Non-conserved Ca$^{2+}$/calmodulin binding sites in Munc13s differentially control synaptic short-term plasticity.


Munc13s are presynaptic proteins that mediate synaptic vesicle priming and thereby control the size of the readily releasable pool of vesicles. During high synaptic activity, Munc13-1 and its closely related homolog ubMunc13-2 bind Ca$^{2+}$/calmodulin, resulting in enhanced priming activity and in changes of short-term synaptic plasticity characteristics. Here, we studied whether bMunc13-2 and Munc13-3, two remote isoforms of Munc13-1 with a neuronal subtype-specific expression pattern, mediate synaptic vesicle priming and regulate short-term synaptic plasticity in a Ca$^{2+}$/calmodulin-dependent manner. We identified a single functional Ca$^{2+}$/calmodulin binding site in these isoforms, and provide structural evidence that all Munc13s employ a common mode of interaction with calmodulin, despite the lack of sequence homology between their Ca$^{2+}$/calmodulin binding sites. Electrophysiological analysis showed that, during high frequency activity, Ca$^{2+}$/calmodulin binding positively regulates the priming activity of bMunc13-2 and Munc13-3, resulting in an increase in the size of the readily releasable pool of vesicles and subsequently in strong short-term synaptic enhancement of neurotransmission. We conclude that Ca$^{2+}$/calmodulin-dependent regulation of priming activity is structurally and functionally conserved in all Munc13 proteins, and that the composition of Munc13 isoforms in a neuron differentially controls its short-term synaptic plasticity characteristics.