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The role of dopamine D_1- and D_2-like receptors related to muscarinic M_1 receptors in impulsive choice in high-impulsive and low-impulsive rats

Lin Tian[a,b], Xinhe Liu[a], Xiaolin Mei[a], Ruisi Cui[a], Xinwang Li[a,*]

[a] Beijing Key Laboratory of Learning and Cognition, School of Psychology, Capital Normal University, Beijing 100048, China
[b] Library, Capital Normal University, Beijing 100048, China

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ABSTRACT

The non-selective muscarinic receptor agonist oxotremorine-M has been found to decrease impulsive choice in high-impulsive (HI) rats and increase impulsive choice in low-impulsive (LI) rats, but little is known about the muscarinic M_1 receptor agonist *N*-desmethylclozapine (NDMC). This study investigated effects of NDMC on impulsive choice, and the effect of co-administration of NDMC with the dopamine D_1-like receptor antagonist SCH 23390 or D_2-like receptor antagonist raclopride on impulsive choice in HI and LI rats, characterized by basal levels of impulsive choice in a delay-discounting task. The results revealed that NDMC (1 and 2 mg/kg) significantly increased impulsive choice in HI, but not LI rats. SCH 23390 significantly promoted impulsive choice in HI rats at 0.01 mg/kg, and in LI rats at 0.0075 and 0.01 mg/kg. Moreover, SCH 23390 (0.005 and 0.0075 mg/kg) significantly inhibited the increase in impulsive choice induced by NDMC (1 mg/kg) in HI rats, whereas the increase in impulsive choice produced by SCH 23390 (0.0075 mg/kg) was significantly reversed by NDMC (1 mg/kg) in LI rats. Raclopride (0.04, 0.08, and 0.12 mg/kg) did not affect choice in both HI and LI rats, but significantly antagonized the increase in impulsive choice induced by NDMC (1 mg/kg) in HI rats. These findings suggest that D_1- and D_2-like receptors might be involved in different effects of the M_1 receptor agonist on impulsive choice between HI and LI rats.

1. Introduction

Impulsive choice is generally defined as a preference for a small immediate or large risky reinforcer versus a large delayed or small likely reinforcer (Zeeb et al., 2010). Moderate impulsive choice belongs to adaptive behavior, whereas an excessive one is a prominent feature of neuropsychiatric conditions such as attention deficit hyperactivity disorder (Rosch and Mostofsky, 2016), schizophrenia (Weller et al., 2014), addiction (Moody et al., 2016), and eating disorders (Cano et al., 2016).

Previous studies have only investigated effects of non-selective cholinergic compounds on impulsive choice. For example, muscarinic receptor antagonists scopolamine and atropine reduced the choice of the large delayed reinforcer, and the muscarinic receptor agonist oxotremorine-M produced no effect on choice (Mendez et al., 2012). The nicotinic receptor agonist nicotine (Anderson and Diller, 2010; Ozga and Anderson, 2018), but not the nicotinic receptor antagonist mecamylamine (Kolokotroni et al., 2011), decreased impulsive choice. In addition, the influence of these cholinergic compounds might be dependent on the baseline levels of impulsive choice (Kayir et al., 2014; Kolokotroni et al., 2014; Mendez, 2010; Tian et al., 2016). Previous research indicates that oxotremorine-M decreases impulsive choice in high-impulsive (HI) rats, and increases impulsive choice in low-impulsive (LI) rats (Tian et al., 2016); however, atropine could promote impulsive choice in both HI and LI rats (Mendez, 2010). Furthermore, nicotine has shown to enhance impulsive choice in LI, rather than HI rats (Kayir et al., 2014; Kolokotroni et al., 2014).

The dopaminergic (DAergic) system has been found to play an important role in impulsive choice (Cardinal et al., 2000; Evenden and Ryan, 1996; Koffarnus et al., 2011; Li et al., 2015; Madden et al., 2010). For instance, the D_1-like receptor antagonist SCH 23390 and D_2-like receptor antagonists haloperidol and L-741626 have shown to promote impulsive choice (Evenden and Ryan, 1996; Koffarnus et al., 2011; Li et al., 2015). Additionally, SCH 23390 and the D_2-like receptor antagonist raclopride have been found to increase impulsive choice in LI rats, with no effect on HI rats (Zaichenko and Merzhanova, 2013), suggesting that the effect of DAergic compounds may also be dependent on the baseline rates of impulsive choice in rats.

The interactions between the cholinergic and DAergic systems are thought to mediate impulsive choice. Several studies revealed that

* Corresponding author.
E-mail address: 5206@cnu.edu.cn (X. Li).

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subcutaneous injections of muscarinic M_1 receptor agonists *N*-desmethylclozapine (NDMC), xanomeline, sabcomeline, and AC260584 increase DA release in the medial prefrontal cortex (mPFC), the ventral hippocampus (vHPC), and the nucleus accumbens (NAc) in rats (Li et al., 2009, 2008, 2007, 2005). Moreover, D_1- and D_2-like receptors are distributed throughout these brain regions (Bentivoglio and Morelli, 2005), which are important in mediating impulsive choice (Abela and Chudasama, 2014; Bezzina et al., 2007; Cardinal et al., 2001; da Costa Araújo et al., 2009; Gill et al., 2010; McHugh et al., 2008; Pothuizen et al., 2005). Therefore, it has been speculated that DA receptors are likely to have a role in the effect of acetylcholine receptors on impulsive choice.

The present study aims to examine the effect of NDMC on impulsive choice in HI and LI rats. Additionally, an effort is made to block the effect of NDMC with SCH 23390 or raclopride to investigate which DA receptors NDMC is working on to affect impulsive choice in HI and LI rats.

2. Materials and methods

2.1. Subjects

Sixty male adult Sprague-Dawley rats were obtained from the Academy of Military Medical Sciences (Beijing, China), weighing 250 ± 20 g upon arrival. In each of the three experiments, 20 rats served as subjects. Rats were housed in groups of two per cage in a temperature- (22 ± 1 °C), humidity- (50 ± 10%), and light- (lights on 08:00–20:00) controlled animal facility. On arrival in the laboratory, rats were habituated to vivarium conditions with free access to food and drinking water for one week. Subsequently, a food deprivation schedule of 15 g per day (inclusive of food earned during training and testing) maintained rats at 85% of their free-feeding weight (Mendez et al., 2012). Animals had access to drinking water ad libitum in home cages. Training and testing were conducted during the light period. The experimental protocol was approved by the Institutional Animal Care and Use Committee of the Capital Normal University in Beijing and followed the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Drugs

NDMC (1, 2, and 4 mg/mL; Sigma) was dissolved in 0.1 M phosphoric acid, the pH was adjusted to approximately 7 with 0.1 M NaOH, and then the solution was diluted with 0.9% saline solution to final concentrations. R(+)-SCH-23390 hydrochloride (0.005, 0.0075, and 0.01 mg/mL; Sigma) and S(−)-raclopride (+)-tartrate salt (0.04, 0.08, and 0.12 mg/mL; Sigma) were dissolved in 0.9% saline solution. All drugs were intraperitoneally administered in a volume of 1.0 mL/kg.

2.3. Apparatus

All sessions were conducted in four identical rat operant chambers (29 cm × 29 cm × 26 cm) controlled by a computer running AniLab version 4.34, Laboratory Animal Behavioral Analysis System (AniLab Software & Instruments Co., Ltd., Ningbo, Zhejiang, China). Each operant chamber was enclosed in a sound-attenuating cubicle and contained a grid floor, a recessed food trough (1.4 cm above the floor), a food pellet dispenser, two retractable levers (5 cm wide, protruded 1.7 cm into the operant chamber; 4 cm above the floor), two cue lights (28 V, 100 mA; 18 cm above the floor), and a house light (28 V, 100 mA; 24 cm above the floor). The food trough was situated in the center of the front panel, where 45 mg of grain food pellets (Research Diets, New Brunswick, NJ) were delivered. The two levers were 9 cm apart, located on either side of the food trough.

2.4. Procedure

Each rat was able to complete daily sessions in the same operant chamber throughout the experiment. Before the first session, to train rats to retrieve food pellets from the food trough, four pellets were placed there, and rats could explore in the darkness for 3 min with the two levers retracted. The rat that did not eat the pellets was put into the chamber again after all rats received the daily training until it ate the pellets in the food trough.

The procedure was essentially the same as the one used by Mar and Robbins (2007) with some modifications, and was reported in Tian et al. (2016). In the present study, however, there were three phases during the training period.

2.4.1. Phase 1: Two-lever fixed ratio one training

Each session consisted of 90 trials. During each trial (60 s), one of the two levers was randomly extended, and the two levers were presented an equal number of times in each session. When a new trial commenced, rats had 30 s to press the extended lever to immediately obtain one food pellet. The phase was over when all rats satisfied the following criteria: the percentage of lever pressing reached at least 80% (36 times for 45 trials) on each lever in a session.

2.4.2. Phase 2: Reinforcer-magnitude discrimination training and testing

Phase 2 was composed of the training period and the testing period. The training program was similar to the one proposed in phase 1 with some alterations. One lever was designated as the small-reinforcer lever and a press on this lever within 10 s resulted in one food pellet delivered immediately, whereas the other lever was designated as the large-reinforcer lever and a press on this lever within 10 s resulted in three food pellets delivered immediately. The positions of the small-reinforcer lever and the large-reinforcer lever were counterbalanced across all rats and constant for each rat throughout the experiment. Once all rats fulfilled the criteria (see phase 1), the reinforcer-magnitude discrimination test was performed. This program bore close resemblance to the above training program; however, each session consisted of 60 trials, and the two levers were simultaneously extended at the beginning of each trial. As soon as the percentage of lever pressing was at least 80% (48 times) of 60 trials and the percentage of the large-reinforcer choice in lever pressing was at least 80% during two successive sessions, this phase ended.

2.4.3. Phase 3: The delay-discounting task

One session consisted of five blocks, with each of which comprised two forced-choice trials followed by 10 free-choice trials. Trials started every 60 s with the illumination of the house light. During the forced-choice trials, one of the two levers was randomly extended at a time, and each lever was only extended once in a block. During the free-choice trials, the two levers were simultaneously extended. If a rat pressed the extended lever within 10 s, the lever(s) retracted. A press on the extended small-reinforcer lever resulted in one food pellet delivered immediately, whereas a press on the extended large-reinforcer lever resulted in three food pellets delivered after a delay of 0 (block 1), 2 (block 2), 4 (block 3), 8 (block 4), or 16 s (block 5; Slezak and Anderson, 2011). During blocks 2–5, the cue light located above the large-reinforcer lever was illuminated immediately after a rat pressed on this lever, and the light did not turn off until reward delivery. After the delivery, the house light remained on for 6 s. Subsequently, the house light darkened, and an inter-trial interval began. Since trials started every 60 s, the inter-trial interval was variable [inter-trial interval duration = 60 s − (response latency + delay duration); Kayir et al., 2014]. When a rat did not press any extended lever within 10 s, an inter-trial interval was also initiated. The trial omitted by a rat during the free-choice period was scored as an omission.

Rats were trained daily until they met the following criteria: the percentage of lever pressing in all free-choice trials and large-reinforcer

lever pressing in free-choice trials of block 1 were each at least 80%, and showed a stable level of responding based on the percent choice of the large reinforcer recorded during the last five consecutive sessions of phase 3. The percent choice of the large reinforcer was then analyzed via two-way repeated measure analysis of variance (ANOVA; session × delay). Criteria for the stability of performance were met when there was a significant main effect of delay [experiment 1: F (2.549, 48.434) = 122.173, $p < 0.001$, $\eta_p^2 = 0.865$; experiment 2: F (1.965, 37.338) = 91.260, $p < 0.001$, $\eta_p^2 = 0.828$; experiment 3: F (2.022, 38.422) = 145.839, $p < 0.001$, $\eta_p^2 = 0.885$], no significant main effect of session [experiment 1: F (4, 76) = 0.815, *ns*, $\eta_p^2 = 0.041$; experiment 2: F (4, 76) = 1.360, *ns*, $\eta_p^2 = 0.067$; experiment 3: F (3.043, 57.818) = 0.830, *ns*, $\eta_p^2 = 0.042$], and no significant interaction [experiment 1: F (6.960, 132.249) = 0.885, *ns*, $\eta_p^2 = 0.045$; experiment 2: F (7.251, 137.765) = 0.757, *ns*, $\eta_p^2 = 0.038$; experiment 3: F (7.340, 139.456) = 1.000, *ns*, $\eta_p^2 = 0.050$; Mar and Robbins, 2007]. Rats had learned all the tasks in 25–35 sessions, which was in accordance with a previous study (Mendez et al., 2012).

2.5. Animal grouping

In each of three experiments, rats were divided into high and low tertile groups (HI and LI groups, respectively; $n = 6$ each) based on the percent choice of the large reinforcer (averaged over all blocks during the last two consecutive sessions of phase 3; Higgins et al., 2018; Stein et al., 2015; Winstanley et al., 2003). The middle tertile group was excluded from further testing.

2.6. Testing

Experiment 1: Within-subjects Latin square designs were used in both HI and LI groups ($n = 6$ each; Wade et al., 2000). All rats received all drug treatments, and were injected with one of vehicle and 1, 2, and 4 mg/kg NDMC during each testing day. Each drug treatment was given to each rat once (Koffarnus et al., 2011; Mendez et al., 2012). The animals' behavior was tested 20 min after the injection (Li et al., 2009, 2005). The interval between two injections was at least 72 h (Mendez et al., 2012). Animals still performed the delay-discounting task with no pharmacological manipulation during non-testing days.

Experiment 2: The procedure was similar to the one used in experiment 1. However, animals in two groups ($n = 6$ each) received one of vehicle-vehicle, vehicle-NDMC (1 mg/kg), SCH 23390 (0.005 mg/kg)-vehicle, SCH 23390 (0.005 mg/kg)-NDMC (1 mg/kg), SCH 23390 (0.0075 mg/kg)-vehicle, SCH 23390 (0.0075 mg/kg)-NDMC (1 mg/kg), SCH 23390 (0.01 mg/kg)-vehicle, and SCH 23390 (0.01 mg/kg)-NDMC (1 mg/kg) during each testing day. SCH 23390 was administered 10 min before the injection of NDMC (Li et al., 2015; Wade et al., 2000). The animals' behavior was still tested 20 min after administration of NDMC. A minimum of 96 h existed between two testing days (Cardinal et al., 2000).

Experiment 3: The procedure bore close resemblance to that of experiment 1. Nevertheless, HI and LI groups ($n = 6$ each) were administrated one of vehicle-vehicle, vehicle-NDMC (1 mg/kg), raclopride (0.04 mg/kg)-vehicle, raclopride (0.04 mg/kg)-NDMC (1 mg/kg), raclopride (0.08 mg/kg)-vehicle, raclopride (0.08 mg/kg)-NDMC (1 mg/kg), raclopride (0.12 mg/kg)-vehicle, and raclopride (0.12 mg/kg)-NDMC (1 mg/kg) during each testing day. Raclopride was administered 10 min before the injection of NDMC (Li et al., 2015; Wade et al., 2000). The animals' behavior was still tested 20 min after administration of NDMC. There was at least 96 h between two testing days (Cardinal et al., 2000).

2.7. Data analysis

The primary measures were the percent choice of the large reinforcer as a function of delay, the number of trials omitted, and the latency to respond on either lever during free-choice trials. Additionally, discounting curves were created by plotting the percent choice of the large reinforcer on the ordinate versus delay duration in seconds on the abscissa of graphs. The area under the curve (AUC) was calculated to quantify impulsive choice, and was defined as the area under the discounting curve divided by the total area of the discounting graph (Myerson et al., 2001). Thus, AUC values ranged from 0 to 1, with larger AUC values indicating lower impulsive choice. In this study, GraphPad Prism version 5.0 was used to calculate AUC values from discounting curves.

All data were analyzed using SPSS version 19.0. Separate independent samples t-tests were used to analyze the difference of the mean AUC as baseline (obtained from the last two consecutive sessions of phase 3) between HI and LI rats in each of three experiments separately. To examine the effect of drug treatments on AUC, omissions, and response latency (obtained from the testing period) in HI and LI rats, a one-way repeated measure ANOVA was conducted. For the repeated measure ANOVA, Mauchly's test was used to determine if the sphericity assumption was violated. When the sphericity assumption was violated, the Greenhouse-Geisser adjustment was applied. In the event of any significant main effects, post hoc comparisons were carried out with Tukey's Honestly Significant Difference post hoc tests. On occasions when data were not normally distributed, a nonparametric analysis (Friedman ANOVA) was conducted. For all analyses, a significance level of 0.05 was employed, and effect sizes were also calculated.

3. Results

3.1. The AUC for LI rats was greater than that of HI rats

Independent samples t-test showed that the AUC for LI rats was significantly greater than that of HI rats in the three experiments

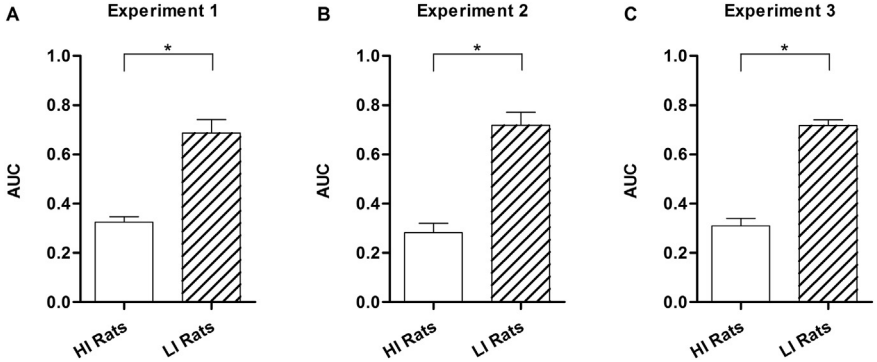

Fig. 1. AUC for HI and LI rats (experiment 1, panel A; experiment 2, panel B; experiment 3, panel C). Each data point represents the mean [± standard error of the mean (SEM)] of AUC among six rats. *$p < 0.05$ compared to HI rats.

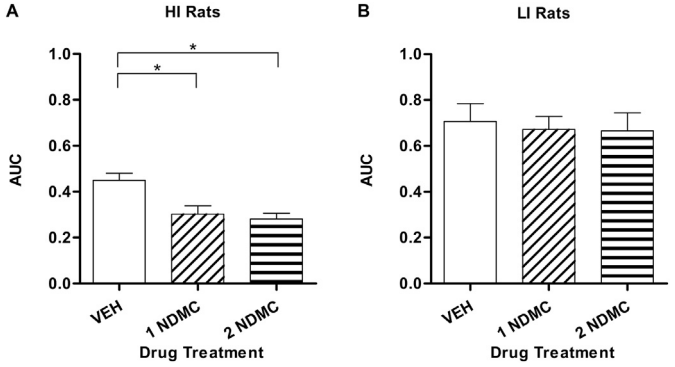

Fig. 2. Effect of NDMC (1 and 2 mg/kg) on AUC (HI rats, panel A; LI rats, panel B). Each data point represents the mean (± SEM) of AUC among six rats. *$p < 0.05$ compared to vehicle. "VEH" and "NDMC" are abbreviations for vehicle and *N*-desmethylclozapine, respectively. The number before the drug name is the dose of the drug (mg/kg).

[experiment 1: t (6.495) = 6.228, $p = 0.001$, $d = 3.597$; experiment 2: t (10) = 6.749, $p < 0.001$, $d = 3.897$; experiment 3: t (10) = 10.746, $p < 0.001$, $d = 6.203$; Fig. 1].

3.2. Experiment 1: NDMC decreased AUC in HI, but not LI rats

Analysis of AUC with HI rats identified a significant main effect of treatment [F (2, 10) = 17.144, $p = 0.001$, $\eta_p^2 = 0.774$; Fig. 2A], with post hoc tests revealing significant reductions in AUC after administration of NDMC (1 and 2 mg/kg). However, for LI rats, NDMC produced no significant effect on AUC [F (2, 10) = 1.088, *ns*, $\eta_p^2 = 0.179$; Fig. 2B].

3.3. Experiment 2

3.3.1. SCH 23390 reduced AUC in HI and LI rats

A one-way repeated measure ANOVA of AUC showed a significant main effect of treatment in HI [F (3, 15) = 8.753, $p = 0.001$, $\eta_p^2 = 0.636$; Fig. 3A] and LI rats [F (3, 15) = 11.627, $p < 0.001$, $\eta_p^2 = 0.699$; Fig. 3B]. Post hoc tests revealed that SCH 23390 produced significant declines in AUC for HI rats at 0.01 mg/kg and for LI rats at 0.0075 and 0.01 mg/kg.

3.3.2. Co-administration of NDMC with SCH 23390 had different effects on AUC between HI and LI rats

For HI rats, SCH 23390 (0.005 and 0.0075 mg/kg) significantly antagonized the decline in AUC produced by NDMC (1 mg/kg). Analysis of AUC with HI rats identified a significant main effect of treatment in Fig. 4A [F (3, 15) = 4.727, $p = 0.016$, $\eta_p^2 = 0.486$] and C [F (3, 15) = 6.601, $p = 0.005$, $\eta_p^2 = 0.569$]. Post hoc tests revealed significant decreases in AUC induced by NDMC alone, relative to vehicle-vehicle and SCH 23390-NDMC. However, administration of SCH 23390 alone or in combination with NDMC had no significant effect on AUC, relative to vehicle-vehicle. For LI rats, NDMC (1 mg/kg) significantly attenuated the reduction in AUC produced by SCH 23390 (0.0075 mg/kg, but not 0.005 mg/kg). Analysis of AUC with LI rats showed a significant main effect of treatment in Fig. 4D [F (3, 15) = 9.427, $p = 0.001$, $\eta_p^2 = 0.653$], but not Fig. 4B [F (3, 15) = 1.142, *ns*, $\eta_p^2 = 0.186$]. Post hoc tests confirmed that SCH 23390 alone significantly reduced AUC, relative to vehicle-vehicle and SCH 23390-NDMC. However, the effect of NDMC alone or in combination with SCH 23390 on AUC did not achieve significance, relative to vehicle-vehicle.

3.4. Experiment 3

3.4.1. Raclopride produced no effect on AUC in HI and LI rats

Analysis of AUC with treatment as a factor revealed no significant main effect of treatment in HI [F (3, 15) = 2.210, *ns*, $\eta_p^2 = 0.307$; Fig. 5A] and LI rats [F (3, 15) = 0.733, *ns*, $\eta_p^2 = 0.128$; Fig. 5B].

3.4.2. Raclopride inhibited the decrease in AUC induced by NDMC in HI, but not LI rats

For HI rats, raclopride (0.04, 0.08, and 0.12 mg/kg) significantly antagonized the decline in AUC produced by NDMC (1 mg/kg). Analysis of AUC with HI rats showed a significant main effect of treatment in Fig. 6A [F (3, 15) = 5.249, $p = 0.011$, $\eta_p^2 = 0.512$], C [F (3, 15) = 6.317, $p = 0.006$, $\eta_p^2 = 0.558$], and E [F (3, 15) = 6.639, $p = 0.005$, $\eta_p^2 = 0.570$]. Post hoc tests revealed significant reductions in AUC induced by NDMC alone, relative to vehicle-vehicle and raclopride-NDMC. However, administration of raclopride alone or in combination with NDMC had no significant effect on AUC, relative to vehicle-vehicle. For LI rats, one-way repeated measure ANOVA of AUC showed no significant main effect of treatment [Fig. 6B: F (3, 15) = 0.726, *ns*, $\eta_p^2 = 0.127$; Fig. 6D: F (3, 15) = 1.030, *ns*, $\eta_p^2 = 0.171$; Fig. 6F: F (3, 15) = 1.067, *ns*, $\eta_p^2 = 0.176$].

3.5. Administration of NDMC (4 mg/kg) alone and co-administration of NDMC (1 mg/kg) with SCH 23390 (0.01 mg/kg) increased omissions in HI and LI rats

A one-way repeated measure ANOVA of omissions revealed a significant main effect of treatment in HI [experiment 1: F (3, 15) = 4.547, $p = 0.019$, $\eta_p^2 = 0.476$; experiment 2: Friedman ANOVA χ^2 (7) = 20.302, $p = 0.005$, $\eta^2 = 0.432$; experiment 3: Friedman ANOVA χ^2 (7) = 3.220, *ns*, $\eta^2 = 0.069$] and LI rats [experiment 1: F (3, 15) = 3.526, $p = 0.041$, $\eta_p^2 = 0.414$; experiment 2: Friedman ANOVA χ^2 (7) = 19.892, $p = 0.006$, $\eta^2 = 0.423$; experiment 3: Friedman ANOVA χ^2 (7) = 5.923, *ns*, $\eta^2 = 0.126$]. Post hoc tests showed that

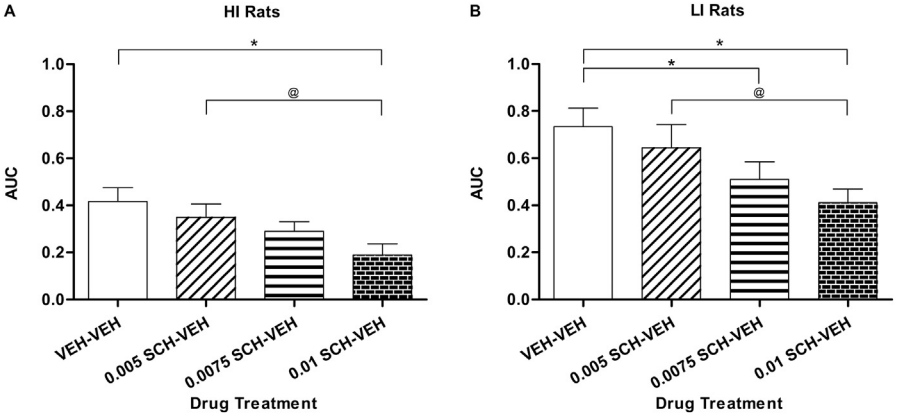

Fig. 3. Effect of SCH 23390 (0.005, 0.0075, and 0.01 mg/kg) on AUC (HI rats, panel A; LI rats, panel B). Each data point represents the mean (± SEM) of AUC among six rats. *$p < 0.05$ compared to vehicle-vehicle, @$p < 0.05$ compared to 0.005 mg/kg SCH 23390-vehicle. "SCH" is the abbreviation for SCH 23390. The number before the drug name is the dose of the drug (mg/kg).

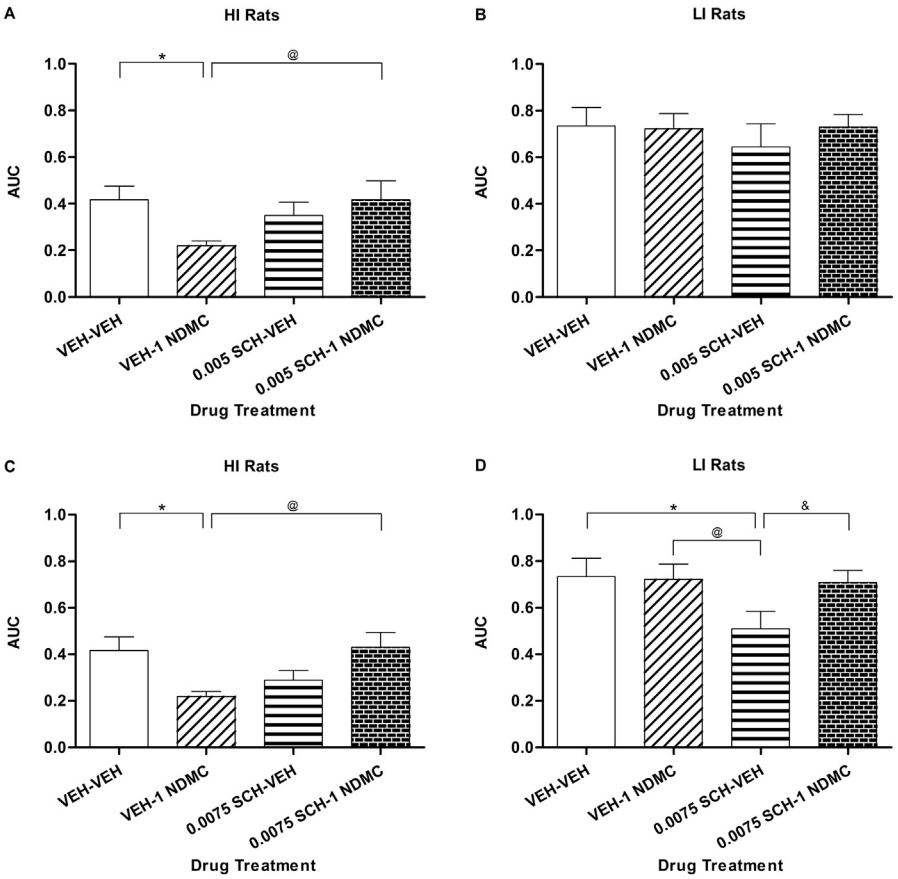

Fig. 4. Effects of the respective and combined administration of NDMC (1 mg/kg) and SCH 23390 (0.005 or 0.0075 mg/kg) on AUC in HI (0.005 mg/kg, panel A; 0.0075 mg/kg, panel C) and LI rats (0.005 mg/kg, panel B; 0.0075 mg/kg, panel D). Each data point represents the mean (± SEM) of AUC among six rats. $^{*}p < 0.05$ compared to vehicle-vehicle, $^{@}p < 0.05$ compared to vehicle-1 mg/kg NDMC, $^{\&}p < 0.05$ compared to 0.0075 mg/kg SCH 23390-vehicle. The number before the drug name is the dose of the drug (mg/kg).

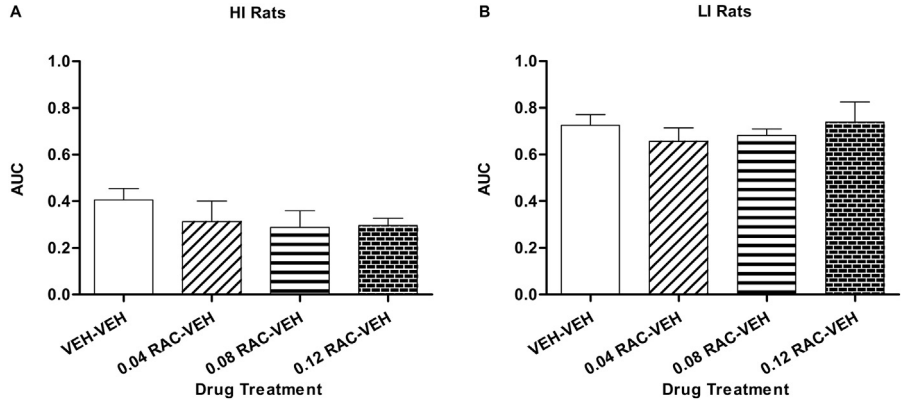

Fig. 5. Effect of raclopride (0.04, 0.08, and 0.12 mg/kg) on AUC (HI rats, panel A; LI rats, panel B). Each data point represents the mean (± SEM) of AUC among six rats. "RAC" is the abbreviation for raclopride. The number before the drug name is the dose of the drug (mg/kg).

administration of NDMC (4 mg/kg) alone and co-administration of NDMC (1 mg/kg) with SCH 23390 (0.01 mg/kg) caused significant increases in omissions in both HI and LI rats (Table 1). When the increase reached a significant level, it was difficult to dissociate drug effects on impulsive choice from drug-induced motor inhibition (Mendez, 2010; Zaichenko and Merzhanova, 2013), drug-induced diminished motivation for food (Mendez et al., 2012; Zaichenko and Merzhanova, 2013), or non-specific drug effects (Cardinal et al., 2000; Tian et al., 2016). Due to this concern, data of the AUC in HI and LI rats after administration of NDMC (4 mg/kg) or SCH 23390 (0.01 mg/kg)-NDMC (1 mg/kg) were excluded from further analyses. Moreover, analysis of response latency with treatment as a factor revealed no significant main effect of treatment in HI [experiment 1: F (3, 15) = 1.255, *ns*, η_p^2 = 0.201; experiment 2: F (7, 35) = 3.158, *ns*, η_p^2 = 0.387; experiment 3: F (7, 35) = 1.409, *ns*, η_p^2 = 0.220] and LI rats [experiment 1: F (3, 15) = 0.886, *ns*, η_p^2 = 0.150; experiment 2: F (7, 35) = 2.435, *ns*, η_p^2 = 0.327; experiment 3: F (7, 35) = 0.718, *ns*, η_p^2 = 0.126] in all three experiments (Table 1).

4. Discussion

This study examined effects of NDMC alone and in combination with SCH 23390 or raclopride on impulsive choice in HI and LI rats using the delay-discounting task. The results revealed that NDMC (1 and 2 mg/kg) significantly increased impulsive choice in HI, but not LI rats. SCH 23390 significantly promoted impulsive choice in HI rats at 0.01 mg/kg and in LI rats at 0.0075 and 0.01 mg/kg. Moreover, SCH 23390 (0.005 and 0.0075 mg/kg) significantly inhibited the increase in impulsive choice induced by NDMC (1 mg/kg) in HI rats, whereas the increase in impulsive choice produced by SCH 23390 (0.0075 mg/kg)

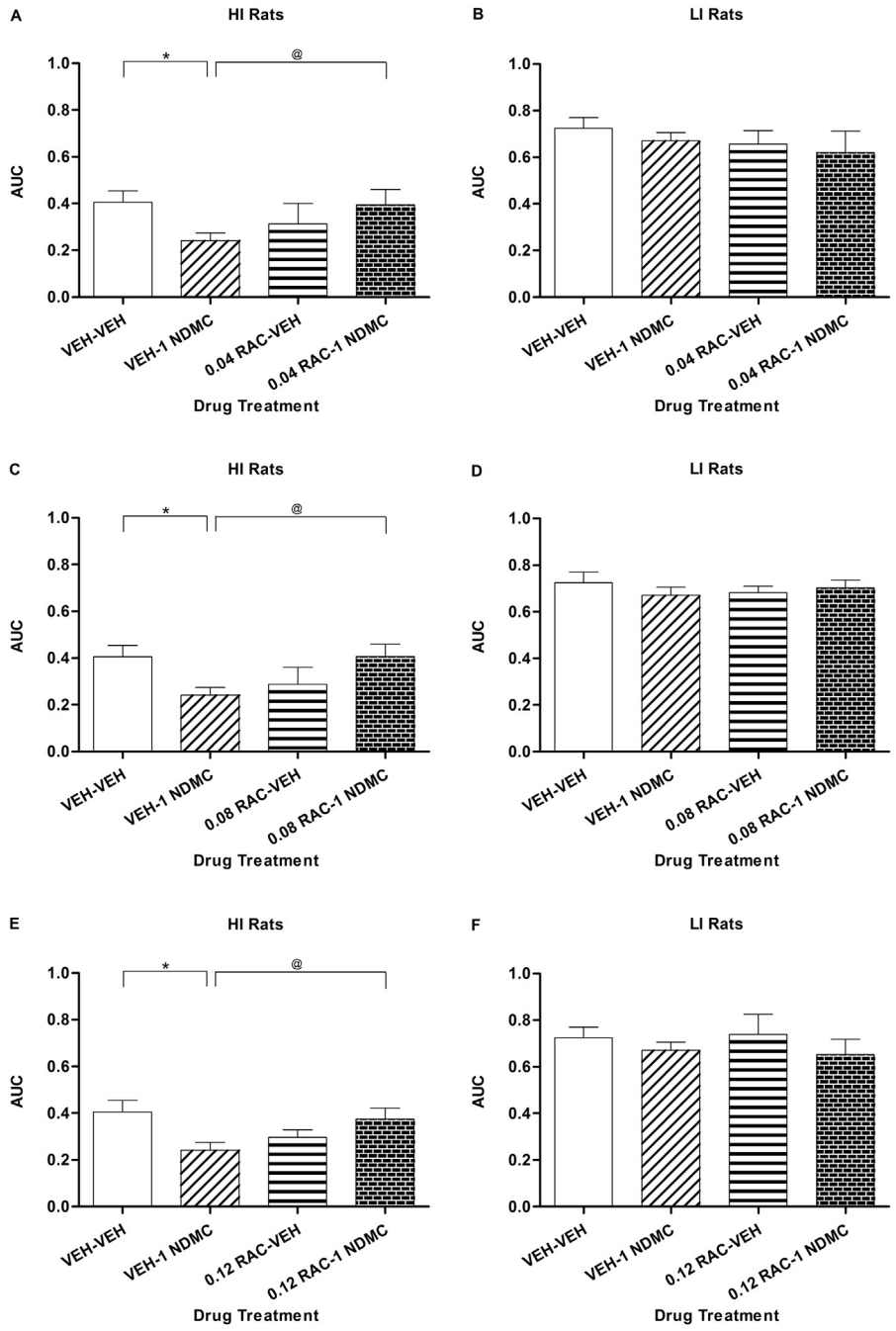

Fig. 6. Effects of the respective and combined administration of NDMC (1 mg/kg) and raclopride (0.04, 0.08 or 0.12 mg/kg) on AUC in HI (0.04 mg/kg, panel A; 0.08 mg/kg, panel C; 0.12 mg/kg, panel E) and LI rats (0.04 mg/kg, panel B; 0.08 mg/kg, panel D; 0.12 mg/kg, panel F). Each data point represents the mean (± SEM) of AUC among six rats. $^{*}p < 0.05$ compared to vehicle-vehicle, $^{@}p < 0.05$ compared to vehicle-1 mg/kg NDMC. The number before the drug name is the dose of the drug (mg/kg).

was significantly reversed by NDMC (1 mg/kg) in LI rats. Raclopride (0.04, 0.08, and 0.12 mg/kg) had no significant effect in both HI and LI rats, but significantly antagonized the increase in impulsive choice induced by NDMC (1 mg/kg) in HI rats.

4.1. The role of M_1 receptors in impulsive choice in HI and LI rats

In experiment 1, NDMC (1 and 2 mg/kg) increased impulsive choice in HI rats, but had no effect in LI rats, suggesting that M_1 receptors might be differentially involved in impulsive choice in HI and LI rats. This supports previous findings; the acetylcholinesterase inhibitor chlorpyrifos has been found to increase impulsive choice in rats (Cardona et al., 2006). Further research showed the important role of muscarinic acetylcholine receptors in impulsive choice (Mendez et al., 2012), and found that the muscarinic receptor agonist oxotremorine-M produced different effects on impulsive choice, with a decrease observed in HI rats and an increase observed in LI rats (Tian et al., 2016). The influence of NDMC on impulsive choice differs to some extent from that of oxotremorine-M, as NDMC is a M_1 receptor agonist. Oxotremorine-M, as a non-selective muscarinic receptor agonist, has affinity for several subtypes (i.e., M_{1-4} receptors; Loudon et al., 1997). Each muscarinic receptor subtype has a unique distribution throughout the brain (Lein et al., 2007), and the roles of these subtypes in cognition are not the same. For example, M_1 and M_3 receptor knockout mice, but

Table 1
Effects of respective and combined administration of the muscarinic M_1 receptor agonist NDMC and the DA receptor antagonist SCH 23390 or raclopride on omissions and response latency in HI and LI rats. The data are averaged omissions or response latency (± SEM) among six rats. *$p < 0.05$ compared to vehicle in experiment 1 or vehicle-vehicle in experiment 2. "HI group", "LI group", "VEH", "NDMC", "SCH", and "RAC" are abbreviations for high-impulsive group, low-impulsive group, vehicle, *N*-desmethylclozapine, SCH 23390, and raclopride, respectively.

Experiment	Rat	Treatment (mg/kg)	Omissions (*n*)	Response latency (s)
1	HI group	VEH	1.17 ± 0.31	2.12 ± 0.13
		1 NDMC	2.67 ± 0.92	2.34 ± 0.18
		2 NDMC	2.83 ± 1.01	2.34 ± 0.10
		4 NDMC	4.50 ± 0.85*	2.51 ± 0.10
	LI group	VEH	1.50 ± 0.76	3.14 ± 0.26
		1 NDMC	5.17 ± 1.68	3.38 ± 0.26
		2 NDMC	5.17 ± 2.24	3.47 ± 0.38
		4 NDMC	7.17 ± 3.12*	3.89 ± 0.53
2	HI group	VEH-VEH	0.33 ± 0.33	2.26 ± 0.12
		VEH-1 NDMC	0.33 ± 0.33	2.13 ± 0.15
		0.005 SCH-VEH	0.50 ± 0.22	2.37 ± 0.14
		0.005 SCH-1 NDMC	1.00 ± 0.82	2.45 ± 0.20
		0.0075 SCH-VEH	1.33 ± 0.61	2.43 ± 0.17
		0.0075 SCH-1 NDMC	0.67 ± 0.49	2.44 ± 0.20
		0.01 SCH-VEH	4.33 ± 1.33	3.19 ± 0.38
		0.01 SCH-1 NDMC	4.67 ± 1.52*	3.05 ± 0.20
	LI group	VEH-VEH	0.83 ± 0.48	2.80 ± 0.16
		VEH-1 NDMC	2.33 ± 1.20	2.96 ± 0.27
		0.005 SCH-VEH	1.17 ± 0.48	2.97 ± 0.16
		0.005 SCH-1 NDMC	1.83 ± 0.87	2.87 ± 0.20
		0.0075 SCH-VEH	1.17 ± 0.98	2.78 ± 0.22
		0.0075 SCH-1 NDMC	2.17 ± 0.70	2.92 ± 0.19
		0.01 SCH-VEH	6.67 ± 2.32	3.60 ± 0.34
		0.01 SCH-1 NDMC	7.17 ± 1.62*	3.55 ± 0.26
3	HI group	VEH-VEH	0.83 ± 0.48	2.45 ± 0.24
		VEH-1 NDMC	1.17 ± 0.48	2.21 ± 0.23
		0.04 RAC-VEH	1.50 ± 0.67	2.40 ± 0.28
		0.04 RAC -1 NDMC	1.67 ± 0.61	1.98 ± 0.18
		0.08 RAC-VEH	1.17 ± 0.65	2.36 ± 0.26
		0.08 RAC -1 NDMC	1.83 ± 1.28	2.41 ± 0.33
		0.12 RAC-VEH	1.33 ± 0.99	2.49 ± 0.28
		0.12 RAC -1 NDMC	2.17 ± 1.08	2.64 ± 0.36
	LI group	VEH-VEH	1.00 ± 0.26	2.69 ± 0.25
		VEH-1 NDMC	1.67 ± 0.88	2.44 ± 0.34
		0.04 RAC-VEH	0.83 ± 0.31	2.75 ± 0.19
		0.04 RAC -1 NDMC	0.67 ± 0.33	2.44 ± 0.18
		0.08 RAC-VEH	2.33 ± 0.92	2.79 ± 0.30
		0.08 RAC -1 NDMC	1.33 ± 0.61	2.32 ± 0.40
		0.12 RAC-VEH	2.50 ± 0.92	2.91 ± 0.35
		0.12 RAC -1 NDMC	2.83 ± 1.35	2.96 ± 0.48

not M_2, M_4, and M_5 receptor knockout mice, show more antidepressant-like behavior than do wild-type mice (Witkin et al., 2014). Therefore, we speculate that the different roles of muscarinic receptor subtypes in impulsive choice are a potential contributor to distinct behavioral effects between NDMC and oxotremorine-M.

In the present study, NDMC affected impulsive choice in HI, but not LI rats. Our task is the same as the cue version of the delay-discounting task used by Zeeb et al. (2010). They found that when the duration of delay was cued, LI rats attributed more incentive salience to the cue, thereby leading to a higher preference for the large delayed reinforcer. In contrast, HI rats did not respond to the incentive properties of the cue like LI rats. Drugs may affect impulsive choice in HI rats by altering the sensitivity to reinforcer magnitude or delay (Zeeb et al., 2010). First, in our study, the duration of delay to the large reinforcer was cued. During the training period, a previously neutral stimulus (i.e., cue) that repeatedly paired with an unconditioned stimulus (i.e., food) became a conditioned stimulus. Moreover, a conditioned stimulus could gain reinforcing properties of its own, and thus functioned as a conditioned reward (Nisanov et al., 2016). Several studies found that muscarinic acetylcholine receptor stimulation was involved in the acquisition of conditioned reward learning, but not the expression of conditioned reward (Galaj et al., 2017; Nisanov et al., 2016; See et al., 2003; Sharf et al., 2006). For instance, scopolamine impaired acquisition of lever pressing for food pellets, but not expression of food approach-related behavior (Galaj et al., 2017; Nisanov et al., 2016). In the current study, NDMC was administered after the conditioned reward learning was acquired, thereby possibly leading to no effect on the expression of conditioned reward. After administration of NDMC, LI rats might still attribute incentive salience to the cue, and preference for the large delayed reinforcer was not altered. Second, for HI rats, NDMC had no effect on the sensitivity to reinforcer magnitude. In experiment 1, the analyses did not show any significant main effect of treatment on the large-reinforcer choice during the 0-s delay block, and the percent large-reinforcer choice was still > 80% in NDMC-treated HI rats (data not shown). The results suggest that HI rats could discriminate between the small and large amounts after administration of NDMC. In addition, previous studies confirmed the role of muscarinic acetylcholine receptors in time estimation (Berz et al., 1992; Ruske et al., 1997). Based on the above analyses, NDMC (1 and 2 mg/kg) may increase impulsive choice in HI rats by reducing tolerance to delay.

NDMC is thought to influence impulsive choice via M_1 receptor-mediated mechanisms. Previous studies have found that M_1 receptors are abundant in various rat brain regions such as the cerebral cortex (Levey et al., 1991; Yamasaki et al., 2010), the hippocampus (Levey et al., 1995; Rouse and Levey, 1997), and the amygdala (McDonald and Mascagni, 2010) which are crucial to impulsive choice (Abela and Chudasama, 2013; Cardinal et al., 2001; Cheung and Cardinal, 2005; Ghods-Sharifi et al., 2009; Gill et al., 2010; Mariano et al., 2009; McHugh et al., 2008; Mobini et al., 2002; Rawlins et al., 1985; Winstanley, 2004; Zeeb et al., 2010). In addition to the M_1 receptor agonist, NDMC also acts as an agonist of serotonin 1A (5-HT_{1A}) receptors (Li et al., 2009, 2005). The 5-HT_{1A} receptor agonist 8-OH-DPAT has been reported to produce a decrease (Bizot et al., 1999) or no effect (Mori et al., 2018) on impulsive choice. After further investigation, Zaichenko et al. (2013) found that 8-OH-DPAT decreased impulsive choice in HI, but not LI rats. Considering separate effects of NDMC and 8-OH-DPAT, we suppose that the effect of NDMC on impulsive choice is likely mediated by M_1 receptors, and not due to its affinity for 5-HT_{1A} receptors.

4.2. The impact of D_1- or D_2-like receptors on impulsive choice in HI and LI rats

In experiments 2 and 3, SCH 23390 promoted impulsive choice in HI rats at 0.01 mg/kg and in LI rats at 0.0075 and 0.01 mg/kg, whereas raclopride (0.04, 0.08, and 0.12 mg/kg) had no effect on impulsive choice in HI and LI rats. Our experiment is congruent with previous results. For example, Koffarnus et al. (2011) and Li et al. (2015) found that SCH 23390 increased impulsive choice in rats. Additionally, Li et al. (2015) reported the D_2-like receptor antagonist eticlopride did not affect impulsive choice. However, our results differ slightly from those of Zaichenko and Merzhanova (2013), which showed that SCH 23390 (0.05 mg/kg) and raclopride (0.08 mg/kg) produced reductions in the percent choice of the large reinforcer in LI, but not HI rats. One reason for this difference is that Zaichenko and Merzhanova (2013) used a higher dose of SCH 23390 which increased trial omissions. When a rat omitted several trials in a session, it was unclear whether the rat's remaining choices accurately represented the rat's choice or if other

factors, such as drug-induced motor inhibition (Mendez, 2010; Zaichenko and Merzhanova, 2013), drug-induced diminished motivation for food (Mendez et al., 2012; Zaichenko and Merzhanova, 2013), or non-specific drug effects (Cardinal et al., 2000; Tian et al., 2016), had confounded the results. Therefore, it is difficult to judge the effect of SCH 23390 (0.05 mg/kg) on impulsive choice in HI and LI rats. Furthermore, the inconsistent results are possibly due to the differences in rearing conditions (two rats per cage versus five rats per cage), the number of delay blocks in a session (five versus one), and the total trial length (constant versus variable) between these two studies.

4.3. The different roles of D_1- and D_2-like receptors in the M_1 receptor agonist-induced impulsive choice in HI and LI rats

Some researchers have speculated that cholinergic compounds affect impulsive choice via DA receptor-mediated mechanisms (Kolokotroni et al., 2011; Mendez, 2010). Tian et al. (2016) confirmed that SCH 23390 reversed the inhibition of impulsive choice induced by oxotremorine-M in HI rats, but promoted the enhancement in LI rats.

Experiment 2 revealed that D_1-like receptors might be involved in effects of the M_1 receptor agonist on impulsive choice in HI and LI rats. Several studies indicated that injections of M_1 receptor agonists NDMC, xanomeline, sabcomeline, and AC260584 increase DA release in the mPFC, vHPC, and NAc in rats (Li et al., 2009, 2008, 2007, 2005) and prefrontal DA release in mice (Koda et al., 2011). Further studies have found that the NDMC-induced DA release in the mPFC was mediated directly by mPFC M_1 receptors (Li et al., 2009). Since functional M_1 receptors and DA receptors coexist on DA cell bodies (Gronier and Rasmussen, 1998; Weiner et al., 1990), previous studies have suggested that the M_1 receptor agonist increases DA release in the mPFC and NAc possibly by activation of M_1 receptors on DA neurons (Perry et al., 2001; Shannon et al., 2000). In addition, previous research shows that the mPFC (Cardinal et al., 2001; Gill et al., 2010), vHPC (Abela and Chudasama, 2014; McHugh et al., 2008), and NAc core (Bezzina et al., 2007; Cardinal et al., 2001; da Costa Araújo et al., 2009; Pothuizen et al., 2005) are implicated in mediating impulsive choice. D_1-like receptors are distributed throughout these brain regions (Bentivoglio and Morelli, 2005). This might be the neurobiological basis of the involvement of D_1-like receptors in the effect of the M_1 receptor agonist on impulsive choice. In experiment 2, NDMC and SCH 23390 was found to easily affect HI and LI rats at a lower dose, respectively, which might be a contributor to different mutual inhibitory effects of NDMC and SCH 23390 between HI and LI rats.

In experiment 3, raclopride had no effect on choice itself, but it inhibited the increase in impulsive choice induced by NDMC in HI rats. This concurs with Li et al. (2015), where they found that eticlopride did not alter impulsive choice, but reversed the impulse inhibition induced by acute cocaine intake. The role of D_2-like receptors in impulsive choice seem to be quite complex. As mentioned above, NDMC increases DA release in the mPFC and vHPC in rats (Li et al., 2009, 2005). Furthermore, systemic administration of raclopride blocked D_2-like receptors. Blockage of D_2-like receptors in the mPFC has been found to evoke output of pyramidal neurons directly (Law-Tho et al., 1994) and indirectly (Grobin and Deutch, 1998) via gamma-aminobutyric acid (GABA) release. Blockage of D_2-like receptors in the basolateral amygdala enhanced inhibition of mPFC neurons evoked by GABAergic interneurons (Li et al., 2015). The evidence indicates that systemic administration of NDMC and raclopride affect rat brain regions such as the mPFC (Cardinal et al., 2001; Gill et al., 2010), vHPC (Abela and Chudasama, 2014; McHugh et al., 2008), and the basolateral amygdala (Ghods-Sharifi et al., 2009; Winstanley, 2004) which mediates impulsive decision making.

5. Conclusion

The present study examined effects of NDMC alone and in combination with SCH 23390 or raclopride on impulsive choice in HI and LI rats using the delay-discounting task. The results revealed that NDMC produced different effects on impulsive choice between HI and LI rats. The mutual inhibitory effect between NDMC and SCH 23390 in HI rats was different from that in LI rats. Raclopride inhibited the NDMC-induced impulsive choice in HI rats. These findings suggest that D_1- and D_2-like receptors differentially mediate effects of the M_1 receptor agonist on impulsive choice in HI and LI rats. This study contributes to the understanding of the neurobiological mechanisms of impulsive choice. Further studies will aim to understand the involvement of D_1- and D_2-like receptors in specific brain regions in the effect of NDMC on impulsive choice.

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Declarations of interest

None.

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