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Orally-active, highly effective, fast-onset, long-acting dopamine D3/D2 agonists in translational experimental models of Parkinson's disease displays specific biased agonism profile

T. Blackburn. Motac Neurosciences Ltd, Manchester, United Kingdom.

Introduction: Dopamine replacement therapy with L-DOPA or D2/D3 dopamine receptor agonists remains the gold standard treatment for Parkinson's disease. We present a new dopamine 'biased' D2/D3 agonist, MCT001, addressing the poor efficacy, short duration of action and side effects associated with current therapy.

Methods: *In vitro & in vivo:* Parkinsonian symptoms (PS) were produced in rats by 6-OHDA and in Macaca fascicularis by MPTP. Regular treatment with L-DOPA resulted in the development of abnormal involuntary movements and dyskinesia. PS motor disability, dyskinesia and on-time were assessed following MCT001 (0.1-10 mg/kg p.o.) in comparison to L-DOPA, ropinirole and pramipexole at therapeutically relevant doses. Biased agonism was assessed through G protein activation and β-arrestin translocation assays in Flp-In-HEK 293 cells.

Results: MCT001 demonstrated dose-dependent, rapid improvement of PS in both experimental models, decreased disability score comparable to L-DOPA, dramatically increased over-time while also increasing the "good on-time" (i.e. with less dyskinesia) compared to L-DOPA, ropinirole, and pramipexole. Analysis of biased agonism profile with an operational model of agonism revealed that, as compared to dopamine, MCT001 displayed significant 8.6-fold bias ($\Delta\Delta\log[\tau/K_A]$ = 0.94 ± 0.2, one way ANOVA, $P < 0.001$) towards $G\alpha_{i2}$ activation over β-arrestin-2 recruitment whereas pramipexole displayed no bias.

Conclusions: MCT001, represents the first novel dopamine receptor agonist therapeutically superior to both L-DOPA and existing agonists, with the added potential of once daily (*o.d.*) administration**.** In vitro investigations also indicated MCT001 to be a potent high intrinsic efficacy DR2 agonist that is significantly biased towards activation of Gαi2 and GαoA G proteins over the recruitment of β-arrestin-2. MCT001 also displayed similar high DR3 efficacy as compared to dopamine and pramipexole. However, we observed a large gain in the potency of this ligand over a 30 minute timescale. We hypothesize that such a gain in potency may reflect a slow dissociation rate from this receptor.[1] 1. Klein Herenbrink, et al., (2016). The role of kinetic context in apparent biased agonism at GPCRs. *Nature Communications*, *7*, 10842.