Selective action of an atypical neuroleptic on the mechanisms related to the development of cocaine addiction: a pre-clinical behavioural study

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Abstract
An increased function in the mesolimbic dopaminergic system has been extensively associated with the rewarding effects of both natural stimuli and drugs of abuse. Thus, dopamine receptor blockers, such as neuroleptic drugs, can be proposed as candidates for potential therapeutic approaches to treat drug dependence. Notwithstanding, this therapeutic potential of neuroleptics critically depends on a selective action on the specific mechanisms related to the development of addiction. We compared the effects of different doses of haloperidol, ziprasidone and aripiprazole (first-, second- and third-generation neuroleptics, respectively) on spontaneous locomotor activity of mice in a novel environment, hyperlocomotion induced by acute cocaine administration and cocaine-induced locomotor sensitization by a two-injection protocol. Whereas high doses of haloperidol abolished the three behavioural paradigms without selectivity, low doses of ziprasidone selectively abolished the development of the behavioural sensitization phenomenon. Finally, low doses of aripiprazole inhibited acute cocaine-induced hyperlocomotion and behavioural sensitization without modifying spontaneous locomotor activity. Thus, aripiprazole at lower doses was the most selective antipsychotic drug concerning the inhibition of the development of behavioural sensitization to cocaine. Because locomotor sensitization in rodents has been proposed to share plastic mechanisms with drug addiction in humans, our data provide relevant suggestions to the clinical practice.

Key words: Animal models, atypical neuroleptics, behavioural sensitization, cocaine, typical neuroleptics.

Introduction
Most common drugs of abuse increase dopamine levels in the mesoaccumbens dopaminergic system, which modulates both their rewarding and psychomotor arousal effects (Wise and Bozarth, 1987; Alcaro et al., 2007). Therefore, dopaminergic drugs play an important role in the efforts to develop pharmacological therapies for the treatment of addiction. Based on pre-clinical studies, dopamine agonists and antagonists have been proposed as either drug substitutes, maintenance drugs or cocaine antagonists (Mendelson and Mello, 1996; Karila et al., 2008). Dopamine agonists, medications that directly stimulate dopamine receptors or increase the levels of synaptic dopamine, have a mechanism of action similar to stimulants, although they do not necessarily have the same activating effects on behaviour (Mariani and Levin, 2012). Within this context, agonist replacement therapy uses a drug from the same pharmacological family as the abused drug to suppress withdrawal and drug craving (Grabowski et al., 2004). This therapeutic approach has been showing as a promising treatment for cocaine dependence (Mendelson and Mello, 1996; Karila et al., 2008). However, most of these drugs are controlled substances with inherent risks of misuse and diversion, and their use in patients with substance use disorders is complex.

Regarding dopaminergic antagonists, although antipsychotics have an elevated therapeutic potential for the treatment of drug dependence, their use can lead to plastic alterations in dopaminergic systems that can increase addictive behaviour. Several studies have demonstrated that chronic treatment with conventional
neuroleptics such as haloperidol results in post-synaptic dopaminergic supersensitivity after chronic treatment (Burt et al., 1977; Prosser et al., 1988; Vital et al., 1998), a phenomenon known as dopaminergic supersensitivity because it leads to an increased responsiveness to dopaminergic agonists (Gianutsos et al., 1974; Frussa-Filho and Palermo-Neto, 1990; Waddington and Gamble, 1980; Chinen and Frussa-Filho, 1999; Andersen et al., 2005).

Within this context, neuroleptic-induced mesolimbic dopaminergic supersensitivity would enhance the effects of all drugs with the potential for abuse because, as mentioned above, all drugs of abuse increase dopamine release in the mesoaccumbens system. Indeed, the high lifetime prevalence of substance abuse disorders observed among schizophrenics has been proposed to be related to the dopaminergic supersensitivity occurring in the mesolimbic system in neuroleptic-treated patients (LeDuc and Mittleman, 1995; Kosten et al., 1996; Fukushiro et al., 2007, 2008).

Although chronic treatment with conventional neuroleptics has been related to the development of dopaminergic supersensitivity, newer atypical neuroleptics do not appear to induce the supersensitivity phenomenon (Rupniak et al., 1985; Fukushima et al., 2007, 2008; Carvalho et al., 2009). For example, ziprasidone—a second-generation antipsychotic drug that has high affinity for serotonin (5-HT) receptors, including 5-HT2A, 5-HT2C, 5-HT1A and 5-HT1B/1D, as well as dopamine D2 receptors (Schmidt et al., 2001)—and aripiprazole—a third-generation neuroleptic that appears to act as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors as well as an antagonist at the 5-HT2A receptor (Burris et al., 2002; Mamo et al., 2007)—are two of the newer atypical antipsychotics that do not appear to result in dopaminergic supersensitivity after repeated treatment (Tadokoro et al., 2001; Fukushima et al., 2007, 2008).

Apart from not producing mesolimbic dopaminergic supersensitivity after chronic treatment, a potential anti-craving neuroleptic agent must present selectivity to the plastic mesolimbic neuronal alterations that contribute to the development of drug dependence. Mesolimbic dopaminergic neurotransmission also plays a fundamental role in natural rewards such as sex (Becker, 2009), maternal behaviour (Silva et al., 2003) and novelty (Bardo et al., 1996). As a consequence, non-selective blockade of mesolimbic dopaminergic receptors could lead to a marked impairment of spontaneous behaviour. If a neuroleptic agent non-selectively blocks the neuronal mechanisms related to both the acute rewarding effects of drugs of abuse and the development of drug dependence, addictive patients will be at the risk of auto-administering overdoses as well as presenting poor adherence to neuroleptic treatment.

In rodents, locomotor stimulation has been extensively related to increased dopaminergic neurotransmission in the mesoaccumbens system (Kelly et al., 1975; Delfs et al., 1990). As a consequence, both novelty exposure and acute administration of most common drugs of abuse stimulate locomotor activity in rats and mice (Frussa-Filho and Palermo-Neto, 1991; Frussa-Filho et al., 1996; Quadros et al., 2002; Wu-Silva et al., 2011). Importantly, while there is tolerance to many of the effects of repeated drug treatments, the psychomotor and positive reinforcing effects of cocaine and other drugs of abuse often become progressively greater with repeated administration (Robinson and Berridge, 1993, 2001; De Vries et al., 1998). This phenomenon, called behavioural sensitization, has been suggested to be useful for studying the mechanisms underlying dopaminergic mesoaccumbens plasticity (Henry and White, 1991; Kalivas and Stewart, 1991; Wolf et al., 1994), which appears to share neuronal mechanisms with drug craving in humans (Robinson and Berridge, 1993). Remarkably, it has been demonstrated that it is unnecessary to repeatedly administer drugs of abuse for long periods of time to produce behavioural sensitization. Indeed, a single injection of cocaine (Valjent et al., 2010), amphetamine (Frussa-Filho et al., 2004; Chinen et al., 2006), morphine (Vanderschuren et al., 2001; Valjent et al., 2010), ethanol (Fukushiro et al., 2010) or nicotine (Frussa-Filho et al., unpublished observations) enhances locomotor stimulation produced by a subsequent injection of the respective drug given hours, days or weeks later. As shown by Valjent et al. (2010), the two-injection protocol of behavioural sensitization provides an excellent model for investigating the long-lasting effects of drugs of abuse, which is less influenced by some variables that add a level of complexity in the interpretation of behavioural responses resulting from the multiple drug exposure protocols.

The main objective of the present study was to investigate the dose-dependent effects of neuroleptics of the first (haloperidol), second (ziprasidone) and third (aripiprazole) generations in their capacity to selectively inhibit the behavioural sensitization phenomenon at doses that modify neither spontaneous locomotor activity in a novel environment nor acute cocaine-induced hyperlocomotion.

Method

Subjects

Male 3-month-old Swiss EPM-M2 mice (30–35 g) were obtained from the Centre for Development of Experimental Models in Medicine and Biology of our institution (Federal University of São Paulo – UNIFESP). Animals were housed in polypropylene cages (32 cm × 42 cm × 18 cm) under controlled temperature (22–23 °C) and lighting (12/12 h light/dark; lights on at 6:45 a.m.) conditions. Food and water were available ad libitum throughout the experiments. The experiments were performed in accordance with the National Institute of Health Guide for the care and use of laboratory animals (NIH Publications...
No 80-23, revised 1996), and animals were maintained in accordance with the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The experimental procedures were approved by the Institutional Ethical Committee of UNIFESP.

**Drugs**

Cocaine-HCl (Sigma®, Brazil), haloperidol (Janssen-Cilag®, Brazil), ziprasidone (Pﬁzer®, Brazil) and aripiprazole (Bristol-Myers Squibb®, Brazil) were used. Cocaine was diluted in saline. Haloperidol was dissolved in lactic acid and diluted to the correct concentrations in distilled water. Ziprasidone and aripiprazole were dissolved in Tween 80 and diluted in saline. Solutions of saline, lactic acid+distilled water and Tween 80+saline were used as vehicles for cocaine, haloperidol and ziprasidone/aripiprazole, respectively. All solutions were given intra-peritoneally at the volume of 10 ml/kg of body weight.

**Open-field evaluation**

Locomotor activity was measured in the open field apparatus, as previously described by Chinen et al. (2006). It consisted in a circular wooden arena (40 cm in diameter and 50 cm high) with an open top and a floor divided into 19 squares. Hand-operated counters were used to score the locomotion frequency (total number of any square entered) during 10-min sessions by an observer, who was blind to the treatment allocation. Ten-minute sessions were proposed because it has been shown that even shorter periods are effective in reliably evaluating the effects of drugs acting on dopaminergic systems (Frussa-Filho and Palermo-Neto, 1990; Vital et al., 1995; Araujo et al., 2005; Castro et al., 2006), particularly cocaine-induced stimulant effect and behavioural sensitization (Fukushiro et al., 2007, 2008).

**Experimental procedure**

For the first experiment, 70 mice were allocated into five groups that were acutely treated with either vehicle (V; \(n=30\)) or haloperidol (H) at the doses of 0.01, 0.05, 0.10 and 2.5 mg/kg (\(n=10\) for each group) followed by initial exposure to the open-field environment 30 min after treatment to quantify their locomotor activities. The following groups were compared in the first open-field exposure: V-S, V-C, H 0.01-C, H 0.05-C, and H 0.10-C. Once removed from the apparatus, 20 animals from the vehicle group received a saline injection, and the remaining 10 mice were treated with 10 mg/kg cocaine (C). All animals pretreated with haloperidol also received 10 mg/kg cocaine. Five minutes after the injections, mice were placed in the open-field for locomotion quantification. Thus, the following groups were formed: V-S, V-C, H 0.01-C, H 0.05-C, and H 0.10-C-C. Seven days later, 10 animals that were treated with vehicle and saline on the previous week received saline again (forming the V-S-S group) and the other 10 mice were treated with 10 mg/kg cocaine (C). All animals pretreated with haloperidol also received 10 mg/kg cocaine. Five minutes after administration of either saline or cocaine, the animals were returned to the open-field for locomotion quantification. Thus, the following groups were compared in the second open-field exposure: V, H 0.01, H 0.05, H 0.10, and H 0.25. Once removed from the apparatus, 20 animals from the vehicle group received a saline injection, and the remaining 10 mice were treated with 10 mg/kg cocaine (C). All animals pretreated with haloperidol also received 10 mg/kg cocaine. Five minutes after administration of either saline or cocaine, the animals were returned to the open-field for locomotion quantification. Thus, the following groups were formed: V-S, V-C, H 0.01-C, H 0.05-C, H 0.10-C-C, and H 0.25-C-C.

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**Table 1. Design of expt 1**

<table>
<thead>
<tr>
<th>Groups</th>
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<td>H 0.01-C-C</td>
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<td>H 0.05-C-C</td>
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VEH – vehicle, i.p. injection; HAL 0.01 – haloperidol 0.01 mg/kg, i.p. injection; HAL 0.05 – haloperidol 0.05 mg/kg, i.p. injection; HAL 0.10 – haloperidol 0.10 mg/kg, i.p. injection; HAL 0.25 – haloperidol 0.25 mg/kg, i.p. injection; COC – cocaine 10 mg/kg, i.p. injection; SAL – saline, i.p. injection; OFQ – open-field locomotor activity quantification for 10 min. The same experimental design was used for expts 2 and 3, with the exception that haloperidol was replaced with either ziprasidone (at the doses of 0.1, 0.5, 1.0 and 2.5 mg/kg) or aripiprazole (at the doses of 0.1, 0.5, 1.0 and 2.5 mg/kg), respectively.
Expts 2 and 3 were performed following the protocol for expt 1. Haloperidol was replaced with ziprasidone at the doses of 0.1, 0.5, 1.0 or 2.5 mg/kg in the second experiment and with aripiprazole at the doses of 0.1, 0.5, 1.0 or 2.5 mg/kg in the third experiment.

Statistical analysis
Before conducting the parametric tests, all variables were checked for normality (Shapiro–Wilk test) and homogeneity (Levene’s test), which validated the use of the parametric test. Data were analysed by one-way analysis of variance (ANOVA) followed by Tukey’s test for multiple comparisons when necessary. A probability of $p<0.05$ was considered significant.

Results

Experiment 1: effects of haloperidol on spontaneous locomotor activity, acute cocaine-induced hyperlocomotion and cocaine-induced behavioural sensitization

In the first behavioural evaluation (spontaneous locomotor activity in a novel environment), ANOVA revealed significant differences between groups $[F(4,65) = 6.75; p<0.0001]$. Haloperidol at the doses of 0.01 and 0.05 mg/kg did not modify spontaneous locomotor activity compared with the vehicle group (Tukey’s test, $p>0.05$) (Fig. 1a). At the doses of 0.10 and 0.25 mg/kg, haloperidol led to a significant decrease in the locomotion frequency compared with the vehicle group (Tukey’s test, $p<0.05$). These data show that haloperidol significantly reduces spontaneous locomotor activity in a novel environment at the doses of 0.10 and 0.25 mg/kg, but not at lower doses.

In the evaluation of acute cocaine-induced hyperlocomotion after haloperidol treatment, statistically significant differences were observed between groups $[F(5,64) = 11.54; p<0.0001]$. An acute cocaine effect was observed based on the significantly higher locomotion frequency in the vehicle–cocaine group compared with the vehicle–saline group (Tukey’s test, $p<0.01$) as shown in Fig. 1b. Haloperidol at the doses of 0.01 and 0.05 mg/kg did not affect cocaine-induced hyperlocomotion. However, at the doses of 0.10 and 0.25 mg/kg, haloperidol abolished the acute stimulating effect of cocaine (Tukey’s test, $p<0.05$). These data indicate that haloperidol abolishes acute cocaine-induced hyperlocomotion only at doses that also reduce spontaneous locomotor activity in a novel environment.

Fig. 1. Locomotor activity quantification in the open-field apparatus demonstrating the behavioural effects of i.p. treatment with either haloperidol (0.01, 0.05, 0.10 or 0.25 mg/kg) or vehicle on (a) spontaneous locomotor activity in a novel environment and its subsequent effects on (b) acute cocaine-induced hyperlocomotion and (c) cocaine-induced behavioural sensitization after a 7-d interval. Data are reported as mean±S.E.M. $*p<0.05$ compared with vehicle (a), vehicle–saline (b) or vehicle–saline–saline (c); $**p<0.05$ compared with vehicle–cocaine (b) or vehicle–cocaine–cocaine (c); $***p<0.05$ compared with vehicle–saline–cocaine (c). One-way analysis of variance (ANOVA) followed by Tukey’s test.
After 1 wk, cocaine-induced locomotor sensitization was evaluated, and statistically significant differences were observed \([F(6,63)=12.99; p<0.0001]\). As shown in Fig. 1c, an acute cocaine injection promoted an enhanced locomotion frequency (vehicle–saline–cocaine > vehicle–saline–saline), which was potentiated in the vehicle–cocaine–cocaine group (vehicle–cocaine–cocaine > vehicle–saline–cocaine) (Tukey’s test, \(p<0.05\)), indicating the development of behavioural sensitization. Treatment with haloperidol at the doses of 0.01 and 0.05 mg/kg before the first cocaine administration did not affect the cocaine-induced sensitization expressed 1 wk later. However, pre-treatment with 0.10 and 0.25 mg/kg haloperidol prevented the development of behavioural sensitization, as shown by a significant decrease in the locomotor activity of these groups compared with the vehicle–cocaine–cocaine group (Tukey’s test, \(p<0.01\)). These data together indicate that haloperidol prevents the induction of cocaine-induced behavioural sensitization but only at doses that also inhibit spontaneous locomotor activity in a novel environment and acute cocaine-induced hyperlocomotion.

**Experiment 2: effects of ziprasidone on spontaneous locomotor activity, acute cocaine-induced hyperlocomotion and cocaine-induced behavioural sensitization**

In the first behavioural evaluation (spontaneous locomotor activity in a novel environment), ANOVA revealed significant differences between groups \([F(4,65)=11.18; p<0.0001]\). Ziprasidone at the doses of 0.1 and 0.5 mg/kg did not modify spontaneous locomotor activity compared with the vehicle group (Tukey’s test, \(p>0.05\)) (Fig. 2a). At the doses of 1.0 and 2.5 mg/kg, ziprasidone led to a significant decrease in the locomotion frequency compared with the vehicle group (Tukey’s test, \(p<0.01\)). These data show that ziprasidone significantly reduces spontaneous locomotor activity in a novel environment at the doses of 1.0 and 2.5 mg/kg, but not at lower doses.

In evaluating acute cocaine-induced hyperlocomotion after ziprasidone treatment, statistically significant differences were observed between groups \([F(5,64)=10.86; p<0.0001]\). An acute cocaine effect was observed based on the significantly higher locomotion frequency presented by the vehicle–cocaine group compared with the vehicle–saline group (Tukey’s test, \(p<0.001\)) as shown in Fig. 2b. Ziprasidone at the doses of 0.1 and 0.5 mg/kg did not affect acute cocaine-induced hyperlocomotion. However, at the doses of 1.0 and 2.5 mg/kg, ziprasidone abolished the acute stimulating effect of cocaine (Tukey’s test, \(p<0.001\)). These data indicate that, like haloperidol, ziprasidone vehicle–cocaine (b) or vehicle–cocaine–cocaine (c); \(p<0.05\)

compared to vehicle–saline–cocaine (c). One-way analysis of variance (ANOVA) followed by Tukey’s test.
abolishes acute cocaine-induced hyperlocomotion only at doses that also reduce spontaneous locomotor activity in a novel environment.

After 1 wk, cocaine-induced locomotor sensitization was evaluated and statistically significant differences were observed [F(6,63)=9.03; p<0.0001]. As shown in Fig. 2c, an acute cocaine injection promoted an enhanced locomotion frequency (vehicle–saline–cocaine>vehicle–saline–saline), which was potentiated in the vehicle–cocaine–cocaine group (vehicle–cocaine–cocaine>vehicle–saline–cocaine) (Tukey’s test, p<0.05), indicating the development of behavioural sensitization. Treatment with ziprasidone at all doses (0.1 to 2.5 mg/kg) before the first cocaine administration prevented the development of behavioural sensitization, expressed 1 wk later. Indeed, the locomotor activity of groups pre-treated with ziprasidone was significantly lower than that observed in the vehicle–cocaine–cocaine group (Tukey’s test, p<0.05). These data together indicate that, unlike haloperidol, low doses of ziprasidone selectively prevent the development of cocaine-induced behavioural sensitization without modifying either spontaneous locomotor activity in a novel environment or acute cocaine-induced hyperlocomotion.

**Experiment 3: effects of aripiprazole on spontaneous locomotor activity, acute cocaine-induced hyperlocomotion and cocaine-induced behavioural sensitization**

In the first behavioural evaluation (spontaneous locomotor activity in a novel environment), ANOVA revealed significant differences between groups [F(4,65)=7.50; p<0.0001]. Aripiprazole at the doses of 0.1 and 0.5 mg/kg did not modify spontaneous locomotor activity compared with the vehicle group (Tukey’s test, p>0.05) (Fig. 3a). At the doses of 1.0 and 2.5 mg/kg, aripiprazole led to a significant decrease in the locomotion frequency compared with the vehicle group (Tukey’s test, p<0.01). These data show that aripiprazole significantly reduces spontaneous locomotor activity in a novel environment at the doses of 1.0 and 2.5 mg/kg, but not at lower doses.

In the evaluation of acute cocaine-induced hyperlocomotion after aripiprazole treatment, statistically significant differences were observed between groups [F(5,64)=38.25; p<0.0001]. An acute cocaine effect was observed based on the significantly higher locomotion frequency in the vehicle–cocaine group compared with the vehicle–saline group (Tukey’s test, p<0.001) as shown in Fig. 3b. Aripiprazole at all doses (0.1 to 2.5 mg/kg) abolished acute cocaine-induced hyperlocomotion (b) or vehicle–saline–saline (c); *p<0.05 compared with vehicle–cocaine (b) or vehicle–cocaine–cocaine (c); p<0.05 compared with vehicle–saline–cocaine (c) group. One-way analysis of variance (ANOVA) followed by Tukey’s test.
(Tukey’s test, \( p<0.001 \)). These data indicate that, unlike haloperidol and ziprasidone, low doses of aripiprazole prevent acute cocaine-induced hyperlocomotion without modifying spontaneous locomotion in a novel environment.

After 1 wk, cocaine-induced locomotor sensitization was evaluated, and statistically significant differences were observed [\( F(6,63)=11.11; p<0.0001 \)]. As shown in Fig. 3c, an acute cocaine injection promoted an enhanced locomotion frequency (vehicle–saline–cocaine> vehicle–saline–saline), which was potentiated in the vehicle–cocaine–cocaine group (vehicle–cocaine–cocaine> vehicle–saline–cocaine) (Tukey’s test, \( p<0.001 \)), indicating the development of behavioural sensitization. Treatment with aripiprazole at all doses (0.1 to 2.5 mg/kg) before the first cocaine administration prevented the development of behavioural sensitization, expressed 1 wk later. Indeed, the locomotor activity of the groups pre-treated with aripiprazole was significantly lower than that observed in the vehicle–cocaine–cocaine group (Tukey’s test, \( p<0.05 \)). These data together indicate that, unlike haloperidol and ziprasidone, low doses of aripiprazole prevent both acute cocaine-induced hyperlocomotion and the development of cocaine-induced behavioural sensitization without modifying spontaneous locomotor activity in a novel environment.

**Discussion**

The most important findings of the present study were the following: (1) haloperidol had a non-specific effect on cocaine-induced behavioural sensitization, acute cocaine-induced hyperlocomotion and spontaneous locomotor activity in a novel environment, in that this drug inhibited all of these behavioural phenomena at the same doses; (2) ziprasidone showed higher sensitivity in preventing the development of cocaine-induced behavioural sensitization because it was attenuated by lower doses than those required to reduce acute cocaine response and spontaneous locomotion; (3) aripiprazole was the only drug that showed selectivity to both acute and sensitized cocaine responses in that it blocked these phenomena at doses that did not change the spontaneous locomotor activity in a novel environment.

The three antipsychotics used in the present study have a common feature: they are either full or partial antagonists at dopamine D\(_2\) receptors (Tadori et al., 2002), blocking D\(_2\) autoreceptors as well as D\(_2\) post-synaptic receptors. Antagonism at the autoreceptors increases dopamine transmission, serotonergic transmission is necessary for spontaneous exploratory behaviour (Fink and Smith, 1980). Acutely administered cocaine binds to the dopamine transporter and inhibits its extracellular reuptake (Ritz et al., 1987), prolonging the stimulation of dopamine D\(_2\) receptors by the endogenous neurotransmitter, which results in increased locomotor activity in rodents (Einhorn et al., 1988; Ellinwood et al., 2000). Repeatedly stimulating dopamine D\(_2\) autoreceptors leads to a marked sub-sensitivity of these receptors (Henry et al., 1989, 1998; Ackerman and White, 1990) and an increase in the basal activity of dopamine neurons (Henry et al., 1998). These neuroadaptations have been suggested to be related to sensitized behaviour in mice (Kalivas and Stewart, 1991; Henry et al., 1998; Brown et al., 2011), even in a two-injection protocol (Keller et al., 1992). In this scenario, the behavioural effects of haloperidol, ziprasidone and aripiprazole were distinguished by their selectivity, which can be explained by their different pharmacodynamic features. For instance, haloperidol is a selective antagonist at dopamine D\(_2\) receptors (Niemeegeers, 1983); by blocking these receptors, it had a non-specific effect: the inhibition of cocaine-induced hyperlocomotion and the development of behavioural sensitization only at doses that initially reduced spontaneous locomotion.

Part of the non-specific effect observed after haloperidol treatment was also observed in ziprasidone treatment. Ziprasidone inhibited acute cocaine effects only at doses that also reduced spontaneous locomotor activity. Nevertheless, unlike haloperidol, ziprasidone inhibited the development of cocaine-induced behavioural sensitization at doses that did not affect either spontaneous locomotor activity or acute cocaine-induced hyperlocomotion. Unlike haloperidol, ziprasidone has a high affinity for both dopamine D\(_2\) and 5-HT receptors, acting as a potent 5-HT\(_{2A}\) receptor antagonist (Schmidt et al., 2001). Within this context, there is extensive experimental evidence demonstrating that in addition to dopaminergic transmission, serotonergic transmission is necessary for the development of cocaine-induced behavioural sensitization. It has been shown that repeated cocaine treatment in mice simultaneously leads to an increase in the locomotor activity and in the cortical serotonin response (Lanteri et al., 2008). Importantly, the repeated administration of the 5-HT releaser p-chloroamphetamine resulted in the development of behavioural sensitization in mice (Itzhak et al., 2004). Additionally, some data showed that behavioural sensitization to cocaine can be prevented by the administration of the 5-HT\(_{2A}\) receptor antagonists ritanserin (Ago et al., 2006) and SR 46349B (Salomon et al., 2006; Lanteri et al., 2008) during exposure to this drug of abuse. Taken together, these findings are in line with the higher selectivity of ziprasidone in inhibiting cocaine-induced behavioural sensitization compared with haloperidol.
Aripiprazole was the most selective antipsychotic drug concerning the inhibition of cocaine-induced behavioural effects. It was more effective in blocking the acute effects of cocaine than in attenuating spontaneous locomotion. These results are in line with previous data showing that aripiprazole is effective in preventing the increase in locomotion induced by acute cocaine injection in mice at doses that do not change basal motor activity (Leite et al., 2008). This selectivity could be explained by the fact that aripiprazole acts as a partial agonist at dopamine D2 receptors (Burris et al., 2002), which makes it a dopamine system stabilizer. Partial agonists at D2 receptors selectively antagonize dopaminergic function resulting from high levels of synaptic dopamine (Tadori et al., 2009). In addition, clinical studies have been suggesting that antipsychotic medications such asquetiapine and aripiprazole, which show less D2 antagonism, appear to reduce substance use, whereas those that exert more antagonistic effect at dopamine D2 receptors, such as haloperidol, appear to have limited benefits and perhaps may increase the substance use, as mentioned before (Sattar et al., 2004; Kennedy et al., 2008; Martinotti et al., 2008; Vorspan et al., 2008; Brunetti et al., 2012).

However, with regards to the control group, the spontaneous locomotor activity verified in a novel environment had the same magnitude as that observed after acute cocaine administration in previously habituated mice. These data indicate that synaptic levels of dopamine were at the same magnitude during the recording of the spontaneous locomotion in a novel environment compared with acute cocaine-induced hyperlocomotion after environmental habituation. Therefore, the partial agonist activity of aripiprazole at the D2 receptor alone does not explain the specificity of this drug for the blockade of acute cocaine-induced hyperlocomotion. Indeed, the occupation of the dopamine transporter by selective dopamine reuptake blockers does not lead to cocaine-like behavioural profiles (Rothman et al., 1992; Newman et al., 1994), indicating that an increase in the extracellular dopamine concentrations might be a necessary but insufficient condition for the locomotor stimulant effects of this drug. In this scenario, aripiprazole is also a known serotonin system stabilizer with potent partial agonist activity at serotonin 5HT1A receptors (Inoue et al., 1996; Jordan et al., 2001). Selective drugs for the 5-HT1A receptor have been found to modulate cocaine-induced locomotor stimulation (Herges and Taylor, 1998; De La Garza and Cunningham, 2000). Particularly, specific 5-HT1A receptor antagonism inhibits the locomotor stimulant effect of cocaine without influencing either locomotor baseline behaviour or dopamine release in the nucleus accumbens (Carey et al., 2002; Müller et al., 2002a,b). Thus, the specific action on serotonin 5HT1A receptors could explain the selectivity of aripiprazole in inhibiting acute cocaine effects at doses that do not reduce spontaneous locomotor activity. Importantly, aripiprazole also blocked the development of behavioural sensitization to cocaine at lower doses than those necessary for the inhibition of spontaneous locomotor activity in a novel environment. This was most likely attributable to its action as a serotonin 5HT3A receptor antagonist (Burris et al., 2002; Tadori et al., 2002), as was discussed for ziprasidone.

Although one must always be wary of extrapolating clinical relevance from animal data, from a clinical perspective haloperidol would not be the best choice for preventive addiction therapies. Although it would be effective in inhibiting the mechanisms associated with the development of addiction, this would occur only at doses that per se would produce relevant and harmful collateral effects on natural behaviours related to mesoaccumbens dopaminergic activation. This would not be the case for ziprasidone because this drug blocked the development of behavioural sensitization at doses that did not affect either spontaneous locomotor activity or acute cocaine-induced hyperlocomotion.

Aripiprazole, in its turn, would be expected to induce the same inhibitory effect on the development of addiction-related mechanisms, but always at the expense of the loss of the acute cocaine stimulant effects. This would be dangerous regarding addiction because aripiprazole could lead drug abusers to a state of overdose in an acute relapse to the drug use by enhancing cocaine consumption owing to its lack of effect. This hypothesis is consistent with clinical data demonstrating that aripiprazole increases smoked cocaine self-administration in humans (Haney et al., 2011). In this study, it was suggested that aripiprazole increased self-administration to compensate for a blunted subjective cocaine effect because it decreased the ratings of good drug effect and cocaine quality following cocaine consumption. On the other hand, to feel a blunted effect is not a rewarding strategy, and after an acute relapse, this effect could even prevent the drug use in the long term. Ziprasidone blocked the development of behavioural sensitization at doses that affected neither spontaneous locomotor activity in a novel environment nor acute cocaine-induced hyperlocomotion. Therefore, low doses of this antipsychotic should be expected to impair the progress of addiction mechanisms without attenuating the acute cocaine stimulant effect, preventing overdose in acute relapse events. However, in the long term, this therapeutic strategy would not represent a cure for addiction because the drug abuser might remain using the substance for long periods, which could even represent a risk if the patient quit the use of the medicine. In addition, it has been demonstrated that ziprasidone might have an influence on the QT interval in humans (Tan et al., 2009; Witsil et al., 2012), and its use in cocaine abusers should have to be monitored.

Together, the above-discussed considerations suggest that aripiprazole would be the best choice for clinical preventive addiction therapies, providing relevant suggestions to the clinical practice. This is consistent with recent studies demonstrating that aripiprazole at lower


