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PVN pathways controlling energy homeostasis

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Abstract

Research into the control of energy balance has tended to focus on discrete brain regions, such as the brainstem, medulla, arcuate nucleus of the hypothalamus, and neocortex. Recently, a larger picture has begun to emerge in which the coordinated communication between these areas is proving to be critical to appropriate regulation of metabolism. By serving as a center for such communication, the paraventricular nucleus of the hypothalamus (PVH) is perhaps the most important brain nucleus regulating the physiological response to energetic challenges. Here we review recent advances in the understanding of the circuitry and function of the PVH.

Keywords: Corticotrophin releasing hormone, hypothalamus, leptin, oxytocin, paraventricular nucleus, thyrotropin releasing hormone

INTRODUCTION

To survive and procreate, a biological organism must manage energy resources effectively. When food is abundant, animals can maintain a larger body size, produce and care for many offspring, and expend energy on recreational activity. When food is scarce, calibrating body size, temperature, reproduction, activity, and cellular metabolism to the available resources becomes essential. Given that different mechanisms regulate these functions, a unified control system is essential. The brain, and the hypothalamus in particular, have evolved to serve this role in mammals.

Study of the hypothalamic control of energy balance has had a laser-like focus on the arcuate nucleus (ARC), largely because of the early identification of orexigenic neuropeptide Y/agouti-related protein (NPY/AgRP) neurons and anorexigenic pro-opiomelancortin/cocaine and amphetamine-regulated transcript (POMC/CART) neurons in that location. Activating POMC/CART-expressing neurons suppresses feeding, whereas activating NPY/AgRP-expressing neurons stimulates feeding.[1] bl2xbNofintake and energy expe
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However, the function of the arcuate nucleus must be placed in a wider context. The hindbrain, amygdala, and neocortex play important roles in the regulation of energy balance,[8–10] as do other hypothalamic nuclei. Sensory information about insufficient food or nutrients travels from the viscera to

the pons and medulla in the hindbrain. These areas can trigger a change in feeding behavior and

express NPY, C2 and C3 neurons in the dorsal medulla, and A6 neurons in the pons.[31] The hindbrain induces release of epinephrine from the adrenal gland in response to glucoprivation even if connections to the forebrain have been disrupted.[31] Severe drops in blood glucose levels threaten survival; epinephrine-induced release of glucose stores in liver must occur, regardless of whether an animal possesses large adipose tissue depots. Input from leptin-sensitive ARC pathways is therefore unnecessary for this response.

However, the PVH is required for glucoprivation to promote feeding and corticosterone release while shutting down reproduction.[32] These responses require hindbrain NPY neurons that project prominently to the parvocellular divisions of the PVH.[33] Interestingly, NPY levels in the PVN increase to compensate when brainstem NPY circuits are lesioned.[34] Conversely, NPY fibers and Y1 receptors increase in the hypothalamic paraventricular nucleus after denervating the Arc.[35] Thus, loss of hypothalamic NPY circuits may increase brainstem NPY projections and PVH sensitivity to NPY.

Other triggers of reflexive feeding, such as lipoprivic feeding can activate different hindbrain pathways. However, any urgent physiological need will require a multifaceted response organized by a neural control center. Whether responding to hypoglycemia or more routine energy needs, the PVH has the ability to divert behavior and physiological functions toward the goal of obtaining food. Along with input from CA and non-CA fibers from the spinal cord and brain stem, the PVH also receives input from the ARC and other leptin-sensitive areas of the hypothalamus. These leptin-responsive pathways permit long -term control over body weight by subtly changing the daily drive for feeding and energy use.

Formation of arcuate nucleus-paraventricular nucleus of the hypothalamus connections

Leptin-sensitive ARC POMC and NPY/AgRP neurons project strongly to the PVH in the adult.[36] These connections to the PVH arise at preprogrammed time points during postnatal development. Altered development of these connections can have a profound effect on adult body weight.[37] During the first 3 weeks of life, a leptin surge occurs in mice.[38] Although leptin promotes a-MSH release and suppresses food intake in adults, it apparently has no regulatory effect on food intake and neuropeptide expression at this age.[39] Instead, during the suckling period, leptin promotes growth of axons from ARC.[40] Indeed, leptin-deficient *ob/ob* mice show reduced AgRP and -MSH fiber density in the PVH. Injecting leptin chronically during the first week of life can reverse this effect.[37] In other contexts, leptin stimulates synaptogenesis,[41] neurogenesis,[42] and dendrite formation.[43] Thus, the neonatal leptin surge may also promote neuron differentiation of progenitor cells and their migration.[44]

New data show that environmental factors such as maternal nurturing and nutrition can change these connections. Manipulating nutrients during gestation or lactation modulates the neonatal leptin surge and PVH fiber density in offspring.[45,46] Neonatal overfeeding [illegible] 6(-(oCs6 cs .18431

effects, as POMC neuron numbers rose in the ARC. Ad

pathways tonically stimulate CRH mRNA expression.[75

terminals innervate TRH neurons.[101] Of the TRH neurons located in the medial parvocellular division of the PVH, 50-60% express MC4R mRNA.[102] Administering -MSH ICV can maintain TRH release during fasting.[103] AgRP, an MC4-R antagonist, can cause hypothyroidism by down regulating TRH mRNA expression in the PVH.[98,104] Recent work suggests that TRH neurons also directly sense leptin.[105,106] Leptin directly regulates the TRH promoter[107] and stimulates TRH peptide biosynthesis and release from dispersed hypothalamic neurons and cultured tissue.[106,108] Moreover, fasting animals respond to systemic leptin with increased TRH mRNA in the PVH and normalized TRH peptide and thyroid hormone levels.[109–111] Therefore, leptin may act directly on TRH neurons to increase energy expenditure independent of the anorectic drive from the ARC.

Oxytocin Neurons

OXT neurons modulate reproductive processes involved in birth, lactation, and maternal behavior.

the PVH become active in mice following cold exposure.[137] Central OXT induces hyperthermia in rabbits and mice.[138,139] Moreover, both OXT- and OXT receptor-deficient mice exhibit an impaired thermogenic response to a cold challenge[137] and reduced epinephrine levels resulting from a decreased sympathetic tone.[123] These data suggest that posterior PVH OXT neurons participate in regulating body heat as well as food intake; both functions may participate in the control of energy reserves.

Conclusions

The studies we have highlighted clearly demonstrate the importance of the PVH in coordinating the control of energy balance. Indeed, one should view the PVH as a meeting point for distributed pathways throughout the brain regulating energy use. Melanocortin pathways stretch from the caudal brainstem to the hypothalamus and beyond. Activating any portion of those circuits can change food intake, body weight, heart rate, and body temperature.[140] By passing through the PVH, hunger-sensitive pathways can interact with neuron groups that regulate reproduction, stress, body temperature, and circadian cycles. Additional research into the healthy and pathological interaction of these different systems will advance the understanding of metabolic disease.

The PVH thus presents a crucial target for treating obesity in the future. New techniques allowing targeted silencing or activating of PVH neurons will definitively determine whether the PVH is unique or

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