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Pharmacology Biochemistry and Behavior, Vol. 54, No. 2, pp. 339-341, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02141-8

Methadone Produces Conditioned Place Preference In The Rat

RHEA E. STEINPREIS,[1] AARON L. RUTELL AND FOLAFEMI A. PARRETT

The University of Wisconsin-Milwaukee, Department of Psychology, 138 Garland Hall, 2441 East Hartford Avenue, Milwaukee, WI, 53211 USA

STEINPREIS, R. E., A. L. RUTELL AND F. A. PARRETT. *Methadone produces conditioned place preference in the rat.* PHARMACOL BIOCHEM BEHAV **54**(2) 339-341, 1996.—The appetitive properties of methadone were investigated using the conditioned place preference paradigm. Male Sprague-Dawley rats received conditioned place preference training for a 6-day period. The apparatus consisted of two chambers with distinctive visual and tactile cues, separated by removable doors. Rats received intraperitoneal (IP) injections of methadone (1.0, 2.0, 4.0, 6.0, 8.0, and 10.0 mg/kg methadone HCl) paired with one chamber and saline paired with the other chamber on alternating days. On the seventh day, rats were allowed free run of the entire apparatus and time spent in either chamber was computer recorded. Methadone produced a place preference for the side previously paired with drug in a dose-dependent manner. Place preference for methadone peaked at 4.0 mg/kg and aversion was produced at 10.0 mg/kg. These results indicate that at intermediate doses, methadone does have appetitive properties and is capable of producing a conditioned place preference.

Methadone Place preference paradigm Rats

METHADONE functions to prevent opiate withdrawal and render most opiate supplementation ineffective as a euphoriant (14), and research indicates that methadone programs are effective at reducing the use of illicit drugs (13,15,17,30). However, the concern that methadone maintenance is just the trade of one drug for another has been raised by both scientists (26,27) and drug users (2). Methadone is perceived as being virtually impossible to detoxify from by drug users with and without first-hand experience with methadone (20), and methadone does produce a withdrawal syndrome (39). Methadone addicts sometimes report that the daily infusion of methadone is experienced as a rush (author, unpublished observations).

However the rewarding properties of methadone are not completely understood. Physical dependence on methadone has been established in animals (5,36,37) and rats generalize from morphine to methadone in discriminative stimulus-response paradigms (18). When administered orally, rats demonstrate an aversion to methadone (10,11,28). However, these findings shed minimal light on the appetitive and/or aversive properties of methadone, given that other opiates that are readily self-administered (19) are capable of conditioned aversions to novel-tasting solutions in the same doses that reinforce behavior in operant situations (8,9,12). Researchers have had difficulty getting rats to self-administer methadone (31, 34), while they readily self-administer other drugs of abuse (38). Rats appear to self-inject methadone only following food deprivation (35).

The conditioned place preference paradigm is a method to determine whether or not an organism experiences stimuli as appetitive or aversive. This paradigm has been used to demonstrate the rewarding properties of a number of psychoactive compounds including ethanol (6), cocaine (22), morphine (3), amphetamine (25), nicotine (23), and phencyclidine (29). This paradigm has some important advantages over other procedures for measuring the rewarding properties of drugs, including: 1) positivity can be indexed even when a drug produces motor disturbances (21) because testing is accomplished in a drug-free state; and 2) the positive reinforcing effects of psychoactive compounds with as little as one injection (1,33).

In what appears to be the only study of methadone's effects in the conditioned place preference paradigm, Bilsky et al. (4) found that at a dose of 8 mg/kg, methadone produced neither place preference nor aversion. These authors found that in contrast to naltrexone, which attenuated the appetitive effects of cocaine, methadone potentiated cocaine's appetitive effects. These findings are consistent with the literature indicating greater cocaine use in methadone-treated opioid addicts compared to naltrexone- or buprenorphine-treated opioid addicts (24). The purpose of the present study is to determine the dose-response curve for methadone's effects in the conditioned place preference paradigm.

[1] To whom requests for reprints should be addressed.

METHOD

Subjects

Forty-two male Sprague-Dawley rats served as subjects in this study (Harlan Sprague-Dawley: Indianapolis, IN). All rats were housed individually throughout the experiment. Rats were maintained on a 12 L : 12 D cycle (lights at 0700 h) and at 20°C. Standard rat chow and water were available ad lib.

Apparatus

The apparatus was a square Plexiglas box divided into two distinct chambers. A removable guillotine door separated the chambers. The each chamber was 28 × 31 × 55 cm. One chamber had a wire mesh floor with cedar bedding and walls with inch thick black and white vertical stripes. The other chamber had a wire mesh floor with bed-o-cob and walls with inch thick black and white horizontal stripes. Each chamber was equipped with eight sensors that were used to detect the rats' movement. The sensors were interfaced to a microcomputer which was used for data collection.

Drugs

Methadone hydrochloride was donated by NIDA (Rockville, MD) and was dissolved in 0.9% saline vehicle. The doses of methadone used in this experiment were 1.0, 2.0, 4.0, 6.0, 8.0, and 10.0 mg/kg (n = 6 in each group, including the saline group).

Procedure

Different rats were used for each of the doses tested. Rats were assigned to a side paired with methadone (or saline in the case of the control group) in random fashion, such that half of the rats received methadone in the horizontally striped chamber and the other half received methadone in the vertically striped chamber. Prior to conditioning, each rat was habituated to the entire apparatus with the door opened. Habituation, conditioning, and testing were all conducted in 15-min blocks. The day after habituation conditioning began and lasted for 6 days. On conditioning days, rats were injected IP with either methadone or saline and placed immediately into one of the chambers with the door closed. The order of presentation of methadone and saline was counterbalanced, such that half of the rats were injected with methadone on odd-numbered days and saline on even-numbered days and the reverse order was true of the remaining half of the rats. During conditioning, the doors were closed such that the rats only had access to the target chamber. The seventh day was the test day, during which none of the animals received drug. Rats were placed into the apparatus with the doors lifted and the amount of time spent on each side was computer recorded.

RESULTS

To illustrate the conditioned place preferences, the amount of time the rats spent in each chamber on test day is presented in aggregate form in Fig. 1. However, the results were analyzed using a single-factor between-subjects ANOVA, which compared the times spent in the drug chamber across doses. There was a significant effect for drug treatment, $F(6, 35) = 30.64$, $p < 0.0001$. Post hoc analysis were done using the Tukey test to compare each of the methadone treatment groups to the saline group. Methadone produced significant increases in time spent on the side previously paired with drug compared to the saline group for the 2.0 mg/kg dose ($p < 0.01$), the 4.0 mg/kg dose ($p < 0.001$), the 6.0 mg/kg dose ($p < 0.005$) and the 8.0 mg/kg dose ($p < 0.05$). Methadone produced a significant decrease in time spent on the side previously paired with the drug compared to the saline group for the 10.0 dose ($p < 0.005$).

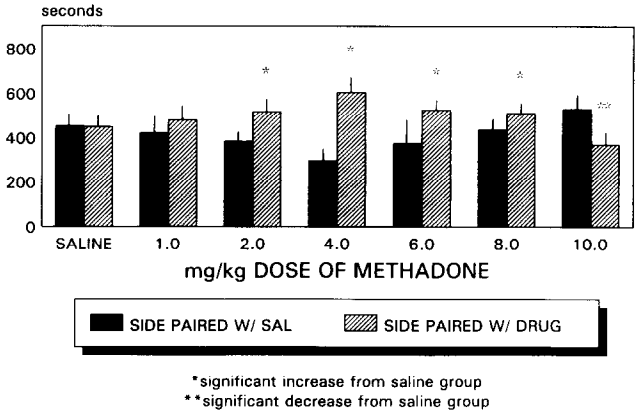

FIG. 1. Mean (+SEM) number of seconds spent on the sides previously paired with methadone or saline.

DISCUSSION

This study represents the first full dose-response curve for the place conditioning range of methadone in rats. Methadone produced a conditioned place preference in the 2.0-8.0 mg/kg dose range. Methadone produced a conditioned place aversion at 10.0 mg/kg. We did attempt a higher dose of methadone to see if we could establish place aversion at higher doses. However, two of five rats died on the first day of conditioning and a third rat died on the third day at a dose of 12 mg/kg so we discontinued training.

These findings are consistent with those of other researchers, indicating that high doses of even abused drugs are experienced as aversive (7,16,29). These results are consistent with the literature on other opiate agonists, indicating that these compounds support conditioned place preferences, including morphine, etorphine, levorphanol, fentanyl, and sufentanil (32,33). These findings underscore the usefulness of the conditioned place preference paradigm, given that the self-administration paradigm has failed to clearly demonstrate the appetitive properties of methadone (31,34,35). It is concluded that the conditioned place preference is a useful method for measuring the rewarding properties of opiate compounds and may be a useful tool in the development of new compounds used to treat illicit drug abuse.

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