



Role of Various Neurotransmitters in the Central Regulation of Food Intake in the Dorsomedial Nucleus of the Hypothalamus

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ABSTRACT

In living organisms, the central control of nutrition is a highly complex and vital mechanism. Central control of nutrition occurs in various regions of the brain, with the hypothalamus being the most important of which is the hypothalamus. The hypothalamus controls feeding behaviors through neural circuits, specialized nuclei, and central neurotransmitters. Different hypothalamic nuclei involved in regulating food intake include ARC, PVN, LHA, VMH, and DMH. The DMH influences feeding behavior by modulating the activity of different neurotransmitters in the brain. This nucleus receives both orexigenic and anorexigenic inputs through neural connections with the ARC and other regions of the brain. Due to its location in the brain, the ARC has access to nutritional inputs from the circulation. Within this nucleus, there exist two distinct neuronal populations, namely NPY and POMC. Different inputs from circulation affect two neuronal populations in the ARC. These inputs are related to second-order neurons, including DMH. The DMH integrates these inputs and sends the final output to PVN and LHA. Therefore, DMH affects the central control of feeding regulation through these neural pathways.

Keywords

Feeding, Hypothalamus, Dorsomedial nucleus, Brain neurotransmitters, Orexigenic, Anorexigenic

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Abbreviations

CNS: Central Nervous System

ARC: Arcuate nucleus

VMH: Ventromedial hypothalamus

PVN: Paraventricular

LHA: Lateral hypothalamus area

DMH: Dorsomedial hypothalamus

Introduction

The ability to maintain a balance between energy intake and consumption is very important in living things. Researchers have conducted many types of research on this subject [1]. It has been shown that CNS plays a key role in controlling this balance [2]. Research conducted on CNS includes brain neuroanatomical constructions, peripheral and central hormonal and metabolic signals, as well as examining cellular and molecular pathways [3]. Among different brain regions, the hypothalamus plays an important role in controlling the mentioned pathways [4].

Numerous neurotransmitters and neuropeptides affect the central control of feeding via the hypothalamus. This region plays a crucial role in monitoring basic behavior patterns, particularly feeding behavior [5]. Different types of stimulating and inhibitory peptides generated in the CNS affect feeding (Figure 1) [6]. The central regulation of feeding behavior and energy homeostasis in the body is a highly complex process that requires extensive research. Neuroscience researchers have discovered that special hypothalamic nuclei, as well as brain neurotransmitters and neuro-modulators, play an important role in the central control of nutritional behaviors [7-15].

Hypothalamus exerts its controlling role through its special nuclei. These nuclei include ARC (first-order neuron), VMH, PVN, LHA, and DMH (second-order neurons) [16-18]. The ARC in the middle eminence is not covered by the BBB, so it has direct access to the signals of energy regulation with blood origin. This nucleus, with its two important neuronal populations (NPY and POMC), plays a very important role in the central control of food intake [19]. By receiving blood signals, the neuronal population in this nucleus sends the necessary message to change the nutritional sta-

tus and neuronal activity of the second-order neuron [4]. The VMH is called the center of satiety and plays a role in energy homeostasis and body weight. It receives different signals from ARC and PVN through its receptors, modulates these messages, and sends appropriate output to ARC, PVN, and other brain regions involved in the central control of feeding [17, 20]. The PVN is the center of hunger and is the main output center of the hypothalamus. It receives multiple inputs from the ARC and subcortical regions. It then issues the appropriate response to the LHA and other brain regions [16, 21]. The most important task of LHA is to control nutrition according to the changes in the body's energy status. This nucleus receives the necessary messages to control the nutritional status of the body, especially from the ARC, PVN [18], and DMH [22, 23]. Then, by integrating these messages, it issues the appropriate stimulus response to VTA and other brain centers involved in the central control of food intake [24].

The DMH plays an important role in controlling feeding, body weight, and digestive behaviors [22, 23]. It is located in the tubular part of the hypothalamus and the area between the periventricular and lateral regions. In rodents, this nucleus is easily divided into several identifiable sub-regions [25]. The DMH contains two important neural populations, namely NPY and CART neurons, which are the most important ones in the central control of food intake [26]. The DMH receives diverse inputs and integrates them and issues the appropriate response through these two neuronal populations [27]. This nucleus has extensive connections with other hypothalamic nuclei in the central control of food intake. This nucleus receives multiple inputs from all the anterior, middle, and posterior nuclei of the hypothalamus [28]. The DMH also receives signals of blood origin through the cerebellum. The cerebellum transmits various inputs from the vagus nerve and signals of blood origin to the DMH. Therefore, through DMH, the hypothalamus is connected to other neural networks involved in the central control of nutrition, including the cerebellum-vagus nerve [29]. The DMH sends extensive nerve projections to all nuclei of the periventricular zone of the hypothalamus, such as PVN, LHA (except ARC), septum, hippocampus, and amygdala [27].

In the field of neurophysiology, several types of research have been conducted on distinct hypothalamic nuclei, and their roles have been investigated separately. The DMH has received little attention among these nuclei [23]. Therefore, considering the role of DMH in the central control of food input, we review the role of this nucleus in controlling central nutritional behavior.

Abbreviations-Cont'd

- BBB: Blood-brain barrier
 NPY: Neuropeptide Y
 POMC: Pro-opiomelanocortin
 VTA: Ventral tegmental area
 CART: Cocaine- and amphetamine-regulated transcript
 GALRs: Galanin receptors
 GPCR: G protein-coupled receptors
 PeH: Periventricular hypothalamic
 ICV: Intracerebroventricular
 GALP: Galanin-like peptide
 L-br: Leptin receptors
 DR: Dopaminergic receptors
 NPYR: NPY receptor
 MCR: Melanocortin receptor
 GHSR 1a: Growth hormone secretagogue receptor 1a
 MBH: Mediobasal hypothalamic
 AgRP: Agouti-related peptide
 α -MSH: alpha-melanocyte-stimulating hormone.

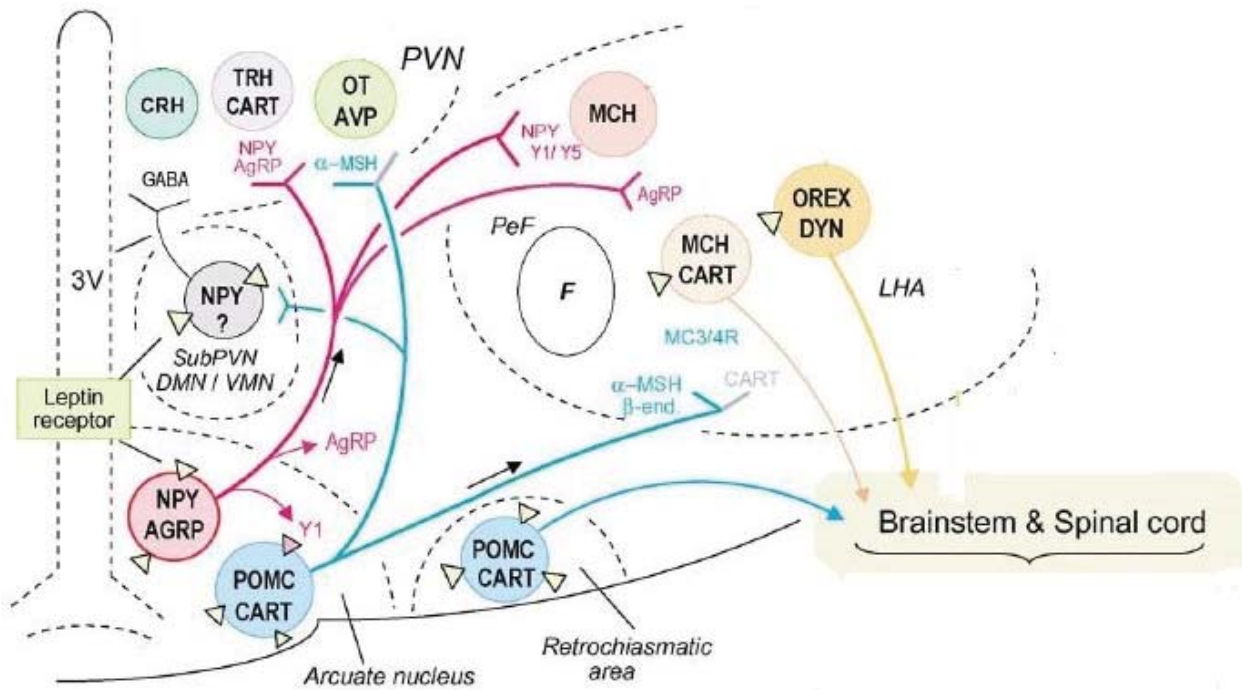


Figure 1. Nutritional status and energy balance hypothalamic peptidergic circuitry in the rat. Receptors and communities of peptidergic neurons with their projections were defined. The middle group of hypothalamic nuclei, including the arcuate nucleus, retrochiasmatic area, dorsomedial, and ventromedial nuclei have long-form leptin receptors (ObrB, open triangles). Arcuate neuron has the mRNA of neuropeptide Y (NPY) and agouti-related protein (AgRP). These neuron populations project output to the paraventricular nucleus (PVN) and the perifornical/lateral hypothalamus (PeF). These neuron populations project output to autonomic and motor areas of the brainstem and spinal cord, PVN and DMH, and other brain areas (not shown). One neuron group that receives input from these ARC projections in the lateral hypothalamus (LHA) involves MCH, CART, orexin-A (OREX), and dynorphin (DYN). Various populations of these neurochemically special cell groups produce ‘ascending’ (cortex, amygdala, hippocampus, thalamus) and ‘descending’ projections to promotor (medullary motor nuclei), locomotor (pedunculopontine locomotor area and spinal cord), and autonomic premotor and motor areas (dorsal motor nucleus of the vagus, A5, RVLM, and ILM) (dorsal motor nucleus of the vagus, A5, RVLM, and ILM) [81].

Study design

Several reliable papers from electronic sources were used in this review article. Creditable articles indexed in the Web of Science, Scopus, PubMed, SID, Google Scholar, and ISI databases using the keywords “feeding central regulation”, “hypothalamic dorsomedial nucleus”, “brain neurotransmitters”, and “brain neuromodulator” were surveyed.

Galanin

Galanin is a neuropeptide found in CNS, especially the hypothalamus, and exerts its effect via GALRs (Table 1). It helps regulate feeding, body weight, reproduction, and growth. The GALRs, as members of the GPCR family, are classified into three types [5, 30]. GALR1 is mostly found in the prefrontal cortex, medial thalamus, and central amygdala. GALR2 is presented in the granule cell layer of the dentate gyrus, cerebellar cortex, and mammillary bodies. GALR3 is found in the hypothalamus [31]. In mice, galanin is distributed in all special nuclei of the hypothalamus,

especially VMH. In rats, galanin is most distributed in DMH and PeH [32]. Galanin stimulates eating through various brain regions, especially DMH [33]. Central administration of galanin increased food consumption in rodents. As well as, intracerebroventricular (ICV) administration of galanin stimulates feeding in various hypothalamic nuclei such as DMH in satiated rats [34]. Moreover, the ICV injection of 1 nmol galanin increased feeding in rats with free access to food and water (Table 2). Galanin causes a central increase in food intake via up-regulating c-FOS in GALR1 in DMH [31].

Galanin-like peptide

The GALP, a 60-amino acid neuropeptide, was discovered in the hypothalamus of pigs and is linked to GALRs (Table 1) [30]. GALR1 is mostly distributed in the CNS, while GALR2 and 3 were distributed to a lesser extent in the CNS and peripheral tissues [35]. GALP has a higher affinity for binding to GALR2 than other receptors and functions in the hypothalamus via GALR2 [36]. In mice, the GLAP neurons are

Table 1.
Basic receptors involved in the central control of feeding in DMH.

Receptor	Receptor Category	Receptor Location (s)	Action (s)	Action Mechanism	Ref.
GALR2	GPCR	DMH	Increased food intake	Increased c-Fos expression	[36]
DR2	GPCR	DMH	Decreased food intake	Inhibits the formation of cAMP	[48]
GHSR	GPCR	ARC, and DMH	Increased food intake	Increased c-Fos expression	[60]
Lb-R	Class 1 cytokine receptor	ARC, and DMH	Decreased food intake	Increased c-Fos expression	[79]
NPYR	GPCR	ARC, PVN, VMH, and DMH	Increased food intake	Increase in the GABA release to the POMC neuron	[74]

distributed in the ARC [37]. Leptin receptors (L-bR) are expressed in the GALP neurons. Therefore, GALP has a direct effect on food intake by communicating with leptin [30, 37]. In rats and mice, GALP seems to have different effects. In rats, this leads to a temporary rise in feeding, followed by a reduction in eating and body weight [38]. This transient increase in feeding is linked to the activation of orexin neurons in LHA and NPY neurons in DMH [36, 39]. In mice, it only reduces food intake and body weight [40]. In mice, the repeated intranasal administration of 2 nmol of GALP reduced food intake, water intake, and body weight in 24 hours [30]. Different doses of GALP have diverse effects on feeding. A low dose (1-2 nmol) reduces food intake, whereas a high dose (4 nmol) does not affect feeding. High doses may reduce receptor expression and sensitivity to GALP [41]. In another study, it has been shown that galanin ICV injection increased food intake for the initial 2 hours in rats. GALP upregulates NPY neurons in the DMH. It also raises the level of c-Fos expression in these neurons and augments food intake (Table 2) [36]. As a result, GALP in mice decreased food intake via communication with leptin neurons. In rats, GALP increased food intake via activating orexin neurons in LHA and c-FOS expression in NPY neurons.

Dopamine

Dopamine is a vital neurotransmitter in the CNS, which is produced from tyrosine amino acid [42]. Dopamine neurons are found in the hypothalamus, especially in ARC, DMH, and LHA [43]. Dopaminergic neurons in the hypothalamus communicate with GABAergic, and POMC neurons in ARC and transmit nerve projections to PVN and LHA [44]. Dopamine exerts its effects on feeding control through DRs, which are GPCR. These receptors include DR1-DR5. Dopamine affects feeding via DR1 and DR2 [45]. DR1 was found in suprachiasmatic nuclei, PVN, LHA, VMH, and DMH. DR2 was expressed in LHA,

PVN, VMH, and ARC (Table 1) [43]. The impacts of dopamine on the central control of eating depend on the type of nucleus, receptor, and overall energy condition of the body [45]. As well, dopamine seems to have diverse effects on feeding in LHA and VMH [3]. In LHA, dopamine levels are high in response to feeding and during feeding. Dopamine levels in VMH increased during fasting and after feeding. DR2 was found in NPY neurons, ARC, and PVN. When dopamine binds to DR2 in NPY neurons in PVN and ARC, inhibits NPY neurons in ARC and PVN. Consequently, NPY level declines and NPY does not bind NPYRs in DMH. The NPY cannot stimulate DMH. Finally, decreased food intake in rat [43, 46]. As well, dopamine binds to DR1 in POMC neurons, stimulating it. POMC via MCR4 inhibited DMH orexigenic output. As a result, food intake is suppressed in mice via indirect effects (Table 2) [43, 46, 47]. Furthermore, DMH sends these neural projections to LHA and suppresses feeding [48]. Dopamine inhibits feeding by inhibiting NPY neurons and stimulating POMC neurons via DMH.

Ghrelin

Ghrelin is a peptide with 28 amino acids derived from the stomach and released in reaction to a change in nutritional status [49]. It is synthesized and secreted in low volumes in the brain [50]. This hormone is orexigenic and increases in response to a massive decrease in energy [51]. Ghrelin is considered a blood glucose regulator, appetite controller, and anti-depressant [52, 53]. Ghrelin neurons transmit nerve projection to hypothalamic nuclei, including ARC, PVN, VMH, and DMH [54]. Ghrelin exerts its multiple and essential functions through GHSR1a, which is a part of GPCR (Table 1) [55]. This receptor is widely expressed in the hypothalamus, especially in MBH, ARC, PVN, VMH, and DMH [56, 57]. Moreover, ghrelin projection is transmitted to extra hypothalamic regions, namely the amygdala and septum [50]. Among different hy-

Table 2. The role of main neurotransmitters in the central control of feeding in the DMH.

Substance Type	Animal Type	Administration Type	Co-transmitter	First Order Neuron	Second Order Neuron	Function (s)	Other Central/Peripheral Action (s)	Action Mechanism (s)	Dosage of the drug (s)	Ref.
GALP	Mice	Intranasal	NPY	ARC	DMH, LHA	Decreased feeding	Decreased water intake, and body weight	Interleukin-1 receptor	2 nmol	[30]
GALP	Rat	ICV	NPY	VMH	PVN	Increased feeding	-	Increased in c-FOS expression	0.3 nmol/5µl	[36]
Sulpiride	Rat	Intra hypothalamic	Serotonin	ARC	LAH	Increased feeding	Increased water intake	cAMP level inhibited	8 µg/0.5 µl	[48]
Ghrelin	Rat	Intraperitoneal	NPY	ARC	DMH	Increased feeding	Increased c-Fos-like-immunoreactivity in PVN	Increased of c-Fos expression	0.3 nmol	[65]
Leptin	Rat	Intravenous	NPY	DMH	PVN	Decreased feeding	Increased energy consumption	Increased of c-Fos expression	1 mg/Kg	[76]
Angiopoietin-like protein 8	Mice	ICV	NPY	ARC	DMH	Decreased feeding	Decreased body weight	Decreased of c-Fos expression	2 µg/ml	[73]

pothalamic nuclei, DMH is sensitive to the regulation of ghrelin secretion in response to feeding behaviors stimuli [58]. Peripheral and central administration of ghrelin increases feed consumption and body weight [59]. GHSR1a expresses NPY/AgRP neurons in ARC [60] and DMH [61]. It increases the activity of these neurons and upregulates NPY. The NPY neurons transmit orexigenic output to DMH. Therefore, DMH sends orexigenic output to the PVN [62]. The ICV and peripheral injection of ghrelin-induced feeding in rats that had free access to food [63, 64], and also upregulated c-Fos in NPY neurons in ARC. Furthermore, induced c-Fos expression in DMH and PVN. Following the stimulation of NPY neurons in ARC, this nucleus sends excitatory projections to DMH, stimulating it. With DMH activation orexigenic output is sent to PVN [65]. Therefore, via this pathway, DMH exerts its orexigenic effect on feeding in rats (Table 2) [66]. Ghrelin also affects nutrition by reducing signaling from dopamine and serotonin [67]. In the brain, ghrelin neurons interact with dopaminergic neurons, and dopamine modulates an increased effect of ghrelin in nutritional behavior [68]. In addition, ghrelin reduces serotonin release to synaptic cleft [69]. Ghrelin raises NPY activity in ARC and DMH via binding to GHSR1a. In addition to directly increasing the level of NPY in the DMH, the level of this neuropeptide is increased in the ARC and sends excitatory input to the DMH. Next, DMH sends orexigenic messages to PVN.

Neuropeptide Y

The NPY is a vital and strong orexigenic compound in CNS and is synthesized in ARC and DMH. DMH contains NPYR [61]. NPY is a 36-amino acid peptide, which is a member of the pancreatic polypeptide family. NPY is distributed in CNS, especially the hypothalamus [7], and plays an orexigenic role with NPYR. The NPYR belongs to the GPCR family. NPY has multiple receptors, including NPYR1, NPYR2, NPYR4, and NPYR5. The DMH contains NPY1R and NPY5R (Table 1) [70]. NPY exerts orexigenic effects via these receptors. The NPY neurons in DMH are considered gabaergic and non-sensitive neurons to leptin [71]. NPY levels in DMH increase in response to food deprivation and stimulate this nucleus. Now, this nucleus transmits orexigenic output to other nuclei [61]. In mice, NPY neurons in DMH are involved in central feeding regulation [72, 73]. It has been shown that POMC neurons in ARC may have an inhibitory role on NPY neurons in DMH. The POMC-GABAergic neurons in ARC send inhibitory output to DMH. In DMH, MCR4 is expressed. The POMC neuron via MCR4 exerts an inhibitory effect on NPY neurons [1]. During starvation in rats, NPY levels are increased in

the ARC [74] and DMH [75]. Also, the GABAergic inhibitory branch inhibits the POMC neurons in the ARC. As a result, their inhibitory effect is removed from NPY neurons in DMH. Then, NPY exerts its additive effect on food intake by sending excitatory outputs to other brain regions [72]. The main brain neurotransmitter for controlling feeding in DMH is NPY. Central injection of NPY augments feeding and body weight (Table 2) [75]. In response to starvation, the NPY level rises in both ARC and DMH. On the other hand, the inhibitory GABAergic branch of ARC inhibits POMC neurons. As a result, NPY stimulates DMH, and DMH exports the necessary orexigenic message.

Leptin

Leptin is an adipose tissue-derived hormone that inhibits ingestion and facilitates weight maintenance. Lack of leptin or reduced sensitivity to leptin causes obesity. Therefore, leptin is a vital hormone in controlling food intake. The Lb-R, which is found throughout CNS, is a member of the class 1 cytokine receptor family (Table 1) [18]. Leptin is highly expressed in the hypothalamus particularly ARC, VMH, and DMH [71]. Leptin has a receptor on GABAergic neurons in DMH. Therefore, leptin inhibits GABAergic neurons via Lb-R and restrains projection transmitted to PVN. Leptin reduces feeding in rats via this pathway [76, 77]. Furthermore, leptin suppresses feeding and promotes energy consumption by activating other neuron populations [78]. Leptin exerts its effect on nutritional behavior via increased c-Fos expression in ARC, DMH, and PVN [79]. The NPY neurons in ARC transmitted nerve projection to DMH. The main site of leptin action is the hypothalamus. It has been shown that the ICV injection of leptin reduces digestion by affecting the hypothalamus (Table 2). Furthermore, circulating leptin enters CNS through MBH, and then exerts its effect on food intake by transmitting nerve projections from ARC to DMH, and then to PVN. Finally, feeding is reduced. Leptin inhibits the expression of NPY mRNA and increases the level of α -MSH in the hypothalamus. It also reduces the level of this neurotransmitter in ARC, DMH, and PVN. Neurons expressing Lb-R in DMH play a key and essential role in feeding control [80]. Leptin inhibits GABAergic neurons in DMH through Lb-R. It also down-regulates NPY and up-regulates α -MSH in ARC and DMH. As a result, through these pathways, the increasing effects of DMH on food intake are inhibited, and it reduces food intake.

Conclusion

DMH plays an important role in the central control of feeding, but it has received very little attention. NPY in this nucleus plays a critical role in the central stimulation of food intake. Galanin and GALP stimulate central feeding behavior via their receptors in this nucleus. The effect of dopamine on the central control of food intake appears to be highly dependent on the nutritional level, receptor type, and nucleus involved. Dopamine inhibits NPY neurons and stimulates POMC neurons via dopaminergic receptors, resulting in a central decrease in digestion. Ghrelin also increases central food intake by raising NPY levels. Leptin reduces central food intake by decreasing NPY levels (graphical abstract).

Future directions

Considering the effect of DMH on the central control of nutritional behavior, the authors recommend that future research be conducted on the effect of other neurotransmitters on the central control of feed intake via this nucleus.

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Statement of Human and Animal Rights

This study has not been performed on any humans or animals.

Authors' Contributions

Farshid Hamidi, and Shiba yousefvand. Farshid Hamidi presented the main idea and plan. Farshid Hamidi and Shiba yousefvand conducted scientific searches. Farshid Hamidi and Shiba yousefvand performed collecting and analyzing information and articles. Shiba Yousefvand wrote the paper. Farshid Hamidi reviewed the paper. Farshid Hamidi and Shiba yousefvand drew an abstract graphical design.

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Competing Interests

The authors do not have conflict of interest.

References

1. Yousefvand S, Hamidi F, Zendehtdel M. The Role of MC3 and MC4 Receptors in Regulation of Food and Water Intake in Broiler Chicks. *Journal of Veterinary Research*. 2021;76(4):459-66. Doi:10.22059/JVR.2021.285656.2949.
2. Zendehtdel M, Parvizi Z, Hassanpour S, Baghbanzadeh A, Hamidi F. Interaction between nociceptin/orphanin FQ and adrenergic system on food intake in neonatal chicken. *International Journal of Peptide Research and Therapeutics*. 2017;23(1):155-61. Doi: 10.1007/s10989-016-9548-2.
3. Vucetic Z, Reyes TM. Central dopaminergic circuitry controlling food intake and reward: implications for the regulation of obesity. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*. 2010;2(5):577-93. Doi:10.1002/wsbm.77.
4. Hamidi F, Yusefvand S. Role of the hypothalamic arcuate nucleus in regulation of food intake (review study). 2017.
5. Jurés A, Cunningham MJ, McClain ME, Clifton DK, Steiner RA. Galanin-like peptide (GALP) is a target for regulation by leptin in the hypothalamus of the rat. *Endocrinology*. 2000;141(7):2703-6. Doi: 10.1210/endo.141.7.7669.
6. Fraley GS, Leathley E, Lundy N, Chheng E, King I, Kofler B. Effects of alarin on food intake, body weight and luteinizing hormone secretion in male mice. *Neuropeptides*. 2012;46(2):99-104. Doi:10.1016/j.npep.2011.12.003.
7. Yousefvand S, Hamidi F, Zendehtdel M, Parham A. Hypophagic effects of insulin are mediated via NPY1/NPY2 receptors in broiler cockerels. *Canadian Journal of Physiology and Pharmacology*. 2018;96(12):1301-7. Doi: 10.1139/cjpp-2018-0470.
8. Yousefvand S, Hamidi F, Zendehtdel M, Parham A. Effects of insulin and somatostatin on water intake in neonatal chickens. *Iranian Journal of Physiology and Pharmacology*. 2018;2(3):165-58.
9. Yousefvand S, Hamidi F, Zendehtdel M, Parham A. Interaction of neuropeptide Y receptors (NPY1, NPY2 and NPY5) with somatostatin on somatostatin-induced feeding behaviour in neonatal chicken. *British Poultry Science*. 2019;60(1):71-8. Doi: <https://doi.org/10.1080/00071668.2018.1547359>.
10. Yousefvand S, Hamidi F, Zendehtdel M, Parham A. Investigating The Role of NPY Receptors on Water Intake in Neonatal Broiler Chicken. *Veterinary Researches & Biological Products*. 2020;33(3):101-7. Doi: 10.22092/VJ.2019.126842.1594.
11. Yousefvand S, Hamidi F, Zendehtdel M, Parham A. Survey the effect of insulin on modulating feed intake via NPY receptors in 5-day-old chickens. *International Journal of Peptide Research and Therapeutics*. 2020;26(1):467-76. Doi:10.1007/s10989-019-09852-0.
12. Zendehtdel M, Hamidi F, Babapour V, Mokhtarpouriani K, Fard RMN. The effect of melanocortin (Mc3 and Mc4) antagonists on serotonin-induced food and water intake of broiler cockerels. *Journal of veterinary science*. 2012;13(3):229-34. Doi: doi.org/10.4142/jvs.2012.13.3.229.
13. Zendehtdel M, Hamidi F, Hassanpour S. The effect of histaminergic system on nociceptin/orphanin FQ induced food intake in chicken. *International Journal of Peptide Research and Therapeutics*. 2015;21(2):179-86. Doi: 10.1007/s10989-014-9445-5.
14. Zendehtdel M, Mokhtarpouriani K, Babapour V, Pourrahimi M, Hamidi F. The role of 5-HT 2A and 5-HT 2C receptors on harmaline-induced eating behavior in 24-h food-deprived broiler cockerels. *Iranian Journal of Veterinary Research*. 2013;14(2). Doi: 10.22099/IJVR.2013.158.
15. Zendehtdel M, Mokhtarpouriani K, Hamidi F, Montazeri R. Intracerebroventricular injection of ghrelin produces hypophagia through central serotonergic mechanisms in chicken. *Veterinary research communications*. 2013;37(1):37-41. Doi:10.1007/s11259-012-9544-8.
16. Yousefvand S, Hamidi F. Role of paraventricular nucleus in regulation of feeding behaviour and the design of intranuclear neuronal pathway communications. *International Journal of Peptide Research and Therapeutics*. 2020;26(3):1231-42. Doi: 10.1007/s10989-019-09928-x.
17. Yousefvand S, Hamidi F. The role of ventromedial hypothalamus receptors in the central regulation of food intake. *International Journal of Peptide Research and Therapeutics*. 2021;27(1):689-702. Doi: 10.1007/s10989-020-10120-9.
18. Yousefvand S, Hamidi F. Role of Lateral Hypothalamus Area in the Central Regulation of Feeding. *International Journal of Peptide Research and Therapeutics*. 2022;28(3):1-9. Doi: 10.1002/npr2.12080.
19. Zendehtdel M, Babapour V, Asadi S. Effects of intracerebroventricular injections of glucose and insulin on food intake in broiler cockerels. *Veterinary Researches & Biological Products*. 2009;22(1):6-12.
20. Iigaya K, Minoura Y, Onimaru H, Kotani S, Izumizaki M. Effects of feeding-related peptides on neuronal oscillation in the ventromedial hypothalamus. *Journal of Clinical Medicine*. 2019;8(3):292. Doi: 10.3390/jcm8030292.
21. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain research reviews*. 2002;39(2-3):107-40. Doi: 10.1016/j.neubiorev.2015.01.014.
22. Bellinger LL, Bernardis LL. The dorsomedial hypothalamic nucleus and its role in ingestive behavior and body weight regulation: lessons learned from lesioning studies. *Physiology & behavior*. 2002;76(3):431-42. Doi: 10.1016/s0031-9384(02)00756-4.
23. Imoto D, Yamamoto I, Matsunaga H, Yonekura T, Lee M-L, Kato KX, et al. Refeeding activates neurons in the dorso-

- medial hypothalamus to inhibit food intake and promote positive valence. *Molecular Metabolism*. 2021;54:101366. Doi:10.1016/j.molmet.2021.101366.
24. Stamatakis AM, Van Swieten M, Basiri ML, Blair GA, Kantak P, Stuber GD. Lateral hypothalamic area glutamatergic neurons and their projections to the lateral habenula regulate feeding and reward. *Journal of Neuroscience*. 2016;36(2):302-11. Doi: 10.1016/j.molmet.2021.101366.
 25. Baroncini M, Jissendi P, Bolland E, Besson P, Pruvo J-P, Francke J-P, et al. MRI atlas of the human hypothalamus. *Neuroimage*. 2012;59(1):168-80. Doi: 10.1016/j.neuroimage.2011.07.013.
 26. Otgon-Uul Z, Suyama S, Onodera H, Yada T. Optogenetic activation of leptin-and glucose-regulated GABAergic neurons in dorsomedial hypothalamus promotes food intake via inhibitory synaptic transmission to paraventricular nucleus of hypothalamus. *Molecular metabolism*. 2016;5(8):709-15. Doi: 10.1016/j.molmet.2016.06.010.
 27. Branch A, Shen P. Central and peripheral regulation of appetite and food intake in *Drosophila*. *Appetite and Food Intake*. 2017:17-38. Doi: 10.1201/9781315120171-2.
 28. Henderson LA, Macefield VG. The role of the dorsomedial and ventromedial hypothalamus in regulating behaviorally coupled and resting autonomic drive. *Handbook of Clinical Neurology*. 2021;180:187-200. Doi: 10.1016/B978-0-12-820107-7.00012-4.
 29. Zhu JN, Li HZ, Ding Y, Wang JJ. Cerebellar modulation of feeding-related neurons in rat dorsomedial hypothalamic nucleus. *Journal of neuroscience research*. 2006;84(7):1597-609. Doi: 10.1002/jnr.21059.
 30. Kageyama H, Shiba K, Hirako S, Wada N, Yamanaka S, Nogi Y, et al. Anti-obesity effect of intranasal administration of galanin-like peptide (GALP) in obese mice. *Scientific reports*. 2016;6(1):1-11. Doi: 10.2174/1381612823666170321095950.
 31. Blackshear A, Yamamoto M, Anderson BJ, Holmes PV, Lundström L, Langel Ü, et al. Intracerebroventricular administration of galanin or galanin receptor subtype 1 agonist M617 induces c-Fos activation in central amygdala and dorsomedial hypothalamus. *Peptides*. 2007;28(5):1120-4. Doi: 10.1016/j.peptides.2007.01.015.
 32. Cheung C, Hohmann J, Clifton D, Steiner R. Distribution of galanin messenger RNA-expressing cells in murine brain and their regulation by leptin in regions of the hypothalamus. *Neuroscience*. 2001;103(2):423-32. Doi: 10.1016/s0306-4522(01)00012-4.
 33. Crawley J. The role of galanin in feeding behavior. *Neuropeptides*. 1999;33(5):369-75. Doi:10.1111/j.1742-4658.2010.07933.x.
 34. Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocrine reviews*. 1999;20(1):68-100. Doi: https://doi.org/10.1210/edrv.20.1.0357.
 35. Parrado C, Diaz-Cabiale Z, Garcia-Coronel M, Agnati LF, Covenas R, Fuxe K, et al. Region specific galanin receptor/neuropeptide Y Y1 receptor interactions in the tel-and dien-cephalon of the rat. Relevance for food consumption. *Neuropharmacology*. 2007;52(2):684-92. Doi: 10.1016/j.neuropharm.2006.09.010.
 36. Kuramochi M, Onaka T, Kohno D, Kato S, Yada T. Galanin-like peptide stimulates food intake via activation of neuropeptide Y neurons in the hypothalamic dorsomedial nucleus of the rat. *Endocrinology*. 2006;147(4):1744-52. Doi: 10.1210/en.2005-0907.
 37. Juréus A, Cunningham MJ, Li D, Johnson LL, Krasnow SM, Teklemichael DN, et al. Distribution and regulation of galanin-like peptide (GALP) in the hypothalamus of the mouse. *Endocrinology*. 2001;142(12):5140-4. Doi: https://doi.org/10.1210/endo.142.12.8542.
 38. Lawrence C, Baudoin FH, Luckman S. Centrally administered galanin-like peptide modifies food intake in the rat: a comparison with galanin. *Journal of neuroendocrinology*. 2002;14(11):853-60. Doi: https://doi.org/10.1046/j.1365-2826.2002.00846.x.
 39. Kageyama H, Kita T, Toshinai K, Guan JL, Date Y, Takenoya F, et al. Galanin-like peptide promotes feeding behaviour via activation of orexinergic neurones in the rat lateral hypothalamus. *Journal of neuroendocrinology*. 2006;18(1):33-41. Doi: https://doi.org/10.1111/j.1365-2826.2005.01382.x.
 40. Krasnow SM, Fraley GS, Schuh SM, Baumgartner JW, Clifton DK, Steiner RA. A role for galanin-like peptide in the integration of feeding, body weight regulation, and reproduction in the mouse. *Endocrinology*. 2003;144(3):813-22. Doi: https://doi.org/10.1210/en.2002-220982.
 41. Sheriff S, Balasubramaniam A. Inhibitory and stimulatory effects of neuropeptide Y (17-36) on rat cardiac adenylate cyclase activity. Structure-function studies. *Journal of Biological Chemistry*. 1992;267(7):4680-5. Doi: https://doi.org/10.1016/S0021-9258(18)42887-6.
 42. Morton G, Cummings D, Baskin D, Barsh G, Schwartz M. Central nervous system control of food intake and body weight. *Nature*. 2006;443(7109):289-95. Doi: https://doi.org/10.1038/nature05026.
 43. Baik J-H. Dopaminergic control of the feeding circuit. *Endocrinology and Metabolism*. 2021;36(2):229. Doi: https://doi.org/10.3803/EnM.2021.979.
 44. Negishi K, Payant MA, Schumacker KS, Wittmann G, Butler RM, Lechan RM, et al. Distributions of hypothalamic neuron populations coexpressing tyrosine hydroxylase and the vesicular GABA transporter in the mouse. *Journal of Comparative Neurology*. 2020;528(11):1833-55. Doi: https://doi.org/10.1002/cne.24857.
 45. Ramos EJ, Meguid MM, Campos AC, Coelho JC. Neuropeptide Y, α -melanocyte-stimulating hormone, and monoamines in food intake regulation. *Nutrition*. 2005;21(2):269-79. Doi: https://doi.org/10.1016/j.nut.2004.06.021.

46. Crowley W, Ramoz G, Keefe K, Torto R, Kalra S, Hanson G. Differential effects of methamphetamine on expression of neuro peptide Y mRNA in hypothalamus and on serum leptin and ghrelin concentrations in ad libitum-fed and schedule-fed rats. *Neuroscience*. 2005;132(1):167-73. Doi: <https://doi.org/10.1016/j.neuroscience.2004.11.037>.
47. Zhang X, van den Pol AN. Hypothalamic arcuate nucleus tyrosine hydroxylase neurons play orexigenic role in energy homeostasis. *Nature neuroscience*. 2016;19(10):1341-7. Doi: <https://doi.org/10.1038/nn.4372>.
48. Meguid MM, Fetissov SO, Varma M, Sato T, Zhang L, Lavinano A, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition*. 2000;16(10):843-57. Doi: [https://doi.org/10.1016/s0899-9007\(00\)00449-4](https://doi.org/10.1016/s0899-9007(00)00449-4).
49. Hosoda H, Kojima M, Kangawa K. Ghrelin and the regulation of food intake and energy balance. *Molecular interventions*. 2002;2(8):494. Doi: <https://doi.org/10.1124/mi.2.8.494>.
50. Carlini VP, Varas MM, Cragolini AB, Schiöth HB, Scimionelli TN, de Barioglio SR. Differential role of the hippocampus, amygdala, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. *Biochemical and biophysical research communications*. 2004;313(3):635-41. Doi: <https://doi.org/10.1016/j.bbrc.2003.11.150>.
51. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. *The Journal of Clinical Endocrinology & Metabolism*. 2002;87(1):240-4. Doi: <https://doi.org/10.1210/jcem.87.1.8129>.
52. Chuang J-C, Perello M, Sakata I, Osborne-Lawrence S, Savitt JM, Lutter M, et al. Ghrelin mediates stress-induced food-reward behavior in mice. *The Journal of clinical investigation*. 2011;121(7):2684-92. Doi: <https://doi.org/10.1172/JCI157660>.
53. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, et al. Ghrelin. *Molecular metabolism*. 2015;4(6):437-60. Doi: <https://doi.org/10.1016/j.molmet.2015.03.005>.
54. Menyhért J, Wittmann G, Hrabovszky E, Szlávik N, Keller É, Tschöp M, et al. Distribution of ghrelin-immunoreactive neuronal networks in the human hypothalamus. *Brain research*. 2006;1125(1):31-6. Doi: <https://doi.org/10.1016/j.brainres.2006.09.048>.
55. Chow KB, Sun J, Chu KM, Cheung WT, Cheng CH, Wise H. The truncated ghrelin receptor polypeptide (GHS-R1b) is localized in the endoplasmic reticulum where it forms heterodimers with ghrelin receptors (GHS-R1a) to attenuate their cell surface expression. *Molecular and cellular endocrinology*. 2012;348(1):247-54. Doi: <https://doi.org/10.1016/j.mce.2011.08.034>.
56. Mani BK, Osborne-Lawrence S, Mequinion M, Lawrence S, Gautron L, Andrews ZB, et al. The role of ghrelin-responsive mediobasal hypothalamic neurons in mediating feeding responses to fasting. *Molecular metabolism*. 2017;6(8):882-96. Doi: <https://doi.org/10.1016/j.molmet.2017.06.011>.
57. Sun Y, Wang P, Zheng H, Smith RG. Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proceedings of the National Academy of Sciences*. 2004;101(13):4679-84. Doi: <https://doi.org/10.1073/pnas.0305930101>.
58. Blum ID, Patterson Z, Khazall R, Lamont EW, Sleeman MW, Horvath TL, et al. Reduced anticipatory locomotor responses to scheduled meals in ghrelin receptor deficient mice. *Neuroscience*. 2009;164(2):351-9. Doi: <https://doi.org/10.1016/j.neuroscience.2009.08.009>.
59. Tanaka M, Naruo T, Muranaga T, Yasuhara D, Shiiya T, Nakazato M, et al. Increased fasting plasma ghrelin levels in patients with bulimia nervosa. *European Journal of Endocrinology*. 2002;146(6):R1-R3. Doi: 10.1530/eje.0.146r001.
60. 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(4):649-61. Doi: 10.1016/s0896-6273(03)00063-1.
61. Bi S, Kim YJ, Zheng F. Dorsomedial hypothalamic NPY and energy balance control. *Neuropeptides*. 2012;46(6):309-14. Doi: <https://doi.org/10.1016/j.npep.2012.09.002>.
62. Rüter J, Kobelt P, Tebbe JJ, Veh R, Wang L, Klapp BF, et al. Intraperitoneal injection of ghrelin induces Fos expression in the paraventricular nucleus of the hypothalamus in rats. *Brain research*. 2003;991(1-2):26-33. Doi: <https://doi.org/10.1016/j.brainres.2003.07.005>.
63. Shintani M, Ogawa Y, Ebihara K, Aizawa-Abe M, Miyanaga F, Takaya K, et al. Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuro-peptide Y/Y1 receptor pathway. *Diabetes*. 2001;50(2):227-32. Doi: <https://doi.org/10.2337/diabetes.50.2.227>.
64. Wren AM, Small CJ, Abbott CR, Dhillo WS, Seal LJ, Cohen MA, et al. Ghrelin causes hyperphagia and obesity in rats. *Diabetes*. 2001;50(11):2540-7. Doi: 10.2337/diabetes.50.11.2540.
65. Kobelt P, Wisser A-S, Stengel A, Goebel M, Inhoff T, Noetzel S, et al. Peripheral injection of ghrelin induces Fos expression in the dorsomedial hypothalamic nucleus in rats. *Brain research*. 2008;1204:77-86. Doi: 10.1016/j.brainres.2008.01.054.
66. Lawrence CB, Snape AC, Baudoin FM-H, Luckman SM. Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers. *Endocrinology*. 2002;143(1):155-62. Doi: 10.1210/endo.143.1.8561.
67. Al Massadi O, López M, Tschöp M, Diéguez C, Nogueiras R. Current understanding of the hypothalamic ghrelin pathways inducing appetite and adiposity. *Trends in neurosciences*. 2017;40(3):167-80. Doi: 10.1016/j.tins.2016.12.003.

68. Perello M, Dickson S. Ghrelin signalling on food reward: a salient link between the gut and the mesolimbic system. *Journal of neuroendocrinology*. 2015;27(6):424-34. Doi: 10.1111/jne.12236.
69. Brunetti L, Recinella L, Orlando G, Michelotto B, Di Nisio C, Vacca M. Effects of ghrelin and amylin on dopamine, nor-epinephrine and serotonin release in the hypothalamus. *European journal of pharmacology*. 2002;454(2-3):189-92. Doi: 10.1016/s0014-2999(02)02552-9.
70. Fetissov SO, Kopp J, Hökfelt T. Distribution of NPY receptors in the hypothalamus. *Neuropeptides*. 2004;38(4):175-88. Doi: 10.1016/j.npep.2004.05.009.
71. Zieba DA, Biernat W, Szczesna M, Kirszt K, Barć J, Misztal T. Changes in expression of the genes for the leptin signaling in hypothalamic-pituitary selected areas and endocrine responses to long-term manipulation in body weight and resistin in ewes. *International Journal of Molecular Sciences*. 2020;21(12):4238. Doi:10.3390/ijms21124238.
72. Trotta M, Bello EP, Alsina R, Tavella MB, Ferrán JL, Rubinstein M, et al. Hypothalamic Pomc expression restricted to GABAergic neurons suppresses Npy overexpression and restores food intake in obese mice. *Molecular metabolism*. 2020;37:100985. Doi: 10.1016/j.molmet.2020.100985.
73. Wang R, Yuan J, Zhang C, Wang L, Liu Y, Song L, et al. Neuropeptide Y-positive neurons in the dorsomedial hypothalamus are involved in the anorexic effect of Angptl8. *Frontiers in Molecular Neuroscience*. 2018;11:451. Doi: 10.3389/fnmol.2018.00451.
74. Acuna-Goycolea C, Tamamaki N, Yanagawa Y, Obata K, van den Pol AN. Mechanisms of neuropeptide Y, peptide YY, and pancreatic polypeptide inhibition of identified green fluorescent protein-expressing GABA neurons in the hypothalamic neuroendocrine arcuate nucleus. *Journal of Neuroscience*. 2005;25(32):7406-19. Doi: 10.1523/JNEUROSCI.1008-05.2005.
75. Yang L, Scott KA, Hyun J, Tamashiro KL, Tray N, Moran TH, et al. Role of dorsomedial hypothalamic neuropeptide Y in modulating food intake and energy balance. *Journal of Neuroscience*. 2009;29(1):179-90. Doi: 10.1523/JNEUROSCI.4379-08.2009.
76. Elmquist JK, Ahima RS, Elias CE, Flier JS, Saper CB. Leptin activates distinct projections from the dorsomedial and ventromedial hypothalamic nuclei. *Proceedings of the National Academy of Sciences*. 1998;95(2):741-6. Doi: 10.1073/pnas.95.2.741.
77. Vong L, Ye C, Yang Z, Choi B, Chua Jr S, Lowell BB. Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. *Neuron*. 2011;71(1):142-54. Doi: 10.1016/j.neuron.2011.05.028.
78. Dodd GT, Worth AA, Nunn N, Korpak AK, Bechtold DA, Allison MB, et al. The thermogenic effect of leptin is dependent on a distinct population of prolactin-releasing peptide neurons in the dorsomedial hypothalamus. *Cell metabolism*. 2014;20(4):639-49. Doi: 10.1016/j.cmet.2014.07.022.
79. Raman PG. Central nervous system control of glucose homeostasis. *Open Journal of Endocrine and Metabolic Diseases*. 2017;7(12):227-34. Doi: 10.4236/ojemd.2017.712020.
80. Faber CL, Deem JD, Phan BA, Doan TP, Ogimoto K, Mirzadeh Z, et al. Leptin receptor neurons in the dorsomedial hypothalamus regulate diurnal patterns of feeding, locomotion, and metabolism. *Elife*. 2021;10. Doi: 10.7554/eLife.63671.
81. Berthoud H-R. Multiple neural systems controlling food intake and body weight. *Neuroscience & Biobehavioral Reviews*. 2002;26(4):393-428. Doi: 10.1016/S0149-7634(02)00014-3.

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