

## Regulation of Neuronal Activities within REM Sleep-Sign Generators

Commentary on Heister et al. Cholinergic modulation of GABAergic and glutamatergic transmission in the dorsal subcoeruleus: mechanisms for REM sleep control. *Sleep* 2009;32:1135-1147.

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OVER THE LAST TWO DECADES, MODERN NEUROSCIENCE RESEARCH ON SLEEP HAS REALIZED THAT THE REGULATION OF RAPID EYE MOVEMENT (REM) SLEEP involves a distributed network, rather than a single center.<sup>1,2</sup> Each of the individual signs of REM sleep is executed by the activation of distinct cell groups in the brainstem. Each group of these executive neurons functions as a generator for a specific sign of REM sleep. Phasic pontine-waves (P-waves) and tonic muscle atonia are two of the most definitive physiologic signs of REM sleep.<sup>3</sup> In this regard, the subcoeruleus area (SubC) of the pons is an important region for the regulation of REM sleep. The REM-sleep muscle-atonía generator is located in the pericoeruleus/locus coeruleus alpha part of the SubC.<sup>1</sup> These REM-sleep atonia-generating neurons are mainly GABAergic. In prey animals (such as the rat), P-wave-generating neurons are located within the dorsal part of the SubC.<sup>4</sup> These P-wave-generating neurons are glutamatergic.<sup>5</sup> Within the SubC, these muscle-atonía and P-wave generators are next to each other, and it is very difficult to separate them into two discrete anatomic areas. In the rat, all of these individual REM sleep-sign generators receive cholinergic inputs from the pedunculopontine tegmental (PPT) cholinergic cells and aminergic inputs from the locus coeruleus and raphe nucleus.<sup>6</sup> Single-cell recordings and functional anatomic studies have demonstrated that these PPT cells are REM-on type and that the aminergic cells of the locus coeruleus and raphe nucleus are REM-off type.<sup>2,7</sup> The expression of REM-sleep signs are tightly regulated by the ratio of cholinergic and aminergic neurotransmitter presence within individual generators. One of the most important recent discoveries in neuroscience is that the activity of the P-wave generator is critical for the synchronization of hippocampal and amygdalar activities, which in-turn are critical for the consolidation of memory.<sup>5, 8, 9</sup> Therefore, it is very important to understand how neuronal activities in those REM sleep-sign generators are regulated.

In this issue of *SLEEP*, Heister and colleagues<sup>10</sup> from Edgar Garcia-Rill's lab present a detailed analysis of the synaptic effects of descending cholinergic input, presumably from the PPT, to the SubC. This publication provides an impressive

number of control experiments that leave little doubt about the accuracy of the results. Briefly, some SubC cells are depolarized by cholinergic input, whereas others are hyperpolarized; however, cholinergic input appears to decrease the amplitude of evoked and spontaneous excitatory currents and increases the amplitude of inhibitory currents. Put another way, cholinergic input increases GABAergic and perhaps glycinergic transmission while decreasing glutamatergic transmission. Placed in the context of electrical coupling, the main effect of cholinergic afferents to SubC would be to activate inhibitory neurons, some of them known to exhibit spikelets (putative electrically coupled cells). By depolarizing GABAergic, presumably coupled, cells and hyperpolarizing glutamatergic cells, especially those with low-threshold spikes, the net effect would be to produce rhythmic oscillations. Previous studies have described cholinergic agonist-induced inhibition of reticular formation neurons, many with low-threshold spikes, that included neuronal sampling of not only SubC, but also of cholinergic and noradrenergic neurons not normally belonging to SubC.<sup>11</sup> The present report by Heister et al. appears to be of cells strictly localized to the very small region of the SubC. The authors suggest that PPT "REM-on" neurons may induce rhythmic activity in SubC underlying P-waves. Although this is a perfectly reasonable, and probably correct, suggestion, studies recording single cells as well as population responses are needed to bolster this hypothesis. Nevertheless, this is an important contribution to detailing the synaptic interactions that lead to REM-sleep signs.

Knowledge of the synaptic organization of the SubC, such as that provided by Heister et al., is essential for determining how these neurons change their firing across different sleep-wake states. Although neurons in the SubC and other regions involved in sleep-wake modulation exhibit synchronization of low (theta, alpha) and higher frequencies (gamma), we do not know how these frequencies are generated. Is gamma-band activity an intrinsic property of some cells in these regions, such as is evident in cortex?<sup>12</sup> Do groups of neurons shift firing from theta to alpha to gamma, or do different populations of cells kick in to induce the new frequency? Do all of these frequencies require electrical coupling for promotion of ensemble activity? If these neurons are capable of generating such activity, what is the role of such activity, and how does it interact with thalamocortical rhythms and/or rhythmic activities within the hippocampus and amygdala? We still have much to learn about how mesopontine rhythms are manifested within the P-wave generators and even more to learn about how dysregulation of such rhythms could lead to disease processes.

Submitted for publication July, 2009

Accepted for publication July, 2009

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This article represents a continuation of some of the most important contributions to the sleep field from the Garcia-Rill laboratory. Garcia-Rill et al.<sup>13,14</sup> were the first to describe the presence of electrical coupling in cell groups of the reticular activating system, namely, the PPT, and an ascending target of the PPT, the parafascicular nucleus, as well as a descending target of the PPT, the SubC nucleus. They were the first to report that the stimulant modafinil, among other actions, may increase electrical coupling, particularly in putative GABAergic neurons in these regions. Similar findings for modafinil have been reported for cortical, cerebellar, and reticular thalamic neurons.<sup>15</sup> Increasing coupling would have the effect of decreasing input resistance and, consequently, GABA release while increasing ensemble activity and promoting rhythmic activity. This represents a novel mechanism for sleep-wake control, especially since some anesthetics act by blocking gap junctions. This discovery could presage the development of a new class of stimulants and anesthetics. A review of the role of electrical coupling in the development of REM sleep has also been published by this group in *SLEEP*.<sup>16</sup>

#### DISCLOSURE STATEMENT

Dr. Datta has received research support from and has participated in speaking engagements for Sepracor.

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