The effects of arginine-vasopressin V1A antagonism on social and repetitive behaviors in a mouse model of autism spectrum disorder

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Introduction

There are no drugs that treat the core symptoms of autism spectrum disorder (ASD), a developmental disability characterized by deficits in social communication, and restricted, repetitive patterns of behaviors and/or interests. Pharmacological research is being conducted to find therapies to alleviate the core symptoms of ASD. Past studies have linked arginine-vasopressin and oxytocin to the regulation of social behavior. To examine the effects of blocking the arginine-vasopressin V1a receptor, SR-49059 (relcovaptan) was administered to a mouse model of ASD. While it is not yet approved for clinical usage, relcovaptan targets the same receptor as balovaptan, a drug that has been shown in clinical trials to improve social behavior.

The aim of these experiments was to see if the antagonism of the V1a receptor would lead to improvements in social and learning behaviors. Oxytocin is implicated in the regulation of social behavior, and arginine vasopressin, which is closely related, may have the same effect. Relcovaptan blocks activation of the V1a receptor. Thus, we hypothesize that antagonism of this receptor might result in prosocial behavior in the BTBR mouse model of autism.

Methods

Treatment: Mice were randomly assigned to three treatment groups: control (vehicle: 15% DMSO, 2% Tween 80, and 83% distilled water), 5, or 10 mg/kg relcovaptan. Drug was administered by intraperitoneal injection 30 minutes prior to starting either the social approach or marble burying tests. The same mice were used in both tests and received the same dose of relcovaptan for each for at least a week in between tests.

Subjects: The mouse model of ASD used in these studies is the BTBR T+gmr/J (BTBR) inbred strain of mice, as these mice exhibit high levels of repetitive behavior and reduced social behaviors. The effects of relcovaptan were also tested in C57BL/6J (B6) mice, an inbred mouse strain commonly used as a control, as B6 mice exhibit fewer repetitive behaviors and more social behavior.

Social Approach. Test results showed that relcovaptan administration exhibited a decrease in sociability for BTBR mice and an increase in sociability for B6 mice.

Marble Burying. Relcovaptan had an effect of reducing marble burying activity in the B6 mice but displayed no effect in the BTBR.

Social Approach Methods

- Social approach uses a three-chambered apparatus to evaluate social behavior in mice. The test is divided into three ten-minute phases.
- Center Habituation: the first phase where the mouse is allowed to habituate to the center of the apparatus.
- Habituation: the mouse can explore all three chambers freely.
- Sociability: inverted wire pencil cups are placed on either side of the apparatus. One is empty, and one contains a same-sex 125 g/l/JLm mouse. The mouse is allowed to explore all of the chambers and given a choice between exploring a novel object or the stranger mouse.

Marble Burying Methods

- The marble burying test is a test used to measure a mouse’s level of repetitive behaviors.
- A 4 x 5 array of 20 marbles is placed on top of 5 cm of bedding. The mice are allowed to explore the cage freely for 30 minutes.
- The number of marbles that are buried by repetitive digging behaviors are scored. Any marble that is at least ¼ covered by the bedding is counted as a “buried” marble.

Summary

In the social approach results, the mice overall preferred to spend time in the stranger mouse chamber (p < .005). There was an interaction between chamber, treatment, and strain (p < .05). When the treatment was 10 mg/kg relcovaptan there was a decrease in time spent in the stranger chamber and an increase in the time spent in the object chamber for the BTBR mice. Conversely, an increase in stranger chamber time and slight decrease in object chamber time at the same dose was observed in the B6 mice.

For marble burying results, while there is a significant difference (p < 0.001) between strains for the number of marbles buried, there appears to be no significant effect regarding the dose. A trend was found in the B6 data, where the number of marbles buried decreased as the dose of relcovaptan increased. However, no such trend was found in the BTBR mice. The number of marbles buried stayed fairly consistent, and peaked at the highest dose.

Riluclovaptan had an effect of reducing marble burying in the B6 mice but no effect in the BTBR mice. Test results also showed that relcovaptan administration led to a decrease in sociability for BTBR mice and an increase in sociability for B6 mice. The results indicate a complicated set of effects in both the control and ASD-like mice that needs to be further studied.

Acknowledgments

This work was supported by the New York State Office for People with Developmental Disabilities (OPWDD). Thanks to everyone for their assistance.

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References


A diagram showing the apparatus set-up of the sociability stage in the social approach test.