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PRENATAL BINGE-LIKE ALCOHOL EXPOSURE ALTERS BRAIN AND SYSTEMIC RESPONSES TO REACH SODIUM AND WATER BALANCE

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Abstract—The aim of the present work is to analyze how prenatal binge-like ethanol exposure to a moderate dose (2.0 g/kg; group Pre-EtOH) during gestational days (GD) 17–20 affects hydroelectrolyte regulatory responses. This type of exposure has been observed to increase ethanol consumption during adolescence (postnatal day 30–32). In this study we analyzed basal brain neural activity and basal-induced sodium appetite (SA) and renal response stimulated by sodium depletion (SD) as well as voluntary ethanol consumption as a function of vehicle or ethanol during late pregnancy. In adolescent offspring, SD was induced by furosemide and a low-sodium diet treatment (FURO + LSD). Other animals were analyzed in terms of immunohistochemical detection of Fra-like (Fra-LI-ir) protein and serotonin (5HT) and/or vasopressin (AVP). The Pre-EtOH group exhibited heightened voluntary ethanol intake and a reduction in sodium and water intake induced by SD relative to controls. Basal Na and K concentrations in urine were also reduced in Pre-EtOH animals while the induced renal response after FURO treatment was similar across prenatal treatments. However, the correlation between urine volume and water intake induced by FURO significantly varied across these treatments. At the brain level of analysis, the number of basal Fra-LI-ir was significantly increased in AVP magnocellular neurons of the paraventricular nucleus (PVN) and in 5HT neurons in the dorsal raphe nucleus (DRN) in Pre-EtOH pups. In the experimental group, we also observed a significant increase in Fra-LI along the nucleus of the solitary tract (NTS) and in the central extended amygdala nuclei. In summary, moderate Pre-EtOH exposure produces long-lasting changes in brain organization, affecting basal activity of central extended amygdala nuclei, AVP neurons and the inhibitory areas of SA such as the NTS and the 5HT-DRN. These changes possibly modulate the above described variations in basal-induced drinking behaviors and renal regulatory responses. © **2015 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: prenatal ethanol exposure, sodium balance, serotonergic neurons, vasopressinergic neurons.

INTRODUCTION

It has been widely demonstrated that the effects of prenatal alcohol exposure on offspring are mainly related to the amount of drug consumed and to the period of pregnancy in which exposure occurs. A recent meta-analytical study shows that, despite the well-known consequences of high prenatal alcohol exposure during most of the pregnancies (Bailey and Sokol, 2008; U.S. Department of Health and Human Services, 2000), which include fetal alcohol syndrome and other fetal alcohol spectrum disorders (FASDs), the effects of mild to moderate prenatal alcohol exposure on neurodevelopment and neurophysiological order are inconsistent in the literature (Flak et al., 2014). Mild or moderate drinking patterns are more frequent in the pregnant population and therefore it is important to determine whether these patterns induce behavioral and physiological disruptions in the progeny. In the United States, for example, from 1991 through 2005, 12% of pregnant women reported consuming at least one alcoholic drink a month (Center of Disease Control and Prevention, 2009).

Our previous studies with rats showed that administration of mild-to-moderate doses of ethanol (2 g/kg) in pregnant females (gestational days 17–20) has behavioral consequences in the offspring. This prenatal binge-like ethanol exposure increases alcohol intake during infancy and adolescence (Molina et al., 1995; Chotro and Spear, 1997; Chotro and Arias, 2003; Spear

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Abbreviations: 5HT, serotonergic system; 5-HT-ir, 5-HT immunoreactivity; AP, area postrema; AVP, vasopressinergic system; BNSTL, lateral division of the bed nucleus of the stria terminalis; CD, sham-depleted rats; CeA, central amygdaloid nucleus; CVOs, circumventricular organs; DAB, diaminobenzidine hydrochloride; DRN, dorsal raphe nucleus; DRV, ventral subdivisions of DRN; Fra-LI, Fra like immunoreactivity; FURO, Furosemide; FURO + LSD, Furosemide and low-sodium diet; GD, gestational day; LPBN, the lateral parabrachial nucleus; MnPO, median preoptic nucleus; Na, sodium; NHS, normal horse serum; NTS, nucleus of the solitary tract; OT, immunoreactivity; OVLT, organum vasculosum of the lamina terminalis; PaLM, lateral magnocellular group; PaMM, medial magnocellular group; PB, phosphate buffer; PDN, postnatal day; Pre-EtOH, prenatally exposed animals; Pre-Water, prenatally control animals; PVN, paraventricular nucleus; SA, sodium appetite; SD, sodium depletion; SFO, subfornical organ; SON, supraoptic nucleus; Veh, vehicle.

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and Molina, 2005; Fabio et al., 2013). In addition and as indicated by Flak et al. (2014), there is increasing evidence that early exposure to moderate ethanol doses affect neural plasticity and consequently has negative physiological and neurological effects throughout the life span of an organism.

Thirst and sodium appetite (SA) are the motivational states leading to the search for and consumption of water and sodium in order to reestablish hydroelectrolyte balance. When body sodium depletion (SD) occurs, hypovolemia and hyponatremia activate the renin–angiotensin–aldosterone system (''RAAS''). This system stimulates vasoconstriction and releases aldosterone (ALDO) and vasopressin (AVP) into the bloodstream, thus increasing renal reabsorption of sodium and water to restore the volume of the extracellular space (Vivas et al., 2013). We have previously investigated the brain areas and neurochemical systems involved in the control of SA following SD (Franchini and Vivas, 1999; Franchini et al., 2002; Godino et al., 2007; Margatho et al., 2015). In these studies, the CVOs of the lamina terminalis, subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), were found to be activated (as shown by Fos immunoreactivity; Fos-ir) during SA stimulation. On the other hand, the brainstem nuclei (such as the nucleus of the solitary tract (NTS), area postrema (AP) and the lateral parabrachial nucleus (LPBN)) and the serotonergic (5HT) neurons in the dorsal raphe nucleus (DRN) were also activated during the inhibition or satiety phase of SA.

It has been demonstrated that the neural circuit involved in the control of both ethanol and sodium consumption behaviors shares common pathways and neurochemical systems. For example, the bed of the stria terminalis and the central amygdala nucleus that form part of the extended amygdala complex are involved in the modulation of ethanol preference and SA (Johnson et al., 1999; Ryabinin et al., 1997). In addition, the AVP and 5HT neurochemical central systems participate in the control of hydroelectrolyte homeostasis and alcohol abuse (Druse et al., 1991; Sari et al., 2001; Knee et al., 2004; Kim et al., 2005; Bird et al., 2006; Sanbe et al., 2008; Oreland et al., 2011).

It has also been shown that prenatal ethanol exposure affects the central AVP and 5HT systems. Previous studies in prenatally ethanol-exposed animals have shown a reduction in synthesis, storage, and release of AVP in response to hyperosmolality and hemorrhage (Knee et al., 2004; Bird et al., 2006). Moreover, effects of *in utero* ethanol exposure produced: (a) decreases of 5HT and tryptophan hydroxylase expression within the DRN of rat offspring (Kim et al., 2005); (b) reductions in the number of 5HT DRN neurons and the density of serotonergic fibers in the forebrain (Sari et al., 2001), and (c) a decline of 5-HT1A receptors in the brain stem and cortex (Druse et al., 1991). These results were obtained using high-to-moderate ethanol doses administered for prolonged periods of time during pregnancy; a procedure known to induce serious teratological alterations.

The aim of the present study is to determine the effect of prenatal binge-like ethanol exposure (2 g/kg) during gestational days 17–20, a procedure known to increase postnatal ethanol affinity (Molina et al., 1995; Chotro and Spear, 1997; Chotro and Arias, 2003; Spear and Molina, 2005; Fabio et al., 2013), upon hydroelectrolyte regulatory responses. Specifically we evaluated sodium intake and renal responsiveness induced by body SD during adolescence. In addition, we also examined the impact of prenatal ethanol exposure upon neuroanatomical substrates via immunohistochemical detection of Fra-LI, alone or combined with 5HT and AVP at the brainstem and forebrain levels, respectively.

EXPERIMENTAL PROCEDURES

Subjects

All animals employed in this study were Wistar-derived rats born and reared at the vivarium of the Instituto Ferreyra (INIMEC-CONICET-UNC), Córdoba, Argentina. The animal colony was kept at 22–24 °C and under artificial lighting conditions (lights on 08:00–20:00 h). Maternal-enriched lab chow (Cargill, Buenos Aires, Argentina) and water were available *ad libitum*. Vaginal smears of adult female rats were microscopically analyzed on a daily basis. On the day of proestrus, females (pre-pregnancy body weight: 200–300 g) were housed during the dark cycle with males (three females per male). Vaginal smears were checked the following morning (10:00–12:00 h) and the day of sperm detection was considered as gestational day 0 (GD 0). Births were checked daily (10:00–12:00 h) and the day of parturition was considered as postnatal day 0 (PD 0). On PD 1, each litter was randomly culled to eight pups (four males and four females, whenever possible). Pregnant females or litters were individually placed in standard maternity cages filled with wood shavings.

At all times, animals used in this study were maintained and treated according to the guidelines for animal care established by the Guide for Care and Use of Laboratory Animals (National Institutes of Health, Institute of Laboratory Animal Resources, 1996).

Maternal treatments

From GDs 17 to 20, pregnant females were weighed and intragastrically intubated with 2.0 g/kg ethanol (Pre-EtOH group). This dose was delivered on a daily basis and was achieved by administering 0.015 ml/g of a 16.8% v/v ethanol solution. The vehicle (Veh) used was room temperature tap water. Control females (Pre-Water group) were administered with this Veh. The ethanol dose and the days of administration were selected on the basis of prior studies demonstrating fetal chemosensory and interoceptive processing of the drug under similar experimental circumstances and the general lack of deleterious effects of ethanol upon different infantile gross morphological and behavioral parameters (Abate et al., 2008; Molina et al., 1995; Domínguez et al., 1996, 1998; Pueta et al., 2005). Intragastric intubations were performed employing a polyethylene cannula (PE 50; Clay Adams, Parsippany, New Jersey, U.S.A.) attached to a disposable 5-ml syringe.

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