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The trace amine associated receptor 1 agonist RO5263397 attenuates the induction of cocaine behavioral sensitization in rats

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HIGHLIGHTS

- The TAAR 1 agonist RO5263397 did not alter the spontaneous locomotor activity in rats.
- RO5263397 did not decrease acute cocaine-induced hyperactivity.
- RO5263397 attenuated the induction of behavioral sensitization to cocaine.

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ABSTRACT

The trace amine associated receptor (TAAR) 1 is a new G protein coupled receptor that critically modulates central dopaminergic system. Recently, several selective TAAR 1 ligands have been described to possess antipsychotic and antidepressant-like activities. However, it is unknown of the role of these ligands in modulating psychostimulant-induced neurobehavioral plasticity. This study examined the effects of a selective TAAR 1 agonist, RO5263397, on cocaine induced behavioral sensitization in rats, a rodent model of drug-induced behavioral plasticity. Daily treatment with 15 mg/kg cocaine (i.p., 7 days) induced robust locomotor sensitization in rats. RO5263397 (1–10 mg/kg, i.p.) alone did not significantly alter the locomotor activity. Acute treatment with RO5263397 (3.2 and 10 mg/kg) did not significantly modify cocaine-induced hyperactivity; however, the induction of locomotor sensitization was significantly blocked after 7 days of daily RO5263397 treatment. More importantly, the expression of locomotor sensitization remained significantly attenuated when rats were re-tested 7 days after the last drug treatment. The marked attenuation of cocaine sensitization was also evidenced by the suppression of the dose-effect function (3.2–32 mg/kg) of cocaine sensitization. Together, these data represent the first to report a critical modulatory role of TAAR 1 agonists in cocaine-induced behavioral plasticity, which may be indicative of its potential role for altering other long-lasting behavioral maladaptations of cocaine including drug addiction.

1. Introduction

Trace amines refer to a family of chemically related, low molecular weight, naturally occurring aromatic aliphatic compounds with potent sympathomimetic actions [3,7] that traditionally include β-phenylethylamine, *para*-hydroxyphenylethylamine, octopamine, synephrine and tryptamine [3]. The molecular evidence and the pharmacological roles of trace amines have just been emerging. In 2001, two labs independently reported the cloning and characterization of a trace amine receptor, now known as trace amine associated receptor (TAAR) 1 [4,6]. Thereafter, several different TAARs have been cloned from different species, within which the TAAR 1 receptor is the best characterized [7,25]. TAAR 1 expression is primarily found in dopaminergic and serotonergic brain regions including hypothalamus and preoptic area, ventral tegmental area, amygdala, dorsal raphe nucleus, nucleus of the solitary tract, rhinal cortices and subiculum [13]. Many compounds including trace amines, common biogenic amines and amphetamine-like psychostimulants are TAAR 1 agonists. However, because all these compounds also bind to other pharmacological targets, it is a challenge to tease apart the physiological and pharmacological roles of TAAR 1. In the past several years, genetically modified

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mice have offered important information regarding the role of TAAR 1 in the modulation of monoaminergic systems. The TAAR 1 knockout mice generally appear normal in measures of emotional, motor and autonomic responses but show marked deficits in tests of sensorimotor gating [24]. When challenged with drugs, these mice demonstrate increased sensitivity to amphetamine in inducing hyperactivity and striatal dopamine release [13], increased sensitivity to methamphetamine in inducing hyperactivity and condition place preference [1], and increased sensitivity to ethanol in ethanol drinking preference test and sedation test [14].

Recently, several highly pharmacologically selective TAAR 1 ligands have been described, which show interesting pharmacological effects. For example, a selective TAAR 1 antagonist, EPPTB, increases the firing frequency of dopamine neurons of the ventral tegmental area (VTA) but prevents the reduction of the firing frequency of dopamine neurons induced by a nonselective TAAR 1 agonist *p*-tyramine [5]. A TAAR 1 agonist, RO5166017, inhibits the firing frequency of VTA dopamine neurons and attenuates hyperactivity induced by cocaine and dopamine transporter knockout in mice [17]. Similarly, two newer TAAR 1 agonists, RO5256390 and RO5263397 both attenuate cocaine-induced hyperactivity in mice. Combined, these data suggest that activation of TAAR 1 may suppress the behavioral and electrophysiological effects of psychostimulants (e.g., cocaine) [19].

Repeated intermittent treatment with some drugs of abuse such as psychostimulants and opioids leads to a long-lasting progressively increased motor-stimulant response to these drugs, a phenomenon termed behavioral sensitization [20]. Because the neural circuitry, the neurotransmitter and receptor systems between behavioral sensitization and the reinstatement of drug-seeking behavior, a widely used behavioral paradigm for the study of drug addiction, have significant overlaps, behavioral sensitization remains a useful model for determining the neural basis of drug addiction [22]. Although previous studies have shown that TAAR 1 agonists can attenuate acute cocaine-induced hyperactivity in mice [17,19], it is unclear whether they also inhibit behavioral plasticity induced by repeated (instead of single) drug treatment. This study directly addressed this question by examining the effects of a TAAR 1 agonist RO5263397 on cocaine-induced behavioral sensitization in rats.

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) were housed individually on a 12/12 h light/dark cycle (behavioral experiments were conducted during the light period) with free access to water and food except during experimental sessions. Animals were maintained and experiments were approved by the Institutional Animal Care and Use Committee, University at Buffalo, the State University of New York, and with the 2011 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington DC). All animals were only used in one study, be it acute drug treatment or repeated drug treatment and tests.

2.2. Drugs

Drugs used in this study included cocaine hydrochloride (Research Technology Branch, National Institute of Drug Abuse, Rockville, MD, USA) and RO5263397 (synthesized at Research Triangle Institute, purity >98%). Cocaine hydrochloride was dissolved in 0.9% physiological saline. RO5263397 was dissolved in a mixture of 1 part absolute ethanol, 1 part Emulphor-620 (Rhodia Inc.), and 18 parts physiologic saline. Doses were expressed as the weight of the forms listed above in milligrams per kilogram of body weight and drugs were administered intraperitoneally.

2.3. Experimental protocols

The locomotor activity of the rats was monitored by a video surveillance camera mounted on the ceiling and analyzed with commercially available software (Smart Junior, Panlab SL, Barcelona, Spain). Four black acrylic boxes (40 cm × 40 cm × 30 cm, $L \times W \times H$) were used as test arena throughout the study [10,21,23]. Before tests began, rats were exposed to at least three days of handling by the experimenter. When only RO5263397 was studied, the drug was injected immediately before the rats were put into the test chambers and the locomotor activity was simultaneously recorded for 60 min. When RO5263397 was studied in combination with cocaine, RO5263397 was injected immediately before the animals were put into the test chambers and a dose of cocaine (15 mg/kg) was administered 20 min (habituation period) later, which was followed by a 60 min test period. A separate experiment also examined the effect of RO5263397 on the dose-effect curve of cocaine by using a cumulative dosing procedure [9]. For this experiment, RO5263397 was administered immediately prior to the start of the test session and different doses of cocaine (cumulative doses of 3.2, 10, 32 mg/kg) were given at times 20 min, 40 min and 60 min. The locomotor effects of each dose of cocaine were recorded for 20 min but for each dose the data from the first 5 min immediately after the drug injection were discarded because the rats always demonstrated a brief hyperactivity due to handling and injection. This procedure generates highly consistent and reliable dose response curves of drugs such as morphine, cocaine and methamphetamine [2,9,15].

For behavioral sensitization studies, a similar protocol was used as described in our previous reports [8,11,12]. Briefly, rats were treated with cocaine (15 mg/kg) with or without RO5263397 (3.2 or 10 mg/kg) daily for 7 days under the above-described protocol and allowed to freely explore the locomotion chambers for 80 min. Animals were housed in their home cages without drug treatment between days 8 and 14 and re-tested on day 15 when they received a challenge dose of 15 mg/kg cocaine. Locomotor activity was recorded on days 1, 7 and 15 (Fig. 2). In the experiment that determined the dose-effect curves of cocaine (Fig. 3), 10 mg/kg RO5263397 was treated daily for 7 days and cumulative dose-effect curves of cocaine were determined as described above on days 1 and 7. Rats received 10 mg/kg RO5263397 and 15 mg/kg cocaine daily between days 2 and 6 in their home cages.

2.4. Statistical analyses

The locomotion data were analyzed by one-way analysis of variance (ANOVA) (Figs. 1 and 2) or two-way ANOVA (cocaine dose × RO5263397 treatment, Fig. 3) followed by *post hoc* Bonferroni's test. $P < 0.05$ was considered statistically significant.

3. Results

As shown in Fig. 1, acute treatment with RO5263397 did not alter the locomotor activity in rats within the dose range of 1–10 mg/kg. One way ANOVA revealed that RO5263397 did not significantly change the locomotor activity ($F[3,26] = 0.95$, $P > 0.05$) (inset, Fig. 1). Daily treatment with 15 mg/kg cocaine induced a significant increase of its motor-stimulating effect, as evidenced by the significantly higher locomotion counts on Day 7 as compared to Day 1 and the increased response persisted on Day 15 (compare

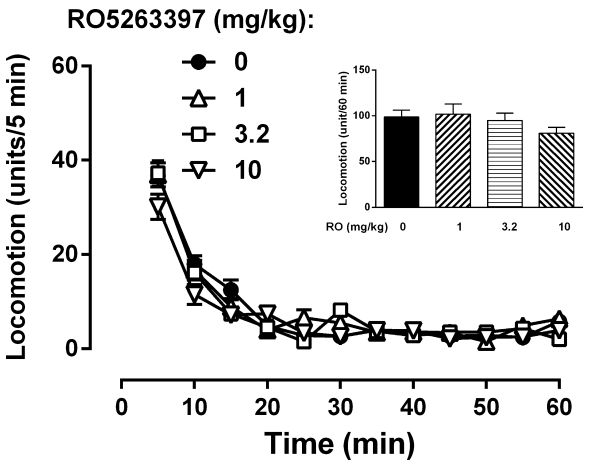

Fig. 1. Effects of RO5263397 on the locomotor activity in rats. Ordinate: locomotion counts/5 min; abscissa: time (min). Inset: total locomotion counts within the period of 60 min. $N = 12$ for control and $N = 6$ for ORG5263397-treated groups.

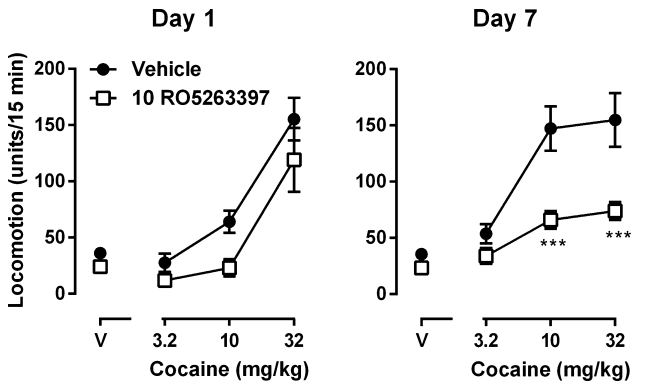

Fig. 3. Effects of RO5263397 on the behavioral sensitization to cocaine in rats. Ordinate: total locomotion counts/15 min; abscissa: cumulative doses of cocaine (mg/kg). $^{***}P < 0.0001$ as compared to corresponding cocaine dose without RO5263397 pretreatment. $N = 8$/group.

black bars from Days 1, 7 and 15, Fig. 2), demonstrating the development of behavioral sensitization. One way ANOVA revealed that the same dose of cocaine (15 mg/kg) induced a significantly higher locomotion counts (F [2,20] = 31.96, $P < 0.0001$). *Post hoc* analysis found that the locomotor activity levels were significantly higher on Day 7 and Day 15 than Day 1 ($P < 0.05$, Fig. 2). Acute treatment with RO5263397 did not significantly alter 15 mg/kg cocaine-induced hyperactivity (left panel, Fig. 2). One way ANOVA revealed no significant effects of RO5263397 on acute cocaine induced hyperactivity (F [2,21] = 1.08, $P > 0.05$). However, the motor-stimulating effects of cocaine were significantly blunted by repeated daily treatment with RO5263397 (middle panel, Fig. 2). One way ANOVA demonstrated a significant effect of RO5263397 (F [2,21] = 38.44, $P < 0.0001$). *Post hoc* analysis found that cocaine-induced hyperactivity was significantly lower in rats that received RO5263397 treatment than those received vehicle treatment and the effect of RO5263397 was dose dependent ($P < 0.05$, middle panel, Fig. 2). More importantly, after one week of drug washout period, cocaine-induced hyperactivity remained significantly lower in rats that were treated with RO5263397 (right panel, Fig. 2). One way ANOVA and *post hoc* analysis demonstrated that rats with a RO5263397 treatment history had a significantly lower response to the same dose of cocaine challenge (15 mg/kg) (F [2,21] = 7.30, $P < 0.01$) with 10 mg/kg RO5263397 reaching statistical significance.

Because the dose-effect curve of cocaine for altering the locomotor activity in rats is bi-phasic with lower dose increasing while higher dose decreasing the locomotion [2], effects of RO5263397 on the dose-effect curve of cocaine were also examined (Fig. 3). Acute RO5263397 (10 mg/kg) slightly attenuated the effects of cocaine (left panel, Fig. 3). Two way ANOVA demonstrated significant main effects of cocaine treatment (F [3,42] = 33.70, $P < 0.0001$) and RO5263397 treatment (F [1,14] = 7.45, $P < 0.05$), but the cocaine × RO5263397 interaction was not significant (F [3,42] = 0.61, $P > 0.05$). However, *post hoc* analysis found no significant effects across the dose range of 3.2–32 mg/kg cocaine. Repeated treatment with RO5263397 for 7 days led to a marked decrease of the entire ascending limb of the cocaine dose-effect curve (right panel, Fig. 3). Two way ANOVA demonstrated significant main effects of cocaine treatment (F [3,42] = 34.11, $P < 0.0001$), RO5263397 treatment (F [1,14] = 16.19, $P < 0.01$) and cocaine × RO5263397 interaction (F [3,42] = 6.50, $P < 0.01$). In addition, *post hoc* analysis found that the effects of 10 and 32 mg/kg cocaine were significantly decreased by RO5263397 treatment.

4. Discussion

The primary findings of the current study were that the selective TAAR 1 agonist RO5263397 alone did not alter the locomotor activity, but markedly attenuated the development of cocaine behavioral sensitization in rats. This represents the first study showing that a TAAR 1 agonist could block repeated cocaine treatment-induced behavioral changes. Given the significant overlap between the neural circuitry of behavioral sensitization and reinstatement of drug-seeking behaviors in rats [22], these data support more detailed examination of the role of TAAR 1 in animal models of drug addiction.

Although TAAR 1 was cloned a decade ago [4,6], the understanding of the pharmacology of this receptor was hampered by the lack of selective ligands. Recent characterization of several highly selective TAAR 1 ligands marks a significant progress of TAAR 1 research [17,19]. RO5263397 is a highly selective TAAR 1 ligand, showing no appreciable binding affinities on a panel of 155 different receptors, enzymes and ion channels [19]. It was shown that oral administration with the TAAR 1 agonist RO5263397

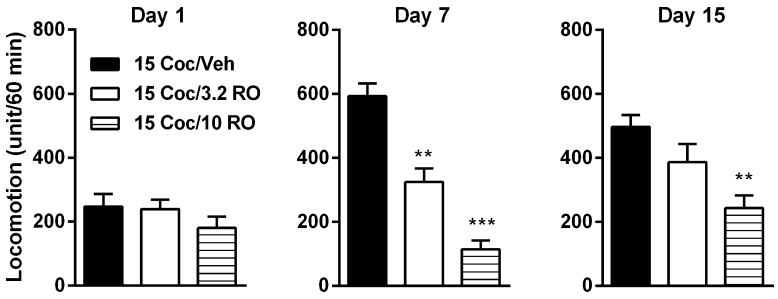

Fig. 2. Effects of RO5263397 on the behavioral sensitization to 15 mg/kg cocaine in rats. Ordinate: total locomotion counts/60 min. Coc: Cocaine; RO: RO5263397; Veh: Vehicle. $^{**}P < 0.01$ as compared to 15 Coc/Veh group; $^{***}P < 0.001$ as compared to 15 Coc./Veh group. $N = 7$–8/group.

significantly decreased the locomotor activity in mice at a dose of 3 mg/kg [19]. However, the same study found no significant effect of oral RO5263397 on the locomotor activity in rats up to a dose of 3 mg/kg. Extending the previous observations, the current study found no significant effect of RO5263397 (i.p.) on the general locomotor activity in Sprague-Dawley rats up to a dose of 10 mg/kg (Fig. 1). Species difference seems to be the logical interpretation of this difference. Interestingly, RO5263397 dose-dependently decreases cocaine-induced hyperactivity in mice, with a dose well below the dose that suppresses spontaneous locomotor activity (0.3 mg/kg, p.o.) significantly attenuating the motor-stimulating effects of cocaine [19]. This is in striking contrast to the effect observed in the current study. In Sprague-Dawley rats, we found essentially no effect of RO5263397 on cocaine-induced hyperactivity within a broad range of cocaine doses (3.2–32 mg/kg) up to a dose of 10 mg/kg RO5263397 (Figs. 2 and 3). This discrepancy is likely due to species difference. Remarkably, repeated RO5263397 treatment produced a long lasting effect for blocking the development of cocaine behavioral sensitization. Seven days after RO5263397 treatment, the motor-stimulating effect of 15 mg/kg cocaine was markedly attenuated, demonstrating no evidence of behavioral sensitization (middle panel, Fig. 2). This effect seems to be due to neurobehavioral adaptations of repeated drug treatment, but not due to other factors such as pharmacokinetics of RO5263397. In rats, the half-life of RO5263397 was 2.6 h after intravenous administration and 4.3 h after oral administration [19]. The current study used intraperitoneal administration, which is expected to have a half-life between those of intravenous and oral administrations. Thus, daily treatment with RO5263397 represents a minimum of 6 half-lives between two injections, and correspondingly >98% of the drug was eliminated from the system when the next-day injection was given. The observed marked attenuation of cocaine-induced hyperactivity on Day 7 was unlikely due to drug accumulation from the previous days. In addition, the rats remained significantly less responsive when cocaine was given on Day 15 (right panel, Fig. 2), which was one week after the last RO5263397 administration. Therefore, RO5263397 genuinely attenuated the induction of behavioral sensitization to cocaine in rats. Importantly, the attenuated sensitization to cocaine by RO5263397 was evident across several doses of cocaine and may represent a shift downward of the entire dose-effect curve of cocaine (Fig. 3).

It remains unclear the mechanism of RO5263397 for attenuating cocaine sensitization. Whole-cell current clamp recordings indicate that RO5263397 increases the firing frequency in the VTA dopamine cells in mice, similar to the TAAR 1 antagonist EPPTB [5], suggesting that RO5263397 might enhance the behavioral effects of drugs acting on dopaminergic systems [19]. This seems to be in consistent with the findings that TAAR 1 knockout mice are more sensitive to amphetamines for their motor-stimulating and rewarding effects [1,13]. However, RO5263397 decreases cocaine-induced hyperactivity in mice. Thus the *in vitro* electrophysiological data do not translate to behavioral results. It is possible that RO5263397 attenuates dopaminergic activity which in turn is hyposensitive to cocaine stimulation. This is supported by the fact that overexpression of TAAR 1 decreases the sensitivity of mice to amphetamine for inducing motoric hyperactivity and catecholamine release [16]. More mechanistic studies are clearly needed. Nonetheless, the current study clearly demonstrated a profound attenuation of repeated cocaine-induced neurobehavioral plasticity by RO5263397.

5. Conclusions

In conclusion, this study represents the first to report the functional consequence of TAAR 1 activation on repeated cocaine treatment induced behavioral plasticity by using behavioral sensitization paradigm. The finding that RO5263397 markedly attenuates the induction of cocaine sensitization strongly suggests the potential role of TAAR 1 in the maladaptive behaviors induced by drugs of abuse. In addition, another TAAR 1 agonist RO5203648 decreases cocaine intake in an intravenous self-administration procedure in rats [18], suggesting that TAAR 1 activation also modulates the motivational properties of cocaine. Given the marked attenuation of RO5263397 on cocaine behavioral sensitization, future studies that examine the effects of RO5263397 on the reinstatement of cocaine taking behaviors are warranted.

Conflicts of interest

None.

Acknowledgements

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