The Potent and Selective A_{2A} 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

- A_{2A} receptor antagonists represent one of the most studies novel symptomatic treatments for Parkinson's disease (PD) over the past several decades
- Multiple A_{2A} 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-Furanyl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]-1-piperazinyl]7H-pyrazolo[4,3-e][1,2,4] triazolo [1,5-c]pyrmidine-5-amine), a potent and selective A_{2A} 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 A_{2A} antagonist induced hypoactivity 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

Altogether 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 2 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.

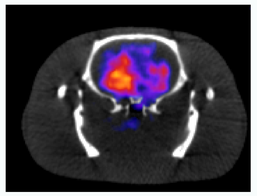
In the **screening tests** on day 14, all rats receive apomorphine 0.5 mg/kg, (s.c.) for the apomorphine screen.

Benzerazide and L-Dopa, as well as preladenant dosings are done only on behavioral testing days.

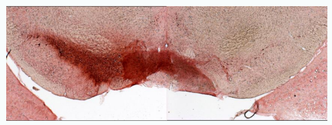
Preladenant (dose 3 mg/kg) will be administered p.o. in dosing volume of 2 ml/kg.

6-OHDA Lesion

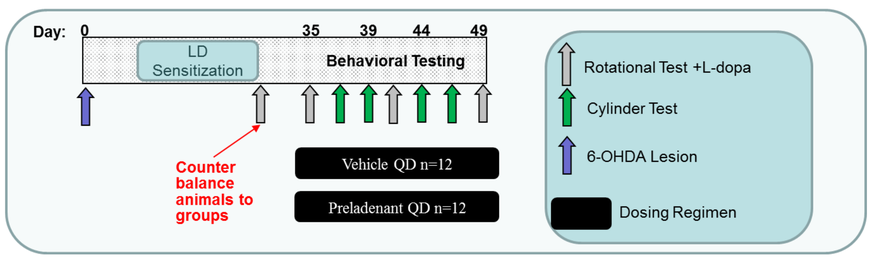
A



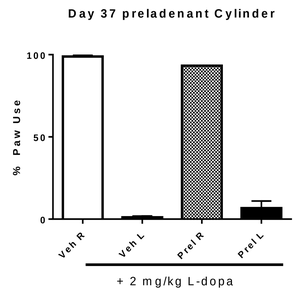
B

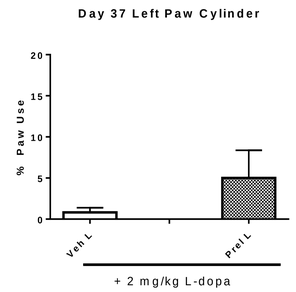


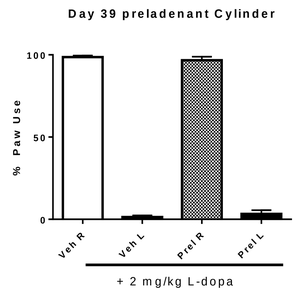
Unilateral delivery of 6-OHDA to the rat MFB produces a (A) significant reduction in the dopamine transporter (DAT) as measured by SPECT and (B) TH in the substantia nigra

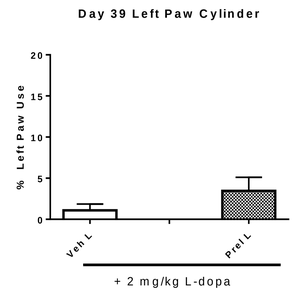


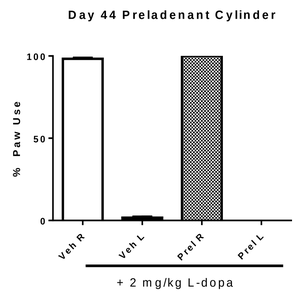
3 CYLINDER TEST

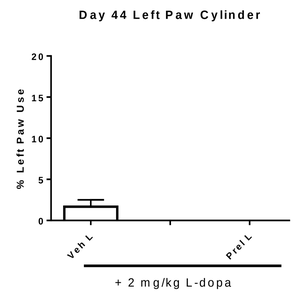


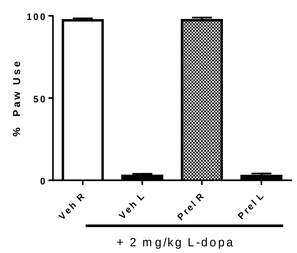


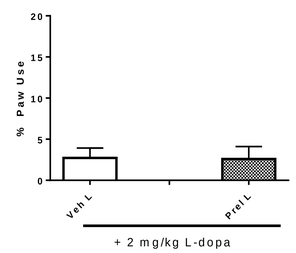






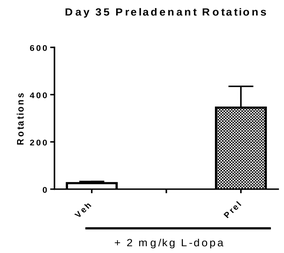




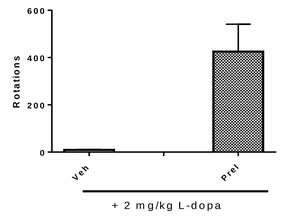


4 ROTATIONAL ASSAY

Day35



Day42



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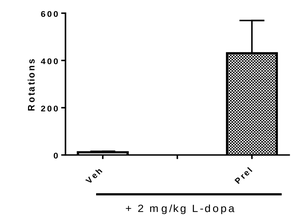

5 CONCLUSIONS

- 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 prelandenant, like other A_{2A} receptor antagonists, produce a significant potentiation of L-dopa-induced turning in this model
- These findings clearly demonstrate that the A_{2A} 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