Tolerance to a paradoxical increase in motor activity induced by PDE10A inhibition under hypodopaminergic conditions

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Abstract

Background and Purpose: Phosphodiesterases (PDEs) are a family of enzymes, which hydrolyze cAMP and cGMP. PDE10A is expressed mainly in the medium spiny neurons of the striatum that provides an opportunity to modulate the movement control pathways of the basal ganglia: “direct” (D1 receptor-dependent) and “indirect” (D2 receptor-dependent). Thus, inhibition of PDE10A can functionally mimic the action of both D1 receptor agonists and D2 receptor antagonists, although much less attention has been paid to the assessment of D1 receptor agonist-like effects. The purpose of the present study was (1) to confirm the motor stimulatory effects of PDE10A inhibitors and (2) to test whether these effects are subject to the development of tolerance. Experimental Approach: The ability of single or repeated (5 or 10 days) administration of selective PDE10A inhibitors, MP-10 (0,3-5 mg/kg) and RO5545965 (0.1-0.9 mg/kg), to stimulate locomotor activity was assessed in rats after single tetrabenazine challenge (3 mg/kg). The study was pre-registered on PreclinicalTrials.eu. Key Results: PDE-10A inhibition exerted paradoxical motor stimulatory properties in a dose-dependent manner. However, repeated administration of PDE10A inhibitors led to a reduction of their effects. Conclusion and Implications: PDE-10A inhibition produces a paradoxical increase in motor activity in animals with low dopamine tone. After repeated administration of PDE-10A inhibitors, these effects disappeared. The development of tolerance similar to that previously observed for D1-receptor agonists may limit the potential clinical use of the stimulatory effects of PDE10A inhibitors. Further studies aimed at analyzing the molecular mechanisms of this tolerance are warrant

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