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Serotonin (2C) receptor regulation of cocaine-induced conditioned place preference and locomotor sensitization

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Abstract

Previous studies have identified an inhibitory regulatory role of the 5-HT_{2C} receptor in serotonin and dopamine neurotransmission. As cocaine is known to enhance serotonin and dopamine transmission, the ability of 5-HT_{2C} receptors to modulate cocaine-induced behaviors was investigated. Alterations in cocaine reward behavior were assessed in the conditioned place preference (CPP) paradigm. Mice were injected with a selective 5-HT_{2C} receptor agonist, Ro 60-0175 (0, 1, 3, 10 mg/kg, i.p.) prior to cocaine administration (10 mg/kg, i.p.) on cocaine-conditioning days. Administration of Ro 60-0175 (10 mg/kg) prior to cocaine attenuated the development of cocaine place preference. To assess the potential of the 5-HT_{2C} receptor to influence cocaine-induced behavioral sensitization, mice were pretreated with either saline or Ro 60-0175 (10 mg/kg, i.p.) and 30 minutes later, administered cocaine (20 mg/kg, i.p.) or saline once daily for 5 days. Locomotor activity was measured daily following cocaine administration. After a 10-day drug-free period, locomotor activity was measured on day 16 following a challenge injection of cocaine (20 mg/kg, i.p.). Pharmacological activation of 5-HT_{2C} receptors with Ro 60-0175 attenuated acute cocaine-induced activity on days 1–5, as well as the development of long-term cocaine-induced locomotor sensitization. Thus, activation of 5-HT_{2C} receptors attenuated the rewarding and locomotor-stimulating effects of cocaine, as well as inhibited the development of sensitization. The current study shows that 5-HT_{2C} receptor activity exerts an inhibitory influence on the short-term and long-term behavioral responses to cocaine.

Keywords

cocaine; reward; hyperactivity; sensitization; 5-HT_{2C} receptor

Introduction

Although the effects of psychostimulants on brain dopamine systems are well recognized, the actions of cocaine on serotonin systems are also important in its addictive properties. Substantial evidence shows that cocaine binds to dopamine transporters and blocks the reuptake of dopamine, leading to increased levels of extracellular dopamine [1–5]. However, cocaine also blocks the reuptake of other monoamines including serotonin [6–10]. Cocaine

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binds to the serotonin transporter and causes increases in extracellular serotonin through this mechanism [11, 12]. Although over fourteen serotonin receptor subtypes are known to exist in the mammalian brain, the serotonin_{2C} (5-HT_{2C}) receptor has been identified as a key regulatory receptor in dopamine neurotransmission and cocaine pharmacology [13–19]. In this study, activity at the 5-HT_{2C} receptor was targeted in the assessment of cocaine-induced behaviors.

Previous studies have demonstrated that stimulation of 5-HT_{2C} receptors results in an inhibition of dopamine neurotransmission. Specifically, activation of 5-HT_{2C} receptors has been shown to decrease synaptic dopamine in mesolimbic brain areas regulating reward circuitry [19, 20]. In this context, administration of 5-HT_{2C} receptor agonists prior to cocaine elicits an attenuation of cocaine-induced conditioned hyperactivity and cocaine self-administration [21, 22]. In the present study, cocaine-induced behaviors were assessed following administration of the selective 5-HT_{2C} receptor agonist, Ro 60-0175. Specifically, the ability of Ro 60-0175 to alter the development of cocaine-induced conditioned place preference as well as cocaine-induced locomotor sensitization was investigated. Results demonstrate that activation of 5-HT_{2C} receptors via Ro 60-0175 prior to cocaine inhibited the development of cocaine-conditioned place preference and attenuated both acute hyperactivity and locomotor sensitization. Thus, results from the current study show that activation of 5-HT_{2C} receptors prior to acute cocaine exposure attenuates the rewarding and locomotor effects of the drug.

Materials and Methods

Animals

Adult male C57Bl/6 mice (Charles River, Inc, 22–24 grams at the start of the experiment) housed 4 per cage were maintained on a 12 hour light/dark cycle and provided food and water ad libitum. Animal use procedures were conducted in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of Temple University.

Drugs

Cocaine hydrochloride, generously provided by the NIDA drug supply program, and Ro 60-0175 (Tocris Bioscience) were dissolved in 0.9% saline and administered intraperitoneally (i.p.) in a volume of 3 ml/kg body weight.

Conditioned Place Preference

A biased conditioned place preference (CPP) procedure was employed using a two compartment place preference apparatus (San Diego Instruments, San Diego, CA). Mice (n=4–12/group) underwent a 30 minute pretest prior to conditioning, in which free access to both compartments of the apparatus was allowed and time spent in each compartment was recorded. The compartment that the mouse spent the lesser amount of time in during the pretest was designated as the cocaine-paired side for the conditioning sessions. The mice were conditioned once daily for 4 days. Mice were pretreated with saline on days 1 and 3 and with Ro 60-0175 (1, 3, 10 mg/kg, i.p.) on days 2 and 4 in their home cages. Thirty minutes after the pretreatment on days 1 and 3, mice were injected with saline and were confined to the preferred side of the CPP chamber. On days 2 and 4, mice received cocaine (10 mg/kg, i.p.) 30 minutes following the pretreatment and were confined to the non-preferred side of the CPP chamber. On day 5, mice had free access to both compartments of the conditioning chamber in a drug-free state for 30 minutes and time in each compartment was recorded. The difference in seconds between the time spent in the cocaine-paired chamber on test day and time spent in the same initially non-preferred compartment during

the pretest was used to measure the degree of place conditioning. A positive number is indicative of a conditioned place preference, whereas a negative number indicates a conditioned place aversion. Data were analyzed by two-way analysis of variance (ANOVA) with pretreatment and treatment as variables (GraphPad Prism V4). Bonferonni's post-hoc analyses were used with a significant ANOVA to identify if there were significant differences between groups in the mean preference for the cocaine-paired compartment.

Locomotor Activity and Behavioral Sensitization

Mice (n=8/group) were placed in activity monitors and allowed 30 minutes to acclimate. After 30 minutes of habituation, mice were injected with either saline or Ro 60-0175 (10 mg/kg) and then 30 minutes later injected with saline or cocaine (20 mg/kg). This was repeated once a day for 5 days. Locomotor activity was measured for 30 minutes after the cocaine or saline injections on each day using the Digiscan Micropro system (Accuscan, Inc., Columbus, OH). The activity monitors consist of transparent plastic boxes (45×20×20 cm) set inside metal frames that are equipped with 16 infrared light emitters and detectors. The number of photocell beam breaks is recorded by a computer interface in 5 minute bins. After a 10-day drug-free period, all mice were injected on day 16 with a challenge dose of cocaine (20 mg/kg) and activity was measured for 60 minutes in order to test the expression of locomotor sensitization. Mean cumulative activity data were analyzed by two-way ANOVA with pretreatment and treatment as variables. Time-course analysis was performed by three-way ANOVA with pretreatment (saline vs. Ro 60-0175), treatment (saline vs. cocaine), and time as variables. Bonferonni's post-hoc analyses were used with a significant ANOVA to identify if there were significant differences between groups in locomotor activity and development of sensitization.

Results

Conditioned Place Preference

In order to test the effects of 5-HT_{2C} receptor activation on the rewarding properties of cocaine, mice were pretreated with saline or the 5-HT_{2C} receptor agonist, Ro 60-0175, prior to cocaine conditioning. The data in Figure 1 represent the mean preference scores for the drug-paired environment for animals in each experimental group. Two-way ANOVA revealed a significant main effect of treatment ($F[1,53]=18.13$; $p<0.0001$) and a significant interaction ($F[3,53]=2.814$; $p=0.0480$); no significant pretreatment effect was revealed ($F[3,53]=1.867$; $p=0.1464$). Post-hoc Bonferonni's analyses show that conditioned place preference was established in cocaine-conditioned animals versus saline controls (sal/sal vs. sal/coc, $p<0.001$, Figure 1). Administration of the 5-HT_{2C} receptor agonist, Ro 60-0175, prior to cocaine on cocaine-conditioning days attenuated the development of conditioned place preference in an apparent dose dependent manner (sal/coc vs. Ro 60-0175 10/coc, $p<0.01$). Administration Ro 60-0175 alone did not produce a significant place preference or aversion (sal/sal vs. Ro 60-0175/sal, $p>0.05$).

Locomotor Activity

The 5-HT_{2C} receptor-mediated influence on the locomotor-stimulating effects of cocaine was evaluated by measuring locomotor activity in the presence of 5-HT_{2C} receptor activation. On days 1–5, animals were injected with either saline or Ro 60-0175 (10 mg/kg) followed 30 minutes later by saline (controls) or cocaine (10 mg/kg) and locomotor activity was measured. The mean activity counts following cocaine administration for mice in each experimental group on days 1 through 5 are displayed in Figure 2. Two-way ANOVAs were conducted using pretreatment and treatment as factors for each day. Significant main effects for treatment were revealed on all 5 days (day 1 treatment, $F[1,28]=5.916$, $p=0.0216$; day 2 treatment, $F[1,28]=14.04$, $p=0.0008$; day 3 treatment, $F[1,28]=32.23$, $p<0.0001$; day 4

treatment, $F[1,28]=68.24$, $p<0.0001$; day 5 treatment, $F[1,28]=163.5$, $p<0.0001$). Significant main effects for pretreatment were also revealed (day 1, $F[1,28]=20.34$, $p=0.0001$; day 2, $F[1,28]=5.681$, $p=0.0242$; day 3, $F[1,28]=4.663$, $p=0.0395$; day 4, $F[1,28]=14.47$, $p=0.0007$; day 5, $F[1,28]=18.01$, $p=0.0002$). A significant interaction effect was revealed on day 5 ($F[1,28]=6.349$, $p=0.0177$). Bonferonni's post-hoc test showed that cocaine significantly increased activity on days 2–5 compared with saline (sal/sal vs. sal/coc, $p<0.05$). Mice pretreated with Ro 60-0175 before cocaine (Ro 60-0175/coc) had significantly lower activity counts than mice receiving cocaine alone (sal/coc) on days 1, 4 and 5. Ro 60-0175 alone significantly decreased activity on day 1 only as compared to saline controls (sal/sal vs. Ro 60-0175/sal, $p<0.05$), but not on other days.

The development of sensitization within groups from day 1 to day 5 was analyzed with two-way ANOVA using treatment group and day as factors. Significant main effects for treatment group ($F[3,140]=93.19$, $p<0.001$), day ($F[4, 140]=21.03$, $p<0.001$) and interaction ($F[12,140]=7.435$, $p<0.001$) were identified. Bonferonni's post-hoc test showed that mice pretreated with saline before cocaine (sal/coc) demonstrated significantly higher locomotor activity counts on day 5, as compared to day 1 ($p<0.001$). Likewise, mice pretreated with Ro 60-0175 prior to cocaine also exhibited significantly higher activity on day 5 as compared to day 1 ($p<0.001$), though comparison of sal/coc and Ro 60-0175/coc on day 5 yielded significant differences between groups. These data indicate that cocaine-injected mice developed a sensitized response over the 5 days of cocaine administration. Pretreatment with Ro 60-0175 partially, but not completely, attenuated the sensitization.

Sensitization

To test for the expression of behavioral sensitization after 10 days of drug absence, a challenge injection of cocaine (20 mg/kg) was given to all mice on day 16 of the study. No pretreatment injections were given on this day. The mean cumulative activity counts over the first 30 minutes and time course of activity (in 5 minute increments) after cocaine challenge on day 16 are shown in Figure 3A and B. Data from Figure 3A were analyzed by two-way ANOVA with pretreatment and treatment as factors.

There was a significant main effect of treatment ($F[1,28]=14.36$, $p=0.0007$). Mice that received saline/cocaine on days 1–5 exhibited heightened activity as compared to saline/saline controls when challenged with cocaine (Bonferonni's post-hoc test, $**p<0.01$), indicating sensitization. Ro 60-0175 pretreated mice did not show a sensitized response to a cocaine challenge on day 16 (Ro 60-0175/sal vs. Ro 60-0175/coc, $p>0.05$; Figure 3A). Time course data were analyzed by three-way ANOVA with pretreatment on days 1–5 (saline vs. Ro 60-0175), treatment (saline vs. cocaine), and time as factors with repeated measures on time. There was no significant main effect of treatment ($F[3, 28]=1.98$, $p=0.1401$), but a significant time effect ($F[12,336]=55.79$, $p<0.0001$) and interaction ($F[36,336]=6.19$, $p<0.0001$). Post-hoc comparison of sal/sal and sal/coc identified significant differences in response to the cocaine challenge on day 16, such that sal/coc mice exhibited significantly heightened locomotor activity in comparison to sal/sal controls at the 5–15 minute time points ($p<0.001$), the 20 minute time point ($p<0.05$) and the 25 and 30 minute time points ($p<0.01$). As shown in Figure 3B, post-hoc comparison of sal/coc and Ro 60-0175/coc groups revealed significant differences in response to the cocaine challenge on day 16. Mice pretreated with Ro 60-0175 on days 1 through 5 before daily cocaine injections (Ro 60-0175/coc) showed lower activity in response to the cocaine challenge on day 16 than those receiving cocaine alone (sal/coc) despite the absence of Ro 60-0175 on this day; their activity was significantly different from the sal/coc group at the 5 minute time point ($p<0.05$). In addition, the Ro 60-0175/coc group demonstrated significantly elevated levels of locomotor activity in comparison to the sal/sal group only at initial time increments; the 5 minute time point ($p<0.001$), the 10 minute time point ($p<0.01$), and the 15 minute time

point ($p < 0.05$), and in comparison to the Ro 60-0175/sal group at the 10 minute time point ($p < 0.05$). This indicates that Ro 60-0175 administration prior to daily cocaine partially attenuated the development of locomotor sensitization to cocaine.

Discussion

The 5-HT_{2C} receptor has been established in previous studies as a key regulatory receptor of dopamine and serotonin neurotransmission [20, 23, 24]. Studies using in vivo microdialysis have identified differential regulation of cocaine-induced alterations in dopamine neurotransmission through 5-HT_{2C} receptors. A report by Navailles et al. showed that the overall action of 5-HT_{2C} receptors on cocaine-induced dopamine output is dependent on a functional balance between 5-HT_{2C} receptor populations in brain regions regulating reward circuitry, such as the nucleus accumbens and ventral tegmental area [19]. In addition, behavioral studies have shown that administration of 5-HT_{2C} receptor agonists prior to cocaine attenuates cocaine-induced self-administration [25] and conditioned hyperactivity [21].

The present study demonstrates that administration of the highly selective 5-HT_{2C} receptor agonist, Ro 60-0175, attenuated cocaine-induced conditioned place preference, identifying an inhibitory effect of 5-HT_{2C} receptor activation on the rewarding properties of cocaine. Likewise, activation of 5-HT_{2C} receptors by Ro 60-0175 prior to cocaine on days 1–5 of cocaine administration attenuated cocaine-induced hyperactivity and the development of locomotor sensitization. The locomotor effects elicited by cocaine are known to demonstrate sensitization, in that cocaine-induced hyperactivity is elevated upon each time the subject is re-exposed to the drug in a repeated administration paradigm [26, 27]. In this study, Ro 60-0175 pretreatment on days 1–5 attenuated acute cocaine-induced hyperactivity, as well as locomotor sensitization during acute cocaine administration. Following a 10-day withdrawal, mice received a cocaine challenge injection and locomotor activity was assessed. It was evident that Ro 60-0175 pretreatment on days 1–5 partially attenuated the development of long-term cocaine-induced locomotor sensitization, as expressed following a cocaine challenge injection on day 16. Partial attenuation of locomotor sensitization on day 16 by Ro 60-0175 pretreatment on days 1–5 is likely due to the contribution of other neurotransmitter systems not affected by 5-HT_{2C} receptor activity, such as the glutamate system, which is known to contribute to sensitization and neuroplasticity associated with repeated psychostimulant exposure [28, 29].

Previous studies have shown that the functional status of the mesocorticolimbic dopamine system is under a phasic and tonic inhibitory control by the serotonin system, including particularly the 5-HT_{2C} receptor [24, 30]. The inhibitory effect of the 5-HT_{2C} receptor is thought to arise from a negative feedback mechanism through GABA networks. It has been shown that 5-HT_{2C} receptors are not located on serotonin neurons, but are expressed on GABA neurons [31]. 5-HT_{2C} receptor activation leads to heightened GABA activity in the dorsal raphe nucleus, an area that is integral in supplying the main source of serotonin in the brain, projecting to mesolimbic regions largely involved in regulating addictive behaviors [23, 32]. Activation of 5-HT_{2C} receptors enhances the inhibitory effects of GABA by increasing GABA synthesis, decreasing GABA turnover, and inhibiting GABA degradation [23]. Further experimentation is needed in order to evaluate the role of 5-HT_{2C} receptors in cocaine abuse and addiction through this GABA mechanism. It is expected that activation of 5-HT_{2C} receptors leads to increases in GABA activity, which results in inhibition of serotonin and dopamine systems normally contributing to the rewarding properties of cocaine. Targeting 5-HT_{2C} receptors would blunt the euphoric effects of cocaine through this proposed mechanism.

This study supports a role for the 5-HT_{2C} receptor in regulating both the rewarding and locomotor stimulating effects produced by cocaine. The 5-HT_{2C} receptor exhibits an inhibitory mode of action over both the short- and long-term behavioral responses to cocaine, potentially through an indirect GABA mechanism. Future studies will further address the link between serotonin and dopamine systems, and the underlying neurocircuitry occurring via 5-HT_{2C} receptor and GABA interactions in the context of cocaine exposure.

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Highlights

- The 5-HT_{2C} receptor inhibits cocaine-induced behaviors.
- 5-HT_{2C} receptor agonist attenuates the rewarding properties of cocaine.
- 5-HT_{2C} receptor agonist attenuates hyper-locomotion elicited by cocaine.
- 5-HT_{2C} receptor activity reduces locomotor sensitizing effects of repeated cocaine.

Figure 1.

Effect of Ro 60-0175 on cocaine CPP. Mice conditioned with cocaine (10 mg/kg, i.p.) spent significantly more time on the cocaine-paired side of the conditioning chamber than the saline-paired side as compared to saline-injected controls (saline/saline vs. saline/cocaine). Pretreatment with Ro 60-0175 (1, 3, and 10 mg/kg, i.p.) attenuated the development of conditioned place preference (saline/cocaine vs. Ro 60-0175/cocaine). Preference is measured by post-conditioning time in the cocaine-paired side minus pretest time in the same side. Data were analyzed by a two-way ANOVA and Bonferroni post-hoc analysis (** $p < 0.01$, *** $p < 0.001$). Data points represent the mean+SEM ($n = 4-12$ /group).

Figure 2.

Effect of Ro 60-0175 on cocaine-induced activity on Days 1–5 (A–E). Cocaine significantly increased activity on days 2–5 (sal/sal vs. sal/coc). Ro 60-0175 pretreatment significantly attenuated cocaine-induced hyperactivity on days 1, 4 and 5. Data are represented as mean +SEM, and analyzed by two-way ANOVA with Bonferonni post-hoc analysis (n=8, *p<0.05, **p<0.01, ***p<0.001).

Figure 3. Cumulative activity counts/30 minutes (A) and time-course of activity counts (B) on day 16; all groups received a cocaine challenge at time 0 as indicated. Ro 60-0175 (10 mg/kg) pretreatment prior to cocaine on days 1–5 attenuated cocaine-induced hyperactivity on Day 16. Data are represented as mean+SEM, and analyzed by two-way ANOVA (A) and three-way ANOVA (B) with Bonferonni post-hoc analysis (n=8, *p<0.05, **p<0.01, ***p<0.001).