Neuropeptides and the Control of Energy Homeostasis

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**Introduction**

We live in an era of unprecedented advancement in our knowledge of the biological controls over eating and the regulation of body adiposity. This has been accomplished in part by technological innovations that enable probing the workings of individual cells and even molecules, as well as by an enormous investment of funds for basic research by government and industry. Nonetheless, in spite of this wealth of new information, the prevalence of obesity continues to increase [20, 47, 64, 102], as does the incidence of related health consequences [102]. The hope is that the new information being generated may soon lead to new therapeutic approaches. Our intent in this overview is to summarize and discuss what is new and exciting in the realm of the neuroendocrine controls over food intake and energy expenditure (i.e., over energy homeostasis), and to suggest avenues for novel therapeutic strategies.

**Food Intake**

Food intake is a complex behavior with multiple levels and kinds of regulatory control [e.g., 158]. For in addition to providing the calories necessary to enable the body to grow and function, food also provides micronutrients (vitamins and minerals), macronutrients (carbohydrates, fats and proteins), and a certain amount of water. Food intake also occurs in distinct bouts or meals, and different kinds of controls influence the onset *vs.* the offset of
meals. Food intake also addresses both acute energy needs as well as the long-term storage of calories as fat. Finally, whereas many controls over eating are related to energy or caloric homeostasis, others are related to different phenomena. For example, when animals are ill or incapacitated, or preoccupied with other behaviors, they eat less food. The interaction of all of these factors relies upon neural and hormonal signals arising throughout the body and impinging upon regulatory control areas of the brain. The complex array of neuropeptides (as well as other neurotransmitters) thought to be important in this regulation is discussed in a later section of this chapter. Initially, we focus upon the control of meals.

**Meals**

Most animals, including humans, adapt their eating schedule to accommodate their unique environmental conditions. When food is ample and readily available, distinct patterns can be discerned (e.g., consuming three meals a day). However, idiosyncratic activities (such as working or going to school) and constraints (the presence of predators at certain times of day) vary considerably among individuals within a species, and most adapt well by developing eating patterns (the size and timing of meals) that provide necessary nutrients and otherwise optimize fitness [31]. In spite of this variation among individuals, most members of a species develop and maintain a rather consistent body weight as adults [18, 124, 139]. The control system that allows meal patterns to vary while allowing daily caloric intake to meet energy needs and maintain body weight is both simple and elegant. The key factor is that whereas meal size is under the control of physiologic signals important in energy homeostasis, meal onset is normally not. Hence, meals can be initiated at times that are convenient, or that have proven successful in the past, or that are imposed by the environment, and the individual can still eat sufficient calories each day to maintain its weight. The reason is that if an individual’s weight decreases slightly, it will tend to eat larger meals when the opportunity arises. Hence, it regains lost weight over long intervals by increasing meal size. Likewise, an individual whose weight increases slightly over time will have a tendency to eat smaller meals.

As ingested food interacts with receptors in the gastrointestinal tract, it elicits the secretion of enzymes and signals that help orchestrate the digestive process and customize it to the meal that is being consumed. In the early 1970s, Gibbs and Smith and their colleagues [55] provided the first solid evidence that some of these signals additionally provide information to the brain that helps determine when the meal will end. Specifically, they found that when the gut peptide, cholecystokinin or CCK, is administered to animals prior to a meal, the animals eat less food, the magnitude of the decrease increasing with greater doses of CCK. This basic phenomenon has been
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replicated in dozens of labs with multiple species (including humans) [135, 136]. Importantly, doses of CCK that reduce meal size do not cause signs of malaise in animals or humans [135, 136].

As potent and selective agonists and antagonists to CCK receptors became available, two important new findings emerged. The first is that CCK acts uniquely at the CCK-A receptor to reduce meal size [63, 92, 105]. The second is that when antagonists to the CCK-A receptor are administered animals prior to a meal, they eat larger meals [63, 105]. This key observation indicates that endogenous CCK normally contributes to the termination of meals, and it implies that when exogenous CCK is administered, it combines with endogenously secreted CCK to terminate the meal prematurely. Another important new finding is that CCK combines with other factors that limit meal size, such as gastric distension, in a synergistic manner. Hence, the ability of a small dose of exogenous CCK to reduce meal size is greatly enhanced when the stomach is slightly distended [114, 116]. This observation is presumably related to the fact that many sensory nerve fibers from the stomach and intestine have different endings [14] that could be sensitive to molecules such as CCK, at one ending, and to stomach distension at another. There is also evidence that the same sensory axons integrate information from both CCK and gastric distension [114, 116], and that the integrity of these axons (that travel in the vagus nerve) is essential for CCK to reduce meal size [137, 138].

CCK is but one of several peptides secreted from the gut during a meal that is purported to reduce meal size. Others include peptides in the bombesin family (bombesin, gastrin-related peptide or GRP, and neuromedin-B) [54, 136], glucagon [50], somatostatin [80], enterostatin [42, 162], and apolipoprotein A-IV [49, 147]. For many of these, administration of the appropriate antagonists or antibodies has led to increased meal size, suggesting that these peptides contribute to the termination of normal meals [see 134]. This is important because humans (and rats, the species in which meal size has been most extensively investigated) are general omnivores and will eat a wide spectrum of possible foods. The specific cocktail of peptides secreted from the gut to digest and absorb each meal can vary considerably since different peptides presumably signal different mixes or amounts of nutrients. Signals comprised of combinations of peptides that ultimately accumulate and stop the meal would be especially functional for omnivores. Accordingly, combinations of CCK and bombesin [142], and of CCK and glucagon [51], have been reported to combine to reduce meal size.

Eating and Body Weight

It has long been recognized that a strong interrelationship exists between body fat stores (adiposity) and food intake. All things being equal, consuming more than sufficient calories to maintain weight each day leads to increased
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stored energy and *vice versa*. Forced or voluntary overeating for several days elicits weight gain as inevitably as dieting or food restriction elicits weight loss. In this light, body weight (mainly body adiposity) can be considered to be at the mercy of food intake. The other side of that same coin, however, is that when an otherwise weight-stable adult eats insufficient food for a period of time, and necessarily loses weight; s/he will likely overeat when ample food once again becomes available (or when the enthusiasm for dieting wanes). Likewise, if an individual consumes excess calories to the point of weight gain for a prolonged interval, there will be an increasing tendency to eat less food and thus help return body weight and body fat stores to their preintervention levels. Viewed in this light, food intake would seem to be controlled by body weight. There are many reviews of these phenomena [18, 71, 72, 124, 159]. Understanding the causal factors that interrelate food intake and body adiposity is an important goal and the subject of considerable ongoing research.

The link between body fat and food intake was formalized a half century ago when Kennedy [73] postulated that signals proportional to body fat influence the control of appetite and feeding by the brain. Thus, Kennedy’s lipostatic hypothesis stated that adiposity is controlled by a negative feedback system in which food intake is controlled in part by the level of total stored body fat. While the fundamental truism of the lipostatic hypothesis has never been in doubt, an important question over the intervening years has been the nature of the signal or signals that indicate how much fat is present in the body. Because body fat is located in multiple storage depots dispersed widely throughout the body, several possibilities exist by which body fat might be monitored by the brain. For example, sensory nerves could innervate and hence provide information from each fat depot, with the cumulated information from multiple sites in the body integrated within the brain into a reliable ‘total adiposity’ signal. While plausible in principle, in fact adipose tissue is only sparsely innervated, and the majority of the fibers innervating fat depots are motor, controlling the release of stored energy when it is needed. A second possibility is that a single fat depot is sufficiently representative of all of the others that it serves as a bellwether. In this schema, the brain need receive a signal only from this sentinel depot. Such a depot could be located anywhere, and several hypotheses have been based upon such a model. For example, Nicolaidis and his colleagues [43, 94] have hypothesized that cells within the hypothalamus of the brain serve this function and are ideally situated to influence all aspects of energy homeostasis. Unlike most other brain cells, this adipose-tissue homunculus is postulated to act like peripheral adipocytes and thus to be sensitive to insulin’s metabolic actions. There is in fact evidence that some cells in the ventral hypothalamus are insulin-sensitive and that their electrical activity varies with insulin and other metabolic signals [78, 97]. There is also evidence for an energy homunculus being located in the liver (or at least within the influence of hepatic nerves) [48, 75]. While there seems little doubt that
signals related both to stored energy and to ongoing energy utilization can arise in both the brain and the liver (and presumably other tissues as well), it is not clear how much they contribute to the control of most instances of the control of eating. Further, there is compelling evidence for a third signaling pathway, involving hormones secreted in the periphery in proportion to the total amount of fat in the body.

**Adiposity Signals**

When two experimental animals are joined surgically such that a small proportion of the circulation exchanges between them (termed parabiotic animals), the presence of circulating adiposity signals is revealed. For example, when otherwise normal animals with similar body weight (either two lean or two obese animals) are parabiotically joined, each eats normally and maintains its usual (presurgical) body weight. Contrary to this, when an obese animal is joined with a lean animal, their respective body weights, rather than converging, diverge. The obese partner may gain a little weight, but the dramatic effect occurs with the lean partner, which may stop eating and lose body weight precipitously [62]. In fact, unless the two are separated, the lean animal might starve itself to death. Such experiments have been interpreted to indicate that a circulating signal proportional to body fat passes between the two partners. The relatively high titer of the signal entering the lean animal from its obese partner provides a false message that too much fat exists in the lean animal’s body, and the lean animal responds appropriately to the signal by reducing its food intake and losing weight. Hence, a circulating signal can have a powerful influence over eating behavior.

The most reliable circulating indicators of body fat are several peptide hormones that are secreted from peripheral organs and that are transported into the brain from the circulation. The three most investigated are leptin, the hormone secreted from adipose tissue, and insulin and amylin, hormones secreted from the B cells of the pancreas. All three are synthesized and secreted in direct proportion to the amount of fat in the body. In the section below, we review the evidence that each of these peptides satisfies criteria for being an adiposity signal to the brain.

**Insulin As an Adiposity Signal**

To be considered an adiposity signal, a compound should be secreted in proportion to body fat, should have access to appropriate areas of the nervous system, and should influence food intake and body weight in predictable ways [119, 124, 159]. Insulin was the first hormone found to have these properties [see reviews in 122, 155]. Insulin is the body’s predominant controller of blood glucose levels, and its secretion from the pancreas is controlled in large part by ambient glucose. Nonetheless, the responsiveness of the B cells to
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glucose (and to most other compounds as well) is proportional to body fat [4, 100, 101]. A fatter individual secretes proportionally more insulin to a given increase of blood glucose than does a lean individual. Hence, insulin levels in the blood reflect both ongoing metabolic needs as well as how much fat exists throughout the body. Circulating insulin gains access to the brain both via areas with a reduced blood-brain barrier (such as the circumventricular organs) and via a receptor-mediated transport process that moves insulin molecules through the cells that comprise the blood-brain barrier and releases it in the brain’s interstitial fluid [see reviews in 120, 122, 126].

Insulin receptors are expressed in brain regions important in the control of energy homeostasis such as the ventral hypothalamus [10, 35, 45, 77]. Insulin receptors are also expressed in other brain regions (e.g., the olfactory bulbs and the hippocampus) where their function is less understood. Within the hypothalamus, the arcuate nuclei (ARC) have particularly high densities of insulin receptors, and the ARC is the location of at least two major neuronal types that potently influence food intake (see below). When exogenous insulin is administered directly into the brain (either into the ARC itself, into nearby ventral hypothalamus, or into the adjacent third ventricle), animals behave as if they are overweight, i.e., they eat less food and lose weight [90, 121, 149, 156, 157, 160]. This response develops over several hours and is proportional to the amount of insulin administered. When the converse treatment is applied such that local concentrations of insulin are reduced (by administering antibodies to insulin into the brain), animals eat more food [143] and gain weight [89]. Consistent with these observations, the tubby mouse has recently been reported to have a mutation in the intracellular insulin-signaling pathway within the ventral hypothalamus [68]. The tubby mouse is characterized by hyperphagia and obesity, suggesting that endogenous insulin normally acts within the brain to reduce body weight. Perhaps analogously, transgenic mice with hyperactivity of insulin signaling are resistant to diet-induced obesity [37].

Collectively, all of these experiments strongly support the hypothesis that insulin is an adiposity signal to the brain. A key prediction of this hypothesis is that an experimentally induced elevation of circulating insulin should also result in a decrease of food intake. This has been difficult to accomplish in a simple way because when plasma insulin is experimentally increased, it causes a rapid decrease of blood glucose (and frank hypoglycemia) which itself causes animals to eat more food [41, 81, 86]. This scenario does not normally occur naturally since elevations of endogenous insulin occur in response to already elevated blood glucose and hence act to reduce glucose to normal levels (and not create hypoglycemia). However, in support of the hypothesis that insulin is an adiposity signal, when circulating insulin is experimentally elevated and hypoglycemia is circumvented, animals eat less food [95, 150, 161]. As a final but important point, when insulin is administered into the brain at doses that reduce food intake and body weight, a number of control experiments have
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indicated that the animals are neither ill nor incapacitated and rather that they are simply defending a lower body weight [25, 26]. Therefore, insulin satisfies all of the criteria for an adiposity signal to the brain.

**Amylin As an Adiposity Signal**

Amylin (also known as islet amyloid polypeptide, IAPP) is a second pancreatic hormone synthesized in B cells [34, 82, 152]. It is co-secreted with insulin in response to glucose and other nutrients in direct proportion to body adiposity [21, 83, 99]. Like insulin, amylin is rapidly and efficiently transported through the blood-brain barrier into the brain [5, 7]. Although the amylin receptor has not yet been cloned, populations of amylin binding sites have been identified in discrete brain regions, including the hypothalamus [12, 28, 132]. Amylin’s best-known peripheral action is a potent inhibition of stomach emptying [33]. Consistent with the hypothesis that amylin is involved in the regulation of energy balance, the peripheral administration of exogenous amylin causes a dose-dependent decrease of food intake and body weight [3, 84, 163], and amylin-deficient ‘knockout’ mice weigh more than wild-type controls [52, 53]. Our recent finding that administration of very low doses of amylin directly into the brain causes rats to eat less food and lose weight is consistent with a central locus of action [109]. Importantly, and analogously to insulin, amylin reportedly reduces food intake without making animals ill [24, 85], and we have recently found that insulin and amylin combine synergistically to reduce food intake [110]. Therefore, although far fewer experiments exist, there is sufficient and increasing evidence to include amylin with insulin as a circulating adiposity signal to the brain.

**Leptin As an Adiposity Signal**

Leptin is the new kid on the block. Although its existence was inferred from experiments done over 25 years ago on parabiotic mice [30], leptin was not discovered and described until 1994 [164]. Leptin is secreted from adipocytes in direct proportion to the amount of stored fat [32, 107]. However, the actual stimulus is related more to the metabolic activity of the fat cell than to actual fat storage [60, 61] such that dissociations can occur between stored fat and leptin release [1, 17, 154]. Nonetheless, over the course of a day, plasma leptin levels are a reliable indicator of body fat. As is the case with insulin and amylin, circulating leptin is transported through the blood-brain barrier into the brain [6, 23, 56, 69, 123], and leptin receptors are localized (among several other regions) within the ARC and other nuclei in the ventral hypothalamus [9, 11]. Administration of leptin locally into the brain results in decreased food intake and body weight [22, 98, 131]. The response is dose-dependent and is not secondary to illness or incapacitation [146]. Animals with ineffective leptin signaling (either because they do not synthesize leptin, *obob* ‘obese’ mice; or because they have defective leptin receptors, *dbdb* ‘diabetic’ mice and *fafa*
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‘fatty’ rats) are characterized by hyperphagia and obesity. Hence, leptin, like insulin and amylin, satisfies the criteria to be an adiposity signal to the brain.

Central Control Systems

Signals indicative of adiposity, as well as those indicative of ongoing metabolic processes and what is being eaten and processed in the gut, converge on the central nervous system (CNS). Within the CNS, in order to regulate food intake and body weight effectively, these signals need to interact in meaningful ways and to engage neurochemical systems that influence energy intake and energy expenditure. The best known of these CNS systems are in the ventral hypothalamus, and they can be roughly partitioned into those whose activity reduces body fat (catabolic effector systems) and those whose activity increases body fat (anabolic effector systems) [66, 124, 128]. Anabolic effectors elicit increased food intake, decreased energy expenditure and consequently increased stored energy in the form of adipose tissue. They are hypothesized to become more active when energy stores are low as indicated by reduced levels of insulin, amylin and leptin (i.e., when the body is in negative energy balance). Catabolic effectors do just the opposite. Activated by positive energy balance, they decrease food intake, increase energy expenditure and result in decreased adipose tissue mass. A critical aspect of this negative feedback model is that hormones responsive to the level of adiposity inhibit anabolic pathways while activating catabolic pathways, and it is the balance between these two pathways that ultimately determines the animal’s ingestive behavior and defended level of adiposity [128, 159].

The catabolic and anabolic effector systems are in actuality a series of discrete neurotransmitter systems and axonal pathways in the brain, and many of the key details of this overall schema have emerged in the last few years. Although receptors for leptin and insulin and binding sites for amylin are located throughout the CNS, all three are concentrated in the arcuate nucleus (ARC) in the ventral hypothalamus. Hence, ARC neurons are presumably sensitive to these hormones and consequently to the amount of adipose tissue in the body.

Hypothalamic Anabolic Effector Systems

The best-described anabolic effector peptide is neuropeptide Y (NPY). Although NPY mRNA and peptide are distributed widely throughout the CNS, NPY-containing cell bodies in the ARC are especially important in the control of energy homeostasis. Although these ARC NPYergic neurons directly influence several areas of the brain, major projections are to the nearby paraventricular nuclei (PVN) and the lateral hypothalamic area (LHA). ARC NPYergic neurons respond to negative energy balance (e.g., to food deprivation) by synthesizing more NPY mRNA, and they release more NPY in the PVN [67, 111, 127] and
presumably the LHA as well. Importantly, animals in negative energy balance have low levels of adiposity hormones, and the local replacement of either insulin or leptin in the vicinity of the ARC normalizes the elevated NPY mRNA in the ARC [118, 127]. Hence, the activity of these ARC NPY neurons is under the direct influence of at least two adiposity signals.

Consistent with its being an anabolic effector peptide, administration of exogenous NPY into the PVN or into the adjacent third cerebral ventricle elicits a rapid and robust increase in food intake [29, 112, 130, 140, 141] and decrease in energy expenditure [15, 16]. Repeated administration of NPY produces uncompensated increases in food intake, body weight and body adiposity [141]. Importantly, local administration into the ARC of compounds that result in less NPY being synthesized result in reduced food intake and body weight [2]. Hence, NPY satisfies all of the criteria of an anabolic effector peptide.

**Hypothalamic Catabolic Effector Systems**

The catabolic counterpart of the ARC NPY system also resides within the ARC. Considerable evidence implicates the melanocortin system as an important catabolic effector system. Melanocortins are a family of peptides including ACTH and α-melanocyte-stimulating hormone (α-MSH). The precursor molecule for ARC melanocortins is proopiomelanocortin or POMC, and it is synthesized in a group of non-NPY synthesizing ARC neurons [38]. In addition to several other important neuropeptides, ARC POMC encodes α-MSH, a transmitter which functions as an agonist at several classes of melanocortin receptors within the hypothalamus (and especially within the PVN and LHA). When administered into the third ventricle, α-MSH and other melanocortin receptor agonists (including the synthetic drug, MTII) reduce food intake and body weight, whereas administration of synthetic melanocortin receptor antagonists (such as SHU-9119) increases food intake and body weight [44, 129, 145, 148]. POMC gene expression is reduced in negative energy balance [125] and increased in positive energy balance [57]. Consistent with the hypothesis that the melanocortin system is important in mediating the effects of leptin, leptin receptors are found on POMC neurons [27], leptin stimulates POMC mRNA [125], and administration of a melanocortin receptor antagonist blocks the effect of leptin to reduce food intake [129]. All of this evidence points to the endogenous POMC/α-MSH/melanocortin receptor hypothalamic system as being a key catabolic effector pathway capable of eliciting robust effects on food intake and body weight that mediates the effect of adiposity signals in the CNS.

Two melanocortin receptors, termed MC3 and MC4, have been identified within the hypothalamus [93]. Of these, the stronger case can be made for MC4 receptors being involved in the control of energy homeostasis. We have recently found that, when administered into the third ventricle of the rat, selective MC4 receptor agonists inhibit and selective MC4 antagonists
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stimulate food intake [13]. Consistent with this, MC4 receptor ‘knockout’ mice have increased food intake and frank obesity, and they are insensitive to the actions of nonselective MC4 receptor agonists to reduce food intake [65].

Complexities of the Arcuate Nucleus System

An important interaction was recently discovered between the ARC to PVN/LHA NPY system and the ARC to PVN/LHA POMC/α-MSH/MC4 system. NPY-synthesizing neurons in the ARC make and secrete a second neuropeptide, agouti-related peptide or AgRP [59, 96, 133]. As occurs following the administration of exogenous NPY, administration of AgRP potently stimulates food intake and body weight [58, 108]. Interestingly, AgRP is an antagonist of the MC4 receptor [96]. Hence, the same ARC neurons release two different neuropeptides from their axon terminals. NPY acts at one set of receptors to create an anabolic effect whereas AgRP acts at MC4 receptors to inhibit an α-MSH-mediated catabolic effect.

Other Hypothalamic Systems

The subsequent steps in the neuronal system that controls energy homeostasis and that emanates from the ARC are more complex and diverse. However, as indicated above, two important areas are the PVN and LHA. Each of these pairs of hypothalamic nuclei receives rich inputs from the ARC [39, 40], and each synthesizes several neuropeptides which are important players in the equation. The PVN, for example, has neurons that synthesize corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH) and oxytocin, and the administration of any of these causes a net catabolic action [128, 159]. Since ablation of the PVN causes a chronic anabolic condition characterized by hyperphagia and obesity [see 19], a rough generalization is that the PVN is a key component of the catabolic effector system. Analogously, the LHA synthesizes melanocyte concentrating hormone (MCH) [104] and the orexins [36, 113]. These neuropeptides, when administered into the CNS, cause a net anabolic response.

Interaction of Adiposity Signals with Signals That Control Meal Size

A key question concerns how the various control systems described in this chapter are integrated in the control of food intake. That is, what are the interrelationships among the systems that signal ingested calories and control meal size, those that signal adiposity, and those hypothalamic neuropeptides and other neurotransmitters that receive feeding-pertinent inputs from throughout the brain. Although precise answers are obviously not
Fig. 1. [from 128]. Schematic neuroanatomical model of the interaction of adiposity signals with other controllers of energy homeostasis in the brain. Adiposity signals such as insulin and leptin (and presumably amylin as well) are secreted into the blood in direct proportion to the amount of fat stored in the body. These signals are transported through the blood-brain barrier and interact with receptors on NPY and POMC-synthesizing neurons in the ARC. Axons from the ARC then pass to many brain areas, including the PVN, the LHA, and the perifornical area (PFA) around the LHA. Although it has many functions, the PVN generates net catabolic signals, whereas the LHA/PFA generates net anabolic signals. Signals related to acute energy balance as well as to what is currently being consumed (i.e., satiety signals such as CCK) originate in the liver and gastrointestinal (GI) tract and are transported to the brain via vagal and sympathetic nervous system (SNS) afferent nerves. Metabolic, satiety-related and adiposity signals (as converted into catabolic and anabolic influences) converge in the brainstem in or near the nucleus of the solitary tract (NTS) where they are integrated and ultimately influence energy intake and expenditure.

yet at hand, a model is emerging that is consistent with most of the data, and it is summarized in Figure 1.

When rats have free access to food and can eat whenever they want, they generally eat 10 or 12 meals a day, with most intake occurring during the night [74, 76]. West et al. [151] observed that when CCK is administered to free-feeding rats prior to each meal via an automated delivery system over a 1-week interval, the size of each meal was reduced. However, the
rats maintained essentially normal daily caloric intake and body weight by increasing the number of times they initiated meals each day. This suggests that exogenous CCK, by itself, is an ineffective treatment for losing weight. Nonetheless, animals with mutated CCK-A receptors [91] gradually become obese over their lifetime [70], suggesting that an inability to terminate meals appropriately may contribute to a gradual development of body fat [117]. Similarly to what occurs when exogenous CCK is administered alone, when the brains of animals are exposed to very low doses of either insulin or leptin, there is no change of daily food intake or body weight. However, when these animals are additionally administered a low dose of CCK once a day, they eat less food [8, 46, 88, 106] and lose weight over days [87]. This is an important observation and it suggests that the efficacy of CCK (and presumably other signals that reduce meal size as well) is enhanced in the presence of elevated adiposity signaling in the brain. The infusion of a low dose of leptin directly into the brain also increases the sensitivity of the vagus nerve to signals that reduce meal size [115].

These observations have important implications. When an individual goes on a diet and starts losing weight, there is a concomitant reduction of the secretion of adiposity signals (leptin, insulin and amylin) and lower titers of these signals enter the brain. In fact, an acute fast, in and of itself, is sufficient to reduce the transport of insulin [144] or leptin [69] into the brain. One consequence of reduced adiposity signaling is a reduced ability of meal-generated peptides such as CCK to terminate a meal, and the important result is that meals will tend to be larger until adiposity signaling (and body weight) are normalized. Likewise, an individual who overeats and gains weight will have increased adiposity signaling in the brain and will consequently tend to eat smaller meals. Hence, this control system opposes long-term changes of body weight, and it does so by changing the average size of meals. Note that individuals are still able to eat according to whatever schedule best meets their lifestyle and environmental constraints; it is the meal size rather than the meal pattern that is controlled by this regulatory system.

An important unanswered question relates to what happens to this control system when the diet is changed. A strong case can be made that when individuals habitually consume diets rich in fat, they tend to become obese [20, 79, 102, 103, 153]. This indicates that the normal feedback signaling system must become altered or insensitive on a high-fat diet, and this is the topic of intense current research.

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References

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Discussion

*Dr. Fernstrom:* When you give standard appetite-suppressant drugs to animals or humans over an extended period of time, there’s a plateau in the effect on body weight, and the effect on food intake is transitory. What is the outcome in longer term studies with some of these agents? I mean the amphetamine-related compounds.

*Dr. Woods:* As you say, when you give these drugs you reach a plateau with any given dose. If you keep to that dose your body weight is likely to start creeping up again, so you start taking greater doses to maintain the effect. I think what you’re doing is changing the gain of the system to these adiposity signals.

*Dr. Fernstrom:* But take CCK as an example. If you gave CCK on a repeated basis over an extended period of time, would you continue to see body weight fall until the animal weighed nothing?

*Dr. Woods:* No. In fact nothing happens in that instance. The animals simply eat more often, and their food intake is constant over the course of at least a week. Nobody’s done any longer studies than that.

*Dr. Fernstrom:* But when a plateau of effect is reached, does that mean that metabolically there has been a change? The compound has not lost its efficacy, otherwise body weight would all be regained.

*Dr. Woods:* Exactly.

*Dr. Fernstrom:* So there is something going on that no-one has a clue about.

*Dr. Woods:* I think there’s a fundamental difference between the class of drugs that you described as appetite suppressants and those that enhance the satiety effect of a meal. Drugs in the former class reduce your tendency to want to initiate a meal, and not only that but you tend to eat smaller meals as well. In the latter class, and CCK is one of those, there is no effect on the likelihood of initiating a meal. Many studies have looked at that and none has found any effect. All they do is reduce meal size, and if the only manipulation you do is to reduce meal size there’s really no effect.

I think that what you have to do is to change the signal coming from the hypothalamus to the brainstem, or wherever the integration occurs. We know that CCK can reduce meal size simply by acting on the brainstem. And you can change the gain of that effect in the long term, though I don’t know how long exactly. We’ve changed insulin in the brain for as long as 2 months and the effect continues. And even though I only talked about neuropeptides, there’s much crosstalk with monoamines between the brainstem and the hypothalamus. I don’t want to suggest that this is a one-way system. I gave a very simplified view of how we control meals. And I ignored one whole class of compounds.

*Dr. Freeman:* I’m interested in ketogenic diets. What would happen in your system, and to leptins and insulin, if you gave a diet with virtually no carbohydrate, say 90% fat?
**Dr. Woods:** I wish that study had been done. I don’t know the answer. My guess is that if body weight remains constant then leptin wouldn’t change. But that said, I haven’t seen a lot of published controlled studies on these ketogenic diets.

**Dr. Rosenberg:** The relation between leptin secretion and adipose tissue is clearly understandable if the adipocytes are secreting leptin, and so there is a quantitative relation. What is the current thinking about the intermediary signal between the amount of adipose tissue and the islet cells that are secreting insulin?

**Dr. Woods:** My former colleague Dan Porte from Seattle always told me that the relation between insulin and adipose tissue was a Nobel Prize question. Nobody seems to know how the pancreas senses how much fat there is – that is, the nature of the feedback mechanism. People are beginning to understand what controls leptin secretion, but it’s not the amount of fat in the fat cells, it’s the glucose turnover in the fat cells that seems to be important. And this varies, as I indicated, between visceral fat and subcutaneous fat. There are other fundamental differences that are important, for example sex differences: women are more likely to distribute fat subcutaneously and men viscerally. My understanding from some recent reports [1] is that subcutaneous fat makes about three times more leptin per volume of fat cell than visceral fat does; also leptin correlates much better than insulin with total body adiposity in women, while insulin correlates much better with total body adiposity in men. We are starting to understand something about these signals but I don’t even want to speculate how the β cell knows how much fat there is.

**Dr. Bourdel-Marchasson:** Why doesn’t leptin work therapeutically in humans to affect body weight? And what is the physiological implication of high leptin secretion in the human? Does it disturb appetite control.

**Dr. Woods:** This deals with the hypothetical construct of leptin resistance. However, taking a parallel situation, type 2 diabetic patients are insulin resistant but you can still treat them with insulin – you can give them enough insulin to lower their blood sugar a certain amount. My understanding of the clinical trials with leptin is that you can’t give enough leptin to ensure that a sufficient amount will enter the brain to overcome the resistance. That’s why I think it’s a much more exciting possibility to understand where the leptin works in the brain and perhaps design a small molecule that works at the next synapse in the neuronal chain that leptin would normally trigger. In that way you wouldn’t have to worry about leptin resistance or getting enough into the brain, if you can simply bypass the leptin receptor in the central nervous system. I can’t emphasize enough that one of the most important findings that has come out of this research is that you can push appetite in either direction with some of these receptor systems in the hypothalamus. For me that’s very exciting – they are chronically turned on and you can move them either direction.

**Dr. Kaye:** Excluding leptin and insulin, have any other peptides been found in humans that could explain obesity, even in just a few people?

**Dr. Woods:** My understanding is that five different mutations concerned with the α-MSH/MC4 receptor system have now been found. In fact, in most human obesities at which you can find a co-localizing gene associated with that system, it is the MC4 receptor that is affected.

**Dr. Kaye:** How much of the variance does that explain?

**Dr. Woods:** It’s a small percentage of the obese population, but far more than can be accounted for by people who don’t secrete leptin, for example. In each instance there’s one variant associated with being obese, but I’m struck by the fact that there are five different variants related to the central melanocortin system, and of course in mice it doesn’t matter where you intervene in that system, you get profound changes in food intake and body weight.
Dr. Ritz: You said that adipose mass is tightly regulated. We know that normal aging is associated with an increasing fat mass. There are some arguments that fat oxidation is reduced but do you feel that the arcuate nucleus of the brain could be impaired?

Dr. Woods: It’s a very good question what happens in aging, and why in humans there is a tendency to store more fat. There has been very little research on this. We have looked at the ability of plasma insulin to penetrate into the brain as a function of age, and it does go down with age in rats. You could make a story about that, but it would be purely speculative. And we’ve not looked at really old rats; we looked up to 1 year.

Dr. Ritz: Is there any means of estimating the activity of the arcuate nucleus in healthy humans, by PET scanning and so on? Do you think that would be possible?

Dr. Woods: My guess is that it would be possible. It’s straightforward to identify it on a scan because of the bony landmarks around it. However, that’s not my area of expertise.

Dr. Ritz: You’ve shown that there are signals coming from fat telling the brain how much energy is on board. Is it possible that there are also signals from the fat-free mass? This may be very naive. Take, for example, a really heavy sportsman; he might have a very high non-fat mass but eat a huge quantity of food.

Dr. Woods: I think Dr. Fernstrom probably knows far more than I do about the regulation of fat-free mass. My naive way of thinking about this is that you can manipulate the fat-free mass quite readily, for example you can build it up by exercise. This suggests that if there is a negative feedback control, it’s easy to override it – much easier than for fat mass. People who want to diet and lose weight, or people who want to gain weight by overeating, have to work at it literally for their whole life or they’ll be unsuccessful; it’s very difficult to do.

Dr. Rabbo: You said that appetite control is situated in the arcuate and paraventricular nuclei. Do you think that there is a descending input from the cerebral cortex to modify the activity of these nuclei? If not, how can we explain the effect of watching TV on the eating habits of humans?

Dr. Woods: You make an excellent point. I gave a very simplified version, because we don’t have TVs in our rat rooms so we don’t worry about that to a great extent! There are many many connections between the cortex and the nucleus accumbens, where hedonics are thought to be controlled, and the lateral hypothalamus, for example, which I mentioned. There are many things that provide cognitive interaction with this system, based upon learning or on habit. I was simply giving a ‘bare bones’ system to account for a single level of negative feedback control of body fat.

Dr. Fernstrom: If you look at the anthropological literature with respect to primate eating habits in the wild, you come away with the fact that these animals are spending most of their time trying to acquire adequate amounts of dietary protein and energy. I’m struck by the fact that for 99% of evolution and 99% of human evolution there’s been no need for a lipostatic hypothesis or a glucostatic hypothesis, or any of that, because this is a luxury you only need worry about when you have excess food. So why would there be such mechanisms if the evolutionary history is such that the animal is always in a condition of marginal adequacy?

Dr. Woods: You raise a fundamentally important question about why there seems to be a discrepancy between the forces within the body that tend to drive appetite and body weight vs. those that tend to reduce it. When I take an overview of the various studies that have been done, I think it’s clear that the forces tending to reduce body weight simply aren’t as powerful as the ones tending to increase it. There are lots of evolutionary teleological arguments as to why this should be the case. We could talk about the thrifty gene hypothesis; we could talk about how we didn’t evolve to live
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beyond reproductive age and have to deal with all the problems that come with obesity beyond that time. Your speculations would be as good as mine.

Dr. Fernstrom: It seems to me that the important thing is to accrete. How much extra you accrete is irrelevant to the organism because by the time you’ve hit the end of your reproductive life you would have succeeded in your biological role, provided you had enough to begin with. So if there is a regulatory mechanism for the upper reaches, it is either fortuitous or it’s there for some reason. I just wonder whether there are some signals normally present when the animal finds itself having to scrounge for food which disappear when you achieve these upper levels of intake.

Dr. Woods: I believe that there are powerful signals that keep us from eating particularly large meals at any one point of time, but nonetheless we can eat sufficiently large meals in the long term – day in, day out – that we get fat. Why this should be is a key question now in many countries. Is it the diet, or is it the lack of exercise, or what is it that’s leading to this epidemic of obesity? Why does it continue to increase? And what can we do to contain it? I wish I had the answers to that.

Dr. Yamori: I am interested in obesity in the menopausal period, which is closely related to estrogen deficiency. Can you explain how menopausal obesity fits into your comprehensive system?

Dr. Woods: You raise a key point that I didn’t discuss at all. There are many signals that interact with the system and with the ability of insulin and leptin to work in the brain. Gonadal steroids, particularly estrogen, are major examples. There are estrogen receptors in these areas of the hypothalamus, and much work has been done to clarify the role that estrogen plays in the control of appetite and of body weight. And although nobody has looked directly at the leptin/insulin system, those studies are ongoing in several laboratories. From what I understand so far, it appears that estrogens act in concert with leptin to keep body weight down; if you remove the effect of estrogen, body weight will go up because leptin will be less efficient.

Reference