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Journal of Nutritional Biochemistry 26 (2015) 267–276

Journal of Nutritional Biochemistry

Maternal taurine supplementation attenuates maternal fructose-induced metabolic and inflammatory dysregulation and partially reverses adverse metabolic programming in offspring

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Received 26 May 2014; received in revised form 9 October 2014; accepted 30 October 2014

Abstract

Excessive fructose consumption is associated with insulin resistance (IR) and nonalcoholic fatty liver disease (NAFLD), and high fructose intake during pregnancy can lead to compromised fetal development in the rat. Evidence suggests that the amino acid taurine can ameliorate fructose-induced IR and NAFLD in nonpregnant animals. This study investigated the efficacy of taurine supplementation on maternal fructose-induced metabolic dysfunction and neonatal health. Time-mated Wistar rats were randomized to four groups during pregnancy and lactation: (a) control diet (CON), (b) CON supplemented with 1.5% taurine in drinking water (CT), (c) CON supplemented with fructose solution (F) and (d) F supplemented with taurine (FT). Maternal and neonatal weights, plasma cytokines and hepatic gene expression were analyzed. Maternal hyperinsulinemia, increased homeostasis model assessment of IR indices and elevated proinflammatory cytokines were observed in F group and normalized in FT group. Maternal fructose-induced hepatic steatosis accompanied with increased liver weight was ameliorated with taurine supplementation. Maternal hepatic sterol regulatory element-binding protein-1c and fatty acid synthase expression was significantly increased in the F group compared to the CON, CT and FT groups. Neonatal hepatic phosphoenolpyruvate carboxykinase expression was increased in male F neonates compared to the CON, CT and FT groups and was increased in female F and FT neonates compared to CON and CT. Interleukin-1β expression was decreased in male CT and FT neonates compared to other male groups. Hepatic tumour necrosis factor receptor-1 was lower in the male FT group than the F group. These results demonstrate that maternal taurine supplementation can partially reverse fructose-induced maternal metabolic dysfunction and may ameliorate adverse developmental programming effects in offspring in a sex-specific manner.

Keywords: Developmental programming; Taurine; Fructose; Inflammation; Fatty liver disease; Maternal nutrition; Animal models

1. Introduction

Over the last few decades, the use of fructose as a food additive to sweeten beverages and other processed foods has increased globally [1] and correlates closely with the rise in obesity, metabolic syndrome and type 2 diabetes [2]. Given the potential of excessive fructose consumption to induce adiposity and metabolic dysfunction, increased availability of products containing fructose has the potential to fuel the global obesity epidemic [3–5]. Animal studies have shown that high-fructose diets can lead to a series of metabolic disorders including insulin resistance (IR), hypertension and nonalcoholic fatty liver disease (NAFLD) [6,7]. Research from our group and others has shown that fructose consumption during pregnancy and lactation leads to hyperinsulinemia, hyperglycemia and hepatic steatosis in dams [8–10]. However, there are few studies that examine the impact of intervention strategies to combat the detrimental effects of excessive fructose intake on the health and well being of pregnant mothers and their offspring.

Growing evidence from both human and animal studies suggests that the development of metabolic disorders during pregnancy is strongly associated with adverse effects on the long-term health of offspring [11,12]. As proposed by the developmental origins of health and disease (DOHaD) paradigm, altered maternal nutrition during critical periods of developmental plasticity can alter offspring development, which in turn can lead to an increased risk of obesity and metabolic dysfunction in later life [13]. We have previously shown that moderate fructose consumption during pregnancy can lead to changes in placental growth, hyperglycemia and hyperleptinemia in female offspring [8]. Of importance, the fructose load in our experimental model is designed to provide the mother only 20% of total calories, thus highlighting that, even at relatively low concentrations, fructose can induce significant metabolic abnormalities in offspring. Further work by Rodriguez et al. [14] demonstrated that maternal fructose intake could alter fetal leptin signaling. It is also important to delineate between the different forms of fructose. Most studies to date have utilized high-fructose corn syrup (HFCS) which is a commonly used sweetener in food and beverages. However, the terms HFCS and fructose are often, and incorrectly, used interchangeably. While pure crystalline fructose, as used in our previous work [8]

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http://dx.doi.org/10.1016/j.jnutbio.2014.10.015
0955-2863/

and in the present study, contains fructose alone, the most widely used variety of HFCS contains approximately 55% fructose and the rest as glucose.

Taurine (2-aminoethanesulfonic acid) is an amino acid which is produced endogenously in humans and rodents [15]. Several studies have demonstrated that taurine supplementation has potential as a regulator of insulin secretion and promotes insulin sensitivity [16,17]. Furthermore, taurine can ameliorate fructose-induced hyperglycemia, hypertension and hepatic steatosis in nonpregnant rat models [18,19]. In addition to its proximal effects, taurine supplementation to pregnant rats fed a low-protein diet has been shown to normalize pancreatic islet development and glucose and insulin homeostasis in offspring [20–22]. These beneficial effects on glucose metabolism persist into adult life [23]. We have also shown recently that maternal taurine supplementation can modify maternal and offspring markers related to hepatic inflammation and lipid metabolism in the setting of maternal obesity [24].

The current study aims to further evaluate the adverse consequences of excessive fructose consumption during pregnancy and lactation and to determine whether maternal taurine supplementation can reverse the metabolic disorders induced by fructose in dams and neonates.

2. Methods

2.1. Animal model

Details on the protocol utilized for fructose and taurine supplementation have been published previously by our group [8,24]. Virgin Wistar rats were time mated at 100 days of age using an estrous cycle monitor (EC-40; Fine Science Tools, San Francisco, USA, USA), and mating was confirmed by the presence of spermatozoa following a vaginal lavage. Animals were then housed as singletons and randomly allocated to one of four nutritional groups: control group (CON) fed a chow diet (Diet 2018, Harlan Teklad, Blackthorn, Bicester, UK) (n=9); control taurine group (CT) fed chow diet with additional 1.5% w/v taurine supplementation in drinking water (n=7); maternal high-fructose-diet group (F) fed chow diet with an additional fructose solution which was designed to provide 20% calories from fructose (n=8); maternal high-fructose-diet and taurine group (FT) fed chow diet with additional fructose solution and taurine supplementation in drinking water (n=8). All cages had two water bottles which were placed in the same position throughout the trial. In the F and FT groups, one of the water bottles contained a fixed volume (70 ml) of fructose and, based on measured chow intake, aimed to provide an additional 20% of total daily calories from fructose. All maternal diets were maintained throughout pregnancy and lactation. As fructose consumption can potentially affect water intake [8], taurine concentrations in the FT group were adjusted where necessary according to the previous days' water intake. This was essential to ensure that the taurine dose was equivalent across both CT and FT groups. All dams had *ad libitum* access to chow diet and water throughout pregnancy and lactation.

Two distinct time points were investigated. Firstly, effects of maternal taurine supplementation on neonatal outcomes were examined on the day after birth, and secondly, the effects of taurine on maternal metabolic and inflammatory profiles were investigated at the end of the lactation period. Maternal body weight, food and fluid intake were recorded daily. At the time of birth, litter size, sex ratio and birth weight were documented. On postnatal day 2, any neonatal deaths were recorded, and litter size was adjusted to eight pups per litter (four males and four females). Neonatal (nonfasting) plasma and liver samples were collected from randomly chosen pups following decapitation. At the end of lactation, dams were fasted overnight and killed by decapitation following anesthesia with sodium pentobarbitone (60 mg/kg IP). Maternal body composition was evaluated by dual-energy X-ray absorptiometry using dedicated small animal software (DEXA; Lunar Prodigy, Madison, WI, USA). Maternal and neonatal blood glucose and β-hydroxybutyrate (BHB) were measured from tail blood samples using a glucose meter (Optium, Abbott Laboratories) at the time of cull.

Some baseline physiologic and plasma data from the CON and CT groups utilized in this study have been reported elsewhere in a parallel project examining maternal obesity [24]. Ethical approval was obtained from the Animal Ethics Committee at the University of Auckland (Ethical Approval R888).

2.2. Plasma analysis

Plasma insulin and leptin (CrystalChem, USA), tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 (Quantikine; R&D Systems Europe, Abingdon, UK) were measured by rat specific enzyme-linked immunosorbent assay. Plasma uric acid and fructose were measured using commercially sourced assay kits (Cayman Chemical, Ann Arbor, MI, USA; EFRU-100, BioAssay Systems, Hayward, CA). Homocysteine (HcY) was measured via immunoassay (Abbott AxSYM system). Maternal plasma taurine concentrations were analyzed using a Hitachi 902 autoanalyzer (Hitachi High Technologies Corporation, Tokyo, Japan). The homeostasis model assessment of IR (HOMA-IR) was calculated as follows: fasting glucose (mmol/L)×fasting insulin (mU/L)/22.5 [25].

Table 1
Maternal and neonatal weights.

	Groups				Effect		
	CON	CT	F	FT	Diet	Taurine	Interaction
Maternal weight (g)	297.8±6.6^{A}	298.7±8.1^{A}	319.4±9.9^{B}	328.8±10^{B}	***F*=7.88**	*F*=0.14	*F*=0.52
					***P*=.0092**	*P*=.7112	*P*=.4771
Maternal liver weight (% body weight)	3.78±0.11^{a}	3.79±0.11^{a}	4.49±0.12^{b}	3.99±0.08^{a}	***F*=17.47**	***F*=5.96**	***F*=5.52**
					***P*=.0003**	***P*=.0215**	***P*=.0264**
Maternal total fat (%)	10.7±1.7	13.8±2.7	12.37±1.63	10.3±0.88	*F*=0.58	*F*=0.0	*F*=1.46
					P=.4519	*P*=.9782	*P*=.2368
Fat:lean ratio	0.134±0.02	0.167±0.04	0.143±0.02	0.116±0.01	*F*=0.77	*F*=0.01	*F*=1.54
					P=.3873	*P*=.9141	*P*=.2253
Birth weights (male, g)	6.34±0.13^{B}	5.8±0.17^{A}	6.26±0.13^{B}	6.20±0.1^{A}	*F*=1.35	***F*=4.39**	*F*=2.95
					P=.2501	***P*=.0406**	*F*=0.0913
Birth weights (female, g)	6.33±0.15	5.94±0.14	5.94±0.19	5.93±0.12	*F*=1.79	*F*=1.78	*F*=2.95
					P=.1856	*P*=.1871	*F*=0.2157

Values are presented as means±S.E.M, n=7–9 per group. Bold font indicates effect P value <.05 via two-way ANOVA. Uppercase letter ($^{A, B}$) superscripts indicate that comparison procedures were conducted between all groups fed fructose diet and all groups fed CON diet. Lowercase letter superscripts ($^{a, b, c}$) indicate that multiple comparison procedures were conducted for diet and taurine interaction. Groups that do not share the same letter are significantly different from each other (P<.05).