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The effects of continuous cocaine duration on the induction of behavioral tolerance and dopamine autoreceptor function

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Abstract

The current experiment evaluated the duration-dependent nature of the induction of behavioral tolerance and changes in dopamine autoreceptor function by continuously administering cocaine for different durations. For all experiments, rats were exposed to a pretreatment regimen involving the continuous administration of 40 mg/kg/day cocaine. The pretreatment regimen lasted 3, 7, or 14 days. All subjects were then withdrawn from the pretreatment regimen for 7 days. The subjects were placed in activity monitors and ambulation measured. In experiment 1, the subjects were challenged with 0.0, 7.5, or 15.0 mg/kg i.p. cocaine on day 7 of withdrawal from the continuous cocaine administration regimen. The results indicated that all continuous cocaine durations induced significant tolerance to the 7.5 and 15.0 mg/kg cocaine challenge, relative to the control group. However, the magnitude of tolerance was not duration dependent. In experiment 2, the subjects were challenged with 0.063 or 0.125 mg/kg quinpirole. The results indicated that the 0.063 mg/kg quinpirole challenge inhibited activity in both pretreatment groups, while the 0.125 mg/kg quinpirole challenge enhanced behavior in the saline control, but not the cocaine, pretreatment group. In experiment 3, the subjects were challenged with the same doses of quinpirole in combination with 7.5 mg/kg i.p. cocaine. Both quinpirole challenge doses inhibited cocaine-induced hyperactivity. The results suggest that the induction of tolerance by continuous cocaine administration is not duration-dependent. Continuous cocaine administration did induce dopamine autoreceptor supersensitivity. Different continuous cocaine durations may induce differential degrees of dopamine autoreceptor supersensitivity.

Keywords: Cocaine continuous; Behavioral tolerance; Dopamine autoreceptor; Cocaine duration; Rat

1. Introduction

Previous research involving chronic cocaine administration clearly indicates that the continuous administration of cocaine results in tolerance to its behavioral and neurochemical effects (Chen and Reith, 1993; King et al., 1992, 1993, 1994a,b, 1995, 1997; Reith et al., 1987). Most of this research utilized a high-dose, long-duration administration regimen. These doses and durations have generally been selected to model the compulsive cocaine abuser. Indeed, in humans compulsive high-dose abuse is characterized by a binge like pattern of consumption. During the binge the individual will ingest, for several hours up to several days, doses that range from an average of 50 mg/kg/day, to much larger doses in abusers with ready access to cocaine (Gawin and Kleber, 1985).

In spite of the substantial literature indicating that tolerance to many of the effects of cocaine can develop following continuous administration, the parameters of cocaine administration that induce tolerance remain largely uncharted. Indeed, few studies have examined whether the induction of tolerance by continuous cocaine administration varies as a function of the pretreatment regimen. In other words, is the induction of tolerance following continuous cocaine administration duration dependent or is there threshold duration necessary for the induction of tolerance? Our previous experiments, as well as those by Reith et al. (1987) have typically used a 14-day treatment period. While the clinical literature suggests that longer durations induce higher levels of tolerance (see, e.g., Gold, 1992), an exper-

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imental examination of this issue is lacking. In other words, can significant tolerance be induced by a shorter dosing period? This question may be important for understanding the transition from recreational cocaine use to cocaine abuse: For example, would a short term binge (e.g., a weekend binge in a casual user) induce sufficient tolerance to require subsequent escalation of the duration and/or dose to obtain the same euphoric effect, thus triggering the initiation of bingeing.

The literature also indicates that the tolerance induced by continuous cocaine administration is associated with several indices of dopamine autoreceptor supersensitivity. King et al. (1994b) reported that rats given continuous cocaine for 14 days showed an enhanced inhibition of locomotor activity following a low dose challenge of apomorphine. Zhang et al. (1992) found that dopamine neurons in the substantia nigra compacta, recorded from rats that had received continuous cocaine, were supersensitive to the inhibitory effects of apomorphine on cell firing rates. Gao et al. (1998) recently reconfirmed these results using the selective D2/D3 agonist quinpirole. Lastly, Jones et al. (1996), using in vitro fast scan cyclic voltammetry, found that dopamine autoreceptors were supersensitive to the inhibitory effects of quinpirole. We have also reported that induction of tolerance, but not autoreceptor supersensitivity, is dose-dependent (King et al., 1999a,b).

In spite of this literature, several questions remain unanswered. First, King et al. (1994b), reported enhanced inhibition of behavior following an apomorphine challenge. However, apomorphine is not selective for dopamine D2 receptors. The question thus arises as to whether these results can be replicated with a ligand more selective for dopamine D2-like receptors. In addition, if the induction of tolerance induced by the administration different continuous cocaine doses is duration-dependent, is the magnitude of tolerance correlated with differential changes in dopamine autoreceptor supersensitivity?

The present experiments evaluate whether the induction of behavioral tolerance by continuous cocaine administration is duration-dependent, and if it is, whether the tolerance is associated with differential changes in dopamine autoreceptor supersensitivity. In other words, does the magnitude of tolerance vary as a function of continuous administration duration, and if it does, do changes in autoreceptor function also vary as a function of continuous administration duration? In all experiments, the subjects were exposed to a pretreatment regimen involving the continuous administration of 0 or 40 mg/kg/day cocaine for 3, 7, or 14 days. The subjects were then withdrawn from this regimen for 7 days. In experiment 1, behavioral tolerance was assessed by challenging the subjects with vehicle, 7.5, or 15.0 mg/kg i.p. cocaine. Experiments 2 and 3 evaluated changes in dopamine autoreceptor function by challenging the subjects with vehicle, 0.063, or 0.125 mg/kg quinpirole. Experiment 2 evaluated the effects of quinpirole on locomotor activity, while experiment 3 evaluated the effects of quinpirole on cocaine induced (7.5 mg/kg) activity. We predict that quinpirole should inhibit both locomotor and cocaine-induced activity due to selective activation of presynaptic dopamine autoreceptors.

The current experiments evaluated the duration-dependent nature of tolerance and changes in autoreceptor function on day 7 of withdrawal from continuous cocaine administration. This withdrawal time was selected for several reasons. First, tolerance is manifested on days 1 and 7 of withdrawal, but dissipates by day 14 of withdrawal from continuous cocaine administration (King et al., 1999a,b). Second, the majority of our research examining behavioral tolerance following continuous cocaine administration has been conducted on day 7 of withdrawal; thus, to maintain comparability to this research, the current experiment also examined tolerance on day 7. Third, as the introduction points out, most of the research evaluating dopamine neuronal activity following continuous cocaine administration was conducted on day 7 of withdrawal. Thus, to compare the current behavioral data with that electrophysiological data, the current experiment was conducted on day 7 of withdrawal. Lastly, although tolerance is present on days 1 and 7 of withdrawal, dopamine autoreceptors are subsensitive on day 1 and supersensitive on day 7 of withdrawal (e.g, Lee et al., 1988; Lee and Ellinwood, 1989).

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats weighing 150–175 g (Charles River Laboratories), were acclimated to the vivarium (12 h light/dark cycle, light on at 7 a.m.) for 1 week. They were maintained on free-food and water and were housed in pairs. Terminal weights ranged from 275 to 325 g. The current methods were approved by the University of North Texas Health Sciences Center animal use committee and all subjects were treated in accordance to the guidelines in the NIH Guide for Care and Use of Laboratory Animals.

2.2. Drugs

Cocaine HCl (received from NIDA) was dissolved in 0.9% saline, as was quinpirole, which was purchased from Research Biochemicals (Natick, MA).

2.3. Minipump preparation and pretreatment regimen

Alzet Osmotic pumps (model 2ML2 Alza) were filled with 2.5 ml of 100 mg/ml cocaine HCl or isotonic (0.9%) saline. The pumps were slightly modified by adding a microdialysis fiber to the output portal to eliminate tissue necrosis from the cocaine (Joyner et al., 1993). The infusion

rate for the cocaine was 5 μl/h resulting in an overall dose of 0 (control group) or 40 mg/kg/day cocaine. The pumps were primed by warming in a warm water bath (37 °C) for 4 h before pump implantation.

The cocaine pretreatment was for a 3-, 7-, or 14-day period. On day 1 of treatment, animals were implanted with 2ML2 Alzet minipumps continuously infusing cocaine at an average rate of 40.0 mg/kg/day.

2.4. Surgery

Rats were anesthetized briefly by inhalation with methoxyflurane (Metofane). They were then shaved along the dorsal midline and injected with 0.1 cm^3 lidocaine (Abbot) proximal to the incision site. A 2-cm incision was made with scissors and a large subcutaneous pocket was made with the scissors. The minipumps were inserted into the pocket with the delivery portal towards the head and the incision closed with surgical autoclips. Removal of the minipumps entailed the identical procedure. The amount of residual cocaine solution was measured. Subjects that had more than 10% of the drug remaining in the pump were discarded from the study.

2.5. Locomotor activity testing

On day 7 of withdrawal from the continuous cocaine pretreatment regimen, the animals were transported from the vivarium to the test room in a rat transporter. The tranporter has slots for 60 cages, and the rats' home cages are inserted into the slots. The rats 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 (Columbus Instruments, Columbus, OH), and allowed to acclimate to the test cages for an additional 30 min. The activity monitors had 15 photobeams, spaced 2.5 cm apart, along each side of the monitor. For all experiments, the rats received an i.p. injection of the challenge ligand and then placed back into the activity chambers. The session was immediately started for that rat and locomotor activity was recorded for 60 min.

In experiment 1, the subjects were exposed to the pretreatment regimen described above. On day 7 of withdrawal, subjects received a vehicle, 7.5, or 15.0 mg/kg i.p. cocaine injection. The vehicle injection subjects served as the control subjects for all experiments (i.e., experiments 1, 2, and 3). In experiment 2, the subjects were exposed to the pretreatment regimen described above. On day 7 of withdrawal, subjects received a 0.063 or 0.125 mg/kg i.p. quinpirole injection. In experiment 3, the subjects were exposed to the pretreatment regimen described above. On day 7 of withdrawal, subjects received a vehicle, 0.063, or 0.125 mg/kg i.p. quinpirole injection, followed 5 min later by a 7.5 mg/kg i.p. cocaine injection.

2.6. Data analysis

The primary dependent measure for the current experiments is locomotor activity. Locomotor activity was measured as the number of photobeam crossings in a 5-min period, without regard to directionality. This current experiment is a mixed model design. Specifically, there were three group factors (pretreatment drug, treatment duration, and cocaine challenge dose) that produce 18 separate groups (3 cocaine pretreatment durations × 2 pretreatment doses × 3 challenge doses), and one repeated measures factor (Time), per experiment. Data were collected on 10 subjects per group. For all experiments, the subject types (i.e., subjects receiving different continuous cocaine doses and drug challenges) were randomized according to a Latin Square design. Our previous research (King et al., 1999a,b) indicated that tolerance to the behavioral effects of a cocaine challenge are manifested over a substantial portion of the 60-min locomotor monitoring interval. Thus, the time course data are not critical. For these reasons, the ambulation scores were converted to areas under the curve (AUC) over the entire 60 min session by PeakFit (Jandel). The data were then analyzed by standard analyses of variance (ANOVA). Significant differences were analyzed by post-hoc Tukey's tests. The significance level is set at $P \leq 0.05$ for all comparisons.

3. Results

3.1. Effects of continuous cocaine duration on the induction of behavioral tolerance

Fig. 1 presents mean area under the curve (AUC) for the locomotion data as a function of cocaine challenge dose, separately for the continuous cocaine and saline subjects. The top panel of Fig. 1 presents the mean AUC for the 3-day duration, the middle panel presents the data for the 7-day duration, and the bottom panel presents the data for the 14-day duration.

The data in Fig. 1 suggest that there were significant differences between the pretreatment groups in their response to the cocaine challenges. To determine whether there were differences between the pretreatment groups, a three-way ANOVA was conducted on the AUCs. The three factors were drug pretreatment group (cocaine vs. saline), pretreatment duration and cocaine challenge dose. The results of the ANOVA indicated that the main effects of drug pretreatment group [Pretreatment Group: $F(1,162) = 30.23$) and cocaine challenge dose [Cocaine Dose: $F(2,162) = 49.06$] were significant. The Pretreatment Group × Cocaine challenge dose interaction was also significant [Pretreatment Group × Cocaine dose: $F(2,162) = 7.19$]. No other comparison was significant. The results of the post-hoc Tukey's comparisons on the data from the ANOVA in Fig. 1 indicate that for all treatment durations, the cocaine group was significantly

different from the saline control group for both the 7.5 and 15.0 mg/kg cocaine challenges.

The results in Fig. 1 also suggest that the tolerance induced by continuous cocaine administration is not duration dependent. The results of the three-way ANOVA further indicate that the treatment duration had no effect, as the results of the ANOVA indicated that the main effect of duration was not significant.

3.2. Effects of quinpirole on locomotor activity

Similar to Fig. 1, Fig. 2 presents mean AUC for the quinpirole challenges. The top panel of Fig. 2 presents the mean AUC for the 3-day duration, the middle panel presents the data for the 7-day duration, and the bottom panel presents the data for the 14-day duration.

An examination of the data in Fig. 2 suggests that increasing quinpirole doses generally decreased activity

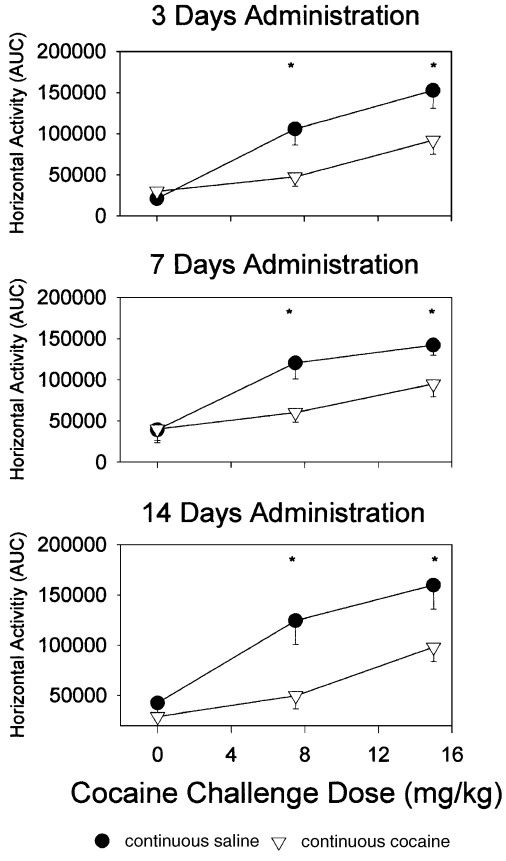

Fig. 1. Locomotor activity (mean area-under-the-curve) a function of cocaine challenge dose for rats treated continuously with either saline (closed circles: ●) or continuous cocaine (40 mg/kg/day; open triangles: ▽). On the behavior testing day, the subjects were challenged with vehicle, 7.5, or 15.0 mg/kg cocaine i.p. The top panel presents the data for the 3-day administration period, the middle panel presents the data for the 7-day administration period, and the bottom panel presents the data for the 14-day administration period. The bars represent 1 S.E.M. An asterisk signifies a significant difference from the saline control group.

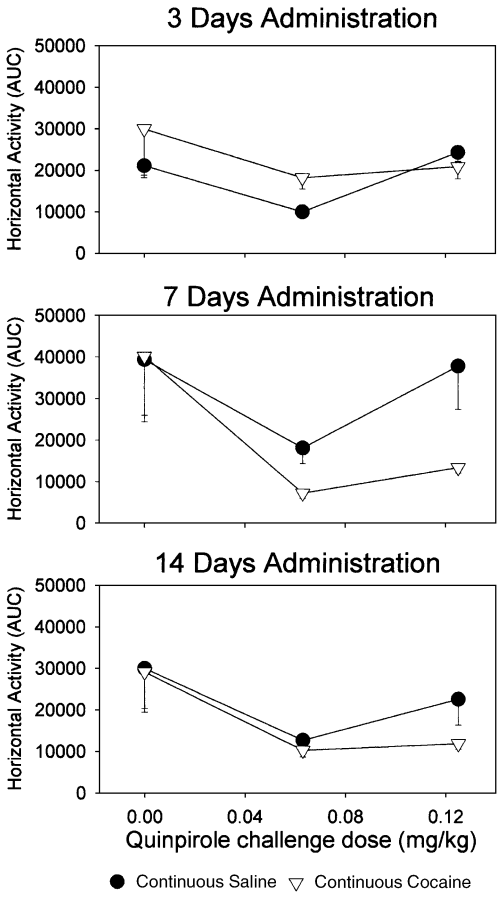

Fig. 2. Locomotor activity (mean area-under-the-curve) a function of quinpirole challenge dose for rats treated continuously with either saline (closed circles: ●) or continuous cocaine (40 mg/kg/day; open triangles: ▽). On the behavior testing day, the subjects were challenged with vehicle, 0.063, or 0.125 mg/kg quinpirole i.p. The top panel presents the data for the 3-day administration period, the middle panel presents the data for the 7-day administration period, and the bottom panel presents the data for the 14-day administration period. The bars represent 1 S.E.M. An asterisk signifies a significant difference from the saline control group.

levels. To determine whether there were significant differences between the pretreatment groups in the behavioral response quinpirole, a three-way ANOVA was conducted on the AUCs for the ambulation data. The three factors were drug pretreatment group (cocaine vs. saline), pretreatment duration and cocaine challenge dose. The results of the ANOVA indicated that only the main effect of quinpirole challenge dose [Quinpirole Dose: $F(2,162) = 12.60$] was significant. No other comparison was significant.

3.3. Effects of quinpirole on cocaine induced hyperactivity

Similar to Figs. 1 and 2, Fig. 3 presents mean AUC for the quinpirole plus 7.5 mg/kg cocaine challenges. The top panel of Fig. 3 presents the mean AUC for the 3-day duration, the middle panel presents the data for the 7-day duration, and the bottom panel presents the data for the 14-day duration.

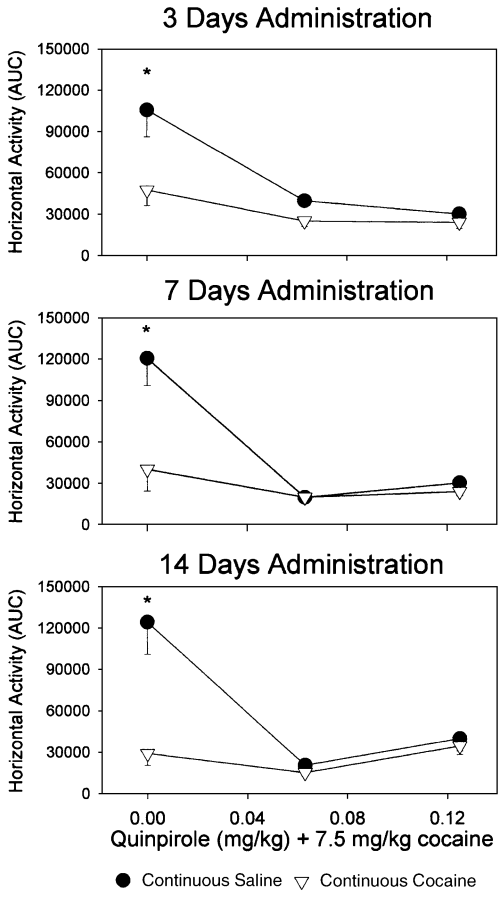

Fig. 3. Locomotor activity (mean area-under-the-curve) a function of quinpirole challenge dose, in combination with a 7.5 mg/kg cocaine challenge for rats treated continuously with either saline (closed circles: ●) or continuous cocaine (40 mg/kg/day; open triangles: ▽). On the behavior testing day, the subjects were challenged with vehicle, 0.063, or 0.125 mg/kg quinpirole i.p., followed 5 min later by a 7.5 mg/kg i.p. cocaine challenge. The top panel presents the data for the 3-day administration period, the middle panel presents the data for the 7-day administration period, and the bottom panel presents the data for the 14-day administration period. The bars represent 1 S.E.M. An asterisk signifies a significant difference from the saline control group.

To determine whether there were differences between the pretreatment groups in the effects of quinpirole on cocaine induced hyperactivity, a three-way ANOVA was conducted on the AUCs. The three factors were drug pretreatment group (cocaine vs. saline), pretreatment duration and cocaine challenge dose. The results of the ANOVA indicated that the main effects of drug pretreatment group [Pretreatment Group: $F(1,162) = 24.30$) and quinpirole challenge dose [Quinpirole Dose: $F(2,162) = 61.37$] were significant. The Pretreatment Group × Quinpirole challenge dose interaction was also significant [Pretreatment Group × Cocaine dose: $F(2,162) = 15.67$]. No other comparison was significant.

The results presented in Fig. 3 suggests that quinpirole inhibited cocaine-induced hyperactivity in all groups. However, the magnitude of the inhibition was greater in the control group as compared to the cocaine-pretreated groups because the cocaine pretreated subjects exhibited tolerance. As can be seen in Fig. 3, the magnitude of quinpirole induced inhibition of cocaine induced hyperactivity is greater in the saline control group than in the cocaine pretreated groups. However, as one can also see, the subjects in the cocaine pretreated groups also exhibited significantly less cocaine induced hyperactivity than the saline control subjects (i.e., the cocaine pretreated subjects exhibited tolerance to the cocaine challenge).

4. Discussion

The current results suggest that, over the duration intervals tested, the induction of behavioral tolerance by continuous cocaine administration is not duration-dependent. In other words, increasing duration of continuous cocaine from 3 to 14 days did not induce increasing levels of behavioral tolerance. The results are also consistent with the hypothesis that continuous cocaine administration induces dopamine autoreceptor supersensitivity. However, the magnitude of this supersensitivity does seem to depend on the continuous cocaine duration.

4.1. Continuous cocaine duration and tolerance

The results of the experiment 1 indicate that all continuous cocaine doses induced tolerance to the 7.5 and 15.0 mg/kg cocaine challenge. This result is consistent with dopamine autoreceptor control of cocaine-induced hyperactivity and the development of dopamine autoreceptor supersensitivity. Activation of dopamine autoreceptors, by higher than normal levels of synaptic dopamine, results in an inhibition of dopamine release. Thus, results suggest that the lower cocaine challenge dose (7.5 mg/kg cocaine) produced sufficient synaptic dopamine levels to stimulate dopamine autoreceptors, which would have the effect of inhibiting cocaine induced hyperactivity.

The results presented in Fig. 1 indicate that, in the current experiment, the magnitude of tolerance to the different cocaine challenges did not vary as a function of the duration of continuous administration. Thus, the induction of cocaine tolerance is not duration-dependent. This pattern of results suggests that even short durations of "high dose" cocaine use may induce sufficient tolerance to trigger binge use in humans.

4.2. Effects of quinpirole on locomotor activity

Experiments 2 and 3 used low doses of quinpirole to probe for changes in dopamine autoreceptor function following different durations of continuous cocaine administration. Low doses of quinpirole will presumably dopamine autoreceptors (Jones et al., 1996). Stimulation of autorecep-

tors would result in an inhibition of dopamine neuronal firing rates and neurotransmission. The behavioral manifestation of this neuronal inhibition is a reduction in locomotor behavior. Dopamine autoreceptor supersensitivity is evident by an enhanced inhibitory response to an autoreceptor selective dose of quinpirole.

Changes in dopamine autoreceptor function have been implicated in mediating the tolerance induced by continuous cocaine and amphetamine administration (Jones et al., 1996; King et al., 1994b; Lee and Ellinwood, 1989; Lee et al., 1988; Zhang et al., 1992). For example, King et al. (1994b) reported that rats pretreated with 40 mg/kg/day cocaine exhibited enhanced behavioral inhibition to autoreceptor selective doses of apomorphine (a D1–D2 agonist). King et al. (1999a,b) reported that rats pretreated with 10–40 mg/kg/day continuous cocaine also exhibited enhanced behavioral inhibition, relative to saline control subjects, following a quinpirole challenge. Zhang et al. (1992) reported similar effects for the effects of apomorphine on dopamine cell firing rate. Lastly, Jones et al. (1996) reported that slices from the caudate were supersensitive to the inhibitory effects of quinpirole on electrically stimulated dopamine release, when assessed with in vitro voltammetry.

The overall pattern of results presented in Fig. 2 tentatively suggests that dopamine autoreceptor supersensitivity developed in the cocaine pretreated subjects, consistent with previous research (e.g., King et al., 1999a,b). In the cocaine-pretreated subjects, both quinpirole doses inhibited locomotor activity. However, in the saline control group the low quinpirole dose inhibited behavior, while the high quinpirole dose induced locomotor activity that was approximately the same as the saline control subjects that received a vehicle challenge. This is most clearly seen for the 7-day cocaine subjects in Fig. 2. This pattern of results suggests the development of dopamine autoreceptor supersensitivity in the cocaine-pretreated subjects.

The increased behavior seen, primarily in the saline control group, after the 0.125 mg/kg quinpirole challenge probably represents activation of post synaptic dopamine receptors which would induce locomotor behavior. The fact that the cocaine pretreated subjects did not show much, if any, increase in behavior following the 0.125 mg/kg quinpirole challenge suggests that dopamine autoreceptors were supersensitive, and still inhibiting behavior even though post synaptic receptors were being stimulated.

4.3. Effects of quinpirole on cocaine-induced locomotor activity

The results of experiment 3 indicate that quinpirole inhibited cocaine-induced hyperactivity in both pretreatment groups. The magnitude of the inhibition was much greater in the control group as compared to the cocaine-pretreated groups because the cocaine pretreated subjects exhibited tolerance. Indeed, inspection of Fig. 3 indicates that, with the exception of the 3-day pretreatment group, both doses of quinpirole inhibited cocaine-induced hyperactivity to the same level, suggesting that these doses of quinpirole were inducing maximal inhibition. It is unlikely that the use of a different cocaine challenge dose, to induce greater hyperactivity, would have produced different results, as a similar pattern of results was found in King et al. (1999a,b) which used a 15.0 mg/kg cocaine challenge.

In spite of such considerations, the data from experiment 3 are mixed regarding the effects of continuous cocaine duration and differential changes in dopamine autoreceptor function. Inspection of the results in Fig. 3 indicate that the functions relating inhibition of cocaine induced hyperactivity and treatment duration are different depending on the quinpirole challenge dose. For the 0.125 mg/kg dose, there is a slight increase in behavior with increasing treatment duration. This does not suggest increasing dopamine autoreceptor supersensitivity with increasing durations. However, for the 0.063 mg/kg quinpirole challenge the magnitude of inhibition increases with increasing cocaine durations. This result does suggest the development of differential autoreceptor supersensitivity following increasing cocaine durations.

4.4. Synthesis of results

The overall pattern of results suggest that, over the continuous cocaine administration durations used in the current experiments, the magnitude of tolerance to the behavioral effects of cocaine are duration independent. However, the results also suggest that the magnitude of dopamine autoreceptor supersensitivity is duration dependent. If dopamine autoreceptor supersensitivity was the only mechanism mediating tolerance, then one would have expected to find that the magnitude of tolerance was duration dependent. Hence, the current results suggest that multiple mechanisms determine tolerance to the behavioral effects of cocaine.

Other research indicates that continuous cocaine administration functionally down-regulates central 5-HT_3 receptors (King et al., 1994a,b, 1995, 1997, 1999a,b; Matell and King 1997). Research indicates that 5-HT_3 receptor agonists will stimulate DA release in vivo (Chen et al., 1991, 1992; Jiang et al., 1990). Further, a variety of 5-HT_3 antagonists (e.g., ICS 205-930, zacopride, ondansetron, MDL 72222) have been shown to block the locomotor stimulating effects of acute cocaine administration (Hagan et al., 1990; King et al., 1994b; Reith, 1990; Svingos and Hitzemann, 1992; Tricklebank et al., 1989). A functional down regulation of 5-HT_3 receptors by continuous cocaine administration should decrease the stimulatory abilities of 5-HT_3 receptors on dopamine release and would contribute to the behavioral tolerance.

The combined research regarding the mechanisms of tolerance to the behavioral effects of continuous cocaine

administration suggests that tolerance is multiply determined. The down regulation of 5-HT_3 receptors would result in lowered synaptic dopamine levels, which might contribute to the reduced behavioral effects early in the session. However, as synaptic dopamine levels increase due the inhibition of dopamine reuptake by cocaine and stimulation of 5-HT_3 receptors, dopamine autoreceptors would be expected to be activated. This activation, in turn, may decrease dopamine release further. However, the enhanced inhibitory effects of dopamine autoreceptors might be attenuated by 5-HT_3 receptor activation and blockade of reuptake. In other words, although dopamine autoreceptors may have a greater inhibitory effect after 14 days, as compared to 7 days, of continuous cocaine administration, this enhanced effect may not be evident when the subjects are challenged with cocaine. The data presented in Fig. 1 support this idea to the extent that the behavioral response to cocaine increased with increasing challenge doses in the cocaine pretreated subjects. If the supersensitive dopamine autoreceptors represented an absolute mechanism (i.e., an absolute limiter of synaptic dopamine levels) then the behavioral response should not have increased, but it did.

In summary, the current results indicate that, over the durations tested, different continuous cocaine durations do not induce differential degrees of tolerance. In other words, all durations induced equivalent magnitudes of tolerance. This tolerance is associated with the development of dopamine autoreceptor supersensitivity. Different continuous cocaine durations may induce differential degrees of dopamine autoreceptor supersensitivity.

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