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ORIGINAL INVESTIGATION

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Characterization of conditioned place preference to cocaine in congenic dopamine transporter knockout female mice

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Abstract *Rationale:* The dopamine transporter (DAT) is thought to play a major role in the rewarding effects of cocaine. Therefore, it is surprising that cocaine reveals conditioned effects in DAT knockout (DAT-KO) mice. *Objectives:* To examine these findings further, we obtained complete dose–effect curves for DAT-KO and DAT wild-type (DAT-WT) mice in a cocaine conditioned place preference (CPP) procedure. *Methods:* Congenic C57BL6 background female DAT-KO and DAT-WT mice were conditioned in a three-compartment place preference apparatus. Conditioning consisted of three 30-min sessions with cocaine (2.5, 5.0, 10.0, 20.0, or 40.0 mg/kg) and three 30-min sessions with saline. The distribution of time in each choice compartment was determined after each pair of conditioning sessions (one cocaine and one saline session). *Results:* DAT-WT mice revealed CPP over a wide range of cocaine doses (5.0–40 mg/kg), whereas DAT-KO mice revealed CPP over a more restricted range of doses, with consistent CPP only occurring with 10 mg/kg of cocaine. *Conclusions:* CPP for cocaine develops in both DAT-KO and DAT-WT mice; however, the dose range at which CPP develops is much more restricted in DAT-KO mice than in DAT-WT mice. These observations corroborate the significant role of DAT inhibition in cocaine's conditioned effects.

Keywords Cocaine · Dopamine · Knockout mice · Dopamine transporter · Conditioned place preference · Reward

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Introduction

Data from a broad range of pharmacological, biochemical, and genetic studies indicate that the dopaminergic system is involved in a number of the effects of cocaine. For example, several studies have shown that cocaine increases the concentration of extracellular dopamine (Di Chiara and Imperato 1988; He and Shippenberg 2000), and this effect is well correlated with cocaine's stimulatory effects (Ritz et al. 1987; Volkow et al. 1997). Specifically, the dopamine transporter (DAT) is thought to play a central role in cocaine's stimulatory effects and has also been closely linked with its rewarding/reinforcing effects (Kuhar 1998; Wise 1998).

One promising technique for investigating the role of the dopamine transporter in cocaine's effects is to examine mice in which the dopamine transporter protein has been inactivated, yielding dopamine transporter knockout mice (DAT-KO) (Giros et al. 1996). It has been shown that the duration of extracellular dopamine is dramatically prolonged in DAT-KO mice (Jones et al. 1998), and that these mice reveal marked increases in spontaneous locomotor activity (Gainetdinov and Caron 2003).

Investigations of the rewarding/reinforcing effects of cocaine in DAT-KO mice have led to a number of interesting findings. For example, Rocha et al. (1998) showed that mice lacking DAT, which exhibit high levels of extracellular dopamine, still self-administer cocaine in an intravenous self-administration paradigm. Nevertheless, the time it takes DAT-KO mice to acquire cocaine self-administration is longer than for dopamine transporter wild-type (DAT-WT) mice. DAT-KO mice were also shown to display a preference for cocaine in a conditioned place preference (CPP) procedure (Sora et al. 1998, 2001; Mateo et al. 2003). Although these studies indicate that cocaine still has rewarding or reinforcing effects in DAT-KO mice, the range of experimental conditions that have been examined are limited. For example, Sora et al. (1998) only examined two doses of cocaine in their study. Also, previous studies included mice of mixed background and used mixed groups of male and female mice. Clearly, a broader range of

conditions needs to be considered when advancing any conclusions about cocaine's effects in DAT-KO mice.

The conditioned place preference procedure provides a case in point. Indeed, whether a drug such as cocaine functions as a conditioned stimulus in this procedure has been shown to depend upon variables such as the duration of the conditioning sessions (Cunningham et al. 1999), the number of conditioning sessions (Laakso et al. 2002), the testing conditions (Bespalov et al. 1999), the housing conditions, and the dose of drug or route of administration (see Tzschentke 1998 and Bardo et al. 1995 for reviews of variables such as these).

Therefore, the current study was conducted to provide more complete dose–effect data regarding the effects of cocaine in DAT-KO versus DAT-WT mice within a conditioned place preference (CPP) procedure. The mice in this study were made congenic through multiple intercrossing to C57BL6 wild-type mice. Because of the availability of a large cohort of age-matched, female mice, but limited availability of male mice, only one sex was examined. Investigations of the development of CPP in female mice are very limited; however, it has been shown that female rats develop CPP to cocaine, and that their sensitivity is even higher compared to male rats (Russo et al. 2003). Also, female rats more readily acquire intravenous cocaine self-administration behavior than male controls (Lynch and Carroll 1999). In mice it has been shown that females develop greater locomotor sensitization to cocaine (Sershen et al. 1998).

Materials and methods

Animals and drugs DAT-KO mice were generated by disruption of the DAT gene through homologous recombination (Giros et al. 1996). DAT-WT and homozygous DAT-KO mice were derived from intercrosses of over 20 generations of heterozygous DAT-KO and C57BL6 mice. Altogether, 61 DAT-WT and 63 DAT-KO mice were used.

Subjects were age-matched, 3- to 5-month-old female siblings weighing between 18 and 30 g and genotype was determined by PCR analysis of DNA extracted from tail tip tissue. In all experiments, DAT-WT littermates served as controls for DAT-KO mice and all genotypes were simultaneously evaluated. Mice were provided food and water ad libitum. All mice were drug-naïve and a new group of mice was used for each dose tested. Experiments were conducted in accordance with the NIH guidelines for the care and use of animals and with an approved animal protocol from the Duke University Animal Care and Use Committee.

Cocaine hydrochloride was purchased from Sigma RBI (St. Louis, MO) and freshly prepared in saline. The following doses were tested: 2.5, 5.0, 10.0, 20.0, and 40.0 mg/kg body weight. Cocaine solution or saline was injected i.p. at a volume of 10 ml/kg body weight.

Apparatus Three-compartment commercially available place preference chambers for mice were used (model ENV-3013, Med Associates, St. Albans, VT). Each place preference chamber was put in a sound-attenuating cubicle, equipped with fan for ventilation and generation of white noise. The location of the mouse was determined by using photobeam strips, and the time spent in each of the three compartments was recorded. The chambers were controlled by an appropriate interface and the data were collected by a PC running a MED-PC IV software package (all from Med Associates, St. Albans, VT). The experiments were conducted in a designated mouse testing room in which no other activities took place during the test times.

Each of three distinct compartments could be separated by a manual guillotine door and each was illuminated with a light source of adjustable intensity. The central compartment was 7.2 cm long, 12.7 cm deep, and 12.7 cm wide, with gray walls and plastic floor. The two flanking choice compartments were 16.8 cm long, 12.7 cm deep, and 12.7 cm wide. One choice compartment was black with a stainless steel rod floor, and the other compartment was white with a stainless steel mesh floor. Each choice compartment also contained a removable, stainless steel waste pan, to which a small amount of corncob bedding was added. An intact "Orange Spice" Bigelow tea bag was included along with the corncob bedding in the waste pan under the grid floor of the black-walled choice compartment (Bohn et al. 2003). Preliminary experiments were performed, at which the stimulus conditions (light intensity and the addition of scent stimuli) were manipulated in order to obtain optimal pretest time distribution in wild-type C57BL6 mice. Under the stimulus conditions selected for these experiments, mice did not reveal a consistent preference for either of the two choice compartments.

Procedure The experimental session began with a pretest session in which the mice's initial preference for the two choice compartments was determined. This was followed by a series of conditioning and test sessions (Fig. 1). Experimental sessions were run every day and both conditioning and testing sessions lasted for 30 min.

Pretest During the pretest phase of the experiment, mice were placed into the central gray compartment and the guillotine doors were removed, so that both black and white choice compartments were accessible. Mice that met the following criteria continued with the experiment: (1) the time spent in the central compartment was less than in any of the choice compartments; (2) the time spent in either of the choice compartments was never less than 25% of the combined time spent in the choice compartments.

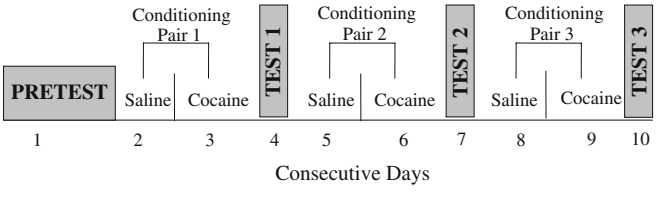

Fig. 1 Experimental procedure

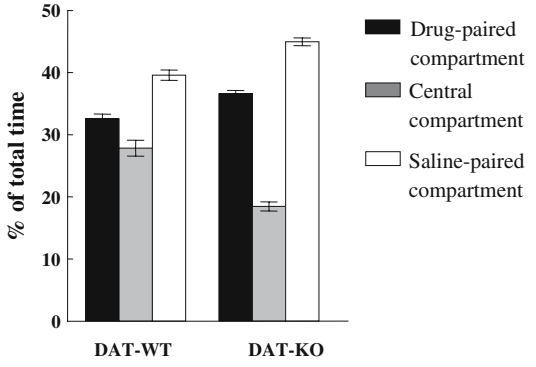

Fig. 2 Distribution of time spent in different compartments of CPP chambers during pretest. *Points* represent the mean (±SEM) of percentage of total time (1,800 s) spent in each compartment. n=38 (DAT-WT), n=41 (DAT-KO)

Conditioning Mice were treated with cocaine at the designated doses on days 3, 6, and 9, and saline on days 2, 5, and 8 of the experiment. After cocaine or saline administration, mice were confined to the compartment designated as cocaine-appropriate or saline-appropriate. Cocaine was always paired with the compartment that was less preferred during pretest. Testing occurred on the day following each set of conditioning sessions (one saline and one cocaine conditioning day).

Tests Mice were handled on the test day in the same manner as during the pretest and received no drug or saline administrations.

Statistical analyses Data were pooled over the 30-min test period for each mouse. CPP data were analyzed as a difference in time spent in the cocaine-paired compartment on test day versus pretest, calculated for each mouse. Data were analyzed using the SAS statistical software (v.6.11, SAS Institute, Cary, NC).

For inferential statistical analyses, a general linear model (GLM) procedure was utilized to correct for different sample sizes under various conditions. Degrees of freedom for a factor and corresponding error are shown for ANOVA analyses.

First, a three-factor global ANOVA with repeated measures was performed with the following factors: genotype, dose, and test (number). This was followed by a two-factor ANOVA for each of the three test sessions and two-factor ANOVA with repeated measures for each of the genotypes. When a significant effect for dose or dose × genotype was revealed, dose–response curves were derived for each test for each genotype, and a one-way ANOVA, followed by Duncan's post hoc test were utilized. When a significant effect for genotype or genotype × test was revealed, pairwise comparisons of genotypes were carried out.

Results

Only the mice that satisfied the criterion set during pretest were used in the experiment. The proportion of mice that satisfied the criterion did not differ between genotypes—41 out of 61 DAT-KO mice and 38 out of 63 DAT-WT mice (χ^2=0.64, df=1, n.s.). The percentages of mice that were conditioned in the black choice compartment also were not significantly different between genotypes—51% of DAT-KO and 57% of DAT-WT mice (χ^2=0.35, df=1, n.s.).

Interestingly, for those mice that met the criterion, the distribution of time spent in different compartments was different between genotypes (Fig. 2). The percentage of total time mice spent in the nonpreferred (cocaine-paired), central, or preferred (saline-paired) compartments differed significantly between genotypes (correspondingly to compartments: $F_{1, 77}$=18.39, p<0.01; $F_{1, 77}$=41.25, p<0.01; $F_{1, 77}$=26.56, p<0.01). DAT-KO mice spent less time in the central compartment than in the choice compartments, whereas the time in all three compartments was more evenly distributed in the DAT-WT mice.

Global ANOVA was performed on the CPP data (Fig. 3). In the pool of data analyzed, there was no significant effect for cocaine dose, genotype, or genotype × dose. There was, however, a progressive change in CPP over consecutive tests ($F_{2, 138}$=5.50, p<0.01) which depended on dose level (dose × test: $F_{8, 138}$=2.71, p<0.01) and genotype (genotype × test: $F_{2, 138}$=7.76, p<0.01). on data obtained in different tests or in different genotypes.

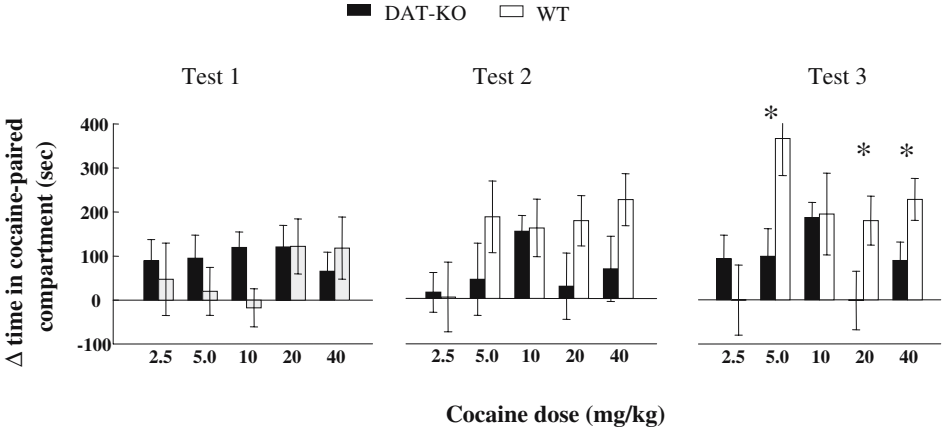

Fig. 3 Conditioned place preference to cocaine in DAT-KO and DAT-WT mice after one, two, or three conditioning pairs. Mice of both genotypes were conditioned with different doses of cocaine in cocaine-paired compartment. Test lasted 1,800 s. *Points* represent the mean (±SEM) of difference in time spent on cocaine-paired side between corresponding test and pretest. n=7–9 (DAT-WT and DAT-KO). *p<0.05 two-tailed Student's t test

Table 1 *F* and *p* values for two-way ANOVAs on conditioned place preference data

	Genotype	Dose	Genotype × Dose
Test 1	$F_{1,\ 69}$=1.23, n.s.	$F_{4,\ 69}$=0.53, n.s.	$F_{4,\ 69}$=0.78, n.s.
Test 2	$F_{1,\ 69}$=4.34, p<0.05	$F_{4,\ 69}$=1.57, n.s.	$F_{4,\ 69}$=0.77, n.s.
Test 3	$F_{1,\ 69}$=6.07, p<0.05	$F_{4,\ 69}$=2.83, p<0.05	$F_{4,\ 69}$=2.55, p<0.05
	Dose	Test	Dose × Test
DAT-KO	$F_{4,\ 36}$=0.90, n.s.	$F_{2,\ 72}$=1.23, n.s.	$F_{8,\ 72}$=1.02, n.s.
DAT-WT	$F_{4,\ 33}$=1.66, n.s.	$F_{2,\ 66}$=10.44, p<0.01	$F_{8,\ 66}$=2.82, p<0.01

Table 1 shows the results of the two-way ANOVA, examining CPP during three different test sessions. Test 1 took place following one pair of conditioning sessions, test 2 following two pairs, and test 3 following three pairs. As shown in Table 1, significant differences between genotypes were revealed during the second and third tests and after the third test, there also was a significant interaction between genotype and dose (Fig. 3) ($F_{4,\ 37}$=3.31, p<0.05) with DAT-WT mice conditioned with 5 mg/kg cocaine being different from the other groups (Duncan test, p<0.05). The dose–response relationship for DAT-KO mice also became evident at test 3 (Fig. 3); however, as with the data obtained after test 2, the dose–response curve for cocaine in the DAT-KO mice was biphasic, which accounts for the lack of significant effect of dose there. When pairwise comparisons were performed, it became evident that the 5.0-, 20-, and 40-mg/kg doses of cocaine revealed more pronounced CPP in DAT-WT than in DAT-KO mice. A separate analysis of the genotypes revealed a dose-dependent increase in CPP in DAT-WT mice that became more pronounced as the number of conditioning sessions increased. DAT-KO mice revealed only moderate CPP throughout the conditioning period.

Discussion

It was shown that a conditioned place preference (CPP) for cocaine developed across a greater range of doses in congenic female DAT-WT mice compared to DAT-KO mice. In general, DAT-KO mice only revealed a consistent CPP at 10.0 mg/kg of cocaine, whereas CPP was observed over a much broader range of doses in the DAT-WT mice (5.0–40 mg/kg). More limited, but parallel effects were reported in a CPP procedure that examined only two doses of cocaine, 5 and 10 mg/kg (Sora et al. 1998). In the Sora study, DAT-KO mice only developed a CPP at 10 mg/kg of cocaine, whereas DAT-WT mice developed a CPP at both 5 and 10 mg/kg of cocaine. In a recent CPP study, DAT-KO mice developed a preference for 20 mg/kg cocaine, but only one dose was tested (Mateo et al. 2003). In another study, which compared intravenous cocaine self-administration in DAT-WT and DAT-KO mice (Rocha et al. 1998), robust cocaine self-administration was observed in both genotypes and appeared to occur over a very similar range of doses. Nevertheless, differences between the genotypes were revealed in terms of the onset of cocaine self-administration with a longer period of time required for DAT-KO mice to initiate cocaine self-administration than for the DAT-WT mice.

A few aspects of the experimental procedure used here are noteworthy. First of all, a biased design was used in which cocaine administration was paired with the non-preferred side of the CPP apparatus. Although some CPP procedures are based on unbiased designs, there also are many CPP studies in which the biased design has been used successfully (Tzschentke 1998). Moreover, while it has been suggested that the biased design may not be appropriate for investigating certain types of compounds, such as anxiolytic compounds (Tzschentke 1998), this caution would not apply to investigations with cocaine. In the present study, the pattern of responding for DAT-WT and DAT-KO mice was somewhat different during the preconditioning phase of the experiment. Whereas DAT-WT distributed their time approximately equally in all three compartments of the place preference apparatus, DAT-KO mice spent significantly less time in the central compartment. This raises further questions about the use of an unbiased procedure in this situation, because the selection of criteria suiting both genotypes becomes complicated.

Another aspect of the experimental protocol that should be noted is the duration of the conditioning interval. It has been shown that DAT-KO mice require extremely long periods to adapt to new environments (Mead et al. 2002) and that habituation plays a major role in the development of CPP (Tzschentke 1998). Although it is possible that the duration of the conditioning interval was an important determinant of the relatively weak CPP observed in DAT-KO mice, it should be noted that CPP was shown to develop in DAT-KO mice with even shorter conditioning intervals (20 min in Sora et al. 1998).

It should be noted that the levels of locomotor activity measured in the CPP apparatus prior to cocaine administration (i.e., during the preconditioning phase of the experiment) did not reveal significant differences in the DAT-KO and DAT-WT mice (data not shown). This finding is in contrast to previous observations that DAT-KO mice are much more active than their wild-type controls (Giros et al. 1996; Sora et al. 1998; Gainetdinov et al. 1999; Spielewoy et al. 2000; Ralph et al. 2001; Mead et al. 2002), revealing pronounced spontaneous locomotor hyperactivity as well as resistance to habituation in novel environments. This discrepancy may be due a number of factors. First of all, the optic pairs used to measure activity in the current experimental apparatus were more sparsely distributed than in a standard locomotor activity apparatus, and second, the small

chambers of the apparatus did not provide a measure of vertical activity, the preferred type of activity of DAT-KO mice in a small chamber (unpublished observations). Therefore, it is possible that the apparatus used in the current experiments was simply not sensitive enough to reveal differences in locomotor activity and therefore these data were omitted.

Taken together, these results complement previous research related to the role of an intact dopaminergic system in cocaine's conditioned effects. Microdialysis studies in DAT-KO mice indicate that extracellular dopamine increases in the nucleus accumbens, but not in the striatum, in response to cocaine treatment (Carboni et al. 2001; Gainetdinov et al. 2002; Mateo et al. 2003), and it has been hypothesized that this increase is linked to cocaine-induced inhibition of the norepinephrine transporter in the nucleus accumbens (Carboni et al. 2001). The work of Budygin et al. (2002) challenges this hypothesis by showing that the rate of dopamine clearance in the nucleus accumbens of DAT-KO mice is unchanged after cocaine treatment. In behavioral experiments, Sora et al. (2001) showed that serotonin transporter/dopamine transporter double knockout mice do not display a place preference for 10 mg/kg cocaine. Also, DAT-KO mice develop a place preference for the serotonin reuptake inhibitor, fluoxetine, whereas DAT-WT mice do not develop a preference for fluoxetine (Mateo et al. 2003). Finally, the current view of mechanisms of cocaine reward in DAT-KO mice is based on serotonin transporter inhibition in the ventral tegmental area, in turn leading to elevations in dopamine levels in the nucleus accumbens (Mateo et al. 2003). Regardless of the mechanism, it is important to note that deletion of the dopamine transporter does not preclude cocaine-induced changes in accumbal dopamine levels.

Electrophysiological and voltammetry studies have shown that the activity of dopaminergic neurons and dopamine release correlate with stimulus conditions associated with food (Hollerman and Shultz 1998; Roitman et al. 2004), sex (Robinson et al. 2001), and cocaine reward (Phillips et al. 2003). Therefore, it was postulated that time-dependent dopamine release plays a role in learning processes, thus complying with a formal learning theory (Waelti et al. 2001). These experimental findings predict that animals with a severely upregulated dopaminergic system (i.e., DAT-KO mice) will show modified responses in behavioral tasks involving learning and memory processes, as was the case with the results reported in this work in a conditioned place preference procedure.

In summary, data from the current study suggest that CPP for cocaine does develop in congenic female DAT-KO mice; however, the dose range and test conditions for cocaine CPP are much more restricted in DAT-KO mice as compared to DAT-WT mice. Consistent CPP was only observed following 10 mg/kg of cocaine in DAT-KO mice and the apparent strength of this CPP did not increase with repeated conditioning sessions. In contrast, CPP developed following a range of cocaine doses in DAT-WT mice with greater CPP observed following multiple conditioning sessions. These finding complement previous results in DAT mice on a mixed background and extend these observations to female congenic mice. It is possible that the weaker cocaine CPP in the DAT-KO mice reflects a reduction in cocaine's rewarding/reinforcing effects in these mice.

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