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The macrocyclic lactones ivermectin and moxidectin show differential effects on rotational behavior in the 6-hydroxydopamine mouse model of Parkinson's disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease characterized by motor and cognitive deficits, the result of dopamine (DA)-depletion within the basal ganglia. Currently, DA replacement therapy in the form of Sinemet (L-DOPA plus Carbidopa) provides symptomatic motor benefits and remains the "gold standard" for treatment. Several pharmacological approaches can enhance DA neurotransmission including the administration of DA receptor agonists, the inhibition of DA metabolism, and enhancing pre-synaptic DA release. DA neurotransmission is regulated by several receptor subtypes including signaling through the purinergic system. P2 × 4 receptors (P2 × 4Rs) are a class of cation-permeable ligand-gated ion channels activated by the synaptic release of extracellular adenosine 5'-triphosphate (ATP). P2 × 4Rs are expressed throughout the central nervous system including the dopaminergic circuitry of the substantia nigra, basal ganglia, and related reward networks. Previous studies have demonstrated that P2 × 4Rs can modulate several DA-dependent characteristics including motor, cognitive, and reward behaviors. Ivermectin (IVM) and moxidectin (MOX) are two macrocyclic lactones that can potentiate P2 × 4Rs. In this study, we sought to investigate the role of P2 × 4Rs in mediating DA neurotransmission by exploring their impact on DA-dependent behavior, specifically rotation frequency in the unilateral 6-hydroxydopamine-lesioned mouse model of DA-depletion. While we did not observe any differences in the degree of lesioning based on immunostaining for tyrosine hydroxylase between sexes, male mice displayed a greater number of rotations with L-DOPA compared to female mice. In contrast, we observed that IVM plus L-DOPA increased the number of rotations (per 10 min) in female, but not male mice. These findings highlight the potential role of pharmacologically targeting the

purinergic receptor system in modulating DA neurotransmission as well as the importance of sex differences impacting outcome measures.

Keywords: ATP; Adenosine; Dopamine; Motor behavior; P2X4 receptors; Purine.

Conflict of interest statement

Declaration of Competing Interest There are no declarations of interests to declare.

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