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REVIEW

New insight into GABAergic neurons in the hypothalamic feeding regulation

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Abstract

Several lines of study have suggested that GABA in the hypothalamic feeding center plays a role in promoting food intake. Recent studies revealed that not only NPY/AgRP neurons in the hypothalamic arcuate nucleus (ARC) that co-express GABA but also other GABAergic neurons act as an orexigenic. Here, we review the progress of studies on hypothalamic GABAergic neurons distributed in ARC, dorsomedial hypothalamus (DMH), and lateral hypothalamus (LH). Three advanced technologies have been applied and greatly contributed to the recent progress. Optogenetic (and chemogenetic) approaches map input and output pathways of particular subpopulations of GABAergic neurons. In vivo Ca^{2+} imaging using GRIN lens and GCaMP can correlate the activity of GABAergic neuron subpopulations with feeding behavior. Single-cell RNA-seq approach clarifies precise transcriptional profiles of GABAergic neuron subpopulations. These approaches have shown diversity of GABAergic neurons and the subpopulation-dependent role in feeding regulation.

Keywords Hypothalamus · Food intake · GABAergic neurons · NPY/AgRP neruons

Introduction

Feeding is regulated by hypothalamic nuclei including the arcuate nucleus (ARC), dorsomedial hypothalamus (DMH), paraventricular nucleus (PVN), ventromedial hypothalamus (VMH), and lateral hypothalamus (LH). ARC is recognized as the first-order center that senses peripheral metabolic signals. DMH and LH are recognized as the hunger centers, VMH as the satiety center, and PVN as the integrative center. GABA (gamma-aminobutyric acid)-ergic neurons are located primarily in ARC, DMH, and LH [1] and regulate energy balance positively. Infusions of GABA and GABA receptor agonist promote food intake, whereas GABA receptor antagonist suppresses it [2]. Here, we review the progress of studies on hypothalamic GABAergic neurons in feeding regulation.

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NPY/AgRP neurons in ARC

Neuropeptide Y (NPY)/Agouti-related protein (AgRP)-expressing neurons in ARC are GABAergic neurons [3, 4]. These neurons play a prominent role in promoting food intake. They are activated by peripheral orexigenic signals such as ghrelin [5, 6], while inactivated by anorexigenic signals such as leptin [4, 7], insulin [8], and glucose [9], and release NPY, AgRP, and GABA in an activity-dependent manner. Intracerebroventricular injection of NPY or AgRP promotes feeding [10, 11]. Conversely, application of their antagonists or GABA receptor antagonist to the projection site of NPY/AgRP neurons suppress feeding [12].

Optogenetics by using light-dependent channels such as channelrhodopsin, halorhodopsin, and variants, and chemogenetics by using designer receptors such as hM3Dq and hM4Di have been used to activate or inhibit the activity in selective neurons, and allow us to analyze the link between the neuronal activity and behavior. Optogenetic or chemogenetic activation of NPY/AgRP neurons promote food intake [13, 14] while chemogenetic inhibition suppresses it [14].

A study using chemogenetic activation of NPY/AgRP neurons in NPY, GABA, and/or melanocortin receptor 4 (MC4R)-deficient mice revealed that ether NPY or GABA is needed to promote food intake in the early phase whereas AgRP plays a role in prolonging feeding [15].

Optogenetics could regulate membrane potential not only in cell bodies but also in axon terminals to generate action potentials and release neurotransmitters. This allows us to identify the neurons that receive monosynaptic transmission from channelrhodopsin-expressing presynaptic neurons. Moreover, this could reveal a behavior that is mediated by the neural circuit. Using this technique, it was determined that AgRP neurons monosynaptically project to the anterior bed nucleus of the stria terminalis (aBNST), PVN, LH, the paraventricular nucleus of thalamus (PVT), the central nucleus of amygdala (CeA), the periaqueductal gray (PAG) [16], and the parabrachial nucleus (PBN) [17]. Among these projection sites, the aBNST, PVN, LH, and PVT were estimated to participate in the core forebrain feeding circuit, since presynaptic activation of AgRP neurons onto these nuclei promoted food intake [16]. Optogenetic activation of presynaptic terminals of AgRP neurons onto MC4R-expressing neurons in PVN but not in LH or aBNST-induced inhibitory postsynaptic current (IPSC) and promoted food intake, suggesting that AgRP neuron-derived hunger is mediated by MC4R neurons in PVN [18]. This study also showed that MC4R was not expressed in oxytocin neurons and that oxytocin neurons and corticotropin-releasing hormone (CRH)-expressing neurons in PVN did not mediate AgRP neuron-derived hunger [18]. This is, however, inconsistent with other reports. Atasoy et al. showed that food intake elicited by optogenetic activation of presynaptic terminal of AgRP was attenuated by additional optogenetic activation of oxytocin neurons in PVN [19]. Immunohistochemical study showed that MC4R is expressed in oxytocin neurons and CRH neurons [20] and that MC4R agonist, α-melanocyte stimulating hormone (α-MSH), and melanotan II (MTII) activates PVN oxytocin neurons [21–23].

Optogenetic activation of presynaptic terminals also clarified the synaptic input onto AgRP neurons from other hypothalamic feeding regulatory nucleus. Glutamatergic neurons that express thyrotropin-releasing hormone (TRH) or pituitary adenylate cyclase-activating polypeptide (PACAP) in PVN but not in VMH and DMH send an excitatory synaptic input onto ARC AgRP neurons, whereas oxytocin, arginine-vasopressin (AVP), or CRH neurons in PVN do not [24]. Chemogenetic activation of TRH or PACAP neurons in PVN promotes food intake via ARC AgRP neurons [24].

In vivo Ca^{2+} imaging with GRIN lens allows us to observe the activity of neurons in deep brain of free-moving mice. Food presentation without consumption acutely suppresses the neural activity of AgRP neurons of fasting mice [25, 26]. The suppression of neural activity was recovered within 10 s but not completely. Several times of food presentation weakened the neural activity, reaching the silent state. Dummy food presentation transiently suppressed and immediately recovered the neural activity. These observations indicate that the fast neurotransmission (probably mediated by GABA) from a sensory system such as vision or smell play a role in regulating AgRP neurons, as well as nutrients and hormones from peripheral organs as a result of food consumption. GABAergic neurons in DMH were reported as one of the sources of the GABA to suppress AgRP neuron activity (see the section of DMH).

POMC neurons in ARC

Approximately half of ARC POMC neurons expressed glutamic acid decarboxylase (GAD) 67, GAD 65, or vesicular GABA transporter (Vgat), the marker of GABAergic neurons, and a small potion of the neurons co-expressed vesicular glutamate transporter (Vglut)2 [27–29]. Additionally, GAD 67-positive POMC neurons increased while Vglut2-positive POMC neurons decreased in a postnatal developing period [30]. Acute and chronic calorie restriction reduced the expression of GAD 67 mRNA, with lesser effect on GAD 65, whereas high-fat diet feeding or stress altered them in POMC neurons [31]. However, the role of GABA release from POMC neurons still remains to be clarified.

Direct GABAergic projection from NPY/AgRP neurons to POMC neurons in ARC has been detected by electron microscopy [4]. Additionally, light-evoked IPSC was observed at POMC neurons in ARC from AgRP neuron selective channelrhodopsin-expressing mice, indicating that POMC neurons received functional synaptic connection from AgRP neurons [19, 32]. However, AgRP neuron-specific inhibition of GABA release by cell type specific deletion of Vgat or expression of botulinum toxin did not alter IPSCs onto POMC neurons [33, 34], suggesting that GABAergic input from AgRP neurons to POMC neurons depends on the states of AgRP neuron activity.

Non-NPY/AgRP, non-POMC GABAergic neurons in ARC

Although NPY/AgRP neurons and POMC neurons in ARC are established as the first-order neurons in sensing leptin, the changes in body weight and food intake in mice deficient of leptin receptor (LepR) selectively in these neurons were smaller than in conventional LepR-deleted mice or Ob/Ob mice, indicating the first-order neurons sensing leptin include new neurons other than NPY/AgRP neurons and POMC neurons. The mice deficient of LepR selectively in the neurons expressing Vgat, which is required for GABA release, showed

similar increases in body weight and food intake with conventional LepR-deleted mice. In contrast, the mice deficient of LepR selectively in the Vglut-expressing neurons showed body weight and food intake comparable to wild-type littermates [1]. These results indicate that the first-order neurons other than NPY/AgRP and POMC neurons are GABAergic.

The role of non-NPY/AgRP, non-POMC GABAergic neurons in feeding regulation was investigated by using several mice lines. The mice with disrupted GABA release from LepR neurons (LepR-Cre::Vgat$^{flox/flox}$) increased body weight caused by increasing food intake and decreasing energy expenditure with lowering leptin sensitivity [35]. Pancreas–duodenum homeobox 1 (Pdx-1) and Rat insulin promoter1 (RIP) are expressed in hypothalamic neurons, except for arcuate NPY/AgRP and POMC neurons [36]. The mice disrupted GABA release from hypothalamic RIP-expressing neurons (RIP-Cre::Vgat$^{flox/flox}$) were obese and extremely sensitive to DIO due to dysregulation of energy expenditure but not food intake. Leptin-induced thermogenesis, but not suppression of food intake, was attenuated in the mice. Most RIP-expressing neurons in ARC are GABAergic, and half of them are LepR-positive [37]. The mice with disrupted GABA release from hypothalamic Pdx-1-expressing neurons (Pdx-1-Cre::Vgat$^{flox/flox}$) showed decreased food intake and body weight in the postweaning period [38]. NPY-induced hyperphagia was attenuated in the mice [38].

GABAergic neurons in DMH

DMH has been considered an orexigenic nucleus since its lesion decreased food intake and body weight. In DMH, however, the principal neuron that promotes food intake has not been identified, in contrast to other feeding regulatory nuclei. A subpopulation of DMH GABAergic neurons expresses leptin receptor [1], which inhibits its activity while it is activated by lowering glucose [39]. These neurons projected to ARC POMC and NPY/AgRP neurons [40] and PVN neurons [39]. Optogenetic activation of GABAergic neurons in DMH showed an increase in food consumption partly via inhibition of PVN neurons [39]. DMH GABAergic neuron projecting to NPY/AgRP neurons expressed leptin receptor while that projecting to POMC neurons did not. Leptin receptor-expressing GABAergic neurons were activated in response to food presentation, which is associated with acute inhibition of NPY/AgRP neurons [40].

GABAergic neurons in LH

Resent studies revealed that three types of GABAergic neurons in LH are associated with feeding behavior. A subpopulation of GABAergic neurons in LH is melanin-concentrating hormone (MCH)-expressing neurons, which also expresses GAD67 and LepR. MCH is an orexigenic neuropeptide that inhibits other hypothalamic neurons [41]. Local injection of MCH to PVN or DMH promotes food intake and body weight gain [42–45]. A chronic infusion of MCH or activation of MCH receptor 1 also increases food intake and body weight gain, and elevates the level of insulin and leptin [46, 47]. Conversely, the mice lacking MCH showed lean phenotype due to decreased food intake [48]. Antagonism of MCH receptor 1 leads to sustained reduction in food intake and body weight gain [47].

Optogenetic activation of axonal projection from Pdx-1-expressing neuron in LH, which also expressed MCH, to PVN promote feeding, whereas it was abolished by disruption of GABA release by deletion of Vgat [49].

Optogenetic activation of Vgat-positive GABAergic neurons in LH produces appetitive and consummatory behavior [50]. In this report, it is also shown that the Vgat-positive GABAergic neurons were distinct from MCH or orexin neurons. However, it is still not clear whether MCH neurons do not express Vgat. Additionally, in vivo Ca^{2+} imaging revealed that the GABAergic neurons from a distinct population that encodes appetitive behavior while others do consummatory behavior [50].

Single-cell RNA-seq analysis in hypothalamic GABAergic neurons

Single-cell RNA-seq technique is quite useful for distinguishing the hypothalamic neurons, since the hypothalamus lacks anatomical characteristics, such as distinct layering or repetitive organization observed in cortical or cerebral neurons. Romanov et al. applied this technique to neural populations of PVN, anterior hypothalamic nucleus (AHA), SCN, DMH, VMH, and ARC [51]. This analysis found 15 clusters of GABAergic neurons, which expressed Gad1, Gad2, and Slc32a1. The 15 clusters included the neurons expressing AgRP/NPY, somatostatin, corticotropin-releasing hormone (CRH), and POMC. Notably, four out of 15 GABAergic neuron clusters showed dopaminergic transcript tyrosine hydroxylase, Slc18a2 (encoding vesicular monoamine transporter 2, VMAT2) and, in some cases, Slc6a3 (encoding dopamine transporter 1, DAT), suggesting that these neuron clusters co-express dopaminergic and GABAergic phenotypes. The GABAergic (Slc17a6-positive) neurons in the ARC and the median eminence were classified into 18 clusters by using single-cell RNA-seq [37]. This analysis firstly observed two subtypes of the AgRP neurons, somatostatin (SST)-positive and -negative ones. Additionally, AgRP-negative SST neuron subpopulation showed a similar transcriptional profile as that of AgRP neurons, and

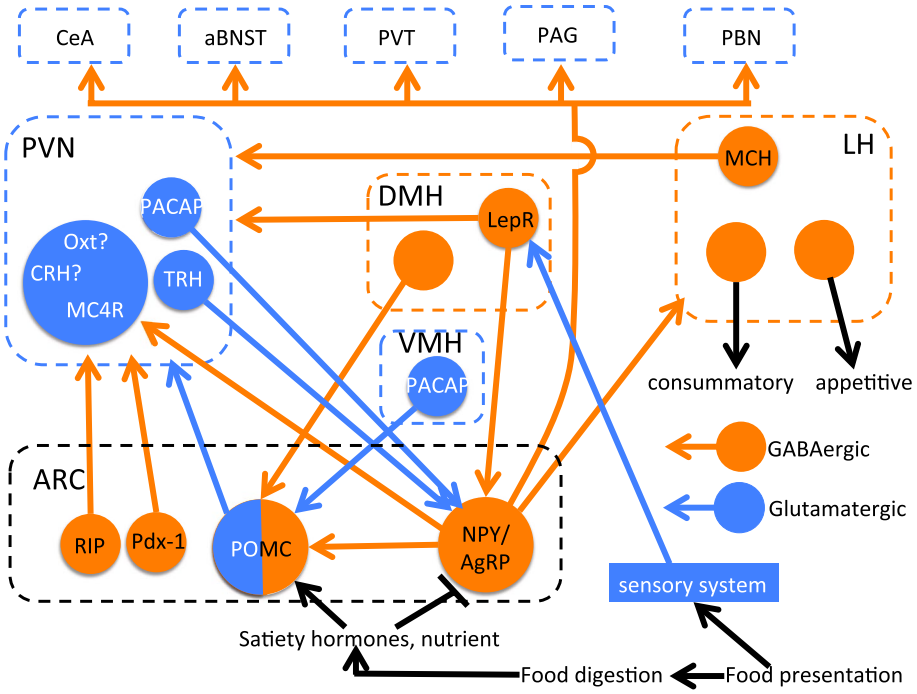

Fig. 1 Schematic overview of circuit of GABAergic neurons in hypothalamus in feeding regulation. *Orange* indicates GABAergic and *blue* indicates glutamatergic neurons. The *dotted lines* indicate nuclei. *ARC* arcuate nucleus, *PVN* paraventricular nucleus of hypothalamus, *DMH* dorsomedial hypothalamus, *VMH* ventromedial hypothalamus, *LH* lateral hypothalamus, *CeA* central nucleus of amygdala, *aBNST* anterior bed nucleus of the stria terminalis, *PVT* paraventricular nucleus of thalamus, *PAG* periaqueductal gray, *PBN* parabrachial nucleus, *NPY* neuropeptide Y, *AgRP* agouti-related protein, *POMC* proopiomelanocortin, *Pdx-1* pancreas–duodenum homeobox 1, *RIP* rat insulin promoter1, *MC4R* melanocortin receptor 4, *PACAP* pituitary adenylate cyclase-activating polypeptide, *TRH* thyrotropin-releasing hormone, *CRH* corticotropin-releasing hormone, *Oxt* oxytocin, *LepR* leptin receptor, *MCH* melanin-concentrating hormone (color figure online)

chemogenetic activation of SST neurons in ARC promoted food intake, similarly to activation of AgRP neurons [37].

These studies showed the diversity of GABAergic neurons in hypothalamus, and demonstrated that the single-cell RNA-seq is a useful method for exploring new subpopulations of neurons.

Perspectives

In the past 5 years, the optogenetic approach has successfully illustrated the neural circuit of GABAergic neurons, particularly GABAergic NPY/AgRP neurons, in feeding regulation. This approach allows us to observe the functional synaptic contact among the neurons of interest and to illustrate the precise neural circuit (Fig. 1). However, the "optogenetically" functional contact is not equal to the "physiologically" functional connection, as suggested from the study of synaptic projection from NPY/AgRP neurons to POMC neurons in ARC [34]. In vivo Ca^{2+} imaging is an effective tool for exploring the neurons that mediate specific behaviors. These new techniques identified an orexigenic GABAergic neuron subtype that expresses neither NPY nor AgRP. Intriguingly, GABAergic neuron subtype that suppresses feeding has not been found by now. In this regard, it remains to be clarified whether or not the GABAergic neurons project to orexigenic GABAergic neurons.

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