

# Anticholinergic Drugs Rescue Synaptic Plasticity in DYT1 Dystonia: Role of M<sub>1</sub> Muscarinic Receptors

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**ABSTRACT:** Broad-spectrum muscarinic receptor antagonists have represented the first available treatment for different movement disorders such as dystonia. However, the specificity of these drugs and their mechanism of action is not entirely clear. We performed a systematic analysis of the effects of anticholinergic drugs on short- and long-term plasticity recorded from striatal medium spiny neurons from DYT1 dystonia knock-in ( $Tor1a^{+/\Delta gag}$ ) mice heterozygous for  $\Delta E$ -torsinA and their controls ( $Tor1a^{+/+}$  mice). Antagonists were chosen that had previously been proposed to be selective for muscarinic receptor subtypes and included pirenzepine, trihexyphenidyl, biperiden, orphenadrine, and a novel selective M<sub>1</sub> antagonist, VU0255035.  $Tor1a^{+/\Delta gag}$  mice exhibited a significant impairment of corticostriatal synaptic plasticity. Anticholinergics had no significant effects on intrinsic membrane properties and on short-term plasticity of striatal neurons. However, they exhibited a differential ability to restore the corticostriatal plasticity deficits. A complete

rescue of both long-term depression (LTD) and synaptic depotentiation (SD) was obtained by applying the M<sub>1</sub>-preferring antagonists pirenzepine and trihexyphenidyl as well as VU0255035. Conversely, the nonselective antagonist orphenadrine produced only a partial rescue of synaptic plasticity, whereas biperiden and ethopropazine failed to restore plasticity. The selectivity for M<sub>1</sub> receptors was further demonstrated by their ability to counteract the M<sub>1</sub>-dependent potentiation of *N*-methyl-D-aspartate (NMDA) current recorded from striatal neurons. Our study demonstrates that selective M<sub>1</sub> muscarinic receptor antagonism offsets synaptic plasticity deficits in the striatum of mice with the DYT1 dystonia mutation, providing a potential mechanistic rationale for the development of improved antimuscarinic therapies for this movement disorder. © 2014 International Parkinson and Movement Disorder Society

**Key Words:** dystonia; striatum; muscarinic receptor antagonists; synaptic plasticity