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Research report

Effects of lurasidone on ketamine-induced joint visual attention dysfunction as a possible disease model of autism spectrum disorders in common marmosets

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HIGHLIGHTS

- JVA function was evaluated in common marmosets using the apparatus we developed.
- Subanesthetic doses of ketamine induced JVA-specific impairment rather than amnesia.
- Lurasiodone, an antipsychotic agent, was effective against the dysfunction.
- Our experimental system could be a useful animal model of autism spectrum disorder.
- Lurasidone might be effective on some aspects of autism spectrum disorder.

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ABSTRACT

Infants with autism have difficulties performing joint visual attention (JVA), defined as following another person's pointing gesture and gaze. Some non-human primates (NHPs) can also perform JVA. Most preclinical research on autism spectrum disorders (ASD) has used rodents as animal models of this social interaction disorder. However, models using rodents fail to capture the complexity of social interactions that are disrupted in ASD. Therefore, JVA impairment in NHPs might be a more useful model of ASD. The aim of this study was to develop an appropriate and convenient ASD model with common marmosets. We first tested whether marmosets were capable of performing JVA. Subsequently, we administered ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, to induce JVA impairment and investigated the effects of lurasidone, a newer antipsychotic agent, on the JVA impairments. An apparatus was constructed using 4 white boxes, which were attached to the corners of a frame. All boxes had a hinged door, and marmosets could easily obtain a reward by pushing the door. An experimenter pointed and gazed at the boxes to inform the marmosets which box contained the reward. Their behavior was scored according to the number of incorrect choices. The JVA score was significantly higher in the cued vs. uncued tasks. Ketamine significantly decreased the JVA score, but lurasidone significantly reversed this effect. These findings suggest that this experimental system could be a useful animal model of neuropsychiatric disorders characterized by NMDA-receptor signaling, including ASD, and that lurasidone might be effective for some aspects of ASD.

1. Introduction

Autism spectrum disorder (ASD) is a developmental disorder involving impairments in sociability and communication, as well as restricted, repetitive behavior patterns. Children with autism are known to show social behavior impairments, including

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impairments of joint visual attention (JVA) [1–4]. JVA, defined as following another person's pointing gesture and gaze, is the basis for language development in infants [5,6] and is a pivotal social interaction skill. Two types of JVA behaviors, responding to joint attention (RJA) and initiating joint attention (IJA), emerge in the first months of life [7,8]. RJA refers to an infant's ability to follow the direction of gaze, head posture, or pointing gestures of others to share a common point of visual reference. On the other hand, IJA refers to an infant's ability to create or indicate a shared point of reference by pointing at an object or alternating their gaze between that object and another individual. JVA must occur within the context of a social interaction. A decreased score on the tests using the RJA or IJA function has been observed in children with autism [9,10]; therefore, these impairments are known to be an early sign of ASD [3,9].

In this way, developmental delay due to ASD results in a significant disadvantage for social independence; however, drugs for the core symptoms of ASD have not yet been approved despite the severity of the disease. This might be because the pathogenic mechanism of ASD is not well understood, and because animal models of ASD using rodents are inappropriate in some points. For example, it has often been reported that the valproate-exposed offspring of rodents show social interaction impairments [11]; however, it is difficult in rodent models to capture the complex behaviors seen in infants with autism like JVA impairment. In addition, considering that the prefrontal cortex (PFC) of rodents is less developed than that of humans [12,13], it may be difficult to directly predict clinical effects based on the results of rodent studies because ASD is thought to involve PFC function. On the other hand, some non-human primates (NHPs), for example, chimpanzees, rhesus monkeys, and Japanese monkeys, can reportedly perform JVA tasks [14–16]. Moreover, the PFC of NHPs is more developed than the PFC of rodents [17], thus it is important to conduct experiments that evaluate the behaviors of NHPs that are also commonly seen in humans, such as JVA, to bridge the gap between rodents and humans. To date, most previous preclinical studies of cognition have used large monkeys; however, they are difficult to handle and require a large quantity of test drugs. Therefore, in this study, we used common marmosets (small monkeys) instead. Marmosets are highly social primates, and since the brain anatomy and the genetic and immunological characteristics of marmosets are similar to those of humans, marmosets have recently been recognized as useful experimental animals. However, it is unknown whether marmosets can perform JVA tasks.

Although it is well known that hypofunction of *N*-methyl-D-aspartate (NMDA) receptors is associated with schizophrenia, recent reports have indicated that impaired neural transmission caused by dysfunctional NMDA receptors may be also related to ASD [18–21]. Therefore, we focused on the relationship between ASD and NMDA receptors, and hypothesized that NMDA receptor antagonist-induced JVA impairment in marmosets might be a pathological model of ASD. In this study, we attempted to develop a new animal model of ASD using marmosets. First, we constructed an apparatus to evaluate JVA function, and tested whether marmosets could perform JVA tasks by comparing the scores between the tasks performed with and without cues (pointing gestures and gaze). Subsequently, we investigated whether ketamine, an NMDA receptor antagonist, induced impairment in JVA. However, it was possible that the impairment effect of ketamine was the result of amnesia rather than JVA impairment. If amnesia was the cause, then ketamine might decrease the score even if a cue that does not involve social communication with an experimenter is used. Therefore, we evaluated the effect of ketamine using lights as a non-social cue instead, to demonstrate whether the ketamine-induced decrease in the JVA score resulted from amnesia or JVA-specific impairment. Moreover, we evaluated the effects of lurasidone, an antipsychotic agent approved by the American Food and Drug Administration in 2010, on the ketamine-induced JVA impairment. We have previously reported that lurasidone has procognitive effects in rodents and marmosets [22–26]. In addition, we have recently reported that lurasidone increased the cortical efflux of glutamate [27]. Considering the relationship between NMDA receptor hypofunction and ASD, lurasidone might be effective on ketamine-induced JVA impairment. Therefore, the present study investigated whether lurasidone ameliorated the ketamine-induced JVA impairment.

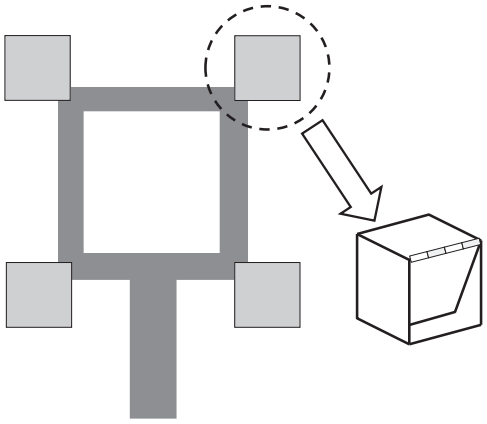

Fig. 1. Schematic illustration of the apparatus. Four white-colored boxes, which each had a door, were attached to the corners of a square frame. There was a food reward behind the door.

2. Materials and methods

2.1. Animals

Two male and three female adult common marmosets (*Callithrix jacchus*, 5–7 years old) obtained from CLEA Japan Inc. (Tokyo, Japan) were used in this study. The animals were housed in an air-conditioned room maintained at a temperature of $28 \pm 2\,^{\circ}C$ and a humidity of $50 \pm 20\%$ under a 12/12, light/dark cycle (lights off at 19:00). Food (CMS-1M, CLEA Japan, Inc.) was administered once daily, and water was available ad libitum. After all experiments for this study were complete, the animals were used in other experiments. All experimental procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of Sumitomo Dainippon Pharma, Co., Ltd.

2.2. JVA task

2.2.1. Apparatus and procedure

The apparatus was constructed using 4 white-colored acrylic boxes ($4 \times 4 \times 4$ cm, each box was numbered), which were attached to the 4 corners of a square frame (10×10 cm). All of the boxes had a door with a hinge (Fig. 1) and the marmosets could easily obtain a food reward (a piece of kneaded cake, about 0.5 cm^3) by pushing the door forward. All experiments were conducted in the animals' home cages, and all doors and inside surfaces of the boxes were wiped down when one session was finished. An experimenter stood in front of the marmoset's home cage with the apparatus facing the marmoset. Subsequently, the experimenter moved the apparatus closer to the marmoset, and informed the animal which box had the reward by pointing and gazing toward the box. We scored the marmosets' JVA ability using the following conditions: 10, obtained the rewards without any mistakes; 3, obtained the rewards with only one mistake; 1, two mistakes; or 0, more than three mistakes. When the marmosets sequentially opened the same door more