Intravenous cocaine induced-activity and behavioural sensitization in norepinephrine-, but not dopamine-transporter knockout mice

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Abstract

Previously, it was reported that both norepinephrine transporter (NET) and dopamine transporter (DAT) knockout (KO) mice were sensitive to the reinforcing effects of cocaine. However, assessing the locomotor-stimulant effects of cocaine in these subjects has proven difficult due to significant differences in their baseline activity compared to wild-type controls. The present studies were designed to clarify the role of NET and DAT in the stimulant effects of acute and repeated cocaine utilizing these knockout mice, and thereby assess the role of these substrates in the locomotor stimulant effects of cocaine. Mice were habituated to the test environment for sufficient time to ensure equal baselines at the time of cocaine administration. Mice then received cocaine (3–25 mg/kg) intravenously according to a within-session cumulative dose–response design. Cocaine dosing was repeated at 48-h intervals for four sessions to assess behavioural sensitization. NET-KO mice exhibited a reduced response to acute cocaine administration compared to wild-type (WT) controls. However, comparable sensitization developed in NET-KO and WT mice. The DAT-KO and DAT-heterozygote (HT) mice displayed no locomotor activation following either acute or repeated cocaine administration. These data suggest a role for the NET in the acute response to cocaine, but no involvement in sensitization to cocaine. In contrast, DAT appears to be necessary for both the acute locomotor response to cocaine and the subsequent development of sensitization. In addition to existing data concerning the reinforcing effects of cocaine in DAT-KO mice, these data suggest a dissociation between the reinforcing and locomotor stimulant effects of cocaine.

Introduction

The generation of mice lacking either the norepinephrine transporter (NET) or the dopamine transporter (DAT) has provided an additional tool in attempts to understand the role of these neurotransmitters in drug-induced or maintained behaviours. Initial studies of these knockout (KO) mice have provided surprising, and in some cases conflicting data. For example, Rocha et al. (1998a) reported that DAT-KO mice would self-administer cocaine intravenously, despite the fact that the DAT was considered to be the primary site for the reinforcing effects of cocaine. Further, Sora et al. (1998) demonstrated that cocaine established a conditioned place preference in DAT-KO mice. While these studies do not rule out the possibility that the DAT is a critical substrate for the reinforcing effects of cocaine in humans, they do suggest that other substrates may also be sufficient for these behavioural effects related to the abuse liability of cocaine. Furthermore, Carboni et al. (2001) reported that both cocaine and amphetamine increase extracellular levels of dopamine (DA) in the nucleus accumbens (NAcc) of DAT-KO mice. In the absence of DAT, this effect was attributed to the ability of cocaine and amphetamine to prevent dopamine (DA) uptake via the NET.

Studies of psychostimulant-induced activity in DAT-KO mice have provided conflicting results. Giros et al. (1996) and Sora et al. (1998) reported that cocaine and amphetamine had no effect on activity levels in the DAT-KO mouse, while Gainetdinov et al. (1999) and Spielewoy et al. (2001) demonstrated that cocaine and amphetamine suppressed activity in these mutants. However, interpretation of these results is complicated due to the basal hyperactivity of DAT-KO mice, as the effects of stimulants were studied from different baseline levels of activity; a variable that is known to influence the effects of stimulants on locomotor activity (Dews & Wenger, 1977; Robbins, 1977).

Presently, very little data exists concerning the response of NET-KO mice to psychostimulant administration. With the discovery that the actions of cocaine in the DAT-KO mouse may be due to its ability to prevent DA uptake via NET (Carboni et al., 2001), the NET-KO mouse has the potential to provide valuable insights into the actions of cocaine. Xu et al. (2000) examined the effects of cocaine and amphetamine in the NET-KO, and found that these mice showed a
greater locomotor stimulation and conditioned place preference induced by cocaine. Furthermore, repeated cocaine administration only resulted in sensitization to the stimulant effects of cocaine in wild-type (WT) mice, leading Xu and colleagues to conclude that the NET-KO mouse was presensitized to cocaine. These findings suggest a potentially important role for the NET in psychostimulant drug actions.

The purpose of the present study was to investigate the stimulant effects of repeated cocaine administration in both DAT- and NET-KO mice using intravenous (i.v.) drug administration. Adequate habituation prior to drug administration and administration of cocaine via a chronically indwelling i.v. catheter allowed baseline levels of activity to be normalized prior to drug administration, and minimized the effects on activity of handling and injection procedures.

### Materials and methods

#### Subjects

Experiment 1 was performed with NET-WT (*n* = 9) and homozygous NET-KO (*n* = 12) male mice, originally generated at Howard Hughes Medical Institute Laboratories, Durham, NC (Wang et al., 1999). Experiment 2 was performed with DAT-WT (*n* = 8), DAT-HT (*n* = 4) and DAT-KO (*n* = 6) male mice (Cord et al., 2002). All mice were obtained from heterozygous breeding pairs, and genotypes of offspring were confirmed using PCR. Upon arrival into the animal colony, all mice were housed individually and allowed a minimum of 14 days habituation prior to any experimental testing. Mice were housed under a 12-h light : 12-h dark schedule, with lights on at 07.00 h. Throughout the course of the experiment, mice had *ad libitum* access to standard laboratory chow and water (including test-sessions for experiment 2), in a temperature (70 ± 5°F) and humidity (50 ± 15%) controlled room. Testing for experiment 1 took place during the light-phase between 08.00 h and 16.00 h. Testing for experiment 2 occurred during the dark-phase between 18.00 h and 07.00 h. Mice were transferred to the separate testing room approximately 30 min prior to test sessions. All experiments were conducted in strict accordance with the Principles for Care and Use of Laboratory Animals provided by the NIH, and received prior approval from the local Animal Care and Use Committee.

#### Drugs

Ketamine-xylazine anaesthesia (65 mg/kg ketamine and 18 mg/kg xylazine diluted in 0.9% saline) was administered intraperitoneally (i.p.) at a volume of 13 mL/kg. Cocaine hydrochloride was dissolved in 0.9% saline for a final concentration of 2.3–4.5 mg/mL (100 mg/kg/mL). Weibull

#### Apparatus

Four activity monitors (Digiscan system, AccuScan instruments Inc., Ohio, USA) were divided into quadrants by two perpendicular Plexiglas divisions crossing the mid-point of the monitor. This resulted in four testing regions (20 cm × 20 cm × 31 cm) per monitor, of which only two were used concurrently for activity monitoring. Floors and walls were made of smooth clear Plexiglas. Sixteen regularly spaced photocells (eight along each axis) located 2 cm above the floor detected horizontal movements (total distance travelled). Each monitor was enclosed in a sound and light-attenuating chamber, and was connected to a PC running Digipro software (AccuScan instruments Inc. Ohio, USA) for data acquisition.

For i.v. infusions, a multisyringe Harvard Pump 22 (Harvard Apparatus, MA, USA) was connected to the same PC, and controlled using a program written in Q-Basic software. Syringes were connected to single-channel fluid swivels (Instech Laboratories Inc., Plymouth Meeting, PA, USA) via Tygon tubing (0.06-inch o.d.; Tygon Microbore Tubing, Norton Performance Plastics, Akron, OH, USA). The swivel was mounted on a counterbalanced arm (Instech Laboratories Inc., Plymouth Meeting, PA, USA), and a Tygon line exited the swivel and entered the testing region of the activity

#### Table 1. Infusion summary for cocaine sessions

<table>
<thead>
<tr>
<th>Time into session (min)</th>
<th>Infusion rate (µL/min)</th>
<th>Actual cocaine dose (mg/kg)</th>
<th>Cumulative cocaine dose (mg/kg)</th>
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</thead>
<tbody>
<tr>
<td>Experiment 1 (NET)</td>
<td>Experiment 2 (DAT)</td>
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<tr>
<td>60</td>
<td>720</td>
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<td>105</td>
<td>765</td>
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<td>10</td>
</tr>
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### Behavioural Testing

The general methods have been described previously (Mead et al., 2002). Mice were placed into the activity monitors for six sessions. Sessions 1–3 occurred on consecutive days (days 1–3), while sessions 4–6 were performed at 2-day intervals (on days 5, 7 and 9). During the first 60 min (Experiment 1) or 720 min (Experiment 2) of each session, no infusions were administered (habituation phase). At 60, 75, 90 and 105 min (Experiment 1) or at 720, 735, 750 and 765 min (Experiment 2), mice received i.v. infusions of either saline or cocaine. During sessions 1 (novel), and 2 (saline), mice received saline infusions, while during sessions 3–6, mice received cocaine infusions in an ascending cumulative dose sequence. All infusions occurred over 60 s and the rate of infusion was varied to control the dose. For cocaine sessions, doses of 3, 5, 7 and 10 mg/kg cocaine were administered. Therefore, the maximum cumulative dose reached at each infusion time was 3, 8, 15 and 25 mg/kg cocaine, respectively. Table 1 provides a summary of the infusion details.

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Statistical analysis
The dependent variable measured was total distance travelled, and all data were square root transformed prior to analysis in order to produce homogeneity of variance and allow parametric analysis. Responses to novelty were analysed using two-way mixed factor ANOVA with genotype and time as factors. Data for analysis of the novelty response was taken from the first hour of session 1. For analysis of dose–response functions following acute administration of cocaine, data from the 15-minute period following each infusion was pooled, with data from the saline session (session 2) being compared to data from the first cocaine session (session 3). Dose–response data were analysed using three-way ANOVA with dose (3, 8, 15 or 25 mg/kg or saline control infusions) and drug (saline or cocaine) as within-subjects factors, and genotype as a between subjects factor. Data from repeated cocaine treatments were analysed using two-way repeated measures ANOVA with dose and session (cocaine sessions 1–4) as factors. Significant main-effects of session were further investigated using one-way repeated measures ANOVA followed by post hoc comparisons of each session with cocaine session 1 (Dunnett’s test).

Results
Response to novelty
Experiment 1 revealed that NET-KO mice displayed a reduced activity response compared to WT controls when placed into a novel environment. This difference was apparent over the first hour of exposure to the novel environment in Session 1 (Fig. 1A) as indicated by a significant difference between genotypes ($t_{1,20} = 2.175$, $P < 0.05$). In Experiment 2, DAT KO mice showed significantly greater levels of activity than both WT and DAT-HT mice when placed into a novel environment (main-effect of genotype, $F_{2,15} = 5.14$, $P < 0.05$; Student Newman–Keuls, $P < 0.05$; Fig. 1C). This increased response was apparent for approximately 10–12 h, suggesting a reduced rate of habituation, rather than an enhanced response to novelty, and it was because of this prolonged hyperactivity that infusions were not administered until 12 h after placement in the apparatus during Experiment 2. During the twelfth hour, there were no significant differences in activity between genotypes (mean total distance traveled $\pm$ SEM: WT $321.3 \pm 106.6$; HT $369.5 \pm 252.4$; KO $328.0 \pm 243.5$, One-way ANOVA, $F_{2,17} = 0.017$, $P = 0.98$).

Response to acute cocaine administration
In Experiment 1, the first session of cocaine infusions (session 3) produced a dose-dependent increase in total distance travelled in WT and NET-KO mice (dose by drug interaction, $F_{3,57} = 21.93$, $P < 0.01$; Fig. 2A). However, the magnitude of this effect differed between genotypes, with the response in NET-KO mice being lower than that seen in WT mice (drug by genotype interaction, $F_{1,19} = 4.80$, $P < 0.05$). Post hoc analysis revealed that the activity response was significantly greater in WT mice at a dose of 8 mg/kg cocaine ($P < 0.05$). This difference was also
apparent at doses of 15 and 25 mg/kg cocaine, but failed to reach statistical significance (compare filled and open circles in Fig. 2A). There were no significant differences between genotypes following saline infusions.

In Experiment 2, cocaine produced a dose-dependent increase in activity compared to saline infusions in WT mice, although this effect was not observed in DAT-HT or DAT-KO mice (dose by genotype interaction, \( F_{5,51} = 3.81, P < 0.01 \); drug by genotype interaction, \( F_{2,17} = 10.44, P < 0.01 \); Fig. 2B). While cocaine produced a significant enhancement in activity in WT mice at doses of 8–25 mg/kg, no enhancement in activity was seen at any dose of cocaine in DAT-HT or DAT-KO mice, when compared to saline infusions. Although this difference between genotypes only reached significance at the 25 mg/kg dose of cocaine \((P < 0.05)\), it was also apparent at the 15 mg/kg dose (compare filled and open circles in Fig. 2B). There were no significant between-genotype differences in activity following any of the saline infusions.

**Response to repeated cocaine administration**

In Experiment 1, repeated cocaine administration produced a progressive increase in activity, indicative of behavioural sensitization (Fig. 3A–B). This increase was observed in both NET-WT and -KO mice (main-effect of session; \( F_{3,57} = 18.07, P < 0.01 \)), and the effect was similar between genotypes (main-effect of genotype; \( F_{1,19} = 0.15, n.s. \)). In WT mice, a significant enhancement in activity compared to cocaine session 1 was observed at doses of 3–15 mg/kg (session by dose interaction; \( F_{9,72} = 2.24, P < 0.05 \)). In NET-KO mice, sensitization occurred at all doses (main effect of session; \( F_{3,33} = 13.48, P < 0.01 \), session by dose interaction; \( F_{9,99} = 1.45, n.s. \)). The lack of sensitization at the 25 mg/kg cocaine dose in WT may have been due to a ceiling effect, suggesting that this dose produced an activity response close to maximum acutely, and further increases could not be observed (Fig. 3A).

In Experiment 2, repeated cocaine administration only produced sensitization in WT mice (main-effect of session, \( F_{3,21} = 11.86, P < 0.01 \); dose by session interaction, \( F_{9,63} = 2.49, P < 0.05 \)). This increase across sessions was observed at doses of 3–15 mg/kg \((P < 0.05)\) (Fig. 3C). In DAT-HT and -KO mice, there was no significant effect of session \((F_{3,9} = 2.55; F_{3,15} = 1.03, respectively)\) or session by dose interaction \((F_{9,27} = 0.93; F_{9,45} = 0.43, respectively)\), indicating that repeated cocaine did not result in an enhancement in cocaine’s stimulant effects (Fig. 3D–E).

**Discussion**

The results of the present study showed that NET-KO mice displayed a decreased locomotor response to a novel environment, a decreased locomotor response to an acute administration of cocaine, but comparable behavioural sensitization compared to WT controls. In contrast, DAT-KO mice displayed a reduced rate of habituation to the novel environment. Cocaine administration had no effect on activity levels in DAT-KO or DAT-HT mice following either acute or repeated administration, although DAT-HT mice did not differ from WT controls in their response to novelty, or rate of habituation.

The observation that NET-KO mice displayed a reduced level of activity when placed in a novel environment is similar to that reported by Xu et al. (2000), who observed that NET-KO mice displayed lower levels of activity than WTs during the first 35 min of exposure to a novel environment. The observation that NET-KO mice displayed a reduced activity response following an acute cocaine administration was unexpected as Xu et al. (2000) reported that these mice showed an enhanced response to acute cocaine administration. It is unlikely that this difference is due to differences in the NET-KO’s since the two studies used mice from the same source. In addition, mice were bred according to the same strategy (i.e., heterozygous breeding pairs). One obvious difference between the two studies is the route of drug administration, with Xu and colleagues giving cocaine via the i.p. route. The route of drug administration may account for differences in results in a number of ways. One possibility concerns the kinetics of drug distribution and concentration. Following i.v. administration, one would expect a more rapid rise in drug levels and a higher peak drug concentration. However, no data exists on cocaine concentrations in the brain following systemic cocaine administration in NET-KO mice, so further testing is needed to examine this possibility. A second explanation is that NET-KO...
mice respond differently to the handling and injection procedure associated with i.p. drug administration. However, neither Xu et al. (2000) nor Bohn et al. (2000) observed such differences following vehicle injections. Despite this, the possibility remains that there is an interaction between the injection procedure and the effects of cocaine, such that stress only influences activity in the presence of the drug. In order to test this hypothesis, a full investigation into the physiological response to the injection procedure in NET-KO is needed. In support of this possibility is the known involvement of norepinephrine (NE) in the response to stressors, and in particular, the ability of the injection procedure to increase extracellular hypothalamic NE levels in rats (Pacak et al., 1995). In the context of the present study, these findings would suggest that the injection procedure would have a more pronounced effect in the NET-KO than in the WT, as clearance of NE would be reduced substantially in the absence of NET. Furthermore, systemic cocaine administration has been demonstrated to increase extracellular NE levels in the NAcc and ventral tegmental area of rats (Chen & Reith, 1994; Reith et al., 1997; Pepper et al., 2001). Therefore, the combination of injection procedure and cocaine-induced NE increases may explain the more pronounced activity in the NET-KO following i.p. cocaine, while in the present study, the absence of injection procedure-induced NE increases would have resulted in a lower NE response to cocaine.

Following repeated cocaine administration, both NET-KO and WT mice displayed a progressive increase in response to cocaine, indicative of behavioural sensitization. Again, this contrasts with previous findings, where NET-KO mice failed to show an increased locomotor response following repeated cocaine administrations (Xu et al., 2000). One explanation for this difference is that in the study by Xu and colleagues, the dose of cocaine chosen produced a response which may well have been at maximum following the first drug administration, and therefore further increases could not be observed. The dose of 20 mg/kg chosen by Xu et al. is at or near maximal effectiveness in several mouse strains (Rocha et al., 1998b; Chausmer & Katz, 2001). Such a ceiling effect would have obscured any evidence of behavioural sensitization, at least with the single dose studied. As we observed that NET-KO mice displayed sensitization similar to that observed in WT controls, it appears that the NET does not play a role in the development of sensitization to cocaine. However, the reduced response of NET-KO mice to an acute administration of cocaine suggests that the NET does have a role in mediating the acute effects of cocaine on activity.

The initial results from DAT-KO mice were comparable with previous reports using these mice, in that they are hyperactive when exposed to a novel environment, and habituate more slowly than controls (Gainetdinov et al., 1999; Giros et al., 1996; Sora et al., 1998). This hyperactivity has been attributed to hyperdopaminergic tone in the KO mouse. Interestingly, DAT-HT mice do not differ from WTs in their activity response to novelty despite a significant reduction in levels of DAT as assessed by [³H]CFT binding (Sora

![Fig. 3. Effects of repeated cocaine administration on activity in NET- and DAT-KO mice. Data show the mean square-root total cm travelled (± SEM) over a 15-min period following repeated administration of cocaine for NET- (A and B) and DAT- (C-E) KO mice, over four successive sessions. Doses of cocaine represent cumulative doses, with individual infusions of 3, 5, 7 and 10 mg/kg administered at 15-min intervals. Cocaine sessions occurred at 48-h intervals. Both NET-KO and WT mice displayed significant behavioural sensitization following repeated cocaine (A and B). In DAT-KO and DAT-HT mice, no sensitization occurred following four treatments. In WT mice, sensitization occurred at doses of 3–15 mg/kg *P < 0.05 compared to cocaine session 1 at respective dose (indicating significant behavioural sensitization). P < 0.05 compared to cocaine session 1 for all doses.](image-url)
et al., 1998) and reduced DA uptake in striatal synaptosomes (Giros et al., 1996).

Previous reports of the effects of psychostimulants on activity in DAT-KO mice have been complicated by this basal hyperactivity of the KO phenotype. As this hyperactivity is often of a similar magnitude to the hyperactivity seen in WT mice following stimulant administration, it is not clear whether the basal level of activity is masking any effects of drug in DAT-KO mice. However, by using i.v. administration of cocaine and providing an adequate habituation time period, this problem was averted in the present study. In order to ensure that activity levels across genotypes were comparable at time of drug administration, mice in this study were allowed 12 h habitation to the testing environment prior to the first drug administration. As the results of the saline infusions show, this period was sufficient to provide equal baselines across genotypes.

Results from the first cocaine session indicated that within the dose-range tested, cocaine stimulated activity in WT mice, but not in either the DAT-KO or DAT-HT mice. It is unlikely that the range of doses chosen was too low to observe a stimulant effect of cocaine in the DAT-KO or DAT-HT as pilot studies indicated that higher doses induced seizures in WT mice. While the results for DAT-KO mice are consistent with previous findings (Giros et al., 1996; Sora et al., 1998), the lack of effect in DAT-HT mice is surprising, as cocaine has previously been reported to increase activity in DAT-HT mice (Giros et al., 1996; Sora et al., 1998). One possibility is that the presence of stereotyped behaviours interfered with the expression of ambulatory behaviour in the present study, however, this is unlikely as no cocaine-induced activity was seen at the lower doses, at which stereotypy was unlikely to occur. Indeed, this discrepancy does not appear to be due to the dose of cocaine used, as we tested over a wide range of doses, and previous studies had utilized doses of 10 mg/kg (subcutaneous), and 40 mg/kg (i.p.). It is possible that the injection procedure may influence the response of the DAT-HT to cocaine administration. Although there are no reports of a saline injection increasing activity in the DAT-HT mice, reconciling the published results with the present ones suggests that the procedure associated with the injection is sufficient to enhance the stimulant effects of an otherwise inactive dose of cocaine.

The repeated administration of cocaine produced behavioural sensitization to the drugs stimulant effects in WT, but not in DAT-KO or DAT-HT mice. These results are consistent with the known role of DAT in mediating the stimulant effects of acute cocaine. The observation that DAT-HT mice displayed no cocaine-induced activity shows that even a reduction of approximately 50% in the level of DAT is sufficient to abolish the stimulant effects of cocaine. This finding is consistent with observations of in vivo displacement of the DAT ligand, WIN 35,428, and locomotor stimulation both produced by the cocaine analogue, RTI-31 (Cline et al., 1992). In that study, maximal stimulation of horizontal activity was obtained at a dose of RTI-31 that virtually displaced [(3)H]WIN 35 428 fully. Doses that produced less than half occupancy were not particularly effective in stimulating activity.

In light of recent findings showing that cocaine is still capable of producing increases in extracellular DA in the NAcc of DAT-KO mice by acting at NET (Carboni et al., 2001), the lack of stimulant effect observed in the DAT-KO and DAT-HT mice is maybe surprising, as stimulant-induced hyperactivity has often been associated with increased extracellular DA levels in the NAcc (Sharp et al., 1987; Kuczenski et al., 1991). However, there is also evidence suggesting that locomotor activity levels are not simply a reflection of NAcc DA concentrations. First, it has been reported that DA levels in the NAcc do not increase proportionately with behavioural activity ratings (Kuczenski et al., 1991; Hemby et al., 1995; Kimmel et al., 2001), suggesting that NAcc DA is not mediating the locomotor response per se. Second, while D1 antagonism with SCH-23390 in the NAcc prevented the reinforcing effects of cocaine (Baker et al., 1998), it had no effect on the locomotor stimulant effects of cocaine (Baker et al., 1998; Neisewander et al., 1998), suggesting that areas other than the NAcc mediate the locomotor response to cocaine. These observations are compatible with the findings that DAT-KO mice will self-administer cocaine (Rocha et al., 1998a) and display a conditioned place preference to cocaine (Sora et al., 1998), but do not display a locomotor response to cocaine. As there are differences in regional cocaine-induced extracellular DA levels between DAT-KO and WT mice (e.g., caudate putamen), further analysis of these differences may provide insight into the regions ultimately responsible for mediating the locomotor response to cocaine.

In summary, we observed that the stimulant effects of cocaine are reduced in the NET-KO mouse, while sensitization to cocaine remains unaltered. Therefore, while there appears to be a minor role of NET in the acute hyperactivity response to cocaine, the NET is not important in the development of sensitization to cocaine. In the DAT-KO and DAT-HT mice, cocaine does not induce hyperactivity following either acute or repeated administration. These results confirm that the normal levels of DAT are crucial for cocaine-induced hyperactivity and subsequent behavioural sensitization, and in light of recent findings, provide evidence for a dissociation between cocaine induced activity and reinforcing effects, at the level of the NAcc.

Acknowledgements

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Abbreviations

DA, dopamine; DAT, dopamine transporter; HT, heterozygote; KO, knockout; NAcc, nucleus accumbens; NE, norepinephrine; NET, norepinephrine transporter; WT, wild-type.

References


