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European Journal of Pharmacology 449 (2002) 253–259

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The effects of continuous 5-HT_3 receptor antagonist administration on the subsequent behavioral response to cocaine

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Received 9 January 2002; received in revised form 7 May 2002; accepted 26 June 2002

Abstract

A functional down-regulation of central serotonin3 (5-HT_3) receptors represents a partial mechanism of the tolerance to cocaine induced by the continuous administration of cocaine. Blocking this down-regulation by co-administering continuous cocaine and daily injections of 5-HT_3 receptor antagonists blocks the development of tolerance. The present experiment evaluated the ability of continuously administered 5-HT_3 receptor antagonists, to induce sensitization (reverse tolerance) to the behavioral effects of cocaine, based on the hypothesis that chronic blockade of 5-HT_3 receptors should induce an up-regulation of these receptors. In all experiments, rats received a 14 day pretreatment involving the continuous administration of tropisetron (0.0, 1.0, 4.0, or 8.0 mg/kg/day) or LY 278,584 (0.001, 0.01, or 0.1 mg/kg/day). The rats were withdrawn for 7 days from this pretreatment regimen. On day 7 of withdrawal from the pretreatment regiment, the rats received a 0.0, 7.5, or 15.0 mg/kg i.p. cocaine challenge. Ambulatory behavior was automatically recorded for 60 min. Both continuous tropisetron and LY 278,584, opposite to the initial hypothesis, induced tolerance, and not sensitization, to the behavioral effects of cocaine. The results clearly indicate that central 5-HT_3 receptors are critical for the effects of chronic cocaine administration.

Keywords: 5-HT_3 receptor; Cocaine; Tropisetron; LY 278,584; Sensitization; Tolerance; (Rat)

1. Introduction

Previous research involving chronic cocaine administration clearly indicates that the continuous administration of cocaine via osmotic minipump induces tolerance to its behavioral and neurochemical effects (Chen and Reith, 1993; King et al., 1993; Reith et al., 1987). Behavioral tolerance is determined by decreased locomotor activity (measured with activity monitors) and/or a decrease in the presence of stereotypies (as measured by the Ellinwood and Balster, 1974 rating scale), following a cocaine challenge. Tolerance to the neurochemical properties of cocaine is determined by a decreased ability of cocaine to enhance synaptic dopamine levels. The contribution of different mechanisms mediating this tolerance has not been clearly established.

Our research has focused on the role of central serotonin3 (5-HT_3) receptors in the development and expression of cocaine tolerance induced by continuous cocaine administration. We have focused on the 5-HT_3 receptor because previous research has shown that a variety of 5-HT_3 selective antagonists (tropisetron, zacopride, ondansetron, MDL 72222) can alter the behavioral stimulating effects of stimulants (Hamon, 1991; Reith, 1990; Reith et al., 1982; Svingos and Hitzemann, 1992), and that 5-HT_3 receptor activation modulates dopamine release in mesolimbic areas important for the effects of cocaine (e.g., Blandina et al., 1988, 1989; Chen et al., 1991, 1992; Jiang et al., 1990).

Our research is based on the hypothesis that the tolerance induced by continuous cocaine administration is significantly mediated by a down-regulation of 5-HT_3 receptors. Continuous cocaine administration should result in prolonged, elevated synaptic levels of 5-HT, due to the 5-HT uptake inhibiting properties of cocaine. The increased syn-

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PII: S0014-2999(02)02036-8

aptic levels of 5-HT would result in prolonged occupancy of 5-HT_3 receptors over the continuous infusion period. This prolonged occupancy of 5-HT_3 receptors would have the effect of further increasing synaptic dopamine levels because of the dopamine releasing effects of 5-HT_3 receptor activation described above. Because of prolonged receptor occupancy, 5-HT_3 receptors would presumably be down-regulated or desensitized as a neuroadaptation to counteract the excitatory effects of prolonged 5-HT_3 receptor occupancy. Such decreased stimulatory abilities of 5-HT_3 receptors would contribute to the behavioral and dopaminergic tolerance produced by the continuous infusion of cocaine because the ''normal'' stimulatory effects of 5-HT_3 receptor activation on dopamine release would be attenuated or eliminated.

The research conducted in this laboratory is consistent with this hypothesis (King and Ellinwood, 1999; King et al., 1994, 1995, 1997, 1999; Matell and King, 1997). For example, we reported that continuous cocaine administration attenuates the ability of the selective 5-HT_3 receptor agonist, 1-(*m*-chlorophenyl-biguanide HCL (mCPBG), to induce dopamine release in the caudate-putamen (King et al., 1995) and the nucleus accumbens (Matell and King, 1997) on day 7 of withdrawal from continuous cocaine administration. These results indicate that continuous cocaine administration does functionally down-regulate 5-HT_3 receptors. Furthermore, we reported that ondansetron, a selective 5-HT_3 receptor antagonist, co-administered with continuous cocaine, blocks the development of behavioral tolerance (King et al., 1997), as well as the functional down-regulation of accumbens 5-HT_3 receptors (King and Ellinwood, 1999). We have also reported that ondansetron, administered during the first 5 days of withdrawal from continuous cocaine, blocks the expression of behavioral tolerance (King et al., 1998). Lastly, we have reported that the time course of behavioral tolerance and 5-HT_3 receptor down-regulation are correlated (King et al., 1999).

These results suggest that a functional down-regulation of central 5-HT_3 receptors represents a significant mechanism of cocaine tolerance. Pharmacological theory predicts that chronic administration of a receptor antagonist should up-regulate receptors (Stahl, 2000). To the extent that this is true, the continuous administration of a 5-HT_3 receptor antagonist should up-regulate 5-HT_3 receptors. Such an up-regulation should induce sensitization (reverse tolerance) to the behavioral effects of cocaine because 5-HT_3 receptor agonists induce dopamine release in mesolimbic and striatal brain regions; the cocaine challenge will block 5-HT reuptake, which will activate 5-HT_3 receptors. This stimulation will produce enhanced dopamine release due to up-regulated 5-HT_3 receptors, which would result in enhanced locomotor activity. Consistent with this hypothesis, Allan et al. (2001) recently developed a mouse strain that over expresses 5-HT_3 receptors. These mice exhibited a significantly enhanced locomotor response to cocaine (there was a significant leftward shift in the dose–response curve for cocaine-induced locomotion) as compared to the wild-type mice.

The current experiments evaluated whether the continuous administration of tropisetron or LY 278,584, both potent 5-HT_3 receptor antagonists, would induce sensitization to the behavioral effects of a subsequent cocaine challenge. The rats received different doses of continuous tropisetron or LY 278,584 for 14 days. The subjects were then withdrawn from the tropisetron regimen for 7 days. On day 7 of withdrawal, the rats received a cocaine challenge, and their behavior recorded in automated activity chambers.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats, initially weighing 200 to 225 g (Charles River Laboratories), were acclimated to the vivarium on a 12 h light/dark cycle (light between 7 AM to 7 PM) for 1 week prior to treatment. They were housed singly in plastic cages with continuous access to food and water. All subjects were treated according to the guidelines for the ethical treatment of subjects proposed by the American Psychological Association. The research was conducted under a protocol approved by the University of North Texas Health Sciences Center IACUC.

2.2. Drugs

Cocaine HCl (received from NIDA) was dissolved in 0.9% sterile saline. Tropisetron and LY 278,584 (RBI, Nattick, MA) were dissolved in distilled water. All doses are calculated as the salt, and injection volume was based on the body weight.

2.3. Minipump preparation

Alzet Osmotic pumps (model 2ML2) from Alza (Palo Alto, CA) were filled with 2 ml of a solution containing tropisetron (0, 1, 4, or 8 mg/kg/day) or LY 278,584 (0.001, 0.01 or 0.1 mg/kg/day). The pump was primed by warming it in a beaker of saline in a waterbath at 37° for 4 h prior to surgical implantation. The minipumps were modified by adding a microdialysis fiber to the output portal to increase the surface area over which the ligand is distributed (Joyner et al., 1993).

2.4. Surgery

The animals were shaved and injected locally with (0.2 cc) lidocaine (Abbott, North Chicago, IL) at the dorsal midline incision site. The animals were then anesthetized by inhalation with methoxyflurane (Metofane). A 2-cm

vertical incision was made with scissors and a large subcutaneous pocket was formed with the scissors. The minipump was inserted into this pocket with the delivery portal toward the head. The opening was closed with metal surgical autoclips. On day 14 of the treatment regimen, the pumps were surgically removed using the same procedure and the residual amount of the respective 5-HT_3 receptor antagonist was measured; this was done by measuring the residual amount of fluid in the pump. In other words, if more than 0.25 ml remained in the osmotic minipumps, that subject was dropped from the experiment.

2.5. Pretreatment regimen

The tropisetron and LY 278,584 pretreatment regimen was for a 14-day period. On day 1 of treatment, the animals were implanted with a 2ML2 Alzet minipump continuously infusing tropisetron at a rate of 0, 1, 4, or 8 mg/kg/day or LY 278,584 at a rate of 0.01 or 0.1 mg/kg/day (continuous administration group). At the end of the 14-day pretreatment period, the subjects were exposed to a 7-day withdrawal period.

2.6. Behavioral testing

On day 7 following the tropisetron pretreatment regimen, the animals were acclimated to the test room in their home cage for 30 min under normal light conditions. The animals were then transferred to the center of plexiglas boxes (43.2 × 43.2 × 21 cm) inside Opto-Varimex "minor" activity monitors, and allowed to acclimate to the test cages for an additional 30 min. The activity monitors were enclosed in a sound-attenuating chamber. The activity monitors had 15 photobeams, spaced 2.5 cm apart, along each side of the monitor. All subjects received a 0.0, 7.5, or 15.0 mg/kg i.p. cocaine injection. Activity counts (horizontal movements and ambulation) were taken in 5-min bins for 60 min.

2.7. Data analysis

The current experiment is a mixed model design. Specifically, there were two group factors (tropisetron or LY 278,584 dose and cocaine challenge dose) that produce 12 separate groups (four tropisetron doses × three cocaine challenge doses; four LY 278,584 doses × three cocaine challenge doses), and one within subjects factor (Time). There were 10 rats per group. In the current experiment, the subjects were randomized according to a Latin Square design. All data were analyzed using a two-between, one-within ANOVA. The between subjects factors were pretreatment drug dose (e.g., tropisetron or LY 278,584 dose) and cocaine challenge dose, and the within subjects factor was time. Differences between specific groups were determined by post-hoc Tukey's *t*-tests. The significance level is set at $P < 0.05$ for all comparisons.

3. Results

3.1. Effects of continuous tropisetron administration on cocaine induced locomotion

Fig. 1 presents mean horizontal activity as a function of time after the challenge, separately for each cocaine challenge dose. An examination of Fig. 1 suggests that continuous tropisetron induced tolerance to the behavioral effects of the cocaine challenge. The results of the ANOVA indicated that the main effects of Tropisetron Dose ($F(3,108) = 6.93$), Cocaine Challenge Dose ($F(2,108) = 44.53$) were significant. However, the Tropisetron Dose × Cocaine Dose interaction was not significant ($F(6,108) = 1.76$). The results of the ANOVA also indicated that the

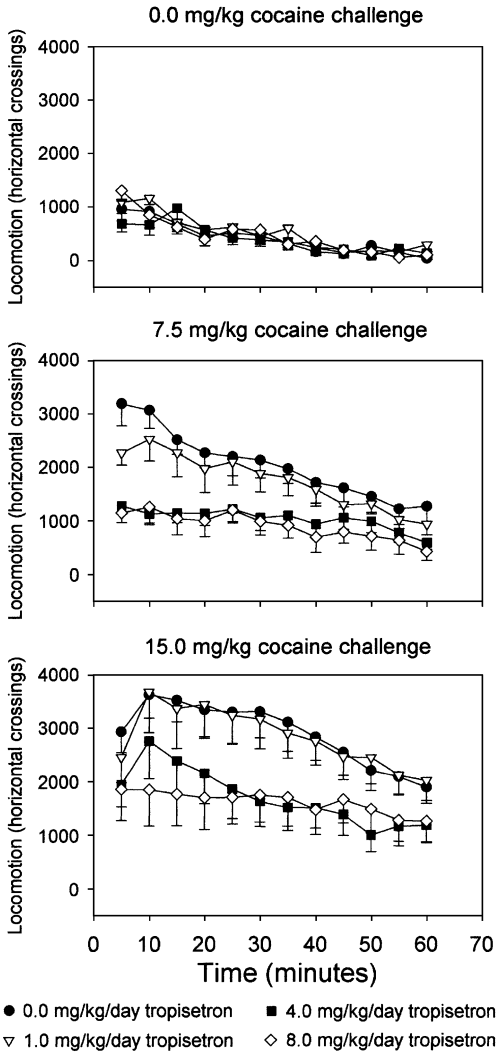

Fig. 1. Presents the mean ambulation (horizontal crossings) as a function of time for each pretreatment group, separately for each cocaine challenge dose. The filled circles (●) represent the saline control subjects. The open, inverted triangles (▽) represent the 1.0 mg/kg/day tropisetron subjects, the filled squares (■) represent the 4.0 mg/kg/day tropisetron subjects, and the open diamonds (◇) represent the 8.0 mg/kg/day tropisetron subjects. The bars represent one S.E.M.

main effect of Time was significant ($F(11,98) = 17.09$), as was the Time × Cocaine Dose interaction ($F(22,198) = 2.99$). Neither the Time × Tropisetron ($F(33,300) = 1.18$), nor the interactions of Time × Tropisetron Dose × Cocaine Dose interactions ($F(66,618) = 1.03$) were significant. The results of post-hoc Tukey's tests indicate that both the saline control and 1.0 mg/kg/day tropisetron doses are significantly different than the 4.0 and 8.0 mg/kg/day tropisetron doses. Post-hoc Tukey's tests also indicate that the 0.0 mg/kg cocaine challenge group is significantly different than the 7.5 and 15.0 mg/kg cocaine challenge groups, and that the 7.5 mg/kg cocaine challenge group is significantly different from the 15.0 mg/kg cocaine challenge group.

3.2. Effects of continuous LY 278,584 administration on cocaine induced locomotion

Similar to Fig. 1, Fig. 2 present the mean horizontal activity as a function of time after the challenge, separately for each cocaine challenge dose. An examination of Fig. 2 suggests continuous LY 278,584 induced tolerance to the behavioral effects of the cocaine challenge. The results of the ANOVA indicated that the main effects of LY 278,584 Dose ($F(3,108) = 13.71$), Cocaine Challenge Dose ($F(2,108) = 46.71$) were significant, as was the LY 278,584 × Cocaine Dose interaction ($F(6,108) = 6.91$). The results of the ANOVA also indicated that the main effect of Time was significant ($F(11,98) = 27.18$), as were the Time × LY 278,584 ($F(33,300) = 1.99$) and Time × Cocaine Dose ($F(22,198) = 1.88$) interactions. However, the interaction of Time × LY 278,584 × Cocaine Dose interactions ($F(66,618) = 1.13$) was not significant. The results of post-hoc Tukey's tests indicate that the saline control group is significantly different from the 0.001, 0.01, and 0.1 mg/kg/day LY 278,584 groups. Post-hoc Tukey's tests also indicate that the 0.0 mg/kg cocaine challenge group is significantly different than the 7.5 and 15.0 mg/kg cocaine challenge groups, and that the 7.5 mg/kg cocaine challenge group is significantly different from the 15.0 mg/kg cocaine challenge group.

3.3. Effects of continuous tropisetron administration on cocaine induced stereotypies

Fig. 3 presents the mean stereotypy counts as a function of time after the challenge, separately for each cocaine challenge dose. An examination of Fig. 3 suggests that continuous tropisetron did not induce any differential effects on cocaine-induced stereotypies. The results of the ANOVA indicated that the main effect of Cocaine Challenge Dose ($F(2,108) = 35.81$) was significant. Neither the main effect of Tropisetron Dose ($F(3,108) = 2.43$), nor the Tropisetron × Cocaine Dose interactions were not significant ($F(6,108) = 1.46$). The results of the ANOVA also indicated that the main effect of Time was significant

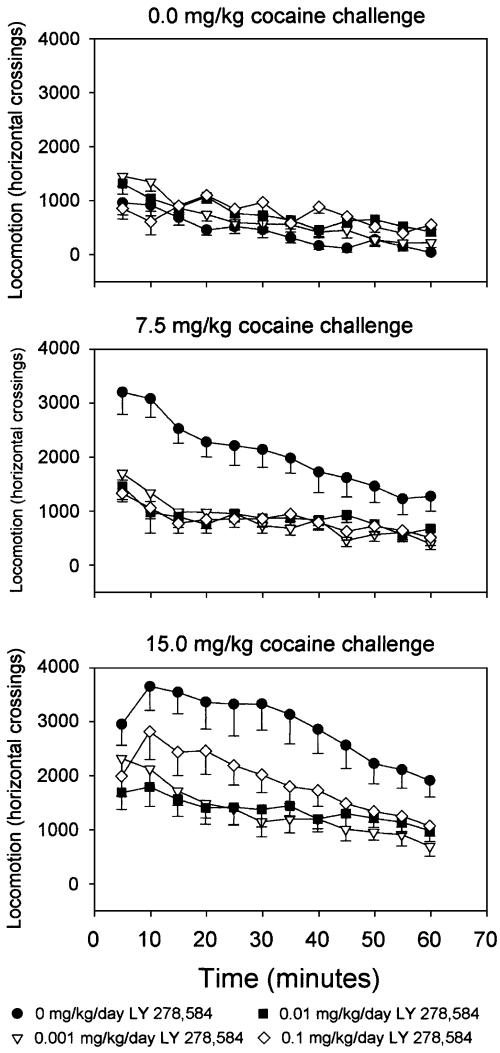

Fig. 2. Presents the mean ambulation (horizontal crossings) as a function of time for each pretreatment group, separately for each cocaine challenge dose. The filled circles (●) represent the saline control subjects. The open, inverted triangles (▽) represent the 0.001 mg/kg/day LY 278,584 subjects, the filled squares (■) represent the 0.01 mg/kg/day LY 278,584 subjects, and the open diamonds (◇) represent the 0.1 mg/kg/day LY 278,584 subjects. The bars represent one S.E.M.

($F(11,98) = 18.96$), as were the Time × Cocaine Dose interaction ($F(22,198) = 2.41$) and the Time × Tropisetron ($F(33,300) = 1.5$) interactions. However, the interactions of Time × Tropisetron Dose × Cocaine Dose interactions ($F(66,618) = 0.91$) were not significant. Post-hoc Tukey's tests indicate that the 0.0 mg/kg cocaine challenge group is significantly different than the 7.5 and 15.0 mg/kg cocaine challenge groups, and that the 7.5 mg/kg cocaine challenge group is significantly different from the 15.0 mg/kg cocaine challenge group.

3.4. Effects of continuous LY 278,584 administration on cocaine induced stereotypies

Fig. 4 presents stereotypy counts as a function of time after the challenge, separately for each cocaine challenge

dose. An examination of Fig. 4 suggests that continuous LY 278,584 induced did not induce any differential effects on cocaine-induced stereotypies. The results of the ANOVA indicated that the main effects of LY 278,584 Dose ($F(3,108) = 10.42$), Cocaine Challenge Dose ($F(2,108) = 40.32$) were significant, as was the LY 278,584 × Cocaine Dose interaction ($F(6,108) = 6.08$). The results of the ANOVA also indicated that the main effect of Time was significant ($F(11,98) = 29.32$), as were the Time × LY 278,584 ($F(33,300) = 1.88$) and Time × Cocaine Dose ($F(22,198) = 2.15$) interactions. However, the interaction of Time × LY 278,584 × Cocaine Dose interactions ($F(66,618) = 1.78$) was not significant. The results of post-hoc Tukey's tests indicate that the saline control group is significantly different from the 0.001, 0.01, and 0.1 mg/kg/day LY 278,584 groups. Post-hoc Tukey's tests also indicate that the 0.0 mg/kg cocaine challenge group is significantly different than the 7.5 and 15.0 mg/kg cocaine challenge groups, and that the 7.5 mg/kg cocaine challenge group is significantly different from the 15.0 mg/kg cocaine challenge group.

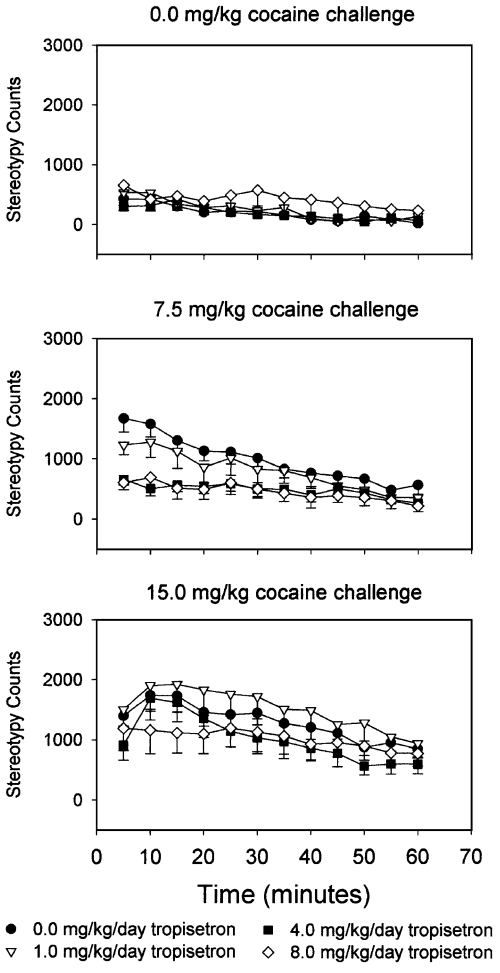

Fig. 3. Presents the mean stereotypy counts as a function of time for each pretreatment group, separately for each cocaine challenge dose. The filled circles (●) represent the saline control subjects. The open, inverted triangles (▽) represent the 1.0 mg/kg/day tropisetron subjects, the filled squares (■) represent the 4.0 mg/kg/day tropisetron subjects, and the open diamonds (◇) represent the 8.0 mg/kg/day tropisetron subjects. The bars represent one S.E.M.

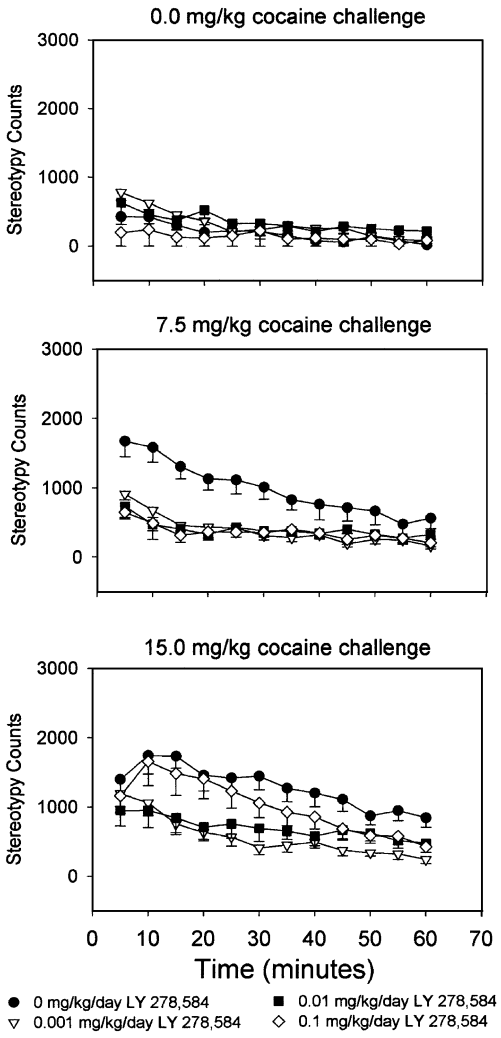

Fig. 4. Presents the mean stereotypy counts as a function of time for each pretreatment group, separately for each cocaine challenge dose. The filled circles (●) represent the saline control subjects. The open, inverted triangles (▽) represent the 0.001 mg/kg/day LY 278,584 subjects, the filled squares (■) represent the 0.01 mg/kg/day LY 278,584 subjects, and the open diamonds (◇) represent the 0.1 mg/kg/day LY 278,584 subjects The bars represent one S.E.M.

4. Discussion

The present results are consistent with the previous findings, which suggest a role for 5-HT_3 receptors in the behavioral effects of cocaine. The current results demonstrate that continuous administration of the 5-HT_3 receptor antagonists tropisetron and LY 278,584 induces tolerance to the behavioral effects of a subsequent cocaine challenge.

4.1. Effects of continuous 5-HT_3 receptor antagonist administration on locomotor behavior

The current experiment was based on the hypothesis that continuous 5-HT_3 receptor antagonists would result in an up-regulation of 5-HT_3 receptors, which in turn would produce sensitization (reverse tolerance) to the behavioral effects of a cocaine challenge. The rationale has some support, as Allan et al. (2001) reported that mice over-expressing 5-HT_3 receptors exhibit significantly enhanced locomotor responses to cocaine challenges, indicating that increased (or up-regulated) 5-HT_3 receptors potently modulate that behavioral effects of cocaine.

The hypothesis was not supported. Continuous tropisetron and LY 278,584 produced tolerance to the behavioral effects of the cocaine challenge, similar to the effects of continuous cocaine administration (e.g., King et al., 1998; Reith et al., 1987). This result suggests that continuous 5-HT_3 receptor antagonist administration functionally down-regulated 5-HT_3 receptors. The basis of this effect is not clear, but is probably not due to alterations in 5-HT_4 receptors. Tropisetron is a high affinity 5-HT_3 receptor antagonist, but also has micromolar affinity for 5-HT_4 receptors. Thus, one might argue that the effects of tropisetron are due to alterations in 5-HT_4 receptors. However, LY 278,584 is a highly selective 5-HT_3 receptor antagonist, with no apparent affinity for other 5-HT receptor subtypes (Wong et al., 1989). Thus, the results suggest that the tolerance induced by continuous 5-HT_3 receptor antagonist administration results from a functional down-regulation of 5-HT_3 receptors.

The effects of tropisetron and LY 278,584 on the induction of tolerance to cocaine were not dose-dependent. Rather, there was a step-function, in which the two highest doses of tropisetron induced nearly identical magnitudes of tolerance, and the lowest dose did not produce any evidence of tolerance. In addition, all doses of LY 278,584 induced roughly equal magnitudes of tolerance. This result is similar to our previous report (King et al., 1999), which examined different doses of continuous cocaine on the induction of behavioral tolerance to cocaine challenge. In that experiment, the induction of cocaine tolerance was not entirely dose-dependent: there was no evidence of tolerance for the 7.5 mg/kg cocaine challenge. For the 15.0 mg/kg cocaine challenge, all pretreatment groups exhibited tolerance, as compared to the saline control group; however, only the 5.0 and 40 mg/kg/day cocaine groups were significantly different from each other, suggesting a dose-dependent effect. In other words, although different continuous cocaine doses induced tolerance, the two highest doses (20 and 40 mg/kg/day cocaine) did not induce differential magnitudes of tolerance. The similarity of results between the current and previous findings suggests that continuous tropisetron and LY 278,584 are acting similar to cocaine. This result is not entirely surprising as cocaine is also a weak 5-HT_3 receptor antagonist (Rocha E Silva et al., 1953; Ross and Renyi, 1969; Gaddum and Piccarelli, 1957).

The current results are not consistent with the previous findings reported by Costall et al. (1987). In that experiment, Costall et al. (1987) perfused ondansetron, another selective 5-HT_3 receptor antagonist, and dopamine into the nucleus accumbens for 13 days. They did not find any effect of continuous ondansetron on subsequent behavior. There are several procedural differences between the current and previous experiments that may account for the differences in results. First, Costall et al. (1987) used ondansetron, while the current experiment used tropisetron and LY 278,584. It is unlikely that the choice of drug represents a significant determinant of the differences, as all of the ligands are high affinity 5-HT_3 receptor antagonists. Second, Costall et al. (1987) experiment used local administration into the nucleus accumbens, while the current experiment used systemic administration. It is possible that the current results are due to a down-regulation of 5-HT_3 receptors in a different area such as the ventral tegmental area. Changes in ventral tegmental area 5-HT_3 receptors is a possibility as Steketee and Crissman (1997) reported that intra-ventral tegmental area tropisetron blocked the development of cocaine sensitization. Future research should evaluate this prospect.

4.2. Effects of continuous 5-HT_3 receptor antagonist administration on locomotor behavior

In sensitized subjects, stimulant challenges often induce stereotypies, which are focused repetitive behaviors such as sniffing or grooming. In other words, there is little or no locomotion while an organism engages in a stereotypy. Hence, it is possible that continuous 5-HT_3 receptor antagonist administration did sensitize the subjects, and the decreased locomotor response is the result of stereotypy induction by the cocaine challenges. However, the current results indicate that continuous 5-HT_3 receptor antagonist administration did not increase the number of cocaine-induced stereotypies. There were no significant differences between the pretreatment groups in terms of cocaine-induced stereotypies. Thus, the tolerance to the locomotor effects of cocaine challenges following continuous 5-HT_3 receptor antagonist administration does reflect a "real" decrease in locomotion, and this tolerance is not an "apparent" tolerance due to the induction of stereotypies.

In summary, the current results indicate that continuous tropisetron and LY 278,584 administration induced tolerance to the behavioral effects of a subsequent cocaine challenge. The effects of continuous 5-HT_3 receptor antagonist administration were not dose-dependent. The results extend previous findings indicating that 5-HT_3 receptors are critical to the acute and chronic effects of cocaine.

Acknowledgements

This research was supported by NIDA grants, 1R29-DA08899 and 1R01-DA10468.

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