Targeted expression of a toxin gene to D1 dopamine receptor positive neurons

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The dopaminergic system of the brain is prone to several degenerative conditions that disrupt normal basal ganglia function resulting in progressive motor impairment. Mice were generated in which the attenuated form of the diphtheria toxin gene was expressed exclusively in D1 dopamine receptor (D1R) positive cells to determine the contribution that the loss of this genetically defined striatal cell subpopulation makes to the clinical phenotype. Consistent with the D1R expression pattern, the striatum of mutant mice was reduced in size and the Islands of Calleja did not develop whereas the cortex was normal. D1R is not detectable in mutants by ligand autoradiography whereas D2 dopamine receptors (D2R) are expressed in the striatum. In addition, substance P, a neuropeptide known to be expressed in D1R positive projection neurons is not detectable whereas enkephalin, a marker found in D2R positive projection neurons is expressed normally in the mutant brain. The findings are consistent with a dual pathway model of basal ganglia circuitry and suggest a previously unappreciated role of D1R positive neurons in the regulation of movement and in the genesis of dystonia in particular.

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