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Brain energetics during the sleep–wake cycle

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Brain activity during wakefulness is associated with high metabolic rates that are believed to support information processing and memory encoding. In spite of loss of consciousness, sleep still carries a substantial energy cost. Experimental evidence supports a cerebral metabolic shift taking place during sleep that suppresses aerobic glycolysis, a hallmark of environment-oriented waking behavior and synaptic plasticity. Recent studies reveal that glial astrocytes respond to the reduction of wake-promoting neuromodulators by regulating volume, composition and glymphatic drainage of interstitial fluid. These events are accompanied by changes in neuronal discharge patterns, astrocyte–neuron interactions, synaptic transactions and underlying metabolic features. Internally-generated neuronal activity and network homeostasis are proposed to account for the high sleep-related energy demand.

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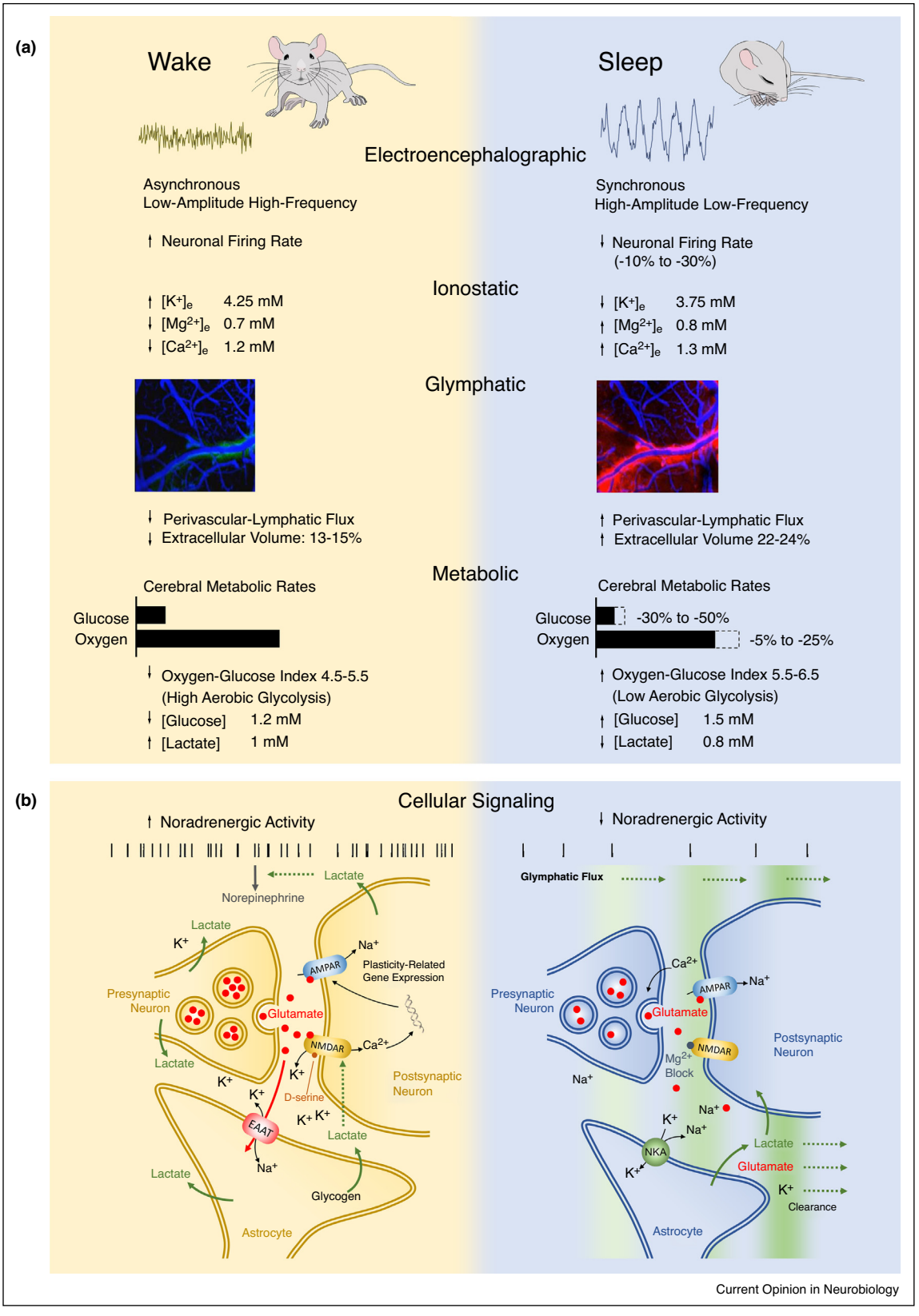
Introduction

Sleep is a universal and evolutionarily conserved behavior shared by species in the animal kingdom regardless of the great diversity of their ecological constraints. Although we do not yet have a fundamental understanding of why animals need to sleep, it is generally accepted that sleep allows the brain to perform critical operations that are largely incompatible with wakefulness [1]. The brain is a constant energy sink, accounting for up to one fifth of total body metabolism. Most of this energy utilization is due to information processing by neuronal-glial networks in the cortical grey matter [2]. The latter is necessary to implement appropriate behavioral responses to the afferent stimuli that are constantly barraging sense organs during wakefulness. Sleep interrupts the connection with the external world, but not the high cerebral metabolic demand. First, brain energy expenditure in non rapid eye movement (NREM) sleep only decreases to ~85% of the waking value, which is higher than the minimal amount of energy required to sustain consciousness [3••]. Second, rapid eye movement (REM) sleep is as expensive as wakefulness and the suspension of thermoregulation during REM sleep is paradoxically associated with increases in brain metabolic heat production and temperature [4]. Third, neither torpor/hibernation (for instance, in mammals undergoing daily hypothermia) [5] nor several anesthetic states [6] can completely redeem sleep need and recovery, in spite of the loss of consciousness and the accompanying decrease of energy use. Sleep must be related to some essential functions that are adaptive to the organism in the face of their relatively high energy requirements. Here we discuss how the glymphatic and ionostatic functions of the brain contribute to shape the metabolic correlates of sleep and associated neuronal network homeostasis.

Oxidative shift in brain energy metabolism during state transitions

Cerebral energy production is reliant on uptake and metabolism of circulating glucose as well as oxygen diffusing from bloodstream supporting the near-complete oxidation of the sugar. The oxygen–glucose utilization stoichiometry (oxygen–glucose index, OGI) is about 5.1–5.4 in quiet waking conditions (note that 6 mol of oxygen are required to fully oxidize 1 mol of glucose). The excess carbohydrates are processed through aerobic glycolysis, so termed because the pyruvate generated from glucose is reduced to lactate instead of being oxidized within the tricarboxylic acid cycle, regardless of adequate oxygenation (i.e. independent of oxygen availability) [7]. Aerobic glycolysis produces only 6% the amount of ATP generated by oxidative phosphorylation, yet it is substantially upregulated during active waking resulting in elevated production of lactate. Advances in amperometric substrate-specific biosensors technology have allowed to monitor on a second-by-second time resolution the extracellular concentration of several important metabolites in the brain of freely-behaving rodents. Together with microdialysis and biochemical assays, these studies show that during NREM sleep cerebral glucose increases [8–10,11•] and lactate decreases [8,11•,12–16] relative to quiet waking. Glucose and lactate levels are reported to be somewhat similar in REM sleep and waking [9,17], although during engagement in complex tasks glucose drops [17,18] and lactate rises [13,17] further than during quiet waking. The extracellular glutamate concentration

Figure 1


(a)
Wake
Sleep
Electroencephalographic
Asynchronous
Low-Amplitude High-Frequency
↑ Neuronal Firing Rate
Synchronous
High-Amplitude Low-Frequency
↓ Neuronal Firing Rate
(-10% to -30%)
Ionostatic
↑ [K+]e 4.25 mM
↓ [Mg2+]e 0.7 mM
↓ [Ca2+]e 1.2 mM
↓ [K+]e 3.75 mM
↑ [Mg2+]e 0.8 mM
↑ [Ca2+]e 1.3 mM
Glymphatic
↓ Perivascular-Lymphatic Flux
↓ Extracellular Volume: 13-15%
↑ Perivascular-Lymphatic Flux
↑ Extracellular Volume 22-24%
Metabolic
Cerebral Metabolic Rates
Glucose
Oxygen
↓ Oxygen-Glucose Index 4.5-5.5
(High Aerobic Glycolysis)
↓ [Glucose] 1.2 mM
↑ [Lactate] 1 mM
Cerebral Metabolic Rates
Glucose
Oxygen
-30% to -50%
-5% to -25%
↑ Oxygen-Glucose Index 5.5-6.5
(Low Aerobic Glycolysis)
↑ [Glucose] 1.5 mM
↓ [Lactate] 0.8 mM
(b)
Cellular Signaling
↑ Noradrenergic Activity
↓ Noradrenergic Activity
Norepinephrine
Lactate
K+
Na+
AMPAR
Plasticity-Related
Gene Expression
Presynaptic
Neuron
Glutamate
NMDAR
Ca2+
D-serine
Postsynaptic
Neuron
EAAT
Glycogen
Astrocyte
Glymphatic Flux
Mg2+
Block
NKA
Clearance
Current Opinion in Neurobiology

is lower during NREM sleep compared with wakefulness and REM sleep, supporting a decrease in glutamatergic neurotransmission [11•,19,20]. Finally, the transition from wakefulness to sleep comes along with a transient surge in ATP levels in wake-active brain regions [21] that likely reflects the initial decrease in ATP degradation as sleep supervenes [22].

The above-mentioned changes in brain metabolite levels confirm and extend previous reports obtained in human subjects (but also in other mammals) that measured alterations in cerebral metabolic rates in different states relative to resting conditions. Specifically, active waking (e.g., sensory stimulation) is accompanied by much higher increases in metabolic rate of glucose than oxygen (with OGI decreasing to 4–5) [23–26]. Opposite, sleep is characterized by much higher decreases in metabolic rate of glucose than oxygen (with OGI approaching or exceeding 6; OGI $>$ 6 implies oxidation of substrates other than glucose, e.g., fatty acids) [27–34]. To summarize, state transitions are associated with changes in brain energy metabolism whose magnitude is governed by oxygen consumption and is thus relatively modest (about 15%). However, on top of these absolute changes there is a state-dependent metabolic shift affecting the degree of aerobic glycolysis, with sleep being more oxidative than wakefulness [35] (Figure 1). For comparison, body metabolic rates fall at least by 25% from quiet wakefulness to sleep, and by much more when physical activity is taken into account. Interestingly, the physiological changes taking place during sleep (e.g., decrease in muscle activity and thermogenesis) come with a slight reduction in respiratory quotient, indicating a transition to lower carbohydrate/fat oxidation ratio at the whole body level.

Coupling between aerobic glycolysis and plasticity by norepinephrine

The benefits for adopting the inefficient metabolic strategy of aerobic glycolysis during active waking behavior are presently unknown, but aerobic glycolysis is abolished by noradrenergic blockade, suggesting that it is related to the processing of sensory information [reviewed by 7]. Indeed, responsiveness to and discrimination between meaningful and meaningless environmental stimuli hinges on the activation of wake-promoting systems. During NREM sleep, firing of cholinergic and noradrenergic neurons is dramatically suppressed and forebrain acetylcholine (Ach) and norepinephrine (NE) levels are reduced (during REM sleep cholinergic activity is reinstated while noradrenergic neurons cease firing altogether). As a result, in the sleeping state the brain no longer process information in a task-relevant manner [e.g., 36] and memory encoding (i.e. formation) is set aside [37].

Aerobic glycolysis is developmentally regulated and correlates with expression of genes involved in synaptic growth and plasticity [38]. In the adult human brain, aerobic glycolysis is elevated in sites exhibiting intense plasticity genes expression and sustained activity like the medial prefrontal cortex, an area extensively implicated in learning and memory [39]. A recent human study reported high levels of aerobic glycolysis in task-relevant neocortical regions that strongly correlated with behavioral adaptation and functional connectivity [40••]. In rodent hippocampus and amygdala, increased glucose utilization and degradation of astrocytic glycogen contribute to the increase in extracellular lactate concentration required for memory processing [41–43]. Lactate potentiates neuronal N-methyl-D-aspartate (NMDA) receptor signaling (necessary for long-term potentiation) and triggers the expression of genes involved in synaptic plasticity [44,45]. The induction of plasticity-related genes depends on the activity of the noradrenergic system and thus can only occur during wakefulness [46]. In turn, lactate can regulate NE availability by stimulating its release from locus coeruleus axonal varicosities [47]. Notably, sleep stimulates the clearance of brain lactate through the glymphatic system [48•], a process dependent on reduced noradrenergic activity and mediated by astrocytic aquaporin-4 (AQP4) water channels [49]. Cerebral perivascular-lymphatic drainage is an important route for lactate dispersal [50] and its suppression during wakefulness may thus contribute to maintain brain lactate

(Figure 1 Legend) Physiological correlates of brain state changes across the sleep–wake cycle. **(a)** Electroencephalographic, ionostatic, glymphatic and metabolic features of wakefulness and sleep states. Sleep is characterized by the appearance of synchronous slow wave activity underlying a reduction in neuronal firing rate and reshaped firing patterns. Neuronal excitability is suppressed through alterations in interstitial fluid ion composition as well as glymphatic clearance of neuroactive compounds. These events are accompanied by a metabolic shifts from elevated aerobic glycolysis during wakefulness to more oxidative metabolism during sleep. Approximate values of main cerebral ions and metabolites are shown. **(b)** Schematics of state-dependent astrocyte–neuron interactions. Noradrenergic tone drives state transitions and maintains brain state by acting at different targets, including ionostatic and glymphatic control systems. During wakefulness, neuronal and astrocytic metabolism is characterized by high rates of aerobic glycolysis, glycogen degradation and lactate production in a NE-dependent manner. Lactate in turn potentiates NE release by noradrenergic terminals and it is involved in NMDAR-mediated synaptic plasticity mechanisms and expression of plasticity-related genes. During sleep, suppression of noradrenergic activity enhances glymphatic clearance of lactate and possibly also glutamate and K^+. Clearance is facilitated by increased extracellular space volume (i.e. reduced intracellular volume) and decreased synaptic coverage by astrocytic processes. K^+ is also sequestrated by astrocytic NKA, which contributes to the decreased extracellular K^+ and associated neuronal excitability underlying sleep. In this state, increased levels of extracellular Ca^{2+} and Mg^{2+} enhances release probability of vesicles (possibly with reduced quantal content) while blocking NMDAR activation, thereby changing synaptic plasticity rules. EAAT, excitatory amino acid transporter; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NKA, Na^+/K^+–activated adenosine trisphosphatase.

levels, noradrenergic tone and synaptic plasticity [48•,51]. It should be noted that changes in neuromodulatory tone drive brain state changes and influence plasticity-related processes in all brain cell types, including astrocytes, neurons, oligodendrocytes and microglia [reviewed by 52].

State–dependent astrocyte–neuron functional and metabolic interactions

The transition from wakefulness to sleep is accompanied by a marked expansion of extracellular space [49,53] as well as rapid and sustained decrease in extracellular K^+ and increase in extracellular Ca^{2+} and Mg^{2+} [54••]. These changes in interstitial fluid volume and ionic composition are reversed during the transition from sleep to wakefulness and are largely dependent on neuromodulators, while they survive suppression of neuronal firing [49,54••]. As wake-promoting neuromodulators generally decrease membrane K^+ conductance, these findings suggest the involvement of Na^+/K^+-activated adenosine triphosphatase (NKA) activity. During sleep–wake cycle, NE has been reported to stimulate neuronal and inhibit astrocytic NKA [55], advancing the possibility that sleep promotes extracellular K^+ removal and volume increase by a transient disinhibition of the osmogenic astrocytic NKA. Both neurons and astrocytes swell upon elevated extracellular K^+ or oxygen/glucose deprivation, however neurons are remarkably more osmo-resistant than AQP4-expressing astrocytes [56,57]. Interestingly, NE has repeatedly been found to alter astrocytic morphology *in vitro* and *in situ*, a mechanism seemingly associated with increments of distal processes volume and surface area [53 and references therein]. Arousal upregulates genes related to extracellular matrix and cytoskeleton involved in the elongation of peripheral astrocytic processes, bringing them closer to the synaptic cleft during wakefulness compared with sleep [58•]. Alternatively or in addition, alike for lactate the enhancement of glymphatic system may contribute to K^+ clearance during sleep (Figure 1).

The combination of interstitial fluid ionic changes brought about by sleep onset and progression might affect the balance between presynaptic and postsynaptic activation. Low extracellular K^+ is associated with reduced synaptic failures and high extracellular Ca^{2+} is known to enhance transmitter release, whereas high extracellular Mg^{2+} increases blockade of NMDA receptors [54••,59]. The decrease in interstitial K^+ concentration is consistent with widespread neuronal hyperpolarization and consequent reduction in neuronal firing rates. Compared with quiet waking, average neuronal firing rates do indeed slightly decrease during NREM sleep, increase during active waking and do not appreciably change during REM sleep [60,61•]. Declines in neuronal firing rates (e.g., periodic neuronal silence during NREM slow-wave activity) are intrinsically associated with reduced synaptic failures in the majority of central synapses [62]. In addition, decreased Ach and NE levels during sleep might suppress astrocytic release (or astrocyte-mediated neuronal release) of ATP/adenosine and D-serine, thereby abrogating the effects of adenosine in inhibiting presynaptic glutamate release and potentiating postsynaptic responses as well as the effect of D-serine in acting as co-agonist at NMDA receptors [63]. Reduced synaptic coverage by astrocytes during sleep also entails decreased glutamate reuptake and consequent increase in glutamate dwell time and spillover, with profound consequences on neuronal synchronization and synaptic plasticity rules [58•]. Together, these observations indicate that sleep is seemingly characterized by an increase in release probability (i.e. decrease in synaptic failures). Synaptic failures enhance information transmission efficiency [2] and are necessary for basic neuronal computations, such as sensory adaptation, gain control and direction selectivity [64], something that is manifestly important during wakefulness.

Fundamental differences in the balance between presynaptic and postsynaptic activation can be well responsible for the changes in OGI observed during the sleep–wake cycle. The machinery for axonal vesicle transport and presynaptic vesicle recycling largely depends on glycolytic energy [65–68], consistent with low mitochondrial density in presynaptic terminals [69]. Action potential waveform and transmitter release can be modulated by astrocytes [70] and are influenced by glycolytic energy provision [71] as well as axonal mitochondrial trafficking [72]. Uptake of extracellular K^+ (most of which exits neurons via NMDA receptors) and glutamate by astrocytes causes and perhaps requires upregulation of glycogenolysis and glycolysis [73–75]. Dendritic spine remodeling during long term potentiation is to a large extent dependent on astrocytic glycogenolysis [76]. High rates of Ca^{2+} entry (e.g., through postsynaptic NMDA receptors) above the threshold for mitochondrial calcium uniporter stimulate tricarboxylic acid cycle dehydrogenases but at the same time favor lactate production by impairing malate-aspartate NADH shuttle [7,77]. The ability of glycolysis and oxidative phosphorylation to sustain different aspects of neurotransmission has been hitherto difficult to determine, but it likely depends on neuronal presynaptic and postsynaptic transactions [78]. At least in part, the aforementioned events are directly or indirectly the result of astrocytic response to neuromodulators, consistent with the idea that these cells can drive state transitions [79].

Network homeostasis as an energy–consuming facet of sleep

Sleep is an adaptive behavior that increases fitness and behavioral performance, as evidenced by the dramatic adverse effects of sleep deprivation, including reduced alertness and ability to acquire and store information [1]. Adaptation to the environment, a crucial factor impacting on the probability of survival, entails the capacity to

modify behavior to mutating conditions. Refinement of neuronal circuits occur in an experience-dependent manner, whereby synapses constantly undergo Hebbian forms of synaptic plasticity like long-term depression and potentiation. If unopposed such mechanism may result in severe widening of neuronal firing rate distribution [80], so that distinct neuronal populations either fire together or are silent, even in the presence of synaptic rescaling. Against this destabilizing force, homeostatic plasticity mechanisms are proposed to maintain the stability of average neuronal activity by adjusting (i.e. either upscaling or downscaling) synaptic strengths [81].

Sleep and wakefulness have recently been found to produce distinct plasticity effects on neuronal networks. In particular, wakefulness is associated with homeostatic changes targeting average neuronal firing set-points [82•] whereas sleep is associated with homeostatic changes targeting neuronal firing distribution [61•]. It seems that sleep brings about a spike rate homogenization effect, that is, increasing the activity of slow-firing neurons and decreasing the activity of fast-firing neurons. To this end, the drifting levels of NE and other subcortical neuromodulators occurring during sleep have been suggested to shift plasticity rules between depression and potentiation [61•]. These findings can be interpreted in keeping with the concept of predictive coding, in a nutshell being the idea that the brain contains a representation of the reality used during wakefulness for unconscious inference [83]. The role of NE would be that of inducing the processing of the sole residual mismatch between external information and the inner model of the world, something that dramatically improves energy efficiency. Accordingly, NE decreases the influence of the internal representation to the afferent sensory input, suggesting that it prevents the interpretation of sensory information based only on previous learning [84]. The representation of reality is altered during wakefulness in the presence of environmentally-oriented sensory-motor cortical activity and requires NE, lactate and astrocytic participation in synaptic plasticity [51]. As illustrated above, cessation of noradrenergic firing during sleep substantially modifies astrocyte–neuron interactions. The resulting internally-generated neuronal activity may enable environment-independent changes to internal representations, which would otherwise become progressively resistant to, and worsen the efficiency of, reorienting behavioral responses.

Conclusions

The varying degree of aerobic glycolysis between sleep and wakefulness likely reflects the altered astrocytic participation in neuronal activity and the ensuing changes in synaptic plasticity brought about by differences in neuromodulatory tone. During sleep, selective homeostatic changes are obtained by exposing synapses to neuronal discharge patterns that are energy demanding. Overall, both in terms of energy metabolism and neuronal activity, the immediate sleep 'savings' are quantitatively minor as they might support processes necessary to improve and/or restore the ability to learn and remember during subsequent wake periods. The exact biological mechanisms underlying the homeostatic control of cortical synapses are largely unknown, but astrocytes are undoubtedly involved in the remodeling of neuronal activity and synaptic plasticity occurring in response to wake-promoting neuromodulators [85,86].

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Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

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- •• of outstanding interest

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