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Neurobehavioral effects of long-term maternal fructose intake in rat offspring

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ABSTRACT

Background: Previous studies have indicated an association between maternal metabolic conditions and general developmental disturbances of the offspring.
Objective: We aimed to investigate the influence of long-term maternal fructose intake during gestation and lactation on neurobehavioral development of rat offspring.
Methods: Twelve female Sprague Dawley rats were received either 30% fructose enriched water (n = 6) or regular tap water (control, n = 6) for 12 weeks. Then, control and fructose-received females were caged with a fertile male, and received 30% fructose and regular chow throughout pregnancy, delivery and until offspring's weaning. On P21, forty littermates (10 male control, 10 female control, 10 male fructose and 10 female fructose) were separated and housed with *ad libitum* access to standard food and tap water. Following behavioral evaluations at P50, brain levels of TNF-α, neuregulin 1 (NRG1), glutamic acid decarboxylase 67 (GAD67), nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1), and 5-hydroxyindoleacetic acid (5-HIAA) were measured. Histologically, hippocampal neuronal density and GFAP expression were assessed.
Results: Analysis of the behavioral tests (three-chamber social test, open field test, passive avoidance learning test and stereotypy test) revealed significant differences among the groups. Histologically, hippocampal CA1 and CA3 regions displayed significant alterations such as gliosis and neuronal cell death in fructose-exposed groups compare to controls. Biochemical measurements of the brain levels of TNF-α and neurodevelopmental markers showed significant differences between controls and fructose-exposed groups.
Conclusion: These results suggest a possible link between the chronic maternal metabolic stress, such as long-term fructose intake, and neurodevelopmental disturbances in the offspring.

1. Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by deficits in communication and social behaviors coupled with the presence of stereotyped behaviors (American Psychiatric Association, 2013). Despite the huge literature on ASD in the last decade, the underlying etiology remains unknown. Numerous risk factors such as genetic, infectious, metabolic, nutritional, and environmental have been reported in several studies (Wegiel et al., 2010; Jeste, 2011; Lee et al., 2016). Though it is well recognized that ASD has a significant genetic component; for at least 70% of cases the underlying genetic cause is unidentified. Among environmental factors, only some rare viral infections and certain drugs have been conclusively linked to autism. The stimulation of maternal pro-inflammatory cytokines by bacterial or viral agents may lead to significant neurochemical and behavioral alterations in offspring (Ashwood et al., 2011). There is also evidence that maternal metabolic conditions including obesity, diabetes and hypertension may be a risk factor for autism and other neurodevelopmental disorders in children (Krakowiak et al., 2012). More recently, in a clinical study, it has been reported that gestational diabetes mellitus (GDM) diagnosed by 26 weeks' gestation was significantly associated with risk of ASD in offspring (Xiang et al., 2015).

Fructose consumption among adults has considerably increased worldwide. Overconsumption of fructose is linked to several adverse

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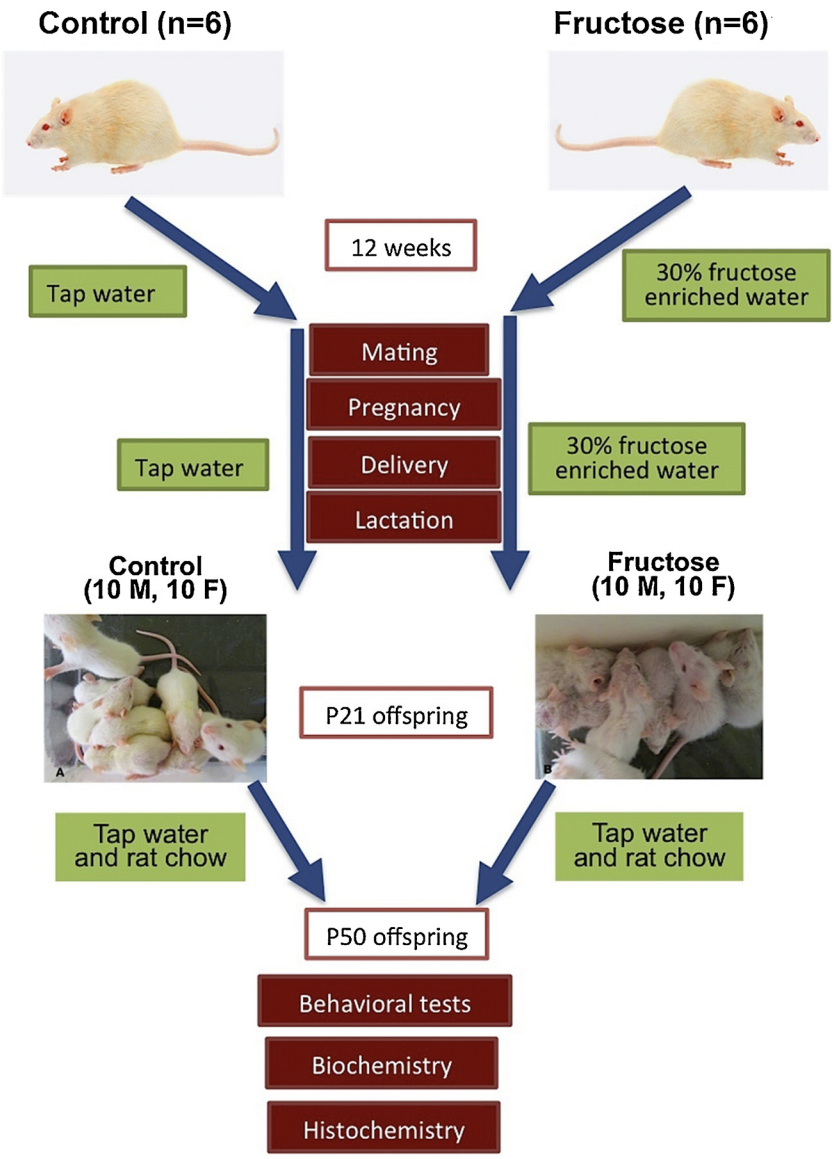

Fig. 1. Schematic diagram of the study design.

metabolic outcomes including hyperglycemia, hyperinsulinemia, insulin resistance, obesity, dyslipidemia, and steatohepatitis in laboratory animals and human subjects (Kolderup and Svihus, 2015). It has been reported that higher consumption of sugar-sweetened beverages, such as soft drinks, has been linked to greater risks for GDM (Chen et al., 2009). Moreover, chronic excessive caloric intake, mainly fructose, contributes to the development of fatty liver disease (steatohepatitis) (Thuy et al., 2008; Spruss et al., 2009). Non-alcoholic fatty liver disease is a condition of fat accumulation in the liver without excessive alcohol consumption. Accumulating evidences reveal that fatty liver is strongly related to low-grade chronic inflammation like some other chronic disorders such as metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus (T2DM), hypertension and some cancers (Rodríguez-Hernández et al., 2013). Animal and human studies suggest that metabolic stresses leading to lipid accumulation in the liver promotes local cytokine production such as interleukins and tumor necrosis factor alpha (TNF-α) (Jahn et al., 2016).

In a previous study, we have reported that long-term fructose-received adult rats revealed significantly higher stereotypy score, elevated levels of brain and liver cytokines and brain dopaminergic activity than those of their normal controls (Erbaş et al., 2015). In the present study, we aimed to investigate the neurodevelopmental effects of long-term maternal metabolic deterioration on offspring using a rat model of fructose-induced metabolic syndrome. We assessed the harmful effects of chronic fructose exposure before, during and after gestational period on the offspring by numerous behavioral parameters such as locomotor activity and anxiety-like behavior (open field test), social interaction (three-chamber test), passive avoidance learning (shuttle box test) and stereotypic behavior (apomorphine-induced stereotypic behavior test). We also measured plasma levels of aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, total cholesterol and triglyceride. In addition, we determined several biomarkers in the brain tissue including tumor necrosis factor alpha (TNF-α), neuregulin 1 (NRG1), glutamic acid decarboxylase 67 (GAD67), nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1), and 5-hydroxyindoleacetic acid (5-HIAA) as serotonin metabolite. Histologically, we evaluated hippocampal neuronal morphology, total neuron count and GFAP immunoexpression in the study groups.

2. Materials and methods

2.1. Animals

Twelve female and 4 male Sprague Dawley adult rats (238 ± 10 g)