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The effects of continuous cocaine dose, treatment, and withdrawal duration on the induction of behavioral tolerance and dopamine autoreceptor function

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Abstract

The present experiment evaluated the interactions between continuous cocaine dose, duration of administration, and duration of withdrawal on the induction of behavioral tolerance and changes in dopamine autoreceptor (DA) function. In the current experiments, rats were exposed to a pretreatment regimen involving the continuous administration of 0, 5, or 20 mg/kg/day cocaine for either 3 or 7 days. All subjects were then withdrawn from the pretreatment regimen for 1 or 7 days. For the experiments examining behavioral tolerance, the subjects received 15.0 mg/kg ip cocaine. For the experiments examining alterations in DA function, the subjects received a 0.063 mg/kg ip quinpirole injection, followed 5 min later by a 15.0 mg/kg ip cocaine injection. For all experiments, the subjects were placed in activity monitors, and ambulation was measured for 60 min. The results indicated that all continuous cocaine durations induced significant changes in cocaine-induced behavior at the 1-day withdrawal period. However, for tolerance to be exhibited on the 7-day withdrawal period, either high-dose or long-duration continuous cocaine had to be administered. This tolerance was associated with an increase in DA sensitivity. However, the change in DAs was dose- or duration-dependently related to tolerance. Overall, the literature suggests that behavioral tolerance following continuous cocaine administration may be mediated by multiple, time-dependent mechanisms that operate in an all-or-none manner.

Keywords: Continuous cocaine; Behavioral tolerance; Dopamine autoreceptors; Cocaine duration; Cocaine dose; Withdrawal duration; Rats

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, where behavioral tolerance is typically exhibited as a decrease in cocaine-induced locomotion, and tolerance to the neurochemical effects is exhibited as a reduction in cocaine-induced dopamine autoreceptor (DA) release (Chen and Reith, 1993; King et al., 1992, 1993, 1994a,b, 1995, 1997; Reith et al., 1987). Most of this research utilized high-dose and/or long-duration administration regimens in an attempt to model chronic cocaine abuse. In spite of the substantial literature indicating that tolerance to many of the effects of cocaine can develop following continuous administration, the parameters that induce tolerance have been systematically explored only recently.

The literature regarding the parameters of continuous cocaine administration that effect tolerance indicates that the magnitude of tolerance induced by a 14-day pretreatment regimen appears to be dose-dependent (King et al., 1999a). In contrast, the magnitude of tolerance is independent of pretreatment duration (3, 7, or 14 days) when high continuous cocaine doses are used (40 mg/kg/day; King et al., 2002). Lastly, the magnitude of tolerance induced by 14 days of 40 mg/kg/day continuous cocaine is present on Days 1 and 7 of withdrawal but dissipated by Day 14 of withdrawal from the pretreatment regimen (King et al., 1999b).

The data also indicate that the tolerance induced by continuous cocaine administration is associated with several indices of DA supersensitivity. Zhang et al. (1992) found that

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dopamine neurons in the substantia nigra compacta from rats that had received continuous cocaine were supersensitive to the inhibitory effects of apomorphine on cell firing rates on Days 1 and 7, but not on Day 14, of withdrawal from continuous cocaine administration. 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 DAs were supersensitive to the inhibitory effects of quinpirole. The behavioral literature suggests that the induction of this supersensitivity is not dose-dependent (King et al., 1999a) but is duration-dependent (King et al., 2002).

The previous research examined the effects of dose, treatment, and withdrawal duration in isolation. However, no studies have examined how the induction of tolerance and DA supersensitivity are jointly determined by the interactions between dose, treatment duration, and withdrawal duration. The central question is whether significant tolerance can be induced by a short-duration, high-dose exposure; and, if so, is this tolerance of the same magnitude and duration as that produced by a long-duration, low-dose exposure?

In all experiments, the subjects were exposed to a pretreatment regimen involving the continuous administration of 0, 5, or 20 mg/kg/day cocaine for 3 or 7 days. The subjects were then withdrawn from this regimen for 1 or 7 days. The subjects were then challenged with 15.0 mg/kg ip cocaine to evaluate the issue of tolerance or 0.063 mg/kg quinpirole, followed 5 min later by 15.0 mg/kg cocaine to evaluate the issue of changes in DA supersensitivity.

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, lights on at 7:00 a.m.) for 1 week. They were maintained on free food and water and were housed singly. Terminal weights ranged from 275–325 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 50 mg/ml cocaine HCl, 2.5 ml of 12.5 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, or 20 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- or 7-day period. On Day 1 of treatment, animals were implanted with 2ML2 Alzet minipumps continuously infusing cocaine at an average rate of 0, 5, or 20 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 an identical procedure.

2.5. Locomotor testing

On Day 1 or 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 transporter 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 30–45 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 were 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 and along the vertical surfaces of the chambers. For all experiments, the rats received a 15.0 mg/kg ip injection of cocaine and were then placed back into the activity chambers. In some experiments, 5 min prior to the cocaine challenge, some subjects received a 0.063 mg/kg ip quinpirole injection to probe for changes in the functional properties of DAs. Locomotor activity was recorded for 60 min.

2.6. Data analysis

The primary dependent measures for the current experiments are horizontal and vertical activity counts. The current experiment is a mixed model design. Specifically, there were three group factors [Pretreatment Dose (0, 5, or 20 mg/kg/day), Pretreatment Duration (3 or 7 days), and Withdrawal Duration (1 or 7 days)], which produce 12 separate groups (3 Cocaine Pretreatment Doses × 2 Pretreatment Durations × 2 Withdrawal Durations), 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.

Previous research (King et al., 1999a,b) indicated that tolerance to the behavioral effects of a cocaine challenge is 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 (AUCs) over the entire 60-min session by PeakFit (Jandel) for statistical purposes. The data were then analyzed by standard three-way analyses of variance (ANOVAs). Significant differences were analyzed by post hoc Tukey's tests. The significance level was set at $P \leq .05$ for all comparisons.

3. Results

3.1. Cocaine-induced locomotor behavior

Fig. 1 presents mean cocaine-induced horizontal activity as a function of time, for each pretreatment dose, separately for each treatment and withdrawal duration.

Fig. 2 presents the mean cocaine-induced horizontal activity on the data transformed to AUCs. The results of the three-way ANOVAs indicate that the main effects of Dose [$F(2,108) = 10.17$], Treatment Duration [$F(1,108) = 12.98$], and Withdrawal Duration [$F(1,108) = 3.94$] are significant, as was the Cocaine Dose × Withdrawal Duration interaction [$F(2,108) = 3.14$]. The results of post hoc Tukey's tests indicate that for the 5 mg/kg/day subjects, the 3- and 7-day treatment durations (collapsed across withdrawal duration, inasmuch as the three-way interaction was not significant) are significantly different. The Tukey's tests also indicate that, for the 1-day withdrawal period, the 5 and 20 mg/kg/day groups are significantly different from the saline control subjects; while for the 7-day withdrawal period, only the 20 mg/kg/day group is significantly different from the saline control group.

3.2. Effects of quinpirole on cocaine-induced locomotor behavior

Fig. 3 presents mean horizontal activity, induced by the Quinpirole plus cocaine challenge, as a function of time, for each pretreatment dose, separately for each treatment and withdrawal duration.

Fig. 4 presents mean quinpirole + cocaine-induced horizontal activity on the data transformed to AUCs. The results of the three-way ANOVAs indicate that the main effects of Dose [$F(2,108) = 16.77$], Treatment Duration [$F(1,108) =$

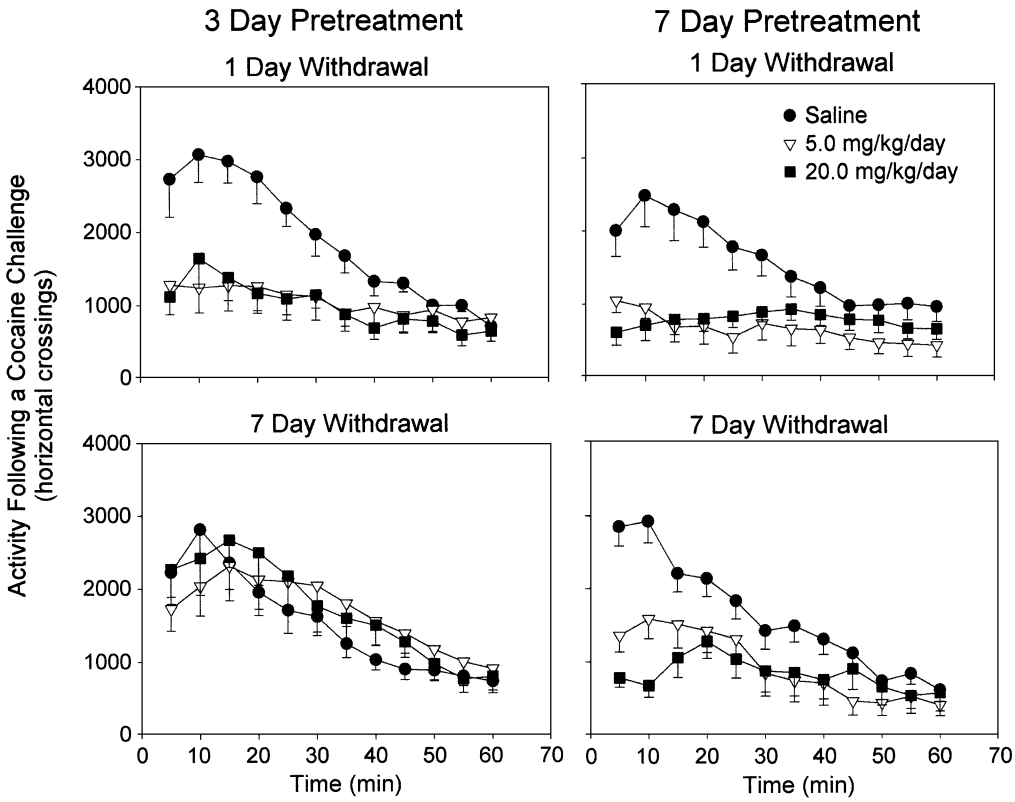

Fig. 1. Mean cocaine-induced horizontal activity as a function of time, for each pretreatment dose, separately for each treatment and withdrawal duration. The filled circles represent the saline control subjects. The open inverted triangles represent the 5.0 mg/kg/day cocaine subjects. The filled squares represent the 20.0 mg/kg/day cocaine subjects. The bars represent 1 S.E. of the mean. The data were collected in 5-min bins. Time 0 is immediately after the cocaine challenge.

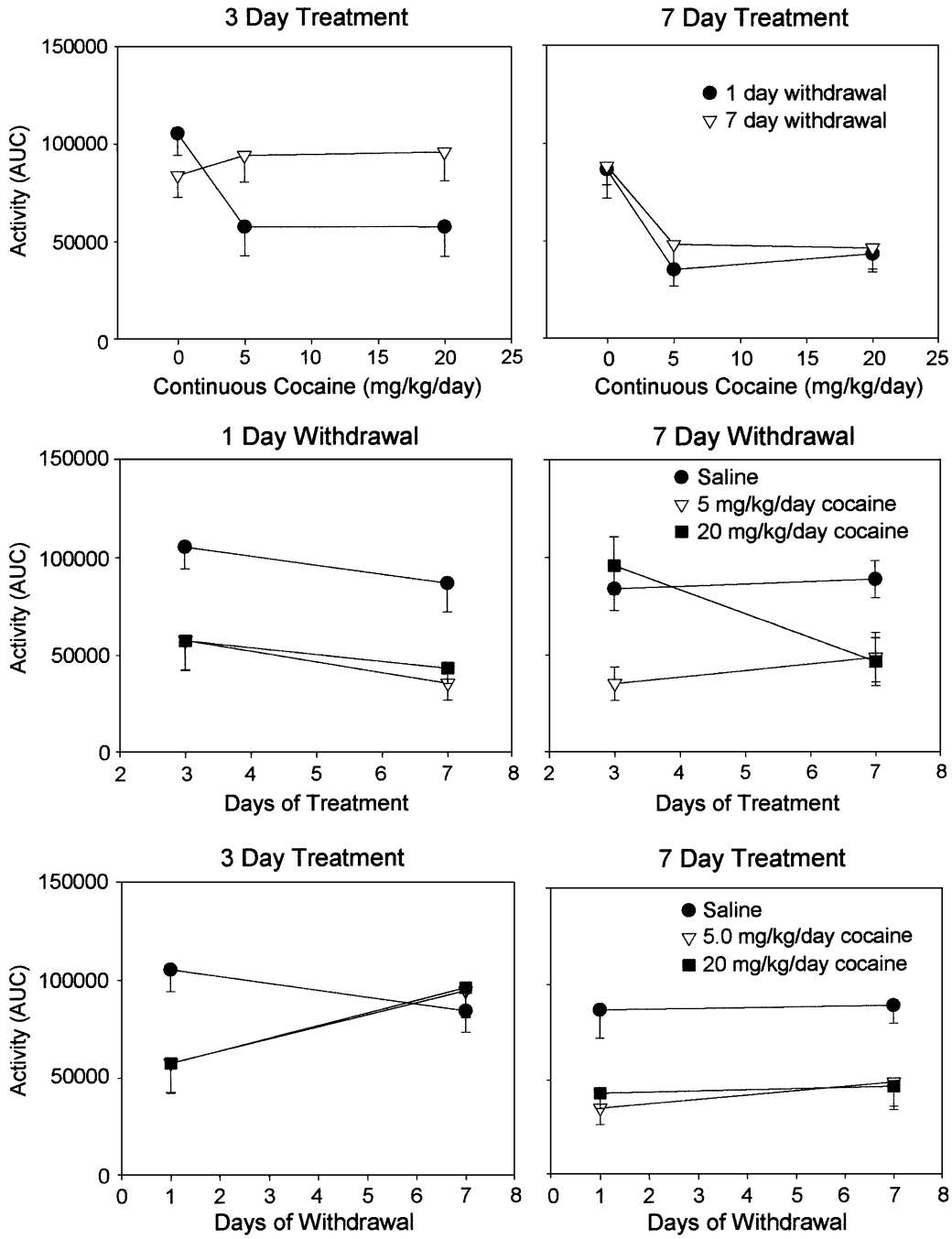

Fig. 2. Mean cocaine-induced horizontal, for each pretreatment dose, separately for each treatment and withdrawal duration. These data are the areas under the curve (AUC) and are the data on which the statistical analyses were conducted. The filled circles represent the saline control subjects. The open inverted triangles represent the 5.0 mg/kg/day cocaine subjects. The filled squares represent the 20.0 mg/kg/day cocaine subjects. The bars represent 1 S.E. of the mean.

9.25], and Withdrawal Duration [$F(1,108) = 4.21$] are significant. No other effect was significant.

4. Discussion

The results suggest that the effects of continuous cocaine dose on locomotor behavior are modulated by the treatment and withdrawal durations. The results indicate that high-dose or long-duration continuous cocaine administration induces tolerance to the behavioral effects of a cocaine challenge. In addition, this tolerance seems to be associated with changes in DA sensitivity. However, the magnitude of change in DA supersensitivity does not seem to be related to continuous cocaine dose, treatment duration, or withdrawal duration.

The present results, as well as our previous research, suggest that the effects of cocaine dose on the induction of tolerance is modulated by the treatment and withdrawal

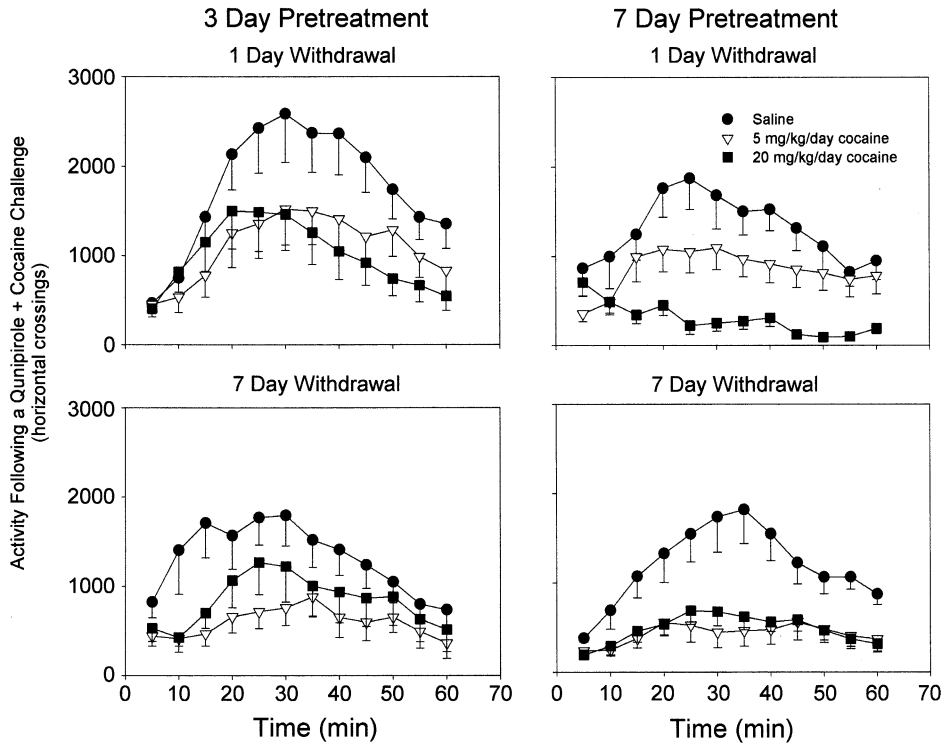

Fig. 3. Mean horizontal activity, induced by the quinpirole plus cocaine challenge, for each pretreatment dose, separately for each treatment and withdrawal duration. The filled circles represent the saline control subjects. The open inverted triangles represent the 5.0 mg/kg/day cocaine subjects. The filled squares represent the 20.0 mg/kg/day cocaine subjects. The bars represent 1 S.E. of the mean. The data were collected in 5-min bins. Time 0 is immediately after the cocaine challenge, which was 5 min after the quinpirole challenge.

durations: 7 days of continuous cocaine administration, regardless of dose-induced behavioral tolerance to a cocaine challenge on Days 1 and 7 of withdrawal. In addition, the values for the magnitude of tolerance on Days 1 and 7 of withdrawal were roughly equivalent for both continuous cocaine doses. This pattern of results is consistent with our previous research (King et al., 2002) indicating that tolerance, assessed on Day 7 of withdrawal, is present following 7 days of continuous cocaine (40 mg/kg/day). However, the fact that tolerance was roughly equivalent for the 5 and 20 mg/kg/day subjects is not consistent with our previous research (King et al., 1999a,b) showing that the induction of tolerance is dose-dependent following 14 days of exposure. However, it is possible that long-duration exposure has greater effects.

In contrast, the results for the 3-day treatment duration are more complicated. Both the 5 and 20 mg/kg/day subjects showed tolerance on Day 1 of withdrawal but not on Day 7 of withdrawal. This pattern would suggest that longer durations are necessary to produce persistent tolerance. However, the results of King et al. (2002) indicate that 3 days of continuous 40-mg/kg/day cocaine induces tolerance on Day 7 of withdrawal. This pattern would suggest that longer durations are necessary to produce persistent tolerance. However, the results of King et al. (2002) indicate that 3 days of continuous 40 mg/kg/day cocaine induces tolerance on Day 7 of withdrawal. This result would indicate that very high dose, short-term exposure to cocaine can induce tolerance but that low-dose, short-duration exposure is not sufficient to induce tolerance. These results are consistent with the work of Ahmed and Koob (1998, 1999) who found that increasing the duration of the cocaine self-administration was stable and consistent. However, when the duration was increased to 6 h, drug intake increased over sessions, there was an increase in drug loading, and an upward shift in the hedonic set point for cocaine, all presumably due to the development of tolerance.

The pattern of results suggests that the casual intermittent user may not develop sufficient tolerance after short-term usage (e.g., one night at a party) to trigger a binge pattern of consumption. However, either protracted low-dose use or high-dose, short-term use could induce tolerance sufficient to induce a binge pattern of use.

4.1. Mechanisms of tolerance

4.1.1. The role of dopamine autoreceptors

The current methods used low doses of quinpirole to probe for changes in DA function following different durations of continuous cocaine administration.

The results presented in Figs. 3 and 4 are consistent with DA control of cocaine-induced hyperactivity and the development of DA supersensitivity. Activation of DAs, by higher-than-normal levels of synaptic dopamine, results in an inhibition of dopamine release in the terminal areas such as

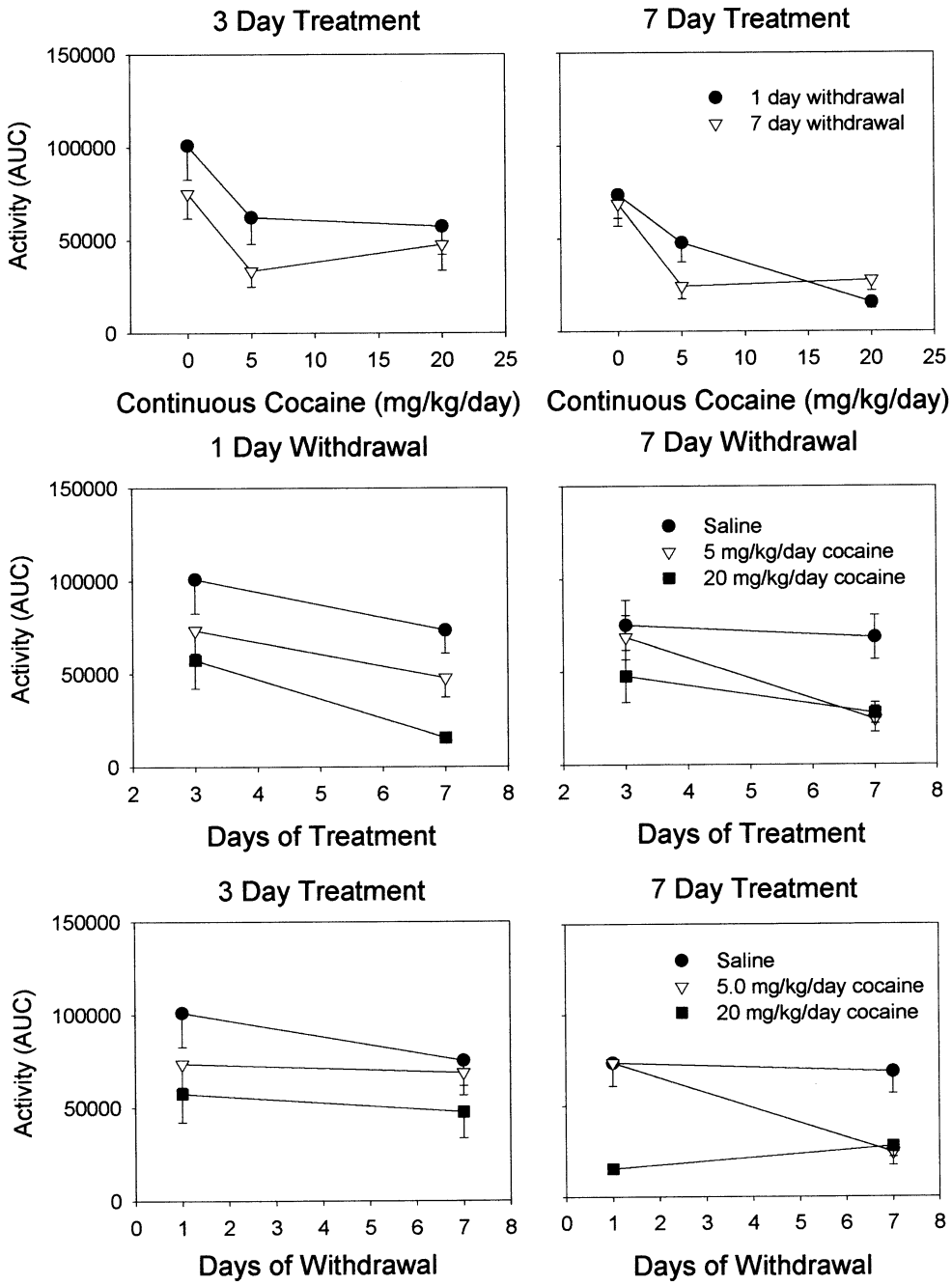

Fig. 4. Mean quinpirole + cocaine-induced horizontal, for each pretreatment dose, separately for each treatment and withdrawal duration. These data are the areas under the curve (AUC) and are the data on which the statistical analyses were conducted. The filled circles represent the saline control subjects. The open inverted triangles represent the 5.0 mg/kg/day cocaine subjects. The filled squares represent the 20.0 mg/kg/day cocaine subjects. The bars represent 1 S.E. of the mean.

the nucleus accumbens or caudate, while activation of soma-dendritic DA autoreceptors in the ventral tegmental area or substantia nigra would inhibit dopamine neuronal firing rates. The overall pattern of results presented in Figs. 3 and 4 tentatively suggest that DA supersensitivity developed in the cocaine-pretreated subjects, which is consistent with previous research (e.g., King et al., 1999a,b). In the cocaine-pretreated subjects, the quinpirole challenge dose generally inhibited locomotor activity for both continuous doses and durations at both withdrawal periods. However, this effect was not duration- or dose-dependent, in that all doses and durations seemed to produce roughly equivalent changes in DA function. Indeed, the lack of any dose- or duration-dependent effects on DAs indicates that this mechanism alone cannot account for tolerance. Lastly, the results for the 3-day treatment, 7-day withdrawal condition presented in

Figs. 3 and 4 indicate that DA supersensitivity developed in the absence of tolerance, suggesting that there may be a dissociation between tolerance and changes in autoreceptor function.

4.2. Synthesis of results

The overall pattern of results from the studies conducted in our laboratory suggests that there are multiple convergent drug use histories that can produce tolerance to the behavioral effects of cocaine, as well as multiple mechanisms mediating tolerance.

4.2.1. Drug-use history

One possible history is lower dose consumption over an extended period of time. This route may model the casual, recreational user who uses during the weekend for a long time. On the other hand, another possible drug consumption history is high-dose use for a short period of time. This might model an individual who "parties hard" over an evening or weekend, consuming a large amount of cocaine during this period. In either case, both individuals would be expected to develop tolerance to the effects of cocaine. The development of tolerance may lead to the initiation of binge cocaine use and, thus, the development of an abuse pattern of consumption (Gold, 1992).

The results also indicate that the magnitude of tolerance and the development of DA supersensitivity were largely dose- and duration-independent but did depend on the withdrawal period. If DA supersensitivity were 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, time-dependent mechanisms determine tolerance to the behavioral effects of cocaine.

4.2.2. Other mechanisms

Other researches indicate that a down-regulation of 5-HT_3 receptors represents another mechanism of the tolerance induced by continuous cocaine administration (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), while 5-HT_3 antagonists will 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.

Another possible mechanism mediating the development of tolerance is changes in the dopamine transporter (DAT). For example, Hitri et al. (1994) reported that continuous cocaine administration for 14 days increased WIN 35,420, but not RTI 55, binding in the caudate. On the other hand, Kunko et al. (1997) reported that WIN 35,428 binding was unchanged in any brain or withdrawal time following continuous cocaine administration (50 mg/kg/day for 7 days). Letchworth et al. (2001) also reported dose-dependent changes in the DAT following chronic self-administration in primates. These results are similar to those found in postmortem tissue samples taken from human cocaine abusers. Little et al. (1993, 1995) reported significantly increased B_{max} for WIN 35,428 in both the caudate and nucleus accumbens. Recent research indicates that chronic cocaine can increase DAT V_{max} and cell surface expression (Daws et al., 2002; Little et al., 2002). Lastly, we have found that continuous cocaine induction increases the B_{max} of the DAT in the VTA and substantia nigra SN in a duration-independent, but dose-dependent, manner (unpublished data). This pattern of results is consistent with the behavioral results indicating that the magnitude of tolerance induced by continuous cocaine administration is independent of the pretreatment duration (King et al., 2002) but does depend on the dose (King et al., 1999a,b).

Overall, the effect of supersensitive somadendritic DAs and increased numbers of DATs in these regions, coupled with down-regulated 5-HT_3 receptors, would produce a dopaminergic system that was largely inhibited, in terms of both firing rate and dopamine release. This combination would result in the behavioral tolerance found following continuous cocaine administration. The pattern of changes in the DA, DAT, and 5-HT_3 induced by different doses and durations of continuous cocaine are generally consistent with the behavioral tolerance exhibited by subjects following the same pretreatment regimens.

In summary, the current results indicate that, over the durations, doses, and withdrawal periods tested, behavioral tolerance was determined by an interaction between the dose, duration, and withdrawal period. In other words, low-dose, long-duration and high-dose, short-duration administration regimens induced tolerance to the behavioral effects of a subsequent cocaine challenge. This tolerance is associated with the development of DA supersensitivity.

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References

Ahmed SH, Koob GF. Transition from moderate to excessive drug intake: change in hedonic set point. Science 1998;282:298–300.

Ahmed SH, Koob GF. Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology 1999; 146:303–12.

Chen N.-H., Reith MEA. Dopamine and serotonin release regulation autor-

eceptor sensitivity in A_9/A_{10} cell body and terminal areas after withdrawal of rats from continuous infusion of cocaine. J Pharmacol Exp Ther 1993;287:1445–53.

Chen J, van Praag HM, Gardner EL. Activation of 5-HT_3 receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res 1991;543:354–7.

Chen J, Paredes W, van Praag HM, Lowinson JH, Gardner EL. Presynaptic dopamine release is enhanced by 5-HT_3 receptor activation in medial prefrontal cortex of freely moving rats. Sypnase 1992;10:264–6.

Daws LC, Callaghan PD, Moron JA, Kahlig KM, Shippenberg TX, Bavitch JA, et al. Cocaine increases dopamine uptake and cell surface expression of dopamine transporters. Biochem Biophys Res Commun 2002;290:1545–50.

Gao W.-Y., Lee TH, King GR, Ellinwood EH. Alterations in baseline activity and quinpirole sensitivity in putative dopamine neurons in the substantia nigra and ventral tegmental area after withdrawal from cocaine pretreatment. Neuropsychopharmacology 1998;18:222–32.

Gold MS. Cocaine (and crack): clinical aspects. In: Lowinson JH, Ruiz P, Millman RB, editors. Substance abuse: a comprehensive textbook. Baltimore: Williams and Wilkins; 1992. p. 205–21.

Hagan RM, Jones BJ, Jordan CC, Tyers MB. Effect of 5-HT_3 receptor antagonists on responses to selective activation of mesolimbic dopaminergic pathways. Br J Pharmacol 1990;99:227–32.

Hitri A, Casanova MF, Kleinman JE, Wyat RJ. Fewer dopamine transporter receptors in the prefrontal cortex of cocaine users. Am J Psychiatr 1994; 151:1074–6.

Jiang LH, Ashby CR, Kasser RJ, Wang RY. The effect of intraventricular administration of the 5-HT_3 agonist 2-methylserotonin on the release of dopamine in the nucleus accumbens: an in vivo chronocoulometric study. Brain Res 1990;513:156–60.

Jones SR, Lee TH, Whitman RM, Ellinwood EH. Effects of intermittent and continuous cocaine administration on dopamine release and reuptake in the striatum: in vitro voltammetric assesstment. Phychoparmacol 1996;126:331–8.

Joyner C, King G, Lee TH, Ellinwood EH. A technique for the continuous infusion of high doses of cocaine by osmotic minipump. Pharmacol Biochem Behav 1993;44:971–3.

King GR, Joyner C, Lee T, Kuhn C, Ellinwood EH. Intermittent and continuous cocaine administration: residual behavioral states during withdrawal. Pharmacol Biochem Behav 1992;43:243–8.

King GR, Kuhn C, Ellinwood EH. Dopamine efflux during withdrawal from continuous or intermittent cocaine. Psychopharmacology 1993; 111:179–84.

King GR, Joyner C, Ellinwood EH. 5-HT_3 receptor modulation of behavior during withdrawal from continuous or intermittent cocaine. Pharmacol Biochem Behav 1994a;47:399–407.

King GR, Ellinwood EH, Silvia C, Joyner CM, Xue Z, Caron M, et al. Withdrawal from continuous or intermittent cocaine: changes in D2 receptor function. J Pharmacol Exp Ther 1994b;269:743–9.

King GR, Xue Z, Calvi C, Ellinwood EH. 5-HT_3 agonist-induced dopamine overflow during withdrawal from continuous or intermittent cocaine administration. Psychopharmacology 1995;117:458–65.

King GR, Xiong Z, Ellinwood EH. Blockade of cocaine sensitization and tolerance by the co-administration of ondansetron, a 5-HT_3 receptor antagonist, and cocaine. Psychopharmacology 1997;130:159–65.

King GR, Xiong Z, Ellinwood Jr. EH. Withdrawal from continuous cocaine administration: time dependent changes in accumbens 5-HT_3 receptor function and behavioral tolerance. Psychopharmacology 1999a;142: 352–9.

King GR, Xiong Z, Douglas S, Ellinwood EH. The effects of continuous cocaine dose on the induction of behavioral tolerance and dopamine autoreceptor function. Eur J Pharmacol 1999b;376:207–15.

King GR, Pinto G, Konen J, Hillburn C, Tran S, Love W, et al. The effects of continuous cocaine duration on the induction of behavioral tolerance and dopamine autoreceptor function. Eur J Pharmacol 2002;446: 111–8.

Kunko PM, Loeloff RJ, Izenwasser S. Chronic administration of the selective dopamine uptake inhibitor GBR 12,909, but not cocaine, produces marked decreases in dopamine transporter density. Naunyn-Schmiedeberg's Arch Pharmacol 1997;356:562–9.

Letchworth SR, Smith HR, Vinsant SL, Moore RJ, Friedman DP, Nader MA, et al. Cocaine self-administration in rhesus monkeys: progression of changes in dopamine transporter binding site density. J Neurosci 2001;21:2799–807.

Little KY, Kirkman JA, Carrol FI, Clark TB, Duncan GE. Cocaine use increases [^{3}H] WIN 35,428 binding sites in human striatum. Brain Res 1993;628:117–25.

Little KY, Carroll RI, Bader BJ. Characterization and localization of [^{125}I]RTI-121 binding sites in human striatum and medial temporal lobe. J Pharmacol Exp Ther 1995;274:1473–83.

Little KY, Elmer LW, Zhong H, Zhang L. Cocaine induction of dopamine transporter trafficking to the plasma membrane. Mol Pharmacol 2002; 61:436–45.

Matell M, King GR. 5-HT_3 agonist induced DA release in the nucleus accumbens during withdrawal from continuous cocaine administration. Psychopharmacology 1997;130:242–8.

Reith MEA. 5-HT_3 receptor antagonists attenuate cocaine-induced locomotion in rats. Eur J Pharmacol 1990;186:327–30.

Reith MEA, Benuck M, Lajtha A. Cocaine disposition in the brain after continuous or intermittent treatment and locomotor stimulation in mice. J Pharmacol Exp Ther 1987;243:281–7.

Svingos AL, Hitzemann R. 5-HT_3 receptor antagonists block cocaine-induced locomotion via a PCPA-sensitive mechanism. Pharmacol Biochem Behav 1992;43:871–9.

Tricklebank MD, Singh L, Loes RJ, Preston C, Iverson SD. The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. Eur J Pharmacol 1989; 167:127–35.

Zhang H, Lee TH, Ellinwood EH. The progressive changes of neuronal activities of the nigral dopaminergic neurons upon withdrawal from continuous infusion of cocaine. Brain Res 1992;594:315–8.