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Mianserin, but not Ondansetron, reduces the locomotor stimulating effect of ethanol in preweanling rats

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ABSTRACT

During infancy rats are highly sensitive to the locomotor stimulating effect of ethanol, an effect particularly observed when they are tested during the rising phase of the blood ethanol curve and in a novel environment. According to a recent study infant rats require some degree of stress to get stimulated after being challenged with ethanol. Ethanol-induced stimulation in preweanling rats required the activation of CRH-1 receptors. Considering these antecedents, we explored modulation of the acute stimulating effect of ethanol (2.5 g/kg) by two anxiolytic drugs, Mianserin (2.5 or 5 mg/kg) and Ondansetron (1 or 3 mg/kg). Mianserin attenuated the stimulating effect of ethanol at a dose that did not affect locomotor activity in water-controls, likely acting through 5-HT2 receptors, while Ondansetron, a 5-HT3 antagonist, did not affect this response. These results are consistent with recent findings indicating that one of the mechanisms by which the CRH-1 receptor modulates anxiety depends on sensitization of the 5-HT2 receptor antagonist, and highlight the importance of stress as a modulator of the effects of ethanol during early developmental stages.

1. Introduction

The pharmacological modulation of ethanol-induced locomotor stimulation has been studied mainly in mice, because some heterogeneous strains of mice get stimulated in response to ethanol while rats normally reduce their locomotion in response to similar ethanol doses (Chuck et al., 2006; Masur et al., 1986). However we recently observed that during early stages of development and under specific parameters rats also increase their locomotion after being challenged with a relatively high ethanol dose (Arias et al., 2009b). These conditions include evaluation of the rat during the rising phase of the blood ethanol curve (usually between minutes 5 and 15 after ethanol administration) and in a novel environment (Arias et al., 2009a). If testing occurs in later stages of the intoxication rats show sedation instead of stimulation (Arias et al., 2009a; Arias et al., 2008). If they are habituated to the testing environment the stimulating effect of ethanol is also significantly reduced (Arias et al., 2009a). This particular effect has been consistently observed during the early development of the rat, although more recently we also observed it in later stages of development (Miller et al., 2009). These findings opened the possibility for analysis of pharmacological modulation of this ethanol effect in an alternative rodent model. An obvious question is whether pharmacological manipulations that regulate this particular ethanol effect in mice are also effective in rats. For example, the acute locomotor stimulation induced by ethanol in mice is reduced by means of dopamine D1 or D2 receptor antagonists (Pastor et al., 2005a), mu opioid antagonists (Pastor et al., 2005b) or GABA-B agonists (Chester and Cunningham, 1999). According to our observations these pharmacological treatments also attenuate the stimulating effect of ethanol in infant rats (Arias et al., 2010a; Arias et al., 2009b; Arias et al., 2010b).

In mice, the CRH-1 receptors are critically involved in the development and expression of locomotor sensitization in mice, although CP154,526 (a CRH-1 antagonist) did not attenuate the acute locomotor effect of ethanol (Fee et al., 2007; Pastor, et al., 2008). In recent experiments we tested the modulatory effect of stress on ethanol-induced locomotor activity in preweanling rats. Results indicated that 15-day-old infant rats require some degree of stress to show this stimulating effect (Arias et al., 2010c). In this study stress was operationalized through social isolation (four hours of maternal separation). Preweanling rats showed locomotor stimulation only if they were stressed (isolated) before testing (Arias et al., 2010c), indicating that the stimulating effect of ethanol in preweanling rats is, in fact, due to a synergism between ethanol and stress. Unlike the previous experiments with mice, ethanol-induced stimulation in preweanling rats required the activation of CRH-1 receptors, since CP154,526 completely blocked this effect (Arias et al., 2010c).

Considering these antecedents, we tested modulation of the acute stimulating effect of ethanol by two anxiolytic drugs, Mianserin and

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Ondansetron. Mianserin is a non-selective serotonin antagonist that binds to 5-HT2a and 5-HT2c receptors (Gleason et al., 2001), both of which are functional by the rat's second postnatal week (Darmani and Ahmad, 1999). In adult mice Mianserin blocked the acute stimulant effect of ethanol (Pietrzak and Kubik-Bogucka, 2002; Risinger and Oakes, 1996) and the development of locomotor sensitization to ethanol in mice (Ferraz and Boerngen-Lacerda, 2008). As mentioned, CP154,526, a CRH-1 antagonist, reduced the acute stimulating effect of ethanol in preweanling rats (Arias et al., 2010c) and the development of locomotor sensitization induced by ethanol in mice (Pastor, et al., 2008). Interestingly, one of the mechanisms by which the CRH-1 receptor modulates anxiety behavior depends on sensitization of the 5-HT2 receptor antagonist (Magalhaes et al., 2010). Overall, these antecedents drove us to hypothesize that Mianserin will reduce the stimulating effect of ethanol in preweanling rats. Ondansetron is a 5-HT3 antagonist that attenuated the development of sensitization induced by ethanol in mice (Umathe et al., 2009), although it did not attenuate the acute locomotor effect of ethanol (Le et al., 1997). For this reason the hypothesis that Ondansetron will modulate the acute locomotor activating effect of ethanol does not have strong empirical support.

2. Material and methods

2.1. Subjects

One hundred and twenty-eight Sprague–Dawley pups, representative of 16 litters, were utilized for analysis of ethanol-induced locomotor activity in the present study. Thirty-two rats representative of 4 litters were included in each of Experiments 1a, 2a and 2b, half males and half females. In Experiment 1b we included 39 pups (19 males and 20 females) derived from 5 litters. Additionally, for analysis of blood ethanol concentrations in Experiment 2b, 12 preweanling rats (6 males and 6 females) derived from 3 litters were employed. In all cases no more than one pup of a given sex from the same litter was assigned to the same experimental condition, to avoid confounding treatment effects by litter effects (Holson and Pearce, 1992). Animals were born and reared at the vivarium of the Center for Developmental Psychobiology (Binghamton University, NY) under conditions of constant room temperature (22 ± 1.0 °C), on a 12-hour light 12-hour dark cycle. Births were examined daily and the day of parturition was considered as postnatal day 0 (PD0). All litters were culled to 10 pups (5 females and 5 males, whenever possible) within 48 h after birth. All procedures were in accordance with the guidelines for animal care and use established by the National Institute of Health (1996).

2.2. Procedures

2.2.1. Locomotor activity test

On PD15 pups were separated from the mother and placed in pairs in a holding maternity cage ($45 \times 20 \times 20$ cm) partially filled with clean wood shavings. The floor of the cage was maintained at 35 °C (± 1 °C) through the use of a heating pad. Ninety minutes later body weights were individually recorded (± 0.01 g) and pups received an intraperitoneal administration of Mianserin (Experiment 1a: 0 or 5 mg/kg; Experiment 1b: 0 or 2.5 mg/kg) or Ondansetron (Experiment 2a: 0 or 1 mg/kg: Experiment 2b: 0 or 3 mg/kg). In all cases, volume injected in each pup was 1.0% of their body weight. Vehicle for both drugs was an isotonic saline solution. Ondansetron dosage was selected on the basis of previous studies using this drug to analyze the role of 5-HT3 receptors in ethanol-mediated sensitization in mice (Umathe et al., 2009). These authors showed that 1 mg/kg blocked the development or expression of sensitization induced by ethanol. The highest dose that we employed (3 mg/kg) is considerably higher than those conventionally used in adult rats in studies on alcohol or in infant rats (see, for example, Wilson et al., 1998). In a pilot study we observed that Mianserin doses (between 5 and 20 mg/kg) employed in prior studies to modulate the stimulating effect of ethanol in mice (Pietrzak and Kubik-Bogucka, 2002; Risinger and Oakes, 1996; Ferraz and Boerngen-Lacerda, 2008) considerably affected locomotion in untreated infant rats. For this reason, for our study we selected doses of 2.5 and 5 mg/kg to minimize the effect on spontaneous locomotion.

After receiving the injection, pups were placed again in pairs in the holding chamber. Thirty minutes after administration of the serotonin antagonist pups received an intragastric (i.g.) administration of 0 or 2.5 g/kg ethanol (volume administered was equivalent to 0.015 ml per gram of body weight of a 21% ethanol solution). Pups assigned to the control condition (0 g/kg) received only vehicle (water). Intragastric administrations were performed using a 10-cm length of polyethylene tubing (PE-10 Clay Adams, Parsippany, New Jersey) attached to a 1 ml syringe with a 27 G × 1/2 needle. This tubing was gently introduced through the mouth and slowly pushed into the stomach. The entire procedure took less than 20 s per pup. Five minutes after ethanol administration locomotor activity was evaluated for 10 min (minutes 5–15 after ethanol administration). The testing environment was a Plexiglas open field ($42 \times 42 \times 30$ cm; VersaMax Animal Activity Monitoring System, Accuscan Instruments, Columbus, OH, USA). In this apparatus, locomotion was detected by interruption of eight pairs of intersecting photocell beams evenly spaced along the walls of the testing environment. This equipment was situated in sound-attenuating chambers ($53 \times 58 \times 43$ cm) equipped with a light and fan for ventilation and background noise. Consecutive photocell beam interruptions were translated to distance traveled in cm by the VersaMax. This dependent variable takes into account the path the animal takes, and is an accurate indicator of ambulatory activity. Immediately after the locomotor activity test pups were returned to their homecage.

2.2.2. Determination of blood ethanol concentrations (BECs)

An independent group of P15 preweanling rats was utilized to determine whether the effect of the lower Mianserin dose (2.5 mg/kg) on ethanol-induced activity may be explained by changes in ethanol's pharmacokinetic potential induced by the serotonin antagonist. The BECs were measured only in response to this Mianserin dose only because it was the only treatment that attenuated the ethanol effect without affecting locomotor activity in water controls. In previous studies it was found that Mianserin can increase ethanol plasma levels in mice (Cott and Ogren, 1980). Procedures were similar to those described for the locomotor activity test. Subjects were treated with Mianserin (0 or 2.5 mg/kg), given the ethanol dose (2.5 g/kg) 10 min later, then were sacrificed. This time-point corresponds to the middle of the locomotor activity test, which was performed between minutes 5 and 15 after being treated with ethanol. Trunk blood was obtained following decapitation. Blood samples were collected using a heparinized capillary tube. The blood samples were immediately centrifuged (6000 rpm; Micro-Haematocrit Centrifuge, Hawksley & Sons LTD, Sussex, England) and stored at −70 °C. BECs were determined using an AM1 Alcohol Analyzer (Analox Instruments, Lunenburg, MA). Calculation of BECs was made by oxidizing ethanol to acetaldehyde in the presence of ethanol oxidase. The apparatus measures the rate of oxygen required by this process, which is proportional to ethanol concentration. BECs were expressed as milligrams of ethanol per deciliter of body fluid (mg/dl = mg%).

2.3. Data analysis

Locomotor activity data from these experiments were analyzed by means of between-factor ANOVAs, in which the factors were sex (male or female), ethanol treatment [0 (water) or 2.5 g/kg] and the corresponding serotonin antagonist dosage (Mianserin: 0 or 5 mg/kg for Experiment 1a, and 0 or 2.5 mg/kg for Experiment 1b; Ondansetron:

0 or 1 mg/kg for Experiment 2a, and 0 or 3 mg/kg, for Experiment 2b). The dependent variable was distance traveled in centimeters. BECs were analyzed by means of a one-way between-factor ANOVA including Mianserin dose (0 or 2.5 mg/kg) as the only variable. Sex did not exert a significant effect in any of the experiments nor did it interact with the remaining factors in any of the analyses performed for the present study. Hence, for a clearer presentation of the results, data were collapsed across this variable. Significant main effects and/or interactions were further analyzed by means of follow-up ANOVAs and post-hoc analysis (Tukey post-hoc tests). All inferential analyses conducted in the present study employed an α level equal to 0.05.

3. Results

3.1. Experiment 1a

The analysis of the data indicated a significant effect of ethanol [$F(1,28) = 8.51$, $p<0.05$] and Mianserin [$F(1,28) = 7,51$, $p<0.05$]. As can be observed in Fig. 1a, ethanol significantly increased locomotor activity (distance traveled) when compared to water controls, regardless the Mianserin treatment. Locomotor activity was reduced by Mianserin about equally whether subjects were given ethanol or water. This effect of Mianserin on water-treated controls precludes a decision of whether the 5-HT2 receptors mediate the stimulating effect of ethanol, so in Experiment 1b we used a lower Mianserin dose that does not affect locomotor activity in water controls.

3.2. Experiment 1b

The ANOVA conducted with the data of the present experiment (Fig. 1b) revealed a significant effect of ethanol [$F(1,35) = 18.96$, $p<0.05$] and Mianserin [$F(1,35) = 14.31$, $p<0.05$] treatments, and a significant interaction between these factors [$F(1,28) = 7.47$, $p<0.05$]. According to the post-hoc analyses, distance traveled by pups given ethanol and vehicle was significantly higher than in the remaining groups. Mianserin at this dose (2.5 mg/kg) did not affect locomotor activity in water-treated controls. This result indicates that Mianserin specifically reduced ethanol-induced locomotor stimulation.

The analysis of BECs as a function of the Mianserin dose indicated no significant effects. These BECs (mean and standard error of the mean) were as follows: Group Mianserin-ethanol: 165.21 ± 11.5 mg%; Group vehicle-ethanol: 173.17 ± 13.1 mg%.

3.3. Experiment 2a

Fig. 2a represents distance traveled by pups as a function of Ondansetron (0 or 1 mg/kg) and ethanol (0 or 2.5 g/kg). The ANOVA

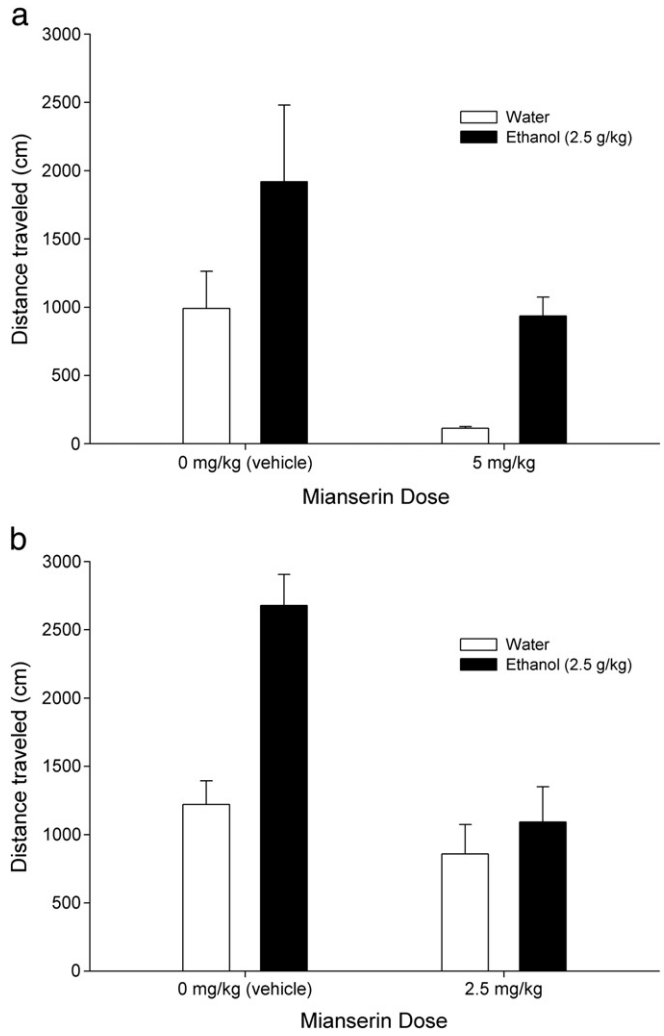

Fig. 1. a: Locomotor activity (distance traveled, cm) as a function of ethanol (0 or 2.5 g/kg) and Mianserin (0 or 5 mg/kg) treatments. b: Distance traveled (cm) as a function of ethanol (0 or 2.5 g/kg) and Mianserin (0 or 2.5 mg/kg) treatments. Vertical lines illustrate standard errors of the means.

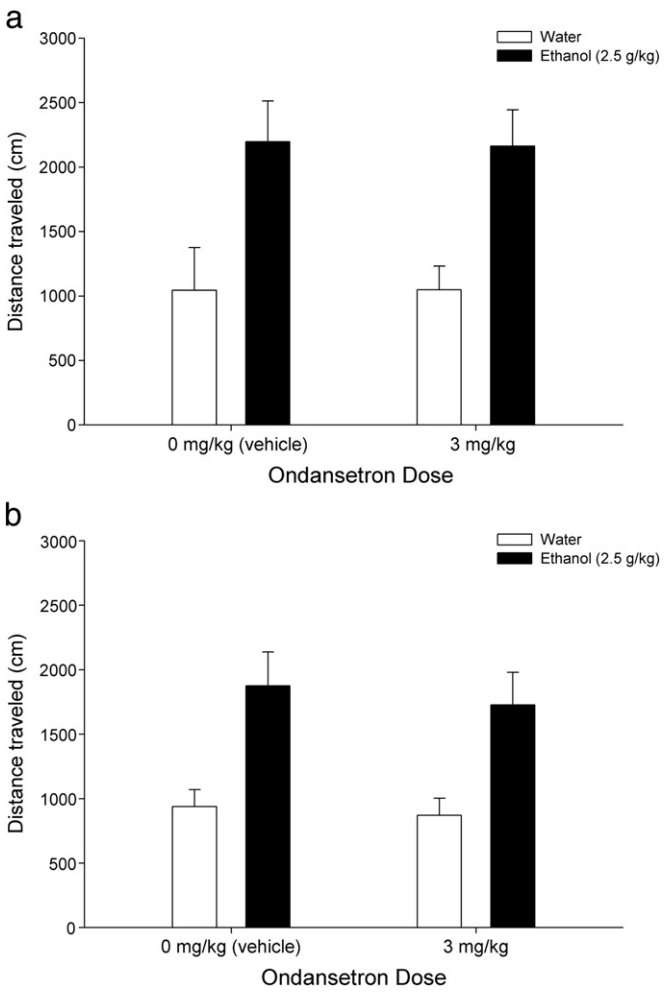

Fig. 2. a: Locomotor activity (distance traveled, cm) as a function of ethanol (0 or 2.5 g/kg) and Ondansetron (0 or 1 mg/kg) treatments. b: Distance traveled (cm) as a function of ethanol (0 or 2.5 g/kg) and Ondansetron (0 or 3 mg/kg) treatments. Vertical lines illustrate standard errors of the means. The ANOVA revealed a significant main effect of ethanol.

revealed only a significant effect of ethanol [$F(1,28) = 15.92$, $p<0.05$], indicating that ethanol significantly increased locomotor activity. Since Ondansetron at the 1 mg/kg dose did not exert any effect in ethanol or water treated pups, in the following experiment we increased the dose of the serotonin antagonist.

3.4. Experiment 2b

Experiment 2b tested whether ethanol-induced locomotor stimulation was attenuated by 3 mg/kg Ondansetron (see Fig. 2b). The ANOVA revealed only a significant effect of ethanol [$F(1,28) = 19.20$, $p<0.05$], indicating that subjects given ethanol traveled significantly more distance than water-controls, but no effect of Ondansetron.

4. Discussion

Ethanol-induced locomotor stimulation was significantly reduced by Mianserin at a dose that did not affect locomotor activity in water-controls (Experiment 1b). According to Experiment 2 this ethanol effect was not modulated by Ondansetron. The present results extend our prior tests of pharmacological modulation of the acute stimulating effect of ethanol in rats during early development. We have shown that this ethanol effect can be reduced by means of dopamine (Arias et al., 2010a) or mu opioid (Arias et al., 2009b; Arias et al., 2010b) antagonists and by GABA B agonists (Arias et al., 2009b). Similar pharmacological manipulations are also effective in attenuating the acute locomotor stimulating effect of ethanol in adult mice (Chester and Cunningham, 1999; Pastor et al., 2005a; Pastor et al., 2005b; Pietrzak and Kubik-Bogucka, 2002; Risinger and Oakes, 1996). Overall these studies suggest that the acute effect of ethanol in mice and preweanling rats is mediated, at least partially, by the same neurochemical systems. However, the mechanisms that regulate this acute effect of ethanol apparently are not identical: CRH-1 antagonists attenuated the acute stimulating effect of ethanol in preweanling rats (Arias et al., 2010c) but not in mice (Fee, et al., 2007; Pastor et al., 2008). This difference may be because the stimulating effect of ethanol in preweanling rats requires a certain degree of stress. Ethanol did not increase locomotor activity in preweanling rats unless they were separated from their homecage before testing (Arias et al., 2010c). Hence, this particular effect of ethanol seems to be more a synergism between ethanol and stress than a mere effect of ethanol (Arias et al., 2010c). This hypothesis is also supported by the fact that prior habituation to the testing environment reduces the stimulating effect of ethanol in infant rats (Arias et al., 2009a).

As mentioned, CP154,526, a CRH-1 receptor antagonist blocked the stimulating effect of ethanol in preweanling rats (Arias et al., 2010c). One of the mechanisms by which the CRH-1 receptor modulates anxiety behavior depends on sensitization of the 5-HT2 receptor antagonist (Magalhaes et al., 2010). CRF acting upon CRF1 receptors sensitizes the 5-HT2 receptor, which is correlated with increased anxiety in mice (Magalhaes et al., 2010). The fact that Mianserin attenuated the stimulating effect of ethanol in the present study is congruent with this finding, since Mianserin, a non-selective 5-HT2 antagonist that binds to 5HT-2a and 5-HT2c receptors, exerts its action partially through 5-HT2 receptors. Both serotonin receptors are functional by the second postnatal week of life (Darmani and Ahmad, 1999). The employment of more specific antagonists will be required to understand more deeply the pharmacological mechanism by which stress and ethanol interact in the preweanling rat to increase locomotor activity.

Ondansetron did not reduce the stimulating effect of ethanol in our study. This result is in agreement with studies conducted with mice (Le et al., 1997). Hence, the 5-HT3 receptor seems not to participate in the interaction between stress and ethanol in preweanling rats.

Campbell and Raskin (1978) reported that at PD15 (the age of the subjects employed in the present study), there is a peak in locomotor activity expressed when the animal is tested alone in an unfamiliar environment. According to these authors this effect reflects fear or distress rather than curiosity (Campbell and Raskin, 1978). The fact that Mianserin, but not Ondansetron, reduced locomotor activity suggests that the mechanism underlying this effect is mediated by 5-HT2 rather than 5-HT3 receptors.

In sum, our study verified that a) Mianserin attenuates the stimulating effect of ethanol, likely acting through 5-HT2 receptors, and b) Ondansetron, a 5-HT3 antagonist, does not affect this response to ethanol in this ontogenetic stage of development. These results expand evidence indicating that stress modulates the stimulating effect of ethanol in preweanling rats. In previous studies we have shown that the capability of ethanol to induce locomotor activating effects in infant rats is restricted to a specific post-administration interval corresponding to the rising phase of the blood ethanol curve, approximately during the first twenty minutes after ethanol administration (Arias et al., 2009a, 2009b, 2009c). When blood ethanol levels reach peak values (30 min after ethanol administration) ethanol induces sedation (Arias et al., 2009a, 2009b, 2009c). Interestingly, this temporal profile of the locomotor response induced by ethanol in preweanling rats seems to correlate with the biphasic motivational properties of the drug. Using a second order procedure Molina and collaborators reported appetitive effects of ethanol during the rising phase of the blood ethanol curve, and aversive effects when blood ethanol levels reached peak values (Molina et al., 2007). Given the apparent association between ethanol-induced locomotor stimulation and reinforcement during this ontogenetic period, the present results also open the question of whether stress is an important component regulating the rewarding effect of ethanol in preweanling rats.

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