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Pharmacology, Biochemistry and Behavior 68 (2001) 701–708

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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A dopamine partial agonist and antagonist block amphetamine self-administration in a progressive ratio schedule

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Received 11 September 2000; received in revised form 18 December 2000; accepted 3 January 2001

Abstract

A recently characterized class of compounds, dopamine partial agonists, have been suggested as potential therapeutic candidates for pharmacological intervention in psychostimulant addiction. These drugs bind to dopamine receptors with high affinity and low intrinsic activity and are thought to behave as functional antagonists in conditions of high dopaminergic tone, and as agonists in conditions of low receptor occupancy by dopamine. The aim of the present study was to characterize the effects of terguride, a partial dopamine agonist at the D2 receptor subtype, on intravenous self-administration of amphetamine in a progressive ratio schedule and to compare it with the effects produced by the dopamine D2 antagonist eticlopride and the dopamine D2 full agonist quinpirole. Terguride at the doses of 0.2 and 0.4 mg/kg ip significantly decreased the maximum number of responses delivered for a single injection of amphetamine (''breaking point''), an effect similar to that produced by the antagonist eticlopride (0.01–0.1 mg/kg sc). In contrast, administration of quinpirole (0.1–1 mg/kg sc) did not significantly modify the breaking point for amphetamine responding. Also, terguride dose-dependently increased responding for amphetamine self-administration on a continuous reinforcement schedule. These data further confirm the effects of terguride on psychostimulant self-administration and indicate that under these conditions partial dopamine agonists act as functional dopamine receptor antagonists.

Keywords: Dopamine; Partial agonist; Amphetamine; Self-administration; Addiction

1. Introduction

Pharmacological attempts to modify the natural history of psychostimulant addiction in humans have met with very limited clinical success. The observation that brain dopamine neurotransmission appears to be critically involved in the acute reinforcing properties of cocaine and amphetamine has stimulated interest in the use of drugs that modify dopamine neurotransmission as possible candidates for the treatment of psychostimulant abuse. However, only limited efficacy has been reported in clinical trials using a number of dopamine agonists and antagonists (for review, see Withers et al., 1995).

A different strategy for pharmacological intervention in psychostimulant addiction has been proposed via the use of drugs with partial agonistic properties at the level of dopamine receptors. These drugs represent a novel class of compounds possessing a unique pharmacological profile since they bind to the dopamine receptor with high affinity but low intrinsic activity (Hoyer and Boddeke, 1993). The functional consequence is that these drugs act as antagonists under conditions of high dopamine tone, such as in the case of intense presynaptic activity or after pharmacological stimulation (e.g., after exposure to cocaine or amphetamine). In contrast, in conditions of low dopamine tone such as after denervation or during functional depletion of the neurotransmitter, partial agonists show agonistic properties since their low intrinsic activity meets with a hyperresponsive receptor system (Clark et al., 1985; Pulvirenti and Koob, 1994). Several compounds with partial dopamine agonistic activity have been characterized to date, including preclamol, terguride, SDZ 208-911, active at the dopamine D2 receptor site (Caine et al., 1997; Hjorth et al., 1983), and SKF 38393, SKF 77434 active at the dopamine D1 receptors (Adachi et al., 1999; Meyer and Shults, 1993)

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0091-3057/01/$ – see front matter
PII: S0091-3057(01)00472-5

Within the context of cocaine abuse dopamine partial agonists may prove particularly versatile. In particular, the presence of various phases during the course of the cocaine addiction cycle, which include phases of intake of high doses of drugs (''drug binges'') followed by period of withdrawal, may represent a specific field of therapeutic application for dopamine partial agonists. It has been proposed that these compounds might indeed counteract the high dopamine levels found during the binging periods of the dependence cycle while their intrinsic agonistic activity might restore the relative functional dopamine hypoactivity thought to occur during the withdrawal phase (Pulvirenti and Koob, 1994).

In this respect, the antagonistic action of dopamine partial agonists has been confirmed and terguride and SDZ 208-911 appear to reduce the acute reinforcing properties of cocaine (Pulvirenti et al., 1994, 1998). Also, a recent report suggests that a novel dopamine partial agonist acting at the dopamine D3 receptor subtype may reduce relapse into cocaine intake produced by drug-associated environmental stimuli (Pilla et al., 1999), while D1 partial agonists reduced self-administration of cocaine in rhesus monkeys in a manner similar to D1 full agonists (Platt et al., 1999).

It is also noteworthy that partial dopamine agonists appear to be devoid of abuse liability (Pulvirenti et al., 1998) and they lack the extrapyramidal side effects that greatly limit the clinical use of classical antipsychotic drugs (Coward et al., 1990). These observations warrant further preclinical investigation of their potential clinical use in psychostimulant abuse.

Most of the work exploring the neuropharmacology of psychostimulant addiction has in recent years utilized cocaine. Amphetamine represents, however, a drug with high abuse liability, which has been present in the illicit market for many years both in its native form and in a number of chemical derivatives. Amphetamine has a pharmacological profile that is only partially similar to that of cocaine. While the primary pharmacological action of cocaine is the blockade of monoamine re-uptake, amphetamine is also a potent dopamine releaser (Fischer and Cho, 1979; Heikkila et al., 1975). In addition, while the effects of cocaine depend upon neuronal impulse flow, those of amphetamine are largely neuronal impulse firing-independent (Fischer and Cho, 1979). These considerations open the possibility that drugs acting at the dopamine receptor level with partial dopamine agonist activity may act differentially on the effects produced by the two different psychostimulants.

The aim of the present study was therefore to investigate the effects of the partial dopamine agonist terguride on intravenous self-administration of amphetamine under a progressive ratio schedule, an operant measure tailored to establish the motivational strength of the organism to obtain an addictive drug (Bedford et al., 1978; Richardson and Roberts, 1996; Stafford et al., 1998). The effects of terguride were directly compared with the effects produced by eticlopride, a dopamine D2 antagonist and by quinpirole, a full dopamine agonist. In addition, the effects of terguride in rats exposed to limited-access daily self-administration of amphetamine on a continuous reinforcement schedule were also evaluated.

2. Methods

2.1. Subjects

Twenty-nine male Wistar rats (Charles River), weighing 200–225 g at the start of the experiment, were housed three to a cage and provided with ad libitum access to food and water and maintained on a 12-h light–dark cycle (lights on 7:00 a.m.–7:00 p.m.).

2.2. Self-administration

Prior to catheter implantation, animals were food-restricted (20 g rat chow per animal per day) and trained under a fixed ratio 5 schedule for food (45 mg pellets) reinforcement. Once stable responding was reached under this schedule (>50 reinforces per 60-min session), animals were catheterized (see below) and thereafter allowed free access to food.

All animals were surgically implanted with a chronic Silastic jugular vein catheter under halothane anesthesia. The techniques used to construct and implant the catheter were those of Caine et al. (1993). The catheter passed subcutaneously to a piece of marlex mesh secured subcutaneously on the animal's back. At the time of the self-administration session (normally 6 days per week), the catheter was connected to a swivel system through a metal spring, which was in turn connected to an infusion pump as described by Caine et al. (1993).

Four days following surgery for the intravenous surgery, the animals were allowed 3-h access each day to a metal lever mounted on the side wall of a standard operant-conditioning cage, 3 cm from the cage floor. The force requirement to press the lever was an average of 30 g (a range of 25 to 35 g in different cages). The cages themselves were housed inside sound attenuated chambers. A lever press resulted in an intravenous injection of 0.1 ml of D-amphetamine sulphate (0.12 mg/kg per injection) dissolved in 0.9% physiological saline and delivered over a period of 4 s. A swivel system allowed free movement of the animal in the cage. Coincident with the onset of the injection, a stimulus light located 1 cm above the lever on the same side wall of the operant chamber was turned on for 20 s during which time the lever became inactive. At the beginning of the session, two noncontingent infusions of amphetamine were delivered automatically by the computer. Thereafter, lever presses during the period when the signal light was not lit were reinforced on a continuous reinforcement schedule (fixed ratio 1). Once the animals demonstrated stable drug

intake for 3 days (a range of less than 15% of the daily intake over 3 days), this was taken as baseline and the study was begun. This baseline amphetamine intake was normally reached within 7–10 days of training. On a test day, the animals were pretreated immediately before the beginning of the session with terguride (a generous gift of Schering, Berlin, Germany). There were four different doses of terguride (0, 0.1, 0.2, 0.4 mg/kg ip). The drug was prepared in a vehicle solution of 0.9% physiological saline with a drop of 1 N HCl and injected in a volume of 1.0 ml/kg of body weight. Each dose was tested only once for each animal ($n = 11$) using a Latin square design. At least 2 days of baseline self-administration separated drug testing days.

In order to avoid possible confounding factors generated by experience with food reinforcement prior to drug self-administration and by the two noncontingent infusions of amphetamine automatically delivered at the beginning of the session, a separate group of animals ($n = 7$) was not exposed to food deprivation and responding for food reinforcement before surgery and did not receive the two noncontingent infusions of amphetamine at the beginning of the session. In addition, two levers were present in each operant chamber for this group of rats; one lever resulted in a drug infusion, while the other remained inactive throughout all sessions. These rats were trained to self-administer amphetamine under a progressive ratio schedule as described below and treated with one, effective dose of terguride (0.4 mg/kg ip).

2.3. Progressive ratio procedure

Rats were allowed to self-administer amphetamine as described above until a stable intake baseline was reached, which usually occurred within 7–10 days. On the following days rats were subjected to a progressive ratio schedule test (12-h session). The design used in the present study employed an increase in response requirement as described by Richardson and Roberts (1996). The ratio requirement increased by the following equation:

$$\text{Response ratio (rounded to the nearest integer)} = [5e^{(\text{injection number} \times 0.2)}] - 5$$

This schedule yields response ratios of 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, etc. The breaking point was defined as the last ratio attained by the rat prior to a 1-h period during which a ratio was not completed. Rats were tested with the progressive ratio schedule until a stable response was obtained (±10% of the average of three successive tests). This required 3–6 days of exposure to the progressive ratio schedule. On a test day, the animals were pretreated immediately before the beginning of the session. There were three different doses of terguride (0, 0.2, 0.4 mg/kg ip). There were three different doses of quinpirole (0, 0.1, 1.0 mg/kg sc) and four different doses of eticlopride (0, 0.01, 0.05, 0.1 mg/kg sc). The doses were chosen following previous results of the literature (Caine and Koob, 1994; Caine et al., 1997). Each dose was tested only once for each animal (terguride $n = 8$; eticlopride $n = 6$; quinpirole, $n = 12$) using a Latin square design. At least 2 days of baseline progressive ratio sessions separated drug-testing days. All rats included in each specific drug test were drug naive at the beginning of testing. The majority of rats were used only in one experiment while some rats, after completion of drug testing in one experiment, were tested in a second experiment once catheter patency was determined and baseline responding were reestablished. In particular nine rats were used in more than one experiment. There were no significant differences between baseline responding of rats with an experimental history and naive rats ($P > .05$, Student's t test). Examination of the response of individual animals to the drug treatment also revealed no interaction with previous drug history. Animals with previous treatments did not differ in their responses from animals that were naive to drug treatments. Therefore, 22 rats account for the total of 37 experimental subjects. Dose was within subject. Each rat in each experiment received each dose of the drug being tested.

2.4. Drugs

Terguride was a generous gift of Schering and was prepared in a vehicle solution of 0.9% physiological saline with a drop of 1 N HCl. Eticlopride (RBI, Natick, MA), quinpirole (RBI) and D-amphetamine sulphate (Sigma) were dissolved in saline. All drugs were injected in a volume of 1.0 ml/kg of body weight.

2.5. Statistical analysis

For the fixed ratio experiment the total number of reinforces earned during the 3-h session was recorded. For the progressive ratio experiment, the maximum fixed ratio values were used for the statistical analysis. These values had an exponential distribution and a logarithmic transformation was therefore applied.

Statistical analysis of the data was computed using a one-way factorial analysis of variance with repeated measures (ANOVA) or Student's t test where appropriate. Individual means comparisons were made using a Newman–Keuls a posteriori test.

3. Results

Terguride induced a dose-dependent increase in responding for amphetamine in a fixed ratio schedule [$F(3,10) = 19.58$ $P < .001$)] corresponding to a dose-dependent decrease in the interinjection interval (vehicle = 35.4 ± 1.62; terguride 0.1 mg/kg = 42.3 ± 1.72; terguride 0.2 mg/kg = 45.0 ± 2.09; terguride 0.4 mg/kg = 56.4 ± 3.2 infusions/3 h). Individual mean comparisons with vehicle revealed that the effect of terguride

reached statistical significance at the doses of 0.1 ($P<.05$), 0.2 and 0.4 mg/kg ($P<.01$, Newman–Keuls test).

Fig. 1 shows the time course of the effect of terguride throughout the 3-h session in one representative rat. In this figure, each mark represents an infusion of the drug. Normally, rats show a relative high number of infusion at the beginning of the session ("load-up" phase) followed by injections at regular intervals. As the dose of terguride was increased, the initial load phase was prolonged and thereafter the regular pattern of responding was generally maintained, though with shorter interreinforcement intervals. This was particularly evident during the first half of the session.

The effects of terguride on responding for self-administration of amphetamine in a progressive ratio schedule are shown in Fig. 2. ANOVA revealed that pretreatment with terguride (0.2 and 0.4 mg/kg) produced a reduction in the maximum fixed ratio ("breaking point") of responding for amphetamine self-administration [$F(2,21)=13.21$ $P<.001$], which reached statistical significance at both doses of 0.2 and 0.4 mg/kg ($P<.01$ Newman–Keuls post hoc test). Terguride did not modify the total time employed by the rats to reach the breaking point (vehicle = 180 ± 18.8 min; terguride 0.2 mg/kg = 128.0 ± 13.81 min; terguride 0.4 mg/kg = 172.5 ± 11.14 min), although ANOVA showed a tendency towards significance [$F(2, 21)=3.4$; $P=.05$].The duration of the progressive ratio session was of 12 h. The actual breaking point for the saline group was 715 ± 282.

Fig. 3 shows the effects of acute pretreatment with the dopamine antagonist eticlopride on responding for self-administration of amphetamine in a progressive ratio schedule. ANOVA revealed that similar to terguride, eticlopride dose-dependently produced a reduction in the maximum fixed ratio of responding for amphetamine self-administration [$F(3,20)=26.09$, $P<.01$] that reached statistical significance at the dose of 0.05 and 0.1 mg/kg ($P<.01$ Newman–Keuls post hoc test).

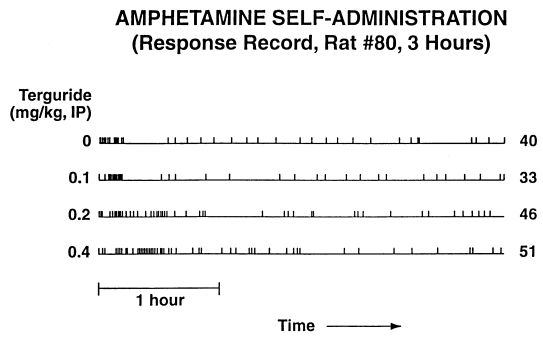

Fig. 1. Time course of the effect of terguride throughout the 3-h session in one representative rat. In this figure, each mark represents an infusion of the drug. As the dose of terguride was increased, the initial load phase was prolonged and thereafter the regular pattern of responding was generally maintained, though with shorter interreinforcement intervals.

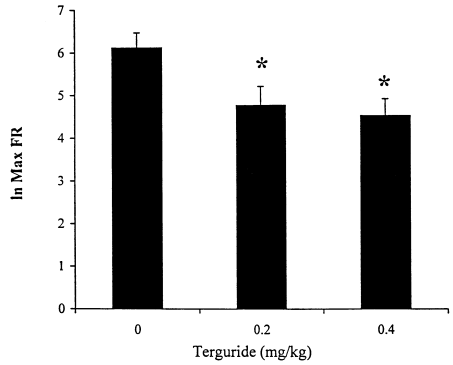

Fig. 2. Effect of acute pretreatment with terguride on progressive ratio responding for intravenous amphetamine self-administration. Values represent the mean ± S.E.M. of the logarithm of the maximum fixed ratio for a single self-injection of amphetamine. $n=8$. * $P<.01$ vs. saline Newman–Keuls test following significant ANOVA

ANOVA also revealed that eticlopride significantly reduced the total time employed by the rats to reach the breaking point (vehicle = 205 ± 17.8 min; eticlopride 0.01 mg/kg = 160 ± 14.4 min; eticlopride 0.05 mg/kg = 80 ± 23.4; eticlopride 0.1 mg/kg = 56.7 ± 42.8) [$F(3,20)=6.57$ $P<.01$].

Fig. 4 shows the effects of acute pretreatment with the dopamine full agonist quinpirole on responding for self-administration of amphetamine in a progressive ratio schedule. ANOVA revealed that, unlike the partial agonist terguride, quinpirole did not significantly modify the breaking point of responding for amphetamine self-administration [$F(2;33)<1$, NS]. ANOVA also revealed that quinpirole significantly increased the time to reach the breaking point (vehicle = 215.8 ± 7.12 min; quinpirole 0.1 mg/kg = 250.9 ± 18.31 min; quinpirole 1 mg/kg = 362.5 ± 31.33 min) [$F(2; 33)=12.86$ $P<.0001$].

The cumulative records of responding during the first 6 h of a single progressive ratio session are represented in

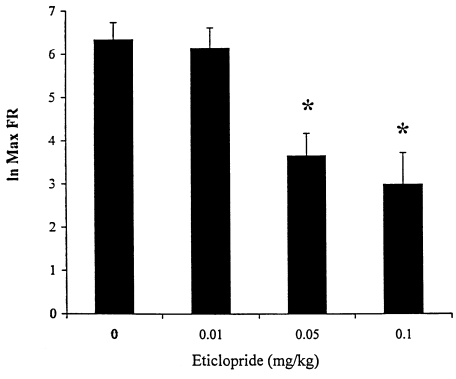

Fig. 3. Effect of acute pretreatment with eticlopride on progressive ratio responding for intravenous amphetamine self-administration. Values represent the mean ± S.E.M. of the logarithm of the maximum fixed ratio for a single self-injection of amphetamine. $n=6$. * $P<.01$ vs. saline Newman–Keuls test following significant ANOVA.

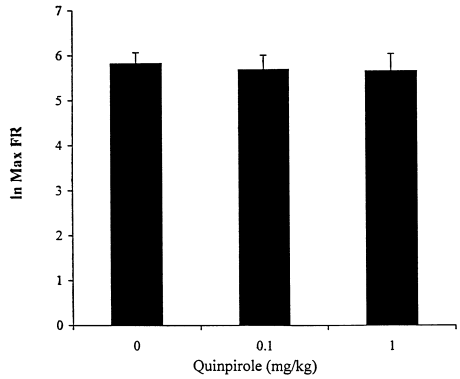

Fig. 4. Effect of acute pretreatment with quinpirole on progressive ratio responding for intravenous amphetamine self-administration. Values represent the mean ± S.E.M. of the logarithm of the maximum fixed ratio for a single self-injection of amphetamine. $n = 12$.

Fig. 5. For each experimental group the effect of vehicle and of the highest dose of the drug tested in one representative rat are shown. The total duration of the progressive ratio session was 12 h. This far exceeded the time employed by individual rats to reach the maximum fixed ratio ("breaking point") under all treatment conditions, as shown by the cumulative records.

In order to avoid possible confounding factors generated during the training phase, a separate group of rats was not exposed to food deprivation and responding for food reinforcement before surgery, did not receive the two non-contingent infusions of amphetamine at the beginning of the session and two levers were present in each operant chamber. The effects of terguride on responding for self-administration of amphetamine in a progressive ratio schedule in these rats were similar to those observed in the group with a history of lever pressing for food (vehicle = 5.61 ± 0.33, terguride 0.4 mg/kg = 4.52 ± 0.37). Student's t test revealed that pretreatment with terguride (0.4 mg/kg) produced a reduction in the breaking point of responding for amphetamine self-administration [$t = 4.0$, $df = 12$, $P < .01$]. The effects of terguride in nondeprived and deprived groups has been compared through a between-subjects t test: no

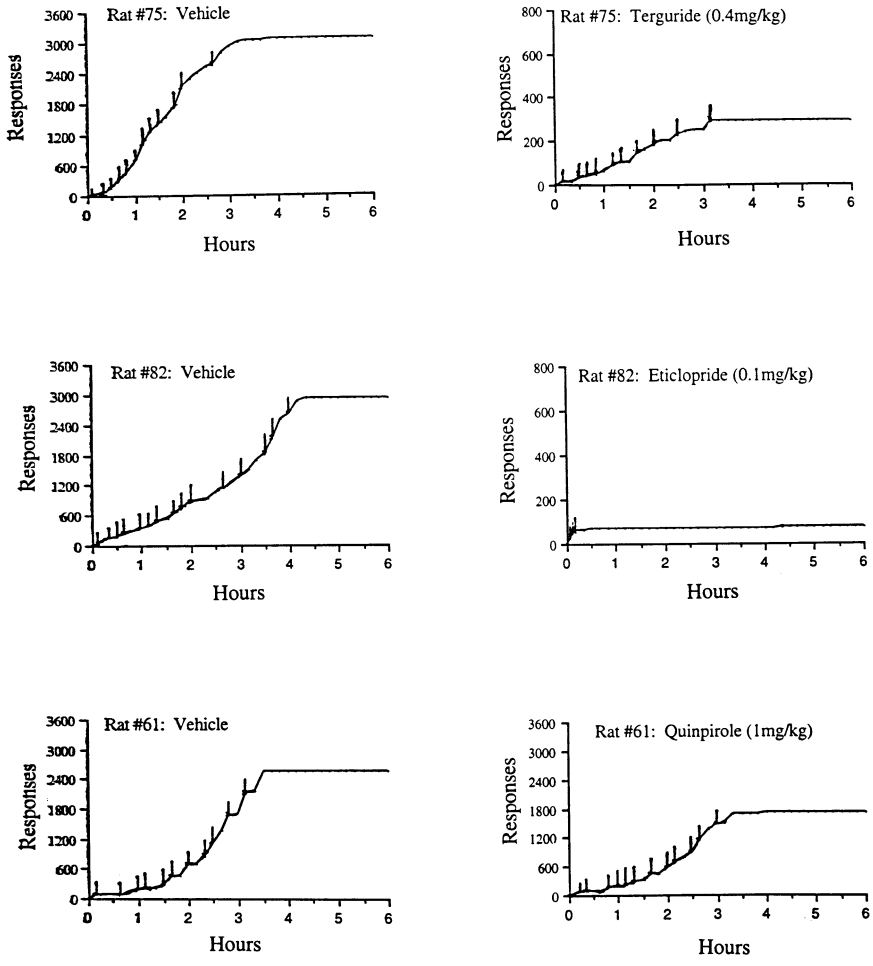

Fig. 5. Effect of terguride, eticlopride and quinpirole throughout the first 6 h of a 12-h progressive ratio session in three representative rats. Each curve represents the cumulative record generated during a single session of progressive ratio schedule of amphetamine self-administration. Each tick mark corresponds to an infusion of the drug. For each experimental group the effect of vehicle and of the highest drug dose tested are shown. Terguride and eticlopride induced a significant decrease of the total cumulative responses (note the change in the scale on the Y-axis) while quinpirole did not change significantly the total cumulative responses compared with vehicle.

significant difference is revealed (nondeprived group = 4.53 ± 0.39; deprived group = 4.52 ± 0.39, NS Student's *t* test).

Also, a low number of operant responses was recorded on the inactive lever and this was not significantly modified by treatment with terguride (vehicle = 14.8 ± 6.26, terguride 0.4 mg/kg = 13.28 ± 5.36, operant responses on the inactive lever, NS Student's *t* test). This revealed that different training schedules did not significantly modify the effects of terguride on responding for amphetamine self-administration under a progressive ratio schedule.

4. Discussion

The results of the present study show that the dopamine partial agonist terguride reduced responding for amphetamine self-administration in a progressive ratio schedule, an effect similar to that of the full antagonist eticlopride, while the full dopamine agonist quinpirole did not modify significantly the breaking point of responding for amphetamine. Animals without a history of lever pressing for food also showed a decrease in breaking point of responding for amphetamine. In addition, terguride dose-dependently increased responding for amphetamine under a continuous reinforcement schedule.

In a previous study it has been shown that terguride significantly modifies various aspects of cocaine self-administration (Pulvirenti et al., 1998). Although cocaine and amphetamine produce similar behavioral effects (Di Ciano et al., 1995; Koob, 1992; Pulvirenti et al., 1998), important differences exist. Pharmacologically, while cocaine is primarily a blocker of dopamine re-uptake and this effect appears to be critical for its reinforcing properties, amphetamine enhances dopamine neurotransmission by producing a massive release of intraneuronal dopamine in addition to its re-uptake blocking effects (Fischer and Cho, 1979; Heikkila et al., 1975). Also, the effects of cocaine depend upon the endogenous firing rate of dopamine neurons, while amphetamine penetrates the neuron and releases the neurotransmitter into the synaptic cleft independently of neuronal firing (Fischer and Cho, 1979). In addition the D2 full antagonist raclopride did not modify responding for cocaine self-administration both in a fixed ratio and in a progressive ratio schedule (Caine and Koob, 1994), but it produced a reduction of the breaking point for amphetamine responding (Fletcher, 1998). These pharmacological differences between cocaine and amphetamine associated with the differential responses obtained under selected tests reflective of different measures of psychostimulant abuse encourage investigation on potential differences within pharmacological treatment of cocaine and amphetamine or methamphetamine addiction.

The increase of responding on fixed ratio schedule of amphetamine self-administration observed in the present study is likely due to a reduction of the reinforcing properties of the drug as attempt to maintain the same level of reward. Accordingly, animals exposed to limited-access daily intravenous self-administration of psychostimulants in a fixed ratio schedule increase the rate of responding for the drug with a reduction of the dose dispensed per injection.

A definitive index of a drug reinforcing efficacy, however, is unlikely to be obtained using a single procedure; instead data generated from several procedures may be useful in characterizing the relative reinforcing efficacy of a drug under different pretreatment conditions. The present study was therefore designed to directly compare the effects produced by terguride with those of the full dopamine agonist quinpirole and the dopamine antagonist eticlopride on responding on a progressive ratio schedule maintained by amphetamine. The progressive ratio measures the maximum response requirement that supports intravenous self-administration, and therefore it may reflect the relative economic value of a drug under specific conditions (Pulvirenti et al., 1998). In this procedure, the subjects must meet increasing response requirements to obtain the drug. Typically, psychostimulant drugs produce an increase in the breaking point with an increase in the unit dose dispensed per injection (Richardson and Roberts, 1996). In light of these considerations, the decrease induced by terguride in the breaking point for amphetamine reinforcement suggests that this dopamine partial agonist reduced the reinforcing magnitude of the drug. This effect is similar to that produced by terguride on progressive ratio responding for cocaine. The identical efficacy of terguride in animals without a history of lever pressing for food eliminates any confounds due to potential generalization from food-reinforcement interactions.

Moreover the present data showed that as the dose of terguride was increased in animals self-administering amphetamine in a fixed ratio schedule, the initial load phase was prolonged and thereafter the regular pattern of responding was generally maintained, though with shorter inter-reinforcement intervals. This was particularly evident during the first half of the session. The full antagonist eticlopride was not tested using a fixed ratio schedule of self-administration in the current report. However, it has been previously shown that eticlopride increased cocaine self-administration in a fixed ratio schedule (Caine and Koob, 1994). It is therefore possible that the effects on the loading phase of amphetamine self-administration of a full dopamine antagonist might be similar to those observed with terguride in the present study. Nevertheless, this point remains to be experimentally addressed.

Dopamine partial agonists are a group of compounds characterized by high affinity on dopamine receptors with low intrinsic activity. The present results show that the effects of terguride are, in this respect, similar to those of the full D2 antagonist eticlopride. Indeed, while eticlopride decreased the breaking point for amphetamine, a full D2 agonist, quinpirole, did not change the maximum fixed ratio for the drug even at the highest dose. Therefore, consistent with earlier results (Pulvirenti et al., 1998; Ranaldi et al.,

1994), the current data suggest that terguride, similar to other dopamine D2 partial agonists, acts as a functional dopamine antagonist in animals self-administering psychostimulant drugs. Moreover while eticlopride significantly reduced the breaking point and the time to reach it, terguride significantly reduced the breaking point but did not modify the time. It is possible that these differences are due to the fact that the doses of eticlopride used caused a greater decrease in the breaking point than terguride at the doses tested, so that the time to reach the breaking point in presence of eticlopride was critically affected.

These results are also consistent with previous observations showing that the full dopamine antagonists haloperidol, flupentixol, spiperone and SCH 23390 decreased the breaking point for cocaine, while they increased the rate of responding for the drug in a fixed ratio schedule of self-administration (Depoortere et al., 1993; Hubner and Moreton, 1991; Richardson et al., 1994). In addition, the reduction of the breaking point of responding for amphetamine produced by eticlopride is similar to the reduction produced by this drug on progressive ratio responding for cocaine self-administration (Ward et al., 1996).

The potential use of dopamine partial agonists for the treatment of psychostimulant addiction has been proposed based on the preclinical observation that the two prototype dopamine D2 partial agonist terguride and SDZ 208-911 increased responding for cocaine in rats exposed to limited-access daily intravenous self-administration of cocaine in a fixed ratio schedule and decreased the breaking point for cocaine in a progressive ratio schedule (Bedford et al., 1978; Pulvirenti et al., 1998). The effects of drugs acting as partial agonists at dopamine receptors other than D2 receptors on psychostimulant dependence has also been recently reported. The dopamine D1 partial agonists SKF 83959, SKF 77434 and SKF 38393 reduced cocaine self-administration in squirrel monkeys trained to respond under a second-order schedule (Platt et al., 1999). In addition, chronic treatment with SKF 77434 produced a downward shift of a cocaine full dose–response function (Mutschler et al., 1999). The dopamine D3 partial agonist BP897, in contrast, did not significantly modify responding for cocaine on a continuous reinforcement schedule but significantly inhibited cocaine-seeking behavior initiated upon the presentation of a cue previously paired with cocaine (Pilla et al., 1999). The present observations lend therefore further support to the emerging evidence showing that drugs that possess the pharmacological profile of partial agonists at the D1, D2 or D3 receptors may represent novel potential candidates for pharmacological intervention in psychostimulant abuse.

Acknowledgments

This is manuscript 12736-NP of the Scripps Research Institute. This work was partially supported by NIDA Grant DA-10072. The authors thank Dr. R. Horowski for helpful discussion.

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