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Review article

Ca^{2+}-dependent hyperpolarization hypothesis for mammalian sleep

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ABSTRACT

The detailed molecular mechanisms underlying the regulation of sleep/wake cycles in mammals are elusive. In this regulation, at least two mechanisms with fast and slow time scales are involved. In the faster time scale, a state of non-rapid-eye-movement (NREM) sleep can be microscopically characterized by the millisecond-to-second-order electrical behavior of neurons, namely slow-wave oscillations described by electrophysiology. In the slower time scale, the total duration of NREM sleep is homeostatically regulated by sleep pressure (the need for sleep), which is usually sustained for hours or even days and can be macroscopically described by electroencephalogram (EEG). The longer dynamics of sleep regulation are often explained by the accumulation of sleep-inducing substances (SISs). However, we still do not have a concrete model to connect fast, microscopic dynamics and slow, macroscopic dynamics. In this review, we introduce a recent Ca^{2+}-dependent hyperpolarization hypothesis, in which the Ca^{2+}-dependent hyperpolarization of cortical-membrane potential induces slow-wave oscillation. Slow dynamics of the Ca^{2+}-dependent hyperpolarization pathway might be regulated by recently identified sleep-promoting kinases as well as classical SISs. Therefore, cortical Ca^{2+}-dependent hyperpolarization may be a fundamental mechanism connecting fast neural activity to the slow dynamics of sleep pressure.

Contents

1. Introduction

The sleep-wake cycle is one of the most fundamental phenomena governing the global state of an animal's brain. The function of sleep remains a mystery, but it apparently involves more than a simple resting of the body; instead, the sleep state is thought to actively guarantee fundamental brain functions such as memory consolidation (Stickgold, 2005). Sleep also appears to play a vital role in other parts of the body, such as the immune system (Bryant et al., 2004). The fundamental physiological importance of sleep would require a homeostatic regulation mechanism to ensure that an organism gets sufficient sleep.

Humans need around eight hours of sleep per day on average (Roenneberg et al., 2012; Walch et al., 2016). Sleep loss leads to increased sleep pressure on the next round of the sleep cycle, indicating that the total sleep amount is regulated homeostatically.

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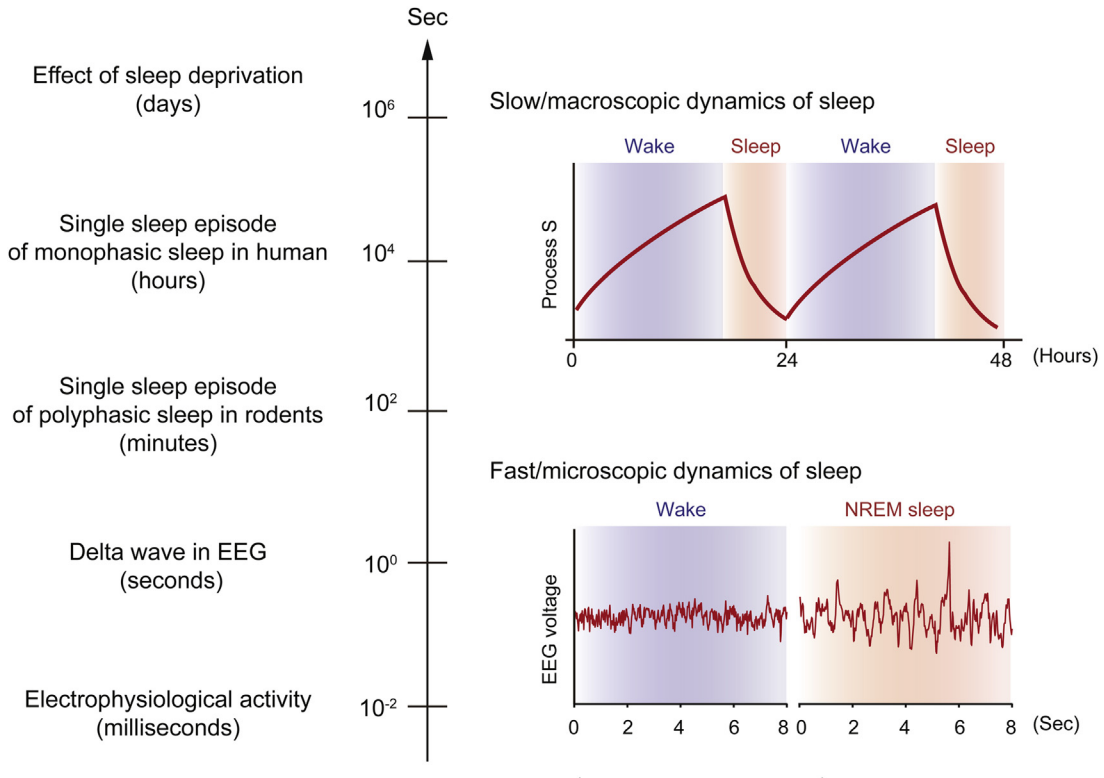

Fig. 1. Regulation of mammalian sleep across a wide range of time scales.
Mammalian sleep is regulated through dynamic, microscopic neuronal electrophysiological activity that occurs on a time scale of milliseconds. The collective activity of cortical neurons during sleep results in slow-wave oscillation in EEG with a frequency around one second. From a macroscopic point of view, the sleep-related behaviors of mammals (e.g., transition from sleep to wake phase) occur on a time scale of minutes to hours. Furthermore, the effect of sleep deprivation lasts for days. One of the most challenging topics of sleep research is constructing a reliable model that accounts for the regulation of the multiple time scales involved in sleep. The upper-right panel shows the conceptual behavior of "process S" as proposed by the two-process model. The lower-right panel shows EEG patterns of mice when sleeping or awake.

In other words, the core of the sleep-wake cycle involves a system with a negative feedback loop in which a prolonged awake period inhibits wakefulness and promotes sleep. With this negative feedback loop, a system output (e.g., sleep duration) can be stable around a fixed set point. In addition, the required sleep duration varies widely among species (Joiner, 2016; McNamara et al., 2008), implying that the set point for the homeostatic regulation of sleep duration is genetically determined. Therefore, one of the goals in a system-level understanding of sleep-wake cycles is to elucidate the molecular components and interactions underlying the homeostatic regulation of sleep duration.

The time scale of the system's dynamics is an important starting point for understanding the system's architecture. The transduction of electrical impulses in neurons occurs on the order of milliseconds. The molecular mechanisms underlying this information processing involve ion fluxes and changes in ion-channel conformation, whereas processes occurring on a longer time scale, such as transcription, translation, degradation, and protein modification, are not directly involved in this electrical system. On the other hand, these longer time-scale processes play more dominant roles in slower biological phenomena, such as learning and memory (Alvarez-Castelao and Schuman, 2015; Bramham, 2008; Bramham and Wells, 2007; Cajigas et al., 2010). Interestingly, the time scales associated with sleep regulation span from milliseconds in the faster dynamics of neural activity to hours/days in the slower dynamics of sleep pressure. Therefore, connecting the wide gap of time scales in sleep regulation is a challenge for sleep studies from both a biochemical (Krueger, 2008; Krueger et al., 2008) and theoretical viewpoint (Olbrich et al., 2011) (Fig. 1). In this review, we introduce the recently proposed "Ca^{2+}-dependent hyperpolarization hypothesis," which proposes roles for neuronal Ca^{2+} in regulating membrane potential during sleep, and discuss how this hypothesis contributes to our understanding of the feedback mechanism underlying the homeostatic regulation of mammalian sleep.

2. Slow dynamics of NREM sleep: process S and sleep-induced substances

Sleep pressure has a long time scale (hours to days), which provides an intuitive clue to understanding sleep-wake dynamics. In fact, the pioneering study of the molecular substances of sleepiness focused on the relatively slow dynamics of the sleep-wake cycle and the recovery process from sleep deprivation. In 1909, Kuniomi Ishimori found that brain extracts from sleep-deprived dogs dramatically induced sleep when injected into dogs without sleep deprivation (Ishimori, 1909), implying that sleep-promoting substances exist that accumulate during periods of (prolonged) wakefulness and promote sleep. The expected dynamics of such sleep-inducing substances (SISs; also called sleep-regulatory substances, SRSs) was designated "process S" in a landmark two-process model describing the relationship between sleep pressure and circadian clocks (Borbely, 1982) (Fig. 1): process S presumably increases during awake time and decreases during sleep time. Increasing process S will prolong sleep duration.

Several candidate SIS molecules have been found since Ishimori's discovery in 1909, including adenosine, nitric oxide, prostaglandin D, tumor-necrosis factor, interleukin 1, and growth-hormone-releasing hormone (Clinton et al., 2011; Krueger et al., 2008; Obal and Krueger, 2003). There is growing cellular and molecular evidence of adenosine's role in promoting sleep. For example, the extracellular adenosine concentration in the basal forebrain was increased during spontaneous wakefulness compared to dur-

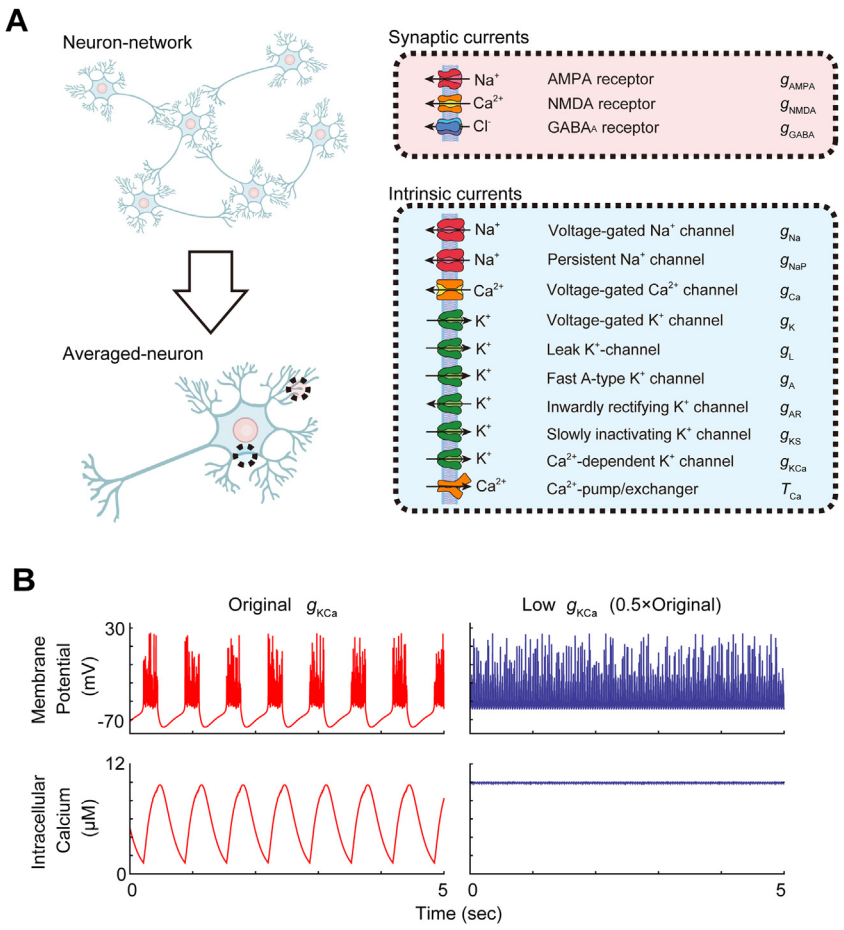

Fig. 2. The averaged-neuron (AN) model predicts that a Ca^{2+}-dependent hyperpolarization pathway plays a pivotal role in non-rapid-eye-movement (NREM) sleep.
(**A**) Diagram showing the AN model. Light red: extrinsic ion channels thought to work mainly at synapses. Light blue: intrinsic ion channels and Ca^{2+}-pumps/exchangers. Compared to the neuron-network (NN) model, which explicitly describes the synaptic connections of excitatory and inhibitory neurons, the AN model assumes that all excitatory and inhibitory neurons are connected to each other. Thus, the model can be described and simulated as if one neuron connected to itself with both excitatory and inhibitory input.
(**B**) Representative firing patterns (slow-wave oscillation) during NREM sleep and the intracellular Ca^{2+} concentration generated from the AN model. Important channels/pumps for inducing or maintaining the silent hyperpolarized state can be searched by changing the parameter corresponding to the activity of each channel/pump. In this figure, reducing g_{KCa} (i.e. reducing the activity of Ca^{2+}-dependent K^+ channels) resulted in the loss of hyperpolarization.

ing NREM sleep in cats (Porkka-Heiskanen et al., 1997). Adenosine's effect on sleep became evident in mice with a conditional knockout of the adenosine A1 receptor in the forebrain and hindbrain; these mice showed impaired enhancement of slow-wave activity upon sleep deprivation (Bjorness et al., 2009). Another adenosine receptor (A2) was shown to be responsible for the effect of caffeine, which is used to promote wakefulness in daily life (Huang et al., 2005). A series of studies by Haydon and colleagues demonstrated that adenosine induces sleep in animals through gliotransmission (Florian et al., 2011; Halassa et al., 2009; Marpegan et al., 2011; Nadjar et al., 2013; Schmitt et al., 2012). These studies suggest that the adenosine signaling pathway functions as a sleep feedback pathway that responds to sleep loss.

However, adenosine may be not involved in the mechanism that determines the set point of amount of sleep; rather, it induces sleep in response to an abnormal sleep status resulting from inflammation or forced sleep deprivation. The basal sleep duration (i.e., under natural conditions) does not differ significantly between adenosine-receptor knockout and wildtype mice (Bjorness et al., 2009; Huang et al., 2005; Stenberg et al., 2003). A similar rationale may be applicable to other SISs: in many cases, knocking out their synthesis, receptors, or signal-transduction pathways has a nonsignificant or only marginally significant effect on the whole-day basal sleep duration, at least for NREM duration (Chen et al., 2003; Eguchi et al., 2002; Fang et al., 1997; Kaushal et al., 2012; Obal and Krueger, 2003). Collectively, these results suggest that although candidate SISs engage the response to sleep loss, other mechanisms may be responsible for ensuring the required sleep amount.

3. Fast dynamics of NREM sleep: electrophysiological neuronal activity

Studies focusing on neuronal activity during sleep, which occurs in the order of milliseconds, provide insight on the electrophysiological regulation of sleep. The collective activity of cortical neurons during NREM sleep is characterized by the EEG pattern (Walter, 1937). During NREM sleep, an EEG displays high-amplitude, low-frequency fluctuations (slow-wave oscillation). This pattern is generated by synchronized slow oscillations of the cortical neuron's membrane potential, in which a depolarized spiking phase and hyperpolarized silent phase occur repetitively with a frequency that corresponds well with that in the EEG pattern (Steriade and McCarley, 2005). Hereafter, we refer to this firing pattern of cortical neurons as slow-wave oscillation (see Fig. 2**B**). The EEG delta power (0.5–4 Hz), which closely matches the major frequency of slow-wave oscillation, is a useful metric to indicate sleep pressure (Borbely et al., 1981; Nakazawa et al., 1978; Webb and Agnew,

1971) and is conserved across different phyla of animals (Shein-Idelson et al., 2016), indicating that the molecular mechanisms underlying the slow-wave oscillation of cortical neurons engage directly in the homeostatic regulation of NREM sleep, and that this oscillation is not simply the trivial output of resting neurons.

There is growing evidence that slow-wave oscillation can emerge from the cortical neuronal assembly: the slow-wave firing pattern was observed in cortical brain slices cultured *in vitro* without electrical/chemical stimulation (Sanchez-Vives and McCormick, 2000). This slow-wave pattern was also observed in an isolated cortical slab maintained in the intact brain of an animal kept under anesthesia (Timofeev et al., 2000). These studies indicate that the cortical region of the brain contains all of the components necessary to elicit the slow-wave firing pattern, and that synaptic inputs from other regions of the brain are not a prerequisite. In addition, the local cortical region can elicit sleep-related neuronal activity *in vivo*, given that the EEG delta power (0.5–4 Hz), which closely matches the major frequency of slow-wave oscillation, can be heterogeneously distributed in the cortex. This distribution, which appears to be determined in an activity-dependent manner in each cortical area and is thus called local sleep, has been observed in various organisms from rodents (Funk et al., 2016; Vyazovskiy et al., 2011) to humans (Huber et al., 2006; Muto et al., 2016). A relevant phenomenon was recently observed in flies: a prolonged wake time inhomogeneously reduces neuronal activity in the Kenyon-cell population in the fly mushroom body, and the cells respond inconsistently to repeated exposure to the same stimulus (Bushey et al., 2015). These results indicate that small and local neuronal circuits may be responsible for inducing the slow-wave oscillation. Sleep pressure might also be stored locally in the cortical neurons. It should be noted that the actual architecture of sleep requires complex neural circuits. The thalamocortical circuit has been implicated as an underlying mechanism for gamma oscillation and the sleep spindle (Traub et al., 2005; Zagha and McCormick, 2014), and cortical-circuit structures are important for synchrony between neurons in different areas of the brain (Amzica and Steriade, 1995; Chen et al., 2012; Hill and Tononi, 2005). Nonetheless, it is useful to investigate the mechanism of slow-wave oscillation by focusing on a small system that is comparable to local cortical-neuronal assemblies and for which the process required for slow-wave oscillation has minimum complexity.

Computational models are a powerful tool for finding explanations for various neuronal electrophysiological behaviors based on the fast/microscopic properties of ion channels/pumps that have been characterized in experiments. Various computational models have attempted to recapitulate slow-wave oscillation based on interactive populations of several types of neurons (Bazhenov et al., 2002; Chen et al., 2012; Compte et al., 2003; Hill and Tononi, 2005; Sanchez-Vives et al., 2010; Timofeev et al., 2000), here referred to as neuron-network models (NN models). Regarding the appearance of the hyperpolarized silent phase, a remarkable property of slow-wave oscillation, three types of mechanisms have been proposed for the transition from firing phase to silent phase. The first is an enhancement of Ca^{2+}- and Na^{+}-dependent K^{+} channels in pyramidal neurons (Bazhenov et al., 2002; Compte et al., 2003; Hill and Tononi, 2005; Sanchez-Vives et al., 2010; Timofeev et al., 2000). This mechanism does not directly involve synaptic inhibition, but rather depends on the activation cascade of cell-intrinsic channels. This prediction is consistent with experimental observations of a relationship between the induction of the silent phase and a series of K^{+} currents, most probably Ca^{2+}-dependent K^{+} currents (Steriade and McCarley, 2005; Timofeev et al., 2001). The second mechanism is a passive inhibition of the excitatory synaptic current at pyramidal neurons due to a limited source of synaptic transmission and the auto-inhibition of ion channels (Bazhenov et al., 2002; Hill and Tononi, 2005). The third mechanism is an active repression of pyramidal neurons through inhibitory synaptic input by interneurons (Timofeev et al., 2000). The role of GABAergic neurons in inducing the hyperpolarized silent phase is questionable, because slow-wave oscillation is resilient to the inhibition of $GABA_A$ receptor activity both *in vivo* (Steriade et al., 2001) and *in vitro* (Chen et al., 2012; Sanchez-Vives et al., 2010). Instead, interneuron-mediated neuronal circuits may be important for the synchronous activity among cortical cells during slow-wave oscillation (Chen et al., 2012). Thus, the question is which mechanism is most influential in inducing slow-wave oscillation and has the greatest impact on the organism's sleep state.

NN models with varying complexities and settings produce different predictions. Although complex and simple models can complement each other, the approaches differ as to purpose and what we hope to learn. The complex model has the advantage when trying to precisely reproduce behaviors observed in experiments. For example, a model with a cortical multilayer structure and thalamocortical circuit has the potential to reproduce not only the slow-wave oscillation of each neuron, but also the collective propagation of neuronal activity that can be compared to EEG patterns (Hill and Tononi, 2005). However, the drawback of complex models is that the huge number of possible combinations of parameters obscures how each component contributes to the system behavior of interest. Thus, it is difficult to comprehensively identify the number and type of parameter sets (and the common critical pathway) that can generate slow-wave oscillation. Such a comprehensive parameter survey requires a reduction in computational complexity of NN models, which means deciding which components should be kept and which should be omitted or simplified. To investigate the molecular details of slow-wave oscillation, equations describing the molecular behavior of neurons should be preserved (i.e., parameters that account for various ion channels and pumps). On the other hand, although an *in vitro* brain slab requires a minimum number of interconnected neurons to exhibit slow-wave oscillation (Timofeev et al., 2000), previous modeling studies suggest that a precise circuit structure may not be necessary for slow-wave oscillation; a randomly connected neuronal assembly can also produce this firing pattern (Compte et al., 2003). Therefore, it is not necessary to explicitly simulate the behavior of thousands of neurons.

4. Ca^{2+}-dependent hyperpolarization as a basis for the fast electrophysiological dynamics of cortical neurons in NREM sleep

We created a simplified NN model, called an averaged-neuron model (AN model) (Tatsuki et al., 2016), in which we applied mean-field approximation to an NN model of a population of neurons (Fig. 2**A**). In other words, the effect of all other neurons on any given neuron is approximated by a single averaged neuron, thus reducing a population of neurons to one averaged neuron. The averaged neuron can interact with itself directly or indirectly through excitatory (Na^{+} currents mediated by AMPA receptors, and Ca^{2+} currents mediated by NMDA receptors) or inhibitory (Cl^{-} currents mediated by $GABA_A$ receptors) synaptic currents. The intrinsic currents incorporate depolarizing Na^{+} and Ca^{2+} currents and hyperpolarizing K^{+} currents. The depolarizing Na^{+} and Ca^{2+} currents are mediated by voltage-gated or persistent Na^{+} channels and voltage-gated Ca^{2+} channels, respectively. On the other hand, K^{+} currents are mediated by several types of K^{+} channels, including voltage-gated, leak, fast A-type, inwardly rectifying, slowly inactivating, and Ca^{2+}-dependent K^{+} channels (Fig. 2**A**). In addition, intracellular Ca^{2+} is transported by Ca^{2+} pumps/exchangers. Although much simpler than current NN models, the AN model recapitulates the slow-wave oscillation with alternating firing and silent phases (Fig. 2**B**).

Since this model has been simplified by mean-field approximation, it requires much less computational power for simulations compared to existing NN models. Over 10,000,000 random parameter sets were generated under each condition. Through a broad and comprehensive parameter search, the AN model provides the following three predictions: 1) Downregulating the Ca^{2+}-dependent hyperpolarization pathway weakens the hyperpolarized silent phase. 2) Voltage-gated Ca^{2+} channels and NMDA receptors play redundant roles in the influx of Ca^{2+} into the neuron to generate slow-wave oscillation. 3) Impaired $GABA_A$ receptor function only marginally affects the appearance of slow-wave oscillation. These predictions are consistent with several NN models as well as previous computational studies of the electric bursting of various types of cells (Arbib, 2003; Izhikevich, 2007). Collectively, the AN model predicts that slow-wave oscillation is established by the cell-intrinsic induction of the silent phase by a Ca^{2+}-dependent hyperpolarization pathway rather than by synaptic inhibition via the $GABA_A$ receptor.

The validity of this prediction is supported by the sleep phenotype of various gene-knockout mice. Interestingly, several studies show that knocking out genes that activate the Ca^{2+}-dependent hyperpolarization pathway shortens sleep duration. A short-sleeper phenotype was reported for mice with a knockout of the NMDA receptor *Nr3a* (Sunagawa et al., 2016) or of the voltage-gated Ca^{2+} channel *Cacna1g* (Anderson et al., 2005; Lee et al., 2004). These channels mediate the inflow of Ca^{2+}, and the Ca^{2+} then activates a Ca^{2+}-dependent K^+ channel. Knocking out *Kcnn2* (a small-conductance Ca^{2+}-dependent K^+ channel) tended to decrease sleep duration, but the decrease was not significant (Cueni et al., 2008). Taken collectively, these phenotypes and AN model predictions suggest a straightforward relationship between animals' sleep phenotypes and the cortical capacity to elicit slow-wave oscillation: the more efficiently cortical neurons induce the Ca^{2+}-dependent hyperpolarization pathway, the longer the animal sleeps.

To evaluate this relationship comprehensively, we created 21 lines of knockout mice to cover all genes in the mouse genome that encode Ca^{2+}-dependent K^+ channels, the α_1 subunit of voltage-dependent Ca^{2+} channels, and plasma-membrane Ca^{2+} ATPases (PMCAs) (Tatsuki et al., 2016), and further investigated the sleep phenotype of mice treated with an NMDA receptor antagonist to assess the sleep-related function of the main NMDA receptor subunits, the knockout of which results in embryonic lethality (Forrest et al., 1994; Li et al., 1994). The phenotypes of these mice were consistent with the predictions based on the AN model: sleep duration was significantly reduced by impairing Ca^{2+}-dependent K^+ channels, the α_1 subunit of voltage-dependent Ca^{2+} channels, or the NMDA receptor, —any of which would reduce the ability to induce Ca^{2+}-dependent hyperpolarization. On the other hand, sleep duration increased significantly in mice with impaired PMCA; thus, in PMCA-mutant mice, the Ca^{2+} efflux rate would decrease to maintain Ca^{2+}-dependent hyperpolarization. Thus, genetic and pharmacological perturbations of the Ca^{2+}-dependent hyperpolarization pathway, which describes the fast dynamics of electrophysiological properties of cortical neurons during sleep, affect sleep duration in mice. Importantly, repressing or activating the Ca^{2+}-dependent hyperpolarization pathway decreases or increases sleep duration, respectively. This bidirectional control of sleep duration indicates that it is possible for the Ca^{2+}-dependent hyperpolarization pathway to be targeted by the slow dynamics of process S. Therefore, the Ca^{2+}-dependent hyperpolarization hypothesis may connect fast and slow time scales between electrophysiological neuronal states and sleep pressure ("process S"). The direct test of the Ca^{2+}-dependent hyperpolarization hypothesis will lie in recording the slow-wave oscillation in cortical-membrane potential *in vitro* or *in vivo*, and testing for its dependency on Ca^{2+} (Cox et al., 2016).

5. Post-translational modification of the Ca^{2+}-dependent hyperpolarization pathway can connect the fast and slow dynamics of sleep regulation

If the Ca^{2+}-dependent hyperpolarization pathway regulates mammalian sleep, it should be homeostatically regulated. In other words, the excitation of (cortical) neurons should directly or indirectly enhance Ca^{2+}-dependent hyperpolarization. Calcium/calmodulin-dependent protein kinase type II (CaMKII) is a strong candidate for sensing neuronal activity and transmitting the information to regulate the efficiency of Ca^{2+}-dependent hyperpolarization. CaMKII, which is activated by the Ca^{2+} signal evoked by neuronal excitation, plays a central role in regulating slower neuron/brain physiologies such as learning and memory (Lisman et al., 2012; Mayford et al., 1996) and circadian rhythm (Kon et al., 2014). Notably, CaMKII is also a well-known protein family that can bind several channels involved in the Ca^{2+}-dependent hyperpolarization pathway in response to Ca^{2+} influx, such as NMDA receptors or L-type Ca^{2+} channels (Leonard et al., 1999; Rose et al., 2009). Indeed, knocking out either the alpha or beta *Camk2* isoform in mice significantly decreased sleep duration (Tatsuki et al., 2016), indicating that CaMKII is, in principle, a sleep-promoting kinase. Thus, intracellular Ca^{2+} signaling may play central roles not only in regulating membrane potential during slow-wave oscillation, but also in the homeostatic regulations connecting neuronal excitability and sleep pressure. The Ca^{2+}-dependent hyperpolarization pathway may integrate SIS signals: for example, growth hormone-releasing hormone (GHRH) stimulation increased intracellular Ca^{2+} levels and delta-wave oscillation during sleep (Liao et al., 2010).

Recent studies have identified other sleep-promoting kinases. A forward genetics study revealed that a gain-of-function mouse mutant of salt-inducible kinase 3 (*Sik3*) has a remarkably long sleep duration (Funato et al., 2016). In addition, a focused screening using an *in vitro* neuron culture mimicking the expression patterns of genes associated with the sleep-wake cycle (Hinard et al., 2012) found that mitogen-activated protein kinases (MAPK), ERK1/2 are sleep-inducing kinases (Mikhail et al., 2017). Although it is not clear how these kinases are regulated during the sleep-wake cycle, they appear to be involved in homeostatic processes. Sleep deprivation upregulates kinase-activated phosphorylation in the case of both SIK3 and ERK1/2 (Funato et al., 2016; Hinard et al., 2012). Several SISs are also plausible factors for activating these sleep-promoting kinases upon prolonged sleep, since the downstream pathways of SIS stimulation are often coupled with the activation of the MAPK signaling cascade—MAPK is involved in the TNF signaling cascade, for instance (Brenner et al., 2015)—or with the activation of G protein-coupled receptors (GPCRs) that regulate SIK3 function through the cAMP-PKA signaling pathway (Funato et al., 2016; Katoh et al., 2006).

In general, having a kinase cascade in a signal-transduction pathway can create a time delay between the signal input and output (Goldbeter, 1991; Kholodenko, 2006). Thus, it would be interesting to investigate whether the above-mentioned sleep-promoting kinases interact with each other to form a sleep-promoting kinase cascade that can bridge the fast dynamics of electrophysiological neuronal activity and the slower dynamics of sleep homeostasis. Furthermore, identifying the kinases and potential substrates that affect animals' sleep duration may provide clues to how different animals adjusted their sleep duration through the course of evolution. In circadian clocks, part of the natural variance on the time scale of the circadian period (nearly 24 h) is caused

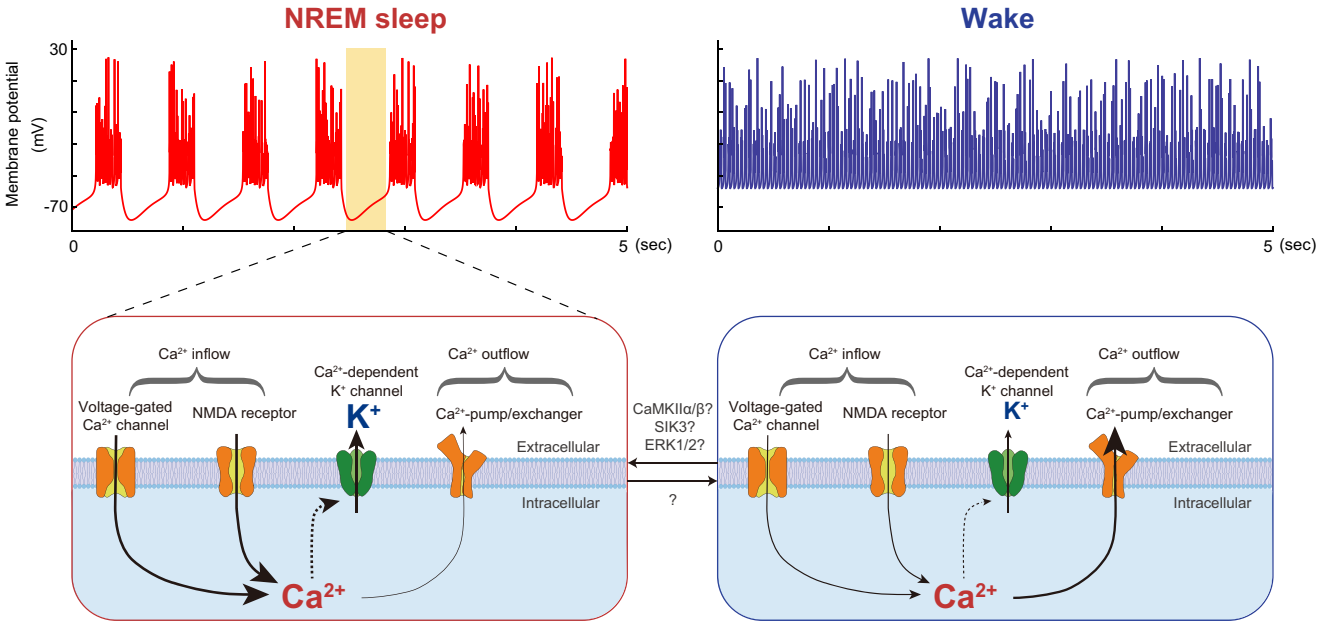

Fig. 3. Schematic diagram of the Ca^{2+}-dependent hyperpolarization pathway.
The efflux of K^+ by Ca^{2+}-dependent K^+ channels generates hyperpolarized states that characterize slow-wave oscillation. Genetic perturbations of factors corresponding to Ca^{2+} inflow into the neurons reduce the sleep duration per day. On the other hand, genetic perturbations of factors corresponding to Ca^{2+} outflow from the neurons increase the sleep duration per day. This Ca^{2+}-dependent hyperpolarization pathway may be the target of sleep-promoting kinases, which are plausible factors for connecting fast, microscopic membrane potential to the slower dynamics of the sleep-wake cycle. Extracellular conditions, including ion concentrations and SIS levels, may be regulated by both neurons and non-neuronal cells.

by single amino-acid substitutions in kinases and their direct substrates (Lowrey et al., 2000; Toh et al., 2001; Xu et al., 2005) that do not change the basic architecture of the circadian molecular network. A similar story might explain the genetic variance in required sleep time between animal species (Siegel, 2005, 2009), where the daily sleep duration can be markedly different in phylogenetically related animal species, while the basic components that regulate sleep duration would be conserved.

An obvious next step is to identify the exact downstream pathway of sleep-promoting kinases, including the substrate that induces sleep. We consider it likely that sleep-promoting kinases target ion channels/pumps. Among these possible targets, it is important to focus on phosphorylation sites that attenuate PMCA activity or potentiate the activity of NMDA receptors, voltage-dependent Ca^{2+} channels, and Ca^{2+}-dependent K^+ channels. In addition, the Ca^{2+}-dependent hyperpolarization pathway may be indirectly regulated by the transcriptional regulation of ion channels/pumps, by the metabolic regulation of neuronal assembly, and by extracellular ion conditions that are important for regulating sleep (Ding et al., 2016). The importance of kinase pathways immediately suggests the involvement of phosphatase activity. Genetic studies using fruit flies found that the NMDA receptor interacts with calcineurin, a Ca^{2+}-dependent protein phosphatase (Tomita et al., 2011; Tomita et al., 2015). In summary, kinase-phosphatase cascades have the potential to connect the time-scale gap between fast/microscopic electrophysiological dynamics and slow/macroscopic sleep homeostasis. Therefore, the Ca^{2+}-dependent hyperpolarization pathway may be the foundation for integrating the intra- and inter-cellular signals that regulate mammalian sleep (Fig. 3).

6. Psychiatric disorders and the Ca^{2+}-dependent hyperpolarization hypothesis

Any new model for regulating physiological processes provides new potential drug targets, and our model for sleep regulation provides possible therapeutic applications for psychiatric diseases that are often associated with sleep abnormalities (Wulff et al., 2010). Interestingly, several factors that regulate the proposed Ca^{2+}-dependent hyperpolarization pathway in sleep/wake cycles have been implicated in the molecular bases of major psychiatric diseases. Schizophrenia-like positive and negative symptoms can be induced by the pharmacological or immunological impairment of NMDA receptors (Dalmau et al., 2008; Jentsch and Roth, 1999); conversely, the pharmacological impairment of NMDA receptors rapidly cures depression (Autry et al., 2011; Berman et al., 2000). Although the underlying molecular and cellular mechanisms of schizophrenia and depression are still under discussion (Coyle, 2012), the Ca^{2+}-dependent hyperpolarization hypothesis may offer clues to the molecular and cellular bases of these diseases. This hypothesis explains how inhibiting Ca^{2+} influx via NMDA receptors by downregulating neuronal hyperpolarization leads to elevated neuronal excitability. This elevation is thought to be due to a direct effect of the attenuated hyperpolarization of cortical neurons, and not to inhibited synaptic repression; this idea has been partly confirmed by whole-brain imaging (Tatsuki et al., 2016). If altered neuronal excitability in cortical pyramidal neurons is causative for the symptoms of schizophrenia and depression, the ion channels/pumps shown in Fig. 3 might be direct drug targets. For example, if the Ca^{2+}-dependent hyperpolarization pathway is impaired in patients with schizophrenia, antagonists against PMCAs and agonists for Ca^{2+}-dependent K^+ channels, voltage-gated Ca^{2+} channels, and NMDA receptors would be potentially therapeutic. Similarly, new compounds developed to inhibit the Ca^{2+}-dependent hyperpolarization pathway might be potential quick-acting drugs to treat depression.

CaMKIIα/β, possible regulators of the Ca^{2+}-dependent hyperpolarization pathway, have been implicated in several mental disorders, including depression, schizophrenia, and bipolar disorder (Hagihara et al., 2016; Purcell et al., 2014; Robison, 2014). Although many studies focus on CaMKIIα/β's function in regulating synaptic plasticity, the causative relationship between CaMKIIα/β

and mental disorders is still unclear. Given that an abnormal sleep pattern is frequently associated with mental disorders (Wulff et al., 2010), impaired Ca^{2+}-dependent hyperpolarization and abnormal sleep structure due to CaMKIIα/β dysfunction might be causative for mental disorders. The sleep-promoting kinases SIK3 and ERK1/2 are also potential drug targets, since impairments of these kinases can also lead to psychiatric disorders.

7. Conclusion

The recent identification of sleep-promoting kinases and the phenotypes of various channel-knockout mice provide a possible connection between electrophysiology and sleep homeostasis via the Ca^{2+}-dependent hyperpolarization pathway. Because several factors that regulate synaptic plasticity (e.g. NMDA receptors and CaMKIIα/β) also regulate the Ca^{2+}-dependent hyperpolarization pathway, further investigation of hyperpolarization in sleep regulation will lead to a quantitative understanding of the physiological significance of sleep for brain information processing and storage through the control of synaptic strength (Krueger et al., 2016; Tononi and Cirelli, 2006). A relationship between sleep pressure and cytosolic Ca^{2+} level via synaptic strength was recently revealed in *Drosophila* (Liu et al., 2016), suggesting that sleep regulation and neuronal plasticity is coupled through Ca^{2+}-dependent signaling across phyla. Therefore, cortical Ca^{2+}-dependent hyperpolarization may be a fundamental mechanism that connects fast, microscopic neuronal activity to the slow, macroscopic dynamics of sleep pressure.

Author contributions

H.R.U., K.L.O., and F.T. wrote the manuscript.

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