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Lorcaserin, a selective 5-HT_{2C} receptor agonist, decreases alcohol intake in female alcohol preferring rats

Amir H. Rezvani *, Marty C. Cauley, Edward D. Levin

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA
Department of Psychology and Neuroscience, Duke University Medical Center, Durham, NC, USA

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ABSTRACT

Serotonergic systems in the brain have been found to be important in the addiction to alcohol. The purpose of this study was to evaluate the efficacy of a novel 5-HT_{2c} receptor agonist, lorcaserin for reducing alcohol consumption in alcohol-preferring (P) rats. Adult female rats were allowed to drink water or alcohol (12%, *v*/*v*) using a standard two-bottle choice procedure. Once stable baselines were established, the acute (0, 0.3125, 0.625 and 1.25 mg/kg, s.c.), and chronic (0, 0.625 mg/kg, sc for 10 days) effects of lorcaserin on alcohol intake and preference were assessed at different time points. In a separate experiment, the effects of lorcaserin on locomotor activity were determined. Our results show that both 0.625 and 1.25 mg/kg lorcaserin significantly reduced alcohol intake at 2, 4 and 6 h. after the drug administration. The chronic administration of 0.625 mg/kg lorcaserin significantly reduced alcohol intake up to 6 h every day after the injection and there was no sign of diminished efficacy of the drug during 10-day treatment. To determine the effects of lorcaserin on sucrose intake, rats were put on a two-bottle choice of water vs a solution of 7% sucrose. The high dose of lorcaserin (1.25 mg/kg, s.c.) reduced sucrose intake only for up to 2 h. When tested for locomotor activity, lorcaserin injected 20 min before testing significantly reduced locomotor activity at all doses. However, when it was injected 5.5 h before the start of the 1-h session, neither dose had a significant effect on locomotor activity. These results show the efficacy of lorcaserin in reducing alcohol intake without a significant effect on water intake and locomotion suggesting the involvement of 5-HT_{2c} receptors in alcohol seeking behavior. Further research is warranted to determine the possible efficacy of lorcaserin or similar drugs as treatments for the treatment of alcoholism.

1. Introduction

In addition to dopaminergic and other neuronal systems, the serotonergic systems in the brain have been shown to play an important role in addiction to alcohol and other addictive drugs (Maurel et al., 1999; McBride et al., 1990; Murphy et al., 1987b; Overstreet et al., 1994; Rezvani et al., 1990; Rezvani and Grady, 1994; Higgins and Fletcher, 2003). Deficiency in central serotonin levels and dysfunction of the serotonin system have been indicated in heavy drinking in rodents, non-human primates and human alcoholics (Borg et al., 1985; Fils-Aime et al., 1996; Heinz et al., 2001; Higley et al., 1996; Rezvani et al.,1990, 2002). There is also evidence that a serotonin deficiency is present in a subgroup of alcoholics and that deficiency is related to negative affect observed in this subpopulation. The deficiency is attributed to reduced serotonin transporter availability (Heinz et al., 2001). Furthermore, it has been shown that early onset alcoholics have lower levels of cerebrospinal fluid 5-HIAA, a major serotonin metabolite, than late-onset alcoholics (Fils-Aime et al., 1996). Hence, drugs that can stimulate the serotonergic systems may reduce alcohol intake in alcoholics with serotonin deficiency. In fact, the treatment with several serotonergic agents has been shown to reduce alcohol intake in both rodents (Meert and Janssen, 1991; Overstreet et al., 1994; Rezvani and Grady, 1994) and a subgroup of human alcoholics (Naranjo et al., 1986; Kranzler et al., 1995). Considering both serotonin and dopamine, it is noteworthy that an inverse relationship between the levels of these transmitters and excessive alcohol intake has been established for several lines of alcohol preferring rats including N/NiH heterogenous stock rats (Murphy et al., 1987a), selectively-bred alcohol preferring P rats and HAD rats (Gongwer et al., 1989). Also, it has been shown that chronic alcohol drinking in selectively-bred alcohol preferring (P) rats decreased the level of serotonin in the nucleus accumbens (Thielen et al., 2004).

Several serotonergic receptor agonists and antagonists have been shown to reduce alcohol intake in rats (See Bell et al., 2012 for an extensive review). However, the usefulness of these compounds has been limited by unwanted side effects. Among the wide variety of serotonergic receptors in the brain, it seems that activation of 5HT2 receptors reduces alcohol intake (Maurel et al., 1999). Selective agonists at 5-HT_2 receptors have been shown to reduce motivational behaviors such as feeding as well as drug taking. Compounds such as Ro 60-0175, MK212 and

* Corresponding author at: Dept. of Psychiatry and Behavioral Sciences, Box 104790, Durham, NC 27710, USA. Tel.: +1 919 668 1880; fax: +1 919 681 3416.
E-mail address: Azadi@duke.edu (A.H. Rezvani).

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WAY-163909 have been demonstrated to reduce cocaine, alcohol and nicotine self-administration in rodents (Grottick et al., 2000, 2001; Higgins et al., 2012; Higgins and Fletcher, 2003). Recently, lorcaserin ((1R)-8-chloro-1-methyl-2,3,4,5, tetrahydro-1H-3 benzazepine HCl) has also been shown to reduce nicotine (Levin et al., 2011; Higgins et al., 2012) and cocaine self-administration (Higgins and Fletcher, 2003) as well as feeding behavior in rats (Higgins et al., 2012), an effect that can be blocked by the selective 5-HT_{2c} antagonist SB-242084 (Higgins et al., 2012).

Based on the fact that neuronal serotonergic receptor agonists have been shown to reduce alcohol, nicotine and cocaine self-administration (Higgins et al., 2012) and 5-HT_{2c} receptors provide an inhibitory input over dopaminergic projections in the ventral tegmental area (VTA), it was hypothesized that lorcaserin will reduce alcohol intake in alcohol preferring rats. To test this hypothesis, both the effects of acute and repeated treatments with lorcaserin on alcohol and water intake in alcohol preferring rats were determined in this project. Furthermore, the effect of lorcaserin on locomotor activity and sucrose intake was also determined. Given that lorcaserin has been approved for human use to combat obesity, evidence that it may be useful for treating drug addictions including alcoholism would offer additional therapeutic uses for this drug.

2. Materials and methods

2.1. Subjects

The animals used in these studies were adult female alcohol preferring rats obtained from the Indiana University. They were maintained in a standard laboratory condition with controlled temperature of 22 ± 1 °C and humidity of 50 ± 10% and reversed 12:12 light–dark cycle (7:00 a.m.–7:00 p.m. dark). The rats were handled briefly for few days upon arrival and then placed in specialized polycarbonate cages that were fitted with two 100-ml graduated Richter drinking tubes for the recording of water and alcohol (12%, *v*/*v*) (Rezvani et al., 2010, 2013). Animals were fed 5001 Rodent Chow (Lab Diet, Brentwood, MO, USA) and water ad libitum. All procedures were approved by the IACUC at Duke University.

2.2. Drug preparation

Lorcaserin was dissolved in saline and administered subcutaneously (1 ml/kg) 20 min before testing. Saline (1 ml/kg) was used as the control vehicle. Solutions of 12% (*v*/*v*) alcohol were prepared twice weekly from a solution of 100% ethanol mixed with tap water. Fresh alcohol and water in Richter drinking tubes were presented to rats 20 min after each treatment. Solutions of 7% sucrose were prepared daily with tap water and were presented to rats in graduated Richter drinking tubes.

2.3. Experimental protocol

The following experiments were carried out to study the effects of acute and repeated administration of lorcaserin on alcohol intake.

2.4. Acute study

After the rats exhibited stable and reliable intakes of alcohol and water for several weeks (approximately 5 weeks), they were injected with one of the doses of lorcaserin (0, 0.3125, 0.625 and 1.25 mg/kg, s.c.) following a cross-over design with random assignment. All injections were given between 9 and 10 a.m. Alcohol and water intakes were recorded at 2, 4, 6 and 24 h after the drug administration. Four days were allowed between injections.

2.5. Chronic study

To determine the effects of repeated administration of lorcaserin on alcohol consumption, based on the outcome of the acute study, a dose of 0.625 mg/kg lorcaserin was selected for the chronic study to be administered subcutaneously for 10 consecutive days. The same group of rats as the acute study was used. After re-establishment of a stable baseline for alcohol and water intake for several weeks rats received lorcaserin or saline for 10 consecutive days. Following a cross-over design, half of the rats received saline first and the other half received lorcaserin first. Thus, all 16 rats received both treatments using a cross-over design. The interval between lorcaserin and saline treatment was 7 days. Alcohol and water intakes were recorded daily at 2, 4, 6 and 24 h after the drug administration.

2.6. Effects of lorcaserin on sucrose intake

To determine the selectivity of lorcaserin effects on alcohol intake, the effects of a high dose of lorcaserin (1.25 mg/kg) on sucrose intake were assessed in a separate group of female rats. Alcohol preferring P rats ($N = 13$) were put on two-bottle choice of water and a solution of 7% sucrose for 6 consecutive days. After the establishment of a stable baseline for sucrose intake, rats were given an acute dose of lorcaserin (1.25 mg/kg, s.c.) or the control saline vehicle following a cross-over design. Sucrose and water intake were measured at 2, 4, 6, and 24 h after the treatment. The interval between lorcaserin and the vehicle treatments was 6 days.

2.7. Locomotor activity

Previously it was shown that lorcaserin at high dose caused sedation-like effects by reducing motor activity in rats (Levin et al., 2011). To find out if the effects of lorcaserin on alcohol intake are the result of its potential sedative-like effects, we investigated the effects of 0.3125, 0.625 and 1.25 mg/kg on locomotor activity. A computerized figure-8 apparatus was used to test the locomotor activity of the rats. This test has been widely shown to be sensitive to the behavioral effects of drugs including nicotine (Levin et al., 2011). Rats were treated with one of the three doses of lorcaserin or saline either 20 min or 5 ½ h before testing. After the treatment, their locomotor activity was monitored for 1 h in an automated figure-8 maze. The maze consisted of continuous enclosed alleys (10 × 10 cm) in the shape of a figure eight with a 21 × 16 cm central arena, a 20-cm high ceiling and two blind alleys extending 20 cm from either side. The maze was equipped with eight infrared photobeams which crossed the alleys. The number of photobeam breaks indicated locomotor activity. The number of photobeam breaks in 5-min block was tallied by computer during the 1-h session (Levin et al., 2011). The linear and quadratic trends across 12 five-minute blocks in the 1-hour test session were used. The average activity counts across the 1-hour session serves as a measure of locomotor activity.

2.8. Statistical analysis of data

The data were assessed by the analysis of variance. Drug treatment (lorcaserin and saline) was a repeated measures factor. Alcohol intake was calculated as g/kg/h from volume of 12% (*v*/*v*) alcohol consumed. Water, alcohol and sucrose intake was calculated as g/kg/h at different time points after treatments. Total fluid intake (alcohol and water) was calculated as ml/kg.

3. Results

3.1. Acute study

Acute lorcaserin caused a significant main effect ($F_{(3,45)} = 9.14$, $p < 0.0005$) decreasing alcohol self-administration (Fig. 1). Significant