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Assessment of the Relative Contribution of Peripheral and Central Components in Cocaine Place Conditioning

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HEMBY, S. E., G. H. JONES, G. W. HUBERT, D. B. NEILL AND J. B. JUSTICE, JR. *Assessment of the relative contribution of peripheral and central components in cocaine place conditioning.* PHARMACOL BIOCHEM BEHAV 47(4) 973–979, 1994.—A balanced place conditioning paradigm was used to assess the contribution of peripheral and central factors mediating place conditioning induced by cocaine HCl. The first experiment was conducted to examine changes in locomotor activity and extracellular dopamine (DA) concentrations in the nucleus accumbens (NACC) following intraperitoneal (IP) injections of cocaine HCl (15 mg/kg) or cocaine methiodide (19.6 mg/kg). IP cocaine HCl significantly increased locomotor activity and extracellular NACC DA, whereas IP cocaine methiodide failed to increase either locomotor activity or extracellular DA in the NACC. In the second experiment, IP cocaine HCl (15 mg/kg) induced a significant conditioned place preference; however, neither IP procaine HCl (25 or 50 mg/kg) nor IP cocaine methiodide (4.9, 9.8, or 19.6 mg/kg) induced preferences for the drug-paired compartment. In the third experiment, intracerebroventricular (ICV) infusions of cocaine HCl (25 μg/2 μl) or cocaine methiodide (1 or 5 μg/2 μl) induced significant place conditioning for the drug-paired compartment. These results suggest place conditioning induced by cocaine HCl is mediated centrally and that the local anesthetic properties alone do not contribute to this effect to any significant degree.

Place conditioning Cocaine hydrochloride Cocaine methiodide Procaine hydrochloride Microdialysis Dopamine Intracerebroventricular infusions Reward Rat

COCAINE administration produces a variety of physiological and behavioral consequences including peripheral effects (e.g., sympathomimetic and local anesthetic) and central nervous system effects (e.g., catecholamine uptake inhibition). At the behavioral level, cocaine can induce psychomotor stimulation and have potent rewarding effects that are thought to contribute to its abuse liability.

Cocaine is readily self-administered by many different species under a variety of conditions (14). In addition, cocaine has been reported to induce a conditioned preference for an environment previously paired with the drug. Place conditioning is considered a reliable indicator of the potential abuse liability of a drug in humans and is commonly used to investigate the rewarding effects of a variety of stimuli (9,28). In this paradigm, drug administration (or the presentation of other stimuli) is paired with a neutral but distinctive environment. The preference for this environment, in the absence of the drug, is taken as the measure of reward.

Terminal regions of the mesocorticolimbic dopamine system and, in particular, the nucleus accumbens (NACC) and medial prefrontal cortex, have been considered to be important neurobiological substrates for the rewarding effects of cocaine (5,30). However, 6-hydroxydopamine (6-OHDA) lesions of the NACC do not attenuate place conditioning induced by intraperitoneal (IP) administration of cocaine HCl (26). This finding, together with the report that procaine HCl, a local anesthetic, can induce a conditioned place preference (26), has led to a two-component hypothesis of cocaine-induced place conditioning (20,26). This hypothesis suggests that both the peripheral effects and the central dopaminer-

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gic effects contribute to cocaine-induced place conditioning. While some of the available evidence appears to support the hypothesis, it should be noted that procaine has been reported to exert mild central effects (8,16).

One approach to further assessing this two-component hypothesis is to compare cocaine HCl with other compounds that share some, but not all, of cocaine's effects such as procaine HCl or cocaine methiodide, a quaternary derivative of cocaine. At physiological pH, quaternary derivatives are ionized and are thereby unable to penetrate cell membranes, such as the blood-brain or blood-CSF barriers (1). However, the sympathomimetic and local anesthetic effects of cocaine HCl do not appear to be altered by the addition of the methyl iodide constituent (25). Thus, the use of cocaine methiodide should allow the separation of the two components (peripheral or central) according to the route of administration.

The present series of experiments was undertaken to further assess the contributions of peripheral and/or central factors mediating cocaine-induced place conditioning. The first experiment was designed to determine whether IP administration of cocaine methiodide would alter extracellular NACC dopamine and locomotor activity to a similar degree as cocaine HCl. For the second and third experiments, cocaine HCl and cocaine methiodide were compared for their ability to induce place conditioning when administered IP or intracerebroventricularly (ICV). It was hypothesized that if the two component hypothesis were true, then IP administration of cocaine HCl, procaine HCl, or cocaine methiodide should induce a conditioned preference for the drug-paired compartment comparable to a conditioned preference induced by ICV cocaine HCl or cocaine methiodide.

GENERAL METHOD

Subjects

Experimentally naive male Wistar rats (n = 103; Sasco/King, Inc.), weighing between 275–350 g at the beginning of the experiment, were used. Subjects were housed two to three per cage in Nalgene plastic animal cages (48 × 27 cm × 20 cm high; Harvard Bioscience) and were maintained on a 12 L : 12 D cycle (lights on 0700) with food and water available ad lib. Experimentation took place during the light phase of the cycle.

Drugs

Cocaine hydrochloride (NIDA), cocaine methiodide (NIDA), and procaine hydrochloride (Sigma, St. Louis, MO) were used in this study. All doses are expressed as the salt. For IP injections, drugs were dissolved in physiological saline and injected in a volume of 1 ml/kg. For ICV infusions, drugs were dissolved in artificial cerebrospinal fluid (CSF) and infused in a volume of 2 μl. Artificial CSF consisted of 130 mM NaCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 2.7 mM KCl, 10 mM *d*-glucose, and 250 μM *l*-ascorbic acid with the pH adjusted between 7.2 and 7.4 with NaOH.

Histology

Following completion of behavioral testing, subjects were sacrificed using a lethal dose of chloral hydrate and intracardially perfused with isotonic saline followed by 10% formalin solution. Brains were removed and placed in 10% formalin solution for a minimum of 72 h before slicing. Coronal sections (75 μm) were mounted on slides and stained with formol thionin. Cannulae placements were verified and subjects with inappropriate placements (n = 3) were excluded from data analysis.

EXPERIMENT 1: EFFECTS OF IP INJECTIONS OF COCAINE HCl OR COCAINE METHIODIDE ON LOCOMOTOR ACTIVITY AND EXTRACELLULAR DOPAMINE CONCENTRATIONS IN THE NACC

Method

Surgical procedure. Rats were anesthetized with sodium pentobarbital (50 mg/kg; Nembutal), secured in a Kopf stereotaxic frame and implanted with unilateral 22 ga guide cannulae (Plastics One, Inc., Roanoke, VA) aimed at the dorsal surface of the nucleus accumbens: anterior = 3.2 mm; lateral = ± 1.5 mm; ventral = 6.1 mm from dura (23). Cannulae were secured to the skull with skull screws and dental cement. Stylets were inserted into the guide cannulae to reduce the probability of blockage. Subjects were allowed a minimum of 5 days to recover before experimentation.

Locomotor apparatus. Locomotor activity was monitored in opaque Plexiglas cages (39 × 25 × 24 cm) equipped with two photocell beams spaced 2 cm above the floor along the long axis of the cage. Locomotor activity counts required the interruption of two beams in succession and were recorded by a microcomputer.

Microdialysis procedure. The microdialysis probe consisted of two sections of fused silica (40 μm i.d., 105 μm o.d., Polymicro Technologies) inserted into a 6 mm section of dialysis membrane (220 μm o.d., 5000 MW cutoff, Spectra/Por, Los Angeles, CA) which was then sealed at both ends with polyimide resin (Alltech Associates). Within the membrane, the ends of the inlet and outlet silica lines were separated by 2 mm, defining the active area of the dialysis probe. The inlet line was connected to a single channel fluid swivel (2). In turn, the swivel was connected to a 500 μl Hamilton syringe via PE-10 tubing mounted on a Harvard syringe pump (model 7724). Dialysate was collected in microcentrifuge tubes from the free end of the outlet line. Artificial CSF was used as the perfusate.

The HPLC apparatus consisted of a 0.5 μl sample loop to deliver sample to a 0.5 mm i.d. × 100 mm column (5μm, C-18 stationary phase). Mobile phase was delivered by an Isco syringe pump (LC-5000) at a flow rate of 0.33 μl/min. Samples were detected by an EG&G/Princeton Applied Research amperometric detector (model 400) with a dual glassy carbon working electrode (MF-1000; Bioanalytical Systems) and a reference electrode (RE-1; Bioanalytical Systems) with an applied potential of +700 mV vs. Ag/AgCl. The mobile phase consisted of 27.2 mM sodium phosphate-monobasic, 10% volume/volume methanol, 4.9 mM triethylamine, 13 mM disodium-EDTA, and 0.99 mM sodium octyl sulfate, with the pH adjusted to 5.75 with 0.1 N phosphoric acid. Under these conditions, dopamine eluted in approximately 4 min.

Behavioral procedures. Subjects were divided into two groups to receive either cocaine HCl (n = 5) or cocaine methiodide (n = 6). Fifteen hours prior to the experiment, a microdialysis probe was inserted through the previously implanted guide cannula and the subject was placed in an activity chamber. The perfusion flow rate was 0.11 μl/min.

At approximately 0800, the experimental chamber was illuminated and the perfusion flow rate was increased to 0.60 μl/min. When a stable baseline level of extracellular dopamine was achieved for at least 30 min, rats were injected with isotonic saline (1.0 ml/kg) followed 90 min later by an IP injection of cocaine HCl (15 mg/kg) or cocaine methiodide (19.6

mg/kg). The dose of cocaine methiodide was equimolar to the cocaine HCl dose. This dose of cocaine HCl has been shown to induce robust locomotor activation (10). Locomotor activity and extracellular dopamine concentrations were monitored throughout the experimental session. Dialysate samples were collected every 10 min. Locomotor counts were recorded in 10-min intervals.

Statistical analysis. Data were analyzed using analysis of variance (ANOVA) with treatment (saline or drug) as the main factor and time as the repeated measure and by a two-way ANOVA, with the drug (cocaine HCl or cocaine methiodide) as the independent measure and time as the repeated measure (29).

Results

The effects of IP cocaine HCl or cocaine methiodide on extracellular dopamine levels in the NACC and locomotor activity are depicted in Fig. 1. ANOVA revealed that cocaine HCl induced significant increases in extracellular dopamine, $F(1, 4) = 13.96$, $p < 0.02$, and locomotor activity, $F(1, 4) = 16.05$, $p < 0.02$, when compared to saline. However, there was no significant difference in extracellular dopamine concentrations, $F(1, 5) = 0.38$, NS, or locomotor activity, $F(1, 5) = 0.56$, NS, following cocaine methiodide when compared to saline injections. The group treated with cocaine HCl showed significantly greater increases in the level of extracellular dopamine in the NACC when compared to the group treated with cocaine methiodide, $F(1, 9) = 5.88$, $p < 0.04$. In addition, the cocaine HCl-treated group had higher levels of locomotor activity than the cocaine methiodide-treated group, $F(1, 9) = 7.16$, $p < 0.03$. The slight increase in locomotor activity following cocaine methiodide was due to an increase in activity in one of six subjects for the 20- and 30-min intervals.

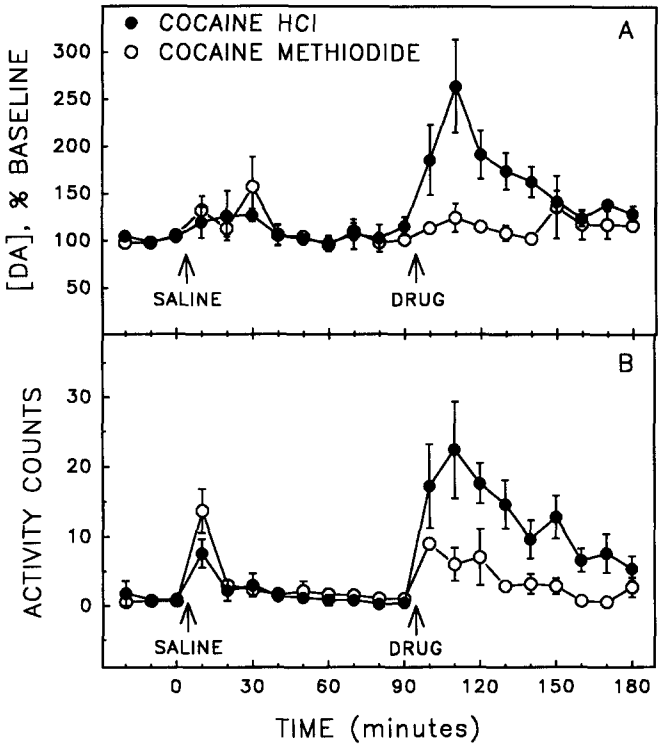

FIG. 1. Effect of IP injections of cocaine HCl (15 mg/kg; $n = 5$) or cocaine methiodide (19.6 mg/kg; $n = 6$) on (A) extracellular dopamine concentrations in the NACC and (B) the effect on locomotor activity. Symbols represent the mean ± SEM for the cocaine HCl- or cocaine methiodide-treated group. The cocaine HCl-treated group exhibited significantly greater locomotor activity ($p < 0.04$) and extracellular dopamine concentrations ($p < 0.03$) than the group treated with cocaine methiodide.

EXPERIMENT 2: COMPARISON OF IP INJECTIONS OF COCAINE HCl, COCAINE METHIODIDE, OR PROCAINE HCl ON PLACE CONDITIONING

Method

Place conditioning apparatus and procedure. The apparatus consisted of an opaque Plexiglas chamber (80 × 25 cm × 36 cm high) divided into three separate compartments (6,7). The two main compartments (35 × 25 cm) were separated by a small neutral compartment (10 × 25 cm) that was used as the place of introduction on the preconditioning and postconditioning days. The neutral compartment had sheet aluminum flooring and gray walls. The openings to the main compartments (12 × 16 cm) were occluded by removable sliding doors during the conditioning trials. One of the main compartments consisted of black walls and a floor of 6.4 mm diameter metal rods spaced 25 mm apart, while the other compartment consisted of white walls and wire mesh floor (6 mm spacing of 1 mm wires). Prior to all experimental phases, a 1.5% acetic acid solution was wiped on the floor of the black compartment to decrease the unconditioned preference for that compartment (6,7,21). All compartments were thoroughly cleaned and the bedding located below the floor was changed after each session.

The experiment consisted of three distinct phases: preconditioning, conditioning, and postconditioning. For the preconditioning phase, subjects were placed in the neutral compartment and the sliding doors were removed to allow complete access to the entire apparatus for 15 min. This phase was videotaped and the amount of time spent in each compartment was monitored and later used to assess unconditioned preferences. Subjects were considered to be in a compartment when both front paws were in that compartment (20,24).

Following the preconditioning phase, subjects were assigned to a treatment group to receive IP administration of cocaine HCl (15 mg/kg), cocaine methiodide (4.9, 9.8, or 19.6 mg/kg), or procaine HCl (25 or 50 mg/kg). The doses of cocaine HCl and procaine HCl are based on those used in previous studies (6,7,26). Treatment groups were counterbalanced according to initial compartment preference, such that half of each group were administered the drug in the initially preferred compartment and half in the initially least preferred compartment. Approximately equal numbers of subjects received drug treatment in the black and white compartments. Each subject received two vehicle and two drug pairings, one pairing per day over a 4-day period. Half of each treatment group received the drug on the first and third day, while the remaining subjects received the drug on days 2 and 4. This type of totally balanced design, in which the mean amount of time spent in the two compartments is equated prior to conditioning, has been suggested to provide a more definitive measure of reward than unbalanced designs in which the drug is paired with the least preferred compartment (3). Immediately following the injections, subjects were placed in the respective compartment for 30 min with access to the neutral

compartment blocked by a sliding door. Following the conditioning trials, subjects were returned to their home cages.

On the test day, the day following the last conditioning trial, rats were tested for conditioned preferences in a drug-free state. Subjects were placed in the neutral compartment, the sliding doors were removed, and unrestricted access to the entire apparatus was allowed for 15 min. Each subject was videotaped during the test trials. The tapes were viewed later by an observer blind to experimental conditions. The amount of time spent in each compartment was monitored and used to assess conditioned preferences.

Statistical analysis. The place conditioning data for the cocaine HCl group were analyzed by Student's *t*-test and the data from the cocaine methiodide and procaine HCl groups were subjected to a two-way, dose × compartment (drug- or vehicle-paired) ANOVA (29).

Results

The place conditioning results for the IP cocaine HCl group are depicted in Fig. 2. This group demonstrated a significant preference for the drug-paired compartment on the test day, $t(16) = 4.09$, $p < 0.001$. The mean difference in the amount of time in the cocaine HCl vs. the vehicle-paired compartment was approximately 183 s. Furthermore, fifteen of 17 rats showed a preference for the drug-paired environment.

Results from IP procaine HCl and IP cocaine methiodide are depicted in Figs. 3 and 4, respectively. In contrast to a previous report (26), procaine failed to induce a significant preference at the doses tested, $F(1, 17) = 0.06$, NS, and there were no significant differences in the amount of time spent in the drug-paired compartment on the test day between the doses of procaine HCl tested, $F(1, 17) = 0.09$, NS. Interestingly, in both procaine groups, four of five subjects who had the drug paired with the initially less preferred compartment exhibited an increase in the amount of time spent in that compartment on the test day. However, this effect was not significant for the 25 mg/kg or the 50 mg/kg dose.

ANOVA revealed that administration of cocaine methiodide failed to induce a significant preference for the drug-paired compartment at the doses tested, $F(1, 27) = 0.33$, NS. Furthermore, there were no significant differences in the amount of time spent in the drug-paired compartment on the test day between the doses of cocaine methiodide, $F(2, 27) = 1.20$, NS.

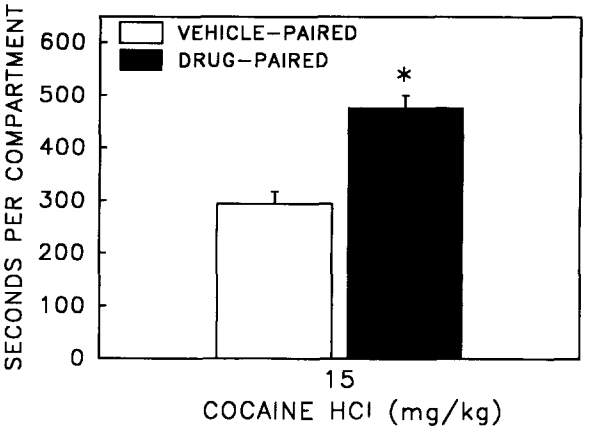

FIG. 2. Effect of IP cocaine HCl injections (15 mg/kg; $n = 17$) on place conditioning. Bars represent the mean amount of time spent in the vehicle- or drug-paired compartment on the test day (±SEM). Cocaine HCl induced a significant preference for the drug-paired compartment (*$p < 0.001$). The mean amount of time spent in the middle compartment on the test day was 129 (±12) s.

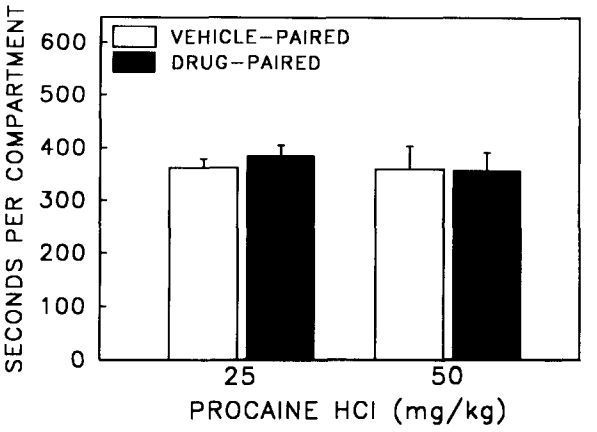

FIG. 3. Effect of IP procaine HCl injections (25 or 50 mg/kg; $n =$ 9 and 10, respectively) on place conditioning. Bars represent the mean amount of time spent in the vehicle- or drug-paired compartment on the test day (±SEM). No dose of procaine induced place conditioning. The mean amount of time spent in the middle compartment (±SEM) on the test day was 151 (±14) and 182 (±14) s for the 25 and 50 mg/kg groups, respectively.

EXPERIMENT 3: COMPARISON OF ICV INFUSIONS OF COCAINE HCL OR COCAINE METHIODIDE ON PLACE CONDITIONING

Method

Surgical and infusion procedure. Rats were anesthetized with sodium pentobarbital 50 mg/kg IP and implanted with a

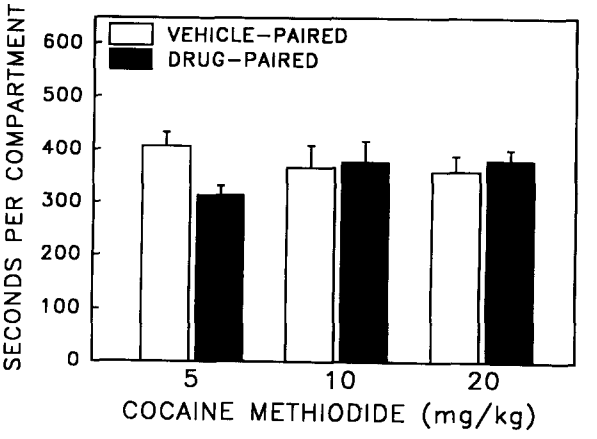

FIG. 4. Effect of IP cocaine methiodide injections (4.9, 9.8, or 19.6 mg/kg; $n = 10$/group) on place conditioning. Bars represent the mean amount of time spent in the vehicle- or drug-paired compartment on the test day (±SEM). No dose of cocaine methiodide induced a significant conditioned preference. The mean amount of time spent in the middle compartment (±SEM) on the test day was 179 (±19), 156 (±18), and 160 (±20) s for the 5, 10, and 20 mg/kg groups, respectively.

22 ga guide cannula (Plastics One, Inc., Roanoke, VA) aimed at the left or right lateral ventricle: anterior = 0.0 mm; lateral = ±1.7 mm; ventral = −2.5 mm from dura (23). Cannulae were secured to the skull surface with screws and dental cement. Subjects were allowed a minimum of 7 days to recover before experimentation.

For microinfusions, rats were loosely held by the experimenter. Stylets were removed and a 30 ga injector cannula (Plastics One, Inc., Roanoke, VA) was lowered through the guide to protrude 1 mm beyond the tip of the guide. The injection cannula was connected via PE-10 tubing to a 10 μl Hamilton syringe mounted on an infusion pump (Sage Instruments, Cambridge MA). A 2 μl infusion was made over a 90-s period and the infusion cannula was left in place an additional minute to allow proper diffusion into the ventricular space. After the infusion, the stylet was reinserted, dust cap secured, and the rat was immediately placed in the appropriate compartment.

Place Conditioning Apparatus and Procedure

The behavioral apparatus and procedure were identical to those used in Experiment 2. Subjects were assigned to one of three groups to receive either cocaine HCl (25 μg; n = 8) or cocaine methiodide (1 or 5 μg; n = 8/group). The dose of cocaine HCl is in the range of doses that has previously been shown to induce a conditioned preference for the drug-paired compartment when administered ICV (20). Following an acute ICV infusion of a dose of cocaine methiodide equimolar to the dose of ICV cocaine HCl (25 μg) in two subjects, simple partial seizures were observed. These seizures were characterized by sudden onset (30–60 s following ICV infusion), clonic jerking of anterior and posterior extremities contralateral to the lateral ventricular infusion site, and preservation of consciousness. This effect may be attributable to the prolonged bioavailability of cocaine methiodide when administered centrally. The doses of cocaine methiodide were, therefore, decreased to 1 or 5 μg to avoid inducing such seizures.

Statistical Analysis

The place conditioning data for the cocaine HCl group were analyzed by Student's t-test and the data from the cocaine methiodide groups were subjected to a two-way, dose × compartment (drug- or vehicle-paired) ANOVA (29).

Results

The results of ICV infusions of cocaine HCl or cocaine methiodide are depicted in Figs. 5 and 6, respectively. The cocaine HCl-treated group spent a significantly greater amount of time in the drug-paired compartment than in the vehicle-paired compartment on the test day, $t(7) = 2.44$, $p < 0.05$. In contrast to peripheral administration of cocaine methiodide, ANOVA revealed that ICV administration resulted in a significant preference for the drug-paired compartment, $F(1, 14) = 16.44$, $p < 0.002$. There was no significant difference in the magnitude of the preference induced by these two doses, $F(1,14) = 0.48$, NS. The difference in the amount of time spent in the drug- paired and vehicle-paired compartment was 166 s for the cocaine HCl treated group, 262 s for the 1 μg cocaine methiodide group, and 186 s for the 5 μg cocaine methiodide-treated group.

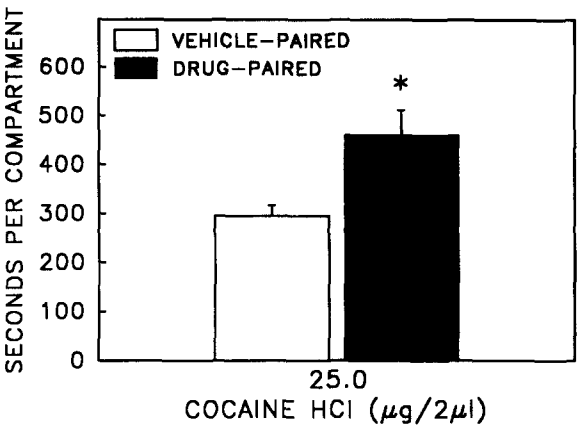

FIG. 5. Effect of ICV cocaine HCl infusions (25 μg/2 μl; n = 8) on place conditioning. Bars represent the mean amount of time spent in the vehicle- or drug-paired compartment on the test day (±SEM). Subjects spent a significantly greater amount of time in the drug-paired compartment than in the vehicle-paired compartment (*$p < 0.05$). The mean amount of time spent in the middle compartment (±SEM) on the test day was 143 (±35) s.

GENERAL DISCUSSION

In confirmation of previous studies, IP administration of cocaine HCl induced a significant preference for the environment previously paired with the drug (6,7,15,21,26). In contrast, neither IP cocaine methiodide nor IP procaine HCl induced a significant conditioned preference at the doses tested. These experiments have also demonstrated that ICV administration of either cocaine HCl (20) or cocaine methiodide-induced significant conditioned preferences. The present results indicate that cocaine HCl place conditioning is mediated centrally with little apparent contribution from the peripheral (sympathomimetic and/or local anesthetic) effects. Therefore, these data do not support the two component hypothesis of cocaine-induced place conditioning.

The present study demonstrates that cocaine-induced place

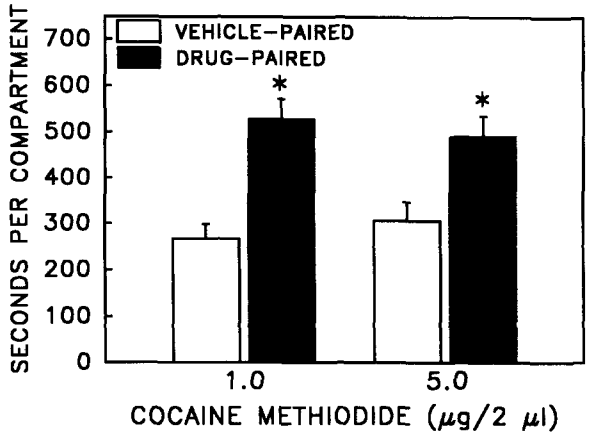

FIG. 6. Effect of ICV cocaine methiodide infusions (1 or 5 μg/2 μl; n = 8/group) on place conditioning. Bars represent the mean amount of time spent in the vehicle- or drug-paired compartment on the test day (±SEM). ICV infusions of cocaine methiodide induced a significant preference for the drug-paired compartment on the test day (*$p < 0.01$). The mean amount of time spent in the middle compartment (±SEM) on the test day was 104 (±14) and 113 (±16) s for the 1 and 5 μg groups, respectively.

conditioning is centrally mediated, presumably via blockade of catecholamine uptake. Using the quaternary derivative cocaine methiodide, the contribution of peripheral and central effects of cocaine place conditioning were assessed. Quaternary salts are unable to penetrate the blood-brain or blood-CSF barriers (1), although the addition of the methyl iodide constituent to cocaine does not appear to alter the sympathomimetic and local anesthetic effects (25). IP cocaine methiodide did not alter extracellular NACC dopamine, a biomarker of cocaine's ability to enter the brain. However, cocaine methiodide infused directly into the brain (via reverse microdialysis) has been reported to elevate extracellular dopamine levels in a manner similar to that observed with cocaine HCl (12). Previous studies have suggested that cocaine place conditioning is attributable to the central dopaminergic effects of the compound (11,20). For example, Morency and Beninger (20) demonstrated that ICV cocaine HCl induced a significant conditioned place preference that was blocked by IP administration of the nonselective dopamine antagonist pimozide. Furthermore, they also showed that ICV procaine HCl does not induce place conditioning. However, attempts to elucidate the critical neural substrates for cocaine place conditioning have not proved successful. For example, 6-OHDA lesions of the NACC (26) or the mPFC (7) do not block IP cocaine HCl place conditioning. Furthermore, direct infusions of cocaine HCl into the NACC failed to induce a conditioned preference (6).

The procaine HCl place conditioning results from Experiment 2 contrast with those of Spyraki et al. (26), who demonstrated that IP administration induced a significant preference for the drug-paired compartment. The discrepancy between the present findings and those of Spyraki et al. (26) may be due to differences in the place-conditioning design. A balanced design was used in the present study, while an unbalanced design was used in the previous study (26). In an unbalanced design, the drug or other stimulus is usually paired with the least preferred compartment and conditioned preferences for the stimulus-paired compartment may reflect decreased aversion rather than reward (3). Such an interpretation has led Morency and Beninger (20) to suggest that procaine and cocaine-induced place conditioning may result from less stimulus aversion with the drug injection as compared to saline injection. In the present study, a balanced procedure was used such that half of the subjects have the drug paired with the less preferred compartment. This design has been argued to more adequately measure reward related processes (3). In the present study, 5 of the 10 subjects within each procaine group were assigned to their initially least preferred compartment. Interestingly, four of these five subjects per group exhibited an increase in the amount of time spent in the initially less preferred compartment. These data support the view that the difference between the present findings and those of Spyraki et al. (26) are due to different experimental designs.

The relative contribution of cocaine's peripheral and central effects have also been assessed in the drug discrimination paradigm. Woolverton and Balster (32) reported that cocaine HCl substituted for procaine HCl; however, in rats trained to discriminate cocaine HCl (10 mg/kg IP) from saline, procaine (10, 20, or 40 mg/kg) did not substitute for cocaine HCl (4,18). Furthermore, IP cocaine methiodide did not substitute for cocaine HCl (10 mg/kg IP) at doses ranging from 10 to 54.6 mg/kg (18,31). These studies suggest that the discriminative stimulus effects of cocaine HCl are also centrally mediated and that the peripheral effects do not contribute to any great extent to this effect.

The present results are consistent with the suggestion that place preferences are dependent on increases in locomotor activity (27,28). However, several studies do not support this view (3). For example, intraaccumbens cocaine HCl infusions were shown to significantly elevate locomotor activity and induce a conditioned locomotor response but fail to induce a conditioned place preference (6). Psychomotor stimulants, such as methylphenidate and nomifensine, induce place conditioning at doses that do not stimulate locomotor activity (17), while phencyclidine produces place aversions at doses that increase locomotor activity (13). Furthermore, two studies have demonstrated that the locomotor effects of drugs can be blocked or attenuated without an observable decrement in place conditioning (19,22).

In conclusion, the present findings suggest that the rewarding effects of cocaine, as measured by the place conditioning paradigm, are mediated centrally and that the peripheral effects do not contribute significantly to this effect.

ACKNOWLEDGEMENTS

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