Negative allosteric modulation of mGlu5 receptor rescues striatal D2 dopamine receptor dysfunction in rodent models of DYT1 dystonia

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Early onset torsion dystonia (DYT1) is an autosomal dominantly inherited disorder caused by deletion in TOR1A gene. Evidence suggests that TOR1A mutation produces dystonia through an aberrant neuronal signalling within the striatum, where D2 dopamine receptors (D2R) produce an abnormal excitatory response in cholinergic interneurons (ChIs) in different models of DYT1 dystonia. The excitability of ChIs may be modulated by group I metabotropic glutamate receptor subtypes (mGlu1 and 5). We performed electrophysiological and calcium imaging recordings from ChIs of both knock-in mice heterozygous for Δ-torsinA (Tor1a$^{+/\Delta gag}$ mice) and transgenic mice overexpressing human torsinA (hMT1). We demonstrate that the novel negative allosteric modulator (NAM) of metabotropic glutamate 5 (mGlu) receptor, dipraglurant (ADX48621) counteracts the abnormal membrane responses and calcium rise induced either by the D2R agonist quinpirole or by caged dopamine (NPEC-Dopamine) in both models. These inhibitory effects were mimicked by two other well-characterized mGlu5 receptor antagonists, SIB1757 and MPEP, but not by mGlu1 antagonism. D2R and mGlu5 post-receptor signalling may converge on PI3K/Akt pathway. Interestingly, we found that the abnormal D2R response was prevented by the selective PI3K inhibitor, LY294002, whereas PLC and PKC inhibitors were both ineffective. Currently, no satisfactory pharmacological treatment is available for DYT1 dystonia patients. Our data show that negative modulation of mGlu5 receptors may counteract abnormal D2R responses, normalizing cholinergic cell excitability, by modulating the PI3K/Akt post-receptor pathway, thereby representing a novel potential treatment of DYT1 dystonia.