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Current Opinion in Neurobiology

Sleep slow oscillation and plasticity

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It is well documented that sleep contributes to memory consolidation and it is also accepted that long-term synaptic plasticity plays a critical role in memory formation. The mechanisms of this sleep-dependent memory formation are unclear. Two main hypotheses are proposed. According to the first one, synapses are potentiated during wake; and during sleep they are scaled back to become available for the learning tasks in the next day. The other hypothesis is that sleep slow oscillations potentiate synapses that were depressed due to persistent activities during the previous day and that potentiation provides physiological basis for memory consolidation. The objective of this review is to group information on whether cortical synapses are up-scaled or down-scaled during sleep. We conclude that the majority of cortical synapses are up-regulated by sleep slow oscillation.

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Current Opinion in Neurobiology 2017, **44**:116–126

This review comes from a themed issue on **Neurobiology of sleep**

Edited by **Yang Dan** and **Thomas Kilduff**

http://dx.doi.org/10.1016/j.conb.2017.03.019

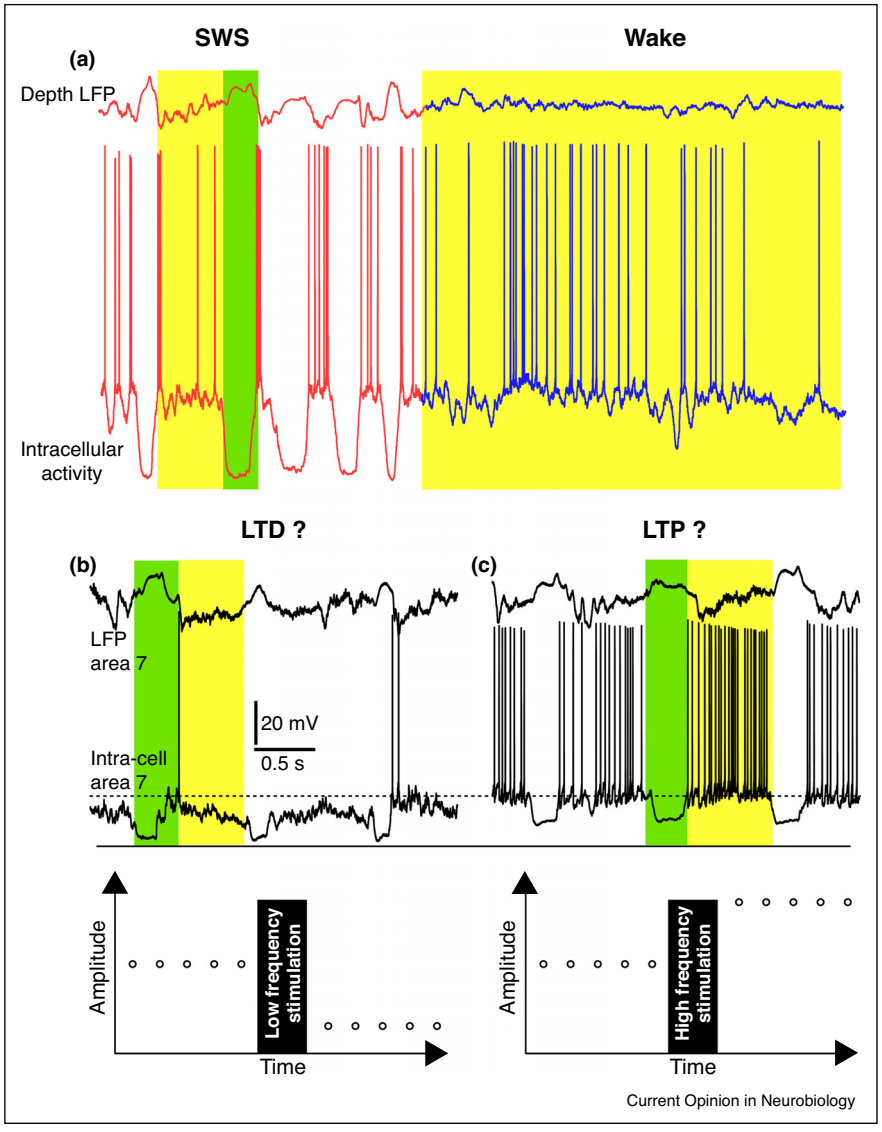
Introduction: neuronal activities during sleep and wake states

During Non-Rapid Eye Movement sleep (NREM, also referred to as slow-wave sleep—SWS) the EEG/LFP activity is dominated by spindles and slow waves, while during Rapid Eye Movement (REM) sleep and waking state it is dominated by activated patterns (low-amplitude, high-frequency activities) [1]. Intracellular recordings in anesthetized cats demonstrated that depth-positive/surface negative components of LFP are associated with hyperpolarization and silence of cortical neurons, while cortical neurons are depolarized and fire spikes during depth-negative/surface positive components of LFP [2]. Identical relation of LFP and intracellular activities was reported during SWS (Figure 1) [3–5].

Waking state and REM sleep are characterized by persistent active states in cortical neurons (Figure 1a) that show continuous synaptic, both excitatory and inhibitory, activities [3,4,6]. It is important to mention that spontaneous or evoked active states in non-anesthetized preparations are dominated by inhibition and spontaneous firing occurs upon a decrease of inhibitory tone [7,8]. Because of a domination of inhibitory activities, a large subset of cortical neurons during waking state display synaptic activities, but they are relatively hyperpolarized and do not fire or rarely fire action potentials [7,9••]. Even neurons with high spontaneous firing rates decrease their firing frequency upon the onset of behavioral tasks [10•]. Intracellular patch-clamp and sharp electrode recordings from various cortical areas of non-anesthetized rats confirmed that large membrane potential fluctuations of cortical neurons were present only when field potential showed large amplitude activities [11], meaning during either sleep or drowsiness. Similar results were also found in V1 cortical area of mice [8,12].

Whole-cell recordings from somatosensory cortex of non-anesthetized mice complicated this picture. It appears that in non-anesthetized, potentially awake mice, the membrane potential of barrel cortex neurons from superficial layers continuously oscillate between depolarized and hyperpolarized voltages (apparently not states, because they are too short) in quiet wake and it becomes persistently depolarized when sensory-motor activities are present [13,14]. It is important to mention that these membrane potential oscillations with a frequency of 3–5 Hz in potentially awake mice were highly correlated with LFP, meaning that large amplitude membrane potential oscillations were present when large amplitude LFP oscillations were present too [14]. The interpretation of these results is a matter of discussion. First, it is unclear how to identify states of vigilance in head-restrained mice as their cortical states are unstable and continuously vary from slow oscillatory to activated pattern [15,16,17••]. Second, due to the technical challenge, usually cells are patched under light isoflurane anesthesia and recorded throughout recovery from that anesthesia; therefore it is unclear whether some remaining effects of the anesthetic influence these recordings. Third, this type of oscillatory activity in mice could be related to well-known rhythmic wake activities like alpha or mu rhythms [18–21]. It is well accepted that spike and wave seizures in rodents occur at a frequency of 6–8 Hz, but in humans their main frequency is 3 Hz [22–24]. It is

Figure 1



Sleep–wake activities and long-term plasticity. **(a)** An example of local field potential (LFP) and intracellular recordings during slow-wave sleep (SWS, red) and its transition to waking state (blue). Yellow background shows examples of active states, green background shows examples of silent states. **(b)** Upper panel shows LFP and intracellular activities of a neuron with relatively low firing rates during active cortical states. Synapses formed by such a neuron can potentially induce long-term depression (LTD, lower panel). **(c)** Upper panel shows LFP and intracellular activities of a neuron with relatively high firing rates during active cortical states. Synapses formed by such a neuron can potentially induce long-term potentiation (LTP, lower panel).

also possible that somatosensory mu rhythm (10–16 Hz) recorded in immobile subjects or occipital alpha rhythms (7–12 Hz) recorded in subjects with closed eyes could be present in mice with different frequencies. The fourth possibility is that mice just lack sufficient number of connections between neurons enabling the maintenance of persistent active states [25–28]. We proposed long time ago that a given number of connections between neurons is needed to maintain regular activity [29] and overall the activity is reduced in reduced cortical preparations [29,30]. It appears that due to reduced intracortical connectivity patterns, it is very difficult to induce regular patterns of activities in slices from rodents and such states are easily recorded in cortical slices obtained from carnivores that exhibit richer intracortical connectivity [31]. Activity of cortical neurons during REM sleep shows species-dependent differences. In cats, fast spiking (normally parvalbumin-containing [32]) neurons increase firing exclusively during eye movements, which causes a decrease in firing in other neuronal types [4]. By contrast,

calcium imaging in mice revealed that parvalbumin-containing neurons increase their activity throughout REM sleep episodes, which causes overall decrease in activity of other neurons [33]. An overall decrease in firing rates during REM sleep was also observed in the CA1 region of hippocampus [34].

Can slow waves, characterized by a silent followed by an active network state, be generated during well-defined behavioral waking? Yes. Slow-wave activity during waking state can be present in epileptic animals or patients [35,36]. Such slow-wave activity is likely generated due to epilepsy-related deafferentation (brain trauma, tumor, *etc.*). Another possibility is sleep deprivation [37] in which the excitatory drive is likely reduced. Indeed, cortical slow-wave activity is replaced by activated pattern upon thalamic activation [38,39] and at least the neurons in mice thalamic VPM nucleus do not fire many spikes during waking state outside whisker movement episodes [40], thus, they lack a thalamic tonic activation during quiet wakefulness. Based on all above, we conclude that during waking state the membrane potential of the majority of cortical neuron does not show major fluctuations and that during slow-wave sleep the membrane potential fluctuates between depolarizing and hyperpolarizing states.

Long-term synaptic plasticity

Long-term potentiation (LTP) was discovered by Lømo in 1966 (first publication dated 1973 [41]) and is the long-lasting improvement in communication between two neurons. Later, the opposite phenomenon, the long-term depression (LTD) was found [42]. A typical experimental stimulation paradigm to induce long-term plasticity is the tetanic stimulation of presynaptic fibers with a train of 100 Hz for 1 s, which induces LTP. LTD can be induced either by low-frequency stimulations (homosynaptic LTD) or as a result of inactivity in synapses formed on a neuron that have active synapses (heterosynaptic LTD). For a long time the long-term synaptic plasticity was considered as a basis of memory formation [43], although hippocampal GluR-A-dependent LTP was not essential for spatial learning in water maze [44]. A recent study demonstrated however a causal link of long-term plasticity in amygdala-dependent fear learning: LTD conditioning—inactivated memory and LTP conditioning reactivated memory [45••].

It was proposed that sleep oscillations induce a down-regulation of synaptic excitability [46,47]. During SWS the dominant frequency of activity is around 1 Hz and some neurons fire on average one spike with this frequency (Figure 1b). Such a frequency of stimulation normally triggers LTD. However, the other neurons fire high-frequency spike trains during active states of cortical slow oscillation and these trains are repeated with a frequency of about 1 Hz (Figure 1c). This pattern of spontaneous firing is normally associated with LTP. Therefore the net synaptic modification induced by sleep slow oscillations remains unclear.

Neuronal plasticity and sleep–wake cycle

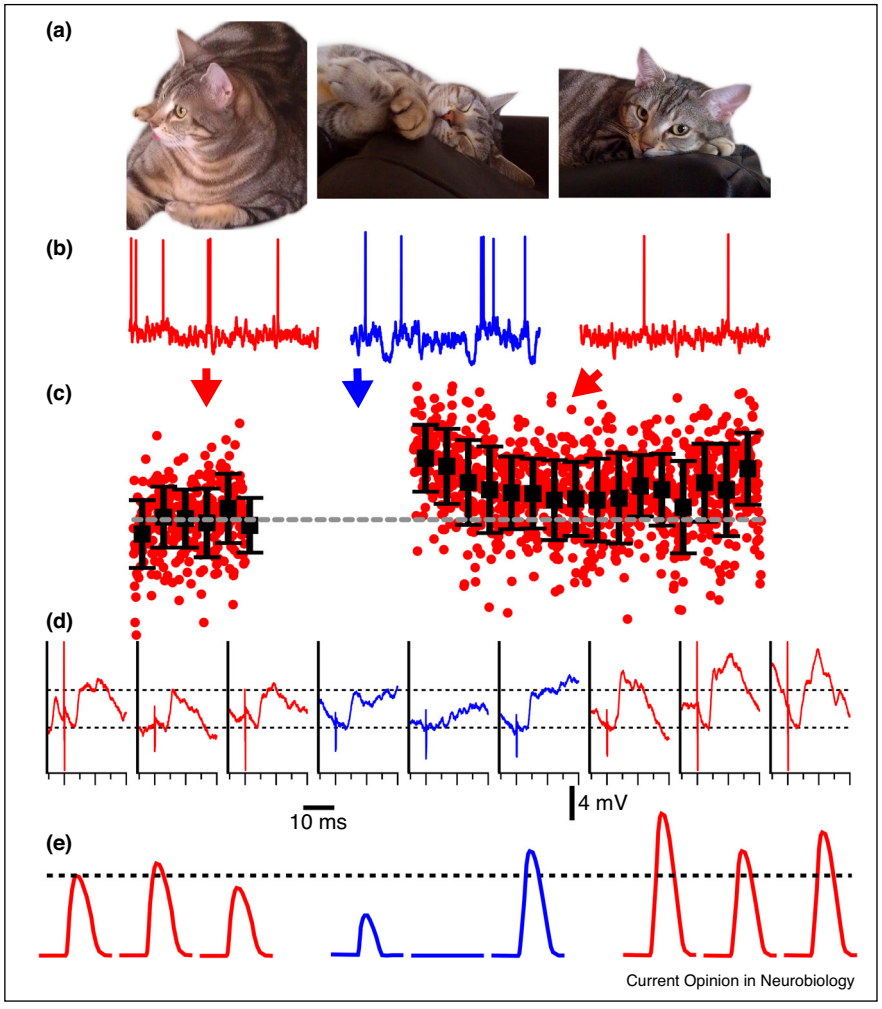
Neuronal plasticity is the ability of neurons to modify their responses to incoming inputs. It can be subdivided to plasticity in the expression of intrinsic neuronal currents and to synaptic plasticity: short-term and long-term. Different experiments evaluated network/neuronal responsiveness during sleep–wake cycle [3,48–51], but the interpretation of these results was mostly ascribed to synaptic changes. It appears that SWS potentiates the overall cortical excitability as synaptically driven field potential and intracellular responses increase after a period of SWS [52] (Figure 2).

State-dependent changes in neuronal plasticity can be attributed to at least three factors. First, changes in neuromodulatory activities that directly affect multiple neuronal channels and thus intrinsic excitability [53•,54–57], second, state-dependent changes in gene expression [58–61] which at the end alter the content of different channels and thus the intrinsic neuronal excitability; third, the presence of hyperpolarizing periods of neuronal activities, which can affect voltage and time-dependent intrinsic neuronal currents.

Short-term synaptic plasticity

A vast majority of studies is focused on synaptic modifications associated with state-dependent changes. During waking state, cortical neurons fire with relatively steady rates [62]. Consistent presynaptic firing induces steady-state synaptic plasticity, which is normally expressed as steady-state synaptic depression [63]. In an active network, overall short-term synaptic dynamics are reduced [64,65]. The main feature of SWS is synchronized neuronal silence occurring over large cortical territories [5,66–70]. A brief silence in steady-state presynaptic firing immediately recovers synapses from steady-state synaptic depression [63,71]. Therefore, it is highly likely that silent states of sleep can reduce or eliminate steady-state synaptic plasticity induced by waking state. The other important mechanism that could mediate sleep-induced short-term facilitation is the presynaptic neuron hyperpolarization-induced facilitation of postsynaptic response due to the recovery from inactivation of Na^+ channels controlling action potential amplitude in the axon [72••]. Indeed, during silent states of the slow oscillation, cortical neurons are hyperpolarized by 5–15 mV [73]. In transition to active state, layer five pyramidal cells are depolarized and fire action potential within just a few milliseconds [5]. Combined with the highest levels of extracellular Ca^{2+} at this period of time [74,75], the elicited EPSPs should be of higher amplitude as compared to the mean EPSPs produced during any other network state. The fact that extracellular Ca^{2+}

Figure 2



Slow-wave sleep induces long-term potentiation. **(a)** Sleep and wake states in a cat. **(b)** Intracellular activities of cortical neuron from somatosensory area in wake – SWS – wake during stimulation of ascending medial lemniscus pathway. **(c)** Dynamics of first depth-negative component of somatosensory evoked potential during wake. Left part corresponds to wake before sleep, empty part corresponds to SWS during which the stimulation was not applied and right part corresponds to wake after SWS. **(d)** Typical examples of intracellular responses during wake – SWS – wake states. **(e)** Artistic representation of typical intracellular voltage responses during wake – SWS – wake states.

concentration is lower in wake as compared to sleep [76••] implies lower synaptic release probability during wake.

Long-term plasticity

A popular hypothesis suggests that waking state is associated with up-regulation of cortical synapses, which are then down-regulated during SWS [46,77•]. Initially, this hypothesis was based on the fact that multiple genes involved in synaptic plasticity were up-regulated during wake, after sleep deprivation [58,78]. However, the time between gene expression, protein synthesis, transport and membrane insertion takes usually hours; therefore, the real effects of wake-dependent gene expression should be sensed more during sleep. The current support for this hypothesis (current name—synaptic homeostasis hypothesis (SHY)) is based on three lines of evidences: molecular, electrophysiological, and structural [77•]. However, the currently available evidences cannot provide a full support for the hypothesis, and therefore are not well accepted by all [79,80••,81].

(1) *Molecular evidence supporting SHY*. Levels of GluA1-containing AMPARs are 30–40% higher after wakefulness than after sleep in rats [51]. This finding was further strengthened by the demonstration that this increase depends on the immediate early gene Homer1a, which controls AMPA-type glutamate receptors and which is itself controlled by noradrenaline and adenosine [82•].

Opposite evidences. High levels of GluA1-containing AMPARs does not necessarily support SHY because of the following reasons. (a) The levels of acetylcholine are high during waking state and high levels of acetylcholine decrease fast (AMPA-dependent) intracortical synaptic currents/potentials [52,83]. Therefore, if any up-regulation of AMPA receptors occurs, this is likely due to homeostatic mechanisms as a response to acetylcholine-induced depression of synaptic efficacy. (b) It is unclear to what extent AMPA receptor up-regulation alone is responsible for long-term synaptic changes. Sleep-dependent memory consolidation requires coactivation of both AMPA and NMDA receptors [84]. (c) The sleep-dependent synaptic strengthening occurs via NMDA receptors, CaMKII, and ERK and PKA activity [85]. Sleep also promote protein synthesis (translation, not transcription) of key plasticity related molecules *ARC* and *BDNF* [86]. Lastly, mGluR5 receptor, a receptor that is implicated in learning and memory is up-regulated at the beginning of sleep phase in rats [87•]. Thus, available molecular evidences do not support SHY.

(2) *A list of electrophysiological evidences presented to support SHY* [77•] *do not support SHY at all*. To support sleep-dependent downscaling of the synaptic response, four types of the experimental evidences are listed. (a) The first negative component of the response evoked by transcallosal electrical stimulation increases with time spent awake and decreases with time spent asleep [51]. The slope of the early (monosynaptic) response evoked by electrical stimulation is a classical measure of synaptic strength when only presynaptic fibers are activated. The interpretation of results with transcallosal stimulation, however, is complex. First, electrical stimulation of grey matter excites primarily axons, but not cell bodies [88,89]. Second, the first component of field potential response induced by callosal stimulation is a reflection of antidromic spike firing, but not synaptic responses [90]. Therefore, this experiment demonstrates that either the axonal excitability is reduced during sleep or that during sleep the antidromic spikes are less ready to invade the soma of cortical neurons. Indeed, during SWS, cortical neurons oscillate between depolarizing and hyperpolarizing states. Somatic hyperpolarization readily blocks somatodendritic component or even the initial component of antidromic spike leaving unaffected only the medullated (M) component (usually just 1–5 mV) of a full antidromic spike [91,92]. Therefore, the first negative component of transcallosal evoked field potential response does not provide information on synaptic processes. (b) The slope of the early response evoked in frontal cortex by transcranial magnetic stimulation (TMS) increases progressively in the course of 18 hours of continuous wake and returns to baseline levels after one night of recovery sleep [93]. It is well accepted that TMS directly excites primarily axons, but not neuronal bodies [94]. Therefore, as in the case of antidromic spikes, a sleep-dependent reduction of earliest phases of TMS-induced evoked potential can be explained by a reduced axonal excitability. (c) In the third type of experiment supporting SHY, patch-clamp recordings of miniature Excitatory Post-Synaptic Currents (mEPSCs) were performed from layer 2–3 pyramidal cells in cortical slices obtained from animals experiencing a long period of control (mainly waking state), sleep, or sleep deprivation. As authors report, the frequency of mEPSCs was different in these conditions: high after wake, higher after sleep deprivation, and lower after sleep [95]. The available results are confusing. First of all, the frequency of mEPSC provides information on presynaptic release; therefore, the explanation cannot be coupled with results on changes in postsynaptic GluA1-containing AMPARs. In different sets of experiments, the frequency of mEPSCs in two control groups was 1.69 ± 0.21 Hz; and 2.31 ± 0.40 Hz, which is about 40% difference in two similar experiments. The frequency of mEPSCs after sleep deprivation was 5.71 ± 1.09 Hz or 2.44 ± 0.48 Hz in two different experiments, which is about a double of difference. The frequency of mEPSCs after sleep deprivation in one of experiments was 2.44 ± 0.48 Hz, which was similar to the frequency of miniature EPSPs in another control experiment (2.31 ± 0.40 Hz). Therefore, most of the provided electrophysiological evidences do not actually support SHY. (d) The firing of cortical neurons progressively increases during wake and decreases during sleep [70]. This appears to be only partially true as this rule can be applied to neurons with relatively high firing rates and neurons with low firing rates, constituting the majority of cortical neurons [96], increase their firing throughout sleep episode [9••].

Other studies demonstrate that SWS increases synaptic efficacy. Somatosensory evoked potential induced by ascending prethalamic stimulation (medial lemniscus) was increased after a period of SWS as compared to pre-sleep waking period (Figure 2c). This field potential response increase was mediated by an increase in the amplitude of intracellularly recorded EPSPs in the majority of investigated neurons pointing to a sleep-dependent increase in synaptic efficacy [52] (Figure 2d,e). An *in vitro* investigation demonstrated that using a natural pattern of synaptic stimulation accompanied with neuronal hyperpolarization that reflects (models) silent phases of the slow oscillation was sufficient to induce this postsynaptic long-term facilitation that is Ca^{2+}-, AMPA-, and NMDA-dependent [52]. Several studies propose/demonstrate that grouping of ripples/spindles by sleep slow-wave activities plays a critical role in sleep-dependent memory

consolidation [97–101]. The high extracellular Ca^{2+} levels during sleep [76••] and in particular at the transition from silent to active states of slow waves [74,75] as well as higher amplitude of spikes elicited at hyperpolarized voltages [72••,102] in addition to higher release probability implies higher Ca^{2+} entry in a postsynaptic neurons and thus an increase in LTP.

Further studies demonstrated that V1 response potentiation, which is associated with a shift in orientation preference, occurs only after sleep suggesting that sleep promotes cortical synaptic potentiation [80••,103]. In addition to direct long-term synaptic facilitation, this sleep-dependent increase in activity during following waking state can be controlled by synaptic disinhibition [104]. Therefore, physiological evidences demonstrate multiple mechanisms of SWS induced synaptic up-regulation, but not down-regulation in neocortex.

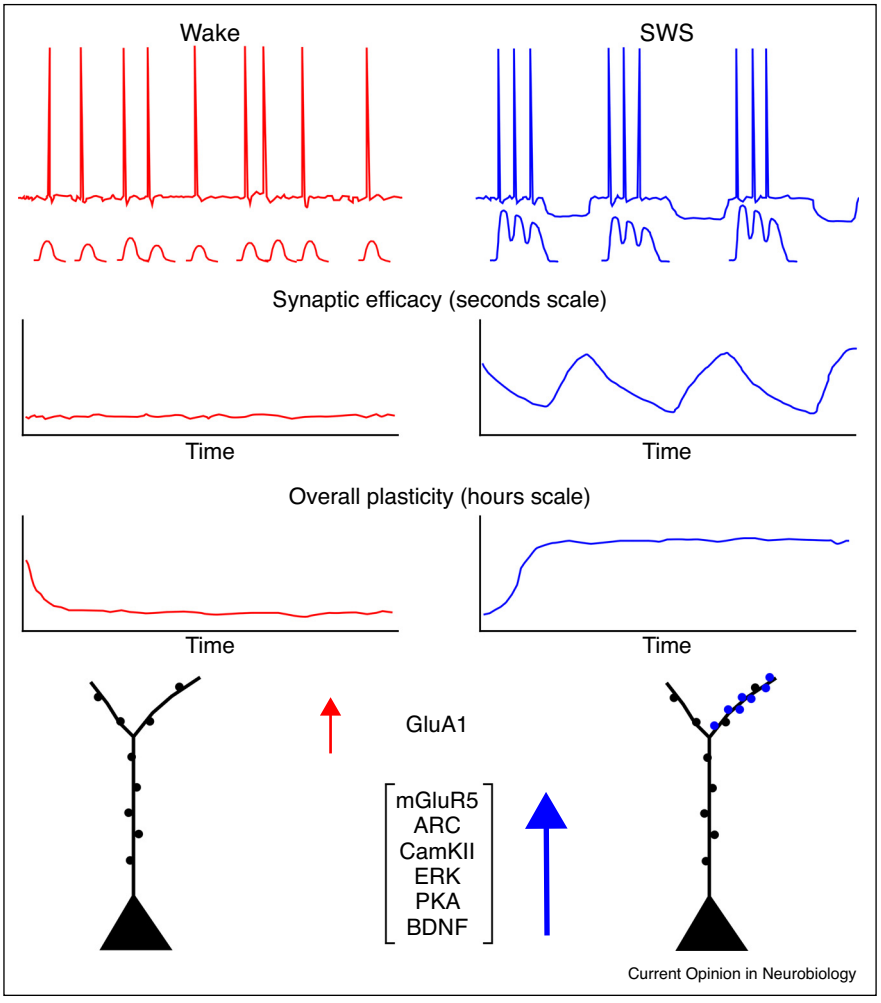
In chemical synapses, it is obvious that presynaptic firing is the only mechanism that initiates synaptic release and thus triggers all further processes responsible for synaptic plasticity. However, a role of overall firing rates in the maintenance of synaptic homeostasis is a matter of discussion. First, it was shown that neuronal firing rates progressively increase during wake and decrease during sleep [70]. However, the opposite is true for the majority of neurons with low firing rates [9••], and neocortical neurons usually show low firing rates [96]. It appears that the overall state-dependent changes in neuronal firing do not contribute to sleep homeostasis [105•,106•,107], but homeostasis in firing rates is promoted exclusively by waking state [108••], therefore these results are incompatible with a general down-scaling of synapses during sleep. Thus, available electrophysiological evidences do not support SHY.

(3) *Structural evidence supporting SHY*. "In adolescent 1-month-old mice, spines form and disappear at all times, but spine gain prevails during wake, resulting in a net increase in spine density, while spine loss is larger during sleep, resulting in a net spine decrease" [109]. The same study shows that spine turnover is not impacted by sleep and wake in adult mice. Again, 1-month-old mice small and medium size axon-spine interface decreases during sleep [110•]. The mechanisms of these changes are unclear, but might be related to a larger extracellular space volume during sleep as compared to wake [76••,111]. One-month-old mice roughly correspond to the end of childhood and beginning of adolescence. There are several issues that have to be taken into consideration here. First, the learning abilities are not lost in adolescence and at later ages: if spines contribute to learning, their change must be seen after learning episodes. Second, the transition from childhood to adolescence is associated with infantile amnesia in human and animals [112,113]. In 9–11 years old children sleep did not play a role in memory consolidation in at least some declarative memory tasks [114]. It is suggested that protracted postnatal development of key brain regions important for memory interferes with stable long-term memory storage [115]. Therefore, the spine plasticity in 1-month old mice might be the mechanisms of forgetting and not learning. Third, an electron microscopy study demonstrates a decrease in the density of excitatory synapses after wake period and its increase after sleep period [116•]. Fourth, a recent study, conducted on adult (3-month old) mice, demonstrated sleep-dependent, branch-specific formation of spines after learning [117••]. Therefore, structural evidences demonstrate that sleep-dependent spine elimination coincides with period of infantile amnesia and that sleep-dependent learning is associated with an increase in excitatory synapse density and branch-specific formation of spines. Overall, all three lines of evidences: molecular, electrophysiological, and structural point to sleep-dependent increase in synaptic efficacy, but not sleep-dependent down-regulation of synapses as suggested by SHY.

Conclusion

Several recent publications suggest that slow-wave sleep is self-organizing, default state of cortical network [67,118,119]. Therefore, the state of plasticity during SWS can be considered as reference level of synaptic efficacy. The maximal synaptic efficacy during slow oscillation occurs during silent states of cortical network. Because of reduced release probability and cortical shunting, the efficacy of synaptic responses is reduced in active states [74,75,120]. These short-term network dynamics are accompanied or lead to an increase in multiple molecular factors contributing to long-term plasticity and increase branch-specific spine/synapse formation (Figure 3). Upon waking up, when network is persistently active the synaptic efficacy appears to be low (Figure 3), but the synaptic failure rates are low too, possibly due to high levels of GluA1 receptors. We suggest that during wake the transmission of information in cortical network occurs at nearly linear fashion and that waking state is associated with steady-state synaptic dynamics, relatively low in amplitude, but highly reliable and not much 'plastic' synaptic state. Because the membrane potential of neurons is relatively depolarized (a few millivolts below threshold) the overall network responsiveness during waking state is high as small amplitude synaptic events can easily lead to action potential generation. Synchronous silent states of SWS reduce/remove steady-state synaptic plasticity, that overall increases synaptic responsiveness (Figure 3), however, the network responsiveness depends on the exact phase of the slow oscillatory cycle [49,121,122].

Figure 3



Overall cortical plasticity during wake and slow-wave sleep (see details in text).

Conflict of interest statement

Nothing declared.

Acknowledgements

Supported by Canadian Institutes of Health Research (grants MOP-136969, MOP-136967) and by National Sciences and Engineering Research Council of Canada (grant 298475).

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

- • of special interest
- •• of outstanding interest

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