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Investigating the Anti-dyskinetic Effects of Serotonin- and Glutamate-acting Compounds, Vilazodone and Amantadine, in Hemiparkinsonian Rats

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Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative movement disorder caused by loss of nigrostriatal dopamine (DA) neurons[1,2].

DA replacement therapy using L-3,4-dihydroxyphenylalanine (L-DOPA) improves motor functioning but often results in L-DOPA-induced dyskinesia (LID), typified by abnormal involuntary movements (AIMs)[3,4].

In this state of DA depletion, serotonin (5-HT) neuron hyperinnervation[5,6] and glutamate overactivity[7] are highly implicated in LID.

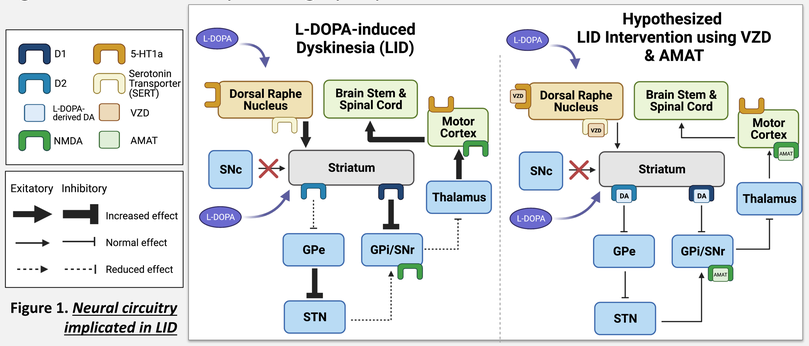


Figure 1. ***Neural circuitry implicated in LID***

This study investigated the anti-dyskinetic effects of Vilazodone (VZD), a 5-HT transport blocker and partial 5-HT1a agonist[8,9], and/or Amantadine (AMAT), an NMDA glutamate antagonist[10], on LID development with L-DOPA administration.

It was hypothesized that alone each would reduce LID, while co-administration at low doses would synergistically reduce LID without compromising L-DOPA efficacy on motor gain of function.

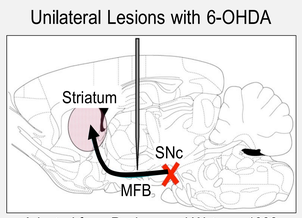
Methods

Subjects:

Male/female Sprague-Dawley (~250-300 g, *n=20*).

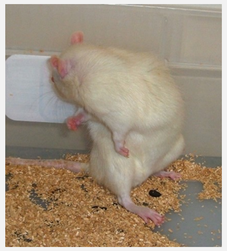
Surgeries:

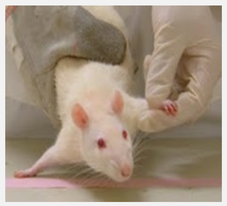
All rats received a unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB) to model late-stage PD-equivalent striatal DA loss.



Drugs:

AMAT (0, 20, 40, 60 mg/kg, s.c.) was administered 100 min prior to L-DOPA. VZD (0, 1, 2.5, 5 mg/kg, s.c.) was administered 5 min prior to L-DOPA. All rats received L-DOPA (6 mg/kg, s.c.) 10 min prior to AIMs.





Behavioral Testing:

Abnormal Involuntary Movements (AIMs) Test:

The AIMs test measures dyskinesia by analyzing 3 behaviors: Axial, Limb, and Orolingual (ALO). Behavior was observed for 1 min, every 10 mins, for a total of 180 mins[11,12].

Forepaw Adjusting Steps (FAS) Test:

The FAS test measures forelimb akinesia and L-DOPA motor efficacy by dragging rats at a rate of 90 cm / 10 s and counting their steps on both lesioned and non-lesioned paws[12,13].

Post-mortem Neurochemical Analysis:

High Performance Liquid Chromatography (HPLC):

HPLC was used to verify lesion efficacy by analyzing DA, 5-HT, and respective metabolite concentrations.

Experimental Timelines

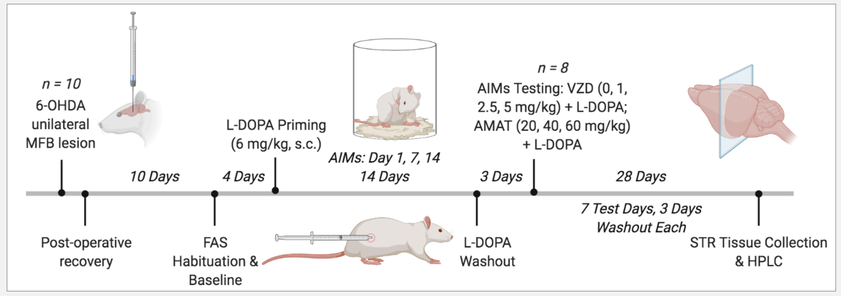


Figure 2. *Experimental Timeline 1: Dose response curves for VZD and AMAT individually administered with L-DOPA.*

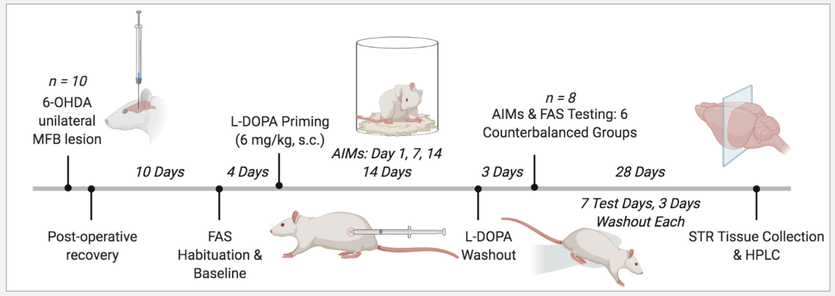


Figure 3. *Experimental Timeline 2: Synergy between low-dose VZD and AMAT on LID reduction and L-DOPA efficacy.*

Results

Experiment 1: Dose Response Curves

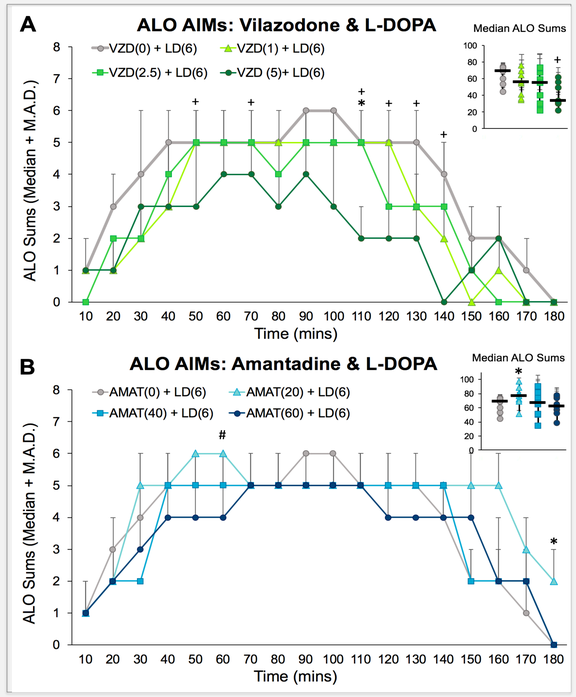


Figure 4. *Experiment 1: Individual dose responses to Vilazodone (VZD) and Amantadine (AMAT) on LID development.* 4A) *P<0.05 VZD (0) vs. VZD (1); +P<0.05 VZD (0) vs. VZD (5). In 4B) *P<0.05 AMAT (0) vs. AMAT (20); +P<0.05 AMAT (0) vs. AMAT (60).

Experiment 2: Co-administration Synergy

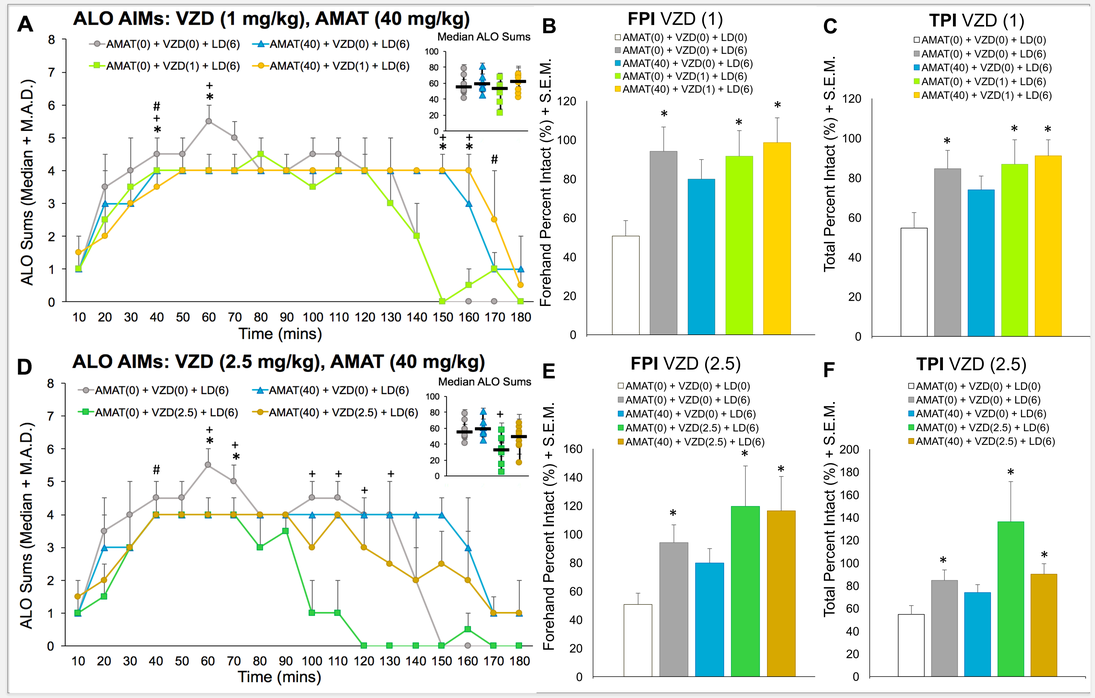


Figure 5. *Experiment 2: The effects of Vilazodone (VZD) and/or Amantadine (AMAT) co-administered with L-DOPA on LID development* 5A) *P<0.05 LD (6) vs. AMAT (40) + VZD (1) + LD (6); +P<0.05 LD (6) vs. VZD (1) + LD (6)#P<0.05 LD (6) vs. AMAT (40) + LD (6). In 5D) *P<0.05 LD (6) vs. AMAT (40) + VZD (2.5) + LD (6); +P<0.05 LD (6) vs. VZD (2.5) + LD (6); #P<0.05 LD (6) vs. AMAT (40) + LD (6). 5B, C, E, F) *P<0.05 any treatment vs. LD (0).

Conclusions

- Acute low-dose VZD administration significantly reduces AIMs while maintaining L-DOPA motor efficacy, suggesting promising treatment of LID without propagating further side effects.
- LID intervention with AMAT does not exhibit the same anti-dyskinetic effects in rodents as it does clinically, thereby complicating the mechanism of action of AMAT and the translation of the 6-OHDA hemiparkinsonian model.
- Sub-threshold doses of VZD and AMAT do not exhibit synergistic reductions on AIMs when co-administered with L-DOPA in a hemiparkinsonian rat model.
- AMAT may dampen the anti-dyskinetic effects of VZD and prolong peak AIMs, while also compromising the motor efficacy of L-DOPA.

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Acknowledgements

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