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Differences in Drug-Induced Place Conditioning Between BALB/c and C57Bl/6 Mice

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BELZUNG, C. AND S. BARREAU. *Differences in drug-induced place conditioning between BALB/c and C57Bl/6 mice.* PHARMACOL BIOCHEM BEHAV **65**(3) 419–423, 2000.—The influence of genotype on the rewarding effects of morphine (0, 1, 3, and 9 mg/kg), amphetamine (0, 0.5, 1, and 2 mg/kg), and cocaine (0, 2.5, 5, and 10 mg/kg) was examined in a place-conditioning paradigm. Two strains of mice, the BALB/cByJIco and the C57BL/6JIco, were used, notably because of their high difference in novelty-seeking behavior. Indeed, high novelty seeking has been associated with an increased risk for using drugs of abuse. Results clearly show that C57BL/6 mice display a conditioned place preference for stimuli paired with morphine, amphetamine, or cocaine. In contrast, BALB/c mice demonstrated place preference to morphine and place aversion to amphetamine, while cocaine was ineffective at the doses tested. No treatment induced differences in the locomotion measured in a drug-free condition. Results may be related to differences at the behavioral (difference in novelty seeking) or neurochemical level (differences in catecholaminergic or opioidergic neurotransmission). © 2000 Elsevier Science Inc.

BALB/c C57BL/6 Morphine Amphetamine Cocaine Conditioned place preference

THERE is considerable evidence, from both animal and human studies, that high novelty seeking is associated with an increased risk for using drugs of abuse (2). For example, rats exhibiting a "high response" to novelty when confronted to an open-field develop acquisition of intravenous amphetamine self-administration more readily then rats that display "low response" to novelty (27–29). However, in these studies, novelty seeking was measured as a locomotor increase in response to forced confrontation to an open-field, while drug-taking behavior was measured using the operant response animal exhibit toward the target compound. Novelty seeking supposes the possibility for a subject to freely approach an unknown stimulus (novel environment, novel object, etc.) from its home base, which is only possible when the animal is given the opportunity to freely move from a familiar to a novel environment. Furthermore, it is generally assumed that the frequency of drug taking behavior is promoted by the sensitivity to the rewarding properties of the drugs. In fact, the ability of drugs to serve as positive reinforcers are supposed to strengthen the operant behavior allowing to obtain them. If this assumption is correct, then the increase in drug seeking behavior observed in rats displaying high novelty seeking should be related to an increase in the sensitivity to the rewarding effects of the drugs. Indeed, individual differences in novelty seeking in a free-choice playground maze predict amphetamine-conditioned place preference (19). This is related to novelty seeking and not activity because it has been shown that rat level of activity in a novel environment does not predict amphetamine-conditioned place preference (10). In fact, rats' activity in an inescapable novel environment may reflect escape behavior rather then exploration (13,19).

Conditioned place preference is a widely used procedure for studying the affective effects of drugs [see (32) for a review] that is based upon the tendency of rodents to approach a stimulus that 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, as preference testing is recorded under drug-free conditions, evaluation of the drug's motivational effects are not confounded by direct effects of the treatments 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.

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Another factor that has been given a particular attention in the etiology of drug seeking is the genetic one. For example, differences in the susceptibility to the reinforcing properties of cocaine, morphine, or ethanol have been described among inbred strains of mice (9,14). Furthermore, marked difference exist among inbred strains of mice for their response to novelty, some strains exhibiting approach responses toward a novel environment while others show avoidance toward novelty. For example, in a free exploratory paradigm in which animals are given the opportunity to choose between familiar or novel places, C57BL/6 mice show preference for novelty while BALB/c mice exhibit a strong neophobia (4,5,13).

The present study was aimed at comparing the susceptibility to the rewarding effects of morphine, cocaine, and amphetamine between a high novelty-seeking strain (the C57BL/6) and a low novelty-seeking strain (the BALB/c) of mice using a conditioned place-preference paradigm.

METHOD

Subjects

Male mice, 7 weeks of age at time of testing, were used. BALB/cByJIco were obtained from Janvier (Le Genest Saint Isle, France). The C57Bl/6JICo were originally obtained from Iffa Credo, and then bred in the laboratory for several generations. 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 article 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 Communities Council Directive 86/609/EEC.

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, a visual, an olfactory and a tactile one were associated with the end compartments. 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, the walls were moistened with an anise tea solution using Kleenex, and the floor was covered with sawdust. The central compartment was painted gray, 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 9 and 12 h, 4–5 days a week, with a 2-day break between the first four and second four conditioning sessions.

During the conditioning phase, mice were injected with one of the treatments (vehicle or drug; 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 (drug if they received saline before the first conditioning session, and saline in they were administered drug before the first conditioning session) immediately before being placed in the other distal compartment. So, a given compartment was paired with a given treatment. 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. Furthermore, the first day, for each dose, half of the subjects experienced drug and half of the animals experienced saline. During this phase, the partitions between the compartments were closed. Two apparatus were used but each mouse was always confronted to the same apparatus.

During the 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 and the time spent in each compartment as well as the number of transitions between the three compartments (locomotion) were recorded during 10 min, using an handheld computer (Psion Organiser). For the group injected with saline in both distal compartments, the paired compartment was chosen arbitrarily, as no spontaneous preference for one or the other distal compartment was observed.

Drugs

All drugs were dissolved in physiological saline (0.9%).

Experiment 1: Effects of Morphine on Place Conditioning in C57BL/6 and BALB/c Mice

Morphine sulfate pentahydrate (SIGMA, France) was administered to C57Bl/6 mice (0, 1, 3, or 9 mg/kg; n = g in all groups) or BALB/c mice (0, 1, 3, or 9 mg/kg; respectively n = 8, n = 9, n = 9, n = 9).

Experiment 2: Effects of Amphetamine on Place Conditioning in C57BL/6 and BALB/c Mice

S(+)-Amphetamine sulfate (RBI, Natick, MA) dosed at 0, 0.5, 1, or 2 mg/kg was administered to C57Bl/6 mice (n = 9 in each group) and BALB/c mice (n = 9).

Experiment 3: Effects of Cocaine on Place Conditioning in C57BL/6 and BALB/c Mice

Cocaine chlorhydrate dosed at 2.5, 5, or 10 mg/kg (Coopération Pharmaceutique, Melun, France) was administered to C57Bl/6 mice (n = 8 per group) and to BALB/c mice (respectively, n = 9, n = 8, n = 9, n = 9).

Statistical Analysis

Results were first analyzed using a two-way ANOVA, with strains and treatments as dependant variables. Further statistical analysis were undertaken in both strains separately. In the case of a significant treatment effect, a posteriori comparisons were made using Tukey test. Furthermore, strains were compared using Student's t-test.

RESULTS

Experiment 1: Effects of Morphine on Place Conditioning in C57BL/6 and BALB/c Mice

For time spent in the drug side, two-way ANOVA revealed a significant effect of treatment, $F(3, 63) = 4.33$, $p < 0.045$, but no effect of genotype, $F(1, 63) = 0.32$, $p = 0.56$, and no genotype × treatment interaction, $F(3, 63) = 1.24$, $p = 0.34$. Morphine induced a conditioned place preference both in C57BL/6, $F(3, 32) = 4.43$, $p < 0.01$, and in BALB/c mice, $F(3, 31) = 3.28$, $p < 0.034$. This effect reached significance for the dose of 3 and 9 mg/kg in C57BL/6 mice, and at the dose of 3 mg/kg in BALB/c mice. Both strains never differed, whatever the dose of morphine injected (Fig. 1).

No genotype × treatment, $F(3, 63) = 0.81$, $p = 0.44$, and effect of treatment, $F(3, 63) = 0.70$, $p = 0.47$, were observed

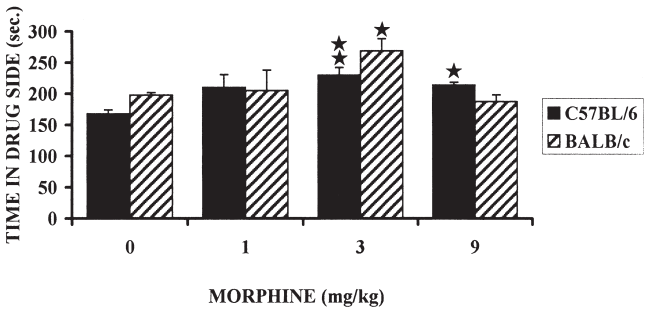

FIG. 1. Effects of morphine on time spent in drug side in C57BL/6 and in BALB/c mice confronted to a place-conditioning paradigm. Mean (+SEM) of time spent in the compartment paired with the drug during the testing phase after various doses of morphine. ★$p <$ 05, ★★$p < 0.01$: different from controls from the same strain.

for locomotion. However, both strains differed for this parameter, $F(1, 63) = 39.21$, $p < 0.001$. This was due to a higher level of activity in C57BL/6 mice, whatever the treatment (results not shown).

Experiment 2: Effects of Amphetamine on Place Conditioning in C57BL/6 and BALB/c Mice

Two-way ANOVA revealed strong statistical differences among groups for time spent in drug side [genotype × treatment interaction, $F(3, 64) = 11.72$, $p < 0.001$; genotype effect, $F(1, 64) = 24.96$, $p < 0.001$; treatment effect, $F(3, 64) = 2.82$, $p < 0.045$]. In fact, C57BL/6 mice displayed a preference for the compartment associated with amphetamine, $F(3, 32) = 6.38$, $p < 0.002$, which was significant at the highest dose (2 mg/kg). BALB/c mice exhibited an aversion for the place previously associated with amphetamine, $F(3, 32) = 7.83$, $p < 0.001$, which reached significance at the dose of 2 mg/kg. Both strains differed at the doses of 1 and 2 mg/kg (Fig. 2).

An effect of genotype was observed for locomotion, $F(1, 64) = 26.24$, $p < 0.001$, which was due to a general difference in basal activity between both strains. However, ANOVA did not reveal an effect of treatment, $F(3, 64) = 0.61$, $p = 0.60$, and no genotype × treatment interaction, $F(3, 64) = 1.87$, $p = 0.14$ (results not shown).

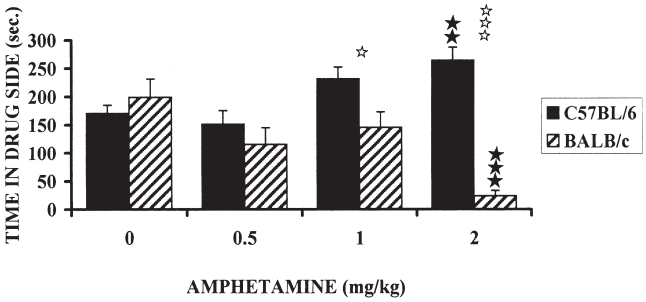

FIG. 2. Effects of amphetamine on time spent in drug side in C57BL/6 and in BALB/c mice confronted to a place-conditioning paradigm. Mean (+SEM) of time spent in the compartment paired with the drug during the testing phase after various doses of amphetamine. ★★$p < 0.01$; ★★★$p < 0.001$: different from controls from the same strain. ☆$p <$ 0.05, ☆☆☆$p < 0.001$: difference between both strains, for the same dose.

Experiment 3: Effects of Cocaine on Place Conditioning in C57BL/6 and BALB/c Mice

For time spent in drug side, two-way ANOVA showed a genotype × treatment interaction, $F(3, 59) = 2.79$, $p < 0.04$, associated with an effect of genotype, $F(1, 59) = 4.18$, $p <$ 0.04. However, no overall effect of treatment appeared in this analysis, $F(3, 59) = 2.04$, $p = 0.11$; in fact, cocaine induced a place preference in C57BL/6 mice, $F(3, 28) = 5.36$, $p < 0.005$, which reached significance at all doses tested. In BALB/C mice, no difference appeared between vehicle and cocaine treated mice for this parameter, $F(3, 31) = 1.38$, $p = 0.26$. Both strains differed in controls and for the dose of 10 mg/kg of cocaine (Fig. 3).

An effect of genotype was observed for locomotion, $F(1, 59) = 17.27$, $p < 0.001$, which was due to a general difference in basal activity between both strains. However, ANOVA did not reveal an effect of treatment, $F(3, 59) = 0.96$, $p < 0.41$, and no genotype × treatment interaction, $F(3, 59) = 0.31$, $p =$ 0.81 (results not shown).

DISCUSSION

Our data clearly demonstrate that both strains showed a reliable conditioned place preference for the compartment previously paired with morphine. However, cocaine induced a conditioned place preference in C57BL/6 mice and not in BALB/C mice while amphetamine elicited place preference in C57BL/6 animals and place aversion in the BALB/c strain. This suggest that morphine, cocaine, and amphetamine may elicit rewarding properties in C57BL/6 mice, while BALB/c mice are sensitive only to the rewarding effects of morphine, amphetamine producing the opposite action.

The ability of C57BL/6 and BALB/c mice to exhibit conditioned place preference to morphine confirms the study of other authors (35). Differences in opioid system have been reported between these two strains. For example, the opiate antagonist naloxone blocks the antianxiety effects of benzodiazepines in C57BL/6 and not in BALB/c mice (1,3). Furthermore, the opiate κ agonist U50488H is a potent analgesic in C57BL/6 and not in BALB/c mice (24,38). In the BALB/c strain, naloxone induces an analgesic response that is blocked by a κ antagonist (39–41). This suggest abnormal functioning of κ opioid receptors in BALB/c mice, because naloxone does not induce analgesia in other strains. However, no difference between strains has been reported in the num-

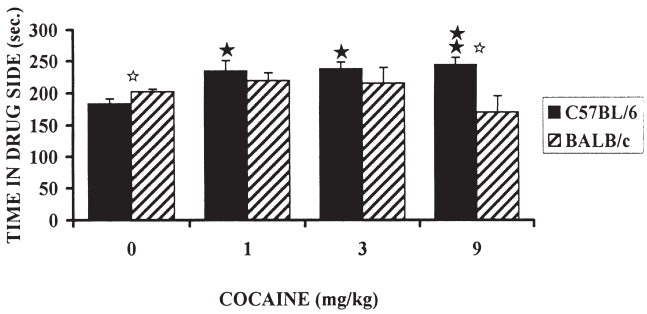

FIG. 3. Effects of cocaine on time spent in drug side in C57BL/6 and in BALB/c mice confronted to a place-conditioning paradigm. Mean (+SEM) of time spent in the compartment paired with the drug during the testing phase after various doses of cocaine. ★$p < 0.05$, ★★$p <$ 0.01: different from controls from the same strain. ☆$p < 0.05$: difference between both strains, for the same dose.

ber and affinity of μ opioidergic receptors (30). Therefore, our data confirm that the rewarding properties of morphine are to be related to the μ (23) and not to the κ opioidergic receptor, because in the second case differences between the two strains were expected.

As to the effects obtained with psychostimulants, other studies have reported aversive effects of amphetamine in mice subjected to a conditioned place preference paradigm. For example, it has been shown (7) that *d*-amphetamine elicited biphasic effects, the dose of 1 mg/kg resulting in place aversion and the doses of 2 or 3 mg/kg resulting in place preference. Therefore, a possible explanation for the opposite effects observed in the C57BL/6 when compared to the BALB/c mice can be related to a difference in sensitivity to the pharmacological effects of amphetamine. However, this seems not to be the case, because amphetamine has been shown to improve performance of mice subjected to a visual discrimination task in the same way in both strains (8). In the same manner, genetic variations in pharmacokinetic may not account for the differences in cocaine responsiveness observed between both strains because no difference in the incorporation of [^{3}H]-cocaine has been found between C57BL/6 and BALB/c mice (33).

Surprisingly, in the BALB/c strain, amphetamine induces place aversion while another psychostimulant, cocaine, does not act as a positive or a negative reinforcer at the doses tested. This difference may be related to the different mechanism of action of these two compounds. Indeed, even if the ability of both cocaine and amphetamine to produce rewarding effects has been associated to the dopaminergic mesolimbic system, differences appear in the action of these two drugs. The dopaminergic mesolimbic system includes dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Rats can self-administer amphetamine directly in the NAc (16), while injections of dopaminergic antagonists in the NAc (22,26) or lesions of dopaminergic neurons projecting from VTA to NAc (20,31) attenuate the rewarding action of intravenously self-administered cocaine. These data provide arguments suggesting that both psychostimulant may act via an identical mechanism. However, contrary to amphetamine, cocaine acts also as a serotonin uptake inhibitor. Serotonin depletion increases the rate of cocaine self administration (21), raising the possibility that the action of cocaine on serotoninergic function may induce an aversive effect that limits its self-administration. Furthermore, contrary to amphetamine, cocaine is not self-administered into the NAc (12), while it can be directly self-administered in the prefrontal cortex (12).

Interestingly, differences in dopaminergic function within the prefrontal cortex have also been reported between C57BL/6 and BALB/c mice. Indeed, the electric foot shock-induced increase in dopaminergic turnover within this structure is higher in BALB/c then in C57BL/6 mice (15). It is to be noticed that the locomotor response of both strains after administration of psychostimulants is quite opposite. Indeed, C57BL/6 mice exhibit an increase in activity and BALB/c mice an inhibition of activity after amphetamine administration (18,25). The same difference is found in response to the amphetamine-like compound phenylethylamine (17), to cocaine (33,34), and to phencyclidine (11). Such effects could not be observed in these experiments, as locomotion is recorded in a drug-free state. However, these differences in locomotion action of psychostimulants may not account for the difference in the rewarding action of cocaine and amphetamine in these two strains because the same difference exists for morphine-induced effects on activity, the C57BL/6 mice being described as runners while BALB/c exhibit a poor response (6,36,37). Therefore, drug-induced place preference can be associated with the failure of a drug to induce hyperactivity, which contradicts the psychomotor stimulant theory of addiction (42).

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