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Role of Paraventricular Nucleus in Regulation of Feeding Behaviour and the Design of Intranuclear Neuronal Pathway Communications

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Abstract

Food consumption and body weight regulations are done in the hypothalamus. Indeed, hypothalamus is the brain's main area in controlling food intake. Hypothalamus controls food intake via special nuclei such as: ARC, PVN, DMH, VMH and LHA. PVN are second order neurons. This nucleus received multiple inputs from different areas of the brain via specific and non-specific receptors. NPYR and α_2-adrenoceptors are orexigenic receptors, but Melanocortin receptors are anorexigenic receptors. PVN integrated inputs from multiple areas, and then transmitted various outputs for central regulation of food intake. To identify neural pathways and the role of neurotransmitters on central control of food intake in PVN, multiple researches have been done via injection of various neurotransmitters on the laboratory animals. Leptin applies its effect on regulation of feeding behaviours through arcuate nucleus-paraventricular nucleus axis and MC4R receptor. Also, Insulin is a hypophagic neurotransmitter, and its hypophagic effect applied in PVN via NPY_1 and MC4R receptors. Ghrelin has a biphasic effect on food intake in birds and mammals. In birds, ghrelin inhibits food intake, but in mammals stimulated food intake. In birds, ghrelin via $5HT_{2A}$ receptor on CRF neurons located on PVN reduced food intake. In mammals via GHSR (ghrelin receptor) and NPY_1 receptors increased food intake. Somatostatin acts in the brain as an inhibitory and hyperphagic neurotransmitter. Hyperphagic effect of Somatostatin on PVN exert via $SST_{2,}$ OX_1 and NPY1 receptors respectively. Therefore, PVN has an important effect on central regulation of food intake via different neurotransmitters and pathway.

Graphic Abstract

The role of PVN in central regulation of food intake. *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *LHA* lateral hypothalamus area, *CRF* Corticotropin-realising factor, *POMC* pro-opiomelanocortin, *CART* Cocaine and amphetamine-regulated transcript, *NPY/AgRP* neuropeptide Y/agouti-related protein, Y_1R NPY_1 receptor, *GHSR* growth hormone secretagogues

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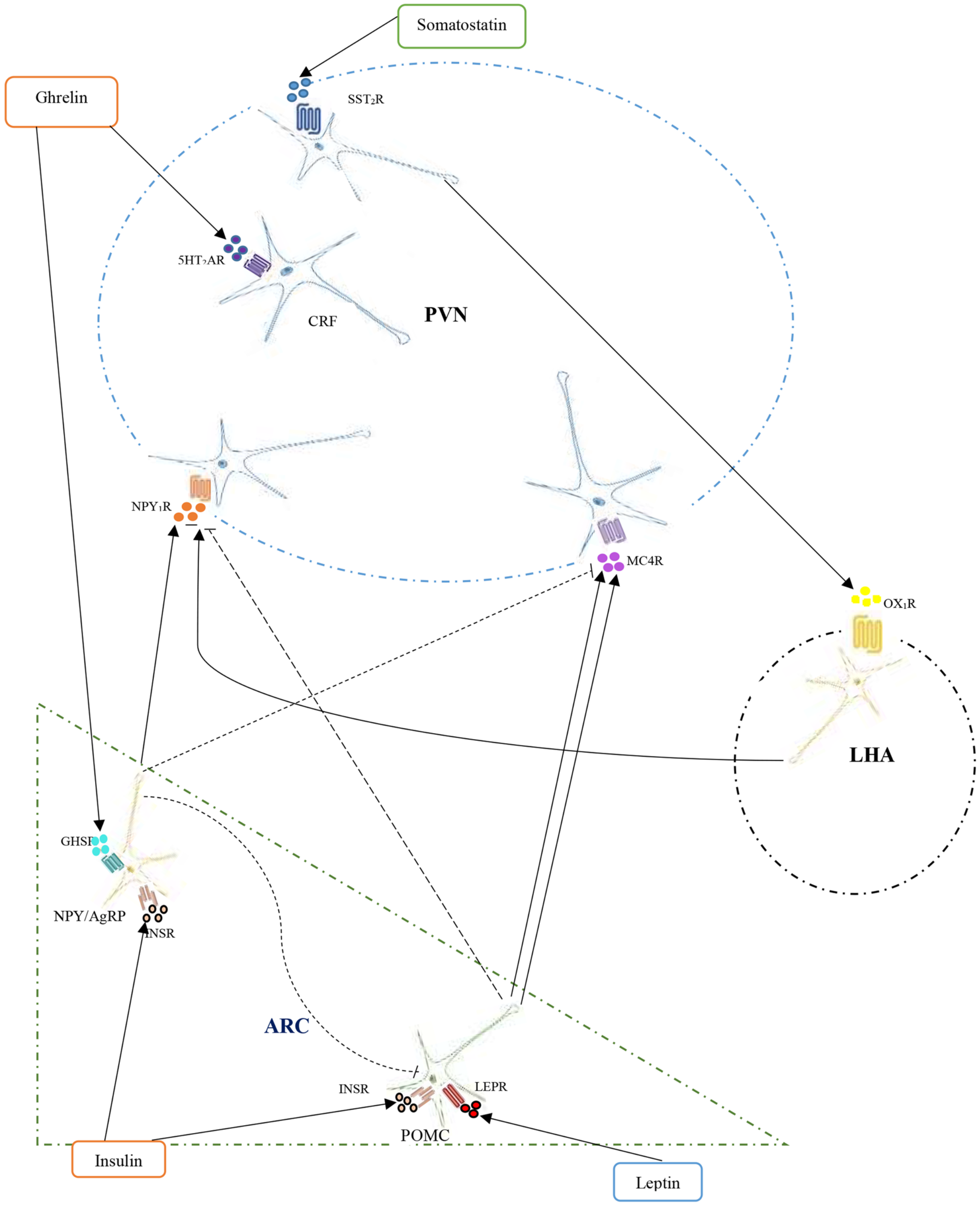
receptor, *LEPR* Leptin receptor, *INSR* Insulin receptor, *OX_1R* orexin receptor, *MC_4R* Melanocortin$_4$ receptor, *SST_2R* Somatostatin$_2$ receptor.



Keywords Feeding behaviours · Hypothalamus · PVN · Neurotransmitters · Central regulation

Abbreviations

VMH	Ventromedial hypothalamus
LHA	Lateral hypothalamus area
ARC	Arcuate nucleus
PVN	Paraventricular nucleus
DMH	Dorsomedial hypothalamus

NTS	Nucleus of solitary tract
TRH	Thyrotropin- releasing hormone
NPY	Neuropeptide Y
CNS	Central nervous system
MC	Melanocortin
POMC	Pro-opiomelanocortin
α-MSH	α-Melanocyte-Stimulating Hormone
AgRP	Agouti related protein
AMPK	AMP-activated protein kinase
TRHN	Thyrotropin releasing hormone neurons
CREB	cAMP response element binding Protein
Pro-TRH	Pro-thyrotropin-releasing hormone
ICV	Intracerebroventricular
$5HT_{2A}$	$5Hydroxytryptamin_{2A}$
CRF	Corticotropin-releasing factor
GHSR	Growth hormone secretagogues receptor
SST	Somatostatin receptor
OX_1R	Orexin receptor
AVP	Arginine vasopressin
N/OFQ	Nociceptin/orphanin FQ
CART	Cocaine and amphetamine-regulated transcript
mRNA	Messenger ribo nucleic acid
NEP	Norepinephrine
DA/Ach	Dopaminergic/Cholinergic/Nucleus accumbens
CRH	Corticotropin releasing hormone
HR	Histaminergic receptor

Introduction

Regulation of food intake and body weight due to the ability of the brain, especially the hypothalamus to integrate endocrine, behavioural, and autonomic functions via afferent and efferent pathways from brainstem and peripheral organs done (Elmquist et al. 2005; Jalali et al. 2019). It has been shown that the hypothalamus is the brain's main area in controlling food intake. The peripheral and central signals are integrated together in the hypothalamus, and they regulate the level of central neuropeptides for managing energy expenditure and food intake (Wynne et al. 2005; Denbow and Cline 2014). Various studies have been shown that, ventromedial hypothalamus (VMH) is an anorexigenic center and lateral hypothalamus area (LHA) is an orexigenic center (Sohn 2015).

The hypothalamus control of food intake via special nuclei such as: arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), VMH, and LHA (Fig. 1) (Wynne et al. 2005). ARC is a hypothalamic nucleus involved in controlling food intake. It is located in the vicinity of the third ventricle of the brain. This nucleus receives appetite-related signals from the peripheral circulation system (through the incomplete blood–brain-barrier) and other areas of the brain, such as nucleus of tract solitary (NTS). The ARC integrates these signals, and transmitted them as neural projections such as NPY, AgRP, melanocortin, and etc. to the second order neurons. The second

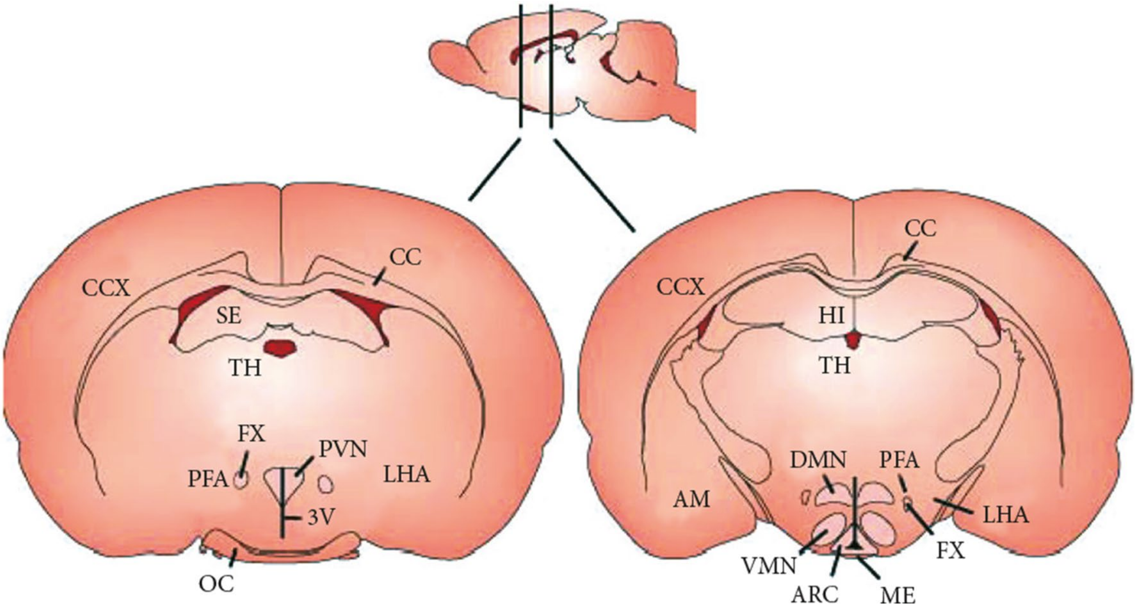


Fig. 1 Different hypothalamic nuclei involved in controlling food intake. *ARC* arcuate nucleus, *AM* amygdala, *CC* corpus callosum, *CCX* cerebral cortex, *DMN* dorsomedial nucleus, *FX* fornix, *HI* hippocampus, *LHA* lateral hypothalamic area, *ME* medi-an eminence, *OC* optic chiasm, *PFA* perifornical area, *PVN* paraventricular nucleus, *SE* septum, *3 V* third ventricle, *TH* thalamus, *VMN* ventromedial nucleus (Yu and Kim 2012)

order neurons are PVN, VMH, DMH, and LHA (Fig. 2). These projections and other information from the brain stem and cortex integrated in second order neurons (especially in the PVN), and via changes in other neuroendocrine systems, effect on energy homeostasis (Fekete et al. 2000; Jensen 2001; Wynne et al. 2005; Hamidi and Yousefvand 2017).

PVN, the main place of the hypothalamus to send the multiple outputs to control of food intake, and it is located in the dorso rostral hypothalamus, and adjust to the third brain ventricular (Cone 2005; Ferguson et al. 2008; Sohn 2015). PVN is an anorexigenic center. Indeed, researchers have shown that the damage to this nucleus causes overeating and obesity in rodents (Duplan et al. 2009). This nucleus receives the series of axons from the subcortical regions of the areas involved in motor behaviour including hypothalamus, hippocampus, amygdala, locus coeruleus, periaqueductal gravy matter and the raphe nucleus (Van der werf et al. 2002). As well, receive various inputs (such as insulin, leptin, and etc.) from other parts of the hypothalamus, and through this effect on food intake (Sutton et al. 2016). Therefore, PVN is a key area in the control of appetite. Projections from NPY-containing neurons in the ARC, are sent to the PVN, and through these regulate energy intake via other pathways such as Thyrotropin- releasing hormone (TRH) secretion (Nillni 2010). In addition, PVN is involved in the regulation of osmotic balance and water intake regulation. Numerous neurotransmitters effects water intake through this nucleus (De Arruda et al. 2003; De Souza Villa et al. 2008; Karasawa et al. 2014).

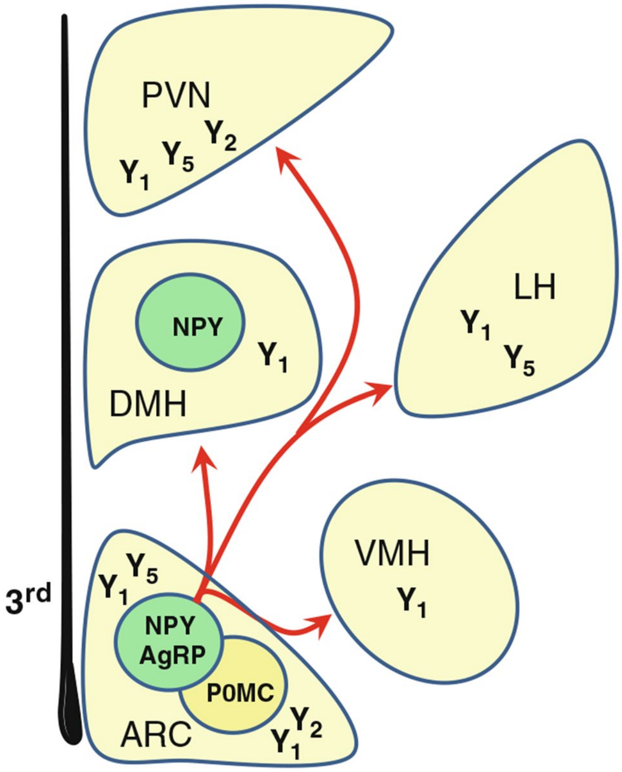


Fig. 2 NPY projections in arcuate nucleus to second order neurons. *3rd* third ventricle of the brain, *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *DMH* dorsomedial hypothalamus, *LH* lateral hypothalamus, *VMH* ventromedial hypothalamus, *NPY/AgRP* neuropeptide Y/agouti-related protein, *POMC* pro-opiomelanocortin, Y_1 NPY_1 receptor, Y_2 NPY_2 receptor, Y_5 NPY_5 receptor (Joost 2012)

Considering the importance of PVN as a place for integrate multiple inputs to the hypothalamus and exporting appropriate hypothalamic outputs for central regulation of feeding behaviours, this study examined the role of PVN in the central regulation of nutritional behaviours.

Therefore, this paper will discusses about the non-specific receptors involved in PVN function in food intake, the signalling process related to central control of food intake, and finally the role of this nucleus in central control of feeding behaviours.

Study Methodology

In this overview, various valid papers from electronic sources used, which in them the role of paraventricular nucleus in regulation of feeding behaviours investigated. Authentic articles indexed in the Web of Science, Scopus, PubMed, SID, Google scholar, and ISI databases by using of Key words: Central regulation of food intake, Hypothalamus, Paraventricular nucleus, Brain ventriculars, Brain neurotransmitters, and Feeding behaviours studied (Fig. 3). The review articles entered in this study are presented in Table 1.

The Role OF Some Non-specific Receptors on PVN in Central Regulation of Food Intake

Central regulation of food intake is carried out in different nuclei of the hypothalamus by multiple inputs from various regions of the brain. Among the different nuclei of the hypothalamus, PVN plays a critical role in receiving and integrating these inputs. These inputs apply their effects on PVN through their specific and non-specific receptors located on the PVN (Lenard and Berthoud 2008; Sorrentino and Ragozzino 2017). Therefore, the receptors located on PVN play the important roles in the function of this nucleus in central regulation of food intake. Then, briefly discuss the roles of some of non-specific receptors.

1.1. Neuropeptide Y (NPY) receptors: NPY receptors are important receptors in the central regulation of food intake. These receptors are distributed throughout the central nervous system (CNS). Among the NPY receptors involved in central food intake regulation (NPY_1, NPY_2, and NPY_5), NPY_1 and NPY_5 receptors are

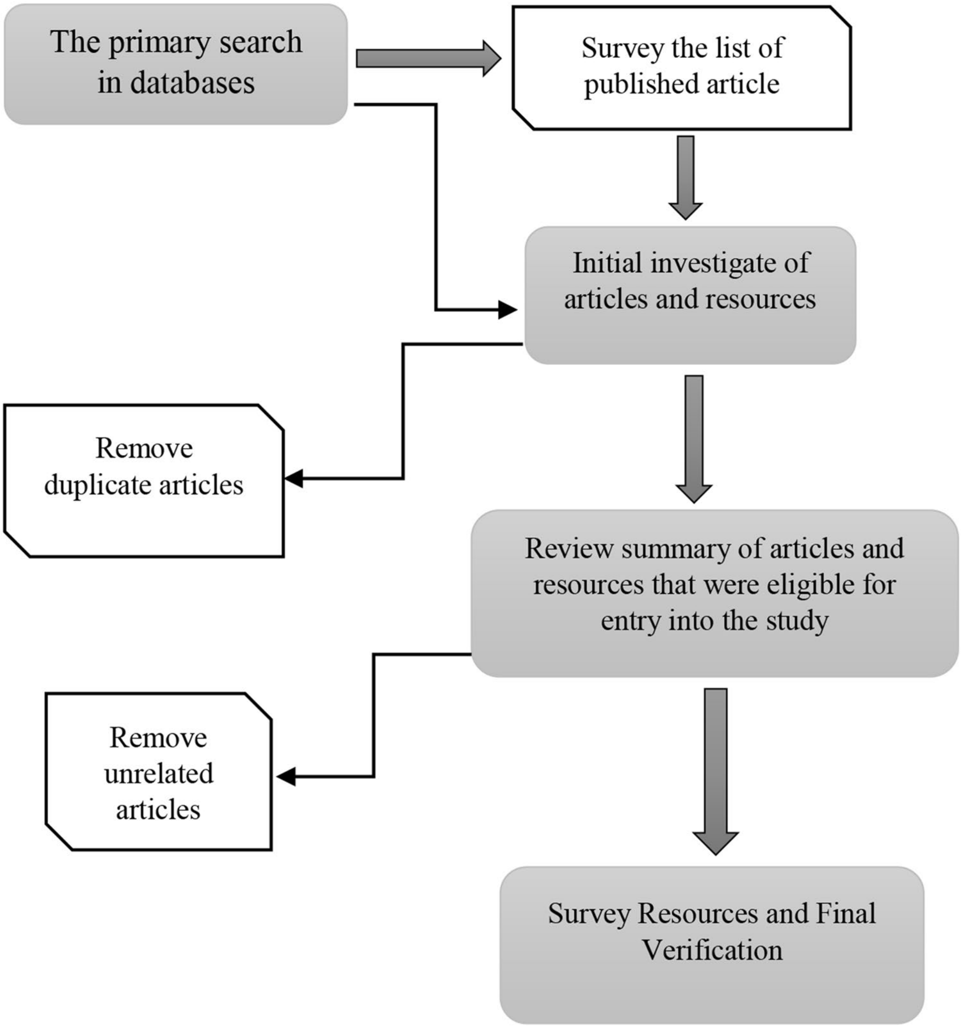


Fig. 3 The flowchart of stages to import recourses into review article

located in the PVN. NPY receptors are G-protein coupled receptors. By attaching the ligand to these receptors, the output of PVN is a central increase in food intake. In fact, these receptors are orexigenic receptors (Henry et al. 2005; Yousefvand et al. 2018a, b, 2019).

1.2. Melanocortin (MC) receptors: Hypothalamic melanocortin system consists of pro-opiomelanocortin (POMC), and central melanocortin receptors include: MCR3 and MCR4. These two receptors are important mediator of the effects of melanocortin ligands such as: alpha-melanocyte-stimulating hormone (α-MSH) and agouti related protein (AGRP) on nutritional behaviour and energy balance. In birds, only MC4R plays an important role in controlling energy balance (Strader et al. 2003; Lee et al. 2008). These receptors are located on PVN, and by their activation, reduce food intake and increase energy consumption. So these receptors are anorexigenic receptors, which located in the PVN (Kim et al. 2014).

1.3. α_2-adrenoceptors: α_2-adrenoreceptors are involved in the central control of food intake, and from the G-protein coupled receptors family. These receptors are located on the PVN. α_2-adrenoreceptors mediated the hyperphagic effects of noradrenaline, and other α_2-adrenoreceptors mimics. Activation of these receptors leads to exit of orexigenic messages from PVN (Taksande et al. 2011). Therefore, these receptors are orexigenic receptors.

Signalling Mechanisms in the Paraventricular Nucleus

The signalling pathway of the neurotransmitters related to regulation of food intake in the PVN maybe is AMP-activated protein kinase (AMPK) signal. This signal is a heterodimer which including catalytic and regulatory subunits. Some factors such as leptin, insulin and MC3/MC4 agonist inhibits

Table 1 The Review articles entered in this study

Number	Authors of study (year)	Studied	Subject
1	Ahima et al. (2000)	Feeding behaviour	Neuroendocrine circuit
2	Jensen (2001)	Feeding behaviour	Regulatory peptides
3	Van der Werf et al. (2002)	Brain functions	Thalamus
4	Wynne et al. (2005)	Energy homeostasis	Central neural and peripheral signals
5	Cone (2005)	Energy homeostasis	Melanocortin system
6	Elmquist et al. (2005)	Feeding regulation	Hypothalamic pathways
7	Richards and Proszkowiec-Weglarz (2007)	Feeding regulation	Energy homeostasis
8	Ferguson et al. (2008)	Autonomic dysfunction	Neural circuits involved in pathology diseases
9	Viollet et al. (2008)	Somatostatinergic system	Circuit network and function
10	Nillni (2010)	Metabolism and thermogenesis	TRHN
11	Yu and Kim (2012)	Appetite regulation	Molecular mechanism
12	Schellekens et al. (2012)	Ghrelin and obesity	Neuronal circuitry modulate rewarding properties
13	Hussain and Bloom (2013)	Feeding regulation	Gut-brain axis
14	Denbow and Cline (2014)	Feeding behaviour	Food intake regulation in birds
15	Zendehdel and Hassanpour (2014)	Feeding behaviour	Neurotransmitters and peptides
16	Schneeberger et al. (2014)	homeostatic energy balance	Neural circuit controlling
17	Sohn (2015)	Control appetite	Neural networks of the hypothalamus
18	Stengel et al. (2015)	Feeding and drinking behaviour	SST_2
19	Sutton et al. (2016)	Energy balance	Leptin action
20	Miller (Miller 2017)	Appetite regulation	Obesity
21	Hamidi and Yousefvand (2017)	Feeding regulation	Arcuate nucleus

2AMPK activity in the ARC nucleus and PVN, while another factors such as AgRP, stimulate 2AMPK. Indicated that, increasing in AMPK level in the PVN leads to accretion food intake. Activity of 2AMPK perhaps controlled with MC4R (Andersson et al. 2004). PVN with integration of multiple signals, initiates changes in other neuroendocrine systems.

Thyrotropin releasing hormone neurons (TRHN) in the PVN are innervated with NPY/AgRP and melanocortin projections from the ARC. NPY via inhibiting of phosphorylation of cAMP response element binding Protein (CREB), has an inhibitory effect on gene expression of pro-thyrotropin-releasing hormone (pro-TRH) in PVN (Fig. 4), while MSH projections apply motivatory effcet on gene expression of pro-TRH (Fekete et al. 2000). In fact MSH via increased phosphorylation of CREB, has a stimulatory effect on gene expression of pro-TRH. Therefore, there is an interaction between NPY and MSH neurons in regulating gene expression of pro-TRH in PVN. Projections of NPY to the PVN operate on corticotrophin releasing hormone-expressing neurons which effect on energy homeostasis (Sarkar and Lechan 2003).

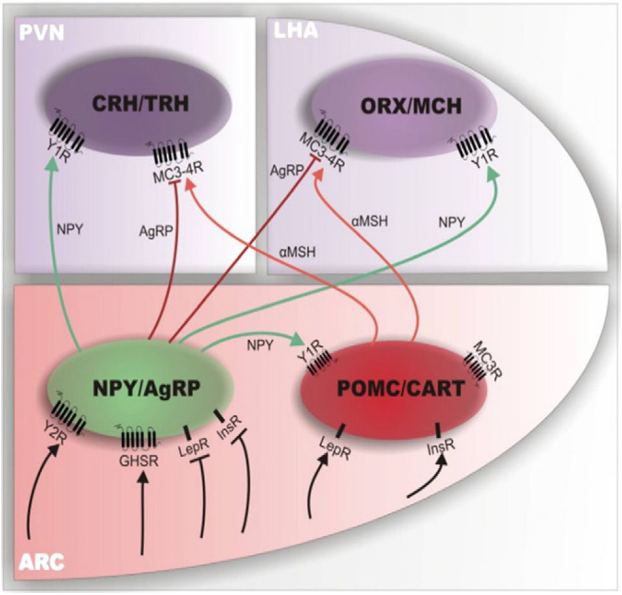


Fig. 4 The key appetite signal which integration in the special nuclei of the hypothalamus. *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *LHA* lateral hypothalamus area, *POMC* pro-opiomelanocortin, *CART* Cocaine and amphetamine-regulated transcript, *Y_2R* NPY_2 receptor, *GHSR* growth hormone secretagogues receptor, *LepR* Leptin receptor, *InsR* Insulin receptor, *ORX* orexin receptor, *TRH* Thyrotropin-releasing hormone, *CRH* Corticotropin-releasing hormone, *MCH* Melanin-concentrating hormone (Schellekens et al. 2012)

The Role of Paraventricular Nucleus in Regulation of Feeding Behaviour

Many factors in the CNS are affected in regulating food intake in mammals and birds. In these species central regulation of food intake is complicated and impressed by many neurotransmitters (Richards et al. 2007; Hussain and Bloom 2013; Zendehdel et al. 2013a, c); although there are differences between these two species in regulation of feeding behaviour (Zendehdel and Hassanpour 2014). Mostly, feeding control neurons are located in the hypothalamus. It's obvious that, the hypothalamus plays the major role in central regulation of food intake (Jensen 2001). Among the hypothalamus nuclei, PVN is very sensitive to injection of various neurohormones or neurotransmitters involved in feeding behaviour (Lawrence et al. 2002; Wynne et al. 2005). To identify neural pathways and the role of neurotransmitters on central control of food intake, various studies have been conducted on the laboratory animals (Table 2). These studies performed on regulation of food intake by direct injection into the nucleus, intracerebroventricular (ICV) injection, and injection to the third ventricular of the brain (Hamidi and Yousefvand 2017; Zendehdel et al. 2013b, 2015). Water intake and energy balance are important topics in physiology. Water is a critical component for living organisms and plays an important role in metabolic processes and temperature regulation (Biranvand et al. 2014; Yousefvand et al. 2017). In central control of water intake and osmotic pressure, different brain areas such as PVN are involved. Several studies in this field confirm the role of PVN in regulating water intake (Silverstein and Plisetskaya 2000; Hajdu et al. 2000; Hashimoto et al. 2007; Mietlicki et al. 2009; Karasawa et al. 2014b). The current review study was designed to summarize various studies performed on the PVN. The following is an explanation of the effect of some important neurotransmitters, which very effective in the processes involved in regulation of food intake, and numerous studies have been done them (Table 2) on central regulation of feeding behaviour and their mechanism of action in the PVN. However, in some cases the contradictory effects of these neurotransmitters in central control of food intake have been reported.

Leptin is the most important mediators involved in controlling energy homeostasis. This mediator acts on central control of energy expenditure through arcuate nucleus-paraventricular nucleus axis (Ahima et al. 2000). Leptin directly controls the circuits involved in controlling energy balance which from the arcuate nucleus to the paraventricular nucleus. This Probabilistic control is done via MC4R receptor and in three ways: (1) direct postsynaptic modulation by leptin. (2) Regulation of MC4R mRNA expression and α-MSH responsiveness by leptin. (3) Regulation by the constitutive activity of the MC4R signalling (Ghamari-Langroudi and Cone 2011).

Insulin as a hormone secreted from pancreas and controls blood sugar, and it is an important adiposetic signal to the brain. Insulin synthesized in the brain nuclei and has direct effects on central control of food intake and energy consumption (Plum et al. 2005). Several researches have been conducted on the effect of central insulin on regulation of food intake (Benoit et al. 2002; Honda et al. 2007; Shiraishi et al. 2008, Shiraishi et al. 2011; Yousefvand et al. 2018a, 2019). Central insulin reduces food intake and its hypophagic effect as follows: Insulin receptors are located on the POMC and NPY neurons in ARC nucleus, and as well POMC (MC3/4R) and NPY_1 receptors are located on the PVN. Administration of insulin to the ventricles of the brain resulted in POMC neurons stimulated and NPY neurons inhibited, so increased in POMC and decreased in NPY gene expression. After that, POMC level raised and NPY level decreased. Increased in POMC level resulted in stimulated the POMC receptors and decreased in NPY level in synaptic space cussed reduced activity of NPY_1 receptor (Benoit et al. 2002; Yousefvand et al. 2018a). Therefore PVN exported hypophagic output, and cusses reduction in food intake.

Ghrelin neurotransmitter is involved in the central control of food intake. Ghrelin inhibits food intake in birds, but in mammals is a strong stimulant for food intake. This contradiction shows the difference in central regulation of food intake between mammals and birds (Zendehdel and Hassanpour 2014; Denbow and Cline 2014; Thomas et al. 2015). The hypothetical mechanism of inhibition of food intake in birds by ghrelin neurotransmitter: ghrelin (by ICV injection) stimulates the $5Hydroxytryptamin_{2A}$ ($5HT_{2A}$) receptor in Corticotropin-releasing factor (CRF) neurons located on PVN. CRF neurons are anorexigenic neurons in PVN, and receive messages from ARC nucleus through receptors that are located on it. Ghrelin stimulated these neurons, and increase CRF expression. By increasing CRF expression, the PVN exerts an inhibitory message for food intake. Therefore reduced food intake (Saito et al. 2005; Honda et al. 2007; Zendehdel et al. 2013c; Dos-Santos et al. 2018). The assumptive mechanism for increase food intake via ghrelin in mammals: the growth hormone secretagogues receptor (GHSR) (ghrelin receptor) located on AGRP/NPY neurons on ARC nucleus. ICV injection of ghrelin resulted in stimulated AGRP/NPY neurons via GHSR, and increased NPY level and excited NPY_1 receptor on PVN (Thomas et al. 2015). Therefore via stimulation of NPY_1 receptor on PVN, increased food intake. Ghrelin in mammals exert hyperphagic effect on food intake via NPY/AGRP neurons in ARC nucleus and NPY_1 receptor in PVN (Kamegai et al. 2000; Wren et al. 2001; Nakazato et al. 2001).

Table 2 Various studies conducted on feeding behaviour in PVN

Authors of study (year)	Animal	Brain mediator	Brain area	Intermediation/pathway	Effect on feed intake	Another effect
Taksande et al. (2011)	Rat	Agmatine	PVN	α_2-Adrenoceptor & NPY$_1$	Increased	feeding-related disorders
Zendehdel et al. (2013c)	Broiler cockerels	harmaline	right ventricle	5-HT2a and 5-HT2c	Decreased	Increased water intake
Yousefvand et al. (2018a)	Broiler cockerels	Insulin	right ventricle	NPY$_1$ and NPY$_2$	Decreased	No sleepiness and behavioural changes
Haynes et al. (2000)	Rat	Orexin A	Lateral ventricle	OX$_1$R	Increased	Treatment of obesity
Mahzouni et al. (2016)	Neonatal meat-chicken	Methylamine	Lateral ventricle	D$_1$, D$_2$	Decreased	–
Yousefvand et al. (2018b)	Neonatal chicken	Somatostatin	right ventricle	NPY$_1$	Increased	No sleepiness and behavioural changes
Pei et al. (2014)	Rat	Melanocortin	PVN	PVN-AVP	Inhibited	–
Shiraishi et al. (Shiraishi et al. 2011)	Broiler chicken	Insulin	Lateral ventricle	Insulin resistance	No effect	Hyper insulinemia
Bungo et al. (2009)	Layer chicken	N/OFQ	Lateral ventricle	AGRP/CART	Increased	Not effect on NPY and POMC mRNA
Tajalli et al. (2006)	Meat-type chicken	N/OFQ	Lateral ventricle	GABA$_A$	Increased	Increasing GABA flow in the brain
Hajnal et al. (1997)	Rat	NEP	PVN	DA/Ach[a]	Increased	–
Rodgers et al. (2000)	Rat	Orexin A	Lateral ventricle	OX$_1$R	Increased	Effect on micro-structural feeding behaviour
Honda et al. (2007)	Leghorns chicken	Insulin	Lateral ventricle	α-MSH, CART and CRF	Reduced	Not influence on NPY mRNA level
Shiraishi et al. (2011)	Broiler chicken	Insulin	Lateral ventricle	Insulin resistance	Reduced	Hyper insulinemia
Thomas et al. (2015)	Hamster	Ghrelin	The third ventricle	GHSR	Increased	Neural activation in PVN
Rayatpour et al. (2017)	Rat	CRH	PVN	Hypothalamic–pituitary–adrenal axis	Increased	Increased food intake in stressful condition
Yousefvand et al. (2019)	5-old-day chicken	Insulin	Right ventricular	NPY$_1$ and NPY$_2$	Reduced	–
Yousefvand et al. (2017)	5-old-day chicken	Insulin and Somatostatin	Right ventricular	–	–	Decreased water intake
Hashimoto et al. (2007)	Rat	Ghrelin	Right ventricular	–	Stimulated	Inhibited water intake
Karasawa et al. (2014)	Rat	Somatostatin	Right ventricular	Orexin-1	Increased	Increased water intake
Hajdu et al. (2000)	Rat	Somatostatin	Right ventricular	SST$_2$ or SST$_5$	Without effect	Increased water intake
Zendehdel et al. (2012a)	broiler cockerels	Serotonin	Right ventricular	–	Decreased	Increased water intake
Zendehdel et al. (2017)	Neonatal chicken	N/OFQ	Right ventricular	B$_2$-adenergic	Increased	–
Shiraishi et al. (2008)	Layer chicken	Insulin	Lateral ventricle	POMC and NPY	Reduced	Not effect on peripheral glucose levels

Table 2 (continued)

Authors of study (year)	Animal	Brain mediator	Brain area	Intermediation/pathway	Effect on feed intake	Another effect
Mietlicki et al. (2009)	Rat	Ghrelin	Right ventricular	–	Increased	Reduced water intake
Zendehdel et al. (2012b)	broiler cockerels	Serotonin	Right ventricular	MC_3/MC_4	Decreased	Stimulated water intake
Zendehdel et al. (2014a)	broiler cockerels	Dopamine	Right ventricular	D_1 and 5-HT_{2C} receptors	Decreased	The effect of 5HT on dopamine release
Nakazato et al. (2001)	Rat	Ghrelin	Right ventricular	NPY neurons	Increased	Raised body weight
Stengel et al. (2010a)	Rat	Somatostatin	Right ventricular	SST_2	Increased	NPYand opioid signalling pathway
Stengel et al. (2010b)	Mice	Somatostatin	Right ventricular	SST_2	Increased	shortened inter-meal interval
Maejima et al. (2009)	Rat	Nesfatin-1	PVN	Melanocortin pathway	Anorexia	Inhibited oxytocin release in PVN
Wirth et al. (2001)	Rat	MTII and a-MSH	PVN	MC3/4R	Reduced	without causing aversive effects
Mortezaei et al. (2013)	Broiler cockerels	Serotonin	Right ventricular	NMDA, AMPA/K, and $GABA_A$ receptors	Decreased	–
Alimohammadi et al. (2015)	Neonatal layer type chick	L-Arginine	right ventricle	μ-opioid receptor	Decreased	The relationship between nitrergic and opioidergic systems
Mirnaghizadeh et al. (2017)	Neonatal meat-type chick	Oxytocin	right ventricle	H1, H3, and β2 receptors	Decreased	–

[a] Dopaminergic/cholinergic/nucleus accumbens

Somatostatin is known to be a hypothalamic inhibitor of the secretion of growth hormone from pituitary gland. Somatostatin acts in the brain as an inhibitory neurotransmitter. This neurotransmitter distributed in multiple areas of the brain, particularly in ARC, PVN, and VMH in hypothalamus. Since these brain regions involved in central control of food intake, the role of somatostatin in central regulation of food intake is not surprising (Viollet et al. 2008; Schneeberger et al. 2014; Stengel et al. 2015). Somatostatin has an increased food intake via a different neural pathway in the PVN. From different somatostatin receptors (SST_1-SST_5), SST_2/SST_3 receptors are located on the PVN (Stengel et al. 2015). Indicated that, SST_2 receptor is the primary role in the orexigenic effect of somatostatin. SST_2 receptor activated $Orexin_1$ receptor (OX_1R) in LHA, and this receptor stimulated NPY_1 receptor on PVN. Therefore PVN increased central food intake (Stengel et al. 2010a, b; Karasawa et al. 2014; Yousefvand et al. 2018b).

Conclusion

The PVN is an important nucleus for central regulation of food intake in the hypothalamus. This nucleus receives many inputs from different areas of the brain such as: hypothalamus, hippocampus, amygdala, locus coeruleus, periaqueductal gravy matter and the raphe nucleus and peripheral circulation include: insulin, leptin, and etc. then, integrated these inputs and transmitted final outputs for other reigns for effect on food intake. On this nucleus, there are several receptors through which they receive different signals and send the required response. Many neurotransmitters, either inside or outside of this nucleus (due to neuromodulators), have their effects on food intake. Because the number of neurotransmitters was high, in this review article just to mention of the most important neurotransmitters, including leptin, insulin, ghrelin, and somatostatin. Leptin and insulin is an anorexigenic, somatostatin is orexigenic neurotransmitters, and ghrelin has biphasic effect: in birds, anorexigenic and in mammals, orexigenic neurotransmitter. These neurotransmitters apply their effects on central regulation of food intake via PVN.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest with the contents of this article.

Research Involving Human Participants and/or Animals The authors declare that there is no conflict of interest regarding the publication of this article.

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