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Calcium Channel Regulation in Synaptic Plasticity and the Fight-or-Flight Response

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P/Q-type calcium currents are conducted by $Ca_v2.1$ channels initiate synaptic transmission at many synapses. These channels are regulated by binding of calmodulin to a bipartite site in the C-terminal domain composed of an IQ-like motif and a calmodulin binding domain (CBD). Brief local increases in calcium support facilitation of calcium channel activity through calcium binding to EF-hands 3 and 4 of calmodulin and interaction with the IQ-like motif of the $Ca_v2.1$ channels. Sustained global increases in calcium cause calcium-dependent inactivation through calcium binding to EF-hands 1 and 2 of calmodulin and interaction with the CBD. Neuronal calcium sensor proteins CaBP1 and VILIP-2 bind to the same site and cause enhanced inactivation or enhanced facilitation, respectively. $Ca_v2.1$ channels expressed exogenously in sympathetic ganglion neurons reconstitute synaptic transmission initiated by P/Q-type calcium currents with typical synaptic facilitation and depression. Both facilitation and depression of synaptic transmission are markedly reduced by mutations that prevent regulation of $Ca_v2.1$ channels by calmodulin and the calcium sensor proteins. Our results show that, at this model synapse, calcium- and voltage-dependent regulation of $Ca_v2.1$ channels through interaction with calcium sensor proteins is responsible for most of short-term synaptic plasticity.

$Ca_v1.1$ and $Ca_v1.2$ channels in skeletal and cardiac muscle, which initiate excitation-contraction coupling, are regulated by the sympathetic nervous system and PKA as part of the fight-or-flight response. PKA must be bound to the distal C-terminal domain via AKAP15, anchored through a modified leucine-zipper motif, in order to up-regulate channel activity effectively. Surprisingly, the distal C-terminal domain with the PKA anchoring site is cleaved by proteolytic processing, but remains noncovalently bound as a potent autoinhibitory domain. Reconstitution of regulation of Ca_v1 channels in nonmuscle cells shows that this novel autoinhibited complex is the probable target for PKA regulation of skeletal and cardiac muscle contraction.

Together, these two sets of results show that two complementary forms of neuromodulation—short-term presynaptic plasticity of synaptic transmission and postsynaptic neuromodulation of excitation-contraction coupling—both result from regulation of Ca channels by distinct signaling complexes.