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Original Article

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# Cocaine-Induced Behavioral Sensitization in Mice: Effects of Microinjection of Dopamine D2 Receptor Antagonist into the Nucleus Accumbens

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To determine the role of dopamine D2 receptor (D2R) in the nucleus accumbens (NAc) core in cocaine-induced behavioral sensitization, D2R antagonist, raclopride was bilaterally microinjected (2.5 or 5 nmol) into the NAc core of WT and $D2R^{-/-}$ mice and the initiation and expression phase of cocaine-mediated locomotor sensitization were analyzed. WT and D2R knockout ($D2R^{-/-}$) mice received bilateral injections of either saline, or raclopride at the NAc core 30 min before each of five daily repeated injections of saline or cocaine (15 mg/kg i.p.). Following 2 weeks of withdrawal after repeated exposure to cocaine, the animals were pre-treated with an intra-accumbal injection of vehicle or raclopride before receiving a systemic cocaine challenge for the expression of sensitization. Animals which had been microinjected raclopride into NAc core displayed the enhancement of cocaine-induced behavioral response for the initiation but also for the expression of sensitization in WT as well as in $D2R^{-/-}$ mice, which was thus unaltered as compared to vehicle-injected control group. These results suggest that D2R in NAc core is not involved in cocaine-induced behavioral sensitization.

**Key words:** dopamine receptor, nucleus accumbens, cocaine, addiction, behavioral sensitization

## INTRODUCTION

An initial exposure to psychostimulant such as cocaine induces enhanced locomotor stimulant effect to subsequent administration, a phenomenon known as sensitization [1, 2], producing enduring molecular, cellular and behavioral plasticity that resembles some addiction-related features in humans [1-5]. Process of behavioral sensitization includes two distinct phase; initiation and expression. The initiation phase refers to the period where the increased behavioral response following daily cocaine administration associated with an increase in extracellular dopamine concentration is observed. Behavioral sensitization continues to increase after cessation of cocaine administration and this procedure produces long-lasting sensitization, known as the expression of sensitization [1, 5, 6]. The expression phase shows a persistent drug hyper-responsiveness after cessation of drug, which is associated with a cascade of neuroadaptation [7-9].

Even though this phenomenon has been studied mostly in experimental animals, the neuronal plasticity underlying behavioral sensitization has been suggested to reflect the neuroadaptations that contribute to compulsive drug craving in human [9, 10].

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Considerable evidences indicated that behavioral sensitization is associated with enhanced dopamine transmission in mesocorticolimbic system comprising thus, ventral tegmental area, prefrontal cortex and nucleus accumbens (NAc) involving also glutamatergic transmission. Animals behaviorally sensitized to cocaine, amphetamine, nicotine, or morphine [7,11] show enhanced dopamine release in the NAc in response to challenge drug exposure. In addition to changes in neurotransmitter release, dopamine binding to its receptors plays a key role in behavioral sensitization [5].

Dopamine is a neurotransmitter which plays an important role in diverse physiological functions such as locomotion, cognition, motivation and reward in central nervous system [12]. Dopamine receptors have been classified five types as D1-like receptor (D1 and D5) or D2-like receptor (D2, D3 and D4) on molecular structure and pharmacology [13]. Dopamine D2 receptor (D2R) is crucial for addictive-related behavior in mesolimbic dopaminergic pathway, consisting of the ventral tegmental area (VTA) and NAc received glutamatergic input from the corticolimbic structures [14-16].

While several studies have sought to elucidate the contribution of the dopamine receptors in NAc to cocaine-induced behavioral sensitization [17-19], relatively few systematic investigations are available for the role of dopamine receptors in specific period of behavioral sensitization, for example. Recently, we have observed that knockdown of D2R expression by infusing a lentiviral vector for encoding a short hairpin RNA (shRNA) specific for D2R mRNA (Lenti-shD2R) into the NAc core did not affect basal locomotor activity of saline-injected mice or cocaine-induced behavioral sensitization, compared with those observed in mice injected with the control virus [15]. As well, continuous infusion of the D2R antagonist in the NAc showed effects similar to those of D2R knockdown at NAc with Lenti-shD2R, displaying that absence of D2R does not affect the cocaine-induced behavioral sensitization [15].

In the present study, we investigated the effect of selective blocking of D2R in the NAc core on the initiation and the expression period of cocaine-induced behavioral sensitization, respectively, in WT and $D2R^{-/-}$ mice in order to dissect the role of D2R in each phase of cocaine-mediated behavioral sensitization.

## MATERIALS AND METHODS

### *Mice*

All experiments were performed with wild-type and dopamine D2 receptor knockout ($D2R^{-/-}$) mice, $D2R^{-/-}$ mice (B6;129S2-*Drd2*tmllow) were purchased from the Induced Mutant Resource at the Jackson Laboratory (Bar Harbor, ME) and produced from heterozygous $D2R^{+/-}$ mice. The mice were kept in a SPF barrier area, and the temperature (22±1°C) and humidity (50%) were carefully controlled with a 12:12 h light/dark cycle. Food (Purina Certified Rodent Diet, USA) and tap water (membrane filtered purified and autoclaved water) were provided ad libitum.

### *Drug*

Cocaine hydrochloride (Macfarlan, U.K, 10 or 15 mg/kg, i.p.) and S(-)-Raclopride L-tartrate (Sigma-Aldrich, 2.5 or 5nmol/side) were dissolved in saline (0.9%).

### *Microinfusion in neucleus accumbens*

Stereotaxic surgery was performed with male $D2R^{-/-}$ and WT control mice at 12 week -old mice. Animals were anesthetized with 1.6 μl/g Zoletil and 0.05 μl/g xylazine (Rompun, Bayer) intraperitoneallyAt least 5~7 day before experiments, all mice were placed in a Kopf stereotaxic frame and implanted with a 26-gauge bilateral guide cannula (plastics One, Inc., Roanoke, VA) at NAc core of the brain. Stereotaxic coordinates according to the atlas of Paxinos and Flanklin (2004): 1.7 mm anterior and 1.3 mm lateral relative to bregma and 4.5 mm depth. Guide cannula was implanted with the tip 0.3 mm above NAc core on each side. Internal cannula (33 gauge) extend 1mm below the tip of the guide cannula. Microinfusion of the raclopride (S(-)-Raclopride (+)-tartrate salt, Sigma-Aldrich, 5 nmol/side) was carried out using an automated syringe pump (KD Scientific Inc.) 30 min before locomotor activity measurement upon saline- or cocaine-challenge. A 22-gauge 25 μl Hamilton microsyringe connected to a 33-gauge internal cannula. 1μl of saline or raclopride was administered bilaterally into the NAc-core at a rate of 0.2 μl/min. The animals have inserted to stylet. Injection site was verified at the end of the experiments by 1% toluidine blue.

### *Cocaine induced behavioral sensitization*

#### Apparatus and locomotor activity

Locomotor activity was evaluated using an Activity Monitor (MED Associates Inc., St. Albans, VT, USA), consisting of an open field chamber (43.2× 43.2×30.5 cm) with 16×16 photocells for measuring horizontal movements. The locomotor activity was measured as the total distance traveled for 30 min at interval of 5 min. The experimental apparatus was cleaned with 70% ethanol between mice to remove odor cues.

#### Behavioral sensitization

For the experiments, age-matched WT and $D2R^{-/-}$ mice (12~20 weeks of age) were housed individually and allowed to acclimatize

to the cage for 1 week. For each manipulation, mice were transferred to the experimental room 60 min before the onset of the experiment in order to allow for habituation and to reduce stress (brightness of the experimental room was 70 lux). All mice were implanted with a guide cannula at NAc core and allowed to recover 5~7 days in home cage. For initiation of sensitization, mice were habituated to saline injections (i.p.) for three consecutive days and were then injected with saline or cocaine (15 mg/kg, i.p) on five consecutive days. For microinjection of D2R antagonist into the NAc core, the mice received raclopride (2.5 nmol or 5 nmol/side) using an infusion pump. After 30 min, the mice have repeated intraperitoneal (i.p.) injection of saline or cocaine (15 mg/kg) and recorded 30 min for each consecutive five days. For the expression of sensitization, the mice received cocaine (15 mg/kg, i.p.) for consecutive five days and after 14 days of withdrawal, raclopride was infused into NAc core and mice were challenged cocaine (10 mg/kg, i.p.) to test the expression of sensitization.

### Criteria for sensitization

Criteria for sensitization were based on the coefficient of variation (standard deviation/mean) for the day 5/day 1 locomotor count ratio in the saline group as described previously[35]. A cocaine-injected mouse was considered sensitized if its increase in activity over the course of cocaine treatment (day 5/day 1 locomotor count ratio) exceeded the coefficient of variation for the saline group. For this analysis, day5/day1 locomotor count ratios were calculated based on locomotor activity during the 30-min period after injection [20].

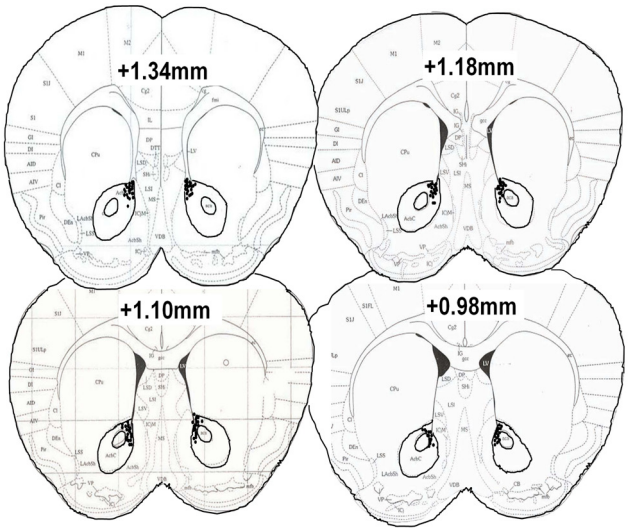


**Fig. 1.** Position of injection cannula in NAc core. Location of the injection needle tips for the mouse included in Fig. 2~4. All mouse included in the data analyses had injection needle tips located bilaterally in the NAc core. CPu, caudate putamen; AcbC, Nucleus accumbens core.

### Assessment of cannula placement

At completion of the experiments, mice were decapitated, brain were removed and frozen at -70°C. Coronal sections (40 μm thick) were cut on a cryotome. Verifying the cannula placement of NAc core injected 1% toluidine blue. Approximate position of cannula tips for animals receiving microinjections in the core of the nucleus accumbens is presented in Fig. 1.

### Statistical analysis

Data are presented as mean±s.e.m. and were analysed with the two-tailed student's t-test, or with two-way analysis of variance followed by Bonferroni's post hoc test. A p-value of $<0.05$ was considered statistically significant.

## RESULTS

### *D2R antagonist did not affect the initiation of cocaine-induced behavioral sensitization*

To determine the role of D2R in the initiation of cocaine-induced behavioral sensitization, we analyzed the development of cocaine-induced behavioral sensitization of WT and D2R knockout ($D2R^{-/-}$) mice with following experimental schedule (Fig. 2A, B).

Mice were received D2R antagonist (Raclopride, 2.5 nmol) at NAc core by microinjection then mice were injected with cocaine (15 mg/kg) on five consecutive days, and locomotor responses were recorded for 30 min after each injection and cocaine-induced behavioral sensitization was analyzed (Fig. 2). Both WT and $D2R^{-/-}$ mice showed a marked increase in locomotor activity in response to the repeated cocaine injection (Fig. 2C). $D2R^{-/-}$ mice thus manifested cocaine-induced behavioral sensitization similar to that apparent in WT mice, despite the lower basal locomotor activity of the mutant animals as previously reported (WT, raclopride effect: $F_{1,22}=0.12$ p=0.7361, $D2R^{-/-}$, raclopride effect: $F_{1,16}=0.55$ p=0.4692, genotype×cocaine interaction: $F_{1,16}=4.29$ p=0.0548) (Fig. 2C, D) [15].

Microinjection of D2R antagonist, raclopride of 2.5 nmol at NAc core (Fig. 2) did not affect the cocaine-induced locomotor activity during the initiation phase of behavioral sensitization in WT mice but also in $D2R^{-/-}$ mice (Fig. 2C), showing no difference between vehicle- and antagonist-injected groups.

We then performed another series of experiment with higher concentration of antagonist, 5 nmol of raclopride. We have observed that higher concentration of D2R antagonist did neither alter the cocaine-induced locomotor activity during the initiation phase


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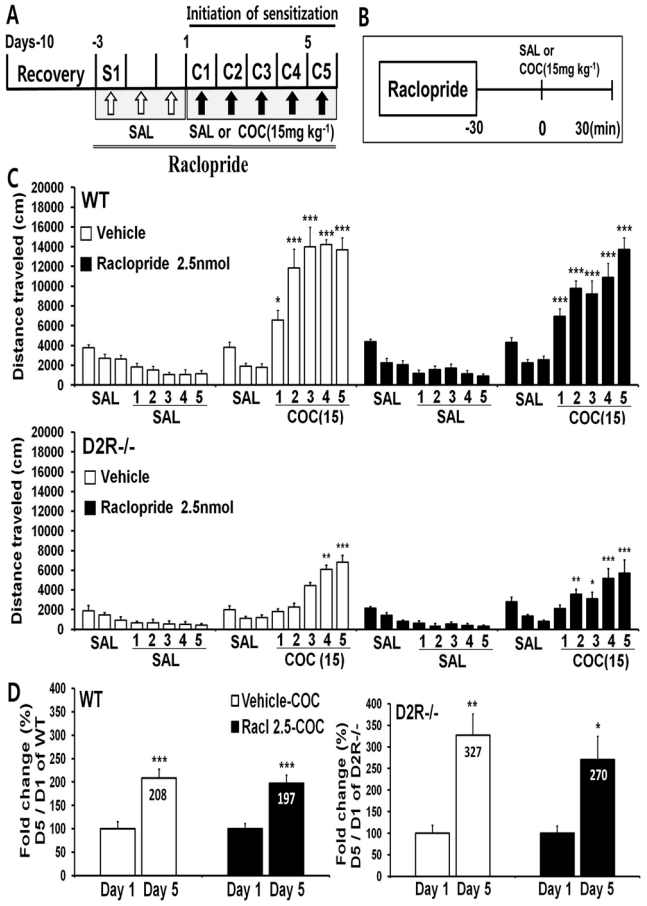


**Fig. 2.** Effect of dopamine D2 receptor antagonist (Raclopride 2.5 nmol) microinjection into NAc core on cocaine-induced behavioral sensitization in WT and D2R$^{-/-}$ mice. (A, B) Experimental protocol of cocaine-sensitization in WT and D2R$^{-/-}$ mice.Mice were injected with vehicle or raclopride (Rac, 2.5 nmol) 30 min before each injection of cocaine or saline in the test sessions. (C) Effect of raclopride (2.5 nmol) on initiation of cocaine-induced behavioral sensitization. Mice were received D2R antagonist (Raclopride, 2.5 nmol) by microinfusion into NAc following repeated i.p. injection of saline or cocaine (15 mg/kg) for 5 days and were measured locomotor activity for 30 min. (D) Fold change (ratio of locomotor activity counts on day 5 to those on day 1) for development of cocaine-induced behavioral sensitization. The mean values±SEM are shown for WT, (racl 2.5 nmol n≥5) and D2R$^{-/-}$, (racl 2.5 nmol n≥5). Two-tailed student's t-test for C *p<0.05; **p<0.01; ***p<0.001.

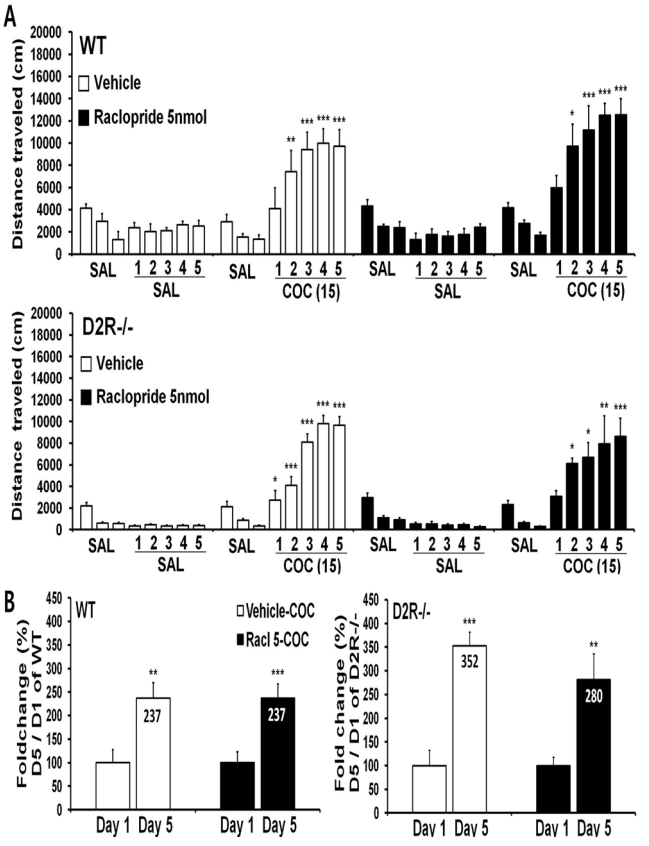


**Fig. 3.** Effect of dopamine D2 receptor antagonist (Raclopride 5 nmol) microinjection into NAc core on cocaine-induced behavioral sensitization in WT and D2R$^{-/-}$ mice. (A) Effect of racloride (5 nmol) on initiation of cocaine-induced behavioral sensitization. Mice were received D2R antagonist (Raclopride, 5 nmol) by microinfusion into NAc following repeated i.p. injection of saline or cocaine (15 mg/kg) for 5 days and were measured locomotor activity for 30 min. (B) Fold change (ratio of locomotor activity counts on day 5 to those on day 1) for development of cocaine-induced behavioral sensitization. The mean values±SEM are shown for WT, (racl 5 nmol n≥6) and D2R$^{-/-}$, (racl 5 nmol n≥6). Two-tailed student's t-test for A *p < 0.05; **p < 0.01; ***p < 0.001.

of behavioral sensitization in WT and D2R$^{-/-}$ mice (WT, raclopride effect: $F_{1.22}$=0 p=0.99990, D2R$^{-/-}$ raclopride effect: $F_{1.20}$=0.96 p=0.3381, genotype×cocaine interaction: $F_{1.18}$=3.49 p=0.0781; Fig. 3B) (Fig. 3).

Therefore, Both WT and D2R$^{-/-}$ mice showed a marked increase in locomotor activity in response to the repeated cocaine injection (Fig. 2, 3), suggesting that the absence of D2R thus did not appear to affect the initiation of behavioral sensitization. As well, blocking the D2 receptor in NAc by the injection of D2R antagonist did not alter the initiation of cocaine-induced sensitization in both WT and D2R$^{-/-}$ mice.

### *Effect of D2R antagonist microinjection at NAc on the expression of cocaine-induced behavioral sensitization*

We next assessed whether blocking of D2R in NAc can alter the expression phase of cocaine-induced behavioral sensitization. After induction of behavioral sensitization by repeated injection of cocaine for 5 days, expression of sensitization was evoked by challenge with a lower dose of cocaine after 14 days of withdrawal period (Fig. 4A). Both cocaine- and saline-treated WT or D2R$^{-/-}$ mice were divided into two groups: one group was injected with vehicle, whereas the other group, subjected to the microinjection

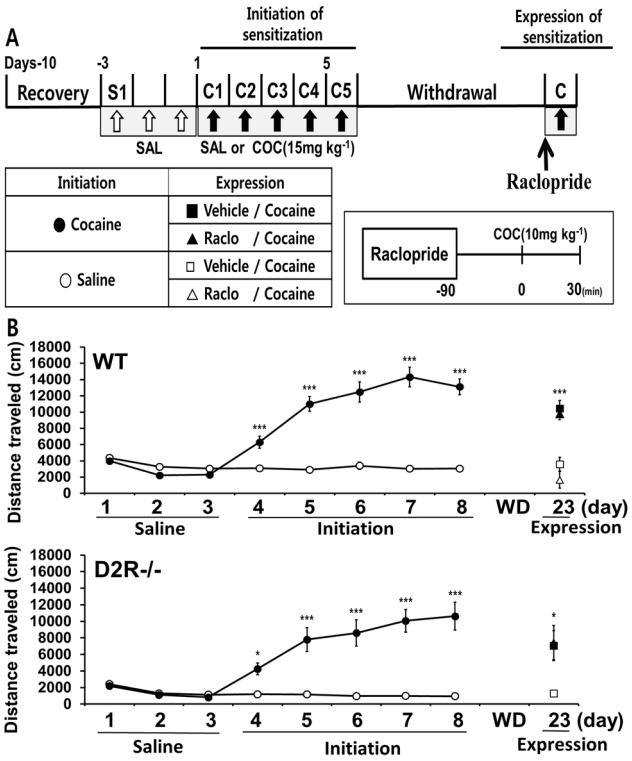


**Fig. 4.** Effect of dopamine D2 receptor antagonist (Raclopride 5 nmol) microinjection into NAc core on expression of cocaine-induced behavioral sensitization in WT and D2R$^{-/-}$ mice. (A, B) Mice were injected cocaine (15 mg/kg, i.p.) for 5-consecutive days. Initiation: Two-tailed student's t-test:cocaine effect *p<0.05; **p<0.01; ***p<0.001. After 14 days of withdrawal from repeated cocaine injection, they were received Raclopride (5 nmol) or saline by microinfusion in NAc following cocaine (10 mg/kg, i.p.) challenge were measured locomotor activity for 30 min.The mean values±SEM are shown for WT, n≥5, and D2R$^{-/-}$, n≥7. Expression: Two-way ANOVA followed by a Bonferroni test, cocaine effect *p<0.05; **p<0.01; ***p<0.001. WT; cocaine effect: $F_{1,20}$=24.90, p<0.0001, raclopride effect: $F_{1,20}$=0.05 p=0.8323, cocaine×raclopride interaction: $F_{1,20}$=0.71, p=0.4100, D2R$^{-/-}$; cocaine effect: $F_{1,25}$=5.32, p=0.0297, raclopride effect: $F_{1,25}$=0.35, p=0.5614, cocaine×raclopride interaction: $F_{1,25}$=0.67, p=0.4191, vehicle group-genotype×cocaine interaction: $F_{1,24}$=0 p=0.9638, Raclopride group-genotype×cocaine interaction: $F_{1,27}$=0.7 p=0.4109.

of raclopride (Fig. 4A). Microinjection of raclopride (5 nmol) into the NAc core was performed before the cocaine challenge at the expression phase (Fig. 4A). A cocaine challenge after 14 days of withdrawal period produced a sensitized locomotor activity response, which corresponds to the expression of cocaine-induced behavioral sensitization in animals previously exposure to cocaine [cocaine (vehicle/cocaine)] as compared to animals which had not been subjected to the cocaine challenge before [saline (vehicle/cocaine)] in both WT and D2R$^{-/-}$ mice group. Animals which had been microinjected raclopride into NAc core did show also an enhancement of cocaine-induced behavioral response to cocaine challenge in WT but also in D2R$^{-/-}$ mice (for expression, WT, raclopride effect: $F_{1,20}$=0.05 p=0.8323, raclopride x cocaine interaction: $F_{1,20}$=0.71 p=0.4100, D2R$^{-/-}$, raclopride effect: $F_{1,25}$=0.35 p=0.5614, raclopride×cocaine interaction, $F_{1,25}$=0.67 p=0.4191, vehicle group-genotype×cocaine interaction: $F_{1,24}$=0 p=0.9638, Raclopride group-genotype×cocaine interaction: $F_{1,27}$=0.7 p=0.4109) (Fig. 4B). Therefore the microinjection of D2R antagonist into NAc core did affect neither the initiation nor the expression of cocaine-induced behavioral sensitization in WT and D2R$^{-/-}$ mice.

## DISCUSSION

In the present study, we determined the role of dopamine D2R in NAc core in the initiation and the expression of behavioral sensitization to cocaine respectively in WT and D2R$^{-/-}$ mice.

The nucleus accumbens is a heterogeneous structure [21], can be separated anatomically into core and shell subdivisions [22]. The distinct pattern of core and shell output targets, suggests that two regions may mediate different behavioral processes. It has been suggested that the nucleus accumbens core (NAcc) is important for the maintenance and induction of cocaine seeking behavior [23].

Recently, we have reported that the effects of knockdown of D2R expression at NAc core by infusing a lentiviral vector for a shRNA against D2R expression into the NAc of WT mice on the cocaine-induced sensitization [15]. Depletion of D2R in the NAc did not affect basal locomotor activity nor the cocaine-induced behavioral sensitization but conferred stress-induced inhibition of the expression of cocaine-induced behavioral sensitization [15]. In a similar set of experiments, the effects of infusion of the D2R antagonist raclopride into the NAc core of WT mice, during whole period of initiation but also for every other day during the withdrawal period of 2weeks before the cocaine challenge at the expression of behavioral sensitization, has been examined [15]. Such pharmacological blockade of D2R in the NAc did not affect the expression of sensitization in the control nonstressed group but only in stress-subjected animal group, the expression of sensitization was significantly attenuated by repeated stress during drug withdrawal [15]. Together with this study, our present investigation which separately examined the effect of D2R antagonist at the initiation and the expression respectively, now strongly suggest that the blockade of D2R in NAc core did not prevent the cocaine-mediated behavioral sensitization while certainly D2R at NAc core plays a key role in regulation of synaptic modification triggered by stress and drug addiction.

As to the locomotor sensitization induced by repetitive injection of cocaine, it has been reported that systemic administration of


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the dopamine D1-like receptor antagonist SCH-23390, or the dopamine D2R antagonists sulpiride, YM-09151-2, eticlopride or raclopride, has been shown to be contradictory, either not to affect or decrease the induction of cocaine sensitization [1, 24-29]. The direct intraaccumbal infusion of D2/D3R antagonist, sulpride in rats have shown that blockade of D2R reverses the acute cocaine-induced locomotion [17, 18], but these studies did not examine the effect on the cocaine-induced behavioral sensitization. Interestingly, it has been reported that the intra-medial prefrontal cortex injection of D2R agonist, quinpirole blocked the initiation and attenuated the expression of cocaine-induced behavioral sensitization [30].

Recent studies using genetically-engineered mice which can express Cre recombinase in cell-type specific manner, revealed some role of D2R-expressing cells in cocaine-addictive behaviors. For example, loss of DARPP-32 in D2R-expressing cells resulted in an enhanced acute locomotor response to cocaine [31]. Using DREADDs (designer receptors exclusively activated by designer drugs) strategies, with viral-mediated expression of an engineered GPCR (Gi/o-coupled human muscarinic M4 designer receptor exclusively activated by a designer drug, hM4D) that is activated by an otherwise pharmacologically inert ligand [32], showed that the activation of striatal D2R-expressing neurons facilitated the development of amphetamine-induced sensitization [32].

It would be possible that NAc D1R may have a more direct role in cocaine-mediated behavioral sensitization. Differently from previous pharmacological or D1R knockout mice studies [1, 24, 25, 33], recent reports using optogentics and other viral-mediated activation/ inactivation of D1 and D2Rs revealed that D1R could be important in cocaine-induced behavioral sensitization [34, 35]. Hikida et al. demonstrated that with reversible inactivation of D1/D2 receptor-expressing MSNs with the tetanus toxin, they observed the predominant roles of the D1 receptor-expressing cells in reward learning and cocaine sensitization, but there was no change in sensitization caused by the inactivation of D2 receptor-expressing cells [34]. Moreover, optogenetically activated with conditional Channelrhodopsin2 viruses injected in NAc of D1-Cre mice showed an enhanced cocaine sensitization while the optogenetic activation of D2 receptor-expressing cells in the NAc induced no change in cocaine-induced behavioral sensitization [19]. As well, optogenetic inactivation of D1 receptor-expressing MSNs using the light activated chloride pump, halorhodopsin eNpHR3.0 during cocaine exposure resulted in an attenuation of cocaine-induced locomotor sensitization [35]. Therefore, on the whole, these evidences suggest that dopaminergic mechanisms critically mediate cocaine-induced addictive behaviors, although the precise contribution of D1 and D2Rs remains to be determined.

Since the common circuitry for behavioral sensitization includes dopamine projections from the VTA to the nucleus accumbens and glutamate projections from the mPFC to the nucleus accumbens [5, 36], it will be important to determine if D2R signaling in NAc also interacts with glutamate signaling in control of cocaine-induced behavioral sensitization, which play a significant role in drug relapse.

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