Neurobiology of Feeding and Energy Expenditure

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Abstract
Significant advancements have been made in the past century regarding the neuronal control of feeding behavior and energy expenditure. The effects and mechanisms of action of various peripheral metabolic signals on the brain have become clearer. Molecular and genetic tools for visualizing and manipulating individual components of brain homeostatic systems in combination with neuroanatomical, electrophysiological, behavioral, and pharmacological techniques have begun to elucidate the molecular and neuronal mechanisms of complex feeding behavior and energy expenditure. This review highlights some of these advancements that have led to the current understanding of the brain’s involvement in the acute and chronic regulation of energy homeostasis.
INTRODUCTION

Feeding, and energy metabolism in general, is the cornerstone of individual and, consequently, species survival. From this perspective, feeding is equivalent in significance with reproductive behavior. The two together represent the backbone for the continuum of most vertebrate species. Therefore, one could argue that the purpose behind the emergence and evolution of the central nervous system was to promote the most effective management of metabolism in support of survival. Both common sense and the experimental data agree with this basic assertion (Clifton et al. 1998). Perhaps then, even higher brain regions, such as the archio- and neocortex, emerged under environmental pressures to support behaviors that more effectively deal with energy balance. Despite this, most of the attention regarding brain regulation of energy homeostasis has focused on more primitive regions of the brain such as the hypothalamus and brain stem (Figure 1). Over the past century, a vast number of observations have been collected, particularly in the past decade owing to the cloning of the ob gene leptin product. This action resulted in a wave of discoveries of new genes and established their relationship to key neuronal structures in the hypothalamus (Seeley & Woods 2003). Recently, investigators have shifted their focus to more complex signal integrations and neuronal adaptations that actually initiate the changes in ingestive behavior and metabolism. This review follows the history behind this line of research and highlights some important new advances.

THE LINK BETWEEN THE PERIPHERY AND THE BRAIN

Brain regions implicated in the regulation of long-term energy balance, by definition, must be able to monitor the amount of available fuel and to communicate this information to the brain. This process involves signal integrations of peripheral metabolic hormones and neuronal responses that arise from peripheral metabolism (Figure 1).
Figure 1
Schematic illustration of brain regions reciprocally connected with the hypothalamus. The hypothalamus is the primary site where metabolic hormones exert their effect. Other brain regions are also targeted by these signals. Key hypothalamic nuclei involved in energy homeostasis include the ARC, VMH, DMH, and LH. The hypothalamic suprachiasmatic nucleus (SCN) serves as the master clock coordinating various central and peripheral functions and the environmental cues. The hypothalamus is reciprocally connected to the cortex and hippocampus, the midbrain dopamine system [the ventral tegmentum (VTA)-nucleus accumbens (NAcc) pathway and the nigrostriatal dopamine projection] and brain stem autonomic regions such as the nucleus of the solitary tract (NST), area postrema (AP), dorsal motor nucleus of the vagus (DX), and the locus coeruleus (LC). Spinal cord projections from the hypothalamus and brain stem are critical regulators of the sympathetic outflow controlling thermogenesis and peripheral metabolism.

Fuel in the body and then use this knowledge to modulate energy intake and expenditure. Which signal(s) convey(s) such information to the brain? Various hypotheses speculated about the nature of these signals. One such proposal, the glucostatic hypothesis (Mayer & Thomas 1967), postulated that small changes in plasma glucose levels trigger meal initiation or termination. This model correlates well with the initiation or termination of feeding per se (the depletion-repletion model of energy intake); however, it does not provide information about, or a mechanism by which to determine, the amount of food
to be consumed, and it correlates poorly with energy expenditure (Woods et al. 1998). Another paradigm that linked food intake to the amount of stored energy (fat mass) in the body was the lipostatic model, which hypothesized that signals proportional to the amount of fat in the body modulate the amount of food eaten at each meal to maintain overall energy balance (Kennedy 1953). Recent developments have supported this model.

Two sets of experiments have been critical to identifying the specific brain structures that are directly involved in energy homeostasis and in linking the “lipostatic” signal to these brain regions. First, various lesion studies that destroyed the hypothalamic ventromedial (VMH), paraventricular (PVN), or dorsomedial (DMH) nuclei induced hyperphagia and obesity (Hetherington & Ranson 1940, Brobeck et al. 1943, Hetherington 1944); whereas lesions in the lateral hypothalamus (LH) led to hypophagia (Anand & Brobeck 1951). This finding led to the proposal of a dual center model that identified the VMH as the “satiety center” and the LH as the “hunger center” (Stellar 1954). Compared with our current knowledge of specific hypothalamic neuronal populations, these lesion studies are strikingly precise in distinguishing between subregions that either promote or suppress feeding and metabolism.

Second, parabiosis studies on hypothalamic lesioned rats concluded the existence of humoral signal(s) in relation to an animal’s lipostatics (Hervey 1959). In these studies, two live animals, one with a lesion in the VMH, were joined by surgical means, which allowed humoral factors to pass from one animal to the other. As obesity developed in the lesioned rat, its partner became hypophagic and lost weight, suggesting that a signal, in proportion to the amount of fat mass, is highly potent in inhibiting food intake. Additional parabiosis studies on genetically obese mutant mice, ob/ob and db/db (Coleman & Hummel 1969, Coleman 1978), concluded that ob/ob mice lack this lipostatic signal, whereas db/db mice are insensitive to it. These hypotheses were later confirmed by cloning the ob gene that encodes leptin (Zhang et al. 1994) and the db gene that encodes leptin receptor (Tartaglia et al. 1995). This soon led to the recognition that all the hypothalamic nuclei associated with energy regulation, i.e., the VMH, DMH, PVN, and LH, are the regions where leptin receptors are highly expressed (Huang et al. 1996, Mercer et al. 1996, Couce et al. 1997). This also promoted gene discoveries, which identified novel neuropeptides, receptors, and transcription factors crucial to mediating leptin effect and led to the detection of the melanocortin system as the key system involved in energy regulation by leptin.

**THE MELANOCORTIN SYSTEM AND LONG-TERM ENERGY BALANCE**

The melanocortin system has been considered the most successful model to explain the neuronal control of long-term energy balance (Figure 2). In this model, the hypothalamic arcuate nucleus (ARC) is critical. The neurons within the ARC are located in an anatomically strategic place, because they are close to fenestrated capillaries at the base of the hypothalamus, giving them access to various humoral signals that are restricted from other portions of the brain (Benoit et al. 2000, Cone et al. 2001). These neurons are innervated by axons containing all major neurotransmitters, synthesize receptors for most metabolic hormones (Benoit et al. 2000, van den Pol 2003), and respond rapidly to nutritional signals (Obici & Rossetti 2003).

Two subsets of neurons that have opposite effects on feeding are found in the ARC; both contain the inhibitory neurotransmitter GABA (Horvath et al. 1997, Hentges et al. 2004). One set of these neurons expresses proopiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART); when stimulated they produce anorectic effects (Boston et al. 1997, Ellacott & Cone 2004). The POMC precursor is cleaved into melanocyte-stimulating hormones (α-, β-,
Figure 2

Schematic illustration of the melanocortin system. The melanocortin system has emerged as the \textit{pinnum movens} in the regulation of energy balance. It consists of two subsets of ARC neurons: the POMC and NPY neurons. Activation of POMC cells by leptin promotes satiety triggered by the release of POMC-driven \(\alpha\)-MSH at target sites where it binds to melanocortin 4 receptor (MC4R). The ARC NPY neurons also express agouti-related peptide (AgRP). These cells are inhibited by leptin but stimulated by ghrelin, which promotes feeding, decreases energy expenditure, and silences POMC neuron firing. The effect of the NPY cells is mediated by three distinct mechanisms: \textit{a}) GABA, \textit{b}) NPY, and \textit{c}) AgRP, an inverse agonist of MC4R antagonizing the anorexigenic effects of \(\alpha\)-MSH. Modified from figure 7 in Cowley et al. 2003.
and γ-MSH), β-endorphin, and adrenocorticotropic hormone (ACTH) (Cone 2005). Of these, α- and β-MSH reduce food intake and body weight and increase energy expenditure in animals and humans (Fan et al. 1997, Biebermann et al. 2006, Lee et al. 2006). Both α- and β-MSH act on melanocortin receptor subtypes 3 and 4 (MC3/4R) (Adan et al. 1994), which are abundant particularly in the ARC, PVN, LH, and DMH (Mountjoy et al. 1994).

The second group of cells in which increased activity leads to orexigenic responses contains neuropeptide Y (NPY) and the agouti gene-related transcript (AgRP) (Ollmann et al. 1997, Baskin et al. 1999a). NPY potently stimulates feeding and reduces energy expenditure (Clark et al. 1984, Stanley & Leibowitz 1984). It is found throughout the central nervous system (Sahu et al. 1988b) with its highest concentration in the ARC (Chronwall et al. 1984). In genetically obese animals, e.g., ob/ob and db/db mice, and animals in a negative energy state, e.g., fasted or lactating animals, the ARC NPY mRNA and protein levels are elevated (Sahu et al. 1988a, Wilding et al. 1993). AgRP is also orexigenic. It acts as a natural antagonist of MC3/4R, thereby reducing the anorectic effect of α-MSH. An ectopic expression of Agouti, an AgRP-like peptide, results in an obese phenotype of the yA agouti mouse (Ollmann et al. 1997).

The use of fluorescent reporter genes that are selectively expressed in specific cells allows the visualization of hypothalamic neuronal subpopulations so that they can be studied in a targeted fashion while they are alive. Using this method, NPY neurons were observed to contact and inhibit nearby POMC cells through the release of GABA (Cowley et al. 2001) (Figure 2). The unidirectional NPY to POMC input (Horvath et al. 1992) may represent a wiring blueprint that favors the tonic inhibition of satiety signals to promote not only feeding, but also overfeeding when food is available in excess.

The POMC and NPY neurons in the ARC function through broad projections to various brain regions, including the PVN, LH, and perifornical hypothalamic region, all of which contain substantial numbers of MC3/4R (Mountjoy et al. 1994, Sahm et al. 1994). The projection from the ARC to the PVN is critical for regulating neurons that produce corticotropic and thyrotropin releasing hormones (CRH and TRH, respectively) and for modulating sympathetic activity, both of which are important mechanisms in energy metabolism (Diano et al. 1998a,b; Cowley et al. 1999). A recent study using a cre/loxP genetic approach showed that mice with mutations to the MC4R gene (loxTB mc4) weighed and ate less if the MC4R gene was restored selectively in the PVN via viral or genetic manipulations (Balthasar et al. 2005). However, the restoration of the MC4R in the PVN was not sufficient to bring energy expenditure levels to those of controls, suggesting that energy expenditure is regulated by melanocortins elsewhere in the hypothalamus or through receptors other than MC4R.

Two independent groups recently showed that intact melanocortin neuronal circuitry is important for acute feeding regulation (Gropp et al. 2005, Luguet et al. 2005). The studies were inspired by the observations that neither NPY nor AgRP single-gene knockout (Erickson et al. 1996) nor NPY/AgRP double-knockout mice (Qian et al. 2002) exhibited the expected hypophagia. To test if the NPY and POMC neurons themselves are crucial in mediating adult energy balance, both groups used the cell-targeted expression of diphtheria toxin receptors that do not exist in mice, making these animals “immune” to diphtheria toxin-induced necrosis. When the otherwise normally developing diphtheria toxin receptor–expressing mice were injected with diphtheria toxin, the targeted hypothalamic neurons rapidly died, resulting in hypophagia in NPY neuron–ablated mice (Gropp et al. 2005, Luquet et al. 2005) and hyperphagia in POMC neuron–ablated animals (Gropp et al. 2005). However, ablation of NPY cells in the early postnatal period did not result in an overt metabolic phenotype (Luguet et al. 2005), contending that the function of degenerated
neurons in critical developmental periods is compensated by reorganization of the circuits.

MODULATION OF MELANOCORTIN CIRCUITS FROM THE SATIETY CENTER, THE VMH

The VMH was implicated in energy balance when electrolytic lesions to this region in rats resulted in hyperphagia and obesity (Hetherington & Ranson 1940, Brobeck et al. 1943). Subsequent studies employing chemical lesions and pharmacological methods have since supported the idea that the VMH is a key hypothalamic nucleus that inhibits feeding and increases metabolism (Tejwani & Richard 1986, Bagnasco et al. 2002). The VMH was later determined as one of a few key regions in the hypothalamus where the long form leptin receptors are highly expressed and, therefore, is the region mediating leptin's effect on homeostasis (Mercer et al. 1996). Despite the early discovery of the anorectic effect of the VMH, little is known regarding the cellular mechanisms by which VMH neurons control homeostasis under the control of leptin or other signals. With the discovery of the importance of ARC NPY and POMC neuronal circuits (Horvath et al. 1992, Elias et al. 1998a, Hahn et al. 1998), research interests shifted from the VMH to the ARC.

Recent studies, however, showed that the antiobesity effect of leptin is only partially mediated by neurons in the ARC, and the cells in the VMH are equally important in mediating leptin's effect on energy control. For example, the animals with the leptin receptor selectively deleted in POMC neurons were, surprisingly, at best only mildly obese and ate amounts of food similar to controls (Balthasar et al. 2004). In contrast, a selective deletion of the leptin receptor gene in the neurons that express steroid factor-1 (SF-1) in the VMH results in mice that are obese and hyperphagic (Majdic et al. 2002, Dhillon et al. 2006). SF-1 is a transcription factor necessary for the development of the VMH (Parker et al. 2002, Davis et al. 2004). Mice with mutations to leptin receptors in both the ARC POMC and the VMH SF1 neurons are more obese than are those with mutations of leptin receptors in either set of neurons alone, suggesting that the VMH's antiobesity function is independent of that of the ARC (Dhillon et al. 2006). This finding is consistent with the early observations from the VMH lesion studies and also helps explain why leptin simultaneously acts on both the ARC and the VMH.

But what exactly is the mode of action of the VMH neurons in the context of hypothalamic feeding circuits? A recent study showed that the VMH may increase the activity of POMC neurons by microcircuits (Sternson et al. 2005) that were previously difficult to detect by conventional tracing methods (Saper et al. 1976, Canteras et al. 1994). Using laser scanning photo-stimulation (LSPS) in combination with slice electrophysiology, the inputs from the VMH neurons were found excitatory upon the POMC cells. The inputs decrease during a fast (Sternson et al. 2005). Further investigation is required to determine whether these VMH neurons receive leptin signaling directly.

Conversely, the activity of the VMH may be modulated by afferent projections from the ARC. The inputs from the ARC to the VMH tend to be less dense than those to other nuclei (Zaborszky & Makara 1979), yet the VMH contains MC4R, as well as NPY Y1, Y2, and Y5 receptors (Bouali et al. 1995, Lopez-Valpuesta et al. 1996, Harrold et al. 1999, Wisialowski et al. 2000), suggesting that both POMC and NPY neurons project to the VMH. Infusions of NPY into the VMH increase feeding, and fasting is associated with elevated NPY in this region (Bouali et al. 1995). Electrophysiological responses of neurons in the VMH to α-MSH are decreased in animals that are fasted or treated with AgRP prior to sacrifice compared with animals that have free access to food (Li & Davidowa 2004).

Notably, brain-derived neurotrophic factor (BDNF), which affects both glucose and
lipid metabolism (Nakagawa et al. 2002, Tsuchida et al. 2002), is highly and specifically expressed in the VMH. Genetic deficiencies of BDNF or its TrkB receptor resulted in obesity in both humans and mice (Rios et al. 2001, Xu et al. 2003). Leptin increases BDNF transcripts (Komori et al. 2006), whereas fasting decreases them selectively in the VMH, suggesting that BDNF is a regulatory component of leptin signaling. The possibility exists that synaptic plasticity in the hypothalamus may be a part of the regulatory mechanism of energy regulation because BDNF in the brain is known to promote synaptic morphology and function (Rios et al. 2001). Remarkably, the anorectic effects of BDNF are not mediated directly by the melanocortin system because BDNF reduces the body weight and food intake of mice that lack the MC4R (Xu et al. 2003), yet neurons in the VMH form excitatory inputs on POMC neurons in the ARC (Sternson et al. 2005); this suggests that the VMH may influence POMC neuroactivity by other means such as classic neurotransmitters and/or plasticity.

THE LATERAL HYPOTHALAMIC AROUSAL/FEEDING SYSTEM

Two subsets of neurons have been identified within the LH: One group contains hypocretin (orexin), a peptide implicated in arousal and feeding, and the other contains melanin-concentrating hormone (MCH), another potent stimulator of food intake. Both populations are connected with POMC and NPY neurons of the ARC, suggesting that their function in motivating food intake is associated with the melanocortin system (Qu et al. 1996, Elias et al. 1998b, Sakurai et al. 1998, Dube et al. 1999, Horvath et al. 1999a, Tritos et al. 2001). Both hypocretin and MCH neurons have a wide projection field and modulate a variety of behavioral responses related to learning, memory, emotion, motivation, and motor responses in association with changes in the energy state (Broberger et al. 1998a, Ludwig et al. 1998, Peyron et al. 1998, Saito et al. 2001). Although the projections of hypocretin and MCH neurons exhibit significant overlap, their overall effects and actual targets are quite different (Broberger et al. 1998a, Horvath et al. 1999a). The activity of hypocretin and MCH neurons is regulated by numerous hormones including leptin and ghrelin, as well as by practically every neurotransmitter system (Elias et al. 1998b, Hakansson et al. 1998, Torrealba et al. 2003, Toshinai et al. 2003, Sakurai et al. 2005). Within the LH, hypocretin and MCH neurons have reciprocal connections with each other and with nearby neurons (Guan et al. 2002). Electrophysiological studies in brain slices or isolated neurons indicated that hypocretin, in general, has a stimulatory effect on LH neurons including MCH neurons (Li et al. 2002, van den Pol et al. 2004), whereas MCH depresses the synaptic activity of glutamate and GABA neurons from the rat LH (Gao & van den Pol 2001). Whether such electrical interactions between hypocretin and MCH neurons, at the intensities and dynamics observed, are relevant to feeding and long-term homeostasis, or if they are related more to arousal behavior, is unclear.

Hypocretin and MCH neurons directly integrate metabolic signals to modulate energy balance, and they do so, more or less, independent of each other, despite their proximate location and physiological interaction in the LH. Hypocretin neurons are rapidly activated by fasting (Diano et al. 2003) and exhibit leptin-dependent synaptic plasticity during fasting (Horvath & Gao 2005). Hypocretin mRNA levels in the LH are upregulated upon fasting (Sakurai et al. 1998). Notably, all the hypothalamic neurons activated by fasting receive strong hypocretin input (Diano et al. 2003). These observations, together with the earlier demonstration of a massive hypocretin input to the ARC, particularly to the NPY cells (Horvath et al. 1999a), the dependence of hypocretin function on NPY Y1 and Y5 receptors (Jain et al. 1999, Yamanaka et al. 2000), and a synergistic action between NPY and
hypocretin (at low concentrations) to induce feeding (Sahu 2002) argue that hypocretin neurons may be upstream to the NPY system with regard to feeding and metabolism. Mice with deletions of the hypocretin gene are hypophagic but maintain normal growth curves, suggesting a reduced metabolic rate in these mice (Willie et al. 2001). This, in association with the critical role of hypocretin neurons to promote arousal (Chemelli et al. 1999) through direct projections to the brain stem including the locus coeruleus (Horvath et al. 1999b), makes it a possibility that the hypocretin neurons provide a link between obesity and insomnia (Horvath & Gao 2005).

MCH, however, shows little or no interaction with NPY or hypocretin in inducing food intake when injected together into the third ventricle of the rat (Sahu 2002). These observations provide physiological evidence concomitant to the preexisting morphological data that shows that the strength of MCH projections to the ARC is limited compared with that of the hypocretin neurons. However, like NPY, MCH does exhibit characteristics of orexigenic genes: Its mRNA levels are increased in obese mutants, fasting further elevates its expression in both normal and obese mutants (Qu et al. 1996), and it has a potent orexigenic effect. Targeted deletion of the MCH gene resulted in a phenotype of hypophagia and leanness with a higher metabolic rate (Shimada et al. 1998). Thus, MCH is a typical “thrift gene” that increases energy intake and reduces energy expenditure simultaneously. Consistent with this finding, MCH suppresses thyroid stimulating hormone (TSH) release (Kennedy et al. 2001).

In contrast to hypocretin, which acts, at least in part, through NPY, MCH competes with the action of α-MSH, a mechanism conserved from skin color regulation in fish to hypothalamic control of energy balance in mammals, such that MCH administration increases feeding, whereas α-MSH acts to decrease it. When the two peptides are administered together, depending on the relative dose, one antagonizes the action of the other (Ludwig et al. 1998). Recently, a mouse model of MCH neuron ablation was generated by expressing a toxin gene, ataxin-3, targeted at MCH neurons (Alon & Friedman 2006). Mice that express this gene have a chronic loss of MCH neurons. The phenotype of these mice highly resembles that of mice lacking only the MCH gene. They exhibit reduced food intake and increased energy expenditure. Moreover, the ablation of MCH neurons in mice with an ob/ob mutant background resulted in improved obesity and glucose tolerance. Thus, the function of MCH cells in energy regulation may be limited to the MCH system itself but not to other aspects of the cells such as their classic neurotransmitter function and synaptic plasticity, which are distinct from NPY cells.

MIDBRAIN DOPAMINE SYSTEM: THE MOTIVATION OR INCENTIVE TO EAT

Dopamine is broadly involved in the regulation of arousal, locomotor activity, mood, and reward (Wise 2002). Dopamine deficiency in mice, generated by selective inactivation of tyrosine hydroxylase, markedly suppresses food intake in a manner similar to that of lesions of the LH (Szczypka et al. 1999). These mice fail to eat in response to acute glucose deprivation (Hnasko et al. 2004), PYY administration, or leptin deficiency (Szczypka et al. 2000), suggesting that dopamine signaling is required downstream of the melanocortin system to promote feeding. Investigators have implicated dopaminergic neurons within the midbrain ventral tegmental area (VTA) that innervate the nucleus accumbens (the ventral striatum) in the rewarding aspect of food, sex, and drugs of abuse (Volkow & Wise 2005). Supporting a role for the mesolimbic reward circuitry in feeding regulation, one study recently found that interfering with ghrelin signaling specifically in the VTA diminished ghrelin-induced feeding (Abizaid et al. 2006). However, the restoration of dopamine production within the dorsal striatum restores feeding on normal chow, whereas restoration
of dopamine in the nucleus accumbens does not. Although these findings may suggest a fundamental difference between feeding for nourishment and food as a rewarding substance (Szczypka et al. 2001), a similar study in human subjects argues in the same vein: By using [(11)C]-raclopride positron emission tomography (PET) scanning, Small et al. (2003) found that feeding is associated with dopamine release in the dorsal, but not the ventral, striatum, and yet the amount of dopamine released correlated with the degree of pleasure experienced. Further investigations are needed to discern the role of VTA versus nigral dopamine neurons in the regulation of feeding and energy homeostasis (Cannon & Palmiter 2003, Sotak et al. 2005).

Nevertheless, feeding is associated with motivational mechanisms, which are important for the behavioral responses necessary for seeking food (Berridge 1996). Hypothalamic peptides such as NPY, α-MSH, AgRP, hypocretin, and MCH, however, modulate the activity of dopaminergic neurons that target the nucleus accumbens (Berthoud 2002). The ARC funnels metabolic information from signals such as leptin to modulate the activity of the mesolimbic dopaminergic system via direct projections to the nucleus accumbens or indirectly through the activation of hypocretin or MCH neurons that also project to both the VTA and the nucleus accumbens (Berthoud 2002). Emerging evidence, however, supports the notion that at least the VTA is sensitive to leptin, insulin, and ghrelin and that the activity of dopaminergic neurons within the VTA can be modulated by these signals (Guan et al. 1997, Figlewicz 2003, Zigman et al. 2006). The implications of these observations and their interpretation remain controversial. Further research may reveal that, in contrast to the funnel hypothesis, metabolic signals could act directly on reward systems, including dorsal striatum, to modulate the motivational aspect of feeding in tandem with homeostatic systems (Fulton et al. 2000, Figlewicz 2003), although perhaps in a more sophisticated way.

OTHER HYPOTHALAMIC REGIONS THAT REGULATE FOOD INTAKE AND BODY WEIGHT

Other hypothalamic nuclei such as the DMH and the suprachiasmatic nucleus (SCN) also express receptors for leptin and ghrelin, suggesting that these hormones directly target these nuclei (Hakansson et al. 1998, Zigman et al. 2006). The DMH has long been implicated in energy regulation, yet its actual role remained vague until recently. The DMH modulates glucocorticoid secretion, body temperature, arousal, and circadian rhythms of locomotor activity (Chou et al. 2003). It receives inputs from cells in the ARC and regions in the brain stem associated with feeding (Bellinger & Bernardis 2002). Lesions restricted to the DMH typically result in hypophagia, although animals can still maintain their body composition (Bellinger & Bernardis 2002). Recently, Gooley et al. (2006) found the DMH to be critical for the entrainment of circadian rhythms to feeding schedules. The DMH of animals with restricted access to food (4 h/day) exhibited an increased expression of c-Fos, indicating an increased cellular activation at a time when the food was presented compared with animals that had free access to food throughout the day. Ibotenic lesions of the DMH resulted in reduced levels of locomotor activity and decreased food intake. When lesioned rats were placed on the restricted feeding schedule, they showed less preprandial increases in food anticipatory locomotor activity than those of sham-operated animals. DMH lesions also blocked the rise in body temperature that is entrained to the timing of food presentation (Gooley et al. 2006). The nature of the cells within the DMH remains obscure. A number of these cells are glutamatergic and project to the PVN and preoptic area; both are involved in the circadian regulation of corticosteroid secretion and body temperature (ter Horst & Luiten 1986, Bellinger & Bernardis 2002). Projections from the DMH...
to the LH and ventrolateral preoptic area may be involved in the control of sleep and arousal and may be related to the enhanced activity of animals in restricted feeding schedules (Chou et al. 2002).

**THE CAUDAL BRAIN STEM: AUTONOMIC CONTROL OF EATING**

The caudal brain stem contains neurons that are involved in autonomic control of ingestion, digestion, and absorption of food (Berthoud 2004), and it does so without the participation of the forebrain (Grill & Kaplan 2002a), just as is the case for respiration and circulation. The regulation of nutrient supply is largely autonomically organized in the brain stem; it generates most of the parasympathetic support for ingestive and digestive processes through the vagus nerve, as well as sympathetic responses related to severe energy depletion and expenditure. The brain stem has immediate access to the locomotor and oromotor apparatus, which enables the approach to food and orchestrates the ingestion of food and fluids that are placed into the oral cavity. Furthermore, it can terminate ingestion when the taste is aversive or when visceral sensors detect noxious stimuli. Thus, complete ingestive behavior and energy balance cannot occur without the circuits within the brain stem (Grill & Kaplan 2001).

The caudal brain stem can sufficiently control meal size, which involves signals arising from the mouth and gastrointestinal tract upon sensing the chemical or mechanical properties of food. These signals are relayed to the nucleus of the solitary tract (NST) via the vagus and other cranial nerves (Travers & Norgren 1991). In a chronic decerebrate rat preparation, the taste concentrations, gastric preloads, and cholecystokinin (CCK; a peptide released from intestinal endocrine cells during feeding) levels all affected the meal size in a manner similar to that of intact rats. Thus, the brain stem isolated from its forebrain connection exhibits the basic behavior of satiety (Grill & Norgren 1978). The specific neural pathways necessary for the satiety response have not yet been identified. CCK is required for this response (Silver et al. 1989), which also involves neurons in the NST as well as the dorsomotor nucleus of the vagus (DMV), and is blocked by vagal deafferentation (Smith et al. 1985). In addition to the control of meal size, decerebrate rats also show a fully formed sympathoadrenal response to systemic 2-deoxy-D-glucose (2-DG) administration, a glucoprivic agent that reduces cellular ATP levels (DiRocco & Grill 1979), indicating that the brain stem houses a complete system responsive to glucoprivation. However, decerebrate rats cannot increase meal size appropriately in response to food deprivation (Seeley et al. 1994) and, therefore, respond inadequately to a long-term homeostatic challenge (Grill & Kaplan 2001).

Consistent with these findings, peripheral hormones such as leptin, ghrelin, and insulin, neuropeptides such as α-MSH and CRH, as well as nutrients such as glucose (administered locally to the brain stem) all yield potent effects on food intake and body weight similar to their effects in the hypothalamus (Grill et al. 2002, Zheng et al. 2005). Consistent with this, the LRb is found throughout the DVC (area postrema, nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve) and in various other structures in the caudal brain stem (Grill et al. 2002). The localized stimulation of these receptors reduces food intake and body weight (Jacob et al. 1997). Ghrelin receptors are expressed in the area postrema and nucleus tractus solitarius of the brain stem (Bailey et al. 2000, Lawrence et al. 2002). Ghrelin delivered to the fourth ventricle significantly increased cumulative food intake, with maximal response ~3 h after injection. In a separate experiment, ghrelin microinjected unilaterally into the DVC significantly increased food intake measured 1.5 h and 3 h after treatment (Faulconbridge et al. 2003). Conversely, unilateral DVC injection of both MC3/4R and CRH1/2R agonists resulted in suppression of food intake, whereas
an MC3/4R antagonist induced hyperphagia (Grill et al. 1998, 2000, Williams et al. 2000). The brain stem also contains glucose-sensitive neurons that are involved in sympathoadrenal and ingestive responses to glucopenia (Ritter et al. 1981). Thus, regions in the brain stem play critical roles in both ascending and descending pathways in association with feeding and energy expenditure.

**SIGNALING MECHANISM OF METABOLIC HORMONES**

Almost all the important metabolic hormones target hypothalamic nuclei associated with energy control (Figure 3). These include leptin, ghrelin, insulin, estrogen, prolactin, glucocorticoids, interleukins, and resistin (Woods et al. 1998, Kojima et al. 1999, Bray 2000), as well as nutrients such as glucose and lipids (Lam et al. 2005a,b, Lee et al. 2005, Seeley & York 2005). Among these, we focus on leptin and ghrelin because of their important and contrasting effects on homeostasis.

**Leptin Signaling through the Long Form Leptin Receptor, LRb**

Leptin receptors (LRs) are encoded by a single gene in both rodents and humans (Tartaglia et al. 1995, Chen et al. 1996). Six variants (Figure 3) have been identified so far, which differ in their 3′ portions of the proteins generated upon alternative splicing (Tartaglia 1997, Chua et al. 1997). The LRb that possesses the longest intracellular domain of 302 residues is evolutionarily conserved among species. Genetic studies of various LR mutations revealed that mice that lack only LRb exhibit a phenotype indistinguishable from that of leptin-deficient and leptin receptor gene–deleted mutants. Thus, energy homeostasis is mediated solely by LRb (Baumann et al. 1996, White et al. 1997). LRb phosphorylation in the intracellular domain (pY1138) by JAKs is necessary to recruit STAT3 to the LRb/JAK complex (Baumann et al. 1996, White et al. 1997, Banks et al. 2000) and STAT3 phosphorylation (pY705). The subsequent dimerization and nuclear transport of STAT3 result in the change of cell transcription (Schindler & Darnell 1995). STAT3 directly activates POMC transcription and inhibits that of NPY, thus exerting an anorectic effect; whereas deficiencies in STAT3 in the brain result in obesity and diabetes (Bates et al. 2003, Gao et al. 2004), a phenotype resembling leptin and leptin receptor mutants.

Leptin activation of the PI3K pathway is mediated by a JAK2-dependent activation of the insulin receptor substrate-2 (IRS-2) protein via a YMXM motif that binds to and activates PI3K (Araki et al. 1994). IRS-2 mutants exhibit increased fat and leptin and are hyperphagic with decreased energy expenditure (Withers et al. 1998), suggesting a functional leptin resistance (Burks et al. 2000). Pharmacological inhibition of PI3K in the hypothalamus blocks the anorectic effect of leptin (Niswender et al. 2001, Zhao et al. 2002). PI3K regulates the electrophysiological properties of hypothalamic neurons (Spanswick et al. 1997, Plum et al. 2006) and the function of the sympathetic nervous system, which contribute to the reduction in feeding (Rahmouni et al. 2003).

Leptin activates the MAPK family of the extracellular signal–regulated kinase (ERK)
pathway in the hypothalamus, which is required for LRβ-mediated c-fos expression in cells (Banks et al. 2000) and leptin-induced c-fos in POMC neurons (Elias et al. 1998a). Phosphorylation of Y985 in the LRβ is crucial for the initiation of MAPK activity by recruiting the SH2 domain-containing tyrosine phosphatase-2 (SHP-2) and its recruitment of the growth-factor-bound protein-2 (GRB2) (Bjorbaek et al. 2001). The STAT3 pathway-induced feedback inhibitor, the suppressor of cytokine signaling 3 (SOCS3) (Song & Shuai 1998, Baskin et al. 2000, Dunn et al. 2004), competes with SHP-2 for Y985. A brain knockout of SHP-2 showed a severe obese phenotype (Zhang et al. 2004), whereas SOCS3 is involved in region-specific leptin resistance in the hypothalamus of diet-induced obese mice (Munzberg et al. 2004). SOCS3 knockout in the brain results in elevated leptin sensitivity and resistance to diet-induced obesity (Mori et al. 2004). How (or whether) these leptin signaling pathways coordinate to modulate the function of hypothalamic feeding circuits is an open question. One position states that the PI3K pathway is crucial for STAT3 phosphorylation in the hypothalamus, which involves phosphodiesterase 3 (PDE3), an enzyme that decreases cyclic AMP levels in the cells (Zhao et al. 2002). We do not yet know whether the MAPK pathway also interacts with STAT3 signaling in energy regulation.

**Ghrelin Signals through GHSR1α Receptors in Energy Metabolism**

Ghrelin, a peptide hormone of 28 amino acids secreted by the stomach, represents an opposing signal to leptin in that its administration increases feeding and adiposity and reduces metabolism (Kojima et al. 1999, Tschop et al. 2000) (Figure 3). Like leptin, ghrelin produces these effects by acting on hypothalamic feeding systems (Tannenbaum et al. 1998, Willesen et al. 1999). In fact, most ghrelin effects can be obtained by its central administration (Tschop et al. 2000). Two ghrelin receptor subtypes have been identified: the growth hormone secretagogue receptor-1a and -b (GHSR 1a and 1b) (Smith et al. 2004). Leptin and ghrelin receptors are both expressed throughout the hypothalamus and central nervous system (Guan et al. 1997) with considerable overlap. The colocalization of LRβ and GHSR1a in the hypothalamic NPY (Mondal et al. 2005) has also been observed, suggesting that these hormones oppose each other in common cells to maintain energy balance (Zigman et al. 2006).

Conceivably, less is known about intracellular signaling of ghrelin in energy homeostasis. This may sound paradoxical because GHSR1 was identified 10 years ago (Howard et al. 1996, McKee et al. 1997). In fact, ghrelin was initially discovered by reverse pharmacology using GHSR1 as a template (Kojima et al. 1999). GHSR1s are G protein-coupled seven-transmembrane domain receptors (Howard et al. 1996). In the brain, they are present on both pre- and postsynaptic membranes. The key receptor involved in feeding responses triggered by ghrelin is GHSR1a, whereas GHSR1b is devoid of signaling in response to ghrelin mimetics (Smith 2005).

Proposed signal transduction mechanisms underlying ghrelin function involve the regulation of ionic currents and protein phosphorylation-based intracellular signaling. The binding of ghrelin to GHSR1a causes conformational changes of intracellular loops of the receptors, which expose binding sites to G proteins. The coupling of G proteins to GHSR1a promotes guanosine diphosphate (GDP) release and guanosine triphosphate (GTP) binding to the G protein α subunit, thus activating G protein subunits to initiate intracellular signaling cascades by acting on various downstream effectors. For example, the regulation of ionic currents may be triggered by a Gaq/11 protein that activates phosphatidylinositol-specific phospholipase C (PI-PLC) to generate inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol...
Intracellular signaling of leptin and ghrelin. (a) Six splice variants of leptin receptors, the LRa–f, have been identified. The long-form, LRb, activates STAT3 and is fully responsible for the leptin-regulated phenotype. (b) Three signal pathways, the JAK/STAT, PI3K, and MAPK, are activated upon leptin binding of LRb. The JAK/STAT3 pathway may play a dominant role in mediating leptin effect. Both PI3K and MAPK are involved in energy homeostasis. (c) The binding of ghrelin to GHS-R1a results in conformational changes of intracellular loops of the receptors, which expose binding sites to G proteins. The coupling of G proteins to GHS-R1a promotes the release of GDP and binding of GTP to the G protein α subunit, thus activating G protein subunits to initiate signaling cascades. The regulation of ionic currents is triggered by a Gaq/11 protein that activates phosphatidylinositol-specific phospholipase C (PI-PLC) to generate inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-diphosphate (PIP2). IP3 mobilizes intracellular Ca2+. Increased calcium and DAG levels activate PKC, which, in turn, inhibits the K+ channels and causes cellular depolarization. (d) Ghrelin activates protein phosphorylation-based intracellular signaling, including the MAPK and PI3K pathways through various G protein subunits, including Gq and a PTX-sensitive G protein (G11iα).
4,5-diphosphate (PIP₂) (Howard et al. 1996, McKee et al. 1997). IP₃ mobilizes intracellular Ca²⁺ from IP₃-sensitive stores. Increased calcium and DAG levels activate PKC, which, in turn, inhibits the K⁺ channels and causes cellular depolarization (Camina 2006) (Figure 3). Ghrelin also activates protein phosphorylation-based cell signaling including MAPK and PI3K cascades in different cellular systems to promote proliferation (Mazzocchi et al. 2004, Kim et al. 2004) through various G protein subunits,

![Diagram](image-url)
including Gq and a PTX-sensitive G protein (G_{i/o}) (Camina 2006). The implication of ghrelin’s effect in energy homeostasis is not clear. In the hypothalamus, ghrelin was recently found to enhance the activity of 5′-AMP-activated protein kinase (AMPK). AMPK activity is strongly implicated in energy homeostasis and is downregulated by leptin administration in the hypothalamus (Andersson et al. 2004, Carling 2005). The mechanism by which ghrelin stimulates AMPK activity is not yet understood.

**NEURONAL RESPONSES TO PERIPHERAL HORMONES**

A large body of data has emerged regarding the intracellular signaling of various hormones in the hypothalamus. Transcriptional events have been described to support overall cellular alterations. However, Cajal’s neuronal doctrine predicts that functional outcomes of circuit alteration should stem from altered firing and/or connection (synaptology) of neuronal networks. Mounting evidence suggests that peripheral hormones accomplish just this in the hypothalamus as well.

**Acute Neuronal Responses to Peripheral Hormones**

With selective labeling of particular neuropeptide-producing cell groups, the two critical components of the melanocortin system, the orexigenic NPY neurons and the anorexigenic POMC neurons, both responded to peripheral hormones in an acute fashion in slice preparations: Firing of POMC cells is enhanced by leptin via both pre- and postsynaptic modes of action (Cowley et al. 2001), whereas the firing frequency of NPY neurons is diminished by leptin (van den Top et al. 2004). The gut-derived, appetite-stimulating hormone, ghrelin, however, was observed to enhance the firing rate of NPY neurons via a direct mechanism while it diminished the frequency of action potential of POMC cells predominantly by a presynaptic mode of action (Cowley et al. 2003) (Figure 4). Leptin’s acute action on neuronal function was tied to a nonspecific cation channel (Spanswick et al. 1997), whereas the mechanism of action of ghrelin is yet to be determined, although it may require GHSR signaling (Abizaid et al. 2006). The pancreas-derived hormone, insulin, also affected neuronal firing in the arcuate nucleus, an event that is mediated by ATP-sensitive potassium channels (Spanswick et al. 2000).

Considering the limitations of slice electrophysiology, whether any of these peripheral signals are present physiologically at quantities high enough to alter action potential generation in the above-described circuitry in vivo is a reasonable yet unresolved question.

**Synaptic Plasticity Driven by Peripheral Metabolic Hormones**

Cajal’s neuronal doctrine also predicts that the output of a neuronal population is greatly influenced by its input organization. Thus, the inquiry into whether various metabolic states might correlate with different synaptology on the melanocortin cells is a logical line of pursuit. Indeed, the hypothalamus retains plasticity throughout life, and immature synapses can frequently be found in the adult hypothalamus (Figure 4). For example, the magnocellular system shows plasticity during changes in water homeostasis (Theodosis et al. 1991, Miyata et al. 1994, Stern & Armstrong 1998); in the ARC, the synaptic organization of unidentified neurons exhibited changes in response to a varying gonadal steroid milieu (Garcia-Segura et al. 1994, Parroduz et al. 2003); the synaptology of the perikarya of luteinizing hormone-releasing hormone neurons varies during changes in the gonadal steroid milieu (Zsarnovszky et al. 2001) or in photoperiod lengths (Xiong et al. 1997). Nevertheless, synaptic plasticity was not considered an important aspect in daily energy regulation. Recent observations, however, suggest that it may be a regulatory component in the hypothalamic control of
Immaturity of synapses on fasted Hcrt perikarya. Electron micrographs (a–g) showing consecutive serial sections of a bouton (red asterisks in a–g) that establishes an ambiguous (immature) synaptic membrane specialization on an Hcrt-immunolabeled neuronal perikaryon (diffuse immunoperoxidase precipitation in the cytosol). The large blue arrowhead in the enlarged inset of panel d points to a postsynaptic density. The synaptic membrane specialization is ambiguous because the typical membrane specialization of an asymmetric connection (also seen between another presynaptic bouton and the Hcrt perikaryon on panel f) is visible only through a limited extent of the synapse. Boxed area on a shows a clathrin-coated pit associated with this synapse. Bar scale on a represents 1 μm for panels a–g.
energy balance. First, leptin replacement in \textit{ob/ob} mice indicated that synaptic rearrangement of feeding circuits is part of an ongoing general phenomena. Furthermore, robust effects of peripheral ghrelin injections on the input organization of POMC neurons of mice led to wiring different from that induced by leptin (Pinto et al. 2004). In addition, leptin robustly regulated the synaptic organization of lateral hypothalamic hypocretin/orexin neurons (Horvath & Gao 2005), and ghrelin produced a rapid effect on synaptic formation in the hippocampus (Diano et al. 2006) and VTA (Abizaid et al. 2006). In these latter studies, ghrelin promoted the propagation of long-term potentiation in the hippocampal formation enhancing learning and memory consolidation (Diano et al. 2006), and it caused the release of dopamine in the nucleus accumbens associated with synaptic changes in the ventral tegmentum (Abizaid et al. 2006) (Figure 5). In addition, estrogen, a gonadal steroid with effects on food intake and energy metabolism, has recently been found to alter energy metabolism by altering the synaptic organization of the arcuate nucleus melanocortin system (Gao et al. 2007).

One important issue remaining unresolved is whether these synaptic alterations have an effect on neuronal activity and then on the metabolic phenotype. Although this remains to be proven, a task that is daunting even still for long-term potentiation and depression (Malenka & Bear 2004), these changes occur both preceding and concomitant to the varying behavioral and endocrine outputs. Even if it does not directly affect action potentials, the change of synaptology on NPY/POMC perikarya may affect the set point of these cells under various circumstances. The intracellular signaling that brings about these rapid changes and the parent cells of the altered inputs in wiring will need further investigation. Another fundamental question regarding synaptic changes is whether ghrelin/leptin signaling is required on the pre- and/or postsynaptic sites. Upon the association between ghrelin-induced synaptic changes and the dependence of ghrelin’s electrophysiological action in the VTA (Abizaid et al. 2006) and hypothalamus (Pinto et al. 2004) on presynaptic mechanisms, these morphological changes likely represent activity-dependent synaptic plasticities (Figure 6). Indeed, the hypothalamic NPY neurons that respond directly to ghrelin without presynaptic mediation (Cowley et al. 2003) showed no synaptic changes on their perikarya (Pinto et al. 2004) in the same ghrelin paradigm that showed synaptic changes on VTA dopamine and hypothalamic POMC neurons. One important conclusion from these studies is that synaptic plasticity is inherent to the circuits that govern appetite. Because this network is becoming well characterized to show a direct relationship between an identifiable set of neurons and a primitive behavior independent of conditioning, for example, learning and memory consolidation paradigms (Gropp et al. 2005, Luquet et al. 2005), it may become more attractive to develop an experimental paradigm that could directly assess the causal relationship between synaptic plasticity and behavior (Malenka & Bear 2004).

**FUEL SENSING AND ENERGY BALANCE**

Hypothalamic neurons, particularly those in the ARC and VMH, directly respond to body metabolic fuels (Oomura & Yoshimatsu 1984; Storlien 1985; McCrimmon et al. 2004; Minokoshi et al. 2004; Lam et al. 2005a,b; Pocai et al. 2006). One of these mechanisms includes an increase in AMPK activity in response to a decrease in the ratio of AMP/ATP (Lee et al. 2005). The activation of AMPK favors cellular responses generated to increase ATP levels including increases in the synthesis and uptake of glucose and fatty acids by most cells. Hypothalamic neurons have a similar nutrient-sensing mechanism (McCrimmon et al. 2004, Minokoshi et al. 2004). Thus, fasting or treatment with 2-deoxy-D-glucose (2-DG) increases the activity of AMPK in the hypothalamus (Kim et al. 2004b).
Figure 5

Fingerprinting the input organization: association between anatomy and electrophysiology. For fingerprinting the input organization of a given set of neurons, the combination of electron-immunofluorescence microscopy, which determines the structural characteristics and neurotransmitter content of synapses (a), and analysis of miniature excitatory/inhibitory postsynaptic currents (mEPSC/mIPSC) is more insightful. For example, we observed that mEPSCs are increased on midbrain dopamine neurons in response to peripheral ghrelin injection, an event that was associated with increased apposition between vesicular glutamate transporter 2 (vGlut2)-containing axon terminals and dopamine perikarya (b). In the same preparation, ghrelin decreased mIPSC frequency paralleled by decreased apposition between glutamic acid decarboxylase (GAD)-containing, putative GABAergic terminals and the dopamine cells.
Hormone action in the brain involves synaptic plasticity. To date, all brain regions directly targeted by metabolic hormones show some extent of plasticities in response to the changes of hormonal milieu. In the arcuate nucleus (a), both leptin and ghrelin alter the synaptology of POMC neurons in support of either satiety (leptin) or hunger (ghrelin). In the lateral hypothalamus (b), leptin-dependent reorganization of excitatory inputs and miniature EPSC were observed on hypocretin (Hcrt) neurons in response to fasting in a manner that promotes increased arousal. In the ventral tegmentum (c), dopamine neurons showed rapid changes in the GABAergic and glutamatergic inputs in response to ghrelin in association with increased dopamine neuronal activity and feeding. Ghrelin also altered synaptic spine density in the hippocampus (d) in parallel with increased propagation of LTP and enhanced performance of animals in various behavioral tasks.

Hypothalamic cells are also sensitive to circulating free fatty acids likely mediated by AMPK (Kim et al. 2004, Landree et al. 2004). Free fatty acids diffuse into hypothalamic neurons and are esterified and transferred into the mitochondria for oxidation, which ultimately leads to increased feeding (Obici & Rossetti 2003). The transfer of esterified fatty acids
into the mitochondria is mediated by the activity of carnitine-dependent acyltransferases 1 and 2 (CPT1 and 2). Although activity is increased upon glucose utilization, malonyl-CoA decreases the activity of CPT1 and thus the oxidation of fatty acids, whereas increases in AMPK activity lead to decreased formation of malonyl-CoA and ultimately increased fatty acid oxidation (Obici & Rossetti 2003, Lam et al. 2005a).

The activation of AMPK may gate hypothalamic responses to peripheral hormones as well, given that leptin decreases and ghrelin increases hypothalamic AMPK activity (Minokoshi et al. 2002, Kola et al. 2005). Like ghrelin, AgRP or mutations in the MC4R also result in increased hypothalamic AMPK activity, whereas MTII, a melanocortin agonist, decreases it, supporting the idea that the melanocortin system is critical for this enzyme to function (Minokoshi et al. 2004).

The relationship between intracellular energy sensing and subsequent biochemical adaptations in hypothalamic neurons is still poorly understood. Mitochondrial uncoupling proteins, e.g., UCP2, may play a role in cellular response generation within the ARC, which ultimately leads to increased activity of the melanocortin system (Horvath et al. 1999b,c; Coppola et al. 2007). UCP2 may modulate the efficiency of metabolic processes in these cells and affect neurotransmission and synaptic remodeling (Fuxe et al. 2005, Andrews et al. 2005). Just how biochemical pathways associated with fuel sensing alter these classic neuronal functions remains to be elucidated. Moreover, cells within the LH also change their activity in response to the fluctuations of extracellular ATP. For example, a local application of ATP depolarized hypocretin neurons and increased their firing frequency (Wollmann et al. 2005). More studies are needed to determine if this effect is mediated by mechanisms of fuel sensing similar to those seen in the ARC neurons.

**SUMMARY**

Peripheral metabolic hormones not only affect brain structures that have been classically linked to endocrine and autonomic functions, but also alter the function of higher brain regions including the hippocampus and cortex. Because of a more direct relationship between hypothalamic circuitry and feeding behavior, the melanocortin system has emerged as a model for the study of synaptic plasticity. A better understanding of the mechanism of feeding and energy expenditure associated with brain structures will also enhance our ability to combat disorders such as diabetes and obesity, which are among the most prevalent medical problems in both developed and developing societies.

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