The pathogenesis of adult onset dystonia has been elusive. Recent genetic studies have implicated mutations in GNAL, which codes for the alpha subunit of the guanine nucleotide-binding protein G(olf). G(olf) is the dominantly expressed stimulatory G protein in the striatum and it mediates intracellular signaling pathways downstream from the D1-type dopamine receptors (D1Rs). Heterozygous knockouts (GNAL +/-) exhibit reduced locomotion during a 5-day period of sensitization to D-amph or cocaine. However, after a 9-day withdrawal, the locomotor behavior in response to a D-amph or cocaine challenge is normalized to that of control animals (GNAL +/+)(Corvol et al. 2007 Neuropsychopharmacology). Although this gross measure of motor function normalizes in the GNAL +/- mice, we hypothesize that other aspects of their motor functions would be pathological. Specifically, we predict that the heterozygous mice would be impaired in instrumental learning tasks, given the putative roles of the basal ganglia in learned action selection and phasic striatal dopamine release in feedback-based learning. At the mechanistic level, we hypothesize that the impaired D1R-G(olf)-AC-PKA signaling pathway in the GNAL +/- mice leads to...
altered patterns of synaptic plasticity. Through a cascade of homeostatic processes downstream from PKA with increasingly longer time constants, short-time constant acute behavior and learning are relatively intact, while long time constant feedback-based learning is subtly altered. In conjunction with repeated patterns of context-specific motor selection, synaptic tagging, remodeling, and synaptogenesis and pruning lead to pathological action selection circuits in the striatum. This model sets the stage for new experimental tests of the GNAL mouse model and a rational basis for future therapeutics development in adult onset dystonias.

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