Special Article

Physiologic Aspects of Hunger and Satiety

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Lusk[1] once pointed out that early nutritional science received considerable impetus from the common-sense observation that man maintains his weight at a fairly constant level despite ingestion of large quantities of food. This observation impelled nutritionists of the nineteenth century to study foodstuffs, their chemical composition and their role in metabolism. They also investigated the excreta and the "invisible exhalations" of the body. In this way, foundations for modern organic and biological chemistry were laid. However, the mechanism responsible for keeping weight constant was not accessible to systematic study at the time, and, despite considerable curiosity about the intricacies of energy balance regulation, little progress was made in understanding this mechanism until the twentieth century.

HYPOTHALAMIC CENTERS

Within the last two decades it has been demonstrated that there is an area in the hypothalamus specifically concerned with the regulation of food intake. When the medial portions of this area are experimentally damaged, food intake increases out of all proportion to energy needs and the experimental animal becomes grossly obese.[2] When lesions are placed in the lateral area the animal may cease to eat and starves to death unless forcibly fed.[3] Electrostimulation of the lateral area induces hyperphagia.[4]

Some investigators have interpreted these results as indicating that there are at least two discrete "centers" in the hypothalamus having to do with energy balance, one a "feeding center" which is directly concerned with feeding behavior and the other a "regulatory center" which governs the activity of the feeding center.

The knowledge that there exists in the hypothalamus a center concerned with regulation of energy balance has stimulated attempts to elucidate the mechanism whereby energy intake presumably is adapted to energy requirements, and the composition of the body is maintained more or less constant.

Investigation of this problem usually has involved two avenues of approach: (1) observations of feeding behavior in experimental animals (rarely eating behavior in man), and (2) attempts to determine how an organism is able to supply information concerning its nutritional status to a regulatory center in the brain.

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FEEDING PATTERNS IN ANIMALS

Clearly, studies of regulation of food intake require as their basis reliable information about the feeding patterns of animals, normal and abnormal. Conventionally, observations of feeding behavior in laboratory animals have consisted of measurements of the quantity of food eaten in twenty-four-hour periods and of daily changes in body weight. Results of such studies have been reviewed by Mayer.[5]

A much better understanding of how certain animals regulate their food intake recently has been obtained by means of technics developed by experimental psychologists. One such technic that has been applied in the study of feeding behavior utilizes the principle of operant conditioning.[6] For example, when a sensitive lever is placed in the cage of the animal to be studied it is observed that the animal operates this device with an appreciable frequency, even in the absence of a history of reward in this situation. This initial rate of responding is known as the "free operant level." When lever pressing responses are rewarded with pellets of food, their frequency tends to increase. When satiety is present, lever pressing activity declines to the free operant level; as hunger returns, lever pressing activity again increases. It is possible by electronic devices to obtain a cumulative temporal record of pellets delivered to the animal and also to schedule pellet delivery so that the animal must press the lever a predetermined number of times before one pellet is delivered. By methods of this kind, detailed analysis of feeding behavior is possible and an estimate of hunger drive can be obtained.[7]

Using such technics, Anliker and Mayer[8] have shown that over a twenty-four-hour period, the normal mouse displays cyclical changes in rate of feeding. There is an initial phase of rapid feeding, followed by a second phase in which the rate of feeding decreases. The twenty-four-hour cycling is largely absent in mice made

hyperphagic by means of hypothalmic lesions; such animals eat almost constantly at the same rate.

Teitelbaum and Campbell[9] have demonstrated that, when eating a concentrated liquid diet, rats with hypothalamic lesions that are actively gaining weight consume meals about twice as large as those taken by normal rats. Under these circumstances, the hypothalamic rats do not eat more frequently than the normal rats. However, when eating a solid diet in which the calorie concentration is reduced, hypothalamic-hyperphagic rats increase both the size and frequency of their meals. Teitelbaum[10] has shown, in confirmation of results of Miller, Bailey and Stevenson,[11] that hyperphagic rats paradoxically show a decrease in their drive to obtain food.

Thus, it seems that normal mice and rats have well-defined, cyclical feeding patterns with alternating periods of feeding activity and relative quiescence. In the hypothalamic-hyperphagic mouse and rat this cyclical pattern appears to be lost until the "static phase" of obesity is reached. Then it may reappear. It seems that in the hypothalamic-hyperphagic animal an inhibiting effect of the ventromedial area on the feeding (lateral area) center is impaired and that the satiety mechanism as manifested in deceleration of normal feeding activity and in termination of normal-sized meals no longer operates properly.

HUNGER VERSUS SATIETY

In contrast to the controlled observations that have been made on feeding behavior in certain laboratory animals, relatively little scientifically acceptable information is available about the regulation of energy balance and body composition in man. In a recent valuable study by Durnin,[12] the daily individual intake and expenditure of calories were compared in four groups of people who differed widely in their ways of life and in their total energy expenditure. In each of the groups there was no significant relationship between expenditure of calories and intake of calories on the same day, the intake on the subsequent day and the intake two days after. Thus, marked variations in day-to-day food intake seem to occur in man independently of proximate energy expenditure.

In addition to the quantitative information that has been collected relating to energy balance in man, there is, of course, common-sense awareness of the fact that body weight tends to remain fairly constant for prolonged periods and that hunger and satiety occur in regular cycles, punctuated by meals.

It is of interest to examine the frequency distribution curves for body weight that are obtainable for various population groups. In the United States, where dietary calories are available in abundance, such curves generally show skewness with more people on the "overweight" side of the curve than on the "underweight" side.[13] In terms of the regulations under discussion, the mechanism that acts to keep man from getting below a certain relative weight is more sensitive and reliable than the mechanism that keeps him from getting above a certain relative weight. Consequently, as many have discovered by personal experience, it is easier to put on weight than to lose it.

From a teleologic standpoint, such an arrangement makes good sense. Man's environment was not always so organized that it was possible to obtain food at will. Under these circumstances, it was entirely appropriate and, indeed, necessary to consume food for storage in the body as well as to meet immediate energy requirements.

There is also some experimental evidence to support the notion that the brake on "overeating" is not a particularly strong one. For example, Bernstein and Grossman[14] have reported that intravenous and oral glucose administrations sufficient to raise blood sugar appreciably did not significantly decrease consumption of a test meal by human subjects. Janowitz and Hollander[15] in studies of the effect of intragastric feedings on spontaneous food intake in dogs showed that, although inhibition of food intake under such circumstances was almost completely compensatory, this adjustment required relatively long periods of time (weeks) to be accomplished. Thus, although a regulation inhibiting food intake most certainly exists, it seems to be elastic in nature, particularly in regard to individual meals.

SIGNALS OF SATIETY

How is the body able to supply information concerning its nutritional status to a regulatory center in the brain?

Several theories have been proposed in an attempt to answer this question (table 1). Before considering them, it might be well to recall that there are only three pathways or modalities by which the body can signal its nutritional status to a regulatory center in the brain. As shown in table 1, three of the current theories postulate a chemical signal to the regulatory center, one a physical signal, and one, tentatively, a neurally transmitted signal. Of the various contending formulations, only one, the glucostatic theory, has provided a comprehensive explanation of how a regulatory center might be able to mediate between calorie needs and food intake.[16] Several of the other theories do not actually have names in any official sense but have been given designations arbitrarily for purposes of discussion. Of the five theories

TABLE 1

Theories concerning the regulation of food intake

Modality	Theory	Signal*
Chemical	Glucostatic[21]	Availability of blood glucose
	Lipostatic[18]	Concentration of circulating metabolite (nature unspecified)
	"Amino acid pattern"[17]	Pattern of available amino acids in blood
Physical	"Thermostatic"[32]	Specific dynamic action of ingested food
Neural	"Liponeurostatic"[33]	Impulses from fibers innervating adipose cells

* to a regulatory center in the hypothalamus.

listed, only two, the glucostatic and thermostatic, have clearly defined the signal transmitted to the hypothalamus. Mellinkoff[17] in his discussion of the role of blood amino acids in determining satiety has referred to a "pattern" of amino acids as being important but has not identified the pattern. Kennedy[18] has singled out the fat stores as being important in regulating food intake but has not explained how such stores provide the appropriate information to the brain. Discussions about what might be called a "liponeurostatic" theory have been based on interesting but as yet unconfirmed reports of a direct neural connection between the central nervous system and adipose tissue.[19,20]

GLUCOSTATIC THEORY

Since the glucostatic theory has been well defined, it seems appropriate in this brief discussion to concentrate on this theory and consider its virtues and shortcomings in the light of the other theories and in terms of various phenomena that any theory of food intake presumably must explain.

The glucostatic theory[21] proposes that the available carbohydrate supply of the body exerts a regulatory influence on food intake via hypothalamic "glucoreceptors"; the urge to eat increases as carbohydrate stores diminish. The hypothalamus probably cannot obtain direct information concerning the status of the carbohydrate stores; however, the rate of carbohydrate utilization by the body as a whole tends to be directly proportional to the supply of this nutrient. Thus, measurement of the rate at which blood glucose is utilized (peripheral arteriovenous glucose differences) provides indirect information about available carbohydrate supply.

Since the stores of carbohydrate in the body are strictly limited and are depleted much more rapidly than are stores of fat and protein, the carbohydrate supply would seem a logical meter of the immediate caloric status of the individual. It is difficult to imagine hunger in the presence of an adequate carbohydrate supply or satiety in the presence of carbohydrate depletion. Moreover, carbohydrate of all the nutrients seems to set the metabolic "tone" of the body; if such terms can be used in this context, carbohydrate is an "active" nutrient while fat seems to be "passive."[22]

In recent years, considerable evidence has been obtained that can be interpreted as supporting the glucostatic theory. Unfortunately, only a part of this material can be mentioned in the present brief discussion. For example, a number of studies have disclosed an association in time (1) between the experience of hunger and a diminished rate of peripheral glucose utilization, and (2) between satiety and an increased rate of glucose utilization.[23-25] Several reports have indicated that the hypothalamus may indeed contain glucose-sensitive areas.[26,27] On the other hand, critics of the glucostatic theory have contended that the temporal relationship between available glucose and satiety is fortuitous and that the hunger associated with hypoglycemia is in the nature of an "emergency mechanism."[28]

CRITERIA

Assuming for the moment that there exists a center in the brain for regulation of food intake, what precisely does such a center have to account for? It would appear to have to account for at least the following observations: namely, that (1) we seem to eat to maintain a certain body composition, regardless of variations in caloric expenditure; (2) hunger develops if our meals during waking hours are separated by more than four or five hours; and (3) apparently normal satiety can be experienced eventually on a carbohydrate-free diet or fat-free diet, provided dietary calories are adequate.

To what extent can the glucostatic theory and other formulations explain the fact that we seem to eat in order to maintain a certain body composition? It is evident that of the body's major components* the most variable is fat. The lability of stores of triglyceride has been well documented in many studies, including those of Keys et al.[29] on the metabolic effects of prolonged semistarvation.

If, in the long term, we eat to maintain our fat stores at a more-or-less constant level, can such a phenomenon be explained by means of the glucostatic theory? Possibly—if the relative amount of fat used for energy (and hence the rate at which carbohydrate is used) is somehow dependent upon the amount of fat stored in the body. If such a relationship between fat stores and

* In terms of quantity, carbohydrate must be regarded as a minor component.

regulation of energy balance were demonstrable, support also would be available for the lipostatic hypothesis but, presumably, not for the thermostatic or amino acid theories.

Blood sugar fluctuations and rates of carbohydrate utilization reflect in part the composition of the meal eaten at the time and in part the current status of the body with regard to carbohydrate stores. They are not, as far as is known, influenced appreciably by fat stores, unless gross obesity is present. Actually, the rate at which fat stores release unesterified fatty acids for metabolism elsewhere in the body seems largely dependent upon the amount of carbohydrate (not fat) that is available at the time.[22] Thus, it seems clear that blood glucose utilization rates, although they might well account for some of the satiety experienced after a meal and might also account for hunger, cannot readily explain the gradual adjustments in food intake in dogs fed by gastrostomy, or the strong tendency, after a period of semistarvation, to return to a certain body composition over a period of months.

Of considerable interest are the changes in feeding behavior that occur in hypothalamic-hyperphagic rats as they become increasingly obese. It is well known that experimentally-induced hypothalamic obesity consists of two phases: (1) a dynamic phase that begins immediately after hypothalamic injury and during which the hyperphagic rat eats enormous amounts of food and gains weight rapidly; and (2) a static phase, that occurs about a month after the onset of the dynamic phase, and which is characterized by a leveling of weight and a decrease in food intake. During the static phase the obese hyperphagic rat, in contrast to his behavior in the dynamic phase, becomes hyper-reactive to positive (sugar) and negative (quinine) stimulus qualities of the diet and decreases his meal size and the number of meals he eats per day.[30]

Since the only known physiologic difference between the dynamic and static hyperphagic animals is in their degree of adiposity, it might seem that the fat depots exert an inhibitory influence on food intake under these circumstances. However, the pathways involved remain obscure.

How well do the various theories of food intake regulation account for the intermittent hunger and satiety that punctuate man's waking hours? It has already been pointed out how the glucostatic theory can account for this kind of periodicity. A lipostatic theory probably is incapable of accounting for the cyclical nature of hunger and satiety since such cycles can occur on a fat-free diet; moreover, the biochemical evidence strongly suggests that the rate of utilization of ingested and depot fat depends largely upon the availability of carbohydrate, not vice versa.

The thermostatic theory is believed by some investigators to explain the periodic nature of hunger and satiety. Booth and Strang[31] showed more than twenty years ago that the rise in skin temperature after eating has the same course in time as that of the specific dynamic action and correlates well with the onset of satiety. Preliminary studies by Strominger and Brobeck[32] suggest that the thermostatic explanation can circumvent some of the difficulties of the "one-nutrient" hypotheses. However, further work is needed to validate the thermostatic formulation.

A "liponeurostatic" theory based on the notion of neural connections between adipose cells and brain would not seem to be able to account for the cyclical nature of hunger and satiety, unless one believes that the hypothalamus can detect exceedingly small changes in the fat depots.

Finally, how can one account for the fact that prolonged satiety can be achieved on a carbohydrate-free diet?[33,34] It is known from the history of the use of pemmican (half and half, by weight, rendered fat and dehydrated lean) for food in the pioneer Northwest and in Arctic exploration that apparently normal satiety can occur on a diet free of carbohydrate.[34] Admiral Peary[35] has written as follows:

> "Too much cannot be said of the importance of pemmican to a polar expedition. It is an absolute sina qua non . . . With pemmican, the most serious sledge journey can be undertaken and carried to a successful issue in the absence of all other foods. . . . It is the most satisfying food I know."

It is not known whether appreciable fluctuations in blood glucose or glucose utilization can occur on a carbohydrate-free diet. Mellinkoff[37] has demonstrated that transient increases in peripheral uptake of glucose take place when amino acid mixtures are administered intravenously to human subjects. There is, as yet, no evidence that rates of glucose release from the liver on a carbohydrate-free diet will correspond to hunger-satiety patterns. It is therefore difficult, in terms of the available information, to see how the glucostatic theory can explain the hunger-satiety cycles that seem to occur with carbohydrate-free meals. Conceivably, the ingestion of protein could affect satiety by virtue of an influence on carbohydrate metabolism.

COMPLEXITY OF THE PROBLEM

It will be noted that in this discussion the complex role played by the digestive tract and particularly the

stomach in regulating hunger and satiety has not been emphasized. It is known that the stomach is dispensable as far as the control of food intake is concerned, and it seems well established that gastrointestinal factors, while important, are secondary in the energy balance scheme.[38]

We have not explained how any signal based on a constituent or effect of a meal can be translated so as to provide quantitative information to the regulatory center about calories consumed or the degree to which caloric requirements have been met. It is difficult to conceive of an immediate precise regulation of calorie intake. The body seems to maintain its composition by a constant process of correction, and the time factors involved suggest that the stimuli that signal satiety after a given meal are not necessarily the same ones that regulate body composition.

Indeed, we are left with the impression that, in terms of current knowledge, no one theory can encompass even the three simple exponible observations set forth earlier in the discussion. To explain the phenomena of hunger and satiety and the regulation of body composition a combination of known or suspected mechanisms may have to be invoked.

At any rate, there is growing evidence that the most productive investigations into the problem of food intake regulation are those which make use of technics from a variety of fields; for example, nutrition, physiology, biochemistry, and psychology. Such a multi-disciplinary approach seems well justified by the complexity of the problem.

SUMMARIO IN INTERLINGUA

Aspectos Physiologic De Fame E Satietate

Es discutite le problema del mechanismos physiologic que es responsabile pro le regulation del balancia de energia in le corpore. Es summarisate le historia del identification—per experimentos animal—de centros hypothalamic functionante como regulatores del ingestion de nutrimento. Es delineate e criticate le varie theorias que tenta explicar le maniera per que le centros hypothalamic recipe signales relative al stato de alimentation e de composition biochimic del organismo total. Le complexitate del problema es illustrate per referentias al cyclicitate del phenomenos de fame e satietate (que non reflecte directmente le requirimentos immediate del corpore). Le autor conclude que nulle theoria individual suffice pro explicar le phenomenos de fame e satietate e le regulation del composition del corpore e opina que un combination de cognoscite e non ancora cognoscite mechanismos participa in le situation total. Ille suggere correspondentemente que futur investigationes del problema procede per combinar e interrelationar technicas disveloppate in varie disciplinas interessate, i.e., per exemplo in le nutritiologia, le physiologia, le biochimia, e etiam le psychologia.

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Metabolism of Essential Fatty Acids

Linoleic, linolenic and arachidonic acids are the three most widely recognized members of the group of higher polyunsaturated fatty acids exhibiting essential fatty acid activity. However, the biological activity of linolenic is known to differ considerably from that of linoleic and arachidonic acids (*Nutrition Reviews* *10*:154, 1952), which suggests that the metabolic fate of linolenic acid is different from that of the other two fatty acids. On the assumption that information about the metabolism of linoleic acid is necessary in order to explain these differences in biological activity, G. Steinberg, W. H. Slaton, Jr., D. R. Howton and J. F. Mead (*J. Biol. Chem.* *224*:841, 1957) have studied the fate of isotopically labeled linoleic acid in the animal body.

About 90 mg. of a mixture containing 40 per cent of methyl linoleate-1-C^{14} and 60 per cent of corn oil were administered to each of a group of ten rats. Eight of the ten were killed after four hours. The other two were retained for respiratory carbon dioxide estimations. The livers, kidneys, hearts, spleens and abdominal fat of the animals were pooled and the higher unsaturated fatty acids were isolated as insoluble polybromides. These were debrominated, hydrogenated and separated by reversed phase chromatography. The arachidic acid (C_{20}) obtained was degraded in such a way that the radioactivity of each of the four carbon atoms, beginning with the carboxyl carbon, could be determined separately. The radioactivity of the carboxy-carbon of the stearic acid was also determined. The linoleic acid was isolated and purified and a fraction of the higher polyene mixture was isomerized.

As much as 30 per cent of the carboxy carbon of linolenic acid was recovered in the respiratory CO_2. However, the low value of 6 per cent for one rat indicates the variability that may be encountered. The measurement of radioactivity in the various lipid fractions isolated indicated that the carboxyl carbon from linolenic acid had been incorporated into the fatty acids of the saturated and various unsaturated fractions.

In sequence of steps, degradation of the C_{20} acids isolated from the unsaturated fatty acid fraction yielded the following information: The carboxyl carbon contained 27 per cent of the total radioactivity present in the C_{20} fraction and, counting from the carboxyl end, C_2 contained 8 per cent; C_3, 60 per cent; C_4, 4 per cent and the 16 carbon residue, 1 per cent. A comparison of the distribution of the labeling in the C_{18} acids isolated from the unsaturated fatty acid fraction with that in the original linolenate revealed that there was labeling beyond the original label in the carboxyl carbon, thus indicating that the labeling in C_4 and in the C_5 to C_{20} chain was real. A similar distribution pattern was found in the carbon skeleton of the polyene mixture. It appeared from these results that the linolenate had undergone several β-oxidations without affecting the double bond system and that the molecule was rebuilt from acetate, some of which arose from β-oxidation of the labeled linolenate. In similar experiments in which carboxy-labeled linoleate was used no radioactivity was detected beyond carbon atom 3 of the C_{20} acids (Steinberg, Slaton, Howton and Mead, *Ibid.* *220*:257, 1956).

From *Nutrition Reviews,* Vol. 16, No. 2, pp. 55-56.