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Effects of Synaptic Frequency and Glutamate Transport on NMDA Receptor Activity at the Shaffer-CA1 Synapse

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Glutamate is the predominant excitatory neurotransmitter in the central nervous system and it plays a central role in many processes including perception, learning, and memory. Glutamate transporters are thought to help maintain synapse specificity in the hippocampus by limiting spillover of glutamate. The NMDA subtype of glutamate receptor (NMDAR) is a key player in neuronal plasticity and serves as a coincidence detector by requiring binding of transmitter in addition to postsynaptic membrane depolarization to relieve Mg^{2+} block. While inhibition of glutamate transport has been shown to cause increased NMDAR activity in conditions permissive for receptor signaling, such as in the absence of extracellular Mg^{2+}, the roles of transport in physiological conditions are less well understood. In this work we show that in Mg^{2+}-free conditions, increasing release site density prolonged the time course of EPSCs and fEPSPs evoked at low frequency by enhancing NMDAR activity, consistent with published work by several groups. However, in physiological [Mg^{2+}], this effect was not observed. NMDAR fEPSPs were selectively enhanced by repetitive activity in a frequency range that closely matched the decay kinetics of [Mg^{2+}]-blocked NMDAR channels monitored with depolarizing voltage pulses. Glutamate transporter inhibition in physiological [Mg^{2+}] increased NMDAR signaling in the same frequency-dependent manner. The data suggest that at low frequencies, Mg^{2+} block rather than glutamate transport plays a dominant role in restricting extrasynaptic NMDAR activity, and that a pool of glutamate-bound and Mg^{2+}-blocked NMDARs signal in a phase-shifted manner during repetitive synaptic activity at frequencies governed by channel desensitization and transmitter unbinding. The data also suggest a potential mechanism contributing to theta frequency-dependent associative LTP.