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# Effects of the κ-opioid receptor agonist U-50,488 on morphine-induced place preference conditioning in the developing rat

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**Abstract**

The ability of the κ-opioid receptor agonist *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide methanesulfonate (U-50,488) to modulate morphine-induced reward was assessed in preweanling (10- and 17-day-old) and periadolescent (35-day-old) rats using the conditioned place preference paradigm. Conditioning and testing were conducted in a three compartment chamber, with each end compartment having its own distinct tactile and odor cues (almond or lemon). An abbreviated conditioned place preference procedure was used in which rats received two saline-odor pairings on the first conditioning day, and two saline- or morphine-odor pairings on the second day. In some experiments, rats were given U-50,488 (2–10 mg/kg, s.c.) 30 min prior to being conditioned with morphine (0.1–8 mg/kg, i.p.). On the third day, rats were allowed free access to the entire chamber for 900 s and compartment preferences were determined. Similar to adult rats, morphine (0.5 mg/kg) was consistently able to induce conditioned place preferences in the two preweanling age groups. This effect was attenuated by κ-opioid receptor agonist pretreatment, as U-50,488 not only enhanced the locomotor activity of 10- and 17-day-old rats, but it blocked the morphine-induced place preference conditioning of these younger animals. In contrast, periadolescent (35-day-old) rats did not exhibit morphine-induced place preferences, nor did they show enhanced locomotor activity after U-50,488 treatment; however, using the same procedure, a different group of similarly aged rats showed conditioned preference produced by 20 mg/kg cocaine (i.p.). Therefore, these results suggest that reward processes are functionally mature in the preweanling rat (at least by 10 days of age), but that periadolescent rats are generally unresponsive to μ- and κ-opioid drugs.

*Keywords:* U-50,488; Morphine; Reward; (Rat); Ontogeny

## 1. Introduction

In adult rats, both the dopamine and opioid systems have been implicated in reward (Wise and Bozarth, 1987; Di Chiara and North, 1992). For example, self-administration, operant and conditioned place preference studies have shown that indirect dopamine agonists (e.g., cocaine and amphetamine) are reinforcing (Gallistel and Karras, 1984; Bardo et al., 1986; Hiroi and White, 1991; Pettit and Justice, 1991). Activation of the various opioid receptor subtypes also affects reward processes. More specifically, agonists at μ- (e.g., morphine and heroin) and δ-opioid receptors will maintain self-administration and produce conditioned place preferences (Ettenberg et al., 1982; Shippenberg and Herz, 1987; Shippenberg et al., 1987; Vezina and Stewart, 1987; Koob, 1992). In contrast, κ-opioid receptor agonists (e.g., *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide methanesulfonate (U-50,488)) do not induce reward and, at certain doses, are aversive (Mucha and Herz, 1985; Shippenberg and Herz, 1991; Bals-Kubik et al., 1993). Interestingly, κ-opioid receptors appear to modulate dopamine and μ-opioid functioning in adult rats, because U-50,488 attenuates cocaine- and morphine-induced place preference conditioning (Suzuki et al., 1992; Funada et al., 1993; Crawford et al., 1995). The mechanisms responsible for U-50,488's actions are uncertain, but κ-opioid receptor agonists probably induce some of their behavioral effects by inhibiting dopamine release in the nucleus accumbens (Di Chiara and Imperato, 1988; Spanagel et al., 1990; Maisonneuve et al., 1994).

Like with adult rats, the reward processes of preweanling animals are also affected by drugs acting on dopamine and μ-opioid receptors. For example, cocaine and am-

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phetamine produce conditioned place preferences in preweanling rats and mice, whereas dopamine receptor antagonists disrupt reward functioning (Smith and Holman, 1987; McDougall et al., 1991, 1992; Laviola et al., 1992; Pruitt et al., 1995). Similarly, systemic and intracerebroventricular injections of morphine produce place preferences and odor conditioning in rats as young as 4–5 days of age (Kehoe and Blass, 1986; Barr and Rossi, 1992; Randall et al., 1992). Curiously, dopamine and opioid receptor agonists have quite different effects in slightly older animals, as periadolescent (30- to 40-day-old) rats show diminished behavioral responses to amphetamine and cocaine and accentuated responses to morphine (Lanier and Isaacson, 1977; Spear and Brick, 1979; Spear et al., 1982).

At present, few studies have investigated the effects of $\kappa$-opioid receptor agonists on the reward processes of preweanling rats; however, there is some evidence that these drugs do not affect young rats in an adult-like manner. More specifically, U-50,488 depresses the locomotor activity of periadolescent and adult rodents (VonVoigtlander et al., 1983; Ukai and Kameyama, 1985; Di Chiara and Imperato, 1988; Schnur and Walker, 1990), while the same drug markedly enhances the motor activity of fetal and preweanling rats (Jackson and Kitchen, 1989; Carden et al., 1991, 1994; Smotherman et al., 1993; Kehoe and Boylan, 1994). This ontogenetic difference indicates that the $\kappa$-opioid system may not become fully mature until after the preweanling period, and it brings into question whether the $\kappa$-opioid receptors of preweanling rats are capable of modulating $\mu$-opioid-mediated reward in an adult-typical manner. To examine this issue, the conditioned place preference paradigm was used to assess morphine's reinforcing properties in preweanling (10- and 17-day-old) and periadolescent (35-day-old) rats. The ability of U-50,488 to attenuate place preference conditioning was then determined for all three age groups.

## 2. Materials and methods

### 2.1. Animals

Subjects were 256 male and female rats of Sprague–Dawley descent (Harlan), born and raised at California State University (San Bernardino, CA, USA). Litters were culled to 8–10 pups at 3 days of age. Rats were initially conditioned when 10, 17 or 35 days of age. The 10- and 17-day-old rats were kept with the dam throughout behavioral testing, while the 35-day-old rats were weaned at 21 days of age and group housed away from the dam. Assignment of subjects was random, with no more than one rat from each litter being placed into a particular treatment group. There were an equal number of male and female rats in each group. The colony room was maintained at 23–25°C and kept under a 14:10 light:dark cycle. Testing occurred in a separate experimental room and was conducted during the light phase of the cycle.

### 2.2. Apparatus

Conditioning and testing were done in rectangular plywood chambers that had three compartments separated by removable partitions. For the 10- and 17-day-old rats, the two end compartments measured $15 \times 15 \times 21$ cm high, while the middle compartment measured $9 \times 15 \times 21$ cm high. For the 35-day-old rats, the two end compartments measured $20 \times 20 \times 28$ cm high, while the middle compartment measured $12 \times 20 \times 28$ cm high (the larger chambers were used to somewhat equate for differences in body size). The tactile surface of each compartment varied, as one end compartment had rubberized pebble flooring, whereas the other end compartment had plywood flooring scored (2 cm deep) in a checkerboard fashion. The middle compartment had smooth plywood flooring. All compartments were painted gray and were covered by a clear Plexiglas top. (The number of visual cues in each chamber were minimized, because the eyes of 10-day-old rats are not open.)

Besides the tactile differences, both end compartments were equipped with an odor delivery system. More specifically, beneath each of the end compartments, and connected via 15 small holes in the floor, were rectangular plastic containers ($14 \times 7 \times 4$ cm deep) partially filled with pinewood chip bedding. Lemon or almond extract (Irish) were applied to the pinewood bedding of each container to provide distinctive odor cues for the end compartments (10 cc of the extract was used for conditioning and 1 cc was used for preference testing). During conditioning, solid partitions were used to keep rats in the appropriate compartments; whereas, the partitions were raised during testing (5.5 cm: 10- and 17-day-olds; 8 cm: 35-day-olds), so that each rat could move freely between the compartments.

### 2.3. Drugs

Morphine sulfate, cocaine hydrochloride and U-50,488 (*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide methanesulfonate) were purchased from Research Biochemicals (Natick, MA, USA). Morphine and cocaine were dissolved in saline and injected intraperitoneally (i.p.), while U-50,488 was dissolved in saline and injected subcutaneously (s.c.). For the 10- and 17-day-old rats, both drugs were injected at a volume of 5 ml/kg; whereas, for the 35-day-old rats, the drugs were injected at a volume of 2 ml/kg.

### 2.4. General procedures

In each experiment, conditioning occurred on two consecutive days followed by a single test day. This brief

two-day conditioning procedure, rather than a more extended 4 or 8 day procedure, was done in order to minimize the impact of maturational changes during conditioning (see also Laviola et al., 1992; Randall et al., 1992). On each conditioning day, rats received two 30-min conditioning trials separated by a 4-h interval. On the first conditioning day, all rats were injected with saline immediately prior to their two placements in the almond- or lemon-scented compartment. On the second conditioning day, rats were injected with either saline or morphine immediately prior to being placed in the opposite compartment containing the alternate scent. A second identical conditioning trial occurred 4 h later. Although having two conditioning trials per day is unusual, this procedure allowed two drug trials during the abbreviated conditioning procedure. In a meta-analysis, Bardo et al. (1995) have shown that two drug trials produce a stronger morphine-induced place preference than only a single trial. On the test day, rats were injected with saline and had free access to all compartments for 900 s.

Both conditioning and test trials were videotaped for scoring at a later date by experimenters blind to treatment conditions. Time spent in the drug-paired compartment was assessed on the test day, whereas locomotor activity (line-crosses) was measured continuously during both conditioning and testing. When measuring locomotor activity each compartment was divided into four equal quadrants, with a line-cross being defined as a rat putting both forepaws and snout into an adjacent quadrant.

#### 2.4.1. Experiment 1

In the first experiment we attempted to determine a dose of morphine that would reliably produce a conditioned place preference in the preweanling rat. To that end, 32 ($n = 8$/group) 17-day-old rats (age at initial conditioning) were injected with saline prior to receiving two separate placements in the almond- or lemon-scented compartment. On the second conditioning day, rats were given morphine (0, 0.1, 0.2, or 0.5 mg/kg, i.p.) prior to their two placements in the opposite compartment.

#### 2.4.2. Experiment 2

To determine whether a $\kappa$-opioid receptor agonist would attenuate morphine-induced place preference conditioning, 64 ($n = 8$/group) 17-day-old rats were given two saline conditioning trials as described in the General Procedures. On the second conditioning day, rats were pretreated with U-50, 488 (0, 2, 5, or 10 mg/kg, s.c.) 30 min before the two morphine conditioning trials. Once again, morphine (0 or 0.5 mg/kg, i.p.) was injected immediately prior to the rats being placed in the almond- or lemon-scented compartment.

#### 2.4.3. Experiment 3

In the third experiment, a total of 96 rats ($n = 8$/group) were initially tested when 10, 17, or 35 days of age. Conditioning was again done across two days, with rats receiving two saline conditioning trials on the first day. On the second day, rats were pretreated with U-50,488 (0 or 2 mg/kg, s.c.) 30 min before the two morphine (0 or 0.5 mg/kg, i.p.) conditioning trials.

#### 2.4.4. Experiment 4

Morphine (0.5 mg/kg) did not produce a conditioned place preference in the 35-day-old rats, so higher doses of morphine were used in an attempt to produce place preference conditioning in the 35-day-olds. This experiment was substantially the same as Experiment 1, with the exception that 40 ($n = 8$/group) 35-day-old rats were treated with 0, 1, 2, 4, or 8 mg/kg morphine immediately prior to their placements in the almond- or lemon-scented compartment. U-50,488 was not administered.

#### 2.4.5. Experiment 5

Regardless of dose, a morphine-induced conditioned place preference was not apparent in the 35-day-old rats. Therefore, to determine whether periadolescent rats will exhibit place preference conditioning 24 ($n = 8$/group) 35-day-old rats were tested as in Experiment 1, except that cocaine (an indirect dopamine agonist) was substituted for morphine. Cocaine (0, 10, or 20 mg/kg, i.p.) was injected immediately prior to the rats being placed in the almond- or lemon-scented compartment.

### 2.5. Statistics

Analyses of variance were used to compare line-crosses (collapsed across the two daily conditioning trials) and total time spent in the drug-paired compartment for the various groups of rats. Significant main effects and interactions were further analyzed using Tukey tests ($P < 0.05$). The data were collapsed across male and female rats because no differences due to gender were apparent ($P > 0.05$). In order to determine whether a conditioned place preference was present, Student's $t$-tests ($P < 0.05$) were used to compare the morphine and saline control groups.

## 3. Results

### 3.1. Experiment 1: Effects of morphine conditioning in 17-day-old rats

Morphine (0.1, 0.2, or 0.5 mg/kg) did not affect the line-crosses of 17-day-old rats during conditioning (data not shown). On the test day, 17-day-old rats treated with 0.5 mg/kg morphine spent significantly more total time in the drug-paired compartment than their saline controls, treatment effect, $F(3,28) = 3.12$, $P < 0.05$, and Tukey tests, $P < 0.05$ (Fig. 1). Rats given lower doses of morphine (0.1 or 0.2 mg/kg) did not differ from the saline-

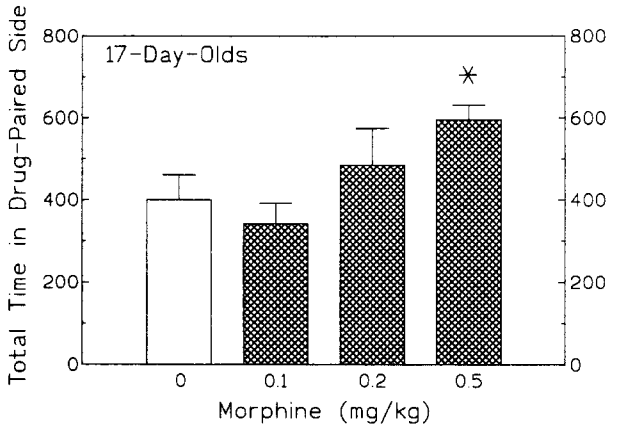


Fig. 1. Total time in seconds (±S.E.M.) spent by 17-day-old rats in the drug-paired compartment on test day ($n = 8$/group). Rats were drug-free on the test day and allowed 900 s access to the three compartment chamber. During conditioning, the rats had been injected with morphine (0, 0.1, 0.2 or 0.5 mg/kg, i.p.) immediately prior to being placed in the almond- or lemon-scented compartment. * Indicates a significant difference from the saline-treated rats ($P < 0.05$).

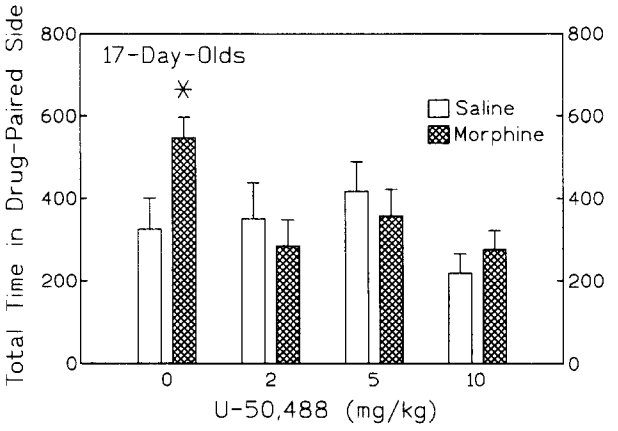


Fig. 3. Total time in seconds (±S.E.M.) spent by 17-day-old rats in the drug-paired compartment on the test day ($n = 8$/group). Rats were drug-free on the test day and allowed 900 s access to the three compartment chamber. During conditioning, rats were treated as in Fig. 2. * Indicates a significant difference from the saline-treated rats ($P < 0.05$).

treated rats, Tukey tests, $P > 0.05$. Separate analyses indicated that almond and lemon were about equally preferred by the various groups of rats ($P > 0.05$).

### 3.2. Experiment 2: Effects of U-50,488 pretreatment on morphine-induced place preference conditioning in 17-day-old rats

Overall, 17-day-old rats receiving U-50,488 (2, 5, or 10 mg/kg) had significantly more line-crosses during conditioning than saline-treated rats, pretreatment main effect, $F(3,56) = 13.40$, $P < 0.001$, and Tukey tests, $P < 0.05$ (Fig. 2). U-50,488's activity enhancing effects were partially, but not completely, blocked by morphine, treatment main effect, $F(1,56) = 12.64$, $P < 0.001$.

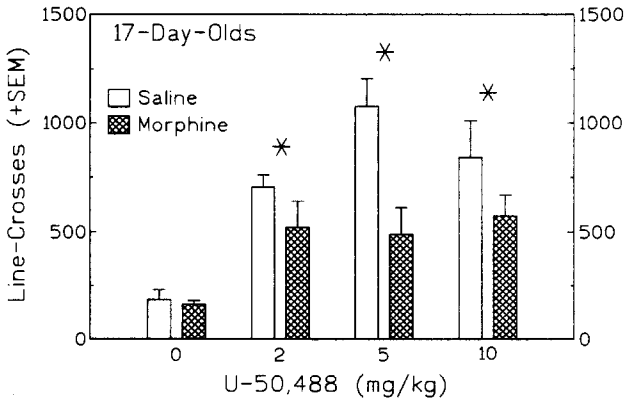


Fig. 2. Mean number (±S.E.M.) of line-crosses in the drug-paired compartment during conditioning ($n = 8$/group). The 17-day-old rats were injected with U-50,488 (0, 2, 5, or 10 mg/kg, s.c.) 30 min prior to conditioning, and morphine (0 or 0.5 mg/kg, i.p.) immediately prior to conditioning. * Indicates a significant difference from the groups receiving 0 mg/kg U-50,488 ($P < 0.05$).

During testing, rats treated with morphine spent significantly more time in the drug-paired compartment than did their saline controls, $t(14) = 2.43$, $P < 0.05$ (Fig. 3). This preference was apparently blocked by U-50,488, because rats given both U-50,488 and morphine did not differ from the saline-treated rats. Overall, rats given 10 mg/kg U-50,488 spent less total time in the drug-paired compartment than rats injected with smaller doses of U-50,488 (2 or 5 mg/kg) or saline, pretreatment main effect, $F(3,56) = 3.22$, $P < 0.05$, and Tukey tests, $P < 0.05$. This suggests that 10 mg/kg U-50,488 produced a place aversion in the 17-day-old rats.

### 3.3. Experiment 3: Effects of U-50,488 pretreatment on morphine-induced place preference conditioning in 10-, 17- and 35-day-old rats

The mean number of line-crosses exhibited by the U-50,488- and morphine-treated 10-, 17- and 35-day-old rats during conditioning are shown in Fig. 4. The 10-day-old rats injected with U-50,488 (2 mg/kg) were significantly more active than their saline-treated controls, pretreatment main effect, $F(1,28) = 91.85$, $P < 0.001$. The U-50,488-induced increase in locomotor activity was partially blocked by morphine, because 10-day-olds given both U-50,488 and morphine had fewer line-crosses than rats receiving the $\kappa$-opioid receptor agonist alone, Pretreatment X Treatment interaction, $F(1,28) = 7.23$, $P < 0.01$, and Tukey tests, $P < 0.05$. Likewise, 17-day-old rats given U-50,488 (2 mg/kg) had significantly more line-crosses during conditioning than same aged rats treated with saline, pretreatment main effect, $F(1,28) = 26.71$, $P < 0.001$. In contrast, neither U-50,488 nor morphine affected the locomotor activity of the periadolescent rats.

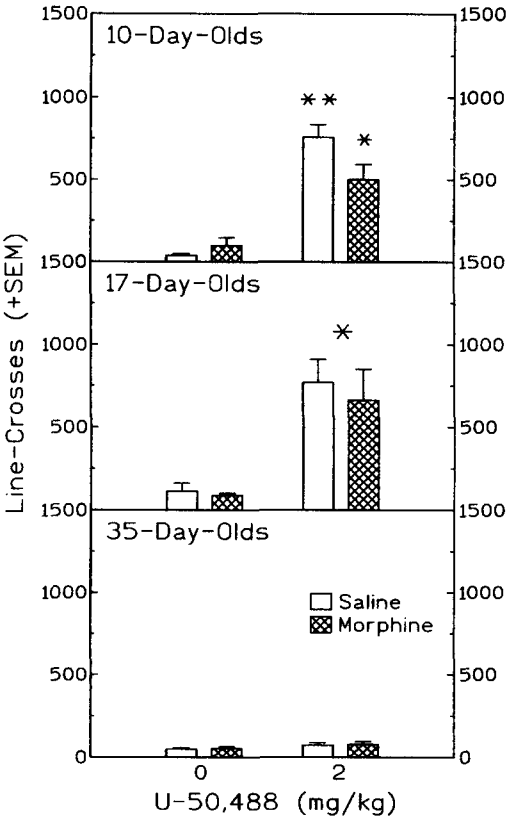


Fig. 4. Mean number (±S.E.M.) of line-crosses in the drug-paired compartment during conditioning ($n = 8$/group). The 10-, 17- and 35-day-old rats were injected with U-50,488 (0 or 2 mg/kg, s.c.) 30 min prior to conditioning, and morphine (0 or 0.5 mg/kg, i.p.) immediately prior to conditioning. * Indicates a significant difference from the groups receiving 0 mg/kg U-50,488 ($P < 0.05$). ** Indicates a significant difference from all other groups ($P < 0.05$).

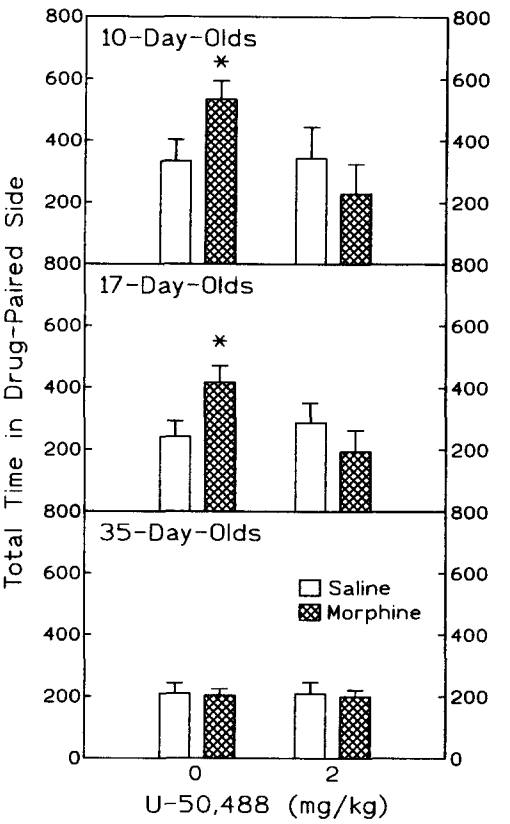


Fig. 5. Total time in seconds (±S.E.M.) spent by the 10-, 17- and 35-day-old rats in the drug-paired compartment on the test day ($n = 8$/group). Rats were drug-free on the test day and allowed 900 s access to the three compartment chamber. During conditioning, rats were treated as in Fig. 4. * Indicates a significant difference from all other groups ($P < 0.05$).

When treated with morphine, 10- and 17-day-old rats spent significantly more total time in the drug-paired compartment than rats given saline, $t(14) = 2.48$, $P < 0.05$, and $t(14) = 2.38$, $P < 0.05$, respectively (upper and middle graphs, Fig. 5). U-50,488 attenuated these morphine-induced preferences in both of the preweanling age groups. More specifically, 10- and 17-day-old rats given both U-50,488 and morphine spent significantly less time in the drug-paired compartment than rats given morphine alone, Pretreatment X Treatment interactions, $F(1,28) = 4.43$, $P < 0.05$, and $F(1,28) = 6.14$, $P < 0.05$, respectively. Morphine did not induce a place preference in the periadolescent rats (lower graph, Fig. 5).

### 3.4. Experiment 4: Effects of morphine conditioning in 35-day-old rats

Morphine (1, 2, 4, or 8 mg/kg) did not affect the locomotor activity of 35-day-old rats during conditioning (data not shown). Similarly, analyses of the test day data indicated that the various doses of morphine (1, 2, 4, or 8 mg/kg) were unable to induce a conditioned place preference in 35-day-old rats (Fig. 6). Once again, separate statistical analyses showed that the rats did not differentially prefer the almond or lemon odors.

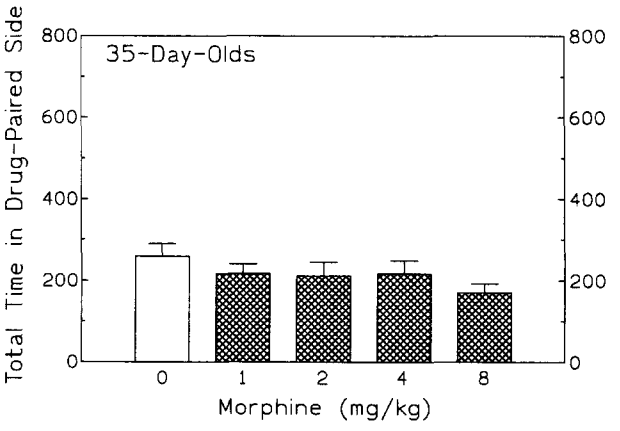


Fig. 6. Total time in seconds (±S.E.M.) spent by 35-day-old rats in the drug-paired compartment on the test day ($n = 8$/group). Rats were drug-free on the test day and allowed 900 s access to the three compartment chamber. During conditioning, the 35-day-old rats had been injected with morphine (0, 1, 2, 4, or 8 mg/kg, i.p.) immediately prior to being placed in the almond- or lemon-scented compartment.

Table 1
Total number of seconds (±S.E.M.) spent by 35-day-old rats ($n$ = 8/group) in the two end compartments on the test day. During conditioning rats in the cocaine groups received cocaine on the drug side and saline on the control side, whereas rats in the saline group received saline on both sides. Rats were drug-free on the test day

| Treatment | Number of seconds per compartment | |
|---|---|---|
| | drug side | control side |
| Saline | 220.1 ± 53.3 | 194.8 ± 19.1 |
| Cocaine (10 mg/kg) | 279.4 ± 52.7 | 224.1 ± 56.1 |
| Cocaine (20 mg/kg) | 486.6 [a] ± 83.4 | 169.4 ± 40.2 |

[a] Significantly different from saline group, $P < 0.05$.

### 3.5. Experiment 5: Effects of cocaine conditioning in 35-day-old rats

In contrast with morphine, cocaine (10 or 20 mg/kg) produced a dose-dependent increase in the locomotor activity of 35-day-old rats during conditioning, treatment effect, $F(2,21) = 25.62$, $P < 0.001$, and Tukey tests, $P < 0.05$ (data not shown). Moreover, 35-day-old rats conditioned with 20 mg/kg cocaine spent significantly more time in the drug-paired compartment than their saline controls, treatment effect, $F(2,21) = 4.67$, $P < 0.05$, and Tukey tests, $P < 0.05$ (Table 1). Rats given 10 mg/kg cocaine did not differ from the saline controls, Tukey tests, $P < 0.05$.

## 4. Discussion

Consistent with past research, morphine was able to induce a conditioned place preference in preweanling (10- and 17-day-old) rats (Kehoe and Blass, 1986; Barr and Rossi, 1992; Randall et al., 1992). The dose range capable of supporting place preference conditioning in these younger animals is relatively narrow, since moderate to high doses of morphine (2–10 mg/kg) result in place aversions rather than place preferences (unpublished data; Randall et al., 1992). Pretreatment with U-50,488 attenuated morphine-induced place preference conditioning in both of the preweanling age groups, indicating that κ-opioid receptors are capable of modulating μ-opioid-mediated reward in rats as young as 10 days of age. U-50,488's actions appear to be due to a direct diminution of morphine's rewarding properties, since pretreatment with U-50,488 (2 mg/kg) did not avert saline-treated rats from the drug-paired compartment. This point is important because κ-opioid receptor agonists induce ultrasonic distress vocalizations in preweanling rats, and higher doses of U-50,488 (10–30 mg/kg) produce place aversions in both 3- and 7-day-olds (Carden et al., 1991, 1994; Barr et al., 1994; Kehoe and Boylan, 1994).

In general, the present results are consistent with models of reward previously proposed by Di Chiara and North (1992) and Spanagel et al. (1992). These researchers have suggested that reward functioning is correlated with the activity of dopamine neurons in the mesolimbic pathway, which projects from the ventral tegmental area to the nucleus accumbens. According to this model, amphetamine and cocaine affect reward by directly increasing synaptic dopamine in the nucleus accumbens; whereas, morphine indirectly enhances dopamine release by binding to μ-opioid receptors in the ventral tegmental area and disinhibiting the dopamine fibers of the mesolimbic pathway (Di Chiara and Imperato, 1988; Di Chiara and North, 1992; Spanagel et al., 1992). In contrast, U-50,488 apparently attenuates cocaine- and morphine-induced reward by stimulating κ-opioid receptors located on dopamine terminals in the nucleus accumbens (Spanagel et al., 1992; Funada et al., 1993). Consistent with this, U-50,488 inhibits both basal and cocaine-induced dopamine release from these terminals (Spanagel et al., 1990; Crawford et al., 1994; Maisonneuve et al., 1994).

That U-50,488 blocks morphine-induced place preference conditioning in preweanling rats supports the model of reward just presented, and suggests that these reward pathways are functionally mature by at least 10 days of age. In contrast, U-50,488 substantially increases the locomotor activity of preweanling animals (Figs. 2 and 4), while either depressing or having little effect on the activity of adults (VonVoigtlander et al., 1983; Ukai and Kameyama, 1985; Di Chiara and Imperato, 1988; Schnur and Walker, 1990; Crawford et al., 1995). The fact that U-50,488 has adult-typical actions on the reward processes of preweanling rats, but has adult-atypical actions on locomotor activity, suggests that the κ-opioid receptors modulating reward are distinct from those modulating activity. One possibility is that reward and activity are mediated by anatomically distinct subdivisions of the nucleus accumbens (see Cameron and Crocker, 1989; Heimer et al., 1991), with these subdivisions becoming functionally mature at different ages. Alternatively, it is possible that κ-opioid receptors located in an entirely different brain region are responsible for U-50,488's activity enhancing effects. Although speculative, the striatum is a likely candidate, because this brain region is known to have a high density of κ-opioid receptors and is involved in the mediation of unlearned behavior (Arnt, 1987; Mansour et al., 1987). Interestingly, Smotherman et al. (1993) have reported that dopamine activation modulates κ-opioid functioning in the fetal rat (day 21 of gestation), rather than the typical κ-opioid-to-dopamine interaction observed in adults. Therefore, it is possible that U-50,488's ability to block reward functioning is due to a κ-opioid-to-dopamine interaction in the nucleus accumbens (i.e., U-50,488 blocks reward by depressing dopaminergic functioning); whereas, U-50,488's ability to paradoxically increase the locomotor activity of the preweanling rat may be due to an immature dopamine-to-κ-opioid interaction in a second brain region (i.e., U-50,488 directly increases the locomotor activity of

the preweanling rat, without modulating a dopaminergic mechanism).

An additional consideration is that morphine was able to induce place preference conditioning, while leaving the locomotor activity of the two preweanling age groups unaffected (see also Caza and Spear, 1980; Jackson and Kitchen, 1989). In some ways this was surprising, since morphine enhanced reward functioning without inducing hyperactivity. This dissociation is not consistent with models of reward which postulate that the rewarding and psychomotor stimulating properties of addictive drugs are mediated through the same biological mechanisms (see Wise and Bozarth, 1987). In the case of morphine, it is possible that the drug's psychomotor properties are masked by the concurrent activation of brain areas which produce sedation (Wise and Bozarth, 1987). In contrast, U-50,488's ability to substantially enhance locomotor activity while inhibiting reward, suggests that forward locomotion and reward are mediated by dissociable processes (see also Stinus et al., 1989; Boyle et al., 1991).

A different pattern of responding was observed in the periadolescent rat, as 35-day-olds showed an almost complete lack of responsiveness to opioid drugs. More precisely, periadolescent rats did not exhibit morphine-induced place preference conditioning even when a broad dose range of morphine (0.5–8 mg/kg) was used (Figs. 5 and 6). Similarly, U-50,488 did not affect the locomotor activity of periadolescent rats (Fig. 4). Very few studies have investigated the effects of $\mu$- and $\kappa$-opioid receptor agonists on periadolescent animals, but the inability of morphine and U-50,488 to induce a place preference or enhance the activity of 35-day-old rats is consistent with the idea that this age group is generally less sensitive to pharmacological challenge (see Spear, 1979; Spear and Brake, 1983, for reviews). This interpretation must be tempered however, because 20 mg/kg cocaine produced a conditioned place preference in the periadolescent rat (Table 1). It is uncertain why this indirect dopamine agonist supported place preference conditioning, while morphine did not. Therefore, it is possible that optimizing the place preference procedure (e.g., adding additional conditioning days, using visual rather than olfactory cues, adjusting the drug dose, etc.) may result in the periadolescent rat showing a morphine-induced place preference (see Bardo et al., 1995, for an analysis of conditioning parameters). At present, however, the inability of morphine and U-50,488 to affect the behavior of the 35-day-olds suggests that periadolescent rats, when compared to both younger and older animals, respond in a qualitatively different manner to opioid drugs.

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