Published in final edited form as:

Front Neuroendocrinol. 2010 January ; 31(1): 1. doi:10.1016/j.yfrne.2009.10.007.

The neuroendocrinology and neuroscience of energy balance

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Keywords

hypothalamus; obesity; mesolimbic; dopamine; satiety; brainstem; leptin; ghrelin; development; inflammation

The past 15 years has witnessed unprecedented growth in our understanding of the neural and neuroendocrine systems that regulate energy homeostasis. In addition to upholding many of the predictions made prior to this period, the field has elucidated hormones, circuits, and processes that contribute to energy balance, and has identified new hypotheses, dilemmas, and predictions to be examined in the near future. The modulation by energy status of variables that govern energy intake (eating) and expenditure have been understood for some time: Animals and humans undergoing caloric restriction exhibit increased “craving” for food (especially calorically dense food) and diminished satiety, promoting increased feeding (Schwartz et al., 2000). Undernourishment simultaneously provokes increased metabolic efficiency, decreased locomotor activity, and diminished activity in endocrine axes (e.g., thyroid, gonadotropic, etc.) that require energy utilization (Ahima et al., 2000). Equally important, overfeeding and acute weight gain decrease feeding and increase parameters of energy expenditure, promoting the rebound of energy stores toward their baseline status (Rosenbaum et al., 2002; Schwartz et al., 2000).

Prior to the recent and ongoing explosion of insight into mechanisms of energy balance was the idea that brain systems integrate signals of energy status and thus appropriately regulate the determinants of energy balance. Indeed, brain systems in the hypothalamus were known to mediate the neuroendocrine response to altered energy balance (Ahima et al., 2000). Nuclei in the basomedial hypothalamus and in the brainstem each contribute to the regulation of satiety, while the lateral hypothalamus and the mesolimbic dopamine system (which mediates the incentive value of food, sex, and other “rewarding” things) contribute to the hedonic response to foods (Schwartz et al., 2000; Kelley et al., 2005; Myers, Jr. et al., 2009). Not as clear 20 years ago were the nature of these energy sensors, the precise identities of the neural

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mediators of energy intake and expenditure, and mechanisms by which the energy sensors regulate the CNS to control feeding and energy utilization.

Beginning with the discovery of leptin in 1994 (Zhang et al., 1994), many of these gaps in our knowledge have been filled. Leptin is an adipocyte-derived hormone that circulates in approximate proportion to long-term energy stores: Increased fat storage promotes increased leptin production, while decreasing adiposity or increased energy utilization blunts the secretion of leptin. Leptin decreases feeding and permits metabolic and neuroendocrine energy expenditure.

Soon after the identification of leptin came the realization that leptin acts within the central nervous system and the elucidation of important leptin-sensitive hypothalamic neural systems, especially neurons located within the arcuate nucleus of the hypothalamus (ARH) (Schwartz et al., 2000; Myers, Jr. et al., 2009). Central to this understanding was the identification of the now extensively-studied anorexigenic melanocortin neurons of the ARH, along with their orexigenic counterparts that express agouti-related peptide and neuropeptide Y.

Insulin, which has been recognized as a signal of energy stores before the discovery of leptin, acts on similar CNS systems (Schwartz and Porte, Jr., 2005). A great deal of recent work has explored the molecular mechanisms by which hormones such as leptin and insulin act to control these important neural systems. The laboratory of Jens Bruning has contributed substantially to our understanding of these mechanisms, and their chapter in this issue summarizes and synthesizes the great deal that we have learned over the last decade about the ARH systems that regulate energy balance, and the molecular mechanisms that control these pathways.

Ghrelin, an octanoylated gut peptide, represents another relatively new and important hormonal signal of acute energy balance (it signals energy deficit), and often functions to oppose the action of leptin (Tschöp et al., 2006). While many issues regarding the regulation of activated (acylated) ghrelin remain to be elucidated, an abundance of evidence supports the importance of this hormone and its receptor to the control of neural systems that affect energy balance. Writing with his colleagues, Matthias Tschöp, who initially discovered the orexigenic action of ghrelin and who continues to work at the forefront of ghrelin biology, synthesizes the history and current understanding of this hormone, as well as identifying important questions for the future.

As signals of energy repletion, such as insulin and leptin, rise with increased adiposity, including in obesity (Considine et al., 1996), many investigators have begun to explore potential mechanisms by which ARH circuitry may become refractory to the action of these hormones. While some of the mechanisms that may promote decreased leptin action in the hypothalamus currently appear to be straightforward (e.g., the increased action of feedback signals with increasing leptin levels), issues surrounding the potential role of hypothalamic inflammation have become particularly vexing: One set of compelling data suggest a role for inflammatory signals in the attenuation of anorectic signaling by ARH circuits, while other (similarly robust) data reveal a role for hypothalamic inflammatory signals to promote anorexia in response to several sickness syndromes. The article by Wisse, et al., in this issue summarizes these confusing findings, and elaborates several hypotheses that may explain these discrepancies, along with important issues that must be addressed to understand the apparently multiple roles for hypothalamic inflammatory signals in the regulation of energy balance.

While processes such as feedback inhibition and inflammation may attenuate anorectic signaling in the ARH in response to energy excess, thereby exacerbating obesity, many other processes likely contribute to the establishment of obesity. In addition to the omnipresence of readily-available, tasty, hedonically “rewarding” foods that contribute to nutritional excess, a variety of data also suggest that altered perinatal nutrition may “program” the organism for

increased adiposity and related metabolic disorders later in life (Myers, Jr. et al., 2005; Simerly, 2008). Work on several fronts during the past several years brought increased attention to neural mechanisms that respond to perinatal hormonal and nutritional factors and may contribute to metabolic programming. Drawing upon a lengthy experience with the developmental programming of multiple CNS systems, Grove, et al., review the evidence for perinatal metabolic programming and the CNS mechanisms that may underlie these processes and their sequelae.

Additionally, it has become clear that hypothalamic systems that respond to leptin, insulin, and ghrelin overlap to a substantial level with many of the brain systems that respond to nutrient levels to modulate peripheral metabolism (Kahn and Rossetti, 1998). The counterregulatory response to hypoglycemia, which stimulates the mobilization of metabolites in the periphery and increases feeding, represents a powerful paradigm with which to elucidate the CNS pathways that control metabolism. The article by Watts and Donovan discusses the organization and regulation of the circuits underlying this important response, focusing on hypothalamic and other limbic centers outside of the ARH. The analysis of these circuits serves not only to remind us that all of the neurons studied by those of us interested in the central mediators of energy balance exist not in isolation, but as nodes in complex and widely-projecting neural systems- many of which operate rather independently of the ARH. As neural pathways that respond to hypoglycemia overlap extensively with largely unexplored neural circuits that respond to hormones such as leptin, the integration of our knowledge of these circuits with recent discoveries on the molecular and hormonal fronts will enhance our understanding of the mechanisms that control energy balance (Myers, Jr. et al., 2009).

Along with non-ARH hypothalamic systems that contribute to the control of energy balance, several non-hypothalamic brain regions play crucial roles in the regulation of feeding. Many of these neural systems respond to a variety of signals of energy status and represent the main sites of historical (pre-leptin) focus for research on food intake; the importance of these centers are now re-emerging from the long shadow cast by the ARH circuitry over the past decade (Myers, Jr. et al., 2009; Kelley et al., 2005; Grill, 2006; Berthoud, 2007). For instance, as detailed by Grill and colleagues, the hindbrain directly receives a plethora of signals to increase satiation and limit feeding. Not only do hindbrain centers such as the nucleus of the solitary tract (NTS) receive information from the vagus and various gut peptides, but the hindbrain responds directly (as well as indirectly via the hypothalamus) to leptin, and modulates meal size even when surgically disconnected from the hypothalamus.

While the control of satiation by the brainstem functions in large part to limit meal size, regions in the midbrain (including dopaminergic neurons in the ventral tegmental area (VTA)), along with their projections into the striatum (nucleus accumbens (NAc), etc.) and elsewhere contribute to the incentive value of food and thus to the inception of feeding (Kelley et al., 2005). These circuits (collectively, the mesolimbic dopamine system), have long represented a major focus for investigations into the neurobiology of reward and behavioral approaches to the study of food intake. The identification of roles for hormonal signals of energy status in the modulation of the mesolimbic DA system has sparked the drive to understand mechanisms by which signals of energy balance modulate the dopaminergic circuitry and associated behaviors. In this issue, we are fortunate to have two reviews directed toward distinct aspects of this important topic: Stephanie Fulton, one of the first to examine roles for leptin in the modulation of dopamine-regulated behaviors, has contributed an elegant and comprehensive discussion of this complicated system, with an informative analysis of critical neuroanatomic/behavioral observations that provide an essential context for data derived from molecular/hormonal approaches. The group of DiLeone has tackled more recent molecular approaches to the mesolimbic DA system, including a variety of ongoing debates regarding roles for specific midbrain neurons. This review integrates a great deal of recent genetic data with some

more classical observations, and offers useful behavioral and pharmacological insights that inform our understanding of how the mesolimbic dopamine system impacts feeding behavior. Taken together, these discussions of the hindbrain and mesolimbic dopamine system will be crucial as we attempt to synthesize a more global and complete model of the neural and neuroendocrine control of energy balance. Just as the discovery of leptin and its central mode of action caused renewed attention on how the nervous system impacts body weight and energy metabolism, the work discussed in this issue demonstrates that the study of energy balance is defining an expanding area of neuroscience research.

Acknowledgments

This work was supported by grants from the American Diabetes Association, the American Heart Association, and NIH DK057631 and DK057768 (to MGM), NIH DK87056 (to MGM and RBS), and by DK065900 (to RBS).

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