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CHAPTER 6

Phasic modulation of cortical high-frequency oscillations by pedunculopontine neurons

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Abstract: Brain states are dynamically shaped by distinct neuronal systems across the brain as a result of an interplay between their intrinsic activity and the environmental demand. Subsets of brainstem and forebrain structures influence the manifestation of specific brain states (e.g., sleep or wakefulness) and contribute to their cyclic alternation. Recent evidence, however, shows that such functional partition is not observed in the brainstem, where neuronal subpopulations engage in particular patterns of activity that contribute to the emergence of phasic components during the cortical slow oscillations. Cholinergic neurons of the pedunculopontine nucleus are functionally associated with the induction of the waking state but discharge during the phase of the slow oscillations that support neuronal activity. Here, we discuss the impact of the phasic signals arising from subcortical structures on the modulation of cortical slow oscillations and their functional significance.

Keywords: pedunculopontine; gamma oscillations; cholinergic; reticular-activating system.

Introduction

The pedunculopontine nucleus (PPN) constitutes one of the main components of the reticular-activating system. It is composed of distinct types of neurons, although its role as an "activating" structure has been traditionally associated with its prominent population of cholinergic neurons. Classic experiments showed that the electrical stimulation of the upper brainstem/lower midbrain in cats produces a short-term change in the amplitude and frequency of neuronal oscillations in the cerebral cortex (Moruzzi and Magoun, 1949). This evidence led to the assumption that ascending projections from subcortical structures drive the activity of cortical neurons in states of cortical activation, such as wakefulness. Subsequent experiments then showed this mechanism to be dependent of acetylcholine transmission, since blockage of acetylcholine receptors was sufficient to abolish the activating response initiated in the brainstem (Curro Dossi et al., 1991).

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Together with other neuronal groups in the brainstem (laterodorsal tegmental nucleus, raphe dorsalis, locus coeruleus) and basal forebrain (nucleus basalis of Meynert, hypothalamus), the PPN is part of a model that explains the subcortical modulation of brain states and regulation of the sleep wake cycle (McCarley, 2007; Saper et al., 2005). Several experiments over the past decades have consistently shown the importance of the drive from these neuronal groups for the activation of the cortex and for the gating of the several neuronal processes that are dependent on such activation in order to be developed (e.g., sensory integration; Munk et al., 1996). In the PPN, neurons increase their firing a few hundred milliseconds before the cortex changes from a slow oscillatory rhythm, typical of slow-wave sleep, to a faster rhythm characteristic of the waking state (Steriade et al., 1990). Pharmacological inhibition of neuronal activity in the PPN is able to reduce the appearance of faster oscillations in the cortex and other subcortical structures, such as the hippocampus (Nowacka et al., 2002). Conversely, and in line with early experiments in cats, electrical stimulation of the PPN produces depolarization of cortical neurons (Steriade et al., 1996) and is typically used to produce activation of the cortex (Curto et al., 2009; Steriade et al., 1991). This has led to the proposal that PPN neurons play a critical role in the promotion of brain state transitions and that their increase in firing rate generates a waking-like pattern of activity in the cortex.

The cholinergic hypothesis of brain activation (for a review, see Steriade and McCarley, 2005) is based on the evidence that ascending axons from cholinergic neurons reach different thalamic structures, most notably the parafascicular and centrolateral thalamic nuclei (intralaminar thalamocortical system; Hallanger et al., 1987; Kobayashi and Nakamura, 2003; Krout et al., 2002; Losier and Semba, 1993; Mena-Segovia et al., 2008). Activation of these thalamocortical neurons produces an increased firing in pyramidal neurons and the emergence of high-frequency oscillations (particularly in the gamma range, 30–50 Hz) in the field activity (Steriade, 1996). Recent evidence, however, shows that the cholinergic nuclei of the brainstem are neurochemically heterogeneous (Mena-Segovia et al., 2009; Wang and Morales, 2009), confirming previous observations of the presence of distinct neurochemical markers (Clements and Grant, 1990; Ford et al., 1995; Vincent, 2000). Indeed, different types of neurons show different functional properties (i.e., dynamic firing properties associated with alternating brain states; Boucetta and Jones, 2009; Ros et al., 2010) and some of them share the thalamus as a common target (Ye et al., 2010). Even though the cholinergic mechanism seems to be sufficient to explain the activation of thalamocortical neurons, it does not take into account the other neuronal subgroups in the PPN that coexist and maintain synaptic connections with the cholinergic neurons. Interestingly, some clues to their complementary functional role might arise from their firing properties during slow-wave activity (SWA).

The firing of PPN neurons during sleep

The PPN is composed of three main types of neurons: cholinergic, GABAergic, and glutamatergic. Cholinergic neurons account for only a small proportion of the total population of PPN neurons, currently estimated at only 20%. However, they delimit the borders of the PPN and are distributed across the entire rostro-caudal extent of the nucleus, intermingled with the other two neurochemical subtypes (Mena-Segovia et al., 2009; Wang and Morales, 2009). This scattering, together with the lack of discernable characteristics in their action potentials, makes the identification of the neuronal subtypes very difficult during *in vivo* extracellular recordings. By means of the juxtacellular labeling method, it is possible to record the spontaneous activity of individual neurons during different brain states and subsequently label them with a neuronal

tracer to identify the cell bodies and neural processes as well as define their neurochemical characteristics by immunocytochemistry. In this manner, it was observed that neurons of distinct neurochemical types show different firing characteristics during urethane-induced SWA (Mena-Segovia et al., 2008; Ros et al., 2010).

SWA tends to entrain the firing of some classes of neurons. As shown in distinct brain regions, neurons with similar functional properties tend to fire together during SWA (e.g., Klausberger et al., 2003; Lacey et al., 2007). The discharge of PPN neurons during SWA was varied: neurons were modulated by the cortical slow oscillations (their firing was temporally correlated to the 1-Hz cycle of cortical activity; Mena-Segovia et al., 2008) or were independent of such modulation in that they fired either tonically or were almost silent (Ros et al., 2010).

Neurons that were modulated during slow oscillations included two categories of cholinergic neurons and one category of noncholinergic (putative glutamatergic) neurons (Fig. 1; Mena-Segovia et al., 2008). About 80% of cholinergic neurons fired preferentially during the active component (up-state) of the cortical slow oscillations. These neurons had a temporal relationship with the nested high-frequency (gamma) oscillations observed during the cortical slow oscillations. The remaining 20% of cholinergic neurons showed an opposite relationship, firing preferentially during the inactive component (down-state) of the slow oscillations. These neurons did not show any temporal relationship with the nested gamma oscillations. A remarkable additional difference between these two populations was the firing rate: whereas active component-coupled cholinergic neurons (ChATa) fired sparsely at $\sim$1 Hz, inactive component-coupled cholinergic neurons (ChATi) fired at least one order of magnitude higher ($\sim$30 Hz). In addition, one category of noncholinergic neuron also showed a strong correlation with the slow cortical oscillations. Slow oscillation-coupled, noncholinergic neurons fired preferentially during the transition from the active component (up-state) to the inactive component (down-state) of the slow oscillations. They did not show a temporal correlation with the nested gamma oscillations. They were identified as putative glutamatergic neurons since some of them formed asymmetric synaptic contacts, suggestive of excitatory connections. These results show the large variability in firing patterns in the PPN during SWA, and suggest a specific functional relationship between the ChATa neurons and the phasic components supported by the cortical slow oscillations, which was not observed with any other neuronal subtype in the PPN.

In terms of the anatomical characteristics, both types of cholinergic neurons (ChATa and ChATi) have profuse local axonal arborizations and give rise to several axonal branches that travel along ascending and descending pathways. These single-cell labeling experiments were also able to show that cholinergic neurons innervate distant targets involved in the regulation of cortical activity and global brain states, such as the intralaminar thalamic nuclei (Mena-Segovia et al., 2008). Thalamic neurons in both parafascicular and centrolateral thalamic nuclei are innervated by abundant cholinergic fibers arising largely from PPN (Parent and Descarries, 2008), and their firing is closely correlated with cortical slow oscillations (Lacey et al., 2007). Thus, the evidence that individual thalamic-projecting cholinergic neurons were temporally correlated with the phasic increases in cortical gamma oscillations during SWA suggest that the cholinergic modulation might be playing a role in structuring the high-frequency activity in thalamocortical systems during slow oscillations.

Cholinergic neurons also produce synaptic contacts arising from local axon collaterals within the PPN, particularly those belonging to the type ChATa. This suggests that the release of acetylcholine from PPN neurons is timed to the active component of the cortical slow oscillations and might have an impact on the firing of thalamocortical neurons and the output of the PPN

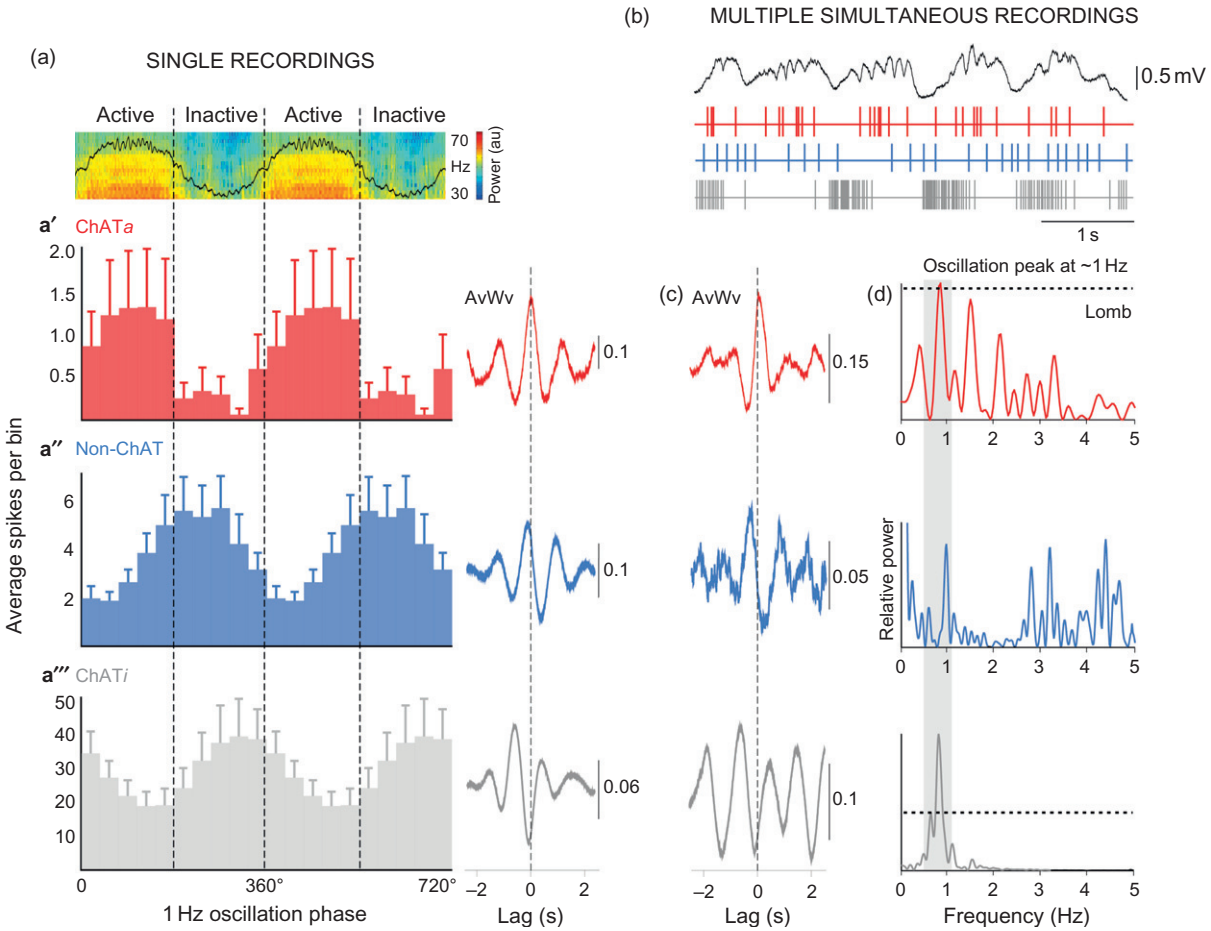

Fig. 1. Distinct types of PPN neurons are differentially modulated during cortical slow oscillations. (a) Individual PPN neurons were recorded and labeled by the juxtacellular method, and then identified by immunohistochemistry as cholinergic (ChAT) or noncholinergic (non-ChAT). The activity histograms show that most cholinergic PPN neurons fire preferentially during the active component of the slow oscillations and thus, phasic increases in gamma oscillations (a′). In contrast, noncholinergic neurons (a″) and a minority of cholinergic neurons (a‴) fired preferentially during the inactive component of the slow oscillation. (b) Traces from the ECoG and the firing of three different neurons (represented as events) recorded simultaneously using high-density multielectrode arrays show that these patterns of activity occur in parallel. (c) The representative spike-triggered averages of ECoG waveforms show the phases of the cortical slow oscillation in which they preferentially fire, allowing the comparison with the juxtacellularly labeled neurons (left), and thus their identification as putative active component-locked cholinergic neurons (ChATa, red), putative noncholinergic neurons (non-ChAT, blue), or putative inactive component-locked cholinergic neurons (ChATi, gray). (d) Even though their firing was timed with different components of the slow oscillation, they all show a peak of oscillation at ~1 Hz, as shown by the Lomb periodograms (dashed line represents level of significance; Mena-Segovia et al., 2008).

through local connections. To test whether local acetylcholine does have an effect on cortical gamma oscillations during SWA, low doses of carbachol were injected into the PPN and the cortical activity was monitored (Mena-Segovia et al., 2008). Intra-PPN injections of carbachol

increased the power of gamma oscillations during the active component (up-state) of the slow oscillations. Importantly, this effect was obtained without disrupting the slow oscillatory structure of SWA, indicating that this phasic increase is constrained to the temporal dynamics of the slow oscillations. Whether this effect is mediated through direct thalamic projections arising from ChATa neurons, or through the ChATa-mediated local modulation of other neuronal subtypes in the PPN remains to be determined, but suggests a functional connectivity within PPN that is able to modulate the high-frequency oscillations in the cortex. Recent evidence from *in vitro* experiments supports the notion that acetylcholine-receptor activation has different effects on PPN neurons, and that this effect is not exclusive to cholinergic neurons (Ye et al., 2010). The subtypes involved and number of neurons recruited to produce this effect remains to be determined.

Subcortical modulation of slow oscillations: A specific role of the PPN or a widespread mechanism in the reticular-activating system?

The idea that neurons of the reticular-activating system discharge during cortical SWA and contribute to the shaping of this activity seems at first counterintuitive. Ascending projection neurons in the brainstem decrease their firing during sleep allowing thalamocortical neurons to hyperpolarize. This means that effective communication from subcortical structures to the cortex via the thalamocortical system is diminished or absent and therefore no sensory information reaches the cortex. The increase in the discharge rate of the neurons in brainstem activating structures switches the overall brain state to a "receptive", activated state (i.e., wakefulness). It has been assumed that neurons in the reticular-activating system *drive* brain state transitions and that their inactivity facilitates sleep (Saper et al., 2005). Recent evidence, however, shows that this is not the case for neurons in the PPN of anaesthetized rats (Aravamuthan et al., 2008; Mena-Segovia et al., 2008; Ros et al., 2010). Specific firing patterns in the different PPN neuronal subtypes are distinctively correlated with discrete components of the cortical slow oscillations (see Fig. 1). This implies that PPN neurons are not, by and large, entrained by the cortical slow oscillations but instead each neuronal subgroup shows a unique modulation that is likely to be the balance between modulatory afferents (Hammond et al., 1983; Scarnati et al., 1987) and intrinsic properties (Leonard and Llinas, 1994; Takakusaki and Kitai, 1997). From all these variants observed in the PPN, only identified cholinergic neurons (ChATa) are precisely timed with nested high-frequency oscillations during SWA (Mena-Segovia et al., 2008).

A similar mechanism seems to be shared by other midbrain and brainstem structures with ascending projections to the forebrain, such as the dopamine neurons in the substantia nigra pars compacta (Brown et al., 2009) and putative noradrenergic neurons in the locus coeruleus (Eschenko et al., 2011). These neurons have the peculiarity of activating/modulating forebrain neuronal networks during different behavioral contexts while also being modulated during cortical SWA. Similar to some of the neuronal subgroups in the PPN, neurons in the locus coeruleus show a strong modulation during cortical slow oscillations in naturally sleeping rats, suggesting also a contribution from putative noradrenergic neurons to the global activity during sleep (Eschenko et al., 2010). Importantly, a recent study in humans using combined electroencephalography and functional magnetic resonance imaging (fMRI) showed a significant increase in the activity of the brainstem during spontaneous slow-wave sleep. This increase was specifically associated with cortical slow oscillations rather than delta waves (1–4 Hz; Dang-Vu et al., 2008). All-in-all, this evidence suggests that the orchestrated activation of midbrain/brainstem networks during the slow oscillations that are characteristic of sleep and anesthesia plays a

role in shaping the global neuronal activity, possibly by modulating the phasic events occurring during SWA.

Is timing important in neuromodulatory systems?

The activation of thalamocortical neurons in the intralaminar thalamic nuclei by stimulation of acetylcholine receptors leads to activation of the cortex. This is evident in the electrocorticogram (ECoG) as a switch from high-amplitude/low-frequency oscillations to low-amplitude/high-frequency oscillations. This effect is considered to be mediated by the activation of muscarinic receptors, which produces a long-lasting depolarization of thalamic neurons over the course of several hundred milliseconds (Curro Dossi et al., 1991; Steriade et al., 1996). Indeed, *in vitro* experiments show that the application of carbachol to thalamic neurons produces an increase in oscillatory activity (Lorincz et al., 2008), suggesting that it is not necessary to preserve intact cholinergic afferents in order to obtain such activation. These reports have contributed to the notion that neuromodulatory systems act upon their target structures by producing a sustained activation that would mask any effect of timing of afferent discharges.

An alternative to this hypothesis is that the frequency and timing of the discharge of cholinergic afferents determines the level of activation in thalamocortical neurons and other targets (e.g., dopaminergic neurons of the midbrain). The maximal discharge rate, as determined by the membrane properties of each neuronal subtype in the PPN, could have a one-to-one effect on the firing rate of thalamic neurons, which would allow thalamic neurons to fire at similar frequencies to those of the PPN afferents (the frequency being determined by the intrinsic properties of PPN neurons). In contrast to the muscarinic-mediated prolonged effect on thalamic neurons necessary to evoke arousal or to sustain wakefulness, this effect on a shorter time scale could be mediated through nicotinic receptors and could denote an immediate but transient response to bind distinct modalities of sensory information at the level of thalamocortical systems. The cellular basis for this hypothetical mechanism has recently been supported by experimental data showing that PPN neurons discharge in the gamma frequency range during *in vitro* pharmacological stimulation (Simon et al., 2010). This implies that thalamic activation by cholinergic afferents occurs by a balance of two mechanisms of distinct temporal dynamics, most likely related to the global brain state and behavioral context.

The gating hypothesis

The data presented in this review poses the question of the functional significance of the excitatory cholinergic afferents to thalamocortical systems during resting states (i.e., sleep and anesthesia). The low discharge rate of cholinergic (ChATa) neurons is unlikely to produce a sustained effect on the activity of thalamic neurons, but rather, a temporally discrete effect on the discharge of thalamocortical neurons. The constraints of such cholinergic activation is correlated to the duration of the active component of the cortical slow oscillations, and in line with the idea that cortical up-states (active components) represent small fragments of the waking state (Destexhe et al., 2007). Neuronal computations occur during up-states across different brain areas during SWA in both sleep and anesthesia, representing complex firing sequences related to memory replay and neuronal plasticity (Lee and Wilson, 2002). Indeed, synchronization of distant cortical areas that have a common functional association occurs in the range of high-frequency oscillations during sleep (Le Van Quyen et al., 2010; Molle et al., 2004).

The range of neuronal computations occurring during sleep is likely to generate waking-like microstates and, along with the intrinsic activity of cortical ensembles (Compte et al., 2008),

produce the alternating patterns of oscillatory activity characteristic of SWA. It is then expected that the effective communication between different neuronal systems will be facilitated or amplified by their synchronization during high-frequency oscillations. Neurons in the PPN, as well as other subcortical structures, could then provide such a common activation mechanism and set the tone required for effective transmission of the information across neuronal ensembles.

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Abbreviations

ChAT	choline acetyltransferase
ChATa	active component-coupled cholinergic neurons
ChATi	inactive component-coupled cholinergic neurons
PPN	pedunculopontine nucleus
SWA	slow-wave activity

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