ALTO-203, a Novel Histamine H3 Inverse Agonist, Increase Sucrose Preference in Dopamine-depleted Rats

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1. Introduction

- Symptoms of reduced experience of pleasure or motivation to engage in rewarding activities, termed anhedonia, are a common component of many neuropsychiatric disorders. Anhedonia is reported in more than 75% of people with depression. It is widely associated with dopaminergic dysregulation and impaired reward processing.
- ALTO-203 is a novel histamine H3 receptor (H3R) inverse agonist in development for major depressive disorder (MDD) with anhedonia.
- ALTO-203 increases dopamine release in the nucleus accumbens in rodents, a property not shared by pitolisant (the only FDA approved H3R inverse agonist, which is indicated for the treatment of excessive daytime sleepiness in narcolepsy).
- However, the behavioral impact of ALTO-203's putative effects on accumbens dopamine remains unclear.

2. Study Design

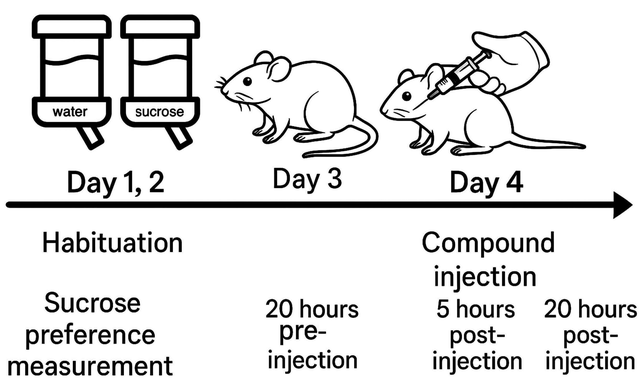
- In dopamine depleted rats, induced by α-methyl-p-tyrosine (AMPT), we evaluated the impact of ALTO-203 versus pitolisant on sucrose preference. The study was designed to further investigate the behavioral relevance of ALTO-203's putative effects on accumbens dopamine.

Treatments

- Rats received either ALTO-203 (0.001, 0.01, 0.3 mg/kg i.p.), pitolisant (2.5, 10, 30 mg/kg i.p.), or vehicle co-administered with AMPT (150mg/kg i.p.).
- N=12 for each treatment and dose group.

Animal Behavior Paradigms

- Male Sprague Dawley rats were tested at 9-weeks of age.
- Animals' weights were monitored daily.
- **Day 1, 2** : **habituation**
- **Day 3 pre-dose preference**: two-bottle choice paradigm (2% sucrose or water) for 20 hours
- **Day 4 compound injection**: measure sucrose preference at 5 hours and 20 hours post injection.

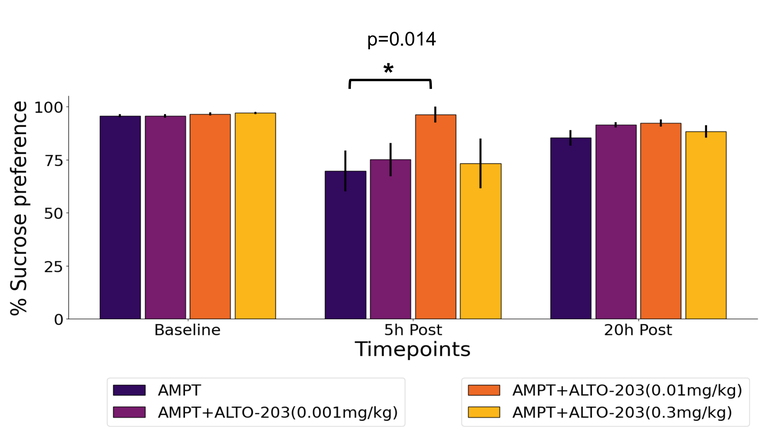


3. Data Analysis

- The percentage of sucrose solution consumed (% sucrose preference) was measured during the pre-dose period, 5 hours and 20 hours after dosing.
- The observations in which animals did not consume any fluid, and outliers outside the 2 interquartile range (IQR) for overall consumption, were removed.
- Since the distribution of the percentage of sucrose consumption is highly skewed, we applied Scheirer-Ray-Hare test (non-parametric ANOVA) to evaluate the effect of Treatment, Time, and Treatment x Time interaction.
- A post-hoc Dunn test was performed between each active treatment and the vehicle group.

4. ALTO-203 (0.01 mg/kg) Increases Sucrose Preference in Dopamine Depleted Animals

- Bar plots of sucrose preference for each treatment at each timepoint (Mean±SE).



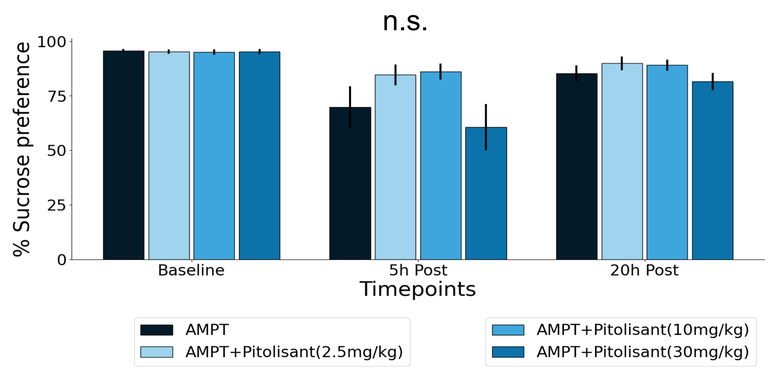
- A two-way ANOVA (non-parametric, Scheirer–Ray–Hare test) found a significant effect of Treatment and Time.

factor	Df	Sum Sq	H	p value
Treatment	3	12901	10.54	**0.0145**
Time	2	17560	14.34	**<0.001**
Treatment X Time	6	12165	9.94	0.127

- A post-hoc Dunn test at 5 hours post treatment showed that 0.01 mg/kg ALTO-203 significantly increased sucrose preference compared to the AMPT only group (from 70% to 96%, p=0.014).

5. Pitolisant Does Not Increase Sucrose Preference in Dopamine Depleted Animals

- Bar plots of the percentage of sucrose preference for each treatment group at each timepoint (Mean±SE).



- A two-way ANOVA (non-parametric, Scheirer–Ray–Hare test) found only significant Time effect, no Treatment effect or interaction effect.

factor	Df	Sum Sq	H	p value
Treatment	3	4638	16.05	0.344
Time	2	30987	26.47	**<0.001**
Treatment X Time	6	3212	32.14	0.890

- A post-hoc Dunn test at 5 hours post treatment showed that pitolisant did not change sucrose preference compared to the AMPT only group at any dose (p>0.05).

6. Conclusions

- ALTO-203 effectively reversed anhedonia-like behavior induced by dopamine depletion, while pitolisant did not.
- ALTO-203's distinct behavioral effects may be due to its ability to enhance the function and control of dopamine in the reward system.

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