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

George R. King *, Zhiping Xiong, Scott Douglas, Tong H. Lee, Everett H. Ellinwood

Department of Psychiatry, Duke University Medical Center, Durham, NC 27710, USA

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Abstract

The current experiment evaluated the dose-dependent nature of the induction of behavioral tolerance, and changes in dopamine autoreceptor function, by continuously administering different doses of cocaine. For all experiments, rats were exposed to a 14-day pretreatment regimen involving the continuous administration of either 0, 5, 10, 20, or 40 mg/kg/day cocaine. All subjects were then withdrawn from the pretreatment regimen for 7 days.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 doses induced significant tolerance to the 15.0 mg/kg cocaine challenge, relative to the control group. Furthermore, the 5.0 mg/kg/day group exhibited significantly less tolerance than the 40.0 mg/kg/day group. In experiment 2, the subjects were challenged with 0.0, 0.063, or 0.125 mg/kg quinpirole. The results indicated that the 0.063-mg/kg quinpirole challenge inhibited activity, while the 0.125 mg/kg quinpirole challenge enhanced behavior. The results further suggested that the inhibition of behavior was greater in the cocaine-pretreated subjects than in the saline control group. In experiment 3, the subjects were challenged with the same doses of quinpirole in combination with 15 mg/kg i.p. cocaine. The low quinpirole challenge dose inhibited cocaine-induced hyperactivity, while the higher challenge dose enhanced cocaine-induced hyperactivity. The results suggest that the induction of tolerance by continuous cocaine administration is dose-dependent. Continuous cocaine administration did induce dopamine autoreceptor supersensitivity. However, different continuous cocaine doses did not induce differential degrees of dopamine autoreceptor supersensitivity.

Keywords: Cocaine, continuous; Behavioral tolerance; Dopamine autoreceptor; Cocaine dose; (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 (Reith et al., 1987; King et al., 1992, 1993, 1994a,b, 1995, 1997; Chen and Reith, 1993). Most of this research utilized a high-dose administration regimen. These high doses 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 days, doses that range from an average of 50 mg/kg/day, to much larger doses in abusers with ready access to cocaine (Dackis and Gold, 1985; Gawin and Kleber, 1985; Gawin and Ellinwood, 1988).

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, no study has examined whether the induction of tolerance by continuous cocaine administration is dose-dependent. In other words, is the induction of tolerance following continuous cocaine administration dose dependent or is there a threshold dose necessary for the induction of tolerance? Our previous experiments, as well as those by Ellison et al. (1996), Izenwasser (Izenwasser et al., 1996; Kunko et al., 1997) and Reith and co-workers (e.g., Reith et al., 1987; Chen and Reith, 1993) have typically used high daily cocaine doses (e.g., 40.0 mg/kg/day or greater). Thus, the question remains whether tolerance occurs following the continuous administration of lower cocaine concentrations. While the clini-

* Corresponding author. Department of Pharmacology, University of North Texas Health Sciences Center, 3500 Camp Bowie Blvd., Fort Worth, TX 76107-2699, USA. Tel: +1-817-735-0260; fax: +1-817-735-2091; E-mail: gking@hsc.unt.edu

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cal literature suggests that larger doses induce higher levels of tolerance (see, e.g., Gold, 1992), an experimental examination of this issue is lacking.

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 basal 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 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.

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 D_2 receptors. The question thus arises as to whether these results can be replicated with a ligand more selective for dopamine D_2-like receptors. In addition, if the induction of tolerance induced by the administration of different continuous cocaine doses is dose-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 dose-dependent, and if it is, whether the tolerance is associated with differential changes in dopamine autoreceptor supersensitivity. In all experiments, the subjects were exposed to a pretreatment regimen involving the continuous administration of 0, 5, 10, 20, or 40 mg/kg/day cocaine. 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 basal activity, while experiment 3 evaluated the effects of quinpirole on cocaine-induced (15.0 mg/kg) activity. We predict that quinpirole should inhibit both basal and cocaine-induced activity due to selective activation of presynaptic dopamine autoreceptors.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats weighing 125–150 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 275–325 g. The current methods were approved by the Duke University animal use committee.

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 either 0, 12.5, 25, 50, or 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), 5, 10, 20, 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 14-day period. On day 1 of treatment, animals were implanted with 2ML2 Alzet minipumps continuously infusing cocaine at an average rate of 5.0, 10.0, 20.0, or 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. Behavioral testing

Our previous behavioral research has exclusively utilized the Ellinwood and Balster (1974) rating scale to assess behavioral changes following continuous cocaine administration. However, in the present experiment, the rats were placed in Opto-Varimex 'minor' activity monitors (Columbus Instruments, Columbus, OH), and ambulation was recorded. This recording allowed us to assess whether continuous cocaine administration also induces tolerance to the locomotor activating properties of cocaine.

On day 7 of withdrawal from the continuous cocaine 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 cm × 43.2 cm × 21 cm) inside Opto-Varimex 'minor' activity monitors, 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.

In experiment 1, the subjects were exposed to the pretreatment regimen described above. On day 7 of withdrawal, some subjects received a vehicle, 7.5, or 15.0 mg/kg i.p. cocaine injection. In experiment 2, the subjects were exposed to the pretreatment regimen described above. On day 7 of withdrawal, some subjects received a vehicle, 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, some subjects received a vehicle, 0.063, or 0.125 mg/kg i.p. quinpirole injection, followed 5 min later by a 15.0 mg/kg i.p. cocaine injection.

2.6. Data analysis

This current experiment is a mixed model design. Specifically, there were two group factors (cocaine pre-

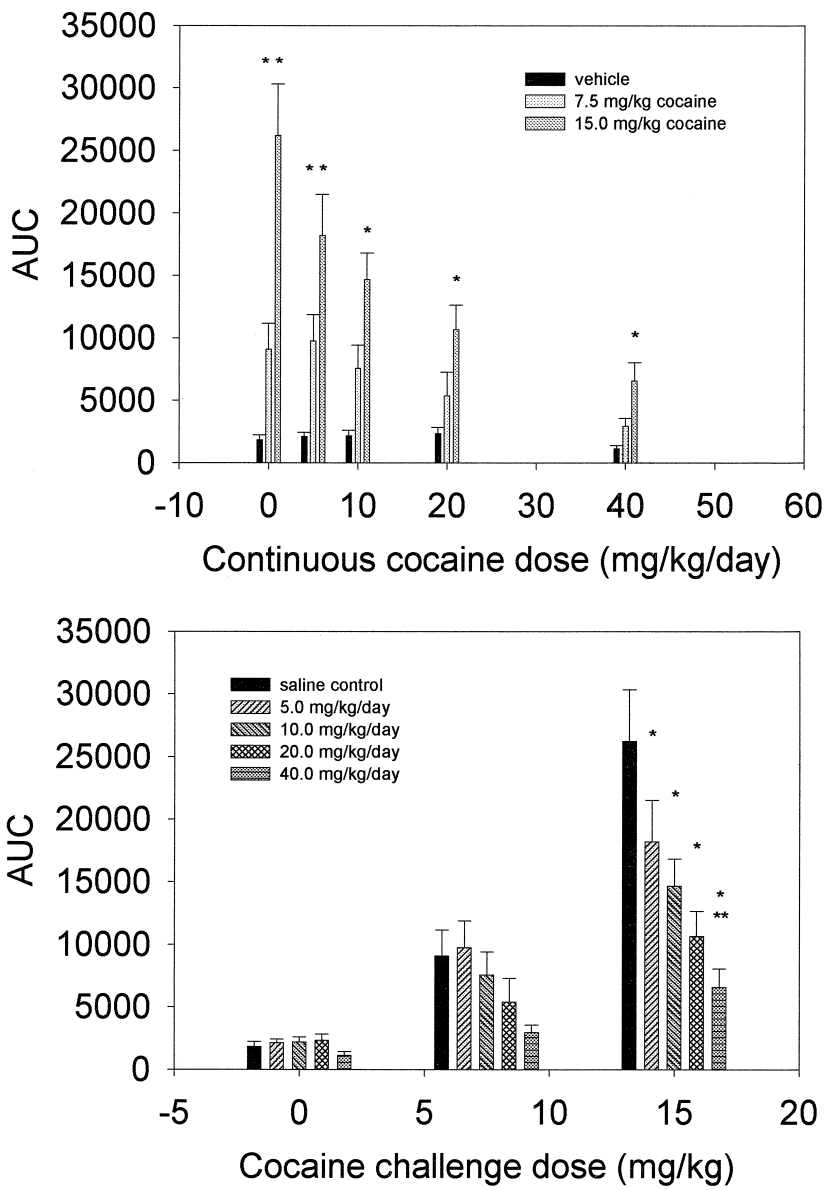

Fig. 1. Mean AUCs for each cocaine challenge as a function of continuous cocaine dose administered during the pretreatment regimen. In the top panel, the black bars represent the vehicle challenge. The light gray bars represent the 7.5 mg/kg cocaine challenge. The dark gray bars represent the 15.0 mg/kg cocaine challenge. In the bottom panel, the black bars represent the saline control group. The light gray, diagonally hatched bars represent the 5.0 mg/kg/day cocaine group. The dark gray, diagonally hatched bars represent the 10.0 mg/kg/day group. The light gray, cross-hatched bars represent the 20.0 mg/kg/day group, and the dark gray, horizontally hatched bars represent the 40.0 mg/kg/day group. The bars represent one S.E.M. In the top panel, an asterisk signifies a significant difference from the vehicle injection. In the bottom panel, a single asterisk indicates a significant difference from the saline control group. A double asterisk indicates a significant difference from the 5.0 mg/kg/day cocaine group.

treatment dose and cocaine challenge dose) that produces 15 separate groups (five cocaine pretreatment doses × three challenge doses), and one repeated measures factor (Time), per experiment. Data were collected on 8–10 subjects per group because one of the activity monitors was not functional. 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. For statistical purposes, the ambulation scores were converted to areas under the curve (AUC) 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. Data consolidation

In experiment 1, some subjects received a vehicle and 15.0 mg/kg cocaine challenge. In experiment 2, some

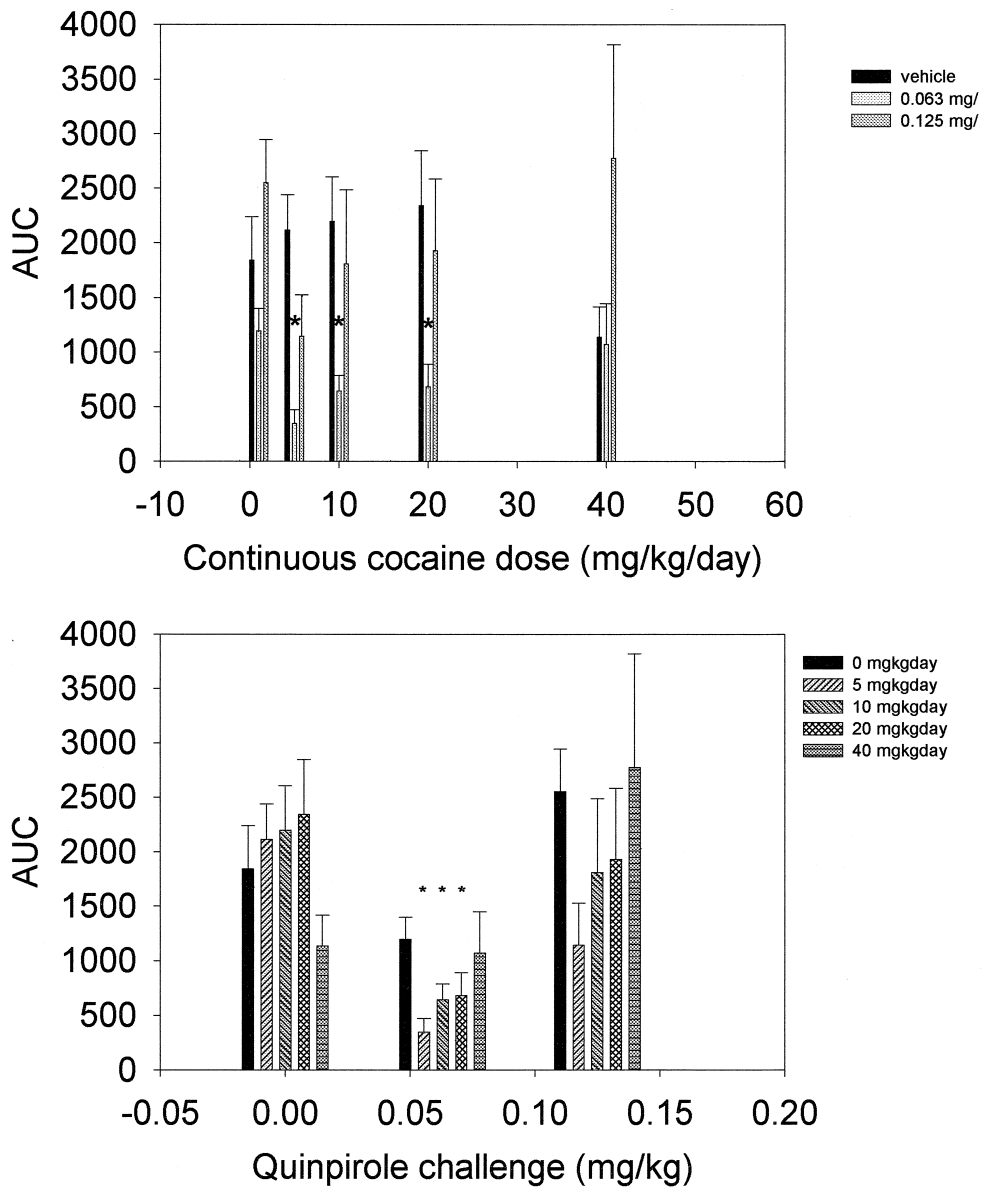

Fig. 2. Mean AUCs for each quinpirole challenge as a function of continuous cocaine dose administered during the pretreatment regimen. In the top panel, the black bars represent the vehicle challenge. The light gray bars represent the 0.063 mg/kg quinpirole challenge. The dark gray bars represent the 0.125 mg/kg cocaine challenge. In the bottom panel, the black bars represent the saline control group. The light gray, diagonally hatched bars represent the 5.0 mg/kg/day cocaine group. The dark gray, diagonally hatched bars represent the 10.0 mg/kg/day group. The light gray, cross-hatched bars represent the 20.0 mg/kg/day group, and the dark gray, horizontally hatched bars represent the 40.0 mg/kg/day group. The bars represent one S.E.M. In the top panel, an asterisk signifies a significant difference from the vehicle injection. In the bottom panel, a single asterisk indicates a significant difference from the saline control group.

subjects also received a vehicle challenge, while in experiment 3, some subjects received a 15.0 mg/kg challenge. To determine whether there were any differences in the replications of these conditions, two-way analyses of variance (ANOVA) were conducted on the AUCs for the ambulation data, separately for the vehicle and 15.0 mg/kg cocaine challenges. The two factors were pretreatment group and replication number (i.e., experiment 1 vs. experiment 2 and experiment 1 vs. experiment 3). The results of the ANOVA for the saline challenge were not significant. The results of the ANOVA for the 15.0 mg/kg cocaine challenge indicated that the main effect of pretreatment group was significant [$F(4.85) = 5.12$], but neither the main effect of replication, nor pretreatment group × replication interaction were significant. Because there were no significant differences in the behavioral response to either the saline or the cocaine challenges across the different experiments, the data were collapsed across experiments for all subsequent graphical and statistical presentations.

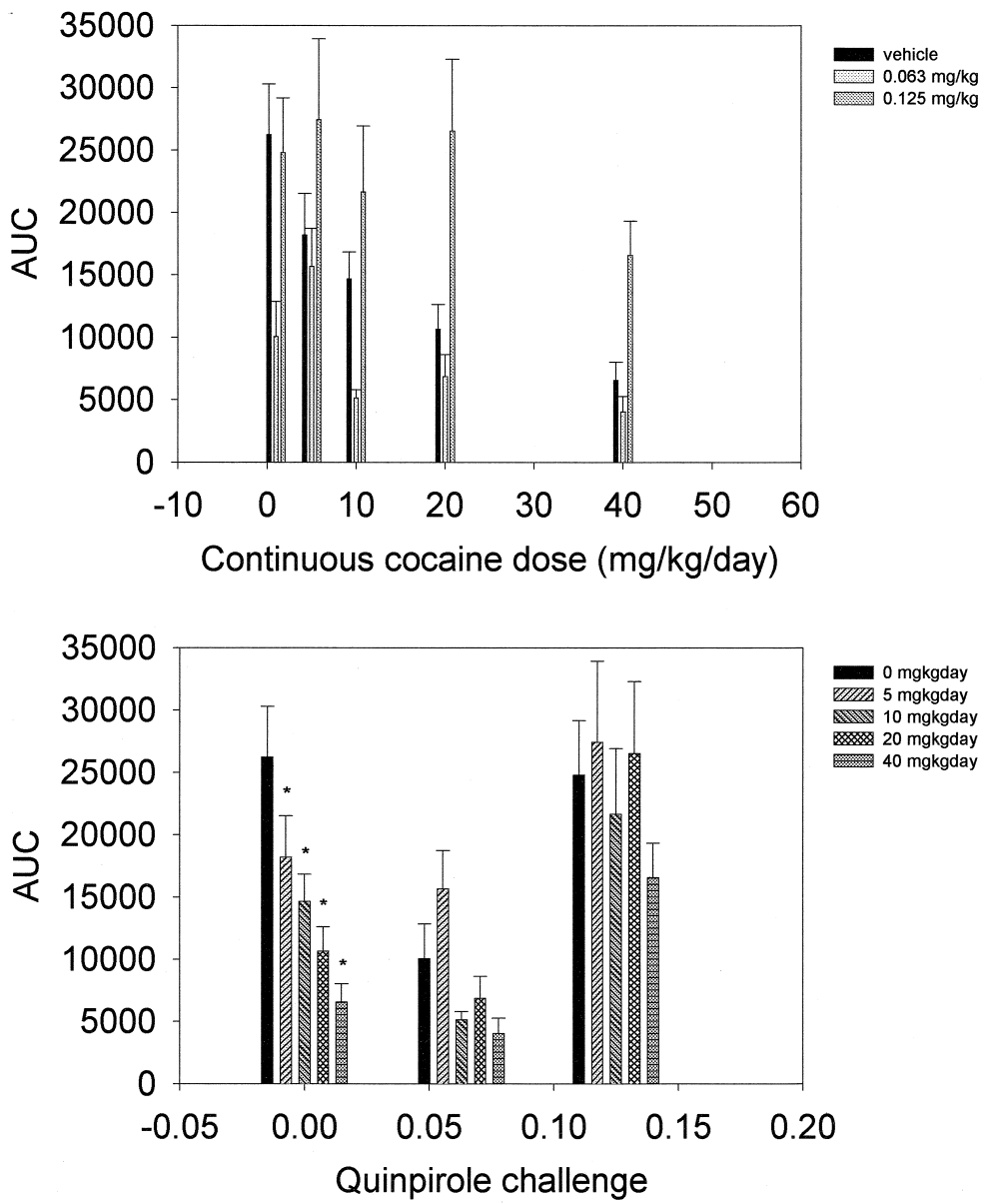

Fig. 3. Mean AUCs for each quinpirole plus 15.0 mg/kg cocaine challenge dose as a function of continuous cocaine dose administered during the pretreatment regimen. In the top panel, the black bars represent the vehicle challenge. The light gray bars represent the 0.063 mg/kg quinpirole challenge. The dark gray bars represent the 0.125 mg/kg quinpirole challenge. In the bottom panel, the black bars represent the saline control group. The light gray, diagonally hatched bars represent the 5.0 mg/kg/day cocaine group. The dark gray, diagonally hatched bars represent the 10.0 mg/kg/day group. The light gray, cross-hatched bars represent the 20.0 mg/kg/day group, and the dark gray, horizontally hatched bars represent the 40.0 mg/kg/day group. The bars represent one S.E.M.

3.2. Effects of continuous cocaine dose on the induction of behavioral tolerance

The top panel of Fig. 1 presents the mean AUC for each continuous cocaine group as a function of cocaine challenge dose. The bottom panel of Fig. 1 presents the mean AUC for each cocaine challenge as a function of continuous cocaine dose administered during the pretreatment regimen.

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, two-way ANOVA was conducted on the AUCs. The two factors were pretreatment group and cocaine challenge dose. The results of the ANOVA were significant [pretreatment group: $F(4.217) = 5.11$; cocaine dose: $F(2.217) = 65.03$; pretreatment group $\times$ cocaine dose: $F(8.217) = 2.93$]. The results of the post-hoc Tukey's comparisons on the data from the ANOVA in Fig. 1 indicate that there were no significant differences between the pretreatment groups for the vehicle and 7.5 mg/kg cocaine challenges. However, for the 15.0 mg/kg cocaine challenge, all cocaine pretreatment groups are significantly different from the control group, and that the 5.0 and 40.0 mg/kg/day cocaine groups are significantly different.

The results in Fig. 1 also suggest that for most pretreatment groups, there was a dose response to the cocaine challenges. In other words, the subjects tended to show increasing behavioral responses to increasing doses of the cocaine challenge. The results of post-hoc Tukey's comparisons indicate that for the control and 5.0 mg/kg/day cocaine groups, the behavioral response to the 15.0 mg/kg cocaine challenge is significantly higher than the behavioral response to both the vehicle and 7.5 mg/kg cocaine challenges. For the 10.0, 20.0 and 40.0 mg/kg/day groups, the behavioral response to the 15.0 mg/kg cocaine challenge is significantly greater than the behavioral response to the vehicle challenge.

3.3. Effects of quinpirole on basal activity

Similar to Fig. 1, the top panel of Fig. 2 presents the mean AUC for each continuous cocaine group as a function of quinpirole challenge dose. The bottom panel of Fig. 2 presents the mean AUC for each quinpirole challenge as a function of continuous cocaine dose administered during the pretreatment regimen.

An examination of the data in Fig. 2 suggests that increasing quinpirole doses increased the variance of the data. Thus, for statistical purposes, the data were logarithmically transformed to normalize the variance. To determine whether there were significant differences between the pretreatment groups in the behavioral response quinpirole, a two-way ANOVA was conducted on the AUCs for the ambulation data. The two factors were pretreatment group and quinpirole challenge dose. The results of the ANOVA indicated that the main effect of was quinpirole dose [$F(2.172) = 6.65$] and the pretreatment group $\times$ quinpirole dose interaction [$F(2.172) = 2.08$] were significant. The main effect of pretreatment group was not significant. The results of post-hoc Tukey's comparisons indicate that for the 5.0, 10.0 and 20.0 mg/kg/day groups, the behavioral response to the 0.063 mg/kg challenge dose is significantly less than the behavioral response to the vehicle challenge. Post-hoc Tukey's comparisons also

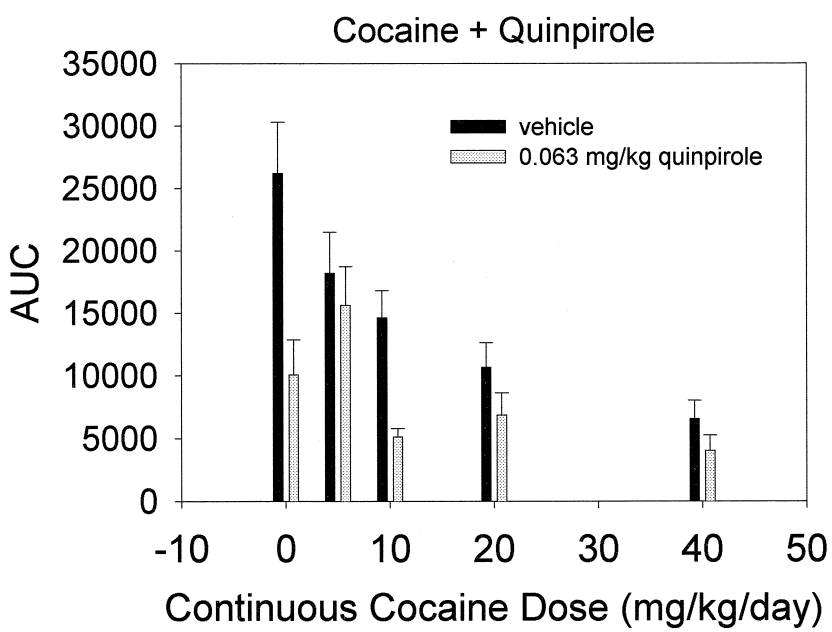

Fig. 4. Mean AUC for each group as a function of continuous cocaine dose for the vehicle and 0.063 mg/kg quinpirole challenges. The black bars represent the vehicle challenge, while the gray bars represent the 0.063 mg/kg quinpirole challenge. The bars represent one S.E.M.

indicated that, for the 0.063 mg/kg quinpirole challenge, the behavioral response to the quinpirole challenge was significantly different from the control group.

3.4. Effects of quinpirole on cocaine-induced hyperactivity

Similar to Figs. 1 and 2, The top panel of Fig. 3 presents the mean AUC for each continuous cocaine group as a function of quinpirole challenge dose administered 5 min before the 15.0 mg/kg cocaine challenge. The bottom panel of Fig. 3 presents the mean AUC for each quinpirole challenge as a function of continuous cocaine dose administered during the pretreatment regimen.

To determine whether there were differences between the pretreatment groups in the effects of quinpirole on cocaine-induced hyperactivity, a two-way ANOVA was conducted on the AUCs. The results of the ANOVA indicated that the main effects of pretreatment group [$F(4.179) = 4.35$] and quinpirole dose [$F(2.179) = 17.83$] were significant. However, the interaction was not significant [$F(8.179) = 1.14$]. The results of post-hoc Tukey's comparisons from the ANOVA, indicate that the 40.0 mg/kg/day cocaine group is significantly different from both the control and 5.0 mg/kg/day groups. Furthermore, all the quinpirole challenge doses are significantly different from each other.

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. To highlight this point, Fig. 4 presents the mean AUC for each continuous cocaine group as a function of continuous cocaine dose for the vehicle and 0.063 mg/kg quinpirole challenge.

As can be seen in Fig. 4, 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 indicate that the induction of behavioral tolerance by continuous cocaine administration is dose-dependent. In other words, increasing doses of continuous cocaine 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 not seem to depend on the continuous cocaine dose.

4.1. Time course of tolerance and changes in dopamine autoreceptor sensitivity

The current experiments evaluated the dose-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 not on day 14 of withdrawal from continuous cocaine administration (King et al., 1999). 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 autoreceptor supersensitivity 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).

This last result has some implications for an analysis of cocaine tolerance. First, this pattern of results suggests that the mechanisms mediating tolerance may be different at different withdrawal times. In other words, there may be time-dependent changes in the mechanisms mediating cocaine tolerance. Second, the pattern of results also indicates that the development of autoreceptor supersensitivity is not necessarily a generalized response to cocaine withdrawal. If this were the case, then one would expect that dopamine autoreceptors would be supersensitive on day 1 of withdrawal, but they are not.

4.2. Continuous cocaine dose and tolerance

The results of the experiment 1 indicate that all continuous cocaine doses induced tolerance, but only to the 15.0 mg/kg cocaine challenge. In other words, behavioral tolerance was not found to the 7.5 mg/kg cocaine challenge. Furthermore, the 5.0 mg/kg/day cocaine induced significantly less tolerance than 40.0 mg/kg/day cocaine. This pattern of results has several implications. First, given that tolerance was only manifested to the highest cocaine challenge dose suggests that the mechanism(s) mediating tolerance is apparent when dopaminergic systems are being driven. In other words, the mechanisms mediating tolerance do not seem to affect basal behavioral levels but, once an increased demand is put on the system (e.g., following a cocaine challenge), dopaminergic systems will no longer be able to compensate.

This result is consistent with dopamine autoreceptor control of cocaine-induced hyperactivity, and the develop-

ment of dopamine autoreceptor supersensitivity. Activation of dopamine autoreceptors, by high levels of synaptic dopamine, results in an inhibition of dopamine release. It is possible that the 7.5 mg/kg cocaine challenge did not produce sufficient synaptic dopamine levels to stimulate dopamine autoreceptors, which would have the effect of inhibiting cocaine-induced hyperactivity. In contrast, the 15.0 mg/kg cocaine challenge seems to result in dopamine autoreceptor activation, with an unmasking of dopamine autoreceptor supersensitivity, because the cocaine-pretreated subjects exhibited significantly less behavioral activation than the saline control subjects.

5.0 mg/mg/day cocaine induced significantly less tolerance than 40.0 mg/kg/day cocaine, suggesting that the induction of tolerance may occur in at least two stages. This pattern indicates that low cocaine doses may induce only a modest degree of tolerance, while higher doses induce tolerance that is more substantial.

4.3. Effects of quinpirole on basal and cocaine-induced behavior

Experiments 2 and 3 used low doses of quinpirole to probe for changes in dopamine autoreceptor function following different doses of continuous cocaine administration. Changes in dopamine autoreceptor function have been implicated in mediating the tolerance induced by continuous cocaine and amphetamine administration (Lee and Ellinwood, 1989; Lee et al., 1988; Zhang et al., 1992; King et al., 1994b; Jones et al., 1996). For example, King et al. (1994b) reported that rats pretreated with 40 mg/kg/day cocaine, were behaviorally supersensitive to the inhibitory effects of autoreceptor selective doses of apomorphine. 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 current results are consistent with this previous research. The results of experiment 2 suggested that dopamine autoreceptor supersensitivity developed in all cocaine pretreatment groups, except for the 40 mg/kg/day cocaine group. The data presented in Fig. 2 indicated that low dose significantly inhibited behavior in the cocaine-pretreated rats, but did not inhibit behavior in either the control or 40.0 mg/kg/day cocaine groups. This pattern of results indicates that continuous cocaine administration induces dopamine autoreceptor supersensitivity. However, the results do not indicate that different continuous cocaine doses induce differential degrees of dopamine autoreceptor supersensitivity.

The failure to find an effect of quinpirole on basal activity in the 40.0 mg/kg/day cocaine subjects may be due to the generally low levels of activity in these subjects. Although there were no significant differences in basal activity across the pretreatment groups, the subjects in the 40.0 mg/kg/day group tended to exhibit markedly less basal activity than the subjects in the other groups. Such lowered activity levels may be indicative of dopamine autoreceptor supersensitivity, and a 'shut-down' dopaminergic system. If such is the case, then these subjects may be at, or near, a floor effect. Under these circumstances, quinpirole would not be expected to have an inhibitory effect in these subjects.

The results of experiment 3 also suggest that continuous cocaine administration induces dopamine autoreceptor supersensitivity. Although quinpirole inhibited cocaine-induced hyperactivity in all 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. This result may be the result of the 15.0 mg/kg cocaine challenge producing levels of synaptic dopamine such that dopamine autoreceptors are maximally (or near maximally) stimulated. Under such conditions, quinpirole would not be expected to induce further inhibition of behavior. Perhaps if the quinpirole challenges had been given with 7.5 mg/kg cocaine challenges, evidence of dopamine autoreceptor supersensitivity would have been found.

In spite of such considerations, the data from experiment 3 do not indicate that different continuous cocaine doses induce differential changes in dopamine autoreceptor function. Inspection of the results in Fig. 3 indicate that the maximum effect of the low dose of quinpirole is obtained in the 10 mg/kg/day cocaine subjects. Thus, in both the 20 and 40 mg/kg/day cocaine subjects, there is no apparent further effect of the low dose of quinpirole on cocaine-induced hyperactivity. Indeed, following the quinpirole challenges, all pretreatment groups exhibited similar levels of activity, suggesting that this may be the 'floor' for the quinpirole cocaine combinations. Under these circumstances, quinpirole would not be expected to have an enhanced inhibitory effect in these subjects.

5. Summary

The current results indicate that different continuous cocaine doses induce differential degrees of tolerance, and that this tolerance is associated with the development of dopamine autoreceptor supersensitivity. However, different continuous cocaine doses did not induce differential degrees of dopamine autoreceptor supersensitivity.

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