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REVIEW ARTICLE

Neuroendocrine Regulation of Energy Metabolism

Marcelo O. Dietrich[1,2], Tamas L. Horvath[1,3,4]

Program on Cell and Neurobiology of Energy Metabolism, Section of Comparative Medicine[1], Yale University School of Medicine, New Haven, CT, USA; Department of Biochemistry[2], Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Departments of Obstetrics, Gynecology and Reproductive Sciences[3] and Neurobiology[4], Yale University School of Medicine, New Haven, CT, USA

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 article 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. (*Endocrinol Metab* 27:268-273, 2012)

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In mammals, energy balance is dictated by energy intake and expenditure. The former is mostly derived from food consumption, even though modern societies have seen an increase in the use of high calorie (energy) drinks that provide an additional source of energy (drink intake). Mammals cannot derive energy from other sources, even though other biological systems can. For example, plants extract energy from sunlight through the process of photosynthesis. Thus, the regulation of energy intake in mammals is quite simple, since only food or drink supplies the energy. On the other hand, energy expenditure is a more complex part of the equation consisting of a basal expenditure that is utilized for autonomic functions, as well as an activity dependent expenditure which is determined by the individual.

The whole organism is involved in the regulation of energy balance, accomplished through cross talk between the peripheral organs and the central nervous system to regulate momentary and long term energy balance. This is a very tightly maintained system, evidenced by the fact that minimal disruptions in energy balance can generate severe consequences to body metabolism. For example, if a typical human consumes 2,000 calories (cal) per day, and expends 1,970 cal, they will have a net positive balance of 30 cal per day (less than a bite of a chocolate bar). This minimal amount of positive balance per day will generate an approximately 12,000 cal positive energy balance over the course of a year. Because this "extra" energy mainly deposits into the adipose tissue of mammals, it is expected that this 12,000 cal will do just that. One gram of fat contains approximately 9 cal, thus this positive balance of 10,000+ cal will accumulate more than 1 kg of fat over 1 year. If this persists, during the course of 10 years, this person will have a very large fat depot as a consequence of a "small" daily positive energy balance. The nature of this imbalance is unknown; however, a modern lifestyle in which high calorie consumption comes mainly from fat and simple sugars and is combined with low energy expenditure (sedentary society) is likely to be a major contributor. Other factors are also implicated, such as high levels of stress and/or sleep deprivation that are prevalent in today's society. This chapter touches upon these issues and delineates our current understanding and some state-of-the-art ideas as to how the brain contributes to the regulation of energy balance (and its imbalance).

Corresponding author: Tamas L. Horvath
Program on Cell and Neurobiology of Energy Metabolism, Section of Comparative Medicine and Departments of Obstetrics, Gynecology and Reproductive Sciences and Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA
Tel: +1-203-785-2525, Fax: +1-203-785-7499, E-mail: tamas.horvath@yale.edu

THE BRAIN AS A CENTRAL REGULATOR OF ENERGY BALANCE

Even though various brain areas are essential for the regulation of both energy intake and expenditure, it is noteworthy that several other tissues produce a myriad of substances (hormones, cytokines, etc.) that will in turn affect the central nervous system. Thus, appropriate signaling between peripheral organs and the brain is critical to maintaining the physiological regulation of energy balance.

As a side note, it is worth looking at this from an evolutionary perspective in that neural cells did not compose the first individuals, or, at least, neural cells were not the first cells to emerge on the evolutionary scale. This fact implies that these cells are a consequent specialization of the evolutionary process based upon a predecessor. Thus, it is a plausible idea that during the course of evolution, not only did brain cells emerge, but the ability of these cells to sense factors being released by other cells of the body did as well. This concept has been explored over the past decades in biological systems and has proven to be correct.

The brain can be described as being composed of a complex network of nuclei that communicate with each other to dictate behavior as well as regulate bodily functions. The first studies to elucidate some of the brain structures that are important in the regulation of energy balance date back to the early 1900's. These earlier findings suggested that the basal part of the brain was involved in the regulation of homeostatic functions. More detailed examinations identified the precise nuclei that regulate energy balance in mammals. Lesions to more medial parts of the basal hypothalamus were found to cause hyperphagia and obesity [1-4]. This region, the ventromedial hypothalamic nucleus was then considered to be the "satiety center" of the brain. On the other hand, bilateral lesions to more lateral areas of the hypothalamus led to a complete cessation of feeding, distinguishing it as the "hunger center" [3,4]. This classic "two-center" hypothesis is still in use today and several reports have confirmed this data using more advanced techniques. Later, chemical lesions caused by monosodium glutamate identified the arcuate nucleus (ARC) within the hypothalamus as a key region in the regulation of food intake [5-7]. Rodents treated with monosodium glutamate became obese, an observation that highlighted the significance of cells within the ARC that were sensitive to this chemical as having an anorexigenic tone. Together with lesion data showing that whole ARC damage causes very little change in energy balance, these results raised the idea of the existence of another group of cells in the ARC with orexigenic properties (not sensitive to monosodium glutamate). This important observation was the earliest footprint of the subsequent elucidation of the melanocortin system of the ARC (see below).

THE ARC MELANOCORTIN SYSTEM AS A KEY METABOLIC SENSOR

The ARC is located in the most basal part of the brain and is a key region in the regulation of several neuroendocrine responses and homeostatic signals [8]. The putative lack of blood-brain barrier in this part of the brain indicates that it can serve as a sensor for peripheral signals [9-12]. Within the ARC are located two groups of neurons that have singular importance in the regulation of energy homeostasis. One of these groups of neurons expresses neuropeptide-y (Npy) and the agouti-related protein (Agrp) [13]. The Npy/Agrp neurons exert an orexigenic tone (stimulate food intake) by sending projections to several brain areas, most importantly the paraventricular nucleus of the hypothalamus [14-17] and the parabrachial nucleus in the brainstem [18]. These neurons have been shown to be inhibitory cells, utilizing gamma amino butyric acid (GABA) as a neurotransmitter [19]. The other population of cells located in the ARC is known to express proopiomelanocortin (POMC) derived peptides, such as alpha-melanocyte stimulating hormone and cocaine amphetamine related peptide. The POMC cells exert an anorexigenic tone, thus their activation leads to cessation of feeding and satiety [20]. The contrasting nature of these two cell populations within the ARC helps explain why lesions to the whole ARC have little effect on food intake. It is also worth emphasizing the intricate network that exists between these cell groups in the ARC, such that the Npy/Agrp neurons send GABAergic projections to the POMC cells [21-23]. Thus, an orexigenic stimulus can induce food intake by activating Npy/Agrp cells and concomitantly inhibiting the neighboring POMC cells. This seemingly redundant network is an important evolutionary outcome comprising a constitutive mechanism by which an orexigenic response is preferred over one which is anorexigenic. This organization of the ARC connections was likely important during periods of limited food availability, maintaining a status of hunger as the default in the brain. As indicated below, the connectivity of these cells in the ARC fluctuates depending on hormone levels and according to energy availability, thus providing evidence of a mechanism by which the brain

senses peripheral signals to coordinate energy balance.

SYNAPTIC PLASTICITY MODULATES THE NEUROENDOCRINE RESPONSE IN THE ARC: HOW THE BRAIN SENSES HORMONES

Earlier studies indicated that peripheral factors were acting in the brain to promote satiety. Indeed, two centuries ago, the famous English physiologist, Sir Charles Sherrington proposed that food intake (and energy expenditure) could be regulated in a similar way as respiration, where peripheral organs produce substances that travel through the blood to signal the brain. Further breakthroughs came in the 1950's with several findings from studies of the obese and diabetic phenotype of the naturally occurring *ob/ob* and *db/db* mice, respectively. The *ob/ob* mice were first described as mice with a massive obese phenotype [24]. The inheritability of this mutant followed a recessive ratio according to Mendel's law [24]. The *obese* (*ob/ob*) gene was later found to occur on chromosome six of these mice.

In the wake of this discovery, some of the first experiments on this mutant mouse provided insight into how the earlier physiologists identified the mechanisms implicated in energy homeostasis. In the 1950's to 1970's, parabiosis was one of the few techniques available to identify blood factors that could influence physiology. Using this method it was possible to combine the blood circulation of two animals and study whether a humoral factor from one could affect the other. Research headed by Coleman and colleague [25,26] utilized parabiosis to investigate the missing factor in the *ob/ob* mouse. When an *ob/ob* mouse was conjoined with a normal mouse, the body weight of the obese mouse slowly approached normal, indicating that a circulating factor from the control mouse was able to signal the obese animal to lose weight. A similar experiment was done using the diabetic mouse (*db/db*). In this case, the *db/db* mouse had no major modification of its phenotype, however, the normal mouse lost weight, so much so that it nearly starved [25,26]. In this case, a factor produced in the *db/db* mouse was traveling into the blood of the control causing it to stop eating. Years later, utilizing more advanced techniques, researchers lead by Dr. Jeffrey Friedman (1994) using point mutation identified the gene involved in the obese phenotype of the *ob/ob* mouse [27,28]. The protein encoded by this gene was called leptin, from the greek *leptos*, meaning thin [28]. Not long after this discovery, the gene missing in the *db/db* mouse was also revealed, and was found to be the receptor for leptin [27,29,30], thus explaining the findings of the parabiosis studies of Coleman [25,26]. Moreover, leptin was found to be produced mainly by the fat tissue, and the *db/db* mouse, which was obese, had high levels of circulating leptin. Thus, in the parabiosis studies, leptin crossed the circulation from the *db/db* mouse and acted in the normal mouse, leading it to starve [25-27].

The discovery of this important anorexigenic protein, leptin, led to a better understanding of how hormones could act in the brain to modulate energy metabolism. Ten years after its discovery, another important finding by the laboratory of Dr. Tamas Horvath (2004) shed light on the brain mechanisms implicated in the sensing of peripheral stimuli [23]. Utilizing POMC-green fluorescent protein (GFP) and Npy/Agrp-GFP transgenic mice (mice in which green fluorescent protein is under the transcriptional control of either the POMC or Npy genomic sequence), they found that leptin induces a rapid rearrangement of the ARC neuronal circuitry that is responsible for governing energy balance [23]. When leptin deficient mice (*ob/ob*, i.e., $Lep^{-/-}$) were compared to wild type mice, they exhibited an increased number of excitatory inputs on the Npy/Agrp cells, with a concomitant decrease in the number of inhibitory inputs on these cells. The opposite profile was observed for the POMC neurons of the ARC. Interestingly, leptin replacement to the $Lep^{-/-}$ mice reversed these neuroanatomical adaptations so that they were like that of the wild type phenotype, thus indicating that these connections were sensitive to peripheral hormones and could modulate energy balance by orchestrating the synaptic inputs onto the ARC neurons [23]. Following this work, another study raised the possibility of targeting this mechanism of synaptic remodeling to treat eating disorders. By administering estrogen to obese mice, Gao et al. [31] mimicked the effects of leptin on the synaptic inputs of POMC and Npy/Agrp cells resulting in decreased body adiposity over time.

The discovery of the brain as a tissue that undergoes constant remodeling [23,31-35] opened avenues for several lines of thinking about how the brain can adapt and regulate energy homeostasis. One of these very interesting hypotheses that take into account the plasticity of the adult brain is the postulation that newly formed neurons in the hypothalamus can have an effect on regulating food intake. The first report to raise this possibility showed that treatment with ciliary neurotropic factor (CNTF), a cytokine known to decrease body weight, induces the proliferation of cells in the hypothalamus [36]. Many of these cells differentiated into neurons that were responsive to hormones, such as leptin. The anorexi-

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genic effect of CNTF was counteracted by the elimination of cell proliferation in the brain, emphasizing the likely importance of cell division in the adult brain under certain circumstances to modulate energy metabolism [36,37]. This study was followed by a recent publication showing that slow ablation of Agrp neurons in the ARC induces cell proliferation in the same area, and part of these new cells differentiate into Agrp neurons [38]. When cell proliferation was inhibited in the brain containing the ablated Agrp neurons, the mice lost weight and decreased their body adiposity. Overall, these data indicate that the hypothalamus is capable of neurogenesis even in the adult brain, and that this process is important for the regulation of food intake [36-38].

HORMONAL CROSS TALK BETWEEN PERIPHERAL ORGANS AND THE BRAIN

So far, this chapter has described the effects of leptin as a model of an anorexigenic molecule that allows for communication between the fat tissue and the brain. However, leptin is not the only hormone important in the regulation of energy metabolism. Indeed, there are a growing number of peptides, proteins, hormones, and cytokines being described as modulators of energy balance.

Contrasting the effects of leptin is a well-known orexigenic peptide, ghrelin. Ghrelin consists of 28 amino acids and is released by the gut [39,40]. Its release from the stomach is mainly at times of negative energy balance. Ghrelin reaches the blood and signals the ARC neurons to induce food intake through the G-protein-coupled growth hormone secretagogue receptor [41-43]. Interestingly, ghrelin is produced as a larger peptide, which is cleaved into at least two small molecules [39,44-46]. The other part of the pre-ghrelin cleavage has been described to have opposite actions to ghrelin, promoting satiety [46]. This peptide has been named obestatin, and is just one example of the complexity of the hormonal network involved in the regulation of energy balance [45,46]. Moreover, the involvement of ghrelin to modulate appetite and metabolism has been a target of intense investigation leading to new concepts in neuroendocrinology. First, it has been shown that the effect of ghrelin to promote appetite is dependent upon fatty acid metabolism in the hypothalamus [47]. This effect was reliant upon mitochondrial energy metabolism, indicating for the first time that a peripheral hormone can alter brain bioenergetics, and thus, can ultimately change energy balance [47]. Intriguingly, fatty acid metabolism through beta-oxidation has been neglected as a pathway involved in the production of energy by neuronal cells. These studies challenge this classic concept, and provide more insight into the flexibility of the brain to adapt to different environmental conditions. Another interesting fact about the physiology of ghrelin is that it needs to be modified to be active. The acylation of ghrelin by the enzyme, ghrelin O-acyltransferase (GOAT), transforms it from its inactive to its active form [48-51]. The availability of GOAT has been shown to be dependent upon the presence of specific lipids in the diet, thereby linking the ingestion of lipids with energy balance [52].

Leptin as a classic anorexigenic, and ghrelin as a representative orexigenic molecule are just a couple of examples of substances involved in the intricate field of metabolic integration of energy balance. Innumerable new molecules that play a role in modulating energy metabolism are regularly being described, thus adding to the already complex neuroendocrine network that regulates food intake and energy expenditure.

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