The Potent and Selective A2A Receptor Antagonist, Preladenant, Produces a Robust Effect in L-dopa Induced Turning, but Only Modest Efficacy in the Cylinder Assay in Unilaterally 6-OHDA Lesioned Rats

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1 BACKGROUND
- A2A receptor antagonists represent one of the most studies novel symptomatic treatments for Parkinson’s disease (PD) over the past several decades
- Multiple A2A receptor antagonists consistently produce robust activity in animal models such as reversal of haloperidol-induced catalepsy and potentiation of L-dopa induced rotations in unilaterally 6-OHDA lesioned rats
- However, those robust positive data in non-clinical models have not translated into robust clinical efficacy
- Preladenant (2-(2-Furyl)-7-(2-(4-(2-methoxyethoxy)phenyl)-1-piperazinyl)[1H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine-5-amine), a potent and selective A2A receptor antagonist did not succeed in a Phase III clinical trial for symptomatic treatment of PD
- Here we hypothesize that the disconnect between the animal and clinical results was that the majority of the animal assays relied on an increase in motor activity, which is something that A2A receptor antagonists induce in rodents whereas there is no evidence of A2A antagonist induced hyporeactivity in human studies
- To test this hypothesis, we assessed the effect of preladenant (3 mg/kg, PO) in unilaterally medial forebrain bundle 6-OHDA lesioned rats in L-dopa induced turning and the cylinder test

2 MATERIALS AND METHODS
Alltogether 84 male CD rats purchased from Charles River, Germany and weighing 250-350 g at lesion date are used for the experiment.
- All lesioned with 6-OHDA

Study groups:
Group 1: 12 rats treated Vehicle (s.c.) and with vehicle (p.o.; QD for 14 days).
Group 2: 12 rats treated with benzerazide (4 mg/kg; s.c.), L-Dopa (2 mg/kg; s.c) and with preladenant (dose 3 mg/kg, QD only on days of testing p.o.)

Dosing-testing for both groups is performed 4 times with cylinder test and 3 times with rotational asymmetry test. Benzerazide and L-Dopa, as well as preladenant, dosings are done only on behavioral testing days.

Sensitization dosings are performed for 4 weeks starting on day 21. Dosings are done only on week days from Mon-Fri, i.e. 5 times/week. On sensitization days, all rats receive benzerazide 12 mg/kg s.c and L-dopa 4 mg/kg s.c.

In the screening tests on day 14, all rats receive apomorphine 0.5 mg/kg. (s.c.) for the apomorphine screen.

Benzerazide and L-Dopa, as well as preladenant dosings are done only on behavioral testing days. Preladenant (dose 3 mg/kg) will be administered p.o. in dosing volume of 2 ml/kg.

3 CYLINDER TEST

Day 37 Preladenant Cylinder

Day 37 Left Paw Cylinder

+ 2 mg/kg L-dopa

Day 39 Preladenant Cylinder

Day 39 Left Paw Cylinder

+ 2 mg/kg L-dopa

Day 42 Preladenant Cylinder

Day 42 Left Paw Cylinder

+ 2 mg/kg L-dopa

Day 44 Preladenant Cylinder

Day 44 Left Paw Cylinder

+ 2 mg/kg L-dopa

Day 46 Preladenant Cylinder

Day 46 Left Paw Cylinder

+ 2 mg/kg L-dopa

Day 49 Preladenant Cylinder

Day 49 Left Paw Cylinder

+ 2 mg/kg L-dopa


4 ROTATIONAL ASSAY

Day 35

Day 35 Preladenant Rotations

Day 35 Preladenant Rotations

+ 2 mg/kg L-dopa

Day 42

Day 42 Preladenant Rotations

Day 42 Preladenant Rotations

+ 2 mg/kg L-dopa

Day 49

Day 49 Preladenant Rotations

Day 49 Preladenant Rotations

+ 2 mg/kg L-dopa


5 CONCLUSIONS
- Consistent with our hypothesis, we found that while we were able to replicate previously published findings that preladenant robustly potentiates L-dopa induced turning.
- This result is consistent with previously published findings that preladenant, like other A2A receptor antagonists, produce a significant potentiation of L-dopa-induced turning in this model
- These findings clearly demonstrate that the A2A receptor antagonists mechanism engages the indirect pathway
- However, the lack of a significant effect in the cylinder test highlights the need to assess not just engagement of the proper pathway but also the positive functional benefit of novel treatments