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Influence of hyper-energetic, high-fat feeding on circulating hepatokines in healthy men: a randomised crossover study

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Introduction: Leukocyte-cell derived chemotaxin 2 (LECT2), fibroblast growth factor 21 (FGF21) and fetuin-A are liver-derived proteins (hepatokines) which can influence substrate metabolism and insulin sensitivity. Hepatokines are modulated by chronic energy status and associated metabolic disease; however less in known about their sensitivity to acute nutrient and energy manipulation. This study explored the influence of hyper-energetic, high-fat feeding on circulating hepatokine concentrations and examined the time-course of these responses.
Methods: In a randomised, counterbalanced, crossover design, 12 healthy men (mean ± SD: age, 24 ± 4 years; BMI, 24.1 ± 1.5 kg/m^2) completed two seven-day diets separated by a three-week washout period: a hyper-energetic, high-fat diet (HE-HFD; +50% excess energy, 65% fat) and a control (habitual) diet. Before (baseline) and after each diet, whole-body insulin sensitivity was assessed during an oral glucose tolerance test using the Matsuda Insulin Sensitivity Index; whilst body fat percentage was measured via bioelectrical impedance analysis. Fasting venous blood samples were obtained at baseline and after 1, 3 and 7 d of each diet for measurement of plasma LECT2, FGF21, fetuin-A, glucose, insulin, triacylglycerol, non-esterified fatty acids, and the homeostatic model assessment of insulin resistance (HOMA-IR).
Results: Anthropometric and metabolic responses to the diets are shown in Table 1. Compared with control, body mass and BMI tended to increase (both $P \leq 0.057$) after the HE-HFD. HOMA-IR was significantly increased after 3 d of the HE-HFD compared to the control diet, whilst whole-body insulin sensitivity was reduced by 31% after 7 d (both $P \leq 0.021$). Fasting plasma LECT2 concentrations were significantly higher than control after both 3 and 7 d of the HE-HFD (both $P \leq 0.004$; Fig. 1A). Furthermore, fasting plasma FGF21 was significantly higher after 1 d ($P = 0.008$) and tended to be higher after 3 d of the HE-HFD ($P = 0.040$, NS after Bonferroni adjustment; Fig 1B); whilst fasting plasma fetuin-A tended to be higher after 7 d of the HE-HFD ($P = 0.028$, NS after Bonferroni adjustment; Fig. 1C).
Conclusion: This study demonstrates that in conjunction with impairments to whole-body insulin sensitivity and fasting glucose metabolism, acute hyper-energetic, high-fat feeding modulates circulating hepatokines in humans. Specifically, both circulating LECT2 and FGF21 are increased rapidly (within 1-3 days) in response to overnutrition; however the FGF21 response appears to diminish after seven days. Subtle increases in circulating fetuin-A may also begin to occur after seven days of high-fat overfeeding.

Conflict of Interest: None.

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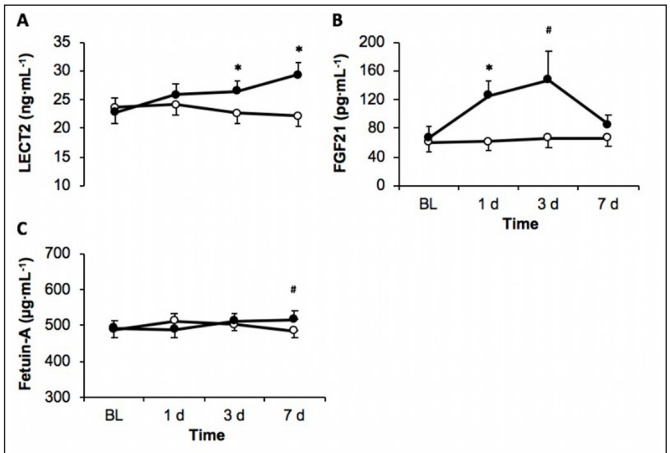

Figure 1. Fasting plasma concentrations of leukocyte cell-derived chemotaxin 2 (LECT2) (A), fibroblast growth factor 21 (FGF21) (B) and fetuin-A (C) during the seven-day control (○) and hyper-energetic, high-fat (●) diets. BL, baseline. Data are presented as means ± SEM. *Significantly different from control diet at same time point ($P < 0.05$). #Tended to differ from control diet at same time point (unadjusted $P < 0.05$, but NS after Bonferroni adjustment).

Fig. 1.

Tab. 1. Anthropometric and metabolic responses during the seven-day control and hyper-energetic, high-fat diets.

	Diet	BL	1 d	3 d	7 d
Anthropometric responses					
Body mass (kg)	Control diet	77.1 ± 4.3	-	-	77.1 ± 4.3
	HE-HFD	76.8 ± 3.7	-	-	78.0 ± 4.1#
BMI (kg/m^2)	Control diet	24.2 ± 1.6	-	-	24.2 ± 1.6
	HE-HFD	24.1 ± 1.5	-	-	24.5 ± 1.5#
Body fat (%)	Control diet	13.5 ± 3.8	-	-	13.3 ± 3.8
	HE-HFD	13.9 ± 3.1	-	-	13.8 ± 3.2
Metabolic responses					
Fasting glucose (mmol/L)	Control diet	4.9 ± 0.4	4.8 ± 0.4	4.6 ± 0.4	4.8 ± 0.4
	HE-HFD	4.8 ± 0.4	5.0 ± 0.3*	5.0 ± 0.5*	5.0 ± 0.3
Fasting insulin (pmol/L)	Control diet	25 ± 12	28 ± 13	22 ± 9	23 ± 7
	HE-HFD	27 ± 11	30 ± 8	30 ± 8	31 ± 11
Fasting TAG (mmol/L)	Control diet	0.75 ± 0.19	0.76 ± 0.19	0.74 ± 0.20	0.86 ± 0.29
	HE-HFD	0.82 ± 0.16	0.63 ± 0.20	0.57 ± 0.16*	0.57 ± 0.16*
Fasting NEFA (mmol/L)	Control diet	0.37 ± 0.13	0.30 ± 0.12	0.33 ± 0.16	0.32 ± 0.13
	HE-HFD	0.31 ± 0.12	0.26 ± 0.14	0.30 ± 0.09	0.25 ± 0.09
HOMA-IR	Control diet	0.8 ± 0.4	0.9 ± 0.5	0.7 ± 0.3	0.7 ± 0.3
	HE-HFD	0.8 ± 0.4	1.0 ± 0.3	1.0 ± 0.3*	1.0 ± 0.4
Matsuda ISI	Control diet	15.1 ± 6.6	-	-	17.1 ± 8.6
	HE-HFD	15.0 ± 6.3	-	-	11.8 ± 5.8*

Data are means ± SD. BL, baseline; HE-HFD, hyper-energetic, high-fat diet; BMI, body mass index; TAG, triacylglycerol; NEFA, non-esterified fatty acids; HOMA-IR, homeostatic model assessment of insulin resistance; ISI, insulin sensitivity index. *Significantly different from control diet at the same time point ($P < 0.05$). #Tended to differ from control diet at the same time point ($P < 0.06$).

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