

SLOW-WAVE SLEEP: SEROTONIN, NEURONAL PLASTICITY, AND SEIZURES

M. STERIADE¹

Laboratoire de Neurophysiologie, Faculté de Médecine, Université Laval, Québec, Canada G1K 7P4

JOUVET'S SEMINAL CONTRIBUTIONS TO SLEEP RESEARCH

This paper is dedicated to my friend Michel Jouvet, the man who performed the first animal experiments (13) to localize the brainstem and forebrain structures responsible for the physiological correlates of the behavioral state he called paradoxical sleep because the increased excitability of higher brain structures was associated with motoneuronal inhibition, an alert yet paralyzed brain. Nowadays, we still use muscular atonia, described by Jouvet and Michel (18), as the physiological sign that most reliably distinguishes paradoxical sleep.

Jouvet hypothesized (15) that paradoxical sleep is a guardian of psychological personality, a reprogramming of individuality during dreaming. He also wrote a novel, *Le Château des Songes* (16), with fabulous dreams and commentaries on them by a character of the 18th century. More recently, Jouvet traced the great moments of his life together with the achievements of other neurobiologists in the field of sleep (17).

Here, I would like to state that even those of Jouvet's ideas that were apparently disconfirmed by subsequent data are now less firmly challenged and some of them are confirmed by detailed analyses at the intracellular level. I specifically refer to the theory implicating neurons in the raphe nuclei and their major transmitter, serotonin (5-hydroxytryptamine, 5-HT), in the generation of slow-wave sleep. Most experimental data supporting this theory were accumulated during the 1960s and were reviewed in Jouvet (14). Subsequent data, mainly recordings from raphe neurons across the waking-sleep cycle, have refuted the role of serotonergic neurons in the genesis of slow-wave sleep since neurons in the dorsal and other nuclei of the raphe system decrease the rates of their regular discharges when the animal passes from waking to slow-wave sleep (25, 27, 57).

While Jouvet's original claims seemed unfounded in the light of subsequent experiments, more recent results may bring back on the scene the raphe and other 5-HT neuromodulatory actions as good candidates for inducing neuronal events related to slow-wave sleep. I shall briefly mention only four series of data.

¹ Corresponding Author: Prof. M. Steriade, M.D., D.Sc., Laboratory of Neurophysiology, Faculté de Médecine, Université Laval, Québec, Canada G1K 7P4 - Tel. 1 (418) 656 5547 - Fax 1 (418) 656 3236 - E-mail: mircea.steriade@pfs.ulaval.ca

(a) The complexity of 5-HT effects on different brainstem neurons is such that, in pontine reticular formation neurons, one population responded with membrane hyperpolarization and decreased input resistance, a response mediated by 5-HT₁ receptors, while another population showed depolarization and increased input resistance, probably a non-5-HT₁ response (53). And, in upper midbrain reticular, mesopontine cholinergic as well as basal forebrain cholinergic neurons, the effects of 5-HT are inhibitory (20, 21, 24), thus shutting down the activity of these neuronal types that are among the most important in ascending activation processes, which would lead to falling asleep (39).

(b) The 5-HT projection to the thalamic reticular (RE) nucleus is of importance in view of generation of oscillatory events within the RE nucleus (46), sleep spindles, associated with rhythmic inhibitory processes in thalamocortical neurons, with the consequence of blocking the transfer of information from the outside world, thus predisposing to cortical deafferentation and sleep. Application of 5-HT to RE neurons results in a prolonged depolarization associated with a decrease in K⁺ currents (26), thus favoring the hypothesis that 5-HT promotes spindling and sleep. Indeed, to decide whether isolated RE neurons are able to generate sleep spindles, as demonstrated *in vivo* (46), or if RE neurons disconnected from the dorsal thalamus are unable to display spindles, as shown *in vitro* (58), computational models have shown that isolated RE neurons can only generate spindles if relatively depolarized by 5-HT (7). Of course, such 5-HT projections are absent in a thalamic slice.

(c) Contrary to the depolarizing action exerted on thalamic RE neurons, 5-HT produced a hyperpolarization of thalamocortical neurons recorded from association nuclei in ferrets, associated with an increased K⁺ conductance; in both ferret and monkey, 5-HT induced barrages of inhibitory postsynaptic potentials (29, 30). Thus, 5-HT contributes to the thalamic blockade of signals arising in the external world and directed to the cerebral cortex and, thus, may promote the process of falling asleep.

(d) Finally, the general conclusion that dorsal raphe neurons diminish their firing rates during sleep (25, 27, 57) was revised by recordings of atypical neurons, distributed unevenly in the cat dorsal raphe nucleus, which displayed the highest discharge frequencies during slow-wave sleep, with suppression of firing in waking and paradoxical sleep (34).

The above data may vindicate Jouvet's data and hypothesis that the action of serotonergic dorsal raphe neurons favors the onset of sleep. Further experiments are needed to assess the chemical code of sleep-active dorsal raphe neurons and to corroborate, in naturally awake and sleeping animals, the data on serotonergic inhibition of thalamic relay cells reported *in vitro*.

SLOW-WAVE SLEEP OSCILLATIONS AND THEIR INTEGRATION
IN CORTICOTHALAMIC NETWORKS

To remain within the frame of slow-wave sleep, a state that, contrary to paradoxical sleep, has been regarded as associated with global inhibition of cortex and sub-cortical structures (33), therefore leading to "abject annihilation of consciousness" (8), let me present some evidence suggesting that these hypotheses became obsolete as they could not resist experimental testing and recent evidence from human studies.

Far from being inactive, intracellularly recorded neocortical neurons display during the depolarizing phase of the slow oscillation (0.5-1 Hz), which typically characterizes slow-wave sleep, firing rates that are as high as during natural states of waking and paradoxical sleep (51). The high activity of cortical neurons in slow-wave sleep leads to a coalescence of several types of brain rhythms during this behavioral state. Instead of analyzing distinct frequency bands of at least three or four distinct oscillations and even dissecting various sub-bands for each rhythm, it is more conceptually rewarding to understand the physiological basis of the grouping, by the slow oscillation, not only of other slow-wave sleep rhythms, such as spindles and delta, but also of fast (beta and gamma) rhythms that are conventionally assumed to only characterize the brain-activated states of waking and paradoxical sleep (40). Below, I discuss some of these grouped rhythms, due to the effect of the slow oscillation that is generated intra-cortically, as it was recorded in neocortical neurons in the absence of thalamus and brainstem (48). Following these initial intracellular recordings in anesthetized animals (47), the slow oscillation was also recorded in naturally sleeping animals (42) and humans (1, 4, 35).

The synchronization of all types of neocortical neurons during the slow oscillation (2, 3), and especially those with thalamic projections, has a powerful impact on thalamic reticular and relay neurons, with the consequence of triggering spindle oscillations. The density of subunits of glutamate receptors is much higher, and the excitatory postsynaptic currents (EPSCs) evoked by corticofugal axons much ampler, in thalamic reticular, compared to thalamocortical, neurons (11). This explains why the synchronous activation of the glutamatergic corticothalamic pathway, as in slow-wave sleep, produces strong excitation of thalamic reticular neurons, as opposed to inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons (Fig. 1 in ref. 38). The excitation of thalamic reticular neurons and the rhythmic IPSPs leading to rebound spike-bursts in thalamocortical neurons represent the cellular basis of sleep spindles. Besides spindle generation by the slow oscillation, the cortex has an important role in spindle synchronization. Thus, spindles propagate in visual thalamic slices (22), whereas they are nearly simultaneous in widespread territories of the thalamus and cortex of both cats and humans (5, 6). After decortication, the thalamic synchronization of spindles is disorganized or completely lost and what remains is accounted for by the synchronizing power of the thalamic reticular nucleus (6).

Another oscillatory type that is grouped within the complex wave-sequence of the slow cortical oscillation is the fast activity in the frequency range of beta (~20-30

Hz) and gamma (~30-60 Hz) rhythms. I consider these two rhythms together because a neuron can pass from beta to gamma frequency in a period as short as 0.5-1 second, due to a slight depolarization (42). The presence of fast activity during slow-wave sleep was surprising to those who consider these oscillations as reflecting high cognitive processes and conscious events during waking and REM sleep. However, the fact that beta/gamma activity is voltage (depolarization) dependent (23, 32, 44) explains the presence of fast activity during the depolarizing phase of the slow sleep oscillation. The grouping of not only spindles, but also relatively fast (beta) activity, by the cortical slow oscillation was also reported during natural slow-wave sleep in humans (28).

To sum up, the slow oscillation has the virtue of coalescing low-frequency as well as fast rhythms due to the properties of neocortical neurons and their intra-cortical and corticothalamic connections.

NEURONAL PLASTICITY AND SEIZURES DURING SLOW-WAVE SLEEP

With the rich (higher than 10 Hz) spontaneous firing of neocortical neurons during slow-wave sleep (51), there is no surprise that these neurons have better to do than to be in a "quiet", "resting" state, as some terms usually applied to slow-wave sleep would suggest. Actually, monkey's motor cortical responses to callosal volleys are not diminished and may even be enhanced during slow-wave sleep, compared to waking (45). This finding indicates that, during slow-wave sleep, at least some cortical neurons maintain an internal dialogue that may explain various forms of mental activities during this state in which there is a complete absence of information from external signals because of synaptic inhibition at the thalamic level (40).

Human studies have also shown that, far from being a period of complete inactivity, slow-wave sleep is implicated in mental processes since dreaming mentation is not confined to paradoxical sleep but also appears, closer to real life events, during slow-wave sleep (12). The recall rate of dreaming mentation in slow-wave sleep is high (31). Also, the idea that slow-wave sleep is implicated in the consolidation of memory traces acquired during the waking state (43) is supported by human studies demonstrating that the overnight improvement of discrimination tasks requires several steps, some of them depending on the early slow-wave stages (54, 55). The enhancement of visual discrimination skills by early stages of sleep led to the conclusion that procedural memory formation may be associated with slow-wave oscillations (9) and, after training on a declarative learning task, the density of human sleep spindles is significantly higher, compared to the non-learning control task (10).

That neuronal plasticity results from spontaneously occurring slow-wave sleep oscillations has been demonstrated using intracellular recordings from thalamic and cortical neurons. Here, I shall focus on cortical neurons. During stages 2-3 of sleep, cortical neurons are targets of thalamic inputs during spindles, but not passive receivers of these rhythmic volleys. Cortical neurons play an active role in amplify-

ing incoming thalamic inputs (19) and elaborate synaptic activities that are primarily dependent, but also outlasting, the spindle-related signals. This was shown with the experimental model of spindling, waxing-and-waning thalamocortical augmenting responses, during which the initial excitatory postsynaptic potential (EPSP) of cortical neurons follows by ~ 3 ms the first action potential in the spike-burst of simultaneously recorded thalamocortical neuron, but the augmentation phenomenon basically consists of a secondary EPSP that is cortical in origin (52). That neocortical neurons display augmenting responses even in the absence of thalamus was demonstrated by progressive depolarization and increased number of action potentials in their rhythmic spike-bursts evoked by repeated, rhythmic callosal volleys in thalamectomized animals (48).

Thus, neocortical neurons have the ability to progressively increase their responsiveness when activated within the frequency range of sleep spindles, even in the absence of spindle generators, thalamic neurons. In the intact brain, testing cortical excitability with repeated pulse-trains revealed that, first, the IPSP of the control response was progressively reduced in amplitude and replaced by an early depolarization and, second, single stimuli applied after the rhythmic pulse-trains elicited exclusively depolarizing responses, an enhancement that remained unchanged for up to 12-15 minutes (56).

The intriguing finding in our experiments was that neuronal plasticity, usually regarded as a beneficial phenomenon implicated in memory and learning, could develop during slow-wave sleep into self-sustained paroxysmal discharges, similar to spike-wave complexes at ~ 3 Hz seen during petit-mal epilepsy or to the more complex electrographic pattern seen during the Lennox-Gastaut syndrome. This unexpected transformation of a normal to a pathological event was first reported in limbic circuits, at which level rhythmic stimulation of basolateral amygdala at 5-6 Hz evoked short-latency hippocampal responses, which progressively increased in amplitude and developed into paroxysmal activity with self-sustained potentials whose shapes were virtually identical to responses evoked in the final stage of stimulation (36). Similarly, the enhanced responsiveness of cortical neurons driven by rhythmic callosal volleys in the frequency range of sleep spindles was followed by paroxysmal activity, which occurred within the same frequencies as in the preceding period of stimulation (48). The changes in neuronal responsiveness that lead to self-sustained oscillations of the paroxysmal type are already initiated during rhythmic stimulation with pulse-trains at 10 Hz and outlast the stimulation period with patterns of spike-wave epileptiform discharges at ~ 3 Hz. Such changes from normal (sleep-like) to pathological (epileptic-like) states have been reported in thalamic neurons driven by cortical volleys (37, 49) and in cortical neurons driven by cortical volleys (50). The behavioral significance of development from "memory" events in the electrical activity of corticothalamic reciprocal circuits to electrographic paroxysmal states that are antinomic to the notion of memory is not yet clearly understood. Let me just mention that slow-wave sleep, a state that is beneficial for the consolidation of memory traces (see above) is also the state during which spike-wave and Lennox-Gastaut seizures preferentially occur (41).

SUMMARY

This article starts by enumerating several data that vindicate Michel Jouvet's hypothesis regarding serotonin as a factor promoting slow-wave sleep. The core of the article is devoted to the description of neuronal bases underlying sleep oscillations, with emphasis on the cortically generated slow oscillation (0.5-1 Hz) that groups both low-frequency (spindles and delta) and high-frequency (beta/gamma) rhythms. The low-frequency rhythms are generated by the synchronous firing of cortical neurons during the depolarizing phase of the slow oscillation, which impacts on the thalamic circuitry to generate spindles and clock-like delta potentials. The fast activity is voltage-dependent and occurs during the depolarization component of the slow cortical oscillation. This coalescence of brain rhythms, discovered in intracellular studies of neocortical and thalamic neurons, is now supported by EEG studies during human sleep. The rich spontaneous activity of neocortical neurons during slow-wave sleep is associated with neuronal plasticity that may play a role in consolidating memory traces acquired during the state of waking. Surprisingly, neuronal plasticity, usually regarded as a beneficial phenomenon implicated in memory and learning, could develop during slow-wave sleep into self-sustained paroxysmal discharges, similar to spike-wave complexes that appear in some epileptic syndromes.

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