Investigation of 1P-LSD as a Novel Drug Therapy for Autism Spectrum Disorders

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Introduction

Autism spectrum disorders (ASD) are defined by repetitive behaviors or impaired social communication. ASD encompasses a series of neurodevelopmental disorders that have various physiological manifestations (Goines & Ashwood, 2013). Due to the heterogeneity of ASD, the true mechanisms leading to the development of ASD and its symptoms remain unclear and require more research (Rossignol & Frye, 2012; Watts, 2008).

Research Problem Statement

There are various disorders that contribute to the symptoms associated with ASD. Hyposerotonemia in the brain and its proposed role in creating dysfunctional NMDA receptor activity is one such disorder. The purpose of this project is to test whether 1-propionyl-lysergic acid diethylamide (1P-LSD), an analogue of lysergic acid diethylamide (LSD) and serotonin agonist, has the potential to treat symptoms of ASD.

1-propionyl-lysergic acid diethylamide

Research Questions

What is the overall efficacy of microdosing 1P-LSD in mitigating the symptoms of ASD?

What is the maximum drug dosage that will not induce a hallucinogenic effect?

How does 1P-LSD influence overexcitation of NMDA receptors?

Hypothesis

In Phase 1 of our experiment, we expect to determine the dosage levels that will be used in Phase 2. We expect to see NR2B receptor subunit levels decrease compared to the control as well as glutamate levels decrease compared to the control throughout Phase 2 of our experiment.

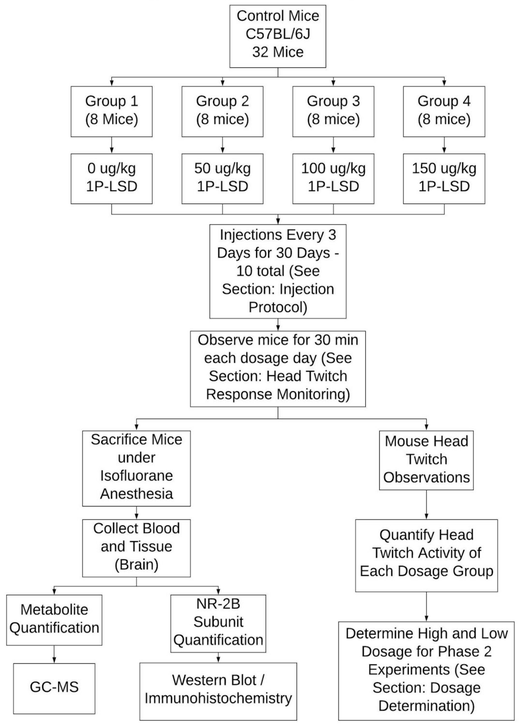
Methodology

Phase 1:

Determine the maximum dose of 1P-LSD to not exhibit hallucinogenic response through behavioral observations

- Composed of 4 cohorts of differential dosages on control mice
- Observing head twitch response as a hallucinogenic indicator

Figure 1: Experimental Design: Phase 1

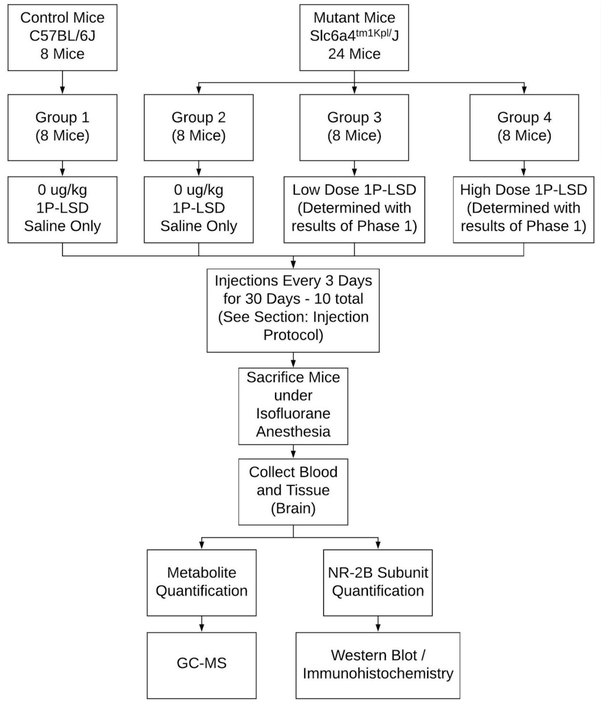


Phase 2:

Measure effect of 1P-LSD on NMDA receptor excitotoxicity

- Composed of 3 cohorts for positive control, negative control, and experimental mutant mice
- Elucidate NR2B receptor subunit activation and glutamate levels in the brain

Figure 2: Experimental Design: Phase 2



1P-LSD Dosing Scheme

Dosage group	Mass of 1P-LSD (µg) /200 µL	Concentration (µg/mL)
Dosage group 1: 0 µg 1P-LSD per kg of body weight	0 µg	0 µg/mL
Dosage group 2: 50 µg 1P-LSD per kg of body weight	1.25 µg	6.25 µg/mL
Dosage group 3: 100 µg 1P-LSD per kg of body weight	2.5 µg	12.5 µg/mL
Dosage group 4 (reconstituted stock): 150 µg 1P-LSD per kg of body weight	3.75 µg	18.75 µg/mL

The 1p-LSD will be purified and dried out under inert gas. The resulting powder will be reconstituted in a vehicle composing of pure ethanol, emulphor, and physiological saline in a 1:1:18 ratio. Mass of 1P-LSD to be dissolved in vehicle and concentration of 1P-LSD for each dosage group. Dosage group 4 will be the same concentration as the reconstituted stock solution that will be securely stored in the Principal Investigator's laboratory. The stock will be diluted to obtain the concentrations for lower dosage groups. Calculations were done using an average 25 g mice and a 0.2 mL injection volume per mouse.

Planned Analyses

We also expect to see a decrease in compounds associated with cytotoxicity pathways, as well as a general increase in metabolites associated with serotonin signaling. Broadly, we expect our measured endpoints for the mutant mice post-treatment to approach those of the control mice before treatment. Specifically we expect to see:

Decreased expression of NR2B receptor subunits in the brain post-treatment. This will be measured using western blotting and immunohistochemistry.

Decreased expression of glutamate in the brain post-treatment. This will be measured using gas chromatography-mass spectrometry.

Future Research Goals

Our results should provide insights into molecular mechanisms through which 1P-LSD improves brain connectivity. This information could be leveraged to mitigate some of the pathology that results in the symptoms associated with ASD. We focused on biological tests, but future research could focus on behavioral tests, such as the anxiolytic (elevated zero maze) test and the partition test. Our research focused on biomarkers surrounding the 5HT1A and NMDA receptors; future research could focus on alternative biomarkers and pathways for 1P-LSD. Our research focused on 1P-LSD as a novel serotonin agonist; future research could focus on LSD itself or other novel serotonin agonists. Future research could also focus on the application of our results from a mouse model to a human model.

References

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