing of sleep and wakefulness to maximize their survival. The probability of an individual entering a particular sleep/wake state depends on multiple factors, including previous sleep history, circadian time, environmental cues, and internal needs (Figure 2). Here, we will focus on homeostatic, circadian, and motivational processes modulating sleep/wake states. A better understanding of these circuits will not only reveal how brain states are regulated, but also how the brain balances conflicting needs. It is important to note that there are additional factors that can modulate sleep/wake behaviors, such as breathing (Morrell and Twigg, 2006; Yackle *et al*, 2017) and immune state (Krueger *et al*, 2011), yet they are beyond the scope of this review.

Homeostatic Regulation of Sleep/Wake States

When wakefulness is extended, sleep pressure accumulates and only dissipates during subsequent sleep. This homeostatic process was initially modeled three decades ago by Borbely in the two-process model of sleep regulation (Borbely, 1982). According to this model, sleep pressure (Process S) increases during wakefulness and declines during sleep in a cycle superimposed over the circadian (~24-h long) cycle of activity (Process C) (Borbely and Achermann, 1999; Borbely *et al*, 2016). While this model has been highly influential, the neuronal substrate(s) of Process S still remain elusive. More than a century ago, researchers revealed that the cerebrospinal fluid of sleep deprived animals contained substances that can promote sleep in other animals (Ishimori, 1909; Legendre and Pieron, 1913). This finding

led to the premise that wake-dependent homeostatic substances accumulate with wakefulness, and when sensed by a homeostatic system promote sleep. Among the homeostatic substances and mechanisms suggested are adenosine and its receptors A1 and $A2_A$, cytokines such as interleukin-1 and tumor necrosis factor-α, prostaglandin D_2, and Nitric oxide (Benington and Heller, 1995; Brown *et al*, 2012; Mang and Franken, 2015; Morairty *et al*, 2013). Nonetheless, it is still unclear how the brain senses and responds to sleep need, where in the brain this process takes place, and whether lack of sleep is sensed by a master control center (ie, a sleep 'homeostat') or by various regulatory neuronal networks. These remain central questions in sleep neurobiology (Allada *et al*, 2017; Mang and Franken, 2015).

Delta oscillations in the EEG are homeostatically regulated and are thought to reflect the accumulation of sleep pressure during wakefulness, and its discharge during sleep (Mang and Franken, 2015; Vyazovskiy *et al*, 2011a). Slow oscillations increase with wakefulness, decline with sleep and reach their peak following sleep deprivation (Dijk *et al*, 1987; Tobler and Borbely, 1986). Interestingly, it has been proposed that sleep intensity, as reflected by delta oscillations during NREM sleep, depends on previous wake time spent in active-motivated wakefulness (theta-dominated wakefulness) rather than only on previous wake duration (Vassalli and Franken, 2017).

Recent studies in *Drosophila* provide important insights regarding the mechanisms and circuits that may mediate the homeostatic drive for sleep (Allada *et al*, 2017; Donlea *et al*, 2017). Sleep in flies can be induced by the activation of sleep-promoting neurons that innervate the dorsal Fan-shaped body (dFB) (Donlea *et al*, 2011). Sleep need was found to be reflected in dFB neuron excitability—it is elevated to promote sleep after prolonged waking and reduced to permit waking once flies are rested (Donlea *et al*, 2014). Furthermore, the changes in excitability of dFB neurons were shown to occur through the antagonistic action of dopamine on two potassium channels, Shaker and Sandman (Pimentel *et al*, 2016). Another study demonstrated that the activation of a subset of Ellipsoid Body neurons elicits a need for sleep that was only apparent following the termination of neuronal activation and not during the activation itself—suggesting a prominent role in sleep drive (Liu *et al*, 2016). Intriguingly, the activation of certain arousal circuits, rather that wakefulness *per se*, has been suggested to drive sleep homeostasis in flies (Seidner *et al*, 2015). Seidner *et al*. induced wakefulness by activating cholinergic, dopaminergic, and octopaminergic neurons, and demonstrated that only wakefulness induced by the activation of cholinergic neurons results in a sleep rebound while octopaminergic and dopaminergic neurons did not (Seidner *et al*, 2015). Moreover, activity in octopaminergic neurons seems to directly inhibit a homeostatic sleep response (Seidner *et al*, 2015). Future studies should further explore these intriguing findings and determine to what extent they can be generalized to mammals.

Recently a forward-genetic approach has been applied to reveal sleep mutants in mammals. By screening sleep patterns in more than 8000 strains of randomly mutagenized mice, researchers revealed two sleep mutants, *sleepy* and *dreamless*, that show altered sleep need (Funato *et al*, 2016). *Sleepy* mutants, that have a gain-of-function mutation in Sik3 serine-threonine protein kinase, show increased NREM sleep (Funato *et al*, 2016). *Dreamless* mutants, that have a mutation in the sodium leak channel NALCN, show a decrease in REM sleep amount and episode duration (Funato *et al*, 2016). Although the precise mechanisms by which these mutations modulate sleep need are still unclear, the use of unbiased forward-genetic screens in mammals will likely lead to major insights into the pathways and mechanisms of sleep regulation, as it did for circadian biology (Allada *et al*, 2001; Susaki *et al*, 2017; Vitaterna *et al*, 1994).

Circadian Regulation of Sleep/Wake States

Circadian rhythms in activity are apparent in the daily organization of sleep and wakefulness into a specific phase of the day-processes C in the two-process model of sleep regulation (Borbely, 1982; Borbely *et al*, 2016). Diurnal species such as humans, zebrafish and flies primarily sleep at night while nocturnal species, such as mice, primarily sleep during the day. This pattern of sleep/wake organization follows the light–dark cycle, but also persists in the absence of environmental time cues—demonstrating the existence of an intrinsic regulatory mechanism. This internal rhythm is generated by the circadian clock which regulates numerous physiological and behavioral processes. The circadian clock can be synchronized to the environment by different cues or *Zeitgebers* (Albrecht, 2012; Saper *et al*, 2010), such as light (Gooley *et al*, 2003; Whitmore *et al*, 2000), temperature (Buhr *et al*, 2010), stress and exercise (Tahara *et al*, 2017), food availability (Stephan, 2002), and social interactions (Bloch *et al*, 2013; Fuchikawa *et al*, 2016). Internal clocks are advantageous to animals, enabling them to anticipate, rather than react to, daily recurring events and align their physiology and behavior to the changing environment (Albrecht, 2012; Sharma, 2003).

How does the circadian system regulate sleep and wakefulness? In mammals, overt rhythmicity is coordinated by the central pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Saper, 2013). Lesions to the SCN abolish the daily rhythm in sleep/wake states and lead to sleep fragmentation, including in non-human primates (Edgar *et al*, 1993). It has been hypothesized that the major output region of the SCN, in regard to sleep/wake regulation, is the dorsomedial nucleus of the hypothalamus (via the subparaventricular zone), which heavily innervates sleep- and wake-promoting nuclei (Deurveilher and Semba, 2005; Saper, 2013). Nonetheless, the precise pathways and roles of the SCN in sleep/wake state synchronization, sleep structure, and sleep quality, remain to be elucidated.

The central circadian clock is comprised of cell-autonomous pacemaker neurons (Allada *et al*, 2001; Takahashi, 2017). The pacemaker neurons contain a molecular transcription–translation-based autoregulatory feedback loop—in which circadian clock genes rhythmically regulate their own expression (Takahashi, 2017), as well as the expression of thousands of other genes (Zhang *et al*, 2014). The core clock genes, in mammals, include the *Period* genes, the *Cryptochrome* genes, *Clock*, and *Bmal1* (Takahashi, 2017). Besides the core molecular loop, there are additional accessory loops that contribute to the overall precision and robustness of the clock. The clock genes are not only expressed in the central pacemaker, instead, their

expression is widespread throughout the body and brain (Dibner *et al*, 2010; Guilding and Piggins, 2007; Mohawk *et al*, 2012). Interestingly, recent findings suggest that clock genes outside the SCN can control sleep/wake state, as well as sleep homeostasis (Ehlen *et al*, 2017; Franken, 2013; Mahoney *et al*, 2013; Mang *et al*, 2016; Yu *et al*, 2014). For example, daily oscillations in the expression of the enzyme histidine decarboxylase in histaminergic TMN neurons depends on *Bmal1* (Yu *et al*, 2014). Deleting *Bmal1* specifically from histaminergic TMN neurons resulted in various alterations to sleep/wake architecture including sleep fragmentation, as well as reduced recovery sleep and delta power following sleep deprivation (Yu *et al*, 2014). A recent study also suggests that *Bmal1* expression in skeletal muscle can regulate sleep (Ehlen *et al*, 2017).

The molecular and neuronal pathways regulating the circadian clock and the sleep/wake cycle in *Drosophila* have been extensively studied over the last decades (Artiushin and Sehgal, 2017). Since the identification of period (Konopka and Benzer, 1971)—a *Drosophila* mutant with altered circadian timekeeping—the fly has served as a prominent model for studies of the molecular and neuronal machinery of the circadian system and sleep regulation (Artiushin and Sehgal, 2017; Bargiello *et al*, 1984; Greenspan *et al*, 2001; Konopka and Benzer, 1971; Liu *et al*, 1992). Intriguingly, reverse genetic analysis in *Drosophila* has also proved a powerful model to study human sleep disorders (Chakravarti *et al*, 2017; Donelson and Sanyal, 2015).

The circadian pacemaker of *Drosophila* contains around 75 pairs of neurons that are organized in several groups among which are the pigment-dispersing factor (PDF)-positive small and large ventral lateral neurons (sLNVs and lLNVs), the dorsal neurons (DN1s, DN2s, and DN3s), and the dorsal lateral neurons (Allada and Chung, 2010). Multiple studies have demonstrated that activity in different clock neurons can modulate sleep and wakefulness (Chung *et al*, 2009; Donlea *et al*, 2009; Parisky *et al*, 2008; Shang *et al*, 2008; Shang *et al*, 2011; Sheeba *et al*, 2008). For example, a *Drosophila* screen identified a cycling gene *wide awake* (*wake*), which links circadian clock output to sleep onset in flies and rodents (Liu *et al*, 2014). WAKE expressed in clock neurons peaks in expression at dusk, and acts downstream of circadian genes to upregulate $GABA_A$ receptors, driving sleep (Funato *et al*, 2016). In addition, PDF secreted from sLNVs neurons was shown to act on DN1s neurons to suppress sleep in anticipation of dawn. Recently, glutamatergic DN1s clock neurons were shown to promote sleep by negative feedback onto key clock neurons that typically promote wakefulness (Guo *et al*, 2016). These essential studies provide mechanistic insight into the regulation of sleep by neurons that control circadian rhythms.

It is important to note that the sleep/wake state itself can also strongly influence the circadian clock, as well as various physiological rhythms, including hormonal secretion (Archer and Oster, 2015; Czeisler and Buxton, 2017). Moreover, the expression of most rhythms at the behavioral, physiologic, and biochemical levels are thought to be regulated by inputs from both the circadian oscillator and sleep/wake states. Misalignment of circadian rhythms and sleep can have adverse health outcomes, including increased risk for all-cause mortality, obesity, type-2 diabetes, and cardiovascular disease, as well as increased risk for various sleep and neuropsychiatric disorders including major depressive disorder (Archer and Oster, 2015; McClung, 2007; Morris *et al*, 2016; Scheer *et al*, 2009; Wulff *et al*, 2010). A better understanding of the neuronal machinery underlying the association between circadian rhythms and sleep regulation will not only reveal one of the most important regulatory processes of arousal states, but would be important for the development of improved therapeutics.

Motivational Regulation of Sleep/Wake States

Motivational processes can powerfully modulate the propensity of animals to stay awake or go to sleep. When motivated, humans can stay awake and engage in various cognitive and physical activities, such as reading a book, working on a grant, or attending a party, far beyond their physiological bedtime while ignoring homeostatic and circadian sleep drives. In the wild, foraging and mating opportunities and the presence of predators drive motivational responses and modulate arousal. Animals can stay awake for extended periods, sleep longer, sleep lighter, or only with half of the brain in response to different internal and external conditions. A better understanding of the processes modulating the propensity to stay awake or go to sleep will not only improve our understanding of brain circuits regulating arousal states but also provide valuable insights into the general problem of balancing conflicting needs.

For studies on the link between motivational processes and sleep/wake regulation, non-model organisms in natural or semi-natural conditions are of particular interest (Aulsebrook *et al*, 2016; Rattenborg *et al*, 2017), as they are typically exposed to an heterogeneous environment in which animals face various competing needs, ie, the need to forage, reproduce, evade predators, and sleep. Laboratory settings rarely provide similar conflicting needs. Moreover, arousal induced by heterogeneous sensory cues could be associated with the activation of neuronal circuits that are not necessarily recruited under standard laboratory conditions.

The energy status of individuals can strongly modulate sleep/wake states. Hunger can drive arousal, locomotor activity, and suppress sleep—probably to favor foraging behavior (Borbely, 1977; Danguir and Nicolaidis, 1979; Dewasmes *et al*, 1989; Jacobs and McGinty, 1971; Rattenborg *et al*, 2016). In contrast, satiety can promote sleep (postprandial sleep) (Jenkins *et al*, 2006; Murphy *et al*, 2016; Varin *et al*, 2015). The presence of predators or predator cues can modulate sleep/wake states (Lima *et al*, 2005), reduce sleep (Lesku *et al*, 2008), or induce frequent arousals (Dominguez, 2003; Gauthier-Clerc *et al*, 1998; Lendrem, 1984). Even the motivation to mate and reproduce can powerfully affect sleep and wake states (Lesku *et al*, 2012). In addition to sleep suppression over long migratory and foraging flights (Rattenborg *et al*, 2004; Rattenborg *et al*, 2016), birds and marine mammals can show unihemispheric sleep (Lyamin *et al*, 2008b; Rattenborg *et al*, 2000)—a state that allows simultaneous engagement in two otherwise mutually exclusive tasks. For example, marine mammals must continuously rise to the water's surface to breath air and take continuous care of their young during critical early life stages—thus unihemispheric sleep enables them to sleep while engaging in these essentail behaviors (Lyamin *et al*, 2008b; Rattenborg *et al*, 2000).

Which neuronal mechanisms modulate the arousal response in face of different environmental and homeostatic needs? Although various wake-promoting neuronal populations have been demonstrated to induce and promote arousal, they vary in their capacity to maintain wakefulness (Eban-Rothschild and de Lecea, 2017a; Luppi *et al*, 2017; Weber and Dan, 2016). Increasing evidence also suggests that different wake-promoting neuronal populations have distinct roles in supporting arousal under specific environmental and motivational conditions (Eban-Rothschild *et al*, 2017b; Joiner, 2016; Jones, 2003; Scammell *et al*, 2017).

In laboratory settings, LH Hcrt neurons have been implicated in mediating the increase in wakefulness in response to stressful conditions (Bonnavion *et al*, 2015; Mahler *et al*, 2014; Winsky-Sommerer *et al*, 2005), including reduced food availability (Yamanaka *et al*, 2003). Hcrt neurons are inhibited by an increase in extracellular glucose concentrations and circulating leptin, while they are excited by elevations in the hunger hormone ghrelin or hypoglycemia (Burdakov and Alexopoulos, 2005; Burdakov *et al*, 2006; Sakurai, 2007; Williams *et al*, 2008). Moreover, the sensitivity of Hcrt neurons to triglycerides, carbon dioxide, and pH further support a role for Hcrt neurons in sensing metabolic factors (Williams *et al*, 2007). Optogenetic stimulation of leptin receptor-expressing (LepRb) GABAergic neurons in the LH produces postsynaptic currents in Hcrt cells (Bonnavion *et al*, 2015), while other GABAergic neurons in the LH, labeled with neurotensin, interact with Hcrt cells to regulate arousal (Grossberg *et al*, 2011; Jennings *et al*, 2015). Remarkably, transgenic mice in which Hcrt neurons are ablated (Hcrt ataxin3 mice) do not show an increase in wakefulness or locomotion following fasting (Yamanaka *et al*, 2003). Together these findings suggest that Hcrt neurons are an important link between metabolism and arousal regulation (Bonnavion and de Lecea, 2010).

VTA dopaminergic neurons are principal regulators of motivational processes (Berridge and Robinson, 1998; Salamone *et al*, 2016; Schultz, 2007), and are well suited to promote arousal for the support of various motivated behaviors, including mate-seeking and predator defense. VTA dopaminergic neurons are strongly activated by salient stimuli in primates and rodents (Salamone *et al*, 2016; Schultz, 2007; Wise, 2004), and their chemogenetic inhibition in mice prevents the maintenance of wakefulness in the presence of various salient stimuli, including a potential mate and predator scent (Eban-Rothschild *et al*, 2016). Intriguingly, chemogenetic inhibition of VTA dopaminergic neurons does not suppress the motivation to engage in sleep-related and goal-directed behaviors, such as nest-building (Eban-Rothschild *et al*, 2016). This finding suggests that the motivation to stay awake, and engage in wake-related behaviors, is regulated by different neuronal circuits than the motivation to sleep or engage in sleep-related behaviors.

Cholinergic neurons have been associated with unihemispheric cortical activation during unihemispheric sleep (Lapierre *et al*, 2007). Northern fur seals (*Callorhinus ursinus*) show unihemispheric sleep preferentially while sleeping in the water (Lyamin *et al*, 2017). Acetylcholine release was found to be lateralized and tightly linked to the hemisphere that was awake, while histamine, serotonin, and noradrenaline were found to be synchronously released from both the awake and asleep hemispheres (Lapierre *et al*, 2013; Lapierre *et al*, 2007; Lyamin *et al*, 2016). These findings suggest that acetylcholine is responsible for unihemispheric EEG activation, and future studies modulating the activity of cholinergic neurons would provide causal evidence.

In the fly, octopaminergic neurons (the *Drosophila* counterpart of noradrenaline), have been shown to mediate sleep suppression by male sexual arousal (Machado *et al*, 2017). Male flies suppress their sleep in the presence of females, and female-induced arousal is attenuated by sexual satiety or elevated sleep drive (Machado *et al*, 2017). Recently, a small number of octopaminergic neurons, designated as male-specific 1 (MS1) neurons, were found to regulate male sleep in a sexual context. The activation of MS1 neurons in isolated males reduces sleep, while their inhibition in the presence of a female attenuate mating-induced arousal (Machado *et al*, 2017).

Taken together, the work reviewed here suggests that different arousal systems support wakefulness under distinct environmental and internal needs. A distinct role for each system in support of a distinct behavioral state could account for the apparent redundancy in wake-promoting circuits (Eban-Rothschild *et al*, 2017a; Jones, 2003).

AN INTEGRATIVE MODEL FOR SLEEP/WAKE REGULATION

In recent years, various theoretical models have been proposed to explain how and where the brain integrates information and computes a decision whether to wake up or stay asleep. The flip/flop model (Saper *et al*, 2010), posits that mutually inhibitory interactions of wake-promoting and sleep-promoting neurons produce a state similar to a flip/flop switch in an electrical circuit. This concept has served as a helpful framework to explain interactions between wake and sleep-promoting neuronal circuits that minimize intermediate states between sleep and wakefulness. However, intermediate and dissociated arousal states do exist, for example in narcolepsy and REM behavior disorder (de Lecea, 2015). In addition, unihemispheric (Lyamin *et al*, 2008b; Rattenborg *et al*, 2000) and local sleep (Huber *et al*, 2004; Krueger *et al*, 2008; Nir *et al*, 2011; Vyazovskiy *et al*, 2011b) phenomena are difficult to explain in a simple binary decision. The flip/flop switch assumes mutual inhibition dynamics with fast synaptic transmission that cannot explain the relatively slow onset of sleep. Furthermore, spontaneous awakening is associated with sleep inertia—a state of impaired cognitive and sensory/motor performance immediately after awakening. Sleep inertia is thought to result from the insertion of sleep-like patterns of cortical neuronal activity into the awake state (Vyazovskiy *et al*, 2014). In view of the complexity of the aforementioned arousal circuits uncovered during the last decade, the binary states proposed by the flip/flop model need to be revised.

Integrator Circuit

As an alternative to the flip/flop binary model, we propose a theoretical framework to predict sleep-to-wake transitions based on an online classification function: depending on inputs with different 'weights', an 'integrator' neuron classifies the state as sleep or wake. We hypothesize that an

'integrator' neuron (eg, LH Hcrt neurons) continuously integrate information from multiple variables and make the decision whether to fire and wake up the animal, or stay silent and facilitate NREM sleep (Figure 2). Comparisons of the latencies to wakefulness following optogenetic stimulations of pairs of neuronal structures (Carter and de Lecea, 2011), has prompted us to build a 'hierarchy' matrix that assigns probabilities of eliciting wakefulness (Sorooshyari *et al*, 2015). A more sophisticated iteration of this model would consider a continuous activation function that reflects probabilities of wakefulness. These probabilities would depend on (i) the functional connectivity between different neurotransmitter systems, and (ii) physiological factors, such as those discussed above (Figure 2). Some of these inputs to the integrator could be associated with individual neuronal circuits, whereas the contribution of other functions whose output depends on sequential input from multiple systems (such as metabolism and limbic structures) may be modeled by hidden layers. Optogenetic interrogations of these circuits will allow us to establish the maximum contribution of each circuit to sleep/wake dynamics (Carter and de Lecea, 2011; Sorooshyari *et al*, 2015).

An essential part of this model is the time scale of integration and information flow. In other words: how long does it take for an integrator neuron to decide whether it is appropriate to fire? Short integration times would be very sensitive to environmental and physiological inputs, but would make sleep bouts short and the sleep cycle fragmented. In contrast, long integration times would result in stable sleep at the expense of disconnection from the environment. The relatively long-time scale of neuromodulators seems to fit optimally with integration times lasting several seconds. These timescales are also consistent with the minimum quantum of sleep continuity necessary for memory consolidation (Rolls *et al*, 2011). The neuromodulation time scale could also explain the dynamics of cortical output circuits and the observed phenomenon of local sleep. A threshold function would determine whether sufficient cortical domains are engaged in local sleep to generate synchronous oscillations associated with NREM sleep.

CONCLUSIONS

The advent of *in vivo* cell type-specific chemogenetic and optogenetic tools and genetically encoded calcium indicators has allowed researchers to interrogate the role of specific neuronal circuits in the control of sleep/wake states. From the first optogenetic experiment in freely moving animals investigating whether the activity of Hcrt neurons is sufficient to induce sleep-to-wake transitions, multiple studies have contributed to our current understanding of the roles of different populations in sleep/wake regulation. Now, it is time to further explore how information from the diverse sleep/wake regulatory populations is integrated to control overt arousal and how diverse external and internal inputs modulate the regulatory capacities of these circuits. These studies would contribute to the understanding of the different functions of sleep and wakefulness.

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