Pharmacology, Biochemistry and Behavior 97 (2010) 222–226

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

The dopamine D_2 partial agonist and antagonist terguride decreases heroin self-administration on fixed- and progressive-ratio schedules

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ARTICLE INFO

Article history:
Received 20 February 2010
Received in revised form 22 July 2010
Accepted 2 August 2010
Available online 10 August 2010

Keywords:
Dopamine D_2 partial agonist
Terguride
Heroin
Self-administration
Fixed-ratio schedule
Progressive-ratio schedule

ABSTRACT

Dopamine partial agonists have been suggested to be potential therapeutic candidates for pharmacological intervention in drug addiction. These drugs bind to dopamine receptors with high affinity and low intrinsic activity and are hypothesized to behave as functional antagonists in conditions of high dopaminergic tone. The aim of the present study was to characterize the effects of terguride, a partial dopamine agonist at the dopamine D_2 receptor, on intravenous heroin self-administration on fixed- and progressive-ratio schedules of reinforcement. The effects of terguride on oral sweet solution (4% sucrose) self-administration on a fixed-ratio schedule were also tested. Terguride dose-dependently decreased heroin self-administration on the fixed-ratio schedule and decreased the maximum number of responses for heroin self-administration on a progressive-ratio schedule. In contrast, terguride did not significantly affect oral sucrose self-administration. These data suggest that terguride may represent a novel pharmacological strategy for the treatment of opiate addiction.

1. Introduction

Converging evidence suggests that brain dopamine neurotransmission is critically involved in the acute reinforcing properties of many addictive drugs (Pierce and Kumaresan, 2006). This observation has stimulated interest in the use of dopaminergic drugs as possible candidates for the treatment of drug abuse. However, dopamine full agonists may have abuse potential in nonhuman models (Self and Stein, 1992; Woolverton and Ranaldi, 2002), and dopamine full antagonists may have undesirable extrapyramidal side effects. Indeed, only limited efficacy has been reported in clinical trials of drug abuse using a number of dopamine agonists and antagonists (Haile et al., 2008). This has prompted research to consider new pharmacological intervention strategies.

Dopamine partial agonists are characterized by high affinity for dopamine receptors and low intrinsic activity. They are thought to behave as functional antagonists in conditions of high dopaminergic tone (e.g., in the case of self-administering addictive drugs) and as agonists in conditions of low dopamine receptor occupancy (e.g., during drug withdrawal) (Pulvirenti and Koob, 1994). The results of several studies have indicated that dopamine partial agonists may be devoid of abuse liability and lack extrapyramidal side effects (Pulvirenti and Koob, 1994; Sorensen et al., 2008). Dopamine partial agonists appear to be promising candidates for the treatment of drug dependence.

Several compounds with dopamine partial agonist activity have been characterized, including preclamol, terguride, SDZ 208-911, SDZ 208-912 (which are active at D_2 receptors), SKF 38393, SKF 77434 (which are active at D_1 receptors), and BP 897 (which is active at D_3 receptors) (Tadori et al., 2007). Several recent studies have shown that D_2 partial agonists decrease the acute reinforcing properties of cocaine and amphetamine, reduce ethanol intake, and restore the decreased motivation to work for natural rewards during psychostimulant withdrawal in rodents (Bono et al., 1996; Hoefer et al., 2006; Orsini et al., 2001; Platt et al., 2003; Pulvirenti et al., 1998). These data suggest that D_2 partial agonists possess a unique pharmacological profile in animal models of dependence and represent a novel pharmacological strategy for intervention in various forms of drug addiction.

Dopamine neurotransmission is an important neuropharmacological component of opiate reinforcement in rodents. Manipulations that alter dopamine activity in the central nervous system frequently modify the reinforcing effects of morphine and other opiate drugs (Pierce and Kumaresan, 2006). Although the action of dopamine agonists and antagonists on opiate addiction has been tested in many studies (Kleber, 2003; Koob et al., 2009; Kreek et al., 2009), the effects of dopamine partial agonists on opiate addiction remain unclear.

The aim of the present study was to investigate the effects of the dopamine partial agonist terguride on intravenous (i.v.) heroin self-administration on a progressive-ratio (PR) schedule of reinforcement,

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doi:10.1016/j.pbb.2010.08.002

an operant measure that assesses the motivational strength of the organism to obtain an addictive drug (Nawata and Yamamoto, 2008; Sanchis-Segura and Spanagel, 2006). Additionally, the effects of terguride in rats exposed to limited-access daily heroin self-administration on a fixed-ratio (FR) schedule were also evaluated. To provide an indication of the specificity of treatment effects on drug self-administration, terguride was also administered to control rats that nosepoked for oral sweet solution (4% sucrose) self-administration on an FR schedule.

2. Materials and methods

2.1. Animals

One hundred eight male Sprague–Dawley rats (inbred, Animal Center of the 2nd Xiangya Hospital, Central South University, Changsha, China), weighing 250–280 g before the experiment, were individually housed in stainless-steel mesh home cages (30×30×30 cm) in a temperature-controlled ventilated colony room with a 12 h/12 h light/dark cycle (lights on 7:00 AM–7:00 PM). Food and water were available *ad libitum*. Experimental sessions were performed between 8:30 AM and 5:00 PM. The data from 12 rats were excluded because seven subjects failed to maintain catheter patency, and five rats failed to reach the training criteria on the PR schedule (i.e., their breakpoints were less than 25 after 20 days of training). All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Diacetylmorphine HCl (heroin) was obtained from the Hunan Public Security Bureau. Terguride (Sigma, St. Louis, MO, USA) was prepared in a vehicle solution of 0.9% physiological saline with one drop of 1 N HCl and was injected intraperitoneally in a volume of 1.0 ml/kg body weight (Hoefer et al., 2006; Orsini et al., 2001; Platt et al., 2003).

2.3. Intravenous heroin self-administration on a fixed-ratio schedule

The animals were implanted with chronically indwelling intravenous catheters under sodium pentobarbital (50 mg/kg, i.p.) anesthesia. Polyurethane intravascular tubing (3.5 cm length, 0.58 mm inner diameter, 0.91 mm outer diameter; BPU-T30, Instech, Plymouth Meeting, PA, USA) was inserted into the right external jugular vein and secured with thread so that the tip reached the right atrium. The other end of the catheter (BPE-T20, Instech, Plymouth Meeting, PA, USA) exited from an incision on the back of the rat. The catheters were flushed daily with 0.2 ml saline containing sterile benzylpenicillin sodium (60,000 units) and heparin (5 units) to prevent bacterial infection and maintain catheter patency. All of the animals were allowed to recover for 4 days. At the time of the self-administration session, the catheter was connected to a swivel (375/22, Instech, Plymouth Meeting, PA, USA) through a metal spring, which in turn was connected to an infusion pump as described by Thomsen and Caine (2005).

The animals were transferred to the operant chambers before each training session and returned to their individual home cages shortly after the session. Training and testing were conducted in stainless-steel operant chambers (30×30×30 cm) in a sound-attenuated, temperature-controlled room. The room light was turned off during training. The chamber was equipped with two holes in the back wall, one of which was selected as the active hole for delivering the reinforcer and the other was the inactive hole. Responding in the active hole resulted in an intravenous heroin infusion (50 μg/kg per infusion) (Greenwell et al., 2009; Wang et al., 2009), whereas responding in the inactive hole had no consequences. A swivel system allowed free movement of the animal in the chamber. Coinciding with the onset of the infusion, a stimulus light and buzzer located 1 cm above the nosepoke hole on the same side wall of the operant chamber were turned on for 2.5 s, during which time the active nosepoke hole became inactive. Locomotor activity counts were measured by 10 passive infrared detectors that were positioned on the side walls of the operant chambers, 5.5 cm above the floor. The infrared beams were arrayed horizontally to allow horizontal locomotion to be detected and recorded. Responses in the active nosepoke hole during the daily 1 h session when the signal light was not lit were reinforced on a continuous reinforcement schedule (FR1). Once the animals demonstrated stable drug infusions for 3 consecutive days (<10% variation in daily infusions over 3 days), the average number of infusions were used as baseline, and the test sessions began. This baseline of heroin infusions was normally reached within 7–10 days of training. Thereafter, these rats were randomly divided into four groups ($n=8$ per group). No significant differences in baseline heroin infusions were observed between the four groups ($F_{3,28}=0.37$, $p>0.05$). On the test day, the animals were pretreated with terguride immediately before the session. Four different doses of terguride were used (0, 0.1, 0.2, and 0.4 mg/kg, i.p.). Each dose was tested only once per animal. The doses were chosen following the results of previous studies (Hoefer et al., 2006; Orsini et al., 2001; Platt et al., 2003).

2.4. Oral sucrose self-administration on a fixed-ratio schedule

The oral sucrose self-administration schedule and treatment were the same as intravenous heroin self-administration under an FR schedule. Once the rat responded in the active nosepoke hole, the pump delivered 0.1 ml sweet solution (4% sucrose) to the fluid receptacle in the cage. The training session was conducted for 1 h daily. No significant differences in baseline sucrose reinforcements were observed between the four groups ($F_{3,28}=0.12$, $p>0.05$).

2.5. Intravenous heroin self-administration on a progressive-ratio schedule

Rats were first trained on an FR schedule 1 h daily for 10 days using the following experimental design: day 1–3 (FR1), day 4–6 (FR3), day7–10 (FR10). After the FR training, rats were subjected to a PR schedule for 4 h daily. The response requirements necessary to receive a single reinforcement increased according to the following progression: $5e^{0.2(\text{total rewards}+1)}-5$ (Nawata and Yamamoto, 2008; Sanchis-Segura and Spanagel, 2006). This resulted in the following progression of response requirements: 1, 2, 4, 6, 9,12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, etc. The breakpoint was defined as the last ratio attained by the rat prior to a 60 min period during which a ratio was not completed. Stable responding maintained for 3 consecutive days (±10% with a breakpoint>25) served as baseline. Rats were then randomly divided into four groups ($n=8$ per group). No significant differences in baseline breakpoints were observed between the four groups ($F_{3,28}=0.55$, $p>0.05$). On the test day, the animals were pretreated with terguride (0, 0.1, 0.2, and 0.4 mg/kg, i.p.) immediately before the beginning of the session.

2.6. Statistical analysis

Data are expressed as mean±SEM. The differences in total active responses, inactive responses, infusions, breakpoints, and locomotor activity were analyzed by one-way analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) *post hoc* test. All statistical analyses were performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p<0.05$.

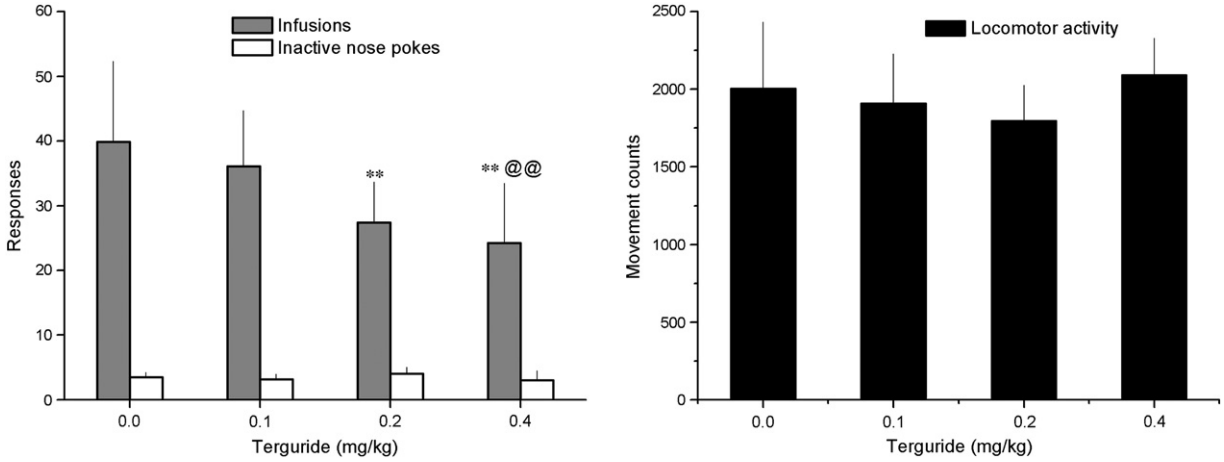

Fig. 1. Effects of pretreatment with terguride on nose poke responding and locomotor activity during intravenous heroin self-administration on a fixed-ratio schedule. Values represent the mean ± SEM of eight animals. $^{**}p<0.01$, significant difference compared with 0.0 mg/kg terguride pretreatment group; $^{@@}p<0.01$, significant difference compared with 0.1 mg/kg terguride pretreatment group (LSD *post hoc* test following significant ANOVA).

3. Results

3.1. Effects of terguride on intravenous heroin self-administration on a fixed-ratio schedule

The effects of acute administration of terguride in rats responding for heroin self-administration on an FR1 schedule are shown in Fig. 1. Terguride dose-dependently decreased the number of heroin infusions ($F_{3,28}=4.83$, $p<0.01$). Individual mean comparisons with vehicle revealed that the effect of terguride reached statistical significance at doses of 0.2 mg/kg ($p<0.01$) and 0.4 mg/kg ($p<0.01$). None of the terguride doses significantly affected inactive nosepoke responses ($F_{3,28}=1.38$, $p>0.05$) or locomotor activity ($F_{3,28}=1.31$, $p>0.05$).

3.2. Effects of terguride on oral sucrose self-administration on a fixed-ratio schedule

Fig. 2 shows that none of the terguride doses significantly affected oral sucrose self-administration. The ANOVA revealed no significant differences between vehicle and three doses of terguride on the number of infusions ($F_{3,28}=1.41$, $p>0.05$), inactive nosepoke responses ($F_{3,28}=0.29$, $p>0.05$), or locomotor activity ($F_{3,28}=2.32$, $p>0.05$).

3.3. Effects of terguride on intravenous heroin self-administration on a progressive-ratio schedule

The effects of terguride on responding for heroin self-administration on a PR schedule are shown in Fig. 3. Pretreatment with terguride reduced the maximum response requirement (i.e., breakpoint) ($F_{3,28}=8.83$, $p<0.01$) and number of infusions ($F_{3,28}=6.86$, $p<0.01$) at all three doses. None of the terguride doses significantly affected inactive nosepoke responses ($F_{3,28}=0.27$, $p>0.05$) or locomotor activity ($F_{3,28}=0.45$, $p>0.05$).

4. Discussion

The results of the present study show that the dopamine partial agonist terguride reduced responding for heroin self-administration on both the FR and PR schedules. This action appears to be functionally specific because sucrose responding was not affected by the same treatments.

In many studies, decreased responding on an FR schedule of drug self-administration was interpreted as the enhanced reinforcing properties of the drug, in which animals attempt to maintain the same level of reward, similar to increasing the dose delivered per

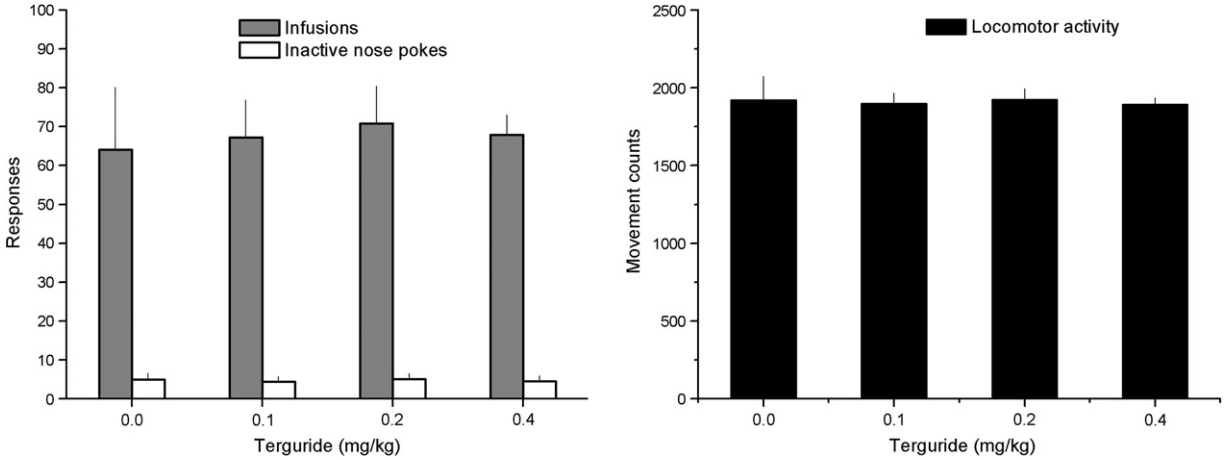

Fig. 2. Effects of pretreatment with terguride on nose poke responding and locomotor activity during oral sucrose self-administration on a fixed-ratio. Values represent mean ± SEM of eight animals.

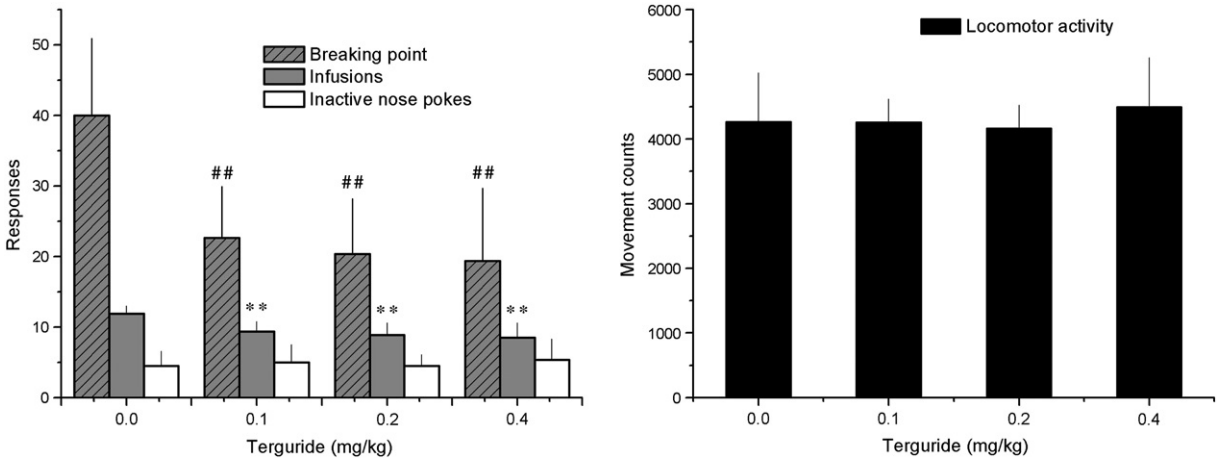

Fig. 3. Effects of pretreatment with terguride on nose poke responding and locomotor activity during intravenous heroin self-administration on a progressive-ratio. Values represent the mean ± SEM of eight animals. $^{**}p<0.01$, $^{\#\#}p<0.01$, significant difference compared with 0.0 mg/kg terguride pretreatment group (LSD *post hoc* test following significant ANOVA).

infusion (Zernig et al., 2007). One question is whether the decreased responding on an FR schedule indicates the enhanced reinforcing properties of heroin. Some studies have shown that neuroleptics caused response deceleration and attenuated intravenous drug reinforcement. For example, the combination of the dopamine antagonist flupenthixol and opioid antagonist quadazocine significantly reduced speedball (cocaine and heroin combination) self-administration without accelerating responding. Considering the pharmacological properties, the researchers concluded that the neuroleptics blocked the reinforcing effect of the speedball combination (Mello and Negus, 1999). Many studies have shown that the mesolimbic dopamine system is hyperactive during the maintenance of intravenous heroin self-administration (Hemby et al., 1995; Leone et al., 1991; Xi et al., 1998). The dopamine D_2 partial agonist terguride may act as an antagonist during this phase. Previous studies found that manipulations that block dopamine activity attenuate the rewarding effect of opiates. For example, systemic treatment with dopamine antagonists blocked the development of opiate-induced conditioned place preference and decreased responding for intravenous heroin self-administration (Liu et al., 2003). Morphine-induced conditioned place preference and intravenous self-administration could not be established in knockout mice lacking dopamine D_2 receptors (Maldonado et al., 1997). In other studies, heroin self-administration was attenuated by systemic treatment with the D_2 antagonist eticlopride (Hemby et al., 1996). Terguride may have decreased the reinforcing effect of heroin on an FR self-administration schedule. However, the interpretation of our manipulation effects on an FR schedule should be integrated with the effects on a PR schedule. Addictive drugs typically increase breakpoints, with an increase in the unit dose delivered per infusion (Stafford et al., 1998). The decrease in breakpoint for heroin self-administration induced by terguride suggests that this dopamine partial agonist reduced the reinforcing magnitude of the drug. Altogether, the consolidated results of the FR and PR schedules suggest that terguride is able to block heroin reinforcement.

An important consideration in the development of a drug dependence pharmacotherapy is the pharmacological specificity of the candidate medication's effect. One technique used to evaluate the specificity of a medication is to compare its effects between the behavior maintained by addictive drugs and the behavior maintained by a non-drug reinforcer, such as food or sucrose (Sanchis-Segura and Spanagel, 2006). Our data show that terguride had no significant effect on sucrose self-administration. The results of the present study are consistent with a previous study in which terguride decreased ethanol but not water intake under free choice non-operant oral self-administration conditions (Bono et al., 1996). Both studies indicate that terguride may selectively affect the reinforcing effects of heroin and ethanol. However, another study found that terguride decreased cocaine-maintained behavior on a second-order schedule of reinforcement in squirrel monkeys and disrupted operant behavior maintained by food. Indicating that terguride may have non-specific behavioral actions (Platt et al., 2003). The different species and schedules may explain the inconsistency of these results. The second-order schedule may be more sensitive than the FR schedule to performance-disrupting effects. These differences encourage more investigations on the pharmacological specificity of terguride in drug dependence pharmacotherapy.

Previous behavioral studies showed that terguride induced contralateral turning in rats with unilateral striatal 6-hydroxydopamine lesions and reduced amphetamine and cocaine-induced locomotor activity (Clark et al., 1991; Sibole et al., 2003). Another study found that terguride significantly reduced the distance traveled in amphetamine-pretreated preweanling rats (McDougall et al., 2005). However, in this study, terguride did not affect locomotor activity in rats self-administering heroin. Previous studies also showed that the dopamine receptor antagonist haloperidol did not attenuate locomotor activation produced by food- or heroin-predictive discriminative cues (McFarland and Ettenberg, 1999). These discrepancies could be attributable to methodological differences, such as the drug administration regimens, treatment doses and courses, and methods of locomotor activity data collection. Specifically, a behavioral sensitization regimen was used in the previous psychostimulant studies, whereas a self-administration model was used in the present study. The locomotor hyperactivity produced by the behavioral sensitization regimen may be more sensitive to the intervention. Moreover, dopamine receptors may undergo different conformational changes between psychostimulant and opiate addiction models (Pierce and Kumaresan, 2006). For example, an early study found that pharmacological blockade of dopamine receptors or lesions of mesolimbic dopamine neurons blocked amphetamine- but not heroin-induced locomotion (Vaccarino et al., 1986). Another possibility is that the rewarding and psychomotor stimulant effects of opiates may have different neural substrates (McFarland and Ettenberg, 1995; Platt et al., 2000; Shabat-Simon et al., 2008). For technical reasons, our locomotion data are expressed as photocell counts instead of distance traveled, and our photocell array was arranged only horizontally. Such a methodology did not allow us to make definitive conclusions about the effects of terguride on locomotor activity in heroin self-administering rats. The future use of more sophisticated apparatuses may yield more valuable information.

Previous studies showed that terguride blocked the reinforcing effects of ethanol and psychostimulants, such as cocaine and amphetamine (Bono et al., 1996; Izzo et al., 2001; Platt et al., 2003). The present observations further suggest that dopamine D_2 partial agonists may represent a novel pharmacological strategy for intervention in various forms of drug addiction. The effects of drugs acting as partial agonists at dopamine receptors other than the D_2 receptor on drug dependence have also been reported. The D_1 partial agonists SKF 83959, SKF 77434, and SKF 38393 reduced cocaine self-administration in squirrel monkeys trained on a second-order schedule (Mutschler and Bergman, 2002; Platt et al., 2001). The D_3 partial agonist BP897, in contrast, did not significantly modify responding for cocaine on a continuous reinforcement schedule but inhibited cocaine-seeking behavior initiated upon presentation of a cue previously paired with cocaine (Gal and Gyertyan, 2003). Notably, these effects were often observed at doses that did not induce catalepsy and maintained self-administration behavior. These observations warrant further preclinical investigation of their potential clinical use in drug abuse. Therefore, the present observations further support that drugs that have a D_1, D_2, or D_3 partial agonist profile may represent novel candidates for pharmacological intervention in drug abuse.

In conclusion, the present data indicate that the dopamine D_2 partial agonist terguride blocked the reinforcing effects of heroin during a self-administration maintenance phase but had no significant effect on oral sucrose self-administration. Our data suggest that D_2-like partial agonists may have pharmacological utility as modulators of heroin reinforcement.

Acknowledgements

The authors thank Keyun Ma for the excellent technical assistance. This work was supported by the Youth Humanities and Social Science Fund of the Education Ministry of China (09YJCXLX019) to D.Z., National Key Basic Research and Development Program (NKBRDP) of China (2009CB522000) to W.H., National Natural Science Foundation (30971050) to W.H., and National Natural Science Foundation (30800360) to J.Z.

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