EFFECTS OF ARIPIPRAZOLE ON ALCOHOL INTAKE IN AN ANIMAL MODEL OF HIGH-ALCOHOL DRINKING

KIMMO INGMAN1*, JOHANNA KUPILA1, PETRI HYYTIÄ2 and ESA R. KORPI3

1Department of Pharmacology and Clinical Pharmacology, University of Turku, FI-20520 Turku, Finland; 2Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland and 3The Institute of Biomedicine, Pharmacology, Biomedicum Helsinki, University of Helsinki, FI-00014 Helsinki, Finland

(Received 7 November 2005; first review notified 3 January 2006; in revised form 6 February 2006; accepted 31 March 2006; advance access publication 9 May 2006)

Abstract — Aims: This study examined the effects of aripiprazole, a novel atypical antipsychotic drug with partial agonist properties at dopamine D2 receptors, on the voluntary limited access alcohol drinking of alcohol-preferring AA (Alko, Alcohol) rats. Methods: AA rats were taught to drink 10% alcohol in a 4 h limited access paradigm. Effects of acute aripiprazole (0, 0.3, 1.0, and 3.0 mg/kg) on the limited access alcohol drinking were studied. In repeated treatment experiment, aripiprazole (0, 1.0, and 6.0 mg/kg) was administered once daily over five successive days. To reveal any effect by aripiprazole not selective for alcohol drinking, 0.025% saccharin solution was substituted for alcohol during the 4 h limited access, and acute treatments were repeated. The effects of aripiprazole on ambulatory locomotor activity were tested with doses that were used in the acute experiments. Results: Acute aripiprazole at the doses of 0.3, 1.0, and 3.0 mg/kg had no effect on alcohol drinking. Repeated treatment with the aripiprazole dose of 6.0 mg/kg significantly diminished alcohol drinking at the 1 h time point. This dose had no effect on saccharin drinking when given acutely. Acute aripiprazole at the doses of 1.0, 3.0, and 6.0 mg/kg significantly suppressed locomotor activity. Conclusions: Aripiprazole decreased limited access alcohol drinking in AA rats, but only at a high dose that also strongly suppressed locomotor activity.

INTRODUCTION

Atypical antipsychotic drugs decrease alcohol drinking and promote abstinence in humans (Hutchison et al., 2003; Potvin et al., 2003; Monnelly et al., 2004). However, in controlled clinical studies the results have been modest (Soyka and De Vry 2000; Potvin et al., 2003; Guardia et al., 2004), and atypical antipsychotics cause adverse effects that may limit their use in alcoholics without an additional psychiatric indication. Aripiprazole, a novel atypical antipsychotic drug, differs from the other atypical antipsychotics in that it is a partial agonist at 5-HT1A receptors (Shapiro et al., 1999; Shapiro et al., 2003) mixed partial agonist–antagonist ligand at dopamine D2 receptors (Burr et al., 2002). Moreover, the type of aripiprazole’s effect at dopamine D2 receptor appears to depend on the environmental context of the receptor (Kikuchi et al., 1995; Lawler et al., 1999). Aripiprazole displays a high affinity for dopamine D3 receptors (Shapiro et al., 2003). Substantial binding by aripiprazole occurs at serotonin receptors. Aripiprazole is a partial agonist at 5-HT1A receptors (Shapiro et al., 2003; Marona-Lewicka and Nichols, 2004), partial agonist at 5-HT2A and 5-HT2C receptors (Shapiro et al., 2003), inverse agonist at 5-HT2B receptors (Shapiro et al., 2003), and an antagonist at 5-HT6 and 5-HT7 receptors (Lawler et al., 1999). It has been suggested that these unique pharmacological characteristics of aripiprazole, possibly making it a stabilizer at pathologically disturbed dopamine and serotonin systems (Burr et al., 2002; Potkin et al., 2003), contribute to its unique properties in the treatment of either negative or positive symptoms in schizophrenic patients (Potkin et al., 2003).

Neuropathology in alcoholism (Liu and Weiss, 2002; Weiss and Porrin, 2002; Gonzales et al., 2004) and schizophrenia (Freedman, 2003) implies alterations in the mesocorticolimbic dopamine transmission. Acute alcohol exposure often increases dopamine release in the mesolimbic dopamine pathway (Weiss et al., 1993; Yim and Gonzales 2000; Boileau et al., 2003). High alcohol consumption is associated with a reduction in the availability of striatal dopamine D2 receptors and altered striatal dopamine function in man (Heinz et al., 2005; Martinez et al., 2005). In animal models, withdrawal from chronic alcohol results in a reduced spontaneous activity of dopamine neurons, and subsequently decreased dopamine release at neuronal terminals (Shen, 2003). This reduced dopamine activity in alcohol withdrawal has been suggested to result from brain overexcitation, followed by depolarization inactivation of dopamine neurons (Shen, 2003). Additionally, it has been suggested that mesolimbic dopamine transmission mediates the motivating and incentive properties of alcohol-associated stimuli and cues (Gonzales and Weiss, 1998; Liu and Weiss, 2002; Heinz et al., 2004). Thus, in this context of altered brain dopamine function in different stages of the pathogenesis of alcoholism, and recovering, the dopamine stabilizing effect of aripiprazole (Lile et al., 2005) might provide a novel therapeutic approach in treating patients abusing alcohol (Brown et al., 2005; Warsi et al., 2005).

This study was designed to investigate the effects of aripiprazole treatment on alcohol drinking in AA rats that represent an animal model of high-alcohol drinking (Sinclair et al., 1989). In addition, the effects of aripiprazole on the limited access saccharin drinking and ambulatory locomotor activity of AA rats were measured in order to assess the selectivity of aripiprazole’s effects on alcohol drinking.

MATERIALS AND METHODS

Experimental animals and housing conditions

Thirty male AA rats were used. Animals were 10 weeks old and weighed between 249 and 300 g when they were transferred from National Public Health Institute, Helsinki, to

© The Author 2006. Published by Oxford University Press on behalf of the Medical Council on Alcohol. All rights reserved
Turku. Animals were individually housed in transparent plastic cages (36 cm × 21 cm, 18 cm high) that were located in an experiment room under controlled housing conditions (temperature 21 ± 3°C, air humidity 55 ± 5%, 12:12 h light/dark cycle). Animals had free access to tap water and food (SDS RMI SQC, Special Diet Service, Witham, Essex, England) during the study, except for the situations as noted below. The laboratory animal committee of University of Turku approved all experimental procedures.

**Drugs**

Alcohol solution (10%, v/v) was prepared by diluting 99.5% ethanol (Primalco, Rajamäki, Finland) with tap water. Aripiprazole (a gift from Bristol-Myers Squibb Company) was suspended in 2.5% Tween-80 (Sigma-Aldrich) solution in distilled water. Aripiprazole suspensions were prepared before each experiment and were kept in a magnetic stirrer throughout the experiment. The aripiprazole suspensions as well as saline and vehicle injections were administered intraperitoneally (i.p.) in a volume of 1.0 ml/kg of body weight.

The drug-free wash-out periods (at least 6 days) between experiments were employed in order to ensure complete elimination of aripiprazole from the brain \([t_{1/2} = 1.8–2.0\ h](\text{Shimokawa et al.}, 2005)\). In the acute experiment, the highest aripiprazole dose (3.0 mg/kg) was chosen because aripiprazole starting at 2.5 mg/kg has been shown to significantly antagonize behavioural dopamine agonistic effects in rats (Semba et al., 1995) but also to decrease dopamine release in the rat brain (Semba et al., 1995; Li et al., 2004) which indicates concomitant dopamine agonistic activity. Aripiprazole 3.0 mg/kg decreases dopamine release in the nucleus accumbens (Li et al., 2004). The aripiprazole dose of 1.0 mg/kg was chosen because doses starting from 0.62 mg/kg have been shown to produce a significant 5-HT1A receptor agonist-like effect (Marona-lewicka and Nichols, 2004) with concomitant dopamine D2 receptor blockade (Semba et al., 1995). The aripiprazole dose of 0.3 mg/kg was chosen because it has been shown to facilitate dopamine release in the prefrontal cortex and hippocampus, which indicates D2 antagonistic activity, but it did not affect dopamine release in the nucleus accumbens (Li et al., 2004).

In the repeated dosing study, the aripiprazole dose of 6.0 mg/kg was chosen because the highest acute dose (3.0 mg/kg) was not effective, and we wanted to see whether the dose increase would cause a reduction in alcohol drinking. This dose was supposed to produce more robust dopamine D2 receptor blockade than the 3.0 mg/kg dose (Semba et al., 1995). The aripiprazole dose of 1.0 mg/kg was included in the experiment because we wanted to see whether repeated administration with this 5-HT1A receptor-activating dose would affect the alcohol drinking.

**Limited access alcohol drinking paradigm**

Animals were trained to voluntarily drink alcohol solution (10%, in tap water) (Sinclair et al., 1992) in a continual access, free choice situation. During this training phase, animals had alcohol as the only drinking fluid available for the first 3 days, and thereafter the animals had a 24 h free choice between alcohol and tap water over 4 weeks. Positions of the bottles on the cages were exchanged every day. During the last 3 weeks of free access, the average alcohol intake was constantly over 50% (v/v) of the total fluid intake, and on the last day of 24 h free choice period the average alcohol preference was 70.8 ± 3.4% (mean ± SEM, n = 30). The average consumption of ethanol over the last 3 days of 24 h free choice was 6.48 ± 0.29 g/kg (mean ± SEM, n = 30) per day. Limited access paradigm (Sinclair et al., 1992), carried out in the light phase between 8 a.m. and 2 p.m., was started by restricting the availability of 10% alcohol solution (in Richter tubes) to 4 h every working day. Rats were weighed prior to each limited access drinking session. Alcohol consumption was recorded to the nearest 0.2 ml at 1 h after the beginning of each session, and at the end of the 4 h session. During the 4 h alcohol drinking session, rats consumed tap water only negligibly, which made the determination so unreliable that only 24 h water drinking (in grams) was recorded.

**Alcohol drinking experiments**

**Acute treatment.** Animals received an i.p. injection of saline (Natrosteril 0.9%, Orion, Finland) 30 min before the beginning of the baseline alcohol drinking session. One hour and 4 h alcohol drinking, and 24 h water drinking were recorded. Thereafter, animals were divided into four treatment groups so that the groups were equal with respect to their 4 h alcohol consumption levels. In the following experiment with active drugs, animals in each treatment group received one of the following treatments: vehicle \((n = 8), 0.3\ mg/kg (7), 1.0\ mg/kg (7),\) or 3.0 mg/kg (7) of aripiprazole 30 min before access to alcohol solution. One hour and 4 h alcohol drinking and 24 h water drinking were recorded.

**Repeated treatment.** After the acute experiment, animals were allowed 6 days of wash-out before baseline limited access drinking session with saline injections was carried out as described above. To test for repeated dosing effects, rats were divided into three treatment groups as follows: vehicle \((10), 1.0\ mg/kg (9),\) and 6.0 mg/kg (10) of aripiprazole. Animals that received high aripiprazole dose in the acute experiment were allocated to vehicle or low aripiprazole dose group in the repeated experiment, and vice versa. Additionally, the animals were assembled into treatment groups so that the baseline 4 h alcohol drinking levels between the groups were balanced. Rats were weighed daily before experimental procedures, and the individual drug dose for each animal was calculated. Animals were daily administered with treatments over five consecutive days, and alcohol as well as water consumption was recorded as described above.

**Saccharin drinking experiment**

The contents of Richter tubes were changed from 10% alcohol to 0.025% (w/v) saccharin/tap water solution, and the 4 h limited access procedure was continued. Saccharin concentration 0.025% was chosen because in previous experiments we have observed that AA rats drink larger volumes of 0.1% saccharin than 10% alcohol solution (Ingman et al., 2003). The total baseline drinking volumes for 1 h and 4 h saccharin
were 4.42 ± 0.88 and 5.66 ± 0.99 ml (mean ± SEM, \( n = 29 \)), respectively. For the sake of comparison, total baseline drinking volumes for 1 h and 4 h alcohol drinking in the acute treatment experiment were 3.95 ± 0.42 and 5.03 ± 0.44 ml (mean ± SEM, \( n = 29 \)), respectively. After 2 weeks of limited access saccharin drinking, rats received saline injections 30 min prior to the saccharin drinking session preceding the experiment with active treatments. Saccharin consumption was recorded at 1 h time point, and at the end of the 4 h drinking session. Twenty-four hour water drinking was recorded. Thereafter, rats were divided into four treatment groups as follows: vehicle (8), 0.3 mg/kg (7), 1.0 mg/kg (7), and 6.0 mg/kg (7) of aripiprazole. Aripiprazole doses were counterbalanced for each animal with respect to treatments the animals received in previous experiments. Saccharin and water consumption was recorded as in the baseline session.

**Determination of locomotor activity**

Locomotor activity was measured using a photobeam activity system (PAS, San Diego Instruments Inc., San Diego, CA, USA), which was composed of eight measurement enclosures consisting of a photobeam frame. The cage rack enclosures were assembled by placing each enclosure around a standard animal cage made of transparent plastic (see above). The frame was positioned 4 cm off the cage floor and contained seven photobeams spaced evenly along the longitudinal axis. A microcomputer counted and recorded the breaks of alternate beams that constituted a measure of horizontal ambulatory locomotor activity.

Rats were allowed 8–11 days of wash-out between saccharin drinking and locomotor activity experiments. Following one 1 h session of acclimatization to the test apparatus, rats were assigned into four treatment groups as follows: vehicle (7), 0.3 (7), 1.0 (7), and 6.0 mg/kg (8) of aripiprazole. The treatments were counterbalanced with respect to the treatments that the animals received in the previous experiments. After the rats were weighed, they received treatment injections and were placed into their home cages located in the experiment room. Thirty minutes locomotor activity measurement session was performed 30 min and 3 h after the injections. For measurement sessions, rats were removed from their home cages and placed into locomotor activity measurement cages. Animals were returned back to their home cages after each measurement session. After these experiments were performed, an identical locomotor activity experiment, in which the vehicle-treated animals received the aripiprazole dose of 3.0 mg/kg, was conducted, although we were aware that this group would not be fully comparable with the other locomotor activity test groups since they were exposed to test conditions for one extra time.

**Statistical methods**

Alcohol consumption data were converted to grams per kilogram body weight, and saccharin as well as water drinking data were presented as millilitres per kilogram body weight. Change from the corresponding baseline consumption was always calculated by subtraction for each animal, and these difference score data were used in the statistical analyses. Effects of acute drug treatments on alcohol, saccharin, and water consumption and on locomotor activity were determined by one-way analysis of variance (ANOVA). Dunnett’s multiple comparison test was used for post hoc comparison. The data from repeated treatment experiment were tested using ANOVA for repeated measurements, using unstructured covariance matrix in the model, and with treatment and day as main effects, the latter being the repeated variable. Pair-wise comparisons were performed with contrast analysis applying Dunnett’s correction. Statistical computations were performed using SAS System for Windows, release 8.02 (Cary, NC, USA).

**RESULTS**

**Alcohol drinking experiments**

Effects of acute aripiprazole on alcohol and water drinking. Aripiprazole (0, 0.3, 1.0, and 3.0 mg/kg) had no statistically significant effect on 1 h or 4 h alcohol drinking, or on 24 h water drinking. (Fig. 1A, B, and C, respectively).

Effects of repeated aripiprazole dosing on alcohol and water drinking. Repeated aripiprazole treatment (0, 1.0, and 6.0 mg/kg) over five successive days significantly decreased 1 h alcohol drinking \( F(2,26) = 3.60, P = 0.0418 \), as shown in Fig. 2A. Pair-wise comparisons with Dunnett’s correction revealed a significant difference between vehicle and aripiprazole at 6.0 mg/kg \( P = 0.0342 \), but the aripiprazole dose of 1.0 mg/kg was ineffective \( P = 0.8876 \). Moreover, there was a significant effect for treatment days \( F(4,26) = 4.91, P = 0.0044 \), and pair-wise comparison showed that day 5 significantly differed from the other test days \( P < 0.05 \), and there was also a significant difference between day 1 and day 3 \( P < 0.05 \).

Repeated aripiprazole treatment (0, 1.0, and 6.0 mg/kg) had a tendency to significantly \( F(2,26) = 3.28, P = 0.0539 \) reduce 4 h alcohol drinking (Fig. 2B). There was a significant treatment day effect \( F(4,26) = 3.37, P = 0.0239 \), and day 5 significantly differed from the other experiment days \( P < 0.05 \).

Treatments had no significant effect on 24 h water drinking \( F(2,26) = 1.01, P = 0.3765 \) (Fig. 2C), but there was a significant effect for treatment days \( F(4,26) = 3.32, P = 0.0254 \). Pair-wise comparisons showed that day 4 significantly differed from the other treatment days \( P < 0.05 \), and there also was a significant difference between day 3 and day 5 \( P = 0.0454 \). Analysis revealed a significant treatment × day interaction \( F(8,26) = 2.34, P = 0.0480 \), which probably was a result from a notable decrease in water intake on the fourth treatment day, concerning both aripiprazole groups, but not the vehicle group. Additionally, water intake in the higher aripiprazole group was almost 50% lower on the fifth treatment day compared with baseline level.

When the difference score data (from baseline) of the first treatment day of repeated experiment were analysed with one-way ANOVA, as in the acute treatment study, it was found that aripiprazole significantly decreased 1 h alcohol drinking \( F(2,26) = 3.42, P = 0.0478 \) (Fig. 2D), and aripiprazole at 6.0 mg/kg differed from vehicle \( P < 0.05 \). Aripiprazole had no significant effect on 4 h alcohol drinking \( F(2,26) = 2.29, P = 0.1316 \) (Fig. 2E).
Aripiprazole (0, 0.3, 1.0, and 6.0 mg/kg) had no effect on 1 h \[F(3,24) = 0.22, \quad P = 0.8821\] or on 4 h \[F(3,24) = 0.13, \quad \]P = 0.9383\] saccharin drinking (Fig 3A and B, respectively). Aripiprazole had no significant effect on 24 h water drinking \[F(3,24) = 1.86, \quad \]P = 0.1637\] (Fig. 3C).

**Effects of acute aripiprazole treatment on locomotor activity**

Aripiprazole was very effective \[F(4,31) = 7.23, \quad \]P = 0.0003\] in reducing locomotor activity 30 min after drug dosing (Fig. 4A). The aripiprazole doses of 3.0 mg/kg \(P < 0.01\) and 6.0 mg/kg \(P < 0.001\) were effective compared to vehicle control. A significant aripiprazole-induced suppression in locomotor activity persisted at 3 h after dosings \[F(4,31) = 4.80, \quad \]P = 0.0040\], and the aripiprazole doses of 1.0 mg/kg \(P < 0.05\), 3.0 mg/kg \(P < 0.01\), and 6.0 mg/kg \(P < 0.01\) were effective compared to control group (Fig. 4B).

**DISCUSSION**

Aripiprazole decreased the limited access alcohol drinking of alcohol-preferring AA rats. However, aripiprazole was only effective at a notably higher dose than what was required to reduce locomotor activity, which makes aripiprazole’s suppressant effect on alcohol drinking non-selective.

We found that acute aripiprazole at doses from 0.3 to 3.0 mg/kg does not decrease the limited access alcohol drinking of AA rats. In the repeated administration experiment, aripiprazole (1.0 and 6.0 mg/kg) significantly decreased 1 h alcohol drinking. The aripiprazole dose of 6.0 mg/kg was effective when compared with control group at the 1 h time point. Moreover, when we compared the aripiprazole effects with vehicle control on the first treatment day, we found that aripiprazole significantly decreased 1 h alcohol drinking. At this time point aripiprazole dose 6.0 mg/kg was effective compared to vehicle control, which reflects the acute effect of this dose.

The alcohol drinking suppressant effect of aripiprazole attenuated on the fifth treatment day of repeated treatment. The 4 h limited access alcohol drinking of rats treated with the aripiprazole dose of 1.0 mg/kg surpassed the alcohol drinking of vehicle-treated control rats. Water drinking of both aripiprazole groups remarkably decreased on the fourth treatment day. These effects appear to be connected with each other, and they probably were caused by aripiprazole since comparable changes were not observed in the control group. It is also possible that a tolerance developed to the alcohol suppressing effect of aripiprazole on the fifth treatment day. It is known that tolerance to the effects of dopamine D2 receptor antagonists can develop during repeated treatment (Csernansky et al., 1993; Ericson et al., 1996). Also, serotonin 5-HT1A receptor agonist buspirone has been found to decrease alcohol drinking in rats, but this effect disappeared with chronic treatment (Hedlund and Wahlstrom, 1999).

Limited access saccharin drinking in the aripiprazole (0.3–6.0 mg/kg) groups decreased no more than that in the control group. Aripiprazole was highly effective in suppressing ambulatory locomotor activity at both 30 min and 3 h time points after drug injections, the aripiprazole doses of 1.0, 3.0, and 6.0 mg/kg being effective in comparison with vehicle control.

Aripiprazole (0.5–5.0 mg/kg) pretreatment has been shown to inhibit yawning behaviour of rats after dopamine agonist challenge (Fujikawa et al., 1996), indicating significant dopamine D2 receptor antagonism by aripiprazole at these doses (Fujikawa et al., 1996). Aripiprazole (5.0 mg/kg) also induced yawns, which is in line with its intrinsic D2 agonistic properties, but aripiprazole has not been able to cause rotational behaviour in 6-OHDA-lesioned rats (Fujikawa et al., 1996) indicating a lack of full postsynaptic D2 agonistic effects. Moreover, aripiprazole (5–20 mg/kg) has been shown to inhibit dopamine agonist-induced stereotypy behaviour in...
we suggest that the dose-dependent suppression of locomotor activity by aripiprazole in the present study is in line with the dose-dependently increasing postsynaptic dopamine D2 receptor blockade by aripiprazole observed in these previous studies (Kikuchi et al., 1995; Fujikawa et al., 1996). In the present study, alcohol drinking behaviour of AA rats decreased only with the highest aripiprazole dose (6.0 mg/kg) which
probably led to an efficient dopamine D2 receptor blockade, but also D2 receptor agonistic effects were likely involved with this dose (Fujikawa et al., 1996). Nevertheless, also other receptor mechanisms, such as 5-HT2 receptor antagonism or 5-HT1A agonism (McKenzie-Quirk and Miczek, 2003), might have contributed to observed results, although the latter effect seems unlikely since the lower aripiprazole dose (1.0 mg/kg) did not reduce alcohol drinking.

The role of dopamine transmission in the alcohol drinking of AA rats is implicated by the findings that limited access voluntary alcohol drinking releases dopamine in limbic and striatal brain areas in the AA rats (Honkanen et al., 1997).

However, in a microdialysis experiment alcohol drinking only marginally elevated dopamine in the nucleus accumbens (Nurmi et al., 1998), which suggests that dopamine is not a pivotal mediator of ethanol reinforcement in these animals. Additionally, autoradiographic binding studies and mRNA assessments of striatal dopamine D2 receptors do not support the idea that the striatal dopaminergic neurotransmission would underlie the high-alcohol drinking phenotype of AA rats in comparison with the alcohol-avoiding ANA (Alko, Non-Alcohol) rats (Korpi et al., 1987; Syvälahti et al., 1994). AA rats have a higher content of serotonin in their brain than ANA rats (Korpi et al., 1988), but these rat strains have comparable binding for 5-HT1 receptors (Korpi et al., 1992). Finally, this kind of a simple rat line comparison may not be valid, since the ANA rats might have various inherited factors, such as greater morbidity (Sarviharju et al., 2004) that just reduce their preference to alcohol even in the presence of functional monoamine systems.

The limited access alcohol drinking paradigm in the present study reflects cued alcohol drinking in these alcohol-prefering rats (Sinclair et al., 1992). The activation of mesolimbic dopamine system is an essential mediator of drug-seeking behaviour in animals (Self, 2004), and alcohol seeking can be abolished by dopamine antagonists (Liu and Weiss, 2002). We have previously observed that atypical
antipsychotics risperidone (Ingman et al., 2003) and olanzapine (Ingman et al., 2006) reduce the limited access alcohol drinking of AA rats, but they additionally suppress locomotor activity. In high-alcohol drinking (HAD) rats acute treatment with dopamine D2 receptor antagonist siperone has been shown to decrease 4 h limited access alcohol consumption only at a high dose, which was suggested to result in a complete dopamine D2 receptor blockade (Dyr et al., 1993). In common stock rats, systemically administered dopamine D2 receptor antagonists have been either effective (Files et al., 1998; Czachowski et al., 2002) or ineffective (Linseman 1990; Silvestre et al., 1996) in reducing alcohol drinking. Dopamine receptor agonists have mostly decreased alcohol drinking (Weiss et al., 1999; Dyr et al., 1993), but also increased alcohol drinking has been reported after a low dose dopamine agonist administration with 7-OH-DPAT, which possibly resulted in a presynaptic dopamine D2 receptor agonistic effect rather than postsynaptic receptor stimulation (Silvestre et al., 1996). Local microinjections of a dopamine agonist quinpirole into the anterior ventral tegmental area, where the cell bodies of mesolimbic dopamine neurons, and thereby also dopaminergic autoreceptors, are situated, significantly and selectively decreased limited access alcohol drinking (Nowak et al., 2000). Acute and repeated systemic administrations with partial dopamine D2 receptor agonists, terguride, and SDZ 208-911 have been reported to decrease limited access alcohol drinking in rats (Bono et al., 1996).

At the therapeutic doses effective against schizophrenia, aripiprazole has been shown to occupy striatal D2 receptors more extensively (up to 95%) than risperidone or olanzapine (60–80%) without any higher incidence for extrapyramidal adverse effects (Gründer et al., 2003). This has been suggested to arise from aripiprazole’s intrinsic agonistic activity at postsynaptic dopamine D2 receptors (Gründer et al., 2003), which might also explain why a higher aripiprazole dose was needed to suppress alcohol drinking compared with locomotor activity in the present study.

Taken together, aripiprazole significantly decreased the limited access alcohol drinking of AA rats, but only at a higher dose than what was needed to suppress locomotor activity. The potential of this putative dopamine transmission stabilizer to positively affect the outcome measures in the animal models of relapse and scheduled operant responding should also be studied to confirm aripiprazole’s efficacy in preclinical conditions.

Acknowledgements — This original study was sponsored by the Finnish Foundation for Alcohol Studies.

REFERENCES


Kikuchi, T., Tottori, K., Uwahodo, Y. et al. (1995) 7-(4-[2,3-Dichlorophenyl]-1-piperazinyl)butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and...


