An atypical role for CRMP-2 in neurotransmitter release via interaction with presynaptic Ca2+ channels

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Abstract

Collapsin response mediator proteins (CRMPs) specify axon/dendrite fate and axonal growth of neurons through protein-protein interactions. Their functions in presynaptic biology remain unknown. Here, we identify the presynaptic N-type Ca2+ channel (CaV2.2) as a CRMP-2-interacting protein. CRMP-2 binds directly to CaV2.2 in two regions; the channel domain I-II intracellular loop and the distal C-terminus, but not to any other regions. Both proteins co-localize within presynaptic sites in hippocampal neurons. Overexpression in hippocampal neurons of a CRMP-2 protein fused to EGFP caused a significant increase in Ca2+ channel current density whereas lentivirus-mediated CRMP-2 knockdown abolished this effect. Interestingly, the increase in Ca2+ current density was not due to a change in channel gating. Rather, cell surface biotinylation studies showed an increased number of CaV2.2 at the cell surface in CRMP-2-overexpressing neurons. These neurons also exhibited a significant increase in vesicular release in response to a depolarizing stimulus. Depolarization of CRMP-2-EGFP overexpressing neurons elicited a significant increase in release of glutamate compared to control neurons. Toxin block of Ca2+ entry via CaV2.2 abolished this stimulated release. Thus, the CRMP-2-Ca2+ channel interaction represents a novel mechanism for modulation of Ca2+ influx into nerve terminals and, hence, of synaptic strength.