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Short Review

Translational insights on developmental origins of metabolic syndrome: Focus on fructose consumption

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ABSTRACT

Metabolic syndrome (MetS) is a highly prevalent complex trait despite recent advances in pathophysiology and pharmacological treatment. MetS can begin in early life by so-called the developmental origins of health and disease (DOHaD). The DOHaD concept offers a novel approach to prevent MetS through reprogramming. High fructose (HF) intake has been associated with increased risk of MetS. HF diet becomes one of the most commonly used animal model to induce MetS. This review discusses the maternal HF diet induced programming process and reprogramming strategy to prevent MetS of developmental origin, with an emphasis on: (1) an overview of metabolic effects of fructose consumption on MetS; (2) insight from maternal HF animal models on MetS-related phenotypes; (3) impact of HF consumption induces organ-specific transcriptome changes; and (4) application of reprogramming strategy to prevent maternal HF consumption-induced MetS. Research into the preventions and treatments of MetS that begin early in life will have a lifelong impact and profound savings in disease burden and financial costs.

The worldwide per capita fructose consumption has grown in the last half-century and its growth has been paralleled by an increase in metabolic syndrome (MetS)-related disorders [1,2]. MetS is a common complex trait comprising of a cluster of medical conditions including hypertension, obesity, dyslipidemia, hyperglycemia, fatty liver, and insulin resistance [3]. Emerging evidence suggests that the origins of susceptibility for MetS in adult can be traced back to the early life, referred to the developmental origins of health and disease (DOHaD) [4]. On the other hand, the DOHaD concept offers a novel approach to prevent MetS through reprogramming, to shift therapeutic interventions from adulthood to early life, even before clinical symptoms are evident [5]. A number of dietary, genetic, surgical, and pharmacological models have been developed to explore the pathophysiology and underlying mechanisms of developmental programming of MetS [6,7]. As rodents fed with a fructose-enriched diet exhibit many features of the MetS, high-fructose (HF) diet becomes one of the most commonly used animal model to induce MetS.

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This review provides an overview of maternal HF consumption-induced programming process contributing to MetS-related phenotypes, with an emphasis on the following areas: metabolic effects of fructose on MetS; effects of maternal HF consumption on developmental programming of MetS-related phenotypes; maternal HF consumption induces transcriptome changes; and application of reprogramming interventions to prevent maternal HF-induced MetS-related disorders.

Metabolic effects of fructose on metabolic syndrome

Fructose is one of the monosaccharides along with glucose and galactose. Fructose is found in all fruits and vegetables. The human body obtains fructose through exogenous supply or endogenously produces fructose from glucose through aldose reductase pathway [8]. Nowadays, most of the increase in fructose consumption is derived from refined sugars and processed foods.

Fructose is absorbed in the intestine through specific glucose transporters such as glucose transporter 5 (Glut 5) and Glut 2. Fructose metabolism differs markedly from glucose metabolism because these two sugars require different enzymes in the initial steps of metabolism. A growing body of evidence indicates that HF diet causes various features of MetS, such as obesity, adiposity, hypertension, hypertriglyceridemia, dyslipidemia, glucose intolerance and decreased insulin sensitivity [2,6,7]. Also, previous studies indicated that glucose or starch-feeding is not as effective as fructose-feeding to induce MetS [2].

Unlike glucose, which is metabolized widely in the body, fructose is converted into glucose, glycogen, lactate, and fatty acids mainly in the liver [8]. Since fructose can be transported and produced by the placenta [9,10], it is considered that the fetal programming process is driven not only by fructose but also by its metabolites [11].

Effects of maternal fructose consumption on developmental programming of metabolic syndrome-related phenotypes

Although a number of epidemiological studies support an association between fructose consumption and adult MetS [12], limited studies have explored the effects of early-life fructose consumption on fetus and disease risk in adult offspring. So far, only a limited number of human studies have shown an association between excessive sweetened food and beverage consumption and poor pregnancy outcome [13]. Notably, human studies have not yet established the direct cause-and-effect relationship between excessive fructose consumption and MetS-related disorders. It stands to reason that the use of animal models is essential to investigate MetS-related programming process and identify reprogramming strategy for further translational research.

Our previous reports showed that adult offspring rats of mothers exposed to 60% HF diet during pregnancy and lactation developed MetS-related comorbidities [14–20], which is in agreement with the results of earlier studies involving fructose-fed adult rats [21]. Fructose appears to induce MetS in part by increasing uric acid [2]. Unlike fructose-induced uric acid generation that induces oxidative stress and nitric oxide (NO) deficiency in adult rats [2,8], we observed that these abnormalities are not present in adult offspring exposed to maternal HF intake [14]. It is speculated that mechanisms underlying maternal HF consumption-induced fetal programming of MetS in offspring might be different from those underlying fructose feeding-induced MetS in adult rats [11].

It is noteworthy that adverse effects of fructose feeding depend on the amount and duration of fructose consumption [22]. Because rats express uricase (which degrades uric acid), fructose does not increase uric acid level very effectively [2]. Despite being viewed as far in excess of a relevant load, most animal studies have been performed using diets containing 50%–60% fructose [8]. However, a recent meta-analysis study showed that various features of MteS can be achieved using diets with as little as 10% w/v fructose in drinking water, independent of variations in study design and duration [21].

This review will primarily be limited to MetS-related phenotypes induced by HF consumption in early life in rodent animal models, some of which are listed in Table 1. Despite fructose alone can alter fetal programming to induce numerous features of MetS [17–19,23,25,26,28–30], some animal studies have often used fructose as a part of diet along with salt [20,24] or fat [27].

HF diet induces hypertension in adult rats have been well reviewed elsewhere [31,32]. However, limited data are available on the effects of maternal HF induced hypertension in adult offspring. Studies listed in Table 1 indicate that consumption of HF alone or as a part of diet by rodent mothers induces programmed hypertension in adult offspring of both sexes [14–17,19,24,27,30]. Several mechanisms have been proposed to interpret HF-induced hypertension, including oxidative stress, NO deficiency, increased sodium absorption, endothelial dysfunction, activation of the renin-angiotensin system (RAS) activation, and sympathetic nervous system stimulation [11].

An obesogenic effect of HF intake was also observed in animal studies [23,30]. Consumption of fructose has been reported to induce obesity by several mechanisms, such as direct effects on adipose tissue, indirect actions on the appetite control and feeding behavior, and by disrupting neuroendocrine signaling between adipose tissue and the hypothalamus [33]. Additionally, often considered the hepatic manifestation of the MetS, non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis in the absence of heavy alcohol use. As shown in Table 1, maternal HF exposure has been reported to induce hepatic steatosis in adult offspring [28–30]. Fructose consumption can upregulate the hepatic lipogenesis program, which is further amplified by hyperinsulinemia in the context of insulin resistance. Also, consumption of HF by rodent mothers induces insulin resistance in adult offspring [16,23,26,30]. Metabolites from fructose metabolism can directly affecting tissue and organ functions; among these uric acid, free fatty acids and lactate play important roles in mediating insulin resistance in systemic and local tissue/organ [34]. Moreover, in several animal