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Neuroscience 2003 Abstract

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Abstract Title:	Anti-calcium channel antibody affects cerebellar synaptic transmission in a model of acquired channelopathy.
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Paraneoplastic cerebellar degeneration (PCD) is an ataxia found in patients with small cell lung carcinoma (SCLC). Antibody to the P/Q-type Ca^{2+} channel (PQCC) has been found in PCD patients, and PCD might be a disease involving altered PQCC function and synaptic transmission, analogous to Lambert-Eaton myaesthenic syndrome (LEMS). Unlike the effects of LEMS antibody (reduction of end-plate potential and facilitation upon repetitive stimulation), effects of PQCC antibody in PCD remain unknown. We tested whether antibody against PQCC can affect cerebellar transmission, consistent with the idea that PCD is a channelopathy. Since anti-α_{1A} antibody has been shown to reduce Ca^{2+} currents in SCLC cells, we made rabbit antibodies against the α_{1A} subunit and tested their effects on cerebellar transmission. We recorded EPSCs at the parallel fiber-Purkinje cell synapse in cerebellar slices during trains of 10 stimuli at 20 or 40 Hz. Repetitive stimulation produced a prominent increase in EPSC facilitation, calculated as the average of the last three EPSCs divided by the initial EPSC ($EPSC_{8-10}/EPSC_1$). The mean frequency-dependent facilitation was 2.9±0.23-fold at 20 Hz and 4.2±0.25-fold at 40 Hz. In the presence of anti-α_{1A} antibody, facilitation was increased respectively to 4.8±0.48- ($p<0.03$) and 7.0±0.14-fold ($p<0.001$). This antibody-mediated enhancement of facilitation was abolished by competitive peptide and occluded by lowering external Ca^{2+}. Accordingly, we postulate that anti-α_{1A} antibody inhibits PQCC function and diminishes Ca^{2+} influx. This deficit can be largely overcome during repetitive firing of the presynaptic terminal, thereby giving rise to enhanced facilitation when referenced to the initial EPSC. Our finding of an antibody effect on central neurotransmission offers encouragement for the use of experimental animals to unravel pathogenic mechanisms in an acquired channelopathy.

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