SYNAPTIC PHYSIOLOGY

Same but different

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GABA (γ-aminobutyric acid), the main inhibitory neurotransmitter in the vertebrate nervous system, has many modes of action. For one of its receptors $GABA_B$ — a heterodimer consisting of $GABA_{B1}$ and $GABA_{B2}$ subunits — functional diversity is achieved by different synaptic localization and physiological action of its subunit isoforms $GABA_{B1a}$ and $GABA_{B1b}$, according to two studies published in *Neuron*.

To uncover the role of different $GABA_{B1}$ versions in inhibitory neurotransmission, Bernhard Bettlers and colleagues used an ingenious approach to generate knockout mice in which $GABA_{B1a}$ and $GABA_{B1b}$ were inactivated one at a time. Electron microscopy studies showed that, in the hippocampus, $GABA_{B1a}$ was predominantly localized at glutamatergic terminals, whereas $GABA_{B1b}$ was mainly found at dendritic spines opposite to the glutamate release sites. This differential localization of $GABA_{B1}$ isoforms correlated with their functional differences: at hippocampal CA3-to-CA1 synapses, $GABA_{B1a}$ assembled receptors that blocked presynaptic glutamate release, while $GABA_{B1b}$ was involved in postsynaptic inhibition of neuronal firing. Intriguingly, the constitutive absence of $GABA_{B1a}$, but not $GABA_{B1b}$, resulted in impaired synaptic plasticity and hippocampus-dependent memory formation. This suggests that different $GABA_B$ receptor compositions might mediate distinct neural functions.

In a companion paper, Perez-Garci and colleagues report similar results of distinct $GABA_{B1}$ receptor functions in pyramidal neurons residing in layer 5 (L5) of the neocortex. These L5 neurons are innervated by numerous inhibitory inputs, including those from interneurons in L1. The researchers first established that extracellular stimulation of L1 inhibited the dendritic Ca^{2+} spikes in L5 pyramidal neurons. Further, the short-lasting component of this inhibitory effect was mediated by $GABA_A$ receptors, whereas the long-term counterpart was mediated by $GABA_B$ receptors. Using the knockout mice generated by Bettler *et al.*, the researchers found that L5 pyramidal neurons from $GABA_{B1a}$-deficient mice showed normal short- and long-lasting inhibitory components in response to L1 stimulation. By contrast, the absence of $GABA_{B1b}$ completely abolished the long-term inhibitory response of L5 pyramidal neurons, but the $GABA_A$-mediated short-term inhibition was unaffected.

These two studies shed fresh light on the apparent contradiction between functional diversity and molecular simplicity of the $GABA_B$ receptor system. It will be interesting to test whether other GABA receptors deploy similar strategies to generate distinct activity under different physiological conditions.

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ORIGINAL RESEARCH PAPERS Vigot, R. *et al.* Differential compartmentalization and distinct functions of $GABA_B$ receptor vaiants. *Neuron* **50**, 589–601 (2006) | Perez-Garci, E. *et al.* The $GABA_{B1b}$ isoform mediates long-lasting inhibition of dendritic Ca^{2+} spikes in layer 5 somatosensory pyramidal neurons. *Neuron* **50**, 603–616 (2006)
FURTHER READING Farrant, M. & Nusser, Z. Variations on an inhibitory theme: phasic and tonic activation of $GABA_A$ receptors. *Nature Rev. Neurosci.* **6**, 215–229 (2005)
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