Characterization of the Effects of the Partial Dopamine Agonist Terguride on Cocaine Self-Administration in the Rat

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ABSTRACT

Dopamine neurotransmission is an important neuropharmacological component of cocaine self-administration in rodents. Terguride is a prototype drug belonging to a recently characterized class of compounds, dopamine partial agonists, which appear to possess a unique pharmacological profile in altering dopamine neurotransmission, where these drugs act as antagonists in conditions of high dopaminergic tone. The aim of the present study was therefore to test the effects of systemic administration of terguride in rats self-administering cocaine intravenously. The different aspects of cocaine self-administration examined after treatment with terguride were (a) the acute reinforcing properties of cocaine in rats exposed to limited-access self-administration of cocaine, (b) a full cocaine dose-effect function, (c) the reinforcing properties of cocaine as measured by a progressive ratio schedule and (d) the ability of terguride to maintain self-administration by itself. Terguride (0.025–0.4 mg/kg i.p.) significantly and dose-dependently reduced the acute reinforcing properties of cocaine as measured by an increase in responding for a single training dose of cocaine and a reduction of the inter-reinforcement interval. In addition, terguride (0.2–0.4 mg/kg) shifted the entire cocaine dose-effect function to the right, thus showing an antagonism of the reinforcing properties of cocaine independent of response rate. Moreover, in rats trained to self-administer cocaine on a progressive ratio schedule, terguride reduced the maximum fixed ratio ("breaking point") for cocaine reinforce- ment, also suggesting a decrease in the reinforcing properties of cocaine. Finally, in rats trained to self-administer cocaine, terguride did not substitute for cocaine, thus indicating that terguride does not maintain intravenous self-administration by itself.

Basic preclinical studies have implicated dopamine neurotransmission as a critical determinant in the acute reinforcing properties of psychostimulant drugs and in the increase in reward threshold associated with abstinence from cocaine abuse, two major components of the psychostimulant dependence cycle (Koob, 1992). However, attempts to modify these important aspects of the natural history of cocaine addiction in humans such as cocaine-seeking behavior and cocaine withdrawal through pharmacological manipulation of the brain dopamine system with agonists or antagonists have met with limited clinical success. This has prompted the search and preclinical testing of novel pharmacological means to modify dopamine function.

Recently, a new class of drugs which possess a unique pharmacological profile on dopamine neurotransmission has been characterized, namely dopamine partial agonists. These drugs bind to the dopamine receptor with high affinity but low intrinsic activity (Hoyer and Boddeke, 1993). The functional consequence is that these compounds 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). This presumably occurs because the low intrinsic activity of these compounds substitutes for the high-activity endogenous agonist at the receptor site. 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 agonist activity have been characterized to date, including preclamol, terguride, SDZ 208–911 and SDZ 208–912, all active at the dopamine D_2 receptor site (Hjorth et al., 1983, Kehr, 1984). Biochemical studies have revealed that SDZ 208–911 and terguride reduced the accumulation of l-dopa in resepcinated rats, an effect similar to that of the full agonist quinpirole, but produced the opposite effect in nonreserpinized rats (Svennson et al., 1991), reflecting their agonistic properties in conditions of denervation supersensitivity. Similarly, be-
havioral studies showed that SDZ 208–911 and terguride induced contralateral turning in rats with unilateral striatal 6-hydroxydopamine lesions, but reduced amphetamine-induced locomotor activity and stereotyped behavior, thus confirming their antagonistic activity in conditions of overstimulation of the dopamine system (Clark et al., 1991).

Compared with pure dopamine receptor blockers, partial dopamine agonists seem to be devoid of the extrapyramidal side effects which greatly limit the clinical use of classical antipsychotic drugs (Coward et al., 1990). This has prompted much attention to the preclinical evaluation of partial dopamine agonists in conditions of altered brain dopamine neurotransmission, including movement disorders and dependence. Previous results suggest that SDZ 208–911 alter the reinforcing properties of cocaine (decreasing the inter-reinforcement interval like an antagonist) and reduce ethanol intake in rodents (Pulvirenti et al., 1994, Bono et al., 1996).

Also, previous studies have assessed the effects of partial dopamine agonists on the discriminative stimulus properties of cocaine. In contrast to compounds exerting full agonistic dopamine agonists on the discriminative stimulus effects of cocaine in squirrel monkeys (Callahan and Cunningham, 1993). Similarly, dopamine partial agonists, including terguride and SDZ 208–911, did not alter the discriminative stimulus effects of cocaine in squirrel monkeys (Spealman, 1995). Interestingly, however, the discriminative stimulus effects of terguride was established and maintained in rats and the dopamine agonist lisuride generalized to the terguride cue (Yamaguchi et al., 1991).

These observations have opened the possibility that partial dopamine agonists may represent a novel treatment strategy for cocaine dependence (Pulvirenti and Koob, 1994). However, previous work has not examined the effects of partial agonists on other aspects of cocaine self-administration, such as dose-effect functions and the progressive ratio procedure, nor has it examined the likelihood that these drugs would support intravenous self-administration themselves.

The aim of the present study was, therefore, to characterize the effects of terguride on different aspects of cocaine self-administration in rats. Terguride is a prototype aminergic which acts as a partial agonist at the dopamine D2 receptor site.

One important issue in the evaluation of the effects of drugs in animal models of cocaine dependence is to use multiple measures of the reinforcing efficacy of the drug to avoid confounds of possible motor impairment on response rate. Consequently, in the present study, experiments in which rats were trained to self-administer cocaine at one dose were extended to incorporate training of the animals at various doses of cocaine, in order to generate a complete cocaine dose-response function. In this context, the effects of treatment with terguride on the reinforcing properties of cocaine were reflected in a shift of the dose-response function. The effects of terguride were studied in a between-session dose-effect paradigm, in which rats were trained on different doses of cocaine on different days. Furthermore, in order to arrive at appropriate interpretations of general increases or decreases in response rate, the reinforcing magnitude of cocaine was assessed in rats self-administering cocaine intravenously in a progressive ratio schedule, a behavioral measure used to establish the relative reinforcing efficacy of different drugs and different treatments on the reinforcing efficacy of a given drug (Bedford et al., 1978, Richardson and Roberts, 1996). Finally, in order to assess the potential abuse liability of terguride by itself, terguride was substituted for cocaine in rats trained to intravenously self-administer cocaine.

**Methods**

Eighty-eight male Wistar rats (Charles River), weighing 200–225 g at the start of the experiment, were housed 3 to a cage and provided with ad libitum access to food and water and maintained on a 12-hr light-dark cycle (lights on 7:00 a.m.–7:00 p.m.).

**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 reinforcers 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 SC 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 and colleagues (1993). Each behavioral paradigm was established in separate groups of rats. Specifically, the effects of terguride in rats self-administering cocaine on a continuous reinforcement schedule were studied in 6 rats; 7 rats were used for the between-session dose-effect curve; 26 rats were used for the progressive ratio experiment; 41 rats for the substitution study and 8 rats to study the effects of cocaine on responding for food. Some of the animals were also implanted with intracerebral cannulae aimed at the nucleus accumbens.

The vast majority of the rats used in the present study were naive animals. Specifically, the 6 rats used in the cocaine self-administration FR-1 experiment and the 8 rats used for the food reinforcement experiment were all naive. Of the 7 animals used in the between-session dose-effect curve experiment, 4 were naive, while 3 had been used for the substitution study of the present paper. Of the 26 rats used in the progressive ratio paradigm, 8 were naive, 11 had received acute treatment with dextromethorphan (25–50 mg/kg i.p.), 5 had received acute treatment with gamma-hydroxybutyrate (100–400 mg/kg IV), 2 had received acute intracerebral microinfusion of aminophosphonovaleric acid (1.5–3.0 μg in the nucleus accumbens), one had been exposed to both dextromethorphan and the substitution study and one had been exposed to both dextromethorphan and gamma-hydroxybutyrate. Finally, of the 41 rats used for the substitution study, 32 were naive, 4 had received acute intracerebral microinjection of aminophosphonovaleric acid as described above, 3 had been exposed to the between-session dose-effect curve of the present study and 2 had received an acute treatment with 7-hydroxyaminoetetraline (7-OH-DPAT, 1.0–4.0 mg/kg i.p.). At least one week separated previous drug injections to the behavioral testing of the present study. There were no significant differences between baseline response 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.

Four days following surgery for the intravenous surgery, all of the animals were allowed 2-hr 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 attenuating chambers. A lever press resulted in an intravenous injection of 0.1 ml of cocaine hydrochloride (0.25 mg/injection) dissolved in 0.9% physiological saline and delivered over a period of 4 sec. 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 sec during which time the lever became inactive. At the beginning of the session, two noncontingent infusions of cocaine (0.25 mg/infusion) 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, FR-1). Once the animals demonstrated stable drug intake for three 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 cocaine 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 AG, Berlin). There were five different doses of terguride (0, 0.025, 0.1, 0.2, 0.4 mg/kg i.p.). Each dose was tested only once for each animal (n = 6) using a Latin-square design. 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. At least two days of baseline self-administration separated drug testing days. The total number of reinforcers earned during the 120-min session was recorded and statistical analysis of the data was computed using a one-way factorial analysis of variance with repeated measures (ANOVA). Individual means comparisons were made using a Newman-Keuls a posteriori test.

Between-session dose-effect paradigm. The animals (n = 7) were trained to self-administer cocaine as described above. The criterion for the start of tests of different unit doses of cocaine (0.06, 0.125, 0.25 and 0.5 mg/injection) or drug pretreatment testing was three consecutive self-administration sessions at the baseline training dose of 0.25 mg/injection with less than 15% variation in the total number of reinforced responses. After changing the dose of cocaine the rats usually reached a new baseline of responding within 3–4 days and drug treatment was begun at the new dose. An effective dose of terguride as established by the previous experiment (0.4 mg/kg) was tested. Dose-effect functions for cocaine were generated using a within-subject Latin-square design to allow analysis of order effects. The total number of reinforcers earned during the 120-min session was recorded and statistical analysis of the data was computed using a two-way factorial analysis of variance with repeated measures on both factors (ANOVA). Individual means comparisons were made using a simple main effects analysis. In addition, doses were transformed into log units and a sigmoidal function was fit using a non-linear procedure (Praam, GraphPAD, San Diego, CA). Sigmoidal functions were constrained to the maximum injection per session (top) and zero (bottom). ED_{50} values and confidence intervals were determined from the fitted function.

Progressive ratio procedure. Rats were allowed to self-administer cocaine 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. In the design used in the present study, the ratio requirement increased by one response per injection for the first eight injections. For the next eight injections the ratio was raised by two for each successive ratio; for the next eight injections the ratio was increased by four and the next eight injections the ratio was increased by eight responses for each successive injection until the ratio requirement reached an FR-120 (Hubner and Koob, 1990). The breaking point was defined as the last ratio attained by the rat prior to a 1-hr 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 4–6 days of exposure to the progressive ratio schedule. The rats were then subjected to treatment with terguride immediately before the beginning of the session. Two effective doses of terguride were used, as established in the first two experiments (0.2 mg/kg, n = 10 and 0.4 mg/kg, n = 16). At least two days of baseline progressive ratio sessions separated drug testing days. Data were analyzed using Student’s t test.

Substitution study. For the substitution study, 41 rats were trained to self-administer cocaine on a continuous reinforcement schedule. Once a stable baseline of responding was obtained, rats were allowed to self-administer cocaine at the training dose of 0.25 mg/injection. Thirty min after the beginning of the session terguride (1.25, 5, 10, 20 or 50 µg per infusion), cocaine (0.12 mg per infusion), apomorphine (30 or 60 µg per infusion) or saline were substituted for cocaine and responding was recorded for the following 150 min. Only one dose of terguride was used for each individual rat and all substitution sessions were single session substitutions. At least 2 regular 2-hr cocaine self-administration sessions separated drug testing days to ensure a return to the previous baseline cocaine intake. The unit doses of terguride were calculated by considering that 1/20 of the behaviorally active doses of various dopamine agonists best maintain self-administration in rodents. For example, a unit dose of 60 µg/injection of apomorphine readily maintains self-administration behavior (see Results). A further dose corresponding to 1/8 of the behaviorally active dose of terguride (50 µg per infusion) was also tested. The number of animals used for each drug substitution is shown in the figure legend.

Food self-administration. A separate group of animals was trained to lever press for food reinforcements. Animals were food-restrained for 48 hr (15 g of food per day per rat) and they were then trained to respond for food in the same operant chambers used for cocaine self-administration. Rats were initially trained to lever press on a continuous reinforcement schedule (FR-1) for one 50 mg food pellet (Noyes) for 30 min daily. At the end of the session, the rats were fed with 15g of food each. The response requirement was gradually increased until a FR-15 schedule was reached. This was usually obtained within one week of training. Once a stable baseline of responding for food was reached under the FR-15 schedule, treatment was begun. Immediately before the beginning of the daily session, all rats received an intraperitoneal injection of either saline or terguride (0.2 or 0.4 mg/kg) in a counterbalanced design. The number of reinforced responses was then recorded. Eight rats were used for the experiment and data were analyzed using a one-way analysis of variance with repeated measures followed by a Newman-Keuls a posteriori test.

Results

The effect of acute administration of terguride in rats responding for cocaine self-administration in a continuous reinforcement schedule is shown in figure 1. Terguride induced a dose-dependent increase in responding for cocaine [F(4,20) = 18.07, P < .001] corresponding to a dose-dependent decrease in the interinjection interval. Individual mean comparisons with vehicle revealed that the effect of terguride reached statistical significance at the doses of 0.2 and 0.4 mg/kg (P < .01, Newman-Keuls test).

Figure 2 shows the time course of the effect of terguride throughout the two-hr session in one representative rat. In this figure, each mark represents an infusion of the drug. Injections were delivered at equal time intervals and, as the dose of terguride was increased, the regular pattern of responding was maintained, though with shorter inter-reinforcement intervals.

Figure 3 shows the effects of acute pretreatment with terguride (0.4 mg/kg i.p.) on cocaine self-administration dose-effect function measured between-session. Pretreatment...
with terguride produced a shift to the right of the cocaine (0.06–0.5 mg per infusion) dose-effect function. ANOVA revealed that there was a significant treatment x dose interaction \( F(3,21) = 4.102, P < .05 \). Simple main effects analysis revealed that pretreatment with terguride produced an increase of the total number of reinforcers earned during the 120-min session at the training doses of cocaine of 0.125 mg/injection \( F(1,7) = 120.6, P < .001 \); 0.25 mg/injection \( F(1,7) = 45.68, P < .001 \) and 0.5 mg/injection \( F(1,7) = 75.89, P < .001 \).

The ED\( _{50} \) for cocaine self-administration after pretreatment saline was 0.201, while the ED\( _{50} \) after terguride was 0.366. The 95% confidence intervals for saline and terguride were 0.174 to 0.232 and 0.268 to 0.500, respectively.

The effects of terguride on responding for self-administration of cocaine in a progressive ratio schedule are shown in figure 4. Pretreatment with terguride (0.2 and 0.4 mg/kg) produced a reduction in the maximum FR (“breaking point”) of responding for cocaine self-administration which reached statistical significance at the dose of 0.4 mg/kg (df = 15, \( t = 2.09, P = .05 \)), but not at the dose of 0.2 mg/kg (df = 9; \( t = 0.417 \) NS). Terguride, however, did not significantly modify the total time employed by the rats to reach the breaking point (sal = 180.6 ± 22.6 min; terguride 0.2 mg/kg = 167.0 ± 32.1 min; sal = 199.1 ± 15.5 min; terguride 0.4 mg/kg = 175.6 ± 21.1 min). This did not reach statistical significance either at the dose of terguride of 0.2 mg/kg (\( df = 9, t = 0.473 \); NS) or 0.4 mg/kg (df = 15, \( t = 0.933 \) NS).

Figure 5 shows the effects of substitution of saline or terguride in rats trained to self-administer cocaine in a continuous reinforcement schedule. Substitution of saline for cocaine produced in all cases a burst of responses followed by suppression of responding. This represents the typical extinction behavior shown by rats self-administering cocaine in a fixed ratio schedule. Similarly, when terguride was substituted for cocaine, the rats showed an extinction-like pattern of self-administration with a burst of responding for approximately 20 min, followed by a cessation of responding for a duration of 30 min by the 90-min time point. This occurred at the doses of terguride of 1.25, 5.0, 10 and 20 µg per infusion, equivalent to the doses administered above in the antagonism study (calculating 20 injections per 2-hr session). ANOVA revealed that there was no significant drug x time interaction \( F(17,102) = 1.262 \) NS at the dose of 1.25 µg/infusion; \( F(17,102) = 1.385 \) NS at the dose of 5.0 µg/infusion; \( F(17,102) = 1.464 \) NS at the dose of 20 µg/infusion], except for the dose of 10 µg/infusion, where erratic behavior in the saline group produced a marginal, isolated statistical significance \( F(17,102) = 1.931, P = .023 \). The dose of terguride of 50 µg per injection produced a similar pattern of extinction as the other doses in that responding for terguride was not maintained. However, the peak of responding during the initial 30 min of the extinction phase was reduced, as revealed by a significant drug x time interaction ANOVA \( F(17,102) = 3.14, P < .01 \). In contrast, substitution of the full dopamine agonist apomorphine for cocaine maintained regular responding and both doses tested (30 and 60 µg/infusion) and regular responding was also maintained when a lower dose of cocaine (0.12 mg/infusion) was substituted for...
drug and that a range of intravenous doses of terguride did not support self-administration on their own. These data extend previous observations showing that SDZ 208–911, another aminoergoline with partial dopamine agonist properties, increased responding for cocaine in rats exposed to limited-access daily intravenous self-administration of cocaine (Pulvirenti et al., 1994). A hypothesis to explain these previous results was that the increase of responding was due to a reduction of the reinforcing properties of cocaine. However, the effects of SDZ 208–911 were tested against only one dose of cocaine. The shift to the right of the full dose-effect function of cocaine self-administration shown in the present study in the between-dose effect paradigm confirms that terguride produced significant increases in cocaine self-administration at all doses of cocaine on the descending limb of the curve and this appears to be independent of the rate of responding.

Experiments using the fixed ratio schedule of responding provide limited information about actions on the reinforcing efficacy of a drug. To measure reinforcing efficacy, the progressive ratio schedule can be used, where the reinforcing efficacy (or magnitude) of a drug is defined as the maximum response requirement (or breaking point) that a self-administered drug can produce (Richardson and Roberts, 1996). Typically, psychostimulant drugs show 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 cocaine self-administration measured in the progressive ratio schedule suggests that this partial dopamine agonist may reduce the reinforcing magnitude of cocaine. This observation is consistent with the hypothesis that terguride is a functional dopamine antagonist in animals self-administering cocaine and is further supported by other observations suggesting that SDZ 208–912 and SDZ MAR 327, two other aminoergolines with partial dopamine agonist properties, reduced the breaking point on a progressive ratio schedule for cocaine self-administration (Ranaldi et al., 1994). The effects of partial agonists are in this respect similar to the effects of dopamine antagonists on responding in the progressive ratio test. Indeed, the full dopamine antagonists haloperidol, flupentixol, spiperone and SCH 23390 decrease the breaking point for cocaine, while they increase the rate of responding for cocaine on a fixed ratio schedule (Hubner and Moreton, 1991, Depoortere et al., 1993, Richardson et al., 1994).

The response rates maintained by cocaine in the present experiments could be a function not only of the reinforcing effects of cocaine but also of other factors such as the behavior disrupting effects, dose titration and possible aversive effects. It is possible that terguride is increasing the number of injections of cocaine and decreasing the inter-reinforcement interval by blocking the decreases in rate of responding (rate-decreasing effects) produced by cocaine (Herling and Woods, 1980). While selective effects of dopamine antagonists and terguride on other schedules of reinforcements, such as the progressive ratio, argue for a selective action on the reinforcing effects of these drugs (Hubner and Moreton, 1991). More studies are needed to explore the basis for these changes.

Finally, the possibility that the agonistic properties of terguride may generate abuse liability was tested in the rat model of self-administration. The fact that terguride did not

Discussion

The results reported here show that acute intraperitoneal pretreatment with terguride reduced the reinforcing effects of cocaine as reflected by an increase in responding for the drug and that a range of intravenous doses of terguride did not support self-administration on their own. These data extend previous observations showing that SDZ 208–911, another aminoergoline with partial dopamine agonist properties, increased responding for cocaine in rats exposed to limited-access daily intravenous self-administration of cocaine (Pulvirenti et al., 1994). A hypothesis to explain these previous results was that the increase of responding was due to a reduction of the reinforcing properties of cocaine. However, the effects of SDZ 208–911 were tested against only one dose of cocaine. The shift to the right of the full dose-effect function of cocaine self-administration shown in the present study in the between-dose effect paradigm confirms that terguride produced significant increases in cocaine self-administration at all doses of cocaine on the descending limb of the curve and this appears to be independent of the rate of responding.

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Finally, the possibility that the agonistic properties of terguride may generate abuse liability was tested in the rat model of self-administration. The fact that terguride did not
support self-administration on its own at all the doses tested suggests that terguride does not possess reinforcing properties in rodents. This observation is of particular significance considering that in the design used in the present study, the rats were trained to self-administer cocaine and apomorphine, a dopamine agonist known to support self-administration in rodents, which is readily substituted for cocaine (see Results). In contrast, responding for intravenous self-administration of terguride was not statistically different from responding for saline, producing in both cases a typical extinction pattern of responding. During substitution for the highest dose of terguride tested, however, a lower peak of responses was recorded during the initial phase of the substitution period. This was followed by extinction as with the other doses of terguride, thus showing that even higher doses of terguride do not support intravenous self-administration.

The fact that partial dopamine agonists elicit discriminative stimulus effects by themselves (Yamaguchi et al., 1991), combined with the observation that terguride does not support drug taking behavior during extinction from cocaine self-administration, might reflect the possibility that the stimulus effects produced by a partial agonist, besides being subjectively different from those of cocaine (Callahan and Cunningham, 1993; Spealman, 1995), also do not support drug-seeking behavior. The possibility that terguride might possess rewarding properties and abuse potential in humans remains to be evaluated clinically. However, the fact that the present data provide no preclinical evidence for terguride self-administration and the fact that no cases of abuse have been reported in preliminary clinical studies with terguride (R. Horowski, personal communication), make the addiction liability of terguride unlikely.

Indeed, an important issue when considering the therapeutic potential of compounds for treatment of cocaine dependence is their discriminative stimulus effects. The discriminative stimulus properties of drugs of abuse have been hypothesized to play a critical role in the acquisition, maintenance and relapse into the dependence process (Stolerman, 1992). The stimulus properties of a drug may also acquire secondary motivational properties and therefore function as a secondary reinforcer. However, the potential therapeutic use of full dopamine agonists for treatment of cocaine dependence (Callahan and Cunningham, 1993) may be limited by the undesirable side effect represented by the possibility that these drugs may reinstate drug self-administration. Since the discriminative stimulus properties of drugs may be important for the maintenance and relapse into the abuse cycle (Stolerman, 1992), partial dopamine agonists which do not appear to possess the same stimulus properties of psychostimulants (Spealman, 1995) may show therapeutic activity without the potential side effect of inducing a cue capable of reinstating cocaine self-administration. Accordingly, the fact that terguride does not appear to share the discriminative

Fig. 5. Effects of substitution of saline or terguride for cocaine during a self-administration session. Thirty min into the session, saline (0.1 ml per infusion) or terguride (1.25; 5.0; 10; 20 or 50 µg per infusion) were substituted for cocaine. Values represent mean of lever presses/10 min intervals. Saline or terguride substitution produced an extinction-like pattern of responding. Left, top: terguride 1.25 µg/injection n = 7, saline n = 7; left, bottom terguride: 5.0 µg/injection n = 7, saline n = 7; middle, top: terguride 10 µg/injection n = 7, saline n = 7; middle, bottom: terguride 20 µg/injection n = 7, saline n = 7 right, top: terguride 50 µg/injection n = 7, saline n = 7; right, bottom: cocaine 0.12 mg/injection n = 6, apomorphine 30 µg/injection n = 6, apomorphine 60 µg/injection n = 6.
stimulus properties of cocaine suggests that terguride might not function to reinitiate cocaine self-administration behavior or, possibly, precipitate craving in humans. Furthermore, the fact that both terguride and SDZ 208–911 did not significantly modify the discriminative stimulus effects of cocaine (Spealman, 1995) suggests that the apparent antagonism of the reinforcing effects of cocaine produced by terguride may not coincide with antagonism or mimicry of cocaine’s subjective effects.

Another important issue is the specificity of the effects of terguride and other partial agonists for the reinforcing effects of cocaine. Previous observations suggest that terguride and SDZ 208–911 also reduced the reinforcing properties of ethanol (Bono et al., 1996). This is not surprising considering that other dopamine receptor antagonists share the same profile of action on cocaine and ethanol self-administration (Hubner and Moreton, 1991, Depoortere et al., 1993, Richardson et al., 1994, Samson et al., 1993) and further suggests that terguride, SDZ 208–911 and, possibly, other dopamine partial agonists act as functional dopamine antagonists in animals exposed to drugs of abuse. In addition, the observation that terguride dose-dependently reduced operant responding for food extends the similarity of the behavioral profile of terguride to other dopamine receptor antagonists (Salamone et al., 1991). It is indeed interesting that in the progressive ratio study, the dose that decreased the breaking for cocaine reinforcement is the same dose that decreased responding maintained by food reinforcement. This may reflect the general reduction in operant responding for reinforcement, associated with pharmacological antagonism at the dopamine receptor site.

Dopamine partial agonists show a unique pharmacological profile since their net effect seems to depend upon the level of existing synaptic activity such as the degree of receptor occupancy by the endogenous transmitter (Clark et al., 1985). Biochemical studies revealed that terguride and SDZ 208–911 act as full agonists with a potency similar to that of the dopamine D2 receptor agonist quinpirole in rats depleted of monoamines after treatment with reserpine, as measured by reduction of DOPA accumulation (Svennson et al., 1991). Both ergolines, however, produced the opposite effect (an antagonist-like action) in nonreserpinized rats (e.g., a compensatory activation of presynaptic tyrosine hydroxylase via a feedback loop), a profile similar to classic dopamine receptor antagonists thought to be dependent upon functional blockade of postsynaptic receptors (Svennson et al., 1991). Electrophysiological evidence supports these results. SDZ 208–911 and terguride weakly inhibited the firing of dopamine neurons of the ventral tegmental area and the substantia nigra in the rat (an agonist-like effect), while they reversed the inhibition induced by quinpirole (an antagonist-like effect) (Piercey et al., 1987; Ackerman et al., 1993). Finally, behavioral studies showed that SDZ 208–911 and terguride produced contralateral turning in rats carrying unilateral striatal 6-OHDA lesions, an agonist-like effect, while they reduced amphetamine-induced locomotor activity and stereotyped behavior (Clark et al., 1991).

It is also interesting that partial dopamine agonists vary in their degree of intrinsic efficacy as determined by a number of electrophysiological, biochemical and behavioral studies (Lahti et al., 1992; Ackerman et al., 1993; Arnt et al., 1990; Baldessarini et al., 1994; Campbell et al., 1992). Different partial dopamine agonists show different intrinsic activities as determined by electrophysiological studies, i.e., the capacity to reduce the firing rate of substantia nigra pars compacta neuron with apomorphine = 100% (Piercey et al., 1987; Ackerman et al., 1993).

According to Lahti and colleagues, the intrinsic activity shown by terguride (16.5%), SDZ 208–911 and SDZ 208–912 (12%) appears to be in the low-intermediate range, compared with the high intrinsic activity of preclamol, apomorphine or quinpirole (34%; 73% and 104%, respectively) (Lahti et al., 1992). Ultimately, it will be important to relate systematically the effects produced by partial dopamine agonists on cocaine self-administration with the intrinsic activity of each individual compound as determined by electrophysiological and biochemical evidence.

Clinical interest for partial dopamine agonists derives from the hypothesis that by occupying the dopamine receptor and exerting low intrinsic activity, these drugs may represent novel therapeutic agents, possibly devoid of extrapyramidal side effects (Coward et al., 1990). In accordance with preclinical studies, terguride was shown in initial clinical studies to possess dopamine antagonistic actions since it reduced levodopa-induced dyskinesias in patients with Parkinson’s disease and decreased the severity of negative symptoms in schizophrenic patients (Baronti et al., 1992; Olbrich et al., 1988). Systematic studies evaluating the effects of dopamine partial agonists in animal models mimicking the different phases of the dependence cycle would therefore be important to assess the potential clinical use of these compounds in cocaine addiction. These studies would be particularly warranted considering the clinical efficacy of the opiate partial agonist buprenorphine in opioid dependence (Johnson et al., 1992). Altogether, the present data support the hypothesis that partial dopamine agonists may represent a novel therapeutic strategy for normalizing dopamine neurotransmission, a basic feature which may be of importance not only during the various phases of the natural history of drug dependence, but, possibly, in the course of other neuropsychiatric disorders characterized by still poorly controllable fluctuations of dopamine neurotransmission.

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