Dual involvement of G-substrate in motor learning revealed by gene deletion

The G-substrate purified from rabbit cerebellum is one of the few preferred substrates for guanosine 3':5'-cyclic monophosphate (cGMP)-dependent protein kinase (PKG). It is positioned at the downstream end of the cascade linking nitric oxide (NO), soluble guanylate cyclase, cGMP, and PKG. Immunohistochemical studies have revealed that G-substrate is uniquely concentrated in cerebellar Purkinje cells. G-substrate Phosphorylated by PKG acts as a potent inhibitor of protein phosphatases (PPs) 1 and 2A. We now have generated G-substrate knockout mice to further investigate functional roles of G-substrate at cellular and behavioral levels. G-substrate-deficient Purkinje cells in slices obtained at postnatal week (PW)10-15 maintained electrophysiological properties essentially similar to those from wild-type littermates. Conjunction of parallel fiber stimulation and depolarizing pulses induced long-term depression (LTD) normally. At younger ages, however, LTD attenuated temporarily at PW6 and recovered thereafter. In parallel with LTD, short-term (1 hr) adaptation of optokinetic response (OKR) temporarily diminished at PW6. Young adult G-substrate knockout mice tested at PW12 exhibited no significant differences from their wild-type littermates in terms of brain structure, general behavior, locomotor behavior on rotor rod or treadmill, eyeblink conditioning, dynamic characteristics of OKR, or short-term OKR-adaptation. One unique change detected was a modest but significant attenuation in the long-term (5 days) adaptation of OKR. The present results support the concept that LTD is causal to short-term adaptation, and reveal the dual functional involvement of G-substrate in neuronal mechanisms of the cerebellum for both short-term and long-term adaptation.