A Functional Link Between the Regulation of Vesicle Priming, Synaptic Short-Term Plasticity, and Working Memory

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Hippocampal mossy fiber (hMF) to CA3 pyramidal cell synapses are thought to support the formation of working memory through presynaptic short-term facilitation (STF) and post-tetanic potentiation (PTP). However, the molecular mechanisms underlying these transient forms of synaptic enhancement remain poorly understood. We found that Munc13-1-mediated priming of synaptic vesicles (SVs) at active zones controls hMF STF and PTP in response to Ca^{2+}-phospholipid and Ca^{2+}-calmodulin (CaM) signaling. Knock-in mice expressing Munc13-1 variants that are insensitive to Ca^{2+}-phospholipid and Ca^{2+}-CaM signaling exhibit severely impaired STF and PTP at hMF synapses. Moreover, the PTP-induction threshold is strongly increased upon the loss of Ca^{2+}-phospholipid-Munc13-1 signaling. Since these synaptic defects are accompanied by working memory deficits, especially in mice expressing the Ca^{2+}-phospholipid-insensitive Munc13-1 variant, we conclude that Ca^{2+}-dependent regulation of Munc13-1-mediated SV priming co-determines hMF short-term plasticity and working memory formation.