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Local Origin of Slow EEG Waves during Sleep

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Neuronal activity mediating EEG slow waves consists of synchronous alternation of intracellular active and silent states. Recent data demonstrate that each active state of a sleep slow wave originates in a particular cortical location and propagate to involve other cortical areas. Preferential sites of origin of these waves are: the frontal cortex in adult humans, the associative cortex in cats and the somatosensory cortex in mice. In the site of origin of these slow waves any neuron can initiate a particular cycle, however there are neuronal groups with high likelihood of triggering a particular cycle. In epileptic patients, these neurons are mostly located in superficial layers, but in healthy experimental animals, populations of intrinsically bursting neurons with a high probability of triggering spontaneous active states have been found in deeper cortical layers.

Keywords: *sleep, wave, electrophysiology, cortex, thalamus, slow oscillation, intrinsic current, synaptic plasticity.*

ЛОКАЛЬНОЕ КОРКОВОЕ ВОЗНИКНОВЕНИЕ МЕДЛЕННЫХ ВОЛН ЭЭГ ВО ВРЕМЯ СНА

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Известно, что нейронная корковая активация, вызывающая медленные волны ЭЭГ во время сна, состоит из синхронного чередования внутриклеточных процессов – активного и пассивного состояний нейронов. В обзоре представлены современные данные, показывающие, что активное возникновение каждой медленной волны во время сна начинается в определенной области коры мозга и распространяется на остальные области коры, вовлекая их в интегральную медленноволновую активность. Существуют предпочтительные зоны возникновения этих волн: лобная кора у взрослого человека, ассоциативная кора у кошек и соматосенсорная кора у мышей. В корковой области генеза медленных волн любой нейрон может начать новый цикл, однако существуют определенные триггерные группы нейронов, у которых более высокая вероятность запуска медленноволновой активности. У пациентов с эпилепсией эти нейроны расположены по большей части в поверхностных слоях коры, но у здоровых экспериментальных животных популяции триггерных нейронов, определяющие генез медленных волн, расположены в более глубоких слоях коры.

Ключевые слова: *сон, волны ЭЭГ, электрофизиология, кора, таламус, медленноволновая активность, внутренние токи, синаптическая пластичность.*

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On a time scale of hundreds of milliseconds, one could detect two major states of cortical network: active and silent. Active network states are characterized by intensive synaptic activities (both excitatory and inhibitory), activation of intrinsic neuronal currents and neuronal firing. Silent network states or periods of disfacilitation are dominated by leak current and some non-inacti-

vating intrinsic currents (i.e. K^+ inward rectifying current). Active states of cortical network can be found during any state of vigilance. In normal conditions, silent network states can be recorded only during slow-wave sleep (SWS) [65, 73, 74]. The major questions of this review are: How the active states are generated when all connected (afferent) neurons are in silent state, and how the cortical silent states are generated when all cortical neurons are depolarized, fire, i.e. interact.

SLOW-WAVES AND SLEEP ANSTHESIA, AND SEIZURES

There are three major states of vigilance: wake, SWS and paradoxical or rapid eye movement (REM) sleep. During both waking state and REM sleep the EEG is activated (therefore these states are called activated states) and cortical neurons are relatively depolarized; most of them fire action potentials [44, 49, 65, 73, 74]. Since early studies it was shown that the majors part of sleep (now called SWS) is dominated by slow waves repeated with a frequency of about 1 Hz [5]. It was later shown on anesthetized animals that the depth-positive (surface-negative) waves of cortical field potential are mediated by a long-lasting hyperpolarization of cortical neurons and that depth-negative (surface-positive) waves of filed potential are mediated by depolarization and firing of cortical neurons. On gross scale a similar behavior was reported for pyramidal cells and interneurons.

Anesthesia is often used as a model of slow-wave sleep [11, 13, 64, 84]. Some features of neuronal behavior observed during sleep and under anesthesia are similar. For example during both these states the depth-positive waves of the EEG are characterized by neuronal hyperpolarization and silence whether depth-negative waves of the EEG are characterized by neuronal depolarization, vigorous synaptic activities and firing [18, 73]. During both states, SWS and anesthesia, the input resistance of cortical neurons is higher during silent states as compare to active states [20, 65]. However, there are also some remarkable differences. The slow-wave and spindle wave power is lower and the gamma power is higher under ketamine-xylazine anesthesia than during sleep. With this anesthesia the duration of silent states is longer than during natural SWS. The amplitude of slow waves is area specific during sleep and it is uniformed under anesthesia [11]. Obviously, different anesthetics induce different patterns of activity that replicate (model) different patterns of sleep. The frequency of slow oscillation is higher under ketamine-xylazine anesthesia as compared to urethane anesthesia [55]. Barbiturate anesthesia induces powerful spindle activities that represent a good model of stage 2 sleep [17, 19]. However, during sleep there are at least two types of spindles (fast and slow), which have different cortical distribution [43]. To the best of my knowledge, there are no experimental models that reproduce two types of spindles. The slow sleep spindles and spindles produced by barbiturate anesthesia have frequency 9–12 Hz. The fast sleep spindles have frequency 12–15 Hz that is faster than spindles recorded under anesthesia. Therefore, using just the criterion of frequency one may consider that barbiturate anesthesia is an excellent model of slow spindles. However, similarly to anesthesia conditions [16, 68], which were also reproduced in modeling experiments [6] the fast but not slow sleep spindles were synchronized with depolarizing components of the slow oscillation [43]. All together this indicates that the known mechanisms of spindle generation investigated in anesthetized animals [62] and thalamic slices [81] may not be identical to the mechanisms of spindles generation in human brain during sleep.

Epilepsy is a term that is used to define a set of about 40 different neurological diseases characterized by occurrence of unprovoked seizures. Because the main focus of the current review is generation of neocortical slow waves, I will focus on neocortical epilepsy. A vast majority of neocortical seizures, the seizures triggered by neocortical activities, are nocturnal, namely they occur either during sleep or during transitions to or from SWS [67]. Neocortical seizures are primarily focal and often become secondarily generalized tonic-clonic seizures [23]. Electrographically, these seizures are most often composed of spike-wave/polyspike-wave (SW/PSW) electroencephalographic (EEG) discharges at 1.0–2.5 Hz and runs of fast spikes at 7–16 Hz. However, on some occasions neocortical seizures are characterized by SW complexes at approximately 3 Hz. Spontaneously occurring SW complexes at 1–2.5 Hz and fast runs at 7–16 Hz develop without discontinuity from slow (mainly 0.5–0.9 Hz) cortically generated oscillations [60, 77]. In ketamine-xylazine anesthetized cats the spontaneous seizures last on average close to 40 s and 70–80% of time they are composed of SW complexes [8]. During fast runs the membrane potential of cortical neurons oscillate with frequencies similar, but not identical to the EEG and the amplitude of these

oscillations is lower as compare to the SW complexes [8]. During SW complexes the membrane potential of cortical neurons oscillate in phase with the EEG and like during sleep slow oscillation the depth-positive EEG waves are associated with neuronal hyperpolarization and silence while depth-negative waves of EEG are associated with neuronal depolarization and firing [59, 77]. Therefore, on gross scale the activity of cortical neurons during SW complexes of seizures resembles their activity during slow oscillation of sleep. However, there are some critical differences. Silent phases of sleep slow oscillation are periods of disfacilitiation, characterized by absence of synaptic activity and dominated by leak current [20, 70, 73]. Active phases of slow oscillation are generated almost exclusively by a well-tuned interplay of excitatory and inhibitory conductances [30, 49, 73]. During seizures, in addition to leak-current-dependent potential the silent phases are also helped with Ca^{2+}- activated (and likely Na^{+}) K^{+} currents [67, 72]. Profound hyperpolarization and increased extracellular concentration of K^{+} strongly activate h-current (hyperpolarization activated depolarizing current) that leads to the generation of the next depolarizing period [69]. Due to reduced extracellular concentration of Ca^{2+} the synaptic activities (excitatory and inhibitory) during depolarizing phases of seizures are reduced, and Cl^{-}-dependent inhibitory potentials become depolarizing; however, persistent Na^{+} and high threshold Ca^{2+} currents strongly contribute to neuronal depolarization [66, 67, 72, 75, 77]. Altogether, it results in a much stronger depolarization of cortical neurons during seizure as compare to sleep slow oscillation. Such a strong depolarization often leads to spike inactivation. These data indicate that despite some apparent similarities at the level of filed potential and intracellular activities, the mechanisms of generation of silent and active phases during slow oscillation and during SW complexes are fundamentally different.

ORIGIN OF SLOW WAVES: CORTEX VS. THALAMUS

Slow waves of slow oscillation orchestrate other oscillatory activities [58]. In fact, the fast spindles, beta, gamma and ripple oscillations occur exclusively over active states of slow oscillation. Thus, the other rhythmic events are secondary to the slow oscillation. The question is where do the slow waves originate? Initial studies pointed to intracortical origin of slow oscillation. This conclusion is based on three main findings: (a) Cortical slow oscillation was observed in cats two days after kainic acid lesion of thalamus [63] or in isolated neocortex [71]; (b) in one hemisphere decorticated cats, the slow oscillation was absent in the thalamus on the side of decortication, but it was present in the thalamus of intact hemisphere [76], and (c) the slow oscillation was obtained in neocortical slices from ferrets [53] and cats [54]. These studies conducted on carnivores point to exclusive cortical origin of the slow oscillation. Slow oscillation was also recorded from cortex in multiple experiments conducted on rodents [13, 36, 42, 55, 82, 83]. Isolated spontaneous active periods were obtained in neocortical slices of rodents [21, 39]. However, despite multiple attempts in multiple labs the reliable robust rhythmic slow oscillation was not reported in neocortical slices of rodent cortex [54]. The absence of reliable slow oscillation in slices obtained from rodent brain can be due to the absence in this order of mammals so-called patchy intracortical connectivity, which is present in cats [29], ferrets [48] and primates [38]. Therefore, the intracortical connectivity of rodents lacks some essential elements that are likely critical for the generation of slow oscillation.

Slow oscillation is essential component of brain activities during sleep. Sleep pressure, measured as power of slow waves progressively increases during day, till the onset of sleep [7]. *In vitro* experiments on cortical slices demonstrate that ability of rodent neocortex to generate slow oscillation is small. It is likely that rodents developed adaptive changes enabling other brain structure to contribute to the establishment of this essential rhythm. Resent studies demonstrated that thalamocortical neurons from thalamic slices from rodent brain, subjected to application of 100 μM trans-ACPD (metabotropic glutamate receptor agonist) were able to generate slow oscillation [33, 85]. This led to a concept of secondary thalamic oscillator contributing to cortical slow oscillation [22]. *In vivo* experiments on anesthetized rats demonstrated that a large number of thalalmocortical neurons could fire prior to the onset of active phases of cortical slow waves [57, 79]. All this indicates that in rodent brain, the thalamus can play an important, if not leading role in the generation of slow oscillation. This might not be the case in carnivores, in which the slow oscillation is generated in different degree isolated cortical preparations [3, 53, 63, 71] and in human in whom isolated cortex may even develop paroxysmal discharges [26, 27].

ORIGIN OF SLOW WAVES: HORISONTAL AND VERTICAL PROPAGATION

Every cycle of slow oscillation can originate from any part of the cortex and propagate toward other areas. However, there are preferential sites of origin of slow waves. In adult human the slow waves can originate at any cortical location, but most commonly they start in frontal areas and from these areas they propagate to involve other cortical regions [9, 40]. The sites of preferential origin of slow waves are not fixed. In young human (2–8 years) the slow waves start preferentially in occipital areas, than strongest power of slow waves move to parietal areas (8–14 years) to become highest in frontal areas after the age of 14 years [35]. In cats, like in human, each active state of slow wave has a preferential site of origin and propagate toward other areas [80]. Most commonly active states in cats originate in parietal cortex at the border of area 5 and 7 [80], where the neurons show longest silent states and the slow waves are of highest amplitude [11]. Propagation of active state onsets was also found in mice, in which active states commonly originate at the border of motor and somatosensory corties [42, 50]. Interestingly, the onset of silent network states occurred more synchronously than onset of active states [80] suggesting implication of long-range synaptic mechanism in termination of active network states during slow oscillation. Pathological processes shift the preferential sites of origin of sleep slow waves. In epileptic patients, most of slow waves are local; preferentially originate in medial prefrontal cortex and if propagate, they invade medial temporal lobe and hippocampus [45]. Seemingly, in cats undergoing trauma-induced epileptogenesis, the slow wave activities start around traumatized cortex [46, 78].

How and where exactly the cortical active states start when all the neurons are silent? There should be a first neuron that is depolarized to the firing threshold and the firing of this neuron must effectively engage target cells into the active state. There are two main possibilities for the neuron to fire. One possibility is that a hyperpolarization achieved during silent state activates h current, that depolarize the first neuron to the firing threshold. Indeed, in neocortical slices from ferret visual cortex the layer 5 pyramidal neurons revel depolarizing sag (suggesting the presence of h current) that bring these neurons to the firing [53]. However, the h current in neocortical neurons is weak [69] and even in conditions of bath solution that increase neuronal excitability it triggers slow oscillation with a period longer than 3 s [53], while a typical period of slow oscillation lasts ≈1 s [64]. Thus, it is unlikely that the h current based mechanism is implicated in the generation of slow oscillation in intact cortex. Another possibility is that spike independent neurotransmitter release (minis [34]) leads to an occasional summation of depolarizing events; activate some inward current (i.e. persistent sodium current) that depolarize neurons to the threshold of action potential generation [12, 71]. Because of stochastic nature of spontaneous neurotransmitter release, this mechanism should be more efficient in neurons possessing larger number of synapses. Indeed, layer 5 neurons are by far the biggest cortical neurons with 50.000–60.000 synapses [25]. Due to multiple mechanisms of dendritic democracy [31, 51], even remote synapses can efficiently depolarize somatic compartment of a neuron. In addition, a large number of layer 5 neurons are intrinsically bursting [15], thus, they are in a position to excite efficiently their targets [37, 71]. Extra- and intracellular recordings from rats and cat neocortex demonstrated that indeed the deep layer (presumably layer 5) neurons are the first to be depolarized at the onset of new active state, they are the first to fire action potentials and they generate larger number of action potentials during active periods of slow waves [12, 52]. Surprisingly, intracortical recordings from human epileptic patients demonstrate that active states start predominantly from superficial cortical layers [10, 24]. Does it suggest that in terms of sleep slow wave the neocortex of human is fundamentally different from animals or that epileptic brain is different from normal brain? Our current experiments on cats with cortical trauma show that during epileptogenesis lasting several months, the most likely site of origin of slow waves moves from deep layers to the more superficial layers (Avramescu, Timofeev, unpublished). This change in the origin of slow waves can be explained by a progressive loss of deeply laying neurons occurring on a background of increased connectivity among remaining neurons [1, 2]. This suggests that in healthy human subjects, the slow waves of sleep can originate in deep cortical layers.

As I mentioned earlier, the active states are maintained via recurrent excitatory and inhibitory interactions [30, 49, 56]. How do active states terminate thus generating silent states and creating slow waves? Previous computational modeling studies suggested that termination of active network states can be mediated via short-term synaptic depression or activation of Ca^{2+}- or Na^{+}-activated K^{+} currents [4, 14, 32]. All these

mechanisms are cell specific and if they are in place the termination of active states should occur at different times in different neurons. Our previous study demonstrated that the termination of active states occurred more synchronously than their initiation [80]. This implies the presence of a network mechanism (s) with abilities of long-range synchronization. Such a mechanism should likely rely on active inhibition. Indeed, the first intracellular study of cortical slow oscillation demonstrated that a modest Cl^--dependent inhibition was detected at the onset of silent states [64]. Two hypothetical mechanisms are possible: (a) Remote cortical territories receive direct widespread inhibitory input from subcortical structures or (b) widespread excitatory inputs provide synchronous activation of a subset of cortical inhibitory interneurons that initiate silent state. In any case, because the active states are maintained by a recurrent interaction of inhibitory and excitatory activities, only a brief, but synchronous inhibition in some subset of excitatory neurons would suffice to stop the active state. In our current experiments, we are testing these two possibilities. To test whether extracortical inhibition play a role in termination of cortical active states, we recorded extracellular unit activities in the magnocellular preoptic nucleus/substantia innominata region, which projects to the cerebral cortex and roughly 50% of these projections are GABAergic. We did not find any relation of spiking of these cells with the cortical slow oscillation (Chauvette, Timofeev, unpublished). These results suggest, although not exclude, that extracortical GABAergic projections do not play a role in the control of cortical slow oscillation. An earlier study described a subset of cortical fast spiking inhibitory interneurons that fire preferentially at the end of cortical active state [47]. These neurons, if synchronously activated over large cortical territories, can terminate active state. In order to terminate it synchronously, these neurons have to receive some common input, which should come from a remote place. To test this possibility we used neocortical slab preparation. Similar to intact cortex, in neocortical slabs the active periods started at some location and propagated to involve the whole isolated island [71]. Our recent field potential experiments show that after isolation of the slab, the active states terminate in different location with significant (hundreds of milliseconds) delays (Lemieux, Timofeev, in preparation), indicating that extracortical inputs are needed to synchronize termination of active states.

CONCLUSIONS

1. During SWS and SW discharges cortical neurons oscillate between active and silent states.

2. Synchronous generation of these states creates slow waves of the EEG.

3. Active cortical states during sleep are triggered by spontaneous, spike-independent mediator release, primarily in large pyramidal neurons. H-current contributes to the triggering of active states during seizures.

4. Preferential location of active state onset varies across species.

5. Active states are maintained by recurrent activities of excitatory and inhibitory neurons with some contribution of intrinsic neuronal currents.

6. Active states are terminated due to synaptic depression and activation of hyperpolarizing intrinsic currents.

7. A subset of intracortical inhibitory neurons, driven by extracortical inputs, contributes to the synchronous termination of active states.

PERSPECTIVE

Most of the listed above statements are confirmed experimentally and further studies will provide a better details and exact values of different currents, synaptic weights etc. that contribute to the generation of active and silent cortical states. The major remaining question is why active states are not terminated during REM sleep and normal (not sleep deprived) waking states? There is no direct answer to this question, thus I will reveal some possibilities. The main factor that might be responsible for the absence of silent states is the high levels of release of neuromodulators in thalamocortical system [61]. Because the silent states are absent during both waking state and REM sleep and out of three classical neuromodulators only acetylcholine levels are high during both these states, the effects of acetylcholine are likely the factors to mediate persistent cortical activities. It is likely that increased levels of acetylcholine reduce hyperpolarizing influences. Two facts are already evident: (a) acetylcholine is known to reduce efficacy of several K^+ currents (M-current and Ca^{2+}-activated K^+ current) [41] therefore reducing hyperpolarizing drive; (b) activation of muscarinic acetylcholine receptors reduces synaptic depression in thalamocortical and intracortical synapses [28]. It is also possible that cholinergic activities reduce firing of extracortical neurons providing synchronous drive to cortical inhibitory interneurons that fire at the onset of si-

lent states. Further investigations need to disclose the exact conditions that prevent generation of cortical silent states mediating waking activties.

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