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Locomotor response to acute nicotine in adolescent mice is altered by maternal undernutrition during lactation

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ABSTRACT

Undernutrition during brain development causes long lasting alterations in different neurotransmitter systems that may alter responses to psychoactive drugs. Despite the recognized effects of early undernutrition on the cholinergic system, no evidence that demonstrates the influence of this insult on nicotine susceptibility has been reported. We investigated the effects of protein/calorie restriction during lactation on the susceptibility to nicotine in adolescent mice. Dams were randomly assigned to one of the following groups: Control (C, 20 litters)—free access to standard laboratory diet (23% protein); Protein Restricted (PR, 12 litters)—free access to a isoenergetic, 8% protein diet; Calorie Restricted (CR, 12 litters)—access to standard laboratory diet in restricted quantities (mean ingestion of PR: pair-fed group). Undernutrition extended from postnatal day 2 (PN2) to weaning (PN21). At PN30, animals either received an i.p. injection of nicotine (0.5 mg/Kg) or saline and were immediately placed in open field (OF). After the OF, adrenal glands and serum were collected for the analyses of stress-related endocrine parameters and leptin concentration. PR and CR offspring showed less body mass gain and visceral fat mass. PR offspring presented reduced serum leptin concentration. In the OF, nicotine increased locomotor activity of C and PR, but not of CR. CR and PR offspring showed decreased adrenal catecholamine content, which was not dependent on nicotine exposure. Our results indicate that early undernutrition interferes with nicotine-elicited locomotor effects in adolescent mice and suggest that endocrine parameters alterations in malnourished animals do not influence the behavioral response to nicotine.

1. Introduction

Undernutrition remains the most prevalent form of nutritional disorder among children in developing countries (FAO et al., 2013), representing an important public health problem. Undernutrition during development has been associated with profound effects on health later in life. In fact, it was found to be associated with alterations such as high blood pressure (Roseboom et al., 1999), obesity (Ravelli et al., 1999), glucose intolerance (Ravelli et al., 1998), dyslipidemia (Roseboom et al., 2000a) and higher risk of coronary disease (Roseboom et al., 2000b). Cognitive, behavioral and emotional impairments during adolescence and adulthood have also been reported (Galler et al., 2013).

A critical period of brain development is lactation. In rodents, there is a surge in brain growth characterized by dendritic arborization, synaptogenesis and the migration of numerous neuronal populations during the first 2 weeks of postnatal life (Dobbing and Sands, 1979), rendering the brain particularly vulnerable to insults. In this sense, it is well established that nutritional insults during the lactation period promote several neurobiological disturbances, resulting in lifelong physiological consequences (Reyes-Castro et al., 2012). It has been described in animal models that protein restriction during lactation promotes alterations in anxiety levels and impairs learning behavior in the adult offspring (Almeida et al., 1993; Reyes-Castro et al., 2011). Several neurochemical systems could be involved in these behavioral

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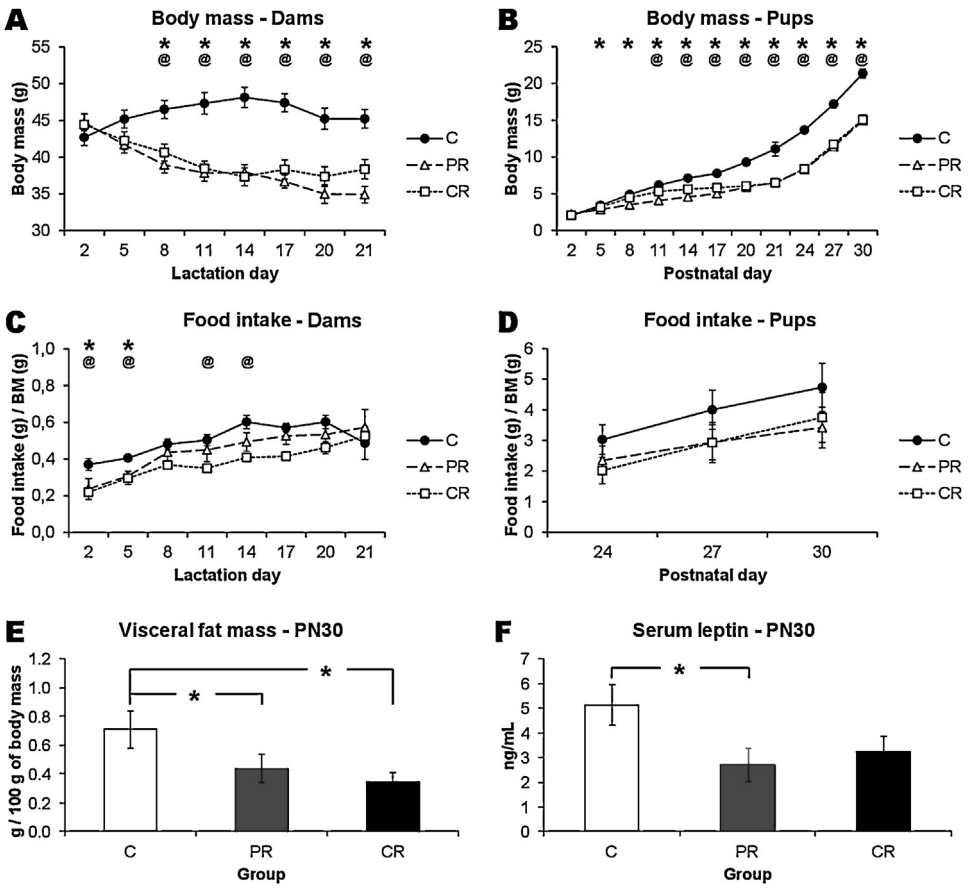

Fig. 1. Effects of undernutrition during lactation on body mass and food intake for dams (A and C, respectively) and pups (B and D, respectively). E, visceral fat mass in the offspring at postnatal day (PN) 30. F, serum leptin levels in the offspring at PN30. Values are means ± S.E.M. Statistical differences between groups were assessed by FPLSD. C, Control group; PR, Protein restricted; CR, Calorie restricted; In A–C, * indicates significant differences between C and PR; @ indicates differences between C and CR; *P* values are indicated in the text of the results section. In E and F, * $P < 0.05$.

alterations (for review see (Almeida et al., 1996)). Previous studies also demonstrated that maternal protein/caloric restriction during lactation disturbs the pattern of food intake and the hypothalamic leptin signaling pathway later in the offspring's life (Lisboa et al., 2012; Passos et al., 2004). These effects suggest that nutritional insults in this period promote changes in mechanisms of reward control. Of note, an association between early undernutrition and the response to psychoactive drugs has been reported in humans: a case-control study indicates a relationship between the prenatal famine during the Dutch hunger winter of 1944–45 and addiction later in life (Franzek et al., 2008). In parallel, animal models of perinatal undernutrition indicate an increased response of the mesocorticolimbic dopaminergic pathway to the rewarding effects of cocaine (Valdomero et al., 2006) and morphine (Velazquez et al., 2010).

Among the drugs of abuse, tobacco consumption is one of the most important public health challenges. Nicotine, an important component of tobacco smoke, is known to be responsible for a wide range of nervous system effects resulting from tobacco use, including tobacco addiction (Benowitz, 1992). Smoking typically begins during adolescence (Centers for Disease Control Prevention, 2010) and, in animal models, it was demonstrated that nicotine exposure in adolescent mice elicits several distinct behavioral and biochemical effects (Ribeiro-Carvalho et al., 2009; Ribeiro-Carvalho et al., 2011; Abreu-Villaca et al., 2007; Abreu-Villaca et al., 2008; Ribeiro-Carvalho et al., 2008), characterizing adolescence as a period of vulnerability to nicotine effects. Interestingly, the cholinergic system, the primary target of nicotine, seems to be particularly sensitive to early undernutrition, exhibiting long-lasting alterations as well as altered responses to a variety of pharmacological treatments (Almeida et al., 1996). In spite of that, to our knowledge, there are no studies that investigate the influence of early undernutrition on nicotine susceptibility.

Here, we investigated the effects of protein and/or caloric restriction during lactation on the acute effects of nicotine exposure on locomotor activity (in the open field test) of adolescent mice. An altered response to stress may influence the stimulatory response of nicotine in the mesolimbic dopaminergic system (Enrico et al., 2013). For this reason, we also evaluated ACTH and corticosterone serum levels, total catecholamine (adrenaline and noradrenaline) content as well as the expression of two catecholamine synthesising enzymes, tyrosine hydroxylase (TH) and phenylethanolamine *N*-methyltransferase (PNMT), in the adrenal medulla. In addition, since it has been consistently demonstrated that undernutrition during development has both short and long-term effects on serum leptin concentration (Bonomo et al., 2007; Carvalho et al., 2014) and that leptin levels have been associated with locomotor activity (Fraga et al., 2011), we also assessed leptin serum concentration.

2. Materials and methods

All experiments were carried out under institutional approval of the Animal Care and Use Committee of the Universidade do Estado do Rio de Janeiro (CEUA/016/2011), in accordance with the declaration of Helsinki and with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National