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Effects of a partial dopamine D_2-like agonist on the cocaine-induced behavioral sensitization of preweanling rats

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Abstract

Partial D_2-like receptor agonists act as functional antagonists when given during periods of high dopaminergic tone (e.g., when self-administering cocaine or amphetamine). For this reason, we determined whether pretreatment with the partial D_2-like agonist terguride would block the induction and/or expression of cocaine-induced behavioral sensitization in preweanling rats. More specifically, we examined (a) whether repeated administration of terguride alone (0.4–1.6 mg/kg) would support behavioral sensitization (Experiment 1); (b) whether injecting preweanling rats with terguride (0.1–1.6 mg/kg) during the pretreatment phase would block the induction and ultimate expression of cocaine-induced behavioral sensitization (Experiment 2); and (c) whether injecting rats with terguride (0.2–0.8 mg/kg) on the test day would block the expression of cocaine sensitization (Experiment 3). Results showed that repeated terguride administration did not induce behavioral sensitization by itself, nor did it block the induction of cocaine sensitization in preweanling rats. Interestingly, terguride reduced, but did not fully attenuate, the locomotor activity of cocaine-treated rats during the pretreatment phase. When given on the test day, terguride also depressed cocaine-induced locomotor activity, but rather than blocking the expression of behavioral sensitization, terguride seemed to cause a general reduction in locomotion. Because partial D_2-like agonists attenuate cocaine- and amphetamine-induced reward, it has been proposed that this class of drug might serve as an effective pharmacotherapy for psychostimulant abuse. Although partial D_2-like agonists may prove useful in this regard, results from the present study suggest that terguride would not block sensitization components of the addiction process.

Keywords: Terguride; Partial D_2-like agonists; Cocaine; Behavioral sensitization; Locomotor activity; Ontogeny

1. Introduction

Partial D_2-like receptor agonists (e.g., terguride and SDZ 208-911) have high affinity but low activity at dopamine D_2-like receptors (Hoyer and Boddeke, 1993; Caine et al., 1997; Newman-Tancredi et al., 2002). Because of these properties, partial D_2-like agonists function as either agonists or antagonists depending on the amount of intrinsic dopaminergic activity (Clark et al., 1991; Campbell et al., 1992; Pulvirenti and Koob, 1994). In a state of low dopaminergic tone (e.g., during amphetamine withdrawal), partial D_2-like agonists have agonist-like actions (Orsini et al., 2001); whereas in a state of high dopaminergic tone (e.g., during cocaine and amphetamine self-administration), partial D_2-like agonists act as functional antagonists (Pulvirenti et al., 1994, 1998; Weissenborn et al., 1996; Izzo et al., 2001).

The ability of partial D_2-like agonists to attenuate the psychopharmacological effects of cocaine and amphetamine has led some researchers to hypothesize that these drugs may have clinical utility for the treatment of psychostimulant abuse (see Pulvirenti and Koob, 1994; Izzo et al., 2001). The drug self-administration paradigm has provided the most compelling evidence for such a role since operant studies have shown that treatment with a partial D_2-like agonist diminishes the reward-inducing properties of cocaine and amphetamine (Pulvirenti et al., 1994, 1998; Izzo et al., 2001; Ranaldi et al., 2001). The behavioral sensitization paradigm has also provided information relevant to psychostimulant abuse because processes underlying behavioral sensitization are important for the incentive-motivational components of addiction (Robinson and Berridge, 1993; Di Chiara, 1995). Behavioral sensitization has been studied in various species and is most frequently observed as a progressive increase in locomotor activity or stereotypy after repeated administration of a psychostimulant drug (Kalivas and Stewart, 1991; Pierce and Kalivas, 1997; Wolf,

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1998). To date, no one has determined whether pretreatment with a partial D_2-like agonist blocks the induction and/or expression of cocaine sensitization, although there is conflicting evidence suggesting that D_2-like receptors play a role in behavioral sensitization. More specifically, full D_2-like receptor antagonists (e.g., haloperidol and raclopride) have alternately been reported to either block the induction of cocaine-induced behavioral sensitization (Weiss et al., 1989; Fontana et al., 1993; Reimer and Martin-Iverson, 1994; Tella, 1994; Mattingly et al., 1996) or leave cocaine sensitization unaffected (Kuribara and Uchihashi, 1993; Mattingly et al., 1994; White et al., 1998). The ability of partial D_2-like receptor agonists to block cocaine sensitization has not been examined. This omission is unfortunate since partial D_2-like receptor agonists, and not full antagonists, are currently being proposed as novel pharmacotherapies for the treatment of cocaine abuse (see Pulvirenti and Koob, 1994; Izzo et al., 2001).

In recent years, the ontogeny of behavioral sensitization has received a substantial amount of empirical attention (for a review, see Tirelli et al., 2003). It was initially reported that young rats were incapable of exhibiting a sensitized response (Fujiwara et al., 1987; Kolta et al., 1990; Ujike et al., 1995); however, it has now become clear that repeatedly exposing rats to cocaine on PD 4, or later, results in behavioral sensitization (Bowman et al., 1997; Tirelli and Ferrara, 1997; Snyder et al., 1998; Wood et al., 1998; Zavala et al., 2000; Tirelli, 2001). Even so, the behavioral sensitization shown by young rats differs from adults in a number of important respects (for a review, see Tirelli et al., 2003), and the neural mechanisms underlying these differences have only begun to be assessed (Duke et al., 1997). The purpose of this study, therefore, was to determine whether the partial D_2-like receptor agonist, terguride, would block the initial induction and ultimate expression of cocaine-induced behavioral sensitization in preweanling rats. Terguride was chosen because this partial D_2-like agonist both diminishes the reward-inducing properties of cocaine (Weissenborn et al., 1996; Pulvirenti et al., 1998) and has been proposed to be of potential therapeutic benefit for cocaine abuse. Since partial D_2-like agonists have agonistic actions in states of low dopaminergic tone, we also assessed whether terguride alone was capable of inducing locomotor sensitization in preweanling rats.

2. Methods

2.1. Animals

Subjects were 194 rats of Sprague–Dawley descent that were born and raised at California State University, San Bernardino. A total of 26 litters were used in the study. Litters were culled to 10 pups at PD 4. Assignment of subjects was random, with one rat from each litter being placed into each treatment group. There were approximately an equal number of male and female rats per group. The colony room was maintained at 22–24 °C and kept under a 12:12-h light/dark cycle. Testing was done in a separate experimental room and was conducted during the light phase of the cycle. Subjects were treated according to the National Institutes of Health *Guide for Care and Use of Laboratory Animals* (Publication No. 85-23, revised 1985) under a research protocol approved by the Institutional Animal Care and Use Committee of California State University, San Bernardino.

2.2. Apparatus

Behavioral testing was done in commercially available (Coulbourn Instruments, Allentown, PA) activity-monitoring chambers (25.5 × 25.5 × 41 cm) consisting of Plexiglas walls, a plastic floor, and an open top. Each chamber included an X–Y photobeam array, with 16 photocells and detectors, that was used to determine distance traveled (locomotor activity).

2.3. Drugs

(−)-Cocaine hydrochloride (Sigma, St. Louis, MO) was dissolved in saline, whereas *R*(+)-terguride (ICN, Aurora, OH) was dissolved in a minimal amount of glacial acetic acid and diluted with saline. Both drugs were injected intraperitoneally at a volume of 5 ml/kg.

2.4. Procedure

2.4.1. Experiment 1: Effects of repeated terguride administration on locomotor activity

The purpose of Experiment 1 was to determine whether repeated exposure to terguride would induce locomotor sensitization in preweanling rats. During the pretreatment phase, which occurred on PD 15–21, rats ($n = 50$) from 10 different litters were habituated to the activity chambers for 5 min each day. After the habituation period, rats were given daily injections of terguride (0.0, 0.4, 0.8, or 1.6 mg/kg ip) and immediately returned to the activity chambers where locomotor activity was measured for 60 min.

A single test day occurred on PD 23 (i.e., after one drug abstinence day). On the test day, rats pretreated with 0.0 mg/kg terguride received a challenge injection of either saline or terguride (0.4 mg/kg ip) 5 min after being placed in the activity chambers. Rats from the other pretreatment groups (i.e., those receiving 0.4, 0.8, or 1.6 mg/kg terguride) received a challenge injection of terguride (0.4 mg/kg ip) on the test day. Locomotor activity was then measured for 60 min.

2.4.2. Experiment 2: Effects of pretreatment injections of terguride on cocaine sensitization

The purpose of Experiment 2 was to determine whether pretreatment injections of terguride would block the initial induction and ultimate expression of cocaine-induced loco-

motor sensitization in preweanling rats. During the pretreatment phase (occurring on PD 15–21), rats ($n=40$) from eight different litters were treated with terguride (0.0, 0.1, 0.2, or 0.4 mg/kg ip), while in a separate experiment, an additional eight litters of rats ($n=40$) were injected with higher doses of terguride (0.0, 0.4, 0.8, or 1.6 mg/kg ip). After being treated with terguride, rats were returned to their home cages for 30 min to allow for drug absorption and distribution (see Clark et al., 1991). Rats were then placed in the activity chambers and allowed to habituate for 5 min each day. After the habituation period, rats were given daily injections of 30 mg/kg ip cocaine and immediately returned to the activity chambers where locomotor activity was measured for 45 min. To assess the occurrence of cocaine sensitization, a separate control group was pretreated with 0 mg/kg terguride and injected with saline after the habituation period.

A single test day occurred on PD 23 (i.e., after one drug abstinence day). On the test day, all rats received a challenge injection of cocaine (15 mg/kg ip) 5 min after being placed in the activity chambers. Locomotor activity was then measured for 45 min.

2.4.3. Experiment 3: Effects of a test day injection of terguride on cocaine sensitization

The purpose of Experiment 3 was to determine whether a test day injection of terguride would block the expression of cocaine-induced locomotor sensitization in preweanling rats. During the pretreatment phase (occurring on PD 15–21), rats ($n=64$) from eight different litters were habituated to the activity chambers for 5 min each day. After the habituation period, rats were given daily injections of saline or cocaine (30 mg/kg ip) and immediately returned to the activity chambers, where locomotor activity was measured for 45 min.

A single test day occurred on PD 23 (i.e., after one drug abstinence day). On the test day, rats were administered terguride (0.0, 0.2, 0.4, or 0.8 mg/kg ip) and returned to their dam in the home cage. After 30 min, rats were placed in the activity chambers and then given a challenge injection of cocaine (15 mg/kg ip) 5 min later. Locomotor activity was then measured for 45 min.

2.5. Statistics

Locomotor activity data from the pretreatment phase were analyzed using two-way analyses of variance (ANOVAs) (Pretreatment Condition × Day). For Experiments 1 and 2, test day data were analyzed using two-way ANOVAs (Pretreatment Condition × Time Blocks). For Experiment 3, test day data were analyzed using a three-way ANOVA (Pretreatment Condition × Test Day Condition × Time Block). Significant higher order interactions were further analyzed using one- or two-way ANOVAs. Body weight data from the initial pretreatment and test day were analyzed using one- or two-way ANOVAs (depending on experiment). In all analyses, litter effects were controlled by using within-litter statistical procedures (i.e., a within analysis using one value/condition/litter) (Zorrilla, 1997). Separate between-subjects statistical analyses showed that neither locomotor activity nor body weight varied according to sex of the animals so these analyses are not presented. Post hoc analysis of the behavioral data were made using Tukey tests ($P<.05$).

3. Results

3.1. Experiment 1

On the first day of the pretreatment phase (i.e., PD 15), the mean body weights of the preweanling rats was 35.0 ($\pm$ 1.3) g. Repeated administration of terguride during the pretreatment phase did not significantly affect body weights since the mean weights of the saline and terguride groups were similar on the test day [overall mean: 58.6 ($\pm$ 1.3) g].

During the pretreatment phase, terguride-treated rats exhibited less locomotor activity (i.e., distance traveled) than saline controls (Fig. 1) [pretreatment condition main effect, $F(3,21)=3.91$, $P<.05$]. Differences between the saline and terguride groups only reached statistical significance on PD 15–17, with the locomotor activity of saline controls declining to approximately the levels of the terguride groups after PD 17 [Pretreatment Condition × Day interaction, $F(18,126)=2.10$, $P<.01$].

When test day data were examined, it was apparent that a challenge injection of terguride depressed the locomotor activity of preweanling rats (Fig. 2), as saline-challenged rats (open circles) exhibited significantly more locomotor activity than terguride-challenged rats (filled symbols) [pretreatment condition main effect, $F(4,28)=5.04$, $P<.01$]. A separate ANOVA, comparing only those groups receiving terguride on the test day, showed that repeated exposure to terguride did

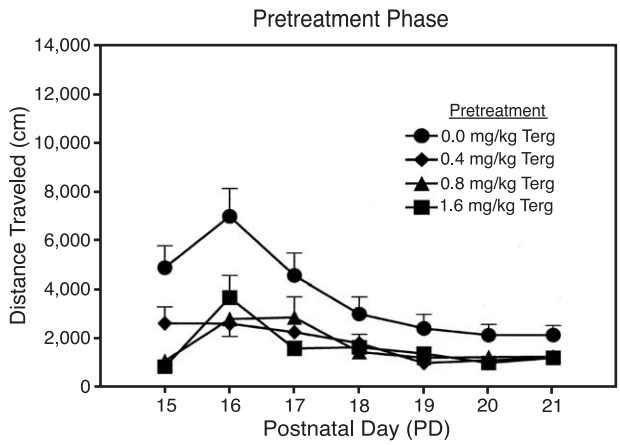

Fig. 1. Mean ($\pm$ S.E.M.) distance traveled (i.e., locomotor activity) of rats injected intraperitoneally with 0.0 mg/kg terguride ($n=20$) or 0.4, 0.8, or 1.6 mg/kg terguride ($n=10$ per group) on PD 15–21. Behavioral testing lasted 60 min and occurred immediately after injections.

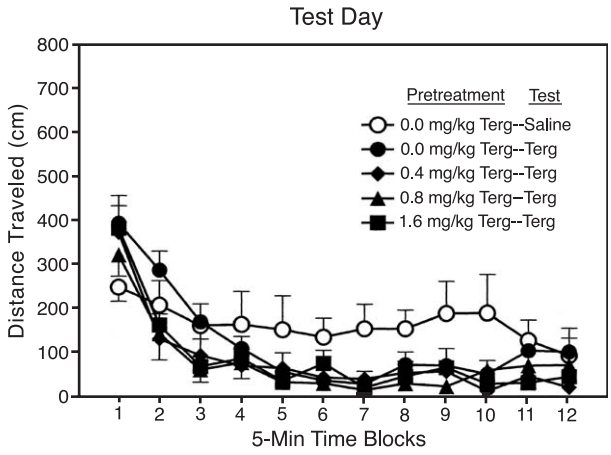

Fig. 2. Mean (± S.E.M.) distance traveled (i.e., locomotor activity) of rats ($n = 10$ per group) receiving a challenge injection of saline (open circles) or 0.4 mg/kg terguride (filled symbols) after one drug abstinence day (i.e., on PD 23). During the pretreatment phase, rats had received daily injections of terguride (0.0, 0.4, 0.8, or 1.6 mg/kg ip) for seven consecutive days (these are the same rats as described in Fig. 1). Behavioral testing lasted 60 min and occurred immediately after injections.

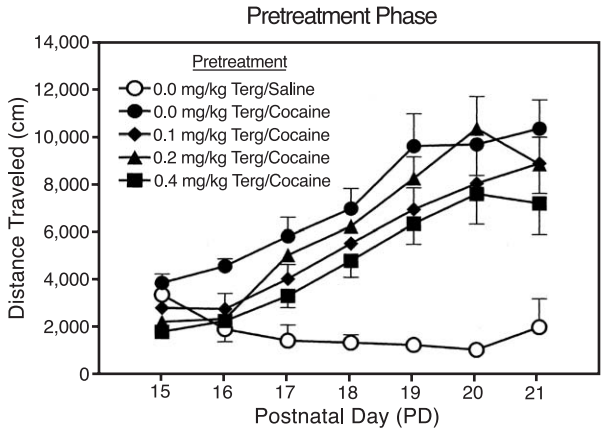

Fig. 3. Mean (± S.E.M.) distance traveled (i.e., locomotor activity) of rats ($n = 8$ per group) pretreated with terguride (0.0, 0.1, 0.2, or 0.4 mg/kg ip) followed, 35 min later, by an injection of 30 mg/kg cocaine (filled symbols). A separate control group was pretreated with 0.0 mg/kg terguride and injected, 35 min later, with saline (open circles). Behavioral testing lasted 45 min and occurred immediately after cocaine or saline injections.

not induce behavioral sensitization. More specifically, rats pretreated with terguride (0.4, 0.8, or 1.6 mg/kg), and later challenged with 0.4 mg/kg terguride, did not exhibit more locomotor activity than acutely challenged terguride controls.

3.2. Experiment 2

The mean body weights of the preweanling rats increased from 34.8 (± 0.5) g on the first day of the pretreatment phase (i.e., PD 15) to an overall mean of 57.1 (± 0.9) g on the test day (i.e., PD 23). Repeated treatment with cocaine was responsible for a nonsignificant ($P < .06$) decline in body weights relative to saline controls [cocaine groups: 56.3 (± 0.9) g, saline group: 60.4 (± 2.3) g].

During the pretreatment phase, rats given cocaine showed a progressive day-dependent increase in locomotor activity (Fig. 3) [pretreatment condition main effect, $F(4,36) = 12.53$, $P < .001$; Pretreatment Condition × Day interaction, $F(24,216) = 4.43$, $P < .001$]. In contrast, locomotor activity of saline controls remained stable across days, with differences between the cocaine- and saline-treated rats reaching statistical significance on PD 17–21. A separate ANOVA, which included only cocaine-treated rats, showed that terguride partially attenuated cocaine-induced locomotor activity during the pretreatment phase. Specifically, rats receiving both cocaine and terguride (0.1, 0.2, and 0.4 mg/kg) exhibited less locomotor activity than rats receiving cocaine alone [pretreatment condition main effect, $F(3,27) = 3.48$, $P < .05$]. Similar results were obtained when higher doses of terguride (0.8 or 1.6 mg/kg) were administered (data not shown).

The pretreatment phase drug regimen affected performance of rats on the test day (Fig. 4) [Pretreatment Condition × Time Block interaction, $F(32,288) = 2.07$, $P < .001$]. Cocaine-induced behavioral sensitization was evident, as a separate ANOVA showed that rats both pretreated and challenged with cocaine (filled symbols), had more locomotor activity than rats given cocaine for the first time on the test day (open circles) [Pretreatment Condition × Time Block interaction, $F(8,72) = 5.30$, $P < .001$]. Importantly, administering terguride (0.1, 0.2, or 0.4 mg/kg) during the pretreatment phase did not affect performance of cocaine-pretreated rats on the test day. Higher doses of terguride (0.8 or 1.6 mg/kg) also did not affect test day locomotor activity (data not shown). Thus, giving young rats a partial D_2-like

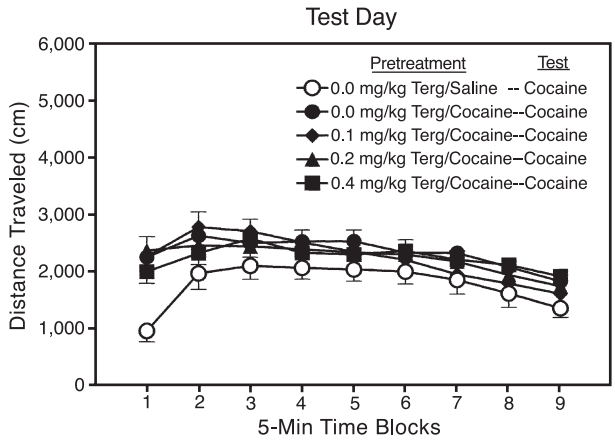

Fig. 4. Mean (± S.E.M.) distance traveled (i.e., locomotor activity) of rats ($n = 8$ per group) receiving a challenge injection of 15 mg/kg cocaine after one drug abstinence day (i.e., on PD 23). During the pretreatment phase, rats had received daily injections of terguride (0.0, 0.1, 0.2, or 0.4 mg/kg ip) followed, 35 min later, by an injection of 30 mg/kg cocaine or saline (these are the same rats as described in Fig. 3). Behavioral testing lasted 45 min and occurred immediately after injections.

agonist during the pretreatment phase did not block the expression of cocaine sensitization.

3.3. Experiment 3

The mean body weights of the preweanling rats were 34.7 (±0.4) g on PD 15. Once again, repeated treatment with cocaine was responsible for a nonsignificant ($P<.09$) reduction in body weight [cocaine groups: 60.0 (±1.0) g, saline group: 63.0 (±1.3) g].

Cocaine-treated rats exhibited a day-dependent increase in locomotor activity across the pretreatment phase (Fig. 5) [pretreatment condition main effect, $F(1,7)=195.89$, $P<.001$; Pretreatment Condition × Day interaction, $F(6,42)=20.93$, $P<.001$]. Differences between the saline and cocaine groups reached statistical significance on all of the pretreatment days (i.e., PD 15–21).

On the test day, cocaine-pretreated rats exhibited more locomotor activity than saline-pretreated rats (Fig. 6) [pretreatment condition main effect, $F(1,7)=17.80$, $P<.01$]. A separate analysis confirmed that preweanling rats showed cocaine-induced behavioral sensitization, as rats both pretreated and challenged with cocaine alone (filled circle) had greater locomotor activity than rats only challenged with cocaine (open circles) [pretreatment condition main effect, $F(1,7)=6.90$, $P<.05$]. Regardless of pretreatment condition, terguride partially attenuated the locomotor activity produced by acute cocaine challenge [pretreatment condition main effect, $F(3,21)=7.49$, $P<.001$]. More specifically, both 0.4 and 0.8 mg/kg terguride reduced cocaine-induced locomotor activity, with the 0.8 mg/kg dose having the greatest impact. Terguride's actions varied according to time block, as 0.4 and 0.8 mg/kg terguride decreased cocaine-induced locomotor activity on Time Blocks 2–7 [Pretreatment Condition × Time Block interaction, $F(24,168)=7.22$, $P<.001$]. The lower dose of terguride (0.2 mg/kg) depressed cocaine's locomotor-activating effects on Time Blocks 3 and 4.

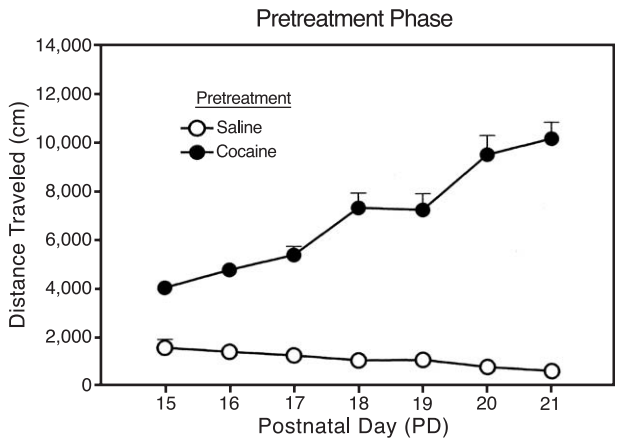

Fig. 5. Mean (±S.E.M.) distance traveled (i.e., locomotor activity) of rats ($n=32$ per group) injected intraperitoneally with saline or 30 mg/kg cocaine on PD 15–21. Behavioral testing lasted 45 min and occurred immediately after injections.

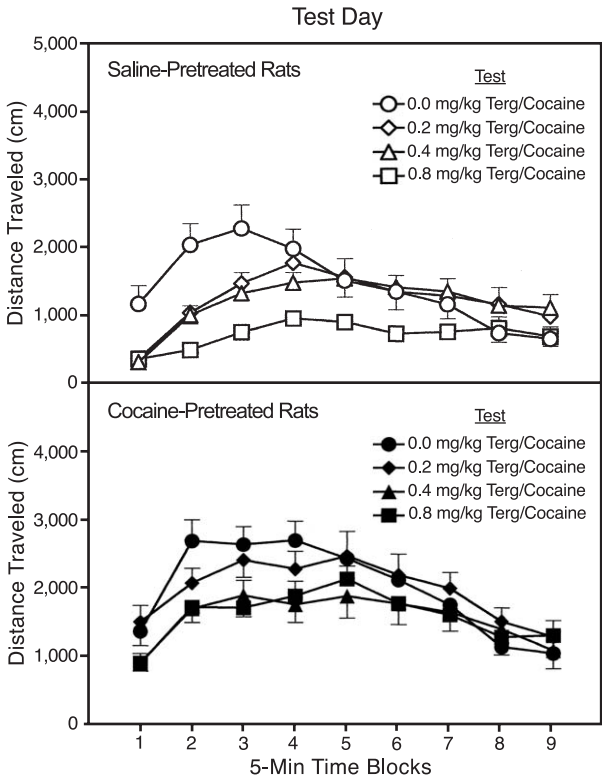

Fig. 6. Mean (±S.E.M.) distance traveled (i.e., locomotor activity) of rats ($n=8$ per group) receiving a challenge injection of 15 mg/kg cocaine on the test day (i.e., PD 23). Rats had received a test day injection of terguride (0.0, 0.2, 0.4, or 0.8 mg/kg ip) 35 min prior to cocaine treatment. During the pretreatment phase, rats had received daily injections of saline (upper graph) or 30 mg/kg cocaine (lower graph) on PD 15–21. Behavioral testing lasted 45 min and occurred immediately after cocaine injections.

4. Discussion

Koob et al. have proposed that partial D_2-like agonists, such as terguride, may be useful for treating psychostimulant abuse (Pulvirenti and Koob, 1994; Izzo et al., 2001). Because terguride has agonistic properties during periods of low dopaminergic tone, we assessed whether repeated treatment with this partial D_2-like agonist would support behavioral sensitization in preweanling rats. Results of Experiment 1 showed that terguride (0.4, 0.8, or 1.6 mg/kg) neither caused a day-dependent increase in locomotor activity, nor did a challenge injection of terguride (0.4 mg/kg) cause a sensitized locomotor response on the test day. Hence, it is apparent that repeated administration of terguride does not induce behavioral sensitization in preweanling rats. The present results do not, however, preclude the possibility that terguride might increase sensitivity to psychostimulant drugs (i.e., support cross-sensitization) because certain dopamine agonists (e.g., SKF 38393), which

are incapable of inducing behavioral sensitization on their own, will cause neural changes that support a cocaine-induced sensitized response (Pierce et al., 1996; Henry et al., 1998).

When administered on the test day, terguride caused a dose-dependent decrease in cocaine-induced locomotor activity. This terguride-induced reduction in locomotion occurred regardless of whether rats had been given saline or cocaine during the pretreatment phase (see Fig. 6). Based on these results, it is possible that terguride blocked the expression of cocaine sensitization. However, because terguride attenuated the cocaine-induced locomotor activity of both sensitized and nonsensitized rats, a more parsimonious conclusion is that the decline in cocaine-induced locomotor activity represented a generalized action of terguride that was independent of the sensitization phenomenon. The latter interpretation is consistent with nonontogenetic studies showing that administering D_2-like receptor antagonists on the test day does not block the expression of cocaine-induced behavioral sensitization in adult rats (Weiss et al., 1989; Fontana et al., 1993; Martin-Iverson and Reimer, 1994; White et al., 1998).

When administered prior to daily cocaine treatments, terguride (0.1–0.4 mg/kg) partially attenuated the cocaine-induced locomotor activity of preweanling rats (Fig. 3); however, no dose of terguride fully eliminated cocaine's locomotor-activating effects. Similar results have been observed in adult animals, as both terguride and SDZ 208-911 only partially attenuated the locomotor activity and sniffing caused by acute treatment with a high dose (8 mg/kg) of amphetamine (Clark et al., 1991). Although terguride reduced cocaine-induced locomotor activity during the pretreatment phase, it did not impact performance of cocaine-challenged rats on the test day. Thus, giving terguride (0.1–0.4 mg/kg) during the pretreatment phase did not block the induction and ultimate expression of cocaine-induced behavioral sensitization. These results were not due to an insufficient dose of terguride being used because higher doses (0.8 and 1.6 mg/kg) were also unable to block the induction of cocaine sensitization. Therefore, these results indicate that terguride reduces the acute locomotor-activating effects of cocaine in preweanling rats, but that this partial D_2-like agonist does not block the induction process.

It is unclear why pretreatment injections of terguride did not disrupt the induction of cocaine sensitization. One possibility is that the partial D_2-like receptor agonist was having agonistic effects in the preweanling rats. This explanation was not supported by the data, however, because terguride consistently acted as a functional antagonist in all experiments (e.g., terguride failed to induce behavioral sensitization and it inhibited both basal- and cocaine-induced locomotor activity). A second possibility is that D_2-like receptor stimulation is necessary for the induction of behavioral sensitization, and that cocaine was still capable of supporting induction despite the administration of terguride. This explanation is based on the finding that no dose of terguride (up to 1.6 mg/kg) fully attenuated cocaine-induced locomotor activity during the pretreatment phase. Alternatively, D_2-like receptor stimulation may not be necessary for the induction of behavioral sensitization. If true, neither a partial D_2-like agonist nor a full D_2-like receptor antagonist would be expected to block the induction of cocaine sensitization. This issue has been examined multiple times, with some studies showing that D_2-like receptor antagonists block the induction of behavioral sensitization (Weiss et al., 1989; Fontana et al., 1993; Reimer and Martin-Iverson, 1994; Tella, 1994; Mattingly et al., 1996) while others report robust cocaine sensitization even after D_2-like antagonist pretreatment (Kuribara and Uchihashi, 1993; Mattingly et al., 1994; White et al., 1998). The present study does not allow for a definitive conclusion about the importance of D_2-like receptors for behavioral sensitization, but our results are consistent with the position that D_2-like receptor stimulation is not necessary for the induction of cocaine-induced sensitization (for a more thorough discussion, see White et al., 1998).

Lastly, it is possible that terguride's inability to block the induction of cocaine sensitization is unique to the preweanling rat and represents a qualitative ontogenetic difference in how rats respond to partial D_2-like agonist drugs. This explanation cannot be discounted because the behavioral sensitization shown by young rats differs from adults in some important respects (e.g., the longevity of the sensitized response and the relative importance of drug-environment Pavlovian associations, etc.), and these differences may reflect ontogenetic changes in mechanisms underlying behavioral sensitization. More generally, however, dopamine-acting drugs produce qualitatively similar effects across ontogeny, as full dopamine receptor agonists (e.g., apomorphine and quinpirole) increase the locomotor activity of rats by PD 4 (Shalaby and Spear, 1980; Camp and Rudy, 1987; Moody and Spear, 1992) and D_2-like receptor antagonists (e.g., haloperidol, flupenthixol, and sulpiride) reduce behavioral activity in both young and adult rats (Camp and Rudy, 1987; Fitzgerald and Hannigan, 1989; McDougall et al., 1990; Nazarian et al., 1999). Dopamine systems mediating reward also become functionally mature early in ontogeny because cocaine and amphetamine potentiate intracranial self-stimulation by PD 3 (Barr and Lithgow, 1986) and cocaine supports place preference conditioning by PD 10 (Pruitt et al., 1995). Therefore, while dopamine-acting drugs often cause similar behavioral effects in young and adult rats, it remains possible that the inability of terguride to block cocaine sensitization reflects an immaturity of neural mechanisms underlying behavioral sensitization.

In conclusion, the behavioral effects of partial D_2-like agonists are being studied intensively because of their proposed utility for the treatment of psychostimulant abuse. The primary basis for this belief is self-administration studies showing that partial D_2-like agonists reduce the rewarding effects of cocaine and amphetamine in adult rats and monkeys (Pulvirenti et al., 1994, 1998; Izzo et al., 2001;

Ranaldi et al., 2001; but see Spealman, 1995). There is other evidence supporting a pharmacotherapeutic role for partial D_2-like agonists since these drugs block the discriminative stimulus properties of cocaine and amphetamine (Exner et al., 1989; Exner and Clark, 1992; Callahan and Cunningham, 1993), reduce ethanol intake (Bono et al., 1996), and reverse amphetamine withdrawal (Orsini et al., 2001). Results from the present study show that partial D_2-like agonists reduce the acute locomotor-activating effects of cocaine in preweanling rats. Terguride did not block the induction of behavioral sensitization in these animals, suggesting that this component of the addiction process is not sensitive to partial D_2-like agonist treatment. Importantly, however, the physiological changes responsible for the induction of behavioral sensitization begin after just one drug exposure (Weiss et al., 1989; Fontana et al., 1993); thus, there may be little utility in developing pharmacotherapies that focus on the initial induction of behavioral sensitization.

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