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Absence of Cocaine-induced Place Conditioning in Serotonin 1B Receptor Knock-out Mice

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BELZUNG, C., K. SCEARCE-LEVIE, S. BARREAU AND R. HEN.—*Absence of cocaine-induced place conditioning in serotonin 1B receptor knock-out mice*. PHARMACOL BIOCHEM BEHAV **66**(1) 221–225, 2000.—A large body of evidence suggests that genetic factors may affect the reinforcing properties of drugs of abuse. This study investigated the involvement of the serotonin 1B (5-HT1B) receptor in modulating cocaine-induced place conditioning by comparing the response of 5-HT1B receptor gene knock-out mice with wild type 129/Sv-ter mice. The rewarding effects of various doses of cocaine (0, 2.5, 5, 10, 20, and 40 mg/kg) were examined in both strains. Results clearly show that 5-HT1B receptor knock-out mice failed to display a conditioned place preference for stimuli paired with cocaine while wild type mice exhibited a conditioned place preference for the compartment paired with cocaine (5 and 20 mg/kg). As other studies showed that 5-HT1B knock-out mice self-administer cocaine, these results suggest a dissociation between the psychologic state linked to self-administration and the one measured in conditioned place preference. © 2000 Elsevier Science Inc.

Conditioned place preference Mice Cocaine 5-HT1B receptor knock-out 5-HT1B receptor

THE CONSIDERABLE inter-individual heterogeneity in drug-seeking behavior is well established. Many factors may be involved in this variability, including psychology (drug-seeking may be related to novelty seeking behaviors) (1,22,23,24), environment, or genes (5). Differences in the susceptibility to the reinforcing properties of cocaine have been described among inbred strains of mice (2,18,33). Recently serotonin 1B receptor (5-HT1B) knock-out mice have been found to display elevated alcohol consumption (6) and increased motivation to self-administer cocaine when compared to 129/Sv-ter wild-type mice (30,31), suggesting a key function of 5-HT1B receptor in drug-seeking behavior.

Conditioned place preference is a widely used procedure for studying the affective properties of drugs (see 32 for a review). This paradigm is based upon the tendency of rodents to approach a stimulus which has previously been paired with an incentive state induced by a drug. This procedure offers some advantages when compared with self-administration. First, it allows the measure of both rewarding and aversive effects of drugs. Second, since preference testing is recorded under a drug-free condition, evaluation of the drug's motivational effects is not confounded by direct effects of the treatment on the target behavior. Third, testing is not based on consummatory behavior and therefore there is no risk of confusion between the motivational and consummatory aspects of reinforcement.

In order to further evaluate the role of 5-HT1B receptors in cocaine-induced reward, the present study compared the susceptibility to the rewarding effects of cocaine (0, 2.5, 5, 10, 20, and 40 mg/kg) between wild-type and 5-HT1B knock-out mice using a conditioned place preference paradigm.

METHODS

Subjects

Male mice of a pure 129/Sv-ter genetic background were tested when they were 9-weeks old. The subjects were housed five per cage under a reversed light/dark cycle (12/12 h, lights on at 2000 h) at a constant temperature (22 ± 1° C). Commercial rodent pellets and water were freely available. The work reported in this paper was conducted in accordance with the Guide for Care and Use of Laboratory Animals established by the National Institutes of Health of the United States of America and with the European Council Directive 86/609/EEC.

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Apparatus and Procedure

The apparatus consisted of a rectangular wooden box divided into three compartments (18.5 × 20 × 18 cm) by guillotine type doors. Three distinctive cues, visual, olfactory, and tactile, were associated with each end compartment. One of the distal compartments was painted black, its walls were swabbed with acetic acid and its floor was covered with plastic. At the opposite end, the compartment was painted white, an anise tea solution was wiped on the walls, and the floor was covered with sawdust. The central compartment was painted grey,the floor was made of wood, and no specific olfactory cue was available. The apparatus was covered with glass.

Experiments included two main phases: conditioning phase (eight sessions) and preference testing (one session). Sessions were conducted between 0900 h and 1200 h, 4 to 5 days a week with a 2-day break after the first four conditioning sessions.

During the conditioning phase, mice were injected with one treatment (vehicle or cocaine; intraperitoneally [IP], in a volume of 10 ml/kg) immediately before being confined to one of the distal compartments of the apparatus for 30 min. On alternate days, mice received the other treatment immediately before being placed in the other distal compartment. Each animal was given four conditioning trials of each type (one trial per day). The number of animals experiencing the drug in the black compartment was counterbalanced with the number of animals experiencing it in the white one. For each dose, half of the subjects experienced drug and half of the animals experienced saline on the first day. During this phase, the partitions between the compartments remained closed.

During preference testing, the guillotine doors were removed, allowing free access to the three compartments. Animals were not injected. Mice were placed in the central compartment. The time spent in each compartment and the transitions between compartments were recorded for 10 min, using a hand-held computer (Psion Organiser). For the group injected with saline in both distal compartments, the paired compartment was assigned arbitrarily before testing, as no spontaneous preference for one or the other distal compartment was observed. Preference testing was recorded 24 hr after the last conditioning session.

Drugs

Cocaine chlorhydrate, at doses of 0, 2.5, 5, 10, 20, or 40 mg/kg (Coopération Pharmaceutique, Melun, France) was dissolved in physiologic saline (0.9%) and administered intraperitoneally to wild-type (respectively $n = 9, n = 8, n = 8, n = 9, n = 8, n = 9$) or to serotonin receptor 1B knock-out mice (respectively $n = 8, n = 8, n = 9, n = 8, n = 8, n = 7$).

Statistical Analysis

Results were first analyzed using a two-way ANOVA, with strains and treatments as dependant variables. Further statistical tests were undertaken in both strains separately. In the case of a significant treatment effect, a posteriori comparisons were made using the Tukey test. Furthermore, strains were compared using a Student *t*-test.

RESULTS

The results concerning time spent in drug side are presented in Fig. 1. Two-way analysis of variance revealed a main effect of genotype ($F(1,86) = 7.31$, $p = 0.008$) and of cocaine ($F(5,86) = 3.05$, $p = 0.014$) but no genotype × treatment interaction ($F(5,86) = 0.58$, $p = 0.70$). In wild type mice, cocaine induced a conditioned place preference ($F(5,45) = 3.06$, $p = 0.018$) which reached statistical significance at the doses of 5 and 20 mg/kg (respectively $p = 0.03$ and $p = 0.03$ when compared with controls) but not at the doses of 10 mg/kg ($p = 0.80$) or 40 mg/kg ($p = 0.11$). In 5-HT1B knock-out mice, cocaine failed to induce place conditioning ($F(5,41) = 0.83$, $p = 0.53$). No difference between genotypes occurred in animals treated with saline, 2.5, 10 or 40 mg/kg of cocaine (respectively $p = 0.99$, $p = 0.14$, $p = 0.39$, $p = 0.73$). Differences between genotypes reached significance at the dose of 5 mg/kg ($p = 0.05$) and marginal significance at the dose of 20 mg/kg ($p = 0.06$). When expressed in percentage (100 × time spent in drug-paired side/time spent in the two distal compartments), wild type and knockout controls respectively exhibited 49.53% and 50.77% of time spent in drug-paired side.

Transition data are presented in Table 1. Two-way ANOVA revealed an effect of treatment ($F(5,87) = 3.73$, $p = 0.004$) but no effect of genotype ($F(1,87) = 1.01$, $p = 0.316$) and no interaction genotype × treatment ($F(5,87) = 1.18$, $p = 0.32$). In fact, transitions during the testing day (in a drug-free condition) was decreased in mice of both strains when previously treated with cocaine, 40 mg/kg ($p = 0.01$).

DISCUSSION

Our data clearly demonstrate that wild type 129/Sv-ter mice showed a reliable conditioned place preference for the compartment previously paired with cocaine (5 and 20 mg/kg) whereas the same treatment did not elicit any effect in 5-HT1B receptor knock-out mice. This suggests that cocaine elicits rewarding properties in 129/Sv-ter mice while 5-HT1B receptor knock-out mice are insensitive to this effect. These results offer strong support for the notion of genetic differences underlying the rewarding action of cocaine.

No effect of cocaine was observed at the doses of 2.5, 10, and 40 mg/kg in wild-type mice. In fact, other studies reported cocaine to elicit an inverted U dose-response curve in the conditioned place preference paradigm (13) and this may explain the failure of our smallest (2.5 mg/kg) and largest (40 mg/kg) doses to induce place preference. As to the failure of 10 mg/kg to elicit conditioned place preference, it must be observed that biphasic changes in cocaine-induced regional cerebral blood flow have been reported in some brain areas such as basolateral and corticomedial amygdala, olfactory tubercule, medial habenula, rostral nucleus accumbens septi, bed nucleus of stria terminalis and ventral pallidum (34) and biphasic changes in local cerebral glucose utilization have been seen in the medial prefrontal cortex and the lateral habenula (25). These regions are critically involved in the rewarding effects of cocaine. Therefore, if biphasic effects of cocaine are observed on drug-induced cerebral activation, biphasic effects may be observed when testing for reinforcing effects as well.

Miner (18) reported that 129/Sv mice did not develop cocaine-conditioned place preference at doses ranging from 2.5 to 10 mg/kg of cocaine. However, Miner used the 129/SvJ substrain whereas we used the 129/Sv-ter substrain. Therefore, differences in place-conditioning may exist between these substrains.

The behavioral phenotype of 5-HT1B knock-out mice is not related to differences at the pharmacokinetic level. The blood and brain levels of cocaine and its metabolites benzoylecognine and norcocaine were identical in 5-HT1B

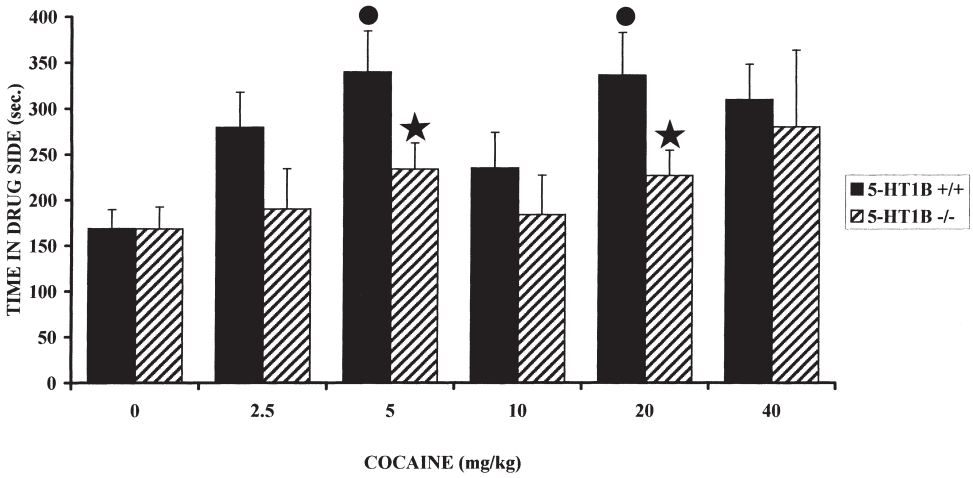

FIG. 1. Effects of cocaine on time spent in drug the compartment associated with drug during conditioning sessions in wild type (5-HT1B +/+) and serotonin 1B receptor knock-out (5-HT1B −/−) mice in a place conditioning paradigm. Mean (+ SEM) of time spent (expressed in seconds) in drug side during the testing phase after various doses of cocaine. Black bars: wild-type mice, stripped bars: serotonin 1B receptor knock-out mice. ★ $p < 0.05$: differences between the two strains, for a same dose of cocaine. ● $p < 0.03$: difference with the controls from the same strain.

knock-out mice when compared with wild types (31). Moreover, cocaine elicits strong pharmacological actions in 5-HT1B knock-out mice, such as increase in locomotion (31). This may interfere with expression of place preference as it might have conditioned 5-HT1B mice to be hyperactive in the training environment, even in the absence of drug, that is on test session. However, this is not the case because there was no genotype × treatment interaction for locomotion on test session. Differential locomotor effects of cocaine in both genotypes could also interfere with the acquisition of place preference: exploration level could be increased; so as to heighten subject's familiarization with the drug-conditioned environment. During the testing phase, animals may exhibit a preference for the most familiar compartment, that is, the drug-associated one (32). In this case, 5-HT1B knock-out mice should display higher place conditioning after cocaine, whereas we observed the contrary.

The failure of 5-HT1B KO mice to display cocaine-induced place preference cannot be attributed to modified anxiety, a learning deficit or a difficulty in making Pavlovian associations. In fact, in the Morris water maze test, these mice show enhanced learning when compared with wild type mice, in contextual or cued fear conditioning and in anxiety tests no genotype differences could be seen (16,26).

Mice lacking 5-HT1B receptors have also been found to display a shorter latency to meet intravenous cocaine self-administration acquisition criteria under a fixed-ratio schedule (30) as well as under a progressive-ratio reinforcement schedule (31). The first one is usually interpreted to reflect an attenuation in the reinforcing properties of the drug while the second one corresponds to an increase of the subjective reinforcing effect of the drug. It has been suggested that animals may compensate for the decrease in reinforcing properties after dopaminergic antagonism when "drug injections can be earned with little effort" (fixed ratio) while the response may extinguish when higher response ratios are required (progressive ratio) (29). One could argue that, because of their increased impulsivity (4) and increased locomotor response to cocaine (31), relatively little effort may be required for 5-HT1B knock-out mice to exhibit high responding under a progressive ratio schedule. Therefore, the increased responding displayed by these mice could, in fact, correspond to a decreased sensibility to the reinforcing action of cocaine. Our results using the place conditioning paradigm confirm these data.

In order to understand the failure of 5-HT1B knock-out mice to display cocaine-induced place conditioning, it is useful to first review the mechanism by which cocaine is believed to induce place-conditioning. Cocaine may induce rewarding effects by stimulating dopaminergic neurotransmission. Injections of dopaminergic antagonists in the NAc (15,21) or lesions of dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (12,28) attenuate the rewarding action of self-administered cocaine. 5-HT1B receptors are expressed on the terminals of GABAergic striatal neurons that project to the substantia nigra and the VTA (3). Therefore, activation of 5-HT1B recep-

TABLE 1

EFFECTS OF COCAINE ON TRANSITIONS IN WILD TYPE (5-HT1B +/+) AND SEROTONIN 1B RECEPTOR KNOCK-OUT (5-HT1B −/−) MICE IN A PLACE CONDITIONING PARADIGM

Treatment	5-HT1B +/+	5-HT1B −/−
Controls	61.77 ± 3.40	57.00 ± 5.08
Cocaine 2.5 mg/kg	63.87 ± 5.33	60.00 ± 9.54
Cocaine 5 mg/kg	48.00 ± 6.05	62.11 ± 7.65
Cocaine 10 mg/kg	50.66 ± 3.74	52.12 ± 7.82
Cocaine 20 mg/kg	41.75 ± 8.47	61.75 ± 6.08
Cocaine 40 mg/kg	36.66 ± 3.18**	33.57 ± 12.64**

Mean (+ SEM) of transitions during the testing phase after various doses of cocaine.

**$p < 0.01$: difference with the controls from the same strain.

tors may inhibit GABA release onto dopaminergic neurons projecting from the VTA to the NAc, thereby stimulating dopaminergic activity within the NAc. Indeed, 5-HT1B stimulation has been shown to enhance dopamine-mediated reinforcement (19) and cocaine self-administration (20). This mechanism could be absent in 5-HT1B knock-out mice. However, there is also evidence than serotonin can oppose the rewarding effects of cocaine (11), which rather suggests that the activation of 5-HT1B receptors reduces brain stimulation reward. For example, serotonin depletion increases cocaine self-administration on a progressive-ratio schedule (14), suggesting that serotonin may decrease the incentive value of cocaine. 5-HT1B autoreceptors inhibit serotonin release at nerve terminals in the frontal cortex, a mechanism that is absent in 5-HT1B receptor knock-out mice (35). Therefore, 5-HT1B knock-out mice may have an increased level of serotonin following cocaine challenge, and therefore display decreased sensitivity to the reinforcing actions of cocaine.

Another possible explanation to the apparent contradiction between results obtained using different procedures (self-administration, intracranial self-stimulation, conditioned place preference) may be that these paradigms measure different psychologic processes. In fact, some experimental data suggest such a dissociation. For example, ethanol is self-administered (17) but elicits aversive properties in conditioned place preference (32). Rats exhibiting "high response" to novelty develop acquisition of intravenous amphetamine more readily the rats that display "low response" (1,22,23,24) whereas they fail to show amphetamine conditioned place preference (8). One may suggest that self-administration measures the motivational motor response to reward while conditioned place preference rather reflects a pavlovian associated between a place and a subjective state.

The present data clearly demonstrates the involvement of the 5-HT1B receptor in the ability of mice to exhibit cocaine-induced place conditioning. Notably, even if 5-HT1B knock-out mice drink more ethanol than wild-type controls (6), they also fail to exhibit ethanol-induced place conditioning (27), which parallels our findings with cocaine. This suggests that the 5-HT1B receptor may be involved not only in the reinforcing effects of cocaine, but more generally in the rewarding effects of different drugs of abuse. However, it is not possible to exclude compensatory processes or genetic background effects (9,10). In fact there are number of evidences that compensatory changes have taken place in the 5-HT1B knockout mice: elevated levels of the transcription factor ΔFosB and of the D1 dopaminergic receptor have been found in the nucleus accumbens of the knockouts (31 and our unpublished results). Finally, it is clear that the effects of an acute antagonist cannot be equated with the chronic absence of a receptor which is found in knockouts (7). We have shown for example that the 5-HT1B antagonist GR127935 decreases the locomotor effects of cocaine whereas the 5-HT1B knockouts are more active in response to cocaine (31). Other tools such as specific pharmacologic agents or conditional knockouts will be necessary to assess the role of these receptors in the reinforcing properties of drugs of abuse.

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