Pharmacology Biochemistry and Behavior, Vol. 60, No. 1, pp. 217–222, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00585-6

Morphine-Induced Conditioned Place Preference in Preweanling and Adult Rats

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Received 21 March 1997; Revised 15 September 1997; Accepted 7 October 1997

RANDALL, C. K., P. J. KRAEMER AND M. T. BARDO. *Morphine-induced conditioned place preference in preweanling and adult rats*. PHARMACOL BIOCHEM BEHAV **60**(1) 217–222, 1998.—The ability of morphine to support a conditioned place preference (CPP) in preweanling (18–22-day-old) and adult (70–90-day-old) rats was assessed. Prior to a 15-min compartment preference test, subjects received a saline-paired, 30-min exposure to a distinct compartment 2 h prior to receiving an injection of 1 or 5 mg/kg of morphine or saline, paired with a 30-min exposure to an alternate compartment for 4 consecutive days. Although overall activity levels differed substantially across age, preweanling and adult rats displayed similar patterns of activity during conditioning. Moreover, only adults exhibited a significant sex difference; females were more active than were males following an injection of 5 mg/kg of morphine. Both doses of morphine supported a comparable CPP in preweanlings and adults, and both ages exhibited relatively low activity levels while in the morphine-paired compartment. These similarities across age suggest that the CPP procedure may prove to be useful in elucidating the ontogeny of learning, memory, and stimulus selection in rats. © 1998 Elsevier Science Inc.

Conditioned place preference CPP Morphine Ontogeny *Rattus norvegicus*

A drug-induced conditioned place preference (CPP) is produced by pairing a drug injection with exposure to a distinct environment, typically composed of visual, olfactory, and tactile stimuli. The drug-paired cues subsequently elicit an approach response (termed the CPP effect), that is presumed to be indicative of the rewarding, or reinforcing, properties of the drug. This procedure has been used primarily as a method for assessing the rewarding effects of drugs of abuse (2,8,10, 27). Consequently, the effects of several parametric manipulations on the magnitude of CPP have been investigated (5,7,22, 26,37). Despite this impressive literature, the CPP procedure has been used as a measure of drug reward almost exclusively in adult subjects.

In contrast, research on drug reward in immature rats has been limited to procedures that employ discrete gustatory, olfactory, or tactile stimuli (9,20,24,29,31,34,39). For example, one recent report (24) from our lab demonstrated that pairing an odor with a single injection of 0.5 mg/kg of morphine in 5-day-old neonates results in a behavioral preference for that odor that is evident 5 days after conditioning. Moreover, we were able to condition an odor aversion in 5-day-old rats by pairing an odor with a single injection of a higher (2.0 mg/kg) dose of morphine. We subsequently replicated these effects with adult rats by conditioning a preference to an odor following a single pairing with a 0.5-mg/kg morphine injection, and an aversion to the odor after a single pairing with a 10-mg/kg morphine injection (25).

This biphasic, dose-dependent effect of morphine has also been observed in a taste-conditioning procedure and does not appear to differ substantially across ontogeny regardless of the conditioning procedure employed (3,15,16). Thus, we believe a systematic comparison of morphine-induced CPP in preweanling and adult rats is timely. Just as ontogenetic differences in learning and memory are often alleviated when the parameters of conditioning are varied (33), the tasks described above may not adequately challenge the associative abilities of developing rats. Ontogenetic differences in learning and memory may provide a window on development that will ultimately assist in the identification of brain–behavior relationships. Moreover, an ontogenetic comparison is a critical component in a comprehensive study of behavior (36). Although the reinforcing properties of morphine have been studied extensively in adult subjects using the CPP procedure, ontogenetic data using the same procedure are presently not available.

Thus, the primary goal of this experiment was to compare the magnitude of a place preference produced by four compartment–morphine pairings in preweanling and adult rats. A

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Videomex-V activity monitor automatically recorded activity during each conditioning day, as well as during the test session, which permitted a comparison of the effects of morphine on locomotor activity during both conditioning and testing. Finally, because a number of studies have reported that adult rats are typically least active while in the drug-paired compartment (1,23,38), an ancillary goal in the present experiment was to determine if that generalization can be extended to preweanling rats.

METHOD

Subjects

Sixty-six male and female preweanlings (18–22 days old) procured from seven litters, and 48 male and female adult (70–90 days old) Sprague–Dawley rats were used in the present study. Subject assignment for preweanlings occurred such that one subject per sex from each litter was assigned to each experimental condition. Preweanling rats were housed with their dam and littermates in a clear maternity cage, and adult subjects were individually housed in wire-mesh cages. Both food and water were continually available in the home cage, which was maintained in a climate-controlled vivarium on a 16-L:8-D cycle. The Institutional Animal Care and Use Committee at the University of Kentucky approved all experimental protocols.

Apparatus

Adjacent compartments of the CPP apparatus measured 30 cm (l) × 15 cm (w) × 31 cm (h) for preweanling rats, and 30 cm (l) × 30 cm (w) × 31 cm (h) for adult subjects. Black- and white-colored Plexiglas provided the visual-cue difference between the two compartments. The floor of the black compartment consisted of plastic rods, each 1.5 cm in diameter and spaced 1 cm apart, suspended above cedar shavings. Pine wood chips were placed under a wire mesh floor in the white compartment. Color-appropriate Plexiglas partitions separated the two compartments during conditioning. Those partitions were removed during the preference test to permit simultaneous access to both compartments of the apparatus. A ceiling-mounted video camera was used to record each conditioning session and the preference test. The apparatus was illuminated with two spotlights mounted on either side of the camera. The video camera was connected to a Videomex-V (Columbus Instruments) activity monitor that recorded the movement of multiple user-defined objects across a video monitor. Activity thresholds for the present experiment were set at values that represent approximately one-half of the average body length of rats in our colony: 2.4 cm for preweanlings and 7.5 cm for adults.

Procedure

Conditioning occurred between postnatal day (pd) 18 and pd 21 for preweanling rats and proceeded for 4 consecutive days for adults. On each day, subjects received an intraperitoneal (IP) injection of saline prior to a 30-min exposure to one of two distinct compartments (the CS− compartment). Following a 2-h interval, subjects were placed in the alternate (CS+) compartment immediately after an IP injection of either saline, 1, or 5 mg/kg morphine sulfate. The dose of morphine was based on the salt form of the drug (obtained from the National Institute on Drug Abuse, Rockville, MD). The assignment of either available compartment as CS+ and CS− was balanced across subjects, and experimental conditions because our pilot research indicated that naive preweanling and adult subjects equally prefer both compartments. Consequently, 12 male and 10 female preweanling rats were randomly assigned to each group, as were equal numbers of male and female adults ($n = 8$). A 15-min preference test was administered on pd 22 for preweanlings and on day 5 for adults. During this test, subjects were afforded simultaneous access to both compartments of the CPP apparatus after being positioned on the midline of the apparatus facing one sidewall. The percent time spent in the CS+ compartment was calculated for each of the three consecutive 5-min intervals of the preference test to assess the persistence of the CPP effect.

RESULTS

Separate mixed-factor ANOVAs were computed on the activity data collected during conditioning, and on the compartment preference data and activity data obtained during the preference test. All statistical analyses were evaluated at $p < 0.05$.

Conditioning Session Activity

Although an attempt was made to equate for the physical differences that exist between preweanling and adult rats, especially with regard to the size of the conditioning and test compartments, adult animals were much more active than were preweanlings. Because these differences preclude a meaningful statistical comparison between the two ages, separate ANOVAs for each age were computed on the distance-traveled data generated during conditioning sessions by the Videomex-V activity monitor.

The mean distance traveled across successive conditioning days according to group assignment is presented in Fig. 1 for preweanlings and in Fig. 2 for male and female adult rats. Because the sex × drug × day interaction was not significant in

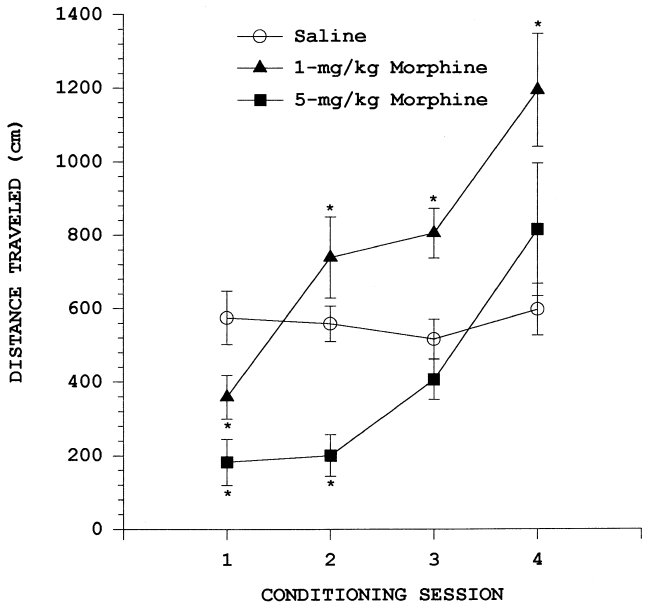

FIG. 1. Mean distance traveled (±SE) for preweanling rats in the CS+ compartment across consecutive conditioning days as a function of the specific US administered. Asterisks (*) denote significant differences from the saline group, $p < 0.05$.

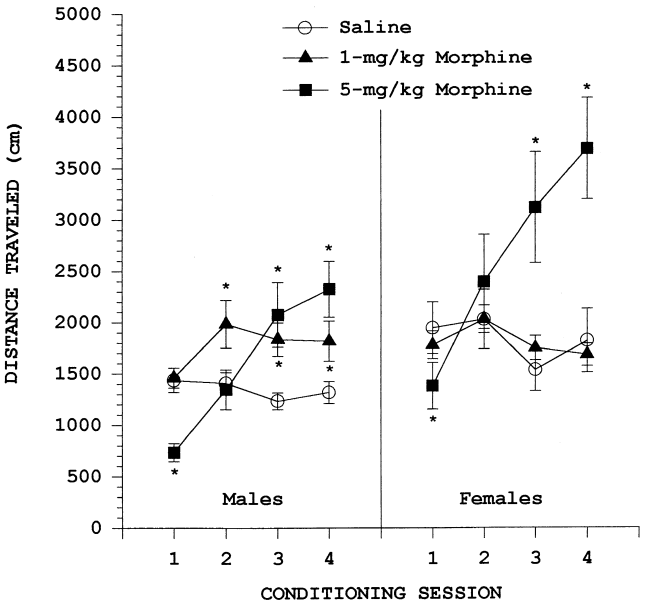

FIG. 2. Mean distance traveled (±SE) for male and female adult rats in the CS+ compartment across consecutive conditioning days as a function of the specific US administered. Asterisks (*) denote significant differences from the saline group, $p < 0.05$.

the preweanling data analysis, $F(6, 180) = 1.44$, the data presented in Fig. 1 are combined for males and females. Not only were adults generally more active than were preweanlings, morphine appears to have had the most pronounced effect on activity at this age. Activity levels among control subjects were relatively stable across conditioning days at each age. In contrast, an injection of either 1 or 5 mg/kg of morphine resulted in an initial suppression of activity, followed by an increase in activity across conditioning days at both ages. These observations were supported by a significant drug × day interaction in preweanlings, $F(6, 180) = 5.65$, by a significant sex × drug × day interaction in adults, $F(6, 126) = 2.93$, and by the appropriate Newman–Keuls post hoc analyses.

In preweanlings, a significant main effect of drug, $F(2, 60) = 9.34$, and post hoc analyses indicated that injections of 1 mg/kg of morphine produced an increase in locomotor activity and injections of 5 mg/kg of morphine resulted in a decrease in locomotor activity relative to animals that received saline injections. Similarly, a significant main effect of day, $F(3, 180) = 21.07$, revealed that activity levels increased across conditioning days independent of the drug administered. The remaining effects in the analysis of the preweanling data were not statistically significant.

As is apparent in Fig. 2, a significant sex × drug interaction, $F(2, 42) = 3.48$, and post hoc analyses revealed that male and female adult rats differed primarily in their response to the locomotor activating effects of 5 mg/kg of morphine across conditioning days. A significant drug × day interaction, $F(6, 126) = 10.48$, confirmed that the high dose of morphine produced the most profound effect on locomotor activity across conditioning days and can be attributed to the differences observed between males and females. In contrast, male rats appeared to be noticeably more sensitive than females to the locomotor activating effects of the 1-mg/kg dose of morphine. Notably, a significant main effect of sex, $F(1, 42) = 9.57$, revealed that females were generally more active than were males, which is consistent with much of the literature on sex differences in rats (4). Overall, only the high dose of morphine produced an increase in activity relative to saline-injected controls, as evidenced by a significant main effect of drug, $F(2, 42) = 4.15$. Finally, activity levels in adults generally increased across conditioning days. This observation was supported by a significant main effect of day, $F(32, 126) = 16.50$. Only the sex × day interaction, $F(3, 126) = 1.73$, failed to reach statistical significance in this analysis.

Compartment Preference Test

Figure 3 depicts the mean percent time both preweanlings and adults spent in the CS+ compartment during the 15-min test session. Both preweanling and adult subjects conditioned with either 1- or 5-mg/kg morphine spent more time in the CS+ compartment than did saline-injected control subjects; however, the dose of morphine used did not differentially affect the resulting CS+ preference. Those observations were supported by an age × sex × drug × interval mixed factor ANOVA that yielded a main effect of drug, $F(2, 102) = 22.65$, and by subsequent post hoc analyses. Although the age × sex × interval interaction, $F(2, 204) = 5.11$, and the main effects of age, $F(1, 102) = 4.50$, and interval, $F(2, 204) = 9.57$, were also statistically significant, those effects collapse over the critical experimental manipulation (drug injection), which diminishes their relevance. The remaining effects in the analysis were not statistically significant.

Preference Test Activity

The Videomex-V activity monitor recorded the time each subject was engaged in ambulation in both compartments of the CPP apparatus during the preference test. This activity

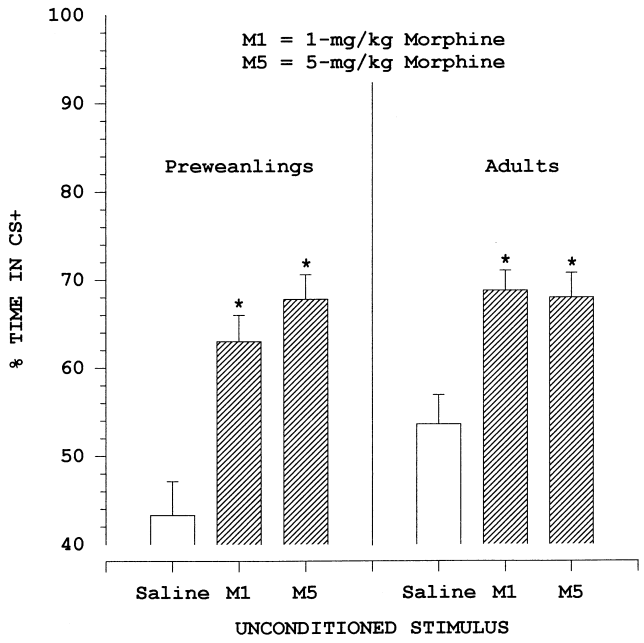

FIG. 3. Mean percent time (+SE) preweanling and adult rats spent in the CS+ compartment as a function of the specific US administered. Asterisks (*) denote significant differences from the saline group, $p < 0.05$.

measure was subjected to two transformations prior to statistical analysis. First, because this measure is influenced by the amount of time spent in that compartment, the time-spent ambulatory in each compartment was divided by the total time spent in that compartment. Separate activity scores were calculated for the three consecutive 5-min intervals of the preference test. Second, at each test interval, the CS+ compartment activity score was subtracted from the CS− activity score to arrive at a single number, an activity difference score (ADS) that reflects the amount of activity that occurred in the CS+ compartment relative to the activity observed in the CS− compartment. Consequently, an ADS of 0 represents no difference in the activity levels in either compartment, a negative ADS indicates that more activity occurred in the CS− compartment than in the CS+ compartment, and a positive score denotes higher activity levels in the CS+ compartment relative to the CS− compartment. Finally, the activity difference scores were converted to percentages to simplify their presentation (see Fig. 4).

At both ages, the mean ADS for control subjects differed substantially from that of subjects conditioned with either 1- or 5-mg/kg morphine. Specifically, control subjects were equally active in both compartments, whereas subjects conditioned with either dose of morphine were markedly less active in the CS+ compartment than in the CS− compartment but did not significantly differ from each other. These observations were supported by an age × sex × drug × test interval ANOVA, which yielded a significant main effect of drug, $F(2, 102) = 5.64$. Although the main effects of age, $F(1, 102) = 5.88$, and interval, $F(2, 204) = 3.44$, the sex × interval interaction, $F(2, 204) = 3.04$, and the age × sex × interval interaction, $F(2, 204) = 4.78$, were also significant, those effects collapse over the critical experimental manipulation (drug injection), which diminishes their relevance. The remaining effects in the analysis were not statistically significant.

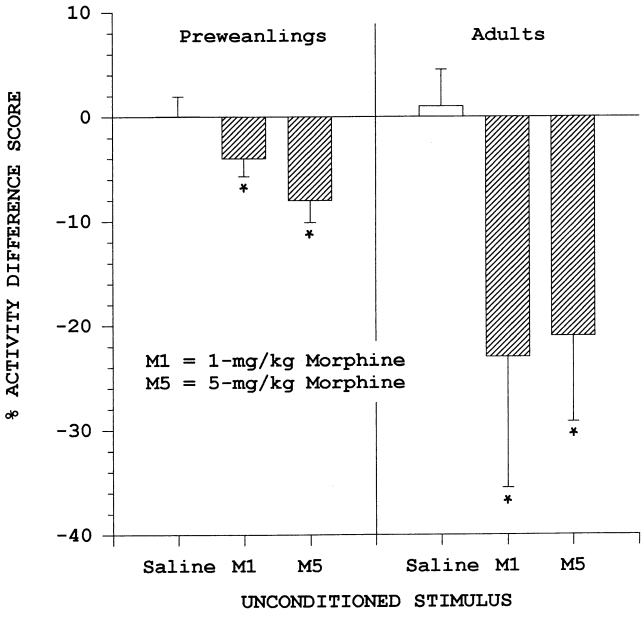

FIG. 4. percent activity difference scores (ADS; ±SE) for preweanling and adult rats as a function of the specific US administered. Asterisks (*) denote significant differences from the saline group, $p <$ 005. ADS were calculated according to the formula:

$$\text{ADS} = \left[\left(\frac{\text{CS + Time Ambulatory}}{\text{TimeVisitingCS+}}\right) - \left(\frac{\text{CS – Time Ambulatory}}{\text{TimeVisitingCS−}}\right)\right] \times 100\%$$

DISCUSSION

The present experiment examined the effect of multiple drug exposures on locomotor activity during conditioning, the magnitude and persistence of the CPP effect, and the effect of place preference conditioning on activity observed during the preference test. Perhaps the most striking result is that preweanling and adult rats differed significantly on only one of these measures. Although morphine differentially affected locomotor activity in preweanlings and adults, an ontogenetic difference was not observed in either the magnitude or persistence of the resulting CPP, or in the activity levels measured during the preference test. Thus, morphine-induced activity does not appear to be correlated with the magnitude of the CPP effect at either age, a finding that has been corroborated in the adult literature (10,28).

The absence of a sex difference among preweanlings in the activity measure was not particularly surprising. At least one other report (11) also failed to observe sex differences in 10- to 24-day-old rats in a number of behavioral measures following an acute injection of one of several doses of morphine (0.1 to 10 mg/kg). Moreover, sex differences in behavior are generally absent during the early neonatal period (6). In contrast, the appearance of a sex difference among adult subjects in morphine-induced locomotor activity was anticipated. Research indicates that females typically exhibit higher baseline activity levels and are more sensitive to the effects of morphine than are adult males (4).

Ontogenetic changes in both the physiological consequences of morphine and stimulus selection have been well documented. Two of those differences are especially relevant to the CPP procedure: immature rats are more sensitive than are adults to the effects of morphine (12,13,19,21). Moreover, they possess both an enhanced tendency to process redundant aspects of a learning episode (30) and a disposition to equate stimuli from different sensory modalities (18). Together, those differences anticipate that preweanlings may be particularly well suited to the demands of the CPP task.

In general, the present results substantiate that characterization of the preweanling rat. Under the present conditions, the magnitude of CPP produced by either 1 or 5 mg/kg of morphine does not appear to differ as a function of age. An alternative interpretation of this finding, however, requires that a distinction be made between the nominal and functional dose of morphine used in the present experiment. Although morphine dose was nominally equated across the ages tested (i.e., 1 and 5 mg/kg), it is likely that these doses differed functionally after administration. Due to the relatively incomplete physiological development of preweanling rats compared to that of adults, the doses of morphine used might have been markedly higher for preweanling subjects. Regardless of this potential for functional differences across age in the dose of morphine employed, preweanling rats appear to be at least as proficient as adults at associating the rewarding effects of morphine with a compartment composed of visual, tactile, and olfactory stimuli.

Finally, preweanling and adult rats conditioned with morphine displayed significantly lower activity levels in the CS+ compartment relative to the CS− compartment during the preference test. Control subjects, on the other hand, were equally active in both compartments of the CPP apparatus. Consistent with the compartment preference measure, activ-

ity levels did not differ across consecutive intervals of the 15-min test session. Although preweanling and adult rats did not differ significantly on this activity measure, the data suggest that locomotor behavior was more profoundly affected in adults. This apparent trend was undoubtedly obscured in the analysis due to the sizable amount of variance in the adult activity scores, relative to that present in the preweanling data.

Research indicates that drugs with rewarding properties generally produce increases in locomotor activity (17,35,40). Moreover, at least in some cases, those locomotor effects may be elicited by the stimuli paired with the drug effect (14). Although the former observation was supported in the present study, the latter was not. A number of studies have also reported that rats tend to be least active while in a preferred chamber (1,23,38). Consequently, the consensus in the literature appears to be that inactivity in the preferred compartment allows the subject to maintain contact with the drug-paired stimuli.

Although the present results indicate that preweanling and adult rats do not differ substantially in the expression of a morphine-induced CPP, several intriguing questions concerning the ontogeny of the CPP effect remain unanswered. In the desire to produce robust drug-induced CPP in adults, researchers have manipulated several stimulus dimensions in alternate conditioning compartments. As a result, conditioning compartments are typically composed of at least visual, tactile, and olfactory stimuli; however, relatively little is known about stimulus selection in this procedure. Development may determine to what particular stimulus, or to what combination of stimuli, drug reward will become associated (32). Therefore, a compelling reason exists to compare conditioned responding to separate elements following CPP conditioning with a compound stimulus in both preweanling and adult rats.

The present results add to a growing body of research that describes striking similarities in the affective consequences of morphine across ontogeny. Although the parameters that influence CPP in adults have been well documented, it is inviting to hypothesize that developing organisms might be differentially affected by similar manipulations. For example, because parametric manipulations often reduce ontogenetic differences in performance (33), potential age-related differences in the present experiment may have been obscured inadvertently. Regardless, the present results appear to indicate that the CPP task may be particularly well suited to subsequent investigations of the ontogeny of drug reward, learning and memory, and stimulus selection in rats.

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