Control of Neurotransmitter Release by Presynaptic NMDA Receptors

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Objective: NMDA receptors are ideal as detectors of coincident pre and postsynaptic activity in Hebbian plasticity, as they require both glutamate and depolarization to open, flux calcium and evoke plasticity. In this classical view, NMDA receptors have to be located postsynaptically. However, at some central synapses, there is evidence for putatively presynaptic NMDA receptors (preNMDARs). The objective of our study was to investigate the expression and functional impact of preNMDARs at excitatory synapses onto several different neuronal classes in layer 5 of mouse visual cortex.

Methods: We examined the impact of preNMDAR blockade on spontaneous release as well as on evoked responses using extracellular stimulation or paired recordings in acute cortical slices. We distinguished cell types based on genetic markers, electrophysiology, and morphology visualized using 2-photon microscopy or biocytin histology.

Results: Several approaches suggested that preNMDAR expression in neocortical layer 5 is cell specific. For example, in pyramidal neurons, preNMDAR blockade reversibly suppressed the frequency of spontaneous release (76 ± 5%; $p<0.01$, $n=10$), but not in a subset of inhibitory interneurons (96 ± 2%, $p=0.14$, $n=7$). Moreover, at synapses where preNMDARs were found, they appeared to help maintain neurotransmission in the face of high-frequency firing.

Conclusions: Given their impact on neurotransmission, preNMDARs may specifically regulate information flow and activity in local microcircuits. This calls the classical view on NMDA receptors into question and suggests that NMDA receptors may have diverse functional roles.