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Keeping Inhibition Timely

GABAergic interneurons play a key role in orchestrating cortical network oscillations. In this issue of *Neuron*, two studies (Bacci and Huguenard and Vida et al.) identify how networks of fast-spiking interneurons can enhance the regularity, precision, and robustness of their own rhythmicity via individual and collective self-innervation.

Neuronal networks of the mammalian cortex are comprised of two main classes of neurons: principal cells and GABAergic interneurons. Whereas principal cells excite other neurons to generate action potentials, the timing of those action potentials is to a large extent controlled by GABAergic interneurons. During active network states, characteristic oscillations in several frequency ranges emerge, at least partly due to the extensive feedback coupling between principal neurons and GABAergic interneurons. Some of the best studied of these network oscillations are the so-called gamma oscillations (30–100 Hz), which have been linked to cognitive processing (see Whittington and Traub, 2003). During gamma oscillations, fast-spiking (FS) GABAergic interneurons maintain a regular rhythm, tightly coupled to the population oscillation, whereas pyramidal neurons fire at a slower pace and are more loosely coupled to the on-going rhythm. How can the network of

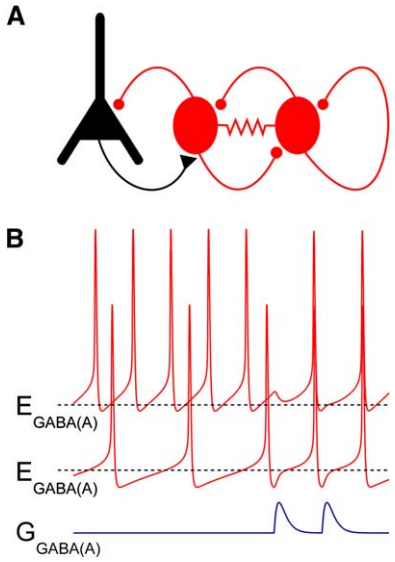

Figure 1. Diverse Mechanisms Underlying Interneuronal Synchrony

(A) Simplified wiring diagram showing autaptic and reciprocal connections between FS interneurons (red) and pyramidal cells (black).

(B) Homogenization and synchronization of firing by shunting inhibition in interneuronal networks. When the reversal potential for GABAergic events (E, dotted lines) is above the resting membrane potential, but below spike threshold, GABAergic conductances (G, lower trace) can decelerate strongly activated neurons (upper trace), while accelerating the firing in weakly activated neurons (middle trace). Computer simulation of Hodgkin-Huxley kinetics in a single-compartment model.

GABAergic interneurons remain in oscillatory synchrony in the presence of barrages of other on-going synaptic activity? By studying isolated GABAergic interneurons in brain slices and simulating their interactions, two new mechanisms have been identified that help achieve this (Bacci and Huguenard, 2006; Vida et al., 2006).

First, Bacci and Huguenard show that self-innervation, or so-called "autaptic" transmission, has the capacity to enhance spike fidelity in individual FS interneurons (Figure 1A). Anatomically, it is well established that FS interneurons innervate themselves (Tamas et al., 1997). These autaptic connections provide a brief GABA(A) receptor-mediated conductance following each action potential (Bacci et al., 2003). The function of this conductance has remained unclear. Now, Bacci and Huguenard link this conductance to network oscillations by showing an enhanced regularity and spike-timing precision mediated by these autaptic connections (Bacci and Huguenard, 2006). Blocking GABA(A) receptors dramatically increased spike jitter in interneurons, and the elegant use of dynamic clamp (Prinz et al., 2004) to mimic the autaptic connections was sufficient to restore the precision in spike timing. The use of dynamic clamp in this study was justified because autaptic connections target the somatic domain. Hence, adding an artificial conductance through the recording electrode at the soma can closely mimic the effect of synaptic input. There is a difficulty in extrapolating to the functional importance of these autapses in active networks, but Bacci and Huguenard also show that autaptic effects on both regularity and spike-timing precision are robust against synaptic noise, suggesting that the

mechanism may well operate in the intact brain (Bacci and Huguenard, 2006).

Autaptic connections add to the repertoire of mechanisms of FS interneurons that ensure regular and temporally precise firing. Other mechanisms include their intrinsic membrane properties, which endow subthreshold resonance and firing frequency preference at gamma frequencies (as discussed by Whittington and Traub, 2003). Furthermore, FS interneurons are vastly interconnected through chemical and electrical synapses, both of which contribute to the synchronization of interneuronal networks (Whittington and Traub, 2003). A second study in this issue of *Neuron*, by Vida et al., demonstrates how GABAergic connections between FS interneurons can enhance the robustness of interneuronal synchronization (Vida et al., 2006). By decreasing firing rates in strongly activated neurons and increasing firing rates in weakly activated neurons, the GABAergic interconnectivity increases homogeneity in neuronal firing rates within the interneuronal network. How is this achieved? The mechanism appears to utilize the dual nature of GABAergic inhibition (Figure 1B).

Synaptic events have two effects on the postsynaptic membrane. One is a shunting effect due to increase of postsynaptic conductance, the other is due to the synaptic "battery" to which this conductance is connected, leading to a depolarizing (excitatory) or hyperpolarizing (inhibitory) current. For glutamatergic excitatory synapses, the current effect is usually dominating, but for GABAergic synapses, for which the reversal potential is close to the resting membrane potential, the shunting effect may be more important, and this is referred to as "shunting inhibition" (Staley and Mody, 1992). Whereas the shunting effect is always inhibitory, the GABAergic current can be hyperpolarizing or depolarizing depending on the reversal potential relative to the actual membrane potential. Thus, the effect of a GABAergic event can sometimes first be inhibitory due to shunting and then excitatory due to depolarization (Gulledge and Stuart, 2003).

In mature pyramidal neurons, the GABA(A) reversal potential is usually negative to the resting membrane potential due to the action of the K^+/Cl^- cotransporter KCC2 (Rivera et al., 1999). In contrast, in FS interneurons of the dentate gyrus, Vida et al. found that the GABA(A) receptor reversal potential is positive to the resting membrane potential (but negative to spike threshold). The functional consequences of this difference in the GABA(A) reversal potential in relation to oscillations are not immediately obvious, as both hyperpolarizing and shunting inhibition have the ability to synchronize firing between neurons. However, Vida et al. convincingly demonstrate that the inclusion of GABAergic events that have the potential to be both shunting and depolarizing adds a highly desirable property to the interneuronal network: both the ability to accelerate weakly activated interneurons and decelerate strongly activated interneurons. This promotes the homogenization of firing rates and enables fast coherent oscillations to be generated even when the tonic drive to the interneuronal network is weak and heterogeneous.

Both studies were done under conditions where fast synaptic excitation would not interfere with the oscillations, either by working with single pharmacologically isolated neurons or by modeling a paradigm where tonic, rather than phasic, excitation drives the interneuronal network (Whittington and Traub, 2003). At the other extreme, gamma oscillations can also emerge from pure feedback loops between pyramidal neurons and GABAergic interneurons (Csicsvari et al., 2003; Mann et al., 2005). Under the latter conditions, the oscillation frequency is slower, as it depends on the summation of both the excitatory and inhibitory synaptic time constants. Of course, in the intact brain, both recurrent excitation and recurrent inhibition are likely to play a role in cellular and network synchronization. Modeling studies show that the population oscillation frequency that emerges in these networks is determined by the recurrent excitation/inhibition balance (Brunel and Wang, 2003). By varying the involvement of phasic excitation, such intracortical networks could potentially support oscillations over a wide variety of frequencies, from beta (15–30 Hz) to fast ripple frequencies (140–200 Hz).

The new insights into interneuronal rhythms provided by the Bacci and Huguenard and Vida et al. studies lend support to the idea that network oscillations are an integral and important part of cortical information processing. Although oscillations are hard to avoid in feedback-coupled networks, such as the cortex, evolution has apparently developed mechanisms that further enhance rather than suppress their oscillatory behavior. The known repertoire of mechanisms possessed by GABAergic interneurons to maintain their spike-timing precision and synchrony continues to expand, and GABAergic interneurons are likely to have more secrets to reveal before we are able to understand their role in neural information processing and cognitive function. Finding this out is as timely as ever.

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