CHAPTER 1

Neuronal Oscillations in the Thalamocortical System during Sleeping and Waking States

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All normal brain processes occur over three main states of vigilance: wake, slow-wave sleep, and REM sleep. These states can be subdivided further to passive and active wakefulness, three to four stages of slow-wave sleep, and active and passive REM sleep. There are also abnormal states of the brain like paroxysmal seizure activities or brain activities generated under anesthesia conditions. The states of vigilance by themselves originate via interaction of circadian and homeostatic processes (Achermann & Borbely, 2003; Borbely, Baumann, Brandeis, Strauch, & Lehmann, 1981) with a leading role of interactions between suprachiasmstic nucleus and hypothalamic regions (Fuller, Sherman, Pedersen, Saper, & Lu, 2011; Saper, Scammell, & Lu, 2005). Different brain states are expressed as different forms of global electrographic activities recorded from a brain surface (elecrocorticogram), which are reflected on a head surface and recorded as an electroencephalogram (EEG). These global electrical activities are mediated by synchronous synaptic activities of neurons. Synchronous de- or hyperpolarization of neighboring neurons will generate large amplitude global waves, the asynchronous activities of neurons will not generate the global field potential signals at all, and intermediates neuronal synchrony will produce field potential waves of intermediate amplitude. While the states of vigilance by themselves originate in suprachiasmstic and hypothalamic regions and are transmitted to the other brain structures via ascending activating systems (Steriade & McCarley, 2005), the top level of the brain, primarily the thalamocortical system, generates the electrical activities that are characteristic to different states of vigilance.

NEURONAL SYNCHRONIZATION

Neuronal synchronization requires some form of interactions between neurons. I will only briefly overview this aspect. To understand the

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processes of neuronal synchronization, one has to separate local and long-range synchronization. Local synchronization is required to produce simultaneous de- or hyperpolarization of a local group of neurons that mediates generation of local field potentials; and long-range synchronization synchronizes the local field potentials generated at some distance. The amplitude of field potential recordings with one electrode will provide information on levels of local neuronal synchrony. Multisite recordings are used to investigate long-range synchronization.

The most investigated aspect of neuronal interactions are *chemical synaptic interactions* (Eccles, 1964). Action potentials generated in excitatory neurons will propagate to synaptic boutons and release excitatory neurotransmitter (mainly glutamate within the thalamocortical system). The amplitude of single-axon induced excitatory postsynaptic potentials (EPSPs) is small from 0.1 to several millivolts with overall mean less than 2 mV (Thomson, West, Wang, & Bannister, 2002). This neurotransmitter will exert depolarizing action on targets. Because each axon forms multiple contacts with target neurons it can produce sufficient local field effects if the target neurons are located in proximity. If several neurons excite the same group of target cells nearly simultaneously, the overall postsynaptic effect will definitely be larger due to spatial summation. That will produce summated effects, which are sensed at the field potential level. Multiple excitatory connections are formed by long-axon neurons; therefore they are well positioned to mediate long-range synchrony. Activities of inhibitory neurons within the thalamocortical system release mainly GABA, an inhibitory neurotransmitter. All known cortical interneurons have a short-axon (Markram et al., 2004; Somogyi, Tamás, Lujan, & Buhl, 1998), which contacts multiple target neurons in a local network. Therefore, cortical interneurons can contribute to local, but not long-range synchronization. This is not the case for other inhibitory cells. During development, GABAergic neurons of thalamic reticular (RE) nucleus form variable patterns of connectivity from a compact, focal projection to a widespread, diffuse projection encompassing large areas of Ventro-Basal complex (VB) (Cox, Huguenard, & Prince, 1996). Indirect action of reticular thalamic neurons that exerts diffuse projections onto thalamocotical neurons could likely be detected as synchronous field potential events over some large cortical areas when thalamocortical neurons will fire action potentials. Neuronal constellations outside the thalamocortical system may also to cortical synchronization. A recent study (Eschenko, Magri, Panzeri, & Sara, 2012) has demonstrated that in rats, the locus coreleus neurons fire in phase with cortical slow waves and they even

preceded onsets of cortical neuronal firing, suggesting a contribution of locus coreleus not only in setting up general cortical excitability, but also in influencing the cortical synchronization processes.

The next mechanism contributing to neuronal synchronization is *electrical coupling* between cells that is mediated by gap junctions. The astrocytic network is tightly connected via gap junctions (Mugnaini, 1986). Gap junctions were also found between multiple groups of cortical interneurons (Galarreta & Hestrin, 1999; Gibson, Beierlein, & Connors, 1999). Electrical coupling was demonstrated between neurons of reticular thalamic nucleus (Fuentealba et al., 2004; Landisman et al., 2002). Dye coupling, presence of spikelets, and modeling experiments suggest the existence of electrical coupling between axons of hippocampal pyramidal cells (Schmitz et al., 2001; Vigmond, Perez Velazquez, Valiante, Bardakjian, & Carlen, 1997). A single study has found spikelets, an accepted signature of electrical coupling, in thalamocortical neurons (Hughes, Blethyn, Cope, & Crunelli, 2002). Indirect data on electrical coupling between thalamocortical neurons and axo-axonal coupling are so far not supported by demonstration of the presence of gap junctions. The gap junctions, mediating electrical coupling, form high resistance contacts between connected cells; therefore, they act as low-pass filters (Galarreta & Hestrin, 2001). Confirmed gap junctions are formed within dendritic arbor of connected cells, therefore, they can contribute to the local synchronization only.

Ephaptic interactions constitute another mechanism of neuronal synchronization. Changes in neuronal membrane potential produce extracellular fields that affect the excitability of neighboring cells (Jefferys, 1995). The extracellular fields produced by a single neuron are weak, however, when a local population of neurons generate nearly simultaneous excitation or inhibition, their summated effects can significantly influence the excitability of neighboring neurons, contributing to local synchronization. External electric field applied with intensities comparable to endogenous fields applied to cortical slices modulated cortical slow oscillation (Frohlich & McCormick, 2010). During seizure activity, the extracellular space reduces and the effects of ephaptic interactions increase (Jefferys, 1995).

Neuronal activities are associated with movement of ions across membrane due to activation of ligand- or voltage-controlled channels. Because extracellular space in the brain is about 20% of total brain volume (Syková, 2004; Sykova & Nicholson, 2008) and an activation of ionic pumps, ionic diffusion, etc., is a time-dependent process, the neuronal activities alter *extracellular concentration of implicated ions* (Somjen, 2002). Changes are

temporal and local, but on a short timescale they affect neuronal excitability. For example, during active states of cortical slow oscillation, due to activation of synaptic currents (primarily NMDA receptor-mediated) and Ca^{2+} gated intrinsic channels, the extracellular concentration of Ca^{2+} decreases from 1.2 mM to 1.0 mM (Crochet, Chauvette, Boucetta, & Timofeev, 2005; Massimini & Amzica, 2001). This leads to a dramatic increase in synaptic failure rates (up to 80%) (Crochet, et al., 2005). Dramatic changes of ionic concentrations occur during seizure activity. In these conditions, the extracellular Ca^{2+} drops to below 0.5 mM (Amzica, Massimini, & Manfridi, 2002; Heinemann, Lux, & Gutnick, 1977; Pumain, Kurcewicz, & Louvel, 1983) and extracellular K^+ increases to 7–18 mM (Amzica et al., 2002; Moody, Futamachi, & Prince, 1974; Prince, Lux, & Neher, 1973). This results in an impairment of chemical synaptic transmission and axonal conduction of action potentials is impaired too (Seigneur & Timofeev, 2010). The reversals potential for ionic currents with implicated ions are shifted affecting overall neuronal excitability. Just some little increase in extracellular K^+ concentration and a decrease in extracellular Ca^{2+} and Mg^{2+} concentration may induce slow oscillation in neocortical slices (Reig, Gallego, Nowak, & Sanchez-Vives, 2006). Stronger changes in ion concentration occurring within physiological/pathological range have profound influence on brain network activities.

Therefore, synaptic potentials (primarily excitatory) are in a position to mediate long-range neuronal synchronization. Synaptic activities and all the other mechanisms of neuronal synchronization are local and they contribute to short-range neuronal synchronization. Local synchronous activities of neuronal groups may create propagating or travelling waves of activities that can involve large neuronal territories and can be detected as synchronous activities with shifts in the phase of oscillations (Boucetta, Chauvette, Bazhenov, & Timofeev, 2008; Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004).

BASIC THALAMOCORTICAL STATES

There are two basic states of thalamocortical network: silent and active.

During *silent states* all active conductances (intrinsic and synaptic) are inactive. Basically, during silent states the membrane potential of neurons is mediated by leak current only. This is a theoretical situation and it is unlikely that it occurs in real life. In practice, some inactivating intrinsic currents, for example inward rectifying current, can also be active.

Activities of these currents preset so-called *resting membrane potential* of neurons. The resting membrane potential of cortical neurons is situated somewhere between −70 mV and −80 mV. Given that equilibrium potential for leak current is around −95 mV (McCormick, 1999), an activation of inward rectifying currents appears to play a role in the mediation of the resting membrane potential. The resting membrane potential can be recorded from neurons in nonoscillating slices maintained *in vitro*; it can also be recorded from cortical neurons during silent phases of sleep slow oscillation (see below). Because very few current are active during network silent states, the input resistance of neurons during silent states is higher as compared to active states (Contreras, Timofeev, & Steriade, 1996; Steriade, Timofeev, & Grenier, 2001).

Active states are generated when active coductances either intrinsic or synaptic or both are activated. Active cortical network states are found in wake, REM sleep and active phases of slow oscillation (sleep or anesthesia). During active network states the mean membrane potential of cortical neurons is situated at somewhere around −62 mV (Steriade et al., 2001). Therefore activities of all conductances accompanying active network states depolarize cortical neurons by about 10 to 15 mV. It appears that under anesthesia conditions the excitatory and inhibitory conductances are balanced (Haider, Duque, Hasenstaub, & McCormick, 2006). However, during natural states of vigilance the inhibitory activities dominate the active network states in the majority of neurons and during all states of vigilance except a few tens of milliseconds at the onset of active states during slow-wave activity (Rudolph, Pospischil, Timofeev, & Destexhe, 2007). Although excitatory neurons outnumber inhibitory ones, the spontaneous firing rate of former is higher (Peyrache et al., 2012; Steriade et al., 2001; Timofeev, Grenier, & Steriade, 2001) and all somatic synapses are formed by inhibitory neurons giving overall stronger inhibitory influence on cell somata. The ratio of activation of intrinsic currents versus synaptic currents during active network states is unclear. Because the membrane potential of cortical neurons during active states is situated close to −60 mV, it is reasonable to assume that persistent Na^+ current (Crill, 1996) contributes to the generation of active states. Indeed, the use of QX-314 (use-dependent blocker of Na^+ channels) reduced active states not only in intact brain (Timofeev, Grenier, & Steriade, 2004), but also in neocortical slabs (Timofeev, Grenier, Bazhenov, Sejnowski, & Steriade, 2000). It is reasonable to believe that hyperpolarization activated depolarizing current and some Ca^{2+} currents also contribute to the generation of active states.

Intracellular recordings demonstrated that neuronal firing occurs during active network states only (Contreras & Steriade, 1995; Steriade et al., 2001). Active network states are accompanied with remarkable increase in membrane potential fluctuations (Steriade et al., 2001; Timofeev, Grenier, & Steriade, 2000) that appear to be mediated by synaptic events. Based on these observations it was even proposed that active network states during sleep are functionally very similar to active network states of wake (Destexhe, Rudolph, & Pare, 2003). Several facts suggest that this assumption may not be true: (a) Patch-clamp recordings from slices obtained from human brain tissue (sub-plate zone) at gestation weeks 20–21 demonstrated that a majority of neurons reveal alteration of active and silent states. However, at this time of development, the chemical synaptic connectivity is not functional (Moore, Zhou, Jakovcevski, Zecevic, & Antic, 2011). Therefore, the synaptic potentials not necessary represent an essential component of active network states. (b) As opposed to REM sleep and waking state, during slow-wave sleep the activity of neuromodulatory systems is reduced (Steriade & McCarley, 2005), which has multiple cellular effects. Among others the input resistance is reduced during active phases of slow-wave sleep as compared to the active phases of waking or REM sleep (Steriade et al., 2001). Accordingly the neuronal responsiveness during active phases of slow-wave sleep differs from that of other states of vigilance. (c) The major feature of waking in higher animals is self-awareness. In order to be self-aware some minimal time is required and this time is about 1 sec (Libet, Alberts, Wright, & Feinstein, 1967). During slow-wave sleep or anesthesia, the active network states last less than 1 sec; therefore, the major characteristic of wake is not present.

The duration of active phases of slow oscillation depends on a variety of factors. Our recent study has shown that under ketamine-xylazine anesthesia active states occupy about 80% of the total time, while during slow-wave sleep they occupy around 90% of the total time. The amplitude of slow waves, the long-range synchrony, and the high frequency oscillations are higher during anesthesia as compared to slow-wave sleep (Chauvette, Crochet, Volgushev, & Timofeev, 2011).

Active network states do not need to be depolarizing. Synchronous activities of inhibitory neurons can impose active inhibitory activities on their targets. Synchronous cortical firing during active phases of slow oscillation strongly excite inhibitory reticular thalamic neurons, which induce inhibitory postsynaptic potentials (IPSPs) in target thalamocortical neurons, which may appear in the form of spindles or long-lasting

hyperpolarization potentials (Contreras & Steriade, 1995; Fuentealba, Crochet, Timofeev, & Steriade, 2004; Timofeev, Bazhenov, Sejnowski, & Steriade, 2001; Timofeev & Steriade, 1996). In thalamocortical neurons spindles represent active hyperpolarizing states. In associative cortical areas the active inhibitory activities dominate cortical neurons during rapid eye movements of REM sleep (Timofeev, Grenier, et al., 2001).

As was mentioned above, the neuronal firing occurs during active network states. Surprisingly, the extent of spontaneous neuronal firing of individual cortical neurons is not clear yet. Intracellular recordings show that the mean firing rates were in the order of 10–15 Hz with lower rates during slow-wave sleep (Steriade et al., 2001). These numbers likely represent some overestimation, because of membrane leak induced by intracellular penetration. Similar results were obtained with extracellular single-unit recordings in which somewhat higher (Noda & Adey, 1970a, 1970b) or lower firing rates were seen (Evarts, Bental, Bihari, & Huttenlocher, 1962). However, in these studies the bias was to record activities of neurons that fire spikes, and the neurons that had sparse firing or did not fire spikes at all were not included in the database. Patch-clamp, optical, and extracellular unit recordings from superficial neurons demonstrated much lower (generally below 0.5 Hz) firing rates (Greenberg, Houweling, & Kerr, 2008; Peyrache et al., 2012; Waters & Helmchen, 2006). Multiunit recordings from different cortical depth demonstrated that indeed superficially laying neurons fire sparsely, and much higher firing rates can be observed in deep layers (Chauvette, Volgushev, & Timofeev, 2010; Sakata & Harris, 2009). However, in these studies a clear-cut separation of firing of individual neurons is impossible due to technical reasons. A number of recent studies attempt to use timing of multispike activity in order to characterize timing of onset and/or termination of active states (Eschenko et al., 2012; Hasenstaub, Sachdev, & McCormick, 2007; Vyazovskiy et al., 2009). The precision of these measurements is questionable. The averaged delay to the first spike in neurons that fire early during active states occurs usually within tens of milliseconds from the onset of active states and most neurons cease firing hundreds of milliseconds prior to the end of active states (Chauvette et al., 2011).

THALAMOCORTICAL RHYTHMIC ACTIVITIES

Thalamocortical rhythmic activities or oscillations are generated in a wide range of frequencies from 0.01 Hz to hundreds of Hz (Fig. 1.1). The mechanisms of thalamocortical oscillations are different. *Infraslow oscillation* has a

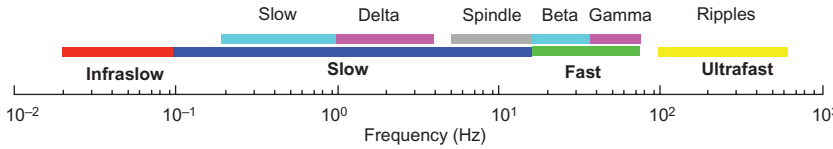

Figure 1.1 Frequency range and groups of thalamocortical oscillations. *(Modified from Bazhenov & Timofeev, 2006)*

period of cycle in the range of seconds to minutes (Aladjalova, 1957, 1962). Infraslow oscillations synchronize faster activities and modulate cortical excitability (Vanhatalo et al., 2004). The mechanisms of infraslow oscillation are unknown. This oscillation likely depends on dynamics of brain metabolism (Aladjalova, 1957; Nita et al., 2004). Multisite recordings indicate that waves of infraslow oscillation can occur nearly simultaneously at different cortical locations (Nita et al., 2004; Vanhatalo et al., 2004) suggesting that long-range synchronizing mechanisms control this type of oscillation.

Slow thalamocortical oscillations are composed of three distinct types of activities: slow oscillation, delta oscillation, and spindle oscillation (Fig. 1.1). During slow-wave sleep and some forms of anesthesia a dominant form of activity within the thalamocortical system is *slow oscillation (0.2–1 Hz)* (Steriade, Nuñez, & Amzica, 1993b; Steriade et al., 2001). During slow oscillation the entire cortical network alternates between silent (hyperpolarizing) and active (depolarizing) states. Depending on cortical area the silent states last between 100 ms and 200 ms and under ketamine-xylazine anesthesia they last between 300 ms and 400 ms (Chauvette et al., 2011). The active states last longer, 80%–90% of a cycle of slow oscillation. During silent cortical states the neurons of both reticular thalamic nucleus and projecting nuclei are also in silent state (Contreras & Steriade, 1995; Contreras, Timofeev, et al., 1996). During active states, cortical firing triggers rhythmic spike bursts of reticular thalamic neurons, which in turn induce rhythmic IPSPs in thalamocortical cells (see Figure 1 in Timofeev & Bazhenov, 2005). Recent experiments on rodents suggest that some thalamocortical neurons can actively participate in the initiation of active states (Crunelli & Hughes, 2010; Slezia, Hangya, Ulbert, & Acsady, 2011; Ushimaru, Ueta, & Kawaguchi, 2012).

Field potential recordings from neocortex in human and animal models during sleep reveal the presence of *delta oscillations (1–4 Hz)*. The delta oscillation likely has two different components, one of which originates in the neocortex and the other in the thalamus. Delta oscillation is distinct from slow oscillation, not only because of some difference in frequencies,

but also because the dynamic of the two rhythms during sleep. During sleep the delta activity declines from the first to second episodes of slow-wave sleep, while this was not observed for slow oscillation (Achermann & Borbely, 1997).

Cortical delta activity. Both surgical removal of the thalamus and recordings from neocortical slabs in chronic conditions result in the significant enhancement of neocortical delta activity (Ball, Gloor, & Schaul, 1977; Villablanca & Salinas-Zeballos, 1972). These experiments suggest that cortex itself is able to generate delta activities.

Thalamic delta is a well-known example of rhythmic activity generated intrinsically by thalamic relay neurons as a result of the interplay between their low-threshold Ca^{2+} current (I_T) and hyperpolarization-activated cation current (I_h) (McCormick & Pape, 1990). As such, the delta oscillation may be observed during deep sleep when thalamic relay neurons are hyperpolarized sufficiently to deinactivate I_T. The mechanism of single cell delta activity is the following: a long-lasting hyperpolarization of thalamic relay neuron leads to slow I_h activation that depolarizes the membrane potential and triggers rebound burst, mediated by I_T, which was deinactivated by the hyperpolarization. Both I_h (because of its voltage dependency) and I_T (because of its transient nature) inactivate during burst, so the membrane potential becomes hyperpolarized after the burst termination. This afterhyperpolarization starts in the next cycle of oscillations. Intrinsic delta oscillations in thalamocortical neurons are generated by individual neurons. Thalamocortical neurons are not connected directly. The intrinsic delta oscillation is not synchronized (Timofeev & Steriade, 1996), therefore, it cannot produce field effects at neocortical level.

Sleep spindle oscillations consist of waxing-and-waning field potentials at 7–14 Hz, which last 1–3 seconds and recur every 5–15 seconds. *In vivo*, spindle oscillations are typically observed during stage 2 of sleep or during active phases of slow-wave sleep oscillations.

In vivo, *in vitro*, and *in silico* studies suggest that the minimal substrate accounting for spindle oscillations consists in the interaction between thalamic reticular and relay cells (Steriade & Deschenes, 1984; Steriade, Deschenes, Domich, & Mulle, 1985; von Krosigk, Bal, & McCormick, 1993). Burst firing of reticular thalamic neurons induces inhibitory postsynaptic potentials in thalamocortical neurons. This deinactivates I_T, inducing burst firing in thalamocortical neurons, which, in turn, excite reticular thalamic neurons allowing the cycle to start again. Spontaneous spindle oscillations are synchronized over large cortical areas during natural sleep and barbiturate

anesthesia. After complete ipsilateral decortication, however, the long-range synchronization of thalamic spindles changes into disorganized patterns with low spatiotemporal coherence (Contreras, Destexhe, Sejnowski, & Steriade, 1996). Although cortical activities help to initiate spindles (Contreras & Steriade, 1996), persistent cortical firing depolarizes thalamic neurons at the second half of spindles, which contributes to the termination of this thalamic rhythm (Bonjean et al., 2011; Timofeev, Bazhenov, et al., 2001).

Beta (15–30 Hz) and gamma (30–80 Hz) activities occur during active cortical states (Mukovski, Chauvette, Timofeev, & Volgushev, 2007). They dominate cortical oscillations during waking state and REM sleep, and they can be found during active phases of slow oscillation. The power of beta/gamma activities under ketamine-xylazine anesthesia is a double of that recorded during natural sleep (Chauvette et al., 2011). Field potential and cellular recordings demonstrate robust synchronization of fast rhythms between connected areas of cortex and thalamus (Steriade, Contreras, Amzica, & Timofeev, 1996). There can be at least two different sources of origin of fast oscillations in neocortex. The first depends on activities in ascending structures. Indeed, it has been shown that synaptic activities in prethalamic pathways display high frequency oscillations (Castelo-Branco, Neuenschwander, & Singer, 1998; Timofeev & Steriade, 1997), which can be effectively transmitted to cerebral cortex when thalamocortical neurons are depolarized (Timofeev & Steriade, 1997). Another possible source of high frequency oscillations is intracortical. Although the exact mechanism of generation of beta/gamma oscillation is unknown, several mechanisms of their origin have been proposed (Timofeev & Bazhenov, 2005). A subset of cortical neurons called fast-rhythmic bursting cells has an intrinsic ability to generate spike bursts repeated with gamma frequency (Calvin & Sypert, 1976; Gray & McCormick, 1996; Steriade, Timofeev, Dürmüller, & Grenier, 1998). Firing of these neurons may entrain target cells into oscillatory activities creating local field potential oscillations. The second intracortical mechanism of gamma activity generation depends on the activity of inhibitory interneurons and was described both *in vitro* and with computational models (Lytton & Sejnowski, 1991; Traub, Whittington, Stanford, & Jefferys, 1996). Transitions between gamma and beta oscillations were simulated by alternating excitatory coupling pyramidal neurons and by change in K^+-conductances (Kopell, Ermentrout, Whittington, & Traub, 2000; Traub, Whittington, Buhl, Jefferys, & Faulkner, 1999).

Ripples are transient oscillations with frequency range between 100 and 600 Hz (Fig. 1.1). They can be recorded with local field potential

electrodes, but not with large EEG electrodes, suggesting that local and not long-range synchronizing mechanisms contribute to their origin. Ripples were described in hippocampus (Buzsaki, Horvath, Urioste, Hetke, & Wise, 1992) and cerebral cortex (Grenier, Timofeev, & Steriade, 2001). Usually, they occur at the beginning of active cortical states (Grenier et al., 2001; Le Van Quyen et al., 2010). In neocortex, ripples with frequency 120–200 Hz occur during normal and paroxysmal activities (Grenier et al., 2001; Grenier, Timofeev, & Steriade, 2003). This is distinct from hippocampus in which paroxysmal activities are associated with high frequency ripples (<300 Hz) (Bragin, Engel, Wilson, Fried, & Mathern, 1999), while in neocortex the high frequency ripples can be recorded in response to sensory stimuli (Jones & Barth, 1999). In addition to active inhibition (Grenier et al., 2001; Ylinen et al., 1995), the electrical coupling mediated by gap junctions contributes to the ripple synchronization (Draguhn, Traub, Schmitz, & Jefferys, 1998; Grenier et al., 2003).

ORIGIN OF SLOW WAVES: CORTEX VERSUS THALAMUS

Slow waves of slow oscillation orchestrate other oscillatory activities (Steriade, 2006). In fact spindle, beta, gamma, and ripple oscillations occur exclusively over active states of slow oscillation. Thus, the other rhythmic events are secondary to 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 with extensive chemical lesion of thalamus (Steriade, Nuñez, & Amzica, 1993a) or in isolated neocortex (Timofeev, Grenier, Bazhenov, et al., 2000); (b) in one hemisphere of 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 (Timofeev & Steriade, 1996); and (c) the slow oscillation was obtained in neocortical slices from ferrets (Sanchez-Vives & McCormick, 2000) and cats (Sanchez-Vives, Reig, Winograd, & Descalzo, 2007). 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 (Clement et al., 2008; Lau et al., 2000; Mohajerani, McVea, Fingas, & Murphy, 2010; Sharma, Wolansky, & Dickson, 2010; Vyazovskiy et al., 2011; Vyazovskiy et al., 2009). Isolated spontaneous active periods were obtained in neocortical slices of rodents (Cossart, Aronov, & Yuste, 2003; MacLean, Watson, Aaron, & Yuste, 2005). However, despite

multiple attempts in multiple labs the reliable robust rhythmic slow oscillation was not reported in neocortical slices of rodent cortex (Sanchez-Vives et al., 2007). The absence of reliable slow oscillation in slices obtained from rodent brain can be due to the absence in this order of mammals of so-called patchy intracortical connectivity, which is present in cats (Gilbert & Wiesel, 1983), ferrets (Rockland, 1985) and primates (Lund, Yoshioka, & Levitt, 1993). Therefore, the intracortical connectivity of rodents lacks some essential elements that are likely critical for the generation of slow oscillation.

Slow oscillation is an essential component of brain activities during sleep. Sleep pressure, measured as the power of slow waves, progressively increases during the day, till the onset of sleep (Borbely et al., 1981). *In vitro* experiments on cortical slices demonstrate that the ability of rodent neocortex to generate slow oscillation is small. It is likely that rodents developed adaptive changes enabling other brain structures to contribute to the establishment of this essential rhythm. Recent 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 (Hughes, Cope, Blethyn, & Crunelli, 2002; Zhu et al., 2006). This led to the concept of a secondary thalamic oscillator contributing to cortical slow oscillation (Crunelli & Hughes, 2010). *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 (Slezia et al., 2011; Ushimaru et al., 2012). 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 isolated cortical preparations (Ball et al., 1977; Sanchez-Vives & McCormick, 2000; Steriade et al., 1993a; Timofeev, Grenier, Bazhenov, et al., 2000) and in human in whom isolated cortex may even develop paroxysmal discharges (Echlin, Arnet, & Zoll, 1952; Echlin & Battista, 1963).

ORIGIN OF SLOW WAVES: HORIZONTAL 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 humans the slow waves originate most commonly in frontal areas and from these areas they propagate to involve

other cortical regions (Carrier et al., 2011; Massimini et al., 2004). 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 the strongest power of slow waves moves to parietal areas (8–14 years) to become highest in frontal areas after the age of 14 years (Kurth et al., 2010). In cats, like in humans, each active state of slow wave has a preferential site of origin and propagates toward other areas (Volgushev, Chauvette, Mukovski, & Timofeev, 2006). Most commonly active states in cats originate in parietal cortex at the border of area 5 and 7 (Volgushev et al., 2006), where the neurons show the longest silent states and the slow waves are of highest amplitude (Chauvette et al., 2011). Propagation of active state onsets was also found in mice (Mohajerani et al., 2010; Ruiz-Mejias, Ciria-Suarez, Mattia, & Sanchez-Vives, 2011). Interestingly, the onset of silent network states occurred more synchronously than the onset of active states (Volgushev et al., 2006) suggesting implication of a 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 the slow waves are local, preferentially originate in medial prefrontal cortex, and if they propagate, they invade the medial temporal lobe and hippocampus (Nir et al., 2011). Seemingly, in cats undergoing trauma-induced epileptogenesis, the slow wave activities start around traumatized cortex (Nita, Cissé, Timofeev, & Steriade, 2007; Topolnik, Steriade, & Timofeev, 2003).

How and where exactly do 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 engages 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 I_h, which depolarizes the first neuron to the firing threshold. Indeed, in neocortical slices from ferret visual cortex the layer 5 pyramidal neurons reveal depolarizing sag (suggesting the presence of h current) that bring these neurons to the firing (Sanchez-Vives & McCormick, 2000). However, the I_h in neocortical neurons is weak (Timofeev, Bazhenov, Sejnowski, & Steriade, 2002) and even in conditions of bath solution that increase neuronal excitability it triggers slow oscillation with a period longer than 3 sec (Sanchez-Vives & McCormick, 2000). Thus, it is unlikely that the I_h-based mechanism is implicated in the generation of slow oscillation in intact cortex. Another possibility is that spike-independent neurotransmitter release (minis (Katz, 1969))

leads to an occasional summation of depolarizing events, activating some inward current (i.e., persistent sodium current) that depolarizes neurons to the threshold of action potential generation (Chauvette et al., 2010; Timofeev, Grenier, Bazhenov, et al., 2000). Because of the 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 (DeFelipe & Farinas, 1992). Due to multiple mechanisms of dendritic democracy (Häusser, 2001; Rumsey & Abbott, 2006), even remote synapses can efficiently depolarize the somatic compartment of a neuron. In addition, a large number of layer 5 neurons are intrinsically bursting (Connors & Gutnick, 1990), thus, they are in a position to efficiently excite their targets (Lisman, 1997; Timofeev, Grenier, Bazhenov, et al., 2000). Extra- and intracellular recordings from rat 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 a larger number of action potentials during active periods of slow waves (Chauvette et al., 2010; Sakata & Harris, 2009). Surprisingly, intracortical recordings from human epileptic patients demonstrate that active states start predominantly from superficial cortical layers (Cash et al., 2009; Csercsa et al., 2010). Does it suggest that in terms of slow wave sleep 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 (Avramescu, Nita, & Timofeev, 2009; Avramescu & Timofeev, 2008). This suggests that in healthy human subjects, the slow waves of sleep can originate in deep cortical layers.

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