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Neurobiology of Feeding and Energy Expenditure

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Key Words

leptin, ghrelin, arcuate nucleus, NPY, POMC, GABA, glutamate

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.

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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

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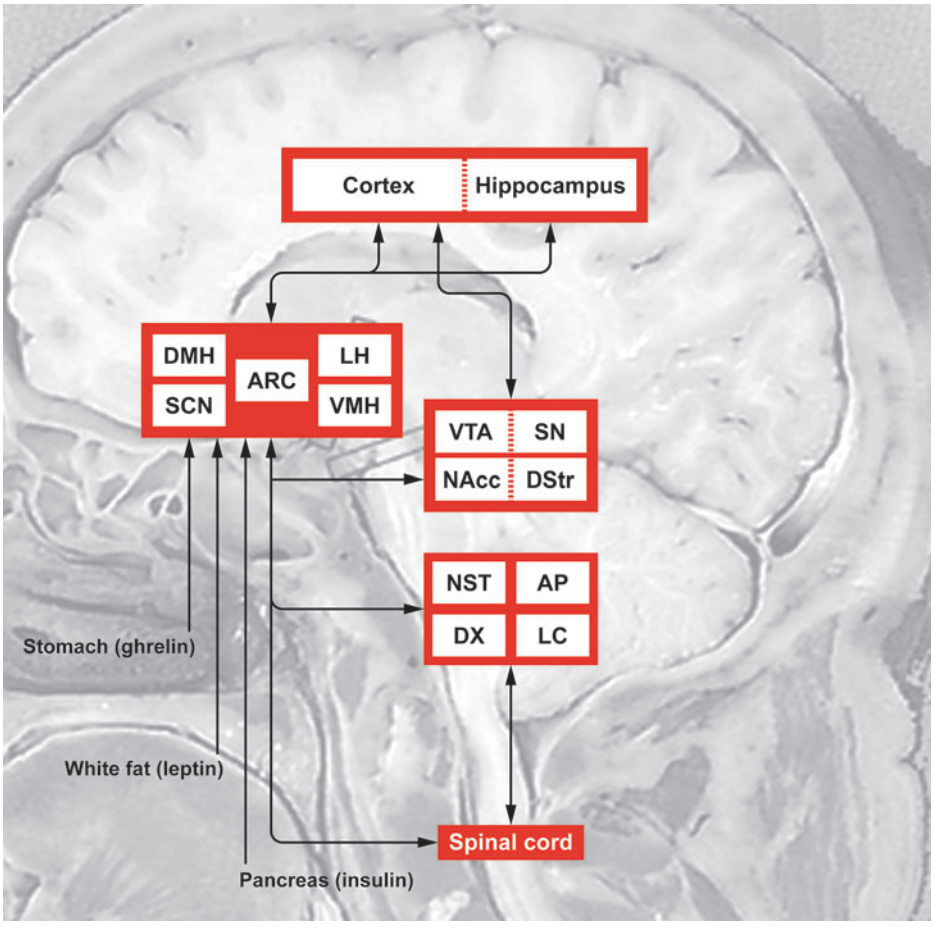

Figure 1

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

VMH: hypothalamic ventromedial

DMH: dorsomedial

PVN: paraventricular

ARC: hypothalamic arcuate nucleus

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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-,

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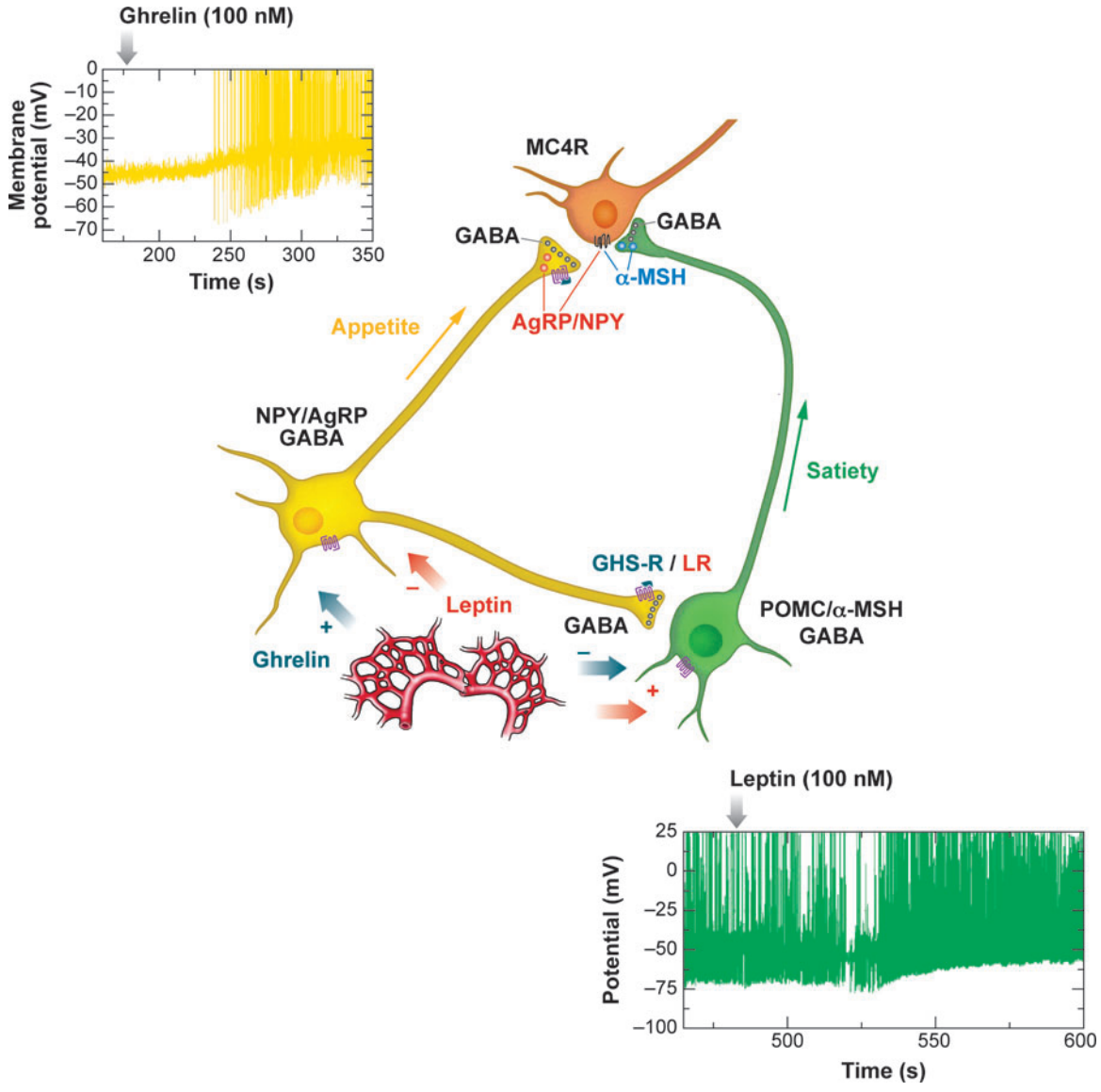

Figure 2

Schematic illustration of the melanocortin system. The melanocortin system has emerged as the *pimum 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 α-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: *a*) GABA, *b*) NPY, and *c*) AgRP, an inverse agonist of MC4R antagonizing the anorexigenic effects of α-MSH. Modified from figure 7 in Cowley et al. 2003.

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and γ-MSH), β-endorphin, and adrenocorticotrophic 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 diphteria 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 in 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

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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

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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 those 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

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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 deafferentiation (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 caudual 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

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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, Banks et al. 2000). LRs belong to the gp130 receptor family of class 1 cytokine receptors, which includes the receptors for interleukin-6 (IL-6), oncostatin M (OSM), leukemia inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF), and ciliary neurotrophic factor (CNTF) (Tartaglia et al. 1995, Taga & Kishimoto 1997) that mediate various functions mainly through JAK/STAT signaling.

In hypothalamic neurons, the LRb mediates the activation of the JAK/STAT3, PI3K, and mitogen-activated protein kinase (MAPK) pathways upon leptin binding (**Figure 3**). STAT3 activation is initiated by the autophosphorylation and activation of JAKs triggered by LRb dimerization (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 anoretic 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)

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pathway in the hypothalamus, which is required for LRb-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 LRb 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). Exactly 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 GHSR1a 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 adipocity 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 LRb 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).

Considerably 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 and 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 $G\alpha q/11$ protein that activates phosphatidylinositol-specific phospholipase C (PI-PLC) to generate inositol 1,4,5-triphosphate (IP_3) and diacylglicerol (DAG) from phosphatidylinositol

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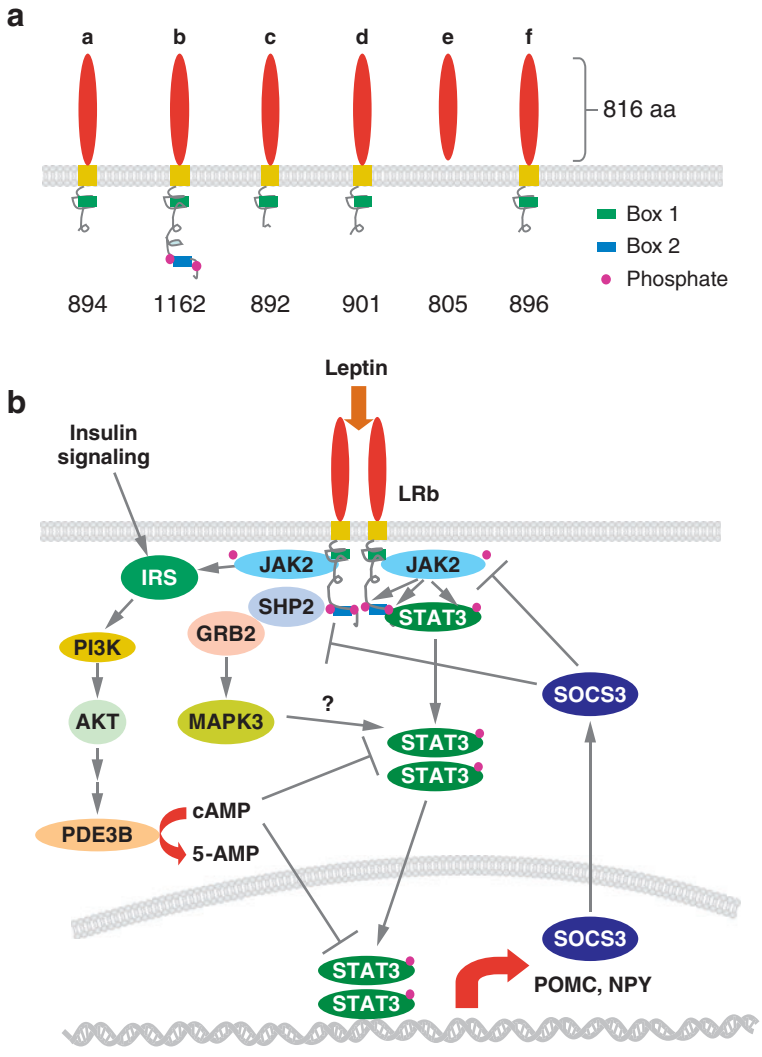

Figure 3

Intracellular signaling of letpin 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 Gαq/11 protein that activates phosphatidylinositol-specific phospholipase C (PI-PLC) to generate inositol 1,4,5-triphosphate (IP_3) and diacylglicerol (DAG) from phosphatidylinositol 4,5-diphosphate (PIP_2). IP_3 mobilizes intracellular Ca^{2+}. 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 ($G_{i/o}$).

4,5-diphosphate (PIP_2) (Howard et al. 1996, McKee et al. 1997). IP_3 mobilizes intracellular Ca^{2+} from IP_3-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,

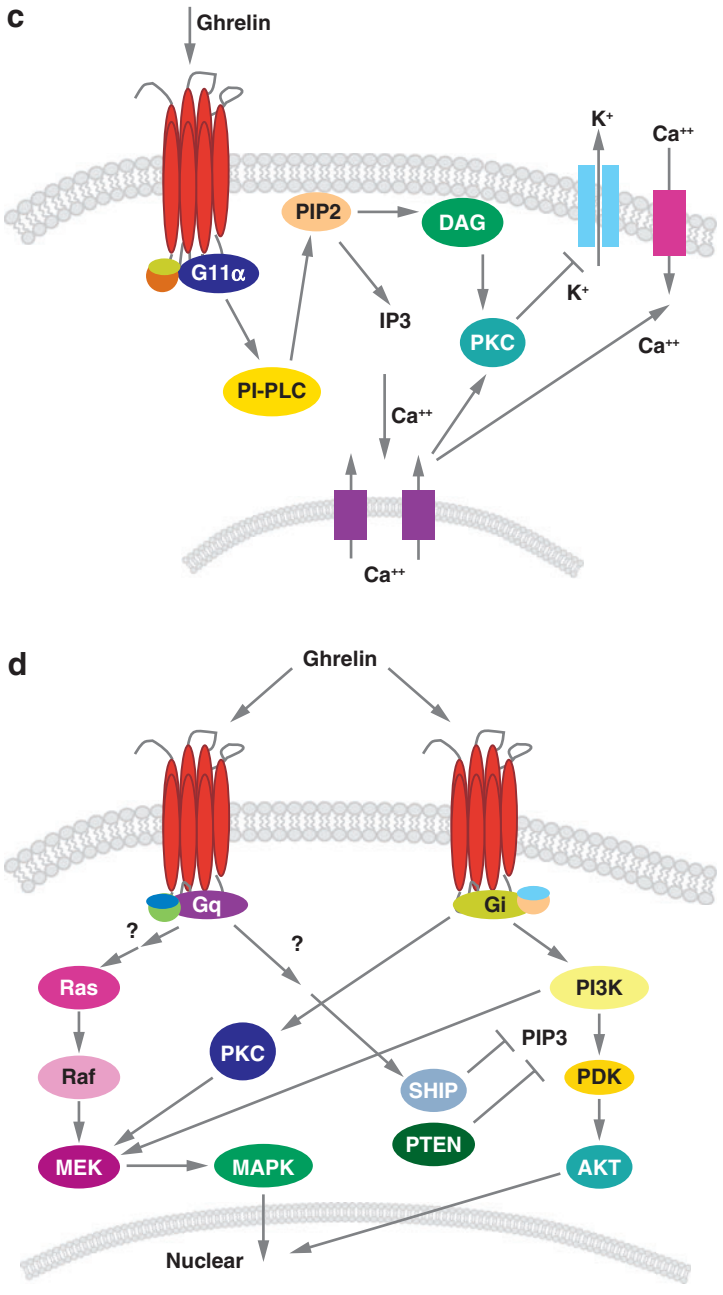

Figure 3
(*Continued*)

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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, Parducz 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

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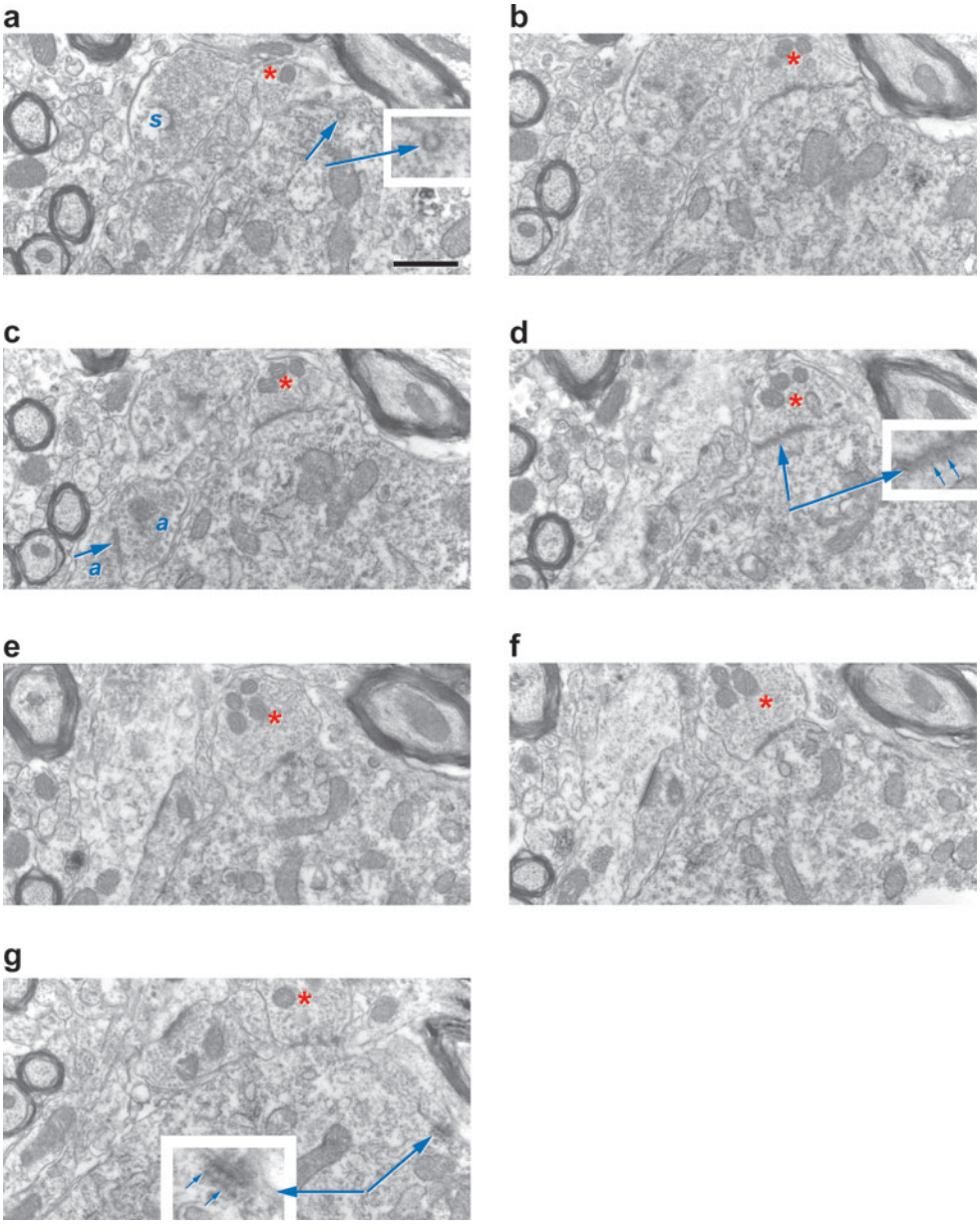

Figure 4

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*.

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energy balance. First, leptin replacement in *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).

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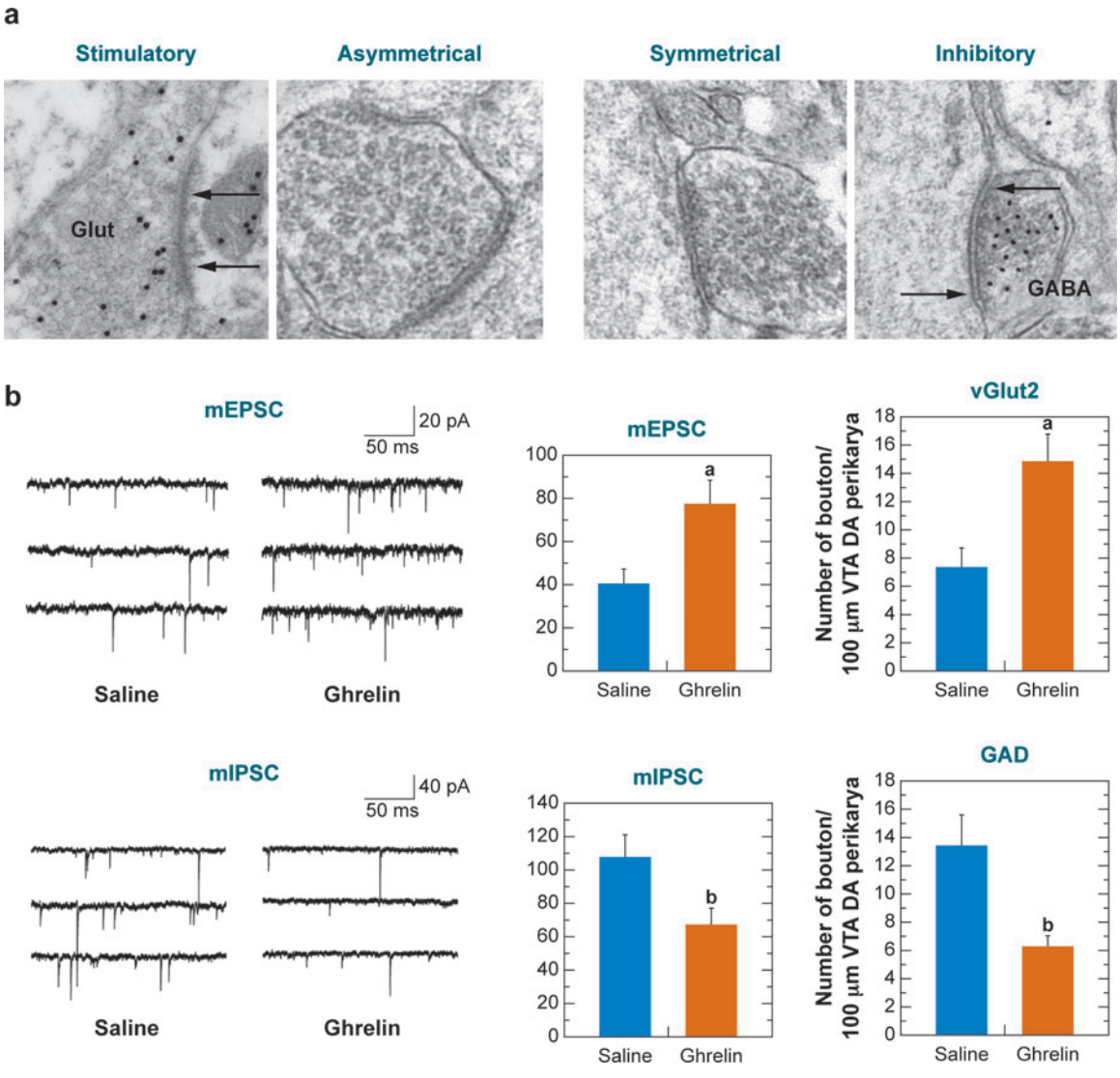

Figure 5

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 apportion between glutamic acid decarboxylase (GAD)-containing, putative GABAergic terminals and the dopamine cells.

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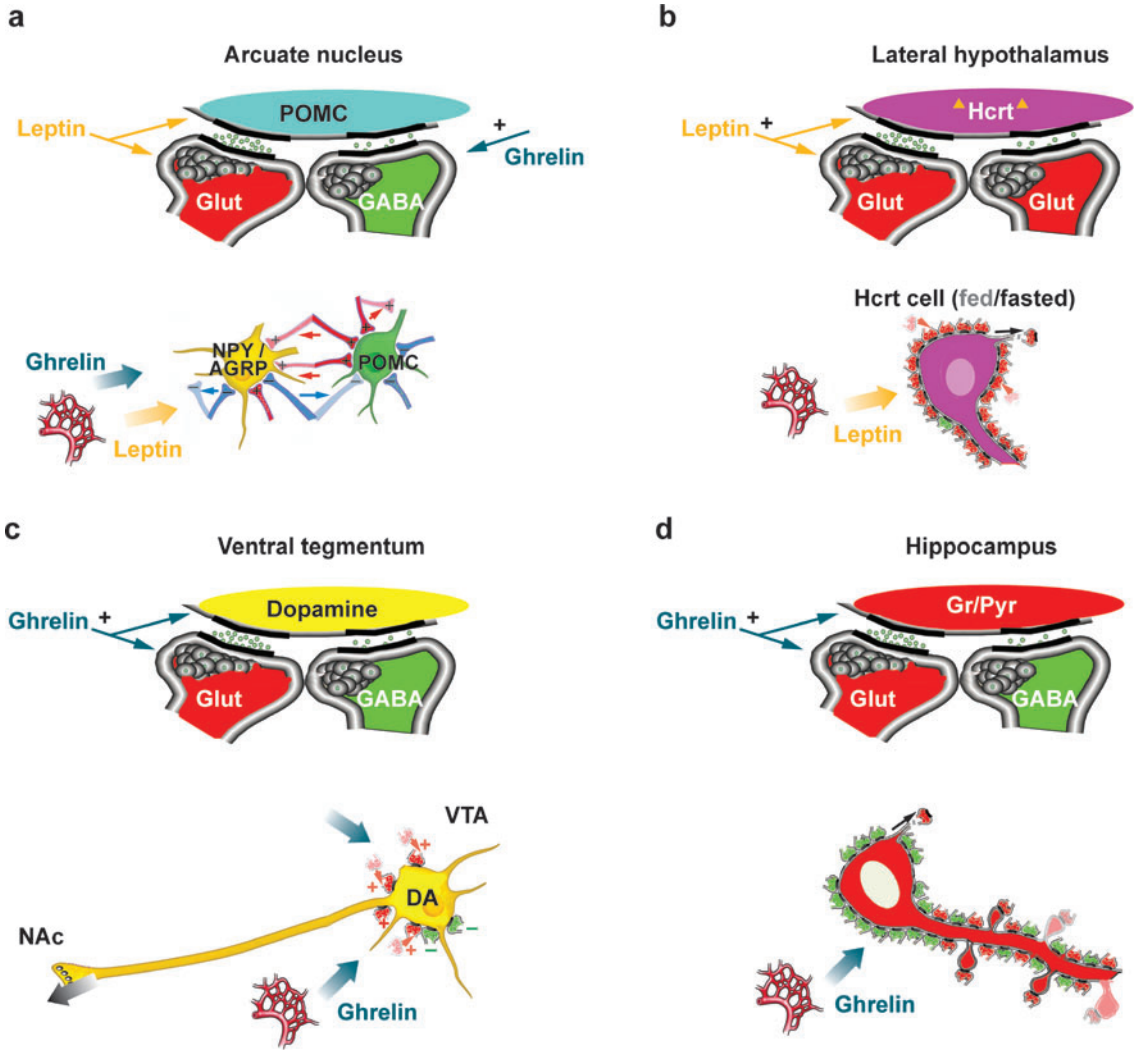

Figure 6

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 parellel 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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LITERATURE CITED

Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, et al. 2006. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J. Clin. Invest.* 116:3229–39

Adan RA, Cone RD, Burbach JP, Gispen WH. 1994. Differential effects of melanocortin peptides on neural melanocortin receptors. *Mol. Pharmacol.* 46:1182–90

Alon T, Friedman JM. 2006. Late-onset leanness in mice with targeted ablation of melanin concentrating hormone neurons. *J. Neurosci.* 26:389–97

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Anand BK, Brobeck JR. 1951. Localization of a feeding center in the hypothalamus of the rat. *Proc. Soc. Exp. Biol. Med.* 77:323–24

Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, et al. 2004. AMP-activated protein kinase plays a role in the control of food intake. *J. Biol. Chem.* 279:12005–8

Andrews ZB, Diano S, Horvath TL. 2005. Mitochondrial uncoupling proteins in the central nervous system: in support of function, survival. *Nat. Rev. Neurosci.* 6(11):829–40

Araki E, Lipes MA, Patti ME, Bruning JC, Haag B 3rd, et al. 1994. Alternative pathway of insulin signaling in mice with targeted disruption of the IRS-1 gene. *Nature* 372:186–90

Bagnasco M, Dube MG, Kalra PS, Kalra SP. 2002. Evidence for the existence of distinct central appetite, energy expenditure, and ghrelin stimulation pathways as revealed by hypothalamic site-specific leptin gene therapy. *Endocrinology* 143:4409–21

Bailey AR, Von Englehardt N, Leng G, Smith RG, Dickson SL. 2000. Growth hormone secretagogue activation of the arcuate nucleus and brainstem occurs via a non-noradrenergic pathway. *J. Neuroendocrinol.* 12:191–97

Balthasar N, Coppari R, McMinn J, Liu SM, Lee CE, et al. 2004. Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. *Neuron* 42:983–91

Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, et al. 2005. Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* 123:493–505

Banks AS, Davis SM, Bates SH, Myers MG Jr. 2000. Activation of downstream signals by the long form of the leptin receptor. *J. Biol. Chem.* 275:14563–72

Baskin DG, Breininger JF, Schwartz MW. 1999a. Leptin receptor mRNA identifies a subpopulation of neuropeptide Y neurons activated by fasting in rat hypothalamus. *Diabetes* 48:828–33

Baskin DG, Breininger JF, Schwartz MW. 2000. SOCS-3 expression in leptin-sensitive neurons of the hypothalamus of fed and fasted rats. *Regul. Pept.* 92:9–15

Baskin DG, Hahn TM, Schwartz MW. 1999b. Leptin sensitive neurons in the hypothalamus. *Horm. Metab. Res.* 31:345–50

Bates SH, Stearns WH, Dundon TA, Schubert M, Tso AW, et al. 2003. STAT3 signaling is required for leptin regulation of energy balance but not reproduction. *Nature* 421:856–59

Baumann H, Morella KK, White DW, Dembski M, Bailon PS, et al. 1996. The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. *Proc. Natl. Acad. Sci. USA* 93:8374–78

Bellinger LL, Bernardis LL. 2002. The dorsomedial hypothalamic nucleus and its role in ingestive behavior and body weight regulation: lessons learned from lesioning studies. *Physiol. Behav.* 76:431–42

Benoit S, Schwartz M, Baskin D, Woods SC, Seeley RJ. 2000. CNS melanocortin system involvement in the regulation of food intake. *Horm. Behav.* 37:299–305

Berridge KC. 1996. Food reward: brain substrates of wanting and liking. *Neurosci. Biobehav. Rev.* 20:1–25

Berthoud HR. 2002. Multiple neural systems controlling food intake and body weight. *Neurosci. Biobehav. Rev.* 26:393–428

Berthoud HR. 2004. The caudal brainstem and the control of food intake and energy balance. In *Handbook of Behavioral Neurobiology*, ed. EM Stricker, SC Woods, pp. 195–240. New York: Plenum

Biebermann H, Castaneda TR, van Landeghem F, von Deimling A, Escher F, et al. 2006. A role for β-melanocyte-stimulating hormone in human body-weight regulation. *Cell Metab.* 3:141–46

Bjorbaek C, Buchholz RM, Davis SM, Bates SH, Pierroz DD, et al. 2001. Divergent roles of SHP-2 in ERK activation by leptin receptors. *J. Biol. Chem.* 276:4747–55

Boston BA, Blaydon KM, Varnerin J, Cone RD. 1997. Independent and additive effects of central POMC and leptin pathways on murine obesity. *Science* 278:1641–44
Bouali SM, Fournier A, St-Pierre S, Jolicoeur FB. 1995. Effects of NPY and NPY2-36 on body temperature and food intake following administration into hypothalamic nuclei. *Brain. Res. Bull.* 36:131–35
Bray GA. 2000. Afferent signals regulating food intake. *Proc. Nutr. Soc.* 59:373–84
Brobeck JR, Tepperman J, Long CNH. 1943. Experimental hypothalamic hyperphagia in the albino rat. *Yale J. Biol. Med.* 15:831–53
Broberger C, De Lecea L, Sutcliffe JG, Hokfelt T. 1998a. Hypocretin/orexin- and melanin-concentrating hormone-expressing cells form distinct populations in the rodent lateral hypothalamus: relationship to the neuropeptide Y and agouti gene-related protein systems. *J. Comp. Neurol.* 402:460–74
Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T. 1998b. The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc. Natl. Acad. Sci. USA* 95:15043–48
Burks DJ, Font de Mora J, Schubert M, Withers DJ, Myers MG, et al. 2000. IRS-2 pathways integrate female reproduction and energy homeostasis. *Nature* 407:377–82
Camina JP. 2006. Cell biology of the ghrelin receptor. *J. Neuroendocrinol.* 18:65–76
Cannon CM, Palmiter RD. 2003. Reward without dopamine. *J. Neurosci.* 23:10827–31
Canteras NS, Simerly RB, Swanson LW. 1994. Organization of projections from the ventromedial nucleus of the hypothalamus: a Phaseolus vulgaris-leucoagglutinin study in the rat. *J. Comp. Neurol.* 348:41–79
Carling D. 2005. AMP-activated protein kinase: balancing the scales. *Biochimie* 87:87–91
Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, et al. 1999. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 98:437–51
Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, et al. 1996. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. *Cell* 84:491–95
Chou TC, Bjorkum AA, Gaus SE, Lu J, Scammell TE, Saper CB. 2002. Afferents to the ventrolateral preoptic nucleus. *J. Neurosci.* 22:977–90
Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J. 2003. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J. Neurosci.* 23:10691–702
Chronwall BM, Chase TN, O'Donohue TL. 1984. Coexistence of neuropeptide Y and somatostatin in rat and human cortical and rat hypothalamic neurons. *Neurosci. Lett.* 52:213–17
Chua SC Jr, Koutras IK, Han L, Liu SM, Kay J, et al. 1997. Fine structure of the murine leptin receptor gene: splice site suppression is required to form two alternatively spliced transcripts. *Genomics* 45:264–70
Clark JT, Kalra PS, Crowley WR, Kalra SP. 1984. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology* 115:427–29
Clifton PG, Vickers SP, Somerville EM. 1998. Little and often: ingestive behavior patterns following hippocampal lesions in rats. *Behav. Neurosci.* 112:502–11
Coleman DL. 1978. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* 14:141–48
Coleman DL, Hummel KP. 1969. Effects of parabiosis of normal with genetically diabetic mice. *Am. J. Physiol.* 217:1298–304
Cone RD. 2005. Anatomy and regulation of the central melanocortin system. *Nat. Neurosci.* 8:571–78

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, Low MJ. 2001. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int. J. Obes. Relat. Metab. Disord.* 25(Suppl. 5):S63–67

Coppola A, Liu ZW, Andrews ZB, Paradis E, Roy MC, et al. 2007. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. *Cell Metab.* 5:21–33

Couce ME, Burguera B, Parisi JE, Jensen MD, Lloyd RV. 1997. Localization of leptin receptor in the human brain. *Neuroendocrinology* 66:145–50

Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. 1999. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. *Neuron* 24:155–63

Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, et al. 2001. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 411:480–84

Cowley MA, Smith RG, Diano S, Tschöp M, Pronchuk N, et al. 2003. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron* 37:649–61

Davis AM, Seney ML, Stallings NR, Zhao L, Parker KL, Tobet SA. 2004. Loss of steroidogenic factor 1 alters cellular topography in the mouse ventromedial nucleus of the hypothalamus. *J. Neurobiol.* 60:424–36

Dhillon H, Zigman JM, Ye C, Lee CE, McGovern RA, et al. 2006. Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. *Neuron* 49:191–203

Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, et al. 2006. Ghrelin controls hippocampal spine synapse density and memory performance. *Nat. Neurosci.* 9:381–88

Diano S, Horvath B, Urbanski HF, Sotonyi P, Horvath TL. 2003. Fasting activates the nonhuman primate hypocretin (orexin) system and its postsynaptic targets. *Endocrinology* 144:3774–78

Diano S, Naftolin F, Goglia F, Csernus V, Horvath TL. 1998a. Monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5′-deiodinase mRNA and the median eminence-projective TRH cells of the rat paraventricular nucleus. *J. Neuroendocrinol.* 10:731–42

Diano S, Naftolin F, Goglia F, Horvath TL. 1998b. Segregation of the intra- and extrahypothalamic neuropeptide Y and catecholaminergic inputs on paraventricular neurons, including those producing thyrotropin-releasing hormone. *Regul. Pept.* 75/76:117–26

DiRocco RJ, Grill HJ. 1979. The forebrain is not essential for sympathoadrenal hyperglycemic response to glucoprivation. *Science* 204:1112–14

Dube MG, Kalra SP, Kalra PS. 1999. Food intake elicited by central administration of orexins/hypocretins: identification of hypothalamic sites of action. *Brain Res.* 842:473–77

Dunn SL, Bjornholm M, Bates SH, Chen Z, Seifert M, Myers MG Jr. 2004. Feedback inhibition of leptin receptor/Jak2 signaling via Tyr1138 of the leptin receptor and suppressor of cytokine signaling 3. *Mol. Endocrinol.* 19:925–38

Elias CF, Lee C, Kelly J, Aschkenasi C, Ahima RS, et al. 1998a. Leptin activates hypothalamic CART neurons projecting to the spinal cord. *Neuron* 21:1375–85

Elias CF, Saper CB, Maratos-Flier E, Tritos NA, Lee C, et al. 1998b. Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J. Comp. Neurol.* 402:442–59

Ellacott KL, Cone RD. 2004. The central melanocortin system and the integration of short- and long-term regulators of energy homeostasis. *Recent Prog. Horm. Res.* 59:395–408

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Erickson JC, Clegg KE, Palmiter RD. 1996. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. *Nature* 381:415–21
Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. 1997. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* 385:165–68
Faulconbridge LF, Cummings DE, Kaplan JM, Grill HJ. 2003. Hyperphagic effects of brainstem ghrelin administration. *Diabetes* 52:2260–65
Figlewicz DP. 2003. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284:R882–92
Fulton S, Woodside B, Shizgal P. 2000. Modulation of brain reward circuitry by leptin. *Science* 287:125–28
Fuxe K, Rivera A, Jacobsen KX, Hoistad M, Leo G, et al. 2005. Dynamics of volume transmission in the brain. Focus on catecholamine and opioid peptide communication and the role of uncoupling protein 2. *J. Neural Transm.* 112:65–76
Gao Q, Mezei G, Nie Y, Rao Y, Choi CS, et al. 2007. Anorectic estrogen mimics leptin's effect on the rewiring of melanocortin cells and Stat3 signaling in obese animals. *Nat. Med.* 13:89–94
Gao Q, Wolfgang MJ, Neschen S, Morino K, Horvath TL, et al. 2004. Disruption of neural signal transducer and activator of transcription 3 causes obesity, diabetes, infertility, and thermal dysregulation. *Proc. Natl. Acad. Sci. USA* 101:4661–66
Gao XB, van den Pol AN. 2001. Melanin concentrating hormone depresses synaptic activity of glutamate and GABA neurons from rat lateral hypothalamus. *J. Physiol.* 533:237–52
Garcia-Segura LM, Chowen JA, Parducz A, Naftolin F. 1994. Gonadal hormones as promoters of structural synaptic plasticity: cellular mechanisms. *Prog. Neurobiol.* 44:279–307
Gooley JJ, Schomer A, Saper CB. 2006. The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. *Nat. Neurosci.* 9:398–407
Grill HJ, Ginsberg AB, Seeley RJ, Kaplan JM. 1998. Brainstem application of melanocortin receptor ligands produces long-lasting effects on feeding and body weight. *J. Neurosci.* 18:10128–35
Grill HJ, Kaplan JM. 2001. Interoceptive and integrative contributions of forebrain and brainstem to energy balance control. *Int. J. Obes. Relat. Metab. Disord.* 25(Suppl. 5):S73–77
Grill HJ, Kaplan JM. 2002. The neuroanatomical axis for control of energy balance. *Front Neuroendocrinol.* 23:2–40
Grill HJ, Markison S, Ginsberg A, Kaplan JM. 2000. Long-term effects on feeding and body weight after stimulation of forebrain or hindbrain CRH receptors with urocortin. *Brain Res.* 867:19–28
Grill HJ, Norgren R. 1978. Chronically decerebrate rats demonstrate satiation but not bait shyness. *Science* 201:267–69
Grill HJ, Schwartz MW, Kaplan JM, Foxhall JS, Breininger J, Baskin DG. 2002. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. *Endocrinology* 143:239–46
Gropp E, Shanabrough M, Borok E, Xu AW, Janoshek R, et al. 2005. Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat. Neurosci.* 8:1289–91
Guan JL, Uehara K, Lu S, Wang QP, Funahashi H, et al. 2002. Reciprocal synaptic relationships between orexin- and melanin-concentrating hormone-containing neurons in the rat lateral hypothalamus: a novel circuit implicated in feeding regulation. *Int. J. Obes. Relat. Metab. Disord.* 26:1523–32
Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, et al. 1997. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. *Brain Res. Mol. Brain Res.* 48:23–29

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Hahn TM, Breininger JF, Baskin DG, Schwartz MW. 1998. Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat. Neurosci.* 1:271–72

Hakansson ML, Brown H, Ghilardi N, Skoda RC, Meister B. 1998. Leptin receptor immunoreactivity in chemically defined target neurons of the hypothalamus. *J. Neurosci.* 18:559–72

Harrold JA, Widdowson PS, Williams G. 1999. Altered energy balance causes selective changes in melanocortin-4 (MC4-R), but not melanocortin-3 (MC3-R), receptors in specific hypothalamic regions: further evidence that activation of MC4-R is a physiological inhibitor of feeding. *Diabetes* 48:267–71

Hentges ST, Nishiyama M, Overstreet LS, Stenzel-Poore M, Williams JT, Low MJ. 2004. GABA release from proopiomelanocortin neurons. *J. Neurosci.* 24:1578–83

Hervey GR. 1959. The effects of lesions in the hypothalamus in parabiotic rats. *J. Physiol.* 145:336–52

Hetherington AW. 1944. Non-production of hypothalamic obesity in the rat by lesions rostral or dorsal to the ventromedial hypothalamic nuclei. *J. Comp. Neurol.* 80:33

Hetherington AW, Ranson SW. 1940. Hypothalamic lesions and adipocity in the rat. *Anat. Record* 78:149

Hnasko TS, Szczypka MS, Alaynick WA, During MJ, Palmiter RD. 2004. A role for dopamine in feeding responses produced by orexigenic agents. *Brain Res.* 1023:309–18

Horvath TL, Bechmann I, Kalra SP, Naftolin F, Leranth C. 1997. Heterogeneity in the neuropeptide Y-containing neurons of the rat arcuate nucleus: GABAergic and non-GABAergic subpopulations. *Brain Res.* 756:283–86

Horvath TL, Diano S, van den Pol AN. 1999a. Synaptic interaction between hypocretin (orexin) and neuropeptide Y cells in the rodent and primate hypothalamus: a novel circuit implicated in metabolic and endocrine regulations. *J. Neurosci.* 19:1072–87

Horvath TL, Gao XB. 2005. Inpur organization and plasticity of hypocretin neurons: possible clues for obesity's association with insomnia. *Cell Metab.* 1:279–86

Horvath TL, Naftolin F, Kalra SP, Leranth C. 1992. Neuropeptide-Y innervation of β-endorphin-containing cells in the rat mediobasal hypothalamus: a light and electron microscopic double immunostaining analysis. *Endocrinology* 131:2461–67

Horvath TL, Peyron C, Diano S, Ivanov A, Aston-Jones G, et al. 1999b. Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. *J. Comp. Neurol.* 415:145–59

Horvath TL, Warden CH, Hajos M, Lombardi A, Goglia F, Diano S. 1999c. Brain uncoupling protein 2: uncoupled neuronal mitochondria predict thermal synapses in homeostatic centers. *J. Neurosci.* 19:10417–27

Howard AD, Feighner SD, Cully DF, Arena JP, Liberator PA, et al. 1996. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science* 273:974–77

Huang XF, Koutcherov I, Lin S, Wang HQ, Storlien L. 1996. Localization of leptin receptor mRNA expression in mouse brain. *NeuroReport* 7:2635–38

Jacob RJ, Dziura J, Medwick MB, Leone P, Caprio S, et al. 1997. The effect of leptin is enhanced by microinjection into the ventromedial hypothalamus. *Diabetes* 46:150–52

Jain MR, Horvath TL, Kalra PS, Kalra SP. 1999. Evidence that NPY Y1 receptors are involved in stimulation of feeding by orexins (hypocretins) in sated rats. *Regul. Pept.* 87:19–24

Kennedy AR, Todd JF, Stanley SA, Abbott CR, Small CJ, et al. 2001. Melanin-concentrating hormone (MCH) suppresses thyroid stimulating hormone (TSH) release, in vivo and in vitro, via the hypothalamus and the pituitary. *Endocrinology* 142:3265–68

Kennedy GC. 1953. The role of depot fat in the hypothalamic control of food intake in the rat. *Proc. R. Soc. London Ser. B* 140:579–92

Kim EK, Miller I, Aja S, Landree LE, Pinn M, et al. 2004. C75, a fatty acid synthase inhibitor, reduces food intake via hypothalamic AMP-activated protein kinase. *J. Biol. Chem.* 279:19970–76

Kim MS, Park JY, Namkoong C, Jang PG, Ryu JW, et al. 2004. Anti-obesity effects of alpha-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. *Nat. Med.* 10:727–33

Kim MS, Yoon CY, Jang PG, Park YJ, Shin CS, et al. 2004. The mitogenic and antiapoptotic actions of ghrelin in 3T3-L1 adipocytes. *Mol. Endocrinol.* 18:2291–301

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 402:656–60

Kola B, Hubina E, Tucci SA, Kirkham TC, Garcia EA, et al. 2005. Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated protein kinase. *J. Biol. Chem.* 280:25196–201

Komori T, Morikawa Y, Nanjo K, Senba E. 2006. Induction of brain-derived neurotrophic factor by leptin in the ventromedial hypothalamus. *Neuroscience* 139:1107–15

Lam TK, Gutierrez-Juarez R, Pocai A, Rossetti L. 2005a. Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science* 309:943–47

Lam TK, Schwartz GJ, Rossetti L. 2005b. Hypothalamic sensing of fatty acids. *Nat. Neurosci.* 8:579–84

Landree LE, Hanlon AL, Strong DW, Rumbaugh G, Miller IM, et al. 2004. C75, a fatty acid synthase inhibitor, modulates AMP-activated protein kinase to alter neuronal energy metabolism. *J. Biol. Chem.* 279:3817–27

Lawrence CB, Snape AC, Baudoin FM, Luckman SM. 2002. Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers. *Endocrinology* 143:155–62

Lee K, Li B, Xi X, Suh Y, Martin RJ. 2005. Role of neuronal energy status in the regulation of adenosine 5′-monophosphate-activated protein kinase, orexigenic neuropeptides expression, and feeding behavior. *Endocrinology* 146:3–10

Lee YS, Challis BG, Thompson DA, Yeo GS, Keogh JM, et al. 2006. A POMC variant implicates β-melanocyte-stimulating hormone in the control of human energy balance. *Cell Metab.* 3:135–40

Li Y, Gao XB, Sakurai T, van den Pol AN. 2002. Hypocretin/orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system. *Neuron* 36:1169–81

Li YZ, Davidowa H. 2004. Food deprivation decreases responsiveness of ventromedial hypothalamic neurons to melanocortins. *J. Neurosci. Res.* 77:596–602

Lopez-Valpuesta FJ, Nyce JW, Griffin-Biggs TA, Ice JC, Myers RD. 1996. Antisense to NPY-Y1 demonstrates that Y1 receptors in the hypothalamus underlie NPY hypothermia and feeding in rats. *Proc. Biol. Sci.* 263:881–86

Ludwig DS, Mountjoy KG, Tatro JB, Gillette JA, Frederich RC, et al. 1998. Melanin-concentrating hormone: a functional melanocortin antagonist in the hypothalamus. *Am. J. Physiol.* 274:627–33

Luquet S, Perez FA, Hnasko TS, Palmiter RD. 2005. NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science* 310:683–85

Majdic G, Young M, Gomez-Sanchez E, Anderson P, Szczepaniak LS, et al. 2002. Knockout mice lacking steroidogenic factor 1 are a novel genetic model of hypothalamic obesity. *Endocrinology* 143:607–14

Malenka RC, Bear MF. 2004. LTP and LTD: an embarrassment of riches. *Neuron* 44:5–21

Mayer J, Thomas DW. 1967. Regulation of food intake and obesity. *Science* 156:328–37

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Mazzocchi G, Neri G, Rucinski M, Rebuffat P, Spinazzi R, et al. 2004. Ghrelin enhances the growth of cultured human adrenal zona glomerulosa cells by exerting MAPK-mediated proliferogenic and antiapoptotic effects. *Peptides* 25:1269–77

McCrimmon RJ, Fan X, Ding Y, Zhu W, Jacob RJ, Sherwin RS. 2004. Potential role for AMP-activated protein kinase in hypoglycemia sensing in the ventromedial hypothalamus. *Diabetes* 53:1953–58

McKee KK, Palyha OC, Feighner SD, Hreniuk DL, Tan CP, et al. 1997. Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors. *Mol. Endocrinol.* 11:415–23

Mercer JG, Hoggard N, Williams LM, Lawrence CB, Hannah LT, Trayhurn P. 1996. Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions by in situ hybridization. *FEBS Lett.* 387:113–16

Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, et al. 2004. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* 428:569–74

Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Muller C, et al. 2002. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 415:339–43

Miyata S, Nakashima T, Kiyohara T. 1994. Structural dynamics of neural plasticity in the supraoptic nucleus of the rat hypothalamus during dehydration and rehydration. *Brain Res. Bull.* 34:169–75

Mondal MS, Date Y, Yamaguchi H, Toshinai K, Tsuruta T, et al. 2005. Identification of ghrelin and its receptor in neurons of the rat arcuate nucleus. *Regul. Pept.* 126:55–59

Mori H, Hanada R, Hanada T, Aki D, Mashima R, et al. 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat. Med.* 10:739–43

Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. 1994. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. *Mol. Endocrinol.* 8:1298–308

Munzberg H, Flier JS, Bjorbaek C. 2004. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology* 145:4880–89

Nakagawa T, Ono-Kishino M, Sugaru E, Yamanaka M, Taiji M, Noguchi H. 2002. Brain-derived neurotrophic factor (BDNF) regulates glucose and energy metabolism in diabetic mice. *Diabetes Metab. Res. Rev.* 18:185–91

Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers MG Jr, Schwartz MW. 2001. Intracellular signaling. Key enzyme in leptin-induced anorexia. *Nature* 413:794–95

Obici S, Rossetti L. 2003. Minireview: nutrient sensing and the regulation of insulin action and energy balance. *Endocrinology* 144:5172–78

Ollmann MM, Wilson BD, Yang YK, Kerns JA, Chen Y, et al. 1997. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science* 278:135–38

Oomura Y, Yoshimatsu H. 1984. Neural network of glucose monitoring system. *J. Auton. Nerv. Syst.* 10:359–72

Parducz A, Zsarnovszky A, Naftolin F, Horvath TL. 2003. Estradiol affects axo-somatic contacts of neuroendocrine cells in the arcuate nucleus of adult rats. *Neuroscience* 117:791–94

Parker KL, Rice DA, Lala DS, Ikeda Y, Luo X, et al. 2002. Steroidogenic factor 1: an essential mediator of endocrine development. *Recent Prog. Horm. Res.* 57:19–36

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, et al. 1998. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J. Neurosci.* 18:9996–10015

Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, et al. 2004. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 304:110–15

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Plum L, Ma X, Hampel B, Balthasar N, Coppari R, et al. 2006. Enhanced PIP3 signaling in POMC neurons causes KATP channel activation and leads to diet-sensitive obesity. *J. Clin. Invest.* 116:1886–901

Pocai A, Lam TK, Obici S, Gutierrez-Juarez R, Muse ED, et al. 2006. Restoration of hypothalamic lipid sensing normalizes energy and glucose homeostasis in overfed rats. *J. Clin. Invest.* 116:1081–91

Qian S, Chen H, Weingarth D, Trumbauer ME, Novi DE, et al. 2002. Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice. *Mol. Cell Biol.* 22:5027–35

Qu D, Ludwig DS, Gammeltoft S, Piper M, Pelleymounter MA, et al. 1996. A role for melanin-concentrating hormone in the central regulation of feeding behavior. *Nature* 380:243–47

Rahmouni K, Haynes WG, Morgan DA, Mark AL. 2003. Intracellular mechanisms involved in leptin regulation of sympathetic outflow. *Hypertension* 41:763–67

Rios M, Fan G, Fekete C, Kelly J, Bates B, et al. 2001. Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. *Mol. Endocrinol.* 15:1748–57

Ritter RC, Slusser PG, Stone S. 1981. Glucoreceptors controlling feeding and blood glucose: location in the hindbrain. *Science* 213:451–53

Sahm UG, Qarawi MA, Olivier GW, Ahmed AR, Branch SK, et al. 1994. The melanocortin (MC3) receptor from rat hypothalamus: photoaffinity labeling and binding of alanine-substituted α-MSH analogues. *FEBS Lett.* 350:29–32

Sahu A. 2002. Interactions of neuropeptide Y, hypocretin-I (orexin A) and melanin-concentrating hormone on feeding in rats. *Brain Res.* 944:232–38

Sahu A, Kalra PS, Kalra SP. 1988a. Food deprivation and ingestion induce reciprocal changes in neuropeptide Y concentrations in the paraventricular nucleus. *Peptides* 9:83–86

Sahu A, Kalra SP, Crowley WR, Kalra PS. 1988b. Evidence that NPY-containing neurons in the brainstem project into selected hypothalamic nuclei: implication in feeding behavior. *Brain Res.* 457:376–78

Saito Y, Cheng M, Leslie FM, Civelli O. 2001. Expression of the melanin-concentrating hormone (MCH) receptor mRNA in the rat brain. *J. Comp. Neurol.* 435:26–40

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, et al. 1998. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92:573–85

Sakurai T, Nagata R, Yamanaka A, Kawamura H, Tsujino N, et al. 2005. Input of orexin/hypocretin neurons revealed by a genetically encoded tracer in mice. *Neuron* 46:297–308

Saper CB, Swanson LW, Cowan WM. 1976. The efferent connections of the ventromedial nucleus of the hypothalamus of the rat. *J. Comp. Neurol.* 169:409–42

Schindler C, Darnell JE Jr. 1995. Transcriptional responses to polypeptide ligands: the JAK-STAT pathway. *Annu. Rev. Biochem.* 64:621–51

Seeley RJ, Grill HJ, Kaplan JM. 1994. Neurological dissociation of gastrointestinal and metabolic contributions to meal size control. *Behav. Neurosci.* 108:347–52

Seeley RJ, York DA. 2005. Fuel sensing and the central nervous system (CNS): implications for the regulation of energy balance and the treatment for obesity. *Obes. Rev.* 6:259–65

Seeley RJ, Woods SC. 2003. Monitoring of stored and available fuel by the CNS: implications for obesity. *Nat. Rev. Neurosci.* 4:901–9

Shimada M, Tritos NA, Lowell BB, Flier JS, Maratos-Flier E. 1998. Mice lacking melanin-concentrating hormone are hypophagic and lean. *Nature* 396:670–74

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
Access provided by University of California - San Diego on 04/23/17. For personal use only.

Silver AJ, Flood JF, Song AM, Morley JE. 1989. Evidence for a physiological role for CCK in the regulation of food intake in mice. *Am. J. Physiol.* 256:646–52

Small DM, Jones-Gotman M, Dagher A. 2003. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage* 19:1709–15

Smith GP, Jerome C, Norgren R. 1985. Afferent axons in abdominal vagus mediate satiety effect of cholecystokinin in rats. *Am. J. Physiol.* 249:638–41

Smith RG. 2005. Development of growth hormone secretagogues. *Endocr. Rev.* 26:346–60

Smith RG, Sun Y, Betancourt L, Asnicar M. 2004. Growth hormone secretagogues: prospects and potential pitfalls. *Best Pract. Res. Clin. Endocrinol. Metab.* 18:333–47

Song MM, Shuai K. 1998. The suppressor of cytokine signaling (SOCS) 1 and SOCS3 but not SOCS2 proteins inhibit interferon-mediated antiviral and antiproliferative activities. *J. Biol. Chem.* 273:35056–62

Sotak BN, Hnasko TS, Robinson S, Kremer EJ, Palmiter RD. 2005. Dysregulation of dopamine signaling in the dorsal striatum inhibits feeding. *Brain Res.* 1061:88–96

Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML. 1997. Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. *Nature* 390:521–25

Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML. 2000. Insulin activates ATP-sensitive K^+ channels in hypothalamic neurons of lean, but not obese rats. *Nat. Neurosci.* 3:757–58

Stanley BG, Leibowitz SF. 1984. Neuropeptide Y: stimulation of feeding and drinking by injection into the paraventricular nucleus. *Life Sci.* 35:2635–42

Stellar E. 1954. The physiology of motivation. *Psychol. Rev.* 61:5–22

Stern JE, Armstrong WE. 1998. Reorganization of the dendritic trees of oxytocin and vasopressin neurons of the rat supraoptic nucleus during lactation. *J. Neurosci.* 18:841–53

Sternson SM, Shepherd GM, Friedman JM. 2005. Topographic mapping of VMH –> arcuate nucleus microcircuits and their reorganization by fasting. *Nat. Neurosci.* 8:1356–63

Storlien LH. 1985. The role of the ventromedial hypothalamic area in periprandial glucoregulation. *Life Sci.* 36:505–14

Szczypka MS, Kwok K, Brot MD, Marck BT, Matsumoto AM, et al. 2001. Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron* 30:819–28

Szczypka MS, Rainey MA, Kim DS, Alaynick WA, Marck BT, et al. 1999. Feeding behavior in dopamine-deficient mice. *Proc. Natl. Acad. Sci. USA* 96:12138–43

Szczypka MS, Rainey MA, Palmiter RD. 2000. Dopamine is required for hyperphagia in Lep(ob/ob) mice. *Nat. Genet.* 25:102–4

Tannenbaum GS, Lapointe M, Beaudet A, Howard AD. 1998. Expression of growth hormone secretagogue-receptors by growth hormone-releasing hormone neurons in the mediobasal hypothalamus. *Endocrinology* 139:4420–23

Tartaglia LA. 1997. The leptin receptor. *J. Biol. Chem.* 272:6093–96

Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, et al. 1995. Identification and expression cloning of a leptin receptor, OB-R. *Cell* 83:1263–71

Tejwani GA, Richard CW 3rd. 1986. Effect of electrolytic and chemical ventromedial hypothalamic lesions on food intake, body weight, analgesia and the CNS opioid peptides in rats and mice. *NIDA Res. Monogr.* 75:497–500

ter Horst GJ, Luiten PG. 1986. The projections of the dorsomedial hypothalamic nucleus in the rat. *Brain Res. Bull.* 16:231–48

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
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Theodosis DT, Rougon G, Poulain DA. 1991. Retention of embryonic features by an adult neuronal system capable of plasticity: polysialylated neural cell adhesion molecule in the hypothalamo-neurohypophysial system. *Proc. Natl. Acad. Sci. USA* 88:5494–98

Torrealba F, Yanagisawa M, Saper CB. 2003. Colocalization of orexin and glutamate immunoreactivity in axon terminals in the tuberomammillary nucleus in rats. *Neuroscience* 119:1033–44

Toshinai K, Date Y, Murakami N, Shimada M, Mondal MS, et al. 2003. Ghrelin induced food intake is mediated via the orexin pathway. *Endocrinology* 144:1506–12

Travers SP, Norgren R. 1991. Coding the sweet taste in the nucleus of the solitary tract: differential roles for anterior tongue and nasoincisor duct gustatory receptors in the rat. *J. Neurophysiol.* 65:1372–80

Tritos NA, Mastaitis JW, Kokkotou E, Maratos-Flier E. 2001. Characterization of melanin concentrating hormone and preproorexin expression in the murine hypothalamus. *Brain Res.* 895:160–66

Tschop M, Smiley DL, Heiman ML. 2000. Ghrelin induces adiposity in rodents. *Nature* 407:908–13

Tsuchida A, Nonomura T, Nakagawa T, Itakura Y, Ono-Kishino M, et al. 2002. Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice. *Diabetes Obes. Metab.* 4:262–69

van den Pol AN. 2003. Weighing the role of hypothalamic feeding neurotransmitters. *Neuron* 40:1059–61

van den Pol AN, Acuna-Goycolea C, Clark KR, Ghosh PK. 2004. Physiological properties of hypothalamic MCH neurons identified with selective expression of reporter gene after recombinant virus infection. *Neuron* 42:635–52

van den Top M, Lee K, Whyment AD, Blanks AM, Spanswick D. 2004. Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. *Nat. Neurosci.* 7:493–94

Volkow ND, Wise RA. 2005. How can drug addiction help us understand obesity? *Nat. Neurosci.* 8:555–60

White DW, Kuropatwinski KK, Devos R, Baumann H, Tartaglia LA. 1997. Leptin receptor (OB-R) signaling. Cytoplasmic domain mutational analysis and evidence for receptor homo-oligomerization. *J. Biol. Chem.* 272:4065–71

Wilding JP, Gilbey SG, Bailey CJ, Batt RA, Williams G, et al. 1993. Increased neuropeptide-Y messenger ribonucleic acid (mRNA) and decreased neurotensin mRNA in the hypothalamus of the obese (ob/ob) mouse. *Endocrinology* 132:1939–44

Willesen MG, Kristensen P, Romer J. 1999. Co-localization of growth hormone secretagogue receptor and NPY mRNA in the arcuate nucleus of the rat. *Neuroendocrinology* 70:306–16

Williams DL, Kaplan JM, Grill HJ. 2000. The role of the dorsal vagal complex and the vagus nerve in feeding effects of melanocortin-3/4 receptor stimulation. *Endocrinology* 141:1332–37

Willie JT, Chemelli RM, Sinton CM, Yanagisawa M. 2001. To eat or to sleep? Orexin in the regulation of feeding and wakefulness. *Annu. Rev. Neurosci.* 24:429–58

Wise RA. 2002. Brain reward circuitry: insights from unsensed incentives. *Neuron* 36:229–40

Wisialowski T, Parker R, Preston E, Sainsbury A, Kraegen E, et al. 2000. Adrenalectomy reduces neuropeptide Y-induced insulin release and NPY receptor expression in the rat ventromedial hypothalamus. *J. Clin. Invest.* 105:1253–59

Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, et al. 1998. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* 391:900–4

Annu. Rev. Neurosci. 2007.30:367-398. Downloaded from www.annualreviews.org
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Wollmann G, Acuna-Goycolea C, van den Pol AN. 2005. Direct excitation of hypocretin/orexin cells by extracellular ATP at P2X receptors. *J. Neurophysiol.* 94:2195–206

Woods SC, Seeley RJ, Porte D Jr, Schwartz MW. 1998. Signals that regulate food intake and energy homeostasis. *Science* 280:1378–83

Xiong JJ, Karsch FJ, Lehman MN. 1997. Evidence for seasonal plasticity in the gonadotropin-releasing hormone (GnRH) system of the ewe: changes in synaptic inputs onto GnRH neurons. *Endocrinology* 138:1240–50

Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, et al. 2003. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat. Neurosci.* 6:736–42

Yamanaka A, Kunii K, Nambu T, Tsujino N, Sakai A, et al. 2000. Orexin-induced food intake involves neuropeptide Y pathway. *Brain Res.* 859:404–9

Zaborszky L, Makara GB. 1979. Intrahypothalamic connections: an electron microscopic study in the rat. *Exp. Brain Res.* 34:201–15

Zhang EE, Chapeau E, Hagihara K, Feng GS. 2004. Neuronal Shp2 tyrosine phosphatase controls energy balance and metabolism. *Proc. Natl. Acad. Sci. USA* 101:16064–69

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–32

Zhao AZ, Huan JN, Gupta S, Pal R, Sahu A. 2002. A phosphatidylinositol 3-kinase phosphodiesterase 3B-cyclic AMP pathway in hypothalamic action of leptin on feeding. *Nat. Neurosci.* 5(8):727–28

Zheng H, Patterson LM, Morrison C, Banfield BW, Randall JA, et al. 2005. Melanin concentrating hormone innervation of caudal brainstem areas involved in gastrointestinal functions and energy balance. *Neuroscience* 135(2):611–25

Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. 2006. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J. Comp. Neurol.* 494:528–48

Zsarnovszky A, Horvath TL, Garcia-Segura LM, Horvath B, Naftolin F. 2001. Oestrogen-induced changes in the synaptology of the monkey (Cercopithecus aethiops) arcuate nucleus during gonadotropin feedback. *J. Neuroendocrinol.* 13:22–28

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