Pharmacology Biochemistry and Behavior, Vol. 66, No. 3, pp. 631–635, 2000
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0091-3057/00/$–see front matter

PII S0091-3057(00)00262-8

Non Reciprocal Cross-Sensitization Between Cocaine and BTCP on Locomotor Activity in the Rat

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Received 22 September 1999; Revised 29 December 1999; Accepted 18 January 2000

MARTIN-FARDON, R., O. BEN-SHAHAR AND F. WEISS. *Non reciprocal cross-sensitization between cocaine and BTCP on locomotor activity in the rat.* PHARMACOL BIOCHEM BEHAV **66**(3) 631–635, 2000.—Measurement of locomotor sensitization was employed to characterize the effect of intermittent treatment with N-[1-(2-benzo[b]thiophenyl)cyclohexyl]piperidine (BTCP) and cocaine in the rat. Like cocaine, BTCP possesses high affinity for the dopamine transporter and inhibits dopamine reuptake. Although both drugs exhibit similar behavioral and neurochemical profiles with acute administration, there is tentative evidence to suggest that following chronic treatment BTCP does not induce neurochemical sensitization, and can attenuate cocaine-induced neurochemical sensitization in the striatum. Male Wistar rats were randomly divided into five groups after determining baseline locomotor activity. Three groups were treated with either saline (saline/saline), cocaine (20 mg/kg; cocaine/cocaine), or BTCP (10 mg/kg; BTCP/BTCP) for 10 days. The remaining two groups were treated with cocaine (20 mg/kg) or BTCP (10 mg/kg) for 3 days, followed by administration of BTCP (10 mg/kg; cocaine/BTCP) or cocaine (20 mg/kg; BTCP/cocaine) for 7 days. Locomotor sensitization was observed in all groups. However, although cross-sensitization on the day of substitution (day 4) was found in the BTCP/cocaine group, cross-sensitization was not observed in the cocaine/BTCP group. These results suggest that although the locomotor-activating effects of BTCP and cocaine are similar, the two drugs do not act identically, and different neural mechanisms may underlie BTCP and cocaine-induced sensitization. © 2000 Elsevier Science Inc.

BTCP Cocaine Locomotor activity Rats Sensitization

IT is widely accepted that the abuse liability of cocaine is related to its ability to increase dopamine neurotransmission by inhibiting the reuptake of dopamine (DA) (14,17,25,26, 42,43,44,53,54). With repeated intermittent administration, cocaine's stimulatory actions are amplified (9,10,50), a phenomenon known as behavioral sensitization or reverse tolerance (37,51). Cocaine-induced motor activity, and the development of sensitization to this effect are thought to be the result of changes in DA transmission in both the dorsal and ventral striatum (2,18,21,22).

N-[1-(2-benzo[b]thiophenyl)cyclohexyl]piperidine (BTCP) is a phencyclidine (PCP) derivative with low affinity for the PCP receptor and very high affinity for the dopamine transporter [DAT; (5,33,52)]. However, like cocaine, BTCP has a rapid onset of action (7), and its potency for inhibition of serotonin and norepinephrine transport is about the same as for inhibition of DA reuptake (23,27). There is much evidence that inhibition of DA reuptake accounts for the behavioral cocaine-like effects of BTCP (13,14,17,47). Thus, as a result of its high affinity (although at a different site than that of cocaine) for the DAT, both drugs exert similar behavioral and neurochemical effects (1,31,32,34). Like cocaine, BTCP potently inhibits DA uptake (5,52) and increases locomotor activity in mice (16,24) and rats (48). BTCP also substitutes for cocaine in drug discrimination studies (24), increases extracellular DA levels in the nucleus accumbens (29), and produces identical breaking points compared to cocaine on a progressive ratio schedule of reinforcement in rats previously trained to self-administer cocaine (12).

Despite the similarities between several of the behavioral and neurochemical effects of cocaine and BTCP, these agents also have been shown to produce differential effects after re-

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peated treatment. Chronic administration of cocaine but not BTCP results in locomotor sensitization in mice, although there is evidence of cross-sensitization between BTCP and cocaine (39). Moreover, unlike cocaine, repeated BTCP administration does not produce neurochemical sensitization on extracellular DA, and can attenuate cocaine-induced sensitization on extracellular DA in the striatum (30). Thus, although tentative in nature, these recent data suggest that BTCP may be able to alter cocaine sensitization, and thus be useful for the treatment of disorders related to sensitization of the mesolimbic DA systems such as drug craving (36,46) and psychostimulant-induced psychosis (11,38). In the view of these previous results, the present study sought to further characterize the effect of repeated intermittent BTCP treatment on locomotor activity in rats and to compare these effects to those of cocaine treatment. In addition, the ability of cocaine and BTCP to produce a full cross-sensitization in rats was examined, as well as the possibility that BTCP may alter cocaine-induced locomotor sensitization.

METHOD

Subjects

Male Wistar rats (Charles River, Kingston, NY, and The Scripps Research Institute, La Jolla, CA) weighing 250–300 g upon arrival were used. The animals were group housed (two to three per cage) with water and food available ad libitum in a humidity- and temperature-controlled vivarium on a 12 L:12 D cycle (lights off at 1800 h). The rats were habituated to vivarium conditions during 1 week, and were handled daily. All procedures were conducted in strict adherence to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Drugs

Cocaine hydrochloride (National Institutes of Health) was dissolved in physiological saline (0.9%, 1 ml/kg). BTCP (generously provided by Dr. Jean-Marc Kamenka, CNRS UPR 1086, France) was dissolved in physiological saline (0.9%, 1.6 ml/kg).

Apparatus

Locomotor activity was measured in 16 identical metal wire hanging cages each measuring 36 cm (L) × 25 cm (W) × 20 cm (H). Each cage contained two sets of infrared emitter-detector photocells positioned along the long axis 1 cm above the grid floor and 8 cm from the front and back of the cage. Movement within the cages produced photocell interruptions, which were automatically recorded by an IBM-compatible computer.

Procedure

Locomotor activity was tested in 10 consecutive daily sessions. The day before the first drug treatment (i.e., day 0), baseline locomotor activity of each animal was measured. Each session consisted of placing animals in the locomotor cages and monitoring their locomotor activity for 60 min. The following 10 sessions were preceded by drug treatments, consisting of IP administration of either 1 ml/kg saline, 20 mg/kg cocaine, or 10 mg/kg BTCP. Drugs were administered 10 min before placing the animals in the locomotor activity cages.

The design and treatment schedule for the experiment is shown in Table 1. Animals were randomly divided into five groups. Groups 1, 2, and 3 received the same drug treatment throughout days 1 to 10, consisting of saline (saline/saline, $n = 6$), cocaine 20 mg/kg IP (cocaine/cocaine, $n = 9$) and BTCP 10 mg/kg IP (BTCP/BTCP, $n = 6$). Groups 4 and 5 received one drug from day 1 to 3 followed by treatment with the other drug from day 4 to 10 (i.e., 20 mg/kg IP cocaine followed by 10 mg/kg IP BTCP for cocaine/BTCP group, $n = 6$ or 10 mg/kg IP BTCP followed by 20 mg/kg, IP cocaine for the BTCP/cocaine group, $n = 6$).

TABLE 1

TREATMENT RECEIVED BY THE FIVE DIFFERENT GROUPS: GROUPS 1 TO 3, SIMPLE TREATMENTS; GROUPS 4 AND 5, CROSS TREATMENTS

	Treatment Day		
Groups	Day 0	Days 1–3	Days 4–10
(1) Saline/saline	baseline	saline	saline
(2) Cocaine/cocaine	baseline	cocaine 20 mg/kg	cocaine 20 mg/kg
(3) BTCP/BTCP	baseline	BTCP 10 mg/kg	BTCP 10 mg/kg
(4) Cocaine/BTCP	baseline	Cocaine 20 mg/kg	BTCP 10 mg/kg
(5) BTCP/cocaine	baseline	BTCP 10 mg/kg	cocaine 20 mg/kg

Data Analysis

Locomotor activity scores were expressed as the number of beam breaks for each animal. Differences among the saline/saline, cocaine/cocaine, and BTCP/BTCP groups were analyzed by a two-way ANOVA followed by Duncan post hoc tests.

RESULTS

The baseline locomotor activity scores for each group determined on day 0 before the beginning of drug treatments (see Table 1 and Fig. 1) were (number of beam breaks ± SEM): saline/saline 1009.2 ± 148.1; cocaine/cocaine 867.9 ± 87.5; BTCP/BTCP 816.7 ± 137.9; saline/cocaine 714.8 ± 67.9; cocaine/BTCP 966.4 ± 132.6, and BTCP/cocaine 721.7 ± 67.8. No differences in baseline locomotor activity were found among groups, $F(4, 28) = 0.8$, $p > 0.05$.

No differences in the time course of locomotor activation between cocaine and BTCP were observed. Therefore, the data were analyzed and are presented in terms of the mean (±SEM) total number of beam breaks. After determination of baseline activity, the first three groups of animals received repeated treatment with either saline, cocaine, or BTCP alone (see Table 1). Animals treated with BTCP (BTCP/BTCP) or cocaine (cocaine/cocaine) for 10 days showed higher rates of activity on days 4 and 10 of treatment compared to day 1 (Fig. 1B and C). In contrast, animals treated with saline (saline/saline) for 10 days exhibited a decrease in locomotor activity (Fig. 1A). The change in locomotor activity over test days in the different groups was reflected by a significant main effect for "treatment groups," $F(2, 18) = 8.2$, $p < 0.01$, and a significant days × groups interaction, $F(14, 126) = 2.6$, $p < 0.01$. Comparison of three different time points (i.e., day 1, 4, and 10) in the first three groups revealed that locomotor sensitization appeared in the BTCP and the cocaine group on day 4 and later up to day 10; whereas, in the saline group, locomotor activity decreased. This was reflected by a significant main effect of "day of treatment," $F(2, 36) = 4.8$, $p < 0.05$. There was also a difference between groups in the amount of locomotor activity on days 1, 4, and 10. The change in locomotor activity between days in the different

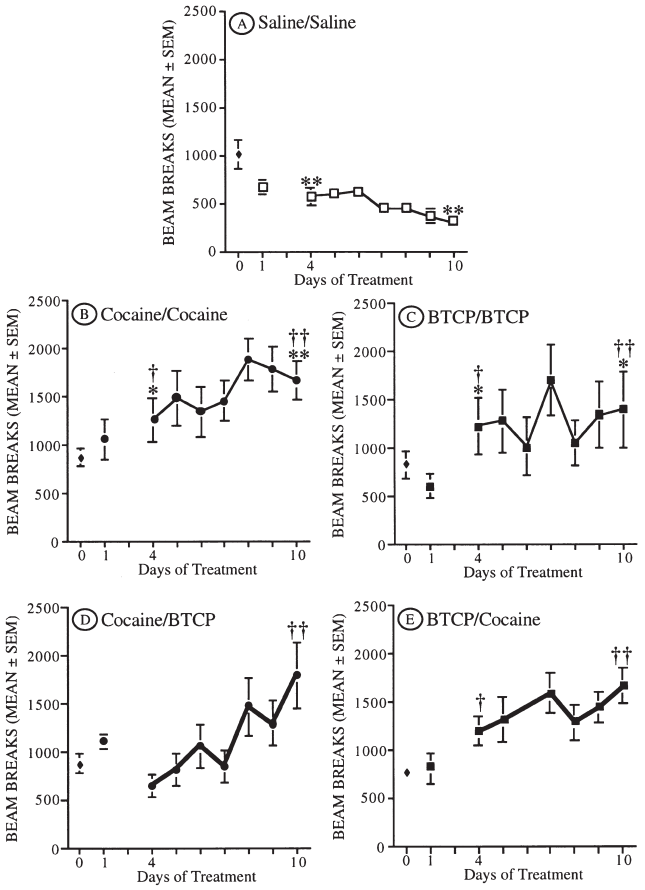

FIG. 1. Locomotor activity induced by repeated treatment with either BTCP or cocaine alone for 10 days (A, B, and C) or with BTCP or cocaine alone for 3 days followed by 7 days of treatment with the opposite drug (D and E). (A) Saline/saline = saline (1 ml/kg throughout the 10-day test). (B) Cocaine/cocaine = cocaine (20 mg/kg, IP throughout the 10-day test). (C) BTCP/BTCP = BTCP (10 mg/kg, IP throughout the 10-day test). (D) Cocaine/BTCP = cocaine (20 mg/kg, IP) for 3 days followed by BTCP (10 mg/kg, IP) for the next 7 days. (E) BTCP/cocaine = BTCP (10 mg/kg, IP) for 3 days followed by cocaine (20 mg/kg) for the next 7 days. Day 0 represents baseline locomotor activity in each group. $*p < 0.05$; $**p < 0.01$ compared to activity on day 1; $^{+}p < 0.05$; $^{++}p < 0.01$ compared to the saline group.

groups was reflected by a significant main effect for "treatment groups," $F(2, 18) = 4.7, p < 0.05$, and a significant day × groups interaction, $F(2, 36) = 5.6, p < 0.01$. Duncan post hoc tests revealed a significant increase of locomotor activity from day 1 to days 4 and 10 (i.e., sensitization) for the cocaine/cocaine group (day 1 vs. day 4, $p < 0.05$; day 1 vs. day 10, $p < 0.01$), the BTCP/BTCP group ($p < 0.05$), and a significant decrease in locomotor activity (i.e., habituation) for the saline–saline group ($p < 0.01$).

After determination of baseline activity, the last two groups of animals received repeated cross-treatments (groups 4 and 5, see Table 1 and Method section, Procedure). The data from day 6 for the BTCP/cocaine group (Fig. 1E) are not presented because they were lost due to a computer failure during the session. The change in locomotor activity in the cross-treatment groups, compared to the vehicle group, was reflected by a significant overall effect of "treatment group," $F(2, 15) = 17.0, p < 0.001$, and a significant day × group interaction, $F(12, 90) = 4.8, p < 0.001$. On day 4 (i.e., the substitution day for the cross-treatment groups, see Table 1) all-groups except cocaine/BTCP exhibited a higher locomotor activity compared to vehicle-treated animals (Fig. 1D and E). Comparison of drug effects among all groups (1 to 5) on day 4 yielded an overall significant main effect for "treatment groups," $F(4, 28) = 2.8, p < 0.05$ (Fig. 1D and E). Duncan post hoc tests revealed a significant increase in all of the groups compared to saline ($p < 0.05$) except for the cocaine/BTCP group. Specifically, cross-sensitization was found the day of substitution (day 4) in the BTCP/cocaine group but not in the cocaine/BTCP group (Fig. 1D and E).

On the last day of the drug treatment (day 10) all groups exhibited increased locomotion except for the saline/saline group. These differences were confirmed by a significant main effect for "treatment groups," $F(4, 28) = 5.6, p < 0.01$ (Fig. 1B, C, D, and E). Moreover, Duncan post hoc tests further confirmed a significantly higher locomotor activity in all of the groups compared to vehicle-treated animals ($p < 0.01$; Fig. 1B, C, D, and E). In other words, pretreatment with one of the drugs did not affect the subsequent locomotor sensitization induced by the other drug (Fig. 1D and 1E).

DISCUSSION

The results indicate that both cocaine (20 mg/kg, IP) and BTCP (10 mg/kg, IP) can induce locomotor sensitization in rats after 10 days of repeated treatment. In the cross-treatment conditions, 3 days of cocaine pretreatment did not result in cross-sensitization to BTCP, whereas 3 days of BTCP administration produced cross-sensitization to cocaine on the substitution day. However, after completion of the 10-day drug treatment period, both BTCP and cocaine induced locomotor sensitization in the cross-treatment condition.

In agreement with numerous previous studies, repeated cocaine administration induced locomotor sensitization [e.g., (20,37,41,49)], and this effect parallels the neurochemical sensitization of DA efflux by cocaine in the caudate nucleus observed after the same repeated-treatment procedure (30). The present results show that 10 days of intermittent treatment with BTCP also produced a significant increase of locomotor activity (i.e., sensitization). These data are consistent with recent findings showing that locomotor sensitization to BTCP occurred in mice after only 3 days of intermittent treatment but at a dose of 20 mg/kg (IP) (40). In the present study, BTCP was administered for a longer period of time, at 10 mg/kg (IP), and the results suggest that at this dose, a longer treatment duration is required to induce significant sensitization of locomotor activity. The differences between the locomotor effect of repeated BTCP treatment observed in the present study and the earlier work (40) may be related to different species used in these two sets of experiments.

The locomotor sensitization to BTCP in the present study does not parallel the tolerance to the elevation in DA levels after repeated BTCP in the caudate nucleus reported previously (30). However, it is well established that cocaine-induced hyperactivity involves DA transmission in the mesoaccumbens, rather than the mesostriatal, dopaminergic system (6,8,15,19,22,35). Similarly, sensitization of locomotor responses induced by repeated administration of stimulants is mediated by changes in dopaminergic function in the mesoaccumbens, rather than the mesostriatal, dopaminergic system (21,45). Thus, it is possible that chronic administration of BTCP affects DA function in the nucleus accumbens and the

caudate nucleus in a different manner. For example, repeated administration of BTCP may produce tolerance in the dopaminergic response in the caudate nucleus, but result in sensitization of locomotor-related DA function in the nucleus accumbens. Consistent with such a differential action are recent findings showing that local perfusion of BTCP produces different effects in both structures. In the caudate nucleus, BTCP increased DA levels but did not change the levels of the DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). In contrast, BTCP produced a smaller increase in DA efflux accompanied by reduced levels of DOPAC and HVA in the nucleus accumbens (32). Also, several studies have shown differences in DAT function in the dorsal striatum vs. nucleus accumbens in terms of DAT maturation (28), regulation of DA clearance or the number of DATs (3), and in the regulation of the DAT after chronic cocaine treatment (4). These observations support the hypothesis that BTCP may act differently in the striatum and nucleus accumbens, a possibility that may provide an explanation as to why BTCP induces sensitization of locomotor activity, but not DA efflux in the striatum.

Cross-sensitization was found between BTCP and cocaine specifically when BTCP-pretreated rats received an injection of cocaine after days of BTCP administration (Fig. 1E). However, when cocaine-pretreated rats received an injection of BTCP after 3 days of cocaine treatment, they did not show increased locomotion (Fig. 1D). Moreover, after the substitution day (day 4), cocaine and BTCP produced locomotor sensitization (Fig. 1D and E), suggesting that pretreatment with either of the drugs did not affect the development of a later locomotor sensitization to the second drug. These observations are only partly in agreement with an early report that described a fully reciprocal cross-sensitization between cocaine and BTCP on locomotor activity (39). A reciprocal cross-sensitization between the effects of BTCP and cocaine on DA levels in the striatum was also found in a previous study, as well as an alteration of cocaine sensitization induced by BTCP cross-treatments (30). However, the latter study examined neurochemical sensitization in the caudate nucleus, and sensitized locomotor activity is thought to be predominantly mediated by changes in nucleus accumbens dopamine transmission (21,45). The apparent tolerance to the stimulatory effect of BTCP after 3 days of cocaine treatment may perhaps be accounted for by the development of stereotyped behavior, which is known to interfere with locomotion (41,50). This possibility, however, is not consistent with findings that BTCP up to 40 mg/kg (IP) produces only little stereotyped activity (24,39,40), and the observation in a previous cross-sensitization test, that repeated pretreatment with cocaine reduced rather than induced BTCP stereotyped behavior (39). The present results, in conjunction with the literature on BTCP actions, suggest, therefore, that there are some similarities in the mechanism of action of cocaine and BTCP after repeated administration, but that the effects of these drugs are not identical. An alternative interpretation for the lack of cross-sensitization may be related to the fact that BTCP and cocaine bind to the DAT on different sites (5,33,52). Specifically, it is possible that after intermittent treatment in rats, cocaine may modify the binding site for BTCP in the nucleus accumbens, and this change may be reversible after a few days (Fig. 1D).

In summary, although in rats both repeated exposure to cocaine and BTCP produced sensitization to each respective drug, no reciprocal cross-sensitization was found between cocaine and BTCP. Cocaine sensitized animals did not cross-sensitize to BTCP, whereas BTCP-sensitized animals showed cross-sensitization to cocaine. These results suggest that there are differences in the mechanism of action by which BTCP and cocaine induce locomotor sensitization.

ACKNOWLEDGEMENTS

This is publication number 12858-NP from The Scripps Research Institute. This work was supported by National Institute on Drug Abuse Grant DA07348 (F.W.), and a fellowship by Singer Polignac and Simone et Cino Del Duca Foundations (R.M.F.). The authors are grateful to Martine Michaud for the synthesis of BTCP, and thank Laurie Michelson and Mike Arends for assistance with the preparation of the manuscript.

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