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Food Intake, Metabolism and Homeostasis

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Abstract

This tribute to Bart Hoebel briefly reviews the following topics. Metabolic processes are intimately intertwined with food intake as well as drug taking. Changes in any of these processes can be adequately adjusted to the environment to preclude major perturbations in homeostatically-regulated systems, but only if the environment is predictable. Learning plays a critical role in adapting these processes to specific situations. The regulatory context plays a critical role in how metabolism and food intake interact.

Keywords

Body weight; addictions; homeostasis

We are pleased to have the opportunity to comment on the career of Bart Hoebel and to document the role that some of his research has had in shaping our views of homeostasis and regulation, as well as in the commonalities of the controls over the ingestion of food and the ingestion of drugs of abuse. In fact, Hoebel himself directly helped kickstart the career of one of us (SCW). When Woods was a junior faculty in Psychology at Columbia University, he wrote a theoretical article on insulin, growth hormone and body weight control with his students, Joe Vasselli and Elisabeth Decke, and somewhat presumptively submitted it to *Psychological Reviews* for review. It was ultimately accepted and published [1]; and he later learned that Bart had been the reviewer that lobbied for its acceptance. More to the point, a prestigious and select invitation-only meeting on the neurobiology of food intake and body weight regulation was to be held in France in late 1973. Having reviewed the manuscript, Bart contacted the organizers, Jacques le Magnen and Stelios Nicolaidis, and suggested they invite Woods to the meeting; and they did. At the meeting Woods met Bart Hoebel and learned the reason for his attendance, and Woods considers the meeting in Ermenonville to have jump-started his career as he was privileged to meet and rub shoulders with many luminaries including (in addition to Hoebel, le Magnen and Nicolaidis) Eliot Stellar, Alan Epstein, Jean Mayer, George Kennedy, Yutaka Oomura and many more. It also sowed the seeds for a career pursuing overlaps in the neurobiology of eating and of drug taking. This article summarizes some of our thoughts on it. What is important is that Hoebel's critical thinking on regulation, initially on the regulation of body weight and its relationship to food

intake (e.g., [2]), then to the interactions of homeostatic and reward aspects of feeding (e.g., [3, 4]), and subsequently to the similarities between food and drug intake (e.g., [5]), predated and stimulated our own.

Food Intake

What controls food intake? Stated another way, what factors or stimuli determine when a meal will occur, and what stimuli determine when it will end and how much will have been eaten? The answers to such questions are vitally important for trying to understand the etiology and potential treatments of the world-wide prevalence of obesity, and they were historically thought to be deceptively simple. Early conceptualizations considered the stomach to be key. When the stomach was empty, hunger occurred and an individual ate so long as food was available; and as food accumulated in the stomach and caused distension during a meal, hunger waned and satiation took over, eventually causing eating to stop. Observations such as the continuous eating by animals with open gastric fistulas, where ingested food exits the body and precludes significant filling of the stomach [6], supported the concept; and bariatric procedures such as gastric banding that reduce the functional volume of the stomach when swallowing are at least partly based on the premise that distending the remaining pouch is instrumental in eating less food [7].

An alternative possibility, and the one championed by most lay people, is that some correlate of energy storage or metabolism governs the start and end of meals. For example, Jean Mayer's glucostatic hypothesis held that the critical controller was the rate of metabolism of glucose by specialized sensory cells in the ventral hypothalamus [8]. With a limited capacity to store glucose, brain cells rely on a steady influx of energy-rich glucose molecules from the blood to drive their cellular activities; hence, low blood glucose (hypoglycemia) was considered sufficient to trigger the sensation of hunger and to elicit eating. Consistent with this, procedures that lower blood glucose, such as administering insulin, elicit the onset of eating [9]. The critical stimulus is not the level of glucose in the blood, however, but rather the ability of some brain cells to derive sufficient energy from glucose. This can be demonstrated by administering drugs like 2-deoxyglucose (2DG) that interfere with brain intracellular glucose metabolism and elicit eating [10].

While there is no doubt that drastically lowering glucose metabolism in the brain is sufficient to cause eating, this experimentally-induced phenomenon bears little relationship to normal eating since virtually all meals begin when blood glucose and brain glucose metabolism are at much higher levels. Hence, eating in response to insulin or 2DG is considered an emergency response, a vital reflex to be activated to enhance long-term survival [9]. Likewise, elevations of available glucose or glucose utilization are not considered to be major controllers of satiation during most ongoing meals.

Brain and Metabolism

In recent years, the possibility that metabolic signals act in the brain to influence food intake has broadened considerably [11, 12]. Glucose received most historical attention as it is the primary energy source for most brain cells, and the signaling activity of some glucose-sensitive neurons in the hypothalamus (as well as elsewhere) changes in association with

changes in local glucose [13]. There is now compelling evidence that neurons in the same areas of the hypothalamus, and perhaps even the glucose-sensitive neurons themselves, also change their signaling activity in response to local changes of some fatty acids [14]; and unlike neurons in general, these cells synthesize the enzymes necessary to synthesize and metabolize fatty acids, and changes in these cellular processes are known to influence cell signaling and to influence food intake [15]. The ventral hypothalamus has also recently been found to be sensitive to local changes of some amino acids, such as leucine [16]. The point is that an area of the hypothalamus known to be important in the regulation of energy homeostasis and body weight contains neurons sensitive to molecules representing all three classes of energy-rich compounds: carbohydrates, fats and proteins. Further, under some conditions, local manipulations of the metabolism of any of these compounds can influence food intake.

A picture that has emerged in recent years is that this area of the hypothalamus can be considered a general energy sensor that integrates information on the metabolism (or potential metabolism) of all major molecular sources of energy [11, 17–19]. While this concept is not new [20, 21], what is perhaps novel is the recognition that most cells in the body share common energy-sensitive enzymatic systems that control their local activity. For example, when ample energy is available from the circulation, a cell is able to put effort into growth and repair as well as carrying out its unique functions. When energy is scarce, nonessential activities are attenuated and energy is targeted into simply staying alive [11, 12].

Two molecules have been identified that determine whether metabolic activity of cells is aimed at growth, maintenance or survival. AMP-activated protein kinase (AMPK) activity increases during energy-need (e.g., during hypoglycemia) whereas mammalian-target of rapamycin (mTOR) activity increases during energy excess. Increased AMPK or decreased mTOR locally within the ventral hypothalamus increases food intake and vice versa, and the balance is influenced by cellular energy metabolism [11, 12].

Food intake and the regulation of body fat

The amount of fat stored in the body is signaled to the brain by means of hormones whose rate of secretion and levels in the blood are proportional to stored fat [22, 23]. The best-known such adiposity signals are leptin, which is secreted by fat cells, and insulin, which is secreted by pancreatic β -cells. Both hormones are transported from the circulation into the brain, and specific receptors for each are expressed by neurons in the ventral hypothalamus as well as elsewhere in the brain [22–24]. Hence, the brain area that is sensitive to local energy-rich fuels and their metabolism is also sensitive to molecules that signify body fat storage. Leptin and insulin increase hypothalamic mTOR and decrease AMPK and vice versa, leading to decreased food intake and weight loss [11, 25, 26]. There is compelling evidence that total body fat itself is regulated in the sense that when it is decreased, homeostatic reflexes are activated to restore fat to normal, and that when it is increased, reflexes with opposite actions are activated to elicit weight loss. These processes account for the relatively stable maintenance of body weight over long intervals.

Control of food intake

Food intake (i.e., the behavioral act of eating) is not a regulated variable; rather, food intake is an effector or response mechanism that can be recruited or turned off in the regulation of body fat [27]. Brain circuits that regulate body weight/fat have several effectors at their command, including exercise/general physical activity and whole-body metabolic rate as well as food intake. When body fat is higher or lower than normal, any of these effectors might be recruited, the exact process(es) depending upon other activities and constraints. An important point is that food intake and other effectors can also be recruited in the service of other regulated variables. Blood glucose and glucose metabolism by some cells in the brain are homeostatically regulated, and as discussed above, when they are experimentally decreased, eating is elicited [27, 28]. Analogously, body temperature is also homeostatically regulated, and when it is decreased, increased physical activity, peripheral vasoconstriction or whole-body metabolism are recruited to defend normothermia [28, 29]. Because of their overlapping and redundant consequences, activating any particular effector is likely to influence multiple regulated variables.

In sum, numerous homeostatic reflexes are available to maintain certain vital parameters in the body within strict limits. When these limits are exceeded in one direction or the other, a subset of available reflexes is recruited, the exact effectors used depending upon environmental and internal conditions [28]. For example, if glucose metabolism decreases, initial defenses might include the secretion of catecholamines or glucagon to increase acute glucose secretion into the blood from the liver; if the hypoglycemia is more persistent, more chronically-acting hormones such as cortisol/corticosterone might be secreted. Increased eating may be recruited, but its glucose restorative ability is relatively slow, and any benefit in terms of increasing available glucose is not immediate. In fact, eating in the face of hypoglycemia might better be viewed as precluding future glucose shortages than correcting an existing one [9, 30].

When body weight is displaced from its usual level, the first effector typically activated is altered food intake. For example, individuals who have dieted and lost weight tend to eat more food (typically larger meals) until weight is restored. Changes of metabolic rate or of exercise are less preferred strategies as they come with other costs, impacting other regulated parameters. Nonetheless, if an individual's weight is above or below the weight the brain is striving to maintain (sometimes called a set point or settling point for weight), and appropriate changes of food intake are not possible, then changes of metabolism and/or exercise are recruited as effectors [31, 32]; and although they may require more time than changes of food intake, they eventually get the job done.

Negative feedback vs. feed-forward control

To summarize, food intake is influenced by metabolic activity in hypothalamic neurons and elsewhere; by hormones that signal the body's fat content to the brain; and by other homeostatic-need situations such as low blood glucose. All of these represent instances of negative feedback. If brain metabolism is too low or too high, eating is impacted; if body fat is too low or too high, eating is impacted; if blood glucose is too low or too high, eating is

impacted; and so on. All are examples of eating being an effector recruited in response to a challenge to a homeostatically-regulated variable. However, this conception fails to capture the predominant influences over eating; i.e., rather than eating being a reflex to correct a homeostatic perturbation, it is better viewed as anticipating and thus circumventing homeostatic perturbations [27, 28, 33].

Eating as an anticipatory behavior

As discussed elsewhere, it is maladaptive to have to rely upon changes in vital parameters and subsequent recruitment of corrective reflexes as a primary mode of regulation [34]. Rather, at least at the behavioral level, most regulation is anticipatory, providing what might be needed before any need arises. In this light, eating can be viewed as stockpiling ample energy-laden nutrients to meet future metabolic needs.

Rather than reacting to homeostatic perturbations through negative feedback, effector activity can be calibrated based on past experience and thereby prevent significant homeostatic deviations from ever occurring. With regard to eating, meal size, meal frequency and dietary choice are highly flexible effector mechanisms that can be adjusted to best maintain body adiposity, blood glucose, brain metabolism and other regulated variables. For example, imposing restrictions that temporally limit food availability (e.g., changing from free food access to a single daily window of time when food is available) results in dramatically increased meal size that mitigates reductions in body fat [35, 36]. For this preventive strategy to be effective, animals use past experience to accurately anticipate environmental challenges so that corrective or compensatory effector activity can be initiated prior to any actual homeostatic perturbation. Learning is the adaptive mechanism enabling these effector changes to be controlled in this way. Learned cues such as the time of day signal a pending change in conditions so that effector activity can be adjusted appropriately to meet the demands of the situation.

This feed-forward strategy has important implications. A highly flexible behavioral effector like food intake can present major challenges to metabolism. As an example, if the environment dictates that food is available only once a day at the same time, in order to maintain body weight an individual must change its behavior and eat only one very large meal each day. In that situation, the animal adapts by learning to make responses that anticipate the arrival of food availability and consequently increase the efficiency and capacity of the digestive system, thereby limiting the impact of absorbing so much new energy into the blood at one time [33, 37].

Eating and drug taking

As pioneered by Bart Hoebel, consuming some substances such as sugar share many properties with addictions to drugs [5]. Importantly, like eating, drug taking presents major challenges to homeostatically regulated variables; i.e., the value of learning to activate effectors to prevent regulated variables from being overly perturbed is as relevant to drug taking as it is to ingestion. The use of effector mechanisms to progressively diminish perturbations caused by drug effects is described as drug tolerance that permits the escalation of drug taking. We have argued [28, 33, 34] that tolerance also develops to foods

in that the physiological disturbances caused by eating can be mitigated by the well-synchronized activation of controlled effectors made possible by learning. An important implication is that highly conditioned individuals, whether tolerant or addicted to drugs or else trained on an extreme meal-feeding schedule, are vulnerable to metabolic mishaps. Making anticipatory responses but failing to get the anticipated drug or food creates symptoms of withdrawal and can lead to an escalating spiral of dependence on both the anticipatory responses and the drug/food effects [28, 38].

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