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Research Report

Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats

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ABSTRACT

Clinical evidence suggests that intrauterine growth restriction (IUGR) can cause persistent changes in the preference for palatable foods. In this study, we compared food preferences, the response to food rewards, and the role of the mesolimbic dopaminergic system in feeding behavior, between IUGR and control rats. Time-mated pregnant Sprague–Dawley rats were randomly allocated to a control group (standard chow *ad libitum*) or a 50% food restriction (FR) group, which received 50% of the control dams' habitual intake. These diets were provided from gestation day 10 to the 21st day of lactation. Within 24 h of birth, pups were cross-fostered and divided into four groups: *Adlib/Adlib, FR/Adlib, FR/FR, Adlib/FR*. Standard chow consumption was compared between all groups. Food preferences, conditioned place preference to a palatable diet, and the levels of tyrosine hydroxylase (TH) phosphorylation and D2 receptors in the nucleus accumbens were analyzed and compared between the two groups of interest: *Adlib/Adlib* (control) and *FR/Adlib* (exposed to growth restriction during the fetal period only). IUGR adult rats had a stronger preference for palatable foods, but showed less conditioned place preference to a palatable diet than controls. D2 receptors levels were lower in IUGR rats. At baseline, TH and pTH levels were higher in FR/Adlib than control males. Measurements taken after exposure to sweet foods revealed higher levels of TH and pTH in FR/Adlib than control females. These data showed

Abbreviations: Adlib, *Ad libitum*; CPP, conditioned place preference; FR, food restriction; GEE, Generalized Estimating Equations; IUGR, intrauterine growth restriction; NAcc, nucleus accumbens; OD, optic density; PFC, prefrontal cortex; pTH, phospho-tyrosine hydroxylase; SGA, small for gestational age; TH, tyrosine hydroxylase; VTA, ventral tegmental area

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that IUGR rats exhibited a preference for palatable foods, potentially due to alterations in their mesolimbic reward pathway. Additionally, the changes observed in the mesolimbic dopaminergic system of IUGR rats proved to be sex-specific.

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1. Introduction

Environmental events in early life, especially those related to nutrition, can lead to adaptations in growth and metabolism which may increase the risk of chronic conditions in adulthood (Barker, 2004), including cardiovascular disease (Barker et al., 2005), hypertension (Law et al., 2002), insulin resistance (Barker, 1999; Eriksson et al., 2002) and obesity (Pilgaard et al., 2011; Ravelli et al., 1999). According to Barker (2006), this developmental programming is more strongly associated with low birth weight for gestational age (*i.e.*, intrauterine growth restriction; IUGR) than with premature birth. The interaction between fetal life events and subsequent environmental factors may also result in an increased or decreased risk for the aforementioned conditions (Barker, 2004). As such, exposure to certain foods over the life course (*e.g.* palatable foods, rich in sugar and/or fat) could modulate the development of chronic non-communicable diseases in adult individuals with IUGR.

Several recent clinical studies have found an association between IUGR and offspring preference for highly palatable foods (rich in sugar and/or fat) throughout the life course. These findings point to a persistent programming effect with behavioral repercussions ranging from impulsiveness for sweet rewards in childhood (Silveira et al., 2012), to a preference for carbohydrates and low fruit and vegetable intake in young adulthood (Barbieri et al., 2009; Kaseva et al., 2013), and higher fat intake in older age (Lussana et al., 2008; Perala et al., 2012; Stein et al., 2009).

IUGR seems to program feeding behavior before metabolic changes (*e.g.* insulin and leptin resistance, obesity) have taken place, as evidenced by the distinct responses to sweet stimuli observed in individuals with IUGR from the very first day of life (Ayres et al., 2012). The preference for palatable foods may lead to subtle but persistent nutritional imbalance, and contribute to the development of obesity and chronic diseases in adulthood (Portella and Silveira, 2014).

The apparent specificity of the effects of IUGR on responses to palatable foods suggests that the brain mechanisms involved in food rewards are likely to be implicated in this phenomenon. Vucetic et al. (2010) found that the offspring of pregnant females exposed to protein restriction during gestation show an increased number of tyrosine hydroxylase (TH) immunoreactive neurons in the ventral tegmental area (VTA), increased expression of DAT in the VTA and nucleus accumbens (NAcc), and higher levels of dopamine in the prefrontal cortex (PFC). Not surprisingly, these changes were associated with dysfunctions in dopamine-dependent behaviors, including preference for sweet solutions and hyperactivity in response to cocaine or a high fat diet. However, as far as we know, the cerebral dopamine mechanisms linked to altered feeding behavior and food choices in animal models of IUGR induced by maternal food restriction have not yet been explored. Therefore, the aim of this study was to evaluate food preferences and food reward, as well as the putative role of the mesolimbic dopaminergic system in these behaviors in IUGR rats.

2. Results

2.1. *Feeding behavior: standard rat chow consumption and food preference*

Rats were habituated to cages equipped with BioDAQ® monitoring systems. During this period, no interactions between group and time were observed (GEE, Wald=12.26; gl=6; $p=0.056$). During these first three days of the study, when only standard chow was available, FR/Adlib males ate more than Adlib/Adlib (Bonferroni $p=0.024$) and Adlib/FR males (Bonferroni $p=0.005$) (interaction group*sex, Wald=16.26; gl=3;$p=0.001$). In females, standard chow consumption was found to be higher in the Adlib/Adlib group than in the FR/Adlib (Bonferroni $p=0.042$) and Adlib/FR groups (Bonferroni $p=0.009$). Habituation was faster in males (Bonferroni $p<0.001$) than females (Bonferroni $p=0.015$) (interaction sex*time, Wald=19.34; gl=2; $p<0.001$) (Fig. 1). In both sexes, food consumption increased over time.

Standard rat chow consumption in the 24 h following habituation was analyzed by two-way ANOVA with group and sex as independent factors and body weight as a covariate. No main effects or interactions were observed on any of the variables except for meal size, which was influenced by a group by sex interaction [F(3,49)=3.64; $p=0.019$],

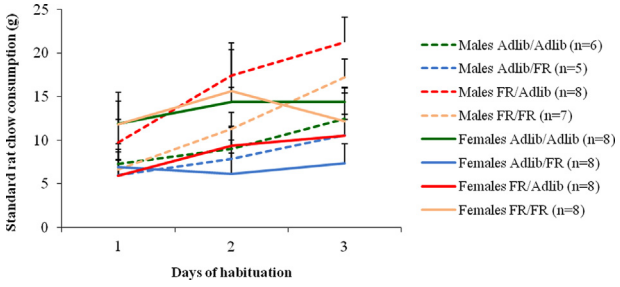

Fig. 1 – Standard rat chow consumption during the habituation period. Data expressed as mean ± SEM. Means adjusted for body weight.