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

A B S T R A C T

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.

Key words: 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] 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.[5-7]

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

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

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.[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 α-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] Neonates exposed to maternal obesity in utero display an amplified and prolonged surge of leptin.[47] In addition, leptin resistance in the offspring of obese mothers causes reduced AgRP-immunoreactivity in the PVH at one month of age.[48] Early malnutrition also increases the risk for obesity.[49] Whereas the ARC of growth-restricted animals remains leptin-sensitive, a low and delayed plasma leptin surge impairs the projection of a-MSH neurons to the PVH.[47,50] Restricting calories during gestation and lactation also enlarges the PVH of offspring by increasing the proliferation of its neurons.[51] Importantly, injecting leptin during the suckling period to growth-restricted rodent neonates prevents adult obesity.[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.[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.[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 satiety 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 satiety. 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 α-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.[75] In addition, dopaminergic NPY fibers originating from the brain stem extensively innervate CRH neurons in the PVH.[76] These brainstem CA projections promote the transcription and release of CRH in response to physical stressors, including hypoglycemia.[77]

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.[78,79] Food intake decreases both neuroendocrine and autonomic CRH output.[80] Conversely, starvation decreases and leptin increases PVH CRH gene expression and peptide levels.[81,82] CRH neurons also interact with leptin-sensitive melanocortin input from the ARC. CRH inhibits NPY/AgRP neurons and NPY gene expression directly.[83,84] 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.[85] 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.[86]

Recent evidence indicates that ghrelin may also play a role in CRH neuronal activity. Mice with genetic deletion of GHSR are unable to respond as wild-type mice to stress-induced alterations of mood, feeding and metabolism, suggesting that elevated plasma ghrelin participates in stress-associated responses.[87-89] Ghrelin is able to activate the CRH neurons of the PVN, and this action is sufficient to acutely increase plasma glucocorticoid levels.[90] 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.[90] 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 also 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.[91] Starvation suppresses TRH gene expression and biosynthesis in these parvocellular neurons.[92] 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.[69,93] Other TRH neurons reside in all parts of the PVH of mice except the periventricular zone. Their axons make reciprocal contacts with CRH axons.[94] In addition, these TRH neurons project to the brain stem and spinal cord.[95] 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.[96] 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,[97] 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.[98,99]

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.[100] In addition, α-MSH nerve 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 α-MSH ICV can maintain TRH release during fasting.[103] AgRP, an MC-4-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. 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.[112-114] This dendritic release has paracrine effects that can excite or change the excitability of neighboring parvocellular OXT neurons that express OXT receptor.[115,116] Thus, magnocellular OXT release may activate parvocellular OXT neurons projecting to the brainstem as well as other circuitry.[112,117,118]

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[119] and ICV OXT[120] dose-dependently reduce food intake in chow-fed rats, an effect prevented in the latter model by ICV pretreatment with an OXT-receptor antagonist.[121] Indeed, mice deficient in either OXT or its receptor[122] exhibit late-onset obesity.[123] Centrally administering OXT induces weight loss and energy expenditure.[124] Furthermore, chronic sucrose intake or a high-fat diet blunts activity of the anorexigenic OXT system.[124,125] Increased OXT signaling in Syt4 mice, which lack a suppressor of OXT release, prevents diet-induced obesity (DIO).[124] 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.[126] Leptin rescues the expression of OXT normally suppressed during fasting[127] and activates OXT-producing neurons in the posterior PVH that express MC4Rs and leptin receptors.[126,128,129] Like leptin, administering α-MSH activates OXT neurons in the PVH.[130] Furthermore, new data show that pretreatment with an OXT receptor antagonist prevents the anorexic effects of α-MSH.[131] 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.[132]

OXT-producing neurons in the posterior PVH project to the NTS and area postrema to innervate hindbrain areas.[72,126,128,129] These areas reduce meal size by integrating gut-derived satiety signals with descending input from the neocortex.[133] Indeed, systemic OXT administration robustly induces c-Fos in the NTS and area postrema and causes weight loss in DIO rats.[132] Furthermore, OXT receptor antagonists block the satiety effects of cholecystokinin (CCK) and increase food intake and meal size.[128] The NTS also provides autonomic innervation to the liver and other tissues.[134,135] This pathway allows the OXT neurons to control glucose homeostasis. OXT$^{-/-}$ mice have higher basal glucose levels, impaired glucose tolerance, and insulin resistance.[123]

OXT neurons in the posterior PVH may also alter thermogenic energy expenditure by projecting postsynaptically to brown adipose tissue via the stellate ganglia.[136] 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.

REFERENCES

1. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci 2011;14:351-5.

2. Ahima RS, Kelly J, Elmquist JK, Flier. JS. Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. Endocrinology 1999;140:4923-31.

3. Cheung CC, Clifton DK, Steiner RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology 1997;138:4489-92.

4. Cowley MA, Smith RG, Diano S, Tschöp M, Pronchuk N, Grove KL, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 2003;37:649-61.

5. Tschöp M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature 2000;407:908-13.

6. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714-9.

7. Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, Riepl RL, et al. Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. Eur J Endocrinol 2001;145:669-73.

8. Boghossian S, Park M, York DA. Melanocortin activity in the amygdala controls appetite for dietary fat. Am J Physiol Regul Integr Comp Physiol 2010;298:R385-93.

9. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: Current knowledge and future directions. Obes Rev 2012;13:43-56.

10. Zhao S, Kanoski SE, Yan J, Grill HJ, Hayes MR. Hindbrain leptin and glucagon-like-peptide-1 receptor signaling interact to suppress food intake in an additive manner. Int J Obes (Lond) 2012;36:1522-8.

11. Blevins JE, Baskin DG. Hypothalamic-brainstem circuits controlling eating. Forum Nutr 2010;63:133-40.

12. Marino JS, Xu Y, Hill JW. Central insulin and leptin-mediated autonomic control of glucose homeostasis. Trends Endocrinol Metab 2011;22:275-85.

13. Larsen PJ, Hay-Schmidt A, Mikkelsen JD. Efferent connections from the lateral hypothalamic region and the lateral preoptic area to the hypothalamic paraventricular nucleus of the rat. J Comp Neurol 1994;342:299-319.

14. Hermes SM, Mitchell JL, Aicher SA. Most neurons in the nucleus tractus solitarii do not send collateral projections to multiple autonomic targets in the rat brain Exp Neurol 2006;198:539-51.

15. Geerling JC, Shin JW, Chimenti PC, Loewy AD. Paraventricular hypothalamic nucleus: Axonal projections to the brainstem. J Comp Neurol 2010;518:1460-99.

16. Saper CB, Loewy AD, Swanson LW, Cowan WM. Direct hypothalamo-autonomic connections. Brain Res 1976;117:305-12.

17. Swanson LW. Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. Brain Res 1977;128:346-53.

18. Jobst EE, Enriori PJ, Cowley MA. The electrophysiology of feeding circuits. Trends Endocrinol Metab 2004;15:488-99.

19. Stanley S, Pinto S, Segal J, Pérez CA, Viale A, DeFalco J, et al. Identification of neuronal subpopulations that project from hypothalamus to both liver and adipose tissue polysynaptically. Proc Natl Acad Sci U S A 2010;107:7024-9.

20. Bamshad M, Aoki VT, Adkison MG, Warren WS, Bartness TJ. Central nervous system origins of the sympathetic nervous system outflow to white adipose tissue. Am J Physiol 1998;275:R291-9.

21. Jansen AS, Hoffman JL, Loewy AD. CNS sites involved in sympathetic and parasympathetic control of the pancreas: A viral tracing study. Brain Res 1997;766:29-38.

22. Song CK, Vaughan CH, Keen-Rinehart E, Harris RB, Richard D, Bartness TJ. Melanocortin-4 receptor mRNA expressed in sympathetic outflow neurons to brown adipose tissue: Neuroanatomical and functional evidence. Am J Physiol Regul Integr Comp Physiol 2008;295:R417-28.

23. Swanson LW, Kuypers HG. The Paraventricular Nucleus of the Hypothalamus-Cytoarchitectonic Subdivisions and Organization of Projections to the Pituitary, Dorsal Vagal Complex, and Spinal-Cord as Demonstrated by Retrograde Fluorescence Double-Labeling Methods. J Comp Neurol 1980;194:555-70.

24. Geerling JC, Shin JW, Chimenti PC, Loewy AD. Paraventricular hypothalamic nucleus: Axonal projections to the brainstem. J Comp Neurol 2010;518:1460-99.

25. Contreras RJ, Stetson PW. Changes in salt intake lesions of the area postrema and the nucleus of the solitary tract in rats. Brain Res 1981;211:355-66.

26. Edwards GL, Ritter RC. Area postrema lesions increase drinking to angiotensin and extracellular dehydration. Physiol Behav 1982;29:943-7.

27. South EH, Ritter RC. Overconsumption of preferred foods following capsaicin pretreatment of the area postrema and adjacent nucleus of the solitary tract. Brain Res 1983;288:243-51.

28. Rogers RC, Hermann GE. Gastric-vagal solitary neurons excited by paraventricular nucleus microstimulation. J Auton Nerv Syst 1985;14:351-62.

29. Roland BL, Sawchenko PE. Local Origins of Some GABAergic projections to the paraventricular and supraoptic nuclei of the hypothalamus in the rat. J Comp Neurol 1993;332:123-43.

30. Csáki A, Kocsis K, Halász B, Kiss J. Localization of glutamatergic/aspartatergic neurons projecting to the hypothalamic paraventricular nucleus studied by retrograde transport of [3H]D-aspartate autoradiography. Neuroscience 2000;101:637-55.

31. Ritter S, Dinh TT, Li AJ. Hindbrain catecholamine neurons control multiple glucoregulatory responses. Physiol Behav 2006;89:490-500.

32. Ritter S, Watts AG, Dinh TT, Sanchez-Watts G, Pedrow C. Immunotoxin lesion of hypothalamically projecting norepinephrine and epinephrine neurons differentially affects circadian and stressor-stimulated corticosterone secretion. Endocrinology 2003;144:1357-67.

33. Sahu A, Kalra SP, Crowley WR, Kalra PS. Evidence that NPY-containing neurons in the brainstem project into selected hypothalamic nuclei: implication in feeding-behavior. Brain Res 1998;457:376-8.

34. Edwards GL, White BD, He B, Dean RG, Martin RJ. Elevated hypothalamic neuropeptide Y levels in rats with dorsomedial hindbrain lesions. Brain Res 1997;755:84-90.

35. Dailey MJ, Bartness TJ. Arcuate nucleus destruction does not block food deprivation-induced increases in food foraging and hoarding. Brain Res 2010;1323:94-108.

36. Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, Low MJ. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. Int J Obes Relat Metab Disord 2001;25:S63-7.

37. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004;304:108-10.

38. Ahima RS, Prabakaran D, Flier JS. Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. J Clin Invest 1998;101:1020-7.

39. Ahima RS, Hileman SM. Postnatal regulation of hypothalamic neuropeptide expression by leptin: Implications for energy balance and body weight regulation. Regul Pept 2000;92:1-7.

40. Bouret SG. Early Life Origins of Obesity: Role of Hypothalamic Programming. J Pediatr Gastroenterol Nutr 2009;48:S31-8.

41. Ahima RS, Bjorbaek C, Osei S, Flier JS. Regulation of neuronal and glial proteins by leptin: Implications for brain development. Endocrinology 1999;140:2755-62.

42. Garza JC, Guo M, Zhang W, Lu XY. Leptin increases adult hippocampal neurogenesis in vivo and in vitro. J Biol Chem 2008;283:18238-47.

43. O'Malley D, MacDonald N, Mizielinska S, Connolly CN, Irving AJ, Harvey J. Leptin promotes rapid dynamic changes in hippocampal dendritic morphology. Mol Cell Neurosci 2007;35:559-2.

44. Udagawa J, Hatta T, Hashimoto R, Otani H. Roles of leptin in prenatal and perinatal brain development. Congenit Anom (Kyoto) 2007;47:77-83.

45. Delahaye F, Breton C, Risold PY, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal perinatal undernutrition drastically reduces postnatal leptin surge and affects the development of arcuate nucleus proopiomelanocortin neurons in neonatal male rat pups. Endocrinology 2008;149:470-5.

46. Yura S, Itoh H, Sagawa N, Yamamoto H, Masuzaki H, Nakao K, et al. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell Metab 2005;1:371-8.

47. Coupé B, Amarger V, Grit I, Benani A, Parnet P. Nutritional programming affects hypothalamic organization and early response to leptin. Endocrinology 2010;151:702-13.

48. Kirk SL, Samuelsson AM, Argenton M, Dhonye H, Kalamatianos T, Poston L, et al. Maternal obesity induced by diet in rats permanently influences central processes regulating food intake in offspring. PLoS One 2009;4:e5870.

49. Rogers I; EURO-BLCS Study Group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord 2003;27:755-77.

50. Delahaye F, Breton C, Risold PY, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal perinatal undernutrition drastically reduces postnatal leptin surge and affects the development of arcuate nucleus proopiomelanocortin neurons in neonatal male rat pups. Endocrinology 2008;149:470-5.

51. Coupe B, Dutriez-Casteloot I, Breton C, Lefevre F, Mairesse J, Dickes-Coopman A, et al. Perinatal undernutrition modifies cell proliferation and brain-derived neurotrophic factor levels during critical time-windows for hypothalamic and hippocampal development in the male rat. J Neuroendocrinol 2009;21:40-8.

52. Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, et al. Neonatal leptin treatment reverses developmental programming. Endocrinology 2005;146:4211-6.

53. Heidenreich KA, Toledo SP. Insulin receptors mediate growth effects in cultured fetal neurons. I. Rapid stimulation of protein synthesis. Endocrinology 1989;125:1451-7.

54. Huck S. Serum-free medium for cultures of the postnatal mouse cerebellum: Only insulin is essential. Brain Res Bull 1983;10:667-74.

55. Schechter R, Yanovitch T, Abboud M, Johnson G 3rd, Gaskins J. Effects of brain endogenous insulin on neurofilament and MAPK in fetal rat neuron cell cultures. Brain Res 1998;808:270-8.

56. Steculorum SM, Bouret SG. Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. Endocrinology 2011;152:4171-9.

57. Ghamari-Langroudi M, Srisai D, Cone RD. Multinodal regulation of the arcuate/paraventricular nucleus circuit by leptin. Proc Natl Acad Sci U S A 2011;108:355-60.

58. Chronwall BM, Dimaggio DA, Massari VJ, Pickel VM, Ruggiero DA, O'Donohue TL. The anatomy of neuropeptide-Y-containing neurons in rat-brain. Neuroscience 1985;15:1159-81.

59. Dube MG, Sahu A, Kalra PS, Kalra SP. Neuropeptide-Y release is elevated from the microdissected paraventricular nucleus of food-deprived rats: An in vitro study. Endocrinology 1992;131:684-8.

60. Tiesjema B, la Fleur SE, Luijendijk MC, Adan RA. Sustained NPY overexpression in the PVN results in obesity via temporarily increasing food intake. Obesity 2009;17:1448-50.

61. Tiesjema B, la Fleur SE, Luijendijk MC, Brans MA, Lin EJ, During MJ, et al. Viral mediated neuropeptide Y expression in the rat paraventricular nucleus results in obesity. Obesity (Silver Spring) 2007;15:2424-35.

62. Shibasaki T, Oda T, Imaki T, Ling N, Demura H. Injection of antineuropeptide-Y gamma-globulin into the hypothalamic paraventricular nucleus decreases food-intake in rats. Brain Res 1993;601:313-6.

63. Stephens TW, Basinski M, Bristow PK, Bue-valleskey JM, Burgett SG, Craft L, et al. The role of neuropeptide-Y in the antiobesity action of the obese gene-product. Nature 1995;377:530-2.

64. Olney JW. Brain lesions obesity and other disturbances in mice treated with monosodium glutamate. Science 1969;164:719-21.

65. Skibicka KP, Grill HJ. Hypothalamic and hindbrain melanocortin receptors contribute to the feeding, thermogenic, and cardiovascular action of melanocortins. Endocrinology 2009;150:5351-61.

66. Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, et al. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell 2005;123:493-505.

67. Ghamari-Langroudi M, Srisai D, Cone RD. Multinodal regulation of the arcuate/paraventricular nucleus circuit by leptin. Proc Natl Acad Sci U S A 108:355-60.

68. Qi Y, Henry BA, Oldfield BJ, Clarke IJ. The action of leptin on appetite-regulating cells in the ovine hypothalamus: Demonstration of direct action in the absence of the arcuate nucleus. Endocrinology 2010;151:2106-16.

69. Ghamari-Langroudi M, Vella KR, Srisai D, Sugrue ML, Hollenberg AN, Cone RD. Regulation of thyrotropin-releasing hormone-expressing

neurons in paraventricular nucleus of the hypothalamus by signals of adiposity. Mol Endocrinol 2010;24:2366-81.

70. Zheng H, Patterson LM, Phifer CB, Berthoud HR. Brain stem melanocortinergic modulation of meal size and identification of hypothalamic POMC projections. Am J Physiol Regul Integr Comp Physiol 2005;289:R247-58.

71. Piekut DT, Joseph SA. Relationship of CRF-immunostained cells and magnocellular neurons in the paraventricular nucleus of rat hypothalamus. Peptides 1985;6:873-82.

72. Sawchenko PE. Evidence for differential regulation of corticotropin-releasing factor and vasopressin immunoreactivities in parvocellular neurosecretory and autonomic-related projections of the paraventricular nucleus. Brain Res 1987;437:253-63.

73. Sawchenko PE, Swanson LW. Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. J Comp Neurol 1982;205:260-72.

74. Szafarczyk A, Guillaume V, Contedevolx B, Alonso G, Malaval F, Paresherbute N, et al. Central catecholaminergic system stimulates secretion of CRH at different sites. Am J Physiol 1988;255:E463-8.

75. Kiss A, Palkovits M, Aguilera G. Neural regulation of corticotropin releasing hormone (CRH) and CRH receptor mRNA in the hypothalamic paraventricular nucleus in the rat. J Neuroendocrinol 1996;8:103-12.

76. Füzesi T, Wittmann G, Liposits Z, Lechan RM, Fekete C. Contribution of noradrenergic and adrenergic cell groups of the brainstem and agouti-related protein-synthesizing neurons of the arcuate nucleus to neuropeptide-y innervation of corticotropin-releasing hormone neurons in hypothalamic paraventricular nucleus of the rat. Endocrinology 2007;148:5442-50.

77. Li HY, Ericsson A, Sawchenko PE. Distinct mechanisms underlie activation of hypothalamic neurosecretory neurons and their medullary catecholaminergic afferents in categorically different stress paradigms. Proc Natl Acad Sci U S A 1996;93:2359-64.

78. Buwalda B, Van Kalkeren AA, de Boer SF, Koolhaas JM. Behavioral and physiological consequences of repeated daily intracerebroventricular injection of corticotropin-releasing factor in the rat. Psychoneuroendocrinology 1998;23:205-18.

79. Arase K, York DA, Shimizu H, Shargill N, Bray GA. Effects of corticotropin-releasing factor on food-intake and brown adipose-tissue thermogenesis in rats. Am J Physiol 1988;255:E255-9.

80. Foster MT, Warne JP, Ginsberg AB, Horneman HF, Pecoraro NC, Akana SF, et al. Palatable foods, stress, and energy stores sculpt corticotropin-releasing factor, adrenocorticotropin, and corticosterone concentrations after restraint. Endocrinology 2009;150:2325-33.

81. Suemaru S, Hashimoto K, Hattori T, Inoue H, Kageyama J, Ota Z. Starvation-induced changes in rat-brain corticotropin-releasing factor (CRF) and pituitary-adrenocortical response. Life Sci 1986;39:1161-6.

82. Uehara Y, Shimizu H, Ohtani K, Sato N, Mori M. Hypothalamic corticotropin-releasing hormone is a mediator of the anorexigenic effect of leptin. Diabetes 1998;47:890-3.

83. Campbell RE, Grove KL, Smith MS. Distribution of corticotropin releasing hormone receptor immunoreactivity in the rat hypothalamus: coexpression in neuropeptide Y and dopamine neurons in the arcuate nucleus. Brain Res 2003;973:223-32.

84. Davidowa H, Plagemann A. Hypothalamic neurons of postnatally overfed, overweight rats respond differentially to corticotropin-releasing hormones. Neurosci Lett 2004;371:64-8.

85. Marsh DJ, Hollopeter G, Huszar D, Laufer R, Yagaloff KA, Fisher SL, et al. Response of melanocortin-4 receptor-deficient mice to anorectic and orexigenic peptides. Nat Genet 1999;21:119-22.

86. Lu XY, Barsh GS, Akil H, Watson SJ. Interaction between alpha-melanocyte-stimulating hormone and corticotropin-releasing hormone in the regulation of feeding and hypothalamo-pituitary-adrenal responses. Journal of Neurosci 2003;23:7863-72.

87. Patterson ZR, Ducharme R, Anisman H, Abizaid A. Altered metabolic and neurochemical responses to chronic unpredictable stressors in ghrelin receptor-deficient mice. Eur J Neurosci 2010;32:632-9.

88. Lutter M, Sakata I, Osborne-Lawrence S, Rovinsky SA, Anderson JG, Jung S, et al. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. Nat Neurosci 2008;11:752-3.

89. Chuang JC, Perello M, Sakata I, Osborne-Lawrence S, Savitt JM, Lutter M, et al. Ghrelin mediates stress-induced food-reward behavior in mice. J Clin Invest 2011;121:2684-92.

90. Cabral A, Suescun O, Zigman JM, Perello M. Ghrelin indirectly activates hy2pophysiotropic CRF neurons in rodents. PLoS One 2012;7:e31462.

91. Simmons DM, Swanson LW. Comparison of the spatial distribution of seven types of neuroendocrine neurons in the rat paraventricular nucleus: toward a global 3D model. J Comp Neurol 2009;516: 423-41.

92. Blake NG, Eckland DJ, Foster OJ, Lightman SL. Inhibition of hypothalamic thyrotropin-releasing hormone messenger ribonucleic acid during food deprivation. Endocrinology 1991;129:2714-18.

93. Vella KR, Ramadoss P, Lam FS, Harris JC, Ye FD, Same PD, et al. NPY and MC4R Signaling Regulate Thyroid Hormone Levels during Fasting through Both Central and Peripheral Pathways. Cell Metab 2011;14:780-90.

94. Hisano S, Fukui Y, Chikamori-Aoyama M, Aizawa T, Shibasaki T. Reciprocal synaptic relations between CRF-immunoreactive and trh-immunoreactive neurons in the paraventricular nucleus of the rat Hypothalamus. Brain Res 1993;620:343-6.

95. Swanson LW, Sawchenko PE, Wiegand SJ, Price JL. Separate neurons in the paraventricular nucleus project to the median eminence and to the medulla or spinal cord. Brain Res 1980;198:190-5.

96. Sawchenko PE, Swanson LW. The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. Brain Res 1982;257:275-325.

97. Toni R, Lechan RM. Neuroendocrine Regulation of Thyrotropin-Releasing-Hormone (Trh) in the Tuberoinfundibular System. J Endocrinol Invest 1993;16:715-53.

98. Fekete C, Kelly J, Mihaly E, Sarkar S, Rand WM, Legradi G, et al. Neuropeptide Y has a central inhibitory action on the hypothalamic-pituitary-thyroid axis. Endocrinology 2001;142:2606-13.

99. Légrádi G, Lechan RM. The arcuate nucleus is the major source for neuropeptide Y-innervation of thyrotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. Endocrinology 1998;139:3262-70.

100. Diano S, Naftolin F, Goglia F, Horvath TL. Segregation of the intra- and extrahypothalamic neuropeptide Y and catecholaminergic inputs on paraventricular neurons, including those producing thyrotropin-releasing hormone. Regul Pept 1998;75-76:117-26.

101. Kishi T, Aschkenasi CJ, Lee CE, Mountjoy KG, Saper CB, Elmquist JK. Expression of melanocortin 4 receptor mRNA in the central nervous system of the rat. J Comp Neurol 2003;457:213-35.

102. Liu HY, Kishi T, Roseberry AG, Cai XL, Lee CE, Montez JM, et al. Transgenic mice expressing green fluorescent protein under the control of the melanocortin-4 receptor promoter. J Neurosci 2003;23:7143-54.

103. Fekete C, Mihaly E, Luo LG, Kelly J, Clausen JT, Mao QF, et al. Association of cocaine-and amphetamine-regulated transcript-immunoreactive elements with thyrotropin-releasing hormone-synthesizing neurons in the hypothalamic paraventricular nucleus

and its role in the regulation of the hypothalamic-pituitary-thyroid axis during fasting. J Neurosci 2000;20:9224-4.

104. Mihaly E, Fekete C, Tatro JB, Liposits Z, Stopa EG, Lechan RM. Hypophysiotropic thyrotropin-releasing hormone-synthesizing neurons in the human hypothalamus are innervated by neuropeptide Y, agouti-related protein, and alpha-melanocyte-stimulating hormone. Journal of Clinical Endocrinol Metab 2000;85:2596-603.

105. Harris M, Aschkenasi C, Elias CF, Chandrankunnel A, Nillni EA, Bjorbaek C, et al. Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. J Clin Invest 2001;107:111-20.

106. Nillni EA, Vaslet C, Harris M, Hollenberg A, Bjorbaek C, Flier JS. Leptin regulates prothyrotropin-releasing hormone biosynthesis. Evidence for direct and indirect pathways. J Biol Chem 2000;275:36124-33.

107. Guo FF, Bakal K, Minokoshi Y, Hollenberg AN. Leptin signaling targets the thyrotropin-releasing hormone gene promoter in vivo. Endocrinology 2004;145:2221-7.

108. Kim MS, Small CJ, Stanley SA, Morgan DG, Seal LJ, Kong WM, et al. The central melanocortin system affects the hypothalamo-pituitary thyroid axis and may mediate the effect of leptin. J Clin Invest 2000;105:1005-11.

109. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest 2003;111:1409-21.

110. Sanchez VC, Goldstein J, Stuart RC, Hovanesian V, Huo LH, Munzberg H, et al. Regulation of hypothalamic prohormone convertases 1 and 2 and effects on processing of prothyrotropin-releasing hormone. J Clin Invest 2000;114:357-69.

111. Légrádi G, Emerson CH, Ahima RS, Flier JS, Lechan RM. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. Endocrinology 1997;138:2569-76.

112. Veening JG, de Jong T, Barendregt HP. Oxytocin-messages via the cerebrospinal fluid: Behavioral effects; A review. Physiol Behav 2010;101:193-210.

113. de Kock CP, Wierda KD, Bosman LW, Min R, Koksma JJ, Mansvelder HD, et al. Somatodendritic secretion in oxytocin neurons is upregulated during the female reproductive cycle. J Neurosci 2003;23:2726-34.

114. Soldo BL, Giovannucci DR, Stuenkel EL, Moises HC. Ca(2+) and frequency dependence of exocytosis in isolated somata of magnocellular supraoptic neurones of the rat hypothalamus. J Physiol 2004;555:699-711.

115. Freund-Mercier MJ, Stoeckel ME. Somatodendritic autoreceptors on oxytocin neurones. Adv Exp Med Biol 1995;395:185-94.

116. Chevaleyre V, Dayanithi G, Moos FC, Desarmenien MG. Developmental regulation of a local positive autocontrol of supraoptic neurons. J Neurosci 2000;20:5813-9.

117. Sabatier N, Caquineau C, Douglas AJ, Leng G. Oxytocin released from magnocellular dendrites: a potential modulator of alpha-melanocyte-stimulating hormone behavioral actions? Ann N Y Acad Sci 2003;994:218-24.

118. Zhang G, Bai H, Zhang H, Dean C, Wu Q, Li J, et al. Neuropeptide exocytosis involving synaptotagmin-4 and oxytocin in hypothalamic programming of body weight and energy balance. Neuron 2011;69:523-35.

119. Arletti R, Benelli A, Bertolini A. Oxytocin inhibits food and fluid intake in rats. Physiol Behav 1990;48:825-30.

120. Olson BR, Drutarosky MD, Stricker EM, Verbalis JG. Brain Oxytocin Receptor Antagonism Blunts the Effects of Anorexigenic Treatments

in Rats: Evidence for Central Oxytocin Inhibition of Food-Intake. Endocrinology 1991;129:785-91.

121. Olson BR, Drutarosky MD, Chow MS, Hruby VJ, Stricker EM, Verbalis JG, et al. Oxytocin and an Oxytocin Agonist Administered Centrally Decrease Food-Intake in Rats. Peptides 1991;12:113-8.

122. Takayanagi Y, Kasahara Y, Onaka T, Takahashi N, Kawada T, Nishimori K. Oxytocin receptor-deficient mice developed late-onset obesity. Neuroreport 2008;19:951-5.

123. Camerino C. Low sympathetic tone and obese phenotype in oxytocin-deficient mice. Obesity (Silver Spring) 2009;17:980-4.

124. Zhang G, Bai H, Zhang H, Dean C, Wu QA, Li JX, et al. Neuropeptide exocytosis involving synaptotagmin-4 and oxytocin in hypothalamic programming of body weight and energy balance. Neuron 2011;69:523-35.

125. Mitra A, Gosnell BA, Schioth HB, Grace MK, Klockars A, Olszewski PK, et al. Chronic sugar intake dampens feeding-related activity of neurons synthesizing a satiety mediator, oxytocin. Peptides 2010;31:1346-52.

126. Blevins JE, Schwartz MW, Baskin DG. Evidence that paraventricular nucleus oxytocin neurons link hypothalamic leptin action to caudal brain stem nuclei controlling meal size. Am J Physiol Regul Integr Comp Physiol 2004;287:R87-96.

127. Tung YC, Ma M, Piper S, Coll A, O'Rahilly S, Yeo GS. Novel leptin-regulated genes revealed by transcriptional profiling of the hypothalamic paraventricular nucleus. J Neurosci 2008;28:12419-26.

128. Blevins JE, Eakin TJ, Murphy JA, Schwartz MW, Baskin DG. Oxytocin innervation of caudal brainstem nuclei activated by cholecystokinin. Brain Res 2003;993:30-41.

129. Blevins JE, Morton GJ, Williams DL, Caldwell DW, Bastian LS, Wisse BE, et al. Forebrain melanocortin signaling enhances the hindbrain satiety response to CCK-8. Am J Physiol Regul Integr Comp Physiol 2009;296:R476-84.

130. Olszewski PK, Wirth MM, Shaw TJ, Grace MK, Billington CJ, Giraudo SQ, et al. Role of alpha-MSH in the regulation of consummatory behavior: Immunohistochemical evidence. American Am J Physiol Regul Integr Comp Physiol 2001;281:R673-80.

131. Yosten GL, Samson WK. The anorexigenic and hypertensive effects of nesfatin-1 are reversed by pretreatment with an oxytocin receptor antagonist. Am J Physiol Regul Integr Comp Physiol 2010;298:R1642-7.

132. Morton GJ, Thatcher BS, Reidelberger RD, Ogimoto K, Wolden-Hanson T, Baskin DG, et al. Peripheral oxytocin suppresses food intake and causes weight loss in diet-induced obese rats. Am J Physiol Endocrinol Metab 2012;302:E134-44.

133. Berthoud HR, Sutton GA, Townsend RL, Patterson LM, Zheng HY. Brainstem mechanisms integrating gut-derived satiety signals and descending forebrain information in the control of meal size. Physiol Behav 2006;89:517-24.

134. Blevins JE, Chelikani PK, Haver AC, Reidelberger RD. PYY[3-36] induces Fos in the arcuate nucleus and in both catecholaminergic and non-catecholaminergic neurons in the nucleus tractus solitarius of rats. Peptides 2008;29:112-9.

135. Moran TH, Ladenheim EE, Schwartz GJ. Within-meal gut feedback signaling. Int J Obes Relat Metab Disord 2001;25:S39-41.

136. Oldfield BJ, Giles ME, Watson A, Anderson C, Colvill LM, McKinley MJ. The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. Neuroscience 2002;110:515-26.

137. Kasahara Y, Takayanagi Y, Kawada T, Itoi K, Nishimori K. Impaired thermoregulatory ability of oxytocin-deficient mice during cold-exposure. Biosci Biotechnol Biochem 2007;71:3122-6.

138. Lipton JM, Glyn JR. Central administration of peptides alters thermoregulation in the rabbit. Peptides 1980;1:15-8.

139. Mason GA, Caldwell JD, Stanley DA, Hatley OL, Prange AJ, Pedersen CA. Interactive effects of intracisternal oxytocin and other centrally active substances on colonic temperatures of mice regulatory. Peptides 1986;14:253-60.

140. Voss-Andreae A, Murphy JG, Ellacott KL, Stuart RC, Nillni EA, Cone RD, *et al*. Role of the central melanocortin circuitry in adaptive thermogenesis of brown adipose tissue. Endocrinology 2007;148:1550-60.

141. Torres N, Chabardès S, Benabid AL. Rationale for hypothalamus-deep brain stimulation in food intake disorders and obesity. Adv Tech Stand Neurosurg 2011;36:17-30.

142. Mantione M, van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: Therapeutic and research implications: Case report. Neurosurgery 2010;66:E218.

143. Melega WP, Lacan G, Gorgulho AA, Behnke EJ, De Salles AA. Hypothalamic deep brain stimulation reduces weight gain in an obesity-animal model. PLoS One 2012;7:e30672.

144. Patterson JT, Day JW, Gelfanov VM, DiMarchi RD. Functional association of the N-terminal residues with the central region in glucagon-related peptides. J Pept Sci 2011;17:659-66.