Review

The Critical Role of Intrinsic Membrane Oscillations

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Abstract
Intrinsic, rhythmic subthreshold oscillations have been described in neurons of regions throughout the brain and have been found to influence the timing of action potentials induced by synaptic inputs. Some oscillations are sodium channel-dependent while others are calcium channel-dependent. These oscillations allow neurons to fire coherently at preferred frequencies and represent the main mechanism for maintaining high frequency network activity, especially in the cortex. Because cortical circuits are incapable of maintaining high frequency activity in the gamma range for prolonged periods, those processes dependent on continuous gamma band activity are subserved by subthreshold oscillations. As such, intrinsic oscillations, coupled with synaptic circuits, are essential to prolonged maintenance of such functions as sensory perception and "binding", problem solving, memory, waking, and rapid eye movement (REM) sleep.

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Introduction

Intrinsic membrane oscillations were discovered in 1986 [1], and, despite a number of excellent studies describing the critical role intrinsic membrane oscillations play, many neuroscientists are unaware of their importance, especially the role of gamma band for higher cognitive function. This mini-review will address the concept that intrinsic oscillations influence the timing of action potentials (AP) induced by synaptic inputs, and represent the main mechanism for maintaining high frequency network activity, especially in the cortex. This is because cortical circuits appear incapable of maintaining gamma frequencies using

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only synaptic inputs. We include a thorough description of findings on intrinsic properties and their underlying mechanisms in mesopontine and hippocampal regions not described in detail elsewhere. These are critical regions that appear to impart high frequency influence on higher centers, thus modulating the incidence and maintenance of gamma activity at the level of the cortex.

History

Rhythmic subthreshold oscillations were first described in the inferior olive [1]. They were calcium-dependent and fired at 1-20 Hz. Soon after, subthreshold oscillations were discovered in entorhinal cortex and these fired in the theta range and were sodium-dependent [2]. These were followed by findings demonstrating gamma band subthreshold oscillations in the cortex and thalamus, both calcium-dependent [3, 4]. Other groups described subthreshold oscillations in the entorhinal cortex [5, 6], and olfactory bulb [7], as well as the dorsal cochlear nucleus [8]. Importantly, these studies established that subthreshold oscillations influenced the timing of APs resulting from synaptic inputs, and triggered the exact occurrence of APs. That is, these membrane oscillations dictated the timing of firing of APs in a circuit [9]. While the amplitude of these oscillations may be low, in the 1-5 mV range, APs are more likely to reach AP threshold, facilitating firing that occurs at the peaks of the oscillations, providing a stable frequency for ensembles of cells [9].

Cortical Synaptic Limits

Sensory perception, problem solving, memory, waking, and rapid eye movement (REM) sleep have all been proposed to involve gamma frequency oscillations [10-14]. Moreover, such coherent events have been proposed to occur at cortical [15], or thalamocortical levels [3]. That is, some of this activity depends on cortico-cortical associations, as well as reverberating cortico-thalamo-cortical activity [16]. The mechanisms involved include inhibitory cortical interneurons manifesting intrinsic oscillatory activity at gamma frequencies [3, 17], and many were found to be electrically coupled [18]. Fast rhythmic bursting pyramidal neurons, some of which are electrically coupled, exhibit intrinsic oscillations [19]. The synchronous activation at gamma band across thalamocortical [20, 21], and other neuronal groups appears to contribute to the merger, or "binding", of information from separate cortical regions [22]. Conversely, disturbances in gamma oscillations are thought to be present in diseases like schizophrenia and Alzheimer's disease [16, 23-25]. Gamma activity is known to occur occasionally during slow wave sleep states and anesthesia, but their brief manifestation of gamma activity may not be sufficient to maintain consciousness [26]. That is, consciousness may be associated with continuous or maintained gamma band activity, but not during interrupted gamma activity [27]. In conclusion, cortical circuits must maintain reverberation at gamma frequencies for prolonged periods for perception and consciousness to occur.

However, there is an unstated assumption that cortical synapses can maintain cortico-cortical association and thalamocortical reverberating signaling at gamma frequencies for prolonged periods. But, cortical synaptic connections alone may not be able to maintain circuit firing at gamma frequencies (~30-90 Hz), so that intrinsic membrane properties appear essential to the maintenance of gamma band activity. For example, considering the primary visual pathway, which manifests high synaptic security, flicker fusion of visual inputs is evidence that cortical circuits cannot "follow" individual visual stimuli presented at rates above 35 Hz [28]. Primary auditory cortex evoked responses can follow stimuli presented up to about 20 Hz [29]. On the other hand, cells with intrinsic membrane properties, coupled with synaptic interactions, may be what allows the circuit as a whole to fire at a high frequency, and is necessary for maintaining high frequencies across the circuit, especially in the gamma range.

Fig. 1. Two cell groups, in one case the population has coherent subthreshold oscillations (A) and in the other, no oscillations are present (B). In both cell groups, output cells receive common inputs, and are electrically connected to adjacent cells through gap junctions. Thus, coherent subthreshold oscillations can arise if each cells manifest subthreshold oscillations.
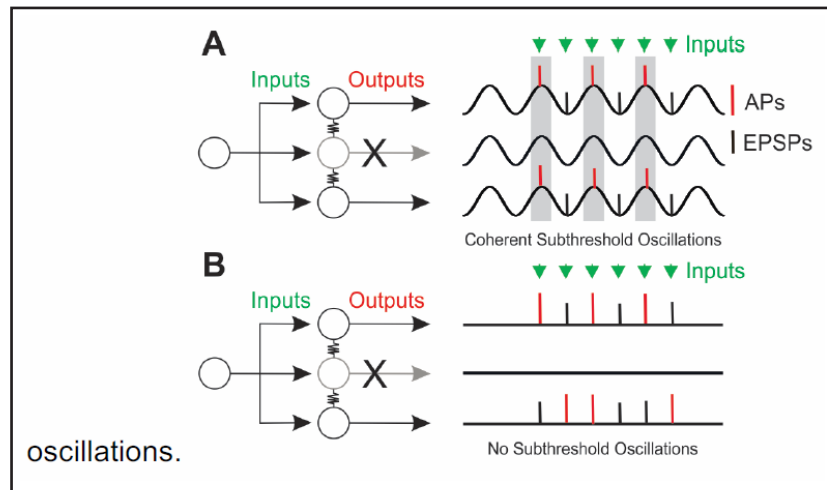
Due to subthreshold oscillations most cells can discharge coherent action potentials at the preferred frequency if excitatory inputs arrive around the peaks when neuronal excitability is high (indicated by the overlapping regions with solid gray bars). In contrast, the cells do not discharge action potentials if excitatory inputs arrive around the trough since neuronal excitability is low. If a synapse fails in one circuit (the middle cell marked by X), the other layers maintain the preferred frequency. If the synapse recovers from the synaptic failures, the circuit ultimately regains coherent firing at that frequency. In contrast, it is likely that neurons, which do not manifest intrinsic subthreshold oscillations, show disrupted coherence of action potential discharges (B), whereas the firing frequency is similar to that of the cell group shown in A. While synaptic failures may not often occur at low frequencies below beta, they will certainly occur at gamma frequencies, particularly in the cortex.

Thus, subthreshold oscillations help circuits maintain a stable frequency rather than generating a range of different frequencies. This point is illustrated in Figure 1, in which two cell groups, in one case the population has subthreshold oscillations (A) and in the other, no intrinsic oscillations are present (B). If there is a synaptic failure from the input to the middle output cell (Xs), the other two output cells will maintain a preferred firing frequency in the case in which oscillations are present. However, in the absence of intrinsic oscillations, the two output cells in Figure 1B will fire at non-coherent times, failing to maintain a stable high frequency.

Ubiquitous Gamma

The cortex and thalamus are not the only regions that manifest gamma frequency activity. Both the hippocampus and the cerebellum possess the intrinsic and synaptic properties necessary for generating gamma band oscillations. There is an association between hippocampal oscillatory activity in the gamma range (30-60 Hz) and afferents from the entorhinal cortex [30]. As mentioned above, entorhinal cortex neurons oscillate at gamma frequencies, suggesting that these afferents are critical for maintaining gamma oscillations in the hippocampus [31]. Gamma frequency activity of cells in the CA1 area has two components, fast (>65 Hz) and slow (~25-60 Hz) components that characterize the CA1 and CA3 subfields, respectively [32]. It has been proposed that, on the one hand, CA1 gamma oscillations from entorhinal cortex at very high frequency are involved in providing information about object and place recognition in rodents [33]. On the other hand, slow gamma oscillations from CA1 are locked to slower frequencies in the CA3 area in charge of memory storage [32, 34]. That is, the two bands subserve different functions.

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The Purkinje cell layer around the apex of the cerebellar lobule manifests gamma band activity [35, 36]. Critical for gamma oscillation generation in Purkinje cells are $GABA_A$ but not glutamate receptors [35]. Coherence between the cerebral cortex and cerebellar cortex at gamma frequencies is present during the performance of a manual precision grip task in monkeys [37]. In addition, cerebello-thalamic activity appears synchronized with neocortical activity at gamma frequencies [38]. Moreover, it was suggested that both cerebellar and thalamo-cortical networks oscillate at similar frequencies to enable coherent information exchange between regions [36].

Gamma band activity in the basal ganglia was observed to lead coherent activity in the cerebral cortex [39, 40]. Several groups concluded that motor cortex gamma synchronization reflects arousal-related activity that enables the initiation of movement [41-43]. Therefore, a region such as the reticular activating system (RAS), which is in charge of arousal, and the thalamus, may together play an early role in the facilitation of movement [44].

Bottom-up Gamma

We found that the pedunculopontine nucleus (PPN), in charge of waking and REM sleep, two states exhibiting gamma frequency activity in the EEG, possesses neurons manifesting gamma frequency activity when stimulated [45]. There is considerable evidence that PPN cells fire at gamma frequencies. Gamma band activity has been observed in the cortical EEG of the cat *in vivo* when the animal is active [17]; in the region of the PPN in humans during stepping, but not at rest [46]; and firing at low frequencies ~10 Hz at rest in the primate, but firing at gamma frequencies when the animal woke up, or when the animal began walking on a treadmill [47]. Thus, the same cells were involved in both arousal and motor control in the PPN *in vitro*, *in vivo*, and across species, including man. We discovered that every PPN neuron exhibited gamma band activity via high threshold, voltage-dependent calcium channels [48]. Later, we found that ~50% of the cells have both P/Q- and N-type calcium channels, while ~25% have only one of the two channels [49]. Early studies (reviewed in [50]), had shown that PPN neurons fire in relation to states of arousal such as "Wake-REM on" cells firing during both waking and REM sleep, while others fire only during waking called "Wake on" cells, and "REM on" cells fire only during REM sleep. We proposed that "Wake-REM on" neurons have both N- and P/Q-type calcium channels, that "Wake on" cells have only P/Q-type channels, and that "REM on" neurons have only N-type channels [50].

The original description of the RAS described the effect of electrical stimulation as inducing "tonic" or "continuous" arousal [51]. Later studies showed that lesions of this region would eliminate "tonic" arousal [52]. Such tonic activity in the PPN probably requires both the channels capable of fast oscillations and the circuitry that involves activating these channels for the maintenance of gamma band activity in the RAS [3, 9, 48, 50, 53-55]. We proposed that the sensory input to the RAS during waking provides the continuous activation of the RAS that allows the maintenance of the background of bottom-up gamma activity. Such activity is necessary to support the process that reliably assesses the world around us on a continuous basis, that is, it is essential for the process of preconscious awareness.

Bottom-up or feed forward brain processes have been proposed to depend on sensory events such as stimuli that activate lower brain centers. The information rises to higher centers to promote perception. Top-down or feedback processing refers to the influence imposed by higher centers on the perception of and attention to incoming stimuli. Gamma frequencies for generating bottom-up, and beta frequencies for inducing top-down, processes were proposed as feed forward and feedback channels, respectively, using different frequency bands [56]. The PPN is likely an early step of the generation of bottom-up gamma activity, which it relays to the intralaminar thalamus. We found that every cell in the parafascicular nucleus manifested high threshold calcium channels [57], a region known to relay gamma activity to the cortex. Cells in the Subcoeruleus region exhibited sodium-dependent gamma oscillations [45], a region known to relay gamma activity to the hippocampus.

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Fig. 2. Diagram of bottom-up gamma projections. Sensory input activates pedunculopontimne nucleus (PPN) dendrites. All PPN cells have N-type channel- and/or P/Q-type channel-dependent subthreshold gamma oscillations and project to the parafascicular nucleus in the intralaminar thalamus (ILT) adjacent to the fasciculus retroflexus (Fr), which projects to upper layers of the cortex (Cx). The PPN also projects to the Subcoeruleus nucleus dorsalis (SubCD), which manifests sodium (Na) channel-dependent subthreshold gamma oscillations (STO) and

projects to the hippocampus (Hipp). The hippocampus also manifests sodium channel-dependent subthreshold gamma oscillations.
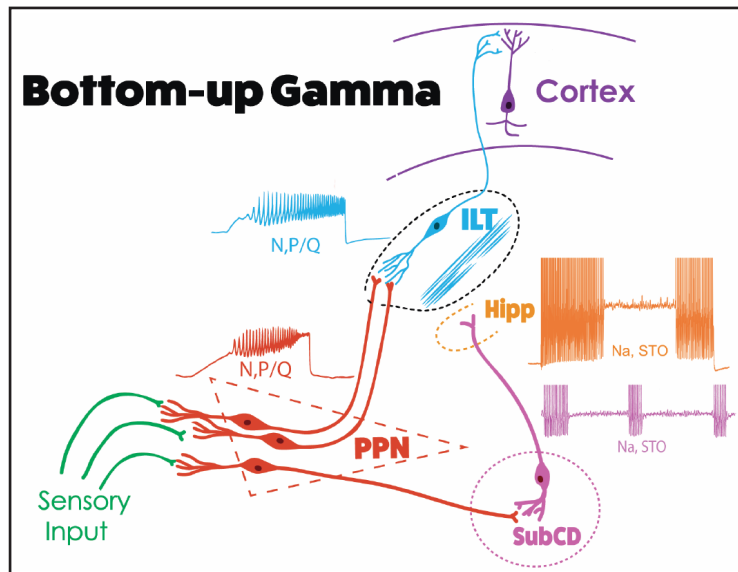
Figure 2 illustrates the organization of arousal-related structures generating bottom-up gamma activity during waking and REM sleep. Sensory input activates PPN neurons, all of which manifest N-type and/or P/Q-type mediated intrinsic membrane oscillations. This information is relayed to the intralaminar thalamus, specifically the parafascicular nucleus, which itself manifests similar calcium channel-dependent intrinsic oscillations. The intralaminar thalamus sends its projections to the upper layers of the cortex. Also, the PPN sends descending projections, especially during REM sleep, to the Subcoeruleus nucleus that manifests sodium-dependent subthreshold oscillations and projects to the hippocampus. How can the synchrony in the gamma oscillations of multiple cell assemblies in above mentioned brain areas be achieved, especially considering the long axon conductance delays? There are excellent review articles describing the mechanisms underlying interregional coherence of network oscillations (see [58] and [56]). In general, it is thought that axon collaterals of glutamatergic projection neurons (e.g., [59]), long-range interneurons (e.g., [60]), and a third region, which is reciprocally connect to two regions (e.g., [61]), contribute to the synchrony between spatially discrete oscillators. Thus, interregional temporal coordination between spatially separate brain regions described in Figure 2 might be achieved via similar mechanisms to those described above.

The issue of coherence between distant cortical sites has received increased attention. Recent findings showed that gamma band activity at the level of the cortex during waking was characterized by coherence across regions, but gamma band activity in the cortex during REM sleep had an absence of coherence [62, 63]. In agreement with the latter, injections of the cholinergic agonist carbachol induced REM sleep with cataplexy (alert wakefulness without muscle tone) that was characterized by decreased gamma band coherence in the cortex [64]. Since the brainstem is the origin of REM sleep drive (for review, see [53]), it is likely that the manifestation of gamma band activity during REM sleep at the level of the cortex begins in the brainstem. We should note that carbachol induced REM sleep which led to decreased coherence, while cataplexy (alert wakefulness without muscle tone) induced increased coherence [64]. Since carbachol will activate both the "waking pathway" and the "REM sleep pathway" discussed above, it is not surprising that these injections induced lack of coherence when REM sleep was elicited and increased coherence when alert wakefulness without muscle tone was elicited. We assume that the manifestation of cortical gamma band activity during waking originates at least in part in the brainstem as well. Therefore, this line

of evidence suggests that, a) brainstem centers drive gamma band activity that is manifested in the cortical EEG; b) during waking, brainstem-thalamic projections are involved in coherence across regions; and c) during REM sleep, brainstem-thalamic projections drive cortical EEG rhythms without coherence between distant sites.

Frequency Specific Hippocampal Interneurons

In the hippocampus, subtypes of GABAergic interneurons represent ~11% of the neuronal population in the subregions [65], and are involved in almost all aspects of hippocampal circuit functions, including coordinated network activity (e.g., theta and gamma oscillations) [66]. We recently found that 5 major subtypes of hippocampal interneurons –parvalbumin-expressing basket cells (PVBCs), cannabinoid type 1 receptor-expressing basket cells (CB_1BCs), Schaffer collateral-associated cells (SCAs), neurogliaform cells, and ivy cell, each produced distinct frequency bands of sodium-dependent intrinsic oscillations [67]. Specifically, a majority of PVBCs (83%) produced intrinsic gamma oscillations near their AP thresholds (see Figure 2). However, the remaining PVBCs (17%), CB_1BCs, SCAs, neurogliaform cells, and ivy cells manifested intrinsic theta, but not gamma, oscillations near their AP thresholds. In the same studies, we demonstrated that a portion of SCAs (17%) and neurogliaform cells (6%) produced intrinsic beta oscillations (15–30 Hz). Our findings suggest not only that major subtypes of GABAergic interneurons manifest cell type-specific intrinsic theta, beta, or gamma oscillations, but also that within-subtype differences in intrinsic membrane oscillations arise in PVBCs, SCAs, and neurogliaform cells. Such information is critical to formulating precise functional models of the generation of specific frequencies related to specific hippocampal operations. Previously [67], we examined the properties of intrinsic oscillations of only 5 of 21 subtypes of GABAergic interneurons in the CA1 subregion. Given that other major subtypes of GABAergic interneurons, e.g., axo-axonic cells, bistratified cells, and oriens-lacunosum molecular interneurons, are known to be also involved in theta and gamma oscillations [68], future studies should determine the properties of intrinsic oscillations of other interneurons.

How is cortical network activity generated? At least two distinct types of models of network activity have been proposed: intrinsic resonance property-based models and circuit-based models. Our findings of cell type-specific intrinsic oscillations in hippocampal GABAergic interneurons are in general agreement with intrinsic resonance property-based theta and gamma models. Neuronal intrinsic resonance properties cause hippocampal interneurons to produce intrinsic subthreshold oscillations without synaptic interactions [67, 69-71]. Although the precise role of intrinsic oscillations of hippocampal interneurons in coordinated network activity is largely unknown, there is evidence indicating that intrinsic subthreshold oscillations are key factors in network oscillations [44, 48, 72-74]. Thus, we hypothesize that intrinsic oscillations of gamma cells (i.e., 83% of PVBCs tested; [67]) may facilitate, or even cause, precise timing of APs during network gamma oscillations. This is particularly true if the oscillations of multiple cells synchronize. Intrinsic oscillations arising from PVBCs and neurogliaform cells can be synchronized in the CA1 network level via electrical synapses, since they are highly coupled with their own or other types of GABAergic interneurons [75-79]. On the other hand, intrinsic theta oscillations of theta cells (i.e., 17% of PVBCs tested; [67], CB_1BCs, SCAs, neurogliaform cells, and ivy cells are conducive to precise AP discharges during hippocampal theta oscillations.

In circuit-based models, GABAergic interneurons are critically involved in gamma oscillations through reciprocal interactions via chemical synapses with pyramidal cells (i.e., pyramidal-interneuron network gamma, as in 'PING' model), or other GABAergic interneurons (i.e., interneuron network gamma, as in 'ING' model) [58]. Similar to models of gamma oscillations, hippocampal theta oscillations are thought to arise primarily from synaptic interactions of GABAergic interneurons with excitatory cells [80-83]. Since not only synaptic and circuit properties of individual neurons, but also intrinsic resonant properties can contribute to hippocampal network activity, the two types of hippocampal models of network activity are not mutually exclusive.

Since precise roles of intrinsic oscillations of hippocampal GABAergic interneurons in hippocampal network oscillations are largely unknown, experimental and computational studies should determine the roles. Our data on intrinsic oscillatory properties of neurochemically identified GABAergic interneurons will be of critical importance in computational models of hippocampal gamma and theta oscillations. It is reasonable to expect that intrinsic theta and gamma oscillations of GABAergic interneurons in the hippocampus are key factors in network theta and gamma activity if these data are incorporated into existing computational models of the CA1 region, such as an innovative full-scale computational model based on experimental results on intrinsic, synaptic, and circuit properties of neurochemically identified neurons [80]. The critical role of intrinsic subthreshold oscillations in network gamma oscillations has been shown in the olfactory bulb using computational and experimental approaches [72, 84]. Accordingly, future studies should also experimentally determine if intrinsic theta and gamma oscillations of hippocampal interneurons simultaneously occur with hippocampal network activity, and determine if hippocampal interneurons, which generate intrinsic oscillations, fire at the peaks of intrinsic oscillations.

Finally, given that network theta and gamma activity are often compromised in a variety of neurological and psychiatric disorders [85-91], and abnormal activities of hippocampal interneurons are often associated with these diseases [92-100], future research should also determine if disruption of intrinsic oscillations in one or more of the major interneuron subtypes occurs in neuropathological conditions such as epilepsy. The results from such research will provide new insights into the mechanisms underlying compromised hippocampal rhythmogenesis in various diseases, and could provide a basis for novel interventions to restore compromised hippocampal theta and gamma oscillations.

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Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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