Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Two Modes of GABA_B: Specific Localized Inhibition and Global Network Inhibition

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Review of Chalifoux and Carter

GABA_B receptors are inhibitory metabotropic receptors that modulate neuronal excitability. Clinically, baclofen, the agonist of the GABA_B receptor, has been used to treat various disorders such as alcohol addiction, epilepsy, and spasticity (Dario et al., 2007). However, GABA_B expression in the brain is widespread and complex, with both presynaptic and postsynaptic components, resulting in a complex clinical phenotype after baclofen administration (Vigot et al., 2006).

Recently Chalifoux and Carter (2011) investigated how activating this GABA_B network influences calcium currents in different dendritic compartments of L2/3 pyramidal cells in prefrontal cortex (PFC). Specifically, they used two-photon calcium imaging in acute brain slices of C57BL/6 mice to look at calcium currents evoked by back-propagating action potentials, the main feedback signal from a soma to its dendrites.

The first main finding was that GABA_B activation by baclofen reduced the amplitude of calcium currents. Although receptor activation decreased membrane resistance via inward rectifying potassium channels

and induced a slow inhibitory current, the decrease in calcium currents resulted primarily from a direct modulation of the voltage-sensitive calcium channels (VSCCs). The second main finding was that the reduction in calcium currents by GABA_B occurred to an equal extent in basal and apical dendritic compartments, and it occurred in both dendritic shafts and spines. The latter is surprising because in hippocampal CA1 pyramidal neurons, GABA_B activation reduced calcium currents only in apical spines, not in apical dendrites, basal dendrites, or basal spines (Sabatini and Svoboda, 2000).

These findings support the hypothesis that GABA_B has different modes of action depending on the cell type and region. The first mode, exemplified by hippocampal CA1 pyramidal cells (Sabatini and Svoboda, 2000), is inhibition of specific synaptic inputs to neurons, allowing a neuron to inhibit some inputs while listening to others. This type of inhibition is suitable for input-specific synaptic plasticity required for hippocampal encoding. The second mode of action of GABA_B, which Chalifoux and Carter (2011) have found in L2/3 pyramidal neurons, is a global inhibition of dendritic excitability of a single neuron or across a small network of neurons (Wang et al., 2010). This might be useful when the brain switches attention from one task to another task requiring a different brain network, a function attributed to prefrontal cortex.

Although these two modes of GABA_B action have not been shown explicitly, multiple lines of evidence support this hypothesis. Electron microscopic analysis has shown that GABA_B receptors are present both at the synaptic cleft and outside synapses on the dendritic shaft (López-Bendito et al., 2002; Kulik et al., 2003). Synaptic GABA_B receptors can keep tight control of synapse dynamics, blocking or mediating the signal coming onto the synapse. Extrasynaptic GABA_B receptors, conversely, can modulate dendritic signals being transmitted to the soma as well as the antidromic back-propagating action potentials.

These two locations of GABA_B receptors are thought to correspond to the two types of inhibitory currents measured in neurons, namely, phasic and tonic inhibition. Phasic GABA_B inhibition is a short, fast, inward current (on the order of hundreds of milliseconds), after activation of an inhibitory synapse (Chalifoux and Carter, 2011). This would correspond to activation of synaptic GABA_B receptors. In contrast, tonic inhibition, which lasts for many minutes, is thought to result from the constant presence of GABA, as mediated by extrasynaptic synapses (Wang et al., 2010). Again, this follows the idea of two functions of GABA_B, one of fast, specific inhibition and another involving slow, more generalized inhibition.

This hypothesis, although supported by some circumstantial evidence, still needs to be tested directly. Immunolabeling of

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GABA_B receptors has shown global expression of the receptor in both cortex and hippocampus (Charles et al., 2001; Vigot et al., 2006). However, this method cannot discriminate between pyramidal cells and interneurons. In addition, GABA_B has a prominent role in presynaptic terminals, influencing release probability, resulting in additional labeling of presynaptic sites (Sakaba and Neher, 2003). Therefore, a full dendritic electron microscopy reconstruction of pyramidal neurons in CA1 hippocampus and layer 2/3 prefrontal cortex with immunogold labeling of GABA_B receptors is essential to establish the synaptic and dendritic localization that could underlie functional differences. Determining the proportion of extrasynaptic versus synaptic receptors will give an indication of whether GABA_B has different local or global functions in the two regions.

From a functional approach, an experiment that monitors global GABA concentration both in L2/3 and in the hippocampus while an animal performs different types of attention tasks using, for example, spectroscopy and fMRI, would be informative (Gaetz et al., 2011). The hypothesis predicts that tonic GABA con-

centrations will remain stable in the hippocampus while varying in L2/3 of PFC.

Learning whether GABA_B can function at local and global inhibitory levels in different brain regions is essential for therapeutic purposes. If the hypothesis holds true, promoting GABA_B activation to reduce dendritic excitability in the cortex in the case of epilepsy might have adverse effects upon dendritic processing underlying hippocampal memory (Dario et al., 2007). Therefore, studies identifying cellular mechanisms of GABA_B-mediated function play an important role in understanding inhibitory effects in the brain at local and global levels.

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