The effects of dopamine D1 and D2 antagonists on cocaine-induced CPP in preweanling rats

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A Thesis
Presented to the
Faculty of
California State University,
San Bernardino

In Partial Fulfillment
of the Requirements for the Degree
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in
Psychology

by
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ABSTRACT

The effects of Dopamine D\textsubscript{1} and D\textsubscript{2} antagonists on conditioned place preference (CPP) and locomotor activity were assessed. Conditioning and testing were conducted in a three compartment chamber, consisting of two large end chambers (15.5 X 15.5 X 21.5 cm) and a smaller middle chamber (9 X 15.5 X 21.5 cm). Each end chamber had its own distinct tactile and odor cues. A total of three experiments were conducted. In each experiment there were two conditioning days followed by a test day. On the conditioning days, two 30-min trials were presented 4-hrs apart. For Experiment 1, 17-day-old rats were given cocaine (20 mg/kg i.p.) or saline and placed in a chamber scented with 10 cc lemon extract. On the other conditioning day, rats were given saline only and placed in the opposite chamber scented with 10 cc almond extract. Cocaine was always paired in the nonpreferred lemon scented chamber. Drug administration was counterbalanced across conditioning days. In Experiment 2, the procedure was identical with the exception that 30-min prior to cocaine or saline treatment, rat pups were injected with the D\textsubscript{1} receptor antagonist SCH 23390 (0.1, 0.3, or 1.0 mg/kg i.p.) or saline. In Experiment 3, the D\textsubscript{2} receptor antagonist sulpiride (50 or 100 mg/kg i.p.) or saline was given 30-min prior to conditioning. The results of Experiment 1 showed that an abbreviated (3-day) CPP paradigm successfully produced a place preference in the 17-day-old
rat \((p < .005)\). In Experiment 2, SCH 23390 blocked cocaine-induced CPP, but not cocaine-induced locomotion. Conversely, in Experiment 3, sulpiride did not block CPP, but did block cocaine-induced locomotion. Thus, these results indicate that DA D_1 and D_2 receptors have distinctly different roles in the mediation of behavior. DA D_1 receptors appear to be critical for reward, but not locomotor activity; whereas DA D_2 receptors are critical for locomotor activity, but not reward. The application of these findings to drug addiction in infants is discussed.
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INTRODUCTION

It is now apparent that dopamine (DA) systems are intimately involved in reward processes. Current research has focused on DA D₁ and D₂ receptor sites in attempts to clarify their respective roles in reward. A recent model proposed by Miller, Wickens and Benninger (1990) suggests that D₁ receptors mediate reward directly, whereas D₂ receptors indirectly affect reward by mediating the motor performance associated with it. However, it was recently shown that the D₁ receptor antagonist SCH 23390, but not the D₂ receptor antagonist sulpiride, blocked reinforced responding in rat pups (McDougall, Crawford, & Nonneman, 1992; McDougall, Nonneman, & Crawford, 1991). This suggests that D₁, but not D₂, receptors are critically involved in the reward processes of preweanling rats.

One criticism of studies designed to assess the role of DA receptors in reward is that blocking these receptors also inhibits motoric function. That is to say, since DA receptor antagonists impair motor performance, conventional measures of reinforcement (e.g. runway response latencies and bar pressing) may reflect changes in the capacity to respond versus the motivation to respond (see Miller et al., 1990, and Wise & Rompre, 1989, for reviews). Hence, a paradigm which could measure reward in the absence of drug impairment would prove superior. The conditioned place preference (CPP) paradigm avoids this problem as the test
for reward is done in the absence of drugs. In addition, locomotor activity can be assessed during the conditioning phase (i.e. prior to testing). This allows for the motor and reward components to be separated. Therefore, the CPP paradigm will be used in the present study to test the effects of DA D₁ and D₂ receptor antagonists on reward and locomotor responses in the preweanling rat.

Drugs and Addiction

Drug addiction is a serious problem and psychomotor stimulants (e.g. cocaine and amphetamine) are some of the most commonly used substances of abuse (Wise & Bozarth, 1987). Several theoretical explanations for the addictive nature of these drugs have been offered (see Wise & Bozarth, 1987, for a review). Drug dependence is one attempt to explain the continued use of psychomotor stimulants (Canada, 1972; Guderman, Shader, & Hemmingway, 1972; Wilson, Elms & Thomson, 1974, 1975). These researchers propose that withdrawal symptoms, usually associated with discontinued use, motivates persistent use of the drug. This model however, does not explain the initial and sustained use of the drug prior to dependence. In addition, the high recidivism rates of addicts who have discontinued use long enough to be free of distress, suggests that withdrawal symptoms are not sufficient to explain the maintenance of addictive behavior (Wise & Bozarth, 1987).

A second model relies on reinforcement theory to explain
the addictive nature of drug use (Griffiths, Brady & Bradford, 1979; Johanson, 1978; Yanagita, 1973). More specifically, an event or stimulus is said to be positively reinforcing when it increases the occurrence of a target behavior and negatively reinforcing when removing the stimulus increases the occurrence of the target behavior (Domjan & Burkhard, 1993, pp. 136-137). Clearly, stimulant drugs could fit into either category. A drug's positive reinforcing properties are apparent when animals perform any number of operant behaviors to receive administration of these drugs. The latter can be inferred, when after dependence has been established, one takes the drug to alleviate the negative symptoms associated with drug withdrawal.

The positive reinforcement model seems to adequately account for addiction processes. But some hold the view that a "euphoria-like" state, often reported by drug users, is a necessary component of addiction (Wise & Bozarth, 1987). Although euphoria cannot be directly measured in animals, approach responses can be used to operationally define positive reinforcement. Wise and Bozarth (1987) explain that approach responses accompany virtually all positively reinforcing events. Further, they state that both the euphoric state and locomotor activity rely on the same, or overlapping, neural substrates.

The neural substrates mediating reward appear to
involve DA receptors. More specifically, both cocaine and amphetamine indirectly activate DA receptors by increasing the amount of DA in the synapse (Heikkila, Orlansky & Cohen, 1975). The DA system also appears to be the substrate for other addictive drugs including: alcohol, opiates, nicotine and caffeine (for a complete review see Wise & Bozarth, 1987). Therefore, cocaine-induced CPP can be used to assess the DA system's role in general addictive processes.

**DA Systems**

DA is discretely located in a number of brain areas, including: the ventral tegmental area (VTA), neostriatum, nucleus accumbens, prefrontal cortex, olfactory tubercles, and hypothalamus (see Cooper, Bloom, & Roth, 1991, for a review). Interestingly, there are only two long DA projection pathways: the nigrostriatal and mesolimbic-mesocortical pathways (Cooper et al., 1991). The nigrostriatal pathway connects the substantia nigra and the striatum at its distal points (Arnt, 1987). DA fiber projections making up the mesolimbic-mesocortical pathway extend from the VTA to several other discrete brain areas including: the lateral hypothalamus, the nucleus accumbens, the frontal cortex and neostriatum (Wise & Bozarth, 1984). The primary focus of the current study is the mesolimbic-mesocortical pathway, because it has often been implicated in reward. However, the striatum, a component of both systems, is included as well. The intent is not to
dissociate DA systems. On the contrary, DA systems appear to be complex interactive brain mechanisms acting in concert to produce behavior.

Models of Reward

Two behaviors which occur after activation of DA systems are quite prominent and distinct: locomotor activity and reinforced responding (Wise, 1983). Older models of reward tended to emphasize one of these components (i.e. locomotor activity or reinforced responding) more than the other (Phillips, 1984; Wise & Bozarth, 1984). For example, Phillips (1984) defined reward as a function of specialized sensory receptor stimulation leading to the "appropriate" motor response and giving rise to "positive affect". Thus, by studying the particular motor response, one could define an event as rewarding. While this does not specify reward as a separate component, this view clearly places emphasis on locomotor activity. Wise and Bozarth (1984), on the other hand, suggested that reinforced responding defined reward. Hence, the operational definition relies more on changes in rates of behavior. Current views of reward more fully incorporate locomotor activity and reinforced responding in their respective definitions of reward. For example, Wise and Rompre (1989) suggest that the initiation of a forward response is both present and necessary for reinforced responding (i.e. reward). Similarly, Miller et al. (1990) propose that locomotor activity indirectly
activates reward at the DA D₂ receptor; whereas direct activation of reward is accomplished through activating DA D₁ receptors. A subtle distinction between these models is apparent. With the former model (i.e. Wise & Rompre, 1989) locomotor activity and reward are seen as inseparable; however, the model of Miller et al. (1990) suggests that locomotor activity is sufficient but not necessary for reward responding to occur. The current study was designed to test the latter proposition.

Assessing Locomotor Activity

Lesion studies provide an excellent way to assess DA's role in mediating locomotor activity. Each of the brain areas mentioned above (i.e. VTA, frontal cortex, nucleus accumbens and hypothalamus) are involved in locomotor activity. For example, when the VTA is lesioned hyperlocomotion and hypolocomotion are observed (Gaffori, Le Moal & Stinus, 1980; Le Moal & Simon, 1991). In addition, the nucleus accumbens and VTA are jointly involved in locomotor responses. Interestingly, both the size and location of lesions produce divergent results. For example, large lesions to either the nucleus accumbens or VTA produce hypolocomotion and effectively block the effects of psychomotor stimulants (Koob, Simon, Herman & Le Moal, 1984; Le Moal, Stinus & Galey, 1976). In contrast, small lesions in the VTA produce hyperlocomotor activity (Koob, Stinus & Le Moal, 1987). When both the VTA and nucleus accumbens are
lesioned, the effects of psychomotor stimulants are potentiated (Koob et al., 1987).

The prefrontal cortex also mediates locomotor responses, as lesions of the prefrontal cortex attenuate locomotor activity (Fink & Smith, 1979). Similarly, DA fibers extending from the lateral hypothalamic-VTA region to the dorsal striatum are crucial in locomotor responses, as lateral hypothalamic-VTA lesions attenuate the initiation of forward locomotion (Fink & Smith, 1979). This was exhibited by the inability of lesioned rats to acquire or demonstrate an active avoidance response to footshock. Challenge with psychomotor stimulants confirmed that the lack of response was not due to motor impairment (Fink & Smith, 1979).

Each of the brain areas mentioned (i.e. prefrontal cortex, nucleus accumbens and lateral hypothalamus) have one common innervation: DA fibers ascending from the VTA. These fibers are known as the medial forebrain bundle (MFB) (Wise & Bozarth, 1984). The MFB is the primary ascending pathway for DA fibers joining the mesocortical-mesolimbic pathway (Wise & Rompre, 1989).

Assessing Reinforced Responding: Bar pressing for ICS, Drug Administration and CPP

Operant Responding for Intracranial Stimulation (ICS). Many researchers have used learning paradigms to define the rewarding nature of DA activation. Specifically, both
operant and classical conditioning paradigms have been used to measure the reinforcing effects of stimulating the DA system. For example, intracranial stimulation (ICS) is a technique where electrodes are implanted in discrete brain areas. Once implanted, a researcher can deliver electrical impulses (ICS) or make delivery dependent upon the organism's response (ICSS). When this electrical impulse is delivered, the neurons in proximity to the electrode are stimulated and subsequently release neurotransmitter (Carlson, 1991, pp. 456-457).

Using the ICSS technique, Olds and Olds (1963; 1969) showed that stimulation of the MFB was extremely reinforcing. Additionally, ICSS in the VTA is so rewarding that it competes with food for bar press responding (Miliaressis & Cardo, 1973). More specifically, heavily food deprived rats (72 hours) showed an increased response for stimulation versus food. Conversely, rats presented with stimulation to the lateral hypothalamus showed a parallel increase in response for both food and stimulation (Miliaressis & Cardo, 1973). Interestingly, when ICSS is presented jointly with psychomotor stimulants the response rate for ICSS is increased. Responding for ICSS in both the MFB and the nucleus accumbens were potentiated by i.p. administration of cocaine (Barr & Lithgow, 1986). Wise and Rompre (1989) indicate that the more proximal the ICSS probe is to DA cells the more rewarding it is. In some cases rats
will starve while bar pressing for ICSS in the MFB or intravenous infusions of cocaine. This suggests that direct DA activation is more rewarding than the peripheral activation of the system by conventional (e.g. food or sex) reinforcers (see Wise & Bozarth, 1987, and Wise, 1982, for reviews).

The rewarding effects of ICSS are potentiated by concurrent administration of DA agonists and attenuated when aversive stimuli are presented. For example, pairing cocaine with ICSS of the VTA and other areas affects the pattern of bar press responding (Barr & Lithgow, 1986). Intermediate doses of cocaine (5-20 mg/kg) led to an initial increase in responding for ICSS, then attenuated the response across time. In contrast, high daily doses (30 mg/kg) of cocaine led to sensitization of ICSS and decreases in the amount of stimulation necessary to maintain the response (Kokkinidis & McCarter, 1990). When ICSS is presented in the nucleus accumbens high response rates are also observed (Prado & Wise, 1984). Conversely, decreases in ICSS responding occurs when an aversive stimulus is presented (Bowers, Zacharko, & Anisman, 1987). For example, when rats were exposed to unavoidable footshock, response rates for ICSS in the nucleus accumbens were attenuated. This suggests that lower response rates were the result of a decrease in the rewarding effects of the stimulation (Bowers et al., 1987).
ICSS in the prefrontal cortex and lateral hypothalamic-VTA is also rewarding. Amphetamine increased extinction bar pressing rates for subjects with electrodes in the prefrontal cortex, but not in the lateral hypothalamic-VTA. These findings suggest that DA activation increases the rewarding properties of stimulation in a site specific manner (West & Michael, 1990).

In summary, research has shown that intracranial stimulation is highly rewarding. Moreover, the increased responding for ICSS when DA agonists are given strongly indicates that the DA system, and not other neurotransmitter pathways, are the primary neurobiological substrate responsible for reward (see Wise & Rompre, 1989, for a review). The combined research also suggests an interactive DA system, as activation of discrete brain areas produces responses nearly identical to activation of the entire system.

Operant Responding for Psychomotor Stimulants. Bar press responding has also been used in conjunction with drug administration. In this paradigm, rather than receiving ICSS for the operant response, the animal receives a small dose of a DA agonist. DA agonists are very reinforcing, as monkeys bar press at extremely high rates for cocaine (Balster, Harris, & Schuster, 1973; Roberts, Corcoran & Fibiger, 1977).

Nonetheless, animals appear to have some internal
limiting process when responding for drug reward (Howell & Byrd, 1991). Bar pressing rates for cocaine or GBR 12909 (a highly selective DA reuptake inhibitor) increase when the dosage is an intermediate amount; whereas pressing rates decrease in response to high doses (Howell & Byrd, 1991). Cocaine elicited bar pressing rates some three times higher than that of GBR 12909 (Howell & Byrd, 1991). This shows the highly rewarding properties of cocaine, as well as an internal monitoring of the dose-response relationship. In other words, it may be that some homeostatic mechanism allows the animal to stop short of self-administering a lethal dose.

Microinjections of cocaine into several discrete brain areas are also reinforcing. For example, rats will bar press for cocaine infusions into the medial prefrontal cortex (Goeders & Smith, 1983; Robertson, 1989). Conversely, microinjections of cocaine into the nucleus accumbens have proven insufficient to establish a bar pressing response (Goeders & Smith, 1983). This finding is of particular interest because amphetamine (another psychomotor stimulant) does produce this response (Hemby, Jones, Justice & Neill, 1992). Nonetheless, cocaine microinjections into the nucleus accumbens potentiate responding for a conditioned reinforcer (Rosenzweig-Lipson, Chu, Delfs & Kelly, 1990). In summary, as with ICSS studies, research shows that the activation of DA pathways
by psychomotor stimulants is rewarding.

The CPP Paradigm as a Measure of Reward. Conditioned Place Preference (CPP) has also been widely employed to test the reinforcing effects of psychomotor stimulants (Bardo, Neisewander, & Miller, 1986; Carr, Phillips, & Fibiger, 1988; Hiroi, & White, 1991). In the CPP paradigm a drug is paired with a novel context during one conditioning trial and an injection of water is paired with a second novel context. After conditioning, the animal is given free access to both of the chambers and the rewarding effects of the drug are revealed by a preference for the drug-paired context. Traditionally, odor, tactile and visual stimuli are used to distinguish compartments of the CPP apparatus.

A number of different reinforcers have been used to produce CPP's. For example, cocaine administration produced a robust CPP; whereas lithium chloride (a highly aversive drug) did not (Mucha, Van Der Kooy, O'Shaughnessy, & Bucenieks, 1982). This indicates that the rewarding properties of the stimulus, rather than its salience produces the CPP response. Many other DA agonists have been shown to reliably produce CPP (for a comprehensive bibliography see Schecter & Calcagnotti, 1993).

A place preference has also been observed when microinjections of psychomotor stimulants are presented. For example, injections of amphetamine into the nucleus accumbens produce CPP (Hemby et al., 1992; Morency &
However, in the same experiment cocaine infusions into the nucleus accumbens failed to produce CPP; rather, only conditioned locomotor activity was observed (Hemby et al., 1992). This study suggests that locomotor and reward components can be separated by directly activating the nucleus accumbens. Further dissociations of the locomotor and reward responses have been shown using the CPP paradigm. For example, when rats were physically restrained from movement in the CPP conditioning chamber, the CPP response was still present. This indicates that CPP can be established without the expression of locomotor activity (Carr et al., 1988).

In summary, CPP reveals the rewarding nature of psychomotor stimulants. However, unlike the previous paradigms, some evidence for dissociation of reward-like behaviors (i.e. locomotor activity and reinforced responding) can be observed.

Evaluation of Models Assessing Reward. ICSS studies indicate that electrical stimulation of the DA system is rewarding. However, even when electrode implantation is made in a discrete area (e.g. the VTA or MFB) several components of the DA system are likely to be activated. Hence, the separate roles that each area or pathway play in overall reward cannot be assessed. In addition, the data indicate that activation of DA systems leads to both increased locomotion and reinforced responding rates.
Therefore, locomotor responding and reward cannot be considered separately with the ICSS paradigm.

Psychomotor stimulant studies with bar press or other operant measures of response (e.g. response latencies or wheel running) also have inherent problems. For example, systemic injections of psychomotor stimulants consistently affect locomotor activity. If hyperlocomotor responding is initiated, then operant response rates cannot be purely attributed to reward. Additionally, when discrete brain areas are infused with psychomotor stimulants, the possibility exists that more than the area at study is being stimulated through diffusion. Thus, separation of behaviors or areas is confounded with these paradigms.

The superiority of the CPP paradigm for assessing the independent effects of psychomotor stimulants on reward and locomotor activity is clear. First, with the CPP paradigm locomotor responding during conditioning can be assessed independently of any reward responses. Second, when reward testing occurs the animal is in a drug-free state. Thus, any locomotor effects of the drug intervention can only be due to learned responses. This superiority is even more apparent when drugs which impair motor performance are used (i.e. DA antagonists).

Effects of DA Antagonists on CPP

DA receptor antagonists include neuroleptics such as haldol and thorazine. While these drugs were initially
developed as antipsychotics, their use in studies of reward have proven beneficial. Antagonists of DA systems abolish reward associated performance. For example, systemic and microinjections of DA antagonists disrupt ICSS (Mackey & Van der Kooy, 1985; Phillips & Broekkamp, 1980). Unfortunately, DA antagonists impair both reinforced responding and locomotor ability. Thus, the effects of DA antagonists on locomotor activity and reward can only be separated with difficulty (a comprehensive discussion is offered by Wise, 1983).

Fortunately, the CPP paradigm can be used to dissociate the effects of DA antagonists on reward and performance. If acquisition of a CPP is blocked by an antagonist (i.e. the antagonist is given prior to agonist treatment) then a measure of reward alone can be assessed by compartment preference on a drug-free test day. By factoring out locomotor effects, CPP studies have shown that neuroleptics are successful in blocking reward (Ettenberg, 1989; but see Spyraki, Fibiger & Phillips, 1982).

**DA Receptor Subtypes D₁-D₅**

DA receptors have been classified into five structurally distinct receptor subtypes: D₁, D₂, D₃, D₄ and D₅ (Clark & White, 1987; Sokoloff, Giros, Martres, Bouthenet & Schwartz, 1990; Sunahara et al., 1991; Van Tol et al., 1991). Of these DA receptor subtypes, the D₁ and D₂ receptors have been differentiated according to anatomical
location, sensitivity to pharmacological actions, effects on second messenger systems and behavioral manifestations (for a comprehensive review see Clark & White, 1987). More specifically, selective activation of DA D₁ and D₂ receptors produces distinctly different behavioral actions. For example, selective D₁ agonists (SKF 38393 or fenoldopam) preferentially induce grooming behaviors (Arnt, 1987; Clark & White, 1987). However, when quinpirole or bromocriptine (selective D₂ agonists) are given changes in locomotion, rearing and sniffing are observed (Arnt, 1987; Hoffman & Wise, 1993). These behavioral differences suggest that cocaine and other psychomotor stimulants primarily affect the D₂ and not the D₁ receptor.

When the rewarding effects of selective (i.e. D₁ or D₂) agonists are tested, seemingly contradictory results have been found. For example, systemic injections of SKF 38393 failed to produce either self administration or CPP (Beaulieu, Itoh, Tepper, Horn & Kebabian, 1984; Krause, van der Weide & Horn, 1986; Woolverton, Goldberg & Ginos, 1984). Conversely, direct injections of SKF 38393 into various brain areas, such as the nucleus accumbens, striatum and substantia nigra support self-administration and have noticeable effects on motor performance (Costall, Eniojukan, & Naylor, 1984; Jackson & Kelly, 1983; Worms, Gueudet, & Biziere, 1986). These contradictory findings, however, are most likely due to route of administration. That is to say,
when drugs are injected peripherally they must cross the blood-brain barrier; whereas central administration bypasses the barrier directly. Thus, the inability of systemically administered SKF 38393 to induce a CPP is probably because a sufficient amount of SKF 38393 did not cross the blood-brain barrier (Arnt, 1987).

Additional studies indicate that D₁ receptors are critical in reward. For example, when the nonselective DA agonist apomorphine was used in a drug discrimination paradigm, parallel generalization to SKF 38393 (a selective D₁ agonist) occurred (Schechter & Greer, 1987). In contrast, bromocriptine, a selective D₂ agonist, only induced a weak generalization after apomorphine treatment.

The use of selective DA antagonists also indicates that D₁ and D₂ receptors have different roles in reward (Gui-Hua, Perry & Woolverton, 1992). These researchers trained rats in a discriminative stimulus task (bar press for food or SKF 38393) prior to treatment with DA antagonists. When rats received chronic treatment with SCH 23390, a D₁ antagonist, or EEDQ (a substance which irreversibly blocks DA receptors) a significant shift toward SKF 38393 was observed. Hence, the D₁ receptor appears to be critical for reinforced responding (Gui-Hua et al., 1992).

Although a good deal of the evidence presented thus far suggests that the D₂ receptor is primarily involved in locomotor activity rather than reward, other studies
indicate that reward may occur in response to selective activation of D₂ receptors. For example, selective D₂ receptor agonists have been shown to support self-administration in both monkeys and rats (Woolverton et al., 1984; Yokel & Wise, 1978). Additionally, CPP has been observed in response to both bromocriptine and quinpirole (Hoffman & Benninger, 1988; Hoffman, Dickson, & Benninger, 1988). Thus, when all of these studies are considered together, the precise role of D₂ receptors in reward is unclear.

A recently proposed model suggests that both D₁ and D₂ receptors are necessary for the full manifestation of reward (Miller et al., 1990). These researchers propose that activation of D₁ receptors directly mediates reward, whereas D₂ activation mediates reward indirectly through motoric activation. More specifically, they suggest that when D₂ fibers in the striatum are stimulated, an inhibitory action is caused at acetylcholine receptors. This inhibition leads to what Miller et al. (1990) describe as a "loosening of the limbs". In turn, hyperlocomotion is induced. The increased locomotor activity is said to then stimulate the VTA through sensory feedback, thus causing the release of DA. If this model is correct, then blocking either D₁ or D₂ should block reinforced responding.

Ontogeny of DA Receptor Systems and Reward

DA receptor stimulation often induces age-dependent
behavioral differences in preweanling and adult animals. For example, joint treatment with D₁ and D₂ agonists, which elicits intense stereotypy in adults, does not do so in preweanling rats (Mashurano & Waddington, 1986; Moody & Spear, 1992). Similarly, when 3-day-old to 21-day-old rats were injected with quinpirole or SKF 38393, or a combination of both, only postweanling pups exhibited adult-like responses (Moody & Spear, 1992). Although some synergistic responding was observed in each age group, increased licking behavior was only exhibited by the 21-day-old pups. Additionally, grooming and vertical movements were not induced by SKF 38393 or quinpirole, except in the oldest group (Moody & Spear, 1992).

Recent studies of reward in preweanling rats also indicates ontological differences. For example, McDougall et al. (1991, 1992) have recently shown that SCH 23390, but not sulpiride, blocked the reinforced responding of 11-day-old and 17-day-old rat pups. These findings suggest that D₁, but not D₂ receptors, are critical for reward processes in rat pups. These results are not consistent with Miller et al.'s (1990) model which indicates that reward should be elicited when D₂ receptors are activated (i.e. increased locomotor activity should ultimately lead to DA release in the VTA).

Summary and Hypotheses

In general, the results of these studies can be
summarized as follows: 1) Activation of the DA system is rewarding; 2) Selective activation of DA receptors increases both locomotion and reward responding; 3) Selective inhibition of DA receptors abolishes or attenuates both locomotor and reward responding; 4) Activation or blocking of DA D₁ and D₂ receptor subtypes produces divergent effects on locomotion and reward responses; 5) Many paradigms (e.g. bar press and response latencies) are confounded by drugs which impair motor performance; 6) With the CPP paradigm locomotor and reward responses can be assessed separately; and 7) Activating or blocking D₁ or D₂ receptors differentially affects the locomotion and reward responding of preweanling and adult rats. Taken together, these premises suggest that selectively blocking D₁ or D₂ receptors prior to cocaine administration in the CPP paradigm will allow a dissociation of locomotor and reward-like responding in preweanling rats. Therefore, I suggest that prior treatment with SCH 23390, but not sulpiride, will block cocaine-induced CPP in preweanling rats. I further propose that prior treatment with sulpiride, but not SCH 23390, will block the hyperlocomotor response normally associated with CPP conditioning.

GENERAL METHOD

Subjects

The subjects were 128 male and female rat pups of Sprague-Dawley descent born and raised at California State
University, San Bernardino. Litters were culled to a maximum of 10 pups at 3 days of age. Assignment of pups was random with no more than one pup from each litter being placed into a particular group. The colony room was maintained at 23°C and was kept under a 12:12 light:dark cycle. Subjects were conditioned during the light cycle at 17 days of age. A protocol for the procedure was approved by the Animal Care and Use Committee.

**Apparatus**

The testing apparatus was a three compartment chamber with two larger end compartments (15.5 X 15.5 X 21.5 cm) and a smaller middle chamber (9 X 15.5 X 21.5 cm). In one of the larger chambers the floor was covered with a rubberized non-slip surface; whereas the other end chamber had the plywood floor scored (2 cm deep) in a checkerboard fashion. Each end chamber was equipped with an odor delivery system. For conditioning the chamber was separated by removable plywood slats. Lemon and Almond odors were purchased from commercial vendors (Schilling, Inc).

**General Procedure**

In each experiment there were two conditioning days followed by a test day. On conditioning days, two 30-min trials were presented 4-hrs apart. For one conditioning day, 17-day-old rats were given cocaine (20 mg/kg i.p.) or saline and placed in a chamber scented with 10 cc lemon extract. On the other conditioning day, rats were given
saline only and placed in the opposite chamber scented with 10 cc almond extract. Cocaine was always paired in the nonpreferred lemon scented chamber. Drug administration was counterbalanced across conditioning days. One day after conditioning, subjects were given saline and had free access to all chambers for 15 min. Both conditioning and test trials were videotaped and scored at a later date by experimenters blind to the treatment condition. For scoring, the conditioning chambers were divided into four equal quadrants.
EXPERIMENT 1

When assessing drug-induced behavior changes in young animals, ongoing maturational changes can be a confounding variable (Laviola, Dell'Omo, Alleva & Bignami, 1992; Spear, 1990). Therefore, an abbreviated CPP procedure is preferable for assessing reward in the young rat. Research has shown that a single injection of cocaine is sufficient to establish a CPP in adults (Bardo et al., 1986) and an abbreviated (4-day) procedure produced CPP in preweanling mice (Laviola et al., 1992). Therefore, in the first experiment an abbreviated cocaine-induced CPP paradigm was tested for the first time using the 17-day-old rat.

Method

Subjects. The subjects were 16 male and female rats of Sprague-Dawley descent. They were born and raised at California State University, San Bernardino.

Procedure and Drugs. The general procedure outlined above was employed for Experiment 1. Cocaine was injected intraperitoneally (i.p.) and was given at a volume of 5.0 ml/kg. Cocaine was obtained from Research Biochemicals INC. (USA) and dissolved in distilled water prior to injection.

Statistical Analysis. An independent t-test was used to assess place preference. CPP was defined as a rat spending significantly more time in the cocaine-paired (lemon) chamber.
Results

Cocaine reliably produced a CPP in preweanling rats (see Figure 1). More specifically, cocaine-treated pups spent a significantly greater percent of time in the drug-paired (lemon) chamber than did saline-treated pups ($t(17) = -3.38$, $p < .005$).
Figure Caption

Figure 1. Mean percent time spent in the lemon scented chamber by 17-day-old rats. Half of the rats received cocaine (20 mg/kg, i.p.) in the lemon scented chamber; whereas the other half received only saline.
EXPERIMENT 2

Previous studies have shown that SCH 23390 blocks reinforced responding in preweanling rats (McDougall et al., 1991, 1992). That study, however, employed a reinforced responding paradigm which did not adequately separate the locomotor and rewarding effects of the D₁ receptor antagonist. Having established in Experiment 1 that a CPP can be induced in the 17-day-old rat, the second experiment was conducted to assess the effects of SCH 23390 on locomotor activity and a cocaine-induced CPP. With the use of the CPP paradigm it is possible to successfully separate locomotor and reward responding. Therefore, I predict that prior treatment with SCH 23390 will not affect locomotor activity, but SCH 23390 will block the acquisition of a cocaine-induced CPP.

Method

Subjects. Subjects were 64 male and female rat pups of Sprague-Dawley descent born and raised at California State University, San Bernardino.

Procedure and Drugs. The general procedure was followed in Experiment 2, with the exception that SCH 23390 (0.1, 0.3, or 1.0 mg/kg i.p.) or saline were given 30-min prior to conditioning trials. All drugs were injected i.p. and were given at a volume of 5.0 ml/kg. Both cocaine and SCH 23390 were obtained from Research Biochemicals INC. (USA) and were dissolved in distilled water prior to injection.
Statistical Analyses. CPP was analyzed by a 2 (agonist) X 4 (antagonist) analysis of variance (ANOVA). CPP was defined as a rat spending significantly more time in the cocaine-paired (lemon) chamber. Locomotor activity data were analyzed in an identical fashion. Line crosses were defined as a pup putting both forepaws and snout into an adjacent quadrant.

Results

CPP. An a priori (Tukeys HSD) analysis of control (saline vs cocaine) groups revealed that cocaine-treated rats spent a significantly greater percentage of time in the lemon (cocaine-paired) chamber (p < .05). CPP was reliably blocked at each dose of SCH 23390, as rat pups receiving SCH 23390 and cocaine responded no differently than pups receiving SCH 23390 alone (see Figure 2).

Locomotor Activity During Conditioning. Locomotor activity of the rat pups was increased by cocaine treatment, agonist main effect $F(1,60) = 102.31$, p < .001. In addition, SCH 23390 pretreatment reduced locomotor activity, but only at the two highest doses tested (0.3 and 1.0 mg/kg), antagonist main effect $F(3,60) = 3.75$, p < .02 and Tukeys post hoc tests (p's < .05). Based on the observed data, a Oneway analysis of variance was performed on the SCH 23390 and saline groups. Rat pups treated with both SCH 23390 (0.1, 0.3 or 1.0 mg/kg) and saline had significantly fewer activity counts than rat pups in the saline and saline
group, $F (3,28) = 12.68, p < .001$ and Tukeys post hoc tests ($p$'s < .05). However, Tukeys post hoc tests indicated that SCH 23390 did not significantly affect the cocaine-induced activity of the pups ($p$'s > .05) (see Table 1).

**Conditioned Locomotor Activity.** Previous treatments with SCH 23390 or cocaine did not affect locomotor activity on the test day. Thus, there was no evidence of cocaine-induced conditioned activity (see Table 2).
Figure Caption

Figure 2. Mean percent time spent in lemon scented chamber by 17-day-old rats. Groups (n = 8) received SCH 23390 (0.1, 0.3, 1.0 mg/kg) or saline followed by cocaine or saline.
Table 1

Mean Number of Line Crossings by Antagonist and Agonist Treated 17-day-old Rat Pups During CPP Conditioning.

<table>
<thead>
<tr>
<th></th>
<th>Line Crossings</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALINE / SALINE</td>
<td>60.375</td>
<td>10.900</td>
</tr>
<tr>
<td>0.1 mg/kg SCH / SALINE</td>
<td>21.375 *</td>
<td>6.674</td>
</tr>
<tr>
<td>0.3 mg/kg SCH / SALINE</td>
<td>8.826 *</td>
<td>2.598</td>
</tr>
<tr>
<td>1.0 mg/kg SCH / SALINE</td>
<td>11.125 *</td>
<td>3.720</td>
</tr>
<tr>
<td>SALINE / COCAINE</td>
<td>337.625</td>
<td>71.074</td>
</tr>
<tr>
<td>0.1 mg/kg SCH / COCAINE</td>
<td>428.250</td>
<td>63.007</td>
</tr>
<tr>
<td>0.3 mg/kg SCH / COCAINE</td>
<td>202.625</td>
<td>47.230</td>
</tr>
<tr>
<td>1.0 mg/kg SCH / COCAINE</td>
<td>268.166</td>
<td>46.234</td>
</tr>
</tbody>
</table>

* indicates a significant difference between SCH 23390 treated pups and saline-treated pups, p < .001.
Table 2
Mean Number of Line Crossings by Antagonist and Agonist Treated 17-day-old Rat Pups During CPP Testing.

<table>
<thead>
<tr>
<th></th>
<th>Line Crossings</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALINE / SALINE</td>
<td>49.750</td>
<td>4.720</td>
</tr>
<tr>
<td>0.1 mg/kg SCH / SALINE</td>
<td>51.500</td>
<td>3.444</td>
</tr>
<tr>
<td>0.3 mg/kg SCH / SALINE</td>
<td>66.375</td>
<td>9.224</td>
</tr>
<tr>
<td>1.0 mg/kg SCH / SALINE</td>
<td>49.875</td>
<td>3.048</td>
</tr>
<tr>
<td>SALINE / COCAINE</td>
<td>50.375</td>
<td>9.723</td>
</tr>
<tr>
<td>0.1 mg/kg SCH / COCAINE</td>
<td>46.375</td>
<td>3.289</td>
</tr>
<tr>
<td>0.3 mg/kg SCH / COCAINE</td>
<td>58.250</td>
<td>8.667</td>
</tr>
<tr>
<td>1.0 mg/kg SCH / COCAINE</td>
<td>46.250</td>
<td>4.259</td>
</tr>
</tbody>
</table>
EXPERIMENT 3

Research has shown that the D₂ receptor antagonist sulpiride does not block reinforced responding in 11- and 17-day-old rats (McDougall et al., 1991, 1992). Sulpiride has, however, been shown to effectively block quinpirole (a D₂ receptor agonist) induced locomotor activity in preweanling rats (McDougall, Arnold & Nonneman, 1990). However, these studies employed paradigms which measured either unlearned behaviors (e.g. grooming and locomotion) or reinforced responding (i.e. alleyway traversal). Hence, the individual effects of sulpiride on locomotor response and reward are not clear. The results of Experiment 2 suggest that assessing sulpiride's effects on cocaine-induced responding will provide clearly separable measures of locomotor activity and reward. Based on the previous research, I predict that prior treatment with sulpiride will not block a cocaine-induced CPP. However, it is expected that sulpiride will block cocaine-induced locomotion in the 17-day-old rat.

Method

Subjects. The subjects were 48 male and female rat pups of Sprague-Dawley descent born and raised in the colony at California State University, San Bernardino.

Procedure and Drugs. The procedure was identical to Experiment 2, with the exception that sulpiride (50 or 100 mg/kg i.p.) or saline was given 30-min prior to conditioning.
trials. Both cocaine and sulpiride were injected i.p. and were given at a volume of 5.0 ml/kg. The drugs were obtained from Research Biochemicals INC. (USA) and were dissolved in distilled water prior to injection. Sulpiride required a small volume of glacial acetic acid for dissolution.

Statistical Analyses. CPP was analyzed by a 2 (agonist) X 3 (antagonist) analysis of variance (ANOVA). CPP was defined as a rat spending significantly more time in the cocaine-paired (lemon) chamber. Locomotor activity data were analyzed in an identical fashion. Conditioning chambers were divided into four quadrants. Line crosses were defined as a pup putting both forepaws and snout into an adjacent quadrant.

Results

CPP. Pups treated with cocaine spent a significantly greater percentage of time in the lemon (cocaine-paired) chamber, agonist main effect, F (1,45) = 11.49, p < .003. Sulpiride did not significantly affect the behavior of the cocaine and saline-treated rats. (see Figure 3).

Locomotor Activity During Conditioning. Overall, cocaine-treated pups had significantly more line crossings than pups given saline, agonist main effect, F (1,45) = 56.07, p < .001 (see Table 3). In addition, pups pretreated with sulpiride had significantly fewer line-crossings than those given saline, antagonist main effect, F (2,45) = 12.76
p < .001. Furthermore, the antagonist pretreatment interacted with agonist, as pups given 100 mg/kg sulpiride followed by cocaine had locomotor activity reduced to saline and saline control levels, Agonist X Antagonist interaction, F (1,45) = 3.77, p < .04 and Tukeys post hoc tests (p's < .05).

Conditioned Locomotor Activity. Previous treatments with sulpiride or cocaine did not affect locomotor activity on the test day. Thus, there was no evidence of a cocaine-induced conditioned activity (see Table 4).
Figure Caption

Figure 3. Mean percent time spent in lemon scented chamber by 17-day-old rats. Groups (n = 8) received sulpiride (50, 100 mg/kg) or saline followed by cocaine or saline.
Table 3
Mean Number of Line Crossings by Antagonist and Agonist Treated 17-day-old Rat Pups during CPP Conditioning.

<table>
<thead>
<tr>
<th></th>
<th>Line Crossings</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALINE / SALINE</td>
<td>85.125</td>
<td>30.669</td>
</tr>
<tr>
<td>50 mg/kg SUL / SALINE</td>
<td>24.250 *</td>
<td>10.631</td>
</tr>
<tr>
<td>100 mg/kg SUL / SALINE</td>
<td>9.875 *</td>
<td>5.921</td>
</tr>
<tr>
<td>SALINE / COCAINE</td>
<td>242.375</td>
<td>24.164</td>
</tr>
<tr>
<td>50 mg/kg SUL / COCAINE</td>
<td>225.625</td>
<td>36.885</td>
</tr>
<tr>
<td>100 mg/kg SUL / COCAINE</td>
<td>83.750 **</td>
<td>17.449</td>
</tr>
</tbody>
</table>

* indicates a significant difference between sulpiride and saline-treated pups, p < .05.
** indicates a significant difference relative to 50 mg/kg and saline-treated pups, p < .05.
Table 4

Mean Number of Line Crossings by Antagonist and Agonist Treated 17-day-old Rat Pups During CPP Testing.

<table>
<thead>
<tr>
<th>Line Crossings</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALINE / SALINE</td>
<td>61.142</td>
</tr>
<tr>
<td>50 mg/kg SUL / SALINE</td>
<td>57.857</td>
</tr>
<tr>
<td>100 mg/kg SUL / SALINE</td>
<td>57.250</td>
</tr>
<tr>
<td>SALINE / COCAINE</td>
<td>47.875</td>
</tr>
<tr>
<td>50 mg/kg SUL / COCAINE</td>
<td>49.125</td>
</tr>
<tr>
<td>100 mg/kg SUL / COCAINE</td>
<td>59.833</td>
</tr>
</tbody>
</table>
DISCUSSION

It was predicted that the selective D₁ antagonist SCH 23390 would block cocaine-induced CPP in 17-day-old rats. Specifically, D₁ receptors were predicted to be critical for reward, but not for locomotor activity. The results of this study support these predictions. All doses of SCH 23390 (0.1, 0.3, 1.0 mg/kg) eliminated the expression of a cocaine-induced place preference (see Figure 2). Importantly, although SCH 23390 reduced line crossings of cocaine-treated pups, activity counts were still quite high. In fact, 0.1 mg/kg potentiated pups line crossings (see Table 1). Hence, SCH 23390 was capable of blocking CPP response even though cocaine-induced activity was still apparent after treatment with this antagonist.

It was also predicted that CPP would be unaffected by pretreatment with the D₂ receptor antagonist sulpiride, whereas cocaine-induced locomotor activity would be blocked. This prediction was also supported, as pups receiving sulpiride still showed a CPP for the cocaine-paired chamber (see Figure 3). As expected, sulpiride did depress the locomotor activity of the cocaine-treated pups. In fact, 100 mg/kg of sulpiride did not block CPP, yet reduced activity levels to that of saline-treated controls (see Table 3).

In general these findings are consistent with McDougall et al. (1991, 1992), as they found that the reinforced
responding of both 11- and 17-day-old rat pups was attenuated by SCH 23390 but not sulpiride. The combined findings of this study and those of McDougall et al. contradict Miller et al.'s (1990) model of reward. For example, in each study there was no evidence that SCH 23390 significantly attenuated locomotor activity. Unfortunately, in the McDougall et al. (1991, 1992) studies no direct measure of locomotor ability was assessed. In the current study, while pups treated with SCH 23390 followed by saline showed a decrease in locomotor activity, pups receiving cocaine after SCH 23390 showed an increase in activity when treated with cocaine (see Table 1). Hence, the increased locomotor response observed in the current study was not sufficient to produce reward through sensory feedback to the VTA.

These findings could be interpreted another way. For example, increased locomotor activity induced by cocaine in the SCH 23390 treated pups could have led to sensory feedback to the VTA and subsequent release of DA. However, this increase in DA would still have been blocked at the D₁ receptors. Therefore, the D₁ receptor would not be activated by either drug treatment or peripheral sensory feedback. If correct, this interpretation also supports the D₁, but not the D₂, receptor as the critical component of reward.

Several studies suggest that D₁ receptor activation is
necessary for the expression of behaviors elicited by D₂ receptor activation (Braun & Chase, 1986; White, Bednarz, Wachtel, Hjorth, & Brooderson, 1987). These researchers suggest that tonic activation of D₁ receptors is a necessary component for the expression of D₂ mediated behaviors. Indeed, DA D₁ and D₂ receptor systems also appear to interact early in development, as D₁ receptor blockade attenuates D₂ mediated locomotor activity in preweanling rats (McDougall et al., 1990). This result is actually inconsistent with the present study, because it suggests that SCH 23390 should have blocked cocaine-induced locomotor activity. This discrepancy may be explained by the immature DA D₁ and D₂ receptor interaction in the preweanling rat. For example, dual activation of D₁ and D₂ receptors does not lead to adult-like stereotypy (e.g. biting, head bobbing and licking) (Moody & Spear, 1990). If this is due to an immature receptor interaction, then effects such as blocking motor activity with D₁ antagonists may only be possible when direct agonists for D₂ receptors are given (as used in the McDougall et al. study). As noted earlier, cocaine is an indirect agonist which affects both D₁ and D₂ receptors (Heikkila et al., 1975).

Although the idea of dual activation of D₁ and D₂ receptors is not new, researchers typically focus on the need of tonic D₁ receptor activation for the expression of D₂ receptor mediated behaviors (i.e. reward). The current
study supports this interpretation, because D2 receptor activation alone was not sufficient to establish a cocaine-induced CPP. In addition, D1 receptor activation alone was not sufficient to produce increased locomotor activity, as indicated by the reduction in line crosses in response to the D2 receptor antagonist sulpiride. Taken together, the results of this study suggest that DA systems act in concert to mediate behavior. Each receptor subtype, D1 and D2, appears to play its own distinct and critical role, yet neither D1 receptors nor D2 receptors fulfill the necessary and sufficient criteria to mediate the full compliment of behaviors associated with the DA systems. In other words, D1 receptor mediated reward (i.e. CPP) was not sufficient to induce heightened locomotor activity, and D2 receptor mediated locomotor activity was not sufficient to induce reward responding (i.e. CPP).

The efficacy of the CPP paradigm for separately assessing motor and reward components was apparent. Whereas operant learning paradigms inherently combine locomotor activity and reward, CPP effectively separates them temporally. In other words, when an animal is responding for DA stimulation, be it ICS or drug infusion, the effects of the reinforcer cannot be solely attributable to reward. As indicated, DA agonists increase locomotion, therefore a high rate of operant responding (e.g. bar press) may reflect a general increase in motor performance and/or reward. CPP,
on the other hand, is tested in the absence of drugs. Therefore, reward responses (i.e. compartment preference) can only be attributed to a learned association (i.e. DA stimulation and a novel context). Furthermore, acute use of DA antagonists induces both motor impairment and a decrement in reward. Therefore, it is difficult to determine whether a DA antagonist is reducing the rewarding nature of a DA agonist or only affecting locomotor ability. Again, with the CPP paradigm these difficulties are eliminated by separating measures of reward from drug treatment temporally.

In this particular study, salience of the novel context played a crucial role in the design of the CPP chamber. Studies of adult rats typically employ color and tactile cues to discriminate conditioning chambers (Schecter & Calcagnetti, 1993). However, with preweanling rats visual cues are not necessarily salient. The visual system of the rat does not mature until after eye opening, which occurs when the pup is approximately 12-days-old. Odor, however, is a salient cue to preweanling rats, as they rely on the odor emitted from their mother to find food prior to vision (Barr & Lithgow, 1984, 1986).

Future studies may wish to address a wider age range of subjects. For example, the DA/acetylcholine receptor complex is not functional in rat pups prior to 14 days of age (Miller et al., 1990). Because of this, Miller et al.
(1990) suggest that the role of D₁ and D₂ receptors in the reward processes of the 14-day-old rat should be disrupted. The use of 10-day-old rat pups would further assess the accuracy of Miller et al.'s (1990) model of reward. In addition, it is becoming more and more clear that as the field of neuroscience advances, the focus on individual neurotransmitter systems will be insufficient for explaining the complex nature of behavior. It is apparent that even within DA systems, interactions abound and behavior is the result of not one discrete brain area or one discrete receptor subtype. In addition, DA systems are not isolated from the rest of the brain. It is obvious that to fully understand reward, future research will have to account for the complexity of interneuronal interactions.

Although speculative, the findings of the current study may be of interest when addressing issues of addiction in infants. In the case of treating infants born with an addiction to psychomotor stimulants the use of general DA agonists may lead to harmful side effects. For example, if a "crack-baby" is treated with a general DA agonist, that child will most likely experience the same "euphoric" feelings reported by drug abusers (Griffiths et al., 1979; Wise & Bozarth, 1987). It has been suggested that the initial feeling produced by psychomotor stimulants creates a psychological drive, and hence motivates subsequent use. Whether this initial effect is experienced in a human infant
cannot be assessed. However, avoiding the possibility would seem prudent. Therefore, if in the infant, as with the preweanling rat, the DA D₁ and D₂ receptor interactions are immature, then it may be possible to alleviate physical withdrawal symptoms without activating reward processes. In other words, activating only D₂ receptors could theoretically inhibit acetylcholine release and thereby produce the "loosening of the limbs" response suggested in Miller et al.'s (1990) model of reward.
References


Schechter, M. D. & Greer, N. L. (1987). Evidence that the stimulus properties of apomorphine are mediated by both D1 and D2 receptor activation. Life Sciences, 40, 2461-2471.


