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Pharmacologically induced N-methyl-D-aspartate receptor hypofunction impairs goal-directed food seeking in rats

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Abstract

Aim: Acute N-methyl-D-aspartate (NMDA) receptor antagonism is an important pharmacological animal model of schizophrenia. In previous studies, schizophrenia patients show impaired goal-directed behavior in an outcome-specific devaluation procedure. In this study, we investigated whether the rat model of the NMDA receptor blockade also showed altered goal-directed behavior in a satiety-induced outcome devaluation paradigm.

Methods: In experiments 1 and 2, we aimed to establish the satiety-induced outcome devaluation test using sucrose and lipid rewards in operant conditioning and free consumption paradigms. In experiment 3, we tested the effect of MK-801 (0.1 mg/kg, i.p.) on outcome-specific devaluation.

Results: Experiments 1 and 2 demonstrated that 1-h ad libitum food consumption is sufficient to induce outcome-specific devaluation in both lever-press and free consumption tests in rats. Experiment 3 showed that the administration of MK-801 impaired satiety-induced devaluation in the lever-press test but not in the subsequent free consumption test.

Conclusions: Our results suggest that acute pharmacological NMDA receptor antagonism in rats is a useful animal model for impaired goal-directed behavior in schizophrenia.

KEYWORDS

devaluation, MK-801, NMDA receptor, rats, schizophrenia

1 | INTRODUCTION

The glutamate hypothesis emphasizes possible dysfunctions in glutamatergic signaling, typically those of the ionotropic N-methyl-D-aspartate (NMDA) receptor, in the central nervous system of schizophrenia patients.[1,2] Human studies have shown that the acute administration of noncompetitive NMDA receptor antagonists, phencyclidine, and ketamine causes hallucinations and delusions seen in the early stages of schizophrenia patients.[3,4] NMDA receptor blockades also cause negative psychological states[3,4] and worsen already expressed cognitive and psychological symptoms in schizophrenia patients.[5,6] Furthermore, a recent genome-wide association

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study (GWAS) has identified 108 sites on the human genome that are closely associated with schizophrenia and genes related to glutamatergic neurotransmission, such as GluN2A (GRIN2A), which is a subtype of NMDA receptors.[7]

Acute administration of NMDA receptor antagonists is one of the pharmacological animal models of schizophrenia inspired by the glutamatergic hypothesis. This animal model has shown various schizophrenic behavioral phenotypes: (1) impaired sensorimotor gating in the pre-pulse inhibition test.[8] (2) Hyperactivity and stereotyped behavior in the open field test,[9] which is regarded as a potential model of the positive symptoms of schizophrenia.[10] (3) Social withdrawal, which is an example of a negative symptom.[11] (4) Cognitive dysfunction in behavioral set-shifting,[12] reversal learning,[13] and paired-associate learning.[14]

In addition to the symptoms mentioned above, schizophrenia patients show dysfunctional decision-making associated with flexible goal-directed behavior.[15,16] Goal-directed behavior is an intentionally executed action that is based on the association between a specific action and causal outcome. Previous studies have quantified goal-directed behavior in an outcome-specific devaluation paradigm in both human and animal subjects.[17-19] In this behavioral paradigm, subjects are first trained in an instrumental conditioning task, where a specific outcome (eg, food) is delivered after the execution of a specific action (eg, button pressing). Goal-directed behavior is measured as the reduction in the likelihood of taking action after the outcome is devalued by the specific satiety or paired with an unpleasant stimulus. Indeed, schizophrenia patients show difficultly in a flexible behavioral change based on updated outcome values in a devaluation paradigm.[20]

The animal model of acute pharmacological blockade of NMDA receptors has shown suboptimal value-based decision making.[21] However, it has not been tested whether this animal model of schizophrenia exhibits an impaired goal-directed behavior in an outcome-specific devaluation paradigm. In the present study, we investigated the effects of the acute administration of an NMDA receptor antagonist, MK-801 (dizocilpine; 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine), on instrumental food-seeking behavior after outcome devaluation.

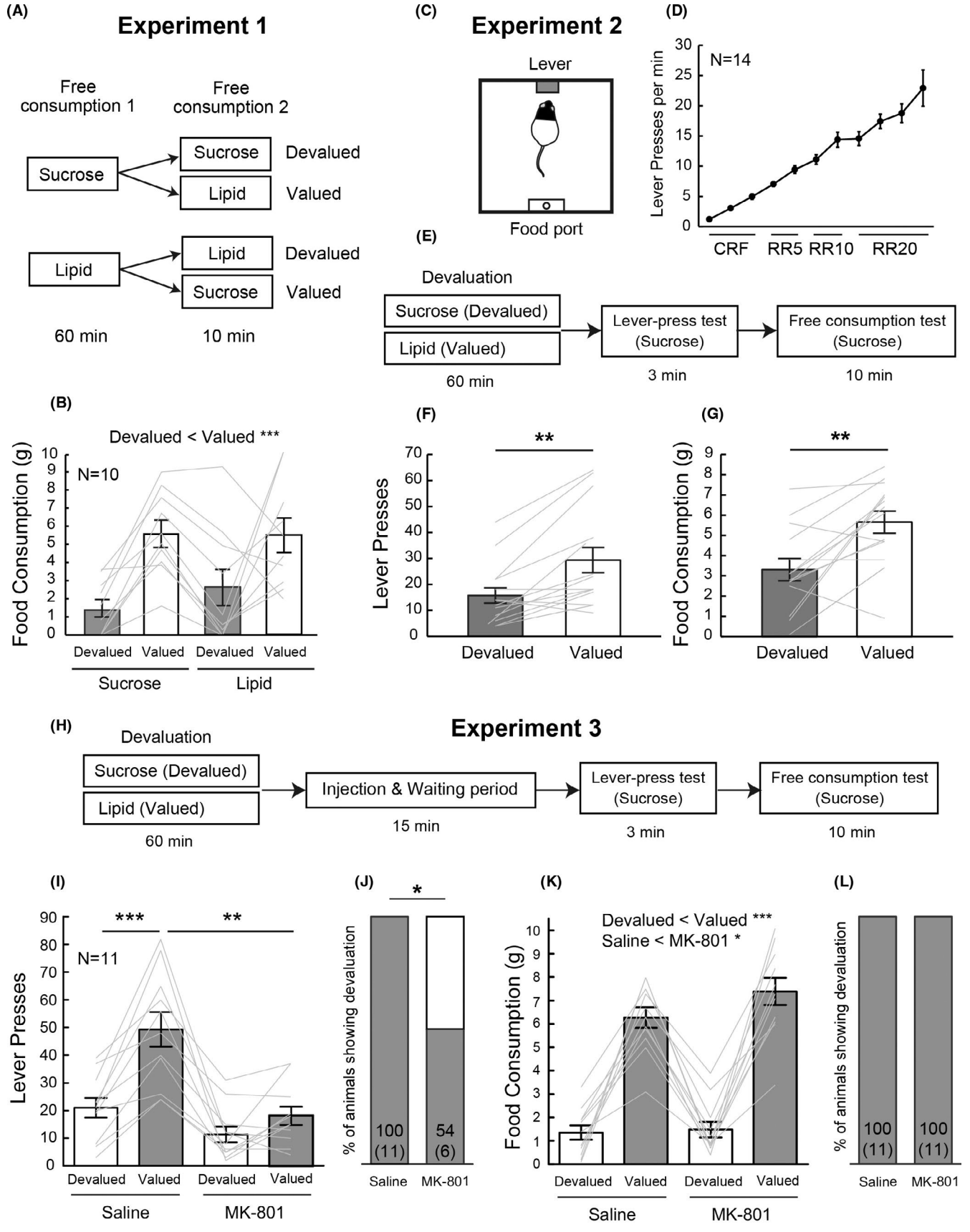
2 | METHODS

Twenty-four male Long-Evans rats (8weeks old) were used. The mean body weight at the start of the experiments was around 280 g. Ten rats were assigned to experiment 1. Fourteen rats were assigned to experiment 2 and experiment 3. However, three rats were removed after the experiment 2 because of health issues. Rats were housed in individual cages on a 12:12 h light-dark cycle (light on: 0800-2000) with free access to water throughout the experiments. Their feeding was limited to maintain 85%-90% of their expected free-feeding weight. All efforts were made to minimize the number of animals used and their suffering. All experiments were approved by the University of Tsukuba Committee on Animal Research.

In the present study, we used MK-801, which is a common and easy-to-use NMDA receptor antagonist, compared to phencyclidine and ketamine that are often regarded as the controlled substances. (+)-MK-801 hydrogen maleate (MK-801; Sigma) was diluted in saline (SAL; Otsuka, Tokyo, Japan) to a final concentration of 0.1 mg/mL. In the experiment, the dose of 0.1 mg/kg was intraperitoneally injected. This low dose of MK-801 was chosen based on a previous report which showed that this dose of MK-801 had no effects on simple discriminative behaviors and motor functions.[22]

In experiment 1, we tested whether satiety for a specific food (sucrose or lipid) induced food-specific devaluation in a free consumption test (Figure 1A). This test consisted of two free consumption periods. In the first period, the food-restricted rat was put in a transparent plastic cage (38 × 21 × 20 cm) and allowed to freely access either sucrose pellets (45 mg, 5TUT; Test Diet) or a 10% soybean lipid solution (Intralipos) for 60 min. The second free food consumption was conducted immediately after the first one in the same manner but only for 10 min. The amounts of food consumed were measured after both periods. Free consumption tests were repeated four times in a within-subject design so that each rat experienced all combinations of devalued food (sucrose or lipid) and tested food (sucrose or lipid). The order of food consumed in each test was counterbalanced.

In experiment 2, we tested whether the satiety for sucrose induced outcome- specific devaluation in both lever-press operant conditioning and free consumption tests (Figure 1C). After 2 days of handling (5 min), rats were allowed to freely explore in an operant chamber (30 × 32 × 36 cm; O'Hara & Co., Ltd.) for 10 min. During this habituation period, rats were able to eat sucrose pellets piled at a food reward port. After the habituation period, rats were given a 2-day magazine training for 30 min. A house light and a mild background white noise were turned on when the training started, and a single pellet was passively delivered to the food reward port every 60 s on average (RT-60 s schedule). Following the magazine training, a single nonretractable lever was set on the wall at the opposite side of the food reward port, and rats were trained to press the lever to get the sucrose rewards for 9 days. Each session finished when rats earned 30 rewards or when 30 min elapsed. In the first 3 days, rats were trained in a continuous reinforcement schedule (CRF), in which a single lever press results in a single sucrose pellet delivery. For the remaining 6 days, rats were trained in a random ratio (RR) schedule where rats were able to earn the reward by pressing the lever with a probability of 0.2 (RR5), 0.1 (RR10), or 0.05 (RR20). Each RR schedule training was conducted for 2 days. After a sufficient lever-press training, rats were tested in a lever press-based outcome-specific devaluation paradigm consisting of 3 periods: devaluation, lever-press test, and free consumption test. On the day of the devaluation test, rats were first allowed to eat lever-press-associated sucrose pellets or a control 10% lipid solution for 60 min in the same manner as the experiment 1 (devaluation). Immediately after the devaluation period, the lever-press test was conducted, where lever-press behavior was measured for 3 min under an extinction condition (ie, no reward delivery) in the operant chamber. Subsequently, rats were moved to a normal cage, and then the amount of sucrose pellet consumed was assessed



(free consumption test). This devaluation test was repeated twice so that rats' food-seeking behavior after satiety by both sucrose and lipid could be assessed.

In experiment 3, the effect of systemic injection of an NMDA receptor antagonist on outcome specific devaluation was tested using the same animals as those used in experiment 2. The procedure of

FIGURE 1 The effect of systemic injection of MK-801 on outcome-specific devaluation. A, and (B) show the results of experiment 1. A, Schematic illustration of the free food consumption test. B, The amount of food consumed during the second period of free consumption test. C-G, show the results of experiment 2. C, Schematic illustration of lever-press operant conditioning. D, The number of lever presses during the lever-press training. E, Time schedule of devaluation tests. F, The number of lever presses during the lever press devaluation test. G, The amount of food consumption during the free consumption devaluation test. H-L, show the results of experiment 3. H, Time schedule of drug treatment and devaluation tests. I, The number of lever presses during the lever-press devaluation test. J, The percentage of animals showing devaluation in the lever-press devaluation test. Numbers in parentheses are the number of animals showing devaluation. K, The amount of food consumption during the free consumption devaluation test. L, The percentage of animals showing devaluation in the free consumption devaluation test. Numbers in parentheses are the number of animals showing devaluation. Data are presented as the mean ± SEM. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$

drug tests was the same as that of the devaluation test; however, rats received intraperitoneal injection of MK-801 or SAL immediately after the devaluation period (Figure 1H). Drug tests were repeated four times so that rats were tested in all four different conditions of devaluation (devalue vs value) and drug treatments (MK-801 vs SAL). The order of each condition was counterbalanced among animals.

In this study, averages of behaviors in different conditions were compared using either of a paired *t* test, one-way repeated measures ANOVA, or two-way repeated measures ANOVA (devaluation × drug) followed by a Bonferroni comparison ($P < .05$). In experiment 3, the percentage of animals showing devaluation between drug conditions was compared using Fisher's exact test. An animal was regarded as "showing devaluation" when it showed a lower lever press or food consumption under the devalued condition compared to the valued condition. All statistical analyses were performed using Prism 9.2.0 (GraphPad Software).

3 | RESULTS

The result of experiment 1 is shown in Figure 1B. Free food consumption for 60 min in the first period was sufficient to induce food-specific devaluation in the second free consumption period. According to two-way repeated measures ANOVA, there was a significant main effect of devaluation [$F(1, 9) = 34.24$, $P < .001$]. The amount of each food consumed decreased when the food was devalued.

Results of experiment 2 are shown in Figure 1D, F, G. In Figure 1D, the number of lever presses per min is shown. One-way repeated measures ANOVA revealed that there was a significant main effect of training days [$F(10, 130) = 44.59$, $P < .001$]. Results of the lever-press test and the free consumption test are shown in Figure 1F, G, respectively. Sixty-min free consumption of sucrose pellets induced outcome-specific devaluation in the operant conditioning and the free consumption test. A paired *t* test revealed that the number of lever presses during the lever-press test [$t(13) = 4.2056$, $P < .01$] and the amount of sucrose pellet consumption during the free consumption test [$t(13) = 3.8256$, $P < .01$] significantly decreased when sucrose was devalued.

Results of experiment 3 are shown in Figure 1H, I, J, K, L. MK-801 impaired outcome-specific devaluation in the lever-press operant conditioning, but not in the free consumption test. According to two-way repeated measures ANOVA, there were significant main effect of devaluation [$F(1, 10) = 44.44$, $P < .001$], main effect of drug administration [$F(1, 10) = 19.97$, $P < .001$], and their interaction [$F(1, 10) = 10.65$, $P < .01$] in the lever-press test (Figure 1I). Subsequent post hoc analysis revealed that the number of lever presses in the SAL-devalued condition was less than that in the SAL-valued condition ($P < .001$). It was also revealed that the number of lever presses in the MK-801-valued condition is less than that in the SAL-valued condition ($P < .01$). Furthermore, Fisher's exact test revealed that fewer animals showed successful devaluation under the MK-801 condition ($P < .05$) (Figure 1J). Regarding the free consumption test, two-way repeated measures ANOVA revealed significant main effects of devaluation [$F(1, 10) = 99.96$, $P < .001$] and drug administration [$F(1, 10) = 5.13$, $P < .05$] (Figure 1K). The amount of sucrose pellets consumed in the devalued condition was lower than that of the devalued condition. Also, the amount of sucrose pellets consumed in the MK-801 condition was higher than that in the SAL condition. In the free consumption test, all animals showed a successful devaluation regardless of drug conditions (Figure 1L).

4 | DISCUSSION

This study investigated goal-directed behavior in a pharmacological animal model of schizophrenia induced by an NMDA receptor blockade. As results, it was found that the acute administration of MK-801 impaired the satiety-induced devaluation when it was measured in the lever-press operant conditioning task, but not in subsequent free consumption test. Our results suggest that acute NMDA receptor blockade is a useful rodent animal model to investigate an impaired value-related decision making in schizophrenia.

In this study, treatment of MK-801 decreased the overall frequency of lever presses compared to the control condition. This result seems to indicate potential nonspecific effects of MK-801 on general cognitive functions or on the motivation for food. However, the dose (0.1 mg/kg) of MK-801 used in our study does not impair discriminative behavior and working memory in rats.[22] Furthermore, the free consumption test following the lever-press test revealed that the amount of food intake significantly decreased in the devalued condition regardless of drug treatment, and MK-801 treatment rather increased general sucrose pellet consumption.[23] These results suggest that MK-801 does not impair general motivation for food nor satiety-induced value updating. To summarize, MK-801 impairs the expression of goal-directed behavior in operant conditioning by

disrupting action-outcome association but not due to its nonspecific side effects.

The systemic MK-801 injection is likely to impair goal-directed behavior by disrupting glutamatergic neurotransmission in the specific regulatory brain area. The striatum, especially the dorsomedial part, is an essential brain structure in regulating goal-directed behavior.[24-26] While the activation of NMDA receptors and its downstream signaling pathway in the dorsomedial striatum is particularly important for the acquisition of action-outcome association,[27] the activity of striatal NMDA receptors may also have some role in the execution of goal-directed behavior, which depends on the action-outcome memory. In addition, the insular cortex is also known to regulate the expression of outcome-specific devaluation.[28] Intra-insular injection of an NMDA receptor antagonist eliminates selective devaluation, suggesting that NMDA receptors in the insular cortex are involved in the expression of goal-directed behavior.[29]

NMDA receptor blockade also changes the level of various neurotransmitters in the brain. Indeed, the systemic MK-801 injection induces significant dopamine, serotonin, and noradrenaline release in the striatum and cortex.[30,31,32,33] Moreover, MK-801 decreases the reuptake of serotonin and noradrenaline.[34] These findings suggest that MK-801-induced excessive monoamine release in the cortico-basal ganglia circuit may cause the impaired goal-directed behavior observed in the present study. Given that the dysfunction in the cortico-striatal circuit is associated with impaired goal-directed behavior in schizophrenia,[20] further research is needed to investigate the relationship between kinetics of neurotransmitters caused by NMDA receptor hypofunction and disrupted optimal value-based decision-making.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

TO conceptualized and designed experiments. TI performed the behavioral tests. TO and TI analyzed the data and wrote the manuscript. KY and YI helped to draft the manuscript. KY and YI supervised all aspects of the present study. All authors have read and approved the final manuscript.

ANIMAL STUDIES

Animal experiments were approved by the University of Tsukuba Committee on Animal Research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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