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Authors:	Liao, Y. J.*¹ ; Safa, P. ¹ ; Boyden, E. S. ¹ ; Tsien, R. W. ¹ ¹ Mol. and Cell. Physiology, Stanford Univ, Stanford, CA
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Antibody (Ab) knock-down of presynaptic voltage-gated calcium channels (VGCC) at the neuromuscular junction is one of the most important pathogenic mechanisms in Lambert-Eaton myasthenic syndrome (LEMS). Some LEMS patients also have a central nervous system disorder called paraneoplastic cerebellar ataxia (PCA), which manifests as problems with balance and coordination. Like LEMS, PCA may be an Ab-mediated channelopathy. Since patients in the early phase of PCA exhibit profound symptoms with a relatively normal-appearing cerebellum on brain imaging, we postulated that calcium channelopathy and altered synaptic transmission, rather than loss of neurons, are the predominant pathogenic mechanisms in the early phase of PCA. To test the hypothesis that exposure to Ab against VGCC is sufficient to alter channel function, we created a function-blocking rabbit polyclonal Ab against the extracellular domain III S5 loop of N- and P/Q-type channels, a site known to be important in LEMS. This Ab rapidly inhibited N- and P/Q-type but not L-type VGCC in cultured cerebellar granule cells and transfected HEK293 cells (see abstract Safa et al.). Exposure of acute cerebellar slices to Ab reduced excitatory synaptic transmission at the parallel fiber-Purkinje cell synapse. During high frequency repetitive stimulation, Ab exposure resulted in an increase in the frequency-dependent facilitation of excitatory postsynaptic currents, consistent with inhibition of the presynaptic VGCC, which are predominantly N- and P/Q-types. Infusion of Ab over the mouse cerebellum duplicated the cerebellar ataxia seen in PCA patients. These results are consistent with our hypothesis that Ab-mediated impairment of presynaptic and possibly somatic VGCC function is an important pathogenic mechanism underlying PCA.

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