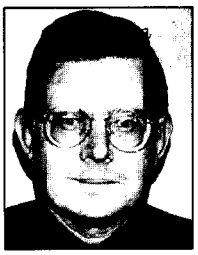

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Hunger and satiation: physiological and pharmacological implications

La faim est un phénomène biologique fondamentalement humain. Elle est un facteur essentiel de la survie, car elle est à l'origine de signaux qui indiquent à l'organisme le moment où il faut apporter des nutriments ou de l'énergie. Son étude est de fait complexe, car elle doit envisager ses multiples aspects qui touchent à la régulation des apports d'énergie, des nutriments et des autres composants alimentaires. La faim est principalement destinée à assurer un bilan énergétique optimal, les objectifs secondaires étant le choix d'aliments ou de boissons essentiels, tout au moins avantageux, d'un point de vue physiologique.

Des progrès ont été indéniablement accomplis dans la compréhension des mécanismes qui sous-tendent la sélection des aliments, qu'il s'agisse de ceux qui participent à la mémorisation alimentaire ou encore au fonctionnement des voies métaboliques et neuro-endocriniennes sous-jacentes. L'identification de neurotransmetteurs, comme la sérotonine, ou d'une apoprotéine A-IV, contenue dans les chylomicrons et reconnue pour son effet dépresseur sur l'appétit, a notamment permis de mieux décrire la balance énergétique sous l'angle homéostasique. Il en est de même avec la découverte de l'entérostatine, pentapeptide qui diminue la consommation de graisses alimentaires. Il manque cependant des données pour appréhender les mécanismes par lesquels les modifications de la composition de l'organisme pourraient affecter ou non la prise alimentaire. L'activité physique intervient de diverses manières pour permettre à ce facteur d'exercer une rétroaction sur les apports alimentaires très probablement en plaçant l'organisme en situation d'alerte. Il faut espérer que les politiques de Santé publique et les stratégies thérapeutiques, qu'elles soient nutritionnelles ou pharmacologiques, seront révisées au fur et à mesure que progressent les connaissances dans le vaste domaine de la physiologie de la faim et de la satiation.

Hunger, satiation, and survival

Hunger is a key factor in human survival, signalling when energy and nutrient replenishment is required. But the fundamental biological question as to how it relates not only to the time since last ingestion, but also to stores or reserves, is poorly understood – both are presumably important. Additionally, hunger can be overridden by what appear to be priority biological needs, as with physical danger, and even suppressed when the needs cannot be met, as in famine. Thus, hunger may not always subserve or be able to subserve physiological needs, but if they continue, it will reassert itself unless there is pathology. Again, without hunger, it is possible to be interested in eating and to eat – a situation where appetite can be distinguished from hunger. In a preferred situation, hunger will contribute to appetite in a major way.

Hunger and energy balance

Mostly, hunger is thought of as directed to achieving a required energy intake, with the intake of essential or biologically advantageous food or beverage factors being secondary. There may be an appetite, rather than hunger, for certain foods (such as fresh fruit or meat), food components, such as salt[16] or fat,[19, 20] certain food factor requirements, but it has the potential for distortion or perversion.

To strike an energy balance as precisely as it is set for many years in most people would be thought to require exquisite adjustment of intake, dependent on the expression and suppression of hunger and/or of energy expenditure. There is increasing evidence that energy balance is better struck at higher levels of energy expenditure, which suggests that the hunger-satiety mechanism may be more sensitive and appropriate at the upper end than at the lower end of the energy intake range.[31]

It would also seem important to preserve hunger as an experience, yet this is less the case with an abundant and regularized intake of food. All in all, it

is worth noting that the evolutionary experience of the human species has been characterized by moving about gathering and hunting for food, and going fishing.

To develop hunger as we go about our exercise, and to have it satisfied as we do, is probably to be preferred. Meals, and the social constraints that go with them, are a relatively new way of achieving energy balance for our species, and are consequent on the agricultural, industrial, transport, and white goods (especially food storage and kitchen) revolutions. The revolutions of food convenience and information technology have yet to realize their full effects on hunger and energy balance, at least by way of new food technology and the new information requirements in food choice.

	Physiological		*Pathology*		
	Process	*End point*	*Excess*	*Misread*	*Inadequate*
Hunger	Satiation	Satiety	Prader-Willi	Bingeing Bulimia	• Under-nutrition • Cachexia
Appetite (orexia)	• Interest • Savoring • Relishing food and beverage	• Satisfaction	• Cravings • Societal overnutrition • Iatrogenic appetite increase (eg, with medication)	• Pica • With food modifiers	• Anorexia • Anorexia nervosa • Secondary to illness or malnutrition • Secondary to medication use

Table I. Physiology and pathology of hunger and appetite.

Appetite or hunger?

The term "appetite" refers to interest in eating food, to which hunger may be contributory, and "hunger" to a sense of the need to eat *(Table I)*.

Appetite may be "satisfied," with the end point "satisfaction," and hunger "satiated," with the end point "satiety."

Disturbances of hunger may occur in states of severe stress or disease where it is not appreciated, leading to undernutrition or even cachexia, or after starvation, or with disturbances of its central nervous system regulation (as in Prader-Willi syndrome) with bingeing.[10] Unfortunately, increased food consumption, after abstinence, at an acceptable level, is sometimes, perhaps increasingly, misread as bingeing, and associated with bulimia.

Disturbances of appetite are characterized by disinterest in food, with disease, even malnutrition (protein energy malnutrition (PEM), thiamine and zinc deficiencies), medication use, or disturbed body image (anorexia nervosa, where hunger may still exist) or excessive interest in food as with certain food cravings in pregnancy (pica) or with social conditioning, or with the enhanced organoleptic properties of food, especially with spices, sweetness, and taste modifiers (at no obligatory necessary food energy density cost) and with textural change of food (eg, fat, with an increased food energy density) and beverages (eg, bubble size and creaminess in beer or stout).

The major contemporary societal factors perturbing hunger expression and satiation are shown in *Table II.*

The mismatch between appetite and hunger is one of considerable importance in resolving the current epidemic of energy overnutrition *(Table III).*

Process of food intake

An understanding of the acquisition, selection, and regulation of food intake is basic to an appreciation of human hunger and satiety.

Chronobiology

The sense of need to eat and actual food intake usually vary in amount and kind from time to time in accordance with season (especially in hunter-gatherer and agricultural societies), day of month in menstruating women,[45] from day to day (especially working as opposed to rest days in a week), and within a day.[11] It is particularly interesting that these variations in food intake are themselves likely to affect subsequent episodes of eating by way, inter alia, of frequency of ingestion, energy density of food eaten, and the difference in food components, nutrient and nonnutrient, which may affect appetite and hunger. For example, food intake at a weekend festive occasion may result in reduced energy intake in the ensuing weekdays: breakfast may influence what is ingested as snacks or as meals later in the day[13,33]; thiamine is mainly ingested at breakfast and zinc at the evening meal by Australian children, both nutrients affecting appetite.[11] Energy needs themselves change across the day for activity and metabolic reasons.[47,57]

1. Continual availability of food
2. Promotion of large serving sizes (culturally, at home, eating out, and with food marketing opportunism)
3. Lack of sensitivity of hunger control at lower levels of energy (calorie) throughput, because of physical inactivity
4. Skewing of food intake towards one with more fat and where more of the population appears to lack appropriate regulatory or feedback control mechanism for appetite as well as hunger.
5. Mismatch between appetite and hunger

Table II. Contemporary societal and clinically relevant factors perturbing hunger expression and satiation.

1. Regular occurrence of hunger
2. Food type and quantity which meet needs for appetite and hunger
3. Phase relationships between appetite and hunger responses to food and other stimuli or suppressants should be in conjunction
4. Minimize non-hunger-satiety signals for appetite

Table III. Requisites for match of appetite and hunger.

Food memory, recognition, and rejection

One of the most intriguing and important contributions to the understanding of food intake comes from Nishijo and Ono at Toyama Medical and Pharmaceutical University in Japan.[48] Their work in nonhuman primates has demonstrated that food memory is located in the amygdala and hippocampus, that it can be recruited and extinguished, and is dependent on an aggregate of inputs (visual, tactile,

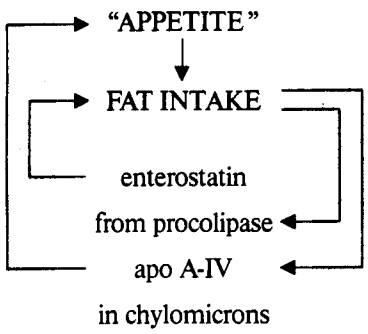
olfactory, taste). It is the mechanism which appears to allow us to make fine distinctions between different kinds of wine or cheese, but also to reject certain items as nonfood.

It is clearly of considerable potential importance in the modulation of hunger.

Regulation of intake

• The *control* of food intake has been thought to be mainly vested in the nuclei of the hypothalamus,[3-9,15,29,30,38-40,42] organizing inputs from the cortex, afferent autonomic nervous system and, we can now probably say, amygdala and hippocampus.[48] This central nervous system (CNS) organization of inputs in the hypothalamus provides the basis for the, as yet, poorly understood feedback loops which allow a remarkably high level of regulation of energy balance in most people over many years *(Figure 1).*

• The *endocrine* and *neuroendocrine* understanding of intake regulation has focussed principally on how energy metabolism might be regulated in relation to energy intake.[34-36,62,63] However, recent developments now suggest that fat intake may be specifically regulated by a pentapeptide, enterostatin, a fragment of procolipase,[19,20,43,50,51] in the following way[12,49,50]:



Other candidates for regulation of fat intake include ACTH (adrenocorticotrophic hormone)[12,42,50] and galanin,[14] a neurohypophyseal peptide (which may also affect body composition by way of growth hormone response.[2,24,25]

The ingestion of fat also stimulates apo A-IV production with chylomicron formation and may regulate appetite.[22,23,27] Similarly, cholecystokinin may decrease appetite after fat ingestion.[1,26] Each of these mechanisms provides an opportunity for gene-food intake interaction through different expression of genetic response to different diets and different ability to handle different diets.

Metabolic

There is a general appreciation that glycemic status, especially hypoglycemia (sometimes due to overinsulinization)[15] may stimulate food intake and that short-chain products of fatty acid catabolism, ketone bodies,[15] may lead to decreases in food intake. Protein, through altering plasma amino acid profiles, may also alter CNS neurotransmitters, especially serotonin formation; so also may carbohydrates through stimulating insulin secretion which selectively alters amino acid transport across the blood-brain barrier in favor of tryptophan, precursor of 5-hydroxytryptophan and serotonin. It is also conceivable that various food-derived peptides may alter gut physiology[26] and, thereby, food intake.[1]

Nutrients

Reference has already been made to the role of certain essential nutrients in appetite regulation *(see above),* in particular thiamine (B_1) and zinc.[15,41,44] In the case of zinc, its importance in taste can also play a role in food intake.

Food factors

There is a growing appreciation that food is extraordinarily chemically com-

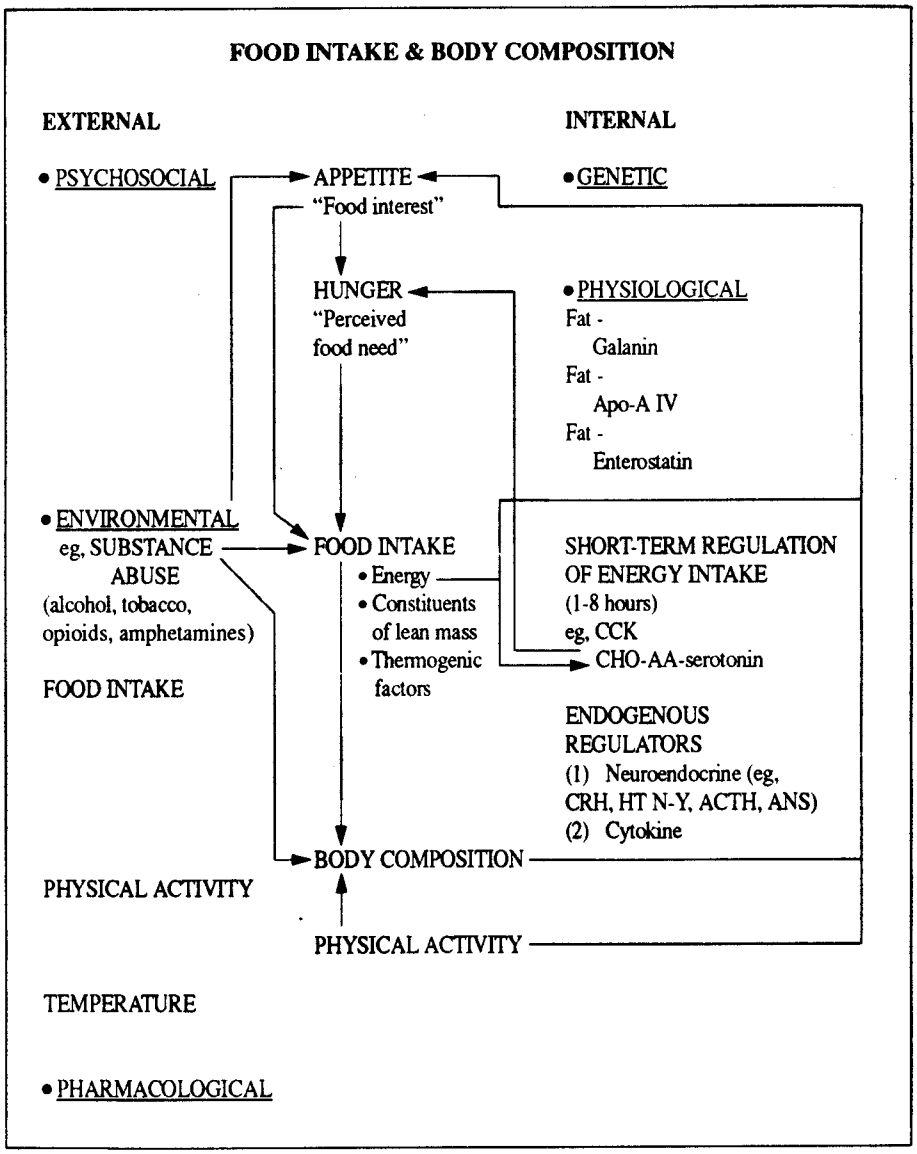


Figure 1. The interplay between food intake and body composition, as affected by external and internal influences on appetite and hunger. *The key missing elements in feedback regulation are tissue-derived factors affecting appetite and hunger. Candidates would be expected to be fatty acids from adipose tissue and their products, ketoacids, and amino acids from muscle.*
Abbreviations: *Apo A-IV = Lipoprotein Apo A-IV; CHO = Carbohydrate; AA = Amino acid; CCK = Cholecystokinin; ACTH = Adrenocorticotrophic hormone; HT N-Y = Hypothalamic neuropeptide Y; CRH = Corticotrophin-releasing hormone; ANS = Autonomic nervous system.*

plex and that nonnutrients may play various biological roles, perhaps including food intake regulation, if not regulation of energy metabolism.[32, 68]

Hunger, food intake, and body composition

Food intake is likely to regulate body composition in ways other than directly laying down energy stores[69-71] *(Figure 1)*. For example, those factors which alter the endogenous production of growth hormone and growth factors will be candidates[10, 17, 58, 61, 67] so might even cell differentiators like vitamin D[21] whose decline with age is associated with body composition changes.

In turn, signals from lean (like amino acids) and fat tissue (like fatty acids as ketone body precursors and adipsin),[15] may influence food intake *(Figure 1)*. In states of malnutrition, however, anorexia may occur[41] whether through nutrition deficiency or cytokine production.[65, 66]

Physiological feedback loops and interference with them

Food intake must be safe and subserve social and basic biological needs, by way of provision of adequate energy, essential nutrients, and other biologically relevant compounds. For safety, food memory,[48] dependent on the sensory properties of food, is likely to be paramount - for example the distinction between bitter and sweet and the preference for sweet.[54, 55, 60] Much is yet to be learned about energy homeostasis and nutrient homeostasis.[16]

The short-term (up to several hours) feedback loops after ingestion of various foods and compounds have been intensively studied in recent years *(see refs in Blundell and Bray)*. It must be acknowledged that these feedback loops are likely to have several dependencies:

1. Genetically dependent;
2. Socioculturally dependent (body image, group dynamics, economics, fashion)[73];
3. Life-style-dependent (physical activity, substance abuse);
4. Gender-dependent;
5. Age-dependent[56, 59, 60];
6. Environment-dependent.

Perhaps one of the most neglected inputs into food intake regulation is physical activity.[18, 52, 72]

There may be several ways in which this may be involved:

1. Influences on the central regulation of appetite;
2. Maintenance of hunger experience;
3. Operation of hunger at higher plane of energy throughput with greater sensitivity;
4. Greater awareness of body shape and size with movement, so providing otherwise unavailable feedback signals.

Functional or designer foods

As the regulation of hunger and ways of inducing satiety are better understood, there will be scope for designing foods to modify human physiology or function.[71] This will lead to a blurring of the boundaries between food and pharmacotherapeutics, a need for clinical nutrition trials, and a new kind of food toxicology, along with appropriate changes in food and drug laws.

Pharmacotherapy

New directions in the identification of regulation of food, and especially fat intake, may lead to new pharmacotherapeutic opportunities.[46] For the moment, selective serotonin agonists, especially dexfenfluramine for the HT_B/HT_C receptors in the hypothalamus, are the most attractive class of agents for induction of satiety. Moreover, with a food supply problem of sweet carbohydrate and fatty foods, there are advantages in a class of agents which decreases their intake as snacks or in meals.

These pharmacotherapeutic findings should not be construed as a case against carbohydrates (unrefined and without fat) or snacks (low in fat) in the overall management of hunger excess, and its consequent health risks.[37] Again, pharmacotherapy, which facilitates food choice without the risks created by "food intake discipline," which competes with other life needs in times of stress (and leads to periods of loss of control)[28, 64] is to be preferred.

It should not be forgotten that, more commonly, in therapeutics, the problem of iatrogenic suppression of food intake is seen.[53] ■

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