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Aripiprazole blocks reinstatement but not expression of morphine conditioned place preference in rats

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ABSTRACT

Aripiprazole is an atypical antipsychotic drug primarily characterized by partial agonist activity at dopamine (DA) D_2 receptors and serotonin-1A (5-hydroxytryptamine, 5-HT_{1A}) receptors and minimal side effects. Based on its pharmacological profile, including stabilization of mesocorticolimbic DA activity (a pathway implicated in drug addiction), we investigated the effects of aripiprazole on relapse to morphine seeking in rats. In experiment 1, rats underwent morphine-induced conditioned place preference (CPP) training with alternate injections of morphine (5 mg/kg, s.c.) and saline (1 ml/kg, s.c.) for 8 consecutive days. To examine the effect of aripiprazole on the expression of morphine-induced CPP, rats received aripiprazole (0, 0.03, 0.1, and 0.3 mg/kg, i.p.) 30 min before testing for the expression of CPP. In experiment 2, rats underwent the same CPP training as in experiment 1 and subsequent extinction training. To examine the effect of aripiprazole on reinstatement of morphine-induced CPP, rats received aripiprazole 30 min before testing for reinstatement of CPP. In experiment 3, to assess the effects of aripiprazole on locomotor activity, aripiprazole was administered 30 min before testing for locomotor activity. Aripiprazole significantly decreased the reinstatement of CPP induced by a priming injection of morphine but had no effect on the expression of morphine-induced CPP or locomotor activity. The D_2 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist properties of aripiprazole likely account for the blockade of relapse to drug seeking. These findings suggest that aripiprazole may have therapeutic value for reducing craving and preventing relapse to drug seeking.

1. Introduction

Drug addiction is regarded as a chronic, recurrent brain disease characterized by relapse. The high rate of relapse to opiate use after detoxification remains a major clinical problem. Intense drug craving and relapse to drug-taking behavior are seen in abstinent heroin addicts even many years after withdrawal (Unnithan et al., 1992). Interestingly, craving and relapse are often accompanied by environmental stimuli previously associated with drug-taking behavior, the drug itself, or stress (O'Brien, 1997; Shaham et al., 2003; Shalev et al., 2002; Weiss, 2005). Drug craving is a subjective feeling experienced by human drug addicts that motivate them to seek drugs and can produce relapse (O'Brien, 1997). Previous research ingeniously elucidated the procedures to directly evaluate craving and relapse in laboratory animals. After the acquisition and subsequent extinction of a particular behavioral response (e.g., pressing a lever or developing a conditioned place preference [CPP]), a laboratory animal reinitiates this response, which is often referred to as reinstatement (Comer and Carroll, 1996; Lu et al., 2003b; Shaham et al., 2003). This recovery of the learned response appears to reflect the re-induction of craving, leading to drug-seeking following a period of extinction of drug use. The CPP paradigm has been used recently to study the relapse to drug use in animals (Lu et al., 2003a; Shaham et al., 2003). In this procedure, animals are first trained to acquire a CPP; afterward, the animals undergo a process of extinction of this preference. Then the same stimuli that induced a drug-paired place preference are able to reinstate CPP.

Recently, several animal and clinical studies have been conducted to investigate whether the antipsychotic aripiprazole can block relapse to drug use (Feltenstein et al., 2007; Ingman et al., 2006; Janiri et al., 2007). Aripiprazole has a unique pharmacological profile that includes partial agonism at dopamine (DA) D_2 receptors with actions on both postsynaptic D_2/D_3 receptors and presynaptic DA autoreceptors with varying degrees of efficacy. Additionally, aripiprazole acts as a partial agonist at serotonin-1A (5-hydroxytryptamine, $5HT_{1A}$) receptors (Jordan et al., 2002) and an antagonist at $5HT_{2A}$ receptors (Davies et al., 2004; Grunder et al., 2003). The primary antipsychotic effects of aripiprazole are believed to involve the "stabilization" of DA neurotransmission in the mesocorticolimbic pathway (Stahl, 2001), a circuitry that is closely related to addiction and relapse (Robinson and Berridge, 2000; White and Kalivas, 1998).

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Acute administration of aripiprazole has been shown to markedly affect the psychomotor effects of psychotomimetics and psychostimulants and the reinforcing effects of cocaine (Leite et al., 2008; Sorensen et al., 2008; Wee et al., 2007), the acute motivational effect of amphetamine during early abstinence (Schwabe and Koch, 2007), and the reinstatement of cocaine-seeking behavior after a period of extinction (Feltenstein et al., 2007). Chronic administration of high doses of aripiprazole also substantially decreased alcohol, but not saccharin, consumption in laboratory animals (Ingman et al., 2006). Aripiprazole has been investigated extensively in alcohol-dependent patients in human laboratory studies and clinical trials. Acute aripiprazole administration altered alcohol's euphoric and sedative effects in healthy volunteers (Kranzler et al., 2008), and chronic aripiprazole treatment reduced compulsiveness (Martinotti et al., 2007) and increased abstinence from alcohol use (Janiri et al., 2007; Warsi et al., 2005) in alcohol-dependent subjects. However, a recent multicenter, double-blind study found that alcohol-dependent patients treated with aripiprazole dropped out of the trial at higher rates than those receiving placebo (Anton et al., 2008). Although the effects of aripiprazole on many drugs of abuse have been studied, including amphetamine (Lile et al., 2005; Stoops, 2006; Stoops et al., 2006; Tiihonen et al., 2007), methamphetamine (Wee et al., 2007), cocaine (Stoops et al., 2007), and ephedrine (Arnold and Yager, 2007), no study has investigated the effects of aripiprazole on opioid dependence.

The present study investigated the effects of aripiprazole on reinstatement of morphine-seeking behavior using a model of relapse with the CPP procedure. To evaluate the selectivity of aripiprazole on motivated morphine-seeking behavior, we also examined its effects on morphine reinforcement during CPP expression and on locomotor activity following exposure to both a novel environment and acute morphine injection.

2. Materials and methods

2.1. Animals

One hundred male Sprague–Dawley rats were purchased from the Center of Laboratory Animal Science, Peking University Health Science Center. The rats weighed 200–220 g upon arrival in the laboratory and were habituated for 7 days prior to the experiments. All animals were housed individually and were allowed free access to food and water. Constant temperature (21±2 °C) and humidity (about 60%) and a 12 h light/dark cycle (lights on at 8:00 am) were maintained throughout the experiments. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Local Committee of Animal Use and Protection of the Peking University Health Science Center.

2.2. Drugs

Morphine hydrochloride was obtained from Qinghai Pharmaceuticals, Ltd. (Xining, China). Morphine was dissolved in saline and administered subcutaneously (s.c.) in a volume of 1 ml/kg. Aripiprazole (powder, kindly supplied by Kanghong Pharmaceutical Group, Chengdu, China) was suspended in vehicle consisting of Tween 5% in saline. The solutions were prepared immediately before use and injected intraperitoneally (i.p.) in a volume of 1 ml/kg.

2.3. Experimental design

2.3.1. Experiment 1: effects of aripiprazole on the expression of morphine-induced CPP

CPP training was conducted in 10 identical Plexiglas boxes, each divided into three chambers by two removable guillotine doors and consisting of one large chamber (27.9×21.0×20.9 cm) on each side with a smaller chamber (12.1×21.0×20.9 cm) in the middle. All three chambers were black with different visual and textural cues. One large chamber had a floor with stainless-steel bars (diameter 4.8 mm, placed every 1.6 cm on center), while the other large chamber had a floor with stainless-steel mesh (1.3×1.3 cm). The smaller middle chamber had a smooth polyvinyl chloride floor. The time spent in each chamber during the test sessions was recorded with a computer. Conditioned place preference was indicated by a preference score that was defined as the difference in time spent in the morphine-paired chamber minus the time spent in the morphine-nonpaired chamber (Wang et al., 2006, 2008; Zhai et al., 2007).

Rats were initially placed in the chamber with the guillotine doors removed for a period of 15 min. Rats that spent 150s more in one large chamber than the other were considered to have chamber bias and were excluded from subsequent testing. Approximately 10% of the rats were excluded based on these criteria.

Place conditioning was conducted with a counterbalanced protocol similar to our previous studies (Lu et al., 2000, 2002; Wang et al., 2006). Briefly, each rat was treated with alternate injections of morphine (5 mg/kg, subcutaneous [s.c.]) and saline (1 ml/kg, s.c.) for 8 consecutive days. On conditioning days, the guillotine doors were closed to restrict the animal to its designated conditioning chamber. The chamber in which morphine or saline was administered was assigned randomly. Rats given either saline or morphine injections were immediately placed into the assigned chambers for 45 min before being returned to their home cages.

The effect of place conditioning was examined in rats with no morphine or saline injections after conditioned training on the ninth day. Rats without any treatment were placed into the middle chamber and allowed to move freely across the three chambers for 15 min.

Four groups of rats (n=8–9/group) were used to assess the effects of aripiprazole on the expression of morphine-induced CPP. Following conditioning training, rats underwent the post-conditioning test. To examine the effects of aripiprazole on the expression of morphine-induced CPP, rats received one dose of aripiprazole (0, 0.03, 0.1, or 0.3 mg/kg, i.p.) in a volume of 1.0 ml/kg 30 min before being placed into the middle chamber and were allowed free access to both conditioning chambers. The doses of aripiprazole were based on a previous study (Feltenstein et al., 2007) and our preliminary results. The experimental procedure for experiment 1 is shown in Fig. 1a.

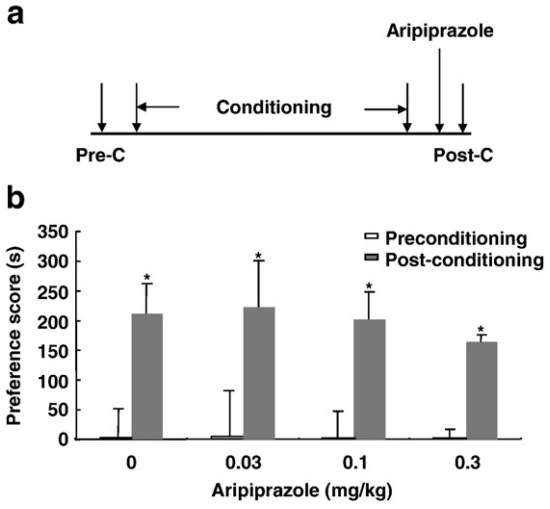

Fig. 1. Effects of aripiprazole on CPP expression. (a) Experimental procedure. CPP tests during preconditioning (Pre-C) and post-conditioning (Post-C) were performed. Different doses of aripiprazole were administered 30 min prior to Post-C. (b) Preference scores during Pre-C and Post-C. Data are expressed as mean±SEM. *p<0.05, compared with preconditioning in the same group.

2.3.2. Experiment 2: effects of aripiprazole on morphine-primed reinstatement of morphine-induced CPP

Following morphine place conditioning and acquisition of CPP, extinction tests were performed. The extinction procedure was identical to training but without morphine or saline administration.

The reinstatement procedure was performed after extinction. The reinstatement phase procedure was identical to the post-conditioning procedure, with the exception that rats were given a priming dose of morphine (3 mg/kg, s.c.) 20 min before CPP testing. The priming dose of morphine was selected based on our previous studies (Zhai et al., 2008).

Four groups of rats (n=7–9/group) were used to examine the effect of aripiprazole on reinstatement of morphine-induced CPP after extinction. During the conditioned training phase, rats underwent morphine or saline conditioning training. Following the extinction training phase, rats were injected with morphine to reinstate their extinguished morphine-induced CPP. To examine the effects of aripiprazole on morphine-induced CPP reinstatement, rats were given a single dose of aripiprazole (0, 0.03, 0.1, or 0.3 mg/kg, i.p.) in a volume of 1.0 ml/kg 30 min before being placed into the middle chamber and were allowed free access to both conditioning chambers (Fig. 2a).

2.3.3. Experiment 3: effects of aripiprazole on locomotor activity

Locomotor activity testing was conducted in the Animal Locomotor Video Analysis System (JLsofttech Co. Ltd. Shanghai, China), which contains eight identical clear Plexiglas chambers (40×40×65 cm). Each chamber was equipped with a video camera on top of the chamber (winfast vc100). Five groups of rat (n=7/group) received one dose of aripiprazole HCl (0, 0.03, 0.1, or 0.3 mg/kg, i.p.) or saline immediately before being placed in a clear Plexiglas chamber for 30 min. Immediately following the 30 min novel environment phase, animals were removed from the chamber, given an injection of morphine HCl (5.0 mg/kg, s.c.), and returned to the locomotor activity chamber for a further 60 min. Horizontal activity (cm) was analyzed in 5 min bins.

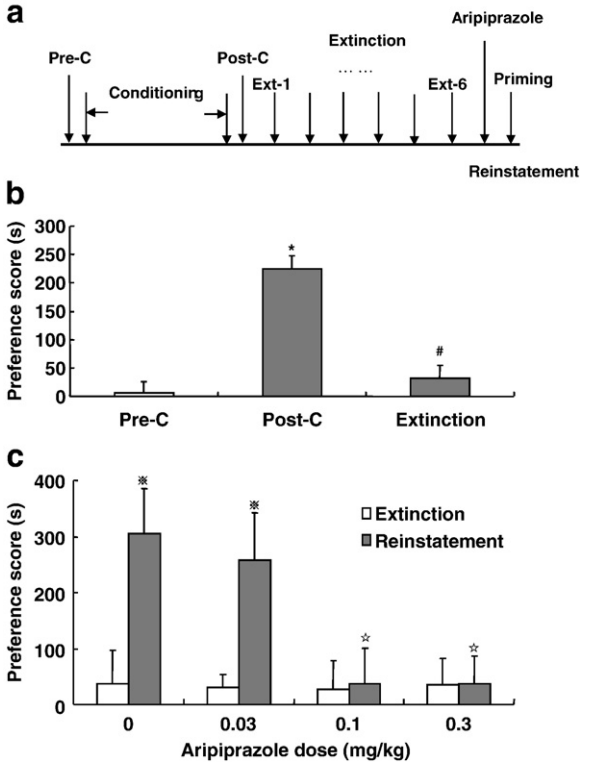

Fig. 2. Effects of aripiprazole on reinstatement of morphine-induced CPP. (a) Experimental procedure. CPP tests were performed during preconditioning (Pre-C), post-conditioning (Post-C), extinction (from Ext-1 to Ext-6), and reinstatement. Different doses of aripiprazole were administered 30 min prior to reinstatement. (b) Preference scores during acquisition and extinction of CPP. (c) Preference scores during extinction and reinstatement of CPP. Following morphine-induced place conditioning and acquisition of CPP, extinction tests were performed. After extinction, 3 mg/kg morphine was used to prime morphine-seeking behavior, and aripiprazole was injected i.p. 30 min before the priming test. Data are expressed as mean±SEM. *p<0.05, compared with Pre-C. $^{\#}p$<0.05, compared with Post-C. p<0.05, compared with extinction. $^{\star}p$<0.05, compared with vehicle in the same phase.

2.4. Statistical analysis

Data are expressed as mean±SEM. CPP score was the dependent variable. For the expression of CPP, a mixed-factor analysis of variance (ANOVA) was used to evaluate the effects of aripiprazole on the expression of CPP. The within-subjects factor was test phase (pre- and post-conditioning), and the between-subjects factor was Dose (0, 0.03, 0.1, and 0.3 mg/kg). The mixed-factor ANOVA was followed by a one-way ANOVA to assess the differences in CPP scores between pre- and post-conditioning. For the evaluation of acquisition and extinction of CPP in the reinstatement experiment, a one-way ANOVA was conducted, with test phase (preconditioning, post-conditioning, and extinction) as the independent factor. For the evaluation of reinstatement of CPP, a mixed-factor ANOVA was conducted, with test phase (extinction and reinstatement) as the within-subjects factor and treatment (different doses of aripiprazole) as the between-subjects factor, followed by a one-way ANOVA to assess the differences in CPP scores between extinction and reinstatement. Fisher's Least Significant Difference (LSD) *post hoc* test was used to evaluate the differences in CPP scores between groups. Locomotor activity data were analyzed using mixed-factor ANOVA, with drug as the between-subjects factor and time as the within-subjects factor. Values of p<0.05 were considered statistically significant (SPSS, v. 13, Chicago, IL, USA).

3. Results

3.1. Effects of aripiprazole on the expression of morphine-induced CPP

As shown in Fig. 1b, CPP score was defined as the difference in time spent in the morphine-paired chamber minus the time spent in the morphine-nonpaired chamber. The ANOVA of CPP score, with the between-subjects factor dose (0, 0.03, 0.1, and 0.3 mg/kg) and the within-subjects factor test phase (pre- and post-conditioning), indicated a significant effect of test phase ($F_{1,33}$=44.67, p<0.001) but not Dose ($F_{3,33}$=0.25, p=0.86) and no Dose×test phase interaction ($F_{3,33}$=0.17, p=0.91). One-way ANOVA of the CPP score indicated a significant difference between pre- and post-conditioning with each of the aripiprazole doses (vehicle: $F_{1,17}$=14.83, p=0.001; 0.03 mg/kg: $F_{1,17}$=9.41, p=0.007; 0.1 mg/kg: $F_{1,17}$=9.86, p=0.006; 0.3 mg/kg: $F_{1,17}$=24.25, p<0.001).

3.2. Effects of aripiprazole on morphine-primed reinstatement of CPP

As shown in Fig. 2b, CPP scores from the four groups during preconditioning, post-conditioning, and extinction were combined. After conditioning training, rats showed significant expression of CPP. After extinction training, CPP was extinguished and returned to preconditioning levels. One-way ANOVA of CPP score indicated a significant effect of test phase ($F_{2,83}$=31.08, p<0.001). LSD *post hoc* tests revealed significant differences between pre- and post-conditioning (p<0.001) and between post-conditioning and extinction (p<0.001) (Fig. 2b). With regard to reinstatement (Fig. 2c), repeated-measures ANOVA of CPP score indicated a significant effect of test phase ($F_{1,24}$=13.02, p=0.001) and Dose ($F_{3,24}$=3.13, p=0.04) and a significant Dose×test phase interaction ($F_{3,24}$=4.05, p=0.02). LSD *post hoc* tests revealed significant differences between vehicle and the 0.1 and 0.3 mg/kg aripiprazole groups (p<0.05) (Fig. 2c). Subsequent one-

way ANOVA revealed significant differences between extinction and reinstatement for the vehicle and 0.03 mg/kg aripiprazole groups ($F_{1,13}$=7.05, p=0.02; $F_{1,13}$=6.61, p=0.03, respectively), but not for the 0.1 mg/kg and 0.3 mg/kg groups.

3.3. Effects of aripiprazole on locomotor activity

Spontaneous and morphine-induced locomotor activity was measured after pretreatment with saline or aripiprazole at doses ranging from 0 to 0.3 mg/kg. Upon exposure to the novel environment, all animals exhibited robust locomotor activity that decreased over a 30 min period (Fig. 3a). Repeated-measures ANOVA revealed significant main effects of time ($F_{5,150}$=158.24, p<0.001) but not dose ($F_{4,30}$=2.16, p=0.098) and no dose×time interaction ($F_{20,150}$=0.95, p=0.53).

Following this novelty phase, animals received a single injection of morphine (5.0 mg/kg) before further measurement of locomotor activity. Repeated-measures ANOVA revealed a significant main effect of time ($F_{11,330}$=4.55, p<0.001) but not dose ($F_{4,30}$=0.38, p=0.82) and no dose×time interaction ($F_{44,330}$=0.59, p=0.89) (Fig. 3b).

4. Discussion

Pretreatment with aripiprazole before a priming injection of low-dose morphine dose-dependently blocked reinstatement of extinguished morphine-induced CPP but had no significant effect on the expression of morphine-induced CPP. In fact, the lowest dose of 0.03 mg/kg aripiprazole had no effect on reinstatement after extinction of morphine-induced CPP, while administration of 0.1 and 0.3 mg/kg aripiprazole before priming with morphine reduced the place preference score in the reinstatement test. Furthermore, aripiprazole pretreatment did not affect either spontaneous or morphine-induced locomotor activity at doses of 0.03, 0.1, and 0.3 mg/kg. This effect is consistent with previous findings in which aripiprazole at 1.0–10.0 mg/kg, but not 0.3 mg/kg, inhibited apomorphine-induced stereotypy (Hirose et al., 2004), decreased D-amphetamine-induced hyperactivity (Natesan et al., 2006), and prevented locomotor hyperactivity induced by psychotomimetics and other psychostimulants, such as cocaine, ketamine, and MK-801 (Feltenstein et al., 2007; Leite et al., 2008).

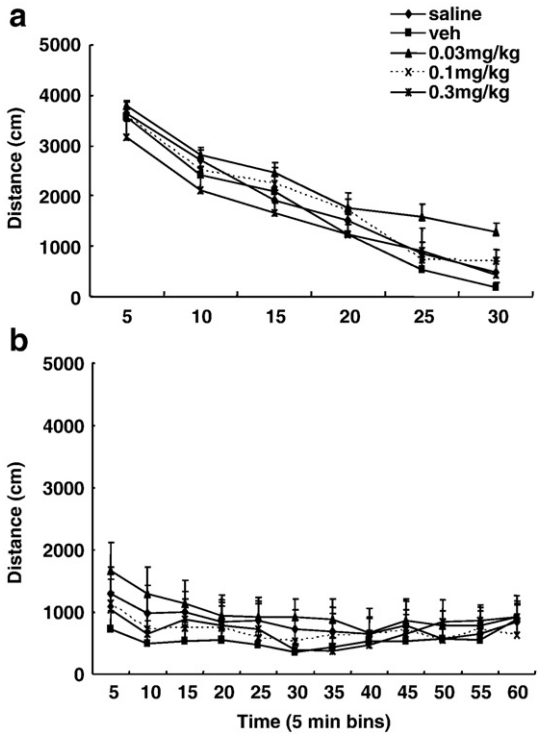

Fig. 3. Effects of aripiprazole on locomotor activity. Locomotor activity (mean±SEM) (measured in centimeters) was analyzed in 5 min sample bins. Animals received an injection of saline or aripiprazole (0–0.3 mg/kg) immediately before testing. (a) Response to initial placement in the test environment. (b) Response to morphine (5 mg/kg, s.c.) injection.

Aripiprazole pretreatment before testing of CPP expression did not significantly change the preference score, although a slight trend toward a decreased preference score was observed. The effect of higher doses of aripiprazole on the expression of morphine-induced CPP was not assessed in the present study. Higher doses may indeed blunt the reinforcing effects of morphine. Previous studies have shown that aripiprazole pretreatment reduced the subjective reinforcing effects of D-amphetamine in human subjects (Lile et al., 2005). Similar to DA receptor antagonists (Roberts and Vickers, 1984), studies using a variety of DA receptor partial agonists have shown increased cocaine self-administration (Gal and Gyertyan, 2003; Mutschler and Bergman, 2002; Pilla et al., 1999; Pulvirenti et al., 1998), suggesting that these drugs may does-dependently act as receptor antagonists in the presence of increased DA levels. The present study suggests that aripiprazole may be beneficial for reducing drug reward during periods of abstinence, rather than reducing preference scores during the expression of morphine-induced CPP, at doses of 0.03, 0.1, and 0.3 mg/kg. The possibility exists that higher doses may block the expression of morphine-induced CPP, and such studies should be conducted in the future.

Numerous reports have shown that morphine administration enhanced 5-HT and DA levels within the nucleus accumbens (Spampinato et al., 1985; Tao and Auerbach, 1995; Wise et al., 1995), but the neurotransmitter systems involved in opiate reward have not been clearly identified. Neurochemical lesions of the DA system or blockade with dopamine receptor antagonists did not affect opiate self-administration (Ettenberg et al., 1982; Gerrits and Van Ree, 1996; Pettit et al., 1984) or morphine-induced CPP (Bozarth and Wise, 1981; Mackey and van der Kooy, 1985; Smith et al., 1985; Spyraki et al., 1983). In contrast, neurochemical lesions of 5-HT terminals in the nucleus accumbens impaired morphine self-administration without affecting responding for food or water (Smith et al., 1987) and also blocked the acquisition of morphine-induced CPP (Spyraki et al., 1988). Additionally, withdrawal from chronic opiate administration decreased both DA and 5-HT transmission in the brain. Notably, reduced 5-HT levels have been linked to both depression (Dolberg et al., 1996; Maes et al., 1995) and compulsive behavior (Dolberg et al., 1996), two disorders that have been proposed to play a role in addictive behaviors (Childress et al., 1994; Koob et al., 1998; Markou et al., 1998;O'Brien et al., 1998).

As a partial agonist, aripiprazole is hypothesized to "stabilize" DA activity by effectively regulating both pre- and postsynaptic D_2/D_3 receptors (Bowles and Levin, 2003; Stahl, 2001). Aripiprazole also has high affinity for both 5-HT_{1A} (partial agonist) and 5-HT_{2A} (antagonist) receptors (Jordan et al., 2002; Lawler et al., 1999). These properties of aripiprazole may contribute to its ability to attenuate reinstatement.

First, aripiprazole preferentially binds to D_2 receptors in the rat brain *in vivo*, based on evidence that aripiprazole occupies other receptor subtypes, including D_1, D_3, 5-HT_{2A}, and 5-HT_{2C}, at 10- to 20-fold higher concentrations compared with D_2 receptors (Langlois et al., 2005). Second, as a D_2 receptor partial agonist, aripiprazole appears to block reinstatement by modulating dopaminergic tone in neural pathways implicated in relapse, including the prefrontal cortex, nucleus accumbens, hippocampus, and amygdala (Ma et al., 2007; Ventura et al., 2005; Wang et al., 2006; Zhou and Zhu, 2006). Some studies have demonstrated that aripiprazole significantly increased DA release in the hippocampus (Li et al., 2004) and prefrontal cortex (Li et al., 2004; Zocchi et al., 2005) at doses as low as 0.1 and 0.3 mg/kg, but not at higher doses up to 40 mg/kg (Assie et al., 2005; Zocchi et al., 2005). In the nucleus accumbens, aripiprazole at 3.0 and 10.0 mg/kg

(but not lower doses) significantly decreased DA release (Li et al., 2004). Interestingly, these effects were somewhat specific to DA. Extracellular levels of norepinephrine (Zocchi et al., 2005), 5-HT (Assie et al., 2005; Zocchi et al., 2005), and acetylcholine (Li et al., 2004) were generally unaltered by aripiprazole. Although no study has examined the effects of aripiprazole on amygdala neurochemistry, a recent pharmacological magnetic resonance imaging study found that aripiprazole dose-dependently decreased brain activity in the entorhinal piriform cortex, perirhinal cortex, nucleus accumbens shell, and basolateral amygdala in a rat model of psychosis (Nordquist et al., 2008). Third, the synergy between $5HT_{1A}$ agonism and $5HT_{2A}$ antagonism may provide aripiprazole with both anxiolytic and affective properties (Carson and Kitagawa, 2004; Levoyer et al., 2007; Ohlsen and Pilowsky, 2005) that may, in turn, contribute to its ability to attenuate the reinstatement of morphine-induced CPP in rats. Previous studies demonstrated that morphine withdrawal produced anxiety-like behavior that was mediated by central serotonergic neurotransmission in morphine-dependent rats. Additionally, the tonic and presynaptic inhibition of serotonergic neurons by central opioidergic neurons was reduced or blocked during morphine withdrawal, and the disinhibition of serotonergic neurons led to the expression of anxiety-like behavior (Zhang, 1997).

Because aripiprazole failed to decrease locomotor activity at doses that inhibited reinstatement of CPP in the present study, we suggest that it may have selective effects on motivated behavior. Aripiprazole failed to produce catalepsy even at high doses in previous studies (Hirose et al., 2004; Kleven et al., 2005; Natesan et al., 2006). Thus, these results suggest that aripiprazole may block the reinstatement of morphine-seeking behavior via a mechanism apart from its sedative or motor inhibitory effects.

In summary, administration of aripiprazole before morphine priming could substantially prevent morphine-induced reinstatement of CPP, with no effect on the expression of CPP or spontaneous or morphine-induced locomotor activity. The current study extends previous findings in which reinstatement of morphine-induced CPP was shown to be modulated by DA and 5-HT receptors. Aripiprazole may have the potential to be effective in preventing relapse in drug-addicted individuals.

Acknowledgments

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