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Short communication

# Effects of Group I metabotropic glutamate receptor antagonists on sensitivity to reinforcer magnitude and delayed reinforcement in a delay-discounting task in rats: Contribution of delay presentation order☆

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ABSTRACT

Metabotropic glutamate receptor 1 ($mGluR_1$) blockade has been shown to decrease impulsive choice, as measured in delay discounting. However, several variables are known to influence an animal's discounting, including sensitivity to delayed reinforcement and sensitivity to reinforcer magnitude. The goal of this experiment was to determine the effects of $mGluR_1$, as well as $mGluR_5$, antagonism on these parameters. Forty Sprague Dawley rats were trained in delay discounting, in which consistently choosing a small, immediate reward reflects impulsive choice. For half of the rats, the delay to the large reinforcer increased across blocks of trials, whereas the delay decreased across the session for half of the rats. Following training, half of the rats received injections of the $mGluR_1$ antagonist JNJ 16259685 (JNJ; 0, 0.1, 0.3, or 1.0 mg/kg; i.p), and half received injections of the $mGluR_5$ antagonist MPEP (0, 1.0, 3.0, or 10.0 mg/kg; i.p.). Administration of JNJ increased sensitivity to delayed reinforcement (i.e., promoted impulsive choice), regardless of which schedule was used. However, the order in which delays were presented modulated the effects of JNJ on sensitivity to reinforcer magnitude. Specifically, JNJ decreased sensitivity to reinforcer magnitude in rats trained on the descending schedule only. MPEP did not alter sensitivity to reinforcer magnitude or sensitivity to delayed reinforcement. These results show that $mGluR_1$ is an important mediator of impulsive choice, and they provide further evidence that delay order presentation is an important variable that influences drug effects in delay discounting.



Impulsive choice is the tendency to choose a small, immediate reward over a large, delayed reward [1] and is often measured using delay-discounting procedures. Recent evidence has implicated the glutamatergic system in impulsive choice, as administration of the glutamate *N*-methyl-D-aspartate receptor (NMDAr) channel blockers ketamine and memantine increase impulsive choice [2,3], whereas the effects of the NMDAr channel blocker MK-801 have been mixed, as some studies have reported a decrease in impulsive choice [4,5] but one study observing no change in impulsivity [6]. Although some evidence has shown that MK-801 decreases impulsive choice, it is a known psychotomimetic [7] that disrupts learning in animals [8].

Instead of targeting the NMDAr, Group I metabotropic glutamate receptors (mGluRs) are a potential mediator of impulsive choice. To our knowledge, only two studies have focused on the contribution of Group I mGluRs in impulsive choice, with results showing that an $mGluR_1$ antagonist decreases impulsive choice [9], whereas $mGluR_5$ allosteric modulators do not alter impulsive choice [10]. Although previous studies have examined the contribution of Group I mGluRs in discounting, they have not examined the effects of mGluR ligands in mediating sensitivity to reinforcer magnitude (i.e., how much an animal responds for the large reinforcer (LR) when its delivery is immediate; see [6] for a full discussion of what this parameter measures) and sensitivity to delayed reinforcement (i.e., what is typically considered to be impulsive

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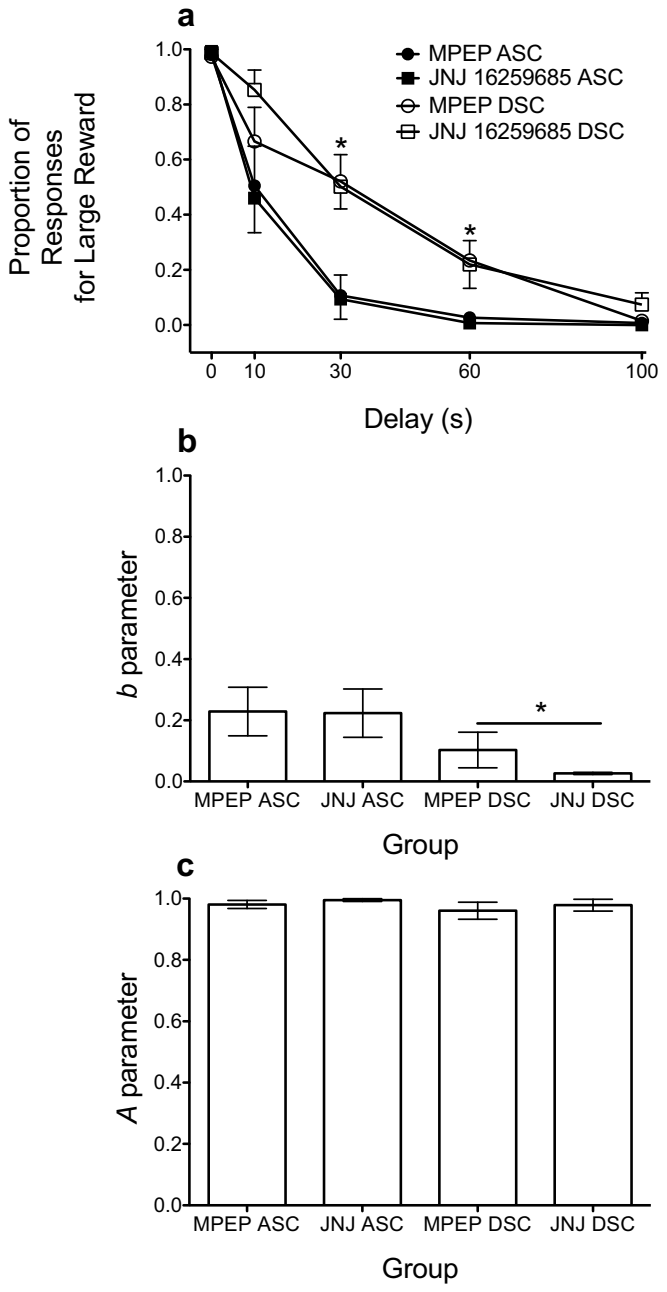


**Fig. 1.** (**a**) Mean (±SEM) proportion of responses for the large, delayed reinforcer, (**b**) mean (±SEM) *b* parameter estimates, and (**c**) mean (±SEM) *A* parameter estimates for each group of rats at the end of baseline. *$p < 0.05$, relative to rats trained on the ascending schedule.

choice), two parameters that influence an animal's discounting [11]. This analysis is important as we can determine the behavioral mechanisms underlying an animal's discounting. For example, previous studies have reported that ketamine and memantine increase impulsive choice [2,3]; however, the use of quantitative analyses revealed that these drugs decrease sensitivity to reinforcer magnitude without altering impulsive choice [6]. Thus, the goal of this study was to further characterize the contribution of Group I mGluRs on these parameters in a delay-discounting procedure. Because the order in which delays are presented can modulate the effects of drugs in discounting [e.g.,12], rats were trained on a task in which the delay to the LR either increased or decreased across the session. Rats received injections of either JNJ 16259685 (JNJ; highly potent and selective $mGluR_1$ antagonist) or MPEP ($mGluR_5$ antagonist).

Forty male Sprague Dawley rats (250–275 g upon arrival in the laboratory) were used. Rats were tested previously in delay discounting and received 12 injections of NMDAr ligands [6]. Rats were individually housed in clear polypropylene cages (51 cm long × 26.5 cm wide × 32 cm high) with metal tops containing food and a water bottle in a room maintained on a 12:12-h cycle. Rats were tested during the light phase and were restricted to approximately 10 g of food each day but had *ad libitum* access to water. All experimental procedures were carried out according to the Current Guide for the Care and Use of Laboratory Animals (USPHS) under a protocol approved by the Northern Kentucky University Institutional Animal Care and Use Committee.

(3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone (JNJ 16259685) and 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP) were purchased from Tocris Bioscience (Ellisville, MO). JNJ was dissolved in distilled water, and MPEP was dissolved in 0.9% NaCl. Because JNJ (0.3 and 1.0 mg/kg) did not stay in solution, it had to be heated and stirred each day prior to the injection. To get MPEP into solution, it was heated and stirred once. All injections occurred at room temperature at a volume of 1 ml/kg.

Eight operant conditioning chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound attenuating chambers (ENV–018 M; MED Associates) were used. A description of the operant chambers has been detailed previously [6].

After completing the experiment described in [6], half of the rats (n = 20) continued training on the discounting task, in which the delay to the LR increased across blocks of trials. Conversely, for half of the rats (n = 20), the delay to the LR decreased across the session. Rats received injections of either the $mGluR_1$ antagonist JNJ (0, 0.1, 0.3 or 1.0 mg/kg, i.p.; n = 20) or the $mGluR_5$ antagonist MPEP (0, 1.0, 3.0, or 10.0 mg/kg; i.p.; n = 20). Each injection occurred 40 min prior to task performance. The doses and pretreatment times were chosen based on previous work [13].

Omissions were analyzed with a two-way ANOVA, with dose as a within-subjects factor and schedule as a between-subjects factor. A main effect of dose was probed using Dunnett's post hoc test, and a significant interaction was probed with additional one-way ANOVAs and Dunnett's post hoc tests, when appropriate.

The proportion of responses for the LR was analyzed with mixed factorial ANOVAs. For baseline data, a three-way ANOVA was used, with delay as a within-subjects factor and drug assignment and schedule as between-subjects factors. Additional two-way or one-way ANOVAs and independent-samples *t* tests were used to probe significant interactions, when appropriate. To determine if JNJ or MPEP altered responses for the LR, separate three-way ANOVAs were conducted, with delay and dose as within-subjects factors and schedule as a between-subjects factor. A main effect of dose was probed using Dunnett's post hoc test, and additional two-way or one-way ANOVAs and independent-samples *t* tests were used to probe significant interactions, when appropriate. For all ANOVA analyses, degrees of freedom were corrected using Greenhouse Geisser estimates of sphericity, if need be.

The exponential discounting function was fit to each subject's data and is defined by the equation $V = Ae^{-bD}$, where V is the subjective value of the reinforcer, *A* is reinforcer magnitude (i.e., responses for the LR when its delivery is immediate), *b* is the rate of discounting (i.e., impulsive choice), and *D* is the delay to delivery of the LR. The exponential function was fit to the data via nonlinear mixed effects modeling (NLME) using the NLME tool in the *R* statistical software package [14], with *A* and *b* as free parameters. To determine if baseline *A* and *b* parameter estimates differed across the four groups of rats, the NLME models defined schedule and drug