WWTF Project LS12-008

Unravelling the pathogenetic mechanisms of fructose consumption as multiple hit in the pathogenesis and progression of non-alcoholic fatty liver disease (NAFLD)

Abstract

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum ranging from simple fatty liver over steatohepatitis (NASH) to liver cirrhosis and cancer (HCC) and is a major and increasing health problem affecting nearly 40% of the general population. Moreover, NAFLD is an important risk factor for progression of diabetes and atherosclerosis. However, the pathomechanisms determining disease progression are poorly understood. The overall aim of this project is to test the central hypothesis that excessive fructose consumption provides a multiple metabolic hit in the pathogenesis and progression of NAFLD/NASH by impairment of hepatic lipid homeostasis and mitochondrial function resulting in hepatic lipotoxicity with inflammasome activation and disturbed interorgan cross-talk among insulin sensitive tissues.

To achieve these goals we will address the following specific hypotheses that - Fructose-induced changes in lipid composition of hepatocellular stores determine lipotoxicity which may be associated with abnormalities in mitochondrial function, energy homeostasis, inflammasome activation and cellular injury in progression to NASH

- Non-invasive characterization of fructose-induced lipotoxic hepatic and extrahepatic metabolic risk profiles (lipid composition and energy metabolism) obtained by magnetic resonance spectroscopy (MRS) will identify patients with NASH
- Severity of fructose-induced lipotoxic lipid and ATP derangements (identified by MRS) critically determines the degree of insulin resistance and abnormalities in hepatic glucose and lipid metabolism
- Compensatory hyperinsulinemia, secondary to skeletal muscle insulin resistance, may be a primary mechanism of hepatic lipotoxicity and progression to NASH
- Gender differences in the hepatic and systemic metabolic response to fructose are mediated by the impact of female sex hormones and their nuclear receptors on hepatic lipid metabolism, mitochondrial function and inflammasome activation.

These key hypotheses will be addressed by a translational research consortium including hepatologists, radiologists, physicists, endocrinologists and specialist in gender medicine allowing an integrated mechanistic approach to NAFLD. The strength of the current proposal comes directly from bridging basic science and clinical perspectives of different disciplines involved in the management of NAFLD, including cutting edge non-invasive technologies such as highfield MRS metabolic profiling ('virtual metabolic liver biopsy') and mechanistic in vitro experiments. This project will provide novel mechanistic insights in the role of fructose as emerging hepatic 'toxin' in the pathogenesis and progression of NASH, as increasing health problem in Western society. Moreover, this study will clarify the impact of sex and gender on fructose-induced alterations in hepatic and systemic metabolism, providing a rational and scientific basis for future dietary interventions and egulatory actions.

Keywords:

Fructose, fatty liver, lipotoxicity, mitochondrial function, inflammasome,oxidative stress, ER stress

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Further links about the involved persons and regarding the project you can find at
https://archiv.wwtf.at/programmes/life_sciences/LS12-008