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The effects of experimental gestational hypertension on maternal blood pressure and fluid intake and pre-weanling hypothalamic neuronal activity

Juan Arguelles [a, *], Carmen Perillan [a], Terry G. Beltz [b], Baojian Xue [b], Daniel Badaue-Passos Jr. [c], Jose A. Vega [d, e], Alan Kim Johnson [b]

[a] Departamento de Biología Funcional, Área de Fisiología, Facultad de Medicina y Ciencias de la Salud, Universidad de Oviedo, Spain
[b] Department of Psychological and Brain Sciences, The University of Iowa, Iowa City, IA, 52242, USA
[c] Currently at Departamento de Fisiologia, Centro C. Biológicas e Saúde, Universidade Federal de Sergipe, Sau Cristovao, SE, Brazil
[d] Departamento de Morfologia y Biologia Celular, Universidad de Oviedo, Spain
[e] Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Santiago de Chile, Chile

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ABSTRACT

To examine the fetal programming effects of maternal hypertension, natriophilia and hyperreninemia [experimentally induced in rats by partial inter-renal aortic ligature (PAL) prior to mating] fos immunoreactivity was studied in 6-day-old offspring of PAL and control mothers. The purposes of the present set of experiments were twofold. The first was to characterize the effects of PAL on the mother's arterial blood pressure and intake of salt (1.8% NaCl solution) and water over the course of gestation. Second, was to study the pattern of neuronal activation in key brain areas of 6-day-old offspring treated with the dipsogen isoproterenol that were from PAL and control mothers. Beta-adrenergic receptor agonist-treated pups allowed the determination whether there were neuroanatomical correlates within the neural substrates controlling thirst and the enhanced water intake evidenced by the isoproterenol treated pups of PAL mothers. Hydromineral ingestive behavior along with blood pressure and heart rate of PAL (M-PAL) and control (M-sPAL) dams throughout gestation was studied. Higher salt and water intakes along with blood pressures and heart rates were found during gestation and lactation in the M-PAL group. Maternal PAL evoked significantly increased isoproterenol-elicited Fos staining in brain regions (e.g. subfornical organ, organum vasculosum of the lamina terminalis, supraoptic nucleus, hypothalamic paraventricular nucleus and median preoptic nucleus) of 6-day-old pups, which is the age of animals shown enhanced thirst responses in PAL offspring. These results indicate that PAL is compatible with pregnancy, producing a sustained increase in blood pressure and heart rate, along with increased water and salt intake. The present study demonstrates that the neural substrates involved in cardiovascular homeostasis and fluid balance in adult rats are responsive in six-day-old rats, and can be altered by fetal programming.

1. Introduction

Many authors have proposed that perturbations in maternal physiology during gestation alters the offspring in ways to make them more vulnerable to disease in adulthood. Intrauterine fetal programming (Fowden, Giussani, & Forhead, 2006; Lucas, 1991) can be induced by physiological challenges or threats to homeostasis that occur to the mother, during critical or sensitive periods of neonatal development. Such challenges affect the structure, physiology or metabolism in a manner that alters function later in life (Barker, 1995; Godfrey & Barker, 2000).

Abbreviations: ANG, angiotensin; AVP, arginine vasopressin; BP, blood pressure; CNS, central nervous system; DOCA, deoxycorticosterone; FLI, Fos-like immunoreactive; Fos-ir, Fos immunohistochemistry; HR, heart rate; LT, lamina terminalis; M-PAL, partial aortic ligated mothers; M-sPAL, sham operated mothers; O-PAL, offspring from PAL mothers; OVLT, organum vasculosum; PAL, partial ligation of the aorta; PRA, paraformaldehyde; PBS, phosphate buffered saline; PVN, paraventricular nuclei; SFO, subfornical organ; SON, supraoptic nucleus.

* Corresponding author.
E-mail address: jal@uniovi.es (J. Arguelles).

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Intrauterine programming has frequently been discussed in relation to cardiovascular diseases (Barker, 1995; Godfrey & Barker, 2000), and it has been hypothesized that such developmental influences on adult vital functions may have influenced population survival in times of drought and famine (Ross & Desai, 2005). Both experimental and natural challenges to maternal and offspring water and sodium distribution and balance and the cardiovascular system during perinatal critical periods, have been shown to have later consequences on body fluid and cardiovascular homeostasis in rats (Contreras, 1989; Contreras & Kosten, 1983; Contreras, Wong, Henderson, Curtis, & Smith, 2000; McCarty & Fields-Okotcha, 1994; Mouw, Vander, & Wagner, 1978; Nicolaidis, Galaverna, & Metzler, 1990; Tucker & Johnson, 1984), sheep (Ross, Desai, Guerra, & Wang, 2005) and humans (Crystal & Bernstein, 1995, 1998).

Most experiments investigating the effects of challenges administered during the perinatal period have been aimed at demonstrating changes in adult systemic and cellular functions. However, recently studies on the effects of manipulations made during fetal development on the responsiveness of behavioral and neural substrates within postnatal period have been investigated by Perillan and colleagues (Perillan, Costales, Diaz, Vijande, & Arguelles, 2004, 2007). These studies made use of earlier work characterizing the ontogenetic calendar of the onset of responsiveness to dipsogenic stimuli in neonates (Mecawi et al., 2015; Wirth & Epstein, 1976).

Wirth and Epstein (Wirth & Epstein, 1976) first described the sequence of the development of water drinking in response to a battery of cellular- and extracellular-depletion-related stimuli that elicit thirst in mature animals. Normal rat pups start to respond to cellular dehydration at 2 days of age, to hypovolemia at 4 days, and to beta-adrenergic receptor activation at 6 days (Wirth & Epstein, 1976). Perillan and colleagues (Perillan et al., 2007) found that pharmacological treatment of the mothers during pregnancy with the mineralocorticoid agonist deoxycorticosterone (DOCA) altered responses to dipsogenic stimuli in neonates. The water intake of the pups of DOCA-treated females at 2 days of age in response to cellular dehydration (hypertonic saline administration) was slightly attenuated. Responding to hypovolemia induced by polyethylene glycol that nevertheless occurs in normal pups at 4 days of age was delayed until 6 days of age in the offspring of treated mothers, but the dipsogenic response to the beta-adrenergic receptor agonist isoproterenol was normal and was not affected by the prenatal maternal DOCA treatment.

Under conditions of mineralocorticoid agonist treatment the levels of circulating renin and angiotensin are suppressed. Perillan and colleagues (Perillan et al., 2007) have used the maternal manipulation-postnatal testing strategy to assess the effects of a condition where the renin-angiotensin system is activated rather than inhibited. In these studies the investigators used partial ligation of the aorta (PAL), a treatment which in adult rat has been shown to elevate plasma renin activity (Fitzsimons, 1998; Perillan et al., 2004), hypertonic saline and water intake (Argüelles, Brime, Lopez-Sela, Perillan, & Vijande, 2000; Costales, Fitzsimons, & Vijande, 1984; Perillan, Nunez, Costales, Vijande, & Arguelles, 2012) and found that the dipsogenic response to isoproterenol was enhanced in 6-day-old pups.

Costales, Fitzsimons and Vijande (Costales et al., 1984) made periodic measurements of arterial blood pressure (BP) by a catheter inserted in the carotid artery after PAL in adult male and non-pregnant female rats over the course of 3 weeks after surgery. Arterial pressure increased rapidly after PAL, but no significant correlation between BP and the increased intake of water and hypertonic saline was found. Although saline and water intakes and renin activities are elevated in pregnant PAL rats, the question of whether BP is elevated over the course of gestation after PAL has not been addressed. This becomes a particularly relevant issue as it is well established that in normal pregnancies the prospective mothers are both volume expanded and remarkably resistant to the hypertensive actions of many pressor agents. The current capability to measure BP continuously over extended periods of time using commercial arterial pressure transducer/telemetered data acquisition systems allow for studying the effects of PAL on blood pressures throughout gestation, while also collecting reliable behavioral information.

The purposes of the present set of experiments were twofold. The first was to characterize the effects of PAL on the mother's BP using continuous monitoring and to characterize the associated intake of salt and water. Second, in the course of conducting these studies it was possible to collect the brains from isoproterenol treated 6-day old offspring of PAL and control mothers. As noted above, the 6-day-old offspring of PAL mothers show enhanced water ingestion. Thus, the material from the beta-adrenergic receptor agonist-treated pups allowed us to determine if there is evidence for a neuroanatomical correlate within key neural substrates [i.e. subfornical organ (SFO), organum vasculosum (OVLT), supraoptic (SON) and paraventricular (PVN) nuclei] controlling thirst and the enhanced water intake evidenced by the isoproterenol treated pups of PAL mothers.

2. Materials and methods

2.1. Animals

Adult Sprague-Dawley male and female rats (10–12 weeks old) were obtained from a commercial supplier (Harlan Sprague-Dawley, Indianapolis, IN). Rats were housed individually in temperature- and light-controlled animal quarters and were provided with rat chow (7013 National Institutes of Health-31 modified rat diet, 0.25% NaCl), tap water and 1.8% NaCl solution ad libitum, except as noted below.

All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Iowa Animal Care and Use Committee.

2.2. Experimental protocol

The animals were divided into two groups: 1) Partial Aortic Ligated Mothers (M-PAL; $n = 6$); and 2) Sham Operated Mothers (M-sPAL; $n = 4$). One week after the surgery, the female rats were mated with adult males to obtain two groups of offspring: 1) Offspring from PAL mothers (O-PAL), and 2) Offspring from Sham Operated Mothers (O-sPAL). Daily water and saline intakes were taken the six days during a baseline period before surgery, four days after surgery, and throughout the pregnancy.

2.3. Surgical preparations

2.3.1. Partial ligature of the abdominal aorta

PAL was produced by following a previously described procedure (Costales et al., 1984). Briefly, the abdominal aorta was approached through a ventral incision. The aorta between the renal arteries was cleared and partially occluded by tying a silk thread (no. 4/0) around it just below the mesenteric artery. A stylus (0.6 mm) was included within the ligature. After the ligatures were tied, the stylus was removed. The abdominal incision was then