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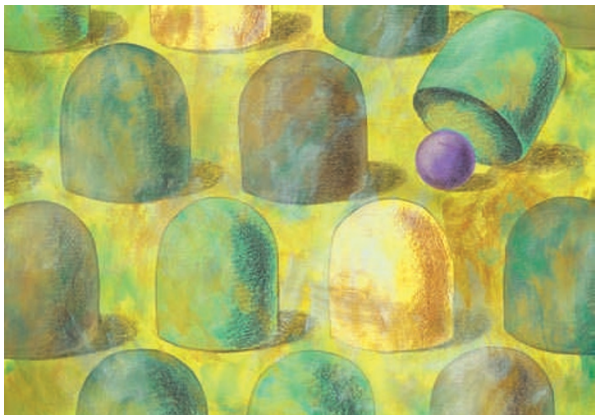
NEUROTRANSMITTER RECEPTORS

Another trick up $GABA_BR$'s sleeve

Metabotropic GABA (γ-aminobutyric acid) type B receptors ($GABA_BRs$) play an important part in the regulation of synaptic transmission as they inhibit presynaptic release and activate postsynaptic K^+ channels. Now, Chalifoux and Carter show that $GABA_BRs$ also suppress postsynaptic Ca^{2+} signals mediated by NMDARs (*N*-methyl-D-aspartate receptors) and inhibit multivesicular release at individual spines.

The authors used two-photon optical quantal analysis to study synaptic transmission at individual spines on the dendrites of layer 2–3 pyramidal neurons from acute prefrontal cortical slices. They found that the $GABA_BR$ agonist baclofen decreased both the probability of release and the synaptic potency (the amplitude of successful release events). Inhibiting signalling downstream of postsynaptic $GABA_BRs$ with the non-hydrolysable GDP analogue guanosine-5′-(β-thio) diphosphate (GDP-βS) did not prevent the decrease in synaptic potency. As this effect of baclofen was no longer evident under conditions of low extracellular Ca^{2+} concentration, these results suggest that $GABA_BR$ signalling regulates multivesicular release at the presynaptic terminal.



To study the effects of $GABA_BR$ activation on postsynaptic NMDAR-dependent Ca^{2+} signals, the authors used two-photon glutamate uncaging. GDP-βS prevented the inhibition of NMDAR-dependent Ca^{2+} signals by baclofen in individual spines, showing that modulation of the postsynaptic Ca^{2+} signal by $GABA_BR$ requires G protein activation. Similar results were obtained using the protein kinase A (PKA) antagonist H89 and the PKA-inhibiting peptide PKI, implicating the PKA pathway in the postsynaptic effects of $GABA_BR$ activation. Finally, $GABA_BR$ activation had no effect on overall synaptic currents mediated either by NMDAR or AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors. Together, these results suggest that $GABA_BRs$ selectively regulate the Ca^{2+} permeability of NMDARs.

By taking advantage of a combination of optical tools, this study identifies novel presynaptic and postsynaptic mechanisms by which $GABA_BRs$ influence synaptic transmission at individual spines. As NMDAR-dependent Ca^{2+} signals in neuronal spines are particularly important for synaptic plasticity and spine excitability, their regulation by $GABA_BRs$ is likely to have wide implications for our understanding of neuronal physiology.

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ORIGINAL RESEARCH PAPER Chalifoux, J. R. & Carter, A. G. $GABA_B$ receptors modulate NMDA receptor calcium signals in dendritic spines. *Neuron* **66**, 101–113 (2010)

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