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Effects of dopamine D_1 and D_2 receptor antagonists on cocaine-induced place preference conditioning in preweanling rats

Douglas L. Pruitt [1], Carlos A. Bolanos, Sanders A. McDougall *

Department of Psychology, California State University, San Bernardino, CA 92407, USA

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Abstract

The effects of dopamine D_1 and D_2 receptor antagonists on the reward processes of 10- and 17-day-old rats were assessed 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 and lemon). During six experiments, 10- and 17-day-old rats (age at initial conditioning) were injected intraperitoneally with either saline, the dopamine D_1 receptor antagonist $R(\pm)$-SCH 23390 hydrochloride (0.01–1.0 mg/kg), or the dopamine D_2 receptor antagonists $(\pm)$-sulpiride (1–100 mg/kg) or $S(-)$-eticlopride hydrochloride (0.1–0.5 mg/kg) 30 min prior to being injected with cocaine hydrochloride (20 mg/kg) or saline. After the latter injections, rats were immediately confined in the lemon-scented (nonpreferred) compartment for 30 min. On the alternate conditioning day, rats were injected with saline and confined in the almond-scented compartment. On the third day (i.e., the test day), rats were given saline and allowed free access to the entire chamber for 15 min. The results showed that the dopamine D_1 receptor antagonist SCH 23390 blocked the cocaine-induced place preference conditioning of both 10- and 17-day-old rats. Surprisingly, the dopamine D_2 receptor antagonists sulpiride and eticlopride blocked the place preference conditioning of 10-day-old rats, while leaving the 17-day-old rats unaffected. These results indicate that dopamine D_1 receptors are critically involved in the reward processes of preweanling rats, but that the importance of dopamine D_2 receptors changes across ontogeny.

Keywords: Cocaine; SCH 23390; Sulpiride; Eticlopride; Ontogeny

1. Introduction

A variety of experimental paradigms have provided evidence that the reward processes of adult rats are mediated, at least partially, by dopamine neurons; however, the relative involvement of dopamine D_1 and D_2 receptors in reward is of some disagreement (Nakajima and McKenzie, 1986; Nakajima and Baker, 1989; Wise and Rompre, 1989; Miller et al., 1990). Results from operant paradigms indicate that both dopamine D_1 and D_2 receptors are necessary for the full expression of reward. For example, intracranial or systemic administration of the dopamine D_1 receptor antagonist SCH 23390, or a variety of dopamine D_2 receptor antagonists, will block bar press responding for food, water, and brain stimulation (Beninger et al., 1987; Sanger, 1987; Kurumiya and Nakajima, 1988; Nakajima and Baker, 1989). Instrumental tasks provide similar results, as dopamine D_1 and D_2 receptor antagonists disrupt run-way responding for a previously reinforcing stimulus (Wise et al., 1978; Ettenberg and Camp, 1986; Nakajima and McKenzie, 1986). Unfortunately, both operant and instrumental paradigms require that animals make appropriate, and sometimes complex, motor responses to get reinforced: motor responses that are impaired by dopamine receptor antagonists. Thus, using these paradigms, it can be difficult to determine the extent to which a drug is affecting reward processes or motoric ability (see Ettenberg et al., 1981; Beninger, 1989; Ettenberg, 1989, for a fuller discussion).

The conditioned place preference paradigm avoids these interpretive difficulties, because reward is assessed in a non-drug state (see Hoffman, 1989, for a review). Even so, conditioned place preference studies

* Corresponding author. Tel. (909) 880-5581, fax (909) 880-7003.
[1] Current address: Department of Psychology, Bowling Green State University, Bowling Green, OH 43402, USA.

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typically show that both dopamine D_1 and D_2 receptors are involved in reward. For example, acquisition of an amphetamine-induced place preference is blocked by the dopamine D_1 receptor antagonist SCH 23390 (Leone and Di Chiara, 1987; Hoffman and Beninger, 1989; Hiroi and White, 1991). Similarly, adult rats given dopamine D_2 receptor antagonists prior to conditioning show no preference for the amphetamine-paired compartment on the test day (Hoffman and Beninger, 1989; Hiroi and White, 1991; but see Spyraki et al., 1982). Therefore, results from a number of different experimental paradigms indicate that both dopamine D_1 and D_2 receptors are involved in the reward processes of adult rats.

Although studied less intensively, ontogenetic studies have shown that the dopamine system is critical for reward processes in preweanling animals (Smith and Holman, 1987). For example, Barr and Lithgow (1986) found that amphetamine and cocaine would enhance the self-stimulation of rats as young as 3 days of age. Consistent with this, preweanling mice exhibit a strong conditioned place preference for a compartment previously paired with cocaine (Laviola et al., 1992). Although these studies do not implicate a particular receptor system, there is evidence that dopamine D_1 and D_2 receptors mediate reward in preweanling rats, albeit in an adult atypical fashion. More specifically, using an instrumental appetitive approach paradigm, McDougall et al. (1991,1992a) found that SCH 23390-treated 11- and 17-day-old rats would quickly stop approaching a previously reinforcing lactating dam. Sulpiride did not directly affect the appetitive approach responding of 11- and 17-day-old rats, but it did depress responding when given in combination with SCH 23390 (McDougall et al., 1991,1992a). Thus, in contrast to the adult, selective blockade of dopamine D_2 receptors was not sufficient to affect the reinforced responding of the preweanling rat.

Therefore, to further determine the role of dopamine D_1 and D_2 receptors in the ontogeny of reward, we assessed the effects of selective dopamine D_1 and D_2 receptor antagonists on the cocaine-induced place preference conditioning of 10- and 17-day-old rats (age at initial conditioning). Based on the aforementioned experiments it was predicted that dopamine D_1, but not D_2, receptor antagonists would block the place preference conditioning of preweanling rats.

2. Materials and methods

2.1. Animals

Subjects were 384 ($n = 8$) 10- and 17-day-old (age at initial conditioning) male and female rats of Sprague-Dawley descent (Harlan Industries, Indianapolis, IN, USA). The rats were born and raised at California State University, San Bernardino. Litters were culled to a maximum of 10 pups at 3 days of age. The colony room was maintained at 23–25°C and kept under a 14:10 h light:dark cycle. Testing occurred in a separate experimental room which was maintained at approximate thermoneutrality for rats of these ages (Conklin and Heggeness, 1971). In this case, 10-day-old rats were maintained at 31°C, while 17-day-olds were kept at 24°C.

2.2. Apparatus

The testing apparatus was a rectangular plywood chamber that had three compartments separated by removable partitions. The two end compartments measured 15 × 15 × 21 cm high, while the middle compartment measured 9 × 15 × 21 cm high. All compartments were painted gray and were covered by a clear Plexiglas top. One end compartment had rubberized non-slip flooring, whereas the other end compartment had plywood flooring scored (1 cm deep) in a checkerboard fashion. The middle compartment had smooth plywood flooring. Besides the tactile differences, both end compartments were equipped with an odor delivery system. More specifically, beneath each end compartment, and connected via 15 small holes in the floor, were rectangular plastic containers (14 × 7 × 4 cm deep) partially filled with pinewood chip bedding. Lemon and almond extracts 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, during testing, the partitions were raised 5.5 cm, so that each rat could move freely between the compartments. Visual cues were minimized, because the eyes of 10-day-old rats are fully closed.

2.3. Drugs

Cocaine hydrochloride, *R*(+)-SCH 23390 hydrochloride, (±)-sulpiride, and *S*(−)-eticlopride hydrochloride were purchased from Research Biochemicals (Natick, MA, USA). All drugs were dissolved in saline, with sulpiride requiring a small volume of glacial acetic acid. Drugs were injected intraperitoneally at a volume of 5 ml/kg.

2.4. Behavioral testing

In each experiment, rats were randomly assigned to the various groups, with no more than one rat from each litter being placed into a particular group. Condi-

tioning occurred on two consecutive days followed by a single test day. On each conditioning day, rats received two 30 min conditioning trials separated by a 4 h interval. On one of the conditioning days, 10- or 17-day-old rats (age at initial testing) were injected intraperitoneally with either saline, SCH 23390 (0.01–1.0 mg/kg), sulpiride (1–100 mg/kg), or eticlopride (0.1–0.5 mg/kg) and returned to their home cage. After 30 min, rats were injected with cocaine (20 mg/kg) or saline and immediately placed in the lemon-scented compartment for an additional 30 min. The identical procedure was repeated 4 h later. On the other conditioning day, the same rats were given two saline injections (30 min apart) and then placed in the almond-scented compartment for 30 min. Treatment order was counterbalanced, so that half of the rats received drug treatments on the first conditioning day, while the other half received drug treatments on the second conditioning day. Importantly, drug treatment was always paired with the lemon-scented compartment, because initial testing showed that this compartment was nonpreferred. On the test day, rats were given two injections of saline (30 min apart) and then tested for a place preference. For the preference test, rats were placed in the middle compartment and allowed free access to the entire apparatus for 15 min. Both the conditioning and testing sessions were videotaped for behavioral assessment at a later time.

2.5. Data analysis

Total time spent in each compartment was measured by a rater blind to treatment conditions. Total time and percent time spent in the drug-paired compartment were analyzed at each age by two-way analyses of variance (antagonist pretreatment × agonist treatment). (These dependent measures provided similar results, so percent data were not presented.) The place preference data were collapsed across male and female rats, because no differences due to gender were apparent. Significant main effects and interactions were further analyzed using Tukey tests ($P < 0.05$). In order to determine whether a conditioned place preference was present, Student's t-tests ($P < 0.05$) were used to compare the saline and cocaine control groups.

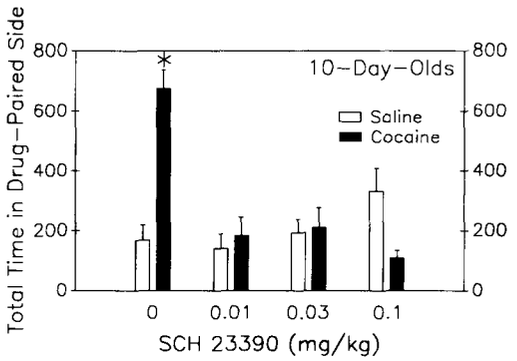

Fig. 1. Total time in seconds (±S.E.M.) spent by the 10-day-old rats in the drug-paired (lemon-scented) compartment on the test day. Rats were drug-free on the test day and allowed 900 s access to the three compartments. On conditioning days, rats were injected with cocaine (20 mg/kg) or saline and placed in the lemon-scented compartment or injected with saline and placed in the almond-scented compartment. Rats were injected with SCH 23390 (0, 0.01, 0.03, or 0.1 mg/kg) 30 min prior to being placed in the lemon-scented compartment. *Significant difference between the cocaine- and saline-treated 10-day-old rats ($P < 0.05$).

3. Results

3.1. Effects of the dopamine D_1 receptor antagonist SCH 23390 on the place preference conditioning of 10-day-old rats

Conditioned place preference was assessed by comparing the total time spent in the drug-paired (lemon-scented) compartment for the various groups. As can be seen in Fig. 1, cocaine-treated 10-day-old rats spent significantly more time in the drug-paired compartment then did their saline controls, $t(14) = 6.42$, $P < 0.001$. Pretreatment with the dopamine D_1 receptor antagonist SCH 23390 completely blocked the preference for the cocaine-paired compartment, as 10-day-old

Table 1
The effects of the dopamine D_1 receptor antagonist SCH 23390 and the dopamine D_2 receptor antagonist sulpiride on the cocaine-induced place preference conditioning of 10-day-old rats

Pretreatment	Agonist	Total time in the drug-paired compartment
Saline	Saline	192.12 + 57.89
Saline	Cocaine (20 mg/kg)	474.12 + 82.90[a]
SCH 23390 (1.0 mg/kg)	Saline	345.38 ± 29.67
SCH 23390 (1.0 mg/kg)	Cocaine (20 mg/kg)	319.25 ± 66.06
Sulpiride (100 mg/kg)	Saline	261.25 ± 35.82
Sulpiride (100 mg/kg)	Cocaine (20 mg/kg)	295.00 ± 69.06

All rats were injected with saline on the test day and allowed 900 s access to the three-compartment chamber. The test day occurred when the rats were 12 days old. Values are the means (±S.E.M.) of 8 rats per group. [a]Significant difference from the saline-treated control group, $P < 0.05$.

rats receiving both cocaine and SCH 23390 (0.01, 0.03, and 0.1 mg/kg) spent significantly less time on the drug-paired side than rats given cocaine alone, Antagonist × Agonist interaction, $F(3,56) = 14.88$, $P < 0.001$, and Tukey tests. In all cases, the preference scores of rats given either SCH 23390 alone or SCH 23390 plus cocaine did not differ, although rats given 0.1 mg/kg SCH 23390 did show a curious nonsignificant increase in the amount of time spent in the drug-paired compartment. In an additional experiment, a higher dose of SCH 23390 (1.0 mg/kg) blocked preferences for the cocaine-paired compartment, Antagonist × Agonist interaction, $F(1,28) = 6.14$, $P < 0.05$ (Table 1). Once again, SCH 23390-treated 10-day-old rats had a nonsignificant tendency to spend more time in the drug-paired compartment (relative to saline controls).

3.2. Effects of the dopamine D_2 receptor antagonists sulpiride and eticlopride on the place preference conditioning of 10-day-old rats

As can be seen in Fig. 2, cocaine-treated 10-day-old rats spent significantly more time in the drug-paired compartment then did their saline controls, $t(14) = 5.31$, $P < 0.001$. Pretreatment with the dopamine D_2 receptor antagonist sulpiride blocked this preference in a dose-dependent manner, as rats given both cocaine (20 mg/kg) and sulpiride (5 and 25 mg/kg) had preference scores which were significantly lower than rats given cocaine alone, Antagonist × Agonist interaction, $F(3,56) = 4.99$, $P < 0.01$, and Tukey tests. In an additional experiment, 10-day-old rats were treated with a higher dose of sulpiride (100 mg/kg) prior to cocaine conditioning (Table 1). Overall, cocaine-treated rats spent significantly more time in the drug-paired compartment then did their saline controls, agonist main effect, $F(1,28) = 6.13$, $P < 0.05$. Although the interaction was not significant, rats given both cocaine and sulpiride (100 mg/kg) appeared to have preference scores which were similar to rats given sulpiride alone. Thus, various doses of the dopamine D_2 receptor antagonist sulpiride (5–100 mg/kg) are capable of blocking the cocaine-induced place preference conditioning of 10-day-old rats.

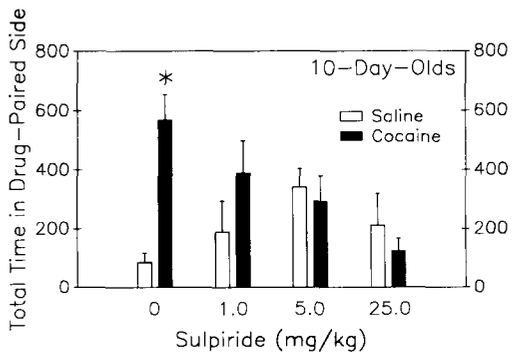

Fig. 2. Total time in seconds (±S.E.M.) spent by the 10-day-old rats in the drug-paired (lemon-scented) compartment on the test day. Rats were treated as in Fig. 1 except that sulpiride (0, 1, 5, or 25 mg/kg) was injected 30 min prior to placement in the lemon-scented compartment. *Significant difference between the cocaine- and saline-treated 10-day-old rats ($P < 0.05$).

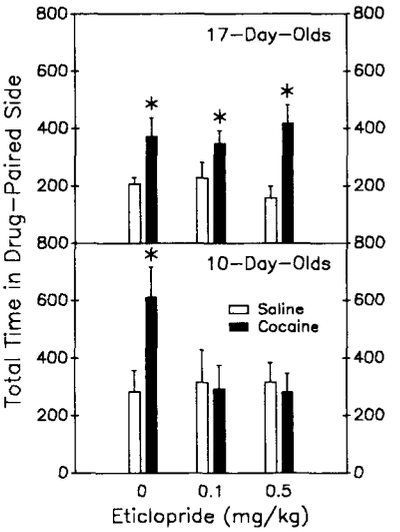

Fig. 3. Total time in seconds (±S.E.M.) spent by the 10-day-old (lower panel) and 17-day-old (upper panel) rats in the drug-paired (lemon-scented) compartment on the test day. Rats were treated as in Fig. 1 except that eticlopride (0, 0.1, or 0.5 mg/kg) was injected 30 min prior to placement in the lemon-scented compartment. *Significant difference between the cocaine- and saline-treated rats ($P < 0.05$).

The place preference conditioning of 10-day-old rats was also blocked by the dopamine D_2 receptor antagonist eticlopride (lower graph, Fig. 3). Once again, cocaine produced a conditioned place preference, as 10-day-old rats spent significantly more time in the drug-paired compartment than their saline controls, $t(14) = 2.54$, $P < 0.05$. This cocaine-induced preference was blocked by both doses of eticlopride (0.1 and 0.5 mg/kg). Thus, in the 10-day-old rat, blockade of dopamine D_2 receptors with either sulpiride (1–100 mg/kg) or eticlopride (0.1–0.5 mg/kg) was sufficient to disrupt cocaine-induced place preference conditioning.

3.3. Effects of the dopamine D_1 receptor antagonist SCH 23390 on the place preference conditioning of 17-day-old rats

As can be seen in Fig. 4, 17-day-old rats spent more time in the cocaine-paired compartment then did their saline controls, $t(14) = 3.00$, $P < 0.01$. Pretreatment with the dopamine D_1 receptor antagonist SCH 23390 blocked this cocaine-induced place preference. More

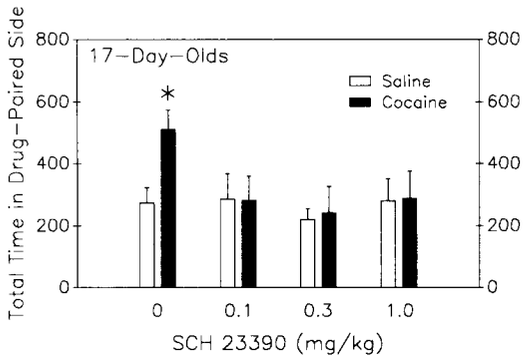

Fig. 4. Total time in seconds (±S.E.M.) spent by the 17-day-old rats in the drug-paired (lemon-scented) compartment on the test day. Rats were treated as in Fig. 1 except that SCH 23390 (0, 0.1, 0.3, or 1.0 mg/kg) was injected 30 min prior to placement in the lemon-scented compartment. *Significant difference between the cocaine- and saline-treated 17-day-old rats ($P < 0.05$).

precisely, 17-day-olds treated with both cocaine (20 mg/kg) and SCH 23390 (0.1, 0.3, or 1.0 mg/kg) had preference scores similar to saline-treated rats.

3.4. Effects of the dopamine D_2 receptor antagonists sulpiride and eticlopride on the place preference conditioning of 17-day-old rats

Once again, 17-day-old rats spent significantly more time in the cocaine-paired chamber than did their saline controls, $t(14) = 3.40$, $P < 0.01$ (Fig. 5). This effect was apparent in all of the cocaine-treated groups, regardless of whether sulpiride (50 or 100 mg/kg) was also administered, agonist main effect, $F(1,42) = 11.49$, $P < 0.01$. Thus, blocking dopamine D_2 receptors with sulpiride did not significantly affect cocaine-induced place preference conditioning.

To determine if this pattern of effects was unique to sulpiride, we tested whether a second dopamine D_2 receptor antagonist, in this case eticlopride (0.1 or 0.5 mg/kg), would block cocaine-induced place preference conditioning (upper graph, Fig. 3). Regardless of whether they received eticlopride or saline pretreatment, cocaine-treated 17-day-old rats spent significantly more time in the drug-paired compartment than did their saline-treated controls, agonist main effect, $F(1,42) = 23.62$, $P < 0.001$. Thus, eticlopride (0.1 or 0.5 mg/kg) and sulpiride (50 or 100 mg/kg) were unable to block cocaine-induced place preference conditioning. In a subsequent replication, we again found that 0.1 and 0.5 mg/kg eticlopride did not disrupt the place preference conditioning produced by cocaine (data not shown).

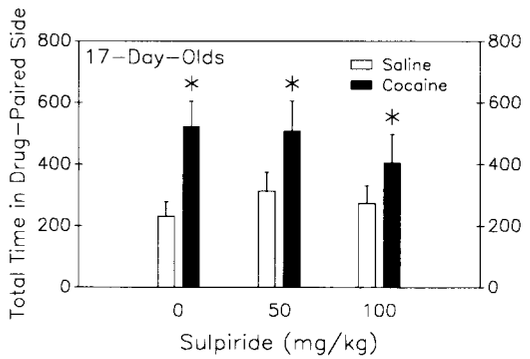

Fig. 5. Total time in seconds (±S.E.M.) spent by the 17-day-old rats in the drug-paired (lemon-scented) compartment on the test day. Rats were treated as in Fig. 1 except that sulpiride (0, 50, or 100 mg/kg) was injected 30 min prior to placement in the lemon-scented compartment. *Significant difference between the cocaine- and saline-treated 17-day-old rats ($P < 0.05$).

4. Discussion

In adult rats, dopamine agonist-induced place preference conditioning is disrupted by pharmacological blockade of either dopamine D_1 or D_2 receptors (Leone and Di Chiara, 1987; Hoffman and Beninger, 1989; Hiroi and White, 1991). In the present study, dopamine D_1 receptor blockade affected preweanling rats in an adult-typical fashion, as the dopamine D_1 receptor antagonist SCH 23390 (0.1–1.0 mg/kg) attenuated cocaine-induced place preference conditioning in both 10- and 17-day-old rats (Fig. 1 and Fig. 4, Table 1). In contrast, the effects of dopamine D_2 receptor blockade varied according to preweanling age. More specifically, both sulpiride (5–100 mg/kg) and eticlopride (0.1 and 0.5 mg/kg) blocked place preference conditioning in the 10-day-olds (Fig. 2 and Fig. 3, Table 1), whereas these dopamine D_2 receptor antagonists were without significant effect in 17-day-old rats (Fig. 3 and Fig. 5). In addition, there was no evidence of any antagonist-induced place aversions in either the 10- or 17-day-old rats.

When considered together, these developmental and nondevelopmental place preference studies indicate that dopamine D_2 receptor antagonists disrupt the place preference conditioning of 10-day-old and adult rats, while leaving 17-day-old rats unaffected. This pattern of ontogenetic effects was not predicted and suggests that a simple linear maturation of receptors (or other neuronal elements) cannot account for these age-dependent differences. Instead, it is possible that 17-day-old rats have a temporary excess of dopamine D_2 receptors, making place preference conditioning resistant to dopamine D_2 receptor blockade. Consistent with this, ontogenetic studies using the irreversible receptor antagonist *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) indicate that a large reserve of dopamine D_2 receptors may be present in the 17-day-old rat (McDougall et al., 1992b,1993; McDougall and Bolanos, 1994). Although intriguing, a receptor reserve

explanation may not be adequate, because other cocaine-induced behaviors were attenuated by sulpiride and eticlopride. For example, cocaine substantially enhanced the locomotor activity of 17-day-old rats during conditioning, an effect blocked by the two dopamine D_2 receptor antagonists (data not shown). Of course, a receptor reserve explanation would still be tenable if one postulates that the population of dopamine D_2 receptors mediating reward is distinct from those receptors mediating locomotor activity.

Alternatively, it is possible that the dopamine D_1 and D_2 receptors mediating reward are normally coupled in some way, but that this 'coupling' is not constant across ontogeny. In the typical case (e.g., when mediating various unlearned behaviors), the dopamine D_1 and D_2 receptors of preweanling and adult rats interact in a cooperative fashion, with each receptor system providing the necessary tonic background activity for the full manifestation of behavior (Arnt, 1987; Clark and White, 1987; Murray and Waddington, 1989; McDougall et al., 1990; Moody and Spear, 1992). Unfortunately, it is still uncertain whether the dopamine D_1 and D_2 receptors mediating reward are coupled in a similar fashion (see Koechling et al., 1988; Wise and Rompre, 1989; McDougall et al., 1991). If they are, a temporary uncoupling of these receptors at 17 days of age may cause the dopamine D_1 receptor to be both necessary and sufficient for reward. Consistent with this, we have previously shown that sulpiride alone does not affect the appetitive approach responding of 17-day-old rats, but that sulpiride combined with SCH 23390 maximally disrupts reinforced responding (McDougall et al., 1991). A third possibility is that cocaine's nondopaminergic actions might have been responsible for these age-dependent behavioral differences. More specifically, besides affecting dopamine neurons, cocaine also blocks the reuptake of norepinephrine and serotonin (Hadfield et al., 1980; Cunningham et al., 1992). Hence, maturational changes in noradrenergic and serotonergic systems might account for some of the behavioral differences observed in the present study.

In summary, the present results suggest that the underlying mechanisms mediating reward change across the preweanling period. While dopamine neurons and receptors are known to mediate, at least partially, the reward processes and unlearned behaviors of rats as young as 3 days of age, the behavioral actions of dopamine agonists and antagonists are often found to exhibit pronounced age-dependent differences (Shalaby and Spear, 1980; Barr and Lithgow, 1986; Camp and Rudy, 1987; McDougall et al., 1992b; Moody and Spear, 1992). Thus, the present study, like other developmental psychopharmacological studies, indicates that dopamine-acting drugs can have qualitatively different effects across ontogeny which, presumably, are the product of maturational changes in the neurobiological mechanisms underlying these behaviors (see also Spear, 1979).

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