PVN pathways controlling energy homeostasis

Jennifer W. Hill

Department of Physiology and Pharmacology, Center for Diabetes and Endocrine Research, University of Toledo Medical Center, Obstetrics-Gynecology, University of Toledo, USA

Corresponding Author: Dr. Jennifer W. Hill, University of Toledo College of Medicine, Mail Stop 1008, 3000 Transverse Avenue, Toledo, OH 43614, USA. E-mail: JenniferW.Hill@utoledo.edu

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-opiomelanocortin/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] Both of these neuronal groups respond to the circulating adiposity signal leptin, released by fat tissue,[2,3] and ghrelin, released by the stomach.[4] By altering ARC neuronal activity, leptin powerfully inhibits food intake and energy expenditure. In contrast, plasma ghrelin concentrations increase under conditions of negative energy balance to stimulate feeding and lower energy expenditure.[5–2]

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 metabolism directly. The hypothalamus and higher order areas also process this sensory information to refine behavioral and metabolic responses.[11] Finally, the hypothalamus and the more ancient hindbrain regions each process humoral input from the pancreas, liver, adipose tissue, and other sources.[12] As this review will illustrate, the paraventricular nucleus of the hypothalamus (PVH) serves as a linchpin in this system for regulating the physiological response to energy scarcity.

The role of the paraventricular nucleus of the hypothalamus

The PVH receives afferent inputs from many centers of the hypothalamus including the ARC, lateral hypothalamic area, subfornical organ, organum vasculosum of the lamina terminalis, medial septum/diagonal band of broca, medial preoptic area, and suprachiasmatic nucleus.[13,14] The hindbrain also communicates with the PVH. For instance, the lateral parabrachial nucleus of the pons sends projections to the PVH. From the medulla, the A5 sympathetic premotor region, nucleus tractus solitarius (NTS), dorsal motor nucleus of the vagus, and the ventrolateral medulla project to the PVH as well.[13,14]

As recently determined through anterograde tracing,[15] neurons from the PVH project widely throughout the brainstem. The rat PVH contains two major sections, the parvocellular (“small cell”) and the magnocellular (“large cell”) divisions. Parvocellular autonomic neurons project to the NTS,[16,17] to the dorsal motor nucleus of the vagus (the origin of parasympathetic preganglionic cells), and to the intermediolateral cell column of the spinal cord (that contains sympathetic preganglionic fiber cell bodies).[18] White adipose tissue,[19,20] pancreas,[21] liver[19] and brown adipose tissue[22] are thereby linked multi-synaptically with the PVH. Though partly interspersed with parvocellular neuroendocrine neurons, these caudally projecting cells form an entirely separate subpopulation.[23] Through these connections, the PVH directs autonomic systems controlling pancreatic secretion, adipose storage, thermogenesis, peripheral glucose uptake, and hepatic glucose flux.[12,19,24] For instance, the PVH tonically inhibits ingestive behavior via its massive projections to the NTS and via relay neurons to the lateral parabrachial nucleus.[15] These connections also transmit viscerosensory feedback to regulate the amount of food, water, and salt ingested.[25–27] For example, the PVH can reduce feeding by increasing the response of the NTS to vagal signals of gastric distention from the stomach.[28] Therefore, the PVH can perceive and modify a wide variety of autonomic signals related to energy balance.

The PVH also acts as the primary endocrine control center of the brain. Magnocellular neuroendocrine neurons, located primarily in the ventrolateral portion of the PVH, send their axons into the posterior pituitary. There they release either vasopressin or oxytocin (OXT) into the systemic circulation to influence fluid balance or the reproductive axis. In addition, medial parvocellular neuroendocrine neurons release signaling peptides at the median eminence. These peptides pass through the pituitary portal system to the anterior pituitary, where they regulate the production of pituitary hormones that control many physiological axes. Specifically, corticotrophin-releasing hormone (CRH) neurons regulate the adrenal axis, thyrotropin-releasing hormone (TRH) neurons regulate the thyroid axis, dopamine neurons regulate the reproductive axis, and somatostatin neurons regulate growth and development.

Neurons within the PVH also communicate with each other. Many gamma-aminobutyric acid (GABA) interneurons reside in the halo zone surrounding the PVH and occasionally inside the nucleus.[29] In addition, glutamate interneurons exist within the PVH.[30] The PVH uses this connectivity to integrate afferent input and to sculpt an integrated response to energy deficits.

Hindbrain-paraventricular nucleus of the hypothalamus communication

Strong physiological stimuli, such as glucoprivation, can sometimes trigger responses without input from the hypothalamus. Glucoprivation selectively activates subgroups of hindbrain neurons that produce catecholamines (CAs). These groups include A1/C1 neurons in the ventrolateral medulla, which co-
express NPY, C2 and C3 neurons in the dorsal medulla, and A6 neurons in the pons.\cite{31} The hindbrain induces release of epinephrine from the adrenal gland in response to glucoprivation even if connections to the forebrain have been disrupted.\cite{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.\cite{32} These responses require hindbrain NPY neurons that project prominently to the parvocellular divisions of the PVH.\cite{33} Interestingly, NPY levels in the PVN increase to compensate when brainstem NPY circuits are lesioned.\cite{34} Conversely, NPY fibers and Y1 receptors increase in the hypothalamic paraventricular nucleus after denervating the Arc.\cite{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.\cite{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.\cite{37} During the first 3 weeks of life, a leptin surge occurs in mice.\cite{38} Although leptin promotes α-MSH release and suppresses food intake in adults, it apparently has no regulatory effect on food intake and neuropeptide expression at this age.\cite{39} Instead, during the suckling period, leptin promotes growth of axons from ARC.\cite{40} Indeed, leptin-deficient ob/ob mice show reduced AgRP and α-MSH fiber density in the PVH. Injecting leptin chronically during the first week of life can reverse this effect.\cite{37} In other contexts, leptin stimulates synaptogenesis,\cite{41} neurogenesis,\cite{42} and dendrite formation.\cite{43} Thus, the neonatal leptin surge may also promote neuron differentiation of progenitor cells and their migration.\cite{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.\cite{45,46} Neonates exposed to maternal obesity in utero display an amplified and prolonged surge of leptin.\cite{47} In addition, leptin resistance in the offspring of obese mothers causes reduced AgRP-immunoreactivity in the PVH at one month of age.\cite{48} Early malnutrition also increases the risk for obesity.\cite{49} Whereas the ARC of growth-restricted animals remains leptin-sensitive, a low and delayed plasma leptin surge impairs the projection of α-MSH neurons to the PVH.\cite{47-50} Restricting calories during gestation and lactation also enlarges the PVH of offspring by increasing the proliferation of its neurons.\cite{51} Importantly, injecting leptin during the suckling period to growth-restricted rodent neonates prevents adult obesity.\cite{52} Thus, it appears that the developmental effects of an excessively large or small neonatal leptin surge can ultimately lead to obesity.

Other factors such as insulin may also program long-term energy balance. Insulin acts as a neurotrophic factor that promotes neurite outgrowth, protein synthesis, and neuronal survival.\cite{53–55} Steculorum and Bouret recently demonstrated that offspring of insulin-deficient diabetic rats have a decreased density of both AgRP and α-MSH fibers in the PVH.\cite{56} Reduced cell numbers did not cause these
effects, as POMC neuron numbers rose in the ARC. Additional research is needed to provide a complete understanding of the postnatal programming of PVH connections.

**Arcuate nucleus input to the paraventricular nucleus of the hypothalamus in the adult**

Leptin also plays a well-recognized role in modulating excitatory and inhibitory input to the PVH in the adult. Both the magnocellular and parvocellular neurons of the PVH express receptors for a-MSH.\[57\] a-MSH, released by POMC neurons originating in the arcuate, promotes satsiy by binding to these melanocortin 4 receptors (MC4Rs). A large number of inhibitory NPY fibers also directly innervate parvocellular neurons of the PVH.\[58\] Increased NPY release is seen in the PVHs of food-deprived rats.\[59\] Likewise, injection of NPY or AAV-mediated overexpression of NPY in the PVH can induce a strong feeding response.\[60,61\] Conversely, reducing levels of NPY in the PVH with anti-NPY antibodies leads to reduced food intake in rats.\[62\] By acting on ARC NPY neurons, leptin suppresses the synthesis and release of their inhibitory products NPY, AgRP, and GABA.\[63\] a-MSH can then maintain an excitatory effect to promote satsiy. Destroying ARC neurons has been presumed to increase energy intake by decreasing this excitatory input to the PVH.\[64\] Indeed, Skibicka and Grill showed recently that an MC4R agonist decreases food intake when injected into the PVH.\[65\] Furthermore, selectively re-expressing MC4R in the PVH of globally deficient mice can prevent hyperphagia and obesity from developing.\[66\]

However, recent analysis adds complexity to this model of leptin-sensitive ARC input. Leptin acts directly on the PVH with no ARC input necessary.\[67,68\] In addition, Ghamari-Langroudi and colleagues have found that neuronal type and location in the PVN alters the effects of leptin. As expected, fasting suppresses and leptin depolarizes anterior PVH MC4R neurons that co-express TRH. However, in the midposterior PVH, leptin reduces the activity of parvocellular MC4R-expressing neurons that co-express OXT/vasopressin or CRH. In contrast, a-MSH appears to increase neuronal activity consistently and oppose NPY/AgRP input in both locations. Since in vitro and in vivo ip leptin decreases the activity of MC4R-expressing neurons in the midposterior PVH, direct leptin actions dominate over leptin's effects on melanocortin input from the ARC.\[67,69\] These results call into question the importance of ARC melanocortin input to the midposterior PVH in food intake control. Alternatively, direct ARC projections to hindbrain sites may mediate the profound effect of a-MSH on food intake. Indeed, the NTS receives direct descending a-MSH containing projections from POMC neurons in the ARC.\[70\] Additional work is necessary to update the prevailing model of how leptin acts in the PVH.

**Metabolic Control via Corticotrophin-Releasing Hormone, Thyrotropin-Releasing Hormone, and Oxytocin Pathways**

CRH, TRH, and OXT circuitry in the PVH has long been considered secondary to “dedicated” pathways controlling food intake and energy expenditure. However, new data highlight the role of these circuits in the control of food intake and energy use. These neurons respond to energy deficits in two ways. First, they alter neuroendocrine outflow. Second, they alter activation of brainstem and spinal sympathetic or parasympathetic preganglionic neurons. These connections allow them to influence energy balance by changing white adipose tissue,\[19\] pancreas,\[21\] liver\[19\] and brown adipose tissue\[22\] function.

**Corticotrophin-releasing hormone neurons**

CRH neurons predominate in the medial parvocellular component of the PVH.\[71\] These neurosecretory neurons control the HPA axis by releasing CRH from the median eminence. CRH triggers ACTH production by the pituitary and glucocorticoid production by the adrenal gland. In addition, subgroups of CRH immunoreactive neurons in the PVH project to autonomic targets in the brainstem and spinal cord.\[72,73\] In turn, CRH neurons receive ascending input from the brainstem. CRH neurons in the paraventricular nucleus and CRH terminals in the median eminence receive extensive excitatory inputs from CA nuclei located in the medulla and brainstem.\[74\] Indeed, adrenergic and noradrenergic
pathways tonically stimulate CRH mRNA expression. In addition, dopaminergic NPY fibers originating from the brain stem extensively innervate CRH neurons in the PVH. These brainstem CA projections promote the transcription and release of CRH in response to physical stressors, including hypoglycemia.

Along with its actions in response to stress, CRH serves an anorexigenic and catabolic role. Intracerebroventricular CRH decreases food intake and body weight gain and induces locomotor activity, brown adipose tissue thermogenesis, and sympathetically-mediated lipolysis. Food intake decreases both neuroendocrine and autonomic CRH output. Conversely, starvation decreases and leptin increases PVH CRH gene expression and peptide levels. CRH neurons also interact with leptin-sensitive melanocortin input from the ARC. CRH inhibits NPY/AgRP neurons and NPY gene expression directly. Thus, in times of fasting, decreased CRH encourages NPY's orexigenic actions. However, CRH does not depend on melanocortin pathways to inhibit feeding; CRH can reduce food intake even in obese MC4R-deficient mice. On the contrary, activity of CRH neurons may mediate some effects of ARC POMC and NPY circuitry; CRH receptor antagonism partially blocks the actions of the melanocortin agonist MTII on food intake, potentially by acting on a small subset of PVH neurons that co-express CRH and MC4R.

Recent evidence indicates that ghrelin may also play a role in CRH neuronal activity. Mice with genetic deletion of GHSR are unable to respond to stress-induced alterations of mood, feeding and metabolism, suggesting that elevated plasma ghrelin participates in stress-associated responses. Ghrelin is able to activate the CRH neurons of the PVN, and this action is sufficient to acutely increase plasma glucocorticoid levels. However, the lack of detectable CRH and ghrelin receptor co-expressing neurons suggests that stimulation by ghrelin of the HPA axis occurs via an indirect mechanism. Activation of ARC NPY neurons may mediate the ghrelin-induced activation of the CRF neurons. Alternatively, ghrelin action on non-CRF-containing PVN neurons that synapse onto CRH-neurons might explain the ability of intra-PVN ghrelin administration to activate the HPA axis.

Thyrotropin-releasing hormone neurons

The hypothalamic-pituitary-thyroid axis plays an important anorexigenic and catabolic role in energy homeostasis. TRH induces release of thyroid stimulating hormone (TSH) from the pituitary and thyroid hormone from the thyroid. Thyroid hormone, essential for thermogenesis during cold exposure, helps to maintain protein synthesis and metabolic activity in peripheral tissues. Given that it determines roughly 30% of resting energy expenditure, TH plays an important role in maintaining overall energy balance.

In mice, the TRH neurons that regulate the TSH secretion reside in the mid-level of the PVH. Starvation suppresses TRH gene expression and biosynthesis in these parvocellular neurons. The resulting drop in thermogenesis conserves energy until feeding occurs. Recent studies show that NPY reduces TRH expression and release, whereas leptin, α-MSH, and CART directly increase its expression. Other TRH neurons reside in all parts of the PVH of mice except the periventricular zone. Their axons make reciprocal contacts with CRH axons. In addition, these TRH neurons project to the brain stem and spinal cord. This output activates uncoupling protein-1 (UCP-1) in brown adipose tissue, which, along with TH, regulates body temperature. TRH neurons in the PVH also receive input from the brainstem. CA neurons, originating mostly from A1/C1 groups in the medulla, contribute around 20% of all synapses on these cells. In addition to stimulating TRH secretion via these connections in the PVH, NorEpi axon terminals form close contacts with TRH axon terminals in the median eminence. Additional hindbrain input includes dopaminergic NPY neurons, whose activity suppresses TRH production.

ARC neuropeptides play an essential role in the response of the thyroid axis to both starvation and illness. TRH neurons receive robust, inhibitory NPY input from the ARC. In addition, α-MSH nerve...
terminals innervate TRH neurons. Of the TRH neurons located in the medial parvocellular division of the PVH, 50-60% express MC4R mRNA. Administering α-MSH ICV can maintain TRH release during fasting. AgRP, an MC4-R antagonist, can cause hypothyroidism by down regulating TRH mRNA expression in the PVH. Recent work suggests that TRH neurons also directly sense leptin. Leptin directly regulates the TRH promoter and stimulates TRH peptide biosynthesis and release from dispersed hypothalamic neurons and cultured tissue. Moreover, fasting animals respond to systemic leptin with increased TRH mRNA in the PVH and normalized TRH peptide and thyroid hormone levels. 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. Residing in the PVH and supraoptic nucleus (SON) of the hypothalamus, these magnocellular neurons project to the posterior pituitary where they release vasopressin and OXT into the general circulation. However, a much greater amount of OXT is released from their dendrites and somata. This dendritic release has paracrine effects that can excite or change the excitability of neighboring parvocellular OXT neurons that express OXT receptor. Thus, magnocellular OXT release may activate parvocellular OXT neurons projecting to the brainstem as well as other circuitry.

A growing body of data suggests caudally projecting OXT neurons respond to energy balance and modulate food intake and energy expenditure. Pharmacological studies demonstrate that both systemic and ICV OXT dose-dependently reduce food intake in chow-fed rats, an effect prevented in the latter model by ICV pretreatment with an OXT-receptor antagonist. Indeed, mice deficient in either OXT or its receptor exhibit late-onset obesity. Centrally administering OXT induces weight loss and energy expenditure. Furthermore, chronic sucrose intake or a high-fat diet blunts activity of the anorexigenic OXT system. Increased OXT signaling in Syt4 mice, which lack a suppressor of OXT release, prevents diet-induced obesity (DIO). Conversely, overexpression of Syt4 in OXT neurons increases food intake and body weight gain. These studies suggest that OXT should be regarded as a neuropeptide involved in energy balance regulation as well as reproduction.

OXT neurons in the PVH serve as a component in a leptin-sensitive signaling circuit. An OXT receptor antagonist blocks leptin’s suppression of food intake. Leptin rescues the expression of OXT normally suppressed during fasting and activates OXT-producing neurons in the posterior PVH that express MC4Rs and leptin receptors. Like leptin, administering α-MSH activates OXT neurons in the PVH. Furthermore, new data show that pretreatment with an OXT receptor antagonist prevents the anorexic effects of α-MSH. However, OXT may have effects not attributable to leptin-sensitive circuitry. New work shows that OXT dose-dependently reduces food intake and body weight to a similar extent in leptin receptor-deficient Koletsky (fak/fak) rats relative to their lean littermates.

OXT-producing neurons in the posterior PVH project to the NTS and area postrema to innervate hindbrain areas. These areas reduce meal size by integrating gut-derived satiety signals with descending input from the neocortex. Indeed, systemic OXT administration robustly induces c-Fos in the NTS and area postrema and causes weight loss in DIO rats. Furthermore, OXT receptor antagonists block the satiety effects of cholecystokinin (CCK) and increase food intake and meal size. The NTS also provides autonomic innervation to the liver and other tissues. This pathway allows the OXT neurons to control glucose homeostasis. OXT mice have higher basal glucose levels, impaired glucose tolerance, and insulin resistance.

OXT neurons in the posterior PVH may also alter thermogenic energy expenditure by projecting postsynaptically to brown adipose tissue via the stellate ganglia. Indeed, OXT-expressing neurons in
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 serves as one among several redundant integrative centers in the hypothalamus. Although medicine cannot yet target precise nuclei for treating obese patients, clinical researchers have a growing interest in using deep brain stimulation as an obesity therapy.[141–143] In addition, pharmacological treatments may one day target neuron types with engineered agonists or antagonists.[144] Given the rising rates of obesity and related diseases around the world, this work may hold the key to balancing the diverse influences that can promote weight gain throughout a lifetime.

**Footnotes**

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