

M₅ muscarinic acetylcholine receptors as a modifier of dopamine neurotransmission in early and late-stage mouse models of Parkinson's disease

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Parkinson's disease (PD) is characterized by debilitating motor and gait symptoms and the death of nigrostriatal DA neurons. The Gq-coupled M₅ muscarinic acetylcholine receptor (M₅) is an intriguing and under-investigated therapeutic target for mitigating PD motor symptoms. M₅ is located on the soma of nigral DA neurons and on nigrostriatal DA terminals. Using the 6-OHDA lesioned hemiparkinsonian mouse model and the preformed fibril mouse model, we investigated how modulating dopamine neuron activity and nigrostriatal DA release via M₅ can modify Parkinsonian-like motor phenotypes. Overall, we found that M₅ positive allosteric modulation alleviates gait deficits in both models, and that it does not affect motor recovery with L-DOPA. Furthermore, M₅ PAM does not affect L-DOPA's motor benefit or L-DOPA-induced dyskinesia, and it does not cause dyskinesia on its own. Finally, in our PFF model, we observed time-dependent changes in nigral dopamine neuron activity and in striatal DA binding. Overall, these results suggest M₅ PAM as a promising and novel therapeutic strategy for reducing gait deficits in early and late-stage PD.

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