

IN THIS EDITION

Satiety and appetite Role of gastro-intestinal peptides

The brain plays an essential role in the control of appetite and satiety. Several monoamines are considered as key neuromediators, involved in the decrease in hunger and/or induced satiety.

Several nutrients are prone to exert an effect on food behaviour namely by modulating gastro-intestinal peptides secretion.

It can also be illustrated by taking into account the role of dietary fat as key nutrients influencing the energy balance. Even dietary fibers could have interesting nutritional properties in the management of obesity.

Studies devoted to approach the putative targeting of gut peptides by nutrients in human are really encouraging.

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APPETITE REGULATION BY NUTRIENTS WHEN GUT PEPTIDES DIALOGUE WITH THE BRAIN...

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The brain plays an essential role in the control of appetite and satiety. Several monoamines are considered as key neuromediators,

involved in the decrease in hunger and/or induced satiety (noradrenaline, dopamine, serotonin, histamine...).

The way by which the brain responds to nutritional state and to the ingestion of nutrients, requires molecular, and neural connections between peripheral organs and specific area of the central nervous system, to adapt food intake behaviour to "acute situations" (fasting, ingestion of carbohydrates/lipid/energy dense meal), but also to "chronic situations" (accumulation of fat, starving). Since the discovery of leptin, the crucial role of the hypothalamus, and of the "dialogue" between peripheral tissue and brain, in the regulation of food intake and energy balance, has been reconfirmed.

This area of research in nutrition brings a "physiological" and "biochemical" explanation to human behaviour and food habits. Several experimental models in animals exist, proving that leptin deficiency, or alterations of leptin receptor

functionality leads to the abnormal food intake and/or energy expenditure, with, as consequences, the development of obesity and fat mass accumulation. The large panel of peptides secreted by the adipose tissue (adipocytokines), reflecting the long-term nutritional status of the body, are clearly implicated in the pathologies associated with obesity (Trayhurn, 2005).

Recent Progresses

On the other hand, recent progresses have been made in the comprehension of the relation between events occurring in the gut, and the central effect of gastro-intestinal peptides involved in the control of food intake (Badman & Flier 2005). Endocrine L-cells are distributed all along the intestinal tract, and are also and mostly present in the caeco-colon, where fermentation of dietary fibres occurs (Orskov et al. 1989). Endocrine cells present in the intestinal mucosa secrete peptides involved in the regulation of food intake, and/or pancreatic functions - the later being called incretins (GLP-1 for glucagon-like peptide 1 and GIP or glucose-independent insulinotropic peptide). Among those peptides, GLP-1,



PYY and oxyntomodulin, have recently been proposed as important modulators of appetite, through their peripheral effect (vagal nerve) and/or by acting directly on the arcuate nucleus (Druce et al. 2004; Wynne et al. 2005). GLP-1 is also involved in the regulation of pancreatic secretion of insulin, and in the differentiation and maturation of β -cells (Brubaker & Drucker 2004). Other gastro-intestinal peptides are implicated in the regulation of body weight and food intake such as a gastric orexigenic derived hormone, Ghrelin.

Several nutrients are prone to exert an effect on food behavior – but also on some components of metabolic syndrome- namely by modulating gastro-intestinal peptides secretion.

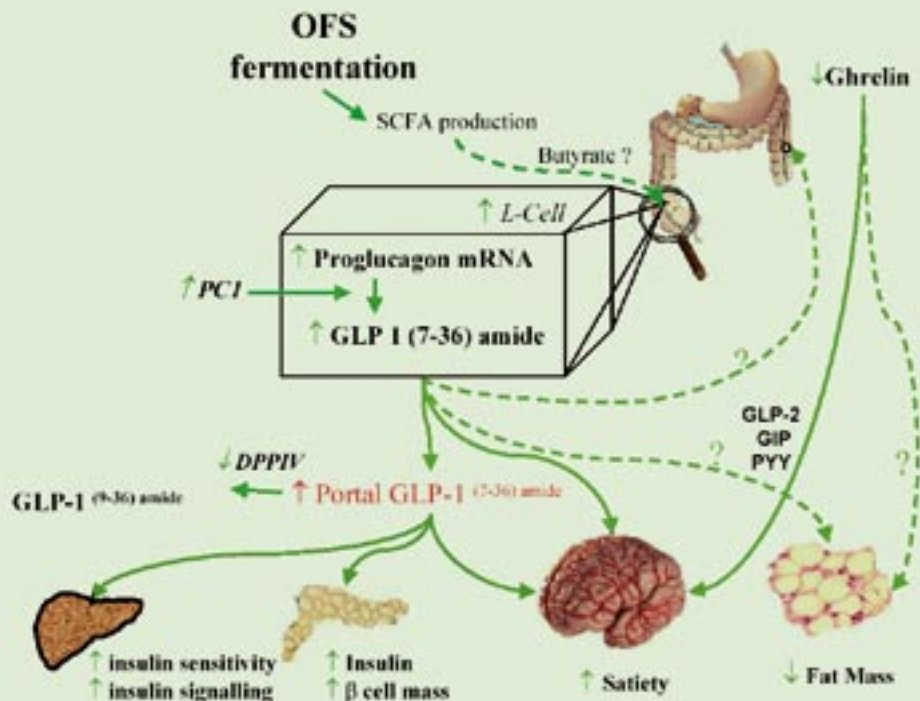
This can be illustrated by taking into account the role of dietary fat as key nutrients influencing the energy balance since it has been a topic of interest for researchers and public health. Hyperphagia might be one important mechanism by which high-fat diets promote obesity, since fat is less satiating than carbohydrate, leading to passive diet over-consumption (Blundell 1996). The reduction in plasma ghrelin levels observed through high-fat diet consumption agrees an article showing decreased circulating ghrelin levels in obese humans (Lee et al. 2002; Tshop et al. 2001). Some authors suggest that the reduced plasma ghrelin levels reflect an adaptation to the excessive caloric intake in obese subjects.

Dietary Fibers

Even if they escape to the digestion, dietary fibers (DF) could also have interesting nutritional properties in the management of obesity, namely through the modulation of gut peptides. The Framingham Offspring Study reported that the prevalence of metabolic syndrome – defined following the National Cholesterol Education Program criteria- was improved by high cereal dietary fibres intake (contributing to the beneficial effect of whole grain) (McKeown et al. 2004). The knowledge of the biochemical mechanism allowing DF to modulate satiety, glucose or lipid metabolism and hypertension is essential to propose key

Potential mechanism of action of dietary fermentable fibre, such as dietary fructans (oligofructose) on peptides production. Their feeding modulates several gastro-intestinal peptides (glucagons like peptide 1 (GLP-1), PYY, ghrelin), being involved namely in the control of food intake.

*OFS fermentation : Oligofructose fermentation
 SCFA production : Short Chain Fatty Acid production
 PC1 : Prohormone Convertase 1
 GLP 1 : Glucagon-like peptide 1
 GLP-2 : Glucagon-like peptide 2
 GIP : Glucose-independent insulinotropic peptide
 PYY : Peptide YY
 DPPIV : Dipeptidyl peptidase IV*



nutritional advice for specific disorders associated to the metabolic syndrome. It was proposed, more than thirty years ago, that DF act as a physiological obstacle to energy intake by an effect on satiation and/or satiety (Gerstein et al. 2004). The mechanism and relevance of endogenous modulation of gut peptides mentioned before (GLP-1, PYY, ghrelin...) by DF is poorly documented, but several experimental data suggest that those peptides could constitute a link between the outcome of fermentation in the lower part of the gut and systemic consequences of "colonic food" intake. An example will be given through the analysis of the metabolic and satietogenic effect of fructans-type non digestible

oligosaccharides (Cani et al. 2004, 2005; Delzenne et al. 2005).

Studies

Studies devoted to approach the putative targeting of gut peptides by nutrients in human are really encouraging. This would finally lead up to a nutritional approach (including functional food) devoted to improve insulin sensitivity, satiety and body weight gain in obese and type 2 diabetes patients. But further human studies are clearly necessary to prove the relevance of the animal data available until now.

References

- (1) Badman MK & Flier JS 2005 **The gut and energy balance: visceral allies in the obesity wars.** *Science* 307 1909-1914.
- (2) Blundell JE, Lawton CL, Cotton JR & Macdiarmid JI 1996 **Control of human appetite: implications for the intake of dietary fat.** *Annu.Rev.Nutr.* 16 285-319.
- (3) Blundell JE & Macdiarmid JI 1997a **Fat as a risk factor for overconsumption: satiation, satiety, and patterns of eating.** *J.Am.Diet.Assoc.* 97 563-569.
- (4) Blundell JE & Macdiarmid JI 1997b **Passive overconsumption. Fat intake and short-term energy balance.** *Ann.N.Y.Acad.Sci.* 827 392-407.
- (5) Brubaker PL & Drucker DJ 2004 **Minireview: Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system.** *Endocrinology* 145 2653-2659.
- (6) Cani PD, Daubioul CA, Reusens B, Remacle C, Catillon G & Delzenne NM 2005a **Involvement of endogenous glucagon-like peptide-1(7-36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats.** *J.Endocrinol.* 185 457-465.
- (7) Cani PD, Dewever C & Delzenne NM 2004 **Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats.** *British Journal of Nutrition* 92 521-526.
- (8) Cani PD, Neyrinck AM, Maton N & Delzenne NM 2005b **Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1.** *Obes. Res.* 13 1000-1007.
- (9) Delzenne NM, Cani PD, Daubioul C & Neyrinck AM 2005 **Impact of inulin and oligofructose on gastrointestinal peptides.** *Br.J.Nutr.* 93 Suppl 1 S157-S161.
- (10) Gerstein DE, Woodward-Lopez G, Evans AE, Kelsey K & Drewnowski A 2004 **Clarifying concepts about macronutrients' effects on satiation and satiety.** *J.Am. Diet.Assoc.* 104 1151-1153.
- (11) Lee HM, Wang G, Englander EW, Kojima M & Greeley GH, Jr. 2002 **Ghrelin, a new gastrointestinal endocrine peptide that stimulates insulin secretion: enteric distribution, ontogeny, influence of endocrine, and dietary manipulations.** *Endocrinology* 143 185-190.
- (12) McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW & Jacques PF 2004 **Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort.** *Diabetes Care* 27 538-546.
- (13) Orskov C, Bersani M, Johnsen AH, Hojrup P & Holst JJ 1989 **Complete sequences of glucagon-like peptide-1 from human and pig small intestine.** *J.Biol.Chem.* 264 12826-12829.
- (14) Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E & Heiman ML 2001 **Circulating ghrelin levels are decreased in human obesity.** *Diabetes* 50 707-709.
- (15) Trayhurn P. 2005 **The biology of obesity.** *Proc Nutr Soc.* 64(1)31-8.
- (16) Wynne K, Stanley S, McGowan B & Bloom S 2005 **Appetite control.** *J.Endocrinol.* 184 291-318.

RECENT PUBLICATIONS

Dietary phytoestrogens and lung cancer risk.

Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. JAMA. 2005 Sep 28;294(12):1493-504. PMID: 16189362

Dietary phytoestrogen intake and mammographic density – results of a pilot study.

Eur J Med Res. 2005 Sep 12;10(9):389-94. Nagel G, Mack U, von Fournier D, Linseisen J. PMID: 16183551

Insulin-like growth factor-1 and binding protein-3 in a 2-year soya intervention among premenopausal women.

Maskarinec G, Takata Y, Murphy SP, Franke AA, Kaaks R. Br J Nutr. 2005 Sep;94(3):362-7. PMID: 16176606

Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women.

Zhang X, Shu XO, Li H, Yang G, Li Q, Gao YT, Zheng W. Arch Intern Med. 2005 Sep 12;165(16):1890-5. PMID: 16157834

Soy protein containing isoflavones does not decrease colorectal epithelial cell proliferation in a randomized controlled trial.

Adams KF, Lampe PD, Newton KM, Ylvisaker JT, Feld A, Myerson D, Emerson SS, White E, Potter JD, Lampe JW. Am J Clin Nutr. 2005 Sep;82(3):620-6. PMID: 16155276

Effect of soy protein-rich diet on renal function in young adults with insulin-dependent diabetes mellitus.

Stephenson TJ, Setchell KD, Kendall CW, Jenkins DJ, Anderson JW, Fanti P. Clin Nephrol. 2005 Jul;64(1):1-11. PMID: 16047639

A follow-up study of nutrient intake, nutritional status, and growth in infants with cow milk allergy fed either a soy formula or an extensively hydrolyzed whey formula.

Seppo L, Korpela R, Lonnerdal B, Metsaniitty L, Juntunen-Backman K, Klemola T, Paganus A, Vanto T. Am J Clin Nutr. 2005 Jul;82(1):140-5. PMID: 16002812

Effect of soybean protein on blood pressure: a randomized, controlled trial.

He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Ann Intern Med. 2005 Jul 5;143(1):1-9. Summary for patients in: Ann Intern Med. 2005 Jul 5;143(1):11. PMID: 15998749

Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study.

Boyapati SM, Shu XO, Ruan ZX, Dai Q, Cai Q, Gao YT, Zheng W. Breast Cancer Res Treat. 2005 Jul;92(1):1-7. PMID: 15980986

Meta-analysis of soy food and risk of prostate cancer in men.

Yan L, Spitznagel EL. Int J Cancer. 2005 Nov 20;117(4):667-9. PMID: 15945102

Soybean products and reduction of breast cancer risk: a case-control study in Japan.

Hirose K, Imaeda N, Tokudome Y, Goto C, Wakai K, Matsuo K, Ito H, Toyama T, Iwata H, Tokudome S, Tajima K. Br J Cancer. 2005 Jul 11;93(1):15-22. PMID: 15942624

Oral food challenges in children in Italy.

Martelli A, Bouygue GR, Isoardi P, Marelli O, Sarratud T, Fiocchi A. Allergy. 2005 Jul;60(7):907-11. PMID: 15932381

Beef and soy-based food supplements differentially affect serum lipoprotein-lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resistive-train.

Haub MD, Wells AM, Campbell WW. Metabolism. 2005 Jun;54(6):769-74. PMID: 15931612

Long-term dietary habits affect soy isoflavone metabolism and accumulation in prostatic fluid in caucasian men.

Hedlund TE, Maroni PD, Ferucci PG, Dayton R, Barnes S, Jones K, Moore R, Ogden LG, Wahala K, Sackett HM, Gray KJ. J Nutr. 2005 Jun;135(6):1400-6. PMID: 15930444

Effects of soy supplementation on blood lipids and arterial function in hypercholesterolaemic subjects.

Hermansen K, Hansen B, Jacobsen R, Clausen P, Dalgaard M, Dinesen B, Holst JJ, Pedersen E, Astrup A. Eur J Clin Nutr. 2005 Jul;59(7):843-50. PMID: 15900307

Direct comparison of dietary portfolio vs statin on C-reactive protein.

Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Josse AR, Wong JM, de Souza R, Emam A, Parker TL, Li TJ, Josse RG, Leiter LA, Singer W, Connelly PW. Eur J Clin Nutr. 2005 Jul;59(7):851-60. PMID: 15900306

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