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From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior

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Abstract

Over the past two centuries, prevalent models of energy and glucose homeostasis have emerged from careful anatomical descriptions in tandem with an understanding of cellular physiology. More recent technological advances have culminated in the identification of peripheral and central factors that influence neural circuits regulating metabolism. This Review highlights contributions to our understanding of peripheral and central factors regulating food intake and energy expenditure.

The French physiologist Claude Bernard is often credited for introducing the concept of homeostasis when he coined the phrase “milieu intérieur” more than 150 years ago. He also first suggested that the CNS directly regulates blood glucose levels^{1,2}. Subsequent investigators outlined a series of models that supported a role for glucose as well as other peripheral signals in the central regulation of food intake, energy expenditure and glucose homeostasis^{3,4}. This was epitomized by the work of Douglas Coleman and Jeffrey Friedman and culminated in the identification of the fat-derived hormone leptin^{5–7}. As highlighted in this Review, the discovery of leptin and concurrent advances in molecular tools used to manipulate circuits in a cell-specific manner have been a catalyst in the study and understanding of the central regulation of food intake, as well as energy balance and glucose homeostasis. Moreover, application of similar strategies to investigate other peripheral and central factors has been and will continue to be essential in the understanding of, as well as the advancement of potential therapeutic strategies for, obesity and diabetes.

Melanocortins: regulating food intake and energy balance

Early reports identified nuclei in the medial basal hypothalamus as key regulators of food intake and body weight, as well as energy and glucose homeostasis⁴. In the past two decades the field has turned its attention to the hypothalamic arcuate nucleus, which has been extensively studied in the context of the central regulation of energy balance^{1,3,8}. This focus is largely because the arcuate nucleus is where two prototypical regulators of energy balance, cell types expressing either proopiomelanocortin (POMC) or neuropeptide Y and agouti-related peptide (NPY/AgRP), reside⁹. Since the identification of POMC and associated neuropeptide products, researchers have been trying to discern the functions of

the various projections of these neurons⁴. Recent work has suggested that these projections of melanocortin neurons to melanocortin (MC3 and MC4) receptors in the CNS determine feeding behavior, as well as energy and glucose homeostasis (Fig. 1)^{4,10–16}. Additional work has suggested a differential regulation of these biological activities by the six distinct G protein–coupled NPY receptors¹⁷. Not surprisingly, researchers have been interested in compounds that manipulate the melanocortin and/or NPY/AgRP circuit to facilitate drug discovery for the treatment of metabolic disorders. The gastrointestinally derived peptide YY and the pancreas-derived pancreatic polypeptide elicit their physiological effects by interacting with specific Y receptors¹⁷. These results suggest that melanocortin and Y receptors, with their various agonists, act in a distributed fashion to regulate food intake, energy expenditure and glucose homeostasis^{4,18–20}.

Important recent evidence suggests a differential regulation of energy and glucose homeostasis by melanocortin and Y receptors during development^{21,22}. For instance, mice deficient in POMC or the downstream melanocortin receptors (MC3 or MC4 receptors) have profound deficits in energy expenditure^{12,15}; however, deficiency of either AgRP and/or NPY does not influence food intake, body weight or adiposity^{21,23}. Similarly, toxin-induced ablation of AgRP/NPY neurons during development only modestly affects food intake²¹. Toxin-induced ablation of NPY/AgRP neurons in adulthood, however, profoundly alters food intake²¹, suggesting that NPY/AgRP neurons do regulate food intake and energy expenditure in the adult. These data emphasize developmental compensatory mechanisms as a potential confounder in the use of genetic modifications. Recent work has also suggested that neurons that normally express POMC during development may undergo a change in cell fate, adopting a non-POMC fate in adult mice.^{22,24} Together, these data suggest that, to better delineate the regulation of energy and glucose homeostasis, future research will require newer molecular tools to discern the functions of specific neuronal populations in the adult versus the embryo.

Leptin and central melanocortin signaling

Rodents and humans with mutations in leptin (*Lep^{ob/ob}*) or its receptor (*Lep^{db/db}*) are hyperphagic and severely obese^{5,6,25–28}. After the discovery of leptin, investigators began embracing the study of energy and glucose homeostasis through molecular tools including both conventional knockout models and Cre-*loxP* technology. This molecular era of obesity research accelerated the identification of neural networks regulating food intake and energy and glucose homeostasis. Mice selectively deficient for leptin receptors in POMC neurons were found to exhibit a more modest obesity than mice globally deficient in leptin receptors²⁹. This increase in adiposity is dependent on decreased energy expenditure and independent of changes in food intake²⁹. Interestingly, arcuate-specific reactivation of leptin receptors in mice and rats with mutant leptin receptor alleles was found to result in only modest improvements in body weight^{30,31}, whereas expression of leptin receptors in the arcuate was found to result in marked improvements in hyperinsulinemia and blood glucose levels^{30–32}. These data were further supported by observations that expression of leptin receptors in POMC neurons alone results in modest improvements in body weight and complete normalization of blood glucose^{28,33}. Moreover, hyperinsulinemic-euglycemic clamps revealed that re-expression of the endogenous leptin receptor gene in POMC neurons results in increased insulin sensitivity and decreased hepatic glucose production independent of changes in serum insulin²⁸, supporting regulation by leptin of glucose homeostasis owing to direct actions on POMC neurons.

Accumulating evidence suggests that hypothalamic and extrahypothalamic sites contribute to the effects of leptin on food intake and energy balance^{4,28,29,34–45}. Notably, the dorsal vagal complex (DVC) has been classically associated with feeding behaviors owing to the

vago-vagal reflex linking the CNS with the viscera^{46,47}. Moreover, the DVC, similarly to the arcuate nucleus, is well positioned to receive and integrate peripheral signals such as leptin^{38,45}. Interestingly, knockdown of leptin receptor expression in the hindbrain results in hyperphagia on both standard chow and high-fat diet (HFD), resulting in weight gain⁴¹. In support of these data, selective deletion of leptin receptors in the DVC has modest effects on food intake; however, it fails to influence body weight largely owing to an increase in energy expenditure (Fig. 1)⁴⁰. Recent work also suggests that melanocortin and leptin signaling may converge in the hindbrain to regulate food intake and meal size and frequency^{44,41,48}.

Peripheral factors regulate food intake, energy expenditure

As reviewed above, leptin and melanocortin signaling have received much of the attention as concerns the regulation of food intake as well as glucose homeostasis and energy expenditure. Understandably, this attention is based on the importance of leptin and melanocortin signaling in regulating these biological activities across species. Moreover, these data have provided a framework for the investigation of other metabolic cues that may regulate similar biological activities. The regulation of food intake, as well as glucose homeostasis and energy expenditure, requires the coordinated response of various peripheral and central factors including hormones, (neuro)peptides and neurotransmitters. As outlined below, the list of peripheral factors includes but is not limited to insulin, ghrelin, glucagon-like peptide-1 (GLP-1) and cholecystokinin (CCK)⁴⁹. Together, the data support a role for several peripheral factors in the coordinated control of food intake, as well as energy and glucose homeostasis.

Insulin

The beta cell–derived hormone insulin has classically been linked to glucose homeostasis⁴. Interestingly, insulin has been suggested to regulate food intake and ingestive behaviors, an effect likely dependent on direct action in the CNS and possibly occurring through similar signaling mechanisms as those of leptin, for the maintenance of glucose and energy homeostasis^{4,35,50–54}. Not surprisingly, investigators have been intrigued by insulin action in the hypothalamus and interested in further examining the melanocortin circuit to better delineate the molecular and cellular mechanisms involved in the central control of energy and glucose homeostasis by insulin. However, loss of insulin receptors selectively in POMC neurons does not influence energy and glucose homeostasis^{35,51}. Loss of both leptin and insulin receptors in POMC neurons results in modest effects on body weight but in profound effects on glucose balance, inducing hepatic insulin resistance and severe diabetes not present upon either single deletion alone³⁵. Moreover, reports suggest that the primary effects of leptin on energy expenditure and body weight may depend on Janus kinase/signal transducer and activator of transcription (Jak/STAT) signaling, whereas the acute effect of leptin and insulin on cellular activity and feeding behavior may require phosphatidylinositol-3-OH kinase (PI3K) signaling^{4,36,55,56}. Notably, leptin- and insulin-dependent activation of the PI3K signaling cascade in a distinct subpopulations of POMC neurons alters the acute activity of arcuate POMC neurons^{4,16,55,57}. Leptin signaling in POMC neurons may compensate for deficiencies in insulin signaling, likely through shared intracellular signaling cascades and possibly by means of distinct subpopulations of melanocortin neurons. Perhaps less surprisingly, and similarly to leptin receptors, insulin receptors require a distributed network in the CNS to regulate energy and glucose homeostasis. For instance, mice deficient for insulin receptors selectively in steroidogenic factor-1 (SF-1) neurons of the ventromedial nucleus of the hypothalamus (VMH) are protected from diet-induced leptin resistance, weight gain, adiposity and impaired glucose tolerance⁵⁸. Moreover, the acute effects of leptin and insulin in the VMH mimic those observed in arcuate POMC neurons⁵⁸. However, it is apparent that deficiency of insulin

receptors in arcuate POMC or VMH SF-1 neurons accounts for only a fraction of the effects observed upon loss of insulin receptors throughout the CNS^{35,52,58–60}. Thus, although these data have illuminated leptin and insulin signaling to regulate food intake and body weight, as well as glucose and energy homeostasis, further studies are needed to better understand the coordinated actions of these hormones in the CNS.

Ghrelin

The stomach-derived peptide hormone ghrelin has emerged as the ‘hunger hormone’^{61–63}. Ghrelin’s cognate receptor, the growth hormone secretagogue receptor (GHSR), is found in many of the same hypothalamic and extrahypothalamic regions in which the leptin receptor is expressed^{62,63}. Mice deficient for GHSRs are hypophagic and lean and store fewer consumed calories when fed a HFD⁶⁴. Moreover, GHSR-null mice exhibit elevated locomotor activity and improved glucose homeostasis⁶⁴. Ghrelin acutely activates arcuate NPY/AgRP neurons and inhibits arcuate POMC neurons^{62,63}. Moreover ghrelin and its mimetics, the growth hormone secretagogues, increase food intake and adiposity by acting on the hypothalamus. Thus, these data, in addition to the GHSR-dependent regulation of weight gain, support the involvement of various hypothalamic (including melanocortin neuron) and extrahypothalamic sites in the ghrelin-induced coordinated control of energy and glucose homeostasis⁶⁴. Notably, recent work suggests that ghrelin may directly counter-regulate leptin and insulin signaling in the hypothalamus^{62,63}. In addition to actions in the hypothalamus, ghrelin may influence the rewarding properties of food through actions in the VTA, as well as modify peripheral appetite by acting on visceral vagal afferents that ultimately modify the activity of neurons in the DVC. Thus the hunger hormone ghrelin is an important counter-regulator of many of the same biological activities modified by leptin through actions on the hypothalamus, VTA and DVC, ultimately contributing to the coordinated control of energy and glucose homeostasis.

Glucagon-like peptide-1

Incretins are factors that are produced by the intestinal mucosa in response to nutrient ingestion and that lower plasma glucose and raise insulin compared to levels produced by parenteral glucose^{65,66}. Glucagon-like peptide-1 (GLP-1), produced primarily by L cells of the intestine, is an incretin that is derived from the cleavage of the proglucagon peptide⁶⁵. Notably, GLP-1 neurons have been identified in the CNS and exhibit an expression pattern tightly restricted to the hindbrain: namely, in the nucleus of the solitary tract (NTS) and the ventrolateral medulla⁶⁷. GLP-1 and its mimetics (or receptor agonists) enhance glucose-dependent insulin secretion, slow gastric emptying and inhibit gastric acid secretion⁶⁵. GLP-1 reduces food intake, increases satiety and promotes weight loss, possibly by modulating central circuits involved in the control of energy homeostasis^{66,68–70}. Perhaps less surprisingly, GLP-1 receptors are distributed in the CNS in hypothalamic centers involved in the central control of energy and glucose balance, such as the arcuate nucleus and the paraventricular nucleus of the hypothalamus^{66,71}. Leptin may stimulate the activity of GLP-1 neurons in the hindbrain, and leptin receptors in a subpopulation of GLP-1 neurons in the NTS are required for leptin-induced effects on food intake^{40,72}. However, recent work has been limited its ability to illuminate the role of the CNS in the GLP-1 induced regulation of food intake, as well as energy and glucose balance, owing to complications in experimental models⁶⁶. Quite possibly Cre-*loxP* technology or similar strategies may hold the most promise in gaining a necessary understanding of GLP-1 physiology⁶⁶. Thus GLP-1 and its receptors are important in the regulation of energy and glucose balance; however, further research is necessary to delineate the actions of GLP-1 in the periphery as well as the CNS (including melanocortin neurons).

Cholecystokinin

The gastrointestinally derived peptide CCK has been of considerable interest in the regulation of food intake. CCK is released after a meal and suppresses food intake and meal size independently of nausea^{46,73–75}. Specifically, lesions of the vagus nerve blunt the CCK-induced reduction in food intake^{75–77}, suggesting that CCK activates receptors on viscerosensory afferents that signal fullness to the brain, resulting in meal termination and initiating satiety⁷⁵. In addition, CCK receptors are distributed throughout the brain and have been implicated in a variety of biological activities, from anxiety to nociception⁷⁵. Recent evidence supports direct CCK-induced regulation of DVC activity, possibly through activity of GLP-1 neurons in the NTS^{78–80}. Not surprisingly, the effects of CCK on food intake may also involve crosstalk with melanocortin signaling through MC4 receptors of the DVC⁸¹. Thus, CCK is important in the regulation of feeding behavior through its action on viscerosensory afferents and on potential signaling mechanisms shared by GLP-1, leptin and other factors implicated in regulating feeding behavior.

Neurotransmitters regulate food intake, energy expenditure

Understanding feeding behavior, as well as glucose and energy homeostasis, will require a detailed understanding of the neural circuits targeted by peripheral and central factors regulating these biological activities. Much of the recent investigation in the central regulation of energy and glucose balance has centered on neuropeptide expression and/or activity profiles. Recent evidence suggests, however, that the influence of classical neurotransmitters in the brain in regulating disease states such as obesity and type II diabetes may have been underestimated⁸². For instance, the neurotransmitter GABA, which is also produced by NPY/AgRP neurons, may be critical in regulating feeding behavior and/or energy balance at sites outside of the hypothalamus, including the parabrachial nucleus (Fig. 1)^{21,83}. Consistent with this observation, selective deletion of the GABAergic vesicular transporter (VGAT) alone from AgRP neurons results in a lean phenotype and mice that are resistant to HFD-induced obesity, independently of changes in food intake⁸⁴. The lean phenotype is accompanied by increased locomotor activity, and increased HFD-induced thermogenesis contributes to the resistance to HFD-induced obesity⁸⁴. These mice also eat less in response to ghrelin, which was attributed to an inability of AgRP neurons to antagonize POMC neuronal activity⁸⁴. A subsequent study demonstrated that selective deletion of leptin receptors from all neurons that express VGAT produces a massive increase in body weight and adiposity that is associated with marked hyperphagia³⁴. This increase in body weight and fat mass represents ~90% of that observed in mice globally lacking leptin receptors³⁴. Contrary to its effects in neurons that express VGAT, selective deletion of leptin receptors from neurons that express the glutamatergic vesicular transporter 2 (VGLUT2) has modest effects on body weight and adiposity³⁴.

Notably, several recent studies have investigated the loss or re-expression of leptin receptors in neuronal populations chemically identified by neuropeptide expression and determined that leptin receptors in these various cell populations modestly contribute to leptin-induced effects on energy and glucose balance (leading to changes 10–20% of those produced by global leptin deficiency)^{28,29,37,40}. The profound effects observed when GABAergic neurons alone are deficient for leptin receptors suggests that inhibitory neurons (and GABAergic synaptic transmission) are important for the leptin-induced regulation of energy and glucose balance. Recent work demonstrated that the presence or absence of leptin and fed or fasted states may be important for the synaptic (re)organization of the arcuate nucleus, with regard to both number of synapses formed and post-synaptic spine density, suggesting regulation of synaptic inputs that includes neurotransmitters^{85,86}. Another neurotransmitter, serotonin, has been studied in a variety of neuropsychological diseases; recent evidence suggests that it also regulates food intake, as well as energy and glucose homeostasis, by

acting directly in a subpopulation of arcuate POMC neurons^{87–90}. Notably, 5HT_{2C} serotonin receptors on POMC neurons regulate body weight by means of changes in feeding behavior and locomotor activity, independently of alterations in energy expenditure^{89,90}. Conversely, leptin receptors on POMC neurons regulate body weight by means of changes in energy expenditure, independently of alterations in food intake^{28,29}. Moreover, leptin and serotonin acutely activate distinct subpopulations of arcuate POMC neurons by means of a putative transient receptor potential cation (TRPC) channel⁹¹. These data may provide a functional model that highlights distinct roles of serotonin and leptin in regulating energy and glucose homeostasis, as well as feeding behaviors, through melanocortin signaling (Fig. 1). Together, these data suggest that, although the study of (neuro)peptides has been critical in understanding the regulation of feeding behavior and energy and glucose balance, it is also important to (re)consider the influence of neurotransmitters (both excitatory and inhibitory) on these behaviors⁸².

Conclusions and perspectives; future directions

In the past two centuries, researchers have extended our understanding of the central regulation of energy and glucose homeostasis through significant advances in innovation and technology. Advances such as optogenetics and designer channels (for example, designer receptors exclusively activated by designer drugs (DREADDS)), have culminated in the selective stimulation and/or inhibition of identified cell populations, furthering our understanding of the neuronal circuitry regulating many biological activities, including feeding behavior^{83,92–94}. Combinatorial implementation of these strategies have begun to delineate a ‘feeding/hunger circuit’ in the hypothalamus and brainstem^{83,94–96}. In the future, these technologies have immense potential to illuminate in greater detail the mechanisms involved in the central regulation of biological activities such as locomotion, energy expenditure and glucose homeostasis.

Obesity and diabetes are commonly associated with resistance to or diminished production of peripheral and central regulators of food intake, as well as of energy and glucose homeostasis. The molecular tools used to selectively ablate and/or restore the expression of enzymes or peptides and their cognate receptors have been vital in establishing an understanding of the cellular and molecular mechanisms involved in obesity and diabetes. However, recent work has highlighted inherent limitations of present strategies; these include developmental compensation and developmental heterogeneity of gene expression^{21,24,96–98}. Collectively, these studies suggest that compensatory mechanisms must be considered in the interpretation of adult and embryonic expression. In addition, conclusions must take into account variation between species and the complexity of intra-species strain differences⁹⁹. In an effort to alleviate possible confounding effects, recent work has suggested the use of congenic backgrounds and establishing standards for the interpretation of data generated from metabolic models¹⁰⁰. Thus future investigation will undoubtedly focus on describing the functions of peptides, hormones, receptors, neurotransmitters, enzymes and other factors in the proper regulation of food intake, as well as glucose and energy homeostasis, further distinguishing effects in the adult from neonatal developmental compensatory mechanisms.

In summary, the proper regulation of energy balance and glucose homeostasis requires a coordinated effort of many peptides, hormones, neurotransmitters and cell populations in various nuclei throughout the brain. This includes a distributed network of melanocortin signaling in tandem with segregated populations of arcuate POMC neurons with respect to their acute responses to leptin, insulin, serotonin and other factors required for proper energy and glucose homeostasis. These data underscore the need to identify both the means by which peptides, hormones and neurotransmitters acutely modify the cellular activity of

arcuate POMC neurons and the downstream targets of melanocortin neurons to better understand the central regulation of energy and glucose balance. These data also suggest that the melanocortin system does not act alone; rather, future investigation will have to further delineate how melanocortins intertwine with other systems to regulate food intake, energy and glucose balance.

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Figure 1. Central regulation of food intake and energy expenditure

(a) Multiple peripheral factors have been shown to modify food intake and energy expenditure through direct effects on the CNS. (b) Evidence suggests that melanocortin signaling regulates these physiological processes by means of distinct projection patterns originating from POMC neurons in the arcuate nucleus (Arc). Ultimately, MC4 receptor (MC4R)-expressing neurons downstream of POMC neurons act to suppress food intake and increase energy expenditure. Hypothalamic NPY/AgRP, paraventricular nucleus of the hypothalamus (PVH) and VMH neurons, as well as hindbrain DVC, parabrachial nucleus (PBN) and spinal cord intermediolateral cell column (IML) neurons, also regulate or counter-regulate these activities. PP, pancreatic polypeptide; PYY, peptide YY; 3V, third ventricle.