Effects of short-term overfeeding with fructose, fat and fructose plus fat on plasma and hepatic lipids in healthy men

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Abstract

Aims. – The present study aimed to assess the effects of excess fat, fructose and fat-plus-fructose intakes on intrahepatocellular lipid (IHCL).

Methods. – Healthy male subjects were studied after an isocaloric diet or a 7-day high-fructose (Fru: +3.5 g fructose/kg fat-free mass/day, +35% energy), high-fat (Fat: +30% energy as saturated-fat) or high-fructose, high-fat diet (FruFat: +3.5 g fructose/kg fat-free mass/day, +30% energy as fat, +65% total energy). IHCL was measured by 1H magnetic resonance spectroscopy.

Results. – All hypercaloric diets increased IHCL (Fru: +16%; Fat: +86%; FruFat: +133%; P<0.05). Very low-density lipoprotein (VLDL) triacylglycerols increased after Fru (+58%; P<0.05), but decreased after Fat (−22%; P<0.05), while no change was observed after FruFat.

Conclusion. – Fat and fructose both increased IHCL, but fructose increased, while fat decreased, VLDL triacylglycerols. However, excess fat and fructose combined had additive effects on IHCL and neutralizing effects on VLDL triglycerides. This suggests that fructose stimulates, while fat inhibits, hepatic VLDL triacylglycerol secretion.

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Keywords: Hepatic steatosis; High-fat diet; High-fructose diet; Healthy males; VLDL triglycerides; Fructose

Résumé

Effets d’une alimentation hypercalorique riche en fructose et en lipides ou en fructose + lipides sur les triglycérides intrahépatiques et plasmatiques chez l’homme sain.

Objectifs. – Comparer les effets d’une suralimentation hypercalorique riche en fructose, en lipides, et en fructose + lipides sur les triglycérides intraépatisques et plasmatiques.

Méthodes. – Des volontaires sains de sexe masculin ont été soumis à des suralimentations riches en fructose pendant sept jours (Fru: +3.5 g fructose/kg masse maigre/j ; +35% des apports énergétiques), en lipides (Fat: +30% des apports énergétiques sous forme de lipides saturés), ou en fructose + lipides (FruFat: +3.5 g fructose/kg masse maigre/j +30% des apports énergétiques sous forme de lipides saturés, +65% des apports énergétiques totaux). Les concentrations de very low-density lipoprotein (VLDL)-triglycérides (VLDL-TG) plasmatiques et de triglycérides intraépatisques (mesurés par résonance magnétique spectroscopique) ont été mesurées au terme de chaque période de suralimentation.

Résultats. – Les trois types de suralimentation ont augmenté les concentrations de triglycérides intraépatisques (Fru: +16% ; Fat: +86% ; FruFat: +133% ; P<0.05). Les concentrations de VLDL-TG ont augmenté après Fru (+58% ; P<0.05), diminué après Fat (−22% ; P<0.05), et n’ont pas changé après FruFat.

Conclusions. – La suralimentation en fructose et la suralimentation en lipides augmentent toutes deux, et de manière comparable, les concentrations de triglycérides intraépatisques, mais seule la suralimentation en fructose augmente les concentrations de VLDL-TG. Lors d’une
suralimentation combinée, le fructose et les lipides ont un effet additif sur les triglycérides intrahépatiques, et un effet neutralisant sur les concentrations de VLDL-TG. Ces résultats suggèrent que la sécrétion de VLDL-TG est stimulée par une suralimentation de courte durée en fructose, et inhibée par une suralimentation de courte durée en graisses.

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Mots clés : Stéatose hépatique ; Régime riche en fructose ; Régime riche en graisses ; Hommes sains ; Triglycéridémie ; Fructose

1. Introduction

Ectopic lipid deposition in the liver (intrahepatocellular lipids [IHCL]) is frequently encountered in obese patients, and is associated with insulin resistance and dyslipidaemia [1,2]. In rodents, both high-sucrose and high-fat diets induce obesity, higher very low-density lipoprotein (VLDL) secretion, hypertriglyceridaemia and ectopic lipid deposition [3,4]. In humans, high-fructose and high-fat diets increase IHCL, while a fructose–but not high-fat–diet will rapidly increase VLDL triacylglycerols [5,6]. Increased VLDL triacylglycerol secretion is associated with an increased production of small, dense low-density lipoprotein (LDL) particles, which have high atherogenic potential [7]. Also, it has recently been shown that fructose consumption is associated with increased small dense LDL in overweight children [8]. Obesogenic diets are, however, characterized by both high-fat and high-sugar contents, but how these nutrients interact to cause ectopic lipid deposition and dyslipidaemia is still unknown. Therefore, the present study aimed to assess the respective effects on IHCL of high-fructose, high-saturated-fat and high-fructose plus high-saturated-fat diets in healthy, non-obese, young male volunteers.

2. Methods

Thirty healthy men, aged 23.9 ± 0.4 years, were evaluated after a 7-day isocaloric control diet that was 55% carbohydrate (10% simple sugars), 30% fat (10% saturated-fat) and 15% protein, as well as after this same diet supplemented with one of the following: a high-fructose diet for 7 days (Fru: +3.5 g fructose/kg fat-free mass/day, +35% energy, n = 12); a high-fat diet for 4 days (Fat: +30% of total energy as fat, +18% as saturated-fat, n = 10); or a high-fructose, high-fat diet for 4 days (FruFat: 3.5 g fructose/kg fat-free mass, +30% energy as saturated-fat, n = 8). All subjects had a normal body mass index (BMI) score (22.6 ± 0.2 kg/m²), no family history of diabetes, were non-smokers and not taking any drugs or medications. Some subjects in the Fru and Fat groups had been included in other studies, as reported elsewhere [5,6]. After each diet period, IHCL concentrations were measured by 1H magnetic resonance spectroscopy (MRS) [9], and fasting hepatic glucose output (HGO) by a 2-h 6,6-2H₂-glucose infusion. Fasting plasma glucose, insulin and VLDL triacylglycerols were measured by standard clinical-chemistry methods. The non-parametric Wilcoxon’s paired signed-rank test was used to evaluate the effects of the isocaloric vs hypercaloric diets in each study group. Differences between groups under isocaloric conditions were assessed using non-parametric one-way analysis of variance (ANOVA; Kruskal–Wallis test), and P < 0.05 was considered statistically significant.

3. Results

Anthropometric and metabolic variables were similar across the three groups under isocaloric conditions. Body weight increased on average by 0.3 ± 0.1 kg and was not significantly different across the three dietary conditions. However, VLDL triacylglycerols significantly increased after the Fru diet (from 0.55 ± 0.07 to 0.87 ± 0.14 mmol/L; P < 0.05) and decreased after the Fat diet (from 0.58 ± 0.07 to 0.45 ± 0.05 mmol/L; P < 0.05), but did not change after the FruFat diet (0.51 ± 0.07 mmol/L; not significant [NS]; Fig. 1A). Fasting glycaemia remained unchanged after all three hypercaloric diets, whereas insulin tended to increase (Fru: from 8.7 ± 0.6 to 9.6 ± 0.4 mU/L; Fat: from 8.3 ± 0.5 to 8.8 ± 0.7 mU/L; and

![Fig. 1. Changes in (A) very low-density lipoprotein (VLDL) triacylglycerols (VLDL-TG) and in (B) intrahepatocellular lipids (IHCL) under isocaloric vs hypercaloric dietary conditions. Data are presented as means ± SEM. Fru: n = 12; Fat: n = 10; FruFat: n = 8. *P < 0.05 (Wilcoxon’s paired signed-rank test) between groups.](image-url)
FruFat: from 8.8 ± 0.8 to 11.1 ± 1.2 mU/L). Also, all three diets significantly (P < 0.05) decreased plasma non-esterified fatty acids (Fru: from 555 ± 36 to 346 ± 22 mmol/L; Fat: from 540 ± 44 to 399 ± 35 mmol/L; and FruFat: from 518 ± 66 to 271 ± 66 mmol/L). However, only the FruFat diet increased alanine aminotransferase (ALT; by +70%). Fasting glucose production remained unchanged with all of three diets from the control condition (isocaloric: 2.1 ± 0.1 mg/kg per minute; Fru: 2.3 ± 0.1 mg/kg per minute; Fat: 2.2 ± 0.1 mg/kg per minute; and FruFat: 2.2 ± 0.1 mg/kg per minute; NS). IHCL significantly increased after all three hypercaloric diets (Fru: +16%; Fat: +86%; and FruFat: +133%), and the latter increase was significantly higher than those after the other two diets (P < 0.05; Fig. 1B).

4. Discussion

Compared with the isocaloric condition, the three study diets were hypercaloric (around +30–35% greater energy intake with Fru and Fat, and around +65% energy intake with FruFat). Given the short duration of the study, however, changes in body weight were small, and cannot be considered responsible for any major changes in tissue or plasma lipids. Both Fru and Fat increased IHCL, although the increase tended to be greater with Fat. The mechanisms underlying hepatic fat deposition are likely to differ according to the nutrients consumed: with a high-fat diet, the accumulation of hepatic lipids is most likely due to hepatic deposition of dietary fat, whereas stimulation of de novo lipogenesis [10,11] and inhibition of lipid oxidation [12,13] are likely to be involved with a high-fructose diet. When excess fructose and fat intakes were combined, both the excess energy load and increase in IHCL were nearly doubled, indicating an additive effect of fat and fructose calories. These observations clearly indicate that excess sugar and lipid intakes can acutely increase ectopic fat before any significant change in body composition occurs. Interestingly, however, hepatic glucose production did not change, suggesting that intrahepatic lipid content is not directly related to hepatic insulin sensitivity.

The effect of the diets on plasma VLDL triacylglycerol concentrations did not parallel the changes in IHCL. VLDL triacylglycerols were increased after a high-fructose diet, as reported elsewhere [9,14]. In contrast, however, they were significantly decreased after a 4-day high-fat diet. This suggests that the high plasma triacylglycerol concentrations associated with high-fat diets in animal models or in obese patients may be due to long-term changes in response to chronic fat exposure such as increased body weight or insulin resistance. Surprisingly, and in spite of a higher total energy intake, excess fat on top of a high-fructose intake completely abolished the fructose-induced increase in VLDL triacylglycerol concentrations. This suggests that fructose may primarily stimulate de novo hepatic lipogenesis and VLDL triacylglycerol secretion [11,15], while a high-saturated-fat intake may decrease VLDL triacylglycerol secretion. In support of this hypothesis, it has been reported that, in rodents, a high-fat intake inhibits VLDL triacylglycerol assembly and secretion [16]. Therefore, the combination of reduced VLDL triglyceride export by fat plus increased fructose-induced lipogenesis de novo could account for any additive effects of fat and fructose on IHCL content, with an opposite effect on plasma triglycerides.

Altogether, these results indicate that nutrient overloading can, over a short period of time, significantly stimulate hepatic fat deposition independent of any changes in body composition or development of hepatic insulin resistance. Furthermore, fat and fructose have additive effects on IHCL, but opposite effects on plasma triglycerides, indicating a complex interaction between these two classes of nutrients.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgments

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