# New and Notable

## A Cerebellar Synapse for ''Heavy Duty'' Transmission

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Purkinje cells are GABAergic neurons that provide the major output of the cerebellar cortex and can sustain very high action-potential firing rates (Eccles et al., 1967). How inhibitory synapses made by Purkinje cells axons can sustain such a ''heavy duty'' task has remained a puzzle until now. The article by Pugh and Raman in this issue (page 1740) complements the work performed by this laboratory in the past three years (Telgkamp et al., 2004; Telgkamp and Raman, 2002) that revealed the striking adaptive changes that this inhibitory synapse must make to allow the flow of a well-timed and effective cerebellar output. The fast rate of presynaptic vesicle release exceeds vesicle replenishment, and the rapid desensitization of postsynaptic $GABA_A$ receptors further limits the capacity of individual release sites to sustain high-frequency synaptic transmission. These limitations are compensated by the peculiar anatomical structure of the Purkinje terminal-deep nuclei GABAergic inhibitory synapse. These terminals are very large, contain multiple release, and the GABA transporters that clear GABA from the synaptic cleft are located exclusively at the periphery of the synapse. This anatomical structure allows an effective GABA spillover to occur, minimizing short-term depression (Telgkamp et al., 2004; Telgkamp and Raman, 2002). Once established that spillover occurs during synaptic transmission at these synapses, the logical question that comes to mind is: How do the specific biophysical properties of the postsynaptic $GABA_A$ receptor regulate the efficacy of spillover, and particularly, desensitization? Different $GABA_A$ receptors are endowed with distinct desensitization properties that have proven crucial in regulating the duration of synaptic currents (Jones and Westbrook, 1996). Using ultrafast GABA applications to excise membrane patches from neurons in the cerebellar deep nuclei, Pugh and Raman describe the GABA current at various application frequencies and durations. The results obtained are then used to model the pre- and postsynaptic biophysical parameters that characterize the basic kinetics of synaptic transmission at low and high frequencies, taking into account the multiplicity of release sites, spillover constraints, and the gating kinetics of postsynaptic GABA channels.

The extent to which desensitization regulates the amplitude of a stimulus train depends on the recovery rate. The ultrafast GABA application studies in this work indicated that while consistent desensitization can occur during each synaptic pulse, the fast recovery from desensitization allows ~80% of receptors to be available within 100 ms. In addition, vesicular release probability and the extent of spillover finely tune the concentration that distant receptors feel during trains of stimuli. Therefore the response in excised membrane patches to trains of GABA application at low concentrations also had to be measured. The striking result, as seen in Fig. 4 of the article, implies that high frequency trains of inhibitory synaptic currents do not decline in amplitude at a low GABA concentration.

To model these results, it was necessary to account for diffusion, the number of release sites, and their relative independence. Although in general terms this model works well, the experimental data can best be described only with a particular combination of parameters for presynaptic release probability, postsynaptic occupancy, and gating. The outcome of this study indeed proves that presynaptic vesicle depletion and postsynaptic receptor desensitization both contribute to decrease in synaptic efficacy at high stimulation frequency, but spillover and the rapid recovery from desensitization are effective in minimizing short-term depression. An intriguing finding was made, however, when the depression measured from real trains of synaptic responses recorded from nuclear neurons (Telgkamp et al., 2004; Telgkamp and Raman, 2002) were compared to the simulation. To match the characteristics of the experimental data with the simulated data, it was necessary to ''destabilize'' a rapid desensitization state. This was not due to a fault of the model, but to the fact that the model was built on data from currents recorded from excised patches that matched, only superficially, the gating kinetics of synaptic receptors. The outcome of these findings is quite exciting, as it implies a specific form of regulation of the biophysical properties of synaptic receptors with a precise functional role. What this regulation is, and how it changes synaptic receptors, remains to be elucidated. Indeed, for several neurotransmitters the properties of synaptic receptors differ from those of extrasynaptic receptors. However, since extrasynaptic receptors are more amenable to studies with rapid application, this poses a formidable challenge to the field. Perhaps the discovery of molecules that are involved in synapse formation will allow us to reconstitute synaptic function in heterologous systems, and dissect out the mechanism by which synaptic receptors are rendered unique.

In summary, the work of Pugh and Raman provides important evidence for a mode of action of an inhibitory synapse that is needed to sustain the load required to translate the main cerebellar output from Purkinje neurons. Most importantly, it demonstrates that $GABA_A$ receptor properties are adapted to allow

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responses to be generated by spillover from distant synaptic sites.

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