Epilepsy & Behavior 14 (2009) 47–53

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Synaptic plasticity along the sleep–wake cycle: Implications for epilepsy

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ARTICLE INFO

Article history:
Received 16 August 2008
Revised 22 September 2008
Accepted 23 September 2008

Keywords:
Epilepsy
Seizure
Synaptic plasticity
Sleep
Waking
Memory

ABSTRACT

Activity-dependent changes in synaptic efficacy (i.e., synaptic plasticity) can alter the way neurons communicate and process information as a result of experience. Synaptic plasticity mechanisms involve both molecular and structural modifications that affect synaptic functioning, either enhancing or depressing neuronal transmission. They include redistribution of postsynaptic receptors, activation of intracellular signaling cascades, and formation/retraction of dendritic spines, among others. During the sleep–wake cycle, as the result of particular neurochemical and neuronal firing modes, distinct oscillatory patterns organize the activity of neuronal populations, modulating synaptic plasticity. Such modulation, for example, has been shown in the visual cortex following sleep deprivation and in the ability to induce hippocampal long-term potentiation during sleep. In epilepsy, synchronized behavioral states tend to contribute to the initiation of paroxystic discharges and are considered more epileptogenic than desynchronized states. Here, we review some of the current understandings of synaptic plasticity changes in wake and sleep states and how sleep may affect epileptic seizures.

1. Introduction

The evolving complexity of the nervous system along phylogeny has endowed mammals with a vast repertoire of responses to a myriad of ecological demands. Their ability to express adaptive behaviors is closely associated with the capacity of their neural circuits to dynamically modify their functions [1,2]. Such neural plasticity provides the brain with the ability to modify its organization and activity in the face of different experiences, be it for good, in daily behavioral adjustments, or for bad, as maladaptive plasticity in response to brain insults. In particular, activity-dependent changes in synaptic efficacy, i.e., synaptic plasticity, affect the efficiency of neuronal transmission and seem to be an important mechanism to regulate information flow and, ultimately, behavior [3–5].

A number of studies have shown that synaptic plasticity is a widespread phenomenon that occurs in virtually all brain regions [6–9]. It plays an important role during ontogenetic development and is involved in the formation of new memory traces [10–12]. In addition, it can also contribute to the pathophysiology of epilepsy and other neurological and psychiatric disorders [13–16]. Among the different modulators of synaptic plasticity, the sleep–wake cycle is of special interest because it is a natural circadian regulator of activity and metabolism, associated with specific behavioral, neurochemical, and neuronal firing pattern changes [17–21]. Studies during the past two decades have accumulated showing that synaptic plasticity is profoundly altered by disturbances in the regular sleep–wake cycle [22–30]. Moreover, oscillatory patterns observed in various behavioral states have distinct effects on the expression of interictal discharges and the initiation of paroxystic hypersynchronization both in animal models and in epileptic patients [31–35]. In this article, we will focus on how synaptic plasticity can be modulated during the sleep–wake cycle and how this modulation could affect the susceptibility to epileptic seizures (Fig. 1).

2. Forms of synaptic plasticity

Different forms of synaptic plasticity have already been described in the hippocampus and cortex [36]. They can be subdivided into two main categories according to the duration of their effects: short-term plasticity and long-term plasticity (Fig. 2). Short-term synaptic plasticity can be expressed as paired-pulse facilitation (PPF), paired-pulse inhibition (PPI), or posttetanic potentiation (PTP). PPF and PPI occur when two closely spaced pulse stimuli are applied to a presynaptic terminal, promoting an enhancement or reduction in the postsynaptic neuronal response to the second pulse compared to its initial response to the first pulse [37,38]. It usually lasts milliseconds and can be measured by quantifying the amplitude of the excitatory postsynaptic potentials (EPSPs) recorded after each stimulus. They are thought to reflect a presynaptic form of short-term plasticity affecting the probability of synaptic vesicle release. Both facilitation and

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doi:10.1016/j.yebeh.2008.09.026

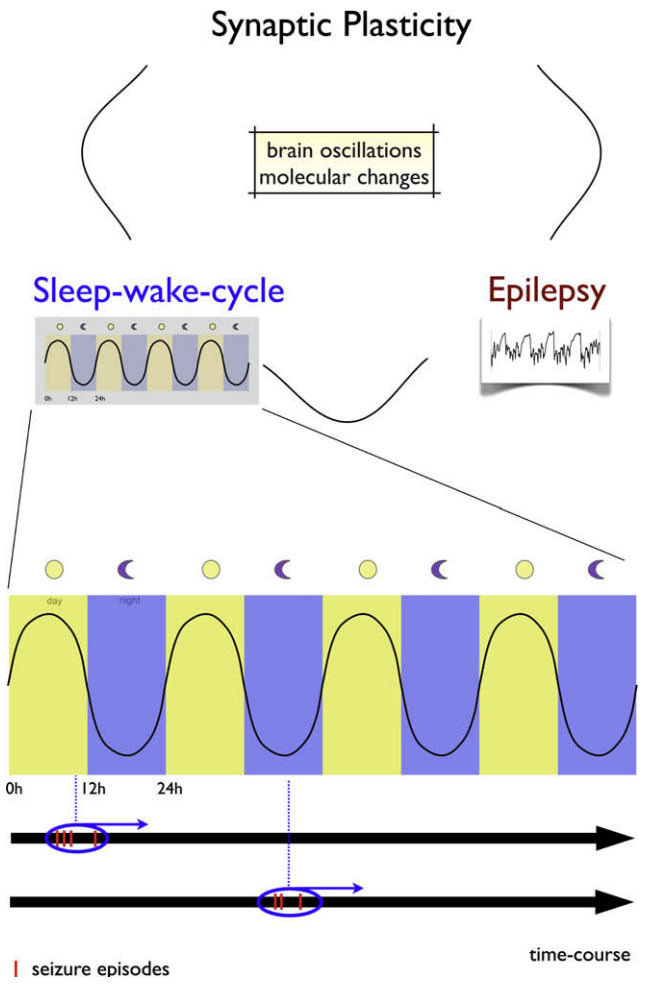

Fig. 1. Synaptic plasticity along the sleep–wake cycle and its relationship to seizure episodes. Do epileptic seizures occurring at different times of the cycle have the same effect on the brain circuitry.

inhibition depend on the recent history of activation of the neuron. In general, inhibition occurs for time intervals shorter than 20 ms and is thought to be the result of inactivation of Na^+ channels or voltage-dependent Ca^{2+} channels or synaptic vesicle depletion. Facilitation, on the other hand, occurs for intervals longer than 20 ms and seems to be caused by residual Ca^{2+} in the presynaptic terminal that contributes to increased synaptic vesicle release. PTP can be induced by the application of repetitive trains of stimulation (10–200 Hz) in the projections to a target neuron. It can last from seconds to minutes and is also thought to involve changes in the probability of synaptic vesicle release. As a functional consequence of all forms of short-term synaptic plasticity, highly active synapses will tend to act as low-pass filters and depress when high-frequency action potentials impinge on them, whereas less active synapses will tend to act as high-pass filters and get facilitated at lower frequency action potentials [36].

Two forms of long-term synaptic plasticity have been the focus of many studies in the past 20–30 years: long-term potentiation (LTP) and long-term depression (LTD). LTP was initially observed in the rabbit hippocampus as a long-lasting potentiation of field EPSPs (fEPSPs) recorded in the dentate gyrus after perforant path stimulation [39]. However, it has been described in many other subcortical and cortical regions such as the amygdala, striatum, visual cortex, perirhinal cortex, and prefrontal cortex [6–9,40]. It was shown to occur when pre- and postsynaptic neurons are coactivated or when tetanic stimulation is applied to the presynaptic terminal. In the hippocampus, it usually requires the activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (except at mossy fiber–CA3 synapses) and a high Ca^{2+} influx into the dendritic spine compartment, triggering a cascade of phosphorylation events and the production of second-messenger molecules [41]. Stimulation protocols used to induce LTP vary from one region to another, being induced by theta burst, primed burst, or high-frequency stimulation of afferents (e.g., 100- to 200-Hz pulses; 5-Hz trains). Many lines of evidence support the idea that LTP is a cellular correlate of memory storage: (1) LTP is easily induced and maintained for days in the hippocampus, which is a brain region required for the formation of new memories; (2) LTP can be induced by patterns of stimulation that mimic oscillatory neuronal activity occurring during exploratory behavior and learning; (3) LTP inhibitors produce learning deficits and impairment in memory tasks; (4) similar biochemical events occur after LTP and learning; and (5) pharmacological blockade of such signaling cascades affects both LTP and memory acquisition [41–43].

LTD, on the other hand, was originally described as a long-lasting depression of fEPSPs recorded in the cerebellum after simultaneous low-frequency stimulation of granule cell fibers (parallel fibers) and climbing fiber projections to Purkinje neurons [44]. However, it has been described in many of the regions where LTP has been found, such as the amygdala, striatum, perirhinal cortex, and prefrontal cortex [45]. Stimulation protocols used to induce LTD vary from one region to another, but most of the time they require prolonged low-frequency stimulation of afferents (600–900 pulses; 1–5 Hz). Additional requirements include the activation of NMDA receptors, followed by postsynaptic Ca^{2+} influx, and activation of a cascade of protein phosphatases [45–47]. Dephosphorylation of GluR1 and receptor removal from the spine membrane by endocytosis have also been demonstrated [46] (Fig. 2).

3. Sleep–wake cycle

The waking state (AW) is characterized by cortical EEG desynchronization with the presence of low-amplitude oscillations in the frequency range of 4–200 Hz, corresponding in humans to the theta (4–7 Hz), alpha (8–13 Hz), beta (13–25 Hz), and gamma (>25 Hz) oscillations. In rats, spontaneous field potentials recorded in the hippocampus can further subdivide AW into two states (Fig. 3): AW during immobility (AWi), consisting of intermittent populational bursts in the CA3–CA1–subiculum–entorhinal cortex axis, associated with sharp-waves in the dendritic layers and with fast-ripple (140–200 Hz) oscillations in the somatic layers, respectively [48–50], and AW during exploratory behavior (AWe), consisting of extracellular field potential oscillations in the theta band (4–12 Hz) generated by entorhinal afferents to the granule cells and CA1–CA3 pyramidal cells [48].

In mammals, sleep can be characterized by two main stages based on the brain electrical activity, muscle tonus, body temperature, and respiratory frequency: slow-wave sleep (SWS) and rapid-eye-movement sleep (REMS) [20]. SWS is characterized by three major rhythms: slow oscillations (~0.5–1 Hz), delta waves (1–4 Hz), and spindles (7–15 Hz). Although they stem from distinct neuronal networks, they appear as a combined oscillation in the intact brain [51]. Slow oscillations seem to be generated in the cerebral cortex and organize the other rhythms during SWS, whereas delta waves are generated by intrinsic cortical and thalamic neurons. Sleep spindles, on the other hand, are induced by a recurrent circuit involving neurons in the reticular nucleus of the thalamus, thalamocortical neurons, and corticothalamic neurons, in addition to intrinsic thalamic and cortical neurons [52,53]. During this stage, sensory inputs are mostly inaccessible to the brain and high-amplitude waves can be recorded in the EEG. They reflect the synchronous burst of neuronal activity resultant from

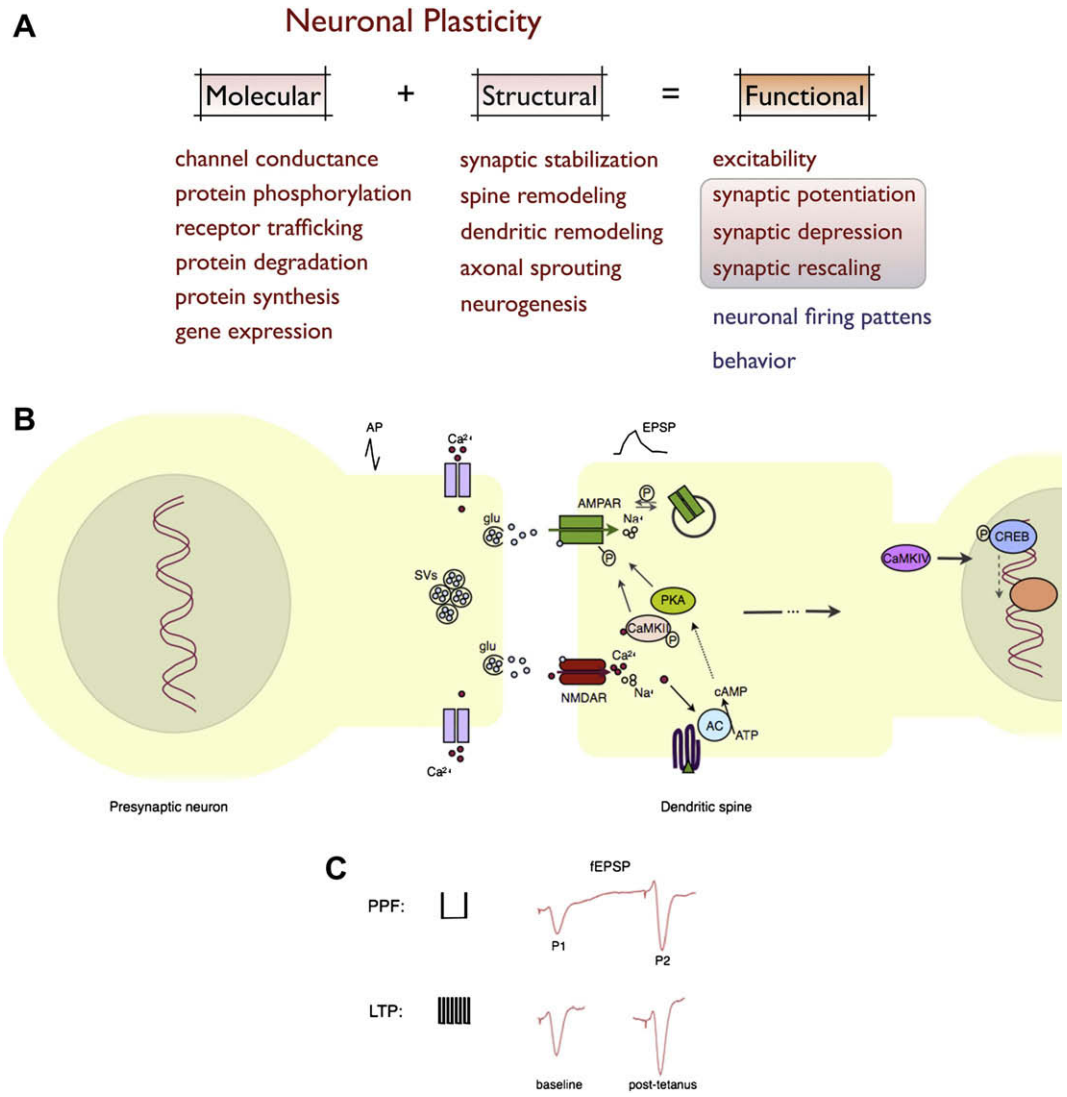

Fig. 2. (A) Structural and molecular changes involved in experience-dependent neuronal plasticity. (B) Schematic illustration of a synapse. Molecular machinery associated with the synaptic transmission and synaptic plasticity phenomena. (C) Short- and long-term plasticity measured in the projections from the hippocampus to the prefrontal cortex in rats. Application of paired-pulses (80-ms delay) induces an enhanced response at P2 compared to P1. Tetanic stimuli induce a long-lasting potentiation of fEPSPs in the prefrontal cortex. AP, action potential; EPSP, excitatory postsynaptic potential; fEPSP, field EPSP; AC, adenylyl cyclase; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid type of glutamate receptor; CaMKII/IV, calcium–calmodulin kinase II/IV; CREB, cAMP-responsive-element binding protein; NMDAR, *N*-methyl-d-aspartate type of glutamate receptor; PKA, protein kinase A; PPF, paired-pulse facilitation; LTP, long-term potentiation; P1, P2, first and second evoked cortical responses; SVs, synaptic vesicles.

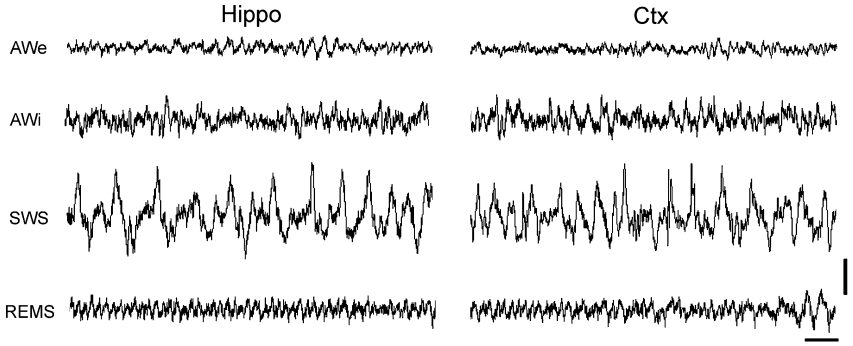

Fig. 3. Local field potentials (deep EEGs) recorded along the sleep–wake cycle in rats. Notice: (1) low-frequency oscillations during SWS; (2) strong theta (7–8 Hz) synchronization during REMS; and (3) distinct signatures of AWe and AWi. Recordings were obtained from the hippocampus (Hippo) and prefrontal cortex (Ctx). Behavioral states correspond to AWe, waking exploration; AWi, waking immobility; SWS, slow-wave sleep; and REMS, rapid-eye-movement sleep. Calibration: 1 s, horizontal bar; 500 μV, vertical bar.

thalamocortical synchronization. Neocortical pyramidal neurons are less active and responsive than in waking and REMS, generally firing single action potentials or bursts during depolarization that is followed by a long-lasting hyperpolarization phase. In the hippocampus, the most prominent pattern during SWS is sharp-waves associated with fast-ripples generated by transient bursts of CA3–CA1 pyramidal cells, similar to those observed in AWi [54,55]. It is also known that neuronal bursts in deep cortical layers, associated with sleep spindles and delta waves and slow rhythms, effectively trigger hippocampal discharges related to ripple oscillations [56]. This cooperative and converging activity can induce localized fast spikes and associated calcium influx in the apical dendrites of CA1 pyramidal cells, which is a necessary condition for the induction of synaptic plasticity. The subcortical effects of hippocampal sharp-wave bursts may be critical in the release of various hormones, which, in turn, may affect synaptic plasticity [57]. In addition, a recent study detected infraslow cortical oscillations (0.02–0.2 Hz) during SWS that were strongly synchronized to fast EEG activity and interictal epileptic events in humans [58].

REMS, on the other hand, shows neuronal activity very similar to that observed during waking [59,60]. Neocortical pyramidal neurons are tonically depolarized and fire single action potentials. In addition, the EEG during REMS consists of high-frequency/low-amplitude waves, reflecting neocortical desynchronization [61]. In the hippocampus, tonic neuronal depolarization produces a characteristic theta oscillation similar to that observed during AWe. When in REMS, animals also show the absence of muscle tonus—except for finger twitching and whisker and ocular movements—and irregular breathing [19]. In addition, a phasic activation of pontine tegmentum neurons, at the onset and throughout REMS, can be observed generating a prominent response in the lateral geniculate body of thalamus and occipital cortex—PGO waves [62,63]. In rats, PGO waves are called P-waves owing to the lack of thalamic activation [64,65]. It was demonstrated that P-wave generator cells fire at bursts just prior to each P-wave and project to the hippocampus, amygdala, and entorhinal cortex, where it could be involved in REMS synchronization [64,66]. Such phasic activity has been proposed to be involved in sensorimotor integration, learning, and memory [67,68]. In rats, a transitional stage between SWS and REMS, the intermediate stage, can be detected, which makes up ~3% of the total sleep cycle [69].

4. Synaptic plasticity in the sleep–wake cycle

In waking, theta and gamma (25–100 Hz) oscillations have been considered hallmarks of cognitive processing. During theta oscillation, hippocampal CA1 cells fire in a specific relationship to the ongoing rhythm and their spikes usually occur coupled to the peak phase of the extracellular field depolarization [48]. In vivo and in vitro experiments showed that LTP is preferentially induced when trains of high-frequency pulses are applied to the theta wave peak [70]. In contrast, LTD can be generated by trains applied to the trough of theta oscillation, allowing the network to undergo a bidirectional modulation dependent on spike timing [71]. In another set of experiments, Poe et al. [72] showed in freely behaving rats that hippocampal neurons displayed a theta peak-firing activity, during waking and REMS, if exposed to a novel environment, but reversed to trough-firing patterns as the rats got acquainted to the place. Such phase precession suggests a mechanism in which LTP encodes memory for novelty, whereas LTD encodes the lack of new features to memorize. Other studies have shown that spike-phase precession naturally occurs when animals traverse place fields of CA1 cells, pointing out that this phenomenon can contribute to a more general synaptic plasticity modulation [73,74]. Gamma oscillations, on the other hand, are thought to synchronize spatially distant neuronal populations and organize their activity in order to build multimodal perceptual representations, attention, and memory [75–79]. Direct support for the participation of gamma rhythm in synaptic plasticity events has been provided by works showing that synchronous gamma oscillations in two brain regions can cause long-lasting (>1 h) potentiation of recurrent excitatory synapses in hippocampal area CA1 [80,81]. In humans, chronic intracranial electrodes implanted in the mesial temporal lobe for seizure monitoring have shown that gamma activity is specifically modulated during a word recognition memory task and entrained to the ongoing theta cycle [82].

Studies in behaving animals showed that perforant path stimulation applied during AWi and SWS induced larger fEPSPS in the dentate gyrus than stimulation applied during AWe and REMS [83,84]. After avoidance learning, LTP could not be induced during alert wakefulness, but occurred in REMS. Also in the dentate gyrus, LTP was easily induced in waking and REMS but not in SWS [85]. Similar results were also obtained in CA1, showing that population-spike PPF could be induced during AWe and REMS, but were reduced or absent during AWi and SWS [86,87]. A possible explanation for these findings is that in SWS, burst firing of CA3–CA1 associated with sharp-wave synchronization and ripple transients is involved in ongoing synaptic plasticity, obliterating further synaptic changes. In fact, it has been proposed that a high Ca^{2+} influx in the hippocampus during SWS, caused by burst activity during sharp-waves, could lead to a cascade of events that are sufficient to induce synaptic plasticity in the most active connections [57]. Several lines of experimental evidence also suggest that synaptic reorganization associated with waking experiences takes place during REMS. They include: (1) increase in REMS following learning [88,89]; (2) memory retrieval impairment after REMS deprivation [23–25,27,90–93]; (3) synaptic plasticity impairment following REMS deprivation [30,94,95]; (4) learning improvement after activation of the pontine P-wave generator [96]; (5) activity-dependent neuronal reactivation during sleep following experience [97–101]; and (6) experience- and plasticity-dependent gene expression in REMS [102,103]. Other molecular changes that characterize sleep compared to waking state may also contribute to its role in offline synaptic reorganization [104–106].

5. Interactions between epilepsy and the sleep–wake cycle

It is well demonstrated that there is a reciprocal interaction between epilepsy and sleep. Epileptic seizures interfere with normal sleep patterns, possibly affecting the arousal level and daytime cognitive performance, whereas various sleep states have particular effects on the appearance of interictal epileptiform discharges (IEDs) and the occurrence of certain types of seizures [34,107,108] (Fig. 4). In general, IEDs are more likely to start and propagate during the synchronized SWS state than during REMS asynchrony. Although IEDs may also occur during REMS, its typical atonia prevents seizure expression [32]. Clinical studies have shown that a number of epileptic syndromes express themselves more often during SWS [107]. One of the most striking cases is the syndrome of continuous spike-wave activity during slow-wave sleep, defined by having an EEG pattern consisting of generalized slow-spike-wave discharges present for 85–90% of slow-wave sleep and relatively suppressed during REM sleep and wakefulness [34]. A high incidence of spike-wave seizures during sleep is also reported in children with absence epilepsy [109] and Lennox–Gastaut syndrome [110]. In these cases, recurrent spike-wave complexes dominate the EEG and are thought to be the transformation of slow sleep oscillations into paroxysmal discharges [111,112]. Frontal seizures are also known to occur more often during sleep. A review of 100 frontal cases showed that sudden awakening was associated with seizures in 28% of the pa-

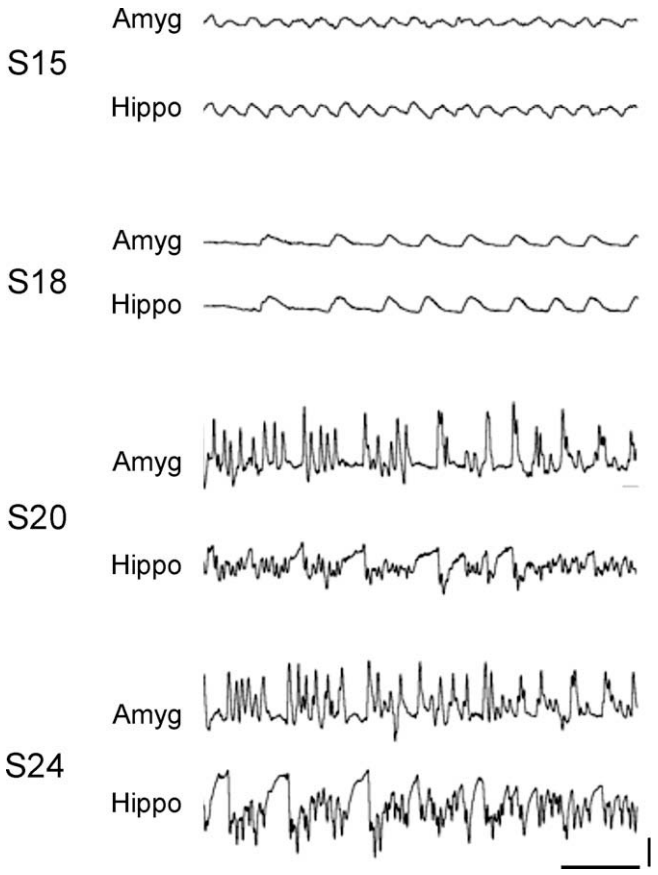

Fig. 4. Ictal EEGs recorded from the hippocampus (Hippo) and amygdala (Amyg) during audiogenic kindling in rats. S15–S24 correspond to recordings during sound stimuli Nos. 15, 18, 20 (From a total of 32 sound stimuli; 110dB SPL; 2x/day, 16days), and 24. Early-seizures (S15, S18) were short and associated with low-frequency (1 Hz) synchronization between Hippo and Amyg during postictal period. In S20 and S24, animals underwent stereotyped limbic seizures: head and forepaw myoclonus associated with high-frequency paroxysms in the Hippo and low-frequency synchronization in Amyg. Calibration: 0.5 s, horizontal bar; 400 μV, vertical bar.

tients during SWS (stages 3 and 4), but only 3% during REMS. In addition, compared to routine EEG, polysomnography had a better discriminative power to detect patients with clear ictal IEDs [113]. In a group of 188 patients with complex partial seizures (1116 seizures in total, including both frontal and temporal lobe seizures), it was shown that 35% of sleep seizures underwent secondary generalization compared to 18% of those starting in wakefulness [114]. In addition to the synchronization role of slow-waves during sleep, a recent study showed the involvement of ripple oscillations (~100–200 Hz) in temporal lobe epilepsy. Interestingly, ripples were associated with the epileptogenic focus and correlated with the degree of hippocampal sclerosis and neuronal loss [115,116].

6. Can synaptic plasticity during sleep affect epileptic circuits?

Most of the studies reported so far were limited to showing correlations between sleep states and IEDs/seizures and vice versa. They did not try to answer the question of whether seizures occurring in sleep have a different impact in the epileptic circuit compared to seizures occurring in wakefulness. Such investigation would give us a better insight into the cellular phenomena activated following seizures during sleep and waking and help us to evaluate pathophysiological brain responses observed in sleep- and wake-prevalent epilepsies.

Some of the questions we may want to answer are: (1) Do synaptic reorganization events that normally occur during sleep affect epileptogenic networks? (2) Are epileptogenic circuits reactivated during sleep? (3) If so, are they reamplified, attenuated, or unaffected during sleep? (4) Is seizure-induced molecular plasticity amplified during sleep? (5) What is the effect of the particular sleep neurochemistry? (6) Do seizures during development impair synaptic stabilization supposed to occur in sleep? (7) Does sleep contribute to axonal sprouting through neurotrophin expression? To our knowledge, very little is known about such interactions. So, considering what we have discussed before, we will present some ideas and possible ways to test the effect of sleep on epileptic circuits.

As mentioned before, the same neurons that are active during the waking state tend to be reactivated during the subsequent SWS state. If that occurs following regular exploratory spatial behavior, we suppose that a much stronger reactivation should take place in a recently active epileptic network, during either wakefulness or sleep. In the case of memory formation, it is postulated that such reactivation would be important for memory consolidation during sleep. However, in epileptic circuits, that could strengthen a set of unstable connections and reverberate IEDs in sleep, with the eventual recruitment of nonepileptic networks over days or years. Seizure expression would depend on the degree of reactivation and if it occurred in SWS or REMS. In addition, such reactivation could also be accompanied by molecular changes in the same circuitry as a result of high Ca^{2+} influx and activation of signaling cascades during SWS, promoting structural changes in specific epileptic connections [57,117]. All these events would be taking place under low levels of the major modulatory brain systems: acetylcholine, serotonin, noradrenalin, dopamine, and histamine. During REMS, the cholinergic and dopaminergic activity could modulate synaptic plasticity in those preactivated synapses and amplify them. In addition, sleep is usually associated with a reduced background level of brain gene expression in the absence of new experiences for the animal. This would also contribute to a higher signal-to-noise gene expression ratio in sleep for those epileptic circuits previously activated in the waking state.

In this context, sleep and waking seizures can differ from each other in the neuronal activation pattern, the neurochemical/molecular environment in which seizures occur, and the time to sleep onset. Seizures occurring in sleep eventually lead to abrupt waking or sleep disturbance, which can reset the brain to a state similar to AWi and then return to sleep again. In seizures during waking, it would take much longer until the next sleep onset. These differences could affect the degree of neuronal reactivation and synaptic plasticity during sleep.

Considering the need to use animal models in which we can control the exact moment of each seizure, the kindling model would be a good choice [118–120]. Amygdaloid, hippocampal, or audiogenic kindling induces a gradual recruitment of circuits that are amenable to study the epileptogenesis process (Fig. 4). In some cases, it is also known to produce spontaneous seizures, which should be avoided. In such models, it would be possible to trigger seizures during "daytime" or "nighttime" and investigate their effects on neuronal reactivation, synaptic plasticity (PPF, PPI, LTP, and LTD) in specific neural pathways, and the anatomical, cellular, and molecular changes in different brain regions in both sleep and wakefulness.

Therefore, it is possible that part of our interpretation and approach to sleep-prevalent epilepsies is lacking in a better knowledge of brain plasticity events occurring during sleep. Both sleep and waking seizures can be affected by brain activation during sleep, but we still do not know what happens in the brain at that time. Further questions still remain unanswered regarding (1) the mechanisms by which SWS oscillations interact with cortical

and subcortical epileptic circuits seen in various types of epilepsy; (2) the effects of sleep-associated IEDs and awake-associated IEDs on the patient's cognitive performance; and (3) the short- and long-term effects of sleep-associated IEDs in the organization of adjacent nonepileptic circuits compared to the effects of awake-associated IEDs.

Acknowledgments

We thank all the students from the lab for fruitful discussions. We acknowledge grant support from CAPES-PRODOC, FAPESP, and CNPq.

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