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RAPID COMMUNICATION

# Cocaine Enhances One-Way Avoidance Responding in Mice

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WEINBERGER, S. B., C. A. RIEDEL, P. H. JANAK AND J. L. MARTINEZ, JR. *Cocaine enhances one-way avoidance responding in mice.* PHARMACOL BIOCHEM BEHAV **41**(4) 851–854, 1992.—We reported previously that posttraining cocaine injections enhance subsequent performance of an automated jump-up avoidance response and a trough avoidance response in rats. In the present study we examined the species generality of the cocaine enhancement by investigating the effects of posttraining cocaine injection on subsequent performance of a one-way active avoidance response in mice. Cocaine (30 mg/kg, IP) administered to mice immediately following completion of two escape-only trials on day 1 significantly enhanced avoidance response performance on day 2. Neither lidocaine nor cocaine methiodide, when administered in doses equimolar to the effective cocaine dose, altered performance on day 2. These data indicate that cocaine's enhancement of avoidance responding in mice probably is neither peripherally mediated nor attributable to its local anesthetic properties.

Cocaine Memory One-way active avoidance Lidocaine Cocaine methiodide Mice

WHEN administered systemically prior to training, cocaine enhances performance of simple operant behaviors in several species (1,2,7,8,15). However, because cocaine also enhances activity levels, it is difficult to determine whether the observed improvement in performance is caused by enhanced learning or simply is due to a performance effect. Recent studies in our laboratory employing posttraining cocaine injections, which enabled us to train the animals in a drug-free state, demonstrated that cocaine enhances subsequent performance of an automated jump-up response (5) and a trough avoidance response (4) in rats. In the present study we investigated the species generality of this enhancement by examining the effect of posttraining cocaine administration on subsequent one-way active avoidance responding in mice.

## METHODS

### *Subjects*

The subjects were male Swiss-Webster mice (Simonsen Labs, Gilroy, CA), aged 56–60 days on arrival. The animals were housed individually, with ad lib access to food and water, in accordance with NIH guidelines. All animal use and testing procedures were approved in advance by the Institutional Animal Care and Use Committee at the University of California at Berkeley. Behavioral testing began 3–5 days after the animals' arrival at our vivarium.

### *One-Way Active Avoidance Task*

Mice were trained on a one-way active avoidance task as detailed in Martinez and de Graaf (9). The apparatus is a two-chamber box with a floor comprised of two metal plates. The chamber design requires the animal to make contact with both plates at all times.

Testing on day 1 consisted of two escape-only trials, which began by placing the animal in the darkened start compartment. After 10 s the door connecting the two chambers was opened and a constant current footshock (330 $\mu$A) was delivered across the metal floor plates. The shock was terminated when the animal escaped into the safe white compartment. The two trials were separated by a 20-s intertrial interval.

On all trials on day 2 the animal could make either an avoidance or an escape response. For these trials the intercon-

These data are reported in abstract form in Weinberger, S. B., Riedel, C. A., Janak, P. H., Martinez, J. L., Jr. Cocaine enhances retention of a one-way avoidance response in mice. Soc. Neurosci. Abstr. 17:871; 1991.

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TABLE 1

EFFECTS OF 0.1-3.0 mg/kg DOSES OF COCAINE ON SUBSEQUENT PERFORMANCE OF A ONE-WAY AVOIDANCE RESPONSE

| Treatment | Mean Avoidances ± SE | N |
|---|---|---|
| Saline | 1.87 ± 0.65 | 15 |
| Cocaine 0.1 mg/kg | 2.53 ± 0.51 | 15 |
| Cocaine 0.3 mg/kg | 2.40 ± 0.69 | 15 |
| Saline | 2.00 ± 0.52 | 28 |
| Cocaine 1.0 mg/kg | 1.73 ± 0.35 | 33 |
| Cocaine 3.0 mg/kg | 1.74 ± 0.48 | 27 |

necting door was opened at the start of the trial and the animal was given 10 s to move into the safe compartment (avoidance response) before the shock was activated and subsequently terminated by an escape response or the passage of 20 s. Animals remained in the safe compartment throughout each 20 s intertrial interval and then were moved by the experimenter to the start compartment to begin the next trial. Each animal completed 14 trials on day 2. The number of avoidances made by each animal on day 2 was used to measure avoidance performance.

*Drugs*

Each animal was given an IP injection of saline, cocaine hydrochloride (0.1-30 mg/kg), lidocaine (8 or 24 mg/kg), or cocaine methiodide (13.1 or 39.3 mg/kg) immediately after completion of the two escape-only trials on day 1. The number of animals in each treatment group is reported in Table 1 and Fig. 1. Cocaine was purchased from Sigma (St. Louis, MO), lidocaine was purchased from Veterinary Companies of America (Tempe, AZ), and cocaine methiodide was provided by the National Institute on Drug Abuse.

*Data Analysis*

Each experimental session included a saline control group and two drug treatment groups. Studies with all doses of all drugs were replicated in at least two separate experimental sessions. The comparability of saline means obtained in these replications was tested with an analysis of variance (ANOVA). When the saline means did not differ significantly, combining drug treatment data obtained in different experimental sessions was deemed appropriate. The significance of differences between combined saline and drug treatment means was tested with a single degree of freedom ANOVA (6).

## RESULTS

*Effects of Posttraining Injection of Cocaine on Subsequent Performance of a One-Way Avoidance Response*

Initial studies examined the effects of cocaine doses between 0.1 and 3.0 mg/kg on subsequent one-way active avoidance conditioning. Because saline means obtained in separate experimental replications did not differ significantly [replications of cocaine 0.1 and 0.3 mg/kg: $F(1, 13) = 3.09$, $p > 0.05$; replications of cocaine 1.0 and 3.0 mg/kg: $F(3, 24) = 2.43$, $p > 0.05$], data from the individual replications were combined. Cocaine doses between 0.1 and 3.0 mg/kg did not alter subsequent avoidance performance, cocaine 0.1 mg/kg: $F(1, 28) = 0.66$, $p > 0.05$; cocaine 0.3 mg/kg: $F(1, 28) = 0.32$, $p > 0.05$; cocaine 1.0 mg/kg: $F(1, 59) = 0.20$, $p > 0.05$; cocaine 3.0 mg/kg: $F(1, 53) = 0.13$, $p > 0.05$. These data are summarized in Table 1.

No statistically significant differences among saline means were obtained in the three experimental replications in which

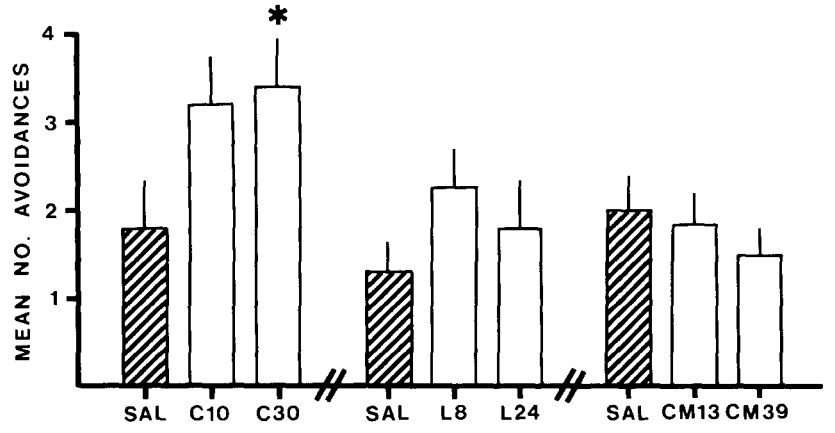


FIG. 1. Effects of cocaine, lidocaine, and cocaine methiodide on subsequent performance of a one-way active avoidance response. A 30 mg/kg (C30; $n = 22$) but not a 10 mg/kg (C10; $n = 21$) dose of cocaine administered after completion of two escape-only trials on day 1 significantly improved day 2 performance (*$p < 0.05$), as measured by mean number of avoidances made during 14 trials, as compared to saline-treated (SAL; $n = 19$) animals. Neither an 8 mg/kg (L8; $n = 30$) nor a 24 mg/kg (L24; $n = 26$) dose of lidocaine altered avoidance responding, as compared to saline ($n = 28$) treatment. Neither a 13.1 mg/kg (CM13; $n = 32$) nor a 39.3 mg/kg (CM39; $n = 33$) dose of cocaine methiodide altered avoidance responding, as compared to saline ($n = 35$) treatment. Both the 24 mg/kg lidocaine dose and the 39.1 mg/kg cocaine methiodide dose are equimolar to the effective 30 mg/kg dose of cocaine.

the effects of 10 and 30 mg/kg doses of cocaine on avoidance performance were tested $F(2, 16) = 1.35, p > 0.05$. Combining data from these three replications therefore was deemed appropriate.

The effects of 10 and 30 mg/kg doses of cocaine on day 2 one-way avoidance responding are presented in Fig. 1. When compared with the saline control animals, the 30 mg/kg cocaine dose was found to significantly enhance avoidance performance, $F(1, 39) = 4.49, p < 0.05$, while the 10 mg/kg cocaine dose was without significant effect, $F(1, 38) = 3.12, p > 0.05$.

*Effects of Posttraining Injection of Lidocaine or Cocaine Methiodide on Subsequent Performance of a One-Way Avoidance Response*

No significant differences among the saline means were obtained in the four experimental replications in which the effects of lidocaine were examined, $F(3, 24) = 1.45, p > 0.05$, or the five experimental replications in which the effects of cocaine methiodide were examined, $F(4, 30) = 1.29, p > 0.05$. Combining data from different experimental sessions therefore was deemed appropriate.

As may be seen in Fig. 1, when administered at doses equimolar to the 10 or 30 mg/kg cocaine doses, both lidocaine and cocaine methiodide did not significantly affect subsequent one-way active avoidance responding, lidocaine 8 mg/kg: $F(1, 56) = 2.83, p > 0.05$; lidocaine 24 mg/kg: $F(1, 52) = 0.69, p > 0.05$; cocaine methiodide 13.1 mg/kg: $F(1, 65) = 0.13, p > 0.05$; cocaine methiodide 39.3 mg/kg: $F(1, 66) = 1.24, p > 0.05$.

## DISCUSSION

The results of the present study demonstrate that posttraining administration of cocaine enhances subsequent performance of a one-way active avoidance response in mice. We observed previously that posttraining cocaine administration also enhances subsequent avoidance performance in rats (4,5), indicating that cocaine's performance-enhancing properties have species generality. Because in both the rat and mouse studies cocaine was administered immediately after the completion of shock-escape response training on day 1, we interpret the enhancement of day 2 performance to be an enhancement of the retention of the shock-escape response. The effective dose of cocaine in mice trained on the one-way active avoidance task is approximately six times the effective dose of cocaine in rats trained on the same task. This interspecies difference in effective dose is a common finding in our laboratory for other classes of drugs as well [e.g., (14)].

Introini-Collison and McGaugh (3) recently reported that a 0.1 mg/kg IP dose of cocaine, administered posttraining to mice, enhanced subsequent performance of a passive avoidance task. In contrast, in the present study we found that although a 30 mg/kg dose of cocaine enhanced subsequent active avoidance responding, posttraining cocaine doses between 0.1 and 10 mg/kg did not affect one-way avoidance task performance. Marked differences in effective dose for passive versus active avoidance are a common finding for other classes of drugs as well (12).

In contrast to the effects produced by cocaine, the results of the present study demonstrate that the local anesthetic lidocaine, when administered posttraining to mice at a dose equimolar to the effective cocaine dose, does not affect subsequent one-way active avoidance performance. Lidocaine administered at a dose equimolar to the effective cocaine dose also does not enhance clearly subsequent avoidance performance in the rat (4). These data indicate that cocaine's local anesthetic properties most likely do not account for its avoidance performance-enhancing properties.

Cocaine methiodide, a cocaine analog with limited ability to cross the blood-brain barrier (13), also did not alter subsequent avoidance performance when administered to mice at a dose equimolar to the effective cocaine dose. These data indicate that cocaine's peripheral stimulant properties most likely do not account for its avoidance performance-enhancing properties. This result contrasts with the finding that the amphetamine analog, 4-OH amphetamine, which also has limited ability to cross the blood-brain barrier, enhances active avoidance performance in rats when administered at a dose equimolar to the effective amphetamine dose (10,11). This latter finding suggests there may be both a central and a peripheral contribution to amphetamine's performance-enhancing properties, while cocaine's effects on subsequent avoidance responding are probably centrally mediated.

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