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Neuronal control of energy homeostasis

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Abstract

Neuronal control of body energy homeostasis is the key mechanism by which animals and humans regulate their long-term energy balance. Various hypothalamic neuronal circuits (which include the hypothalamic melanocortin, midbrain dopamine reward and caudal brainstem autonomic feeding systems) control energy intake and expenditure to maintain body weight within a narrow range for long periods of a life span. Numerous peripheral metabolic hormones and nutrients target these structures providing feedback signals that modify the default “settings” of neuronal activity to accomplish this balance. A number of molecular genetic tools for manipulating individual components of brain energy homeostatic machineries, in combination with anatomical, electrophysiological, pharmacological and behavioral techniques, have been developed, which provide a means for elucidating the complex molecular and cellular mechanisms of feeding behavior and metabolism. This review will highlight some of these advancements and focus on the neuronal circuitries of energy homeostasis.

Keywords

Leptin; Ghrelin; Arcuate nucleus; NPY; POMC; GABA; glutamate

1. Introduction

Feeding and energy metabolism is a basic and vital life process essential for individual and, consequently, species survival. It could be argued that the emergence and evolution of the central nervous system is to promote the most effective means of dealing with feeding and metabolism in support of survival. Accumulating experimental evidence is in agreement with this basic assertion. Thus, it is not unreasonable to claim that even higher brain regions, such as the archio- and neocortex, emerged under environmental pressures to support

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behaviors that more effectively deal with available energy resources. The pursuit to understand the role that the brain plays in the control of body energy balance has continued for more than a century, when patients with pituitary adenomas were initially observed to rapidly gain body weight (1, 2). Increasingly sophisticated technologies and methods have since been brought to bear on the topic and a vast number of observations have been made, particularly within the last decade due to the cloning of the product of the *obesity* (*ob*) gene, leptin, the mutation of this gene causes obesity in rodents (3), which brought about a wave of discovery of other metabolic hormones, neuropeptides and signaling pathways, and established their relationship to key neuronal structures in the hypothalamus (4, 5, 6, 7). Based upon these fundmental findings, the studies of more complex signal intergrations and neuronal adaptations that actually initiate changes in ingestive behavior and metabolism have become possible. This review will follow this line of research history and highlight some important new advances.

2. Discovery of the brain regions that control energy balance

The initial observations of Mohr (1840) and Frohlich (1901) regarding pituitary adenomas led to the hypothesis that adenoma-related obesity is caused by damage to the hypothalamus (8). This important idea was supported by the observation that obesity developed in an experimental dog given that underwent a hypothalamic lesion (9). The actual identification of specific hypothalamic structures that are directly involved in energy homeostasis, however, was accomplished about three decades later, when a set of systematic lesion experiments was performed in rats, in which various hypothalamic nuclei that include the hypothalamic ventromedial (VMH), paraventricular (PVH) and dorsomedial (DMH) nuclei were destroyed. The lesions of these nuclei induced hyperphagia and obesity (10, 11, 12); whereas, lesions in the lateral hypothalamus (LH) led to hypophagia (13). This study, which stands as a milestone in linking brain function to body energy balance, led to the proposal of a “dual center model” that identified the hypothalamic VMN as the “satiety centre,” and the LH as the “hunger centre” (14). More studies, including chemical lesions as well as pharmacological applications of various hormones and drugs, which either stimulate or inhibit the neuron populations locally, have since been done and all supported the initial observations that lead to the proposed “dual center model.” In retrospect to our current knowledge of specific hypothalamic neuronal populations, these lesion studies are strikingly precise in distinguishing between subregions that contain circuits that either promote or suppress feeding. These findings have since been used as a road map for studies concerning the neurobiology of feeding and metabolism.

3. Linking the periphery to the brain

The brain regions that control energy homeostasis, by definition, need to “know” the amount of pre-existing body energy stores in order to “wisely” determine the levels of energy intake and expenditure. The nature of the signal(s) that conveys such information to the brain was the subject of a couple of hypotheses. The “glucostatic hypothesis,” (15) suggested that small changes in plasma glucose levels trigger meal initiation or termination. This “depletion-repletion” model of energy intake correlated well with the initiation or termination of feeding per se, however, it did not provide information about or a mechanism

by which to ensure that food consumption with respect to existing energy stores would be appropriate and it correlated poorly with energy expenditure (16). The “lipostatic model,” on the other hand, hypothesized that signal(s) proportional to the amount of fat in the body modulates the amount of food eaten at each meal to maintain overall energy balance (17). Later discoveries have supported this hypothesis that food intake is controlled within a lipostatic system to maintain energy homeostasis.

The findings from the initial parabiosis studies on hypothalamic lesioned rats appear to be essential to the conclusion of the existence of humoral signal(s) in relation to an animal’s lipostatics (18). In these studies, two live animals, one with a lesion in the VMH, were joined by suturing, which allowed humoral factors to pass from one animal to the other. As obesity developed in the lesioned rat, its partner became hypohagic 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* (19, 20), concluded that *ob/ob* mice lack this lipostatic signal, whereas *db/db* mice are insensitive to it. These hypotheses were later confirmed by the discoveries of the *ob* gene that encodes leptin (3) and the *db* gene that encodes leptin receptor.

The detection of leptin and its receptor soon led to the recognition that all of the hypothalamic nuclei associated with energy regulation, i.e., the VMH, DMH, PVN and LH, are regions where leptin receptors are highly expressed. This promoted a new flourish of gene discoveries, which identified novel neuropeptides, their receptors and transcription factors that mediate leptin function in the hypothalamus and subsequently, led to the discovery of the hypothalamic melanocortin system, the key neuronal system in the control of energy balance by leptin signaling. Other metabolic signals, such as insulin, ghrelin, estrogen, prolactin, glucocorticoids, resistin and interleukins, etc., as well as nutrients such as glucose and free fatty acids (21, 22, 23), which, to a certain extent, modify energy balance and body weight, also target the hypothalamic melanocortin system (16, 5 24, 25, 26), presumably in coordination with leptin function.

4. The importance of the melanocortin system in energy homeostasis

The melanocortin model has held the most significance in explaining the neuronal control of energy balance. In this model, the hypothalamic arcuate nucleus (ARC) is considered a critical region for various reasons. First, the neurons within the ARC are anatomically placed in close proximity to fenestrated capillaries at the base of the hypothalamus, giving them access to humoral signals that are restricted from other regions of the brain (27, 28). Indeed, they respond rapidly to fluctuations in neutrients (7, 29) and metabolic hormones. These neurons are also innervated by axons containing all major neurotransmitters and express receptors for most metabolic hormones (5, 27, 30, 31), implying that an extensive neuronal control exists. Finally, they project broadly to the brain and pheriphery both directly as well as indirectly.

Two sets of neurons, with opposite effects on feeding, have been identified in the ARC. The neurons that express proopiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART) are anorexigenic (32, 33, 34), due to the release of the cleavage products

of POMC precursor, α-, and β-melanocyte stimulating hormones (α- and β-MSH) (34). These, in turn, reduce food intake and body weight as well as increase energy expenditure in animals and humans (35, 36, 37) by acting on melanocortin receptor subtypes 3 and 4 (MC3 and 4R) (38), found to be abundant in the ARC, PVN, LH and DMH (39). In contrast, cells containing neuropeptide Y (NPY) and the agouti gene related transcript (AgRP) are orexigenic (40). NPY potently stimulates food intake and reduces energy expenditure (41). In genetically obese animals, i.e., *ob/ob* and *db/db* mice, as well as those in a negative energy state, i.e., fasted or lactating animals, the ARC NPY mRNA and protein content are elevated (42, 43, 44, 45). AgRP acts as a natural antagonist of MC3R and MC4R, thereby, reducing the anorectic effect of α-MSH (40, 46, 47, 48). An ectopic expression of Agouti, an AgRP like peptide, results in an obese phenotype of the *yA* agouti mouse (40).

The selective expression of fluorescent reporter genes in specific neurons allows for the visualization of hypothalamic neuronal subpopulations so that they can be studied in the context of feeding circuits while the cells are still alive. Through the use of this method, substantial neuroanatomical and electrophysiological data have been generated, which demonstrate that NPY neurons contact nearby POMC cells and inhibit them through the release of GABA (49). This unidirectional NPY to POMC interaction (50) may represent a wiring blueprint that favors the tonic inhibition of satiety signals to not only promote feeding, but also overfeeding when food is available in excess (51).

The ARC POMC and NPY neurons project to various parts of the brain, e.g., the PVN, LH and perifornical hypothalamic region, all of which contain substantial numbers of MC3 and 4 receptors (39, 52). The projection from the ARC to the PVN is important for the regulation of neurons that produce corticotropic and thyrotropin releasing hormones (CRH and TRH, respectively) and for the modulation of sympathetic activity, both of which are significant mechanisms in energy metabolism (53, Fig. 2). A recent study using a *cre/loxP* genetic approach showed that mice with mutations to the MC4R gene (loxTB *mc4*) ate and weighed less if the MC4R gene was restored selectively in the PVN (54). However, it was not sufficient to bring energy expenditure levels to those of controls, suggesting that energy expenditure is regulated by melanocortins elsewhere in the hypothalamus and/or through receptors other than MC4R (54).

Recent studies showed that intact melanocortin neuronal circuitry is important for acute regulation of feeding (55, 56). These studies stemmed from the considerable frustration encountered due to the fact that neither NPY nor AgRP single gene knockout mice (57) nor NPY/AgRP double knockout mice (58) exhibited the expected hypophagia. To examine whether the NPY and POMC neurons themselves are crucial in adult energy regulation, whereas the loss of NPY/AgRP or POMC genes may be compensated for during development, both groups had 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 two subsequent doses of diphtheria toxin, the targeted hypothalamic neurons rapidly died resulting in hypophagia in NPY neuron–ablated mice (55, 565) and hyperphagia in POMC neuron-ablated animals (55). Interestingly, the ablation of NPY neurons during the early postnatal period did not result in an overt metabolic phenotype,

indicating that functional effects of degenerated neurons in critical developmental periods may be overcome by re-organization of the circuits.

5. The function of satiety center, VMH: does it modulate the melanocortin circuits?

The VMH was directly implicated in feeding when Hetherington and Ranson showed that electrolytic lesions to this region in rats resulted in rapid development of obesity (10, 59, 11, 12). Chemical lesions as well as pharmacological studies have since supported the notion that the VMH inhibits feeding and increases metabolism and by doing so, restricts the amount of body fat (60, 61). The VMH was found to highly express the long form leptin receptor, LRb, and, therefore, is the region that mediates leptin's effect on homeostasis (62, 63). Despite the early discovery of the anorexic effect of the VMH, little is known regarding the cellular mechanisms by which VMH neurons contribute to homeostasis under the control of leptin signals.

Recent studies, however, show that the VMH is equally important and functions alongside the ARC in energy regulation in response to leptin (64). These studies examined the behavioral and metabolic phenotype of animals with the leptin receptor selectively deleted in POMC neurons (65). Surprisingly, these animals were at best only mildly obese and ate similar amounts of food as controls. 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 not only obese but also hyperphagic (66, 67). SF-1 is a transcription factor necessary for the development of the VMH (68, 69, 70). Mice with mutations to leptin receptors in both the ARC POMC and the VMH SF1 neurons are more obese than those with mutations of leptin receptors in either set of neurons alone (67).

How do VMH neurons act to deliver the anorectic effect in the context of hypothalamic feeding circuits? A recent study showed that the VMH may directly increase the activity of POMC neurons via microcircuits (71) that were previously difficult to detect by conventional tracing techniques (72, 73, 74). Using laser scanning photo-stimulation (LSPS) in combination with slice electrophysiology, these authors showed that the inputs from the VMH neurons are mostly excitatory, thus increasing the activity of POMC cells; during a fast, these inputs decrease (71). Whether or not these VMH neurons receive leptin signaling requires further investigation.

Conversely, the ARC may also modulate the activity of the VMH. Although afferent projections from the ARC to the VMH are sparser than those to other nuclei (73), the VMH contains MC4R as well as NPY Y1, Y2 and Y5 receptors (75, 76, 77, 78, 79, 80), suggesting that both POMC and NPY neurons project to the VMH. Infusions of NPY into the VMH increase feeding; fasting is associated with elevated levels of NPY in this region (75, 5), whereas electrophysiological responses of neurons in the VMH to α-MSH are decreased in animals that are fasted and/or treated with AgRP prior to sacrifice than in animals that have free access to food (80).

A notable characteristic of the VMH is that it highly and specifically expresses the brain-derived neurotrophic factor (BDNF) that has been shown to affect the metabolic functions regulated by the VMH. Genetic deficiencies of BDNF or its TrkB receptor resulted in obesity in both humans and mice (81, 82). Interestingly, leptin increases BDNF transcripts (83, 84, 85, 86), whereas fasting decreases them selectively in the VMH, suggesting that the BDNF is a regulatory component of leptin signaling. Since BDNF in the brain is known to promote synaptic morphology and function (81), this raises the possibility that synaptic plasticity in the hypothalamus may be a part of the regulatory mechanism of energy regulation. Notably, the anorectic effects of BDNF are not directly mediated by the melanocortin system since BDNF reduces the body weight and food intake of mice that lack the MC4R (82), yet neurons in the VMH form excitatory microcircuits with POMC neurons in the ARC (71), suggesting that the VMH may influence POMC neuroactivity by other means, such as classic neurotransmitters and/or plasticity. Indeed, leptin and other hormones increase the number of excitatory synapses on POMC cells (87, 88).

6. The lateral hypothalamic arousal-feeding system

In the lateral hypothalamus (LH), two sets of neurons that contain either hypocretin (orexin), a peptide implicated in arousal and feeding, or melanin-concentrating hormone (MCH), another potent stimulator of food intake, have been identified. These neurons are innervated by both POMC and NPY terminals, suggesting that their function in motivating food intake is also within the confines of the ARC melanocortin system (89, 90, 91, 92, 93, 48, 94, 95, 96, 97, 98, 99). Both MCH and hypocretin 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 (100, 92, 101, 102, 97). Although the projections of MCH and hypocretin neurons exhibit significant overlap, their overall effects and actual targets are quite different (100, 96). Like that of the NPY and POMC neurons, the activity of MCH and hypocretin neurons is regulated by numerous hormones that include leptin and ghrelin, as well as by practically every neurotransmitter system (91, 103, 104, 105, 106). Within the LH, MCH and hypocretin neurons have reciprocal connections with each other, and with nearby neurons (99). Electrophysiological studies in brain slices or isolated neurons indicated that hypocretin, in general, has a stimulative effect on LH neurons including MCH neurons (107, 108), whereas MCH depresses the synaptic activity of glutamate and GABA neurons from the rat LH (109). It is not clear whether such electrical interactions between hypocretin and MCH neurons, at the intensities and dynamics observed, are more relevant to feeding or arousal behavior.

MCH and hypocretin neurons are able to integrate metabolic signals to modulate energy balance, more or less, independent of each other, despite their proximate location and physiological interaction in the LH. The mRNA levels of hypocretin in the LH are up-regulated upon fasting (93). Hypocretin neurons are rapidly activated by fasting in rodents and non-human primates (110) and exhibit leptin-dependent synaptic plasticity during fasting (111). Moreover, all of the hypothalamic neurons that are activated by fasting receive strong hypocretin input. These observations, together with the earlier demonstration of a massive hypocretin input to the ARC, particularly to the NPY neurons (112), as well as the dependence of hypocretin function on NPY signaling (in particular on the Y1 and Y5

receptors) (113, 114), and a synergistic action between NPY and hypocretin (at low concentrations) to induce feeding (115) 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 that their metabolic rates are reduced (116). This, in association with the critical role of hypocretin neurons to promote arousal (117) through direct projections to the brain stem, including the locus coeruleus (112) make the hypocretin neurons a likely candidate to provide the link between obesity and insomnia.

The orexigenic peptide MCH, on the other hand, shows little or no interaction with NPY or hypocretin in inducing food intake when injected together into the third ventricle of the rat (115). This observation provides a physiological component concomitant to the pre-existing morphological data that shows that the strength of MCH projections to the ARC is limited compared to that of the hypocretin neurons. Thus, the action of MCH on feeding is likely independent of NPY and hypocretin. However, like NPY, MCH does exhibit characteristics of orexigenic genes: its mRNA levels are increased in obese mutant animals and fasting further increases its expression in both normal and obese animals (89); and it has a potent orexigenic effect. Targeted deletion of the MCH gene resulted in a phenotype of hypophagia and leanness with an inappropriately high metabolic rate (118), suggesting that MCH is a typical “thrift gene” that increases energy intake and reduces energy expenditure simultaneously. Consistent with this idea, MCH suppresses thyroid stimulating hormone (TSH) release (119).

The orexigenic effect of MCH appears to compete 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, while α-MSH acts to decrease it. When the peptides are administered together, depending on the relative ratios, one antagonizes the action of the other (92). Recently, a mouse model of MCH neuron ablation was generated by expressing a toxin gene, ataxin-3, targeted at MCH neurons (120). Mice that express this gene have a chronic loss of MCH neurons. Interestingly, the phenotype of these mice highly resembles that of mice lacking only the MCH gene, exhibiting reduced food intake and increased energy expenditure. Moreover, the ablation of MCH neurons in mice with an *ob/ob* mutant background improved obesity and glucose tolerance. These results suggest that the function of MCH cells in energy regulation is limited to the MCH system itself, but not to other aspects of the cells such as their classic neurotransmitter function and/or synaptic plasticity, which are distinct from NPY cells.

7. Other hypothalamic regions that regulate food intake and body weight

Receptors for leptin and ghrelin are also found in other hypothalamic nuclei including the DMH and the suprachiasmatic nucleus (SCN) (103, 121). The DMH has been implicated in the regulation of energy balance, however, its actual role remained obscure until recently (122, 123, 124). The DMH is involved in a variety of regulatory mechanisms that include the modulation of glucocorticoid secretion, body temperature, arousal, and circadian rhythms of locomotor activity (123). The DMH receives inputs from cells in the ARC and from brain stem centers that are also implicated in feeding (122). Lesions restricted to the

DMH typically result in hypophagia, although animals can still maintain their body composition (122). Recently, the DMH was shown to be critical for the entrainment of circadian rhythms to feeding schedules (124). The DMH of animals with restricted access to food (4 hours/day) had increased expression of c-Fos, indicating an increased cellular activation at a time when the food was regularly presented compared to 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. Furthermore, when lesioned rats were placed in 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 (124). The phenotype of cells within this region remains obscure. A number of these cells produce glutamate as a neurotransmitter and project to the PVN as well as to the preoptic area, both thought to be involved in the circadian regulation of corticosteroid secretion and body temperature (125, 122). Projections from the DMH to the LH and to the ventrolateral preoptic area have been implicated in sleep and arousal and could presumably relate to the enhanced activity of animals in restricted feeding schedules (126).

The role of the SCN in energy balance has been overshadowed by the critical role of this region as a master clock that mediates circadian patterns of biological function (127). Among these, the SCN controls the circadian secretion of metabolic hormones and is thought to regulate seasonal adipose tissue content and maintain patterns of glucose levels (128, 129). The SCN projects to most hypothalamic nuclei, with a strong projection that terminates in the PVN and DMH (127). Recent evidence suggests that the ARC projects to the SCN as well, indicating that the melanocortin system can influence its activity (130). Importantly, mice with mutations of the *clock* gene, a transcript expressed in the SCN and critical for the generation of circadian rhythms, exhibit an obese phenotype (131). Hypothalamic *clock* gene expression is highest in the SCN, thus directly implicating this region in obesity caused by this mutation (132, 133).

8. Midbrain dopamine system-the motivation or reward to eat

The midbrain dopamine system is known to be involved in the regulation of arousal, locomotor activity, mood and reward (134). 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 (135, 136). These mice fail to eat in response to acute glucose deprivation (137), as well as to PYY administration or leptin deficiency (138), suggesting that dopamine signaling is absolutely required for promoting feeding and acts downstream of the melanocortin system. Among the various functions of the dopamine system, the reward pathways have received particular attention in explaining feeding behavior given the universality of food as a natural reinforcer. Dopaminergic neurons within the midbrain ventral tegmental area (VTA) that innervate the nucleus accumbens (the ventral striatum) have been implicated in the rewarding aspects of food, sex, and drugs of abuse (139). In support of a role for the mesolimbic reward circuitry in feeding regulation, it was recently found that interfering with ghrelin signaling specifically in the VTA diminished ghrelin-induced feeding (140). Surprisingly, however, the restoration of dopamine production within the dorsal striatum restores feeding on normal chow, whereas

restoration of dopamine in the nucleus accumbens does not. While these findings may suggest a fundamental difference between feeding for nourishment and food as a rewarding substance (141), a similar study in human subjects argues in the same vein: by using [(11)C]raclopride positron emission tomography (PET) scanning, feeding was found to be 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 (142). Thus, further investigations are needed to discern the role of VTA versus nigral dopamine neurons in the regulation of feeding and energy homeostasis in general (143, 144).

Nevertheless, feeding is associated with motivational mechanisms important for the behavioral responses necessary for seeking food (145). Hypothalamic peptides like NPY, α-MSH, AgRP, hypocretin and MCH, on the other hand, modulate the activity of dopaminergic neurons that target the nucleus accumbens (146). The ARC funnels metabolic information from signals like 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 nucleus accumbens (146). Emerging evidence, however, supports the idea 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 (147, 148, 121). The implications of these observations remain controversial. Further research may reveal that, in contrast to the funnel hypothesis, metabolic signals could act directly on reward systems, including the dorsal striatum, to modulate motivational aspects of feeding in tandem with homeostatic systems (149, 148).

9. The caudal brainstem: autonomic control of eating

The caudal brainstem contains neurons and circuits that involve autonomic control of ingestion, digestion, and absorption of food (150), and do so without forebrain influence (151), just as for respiration and circulation, the functions essential for survival. Thus, the regulation of nutrient supply is to a large extent autonomically organized within the brainstem that generates most of the parasympathetic support during ingestive and digestive processes through the vagus nerve, as well as sympathetic responses related to severe energy depletion and energy expenditure. It has immediate access to the locomotor and oromotor apparatuses that enable approach of food and orchestrate ingestion of food and fluid placed into the oral cavity. Furthermore, the brainstem 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 of the brainstem (152).

Interestingly, the caudal brainstem is involved in the control of meal size by signals arising from the mouth and gastrointestinal tract based upon the chemical or mechanical properties of food, which are relayed to the nucleus of the solitary tract (NST) via the vagus and other cranial nerves (153). In a chronic decerebrate rat preparation, the taste concentrations, gastric preloads and cholecystokinin (CCK; a peptide released from intestinal endocrine cells during feeding) all affected the meal size in a manner similar to that of intact rats. Thus, the brainstem isolated from its forebrain connection exhibits the basic behavior of satiety (154). This challenges the classic view that hypothalamic integration of visceral signals is necessary for the behavioral output that determines meal size. The specific neural

pathways necessary for the “satiety” response have not yet been identified. CCK appears required for the “satiety” response (155), which also involves neurons in the NTS as well as the dorsomotor nucleus of the vagus (DMV), and is blocked by vagal deafferentiation (156). In addition to meal size control, decerebrate rats also show a fully formed sympathoadrenal response to systemic 2DG administration (157), indicating that the brainstem houses a complete system responsive to glucoprivation. However, decerebrate rats are not able to increase meal size appropriately in response to food deprivation (158), and, therefore, have an inadequate response to a long-term homeostatic challenge, which requires interactions between hypothalamic and caudal brainstem nuclei (152).

Consistent with these findings, the peripheral hormones leptin, ghrelin and insulin, neuropeptides α-MSH and CRH as well as nutrients such as glucose all yield potent effects on food intake and body weight similar to their effects in the hypothalamus (152, 151). LRbs are found throughout the dorsal vagal complex (DVC, area postrema, nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve) and in various other structures in the caudual brainstem (159). Localized stimulation of these receptors reduces food intake and body weight (160); Ghrelin receptors, GHS-R are expressed in the area postrema and nucleus tractus solitarius of the brainstem. Stimulation of GHS-R in the caudal brainstem led to a hyperphagic response (161, 162). Ghrelin delivered to the fourth ventricles significantly increased cumulative food intake, with maximal response approximately 3 h after injection. In a separate experiment, ghrelin microinjected unilaterally into the dorsal vagal complex (DVC) significantly increased food intake measured 1.5 and 3 h after treatment (163). Insulin receptors are also found in the NST (164). Furthermore, unilateral DVC injection of both MC3/4R and CRH1/2R agonists resulted in suppression of food intake, while a MC3/4R antagonist induced hyperphagia (165, 166, 167). The innervation of the brainstem by the perifornical and far-lateral hypothalamic MCH neurons has recently been identified (168). Lastly, it is noteworthy that the brainstem also houses glucose-sensitive neurons that are involved in the sympathoadrenal and ingestive responses to glucopenia in rodents (169).

10. Concluding remarks: questions on which to focus

Despite the complex and extensive involvement of the brain in energy homeostasis, a basic picture of the neuronal control behind this process is emerging. In this representation, the melanocortin system, broadly defined to include the hypothalamic ARC, VMH, DMH, PVN and LH, is positioned at the center, with the other brain regions, such as the midbrain dopamine system (controlling the motivation to eat or reward of eating) and the caudal brainstem (autonomic control of eating) positioned downstream. The key molecule that connects the entire network is the adipokine leptin, which conveys information from the periphery regarding pre-existing energy stores to the brain. These neuronal structures are all targeted, differentially, by leptin to modify their default settings, which otherwise tend to increase energy intake and reduce energy expenditure. Although close interactions between individual nuclei have been found, these nuclei and neuronal subpopulations act more or less in parallel but are not hierarchical.

This relatively simplified representation of the neuronal control of energy regulation highlights several issues that still need to be addressed. These include: 1) an intricate and

detailed labeling of all of the LRb expressing neurons in the brain, with particular attention given to the hypothalamus, midbrain and brainstem, in order to identify novel neuronal subpopulations, specifically in the VMH, DMH and LH. In fact, this work is already quickly progressing (personal communication, Myers); 2) focusing on neuronal adaptations, e.g., electrophysiological and plastic, directly induced by the metabolic hormones, leptin and ghrelin, that actually alter feeding behavior and/or metabolism; 3) discerning the particular effect of each nucleus and/or neuronal subpopulation in relation to homeostasis; identifying the niche, through which different neuronal circuits interact, and, more importantly, addressing the logic behind the parallel arrangement of brain structures/systems that control long-term energy balance.

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