2020

The effects of 5-HT2AR stimulation on psychosis-associated behaviors in naive and L-DOPA treated hemiparkinsonian rat

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The effects of 5-HT_{2A}R stimulation on psychosis-associated behaviors in naive and L-DOPA treated hemiparkinsonian rats

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Background

- Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of nigrostriatal dopamine (DA) neurons.[1]
- L-3,4 dihydroxyphenylalanine (L-DOPA) is the current gold standard treatment for the symptoms of PD.[2]
- Unfortunately, L-DOPA can exacerbate non-motor features of PD such as PD-associated hallucinations (PDAP). These might be due to changes in the 5-HT system, specifically upregulation of 5-HT_{2A} receptors (5-HT_{2A}R).[3]
- In rodents, hallucinogenic like behavior can be expressed by head twitch responses and changes in novelty-induced exploratory behavior.[4]
- Psychedelic drugs or specific agonists that stimulate 5-HT_{2A}Rs (like LSD and DOI) can produce hallucination-like behaviors, but it is unknown how 5-HT_{2A}R stimulation might be differentially affected by DA lesions and/or L-DOPA-treatment in parkinsonian rats.[5]
- Additionally, it is unclear how 5-HT_{2A}R stimulation affects general locomotive activity in lesioned and L-DOPA-treated subjects. Changes to exploratory behaviors can be used as a proxy for anxiety and other non-motor behaviors, providing valuable information about 5-HT_{2A}R's actions.

The current investigation examined whether 6-OHDA lesion and/or L-DOPA treatment differentially affect 5-HT_{2A}R induced unconditioned responses such as head twitch response, rearing and locomotion.

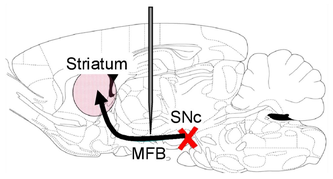
Methods

Subjects:

Adult Male/Female Sprague-Dawley or LE rats (Dose-response n=7, Experiment 1 n=18, Experiment 2 n=16). All ~300-400g

Surgeries:

All rats received a unilateral injection of 6-hydroxydopamine (6-OHDA) or saline into the medial forebrain bundle (MFB) to deplete striatal DA.

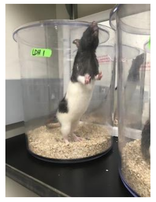


Exploratory Behavior (Rearing)[4]

Exploratory rearing test was used to measure unconditioned hallucinogenic behavior. This response is based on the animal's motivation to explore it surroundings.

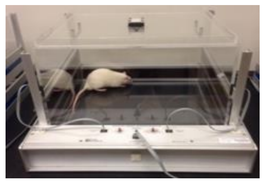
Head Twitch Response (HTR)[4]

The HTR test was used to measure unconditioned hallucinogenic behavior. The HTR is a paroxysmal rotational shaking of the head. The response is a mixture of head shakes and whole-body shakes.



Locomotor Activity Chamber (LAC)

Before testing, rats were habituated 3x in the activity chamber. Rats were placed in activity chambers immediately after injection and locomotor behaviors were quantified based on infrared beam breaks.



Experiment 1

Figure 1: Experimental Design

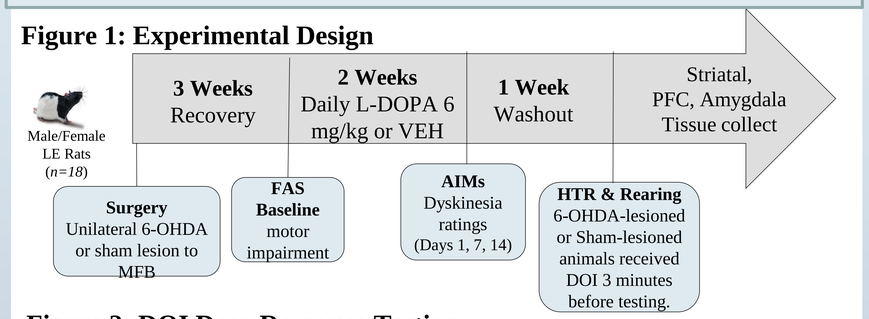


Figure 2: DOI Dose-Response Testing

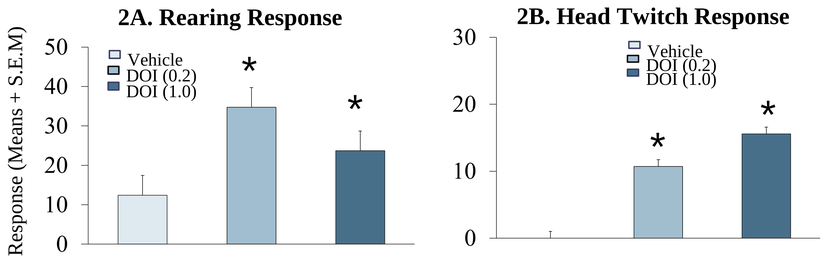


Figure 2. Prior to Experiment 2, doses were established for DOI in intact SD rats (n=7). **A)** increases in rearing at the low (0.2) dose. (p<*0.05 vs Vehicle) **B)** DOI (Vehicle, 0.2, 1.0 mg/kg) induces dose-dependent increases in HTR and

Figure 3: Effect of Lesion and L-DOPA on DOI-Rearing and HTR

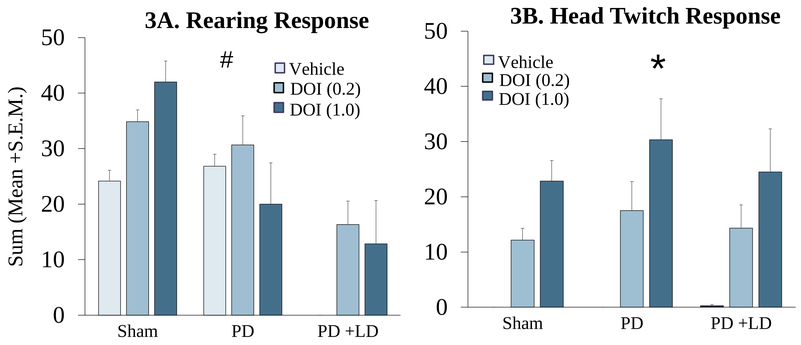


Figure 3. DOI effects (Vehicle, 0.2 & 1.0 mg/kg) in Sham, DA-lesioned and L-DOPA-treated DA-lesioned rats (n=9/group). A 3 (group) x 3 (treatment) ANOVA was performed for Rearing and HTR **A) For rearing,** a main effect of group was found. PD + LID subjects displayed decreased rearing regardless of treatment **B) For HTR,** a main effect of treatment was found. Subjects displaying dose-dependent increases in rearing regardless of group (*p<0.05 main effect of treatment, #p<0.05 main effect of group)

Experiment 2

Figure 4: Experimental Design

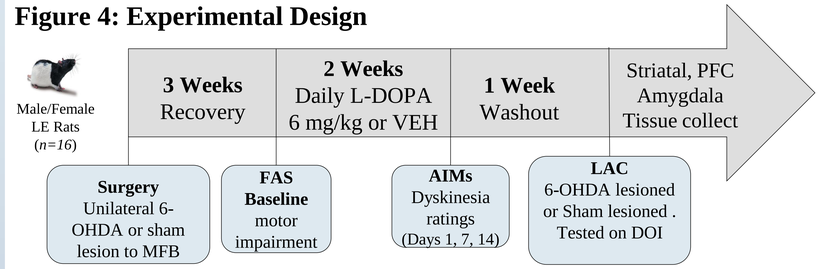
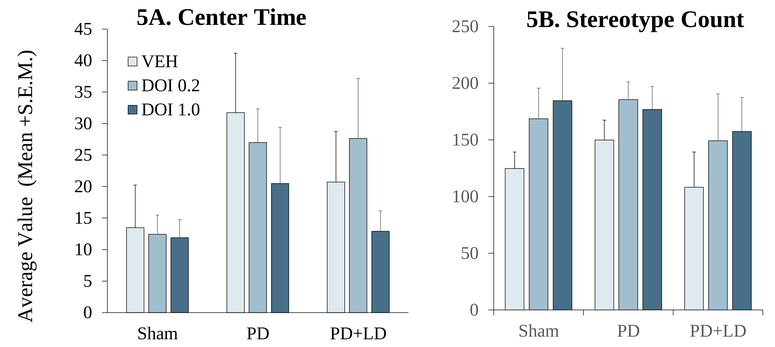


Figure 5: Effect of Lesion and L-DOPA on Locomotor Activity



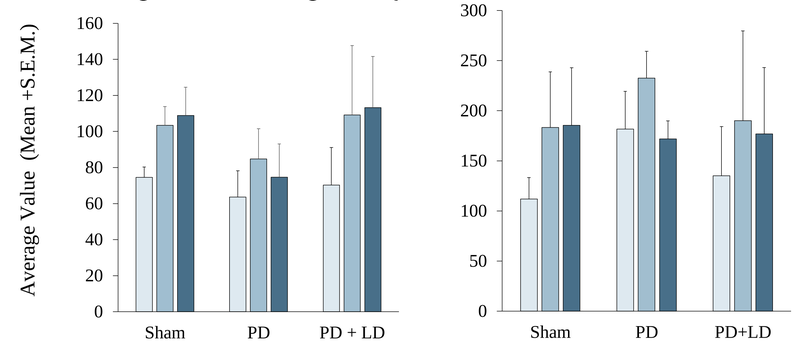


Figure 5. DOI effects (Vehicle, 0.2 & 1.0 mg/kg) in Sham, DA-lesioned and L-DOPA-treated DA-lesioned rats (n=5-6/group)**A.)** Center time or **B.)** Stereotype Count. **C.)** Rearing activity **D.)** Total distance

Conclusions

- DOI dose-dependently increased HTR (**Fig. 2B)** and modified the rearing response in intact subjects (**Fig. 2A**).
- Rearing response was reduced in PD + LID groups and not affected by varying DOI doses (**Fig. 3A).**
- Like in the dose-response testing, DOI dose-dependently increased HTR. Though these effects were not exacerbated by DA lesion or L-DOPA (**Fig. 3B**), it supports a role of 5HT_{2A}R involvement in hallucinogenic-like behavior.[4]
- DOI increases time spent at the center, dopamine depletion and L-DOPA exposure appears to increase this behavior. (**Fig. 5A)**
- Treatment increases stereotype count regardless of dopamine loss or L-DOPA exposure. (**Fig. 5B)**
- Total distance travelled increased regardless of group, indicating that there is an effect of treatment. (**Fig. 5D**)
- More subjects need to be added to Experiment 2 in order to better delineate effects of 5-HT_{2A}R stimulation in DA-depleted and L-DOPA-primed subject.

These data highlight how 5-HT_{2A}R stimulation produces altered exploratory and hallucinogenic behaviors and suggest DA depletion/L-DOPA might uniquely modify these effects with implications for studying and treating PDAP in patients.

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Supported by NIH Bridges to Baccalaureate Grant R25 GM056637 and the Center for Development and Behavioral Neuroscience at Binghamton University.