TOXICOLOGICAL IMPACT OF HIGH FRUCTOSE INTAKE ON GUT MICROBIOTA AND LIVER/INTESTINE INTEGRITY: ANY DIFFERENCES BETWEEN SOLID AND LIQUID FORMULATIONS?

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We previously demonstrated the deleterious effects of fructose feeding on liver through production of advanced glycation end products (AGEs) and the induction of hepatic steatosis and inflammation. Moreover, it has been reported that high fructose intake alters microbiota composition, resulting in reduced bacterial diversity and altered expression of genes involved in specific metabolic pathways. A recent paper demonstrated that liquid high-sugar diets compared to solid high-sugar diets differentially modulate intestinal sugar transporters and hormone expression. To date, however, the peculiar effects evoked by the intake of different formulations of fructose, liquid or solid, on gut integrity and microbiota as well as on the related hepatic outcomes, have never been investigated. Hence, the present study was designed not only to elucidate the toxicological profile of high fructose intake in both intestine and liver but also to determine potential differences due to the texture of the sugar.

Male C57Bl/6j mice were fed a standard diet (SD) plus water to drink, a standard diet plus 60% fructose syrup (L-Fr), or a 60% fructose solid diet plus water (S-Fr), for 12 weeks. At the end of protocol, liver lipogenesis, fibrosis, and inflammation were evaluated by western blotting and histological analysis. Intestinal absorption, accumulation of AGEs, and integrity were assessed by immunofluorescence and histology. Gut microbiota population was characterized by metagenomic sequencing.

L-Fr intake induced higher levels of hepatosteatosis (liver TG: +80% vs. SD, +33% vs. S-Fr, $p<0.05$) associated to a greater expression/activation of the lipogenic SCAP/SREBP signaling pathway and fibrogenic markers than the S-Fr administration. In contrast, S-Fr evoked a stronger local AGEs accumulation, RAGE expression, and barrier injury in the ileum intestinal mucosa, leading to higher concentration of LPS in the portal plasma (+300% vs. SD, +210% vs. L-Fr, $p<0.05$). The S-Fr related impairment of gut integrity was associated to a stronger activation of the LPS-dependent pro-inflammatory pathway NLRP3 inflammasome in the liver of S-Fr mice than L-Fr mice. Interestingly, the local accumulation of fructose in the intestine led to alterations of the gut microbiota depending on the fructose formulation, with increase in the saccharides metabolizing Lactobacillus genus in the L-Fr, and increased colonization by populations related to intestinal inflammation and barrier diysruption, such as Clostridium, in the S-Fr group.

Overall, these results convincingly show that consumption of different fructose formulations, liquid or solid, may evoke different impact on gut integrity, thus differently affecting liver homeostasis. Our results suggest that the liquid fructose formulation is more rapidly absorbed by intestine and metabolized by the liver, leading to lipogenesis. In contrast, the solid fructose

formulation is slowly absorbed by enterocytes producing glycated proteins and affecting gut barrier integrity, leading to systemic inflammation.