Effect of fructose overfeeding and fish oil administration on de novo lipogenesis and insulin sensitivity in healthy males

David Faeh[1,2], Kaori Minehira1, Jean-Marc Schwarz[3,4], Raj Periasami4, Park Seongsu[3], Luc Tappy[1]

[1]Department of Physiology, University of Lausanne, Lausanne, Switzerland, [2]University Institute of Social and Preventive Medicine, Lausanne, Switzerland, [3]Department of Medicine, University of California at San Francisco, San Francisco, USA, [4]Basic Science, Touro University, Mare Iland, CA, USA

Introduction

High fructose diets (Hfr) may stimulate hepatic de novo lipogenesis (DNL), and cause hypertriglyceridemia and insulin resistance (IR) in rodents. It can therefore be hypothesized that fructose-induced IR is secondary to alterations of hepatic and extra-hepatic lipid metabolism. Since fish oil supplementation (FO) is known to suppress lipogenic enzymes and to decrease TG, it may improve insulin sensitivity.

Objective

To study the effect of Hfr and FO on DNL and VLDL-TG and their impact on insulin sensitivity.

Methods

Seven normal men were studied on four occasions: after FO for 28 d (7.2 g/day), after a six-day Hfr (corresponding to an extra 25% of total calories), after FO plus Hfr and after control conditions. Following each condition, basal fractional DNL and endogenous glucose production (EGP) were evaluated using 1-^{13}C sodium acetate and 6,6 $^{2}H_2$ glucose. Thereafter, a two-step euglycemic hyperinsulinemic clamp was performed to assess adipose tissue, hepatic, and whole body insulin sensitivity.

Methods

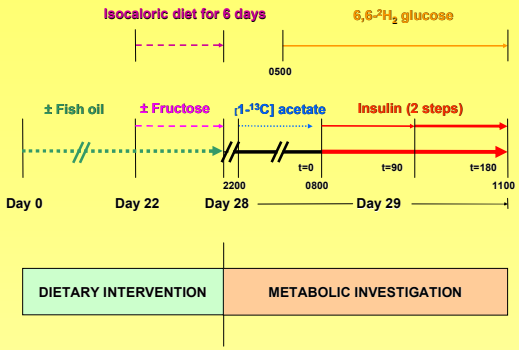

Figure 1. Experimental protocol. After each of the four types of dietary interventions a 13-hour metabolic study was started: At 2200, 0.5g/h of [1-^{13}C] acetate was infused until 0730. 6,6-$^{2}H_2$ glucose (bolus: 2 mg/kg; continuous: 20 µg/kg/min) was infused between 0500 and 1100. Indirect calorimetry was carried out from 0700 to 1100. Between 0800 (t=0 min) and 1100 (t=180 min) a two step (0.2 mU/kg/min and 0.5 mU/kg/min) hyperinsulinemic, euglycemic (5.3 mmol/L) clamp was performed.

Results

Under fasting conditions, Hfr significantly increased fasting glycemia (7 ± 2%, $P < 0.05$), TG (79 ± 22%, $P < 0.05$), DNL (six fold, $P < 0.05$) and EGP (14 ± 3%, $P < 0.05$). At high insulin concentrations, Hfr was associated to an impaired suppression of adipose tissue lipolysis ($P < 0.05$) and with a trend toward a decreased suppression of EGP compared to control but had no effect on whole body glucose disposal. FO significantly decreased TG (37%, $P < 0.05$) and tended to reduce DNL (21%, P = ns) in combination with Hfr compared to sole Hfr but had no other significant effect.

Results

	Control (15:35:50)[2]	Fish oil (15:35:50)[2]	High-fructose (11:26:63)[2]	Fish oil & high-fructose (11:26:63)[2]
Body weight (kg)	71.5 ± 4.0 [a]	72.6 ± 3.7 [a]	72.1 ± 4.1 [a]	73.1 ± 3.4 [a]
Body fat (%)	16.5 ± 0.7 [a]	17.2 ± 0.7 [a]	16.5 ± 0.8 [a]	17.2 ± 1.0 [a]
Waist circ. (cm)	80.0 ± 2.9 [a]	81.1 ± 3.3 [a]	81.0 ± 2.7 [a]	81.2 ± 2.6 [a]
Fasting NEFA* (µmol/l)	392 ± 43 [a]	375 ± 48 [a]	243 ± 43 [b]	212 ± 26 [b]
(% of controls)	(100 ± 0) [a]	(101 ± 14) [a]	(61 ± 6) [b]	(55 ± 5) [b]
Fasting insulin (pmol/l)	53 ± 7 [a]	49 ± 6 [a]	61 ± 9 [a]	58 ± 4 [a]
(% of controls)	(100 ± 0) [a]	(96 ± 11) [a]	(117 ± 14) [a]	(116 ± 13) [a]
Fasting glucose (mmol/l)	4.6 ± 0.1 [a]	4.7 ± 0.1 [a]	5.0 ± 0.1 [b]	5.0 ± 0.1 [b]
(% of controls)	(100 ± 0) [a]	(101 ± 4) [a]	(107 ± 3) [b]	(108 ± 3) [b]
Fasting lactate (mmol/l)	0.7 ± 0.1 [a]	0.7 ± 0.1 [a]	1.1 ± 0.1 [b]	1.0 ± 0.1 [b]
(% of controls)	(100 ± 0) [a]	(107 ± 9) [a]	(158 ± 12) [b]	(141 ± 9) [b]

[1]Data are expressed both as absolute values (mean ± SE of individual data averaged for T-30, T60 and T120) and as % (mean ± SE compared to control condition). Values within a row not sharing the same superscripts are significantly different ($P < 0.05$).
[2]Percentage of total energy from protein, fat and carbohydrate
*Non esterified fatty acids

Table 1. Clinical and biomedical characteristics (fasting) of the 7 subjects (mean age 24.7 ± 1.3 years)[1]

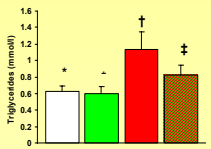

Figure 2. Mean fasting triglyceride concentration. Values are means ± SE represented by vertical bars. Values not sharing the same superscripts are significantly different ($P < 0.05$).

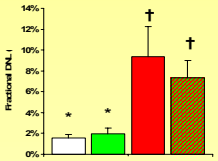

Figure 3. Mean fasting fractional hepatic de novo lipogenesis (DNL). Values are means ± SE represented by vertical bars. Values not sharing the same superscripts are significantly different ($P < 0.05$).

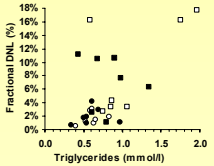

Figure 4. Relationship between fasting fractional hepatic de novo lipogenesis (DNL) and fasting triglyceride concentration (R=0.46, P= 0.013)

○ or white bar: control
● or green bar: fish oil
□ or red bar: high-fructose
■ or striped red and green bar: fish oil & high-fructose

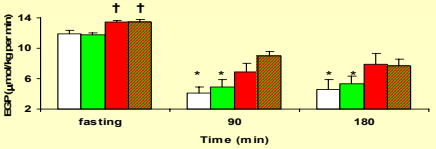

Figure 5. Endogenous glucose production (EGP) in fasting conditions and at 90 and 180 min of euglycemic hyperinsulinemic clamping. Values are means ± SE represented by vertical bars. † $P < 0.05$ vs. fasting C and FO. * significant suppression ($P < 0.05$) vs. fasting C and FO.

Results

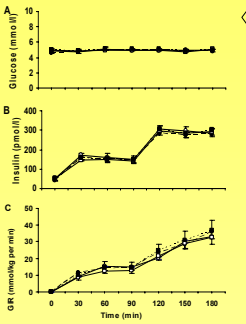

Figure 6. Plasma glucose (*A*) and insulin (*B*) concentrations and glucose infusion rate (GIR) (*C*) during euglycemic hyperinsulinemic clamping. Values are means ± SE represented by vertical bars.

○ control
● fish oil
□ high-fructose
■ fish oil & high-fructose

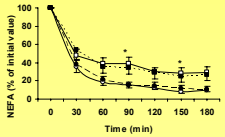

Figure 7. Non esterified fatty acids (NEFA) expressed in percentage of the baseline value during euglycemic-hyperinsulinemic clamping. Values are means ± SE represented by vertical bars. *$P < 0.05$ high-fructose diet vs. control.

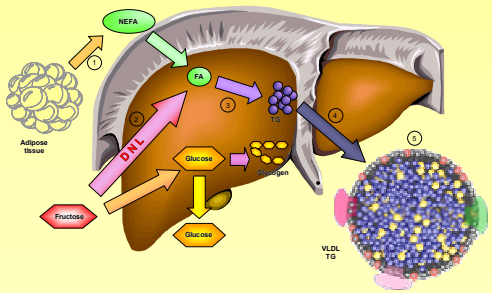

Figure 8. Potential impact of fructose and fish oil on hepatic metabolism: 1, lipolysis; 2, de novo lipogenesis; 3, reesterification of FA; 4, secretion of TG rich VLDL; 5, extrahepatic clearance of VLDL TG. Abbreviations: NEFA, plasma non-esterified fatty acids; DNL, de novo lipogenesis; VLDL, very low-density lipoproteins; TG, triglycerides; FA, fatty acids.

Conclusion

Hepatic and adipose tissue insulin resistance induced by Hfr has not been reversed by FO, despite its hypolipidemic effect on Hfr.