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Dopamine receptors modulate ethanol's locomotor-activating effects in preweanling rats

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Abstract

Near the end of the second postnatal week motor activity is increased soon after ethanol administration (2.5 g/kg) while sedation-like effects prevail when blood ethanol levels reach peak values. This time course coincides with biphasic reinforcement (appetitive and aversive) effects of ethanol determined at the same age. The present experiments tested the hypothesis that ethanol-induced activity during early development in the rat depends on the dopamine system, which is functional in modulating motor activity early in ontogeny. Experiments 1a and 1b tested ethanol-induced activity (0 or 2.5 g/kg) after a D1-like (SCH23390; 0, 0.015, 0.030 or 0.060 mg/kg) or a D2-like (sulpiride; 0, 5, 10 or 20 mg/kg) receptor antagonist, respectively. Ethanol-induced stimulation was suppressed by SCH23390 or sulpiride. The dopaminergic antagonists had no effect on blood ethanol concentration (Experiments 2a and 2b). In Experiment 3, 2.5 g/kg ethanol increased dopamine concentration in striatal tissue as well as locomotor activity in infant Wistar rats. Adding to our previous results showing a reduction in ethanol induced activity by a GABA B agonist or a nonspecific opioid antagonist, the present experiments implicate both D1-like and D2-like dopamine receptors in ethanol-induced locomotor stimulation during early development. According to these results, the same mechanims that modulate ethanol-mediated locomotor stimulation in adult rodents seem to regulate this particular ethanol effect in the infant rat.

Keywords

Dopamine; Sulpiride; SCH23390; ethanol; stimulation; infant rat

Genetically heterogeneous rats are particularly sensitive to ethanol's motivational effects during infancy. Ethanol consumption is much higher in 8-and 12-day-old infant rats than in later stages of development (Sanders & Spear, 2007; Truxell, Molina, & Spear, 2007). In addition, during the first and second postnatal weeks rats are highly sensitive to appetitive reinforcement by ethanol (Arias & Chotro, 2006b; Molina, Pautassi, Truxell, & Spear, 2007; Petrov, Varlinskaya, & Spear, 2003) and seem more resistant to aversive consequences of the drug (Arias & Chotro, 2006b; Hunt, Spear, & Spear, 1991). Acute tolerance to motor impairment effects of ethanol is also more marked in infant than in adult heterogeneous rats (Arias, Molina, Mlewski, Pautassi, & Spear, 2008; Silveri & Spear, 2001). Furthermore, we

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recently reported that infant heterogeneous rats are also sensitive to ethanol's activating effect (Arias, Mlewski, Molina, & Spear, 2009; Arias, Mlewski, Molina, & Spear, 2009a, 2009b; Arias et al., 2008).

Infantile sensitivity to ethanol-induced locomotor stimulation contrasts with the locomotor response induced by ethanol in adult heterogeneous rats. Acute administration of ethanol reduces locomotion in adult outbred rat strains (Chuck, McLaughlin, Arizzi-LaFrance, Salamone, & Correa, 2006; Correa, Arizzi, Betz, Mingote, & Salamone, 2003). Yet ethanol induces locomotor activating effects in adult inbred rats genetically selected for excessive ethanol consumption (Agabio et al., 2001; Colombo et al., 1998; Paivarinta & Korpi, 1993; Quintanilla, 1999; Rodd et al., 2004; Waller, Murphy, McBride, Lumeng, & Li, 1986) or in rats with higher baseline activity levels, referred as high responders (Cools & Gingras, 1998; Hoshaw & Lewis, 2001). In these cases, low ethanol doses (below 1 g/kg) induce locomotor activating effects, while higher ethanol doses suppress locomotor activity. However, during the infant period, moderate to high ethanol doses (1.25 or 2.5 g/kg v/v) induce clear stimulating effects in heterogeneous rat strains (Arias et al., 2009; Arias, Mlewski, Molina et al., submitted; Arias et al., 2008). The stimulant effect of ethanol was observed during the second postnatal week of life, when infants were evaluated in terms of locomotor activity during the initial stage of the acute intoxication (5-20 minutes post-administration, Arias et al., in press-b; Arias, Mlewski, Molina et al., submitted; Arias et al., 2008); in contrast, sedation-like effects were clearly observed in later stages of the intoxication process (30-35 or 60-65 min). It is noteworthy that this time course of ethanol's motor effects in infant rats coincides with the time course of its biphasic motivational effects (Molina et al., 2007) During the rising phase of the blood ethanol curve, relatively high ethanol doses exerted locomotor activating effects (Arias et al., 2008) as well as appetitive reinforcement (Molina et al., 2007). When blood ethanol levels reached peak values, ethanol suppressed locomotion (Arias et al., 2008) and promoted aversive reinforcement (Molina et al., 2007). These results argue in favor of the hypothesis that a common mechanism is responsible for motor-activation and motivational effects of ethanol (Robinson & Berridge, 1993; Wise & Bozarth, 1987). Overall, these antecedents suggest that understanding mechanisms that regulate ethanol-induced stimulation in developing rats may provide insight into mechanisms underlying developing motivational effects of ethanol.

A considerable number of studies have shown that ethanol-induced locomotor stimulation is mediated by the dopaminergic system in adult rodents (Boehm, Piercy, Bergstrom, & Phillips, 2002; Di Chiara, Acquas, & Tanda, 1996; Di Chiara & Imperato, 1985). Systemic or local (in nucleus accumbens or ventral tegmental area, VTA) ethanol administration induces dopamine release in nucleus accumbens (Di Chiara & Imperato, 1985; Tupala & Tiihonen, 2004). In vitro studies have shown that ethanol directly excites dopaminergic neurons in VTA (Appel, Liu, McElvain, & Brodie, 2003; Brodie, Pesold, & Appel, 1999). Ethanol-induced locomotor activating effects in adult rodents also have been modulated by dopaminergic drugs. Antagonists of D1-like receptors (such as SCH23390) or D2-like (such as sulpiride) receptors reduce ethanol mediated locomotor stimulation in adult mice (Le, Tomkins, Higgins, Quan, & Sellers, 1997; Matsuzawa, Suzuki, Misawa, & Nagase, 1999; Pastor, Miquel et al., 2005). These results indicate that both D1-like and D2-like receptors are involved in the locomotor activating effects of ethanol.

The dopaminergic system is functional in modulating motor activity as early as the prenatal period (Moody, Robinson, Spear, & Smotherman, 1993). In the fetal and neonatal rat the dopaminergic system regulates oral capture of the nipple (Becker & Smotherman, 1996) as well as hedonic responses by the fetus elicited by milk (Smotherman & Robinson, 1995). This neurochemical system rapidly develops during the infantile period, particularly during the second postnatal week of life. For example, density of D2 receptors in nucleus

accumbens is significantly higher in 14-day-old rats than in younger infants (7-day-olds, Tarazi & Baldessarini, 2000). By the second postnatal week of life there is evidence that the dopaminergic system participates in locomotor activity and stereotypic behavior (McDougall, Arnold, & Nonneman, 1990) and modulates locomotor and motivational effects induced by psychostimulants (McDougall, Crawford, & Nonneman, 1992; McDougall, Duke, Bolanos, & Crawford, 1994; Pruitt, Bolanos, & McDougall, 1995).

The goal of the present study is to determine in infant heterogeneous rats whether the dopaminergic system is involved in the acute stimulating effect of ethanol. Considering the above antecedents the working hypothesis guiding the present investigation is that both D1-like and D2-like receptor antagonists will attenuate ethanol's activating effects in infant rats. Due to the possible association between ethanol's stimulating and reinforcing effects during the infant period (Arias, Mlewski, Molina & Spear, 2009a; Arias et al., 2009b; Arias et al., 2008), the present study may also contribute to the understanding of mechanisms underlying ethanol's reinforcing effects during this ontogenetic period characterized by heightened ethanol affinity. In Experiment 1 we tested whether specific D1-like (SCH23390) or D2-like (sulpiride) receptor antagonists would attenuate ethanol-mediated locomotor activation in infant Sprague-Dawley rats. In Experiment 2 we assessed possible effects of these drug treatments upon ethanol pharmacokinetics. In Experiment 3 the acute motor response to ethanol was analyzed in infant rats from an alternative rat strain (Wistar) in order to further establish the generality of our results. In this last experiment we also analyzed striatal tissue concentration of dopamine at the same post-administration interval in which hyperactivity induced by ethanol was detected. Considering previous research implicating the dopamine system in the stimulating effects of drugs of abuse (Robinson & Berridge, 1993; Wise & Bozarth, 1987), including ethanol (Imperato and DiChiara, 1986), we expected that the hyperactivity induced by ethanol during the infant period would be associated with increased dopamine activity.

Experiment 1

Relatively high ethanol doses induce clear locomotor activating effects during the second postnatal week of life (Arias et al., in press-a; Arias et al., in press-b; Arias et al., 2008). This ethanol effect was observed when infant rats were tested in a novel environment during the rising phase of the blood ethanol curve (Arias et al., 2008; Arias et al., 2009). In the first experiment we tested the hypothesis that this stimulating effect of ethanol during the infant period is modulated by dopamine receptors. Prior to assessment of ethanol-induced activity, the D1-like receptor antagonist SCH23390 (Experiment 1a) or the D2-like receptor antagonist sulpiride (Experiment 1b) were administered to rats on postnatal day 12 (PD12) 30 min before administration of ethanol (0 or 2.5 g/kg). SCH23390 or sulpiride have been found to attenuate the stimulant and the rewarding effect of ethanol in adult rodents (Le et al., 1997; Matsuzawa et al., 1999; Pastor, Miquel et al., 2005)

Material and Methods

Subjects—Eighty-eight Sprague-Dawley rat pups (40 females and 48 males), representative of 11 litters, were tested in Experiment 1a, and another 120 pups (60 males and 60 females) representative of 15 litters were employed in Experiment 1b. Animals were born and reared at the vivarium of the Center for Development and Behavioral Neuroscience (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 hours after birth. All procedures were in accordance with the guidelines for animal care and use established by the National Institutes of Health

(1986) and maintained by the Institute of Laboratory Animal Resources (1996) as indicated by the Binghamton University's institutional animal care and use committee.

Procedures

SCH23390, sulpiride and ethanol treatments: On PD 12 pups were separated from their mothers and randomly assigned to one of the eight independent conditions defined by orthogonal combination of the following variables: ethanol (0 or 2.5 g/kg), and SCH23390 (Experiment 1a: 0, 0.015, 0.03 or 0.06 mg/kg) or sulpiride (Experiment 1b: 0, 5, 10 or 20 mg/kg) treatments. Pups from a given litter were evenly distributed across drug conditions, and in no case was more than one subject from a given litter assigned to the same group. Pups were placed in a holding maternity cage (45 × 20 × 20 cm) partially filled with clean wood shavings. The floor of the cage was maintained at 33° C (± 1° C) through the use of a heating pad. Thirty minutes later body weights were individually recorded (± 0.01 g) and pups received an intraperitoneal injection of SCH23390 (Experiment 1a: 0, 0.015, 0.03 or 0.06 mg/kg) or sulpiride (Experiment 1b: 0, 5, 10 or 20 mg/kg). Vehicle was an isotonic saline solution for SCH23390, while sulpiride was dissolved in distilled water containing 0.1% acetic acid (Crescimanno, Mannino, Casarrubea, & Amato, 2000). Volume injected was 1.0 % of their body weight. SCH23390 and sulpiride dosage was based on doses previously found effective for attenuating the stimulatory effect of ethanol in adult mice (Pastor, Miquel et al., 2005). In addition, these doses also blocked cocaine-mediated conditioned place preference in preweanling rats (Pruitt, Bolanos and McDougall, 1985). After receiving the injection, pups were placed again in couples in the holding chamber. Thirty minutes after SCH23390 or sulpiride administration 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; vehicle was distilled 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 seconds per pup.

Behavioral assessment: Locomotor activity: Five minutes after ethanol administration, locomotor activity was evaluated in a novel environment consisting of a Plexiglas container (10 × 10 × 12 cm). The floor of this apparatus was lined with absorbent paper. A new piece of paper was employed for each animal. A circuit board (2-cm in width) surrounded the four sides of each chamber. This board had six infrared photo emitters and six infrared photo-receptors. The photo beams crossed the chamber generating a matrix of nine cells that allowed measurement of overall amount of activity. Custom-made software served to analyze the number of beams crossed by each subject every 10th of a second. Each activity test had a total duration of 8 min and data were collected in 1-min bins. In preliminary studies, this measure (number of beams broken per minute) was highly and significantly correlated with time spent wall climbing and walking in 12-day-old Sprague-Dawley rats during a 5-min test ($r_{xy} = 0.84$, $p < 0.001$, $n=15$).

Data analysis—The factorial design was defined by the following variables: SCH23390 (Experiment 1a: 0.00, 0.015, 0.03 or 0.06 mg/kg) or sulpiride (Experiment 1b: 0, 5, 10 or 20 mg/kg) treatment and ethanol treatment (0 or 2.5 g/kg). No significant effect of sex or interaction with the remaining factors was found in any of the analyses performed in these experiments. Hence, for the inferential analysis and descriptive presentation of the results, data were collapsed across sex. Locomotor activity data were analyzed by means of 2 (ethanol treatment) by 4 (SCH23390 or sulpiride treatment) between factor ANOVAs. Significant effects or interactions indicated by the ANOVAs were further analyzed through post-hoc tests (Newman Keuls post-hoc test with a Type I error set at 0.05). When

appropriate and regardless of whether the F test resulted in a significant effect (Wilcox, 1987), planned comparisons using the overall error term from the ANOVA were also conducted to explore effects predicted by the working hypothesis that guides the current study.

Results

Experiment 1a—Figure 1 depicts locomotor activity scores as a function of ethanol and SCH23390 treatments. Ethanol stimulated locomotor activity, an effect that apparently was attenuated by SCH23390. The ANOVA confirmed these impressions, indicating a significant main effect of SCH23390 [$F(3,80) = 19.58$, $p < 0.0001$], which interacted with ethanol treatment [$F(3,80) = 3.63$, $p < 0.05$]. Post-hoc analyses revealed that pups treated with ethanol and vehicle (group EtOH-0) had significantly higher locomotor activity scores than those treated with water and vehicle (group water-0) or those given ethanol and SCH23390 (groups EtOH-0.015, EtOH-0.03 or EtOH-0.06), a result indicating that SCH23390 suppressed locomotor stimulation induced by ethanol. This result was additionally confirmed by the lack of significant difference between pups given ethanol and SCH23390 (groups EtOH-0.015, EtOH-0.03 or EtOH-0.06) and their respective water-treated controls (groups Water-0.015, Water-0.03 and Water-0.06, respectively). Locomotor activity of water-treated pups also varied as a function of the SCH23390 treatment. Pups given water and 0.06 mg/kg moved less than those given water and 0 or 0.015 mg/kg SCH23390.

Experiment 1b—Figure 2 represents locomotor activity scores as a function of ethanol (0 or 2.5g/kg) and sulpiride (0, 5, 10 or 20 mg/kg) treatments. As was the case in Experiment 1a, ethanol increased locomotor activity, an effect that apparently occurred only in vehicle-treated pups. Sulpiride reduced the stimulant effect of ethanol. The ANOVA indicated significant main effects of ethanol and sulpiride treatments [$F(1,112) = 5.82$, $p < 0.05$, and $F(3,112) = 5.90$, $p < 0.001$, respectively]. Post-hoc analyses indicated that pups given ethanol showed higher locomotor activity scores than water treated controls. In addition, locomotor activity scores exhibited by pups given 20 mg/kg sulpiride were significantly lower than those given vehicle or 5 mg/kg sulpiride.

Guided by the working hypothesis of the present study planned comparisons were also conducted to explicitly compare locomotor activity as a function of ethanol and sulpiride treatments. These analyses revealed that pups from group EtOH-0 moved more than their corresponding water controls (group Water-0; $F(1,112) = 7.70$, $p < 0.01$), while groups EtOH-5, EtOH-10 and EtOH-20 did not significantly differ from their respective controls (Water-5, Water-10 and Water-20). In addition, pups given ethanol and vehicle also showed higher activity scores than pups given ethanol and sulpiride (5, 10 or 20 mg/kg; $F(1,112) = 6.96$, $p < 0.01$; $F(1,112) = 5.56$, $p < 0.05$; $F(1,112) = 15.45$, $p < 0.001$, respectively). Pups from group Water-20 showed lower locomotor activity scores than those from group Water-0, indicating that the highest sulpiride dose also affected locomotion.

In the present experiment ethanol again increased locomotor activity in 12-day-old rats. This effect was significantly reduced by peripheral administration of sulpiride or SCH23390 at doses that did not attenuate locomotor activity in rats given vehicle.

Experiment 2

The goal of the second experiment was to test whether the dopamine antagonists utilized in Experiment 1 affect ethanol absorption and metabolism at the time in which pups were tested in terms of locomotor activity. Specifically, we tested whether blood ethanol concentration induced by 2.5g/kg at the post-administration time employed in Experiment 1

is affected by SCH23390 (Experiment 2a) or sulpiride (Experiment 2b) in 12-day-old pups. Pups were injected with either SCH23390 (Experiment 2a: 0, 0.015, 0.03 or 0.06 mg/kg) or sulpiride (Experiment 2b: 0, 5, 10 or 20 mg/kg) before ethanol administration (2.5 g/kg). Blood ethanol levels were determined by taking blood 10.5 minutes after ethanol administration, the time point that coincides with the middle of the activity test conducted in Experiment 1.

Material and Methods

Subjects—Forty-five Sprague-Dawley pups (13 females and 9 males for Experiment 2a, and 9 females and 14 males for Experiment 2b), representative of 6 litters were utilized.Animals were born and reared at the vivarium of the Center for Development and Behavioral Neuroscience (Binghamton University, NY). Housing conditions were the same to those described in Experiment 1.

Procedures—On PD 12 pups were separated from their mothers and randomly assigned to one drug condition: SCH23390 (Experiment 2a: 0, 0.015, 0.03 or 0.06 mg/kg) or sulpiride (Experiment 2b: 0, 5, 10 or 20 mg/kg). Pups were maintained under the same conditions as those described for Experiment 1. SCH23390, sulpiride and ethanol were administered following the procedures employed in Experiment 1. Pups were sacrificed 10.5 minutes after receiving their ethanol dose (2.5 g/kg), a time point that coincides with the middle of the activity test conducted in Experiment 1. Trunk blood was obtained following decapitation. Blood samples were collected using a heparinized capillary tube. They were immediately centrifuged (6,000 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%).

Data analysis—The design of the present experiments were defined by SCH23390 treatment (0, 0.015, 0.03 or 0.06 mg/kg) for Experiment 2a, and sulpiride treatment (0, 5, 10 or 20 mg/kg) for Experiment 2b. Blood ethanol concentrations were analyzed by means of one-way between-factor ANOVAs. Significant effects were further analyzed through post-hoc tests (Newman Keuls post-hoc test with a Type I error set at 0.05).

Results

The corresponding ANOVAs revealed that there were no significant effects of SCH23390 or sulpiride treatments on BECs (see Table 1). According to these experiments, at the time in which subjects of Experiment 1 were tested in terms of locomotion, ethanol pharmacokinetics were not affected by the administration of D1-like or D2-like receptor antagonists.

Experiment 3

Experiment 3 pursued two goals. First, we sought replication of the stimulating effect induced by ethanol in an alternative heterogeneous rat strain (Wistar) during the infant period. All previous studies showing ethanol-mediated locomotor stimulation in infant rats were conducted with Sprague-Dawley rats (Arias, et al., 2008; Arias et al., 2009). The second goal of the experiment was to analyze dopamine concentration in striatum during the post-administration interval in which ethanol induces locomotor stimulation in infant rats. Results derived from this analysis may be relevant for the study of possibly common mechanisms regulating ethanol-induced locomotor stimulation and ethanol-induced

motivation. Dorsal striatum was selected on the basis of prior research showing that during the rising phase of the blood ethanol curve, ethanol increases local cerebral metabolic rates for glucose in this area in Sprague-Dawley rats (Lyons, Whitlow, & Porrino, 1998). Furthermore, in a different study conducted with Wistar rats relatively high ethanol doses (2.25 g/kg) elevated intracellular levels of dopamine in dorsal striatum (Melendez, Rodd-Henricks, McBride, & Murphy, 2003). This ethanol effect upon the dorsal striatum has been associated with the stimulating effect of the drug (Melendez et al., 2003), since increased motor activity leads to similar changes in cerebral metabolism in dorsal striatum (Brown & Sharp, 1995; Ebrahimi-Gaillard, Beck, Wree, & Roger, 1994).

Material and Methods

Subjects—Twenty-five Wistar pups (11 males and 24 females) representative of 7 litters were utilized. Animals were born and reared at the vivarium of the Instituto de Investigacion Medica Mercedes y Martin Ferreyra, (Cordoba, Argentina). Housing conditions were similar to those described for Experiment 1.

Procedures

Locomotor activity assessment: Locomotor activity induced by ethanol (0 or 2.5 g/kg) was evaluated in 16-day-old infant rats. This age was selected on the basis of the results obtained in a preliminary study in which we observed clear locomotor activating effects of ethanol in Wistar rats at this age (Mlewski et al., 2007). According to previous data from our laboratory BALs generated by this ethanol dose 7.5 min after ethanol administration in Wistar rats were 104.14 ± 11.65 mg% (mean ± standard error of the mean, see Mlewski et al., 2007). Procedures utilized to evaluate ethanol-mediated locomotor activity were the same as those described for Experiments 1a and 1b, except for details of the dependent variable. The floor of the testing environment was divided in four quadrants, and two trained researchers blind to the experimental treatments estimated horizontal activity in terms of the number of quadrants crossed. A given subject was considered to cross a specific quadrant when the two forepaws and the head passed through the line that divided the quadrants.

Striatal dopamine concentration analysis: Immediately after behavioral assessment, pups were sacrificed. The striatum was quickly dissected over ice, homogenized and deproteinized in cold 0.2 M perchloric acid (1/40 w/v). After centrifugation (10 min at 15,000 ×g), supernatants were filtered through a 0.22 μm PVDF membrane (Millipore, Sao Paulo, SP, Brazil). Levels of dopamine were analyzed using HPLC with electrochemical detection. Dopamine was separated on a reverse-phase column (Zorbax Eclipse XDB, C-8, 4.6 × 150 mm, 3.5μm, Agilent Technologies, Inc. Santa Clara CA, USA) with a mobile phase consisting of 0.03 M monocloroacetic/citric acid, 0.1 mM EDTA, 5 mM potassium chloride, and 3 % acetonitril (pH 3.2), at a flow rate of 0.8 ml/min and detected by a 3-mm glassy carbon electrode +0.75 V. The volume of injection was 80 μl and the peak heights were measured by HP 1100 ChemStation (Agilent Technologies, Inc. Santa Clara CA, USA).

Data analysis—Locomotor activity and striatal dopamine concentrations were analyzed by means of one-way ANOVAs including ethanol treatment as the only factor. Significant effects were further analyzed through post-hoc tests (Newman Keuls post-hoc test with a Type I error set at 0.05).

Results

The corresponding ANOVAs revealed that ethanol significantly increased locomotor activity [$F(1,23) = 16.34$, $p < 0.0001$, see Figure 3]. In addition, striatal dopamine

concentration was significantly higher in pups given ethanol than in water-treated controls [$F(1,23) = 6.10$, $p < 0.05$, see Figure 4].

Discussion

In the current study a relatively high ethanol dose (2.5 g/kg) induced locomotor stimulating effects in infant (Sprague-Dawley or Wistar) rats. This ethanol effect was attenuated by SCH23390 or sulpiride at doses that did not affect locomotor activity in water-treated controls (see Experiment 1a and 1b). Specifically, 0.015 or 0.03 mg/kg SCH23390 or 5 or 10 mg/kg sulpiride reduced ethanol-induced activation to control levels (Figure 1), but these SCH23390 or sulpiride doses didn't reduce locomotor activity in water treated controls. These results indicate that D1-like and D2-like receptors are involved in ethanol-induced activation in infant rats. These findings are congruent with studies conducted with adult mice, in which systemic administration of D1-like or D2-like receptor antagonists attenuated the enhanced locomotor effects induced by ethanol (Le et al., 1997; Matsuzawa et al., 1999; Pastor, Miquel et al., 2005).

Ethanol significantly increased dopamine concentration in striatum, a result that is consistent with previous research with adult rats showing that relatively high ethanol doses induce an increment in local cerebral rates of glucose metabolism in striatum (Lyons et al., 1998) and elevation of dopamine levels in this area (Melendez et al., 2003). We acknowledge that increases in dopamine content may not reflect dopamine release directly. The technique and procedures employed in the present study had insufficient resolution for completely consistent detection of levels of DOPAC, metabolite of dopamine required to estimate an index of dopamine utilization. From our results we cannot conclude whether the increase in dopamine content induced by ethanol indicates that the dopaminergic pathway was activated by ethanol soon after drug administration, resulting in an increment in dopamine synthesis, or through an alternative mechanism such as reduced metabolism or decreased release of dopamine. Unfortunately, our present experiments cannot discriminate clearly among these hypotheses, which limits our conclusions.

It is interesting that relatively high ethanol doses failed to increase locomotor activity in heterogeneous rats during adulthood, even when animals were tested at postadministration intervals similar to those utilized in the present study (Chuck et al., 2006; Correa et al., 2003). Correa et al. (2003) suggest that given the increase in motor activity induced (in adult rats) by acute central administration of ethanol into the cerebral ventricles, sedation induced by peripheral ethanol administration may be a consequence of peripheral mechanisms that mask the central activating effects of the drug (see also Carmichael et al., 1991). The heightened sensitivity of infants to ethanol's activating effects may be associated with their slower peripheral ethanol metabolism when compared to adults (Hollstedt, Rydberg, Olsson, & Buijten, 1980; Kelly, Bonthius, & West, 1987).

Ethanol's stimulating effects seem to be mediated by the mesolimbic dopaminergic system. In adult rodents, ethanol stimulates dopamine release in striatum and nucleus accumbens (Di Chiara & Imperato, 1986, 1988; Imperato & Di Chiara, 1986). D1-like or D2-like receptor antagonists also reduce ethanol's activating effects in adult mice (Pastor, Miquel et al., 2005). Furthermore, systemic administration of GABA B agonists such as baclofen (Chester & Cunningham, 1999; Quintanilla, Perez, & Tampier, 2008; Shen, Dorow, Harland, Burkhart-KaSCH, & Phillips, 1998), or opioid antagonists (Camarini, Nogueira Pires, & Calil, 2000; Pastor & Aragon, 2006; Pastor, Miquel et al., 2005; Pastor, Sanchis-Segura et al., 2005) attenuate ethanol's stimulating effect on behavior presumably by attenuating the excitatory effect of ethanol upon dopaminergic neurons (Xiao & Ye, 2008; Xiao, Zhang, Krnjevic, & Ye, 2007; Xiao, Zhou, Li, Davies, & Ye, 2008). This hypothesis is supported by the fact that local administration of baclofen in VTA also attenuates ethanol-induced

locomotor stimulation (Boehm et al., 2002). According to the present study the dopaminergic system also seems to modulate ethanol's activating effects early in ontogeny. We recently reported that naloxone and baclofen attenuate ethanol's stimulating effect in prewenaling rats (Arias et al., 2009b) most likely through ultimate action on the dopaminergic system. The current study confirmed that ethanol mediated locomotor stimulation is modulated at some level by dopamine receptors.

The highest SCH23390 or sulpiride doses (0.06 mg/kg and 20 mg/kg, respectively) attenuated locomotion in water treated controls, indicating that D1-like and D2-like receptors are involved in locomotor activity during early development. SCH23390 and sulpiride also reduce locomotion in adult rats (Chandler, Starr, & Starr, 1990; Chandler, Wohab, Starr, & Starr, 1990; Fujiwara, 1992; Meyer, Cottrell, Van Hartesveldt, & Potter, 1993; Meyer, Van Hartesveldt, & Potter, 1993). Results from our study are in agreement with previous suggestion that D1-like and D2-like receptors modulate locomotion very early in life (Moody et al., 1993).

Recent studies indicate that infant rats are sensitive to ethanol's reinforcing effects. During early ontogeny infant rats are highly sensitive to appetitive reinforcement by ethanol (Arias & Chotro, 2006a; Cheslock et al., 2001; Chotro & Arias, 2007; Molina et al., 2007; Petrov et al., 2003). In addition, ethanol consumption is higher during the second postnatal week of life than in later stages of development (Sanders & Spear, 2007; E. Truxell & Spear, 2004; E. M. Truxell et al., 2007). The present study represents an empirical antecedent from which to postulate the participation of the dopaminergic system in ethanol intake and appetitive ethanol reinforcement during early ontogeny.

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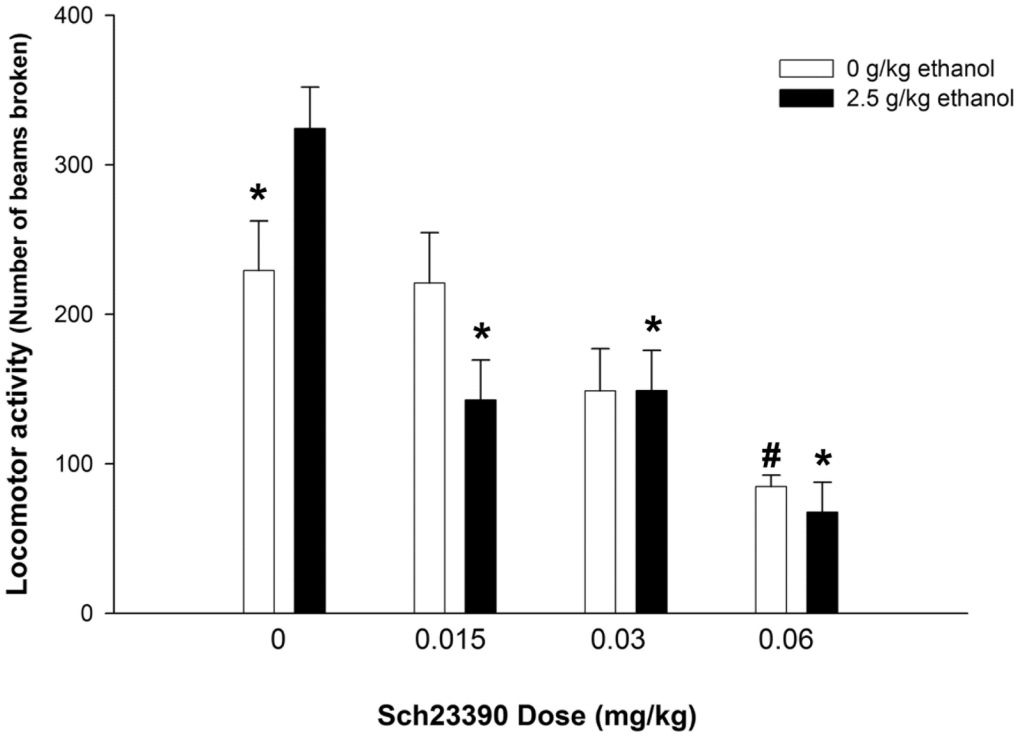

Figure 1.

Locomotor activity scores as a function of ethanol (0 or 2.5 g/kg) and SCH23390 (0, 0.015, 0.03 or 0.06 mg/kg) treatments. Vertical lines illustrate standard errors of the means. * $p < 0.05$ versus 2.5 g/kg EtOH and 0 mg/kg SCH23390; # $p < 0.05$ versus 0 g/kg EtOH and 0 mg/kg SCH23390.

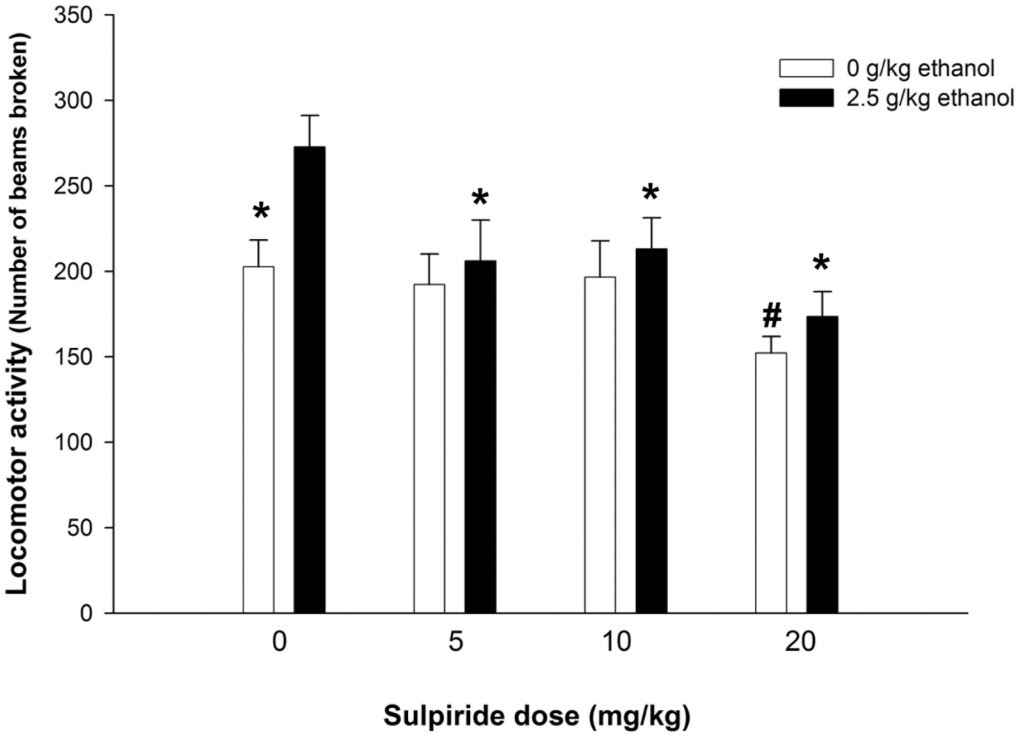

Figure 2.

Locomotor activity scores as a function of ethanol (0 or 2.5 g/kg) and sulpiride (0, 5, 10 pr 20 mg/kg) treatments. Vertical lines illustrate standard errors of the means. * $p < 0.05$ versus 2.5 g/kg EtOH and 0 mg/kg sulpiride; # $p < 0.05$ versus 0 g/kg EtOH and 0 mg/kg sulpiride.

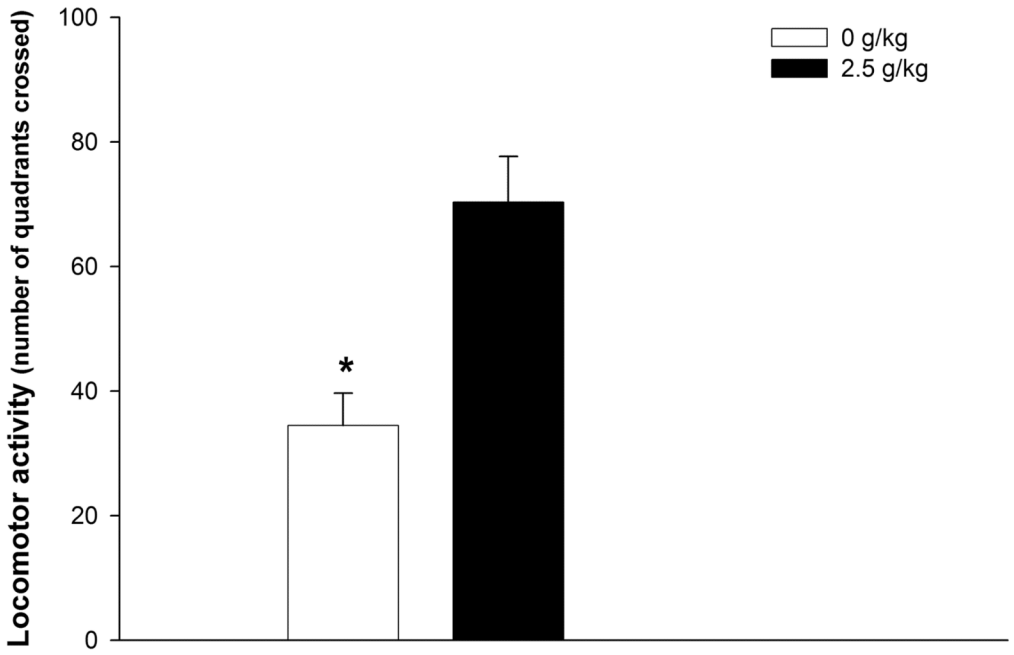

Figure 3.
Locomotor activity as a function of the ethanol dose (0 or 2.5 g/kg). Vertical lines illustrate standard errors of the means. * $p < 0.05$ versus 2.5 g/kg EtOH.

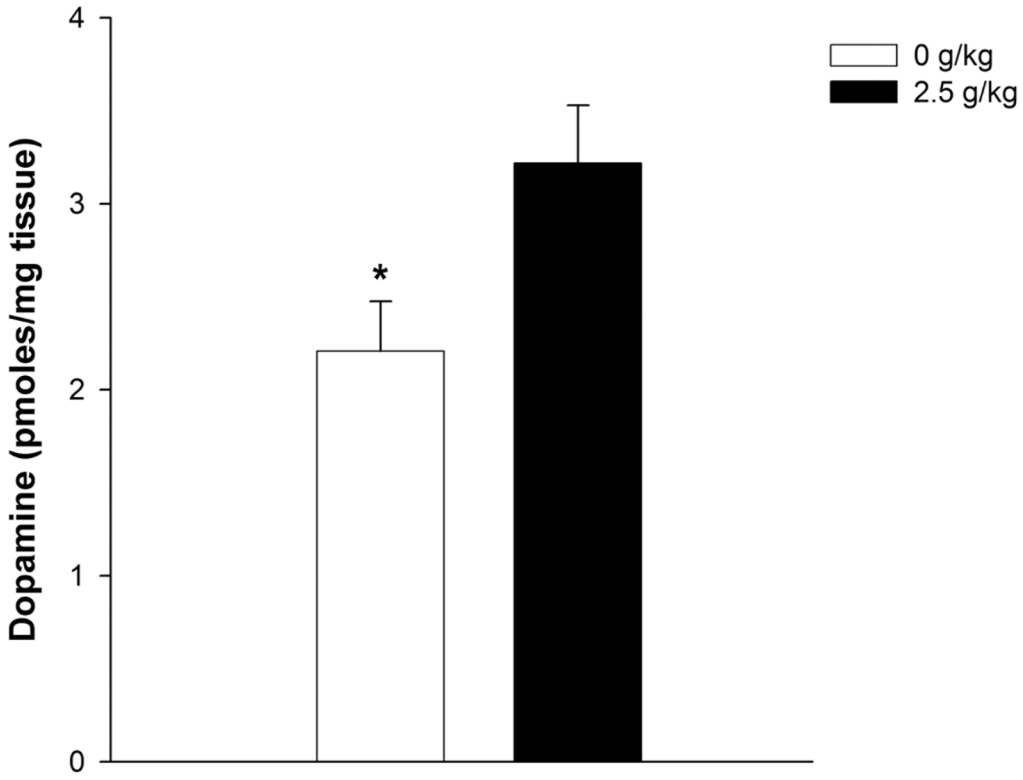

Figure 4.
Striatal dopamine concentration (picomoles/mg tissue) as a function of ethanol treatment (0 or 2.5 g/kg). * $p < 0.05$ versus 2.5 g/kg EtOH.

Table 1

Blood ethanol concentration (mg %) obtained 10.5 minutes after ethanol administration (2.5 g/kg) as a function of SCH23390 (0, 0.015, 0.03 or 0.006 mg/kg; Experiment 2a) or Sulpiride (0, 5, 10 or 20 mg/kg; Experiment 2b) dosage. Values represent mean ± standard error of the mean.

	Dose (mg/kg)	Blood Ethanol Concentration (Mean ± SE)	n
SCH2390	0	150.22 ± 6.39	5
	0.015	160.28 ± 6.09	6
	0.03	150.11 ± 8.81	6
	0.06	146.98 ± 8.35	5
Sulpiride	0	151.43 ± 7.49	6
	5	152.83 ± 7.34	6
	10	166.45 ± 5.03	6
	20	157.20 ± 7.27	5