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**Markedly blunted metabolic effects of fructose in healthy young females  
compared to males**

THESE

préparée sous la direction du Professeur Luc TAPPY,  
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## Rapport de synthèse

*Objectif* : De récentes études ont démontré que l'ingestion de hautes doses de fructose modifie certains paramètres métaboliques. Peu d'entre elles se sont cependant intéressées à déterminer si les effets métaboliques du fructose étaient dépendants du sexe. L'objectif de la présente étude était donc de comparer les effets du fructose chez des volontaires sains, hommes et femmes.

*Méthode* : Le profil métabolique à jeun et la sensibilité hépatique à l'insuline ont été déterminés au moyen d'un clamp hyperglycémique chez un collectif de 16 jeunes hommes et femmes après une période de 6 jours de régime riche en fructose.

*Résultats* : La concentration de triglycérides à jeun après ce régime était augmentée de 71% chez les hommes contre 16% chez les femmes ( $p < 0.05$ ). La production endogène de glucose était augmentée de 12%, l'alanine aminotransférase de 38% et la concentration d'insuline à jeun de 14% chez les hommes ( $p < 0.05$  pour tous). Chez les femmes, ces paramètres n'étaient au contraire pas significativement modifiés. L'oxydation des acides gras libres et des lipides à jeun était inhibée par le fructose chez les hommes, mais pas chez les femmes.

*Conclusion* : Ces résultats indiquent qu'une suralimentation de courte durée en fructose induit chez l'homme une hypertriglycéridémie et une résistance hépatique à l'insuline, alors que chez la femme jeune, ces effets sont nettement atténués. Il reste à éclaircir de manière plus approfondie les mécanismes sous-tendant ces différences.

**Markedly blunted metabolic effects of fructose in healthy young females compared to males**

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**Running Title:** Metabolic effects of fructose and gender

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## ABSTRACT

*Objective:* to compare the metabolic effects of fructose in healthy males and females

*Research Design And Methods:* Fasting metabolic profile and hepatic insulin sensitivity were assessed by means of a hyperglycemic clamp in 16 healthy young males and female subjects after a 6-day fructose overfeeding

*Results:* Fructose overfeeding increased fasting triglyceride concentrations by 71% in males vs 16% in females ( $p < 0.05$ ). Endogenous glucose production was increased by 12%, alanin aminotransferase concentration was increased by 38%, and fasting insulin concentrations was increased by 14% after fructose overfeeding in males (all  $p < 0.05$ ), but were not significantly altered in females. Fasting plasma free fatty acids and lipid oxidation were inhibited by fructose in males, but not in females

*Conclusions:* Short term fructose overfeeding produces hypertriglyceridemia and hepatic insulin resistance in males, but these effects are markedly blunted in healthy young females.

High fructose intake has been associated with adverse metabolic effects (1). Few studies have addressed whether the metabolic effects of fructose are gender-dependant, however. In rats, several reports show that fructose has adverse metabolic effects in males but much less in females (2; 3); similarly, in humans, only men showed fructose-induced hypertriglyceridemia (4; 5). The aim of this study was to further assess whether the effects of a short-term fructose overfeeding on fasting lipid metabolism and insulin sensitivity differ in males and females.

#### RESEARCH DESIGN AND METHODS

**Subjects.** Healthy, non smoking, Caucasian male volunteers (n=8, mean age: 22.5 ± (SD) 0.93 yr, BMI 22.5±1.4, % fat mass 14.2±3.1 %) and female volunteers (n=8, mean age: 22.9 ± (SD) 0.62 yr, BMI 21.0±1.4, % fat mass 24.6±2.5 %) took part to the study. All subjects were in good health, and were not taking any medications (except oral contraception for women).

Each subject was studied on two occasions. On one occasion (control test), they were placed on a balanced, isoenergetic diet (100% energy requirements; 15% proteins, 35% lipids, 40% starch, 10% mono- and disaccharides) for 6 days. On the other occasion they were placed on the same isoenergetic diet supplemented with 3.5 g of fructose per kilogram of fat free mass per day for 6 days (130% energy requirements; 11% proteins, 26% lipids, 30% starch, 8% glucose and disaccharides, and 25% fructose). The two dietary conditions were applied in a randomized order with a 4-week wash-out period. On the seventh day, they underwent a metabolic assessment including basal hormone and substrate concentrations, fasting endogenous glucose, and glucose metabolism during a two-step hyperglycemic clamp (6) Women who were not on oral contraceptive (N=2) were studied during the first 10 days of their menstrual cycle.

**Statistical analysis.** Data are expressed as means ±1SEM. Comparisons between control diet and fructose supplementation were performed using the paired Wilcoxon signrank test. Comparison between males and females was done by using the Wilcoxon ranksum test.

#### RESULTS

Basal metabolic parameters were comparable in females and in males, except for a higher glucose production ( $p < 0.05$ ) and a trend toward higher plasma insulin ( $p = 0.12$ ), triglycerides ( $p = 0.06$ ) and  $\beta$ -hydroxybutyrate ( $p = 0.17$ ) in females.

Body weight was increased by 1.1% in males and 0.7% in females after fructose supplementation. In males, fructose supplementation caused significant ( $P < 0.05$ ) increases in fasting glucose (+5%), insulin (+14%), triglyceride (+71%), alanine amino-transferase (+38%) and lactate (+44%) and decreases in free fatty acids (-43%),  $\beta$ -hydroxybutyrate (-87%) and glucagon (-10%). It also significantly ( $P < 0.05$ ) increased fasting endogenous glucose production (+12%) and basal carbohydrate oxidation (+43%) and decreased basal lipid oxidation (-48%) (table 1).

The metabolic effects of fructose supplementation were markedly attenuated in females, in whom it caused only significant increases in fasting glucose (+4%) and triglyceride (+16%) and decreases in  $\beta$ -hydroxybutyrate (-55%) and glucagon (-9%) while all other parameters showed no significant changes (table 1). The increment in endogenous glucose production and in plasma triglyceride and the decrement in  $\beta$ -hydroxybutyrate were all significantly lower in females than in males ( $P < 0.05$ ).

During the clamp, endogenous glucose production during the first step was significantly higher (+13%,  $P < 0.05$ ) after fructose supplementation in males, but not in females. The first phase insulin secretion, and the plasma insulin concentration at the

first plateau of glycemia were not altered after fructose overfeeding in males and females. During the second plateau of glycemia, plasma insulin concentration was increased by 26% ( $P < 0.05$ ) after fructose supplementation in males, but not in females (table 1).

## **CONCLUSION**

The females participating in this study had, at baseline, slightly higher plasma triglycerides and endogenous glucose production than males, suggesting a lower metabolic fitness. In spite of this, they showed a markedly blunted increase in plasma triglycerides in response to fructose. Several explanations can be proposed for this lesser effect of fructose: first, the effect of fructose on metabolism may be modulated by sex hormones. In support of this hypothesis, studies done in rats showed that intact, but not oophorectomized, female rats were protected against the deleterious metabolic effects of fructose (3). It was also reported that fructose increased plasma triglyceride in post-menopausal, but not in pre-menopausal women (7). Fatty acid synthase gene expression is also lower in hepatocytes of female or estrogen-treated male than of untreated rats, which suggests that fructose-induced hepatic de novo lipogenesis may be attenuated in females (8). Second, females have a larger fat mass than males at comparable BMI, and may have a more efficient removal of triglyceride-rich particles from the circulation (9).

This study was done in small groups of healthy males and females with different baseline metabolic characteristics, and needs to be replicated by larger scale studies. It nonetheless call for attention to gender-related factors in future studies. It is possible that the vascular risk associated with high fructose intake be reduced in young females due to their lower plasma triglycerides. Beside this differential effect on plasma triglycerides, fructose also inhibited lipolysis and lipid oxidation in males, presumably secondary to a slight increase in insulin secretion (10), but failed to do so in females. Furthermore, it increased basal glucose production fasting insulin concentrations, which indicates hepatic insulin resistance, in males, whereas these effects were totally abolished in females. It also failed to increase alanine aminotransferase in females as it did in males. Given the importance attributed to lipotoxicity and to ectopic fat deposition in skeletal muscle and in the liver (11) in the development of insulin resistance, it can be speculated that an enhanced triglyceride removal in subcutaneous adipose tissue and a lesser inhibition of fat oxidation may offer some protection against fructose-induced insulin resistance in young females by reducing fructose-induced lipotoxicity.

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**TABLE 1**

Hormones and substrates concentrations and metabolic parameters observed in males and females after a 6-day isocaloric diet (Control) and a 6-day isocaloric diet supplemented with 3.5g/kg fat-free mass/day (High fructose)

	Men (n=8)		Women (n=8)	
	Control	High fructose	Control	High fructose
Fasting metabolic parameters				
Glucose (mmol/l)	5.0 ± 0.2	5.3 * ± .03	4.7 ± 0.3	4.9 * ± 0.2
Lactate (mmol/l)	0.9 ± 0.2	1.3 * ± 0.3	0.8 ± 0.2	1.0 ± 0.3
Insulin (pmol/l)	44 ± 8.5	50 * ± 5.6	52 ± 5.6	59 ± 8.5
Glucagon (ng/l)	51.5 ± 12.1	46.2 * ± 7.9	52.3 ± 11.6	47.8 * ± 9.6
Triglycerides (mmol/l)	0.79 ± 0.17	1.35 * ± 0.31	1.10 § ± 0.31	1.28 * ± 0.28
Free fatty acids (g/l)	0.14 ± 0.03	0.08 * ± 0.02	0.17 ± 0.03	0.17 § ± 0.06
$\beta$ -hydroxybutyrate ( $\mu$ mol/l)	165 ± 85	21 * ± 8.5	252 ± 74	114*§ ± 62
ALT (U/l)	7.88 ± 3.08	10.88 * ± 4.63	5.38 ± 1.83	4.50 ± 1.72
EGP ( $\mu$ mol/kg/min)	11.1 ± 0.8	12.4 * ± 0.56	12.2 § ± 0.3	12.2 § ± 0.56
Carbohydrate oxidation ( $\mu$ mol/kg/min)	8.3 ± 1.7	11.9 * ± 2.26	8.8 ± 1.2	9.6 ± 1.69
Lipid oxidation (mg/kg/min)	0.54 ± 0.11	0.28 * ± 0.11	0.49 ± 0.08	0.54 ± 0.17
Energy expenditure (cal/kg/min)	13.1 ± 0.84	13.0 ± 0.56	13.2 ± 0.8	13.6 ± 0.85

## Hyperglycemic clamp

1 <sup>st</sup> phase insulin	298 ± 124	318 ± 90	327 ± 113	287 ± 79
2 <sup>nd</sup> phase insulin (at glycemia=7.5 mmol/l)	109 ± 28	116 ± 31	169 ± 45	166 ± 54
2 <sup>nd</sup> phase insulin (at glycemia=10 mmol/l)	225 ± 48	279 * ± 62	318 ± 88	294 ± 71
EGP (at glycemia=7.5 mmol/l)	2.3 ± 2.5	4.4 * ± 1.13	3.6 ± 2.54	3.7 ± 1.41
EGP (at glycemia=10 mmol/l)	1.2 ± 1.1	2.5 ± 0.9	3.1 ± 4.0	2.1 ± 2.26

Values are means ± SD

\* Significantly different High fructose diet vs. control diet ( $P < 0.05$ , by Wilcoxon's signed-ranks test); § significantly different females vs males Abr: Endogenous glucose production, EGP; alanine aminotransferase, ALAT.