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Risperidone reduces limited access alcohol drinking in alcohol-preferring rats

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Abstract

An atypical antipsychotic drug risperidone reduced ethanol drinking of ethanol-preferring Alko, Alcohol (AA) rats in a limited access paradigm. Its effect was transient at a dose known to preferentially antagonize the 5-HT_2 receptors (0.1 mg/kg, s.c.), but long-lasting when the dose was increased to 1.0 mg/kg that also blocks dopamine D_2 receptors. Risperidone also reduced dose-dependently locomotor activity and limited access saccharin intake of the AA rats, indicating that its effect on ethanol drinking was not selective. Risperidone at 0.1 mg/kg given before four successive daily ethanol-drinking sessions significantly reduced the ethanol intake. These data from an animal model of high ethanol intake suggest that risperidone should be tested in various populations of alcoholics for reducing ethanol consumption.

Keywords: (Selected rat line); Alcohol preference; Risperidone; Food consumption; Locomotor activity

1. Introduction

A number of investigations have been conducted in order to elucidate neuronal mechanism underlying ethanol abuse and alcoholism. In spite of rapid progress in this field, we have still a paucity of drugs that are approved by common consent to be effective treatment for alcoholism. Ethanol reinforcement appears to be an outcome of complex interactive network between ethanol and several neurotransmitter systems. Dopaminergic system is considered one of the key mediators of the rewarding effects of ethanol (Wise, 1987; Koob, 1992), although recent findings point out its significance as a mediator of the reward learning process rather than as a target of direct ethanol action (Spanagel and Weiss, 1999; Grace, 2000). Pre-clinical and clinical studies have yielded information suggesting that serotonin system is an important mediator of ethanol reward. Particularly innate deficiencies in brain serotonin contents have been implicated in certain animal models of alcoholism or subtypes of alcoholism (Murphy et al., 1987; Virkkunen and Linnoila, 1990; McBride and Li, 1998; Johnson and Ait-Daoud, 2000).

Animal models of high ethanol drinking provide investigators one possible way to study neurobiological mechanisms needed to be modulated in order to reduce ethanol consumption by drugs (McBride and Li, 1998). Alko, Alcohol (AA) rats represent an outbred rat line that exhibits high voluntary ethanol-drinking behaviour (Eriksson, 1968). Studies using dopamine ligands have provided diverse results, but majority of studies suggest that systemically administered dopamine antagonists are ineffective in reducing ethanol intake, except for high doses that reduce consummatory behaviour overall (Silvestre et al., 1996; McBride and Li, 1998). A wide variety of pharmacological compounds acting via serotonergic system affects voluntary ethanol intake in animals and humans (Sellers et al., 1992; McBride and Li, 1998; Wilson et al., 1998; Johnson and Ait-Daoud, 2000). Selective 5-HT_2 receptor antagonist ritanserin has decreased ethanol intake in several investigations (Lin and Hubbard, 1994; Meert, 1994), but on the other hand, it has been shown ineffective in common stock rats (Myers and Lankford, 1993) and also in alcohol-preferring rats (Panocka et al., 1993a). Selective 5-HT_{2A}-receptor antagonist amperozide dose dependently decreased

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ethanol intake in several strains of rodents, including the AA rats, but only at doses that also impair general consummatory behaviour (Overstreet et al., 1997).

Risperidone is an atypical antipsychotic drug that is being used in the treatment of acute psychosis and in the maintenance treatment of schizophrenia (Gupta et al., 1994; He and Richardson, 1995). To our knowledge, it has not been rigorously tested in the treatment of alcoholism. Risperidone has a relatively broad profile of receptor interactions. It effectively occupies 5-HT_2 receptors at low concentrations and additionally dopamine D_2 receptors at higher concentrations in rodents and man (Matsubara et al., 1993; Schotte et al., 1993, 1996; Nyberg et al., 1999; Yamada et al., 2002). It also antagonizes histamine H_1 receptors, α_1- and α_2-adrenoreceptors to a lower extent. Risperidone easily crosses blood–brain barrier after peripheral administration and has a half-life of 3–4 h in the rat frontal cortex and striatum, both areas abundant in 5-HT_2 and dopamine D_2 receptors (van Beijsterveldt et al., 1994). Central pharmacological activity of risperidone is still markedly extended by its major metabolite 9-hydroxy-risperidone (van Beijsterveldt et al., 1994), which has similar pharmacological profile and selectivity as its parent compound (Schotte et al., 1995). Several studies investigating the effects of risperidone on ethanol consumption in experimental animals have given contradictory data, as risperidone decreased ethanol intake in nonselected rats at doses (0.1 mg/kg) that antagonize mainly 5-HT_2 receptors in one study (Panocka et al., 1993b), but was without effect in another study applying genetically selected ethanol-preferring rat strain (Panocka et al., 1993a). However, higher risperidone doses antagonizing effectively both 5-HT_2 and dopamine D_2 receptors, reduced both ethanol intake and other general consummatory behaviour (Panocka et al., 1993b; Silvestre et al., 1996).

The present study was conducted in order to determine whether risperidone is effective in reducing limited access ethanol drinking in the AA rats at two doses: a low dose (0.1 mg/kg) that should be selectively blocking the 5-HT_2 receptors and a high dose (1.0 mg/kg) that is supposed to block also the dopamine D_2 receptors. In addition, the efficacy of repeated administration of the low risperidone dose on ethanol consumption was studied. To test for the selectivity of the effects for ethanol consumption, the effects of risperidone on spontaneous locomotor activity and limited access saccharin drinking were also ascertained.

2. Materials and methods

2.1. Animals

Adult, male AA (Alko, alcohol) rats weighing 280–400 g were used. They were 3 months old, when they were transferred from Helsinki to Turku and ethanol drinking was commenced. The animals were individually housed in transparent plastic cages (36×21 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). The animals had free access to tap water and food (RM1, Special Diet Service, Witham, Essex, England) except during the initial ethanol-drinking period, when 10% ethanol in tap water was the only fluid with food being freely available. The laboratory animal committee of the University of Turku approved all experimental procedures.

2.2. Drugs and administration of the drugs

Ethanol solution 10% (v/v) was prepared by diluting 99.5% ethanol (Primalco, Rajamäki, Finland) with tap water. Risperidone (a gift of Janssen Research Foundation, Beerse, Belgium) was dissolved in a vehicle containing distilled water and two equivalents of tartaric acid solution. The drug solutions were prepared in the morning of each experimental day and administered subcutaneously (s.c.) in a volume of 1.0 ml/kg of body weight.

2.3. Limited access ethanol-drinking paradigm

After a 2-week habituation to a new environment in the experimental room, animals were trained to drink ethanol according to a protocol described by Sinclair et al. (1992), and Wegelius et al. (1994). First, animals underwent a 6-day forced ethanol-drinking period when the only available drinking fluid was 10% (v/v) ethanol. Thereafter, one tap water bottle per cage (and food) was always available. Then, the animals had an all-day two-bottle free choice between 10% ethanol and tap water until ethanol consumption was regularly more than 50% (ethanol preference 75±24%, mean±S.D., n=24) of the total fluid intake, which took about 6 weeks. Positions of the bottles on the cages were exchanged every day. Limited access paradigm, carried out in the light phase between 10 a.m. and 2 p.m., was started by first restricting the choice between a tap water bottle and a bottle containing 10% (v/v) ethanol to 4 h daily, and after reaching again steady daily ethanol consumption, the access was limited to 4 h every second working day (Monday, Wednesday and Friday). The rats were weighed prior to each drinking session. Ethanol consumption was recorded to the nearest 0.2 ml 1 h after beginning of the session and at the end of the 4-h session. During the 4-h ethanol-drinking session, rats consumed food and tap water only negligible amounts, which made their determination so unreliable that it was not carried out.

2.4. Determination of ethanol consumption after acute risperidone administration

All animals received a vehicle injection (distilled water, s.c., 1.0 ml/kg) 30 min before the beginning of the ethanol-drinking session. Then, animals were divided into three

groups according to their 4-h baseline ethanol consumption so that ethanol consumption was equivalent in each group. In the experiment, 30 min before the access to ethanol, the animals in each group were given one of the following treatments: vehicle (n=7), 0.1 mg/kg (8) or 1.0 mg/kg (8) of risperidone.

To test for repeated dosing effects, seven rats were injected daily 30 min before the access to ethanol with risperidone (0.1 mg/kg) during four daily sessions after the limited access training phase. One- and four-hour ethanol consumptions were determined each day. The rats were weighed daily before experimental procedures to calculate the individual drug doses.

2.5. Determination of saccharin consumption after acute risperidone injections

Rats had free access to food and tap water throughout the entire study. Richter tubes containing 0.1% saccharin–tap water solution were mounted to cages for 4 h everyday for 1 week. Then, saccharin solution availability for rats was restricted to 4 h every second working day. After 2 weeks, the level of saccharin intake by the rats was stabilized. All rats received saline injections (1.0 ml/kg) 30 min prior to the saccharin drinking session preceding the actual experiment and saccharin consumption was recorded at the end of the drinking session. Then, the rats were divided into three comparable groups with respect to their 4-h saccharin consumptions (n=7 in each group). Thirty minutes before the next saccharin drinking session, the rats received subcutaneous vehicle or risperidone injections. Saccharin consumption was recorded at 1 and 4 h after the beginning of the drinking session.

2.6. Determination of locomotor activity

Locomotor activity was measured using a photobeam activity system (PAS, San Diego Instruments, San Diego, CA, USA), which was composed of eight measurement enclosures consisting of a photobeam frame (Vekovischeva et al., 2001). Cage rack enclosures were assembled by placing enclosures around a standard animal cages 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 activity.

Twenty-three male AA rats were used in this experiment. The rats were randomly assigned into three different treatment groups [vehicle (n=8), 0.1 mg/kg (8) and 1.0 mg/kg (7) of risperidone]. After weighing the rats, they received the vehicle or drug injections and were placed into their home cages located in the experiment room. Two 30-min locomotor activity measurement sessions were performed 30 min and 3 h after the injection. For measurement sessions, the rats were removed from home cages and placed into locomotor activity measurement cages. After the 30-min measurement sessions, the animals were returned back to the home cages.

2.7. Statistical methods

Effects of acute drug treatments on the consumption of ethanol or saccharin solutions and on the locomotor activity were determined by one-way analyses of variance (ANOVA). Dunnett's multiple comparison test was used for post-hoc comparisons. Data of repeated risperidone treatment were tested with analyses of variance for repeated measurements followed by Student's t-tests. P-values less than 0.05 were regarded as statistically significant. Statistical computations were performed using SAS System for Windows, release 8.02 (Cary, NC, USA).

3. Results

3.1. Effect of acute risperidone treatment on ethanol consumption

Average ethanol consumption in 4-h baseline drinking session was 1.10±0.10 g/kg (mean±S.E.M., n=23). Fig. 1A shows that risperidone reduced significantly ethanol intake when measured after 1-h ethanol drinking [$F(2,20)=12.9$, $P=0.0003$], risperidone at the doses of 0.1 mg/kg ($P<0.05$) and 1.0 mg/kg ($P<0.01$) decreasing ethanol intake in

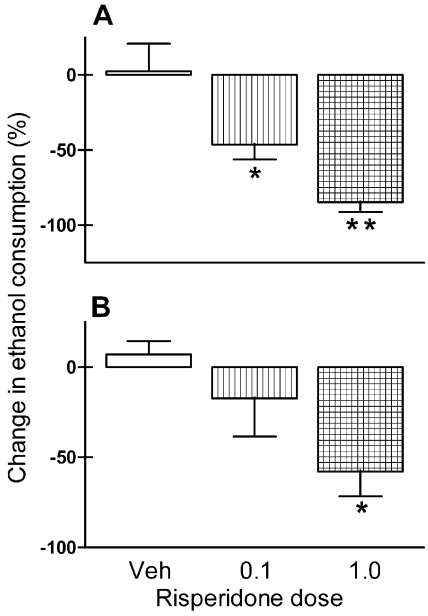

Fig. 1. Suppression of ethanol intake in AA rats by acute risperidone injections (0.1 and 1.0 mg/kg). The bars show mean percentage change (±S.E.M., n=7–8) in ethanol consumption from the baseline levels. The rats received drug or vehicle injections 30 min before ethanol drinking session and ethanol consumption was measured for 1 h after the beginning (A) and at the end of the 4-h drinking session (B). Significant differences from vehicle treatment are denoted by *$P<0.05$ and **$P<0.01$ (Dunnett's test).

comparison with the vehicle treatment (Dunnett's multiple comparison test). The effect of risperidone on 4-h ethanol intake was also significant [$F(2,20)=4.298$, $P=0.0280$] (Fig. 1B), the vehicle and high-risperidone dose groups significantly differing from each other ($P<0.05$, Dunnett's test).

3.2. Effect of subchronic treatment with low dose of risperidone on ethanol drinking

The baseline ethanol drinking during the 4-h drinking session preceding the experiment was 1.12±0.14 g/kg body weight ($n=7$). Ethanol drinking over 4 days of administration of risperidone at 0.1 mg/kg is shown in Fig. 2. Risperidone reduced significantly the 1- and 4-h ethanol-drinking values [$F(4,34)>2.93$, $P<0.05$], and the individual daily comparisons revealed that the risperidone effect was significant at both time points on the last day of the experiment ($P<0.05$).

3.3. Effect of acute risperidone treatment on saccharin consumption

Risperidone had a significant effect on 1-h saccharin intake [$F(2,18)=14.82$, $P=0.0002$] and individual comparisons showed significant difference between vehicle and risperidone dose groups ($P<0.01$, Dunnett's test) (Fig. 3A). At the end of the 4-h drinking session, saccharin intakes were still suppressed after risperidone treatment [$F(2,18)=9.93$, $P=0.0012$] (Fig. 3B). The mean 4-h intake of ethanol was significantly lower after 1.0 mg/kg risperidone administration than after vehicle injection ($P<0.01$, Dunnett's test).

3.4. Effect of acute risperidone treatment on ambulatory locomotor activity

Risperidone significantly decreased locomotor activity 30 min after the drug administration [$F(2,20)=15.79$, $P<0.0001$], the higher risperidone dose significantly affecting locomotor activity as compared to the vehicle ($P<0.01$, Dunnett's multiple comparison test) (Fig. 4A). Risperidone

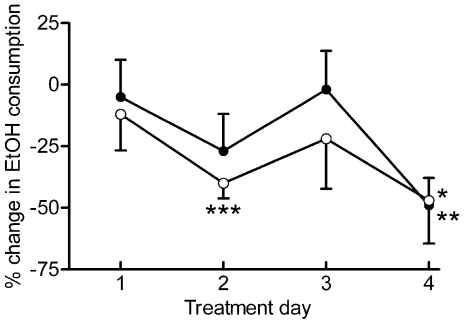

Fig. 2. Effects of repeated treatment with risperidone (0.1 mg/kg, s.c.) on ethanol self-administration during limited access drinking sessions over 4 days. The values are expressed as mean percent change (±S.E.M., $n=7$) from the drinking levels in the baseline session. Animals received drug injections 30 min before access to ethanol solution and ethanol consumption was measured 1 h after the beginning (○) and at the end of the 4 h drinking session (●). Statistically significant differences from the baseline drinking are denoted by asterisks (*$P<0.05$, **$P<0.01$, ***$P<0.001$; Student's t-test).

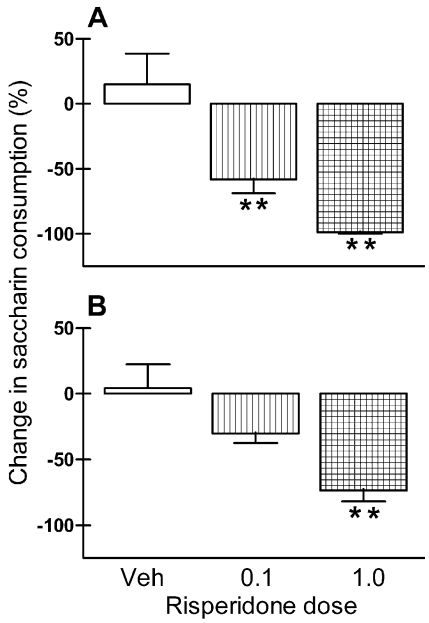

Fig. 3. Effect of acute risperidone treatment (0.1 and 1.0 mg/kg) on 1-h (A) and 4-h (B) saccharin drinking. Animals in the treatment groups were injected with vehicle or risperidone 30 min prior to the limited access drinking session. Values are expressed as percent change relative to the baseline consumption and represent mean percent change±S.E.M. ($n=7$ in each group). Asterisks indicate significant difference in comparison with vehicle treatment (**$P<0.01$; Dunnett's test).

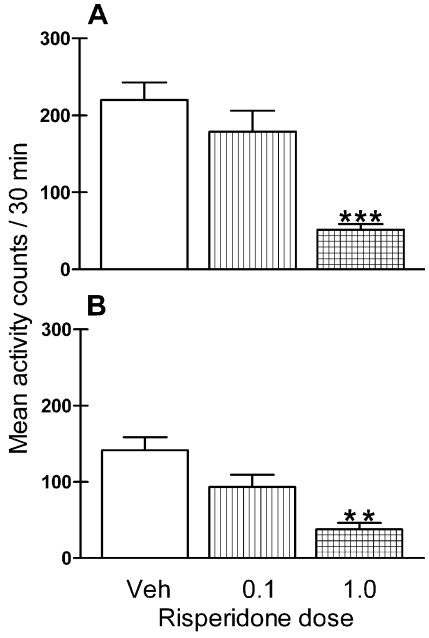

Fig. 4. Effect of risperidone (0.1 and 1.0 mg/kg) on ambulatory locomotor activity in the AA rats. Two 30-min measurement sessions were performed 30 min (A) and 3 h (B) after the drug administration in a novel environment. Data are the mean activity counts±S.E.M. ($n=7-8$). **$P<0.01$, ***$P<0.001$ (Dunnett's test).

significantly reduced locomotor activity still 3 h after drug administration [$F(2,20)=11.73$, $P=0.0004$], the difference between the high-dose risperidone and vehicle treatments being statistically significant ($P<0.01$) (Fig. 4B).

4. Discussion

Risperidone at the dose of 1.0 mg/kg, s.c. produced a marked reduction in spontaneous ambulatory locomotor activity of the alcohol-preferring AA rats. The effect is durable; comparison between effects at 30 min and 3 h after drug administration reveals only slight attenuation. The low risperidone dose (0.1 mg/kg, s.c.) failed to significantly decrease locomotor activity in comparison with vehicle treatment. Reduction of locomotor activity results typically from the blockade of dopamine D_2 receptors and is in agreement with earlier findings, where risperidone at the dose of 0.18 mg/kg started to reduce horizontal locomotor activity (Megens et al., 1988). Lower doses mainly occupy and block the 5-HT_2 receptors. For example, significant serotonergic blockade can be achieved at risperidone doses starting from 0.014 mg/kg (Janssen et al., 1988), which makes risperidone a potent 5-HT_2 receptor antagonist, having more than 10-fold preference to 5-HT_2 receptor than to dopamine D_2 receptors also in occupancy experiments (Schotte et al., 1993). Therefore, it appears that the lower risperidone dose in our study antagonized efficiently 5-HT_2 receptors and affected dopamine D_2 receptors to insignificant extent, while the higher dose produced a long-lasting and robust mixed serotonin 5-HT_2 and dopamine D_2 receptor blockade.

Acutely administered risperidone dose dependently decreased ethanol intake of the AA rats under the limited access paradigm. Both 0.1 and 1.0 mg/kg doses of risperidone were effective in comparison with vehicle treatment in 1-h ethanol drinking, but only the higher dose retained its effect also in 4-h drinking session. While this result may be due to pharmacokinetic factors, the half-life of risperidone being about 3–4 h in rat brain (van Beijsterveldt et al., 1994), it also suggests that the effect of risperidone on alcohol drinking was mediated by the blockade of dopamine D_2 receptors or by both 5-HT_2 and dopamine D_2 receptors rather than 5-HT_2 receptors alone in this study. This is consistent with the important role of increased dopamine release in the limbic brain regions of the AA rats after short bouts of voluntary ethanol drinking (Honkanen et al., 1997). It has been previously shown that risperidone administered repeatedly at doses of 0.1 and 1.0 mg/kg reduces ethanol intake in nonselected Wistar rats under 24-h free choice paradigm (Panocka et al., 1993b). In contrast, risperidone doses of 0.01, 0.1 and 1.0 mg/kg administered twice daily for 4 consecutive days to nonselected Sprague–Dawley rats with free access to ethanol affected ethanol consumption or preference only at the highest dose that significantly reduced also the water intake (Silvestre et al., 1996). Furthermore, alcohol-preferring sP rats are not responding to risperidone under the corresponding test design (Panocka et al., 1993a). Anyway, interpretations for discrepant results might be due to methodological approaches and genetic dissimilarities between animal lines. Indeed, a relationship between innate deficiencies in brain 5-HT content and high ethanol preference has been established in several animal line pairs with differences in ethanol-drinking behaviour (McBride and Li, 1998), but the AA rats have a higher content of 5-HT in several brain areas than their controls, the alcohol-avoiding ANA rats (Korpi et al., 1988). Densities of serotonin receptors also differ between some high and low ethanol-drinking animal lines (McBride and Li, 1998), but the AA and ANA rat lines have similar serotonin receptor densities (Korpi et al., 1992; Ciccocioppo et al., 1997, 1998). Acute administration of 5-HT uptake blocker citalopram failed to reduce ethanol drinking in the AA rats in a limited access paradigm (Wegelius et al., 1994). The AA rat line may thus represent high ethanol-drinking rats without a serotonergic deficiency, associated with an apparent inefficacy of drugs promoting serotonin actions to affect their ethanol-drinking behaviour, while being possibly sensitive to 5-HT_2 receptor blockers (the present study; Overstreet et al., 1997).

Saccharin intake was reduced by risperidone in the AA rats even more than ethanol drinking. Baseline intake volumes for 10% ethanol solution and 0.1% saccharin solution during 4-h limited access period were 4.6 ml and 9.9 ml/kg, respectively, which suggests that saccharin solution was preferred over ethanol by the AA rats. However, a preference test between ethanol and saccharin should be made with both solutions available at the same time at varying concentrations. Additionally, pharmacological effects, e.g., sedation by ethanol may limit its consumption in high volumes. In alcohol-preferring P rats, the 5-HT_{2A} receptor antagonist amperozide produces a greater decline in ethanol than saccharin intake (Biggs and Myers, 1998), suggesting that 5-HT_{2A} receptors might be responsible for reinforcement of palatable substances in P rats (Biggs and Myers, 1998). This is consistent with the serotonin system being responsible for high ethanol intake in P rats (Myers et al., 1993; Lankford et al., 1996). However, the AA rats do not have innate changes in brain 5-HT system that could explain ethanol preference (see above), although that system may be involved in the regulation of saccharin intake also in these animals. When considering the significance of the saccharin results in the present study, one should anyway keep in mind that often preference for alcohol and sweets correlates and might be regulated by similar genetic and neurobiological mechanisms (Kampov-Polevoy et al., 1997; Kranzler et al., 2001). Therefore, the effect of risperidone on saccharin consumption does not necessarily mitigate the importance of its action on alcohol consumption.

Risperidone (0.1 mg/kg) in the repeated treatment experiment reduced the ethanol drinking reaching a statistically significant effect on the 4th day. This suggests that repeated predominant 5-HT_2 receptor blockade can have an effect on

ethanol drinking, but as discussed above, risperidone is only partially selective for 5-HT_2 receptors, and we cannot fully rule out the dopamine D_2 antagonism even in this small dose experiment. However, chronic treatment with dopamine D_2 receptor antagonists has generally failed in the treatment of human alcoholism (Soyka and De Vry, 2000), but acute treatment with these agents can efficiently control conditioned ethanol and drug seeking in animals (Liu and Weiss, 2002). The limited access method used here may measure conditioned responses rather than general consummatory behaviour. Thus, risperidone might prove useful if used acutely in situations, which normally provoke strong alcohol craving in alcoholics.

In conclusion, the present study revealed a strong inhibition of ethanol-drinking behaviour by the atypical antipsychotic risperidone in an alcohol-preferring rat line. Although the study also witnessed that this effect was not selective for ethanol consumption, risperidone should be tested in alcoholics, preferably in subpopulations with different genetic backgrounds.

Acknowledgements

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