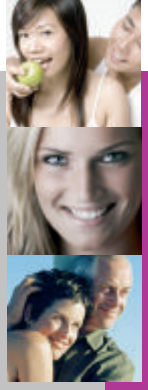


# SCIENTIFIC & MEDICAL NEWSLETTER

SPRING/SUMMER 2008 — #09.

eurodiet
www.eurodiet.com

## SCIENTIFIQUES **NEWS**

### **ADVANCE vs. ACCORD :** absence of risks related to intensive blood sugar lowering therapy.

Given that A1c-related endpoints are similar in the ACCORD and ADVANCE trials and that the ACCORD trial intensive blood glucose lowering program was prematurely discontinued, a special analysis was performed on ADVANCE trial mortality data by the Data Security Committee who concluded that the data did not confirm the mortality risks reported for the ACCORD trial. The ADVANCE trial final results for the intensive blood glucose lowering program are expected earlier than planned, by mid 2008.

### **Obesity increases the risk of infection.**

Obesity increases the risk and severity of infection. This is what emerged from a paper reviewing the links between body mass index (BMI) and risk of infection. Obesity increases the risk for certain minor (intertrigo, furunculosis, folliculitis, athlete's foot) and severe (erysipelas, cellulitis) skin infections. It also increases the severity of numerous other infections as well as the incidence of nosocomial infections such as surgical site infections, sepsis, pulmonary infections, catheter infections, C. difficile colitis ... The risk of infection increases in proportion to the BMI.

Caron F et coll. : Obésité et risque infectieux : BMI et CMI. Réunion interdisciplinaire de chimiothérapie anti-infectieuse (RICAI) (Paris) : 6-7 décembre 2007.

### **An attempted explanation of the rapid improvement of insulin sensitivity during very low calorie diets (VLCD).**

After only 6 days on a VLC diet, a pronounced reduction of intramyocellular lipids (IMCL) was demonstrated in both non-diabetic subjects (56% reduction) and type-2 diabetic subjects (40% reduction). A significant correlation was established between these IMCL levels and insulin sensitivity and waist circumference but none was demonstrated with the BMI or fat mass. Therefore, in the absence of any substantial change in total body fat mass, the rapid improvement of insulin resistance during VLC diets could be partially due to the drop in IMCL levels.

Lara-Castro C. & al., Effects of short-term very low-calorie diet on intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetic subjects, Metabolisme, 2008 Jan ; 57(1):1-8.

### **Lipid metabolism improved by soybean proteins.**

Rats fed a soy-protein based diet gain less weight than those on a casein based diet. This is partly due to an increase of UCP-1 (uncoupling protein-1) mediated thermogenic activity. These results suggest that soy protein improves lipid metabolism in fatty tissue and in the liver.

Torre-Villalvazo I. & al. Soy Protein Ameliorates Metabolic Abnormalities in Liver and Adipose Tissue of Rats Fed a High Fat Diet. J. Nutr. 138:462-468, March 2008.

## DOSSIER :
## THE REGULATION OF FEEDING BEHAVIOURS: BEYOND THE SATIETY CASCADE.

### **The metabolic repercussions of overweight:** VLCD and the benefits of a modest weight loss.

A meta-analysis looked for factors associated with the preferential loss of fat in the visceral adipose tissues (VAT) versus subcutaneous abdominal tissues (SAT) during weight loss. The VAT is indeed much involved in obesity-related metabolic disorders. The only variable found to have an impact on this VAT/SAT distribution was the percentage of weight loss: whereas the visceral adipose tissue was preferentially affected by modest weight losses, this effect decreased when weight loss became more important. This implies that, from a metabolic point of view, modest weight losses do remain interesting targets. The phenomenon was observed independently of the method used, save one: ketogenic management with VLCD where, despite the major weight loss induced by a 4-week VLCD, the preferential impact on VAT persevered, hence the great advantage of this method in cases where obesity is complicated by metabolic repercussions.

Chaston T., Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review, International Journal of Obesity (2008) 32, 619-628

### **Why is ketogenic management (VLCD) so effective?**

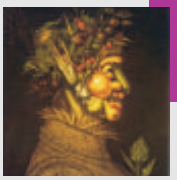
A 4-week trial compared the effects of ketogenic management using VLCD (4% carbohydrates) to those of a non-ketogenic low-calorie diet (30% carbohydrates) in 17 obese men. Ad libitum energy intakes were lower (p=0.02; SED (standard error of difference): 0.27, 7.25 and 7.95 MJ/day, respectively), hunger was significantly reduced (p=0.014, SED: 1.76) and weight loss was significantly increased (p=0.006, SED: 0.62) in the VLCD group (6.34 kg) compared to the group on an average carbohydrate-content diet (4.35 kg).

Johnstone A. & al. Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum, American Journal of Clinical Nutrition, Vol. 87, No. 1, 44-55, January 2008

### **Chewing gum, an appetite suppressant.**

A study of 60 patients demonstrated that chewing gum before an afternoon snack decreased intakes by 8% in average and by up to 14% in subjects under caloric restriction. It also reduced hunger pangs and cravings for sweet snacks. These results confirm the major part played by orosensory stimulation in satiation. However, one should not disregard possible complications, notably dental, that might result from a systematic consumption of such products.

Hetherington M., Regan M., Boyland E. Chewing it over: Effects of chewing gum on appetite. Appetite, 50, 2-3, March-May 2008, p. 560



# DOSSIER / **THE REGULATION OF FEEDING BEHAVIOURS:** BEYOND THE SATIETY CASCADE //

**The aim of feeding behaviours is simple: ensure an adequate supply of the substrates needed by the body to function properly. However, this crucial function involves a complex and fine-tuned set of personal responses to the ingestion of food. Indeed, extremely varied signals are implicated in the physiological control of our food intake:**

| NATURE OF SIGNAL | INDUCING SIGNAL | INHIBITING SIGNAL |
|---|---|---|
| Metabolic | Hunger | Feeling of fullness, satiety |
| Hedonic | Appetite, pleasure | Repulsion |
| Psychological | Anxiety | Fear, repulsion |
| Social | Environment | Prohibition |
| Behavioural | Gratification | Self-concept |
| Environmental | Availability | Shortage |

In opposition to the constant use of substrates by the cells, the intermittent aspect of our food intakes requires a redirection of energy flows throughout the day in order to comply with the regulating mechanisms of energy homeostasis. A food intake episode includes three stages:

- **pre-ingestion** corresponds to the state of internal motivation that precedes food ingestion, when **feelings of hunger** arise.
- **the prandial stage** corresponds to the actual ingestion of food with the associated progressive process of **satiation**, a set of mechanisms and signals which will terminate the ingestion of food.
- **the post-prandial stage** characterized by a state of satiation (i.e. when the subject is not motivated to ingest food) of varying duration.

Homeostatic processes rely on a constant interplay between the hypothalamic regulation centres and the various peripheral signals they receive concerning hunger, satiation, and energy status.

## FROM HOMEOSTASIS ... TO REWARD

**There are two types of homeostatic signals: short-term and long-term. Both categories include feeding triggering signals and feeding discontinuation signals.**

## AT MEALTIMES: SHORT-TERM REGULATION

### THE FACTORS THAT TRIGGER THE INGESTION OF FOOD: hunger

**Hunger seems to be more determined by cultural, social and psychological factors than by a physiological homeostatic urge. Although these mechanisms are not as well understood as those involved in satiation, certain signals have been clearly identified.**

#### The part played by blood-sugar levels

Traditionally, the initiation of feeding was considered as the metabolic response to the perception by the brain of an energy shortage, given that the final objective was to compensate losses. It is now recognised that preprandial blood sugar level variations only reflect the cellular availability of glucose. In fact, the glucosensitive neurones of the hypothalamus use falls in blood-sugar levels as a signal rather than as an energy substrate.

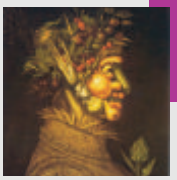
| | Triggering factor | Type of information | Duration | Impact |
|---|---|---|---|---|
| Short-term signals | Directly related to food intake | • Sensory<br>• Neuronal<br>• Hormonal | Interprandial interval | • Volume and duration of food intake<br>• Duration of satiation<br>• Satiation after next food intake |
| Long-term signals | Related to adiposis (stored energy) | Hormonal | Delayed with respect to food intake | • Modulation of the impact of short-term signals<br>• Direct impact on hypothalamic pathways. |

#### Orexigenic neuropeptides

The most potent orexigenic agent know today is the NPY (neuropeptide Y). Its hypothalamic release increases on meal initiation and is decreased by leptin and insulin. However, its absence does not modify food intakes which implies the existence of compensatory systems. Its effect is short-lasting and limited to mealtimes whereas, in the lab, AgRP, another simultaneously released neuropeptide, triggers an increased dietary intake that perseveres for one week. Orexins A & B as well as MCH (Melanin Concentrating Hormone) are also orexigenic. The release of these neuropeptides is stimulated by high-fat-content diets.

#### Ghrelin

Sole orexigenic hormone known to date[1], ghrelin is mainly secreted by the stomach but also by the hypothalamus and the pituitary gland. This appetite-stimulating hormone increases feelings of hunger and, on meal initiation, prepares the gastrointestinal tract for digestion by stimulating gastric motricity, HCl secretion and exocrine pancreatic secretions. Preprandial ghrelin release is thought to depend on psychological, neuroendocrine and metabolic factors. In the hypothalamus, ghrelin antagonizes leptin : it activates NPY-releasing neurones and reduces the anorexigenic effects of leptin. In obese subjects, ghrelin response is reduced but improves after weight loss, notably after ketogenic management by means of a very-low-calorie diet (VLCD)[2].





| PEPTIDE | STIMULUS | SITE PRODUCTION | SITE D'ACTION |
|---|---|---|---|
| CCK | Protéines/Lipides | Enterocytes | Cerveau (N.Vague) |
| PYY 3-36 | Contenu énergétique du repas | Tube digestif distal | Récepteurs Y2R du noyau arqué |
| GLP-1 | Présence de nutriments dans l'intestin. Régimes riches en graisses. | Tube digestif distal | Hypothalamus (NA, PVN) & Tronc Cérébral (NTS) |
| Oxyntomoduline | Présence de nutriments dans l'intestin. | Tube digestif distal | Idem (+ autre voie ?) |
| Apolipoprotéine A-IV | Absorption de lipides et leur transfert dans la lymphe. Formation de chylomicrons. | Grêle | |

## THE DISCONTINUATION OF FEEDING: FEELINGS OF FULLNESS AND SATIETY

**As soon as the meal starts, the nervous system receives peripheral signals which interplay with one another to form the "satiety cascade".**

### Digestive signals: mechanical and chemical receptors

The flow of food into the stomach stimulates **mechanoreceptors** located in the gastric wall which transmit the information to the central nervous system via vagal pathways. The perfusion of nutrients in the digestive tract before and during meals induces an early feeling of satiation and a decreased food intake due to the action of nutrient-specific **chemoreceptors** located in the small bowel. However, this is only a volume and pressure control mechanism, not a true energy regulation process.

### Enteric and digestive peptides

The arrival of food in the digestive tract triggers the secretion of a number of peptides which have a dose-dependent reducing effect on the size of the meal. Their message is transmitted to the cerebral regulating centres via hormonal or nervous pathways.

**Cholecystokinin:** Known since 1973, CCK (cholecystokinin) is a polypeptide made of a variable number of amino-acids (4, 8 or 33). It is a mediator in several physiological processes, notably digestion and satiation[3]. CCK is secreted by the enterocytes of the duodenal-jejunal mucosa in the presence of lipids and proteins. Similarly to neuropeptides, cholecystokinin is a mediator of satiety which acts on specific receptors found throughout the central nervous system. In Man, the administration of cholecystokinin decreases the desire to eat.

**Le Glucagon Like Peptide I :** le GLP-hormone derived from proglucagon secreted by the distal gut cells. High-fat content diets increase GLP-1 levels, probably as a defence against these diets' orexigenic effects[4]. Release occurs in two stages: a first release is triggered by the vagus nerve, fifteen minutes after food ingestion, followed later by a longer-lasting release in response to the presence of nutrients in the gut5. In Man, this results in increased gastric fullness and satiety and also contributes to reduce the energy intake during the next meal. In addition, it stimulates proinsulin secretion and, therefore, insulin secretion. At doses 3 to 4 times higher than the physiological dose, this hormone enables the normalization of glycaemia during feeding as well as a reduction of post-prandial blood-sugar rises.

**Insulin** : its central satiating effect involves an action at the level of the arcuate nucleus. It appears to be a signal indicating an interaction between immediate metabolic processes and the level of adiposis.

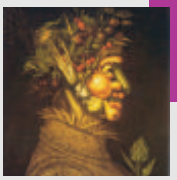
## ADIPOSIS AND LONG-TERM REGULATION

**over long periods of time. In the early Fifties, this phenomenon was found to be influenced by a hormonal factor correlated to the level of fat mass; this demonstration later led to the development of the negative feedback loop model in which "adiposis signals" inform the hypothalamic centres of stored-fat levels. These, in turn, regulate energy expenditure and food intake by modulating the brain's sensitivity to satiety signals. Three hormones are involved in this regulation.**

**Leptin:** is a cytokine secreted by fatty tissues. Its levels are correlated to the importance of the fat mass. A true marker of stored-energy variations, leptin inhibits the food intake and increases energy expenditure by interacting with specific receptors located in the hypothalamus. It activates anorexigenic pathways (POMC) and inhibits orexigenic pathways (NPY/AgRP). In obese people, leptin levels are higher (as they are related to the fat mass) but there is a loss of efficacy of yet unknown origin: a **leptin-resistance** phenomenon has been suggested. The same resistance is also found with high-lipid content diets[4].

**Insulin:** Like leptin, its blood level is correlated to the fat mass. Similarly, obesity does induce insulin-resistance. Insulin receptors are co-expressed with those of leptin in various hypothalamic nuclei: they activate anorexigenic pathways ($\alpha$MSH) and inhibit orexigenic pathways (NPY).

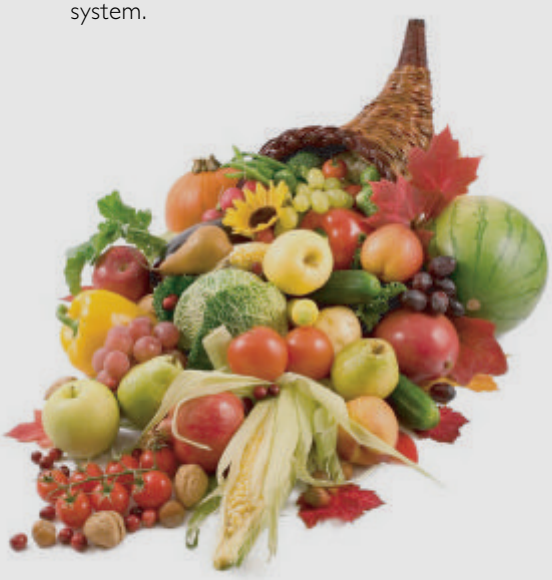
**Ghrelin:** is a counter-regulator of the two above-mentioned hormones. Its plasma level is inversely proportional to the fat mass.





## BEHAVIORAL ASPECTS

Food intake regulation is not only a matter of homeostatic balance; a rewarding system called **behavioural homeostasis** is also involved. Influenced by emotional aspects related to eating, this system is regulated by the brain via the limbic system.



The aspect, smell and texture of foods also play a part in food intake modulation. Pleasing foods will encourage an increased intake, all the more when previous experience has created an association between their taste and their nutritional value and energy content. This phenomenon is called **anticipatory adaptation**. It can also induce aversion with the refusal to eat certain foods associated with negative past experiences. In addition, the attractiveness of a given food decreases with the amounts ingested: this is called **alliesthesia**.

**Palatable** foods (those with a pleasant taste) thus generate sensory gustative data recognised as positive by the brain. This rewarding system mainly involves the dopamine pathways but opiate peptides and endocannabinoids also play a part.

Dopamine pathways could be dysregulated in obese patients which would explain their excessively increased attraction for food which does not correspond to any increase in the pleasure experienced.

## THE HUMAN FACTOR

phenomena and signals involved in hunger and satiety is constantly progressing. One question however remains unanswered: why does a subject eat and why does he or she stop eating?

Feeding behaviour is influenced by the boosting or inhibition of homeostatic signals such as those triggered by moods, the voicing of emotions, anxiety or psychological stress, the recollection of past experiences, family or social conditioning.

Food intake timing and rules are notably influenced by **sociocultural factors**. Indeed, it is not only the duration of satiety which governs the time span between two meals, social conventions regarding mealtimes and work-related imperatives may also lengthen or shorten this time span. Childhood conditioning and family traditions play a part in this behaviour, as does a given society's cultural perception of the ideal body. For instance, Maghrebi women with a traditional lifestyle frequently wish to gain weight, not lose it.

Other sociological factors include the **availability and composition of foods**. A crying example of this is the current "nutritional paradox" observed in developing countries suddenly submitted to Western urban eating patterns which lead to the coexistence of famine and obesity in the same population. Concerning the composition of foods, it is demonstrated that high-lipid content diets tend to induce overeating both through their high energy density and their palatability. Conversely, it is established that selecting **high-fibre, low-energy density and low-glycemic index**[6] foods extends the duration of satiety and may thus contribute to weight management.

As we have seen, **psychological and emotional factors** interact with food-intake related sensory signals. These signals may also take on an emotional dimension and trigger elaborate feelings, such as envy, repulsion, guilt or frustration, that have an impact of the food intake.

Lastly, the entire regulation system is under the influence of the individual's **conscious decision** to eat or not. This cognitive control may lead him or her to delay or cancel a meal; the extreme being hunger-strike situations (or shouldn't one rather speak of eating-strikes?).

The desire to loose weight may also induce a deliberate chronic restriction of food intakes; this is frequently observed in Western-world subjects.

# **NEW** SPRING **2008** PRODUCTS //

**The Eurodiet range expands to include 4 new products for this Spring. The great novelty for 2008 is undoubtedly the launch of two new dietary supplements. Perfectly adapted to the Eurodiet method, these supplements have well defined physiological targets: "Eurodiet Draine" helps limit fluid retention and the new "Satiety Bar" helps relieve hunger pangs. Our two other new products are healthy snacks: "barbecue flavour soya nuts" to brighten up aperitif time and "chocolate chip cookies" for when you feel peckish. Enjoy!**

## **SOYA NUTS** BARBECUE FLAVOUR

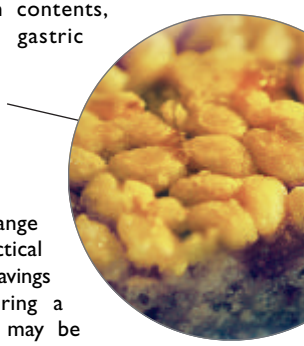
The virtues of soybeans are nowadays broadly recognized: they are an excellent source of vegetable protein, low in energy and high in mono- and polyunsaturated fatty acids. Non-processed soybeans are used to make this high-protein (11.4g/30g), low-lipid (3g/30g) and low glycemic index (15) snack. Spices such as garlic and onion give these appetizers a pleasant taste: to be enjoyed at all times and without misgivings.

## CHOCOLATE CHIP **COOKIES**

Eurodiet has taken up the challenge of creating cookies that are both high in protein (15g for 6 cookies), and low in carbohydrates (2g per 6 cookies) whilst retaining a rich chocolate taste and satisfyingly crunchy chocolate chips. They also supply omega-3 fatty acids (500mg for 6 biscuits) and beta-glucans (1.1g for 6 biscuits). Found notably in oat bran, these soluble fibres contribute to reduce cholesterol levels and have a favourable impact on the carbohydrate metabolism of diabetics. An excellent snack with health-related benefits that provides for patient well-being.

## APRICOT-ORANGE **SATIETY BAR**

This new functional bar combines the optimal nutritional profile of Eurodiet bars (15.2g protein, 11.9g carbohydrates, 3.8g free sugars and 4g lipids per bar) with a specific physiological hunger abating effect. It contains an ingredient derived from the oily fraction of Korean pine seeds, pinolenic acid, which acts directly on the endogenous satiation regulation peptides (CCK & GLP-1). Its soluble-fibre content (4.5g per bar) also contributes to increase satiety by raising the viscosity of stomach contents, thus slowing down gastric emptying.



This tasty apricot-orange cereal bar is a practical solution to sudden cravings or hunger pangs during a Eurodiet program. It may be used as from phase 1 (systematically for instance during ketosis initiation) and is particularly recommended during the phase 3 reintroduction of carbohydrates. During phase 4, your patients will be able to keep one of these bars handy to manage hunger pangs or to control mealtime food intakes in which case the bar should be eaten one hour before the "high-risk" meal.

Pasman W. & al., The effect of Korean pine nut oil on in vitro CCK release, on appetite sensations and on gut hormones in post-menopausal overweight women. Lipids in Health and Disease 2008 Salas-Salvadó J. & al. Effect of two doses of a mixture of soluble fibres on body weight and metabolic variables in overweight or obese patients: a randomised trial. Br J Nutr. 2007 Nov 22:1-8. Astrup A, Vrist E, Quaade F. Dietary fibre added to very low calorie diet reduces hunger and alleviates constipation. Int J Obes. 1990 Feb;14(2):105-12

EURODIET **DRAINE**

**This is the first dietary supplement in the Eurodiet range. It has been specifically designed to meet the needs of patients suffering from fluid retention, a symptom frequently associated with overweight and obesity.**

EURODIET **DRAINE is a natural solution that encourages elimination by supplying the body with :**

- **proanthocynidine oligomers (PCO).** Extracted from grape seeds, PCOs limit fluid and sodium retention in the kidneys. PCOs belong to the polyphenol family, a group of compounds with demonstrated vasoprotective, antiangiogenic, antiatherogenic, vasorelaxing and antihypertensive properties.
- **gamma-tocophérol,** which is a form of vitamin E. This precursor of the natriuretic hormone "gamma-CEHC" stimulates urinary sodium elimination by inhibiting 70pS potassium channels.

**Easy to use,** EURODIET **DRAINE** is packaged in stick packs, each containing 3g of dilutable powder. Each stick pack contains 100 mg of PCO and 33mg of gamma-tocopherol. The content is to be poured directly into a bottle of water (1 stick pack for 1/2 litre water). Loading dose is 3 stick packs per day during fifteen days (1 stick pack per day if symptoms are slight or for maintenance purposes). The orange flavoured drink thus obtained can be sipped throughout the day.

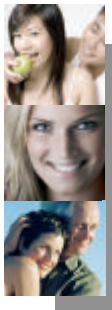
Christie S, Walker AF, Hicks SM, Abeyasekera S. Flavonoid supplement improves leg health and reduces fluid retention in pre-menopausal women in a double-blind, placebo-controlled study. Phytomedicine. 2004 Jan;11(1):11-7. Christie S, Walker AF, Lewith GT. Flavonoids--a new direction for the treatment of fluid retention? Phytother Res. 2001 Sep;15(6):467-75. Stoclet JC, Chataigneau T, Ndiaye M, Oak MH, El Bedoui J, Chataigneau M, Schini-Kerth VB. Vascular protection by dietary polyphenols. Eur J Pharmacol. 2004 Oct 1;500(1-3):299-313. Yoshikawa S, Morinobu T, Hamamura K, Hirahara F, Iwamoto T, Tamai H. The effect of gamma-tocopherol administration on alpha-tocopherol levels and metabolism in humans. Eur J Clin Nutr. 2005 Aug;59(8):900-5

## TOWARDS A MANDATORY EUROPEAN LABELLING

The European Commission proposes a mandatory nutrition labelling of all foodstuffs detailing their content in 5 essential nutrients: energy, carbohydrates (including sugar), fat, salt and saturated fatty acids. The labels should be clearly displayed on the package front. This obligation will not prevent Member States from requesting that other data be displayed, notably that concerning recommended daily allowances. In view of the current increase in obesity rates, the European Consumers' Organisation (BEUC) welcomes this EU recommendation. All that's needed now is its implementation.

## AGENDA

The entire Eurodiet team wishes to thank you for visiting our stand during the 16th European Congress on Obesity in Geneva.

SCIENTIFIC AND MEDICAL NEWSLETTER

SPRING-SUMMER 2008#9



Editorial comitee : **Dr Dominique Périn-Calvao, Emmanuel Frin, Dr Thierry Tranchant.**

Comments, suggestions and articles are very welcome. Please contact our Medical and Scientific Departement : **med@eurodiet.com**

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