Inflammatory Signaling and Insulin Resistance Caused by High Sugar Intake: Modulation by PPAR-δ Agonism

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The use of sugar sweetened beverages has been demonstrated to increase body weight of children and adolescents, and to enhance the risk of obesity in genetically susceptible subjects (Qi et al., 2012; de Ruyter et al., 2012; Ebbing et al., 2012). In attempt to mimic the metabolic derangement induced by ingested sweeteners in the Western diet, and to understand the pathophysiological mechanism(s) of the following insulin resistance and inflammation, an *in vivo* animal models of chronic high sugar intake has been developed. Male C57BL/6J mice received HFCS-55 (containing 55% fructose and 42% glucose) added to the drinking water for 30 weeks, at 15% wt/vol. This amount covers the 10% of the human daily caloric intake, due to sugar-added beverages consumption. In order to identify the molecular mechanisms involved in HFCS-55 induced-dismetabolism, we focused on the liver and kidney. In the liver, HFCS-55 enhanced the expression of fructokinase resulting in hyperuricemia. In addition, it caused abnormalities in known insulin-driven signaling events, increasing the phosphorilation of IRS-2 and reducing the phosphorilation of Akt and GSK-3β. In the kidney, HFCS-55 significantly increased markers of neutrophil infiltration such as MPO activity, iNOS and ICAM-1 expression and enhanced the expression of the NLRP3 (nucleotide-binding domain and leucine-rich-repeat-protein 3) in?ammasome complex, resulting in caspase-1 activation and interleukin-1β production, and subsequent renal inflammation. In order to investigate a target for the pharmacological modulation of HFCS-55-induced damage, we focused on Peroxisome-Proliferator Activated Receptor (PPAR)-δ, whose agonists have never been tested in models of sugar-induced dismetabolism. In this study, we demonstrated for the first time that the previously reported metabolic abnormalities and inflammatory parameters caused by HFCS-55 were attenuated in mice treated with a selective PPAR-δ agonist, GW0742 (1 mg/kg/day for 16 weeks; Collino et al., 2013). PPAR-δ agonism also increased, in the skeletal muscle of HFCS-55 fed mice, both the expression of the glucose transporter GLUT-4 and GLUT-5 and their membrane translocation, were related to the improvement of insulin resistance. Furthermore, it reverted the diet-induced increase of inflammatory markers. These effects were associated with a marked rise in skeletal muscle levels of FGF-21, a recently identified myokine involved in the control of impaired glucose homeostasis and skeletal muscle glucose uptake (Benetti et al., *in press*). Overall, our study contributes to a better elucidation of the inflammatory signaling and insulin resistance and related molecular mechanisms evoked by chronic exposure high sugar intake diet, and adds original piece of evidence to the complex mechanisms by which PPAR-δ regulates several metabolic processes.