Long term regulation of feeding and body weight

While it natural to think that body weight is under the control of feeding behavior, it is becoming increasingly clear that the causal relationship is actually the reverse. Feeding behavior over long periods of time is controlled by body weight. An organism's weight normally does not stray far from a certain value. For instance, Davidson, Passmore and Brock (Human Nutrition and Dietetics, 1972) point out that an average woman gains 24 pounds between the ages of 25 and 65. This corresponds to an excess daily energy intake of .025% of her total needs. Put another way, this represents an average excess energy intake equivalent to 350 mg of food per day over 40 years, a period during which she consumes 20 tons. If one considers the tremendous variety of eating patterns which occur over such a period, the long-term stability of weight is remarkable.

Experimental animals deprived of food (or force-fed), will eat (or starve) their way back to "normal" weight, if allowed ad lib access to food. Thus, body weight can be forcibly perturbed, but if the normal regulatory mechanisms are allowed to function, it tends to return to some "normal" value. This regulatory process can be permanently altered by lesions of the hypothalamus. A lesion of the ventromedial nucleus of the hypothalamus (VMH), results in hyperphagia and obesity in laboratory animals. A similar picture is sometimes seen in humans with hypothalamic or third ventricle tumors. This is often called the **ventromedial hypothalamic syndrome**. A lesion in the lateral hypothalamus will cause an animal to cease eating and drinking, often to the point that it dies of starvation and dehydration. This is called the **lateral hypothalamic syndrome**.

In contrast, if a rat is force-fed until it is very obese, and then given a bilateral lesion of the VMH and free access to food, instead of overeating it will avoid food until it attains a weight which is below its weight at the time of the lesion, but above its original normal weight. If a rat is food-deprived so that its body weight becomes quite low, and then given a lateral hypothalamic lesion and free access to

food, instead of becoming **aphagic** it will eat steadily until it attains a body weight above that at the time of the lesion, but lower than normal.

These results led to the idea that the hypothalamic lesions disturb some kind of **set-point** at which an animal regulates body weight. This abstract set-point is the expression of neural mechanisms in the hypothalamus and the signals to which they are sensitive. When signals reflecting body weight are higher than the set-point, feeding behavior is inhibited. When they drop below the set-point, feeding behavior is initiated to "defend" the normal body weight. There is evidence that a variety of factors can affect the hypothetical set-point mechanisms, and it is not clear that there is just one signal upon which long-term regulation of body weight depends.

When weight is gained or lost, a major component of the change is in adipose tissue mass. Thus, it has long been assumed that some humoral element signals the size of the body's fat mass and the brain regulates feeding to keep this signal constant. This is the so-called **lipostatic hypothesis** of feeding control. The search for such a substance has gone on for years and several candidate substances, such as glycerol, have been examined but set aside. **Insulin** has long been suspected of having a role in body weight regulation because its blood levels increase in proportion to body weight in certain kinds of diabetes. In recent years, evidence has developed that a protein called **leptin** is a circulating signal linking fat mass to the brain's control of energy balance. This protein is missing in certain genetically obese mice and was isolated in experiments designed to find the responsible gene, now known as the *ob* gene. Leptin itself is sometimes referred to as **OB protein**. Circulating leptin concentration in humans is proportional to body weight.

Leptin injection into the cerebral ventricles of normal and genetically obese mice causes a long-lasting decline in feeding and leads to a reduction in body weight. Circulating leptin in mice varies diurnally and is lowest during periods of active food consumption. Leptin receptors have been identified in the choroid plexus and hypothalamus. Its major hypothalamic target appears to be the arcuate nucleus

where it has an inhibitory effect.

The effects of leptin are thought to be mediated, in part at least, through **neuropeptide Y**, a powerful stimulant of food intake when injected into the cerebral ventricles. Hypothalamic neuropeptide Y concentrations and messenger RNA increase in starvation and return to normal with injection of leptin. Leptin inhibits the feeding stimulation induced by neuropeptide Y. Receptors for neuropeptide Y (which occurs in a number of forms), are found in the hippocampus, cingulate cortex, amygdala and in many hypothalamic regions including the lateral hypothalamic area which is known to be involved in feeding. **Melanocyte Stimulating Hormone** (**MSH**) and its receptor also appear to be part of the mechanism by which leptin has its **anorectic** effects.

Leptin has been studied in both humans and rodents carrying genes causing obesity. It appears that the normal function of this protein can be interrupted in at least three ways: (1) failure of the *ob* gene to produce a normal form of leptin; (2) failure of transport of leptin into the CNS and (3) abnormalities in the receptor for leptin on neuronal cell membranes in the brain. It should also be noted that leptin may have functions other than weight regulation because individuals with leptin abnormalities often experience developmental and reproductive abnormalities as well.

Recent research has unearthed another class of hypothalamic peptides that stimulate feeding when injected into the cerebral ventricles. **Orexin**, also called **hypocretin**, comes in at least two forms and activates cells in the arcuate nucleus of the hypothalamus that are inhibited by leptin. Of considerable interest is the fact that orexin may have a major role in the regulation of arousal and sleep and in the major sleep disorder narcolepsy. Some narcoleptic animals appear to have a defective brain receptor for orexin. Many humans with narcolepsy have been found to have no or abnormally low circulating levels of orexin associated with an increased level of the major histocompatibility complex class II antigens in microglia, suggesting that their narcolepsy may be an autoimmune disorder.

Other substances have been found to have large effects on feeding behavior when injected into the brain. One of these is **cholecystokinin** (**CCK**). This peptide is normally present in the brain in addition to being secreted in the gut, where it regulates emptying of the gall bladder. Tiny amounts injected into the brain will inhibit feeding. Also, genetically obese mice have lower levels of CCK in their brains than do non-obese littermates and normals. Their sensitivity to CCK is normal.

How all of this ties together in the control of body weight (and sleeping/waking) is the subject of intense research. In the set-point model of Figure 1, body weight, as signaled through levels of various peptides (such as leptin, orexin, insulin, etc), is compared with some "set point" for the levels of these substances, and feeding behavior is regulated to sustain them at normal levels. Deviations result in the appropriate corrective behavior, either feeding or fasting. The conceptual "set point" is a complex interaction of the sensitivities of hypothalamic cells that trigger feeding (or represent hunger and satiety) with the effects of the various substances on these same cells.

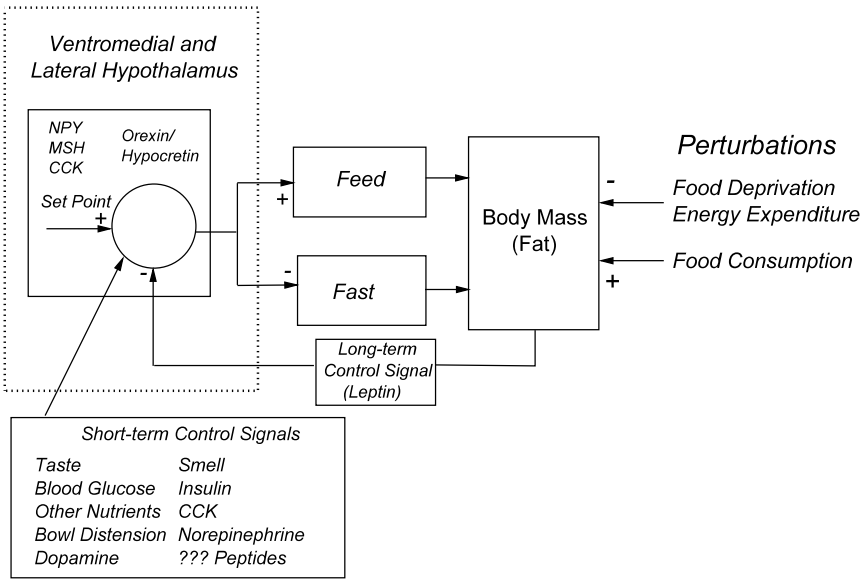

Figure 1 Schematic diagram of feedback system for the control of feeding behavior. The effects of a variety of substances acting on hypothalamic neurons, including insulin, leptin, MSH, CCK, Neuropeptide Y and the orexins, may be thought of as regulating a "set point" for body weight. Changes in the levels of these substances or in their receptors can cause increases or decreases in body weight.

Short term regulation of feeding: control of meal size and frequency.

Acute changes in the blood levels of various nutrient substances can initiate or inhibit feeding. These include certain amino acids, glycerol, and glucose. The one most thoroughly investigated is glucose. The brain needs glucose for its normal function, so one might expect blood glucose to be maintained within narrow limits by ingestion, as well as by glycogenolysis. It has long been established that infusion of glucose i.v. inhibits feeding, while infusion of insulin initiates feeding. Infusion of glucagon, which elevates blood glucose, inhibits feeding. Infusion of 2-DG, a non-metabolized glucose analog, interferes with the access of glucose to cells and increases feeding in the face of normal blood glucose levels. Injection of gold thioglucose destroys the VMH and causes hyperphagia and obesity, suggesting the presence of glucose receptors in the hypothalamus which sense blood glucose levels and initiate or terminate feeding. Such findings led to the hypothesis that the brain uses feeding behavior to control its supply of glucose within normal limits. This is the so-called **glucostatic hypothesis**.

This theory faces the difficulty that changes in blood glucose have to be rather heroic to evoke or inhibit feeding; the behaviors are sensitive to glucose levels, but not that sensitive. Careful studies of monkeys eating a variety of diets show that minute-to-minute control of feeding is relatively independent of blood glucose levels. The available data indicate that a glucostatic mechanism is certainly present, that it is critical in certain situations, but that normally it probably does not play a central role in the regulation of feeding.

In addition to changes in blood levels of various substances, other changes occuring as a direct result of the ingestion of food exert short-term control on meal size. Some of these have been shown to have a significant effect on when the animal will cease to eat. Taste and smell are obviously important in the initiation of feeding. More will be said about them below. The introduction of food into the mouth causes blood glucose to rise, even before any of the nutrient can be absorbed. It is not known if this rise has a control

function, but it could serve as a kind of anticipatory negative feedback through the glucostatic mechanisms discussed above. Feeding can be inhibited by using a balloon to dilate acutely the esophagous, stomach or bowel. Factors, such as CCK, secreted by the gut in response to ingestion may also act via the sensory fibers in the vagus nerve to regulate meal size by inducing satiation. The control of meal size involves a large number of possible factors operating over a time span on the order of minutes. Leptin is not thought to have this kind of role in feeding behavior, but rather participates in a regulatory process that integrates over weeks or months.

Recent studies lend support to the idea that under normal circumstances, taste and smell are important factors in the regulation of ingestive behavior and that these sensations are themselves manipulated after a fashion. An early suggestion of this came from studies of animals with hypothalamic lesions. It was found that these animals are extraordinarily fussy about the palatability of the food presented to them. The aphagic animal with a lateral hypothalamic lesion can be made to eat if the food is very tasty. Similarly the VMH lesioned animal is also very picky about the food it will eat to become obese. Such studies led to the idea that the lesions were having a large effect on the capacity of various foods to positively or negatively reinforce eating behavior.

That such a mechanism might actually be operating is suggested by the effects of intracranial electrical stimulation. If a rat is allowed to stimulate certain areas in and around the hypothalamus, it will do so continuously until it drops of hunger, dehydration or exhaustion. A male rat will do this in the presence of a receptive female and will cross an electrified grid to reach the lever controlling the stimulation. In contrast, there are other sites which the animal will only stimulate once and then never again. These observations have given rise to the idea that there are "pure" reinforcement systems in the brain, systems which when activated will increase (or decrease) the probability of recurrence of whatever behavior led to their activation. Presumably, behaviors that are good for the organism activate the positive reinforcement mechanism, those that

are harmful activate the negative mechanism. Addictive behaviors may be traceable to the effects of addictive substances on these systems.

Recent work indicates that behaviors classified as "foraging" (seeking, wanting) may be different from those classified as "consummatory" (liking). This makes sense because an animal has to forage in the absence of food reinforcement, so the foraging itself must be "its own reward," so to speak. The 'wanting' system appears to do this. The dopaminergic projection from the ventral tegmental area (Martin, pp. 87,525) to the nucleus accumbens (Martin, p 463) appears to be essential to 'wanting' but not to 'liking'. Thus, lesions here will decrease the probability that an animal will seek out food, but will not decrease the amount of food eaten when it is made available. The role of such systems in addiction is under intense study.

The basic idea of a control system based on hedonic mechanisms reveals what Walter B. Cannon called the "wisdom of the body." Pleasure and pain, or better, comfort and discomfort, are experiences that can be decoupled from the physiological regulatory mechanisms that maintain such vital parameters as blood pressure, body temperature, fluid balance and energy stores. By allowing hedonic factors to regulate behaviors related to these vital parameters, the parameters themselves never drift into the danger zone that requires emergency action. Consider how we keep our body temperatures within normal limits by anticipating and thwarting a cold threat. When we feel chilly, we use clothing, shelter, and fire to ensure that we don't have to shiver, vasoconstrict, and piloerect.

The same strategy appears to operate in one of the mechanisms regulating meal size. When appropriate food is available, its taste and smell "reward" feeding behavior and sustain consumption up to a point. After some quantity of the food has been consumed, the brain appears to modify the reinforcing properties of taste and smell, presumably by switching these sensory inputs into circuits that "punish" the feeding behavior. This mechanism will clearly regulate meal size without there ever being a threat to, say, blood sugar levels or the capacity of the gastrointestinal tract to contain

and process the food. It will ensure that eating takes place when tasty food is available and that eating stops before the animal compromises its digestive system or is so full that it can't flee predators.

References:

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