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ORIGINAL INVESTIGATION

Cariprazine (RGH-188), a D_3-preferring dopamine D_3/D_2 receptor partial agonist antipsychotic candidate demonstrates anti-abuse potential in rats

V. Román · I. Gyertyán · K. Sághy · B. Kiss · Zs. Szombathelyi

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Abstract
Rationale Cariprazine (RGH-188) is a D_3-preferring dopamine D_3/D_2 receptor partial agonist antipsychotic candidate for the treatment of schizophrenia and bipolar mania. Substance abuse is a frequent comorbidity of both disorders and is associated with serious health issues. Based on preclinical efficacy, dopamine D_2 and D_3 receptor partial agonists and antagonists are assumed to have relapse-preventing potential in human cocaine addiction.
Objectives We investigated the anti-abuse potential of cariprazine in cocaine self-administration paradigms. Aripiprazole and bifeprunox were used as comparators because of their pharmacological similarity to cariprazine.
Methods The effects of compounds on cocaine's rewarding effect were investigated in a continuous self-administration regimen. The relapse-preventing potential of drugs was studied in rats with a history of cocaine self-administration after a period of complete abstinence in a relapse to cocaine-seeking paradigm.
Results Cariprazine, as well as aripiprazole and bifeprunox, were able to reduce the rewarding effect of cocaine (minimum effective doses were 0.17, 1, and 0.1 mg/kg, respectively) and attenuated relapse to cocaine seeking with half maximal effective dose [ED_{50}] values of 0.2, 4.2, and 0.17 mg/kg, respectively.
Conclusions These results may predict a relapse-preventing action for cariprazine in humans in addition to its already established antipsychotic and antimanic efficacy.

Keywords Cariprazine · Aripiprazole · Bifeprunox · Dopamine receptor · Cocaine self-administration · Cocaine seeking · Relapse · Antipsychotic · Antimanic

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V. Román · I. Gyertyán · K. Sághy · B. Kiss · Z. Szombathelyi
Pharmacology and Drug Safety Research, Gedeon Richter Plc, Budapest, Hungary

V. Román (✉)
Department of Behavioural Pharmacology, Gedeon Richter Plc.,
Gyömrői út 19-21,
H-1103, Budapest, Hungary
e-mail: v.roman@richter.hu

Introduction

Abuse of drugs, such as cocaine, is a frequent comorbidity in psychiatric disorders and is associated with greater morbidity, impairment, and mortality (Drake and Mueser 2000; Schmidt et al. 2011). Because of the huge burden it imposes on psychiatric patients, effective treatment of drug abuse is a high priority. Beyond psychotherapeutic interventions, treatment options are limited; specific and approved pharmacological treatments do not currently exist for cocaine dependence or relapse. Various dopamine receptor ligands, agonists, antagonists, and partial agonists have been intensely investigated in both preclinical settings and human laboratory studies to investigate their potential anti-abuse effect (for review, see Haney and Spealman 2008). Cariprazine is a D_3-preferring dopamine D_3/D_2 receptor partial agonist (Kiss et al. 2010) that has shown efficacy in animal models of psychosis (Gyertyán et al. 2011) and in the treatment of schizophrenia (Bose et al. 2010) and acute mania (Knesevich et al. 2009). The aim of the present study was to determine whether cariprazine shows anti-abuse efficacy in animal models of cocaine dependence.

Dopamine receptor antagonists, such as haloperidol and SCH-23390, increase cocaine self-administration in continuously self-administering animals at low to moderate doses by reducing the reward value of cocaine, thereby inducing a compensatory increase in the number of cocaine self-infusions (Corrigall and Coen 1991; Caine et al. 1995; Gál

and Gyertyán 2003). In contrast, the dopamine receptor agonists R(+)-2-dipropylamino-7-hydroxy-1,2,3,4-tetrahydronaphtalene (7-OH-DPAT) and PD-128907 produce a discriminative stimulus similar to that of cocaine and partially substitute for the drug, decreasing cocaine self-infusions in the self-administration model (Caine and Koob 1995; Gál and Gyertyán 2003). The partial agonist aripiprazole was shown to increase the number of smoked cocaine choices in humans, behaving similarly to dopamine receptor antagonists with respect to self-administration (Haney et al. 2011).

In animal models of cocaine relapse, partial agonists and antagonists at the dopamine D_2 or D_3 receptors have been found to attenuate cocaine-seeking behavior by reducing the effect of dopamine at these receptors. Mounting evidence supports the idea that dopamine mediates the "wanting" aspect of reward-related animal behavior (Berridge 2007); therefore, it is conceivable that inhibition of the dopamine D_2 or D_3 receptors by partial agonists or antagonists diminishes this "wanting," which in turn manifests as attenuated cocaine seeking. Considerable work has been done in animals with D_2 and D_3 receptor antagonists and partial agonists (e.g., S33138, NGB 2904, BP897, raclopride, SB277011A, RGH-237, and haloperidol) that showed these compounds inhibited relapse to cocaine seeking (Cervo et al. 2003; Gál and Gyertyán 2006; Gyertyán et al. 2007; Peng et al. 2009; Xi and Gardner 2007). Aripiprazole, a marketed dopamine D_2/D_3 receptor partial agonist antipsychotic agent, has also been effective in a preclinical model of cocaine relapse (Feltenstein et al. 2009), and the compound is thought to be a potential treatment candidate for cocaine dependence (Beresford et al. 2005; Karila et al. 2011).

We investigated whether cariprazine altered cocaine-taking behavior and compared that effect of cariprazine with a number of reference compounds (i.e., the D_2 receptor antagonist haloperidol, the D_3/D_2 receptor agonist 7-OH-DPAT, and the D_2/D_3 receptor partial agonists aripiprazole and bifeprunox) in a continuous cocaine self-administration paradigm in rats. Additionally, we explored the effects of cariprazine in a relapse to cocaine-seeking paradigm in rats; the effects of aripiprazole and bifeprunox were also investigated in this model.

Materials and methods

Animals

For the cocaine self-administration and relapse experiments, individually housed male Long–Evans rats (Elevage-Janvier, France; 250–300 g upon arrival) were used. Animals were kept in a temperature-controlled environment on a 12:12 light/dark cycle (lights off from 1800 to 0600 hours). Prior to any experimental manipulation, animals were given a minimum of 4 days to habituate to the colony room; during this habituation period, they were weighed and handled. Rats had unlimited access to commercial food pellets and tap water. Access to water was limited when rats were trained to lever press for water (pretraining). All experiments were conducted with approval from the local ethical committee and were in accordance with both local and international rules and principles (86/609/EEC Directive).

Drugs

Haloperidol, aripiprazole, bifeprunox, and cariprazine were synthesized at Gedeon Richter Plc. Cocaine was purchased from Sigma (St. Louis, MO, USA). 7-OH-DPAT was obtained from Tocris Biosciences (St. Louis, MO, USA). Aripiprazole, bifeprunox, and cariprazine were suspended in 5 % Tween-80 and distilled water. Cocaine was dissolved in heparinized (5 U/ml) physiological saline.

Operant apparatus

In the cocaine self-administration and relapse experiments, training and testing took place in six standard operant chambers (25×20×30 cm) housed inside ventilated sound and light-attenuating enclosures (Coulbourn Instruments, USA). Each chamber contained two levers (3 cm wide) on one wall that extended 1.5 cm into the chamber. The levers were 16 cm apart and positioned 3 cm above a grid floor. Above each lever there were three cue lights (green, red, and yellow; 2.5 W, 24 V); a white house light (2.5 W, 24 V) was located on the upper part of the same wall. There was a liquid dipper between the two levers that was used to supply water during pretraining sessions. In order to self-administer cocaine, an intravenous drug delivery system was used. This drug delivery system included a piece of polyethylene tubing covered with a flexible metal spring (PlasticsOne Inc., USA) that was attached to the intravenous catheter of each animal and extended to a liquid swivel (Lomir Inc., USA) mounted on a moveable arm that was fixed outside the operant chamber. The combination of a flexible spring, swivel, and moveable arm allowed the animals unrestrained locomotion inside the chamber. The swivel was connected to a 10-ml Hamilton syringe mounted on an infusion pump (Razel Inc., USA) through special polyethylene tubing (Hamilton Bonaduz AG, Switzerland). The infusion pump was placed outside on the top of the operant chamber. An interfaced computer and software (Graphic State, Coulbourn Instruments) were used to record lever presses and govern levers, cue lights, house lights, and infusion pumps.

Pretraining: operant task learning

Animals were placed on a daily 23-h water deprivation regimen and trained to lever press for water. Training involved a daily 30-min magazine training session on a fixed ratio 1

(FR1) schedule of reinforcement. Responding on both levers was rewarded by the presentation of 0.01 ml of water through a liquid delivery system every time. According to the side preference of the rats, the lever on the preferred side became the active lever (rewarded), and the lever on the other side became the inactive one (response recorded, but unrewarded) in the later cocaine self-administration sessions. Operant task learning was defined as complete when rats obtained more than 100 water drops per session on three consecutive days. All animals received water for 1 h after each experimental session and for 48 h on weekends.

Surgery and recovery

After acquiring the operant task, rats were anesthetized with intraperitoneal pentobarbital (60 mg/kg), and a catheter was implanted into the right jugular vein. Catheters were constructed of an autoclaved, 9-cm piece of silicone tubing (inner diameter, 0.635 mm; outer diameter, 1.194 mm; SEDAT, France). The free end of the implanted catheter was carried subcutaneously, externalized on the back of the animal and attached to a modified plastic pedestal (C313-000, PlasticsOne, Roanoke, USA) with a piece of plastic mesh under it. Animals were given a minimum of 5 days to recover from surgery prior to starting self-administration sessions. Catheters were filled with 55 % polyvinylpyrrolidone to avoid clogging (5.5 g PVP in 10 ml 500 U/ml heparinized saline; Merck). During the 5-day recovery period, animals received subcutaneous antibiotic treatment (10 mg/kg Tylan in physiological saline once per day; Elanco-Ely-Lilly, France); unlimited access to water and food with facilitated reach was available.

Acquisition of cocaine self-administration

Cocaine self-administration was established on an FR1 schedule of reinforcement in daily 2-h sessions. Sessions were performed 5 days per week; before and after sessions, catheters were flushed with sterile, heparinized saline (5 U/ml). During each session, animals were connected to a drug delivery system that allowed unrestricted movement in the chamber. After a priming infusion of 0.5 mg cocaine, every response on the active lever was reinforced (FR1) with sterile cocaine hydrochloride solution (0.25 mg/0.1 ml) delivered in approximately 6 s (Razel pump, model A, 3.33 rpm); response on the inactive lever was recorded but not rewarded. In order to avoid accidental overdosing, the number of self-infusions was maximized at 30 infusions during the 2-h sessions. Infusions were paired with flashing house light pulses lasting 6 s, followed by a 10-s time-out period. During the time-out period, both the chamber house light and cue lights were turned off, and responding was recorded without being reinforced. After 9–12 days of training, a stable self-administration behavior was established. Self-administration behavior was considered stable when there was no more than 15 % variation in the number of self-infusions during three consecutive days and a minimum of ten reinforcing injections were recorded per session.

Pharmacological challenges in the cocaine self-administration paradigm

When animals reached the criteria of stable cocaine self-administration, they were pharmacologically challenged with dopaminergic compounds including haloperidol, 7-OH-DPAT, aripiprazole, bifeprunox, or cariprazine. A session with a pharmacological challenge was identical to the usual self-administration session described above. Rats were assigned to treatment groups based on their baseline performance so that the different groups would have the same baseline with respect to cocaine self-infusing behavior. Rats received 5 % Tween-80 in distilled water or various doses of the investigational compounds. Haloperidol (0.25 mg/kg), aripiprazole (0.3–3 mg/kg), bifeprunox (0.03–0.3 mg/kg), or cariprazine (0.03–1 mg/kg) were given orally, while 7-OH-DPAT (0.1 mg/kg) was administered subcutaneously for pharmacokinetic reasons. Thirty minutes later, the animals were placed in operant boxes, and a cocaine self-administration session was run. Starting the next day, rats participated in cocaine self-administration sessions without pretreatment with compounds or vehicle. Self-administration was followed for at least another 3 days to ensure that a stable pattern of self-administration would return. When stable cocaine self-administration criteria returned (but not earlier than a week later), rats were pharmacologically challenged again with additional drug treatments. An animal typically underwent three to four drug treatments. The same treatment (i.e., same drug, same dose) was never repeated on the same animal.

Relapse test session

Naïve rats that had not previously been challenged with test compounds were used for the relapse assay. When they reached the criteria of stable cocaine self-administration, self-administration sessions were suspended for 14–16 days. The duration of this abstinence period was approximately the same as the duration of the previous cocaine self-administration training period. Rats were abstinent in a different room than the room used for cocaine self-administration. During this period, rats were not exposed to cocaine or environmental and technical cues that could have been associated with drug intake.

After cocaine withdrawal, rats were placed in the operant chambers for a 30-min extinction session where all the conditions were the same as in the acquisition phase except that lever presses were not paired with cocaine infusions. All the secondary cues that were previously paired with cocaine infusions (i.e., presession handling and technical procedures,

sound of the infusion pump, response-contingent house and cue lights, and the time-out period) were present, but the rats were not connected to the drug delivery system. One hour prior to the test session, animals were assigned to treatment groups and received vehicle or various doses of aripiprazole (1–10 mg/kg), bifeprunox (0.1–0.3 mg/kg), or cariprazine (0.1–0.3 mg/kg) orally. All groups consisted of rats that were matched for their previous stable cocaine intake.

Data analysis and statistics

In the cocaine self-administration study, the absolute number of cocaine self-infusions by individual rats was averaged. The 3 days preceding the challenge day constituted the baseline, while the 3 days following the challenge day was the return to baseline. Statistical analysis was done only on the number of cocaine infusions acquired on challenge days by applying one-way analysis of variance (ANOVA) with treatment as the independent variable and the number of cocaine infusions as the dependent variable, followed by the post hoc Duncan test. In the case of bifeprunox, where self-administration behavior did not seem to return to baseline levels, the number of cocaine self-infusions obtained the day after the challenge day was similarly analyzed.

In the relapse to cocaine-seeking experiments, the number of formerly active lever presses at the time of the relapse session was statistically analyzed by one-way ANOVA with treatment as the independent variable and the number of active lever presses as the dependent variable, and the post hoc Duncan test. The number of lever presses at the formerly inactive lever was analyzed independently by one-way ANOVA. Inhibition of active lever pressing was calculated as percentage reduction of lever pressing in comparison to lever pressing after vehicle treatment. Half maximal effective dose (ED_{50}) values for relapse were derived from percentage inhibitions of active lever pressing caused by the agents by applying linear regression.

Results

Effect of cariprazine on cocaine self-administration

The dopamine receptor agonist 7-OH-DPAT and the antagonist haloperidol were used to validate the cocaine self-administration model. For all experiments, during the 3 days preceding the challenge day, baseline self-administration rate was approximately 19–21 infusions (24–30 active lever presses) per 2-h session. Vehicle treatment itself did not alter cocaine self-administration (Fig. 1a–d). In contrast, the dopamine D_2 receptor antagonist haloperidol (0.25 mg/kg) significantly increased the mean number of cocaine infusions compared with vehicle treatment ($F_{(1,22)}=4.842$, $p=0.039$) from baseline to 26 self-infusions (Fig. 1a). Conversely, the dopamine D_3/D_2 receptor agonist 7-OH-DPAT (0.1 mg/kg) significantly attenuated self-administration compared to vehicle ($F_{(1,22)}=27.572$, $p<0.001$) and decreased the number of self-infusions from the baseline to approximately 12 (Fig. 1a). Aripiprazole significantly increased self-administration ($F_{(3,37)}=5.855$, $p=0.002$) at doses of 1 ($p=0.011$) and 3 mg/kg ($p=0.008$) in comparison with vehicle (Fig. 1b). Bifeprunox significantly increased self-administration compared with vehicle ($F_{(4,26)}=8.7983$, $p<0.001$) at doses of 0.1 ($p=0.002$) and 0.3 mg/kg ($p<0.001$) (Fig. 1c). The behavioral effect of bifeprunox was still present on the day following the bifeprunox challenge ($F_{(4,\ 24)}=7.25519$, $p<0.001$) with significantly increased cocaine self-administration at doses of 0.05 ($p=0.0259$), 0.1 ($p<0.001$), and 0.3 mg/kg ($p<0.001$) relative to vehicle treatment. In the cases of both aripiprazole and bifeprunox, maximal effect size (26–28 self-infusions) was comparable to that of haloperidol. Cariprazine dose dependently increased cocaine self-administration ($F_{(5,46)}=6.517$, $p<0.001$). At doses of 0.17 ($p=0.049$), 0.3 ($p=0.002$), and 1 mg/kg ($p<0.001$), cariprazine significantly increased the number of cocaine self-infusions when compared to vehicle treatment (Fig. 1d). The two highest doses of cariprazine showed effect sizes equal to haloperidol, aripiprazole, and bifeprunox.

Effect of cariprazine on relapse to cocaine seeking

By the end of the cocaine self-administration period, animals with stable performance produced 19–23 cocaine infusions (corresponding to 29–32 active lever presses) (see Fig. 2).

In the relapse session, aripiprazole administered in the dose range of 1–10 mg/kg significantly decreased the number of formerly active lever presses in comparison with vehicle treatment ($F_{(3,36)}=3.434$, $p=0.027$) (Fig. 2a). Post hoc analysis revealed that the effect of aripiprazole reached significance at the dose of 3 mg/kg ($p=0.049$) and 10 mg/kg ($p=0.047$). The ED_{50} of aripiprazole for inhibition of active lever pressing was 4 mg/kg, based on linear regression analysis. Bifeprunox, the other dopamine D_2/D_3 receptor partial agonist, was given in the dose range 0.1–0.3 mg/kg, and it significantly reduced cocaine seeking as measured by lever pressing behavior ($F_{(3,43)}=5.649$, $p=0.003$) (Fig. 2b). For this compound, lever pressing was significantly attenuated at doses of 0.17 ($p=0.016$) and 0.3 mg/kg ($p=0.006$); the ED_{50} value was 0.17 mg/kg for bifeprunox. Cariprazine in the dose range of 0.1–0.3 mg/kg significantly decreased the number of formerly active lever presses during a relapse session in comparison to vehicle treatment ($F_{(3,42)}=4.627$, $p=0.007$) (Fig. 2c). Post hoc analysis revealed that the effect of cariprazine reached significance at the dose of 0.3 mg/kg ($p=0.003$). For inhibition of active lever pressing, the ED_{50} of cariprazine was 0.2 mg/kg.

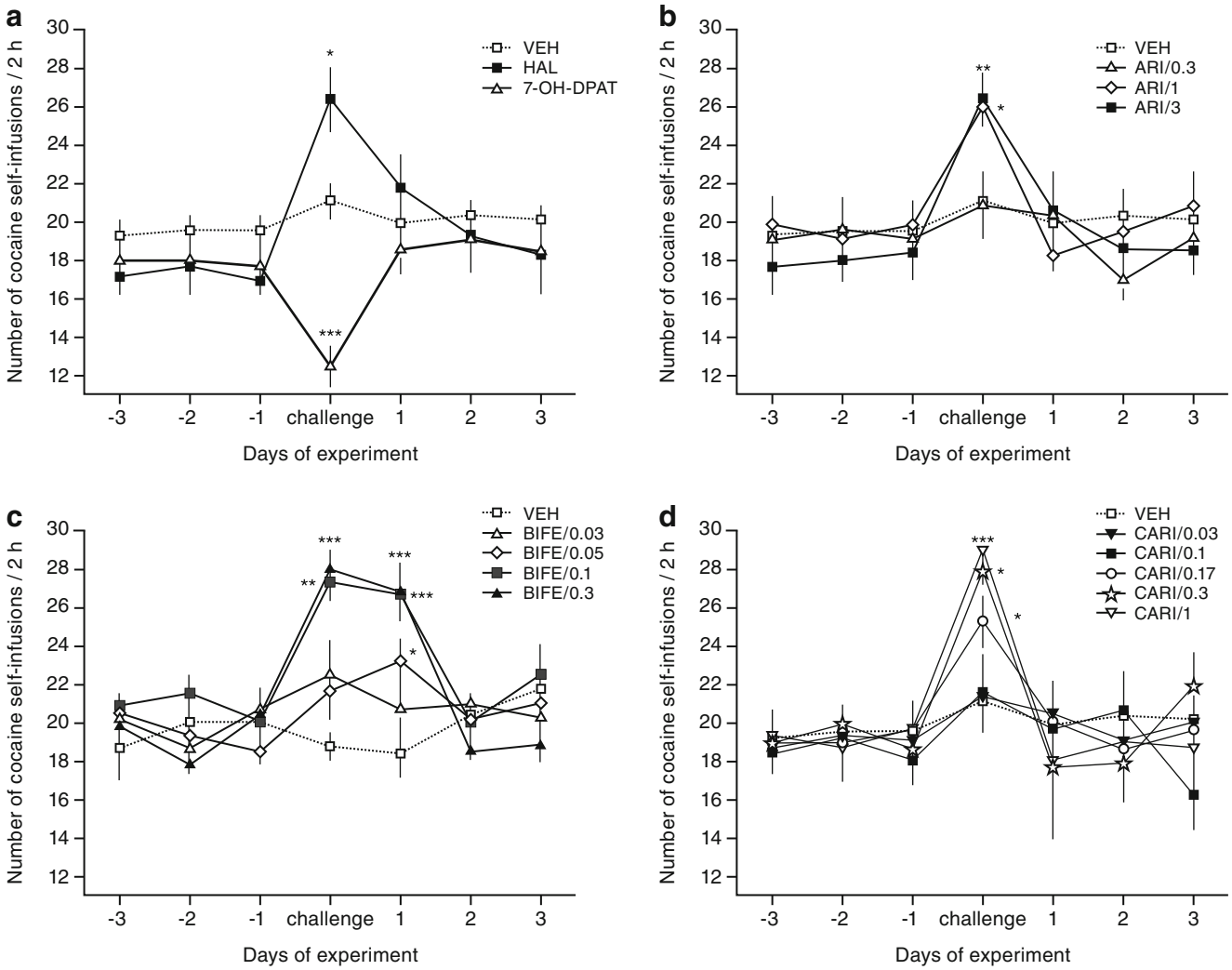

Fig. 1 Effects of dopaminergic compounds on continuous cocaine self-administration in rats: **a** 7-OH-DPAT 0.1 mg/kg (n=8, *open triangle*), haloperidol 0.25 mg/kg (n=8, *black square*), and vehicle (n=8, *open square*); **b** aripiprazole 0.3 (*open triangle*), 1 (*open diamond*), 3 mg/kg (*black square*), and vehicle (*open square*), n=8 for all doses and vehicle; **c** bifeprunox 0.03 mg/kg (n=6, *open triangle*), 0.05 mg/kg (n=6, *open diamond*), 0.1 mg/kg (n=6, *black square*), 0.3 mg/kg (n=5, *black triangle*), and vehicle (n=8, *open square*); **d** cariprazine 0.03 mg/kg (n=8, *black triangle*), 0.1 mg/kg (n=8, *black square*), 0.17 mg/kg (n=8, *open circle*), 0.3 mg/kg (n=8, *open star*), 1 mg/kg (n=3, *open triangle*), and vehicle (n=16, *open square*). Data are presented as average number of cocaine self-infusions ±SEM. *p<0.05 vs. vehicle control of the same day, ***p<0.001 vs. vehicle control of the same day (Duncan post hoc test)

Lever pressing behavior at the inactive lever was not altered significantly by any of the treatments.

Discussion

In the present study, we demonstrated the anti-abuse potential of the antipsychotic candidate D_3/D_2 receptor partial agonist cariprazine. The compound reduced the effect of cocaine in rats on a continuous cocaine self-administration regimen and prevented relapse to cocaine seeking in the same species. The behavioral effects of cariprazine were as potent as bifeprunox and more potent than aripiprazole.

A number of studies have shown that pharmacological modulation of the reward value of cocaine is possible by administration of dopaminergic agents. The dopamine D_3/D_2 receptor agonist 7-OH-DPAT blunts cocaine self-administration after systemic administration (Caine and Koob 1995; Barrett et al. 2004; Gál and Gyertyán 2003) and intraamygdalar injection (Thiel et al. 2010). Other dopamine D_2-like receptor agonists including quinelorane, pramipexole, and PD128, 907 behave similarly and decrease operant responding maintained by high unit doses of cocaine in the rat (Barrett et al. 2004; Caine and Koob 1995). A likely explanation for this reduced cocaine intake is that dopamine receptor agonists produce a cocaine-like discriminative stimulus (Acri et al. 1995; Garner and Baker 1999;

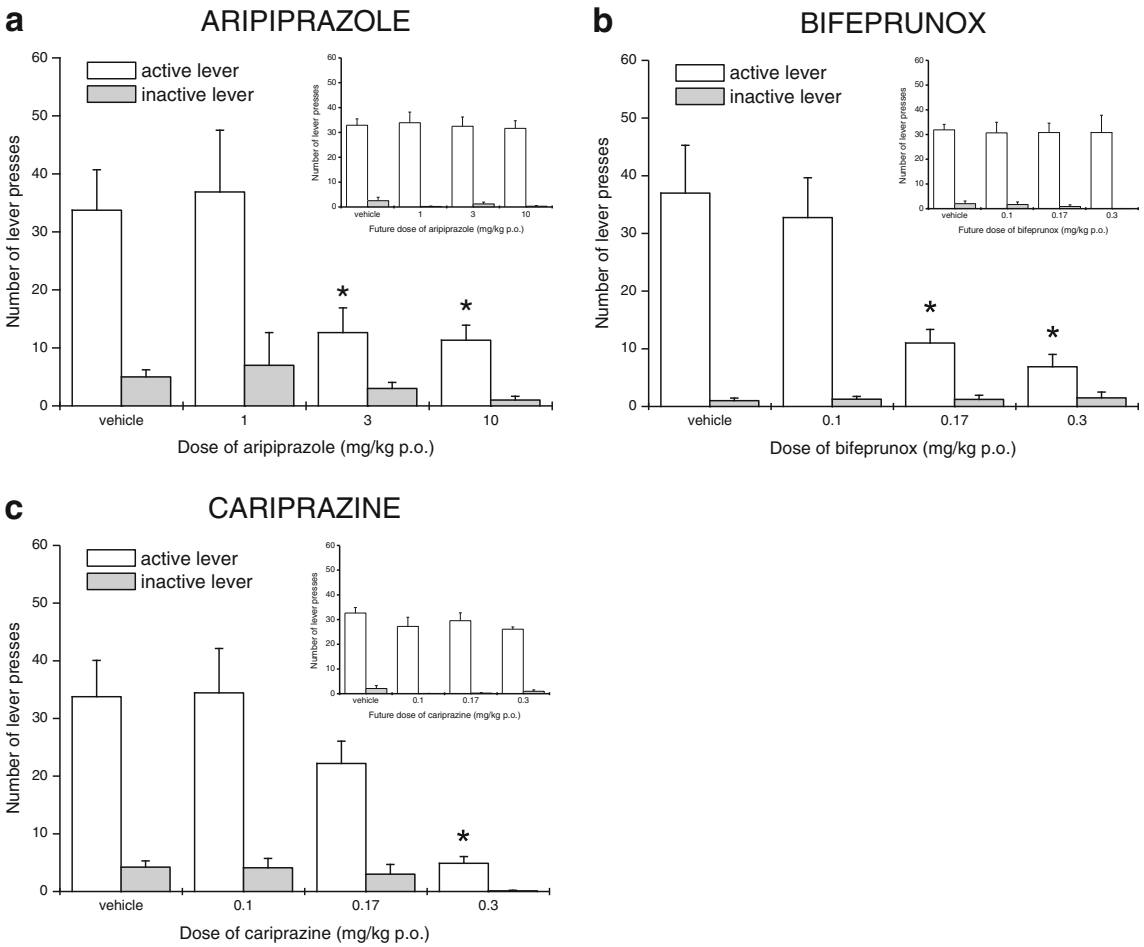

Fig. 2 Aripiprazole (**a**), bifeprunox (**b**), and cariprazine (**c**) were investigated in a model of relapse to cocaine seeking. Relapse to cocaine seeking was induced by placing the animals back in the operant chambers with all cocaine-related cues present after a period of complete abstinence. *Open bars* represent lever pressing behavior at the active lever, while *closed gray bars* indicate lever pressing behavior at the inactive lever. Lever presses at the formerly inactive lever were not significantly affected by any of the compounds. *Insets* show the basal number of active and inactive lever presses during the last 3 days of cocaine self-administration for each treatment group prior to the abstinence period. Data are presented as average lever presses ±SEM. *$p<0.05$ vs. vehicle control (post hoc Duncan test)

Lamas et al. 1996), so intake of less cocaine is satisfactory to achieve the same internal state.

In contrast to agonists, dopamine D_1 and D_2 receptor antagonists increase cocaine intake at low to moderate doses (Barrett et al. 2004; Caine et al. 1997; Corrigall and Coen 1991; Gál and Gyertyán 2003; Peng et al. 2009) by reducing the rewarding effect of cocaine (Norman et al. 2011). When dopamine levels are high due to cocaine self-administration in animals (Bradberry et al. 2000; Hurd et al. 1997) and humans (Cox et al. 2009; Volkow et al. 2007), dopamine D_2 receptor partial agonists (e.g., BP-897, terguride) behave functionally similar to antagonists; therefore, the administration of D_2 receptor partial agonists results in increased cocaine intake in animal models (Gál and Gyertyán 2003; Pulvirenti et al. 1998). The D_2 receptor partial agonists aripiprazole and bifeprunox increased self-administration of cocaine in our study with minimum effective oral doses of 1 and 0.1 mg/kg, respectively. In another study, intraperitoneal aripiprazole (0.5–2.5 mg/kg) caused a mild, nonsignificant trend toward an increase of cocaine intake in rats receiving a 0.5-mg/kg unit dose of cocaine (Feltenstein et al. 2007). A recent human study is also consistent with our finding that aripiprazole increases cocaine self-administration (Haney et al. 2011). Interestingly, cocaine self-administration was also elevated on the day following bifeprunox administration. Since appropriate data are lacking in the literature, we can only speculate on whether the long-lasting effect of bifeprunox may be related to its pharmacokinetic or receptor kinetic properties.

Similar to aripiprazole and bifeprunox, we found that cariprazine elevated the number of self-infusions in rats on a continuous cocaine self-administration regimen suggesting that it reduced the rewarding effect of cocaine. The question arises as to the precise nature of the receptorial action responsible for the behavioral effect of cariprazine. Cariprazine showed affinity to dopamine D_3 receptors

(*p*Ki=9.15) that was about an order of magnitude higher than to D_2 receptors (*p*Ki=8.03) (Kiss et al. 2010). However, earlier investigations showed that pharmacological manipulation of the D_3 receptor does not seem to considerably modulate the acute reinforcing effect of cocaine: neither D_3 receptor antagonists (e.g., SB277011, U-99194A) nor the D_3 receptor partial agonist BP-897 could induce a major alteration in the number of cocaine self-infusions in rats when cocaine was obtained under an FR1 schedule (Di Ciano et al. 2003; Gál and Gyertyán 2003; Le Foll et al. 2005). Based on this, we presume that the pharmacological effect of cariprazine (and also of aripiprazole and bifeprunox) observed in the present study may be associated with their partial agonist behavior at the D_2 receptor and not with effects mediated through the D_3 receptor. This view may be further strengthened by a finding of Etievant et al. (2009) concerning in vivo effects of dopamine receptor partial agonists. That study showed that both aripiprazole and bifeprunox behaved in vivo as partial agonists at D_2 but not at D_3 receptors; only the preferential D_2 receptor antagonist L741, 626, but not the preferential D_3 receptor antagonist GR218, 231, was able to block the inhibitory effect of the two partial agonists on ventral tegmental dopaminergic neuronal activity.

Relapse prevention, another aspect of anti-abuse potential with cariprazine, was assessed in a relapse to cocaine-seeking paradigm. It is known from animal studies that environmental cues associated with drug taking are powerful primes that induce reinstatement of drug-seeking behavior (Stewart 2000; de Wit and Stewart 1981). As such, drug-related environmental cues predicting reward can evoke drug craving in humans, which may in turn trigger a relapse to drug seeking as seen in experimental animals (O'Brien et al. 1992). Preclinical evidence shows that relapse to cocaine seeking can be modulated by pharmacological manipulation of the D_2 and D_3 receptors. Dopamine D_2 and D_3 receptor agonists such as 7-OH-DPAT, R(−)-propylnorapomorphine, quinelorane, and quinpirole, and the nonselective dopamine receptor agonist apomorphine, have all been found to induce reinstatement of extinguished cocaine-seeking behavior in rats or squirrel monkeys (Bachtell et al. 2005; Dias et al. 2004; Khroyan et al. 2000; de Wit and Stewart 1981). Conversely, dopamine receptor antagonists or partial agonists attenuate relapse. Reinstatement of cue-induced cocaine seeking in rats is prevented by the D_2 receptor antagonist raclopride (Cervo et al. 2003; Crombag et al. 2002), the D_3 receptor antagonists SB-277011, S33138, and NGB 2904 (Gál and Gyertyán 2006; Peng et al. 2009; Xi and Gardner 2007), as well as by the selective D_3 receptor partial agonist RGH-237, the D_3/D_2 receptor partial agonist BP897, and the D_2/D_3 receptor partial agonist aripiprazole (Feltenstein et al. 2007; Gilbert et al. 2005; Gyertyán et al. 2007). The D_2 receptor partial agonist bifeprunox has also been reported to attenuate cue-induced nicotine seeking in a rat study (Di Clemente et al. 2011). A limited number of human studies imply that pharmacological manipulation of dopamine receptors may control the motivational value of rewarding cues not only in animals, but also in humans (Ersche et al. 2010; Nathan et al. 2011).

Based on these previous results, we investigated the effect of cariprazine, aripiprazole, and bifeprunox on relapse to cocaine seeking in rats with a previous history of cocaine taking and complete abstinence; the study did not include an extinction training phase. In our study, the three partial agonists were all able to prevent relapse to cocaine seeking after a period of complete withdrawal from cocaine and its related cues. The effects of cariprazine and bifeprunox were equipotent (relapse ED_{50} were 0.2 and 0.17 mg/kg, respectively), while aripiprazole was approximately 20 times less potent than the former two compounds (relapse ED_{50}, 4.2 mg/kg). In contrast to continuous cocaine self-administration, cocaine seeking in relapse models can be inhibited by selective dopamine D_3 receptor ligands as well as by mixed or largely D_2-preferring compounds (see above). The relapse-preventing potency of cariprazine, aripiprazole, and bifeprunox coincide with their inhibitory potency on amphetamine-induced hyperlocomotion (ED_{50} values are 0.12, 3.9, and 0.07 mg/kg, respectively) (Gyertyán et al. 2011). Since inhibition of amphetamine-induced hyperlocomotion is known to be correlated with D_2 receptor affinity (Hoffmann and Donovan 1995), it may be again assumed that dopamine D_2 rather than D_3 receptors mediate the relapse-preventing action of these compounds.

Inhibition of relapse in the present experiment is most likely not due to sedation or motor impairment as pressing on the formerly inactive lever was not significantly reduced during the relapse session. This indicates a conserved level of motor activity, though it cannot be excluded that the lack of significant reduction in lever pressing behavior might be due to a floor effect. In cue-induced cocaine and nicotine reinstatement studies, similar low rates of responding on the inactive lever were found (Feltenstein et al. 2007; Di Clemente et al. 2011). Nevertheless, in the case of the study by Feltenstein et al. (2007), there was a clear separation between the doses inhibiting cocaine seeking (MED 0.1 mg/kg) and the dose causing a significant reduction of inactive lever pressing (MED 15 mg/kg). In the other study by Di Clemente et al. (2011), bifeprunox significantly inhibited active lever pressing in response to nicotine-related cues with a MED of 4 μg/kg while lever pressing at the inactive lever remained unaltered up to the dose of 250 μg/kg. At most, cariprazine may only have mild effects on inactive lever pressing behavior (just like aripiprazole and bifeprunox) that cannot be detected at such low rates of lever pressing.

In summary, the present study demonstrated that the D_3-preferring dopamine D_3/D_2 receptor partial agonist antipsychotic candidate cariprazine reduces the rewarding effect of cocaine and also prevents the relapse to cocaine seeking in rat models of cocaine dependence. Such effects may enhance the therapeutic value of an antipsychotic/antimanic compound since drug abuse is a frequent comorbidity of both schizophrenia and mania. These results suggest that cariprazine may have relapse-preventing potential in addition to its well established antipsychotic and antimanic efficacy.

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