Mesdopetam suppresses sensitization and AIMs in the rodent unilateral 6-OHDA lesion model of Parkinson's disease

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Introduction

- Mesdopetam (aka IRL790) was discovered using a phenotypic screening strategy (1) to find small molecule dopamine (DA) modulators with antidyskinetic and anti-psychotic effects, but devoid of inhibitory effects on normal motor function. The compound is a DA D3 antagonist, however with an agonist-like binding mode, displaying the desired in vivo profile (2). Mesdopetam is well tolerated in Parkinson's disease (PD) patients (3), and currently in clinical development for treatment of L-DOPA induced dyskinesias (LIDs) and PD psychosis.
- Mesdopetam is antidyskinetic in the rodent unilateral 6-OHDA model upon acute administration (2). The present study investigated the effects of chronic administration of mesdopetam + L-DOPA in this model.

Methods

- Female S-D rats were subjected to unilateral 6-OHDA lesions in the MFB (AP -2.5; ML -2.0; DV -8.5 mm). After recovery, responders to apomorphine challenge were treated with L-DOPA/ Benserazide (10/7.5mg/kg, i.p.), mesdopetam (3mg/kg, s.c.), or the combination thereof for 2 weeks. Amantadine (40mg/kg i.p.) was used as a comparator. Rotational L-DOPA response (turns/2.5h), and dyskinesias (AIMs), were recorded on Days 1, 7 & 14 of subchronic treatment. Lesions were verified with DAT autoradiography.

Schedule

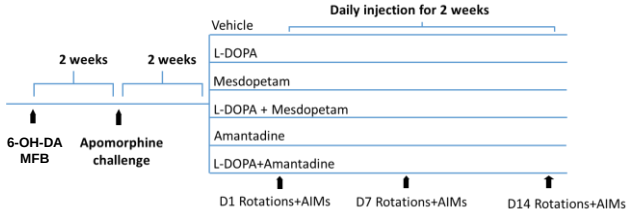

Figure 1. Vehicle: saline by i.p. L-DOPA (10mg/kg)/Benserazide (7.5mg/kg) i.p. N=6-8/group

Rotations were recorded for 2.5 h. Dyskinesia scoring (Adverse involuntary movements, AIMs): 5' videos taken at 01:30. Sacrifice Day 15

Mesdopetam reduces L-DOPA sensitization

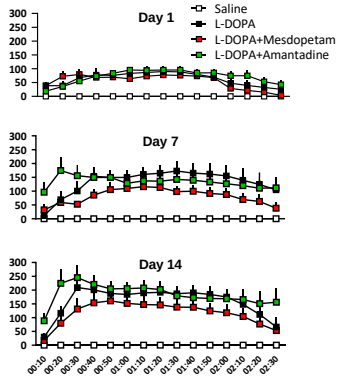

Figure 2. Time course of contralateral turns (Means ± SEM) 0-2.5 h post dose on Day 1, 7 and 14. Repeated administration of L-DOPA resulted in increased contralateral turns. This was attenuated by co-administration with mesdopetam.

Total contralateral turns

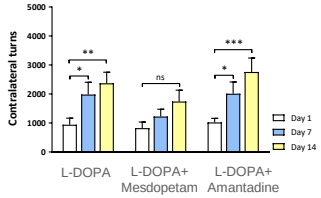

Figure 3. L-DOPA and L-DOPA+amantadine treatment, but not L-DOPA + mesdopetam, significantly increased total number of turns on Days 7 and 14 (ANOVA/Fischers LSD)

Mesdopetam & amantadine improve LIDs

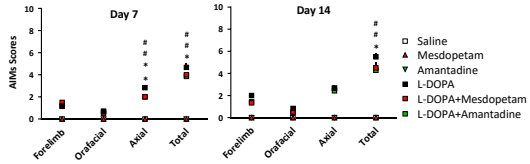

Figure 4. AIMs recorded on 5' videos Day 7 and 14. Both mesdopetam and amantadine significantly reduced total AIMs scores. Mesdopetam 3 mg/is is a submaximal dose for reduction of AIMS (2). Amantadine 40 mg/kg is a maximal dose in this model.

Summary

- Mesdopetam is antidyskinetic upon acute administration in rodents with established LIDs (2). Here we show that the compound also reduces sensitization to L-DOPA upon chronic, low-dose, administration in hemiparkinsonian rats. Compared to L-DOPA alone, the increase in contralateral turns was attenuated upon co-treatment with mesdopetam. Upon acute administration, mesdopetam at this dose does not reduce turns, indicating a specific impact on the sensitisation process with chronic administration (2). Intriguingly, higher acute dosages tend to increase turns, potentially reflecting a biphasic dose-response pattern.
- The comparator amantadine did not share the suppression of L-DOPA sensitization. Chronic mesdopetam at a low dose and amantadine at a fully efficacious dose displayed a similar reduction of LIDs.
- The suppression of L-DOPA sensitization suggests that mesdopetam modifies mechanisms underlying development of LIDs. Thus, mesdopetam has a potential also as a preventive treatment for LIDs.
- Overexpression of DA D3 receptors is involved in the pathophysiology of LIDs. DA D3 receptor antagonism may underlie both acute antidyskinetic effects and the suppression of L-DOPA sensitization observed with mesdopetam.

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References:
1. Waters, S et al. ACS chemical neuroscience vol. 8,4 (2017): 785. 2. Waters et al, JPET 374(1),113 (2020) 3. Svenningsson, P et al. npj Parkinson's Disease 4, 35 (2018)