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Bottom-up gamma and stages of waking

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ABSTRACT

Gamma activity has been proposed to promote the feed forward or "bottom-up" flow of information from lower to higher regions of the brain during perception. The pedunculopontine nucleus (PPN) modulates waking and REM sleep, and is part of the reticular activating system (RAS). The properties of PPN cells are unique in that all PPN neurons fire maximally at gamma band frequency regardless of electrophysiological or transmitter type, thus proposed as one origin of "bottom-up" gamma. This property is based on the presence of intrinsic membrane oscillations subserved by high threshold, voltage-dependent calcium channels. Moreover, some PPN cells are electrically coupled. Assuming that the population of PPN neurons has the capacity to fire at ~40 Hz coherently, then the population as a whole can be expected to generate a stable gamma band signal. But what if not all the neurons are firing at the peaks of the oscillations? That means that some cells may fire only at the peaks of every second oscillation. Therefore, the population as a whole can be expected to be firing at a net ~20 Hz. If some cells are firing at the peaks of every fourth oscillation, then the PPN as a whole would be firing at ~10 Hz. Firing at rates below 10 Hz would imply that the system is seldom firing at the peaks of any oscillation, basically asleep, in slow wave sleep, thus the activation of the RAS is insufficient to promote waking. This hypothesis carries certain implications, one of which is that we awaken in stages as more and more cells are recruited to fire at the peaks of more and more oscillations. For this system, it would imply that, as we awaken, we step from ~10 Hz to ~20 Hz to ~30 Hz to ~40 Hz, that is, in stages and presumably at different levels of awareness. A similar process can be expected to take place as we fall asleep. Awakening can then be considered to be stepwise, not linear. That is, the implication is that the process of waking is a stepwise event, not a gradual increase, suggesting that the brain can spend time at each of these different stages of arousal.

Introduction

The role of gamma band activity

Sensory perception, problem solving, and memory are thought to require gamma band oscillations [1–6]. The coherence of gamma activity may occur at cortical or subcortical levels [7,8], and is thought to contribute to the merger, or "binding", of information originating from separate regions to promote perception [9]. Gamma oscillations were proposed to emerge from the interaction between intrinsic neuronal and synaptic properties of thalamocortical networks [10]. For example, cortical synaptic connections alone may not be able to maintain firing at gamma frequencies, so that intrinsic membrane properties also appear essential to the maintenance of gamma band activity. One example of the limits of cortical synaptic connectivity is flicker fusion of visual inputs such that cortical circuits cannot "follow" individual visual stimuli presented at rates above 35 Hz. Therefore, it is the ability of cells with intrinsic membrane properties, coupled with synaptic interactions, which allows the circuit as a whole to fire at a preferred frequency, and is essential to maintaining frequencies in the gamma range. The neuronal mechanisms behind such activity include inhibitory cortical interneurons with intrinsic oscillatory activity in the gamma range [7,10,11], many of which are electrically coupled [12], as well as of fast rhythmic bursting pyramidal neurons [13], and layer V pyramidal cells that summate dendritic action potentials at gamma frequency [14]. Moreover, thalamocortical excitatory neurons have intrinsic properties needed to generate subthreshold gamma band oscillations [15]. However, other regions are known to manifest gamma band activity in addition to the cortex and thalamus, including the hippocampus, basal ganglia, cerebellum, and the RAS.

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Gamma band activity in the RAS

Recently, two important discoveries were made in the properties of neurons that control waking and rapid eye movement (REM) sleep. During waking and REM sleep, the EEG shows low amplitude, high frequency activity at beta/gamma frequencies (~20–30/30–90 Hz). The pedunculopontine nucleus (PPN) is active during waking and REM sleep [16]. The PPN is the arm of the RAS that modulates ascending projections through the intralaminar thalamus (modulating arousal) and descending projections through the pons and medulla (modulating posture and locomotion) [16]. The PPN is composed of different populations of cholinergic, glutamatergic, and GABAergic neurons [17]. Recordings of PPN neurons *in vivo* identified PPN cells with firing properties related to ponto-geniculo-occipital wave generation [18]. Some neurons had low rates of spontaneous firing (~10 Hz), but most had high rates of tonic firing in the beta/gamma range (~20–80 Hz). PPN neurons also exhibit beta/gamma frequencies *in vivo* during waking and REM sleep, but not during slow wave sleep [18–23]. Moreover, the presence of gamma band activity has been confirmed in the cortical EEG of the cat *in vivo* when the animal is active [17,24]; and in the region of the PPN in humans during stepping, but not at rest [25]. In the monkey, PPN neurons fired at low frequencies ~10 Hz at rest, but the same neurons increased firing to gamma band frequencies when the animal woke up, or when the animal began walking on a treadmill [26]. That is, the same cells were involved in both arousal and motor control. Thus, there is ample evidence for gamma band activity during waking and movement in the PPN *in vitro*, *in vivo*, and across species, including man.

Mechanisms behind PPN gamma activity

A number of articles described the mechanisms behind gamma band activity in the PPN [27–32]. Ramps instead of steps were required to activate high threshold calcium channels in order to keep from activating potassium channels that would prevent sufficient membrane depolarization [30]. In short, gamma oscillations are mediated by voltage-dependent, high threshold N- and P/Q-type calcium channels that are present in every PPN neuron, regardless of cell or transmitter type. These channels are distributed along the dendrites of PPN cells [33]. It has been proposed that afferent input traveling through "specific" sensory pathways diverges to activate "non-specific" reticular pathways to activate PPN dendrites. This generates activity in the beta/gamma range and basically represents one origin or first way station of "bottom-up" gamma activity [34]. However, it appears that gamma band activity during waking has different mechanisms than gamma band activity during REM sleep. Injections of glutamate into the PPN were found to increase both waking and REM sleep [35], but injections of the glutamatergic receptor agonist N-methyl-D-aspartic acid (NMDA) increased only waking [36], while injections of the glutamatergic receptor agonist kainic acid (KA) increased only REM sleep [37]. Intracellularly, CaMKII, which modulates NMDA receptors, was shown to modulate P/Q-type channel function [38], but protein kinase C (PKC), which modulates KA receptors, enhances N-type channel activity and has no effect on P/Q-type channel function [39].

Thus, PPN calcium channel subtypes are modulated by different intracellular pathways, N-type by the cAMP/PK pathway, and P/Q-type via the CaMKII pathway. Moreover, we found three cell types in the PPN, those bearing only N-type calcium channels, those with both N- and P/Q-type, and those with only P/Q-type calcium channels [40,41]. The implications from all of these results is that there is a "waking" pathway mediated by CaMKII and P/Q-type channels and a "REM sleep" pathway mediated by cAMP/PK and N-type channels, and that different PPN cells fire during waking (those with N + P/Q and only P/Q-type) vs REM sleep (those with N + P/Q and only N-type).

The role of "bottom-up" gamma

Early studies on the RAS suggested that it participates in "tonic" or "continuous" arousal [42], and lesions of the RAS were found to eliminate tonic arousal [43]. Recent findings on the presence of intrinsic gamma oscillations and electrical coupling in PPN cells provided the mechanisms required for the maintenance of gamma band activity [27–32]. The PPN, in which every cell manifests gamma band activity, then becomes a gamma-making machine. We speculate that it is the continued activation of the RAS during waking that allows the maintenance of the background of gamma activity necessary to support the state capable of reliably assessing the world around us on a continuous basis – preconscious awareness. That is, RAS bottom-up gamma provides the maintained arousal necessary for higher functions such as attention, learning, and memory. This activity is relayed through the intralaminar thalamus, specifically the parafascicular nucleus (Pf), whose cells were also found to bear high threshold, voltage-dependent calcium channels all along their dendrites [44,45], to the cortex.

At the level of the cortex, the difference between gamma band activity during waking compared to REM sleep seems to be decreased coherence [46]. Basically, brainstem driving of gamma band activity during waking carries with it coherence across distant cortical regions, while induction of gamma band activity during REM sleep does not include coherence across distant regions [46,47]. These findings suggest that brainstem centers drive gamma band activity manifested in the cortical EEG. In other words, brainstem PPN activity is ultimately influencing the characteristics of the cortical EEG. Otherwise, there would be no difference between the gamma band manifested during waking compared to during REM sleep. Mainly because, during waking, brainstem-thalamic projections include coherence across regions, but during REM sleep, it drives cortical EEG rhythms without coherence.

Waking up

Roger Sperry, Nobel Laureate in 1971, proposed that the critical organizational features of the neural circuitry for generating conscious awareness are activated through the RAS, and, once activated, become responsive to changing sensory as well as centrally generated input [48]. Therefore, what happens when we first activate the RAS, when we first wake up? Upon waking, blood flow increases first in the upper brainstem and thalamus, and only later increases in the frontal lobes [49]. That is, the process of awakening entails a rapid re-establishment of consciousness (within a few minutes) followed by a relatively slow (20–30 min) re-establishment of full awareness. Cerebral blood flow measured using positron emission tomography was found to occur soonest upon waking in the brainstem and thalamus, suggesting that the reactivation of these regions underlies the re-establishment of basic conscious awareness. Over the following 15–20 min, increases in cerebral blood flow were evident primarily in anterior cortical regions. These results question ideas that insist that the cortex is solely responsible for achieving conscious awareness.

Changes in arousal state do not occur suddenly unless suprathreshold stimuli ensue. There are relatively slow transitions between waking, slow wave sleep, and REM sleep. The transition from waking to sleep takes time, in the order of minutes, that is, it is not instantaneous. The beginning of REM sleep is also not immediate but appears to be recruited by increasing bursts of