Regulation of Food Intake Through Hypothalamic Signaling Networks Involving mTOR

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Abstract

To maintain normal activity, single cells must assure that their energy needs and utilization are continuously matched. Likewise, multicellular organisms must constantly coordinate energy intake and expenditure to maintain energy homeostasis. The brain, and the hypothalamus in particular, plays a critical role in integrating and coordinating several types of signals, including hormones and nutrients, to guarantee such homeostasis. Like single cells, the hypothalamus also profits from intracellular pathways known to work as fuel sensors to maintain energy balance. One such pathway is the mammalian target of rapamycin (mTOR). mTOR integrates different sensory inputs to regulate protein synthesis rates in individual cells, and it has recently been implicated in the central nervous system to regulate food intake and body weight as well. This review provides an overview of the role of hypothalamic intracellular fuel sensors in the overall control of energy balance and discusses the potential contribution of these fuel-sensing mechanisms to the metabolic dysregulation associated with obesity.

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INTRODUCTION

Primitive unicellular organisms share certain critical properties with even the most specialized cells in multicellular creatures, including the abilities to recognize and capture energy-rich molecules, to convert the energy contained in those molecules into a usable currency, and to expend that currency as needed in the fulfillment of the cell's activities. A common currency in most mammalian cells is the energy-rich molecule adenosine triphosphate (ATP). So long as sufficient nutrients and oxygen are available, along with periodic ebb and flow of the surrounding medium allowing the natural removal of wastes, the creature can thrive. Although evolution to more and more complex organisms enabled delegation of many requisite tasks to specialized cells and organ systems, the need to recognize, acquire, and utilize energy appropriately remains a property of virtually all cells.

In complex organisms, nearly all individual cells lie close to capillaries, which provide local access to nutrients, oxygen, and/or other key molecules supplied via the blood, as well as an avenue to eliminate wastes. Another critical adaptation is based on the challenge of having sufficient nutrients on hand to feed the multitudes of hungry cellular mouths when needed. When faced with insufficient nutrients or oxygen, unicellular organisms either perish or become dormant until conditions improve. Complex organisms have evolved specialized cells such as adipocytes and hepatocytes that function as energy storage depots, sequestering and stockpiling energy-rich nutrients when they are plentiful and doling them out via the circulation when they are scarce. The important point is that in complex, multicellular organisms, individual cells have a continuous need for energy and oxygen; the degree of the appetite varies with local cellular activity. This need is normally met by a steady flow of oxygen, coupled with the secretion into the blood of energy-rich molecules either by intestinal cells that have the capacity to convert ingested food into a form amenable for circulation or else by energy-storage cells. The coordination of these processes, including the ingestion, digestion, and absorption of food and the metabolism, use, and storage of nutrients by various tissues, is termed energy homeostasis, and it is coordinated in a region of the ventral hypothalamus surrounding and including the arcuate nucleus. In this review, we consider one class of molecules that act as key intracellular signals in the overall coordination of energy homeostasis, the mammalian target of rapamycin (mTOR), and how its activity in the hypothalamus relates to the control of food intake.

THE CONTROL OF ENERGY HOMEOSTASIS

Several excellent reviews of the control of energy homeostasis have appeared within the past few years (26, 29, 70, 84, 89, 113), so we present only an overview here. A general schema of energy homeostasis is depicted in **Figure 1**. The brain is in the center of the diagram because it receives a continuous

stream of diverse signals regarding energy status throughout the body and because it influences the entry of nutrients into the blood and their utilization by most tissues. Much of the incoming information is in the form of hormonal or neural signals arising from the gastrointestinal tract, liver, pancreas, adipose tissue, and other organs. The brain integrates information on available energy with data on energetic needs or anticipated needs throughout the body, environmental factors such as where and when food might be available, relevant aspects of the social situation, memory for key relevant information from past experiences, and hedonic factors, among others.

Based on all of this information, an important role of the brain is to ensure adequate circulating energy for immediate tissue needs as well as adequate stored energy to weather long intervals during which access to energy sources is not available (95, 96). As integral pieces of the overall calculus, finding food and ingesting it are behaviors that are tightly coordinated with the control of plasma levels of glucose, fatty acids, and other substrates; the amount of energy already present in various storage organs; and other ongoing behaviors. Under most circumstances, the levels of energy-rich fuels in the blood are relatively constant, as their use by tissues is matched well to their secretion by the liver and adipocytes. This is true even when energy usage increases considerably (such as during exercise), when the turnover but not the absolute levels of blood glucose have the greatest variance. The major exception occurs during and after meals as newly digested and absorbed nutrients enter the blood from the intestine. Therefore, an important consideration of the brain is to limit the size of individual meals so as not to allow too large a perturbation to plasma fuels (105, 110, 111, 121). As depicted in **Figure 1**, this is accomplished by the brain's coordinating ongoing information about the quality and quantity of calories being consumed (via satiation signals), the levels of fuels already in the plasma (via direct sensing by specialized cells in the brain and elsewhere), and the amount of energy present in the various storage depots (via adiposity signals).

Satiation Signals

As has been reviewed elsewhere, numerous endogenous factors related to meals have been implicated as satiation signals (42, 63, 64, 103, 112, 113). The best-known endogenous factor is the intestinal peptide cholecystokinin (CCK), which is secreted in proportion to the lipids and proteins in the meal and which stimulates receptors on the afferent vagus nerve (81). The signal is then relayed to the hindbrain, then relayed further on to the hypothalamus. Although many other gastric and intestinal signals influence satiation, most follow a pattern similar to that of CCK, either stimulating the hindbrain directly or stimulating sensory nerves and then passing to the hindbrain. These collective signals are integrated with the level of available glucose in the hindbrain, where various digestive reflexes are controlled; the information is also relayed to the hypothalamus, where it is integrated with adiposity signals, hedonic and social factors, and local levels of nutrients (5–7, 83). The net effect is that as satiation signals accumulate during a meal, they ultimately activate circuits that cause individuals to stop eating (i.e., to limit meal size). Importantly, this is true even when ample food is available and more could be eaten; the signal works in part to prevent extreme postprandial elevations of plasma fuels (110, 111). When exogenous satiation factors are administered to people or animals as they are eating, they eat smaller meals, and when the activity of endogenous satiation factors is experimentally or therapeutically blocked, they eat larger meals (63, 64, 103, 112, 113).

Adiposity Signals

In contrast to satiation signals, adiposity signals are hormones secreted in proportion to the body's fat depots. The best-known adiposity signals are insulin, from the pancreatic β cells, and leptin, from white adipocytes (4, 67, 69, 73, 89, 113, 115). Increased levels of either

signal in the blood indicate more stored fat. Each signal is transported through brain capillaries to gain access to receptors on neurons in the hypothalamus, the hindbrain, and elsewhere (3, 74, 87, 119). As with satiation factors, when either insulin or leptin is directly delivered into the brain in or near the hypothalamus, less food is consumed and weight is lost over time; when the action of insulin or leptin in the brain is reduced, food intake and body weight increase (88, 89, 117, 118, 120).

THE ARCUATE NUCLEUS

Although many areas of the hypothalamus are important in the control of energy homeostasis, the hypothalamic arcuate nucleus (ARC) is a key area: Here, satiation and adiposity signals are integrated with information on nutrient levels, and the resulting message is relayed to appropriate response elements in other hypothalamic areas and throughout the brain. ARC circuitry has been the subject of intense investigation over the past few years. The major output of the ARC is a pair of parallel neuronal circuits with functionally opposite actions, one providing an anabolic tone to hypothalamic and other brain areas, and the other providing a catabolic tone (10, 17, 18, 95, 96). The balance between these two output systems plays a major role in determining whether more food is ingested and therefore more fat laid down (i.e., anabolic activities) or whether eating is suppressed and stored fat is used for energy, resulting in a net loss of body weight (i.e., catabolic activities).

ARC catabolic neurons synthesize the peptide pro-opiomelanocortin (POMC), which is a precursor for several active neuropeptides. In the ARC, POMC is processed into α-melanocyte-stimulating hormone (αMSH). αMSH released from axons originating in the ARC acts at several areas of the brain on melanocortin (MC) receptors (especially MC4 receptors) to reduce food intake. Administration of αMSH or other agonists of MC4 receptors causes hypophagia and weight loss, whereas administration of MC4 antagonists causes hyperphagia and weight gain. Chronic reduction of αMSH activity results in extreme obesity. There are many excellent reviews describing these phenomena (17, 21, 70).

ARC anabolic neurons synthesize two key peptides, neuropeptide Y (NPY) and agouti-related protein (AgRP). Although NPY plays diverse roles throughout the brain, NPY originating in the ARC acts on Y receptors in several areas of the brain to increase food intake; when NPY is administered chronically, it causes an increase in body weight (reviewed in 19). AgRP, which is synthesized in the same ARC neurons that make NPY, is an antagonist at MC4 receptors and thus functions to curb the activity of αMSH. Administration of AgRP or synthetic MC4 antagonists increases food intake and body weight (19).

What is particularly interesting about these ARC circuits is that under normal conditions, both are active; i.e., both the anabolic and the catabolic systems are turned on, such that manipulation of either the αMSH catabolic system or the NPY/AgRP anabolic system, in either direction, shifts the balance of control and can have profound effects on energy intake, energy expenditure, and energy storage (89, 90, 95, 96, 113). It is as though the ARC simultaneously applies an accelerator and a brake to numerous circuits controlling all aspects of energy homeostasis, especially food intake; however, adjustments can be made to strengthen or lessen either side of the equation in the service of homeostasis. Adiposity signals interact with these ARC circuits in predictable ways. Both POMC and NPY/AgRP cells express both leptin and insulin receptors, and increased levels of either insulin or leptin locally in the vicinity of the ARC cause increased catabolic and decreased anabolic activity (reviewed in 19). Conversely, the ability of either leptin or insulin to reduce food intake is attenuated when the melanocortin system is blocked (17). Analogously, decreased leptin or insulin activity locally within the ARC elicits increased food intake and weight gain (13, 67, 71).

ARC neurons have another important property. As discussed above, all cells share the

ability to sense and respond to nutrients in order to meet their individual needs (the mechanisms mediating these processes, especially the metabolism of nutrients, are discussed below). Some specialized cells, including some ARC neurons, can respond to changes in the activity of their own intracellular metabolic processes by generating messages that are then passed to other cells; i.e., these specialized cells function as receptors for the levels of nutrients present in their local environment. For example, researchers have long known that some neurons change their firing patterns in response to local changes of glucose (55, 58). These glucose-sensing neurons can be subdivided into those whose activity is increased by glucose (glucose-excited) and those whose activity is reduced (glucose-inhibited), but the important point is that through their synaptic connections with other cells, glucose-sensing neurons can influence activities pertinent to energy homeostasis, in particular the control of food intake and plasma glucose levels (55, 58).

Glucose-excited neurons in the ARC synthesize POMC and secrete αMSH (44), whereas glucose-inhibited neurons secrete NPY (68). Like pancreatic β cells, glucose-sensing neurons in the ventromedial hypothalamus (including the ARC) express K_{ATP} channels, and the activity of these K_{ATP} channels can be modified by exposure to glucose as well as to insulin and leptin (53, 55). Increases of either insulin or leptin locally in the vicinity of the ARC cause the K_{ATP} channels in these neurons to open, thereby initiating a chain of responses that reduce blood glucose by inhibiting hepatic gluconeogenesis via a vagal reflex; this effect depends critically on the activation of hypothalamic K_{ATP} channels (77, 100, 101). Conversely, local decreases of available glucose cause these ARC glucose-sensing neurons to induce glucagon secretion from the pancreas and consequently to increase hepatic glucose secretion and blood glucose. Local administration of sulfonylureas in or near the ARC abolishes the activation of K_{ATP} channels induced by either insulin or leptin (77, 100). Thus, modulation of hypothalamic K_{ATP} channels alters blood glucose levels in part by controlling hepatic glucose output, and disruption or pathology within this central nervous system/liver circuit is anticipated to contribute to the development of hyperglycemia or diabetes (77).

Insulin and leptin modulate K_{ATP} channel activity by first activating the Janus kinases/signal transducers and activators of transcription (JAK/STAT) or the tyrosine kinase-coupled pathway, and then activating the downstream phosphoinositide-3-kinase (PI_3K) pathway (53). Phosphatidylinositol 3,4 phosphate and 3,4,5 phosphate, products generated from activation of the PI_3K pathway, in turn decrease ATP binding, inactivating the K_{ATP} channels. Consistent with this action, inhibitors of PI_3K, such as wortmannin, prevent leptin and insulin from opening K_{ATP} channels (53); perhaps related to the same process, neither leptin nor insulin can modulate hypothalamic K_{ATP} channels in obese animals (100, 101), presumably due to dysregulation of the JAK/STAT as well as the PI_3K pathways, which are associated with the development of obesity (67, 76).

An increase in glucose locally in the hypothalamus also inhibits hepatic gluconeogenesis, an effect that requires the conversion of glucose into lactate and pyruvate. Stimulation of the pyruvate pathway, and specifically of the pyruvate dehydrogenase complex, activates hypothalamic K_{ATP} channels, suggesting that the neuronal tricarboxylic acid cycle might function as a biochemical sensor for carbohydrate availability, and that this activity in turn modulates hepatic glucose production (49). Diabetes and/or maintenance on a high-fat diet are associated with decreased pyruvate dehydrogenase activity systemically (80). If this is also true at the hypothalamic level, it could compromise the ability of the hypothalamus to regulate peripheral glucose levels (49).

More recently, it has been found that some ARC neurons can also respond to local changes of some fatty acids, particularly oleic acid and some long-chain acetyl-CoAs, thereby transmitting signals to other brain areas and throughout the body (50, 72). The key point is that ARC neurons are somewhat unique in the

brain. They directly sense and respond to local levels of energy-rich nutrients such as glucose and fatty acids, they have receptors for adiposity signals, they receive information concerning satiation that is relayed from the hindbrain, and they are the site of two major neuronal pathways influencing homeostatic balance.

As might be expected, increases of glucose or oleic acid locally in the ARC elicit decreases in food intake (53, 72). Thus, any of several possible inputs to the ARC reduce feeding, including increased levels of some nutrients, increased satiation signals, or increased adiposity signals. Because of the interrelatedness of many aspects of energy homeostasis, these same types of signals also act in the ARC to influence glucose homeostasis. As an example, the amount of glucose secreted into the blood from the liver is influenced both by local levels of hormones such as insulin and glucagon and by neural signals emanating from the brain. Increases of insulin, leptin, or other nutrients locally in the ARC trigger a neural reflex whereby less glucose is secreted from the liver.

NUTRIENT UTILIZATION

Three major categories of energy-rich molecules or macronutrients provide fuel for mammalian cells: carbohydrates, lipids, and amino acids. When combined with oxygen in the appropriate enzymatic metabolic pathway, these molecules are converted to intermediate metabolites or end products such as carbon dioxide and water, with much of the energy sequestered into molecules of ATP (or their equivalents). Under normal circumstances, most tissues rely predominantly on carbohydrates (mainly glucose) or lipids (primarily fatty acids) for energy. A major factor that determines whether glucose or fatty acids are used for energy is the hormone insulin, which is secreted when fuels (mainly glucose) increase in the blood. Insulin enables most tissues (e.g., skeletal muscle, adipose tissue) to take up glucose and either oxidize it or store it. Low levels of insulin prevent glucose uptake, requiring those same cells to convert to oxidizing lipids. Because blood glucose is elevated primarily during and after meals as ingested carbohydrate enters the blood from the intestine, the prandial period is associated with high insulin and consequently high glucose utilization by many tissues. As the effects of the meal wane, insulin levels fall and cells revert to consuming lipids. Low levels of insulin signal adipose tissue to release stored lipids into the blood.

Two organs constitute important exceptions to this scenario. The first is the liver, which oxidizes mainly lipids at all times (51). The liver can also interconvert energy-rich molecules from one form to another. It packages available lipids into lipoproteins that are secreted into the circulation, providing fat cells and other tissues with lipid energy. After meals when insulin is high, the liver replenishes its glycogen stores and converts excess glucose into glycerol that can be used in the formation of triglycerides (41). Between meals when insulin is low, most cells oxidize lipids, so the need for glucose is reduced. However, as discussed below, there is always a need for glucose, and when its levels get too low, the liver can generate glucose from some amino acids. Liver cells can also store a certain amount of glucose as glycogen to provide energy when a very rapid increase of blood glucose is required.

The second exception is the brain, which relies mainly on glucose for energy. The passage of glucose through the blood-brain barrier and the uptake of glucose by neurons and glia are insulin independent. Moreover, neurons have the support of glial cells that assure energetic needs during fasting or intense neuronal activity. In fact, astrocytes are able to synthesize ketones, which provide additional nutrition to the brain during nutrient deprivation (36).

Given the complexity of ensuring that each tissue has the fuel it needs at the time it needs it as well as the capability of storing fuels and/or interconverting them from one form to another as needed, a complex integrating/coordinating system has evolved to facilitate energy homeostasis. The brain, with considerable help from the liver, bears this responsibility, and in

order to accomplish its task most efficiently it requires a continuous stream of information as to which tissues need what sources of energy and in what amounts, how much carbohydrate and lipid is stored and readily available, how much and what types of fuels are currently being processed in the digestive system, and where and when in the environment potential new sources of energy might be available (31, 54, 95, 96).

THE CONTROL OF MEAL SIZE

Determining when to eat and how much to eat are key challenges of the energy homeostatic circuits. An organism living in a stable environment in which ample food is available has the luxury of establishing regular eating patterns so that its ingestive behavior can be optimally integrated with other behaviors (16, 104, 105, 111). In such an environment, it can optimize the amount of excess fuel to store as well as how much energy to take in during individual meals spread over the day. In an ideal environment, the organism might also have the luxury of selecting foods rich in one or another macro- or micronutrient.

Animals living in stable and hence predictable environments develop strategies that enable them to glean the best and most current information on critical energetic parameters, and they learn to make responses to take in and utilize fuel most efficiently (see 78, 79, 106, 110, 116, 121). They utilize temporal cues to dictate the optimal times to eat in relation to other behaviors. At the same time, signals such as odors or tastes become reliable bellwethers of food quality and energy content, and these relatively distal cues confer the ability to guide food-taking behavior (i.e., how much to eat). These signals are known as distal cues because they have been associated with energy content in the past, but they have no energy content themselves. In a less predictable environment, the association between distal cues and actual energy sources can be tenuous, requiring the individual to rely to a greater extent upon more proximal cues; i.e., to cues more closely tied to actual caloric availability. Satiation signals are an example of intermediate cues, as they are secreted in response to a chemical analysis of ingested food by cells lining the intestines. A certain level of CCK activity, or of gastric distension, indicates the number of calories that can be anticipated to enter the blood from the intestines over the hour or so after eating. The ultimate proximal cues are the actual levels of glucose, fatty acids, or other energy-rich molecules reaching the cell, or else the consequences of their intracellular metabolism (i.e., metabolites, altered enzyme activity). Importantly, an energy-reliability gradient of sorts maps onto the cues that an individual can use to guide energy intake. In a highly predictable world, the individual can use more and more distal cues to dictate when meals should end. This is important because this continuum also correlates with time until ingested nutrients enter the blood and reach the tissues. An individual using taste or other oral cues can stop eating long before most nutrients are digested and absorbed. As it shifts to using more proximal cues, the lag lessens. Controlling intake via distal cues confers the advantage of being able to eat relatively large meals because appropriate anticipatory responses can be made sufficiently far in advance to lessen their metabolic impact. Having to rely upon more proximal cues comes at a cost of having to eat smaller and more frequent meals, thus perhaps interfering with other behaviors (15, 16, 102, 110, 121).

Under normal circumstances, all of these different cues impinge upon the nervous system during meals, albeit with different latencies and different levels of predictability. For an individual living in a variable environment, the reliability of the smell and taste of food in predicting actual caloric content may be low, requiring the individual to rely to a greater extent upon CCK and other satiation factors to know when to stop a meal. Researchers have found that although animals can readily use taste to guide intake, once taste is experimentally dissociated from caloric content animals abandon it as a cue to guide intake (9, 91–94). Moreover, when individuals are confronted with novel-tasting food,

they are neophobic, eating very little at first until their more proximal nutrient sensors have a chance to experience the consequences (8, 43, 85). Likewise, when caloric content of meals is experimentally dissociated from CCK activity, the ability of CCK to control meal size is attenuated (25, 35). Thus, numerous considerations enter into the determination as to when and how much to eat. When to eat is largely dictated by environmental factors, especially time of day (14, 104, 105). How much to eat once a meal is under way is governed by a potentially broad array of signals (63, 103, 112). When the world is highly predictable, signals farther and farther from actual energy content are used, enabling the individual to consume large meals at one sitting with little metabolic perturbation. In more variable worlds, more proximal cues come into play at the expense of eating smaller meals and requiring the individual to eat more often in order to meet its energy requirements.

Key questions relate to which signals take precedence when all are present at once, and how they interact. Normally the messages related to available nutrients in the blood, to a meal being consumed, and to adipose stores all are congruent and the issue is moot, but this does not always hold. For example, how does an individual respond when distal and proximal cues give mixed messages? One obvious possibility is that the more proximal cues should predominate because they are more closely tied to energy-rich foods. Although few experiments have directly assessed this, satiation signals do indeed trump taste signals, for when exogenous CCK is administered to bolster total CCK during meals, animals and people ignore what has passed through the mouth and over the taste buds and eat less food (22, 23, 34, 63, 103, 112). Studies in which local nutrients are reduced in the ARC at the same time CCK is increased would be informative on these points. Experiments considering the interaction of satiation signals with adiposity signals have found that adiposity signals change the brain's sensitivity to satiation signals. For instance, when small amounts of either insulin or leptin are administered near the ARC, the ability of CCK to reduce meal size is greatly enhanced (27, 28, 59, 60, 82).

NUTRIENT UTILIZATION AT THE CELLULAR LEVEL

Analogous to what occurs at the level of the whole animal, individual cells—in addition to responding directly to energy-rich molecules themselves—can also recognize and respond to an array of distal cues. At the cellular level, distal cues are often signals generated in other, often remote, cells or tissues that reflect key parameters related to energy availability. Insulin is an example of such a distal cue, as the hormone reaches receptors on neurons in the brain in proportion to glucose reaching the pancreas and consequently altering food intake. Likewise, leptin's action in the brain reflects the amount of fat stored in white adipose depots. As a general rule, hormones and neurotransmitters impinging on a cell are distal cues, and nutrients and their metabolic consequences are proximal cues. The cell must be able to integrate all of these signals and use the collective information to appropriately adjust its level of energy intake, storage, and utilization.

As energy-rich fuels and energy-related hormones, neurotransmitters and other signals react with cellular receptors, and as intracellular enzymatic cascades become activated or suppressed in response, changes in the levels of downstream molecules function as signals to direct the cell to perform anabolic or catabolic activities. This is a vital property of all cells. For example, when ample fuel is present, enzymatic pathways channel activity into synthesizing new protein for routine cellular maintenance, or for storing energy as glycogen or triglyceride; when fuel is scarce, catabolic enzymatic cascades permit burning stored energy, converting molecules into usable fuels, and so on.

Of particular relevance is that some cells are able to convert activity in one or another fuel-sensitive enzymatic cascade into a signal that can be transmitted to other cells. Hence, some cells function as glucose sensors, fatty acid sensors, or more general energy sensors;

as available energy levels fluctuate, these cells emit proportionate signals to influence activity more globally throughout the body. A common example is the glucose-sensing pancreatic β cell. When glucose levels are high or increasing, β cells respond by secreting insulin that in turn acts as a signal enabling other cells to remove glucose from the blood and utilize it for energy. Likewise, glucose-sensing cells on the taste buds send a neural signal to the brain, engaging circuitry to ingest more of the (palatable) food being sampled. Glucose-sensing cells that convey information to guide other tissues are located in many strategic locations, including the gastrointestinal tract and the liver as well as the pancreas and the tongue. Glucose-sensing cells are also located in the areas of the brain that influence the control of blood glucose levels and food intake, i.e., the autonomic control areas of the hindbrain and the hypothalamus. These cells are neurons that monitor and integrate changes in local glucose concentration over time and regulate their release of neurotransmitters accordingly.

AMP-ACTIVATED PROTEIN KINASE

Perhaps analogous to the balance of activity between anabolic and catabolic circuits in the ARC, nutrient-sensing cells have parallel and functionally opposite intracellular metabolic pathways that direct their signaling, with the balance of relative activity in the two determining the output. Relevant to the control of energy homeostasis is that most cells utilize a pair of protein kinases whose level of activity reflects the overall metabolic activity of the cell. One of these is adenosine monophosphate-activated protein kinase (AMPK), whose activity increases when intracellular ATP is low. AMPK in turn elicits a coordinated pattern of cellular processes to reduce nonessential activities and to acquire new sources of energy (37, 38). AMPK is reviewed elsewhere in this volume (85a) and so is only briefly discussed here.

In neurons, as in most cells, AMPK activity is augmented when cellular AMP:ATP ratios increase (52). Thus, the level of AMPK activity is sensitive to the availability of utilizable fuels such as glucose; when available glucose is low, AMPK activity is elevated (61). Neuronal AMPK levels also rise in response to more distal neurotransmitter signals that are increased in times of nutrient need. For example, elevated levels of AgRP, the gastric hormone ghrelin, or endocannabinoids acting on a cell's receptors increase AMPK activity (1, 48, 61). Each of these signals is increased during fasting and is decreased upon refeeding, and each influences AMPK levels in neurons throughout the brain including the ARC (1, 61). Administration of the adiposity signals leptin or insulin reduces ARC AMPK activity. Actually, recent evidence has shown that central administration of leptin, together with inhibiting AMPK, activates acetyl-CoA carboxylase (ACC) in both the ARC and the paraventricular nucleus of the hypothalamus (32). ACC is the key enzyme regulating fatty acid biosynthesis, and its inhibition blocks leptin-induced anorexia (32). Conversely, increasing local AMPK activity elicits increased food intake and attenuates the anorexigenic action of leptin and α-lipoic acid (45, 61). Although the mechanisms interfacing AMPK to the control of food intake are not known, the NPY/AgRP system seems to be involved, as the catalytic subunits of AMPK are colocalized with NPY in the ARC (45). Interestingly, mice selectively lacking the AMPKα2 subunit in POMC neurons become obese, whereas those lacking the kinase in AgRP neurons develop an age-dependent lean phenotype (12). Even more interestingly, AgRP and POMC neurons lacking a functional AMPKα2 are still responsive to both insulin and leptin, but not to glucose, suggesting that glucose-sensing mechanisms might be distinct from those engaged by insulin and leptin (12).

MAMMALIAN TARGET OF RAPAMYCIN

The macrolide rapamycin is a potent immunosuppressant, and in 1991 investigators found that this drug acts on a ubiquitous protein

kinase consequently named target of rapamycin (TOR). The mammalian isoform (known as mTOR, FRAP, RAFT, RAPT, or SEP) is a ~280-KDa protein in the phosphatidylinositol kinase–related protein kinase family (123). mTOR is a highly conserved serine-threonine kinase that controls critical aspects of the regulation of cell growth, including transcription, translation initiation and elongation, and cell-cycle progression (56, 123). mTOR is an integral component of at least two multiprotein complexes inside the cell. One (mTORC1) contains the protein raptor, and the other (mTORC2) contains the protein rictor (86). mTORC1 is the actual complex susceptible to rapamycin's action (86). When available intracellular energy (i.e., ATP and other energy-rich molecules) is low, mTORC1 stabilizes, resulting in less mTOR kinase activity; conversely, the presence of adequate nutrients increases mTOR kinase activity, which leads to the phosphorylation of its downstream targets such as S6-kinase-1 (S6K1), S6 ribosomal protein (S6), and eukaryotic initiation factor 4E–binding protein (4E-BP1) (40, 123). Thus, mTOR levels of activity fluctuate directly with nutritional status and vary inversely with those of AMPK; i.e., when ample intracellular energy is available, mTOR activity is increased and AMPK activity is decreased, and the converse is true when energy is low. The AMP:ATP ratio is thought to be a critical determinant of both mTOR (24) and AMPK levels (39).

The AMP:ATP ratio can be considered the ultimate proximal energy signal for cells because it is a direct measure of immediately available energy for any cellular activity, and mTOR activity is one of its effectors in cells throughout the body. Increased mTOR phosphorylation (activation) dictates increased cellular anabolic activity such as cellular growth and repair, whereas decreased mTOR activation causes the cell to retreat from such activities. Perhaps not surprisingly, mTOR activity is also sensitive to distal cues, the best known of which is insulin. As discussed above, insulin levels increase when available glucose is high, and activity at the insulin receptor on most cells triggers a cascade of enzymatic events through activation of the PI_3K/Akt cascade, resulting in increased mTOR activity that in turn increases phosphorylation of S6K1, S6, and 4E-BP1 (97, 123) (**Figure 2**).

Like most cells and tissues throughout the body, ARC neurons also express mTOR. However, although mTOR and S6K1 are expressed widely throughout the brain, the phosphorylated forms of these two kinases within the ARC are localized only in NPY/AgRP and POMC neurons (20). Thus, nutrient-sensing neurons in the ARC use the mTOR enzymatic pathway, whose activity varies with feeding status. When animals are fasted, activity of the mTOR pathway in these ARC neurons decreases, and after feeding, mTOR activity increases (20). Thus, the activity of mTOR in nutrient-sensing neurons in the ARC covaries with nutritional state, positioning mTOR to provide a signal dictating whether animals should take in more or less food (20). Consistent with this possibility, downregulation of S6 kinase activity in *Drosophila* neurons that secrete insulin-like peptides elicits increased food intake, and upregulation of S6 kinase activity suppresses feeding (122).

As depicted in **Figure 2**, the PI_3K/Akt signaling pathway is an important intracellular mediator of the two adiposity signals, insulin and leptin (67, 75), and mTOR is a downstream target in the same circuit (97). Moreover, administration of leptin into the third cerebral ventricle adjacent to the ARC causes a time-dependent increase in the phosphorylation of both S6K1 and S6, and the ability of leptin to reduce food intake is attenuated by the mTOR inhibitor rapamycin (20). Thus, mTOR is a necessary mediator of leptin's anorexic action, and presumably of insulin's as well, although this has not been assessed.

Over the past few years, researchers have made the important observation that the mTOR pathway in the ARC is an important link integrating information from adiposity signals with local levels of nutrients in the control of food intake, for, as discussed above, ARC neurons are sensitive to local levels of glucose

and some fatty acids. The mTOR pathway is also sensitive to the other category of nutrients, amino acids, and in particular to branched-chain amino acids (BCAAs) (47). BCAAs are the most abundant of the essential amino acids, and they influence protein synthesis and degradation as well as insulin secretion. The BCAA leucine is especially effective with regard to the stimulation of protein synthesis in skeletal muscle (47), and it was recently demonstrated that when low doses of leucine are administered into the third ventricle, food intake is reduced (20, 66) and levels of S6K1 and S6 phosphorylation are increased in the ARC (20). The reduction of food intake is due to leucine's activating the mTOR pathway, as the anorexic response is attenuated by rapamycin (20).

LEUCINE

Leucine has several important characteristics relevant to its ability to influence energy homeostasis in the brain. Because it cannot be synthesized in the body, its levels reflect dietary leucine, and hence dietary protein intake more generally (47). Like other BCAAs, leucine is not metabolized by liver but is metabolized by muscle and other peripheral tissues (47). Once ingested, therefore, leucine passes relatively unscathed through the liver, and because there is a lack of synthesis in the body, circulating leucine is a reasonably accurate surrogate of ingested protein. Leucine is transported through the blood-brain barrier along with other BCAAs and glutamate by the L-system of transporters (99), and it is rapidly transported into neurons and glia. Because nitrogen in leucine is a precursor for glutamate synthesis, the most abundant and ubiquitous excitatory neurotransmitter in the brain, much of the leucine entering the brain is utilized for that purpose as opposed to forming new protein (11, 33). Finally, leucine can act as a signaling molecule in some cells, based upon its potent and rather selective stimulation of mTOR (46). Hence, when a protein meal is consumed, rising leucine levels herald the opportunity to replenish protein stores in tissues, and elevated mTOR activity acts as the mediating agent.

When available leucine is increased either by its addition to drinking water (124) or by selective deletion of BCAT (branched-chain amino transferase), the enzyme that metabolizes it (98), animals are lean and resistant to diet-induced obesity. However, in neither instance did the animals attain this state by a reduction in energy intake. Mice whose drinking water contained leucine had significantly elevated resting energy expenditure and increased expression of UCP3 in adipose tissue and muscle, but were normophagic on a high-fat diet (124). Mice lacking BCAT developed an energy-wasting futile cycle of increased protein synthesis and breakdown and were also normophagic on a high-fat diet (30, 98). In neither instance is it clear whether the hypothalamic leucine-sensitive mTOR system was impacted, although mitochondrial BCAT (BCATm) is widely expressed in the brain, especially in glutamatergic and GABAergic nerve terminals. Moreover, the cytosolic form of BCAT (BCATc) is found in relatively high concentrations in several nuclei in the ventral hypothalamus including the arcuate (33), suggesting that BCAT may help regulate local leucine levels.

FUEL-SENSING PATHWAYS AND OBESITY

Exposure to a high-fat diet reduces the ability of both hormones (insulin and leptin) and nutrients (glucose, oleic acid, long-chain fatty acids) to modulate food intake and hepatic glucose production when administered centrally (2, 65, 109, 114). This phenomenon appears to be caused by exposure to the diet per se and not by any increased adiposity, as the development of central resistance occurs quickly (within days) (109) and is also present in rats that are fed a high-fat diet but that are calorically and body weight matched to rats fed a low-fat diet (114).

During exposure to a high-fat diet, both leptin and insulin receptors are downregulated

within the ARC, implying that a reduced signal reaching key intracellular circuits may account for the leptin and insulin resistance (67, 71, 75). However, intracellular dysfunctions also seem to contribute to hormonal resistance. For instance, the development of central leptin resistance has recently been associated with an inability of leptin to inhibit hypothalamic AMPK (57), and we have recently found that leptin is also unable to modulate hypothalamic mTOR signaling under exposure to a high-fat diet (D. Cota, S. C. Woods & R. J. Seeley, unpublished observations).

The newly discovered roles of both AMPK and mTOR in the context of food intake regulation make them an interesting research topic, a better understanding of which will aid in determining the function of intracellular signaling cascades in the development of diet-induced obesity. However, although the prevailing data make an excellent case that both kinases play important, and mostly functionally opposite, roles in energy balance regulation, they unfortunately represent a problematic target for the therapy of obesity. In fact, as critical regulatory components of cellular function, they are expressed ubiquitously throughout the body, and their role in peripheral tissues is quite different from their role in the hypothalamus. For instance, it has been shown that whereas leptin decreases AMPK activity in the hypothalamus, thus reducing food intake, it actually induces AMPK in skeletal muscle, an effect that leads to increased fatty acid oxidation (62). Conversely, pharmacological inhibition of hypothalamic mTOR, as well as partial (localized to insulin-sensitive neurons in the *Drosophila*) (122) or total knockout of the S6K1 gene in rodents, is associated with increased food consumption (108). However, chronic activation of mTOR signaling in peripheral tissues, such as muscle and liver, attenuates the PI_3K cascade over time and is associated with the development of insulin resistance (107).

An important implication of these findings is that although it may be attractive to consider developing ligands that either inhibit AMPK or activate mTOR in the central nervous system as a therapeutic approach to weight loss, it may be impractical. Systemically administered compounds might well cause reduced food intake, but at the cost of peripheral insulin resistance; and formulations that are either administered centrally or else work uniquely in the ARC when administered systemically seem impractical and daunting. As a consequence, any use of these pathways for therapy will likely rely on identifying key components of the signaling cascades that are unique to fuel-sensing neurons and that can therefore be targeted without the counterindications discussed above.

CONCLUSIONS

In order to meet the continuous demand for energy, organisms utilize diverse signals at both the organismic and the cellular levels to optimize all aspects of energy homeostasis. As reviewed herein, the overall regulation of these processes relies upon opposing effector systems at every level. ARC neurons integrate distal and proximal signals related to immediately available as well as stored energy with energy demand, and their output changes the balance of anabolic and catabolic circuits directing behavioral, endocrine, and autonomic responses. At the cellular level, nutrient-sensing neurons in the ARC and elsewhere integrate distal and proximal signals to control their own metabolism as well as to generate signals transmitted to other cells and tissues. Mounting evidence implicates both AMPK and mTOR as key cellular fuel sensors whose activity within the hypothalamus, and especially within ARC neurons, affects food intake and body weight in response to both nutrient and hormonal signals. During exposure to a high-fat diet, an organism's hypothalamic circuitry becomes susceptible to hormonal and nutrient resistance, which in turn can predispose the organism both to weight gain and to dysregulated glucose homeostasis. Energy-sensing pathways play a role in the development of this central resistance, although the mechanisms underlying this event have not been completely clarified. Understanding the mechanisms by which

specific diets and the resulting obesity reduce hypothalamic sensitivity to peripheral signals may lead to the development of efficacious pharmacological options to treat obesity as well as insulin resistance. Considering the urgency that our society faces in curtailing the epidemics of obesity and type 2 diabetes, intense research will be needed to understand how dietary constituents and energy content influence hypothalamic sensitivity to hormones and nutrients.

DISCLOSURE STATEMENT

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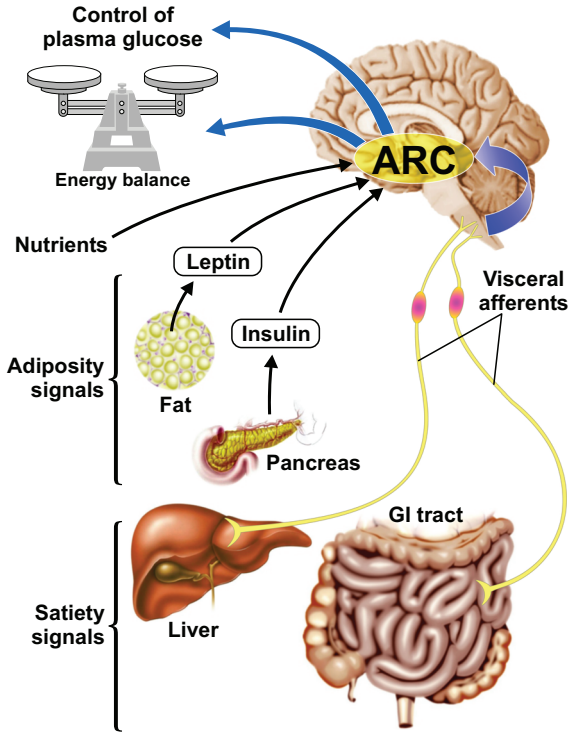

Figure 1

Central nervous system control of energy balance and glucose homeostasis. Satiety signals are generated in the periphery in response to food consumption and lead to the termination of the meal. Signals activate vagal afferents that terminate in the nucleus of the solitary tract in the brainstem. Such information is then integrated with information processed by the hypothalamic arcuate nucleus (ARC) and by other hypothalamic nuclei. Adiposity signals, such as leptin and insulin, and nutrients present in the blood directly target neuronal circuits within the ARC and other hypothalamic nuclei. As a result, food intake and body weight, together with plasma glucose levels and energy expenditure, are regulated to maintain energy homeostasis. GI, gastrointestinal.

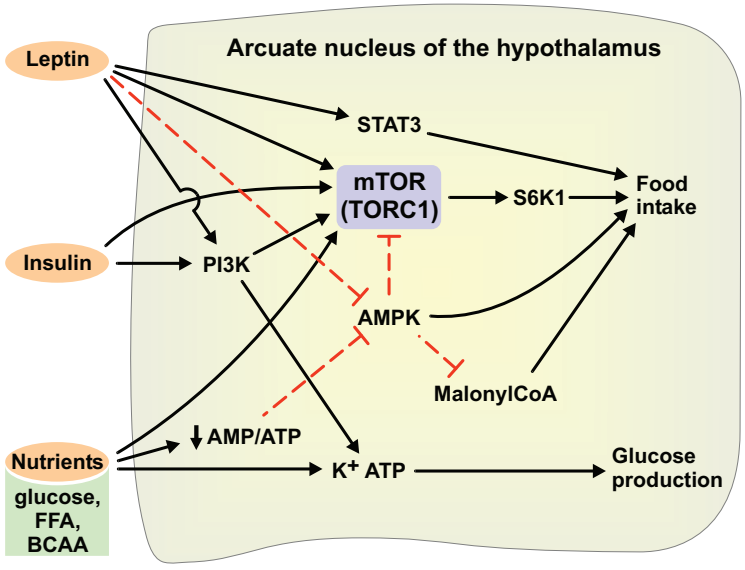

Figure 2

Fuel and hormonal signals converge onto common hypothalamic intracellular pathways. Hormones and nutrients modulate the same intracellular signaling cascades within the hypothalamus to reduce food intake and inhibit hepatic glucose production. Leptin induces activation of hypothalamic signal transducers and activators of transcription (STAT3), an event causally linked to the ability of the hormone to induce anorexia. Furthermore, insulin and leptin both modulate the PI3K cascade. Modulation of this pathway might affect mammalian target of the rapamycin (mTOR) activity as well as KATP channels activity, whose functions can be also affected by nutrients. Decreased adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratios as well as increased leptin levels inhibit AMPK, which is known to negatively modulate mTOR activity and malonyl-coenzyme A (CoA) levels. mTOR activation leads to the phosphorylation of downstream targets, such as S6K1. These and other phenomena, such as increased protein synthesis, are likely involved in determining a decrease in food intake. BCAA, branched-chain amino acid; FFA, free fatty acid.

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