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Fructose-rich diet and insulin action in female rat heart: Estradiol friend or foe?

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ABSTRACT

Increased intake of fructose in humans and laboratory animals is demonstrated to be a risk factor for development of metabolic disorders (insulin resistance, metabolic syndrome, type 2 diabetes) and cardiovascular diseases. On the other hand, estradiol is emphasized as a cardioprotective agent. The main goal of this review is to summarize recent findings on damaging cardiac effects of fructose-rich diet in females, mostly experimental animals, and to evaluate protective capacity of estradiol. Published results of our and other research groups indicate mostly detrimental effects of fructose-rich diet on cardiac insulin signaling molecules, glucose and fatty acid metabolism, nitric oxide production and ion transport, as well as renin-angiotensin system and inflammation. Some of these processes are involved in cardiac insulin signal transmission, others are regulated by insulin or have an influence on insulin action. Administration of estradiol to ovariectomized female rats, exposed to increased intake of fructose, was mostly beneficial to the heart, but sometimes it was ineffective or even detrimental, depending on the particular processes. We believe that these data, carefully translated to human population, could be useful for clinicians dealing with postmenopausal women susceptible to metabolic diseases and hormone replacement therapy.

1. Introduction

Fructose is a monosaccharide naturally present in fruits, some vegetables and honey. Fructose intake in its primary natural form is not associated with adverse effects up to the limits of human consumption (Ludwig, 2013). Namely, besides simple sugars that they contain, fructose-containing natural products also comprise vitamins, minerals, fibers, antioxidants and phytochemicals responsible for their beneficial effects (Sharma et al., 2016). For thousands of years humans consumed fructose up to 20 g per day, largely from fresh fruits, without any adverse effects. Fructose has less influence on serum insulin concentrations than glucose, and no influence on plasma glucose levels, which support fructose as a convenient sweetener for diabetic patients (Schaefer et al., 2009).

However, westernization of diets has resulted in significant increases in added fructose, leading to typical daily consumptions amounting to 85–100 g of fructose (Bray and Popkin, 2014). An increased intake of fructose in human population during last decades is the predominant consequence of wide usage of added sugars in food industry. Two of the most common industrial sweeteners, sucrose and high fructose corn syrup (HFCS), both consist of glucose and fructose. Sucrose is composed of one molecule of glucose and one molecule of fructose, while liquid HFCS usually contains 42% or 55% of fructose (Basciano et al., 2005; Malik and Hu, 2015). A wide spectrum of prepackaged foods contains added sugar, but sugar sweetened beverages are particularly notorious because of high content of sugar and high level of consumption (Bes-Rastrollo et al., 2016). Introduction of HFCS as commercial sweetener coincides with an enormous raise of obesity and obesity-related diseases (Bray and Popkin, 2014; Stanhope, 2012). Therefore, numerous experiments were conducted to elucidate the specific role of fructose in spreading obesity and other metabolic disorders.

Generally, in scientific community there are two opposite standpoints. The first one indicates that fructose has specific adverse effects, which are consequence of its metabolism and the fact that human organism is not evolutionary prepared to deal with the amount of fructose typical for modern diet (Basciano et al., 2005; Malik and Hu, 2015). Human studies indicate that fructose consumption from industrialized foods has significant effects on most components of metabolic syndrome (Kelishadi et al., 2014). Also, consumption of a

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low concentration fructose beverage is sufficient to cause early signs of the metabolic syndrome in adult rats (Toop and Gentili, 2016). Contrary, other authors believe that fructose is equal to glucose as an energy source and that the crucial culprit for the epidemic of obesity is a combination of modern-day unhealthy habits, particularly our inability to control caloric intake (Rippe and Angelopoulos, 2015; Tappy, 2016). They criticize animal and epidemiological studies as unreliable, claiming that studies indicating harmful effects of fructose are performed by using fructose amount that does not reflect real-life diets (White, 2013).

However, several characteristics of fructose metabolism make it particularly lipogenic (Herman and Samuel, 2016; Softic et al., 2016). Fructose is absorbed via portal vein and delivered preferentially to the liver. As reviewed in Malik and Hu (2015), there are crucial differences in the metabolic pathways of glucose and fructose. In the liver, fructose is metabolized into glyceraldehyde and dihydroxyacetone phosphate. These intermediate products converge with the glycolytic pathway. It is of key importance, that fructose is able to by-pass the main regulatory step of glycolysis, the conversion of glucose-6- phosphate to fructose 1,6-bisphosphate, controlled by phosphofructokinase. Accordingly, while glucose metabolism is negatively regulated by phosphofructokinase, fructose continuously enters the glycolytic pathway. Therefore, fructose can uncontrollably produce glucose, glycogen, lactate, and pyruvate, providing both the glycerol and acyl portions of acyl-glycerol molecules. These particular substrates, and the resultant excess energy flux due to unregulated fructose metabolism, will promote the overproduction of triglycerides.

As detailed in Herman and Samuel (2016) fructose increases protein levels of all hepatic *de novo* lipogenesis enzymes during its conversion into triglycerides. Additionally, fructose supports lipogenesis in the insulin resistance milieu because fructose metabolism is insulin independent, and it directly stimulates sterol regulatory element-binding protein 1, a major transcriptional regulator of *de novo* lipogenesis. Furthermore, fructose leads to ATP depletion and suppression of mitochondrial fatty acid oxidation, resulting in increased production of reactive oxygen species. Fructose, also, generates endoplasmic reticulum stress and uric acid formation, additional insulin independent pathways leading to *de novo* lipogenesis (Softic et al., 2016).

Specific metabolism of fructose in the liver and metabolic shift induced by high fructose consumption that leads to obesity, disturbances in insulin action, carbohydrate and lipid metabolism and hypertension, indirectly, but strongly, jeopardize regular heart functioning. In addition, it has been recently observed that cardiomyocytes express fructose transporter GLUT5 implying that cardiomyocyte have the capacity to transport and functionally utilize exogenously supplied fructose (Mellor et al., 2011a). Indirectly and/or directly, fructose-rich diet (FRD) certainly leads to cardiac insulin resistance (Zakula et al., 2011), compromising insulin action in the heart. In the insulin-resistant cardiac milieu, abnormalities in fructose metabolism can contribute directly to myocardial disease development (Delbridge et al., 2016).

Considering the literature from epidemiological, clinical, and experimental perspectives there is an abundance of evidence demonstrating fructose participation in the etiology of diabetic cardiomyopathy, including involvement in cardiac metabolic, structural, and electromechanical pathologies (Mellor et al., 2013). Fructose-rich diet elevates superoxide generation, activates autophagy and suppresses survival signaling, disturbs Ca^{2+} handling and modulates excitation-contraction coupling in the mouse heart (Mellor et al., 2010, 2011a, 2011b, 2012). It is of notice that dysregulated fructose metabolism in the heart, and not specifically systemic glycemic exposure, is associated with the ultimate progression of diabetic cardiomyopathy to cardiac failure state (Delbridge et al., 2016). Considering specifically human studies, dietary fructose increases de novo lipogenesis, promotes dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity in overweight/obese adults (Stanhope et al., 2009), which all may increase cardiometabolic risk. In addition, fructose, but not glucose, elicits an increase in blood pressure that is probably mediated by an increase in cardiac output without compensatory peripheral vasodilatation (Brown et al., 2008).

Effects of FRD are shown to be sex-dependent and mature premenopausal females, in contrast to adult males, are indicated as “fructose-resistant” to some degree, in terms of development of metabolic and other disturbances (Bundalo et al., 2016; Galipeau et al., 2002; Romic et al., 2014). Estradiol (E2) is indicated as responsible for protection against FRD and after ovary removal or in menopause females became sensitive to harmful effects of fructose (Galipeau et al., 2002; Zakula et al., 2011). Furthermore, chronic E2 treatment has some beneficial effects on cardiovascular diseases, which result from improvement of insulin sensitivity (Liu et al., 2004). Estrogen has a number of effects on cardiovascular function and disease. Among its various cardiovascular effects, estrogen modulates vascular function, inflammatory response, metabolism, insulin sensitivity, cardiac myocyte and stem cell survival, and the development of hypertrophy (Murphy, 2011). Although estrogens had long been viewed as cardioprotective (Knowlton and Korzick, 2014), their capacity to prevent or fix cardiac problems induced by high fructose diet is not yet fully elucidated.

Provoked by a lack of reviews on this topic we aimed to summarize current evidence on female's cardiac markers of insulin signaling and insulin-regulated processes (energy metabolism, nitric oxide (NO) production, ion transport), as well as processes implicated in insulin resistance genesis (renin-angiotensin system (RAS) signaling, inflammation), in the light of increased intake of fructose and discuss E2 protective capacity.

2. FRD and insulin signaling pathways

Although a comprehensive understanding of the insulin action mechanisms in the heart is still developing, there is convincing evidence that insulin has an impact on cardiac metabolism by influencing cellular processes such as glucose and fatty acid transport and metabolism, as well as protein synthesis. Insulin also contributes to myocardial contractility, autophagy, cell survival and protection against heart hypertrophy and ischemia-induced necrosis (Westermeier et al., 2016).

As recently reviewed in detail (Saltiel, 2016), insulin receptor is a cell surface protein with intrinsic tyrosine kinase function, activation of which leads to an association with insulin receptor substrates (IRS), signaling scaffolds that facilitate activation of signaling molecules such as phosphoinositide-3-kinase (PI3K). PI3K converts phosphatidylinositol (3,4)-bisphosphate to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) at the plasma membrane. Subsequently, PIP3 interacts with the PH-domain containing protein phosphoinositide-dependent kinase 1 that phosphorylates and activates the serine/threonine kinase Akt. Akt phosphorylates many intracellular targets that include: forkhead box O transcription factor, tuberous sclerosis complex 2, glycogen synthase kinase 3 β, endothelial nitric oxide synthase (eNOS) and Akt substrate AS160. These Akt substrates are involved in regulation of glucose and fatty acid metabolism, protein synthesis, glycogen synthesis, NO production, glucose transport etc. Insulin receptor activation also increases phosphorylation of the mitogen activated protein kinases ERK1 and 2 (extracellular signal-regulated kinases), which regulate gene expression (Riehle and Abel, 2014; Saltiel, 2016).

Even though numerous data indicate FRD impairments of insulin signaling molecules in the male heart (Cheng et al., 2014; Mellor et al., 2011b; Stanisic et al., 2016), studies on female heart are limited to publications of our group. Regarding E2, it was demonstrated that in ovariectomized rats on normal diet, this hormone stimulates cardiac Ser^{473} and Thr^{308} Akt phosphorylation, as well as Thr^{202}/Tyr^{204} phosphorylation of ERK1/2 (Koricanac et al., 2009, 2011; Patten