The Paraventricular Nucleus of the Hypothalamus: Development, Function, and Human Diseases

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The paraventricular nucleus of the hypothalamus (PVH), located in the ventral diencephalon adjacent to the third ventricle, is a highly conserved brain region present in species from zebrafish to humans. The PVH is composed of three main types of neurons, magnocellular, parvocellular, and long-projecting neurons, which play imperative roles in the regulation of energy balance and various endocrinological activities. In this review, we focus mainly on recent findings about the early development of the hypothalamus and the PVH, the functions of the PVH in the modulation of energy homeostasis and in the hypothalamus-pituitary system, and human diseases associated with the PVH, such as obesity, short stature, hypertension, and diabetes insipidus. Thus, the investigations of the PVH will benefit not only understanding of the development of the central nervous system but also the etiology of and therapy for human diseases. (*Endocrinology* 159: 3458–3472, 2018)

The hypothalamus, which is located in the ventral forebrain, plays important roles in regulating energy homeostasis, fluid balance, stress, growth, reproductive behavior, emotion, and circadian rhythms (1). The hypothalamus is composed of several small essential nuclei, including the arcuate nucleus (ARC), paraventricular nucleus of the hypothalamus (PVH), supraoptic nucleus (SON), suprachiasmatic nucleus (SCN), dorsomedial nucleus of the hypothalamus (DMH), ventromedial nucleus of the hypothalamus (VMH), and lateral hypothalamus area. Among these nuclei, there are various subtypes of neurons. Recent studies based on a single-cell RNA-sequencing technique identified at least 34 neuronal and 11 nonneuronal cellular groups with distinct transcriptional signatures in the adult mouse hypothalamus, and even arcuate pro-opiomelanocortin (POMC)–positive neurons are highly heterogeneous populations (2, 3). Abnormal development or function of the hypothalamus leads to many diseases in humans, such as growth defects, obesity, diabetes mellitus and insipidus, hypertension, and amenorrhea (4–9). Moreover, recent studies suggest that changes in the hypothalamus are associated with not only neural degenerative diseases, such as amyotrophic lateral sclerosis, Huntington disease, and Alzheimer's disease (10), but also neurodevelopmental diseases, such as autism and Prader-Willi syndrome (11).

The PVH, which is located in the ventral diencephalon adjacent to the third ventricle, is a brain region highly conserved from zebrafish to humans (12). It is composed of heterogeneous parvocellular neurons, magnocellular

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Abbreviations: AgRP, agouti-related protein; ARC, arcuate nucleus; *Arnt2*, aryl hydrocarbon receptor nuclear translocator 2; AVP, arginine vasopressin; BAT, brown adipose tissue; BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; *Brn2*, brain-2; CART, cocaine- and amphetamine-regulated transcript; CDI, central diabetes insipidus; *COUP-TFII*, chicken ovalbumin upstream promoter transcription factor II; DMH, dorsomedial nucleus of the hypothalamus; DMV, dorsal motor nucleus of the vagus nerve; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide 1; HNS, hypothalamic-neurohypophysial system; HPA, hypothalamic-pituitary-adrenal; HPT, hypothalamic-pituitary-thyroid; IML, intermediolateral column; MC4R, melanocortin receptor 4; Nos1, nitric oxide synthase-1; NPY, neuropeptide Y; Nrp1, neuropilin 1; NTS, nucleus of the solitary tract; *Otp*, orthopedia; OXT, oxytocin; PBN, parabrachial nucleus; POMC, pro-opiomelanocortin; PVH, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus; *Sim1*, single-minded 1; *Sim2*, single-minded 2; SON, supraoptic nucleus; SST, somatostatin; VMH, ventromedial nucleus of the hypothalamus.

neurons, and long-projecting neurons (Fig. 1). The parvocellular neurons send axons to the median eminence and secrete mainly TRH and CRH into the portal vasculature to initiate the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axis, respectively (13). Interestingly, CRH neurons in the PVH are associated with dietary preference for carbohydrate over fat through the activation of AMP-activated protein kinase (14). The PVH also contains some somatostatin (SST)-positive neurons that project to the median eminence and inhibit the secretion of GH and TSH in the anterior pituitary (15). Magnocellular neurons project mainly to the pituitary gland posterior lobe, where they secrete arginine vasopressin (AVP) and oxytocin (OXT) into the hypothalamic-neurohypophysial system (HNS), which regulates fluid balance, breast milk release and uterine contraction, and ejaculation (13). In addition, AVP neurons in the PVH participate in the regulation of feeding behaviors (16). Long-projecting neurons express mainly melanocortin receptor 4 (MC4R) and OXT, which project primarily to the hindbrain to regulate energy balance (17, 18). Most likely, OXT neurons are the main mediator for the hyperphagic obesity of the single-minded 1 (*Sim1*) heterozygous mutant mouse and also are postsynaptic targets of agouti-related protein (AgRP)–positive neurons in the ARC (19, 20). In this review, we focus mainly on the development and function of the PVH in mice and on human diseases associated with abnormalities of this nucleus.

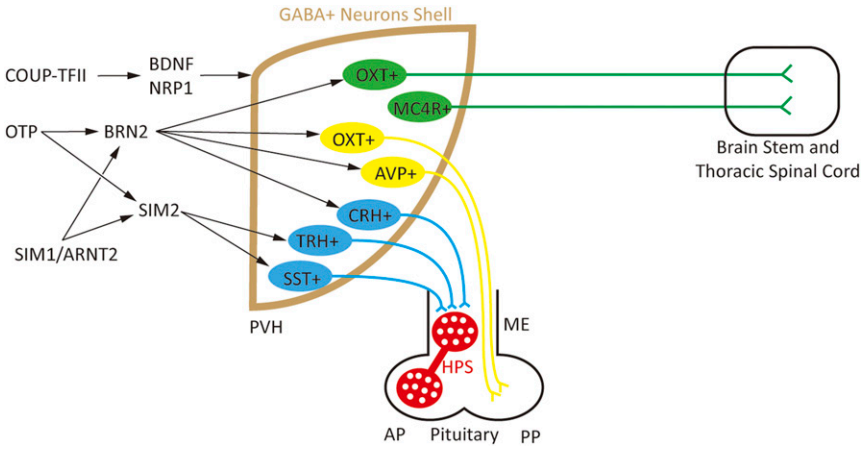

Figure 1. The development of PVH neurons and their projections. *COUP-TFII* controls the survival and migration of PVH progenitor cells through *Bdnf* and *Nrp1* genes. *OTP* regulates the differentiation of OXT+, AVP+, CRH+, TRH+, and SST+ neurons in the PVH, most likely through direct or indirect activation of *Brn2* and *Sim2*. The PVH, which is surrounded by a shell of GABA+ neurons, is composed of three main cell types. Parvocellular neurons, including SST+, TRH+, and CRH+ neurons, project to the medial eminence, where axon terminals connect with the HPS. The magnocellular neurons, including OXT+ and AVP+ neurons, project to the posterior pituitary. The long-projecting neurons, including MC4R+ neurons and one group of OXT+ neurons, project to the brainstem and thoracic spinal cord, where they regulate energy balance. Black arrows represent the positive regulation of gene expression during the development of the PVH neurons. Blue, yellow, and green lines represent the projections from the parvocellular, magnocellular, and long-projecting neurons, respectively. AP, anterior pituitary; *Arnt2*, aryl hydrocarbon receptor nuclear translocator 2; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; *Brn2*, brain-2; *COUP-TFII*, chicken ovalbumin upstream promoter transcription factor II; GABA, γ-aminobutyric acid; HPS, hypophyseal portal system; MC4R, melanocortin receptor 4; ME, median eminence; Nrp1, neuropilin 1; *Otp,* orthopedia; OXT, oxytocin; PP, posterior pituitary; *Sim1*, single-minded 1; *Sim2,* single-minded 2; SST, somatostatin.

Development

Development of the hypothalamus

The hypothalamus is derived from the anterior-most ventral part of the neural tube during early development. Graded responses to levels and timing of WNT signaling may program the subdivision of the anterior neural plate into the telencephalon, eye field, and diencephalon (21). The preoptic area originates from the telencephalon, and other parts of the hypothalamus are generated from the diencephalon (1). According to the gene-expressing profiles along the dorsal-ventral axis, the early primordium of the hypothalamus can be divided into three subregions and one cell band. They are known as the alar plate, basal plate, floor plate, and the intrahypothalamic diagonal (Fig. 2A) (22). The intrahypothalamic diagonal, a parallel band of cells between the alar and basal plates, expresses *Arx* and *Gad67* (23). The alar plate is marked by the expression of *Sim1* and *Pax6* (23, 24). The floor plate is characterized with the expression of *Nkx2.1*, *Tbx2*, and *Tbx3* (15, 25, 26). *Nkx2.1* is also expressed in the basal plate (15). The alar plate gives rise to the SON and PVH, and the basal plate generates the ARC, DMH, and VMH (Fig. 2B and 2C) (22). In contrast with the inside-out layer pattern in the cerebral cortex, the development of distinct nuclei in the hypothalamus has an outside-in formation, as evidenced by the formation of lateral neurons before the medial neurons (27, 28). However, the detailed processes involved in the development of the hypothalamus and PVH have not been fully elucidated.

Several secreted proteins, such as WNTs, SHH, FGFs, and BMPs, participate in the early formation of distinct nuclei in the hypothalamus. Low WNT signaling in the anterior forebrain induces the expression of *Six3* (29), activates the expression of *Shh*, a basal/floor-plate marker, and promotes the development of the vertebrate forebrain,

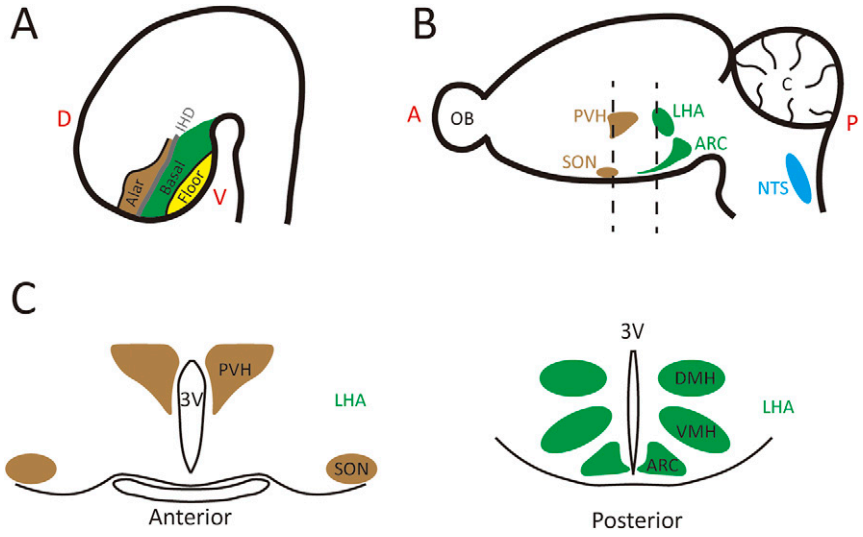

Figure 2. The structure of the hypothalamus at the early embryonic stage and at the adult stage in the mouse. (A) Sagittal view of the hypothalamic primordium in the early mouse embryo. Along the dorsoventral axis, the primordium of the hypothalamus can be divided into the alar plate, intrahypothalamic diagonal (IHD), basal plate, and floor plate. (B) Sagittal view of the PVH and other hypothalamic nuclei in the adult mouse brain. The alar plate gives rise to the SON and PVH, and the basal plate generates the ARC and lateral hypothalamic area (LHA). (C) Coronary views of the PVH and some other hypothalamic nuclei at two sections of the adult mouse brain, indicated by two dashed lines in (B). 3V, third ventricle; A, anterior; C, cerebellum; D, dorsal; NTS, nucleus of the solitary tract; OB, olfactory bulb; P, posterior; V, ventral.

including the hypothalamic primordium (30, 31). Later, the expression of *Shh* is repressed by *Tbx2* and *Tbx3* genes in the ventral floor plate of the posterior hypothalamus, whereas *Shh* is still expressed in the ventral floor plate in other regions of the hypothalamus (25, 26, 32). At the same stage, the expression of BMP4 and FGFs is detected in the ventral floor plate of the posterior hypothalamus, including the infundibulum (26, 33, 34). Therefore, an expression boundary along the ventral midline is established with SHH in the anterior hypothalamus and with BMP4/FGFs in the posterior hypothalamus, which is essential for the appropriate morphogenesis of the pituitary by programming the development of the infundibulum and oral ectoderm (35).

The PVH and SON are located in the anterior hypothalamus. Evidence from rodents supports origination of magnocellular neurons in these two nuclei from a small patch of neural progenitor cells at embryonic day 10.5 to embryonic day 12.5 in mice (36, 37), which is positive for spot 35, a member of the calbindin family (38). During development, one group of cells remains near the third ventricle to give rise to the PVH and the other group migrates ventrolaterally to form the SON (36, 38, 39).

Key regulatory genes in the development of the PVH

Several transcription factor genes, such as *Sim1* and single-minded 2 (*Sim2*), aryl hydrocarbon receptor nuclear translocator 2 (*Arnt2*), brain-2 (*Brn2*), orthopedia (*Otp*), and chicken ovalbumin upstream promoter transcription factor II (*COUP-TFII*), have been identified as key regulatory genes that program the development of the PVH (Fig. 1). In addition to the wide effects of the regulators mentioned previously, there are factors that regulate the development of single neuronal lineages. For example, brain-derived neurotrophic factor (BDNF) promotes the expression of prepro-TRH in the PVH, regulating the development of TRH+ neurons (40).

Sim1 and Sim2

The gene *Sim1*, which encodes a transcription factor of the bHLH-PAS family, is expressed in the anterior periventricular nucleus, posterior hypothalamic nuclei, PVH, SON, and nucleus of the lateral olfactory tract from early embryonic stages to adulthood (41, 42). *Sim1* null mutant ($Sim1^{-/-}$) mice die soon after birth and exhibit severe hypoplasia of the PVH and loss of SST+, TRH+, CRH+, AVP+, and OXT+ neurons (42). Heterozygous mutant ($Sim1^{+/-}$) mice survive until adulthood but develop hyperinsulinemia, hyperleptinemia, hyperphagia, and obesity with modestly decreased neurons in the PVH (43). The SIM1 protein binds to ARNT2 to form the SIM1/ARNT2 dimer, which participates in the final differentiation of PVN and SON neurons (42, 44). In this process, the function of the SIM1/ARNT2 heterodimer is partially mediated by its downstream target gene, *Brn2* (45), which is required for the survival and terminal differentiation of AVP+, OT+, and CRH+ neurons (38, 46). Either the *Sim1* or the *Arnt2* gene is necessary to maintain the expression of the *Brn2* transcript in the prospective PVN/SON region (42, 47). Moreover, the SIM1/ARNT2 dimer directs the extension of hypothalamospinal axons (48). The *Sim2* gene, a paralog of *Sim1*, is also expressed in the PVH (49). As a downstream gene of the *Sim1* and *Otp* genes (50), the *Sim2* gene is vital for the appropriate development of SST+ and TRH+ neurons in the anterior hypothalamus (51).

Arnt2

The gene *Arnt2*, which encodes another basic bHLH-PAS transcription factor, is enriched in the brain and kidneys (52). As in $Sim1^{-/-}$ mice, the development of the PVH also fails in *Arnt2* null mutant ($Arnt2^{-/-}$) mice,

whereas the heterozygous ($Arnt2^{+/-}$) mice do not display any obvious difference from wild-type mice (47). Clearly, the formation of SIM1/ARNT2 heterodimers is essential for the development of the PVH.

Brn2

Brn2 (also known as *Pou3f2* or *N-Oct3*), which encodes a class III POU-homeodomain transcription factor, plays an important role in neurogenesis (53). *Brn2* is widely expressed in the developing central nervous system (54). *Brn2* null mutant ($Brn2^{-/-}$) mice die within 10 days after birth, accompanied by the loss of AVP+, OXT+, and CRH+ neurons in the PVH (46). Although the heterozygous mutants ($Brn2^{+/-}$) exhibit normal PVH nuclei, their expression of *AVP* and *OXT* is half that of the wild-type mice (38), suggesting that BRN2 is important for the expression of *AVP* and *OXT* in adult mice. In addition, BRN2 may bind to the *OXT* and *CRH* genomic loci to promote their expression (55). Thus, BRN2 plays vital roles in both the development of the PVH and the differentiation of AVP+, OXT+, and CRH+ neurons.

Otp

The gene *Otp,* which encodes a homeodomain transcription factor, is highly expressed in the hypothalamus and is essential for its regionalization (56). In *Otp* null mutant ($Otp^{-/-}$) mice, the development of SST+, AVP+, OXT+, CRH+, and TRH+ neuroendocrine neurons is compromised by abnormal cell death after birth. OTP regulates the terminal differentiation, maturation, and survival of the PVH neurons (50). There is no difference in viability and fertility between heterozygous ($Otp^{+/-}$) and wild-type mice (43). *Otp* missense mutation ($Otp^{R108W/+}$) heterozygous mice develop obesity, which may be caused by decreased expression of *OXT* and *AVP* in the adult PVH (57). Most likely, Otp^{R108W} mutation causes not only loss of function but also a potential dominant negative effect, which leads to obesity in $Otp^{R108W/+}$ heterozygous mice (57). Early studies suggested that the role of OTP in the development of PVH neurons may be mediated by BRN2 and SIM2 (50, 51); interestingly, recent studies in zebrafish have revealed that Otp regulates the expression of thyroid hormone (*TH*), *TRH*, *CRH*, *OXT*, *AVP*, and *SST* through cooperation with Sim1 in the neurosecretory preoptic area and posterior tuberculum (58).

COUP-TFII

COUP-TFII, also known as *NR2F2*, is conserved from early metazoans to humans and belongs to the steroid hormone receptor superfamily genes (59). *COUP-TFII* is highly expressed in the early hypothalamic primordium, PVH neural progenitor cells, and early differentiating PVH neurons but not in late-differentiating and mature PVH neurons. The PVH barely forms in $RXCre/+;COUP\text{-}TFII^{F/F}$ mutant mice, which results in growth retardation. Nonetheless, the reduction of growth hormone–releasing hormone neurons in the mutant ARC could also be a likely cause of the growth retardation. COUP-TFII may support the survival and migration of neurons during early development of the PVH by promoting the expression of *Bdnf* and neuropilin 1 (*Nrp1*) (8).

Functions

Food intake

Food intake circuits, which are based mainly on the leptin-melanocortin system, can be divided into three main components: pre-PVH, PVH, and post-PVH (Fig. 3).

Pre-PVH components

The ARC, which has strong projections to the PVH, serves as an essential node for PVH input. Leptin, which is secreted from white adipose tissue and is positively related to total body fat volume, is an important molecule in initiation of the melanocortin signal (60). Leptin receptors are highly expressed in the hypothalamus, especially in the ARC (61). POMC+ and AgRP+ neurons are two primary neuronal types with leptin receptors in the ARC (62). Leptin plays distinct roles in POMC+ and AgRP+ neurons in regulating food intake. After the stimulation of leptin, POMC+ neurons secret α-melanocyte–stimulating hormone, which activates MC4R+ neurons in the PVH to inhibit food intake. In contrast, AgRP+ neurons secrete AgRP, which antagonizes the activity of MC4R+ neurons in the PVH to promote food intake (63). In addition, POMC+ neurons secrete cocaine- and amphetamine-regulated transcript (CART) to reduce food intake (64), and AGRP+ neurons release neuropeptide Y (NPY) and γ-aminobutyric acid (GABA) to rapidly promote food intake (65, 66) (Fig. 3). Both POMC+ and AgRP+ neurons respond to the leptin signal, but only POMC+ neurons express c-Fos, a marker for neural activation (67). Interestingly, one recent report revealed that in either POMC+ or AgRP+ neurons the same signaling pathways are activated by leptin to generate phosphorylated STAT3 and inactivated FoxO1, which promote the expression of *Pomc* but inhibit the expression of *Agrp* (62). AgRP+ neurons also project to adjacent POMC+ neurons to inhibit their activity (65, 68, 69), suggesting that the regulation of the leptin-melanocortin system is not that simple. In addition to leptin, neurons in the ARC express other receptors that respond to different molecular signals, such as insulin,

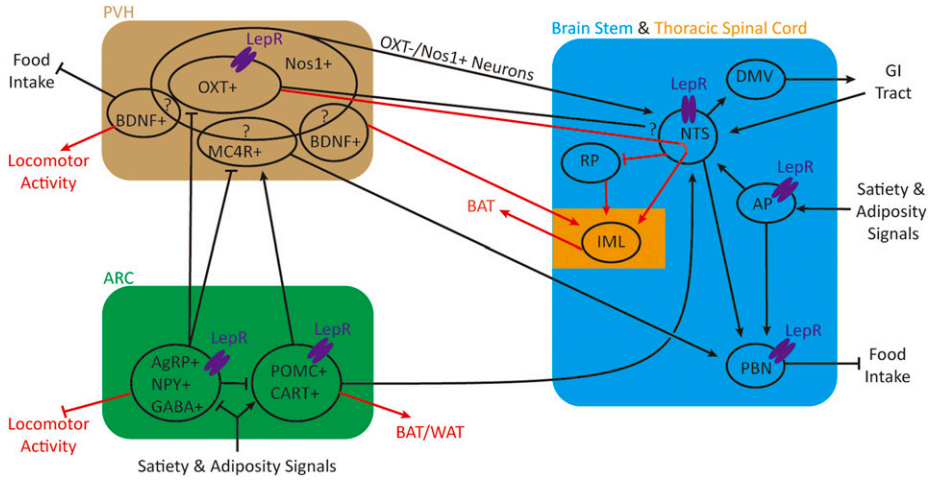

Figure 3. Overview of the melanocortin system in the regulation of food intake and energy expenditure. The two primary cells in the ARC, AgRP+ and POMC+ neurons, sense diverse satiety and adiposity hormonal signals and project to the PVH, which is essential for the regulation of food intake and energy expenditure. AgRP+ neurons also regulate locomotor activity, and POMC+ neurons also modulate thermogenesis. AgRP+ and POMC+ neurons project to the PVH to antagonize or promote the activities of MC4R+ neurons, respectively. In addition, the orexigenic actions of AgRP are partially achieved by releasing GABA to inhibit anorexigenic POMC neurons in the ARC. Long-projecting OXT+ neurons receive projections from AgRP+ neurons. OXT+ neurons are a subset of Nos1+ neurons. BDNF colocalizes with OXT in a few neurons. The anterior BDNF+ neurons regulate food intake and locomotor activity, whereas the medial and posterior BDNF+ neurons project to the IML. MC4R+ neurons project to the PBN, and OXT+ neurons project to the NTS in the brainstem or the IML in the thoracic spinal cord. The brainstem does not simply relay information from the PVH; it also receives diverse hormonal signals through the AP. The AP projects to the NTS and PBN nuclei. The NTS not only relays information from the PVH to regulate food intake but also receives afferents from the gastrointestinal tract and sends efferents through the DMV to regulate gastrointestinal tract motor function. Moreover, it receives projections from POMC+ neurons in the ARC. In addition, the NTS plays a key role in energy expenditure. It indirectly projects to the IML through the RP. Double blue symbols by LepR indicate dimer of Leptin receptor. The lines in red are related to the modulation of energy expenditure. The lines in black are associated primarily with the regulation of food intake. Arrows mean positive regulations. Blunt ends represent inhibitory regulations. AP, area postrema; BAT, brown adipose tissue; CART, cocaine- and amphetamine-regulated transcript; DMV, dorsal motor nucleus of the vagus nerve; GABA, γ-aminobutyric acid; GI, gastrointestinal; IML, intermediolateral column; LepR, leptin receptor; Nos1, nitric oxide synthase-1; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; RP, raphe pallidus; WAT, white adipose tissue.

glucagon-like peptide 1 (GLP-1), oxyntomodulin, ghrelin, melanocortin, and serotonin. Insulin acts on POMC+ and AgRP+ neurons to mediate glucose homeostasis (70). Insulin modulates food intake by sharing the FoxO1 pathway with leptin signaling (62). Specifically, insulin may also regulate STAT3 signaling (71). GLP-1 and oxyntomodulin, both of which are secreted from the gastrointestinal tract after feeding, inhibit food intake through GLP-1 receptors in the ARC (72). Ghrelin, which is produced by the stomach, activates AgRP+ neurons to increase appetite (73). Both POMC+ and AgRP+ neurons express MC3R, an isoform of MC4R that interacts with melanocortin and prevents obesity (74). Serotonin binds to distinct receptors on POMC+ and AgRP+ neurons, which inhibits AgRP+ neurons and stimulates POMC+ neurons to reduce food intake (75).

PVH components

The ARC has wide reciprocal projections with various regions within and outside the hypothalamus, such as the PVH, lateral hypothalamus area, posterior hypothalamus, DMH, nucleus of the solitary tract (NTS) of the brainstem, and the bed nucleus of the stria terminalis (BNST) in the forebrain (76). Among them, the PVH seems to be the center of the melanocortin system. In the PVH, MC4R is expressed on most glutamatergic neurons that project to the parabrachial nucleus (PBN) and dorsal motor nucleus of the vagus nerve (DMV) in the brainstem (77, 78). In general, activated MC4R+ neurons carry feeding-inhibiting signals, whereas the inhibition of MC4R+ neurons results in feeding-promoting signals to the hindbrain. MC4R+ neurons are activated by α-melanocyte–stimulating hormone and inhibited by AgRP (63). In addition, MC4R+ neurons express NPY receptors to transfer feeding-promoting information (79). In addition to MC4R+ neurons, OXT+ neurons in the PVH also sense leptin signaling and project to the NTS (80), elevating the response of the NTS to satiety signaling such as cholecystokinin, which is secreted from the gut after feeding (81). In addition, OXT+ neurons are inhibited by AgRP (20). Interestingly, a recent study suggested that OXT+ neuron projections just pass through the NTS and target the intermediolateral column (IML) in the thoracic spinal cord (17), which plays an important role in energy expenditure (82). Nitric oxide synthase-1 (Nos1)–positive neurons are located in the PVH; OXT+ neurons are a subset of Nos1+ neurons in the PVH. OXT−/Nos1+ neurons, which project to the

NTS, are also involved in feeding regulation (17). However, so far the correlation between MC4R+ and Nos1+ neurons remains unclear. The expression of *Bdnf* has also been detected in the PVH, especially in some previously undefined neurons (83). Among them, BDNF+ neurons in the anterior PVH regulate both locomotor activity and food intake (83) (Fig. 3). In addition, AVP+ neurons in the PVH respond to melanocortin agonists and acutely reduce food intake (16). One recent study showed that IL-6 plays a vital role in inhibiting food intake and controlling obesity by acting on the PVH neurons (84). Nevertheless, how the distinct PVH neurons participate in the regulation of food intake has not been fully elucidated.

Post-PVH components

The hindbrain, especially the NTS, PBN, and DMV, is an essential region where feeding information from the PVH, other brain regions, and peripheral tissue is integrated (85). The area postrema, which projects to the NTS and PBN nuclei, serves as a receiver in the brainstem. Because it is outside the blood-brain barrier, many peripheral signals, such as leptin, amylin, insulin, cholecystokinin, GLP-1, and ghrelin, are detected there (86, 87). Thus, the NTS can receive area postrema–derived gut signals. Vagal afferents from the upper gastrointestinal tract also project to the NTS to deliver satiety-associated signals (88). Furthermore, leptin receptors are located in the NTS and PBN (89, 90), suggesting that the brainstem is not only a simple downstream target of the PVH but also a vital center for feeding regulation. Being downstream of vagovagal neurocircuits, the NTS projects to the DMV, which sends efferent fibers to the gastrointestinal tract to regulate gastric motility (91). The NTS also projects to the PBN (92). The PBN is a central processor that integrates hindbrain information to induce feeding behavior. Furthermore, the PBN is the primary target of MC4R+ neurons in the PVH and plays an indispensable role in the melanocortin system (77). Finally, PBN neurons project widely to other parts of the brain, including the PVH, central nucleus of the amygdala, and BNST (93–95), to regulate feeding behavior. In addition, the ARC projects directly to the brainstem; for example, POMC+ neurons project to the NTS to regulate food intake (96) (Fig. 3). The DMV also contains MC4R+ neurons (97), modulating gastric activity (98). The NTS contains POMC+ neurons as well (99), which receive wide inputs within the brain and regulate energy balance (76). Therefore, the melanocortin system is more complicated than what we currently know.

Energy expenditure

The melanocortin system is also highly associated with the regulation of energy expenditure (Fig. 3). Leptin and insulin act on POMC+ neurons in the ARC to increase energy expenditure by browning white adipose tissue (100). CART promotes energy expenditure through brown adipose tissue (BAT) activation and by stimulating the release of CRH and TRH (101). The activation of STAT3 in AgRP+ neurons by leptin improves locomotor activity and increases energy expenditure (102). In contrast, NPY plays an inhibitory role in energy expenditure (103). In addition, a group of AgRP−/POMC− neurons in the ARC, which exhibit rat insulin-2 promoter activity and respond to leptin, increase thermogenesis by releasing GABA into the PVH (104). In the PVH, OXT+ neurons project to the IML and stimulate sympathetic efferent activity to BAT to increase energy expenditure (17). BDNF+ long-projection neurons in the posterior and medial PVH release BDNF in the IML, which indirectly promotes thermogenesis in BAT (83). Moreover, disinhibition of PVH neurons by stereotactic microinjection of a $GABA_A$ antagonist can repress thermogenesis through activation of GABAergic input to the nucleus raphe pallidus (105); in contrast, microinjection of glutamate stimulates thermogenesis in BAT (106). In addition, observations in some transgenic animal models reveal a correlation between PVH and BAT thermogenesis. In $Sim1^{+/-}$ mice, the expression of *Ucp1* is decreased, which promotes thermogenesis in BAT and leads to obesity (107). In *LXR* null mice, the expression of *Ucp1* in BAT is increased, accompanied by the activation of TRH+ neurons in the PVH, which increases energy expenditure through the HPT axis (108). In the brainstem, the NTS inhibits BAT thermogenesis by repressing sympathetic premotor activity in the nucleus raphe pallidus (109). However, whether the NTS relays the information from the PVH in this process is unclear. Finally, the sympathetic premotor neurons in the raphe regions directly control sympathetic preganglionic neurons in the IML, which innervate BAT and regulate thermogenesis and energy expenditure (110).

The HPT axis

In the HPT axis, TRH derived from the PVH stimulates the secretion of TSH in the anterior pituitary, which then promotes the secretion of T4 in the thyroid gland. In addition, lactotropes in the anterior pituitary are activated by TRH (111). As the primary product of the HPT axis, T3 regulates body growth by enhancing the function of GH (112). Simultaneously, it promotes energy metabolism through both the central nervous system and the peripheral tissue (113). In addition to the negative feedback regulation of thyroid hormone (114), the HPT axis is modulated by other diverse hormonal signals related to different neuronal inputs. TRH+ neurons in the

PVH receive projections mainly from the ARC and DMH nuclei in the hypothalamus and catecholaminergic neurons in the brainstem (115). Both POMC+ and AgRP+ neurons in the ARC innervate TRH+ neurons in the PVH (116, 117). The DMH may not only relay information from the ARC to TRH+ neurons but may also integrate inputs from the SCN, which mediates the circadian regulation of the HPT axis (115). In the brainstem, both adrenergic and noradrenergic neurons innervate TRH+ neurons in the PVH to induce thermogenesis in cold environments (118). In addition, adrenergic neurons release other neural transmitters, such as CART, NPY, and pituitary adenylate cyclase-activating polypeptide, to TRH+ neurons, indicating that adrenergic neurons can respond to different conditions and thus send various signals to TRH+ neurons (119).

The HPA axis

In the HPA axis, CRH derived from the PVH stimulates the secretion of ACTH in the anterior pituitary, promoting the secretion of glucocorticoids in the adrenal gland. As the primary product of the HPA axis, glucocorticoids act primarily as a response to physiological stress (120). They also inhibit the immune response because they are intense anti-inflammatory regulators, modulating energy stores, proteolysis, and lipolysis (121, 122). Interestingly, CRH+ neurons also release AVP and OXT (123), both of which can sufficiently activate ACTH secretion without the presence of CRH (124, 125). In addition to the essential negative feedback of glucocorticoids (126), the HPA axis is also regulated by various hormonal signals and distinct neuronal inputs. In contrast to their roles in the anterior pituitary, AVP and OXT inhibit the HPA axis through dendritic release within the PVH (127). The diurnal rhythm of glucocorticoid secretion depends on the regulation of the SCN (128). CRH+ neurons in the PVH receive the projections of catecholaminergic neurons at the locus coeruleus, NTS, and ventrolateral medulla to activate the HPA axis in the response to stress (129). GLP-1+ neurons in the NTS project to CRH+ neurons in the PVH, which may be associated with the regulation of food intake and stress response (130, 131). Serotonin, derived from the dorsal and median raphe nuclei of the brainstem, activates CRH+ neurons (132, 133). Moreover, to mediate stress regulation, CRH+ neurons are innervated by many limbic areas, such as the indirect innervation of the prefrontal cortex, hippocampus, lateral septum, and medial amygdala, and the direct innervation of the BNST (129). Interestingly, disorders related to the HPA axis exhibit obvious sex differences, as the HPA axis is regulated by sex hormones including androgens and estrogens (129).

The HNS

In the HNS, magnocellular neurons in the PVH and SON nuclei project to the posterior pituitary and release AVP and OXT into the circulatory system (134). In the periphery, OXT promotes milk ejection and uterine contraction, and AVP functions in vasoconstriction and antidiuresis (134). Recent studies suggest that AVP and OXT also participate in the regulation of social behaviors and gastrointestinal motor function (135, 136). Concentrations of AVP and OXT in plasma are affected by various hormonal signals and neuronal inputs. Purinergic and adrenergic agonists, prolactin, carbachol, hypertonic saline, angiotensin II, histamine, and prostaglandin E2 can promote AVP and OXT release; in contrast, serotonin decreases their concentrations in plasma (137–140). The secretion of AVP is affected mainly by changes in plasma osmotic pressure. The subfornical organ and organum vasculosum of the lamina terminalis are two circumventricular organs monitoring osmoreceptor stimulation, and they cooperate with the median preoptic nucleus to regulate AVP secretion in the PVH and SON (141–143). In addition, as another circumventricular organ, the area postrema also senses osmoreceptor information and relays it to the PVH (86). However, neurons in the caudal medulla and NTS in the brainstem, which receive afferents from the baroreceptors in the heart, aortic arch, and carotid sinuses, tonically inhibit AVP secretion and thirst (144–147). AVP functions at the kidney and arterioles to regulate water balance (148, 149) (Fig. 4). The secretion of OXT is regulated by reflex circuits during childbirth and breastfeeding (150). In addition, the release of AVP and OXT has been associated with emotional regulation (135, 151). However, the neural circuits related to emotional regulation that regulate the secretion of AVP and OXT have not been fully clarified.

Diseases

Obesity

Obesity is a medical condition in which excess body fat accumulates to the extent that it can have a negative effect on health (152). The morbidity of obesity has increased significantly in the past several decades. There are two billion overweight people worldwide, and one-third of them are obese, which is an enormous burden for public health (153). Moreover, obesity has a strong correlation with the pathogeneses of type 2 diabetes, cardiovascular diseases, and cancer (154, 155). Therefore, understanding of the etiology of obesity is one of the most prominent topics in both life science and clinical research.

Many clinical observations support the strong association of obesity with an abnormal PVH and melanocortin

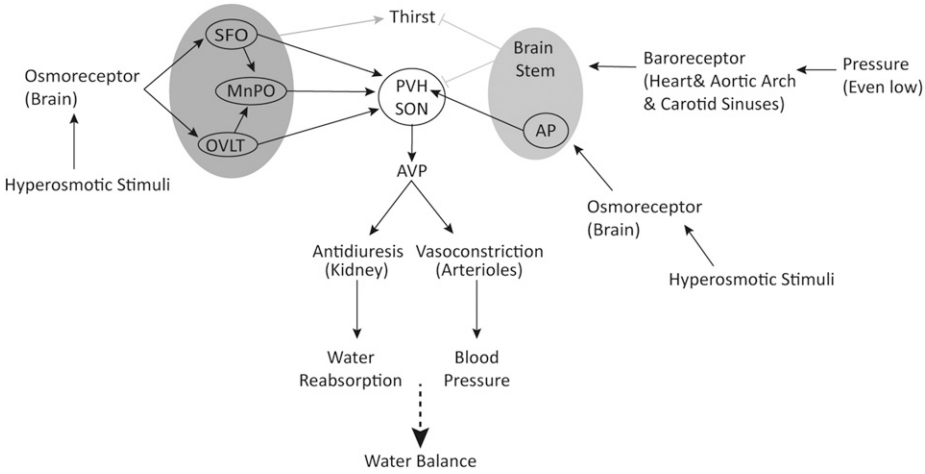

Figure 4. The brief neural network that regulates water balance through AVP secretion. The subfornical organ (SFO), oganum vasculosum of the lamina terminalis (OVLT), and AP are three circumventricular organs monitoring osmoreceptor stimulation. The SFO and OVLT cooperate with the MnPO to regulate thirst and AVP secretion in the PVH and SON. The AP projects to the PVH to control the release of AVP. In addition, the brainstem receives afferents from the baroreceptors to modulate AVP secretion and thirst. AVP functions at the kidney and arterioles, monitoring stimuli on the osmoreceptor and baroreceptor, respectively, to achieve maintenance of water balance. The black solid arrows represent positive regulations. The gray solid arrow indicates positive output from the circumventricular organs. The gray lines with blunt ends represent inhibitory regulation from the brain stem, and the dashed arrow means that water balance is maintained through AVP secretion. AP, area postrema; MnPO, median preoptic nuclei.

system. Monogenetic deficiency of the leptin, leptin receptor, insulin receptor, *MC4R*, or *POMC* genes leads to severe human obesity (155–160). Bardet-Biedl syndrome, in which obesity is the primary feature, is caused by a mutation in a single gene, such as *BBS1* or *BBS10*, which leads to leptin resistance (161). Mutations in chromosome *15q11-q13* lead to Prader-Willi syndrome, which is characterized by hyperphagia because of a severe reduction of OXT+ neurons in the PVH (162, 163). The mutation, translocation, or deletion of *SIM1* leads to hyperphagia and obesity in humans (164–166). Mutation of *ARNT2* has also been identified in human obesity (167). In addition, mutations in the fat mass and obesity-associated, *BDNF*, SH2B adaptor protein 2 isoform 1, or tubby genes also affect normal development or function of the hypothalamus, especially the PVH, which leads to obesity (83, 168–174) (Table 1).

Some neurodegenerative disorders cause obesity as well. For example, frontotemporal dementia leads to atrophy of the right orbitofrontal-insular-striatal circuit, which may affect reward circuits and contribute to abnormal feeding behavior (175). Interestingly, lesions in the right frontal lobe, such as trauma, tumor, or stroke, cause Gourmand syndrome, which is characterized by an obsessive focus on fine eating with an unaffected appetite (176). Thus, a better understanding of energy homeostasis regulation in the brain, especially the hypothalamus, will shed new light on the etiology and therapies of obesity.

Short stature

Short stature, also known as growth defect, indicates a height that is >2 SDs below the mean for age and sex. The clinical manifestation of short stature can be the result of complicated genetic conditions with apparently normal hormonal levels, defined as primordial dwarfism (177, 178). However, a compromised GH/insulinlike growth factor axis, hypothyroidism, and achondroplasia are possible causes of many short stature cases (179–181). The PVH plays an essential role in the formation of the HPT axis, and GH-releasing hormone-positive neurons in the PVH can regulate the secretion of GH in rats (182). Therefore, its aberration could cause short stature. Mutations of *OTX2, HESX1, SOX2, SOX3, LHX3, LHX4, PROP1,* and *POU1F1* genes result in abnormal hypothalamus-pituitary development and then lead to combined hormone deficits, including those of GH and TSH (180). Some recent studies revealed that deficiency of the *COUP-TFII* gene, which is located at chromosome *15q26*, is highly associated with growth defects in humans (183). Our study further demonstrated that the *COUP-TFII* gene participates in regulating the development and function of the PVH and hypothalamic-pituitary axis through modulation of the expression of *Bdnf* and *Nrp1* genes (8). Hormone replacements, such as levothyroxine or recombinant human GH, are current and effective therapies. However, there are still no treatments for primordial dwarfism (178).

Hypertension

Hypertension is a common disease that affects approximately 65 million people in the United States and plays a key role in the progress of irreversible life-threatening cardiovascular diseases (184). There are two types of hypertension: primary hypertension with unknown pathogenesis

Table 1. Human Genes and Obesity Associated With Abnormalities in the Hypothalamus or PVH

Mutant Gene/Region	Main Symptoms	Etiology	References
LEP	Obesity	Abnormal melanocortin system	Farooqi and O'Rahilly (157)
LEPR	Obesity	Abnormal melanocortin system	Farooqi and O'Rahilly (157)
IR	Diabetes, obesity	Insulin resistance	Nikolopoulou and Kadoglou (155) and Taylor *et al.* (158)
MC4R	Obesity	Abnormal melanocortin system	Yeo *et al.* (156)
POMC	Obesity	Abnormal melanocortin system	Krude *et al.* (159) and Mencarelli *et al.* (160)
BBS1	Bardet-Biedl syndrome, obesity	Leptin resistance	Feuillan *et al.* (161)
BBS10	Bardet-Biedl syndrome, obesity	Leptin resistance	Feuillan *et al.* (161)
15q11-q13	Prader-Willi syndrome, obesity	Abnormal development of the PVH, including impaired OXT+ neurons in the PVH	Swaab *et al.* (162) and Angulo *et al.* (163)
SIM1	Obesity	Abnormal development of the PVH	Bonnefond *et al.* (164), Holder *et al.* (165), and Wang *et al.* (166)
ARNT2	Obesity	Abnormal development of the PVH	Swarbrick *et al.* (167)
FTO	Diabetes, obesity	Not very clear (related to an abnormal hypothalamus and many other metabolic events)	Frayling *et al.* (168), Poritsanos *et al.* (169), and Taneera *et al.* (170)
BDNF	Obesity	Impaired BDNF+ neurons in the hypothalamus	An *et al.* (83), Friedel *et al.* (171), and Unger *et al.* (172)
SH2B1	Diabetes, obesity	Leptin and insulin resistance	Doche *et al.* (173)
TUB	Retinal dystrophy, obesity	Unknown (related to abnormal insulin and leptin signal in the hypothalamus)	Borman *et al.* (174)

and secondary hypertension with relatively clear causes. Primary hypertension accounts for the major proportion of hypertension cases. As an important neuronal pathogenic factor, the sympathetic nervous system has been widely studied (185). Abnormal AVP secretion contributes to some types of salt-sensitive hypertension (186). Salt and water homeostasis is necessary for maintaining normal blood pressure level, and disruption of their balance causes hypertension (187). The subfornical organ, median preoptic nucleus, and organum vasculosum of the lamina terminalis are three nuclei that integrate diverse signals, including salt and water homeostasis, to regulate thirst, central sympathetic neuronal circuits, and AVP secretion (141) (Fig. 4). The PVH receives projections from these nuclei to regulate AVP secretion and sympathetic neuronal circuits (188, 189). Many animal studies have demonstrated that an abnormal PVH is highly related to the pathogenesis of hypertension (190, 191). However, no clinical reports have demonstrated isolated PVH disruption in human hypertension. Therefore, PVH defects may be some of the neural factors that contribute to the development of primary hypertension.

Diabetes insipidus

Diabetes insipidus has two main symptoms, polyuria and polydipsia. There are four types of diabetes insipidus: pregnancy-related, nephrogenic, dipsogenic, and central diabetes insipidus (CDI). Among them, CDI is the most common type. CDI is characterized by AVP deficiency, causing dehydration and disturbance of water and electrolyte balances in the body (9). CDI can be caused by a variety of diseases, such as hypothalamic-pituitary Langerhans cell histiocytosis, posttraumatic stress disorder, brain malformations, and germinoma autoimmune hypophysitis (192–195). It can also be a side effect of some drugs, such as temozolomide (196). Some types of familial CDI have been studied, such as *AVP* mutations, Wolfram syndrome, mutations in genes related to the development of HNS, and a *LXR* null mutation mouse model (197–200). AVP+ cell antibodies, found in some patients with CDI, lead to the destruction of AVP+ neurons in the PVH (201). So far, many CDI cases are still classified as idiopathic in clinical medicine, and even their etiological diagnosis is difficult to determine (202). Desmopressin, clofibrate, chlorpropamide, and carbamazepine are the traditional treatments for CDI (9). Recently, orally disintegrating desmopressin tablets have provided better management, improving the quality of life of patients (203, 204).

Conclusions

The hypothalamus, composed of several imperative small nuclei, controls body temperature, hunger, thirst, stress, sleep, and circadian rhythms. Among these hypothalamic nuclei, the PVH plays essential roles in the regulation of food intake and energy expenditure and other activities of the autonomic nervous system, including the function of the hypothalamic-pituitary axis. Accumulating evidence from

clinical and animal studies reveals that an abnormal PVH contributes to growth defects, obesity, diabetes, and hypertension. Thus, a better understanding of the development and function of the PVH will benefit the understanding of the etiology and therapy of human diseases.

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