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Agmatine blocks ethanol-induced locomotor hyperactivity in male mice

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ABSTRACT

Ethanol-induced locomotor activity is associated to rewarding effects of ethanol and ethanol dependence. Agmatine is a novel endogenous ligand at α_2-adrenoceptors, imidazoline and N-methyl-D-aspartate (NMDA) receptors, as well as a nitric oxide synthase (NOS) inhibitor. There is no evidence presented for the relationship between the acute locomotor stimulating effect of ethanol and agmatine. Thus, the present study investigated the effects of agmatine on acute ethanol-induced locomotor hyperactivity in mice. Adult male Swiss–Webster mice (26–36 g) were used as subjects. Locomotor activity of the mice was recorded for 30 min immediately following intraperitoneal administration of ethanol (0.5, 1 and 2 g/kg) or saline (n = 8 for each group). Agmatine (5, 10 and 20 mg/kg) or saline was administered intraperitoneally to another four individual groups (n = 8 for each group) of the mice 20 min before the ethanol injection. In these groups, locomotor activity was also recorded immediately following ethanol (0.5 g/kg) injection for 30 min. Ethanol (0.5 g/kg) produced some significant increases in locomotor activity of the mice. Agmatine (5–20 mg/kg) significantly blocked the ethanol (0.5 g/kg)-induced locomotor hyperactivity. These doses of agmatine did not affect the locomotor activity in naive mice when they were administered alone. Our results suggest that agmatine has an important role in ethanol-induced locomotor hyperactivity in mice. There may be a relationship between the addictive psychostimulant effects of the ethanol and central agmatinergic system.

1. Introduction

Studies examining the effects of ethanol alone have demonstrated that ethanol possesses both excitatory and depressant properties in a dose-dependent manner. Low doses of ethanol produce locomotor stimulant effects in rodents (Frye and Breese, 1981; Uzbay and Kayir, 2003). Psychostimulant properties of drugs can be assessed by measuring locomotor activity, and these psychostimulant effects have been linked to their addictive properties (Wise and Bozarth, 1987).

Agmatine is synthesized following decarboxylation of L-arginine by enzyme arginine decarboxylase in mammalian brain and other tissues. It is a biological active substance that is synthesized, stored, and released in brain. It binds with high affinity to imidazoline and α_2-adrenergic receptors. Namely, it elicits biological actions within the central nervous system by interaction with some receptors and neuronal pathways. Thus, it has been suggested that agmatine meets many criteria as a novel neurotransmitter in brain (Reis and Regunathan, 1998, 2000). It also antagonizes N-methyl-D-aspartate (NMDA) receptors (Yang and Reis, 1999) and inhibits nitric oxide synthase (NOS) (Auguet et al., 1995; Galea et al., 1996).

Systemic administration of agmatine exerts anxiolytic (Lavinsky et al., 2003; Gong et al., 2006), antidepressant (Zomkowski et al., 2002; Krass et al., 2008), antinociceptive (Onal and Soykan, 2001; Yesilyurt and Uzbay, 2001) and antiepileptic (Demehri et al., 2003; Su et al., 2004) effects. In a recent study, Taksande et al. (2010) also demonstrated that agmatine potentiates ethanol-induced anxiolysis and blocks the withdrawal anxiety associated to ethanol withdrawal in rats. Further, several reports have indicated that agmatine attenuated the signs of morphine (Aricioglu-Kartal and Uzbay, 1997) and ethanol (Uzbay et al., 2000a) withdrawal syndrome in rats and it was proposed that it may have a key role in development of physical dependence to ethanol (Uzbay et al., 2000a). Because ethanol-induced locomotor stimulation positively correlated with the rewarding effects of ethanol and ethanol dependence (Wise and Bozarth, 1987; Koob, 1992; Phillips and Shen, 1996), testing the effects of agmatine on ethanol-induced locomotor activity is important. Although the effects of agmatine on locomotor hyperactivity induced by other psychostimulants such as nicotine (Zanizewska et al., 2008; Kotagale et al., 2010) and caffeine (Uzbay et al., 2010) were investigated, no study on the role of agmatine in ethanol-induced locomotor hyperactivity has been published yet. Hence, we hypothesized that agmatine may modulate the ethanol-induced locomotor stimulation.

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The major objective of the present study was to investigate the role of agmatine in ethanol-induced locomotor hyperactivity in mice. This was done by recording ethanol-induced locomotor activity of the mice after ethanol, or after ethanol plus agmatine administration.

2. Material and methods

2.1. Animals and laboratory

All procedures in the present study were performed in accordance with the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (USA) and the Declaration of Helsinki. Local ethical committee approval was also taken, numbered with 05/73 on October 23rd, 2005.

Adult male (26–36 g) Swiss Webster mice were subjects. The animals were supplied from animal facility of Experimental Psychopharmacology Research Unit at Gülhane Military Medical Academy. They were housed eight per cage in Plexiglas cages. They were placed in a quiet and temperature and humidity controlled room (22 ± 2 °C and 60 ± 5%, respectively) in which a 12/12 hour light–dark cycle was maintained (0700 h–1900 h light). Food and water were available ad libitum. All experiments were performed at the same time of day and in the light period (0900–1100 am).

2.2. Drugs

Agmatine was purchased from Sigma Chemical (USA) and dissolved in 0.9% saline. Ethanol was purchased from Merck (USA) and diluted with 0.9% saline. Ethanol, agmatine and saline injected intraperitoneally (i.p.) in a volume of 10 ml/kg. Drug stocks and ethanol solutions were prepared freshly every morning.

2.3. Apparatus

Locomotor activity was measured with an open-field activity monitoring system (MAY 9908 model—Activity Monitoring System—Commat Ltd., TR). This system had eight Plexiglas cages ($42 \times 42 \times 30$ cm) equipped with infrared photocells. Fifteen photocell emitter and detector pairs were located 2 cm above the floor at intervals of 2.5 cm on the both counter sides of each activity cage, and another 15 photocell pairs were located 8 cm above the floor. Interruptions of photocell beams were detected by a computer system, and the location of the animal was calculated by the software at 0.1 s sensitivity. If the calculated locations were completely changed, this was expressed as ambulatory activity. Other behavioral responses that caused interruptions of beams but not changes in location were recorded as horizontal activity. Vertical activity, such as rearing, was detected by the photocells located 8 cm above the cage floor.

2.4. Procedure

The experiments were designed and performed in three stages. For each stage naïve animals were randomly assigned to each treatment group ($n = 7$–8 for each group), and tested in a random order. In the first experiment, acute effects of ethanol on locomotor activity were evaluated by administering ethanol (0.5–2 g/kg) or saline (for control group) to mice and immediately measuring locomotor activity for 30 min. The locomotor stimulating dose (0.5 g/kg) was selected for further experiments. In the second experiment, effects of agmatine pretreatment on ethanol-induced hyperactivity were evaluated. Agmatine (5, 10 and 20 mg/kg) was injected to mice 20 min before ethanol (0.5 g/kg) administration and locomotor activity was recorded for 30 min. In the third experiment, agmatine at doses used for combination experiment was administered to mice 20 min before saline injection followed by 30 min of locomotor activity measurements.

Locomotor activity was recorded as a sum of horizontal, vertical and ambulatory activities of the mice in 5-min bins. In the preliminary work, we observed that increases in locomotor activity of the mice reached a maximum level within 30 min following the ethanol injections. Thus, we used a 30-min observation period for evaluating the effects of drugs.

To evaluate the effects of agmatine (5–20 mg/kg) in naive (not ethanol-treated) mice, the drug and saline were also administered to four independent groups of subjects ($n = 7$ for each group) and locomotor activity was recorded with the same protocol.

2.5. Statistics

Data were expressed as mean ± S.E.M. Time course changes in locomotor activity after saline, ethanol and agmatine treatments were analyzed using two-way analyses of variance (ANOVA) test for repeated measures (treatment × time). Data including the effects of ethanol doses and agmatine on total locomotor activity for 30 min were evaluated by one-way ANOVA test. Dunnett's test was used for post-hoc analyses. Bonferroni correction was applied for the post hoc analysis of two-way ANOVA test. The levels of statistical significance were set at $P<0.05$.

3. Results

Changes in locomotor activity of the mice at 5-min intervals after ethanol treatments have been shown in Fig. 1. A two-way ANOVA test indicated a significant effect of treatment [$F(3,28) = 10.909$; $P<0.0001$] and time [$F(5,140) = 56.196$; $P<0.0001$] on the locomotor activity. However, the treatment × time interaction could not reach statistically significant levels [$F(15,140) = 1.150$; $p = 0.319$]. Post hoc analysis revealed that the locomotor activity of 0.5 g/kg ethanol treated group was significantly higher than saline treated control rats between 5 and 25 min of observation period (Dunnett's test, $P_s<0.05$) (Fig. 1).

We also analyzed the effects of ethanol treatment on the total locomotor activity of mice and the effects of agmatine in ethanol-treated mice for 30 min period. Ethanol produced some significant changes on the locomotor activity of mice [$F(3,28) = 10.909$; $P<0.0001$, one-way ANOVA test]. Ethanol significantly increased the locomotor activity of mice at 0.5 g/kg dose ($p = 0.004$, Dunnett's test). Other doses of ethanol did not produce any significant changes in the locomotor activity ($P_s>0.05$, Dunnett's test). Thus, ethanol dose of 0.5 g/kg was selected for combination treatments with agmatine.

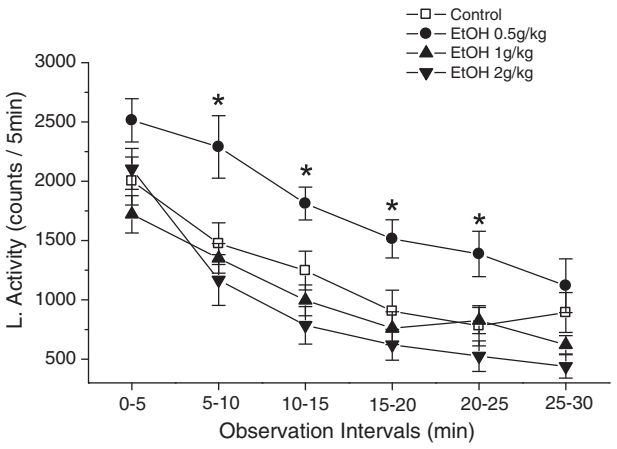

Fig. 1. Time course changes in locomotor activity of mice at 5-min intervals for 30 min ($n = 8$ for each group; EtOH = ethanol; control: saline treatment; *$P<0.05$ significantly different from control).

Agmatine pre-treatment produced some significant inhibitions on ethanol (0.5 g/kg)-induced locomotor hyperactivity in mice [$F(3,28) = 6.503$, $P = 0.002$, one-way ANOVA test]. Post hoc analyses revealed that the inhibitory effects of agmatine were statistically significant for all three doses (Dunnett's test; $P = 0.008$; $P = 0.002$ and $P = 0.003$ for 5, 10 and 20 mg/kg, respectively).

Effects of agmatine (5–20 mg/kg) on ethanol (0.5 g/kg)-induced locomotor hyperactivity at 5-min intervals have been shown in Fig. 2. A two-way ANOVA test indicated a significant effect of treatment [$F(3,28) = 6.503$; $P = 0.002$] and time [$F(5,140) = 22.920$; $P < 0.0001$] on the locomotor activity. However, the treatment × time interaction could not reach statistically significant levels [$F(15,140) = 0.995$; $P = 0.464$]. Post hoc analyses revealed that agmatine (5–20 mg/kg) significantly blocked ethanol (0.5 g/kg)-induced locomotor hyperactivity between 5 and 25 min of observation period (Dunnett's test, $P_s < 0.05$) (Fig. 2).

Agmatine (5–20 mg/kg) did not cause any significant change in the locomotor activity of the naïve (not ethanol-treated) mice [$F(3,24) = 0.124$; $P = 0.945$, one-way ANOVA test] (Fig. 3).

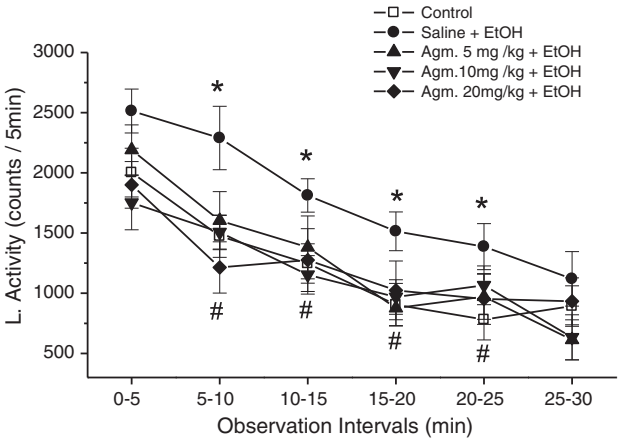

Fig. 2. Time course changes in locomotor activity of mice at 5-min intervals for 30 min after ethanol 0.5 g/kg plus agmatine (n = 8 for each group; control: saline treatment; EtOH = ethanol (0.5 g/kg); Agm.: agmatine; *P<0.05 significantly different from control; #P<0.05 significantly different from ethanol 0.5 g/kg-treated group).

4. Discussion

The results of the present study clearly show that the ethanol-induced locomotor hyperactivity of mice is blocked by agmatine, an arginine metabolite. This is also the first report that indicates the inhibitory effect of agmatine on ethanol-induced locomotor stimulation. The inhibitory effect of agmatine cannot be related to other non-specific effects such as sedation or muscle relaxation involved in its psychotropic properties since it did not cause any significant impairment effect on locomotor activity of the naïve (no-ethanol treated) mice in the present study. Thus, inhibitory effects of agmatine on locomotor hyperactivity induced by a low dose of ethanol are specific.

Doses of ethanol and agmatine used in our study were selected as to the results of our preliminary experiments and previous studies (Kayir and Uzbay, 2002; Uzbay and Kayir, 2003; Uzbay et al., 2010). In our study, because we observed that the locomotor stimulating effect of ethanol was prominent for the first 25 min following the injections and gradually reduced after this time, we selected to use a 30-min observation period to evaluate the effects of ethanol and agmatine on locomotor hyperactivity. Our findings indicate that a significant increase on the locomotor activity by a low dose (0.5 g/kg) of ethanol is consistent with the results of previous studies in which the same dose of ethanol was used in mice (Kayir and Uzbay, 2002; Uzbay and Kayir, 2003).

Responsiveness of the brain reward system and sensitivity to addictive agents are related to gender (Pogun, 2001; Lajtha and Sershen, 2010). Sex-related responses in locomotor activity (Romero and Chen, 2004) and behavioral sensitization (Booze et al., 1999) following nicotine exposure in rats were reported. In our recent study, we also observed sex-related effects of agmatine on caffeine-induced locomotor activity in mice (Uzbay et al., 2010). In this study, agmatine blocked the caffeine-induced locomotor hyperactivity dose dependently in male but not female mice. For this reason, we preferred to use male mice as subjects in the present study.

The inhibitory effects of agmatine on ethanol-induced locomotor hyperactivity may be explained by several mechanisms: First, agmatine binds to α_2-adrenergic receptors (Li et al., 1994) and these receptors are associated with modulation of locomotor hyperactivity in mice (Juhila et al., 2005) and monkeys (Ma et al., 2005). Drugs which bind to these receptors such as clonidine have inhibitory effects on locomotor hyperactivity induced by d-amphetamine (Vanderschuren et al., 2003) and ethanol (Weathersby et al., 1994) in rodents. These data imply that agmatine may inhibit ethanol-induced locomotor hyperactivity by a clonidine like effect. Alternatively, agmatine acts as an agonist at imidazoline receptors (Li et al., 1994; Reis and Regunathan, 1998). This action could be responsible for its inhibitory effects on the locomotor stimulation induced by low dose of ethanol, because imidazoline receptor activity is also shared with clonidine (Ruiz-Ortega et al., 1995; Pineda et al., 1995).

A second explanation may be a central inhibition of NOS by agmatine. Evidences suggest that nitric oxide (NO) plays an important role in the rewarding effects of ethanol. Inhibition of NOS is reported to reduce ethanol consumption (Rezvani et al., 1995) and inhibit ethanol-induced locomotor sensitization (Itzhak and Martin, 2000). Moreover, it has been demonstrated that neuronal NOS knockout mice were resistant to rewarding effects of ethanol (Itzhak and Anderson, 2008; Itzhak et al., 2009). These reports clearly indicate that inhibition of NOS reduces the rewarding effects of ethanol. Moreover, several studies have been shown that NOS inhibitors cause attenuation in locomotor hyperactivity or locomotor sensitization induced by amphetamine (Celik et al., 1999), nicotine (Ulusu et al., 2005), caffeine (Kayir and Uzbay, 2004) and ethanol (Uzbay and Kayir, 2003). As it is known, agmatine inhibits NOS in rat brain (Galea et al., 1996) and NOS inhibition may be responsible for inhibitory effects of agmatine on ethanol-induced locomotor hyperactivity.

Because agmatine selectively blocks NMDA receptor channels in rodents (Yang and Reis, 1999), another possibility explaining the effects of agmatine could be an interaction with NMDA receptors. The role of glutamatergic system and NMDA receptors in development of physical dependence to ethanol is well known (Tsai et al., 1995; Uzbay and Oglesby, 2001). Several authors reported that NMDA receptor antagonists such as MK-801 increase locomotor activity in mice like low doses of ethanol (Irifune et al., 1995; Leriche et al., 2003; Su et al., 2007). These reports complicate to explain via NMDA related mechanisms the agmatine effect on ethanol-induced locomotor hyperactivity. However, it has been shown that ketamine and MK-801, NMDA antagonists, blocked cocaine-induced locomotor hyperactivity in mice (Uzbay et al., 2000b). The results of Uzbay et al.'s (2000b) study support the hypothesis that the NMDA receptor activation contributes to the locomotor hyperactivity produced by psychostimulants. Different doses or animal strains may be the reason for the discrepancy between the studies. Further studies are needed for clarification of this statement.

In conclusion, there was no evidence presented for a relationship between the acute locomotor stimulatory effect of ethanol and agmatine. Thus, our results suggest for the first time that agmatine is able to prevent the acute ethanol-induced hyperactivity in mice.

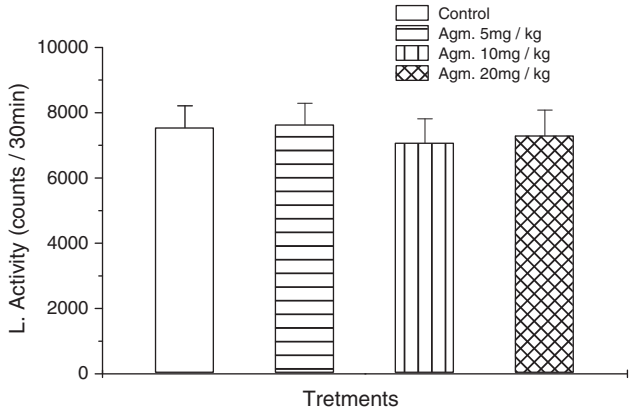

Fig. 3. Effects of agmatine on locomotor activity of naïve (no ethanol-treated) rats (n = 7 for each group).

Because locomotor stimulation is associated with ethanol dependence (Wise and Bozarth, 1987), our data may also provide an evidence for the significance of agmatine in mechanisms of ethanol dependence. However, this is a single set of data that may need further confirmation and extension.

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