Orexigenic Effect of Neuropeptide Y and Its Regulatory Mechanisms: Postprint

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Abstract

Neuropeptide Y (NPY) is a neurotransmitter widely distributed in central and peripheral systems that plays a crucial role in maintaining homeostasis, and exerts a principal role in the regulation of food intake. NPY neurons are primarily located in the arcuate nucleus of the hypothalamus (ARC), with fiber projections extending to nuclei including the paraventricular nucleus (PVN), ventromedial nucleus (VMN), lateral hypothalamic area (LHA), and dorsomedial nucleus (DMN). Through synaptic connections formed between NPY fibers and their corresponding receptors, they exert orexigenic regulatory effects. NPY receptors are Gi/Go-protein-coupled receptors comprising eight subtypes (Y1–Y8), among which the Y1 receptor plays a predominant role in hypothalamic energy metabolism regulation. This article elaborates on the structure of NPY and the NPY-related feeding regulation and molecular mechanisms within the ARC, PVN, VMN, LHA, and DMN nuclei, aiming to provide foundational information for related research.

Full Text

The Orexigenic Role and Regulatory Mechanisms of Neuropeptide Y

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Abstract: Neuropeptide Y (NPY) is a neurotransmitter widely distributed in the central and peripheral nervous systems that maintains homeostasis, playing a principal role in the regulation of food intake. NPY neurons are primarily located in the hypothalamic arcuate nucleus (ARC), and their projections reach the paraventricular nucleus (PVN), ventromedial nucleus (VMN), lateral

hypothalamic area (LHA), and dorsomedial nucleus (DMN). Through synaptic connections formed between NPY fibers and their corresponding receptors, NPY exerts orexigenic regulatory effects. NPY receptors are Gi/Go-protein-coupled receptors comprising eight subtypes (Y1–Y8), among which the Y1 receptor plays a dominant role in hypothalamic energy metabolism regulation. This review elaborates on the structure of NPY and its food intake regulatory functions and molecular mechanisms in the ARC, PVN, VMN, LHA, and DMN nuclei, aiming to provide foundational information for related research.

Keywords: neuropeptide Y; Y receptor; food intake; nuclei

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Neuropeptide Y (NPY) is a neurotransmitter extensively distributed throughout the central and peripheral nervous systems. Within the central nervous system, NPY is found in the hypothalamus, cerebral cortex, hippocampus, striatum, olfactory bulb, and midbrain. In the peripheral nervous system, NPY is present in sympathetic nerves, adrenal nerve fibers, and adrenal chromaffin cells, as well as in nerve fibers innervating the lungs, urethra, spleen, blood vessels, and reproductive organs [1]. NPY was first isolated from porcine brain by Tatemoto in 1982, and Stanley et al. [2] subsequently discovered its involvement in feeding regulation, demonstrating that injection of NPY into the hypothalamic paraventricular nucleus (PVN) increased food intake. Further studies confirmed that intracerebroventricular injection of NPY dose-dependently increased food intake while reducing energy expenditure, and chronic NPY administration led to increased food consumption and obesity. Similar findings have been reported in ruminants; Miner et al. [3] observed that lateral cerebroventricular injection of 2.35 nmol NPY in satiated sheep increased feeding by 154% within 30 minutes, while also increasing leptin expression and decreasing growth hormone levels, indicating that NPY influences mammalian fat production and growth development. Additionally, fasting studies have shown that NPY precursor increased 2.6-fold after 72 hours of fasting, with cellular localization revealing increased NPY precursor mRNA content in the hypothalamic arcuate nucleus (ARC) [4]. NPY expression levels are elevated in both diet-induced obesity rat models and leptin-deficiency obesity models, whereas leptin, an anorexigenic factor secreted by adipose tissue, can reduce NPY-induced feeding. These findings demonstrate that NPY is closely associated with energy intake.

The hypothalamus participates in multiple physiological activities including feeding behavior, thermoregulation, and sleep-wake cycles, with feeding behavior studies dating back to the 1930s. The hypothalamic ARC serves as the primary source of NPY, integrating peripheral nutritional signals to regulate feeding behavior. This review focuses on the structure of NPY and its food intake regulatory roles and mechanisms in the hypothalamic ARC, PVN, ventromedial nucleus (VMN), dorsomedial nucleus (DMN), and lateral hypothalamic area (LHA).

1. NPY Composition and Structure

NPY is a biologically active single-chain polypeptide composed of 36 amino acids, rich in tyrosine, with an α-amide structure at its C-terminus [5]. It shares high homology with two other pancreatic polypeptide family members: pancreatic polypeptide (PP) and peptide YY (PYY), all possessing a hairpin-like three-dimensional structure known as the PP-fold. This structure brings both ends of the molecule together to facilitate receptor binding. Analysis of complete NPY gene sequences across nine species including humans, chimpanzees, cattle, dogs, rats, chickens, frogs, and zebrafish reveals that the NPY gene is highly evolutionarily conserved. At the nucleotide level, humans and zebrafish show the lowest homology at 75%, while amino acid conservation reaches 89% [6]. This high degree of evolutionary conservation indicates that NPY plays a crucial role in maintaining normal physiological functions in organisms.

2. NPY' s Orexigenic Role and Mechanism

NPY is widely distributed in central and peripheral nervous tissues and participates in important physiological functions including locomotion, learning and memory, anxiety, epilepsy, circadian rhythms, and vascular function. Hypothalamic NPY primarily originates from NPY neurons in the ARC, which co-express the orexigenic neuropeptide agouti gene-related protein (AgRP). The ARC projects integrated information through NPY neurons to different hypothalamic nuclei, including the PVN, VMN, LHA, and DMN, thereby playing a role in orexigenic regulation [7].

2.1 ARC Regulation of Food Intake

The ARC is located at the base of the third ventricle, adjacent to the median eminence of the circumventricular organ. The median eminence lacks a blood-brain barrier, and the capillary endothelium in this region is fenestrated, making the ARC more permeable to blood-borne molecules than other hypothalamic regions. Various feeding-related molecules such as ghrelin, leptin, and insulin enter the ARC from the blood and bind to corresponding receptors on neurons to regulate feeding behavior, allowing the ARC to function as an integrator of feeding signals. The ARC contains two types of neurons with opposing functions that participate in energy balance regulation: orexigenic NPY neurons and anorexigenic proopiomelanocortin (POMC) neurons. Additionally, NPY neurons express AgRP and γ-aminobutyric acid (GABA), while POMC neurons express cocaine- and amphetamine-regulated transcript.

NPY/AgRP neurons co-express NPY and AgRP, with 94% of NPY neurons expressing AgRP mRNA in freely fed mice and 99% expressing it under fasting conditions [8]. Studies have shown that the orexigenic effect of NPY/AgRP co-expressing neurons is independent of NPY' s inhibition of POMC neurons [9], indicating that NPY can regulate feeding function through different pathways. Overexpression of NPY in the rat ARC using adeno-associated viral vectors

induces hyperphagia and sustained weight gain, ultimately leading to severe obesity. Targeting NPY with miRNA to downregulate its expression in the ARC does not affect normal food intake or weight gain but attenuates or eliminates the refeeding response after fasting [10]. Selective silencing of NPY/AgRP neurons in the ARC significantly reduces food intake and body weight in adult rats but does not significantly affect food intake in neonatal mice [11], possibly because ARC neural fibers can project to the PVN, DMN, and LHA to regulate feeding, but these projections are not fully mature during early development [12]. This suggests that alternative pathways or compensatory mechanisms for ARC regulation exist before the completion of feeding circuit development. NPY acts directly on postsynaptic Y1 and Y2 receptors on POMC neurons through its nerve fibers, causing membrane hyperpolarization, inhibiting cell firing, and preventing the transmission of anorexigenic signals [13].

2.2 PVN Regulation of Food Intake

The PVN is one of the most important targets of NPYergic fibers from the ARC, and early studies demonstrated that NPY in the PVN is associated with feeding behavior. After three days of fasting, NPY concentrations in the rat PVN significantly increase, while NPY content markedly decreases during food consumption [14]. This indicates that NPY in the PVN can trigger feeding behavior. Injection of NPY into the PVN promotes food intake and reduces the expression of uncoupling protein and phospholipase mRNA in brown adipose tissue [15]. Overexpression of NPY in the rat PVN using lentiviral vectors increases food intake and body weight, predisposing to obesity and glucose metabolism disorders [16]. Under specific conditions, NPY expression patterns in the PVN change: compared with controls, early-weaned rats show high NPY expression in the PVN in adulthood, leading to long-term hyperphagia and increased susceptibility to obesity [17]. This demonstrates that NPY in the PVN plays an important role in appetite regulation and that early nutritional signals are critical for the formation of feeding pathways. Various neurons in the PVN (oxytocin neurons, thyrotropin-releasing hormone neurons, etc.) can stimulate NPY/AgRP neurons in the ARC, and these excited neurons inhibit anorexigenic neurons in the PVN through NPY/AgRP fibers to form an orexigenic circuit [18–19].

NPY regulates neural activity in the PVN through both presynaptic and postsynaptic mechanisms. Regarding the former, NPY in the PVN inhibits GABA release from GABAergic synapses on small cell-body neurons, thereby reducing the orexigenic effect of NPY. This explains why obese rats with high NPY expression show diminished responses to NPY' s orexigenic effects [20]. Regarding the latter, NPY inhibits melanocortin receptor 4-expressing neurons in the PVN through membrane hyperpolarization, thereby regulating feeding behavior [21–22].

2.3 VMN Regulation of Food Intake

The VMN is one of the early-identified hypothalamic regions associated with feeding. Substantial evidence indicates that the VMN plays an important role in feeding behavior. Neuroimaging studies show that VMN activity significantly increases during feeding, while its neuronal activation inhibits feeding behavior. The VMN is highly sensitive to the orexigenic effects of NPY, which binds to receptors and reduces VMN neuronal firing. The VMN contains numerous NPY-positive fibers that form synaptic connections with VMN dendrites. Released NPY activates postsynaptic Y1 receptors, opening potassium channels, causing hyperpolarization, and directly inhibiting VMN neural activity [23]. Excitatory neurons in the VMN project to POMC neurons in the ARC to activate them, thereby inhibiting feeding [24].

2.4 LHA Regulation of Food Intake

The LHA plays a key role in feeding regulation. In contrast to the PVN, electrical stimulation of the LHA induces anorexic behavior, which has been clinically applied for effective weight loss [25]. Injection of NPY into the hypothalamic LHA induces strong feeding behavior. Similarly, injection of adeno-associated virus (AAV) vectors into the LHA to chronically overexpress NPY leads to increased food intake and weight gain [26]. The LHA contains two main types of orexigenic neurons: orexin neurons and melanin-concentrating hormone (MCH) neurons. Orexin neurons are widely distributed excitatory neurons in the hypothalamus that have feedback connections with NPY neurons in the ARC. Immunohistochemical results show that the LHA receives dense NPY fiber projections from the ARC, with fibers projecting to orexin neurons being more abundant than those projecting to MCH neurons [27]. Orexin neurons in the LHA also project fibers to NPY neurons in the ARC, and excited orexin neurons increase NPY expression and food intake. This suggests that the ARC-LHA forms a neural circuit regulating feeding behavior, although NPY axons may also originate from other nuclei such as the brainstem and lateral geniculate body [28].

2.5 DMN Regulation of Food Intake

The DMN contains numerous orexigenic NPY neurons whose fibers project to the PVN, LHA, and perifornical area. Electrical stimulation of the DMN induces substantial feeding, while DMN lesions cause anorexia, indicating that signals from this nucleus are primarily orexigenic. The DMN plays a crucial role in the normal development of feeding circuits in mice: after birth, projections from NPY neurons in the ARC are immature and gradually project to the DMN, PVN, and LHA. Among these, projections from the ARC to the DMN develop the fastest and are fully established by postnatal day 6 [12]. Short-term NPY expression in the DMN may increase energy demand: NPY expression increases during the rapid growth period after birth and decreases to low levels in adulthood, while pregnant females show elevated DMN NPY

content to meet increased energy demands [6]. Yang et al. [29] demonstrated that AAV-mediated overexpression of NPY in both sides of the DMN in lean rats increased food intake and body weight, whereas silencing the NPY gene improved obesity symptoms. This indicates that the DMN plays an important role in NPY-mediated feeding regulation, and its dysregulation can cause metabolic disorders leading to obesity. NPY knockout in the dorsomedial hypothalamus increases insulin sensitivity, improves glucose tolerance, and prevents high-fat diet-induced hyperglycemia and hyperinsulinemia, suggesting that NPY in this nucleus also plays a role in glucose homeostasis [30].

After long-term restricted feeding, NPY gene expression in the DMN increases, whereas short-term food deprivation does not affect its expression [31]. Compared with ARC NPY, which is directly regulated by leptin, DMN NPY is regulated by cholecystokinin and other molecules. Knockdown of NPY in the DMN of obese OLETF (Otsuka Long-Evans Tokushima Fatty) rats using AAV-RNA interference decreases food intake and significantly improves obesity and glucose tolerance. Moreover, NPY knockdown in the rat DMN promotes brown adipose tissue formation, which further prevents diet-induced obesity [32]. Both stimulation and disinhibition of DMN neurons enhance sympathetic activity in scapular brown adipose tissue, thereby increasing brown fat levels and body temperature [33].

3. NPY Receptors Related to Food Intake

NPY receptors are Gi/Go-protein-coupled receptors, referred to as Y receptors, which can also be activated by PYY and PP. The Y receptors comprise eight subtypes (Y1–Y8) [34]. Most species possess Y1, Y2, Y4, and Y5 receptors, with NPY preferentially binding to Y1, Y2, and Y5 receptors and showing relatively weaker affinity for Y4. The Y3 receptor is considered to exist only in pharmacological data and has not been identified in rodents, primates, or humans. The Y6 receptor is non-functional in humans and absent in rats, while Y7 and Y8 receptors have not been found in mammals [35]. Amino acid sequence homology analysis reveals extremely low homology between receptor subtypes: Y1, Y4, and Y6 share relatively high homology at only 50%; Y2 shows only 30% homology with these three receptors and 31% with Y4. Among these receptors, Y4 shows higher variability than Y1, Y2, and Y5, possibly because its endogenous ligand may be PP rather than NPY or PYY. However, Y1, Y2, and Y5 share only 27–32% homology despite binding the same ligands. Although Y1, Y2, and Y5 receptors are widely distributed in the hypothalamus, brainstem, blood vessels, lungs, kidneys, adrenal glands, stomach, colon, heart, pancreas, and intestines, the Y1 receptor plays a dominant role in hypothalamic energy metabolism regulation [36].

3.1 Y1 Receptor and Food Intake Regulation

The Y1 receptor is widely distributed in the brain, including the cerebral cortex, thalamus, hippocampus, amygdala, lateral geniculate body, nucleus of the

solitary tract, and hypothalamus. In the hypothalamus, Y1 receptors are primarily expressed in the ARC, PVN, DMN, and VMN, often co-expressed with Y5 receptors in the same cell [37–38]. Beyond the central nervous system, Y1 receptor mRNA is abundantly expressed in the heart, kidneys, pancreas, skeletal muscle, bone marrow, and lungs of rodents, as well as in the colon, kidneys, adrenal glands, and heart of humans.

In monogenic obese Zucker rats (fa/fa), hypothalamic Y1 receptor mRNA expression is 25% higher compared with lean rats (FA/FA) [39], consistent with reduced feeding responses induced by NPY in obese animals. Y1 receptor expression is increased in diet-induced obesity (DIO)-sensitive rats but decreased in DIO-resistant rats, suggesting that Y1 receptor expression correlates with obesity susceptibility [40]. In DIO mouse models, Y1 receptor mRNA levels change in the ARC but are downregulated in the VMN and DMN, indicating that male obesity susceptibility is associated with altered Y1 receptor expression in the VMN and DMN [41]. Furthermore, fasting or food deprivation downregulates Y1 receptor expression in the ARC and PVN [42–43], demonstrating that Y1 receptor expression changes in these nuclei play important roles in energy balance.

3.2 Y2 Receptor and Food Intake Regulation

Immunohistochemical studies show that Y2 receptors are primarily expressed in the olfactory bulb, nucleus accumbens, amygdala, hippocampus, hypothalamus, and nucleus of the solitary tract in mice. In the mouse hypothalamus, Y2 receptors are mainly expressed in the ARC, PVN, and LHA, with additional expression in the gastrointestinal tract, cardiovascular system, and adipose tissue [44]. Although fasting does not substantially affect Y2 receptor gene expression in the ARC of rats, Y2 receptor expression in the hypothalamus significantly increases in DIO-sensitive models but markedly decreases in DIO-resistant models [40]. These results indicate that Y2 receptors play important roles in long-term energy metabolism balance. Further studies show that knockout of peripheral Y2 receptor genes prevents diet-induced obesity, and high Y2 receptor expression in visceral fat correlates with obesity [45].

3.3 Y5 Receptor and Food Intake Regulation

Y5 receptor mRNA is highly expressed in the PVN, ARC, LHA, DMN, and VMN of humans and rats. Similar to Y1, the Y5 receptor also has orexigenic effects. However, hypothalamic Y5 receptor mRNA expression is downregulated in Zucker obese rats and significantly decreased in the ARC, VMN, and DMN of ob/ob obese rats. In contrast, Y5 receptor mRNA expression is upregulated in DIO-sensitive models compared with genetic obesity models [40]. Moreover, Y5 receptor mRNA expression is downregulated by energy intake restriction. These findings indicate that the role of Y5 receptors in hypothalamic orexigenic regulation is complex and varies with different interventions or inducing factors.

The hypothalamic NPY system plays a crucial role in regulating food intake and energy metabolism. This system integrates energy balance centers with limbic signals in the ARC through the melanocortin system. Subsequently, the NPY system in the ARC projects integrated information via neural fibers to neurons in different hypothalamic nuclei, including the PVN, VMN, DMN, and LHA. Finally, released NPY binds to different receptor subtypes, and through feedback between neurons and peripheral secretory signals, jointly regulates food intake and energy metabolism. The body' s energy status affects hormone levels, and increased NPY expression inhibits luteinizing hormone production, thereby influencing reproductive behavior in livestock [46–47]. In-depth research on energy metabolism and reproduction in livestock can lay the foundation for improving livestock productivity. Additionally, metabolic disease patients are increasing globally, seriously affecting human health and development. Although substantial breakthroughs have been achieved in "feeding and energy metabolism regulation" research, the specific mechanisms of "hypothalamic NPY system involvement in feeding and energy metabolism regulation" require further investigation due to the diversity and complexity of the regulatory network and the interaction of multiple peripheral and central energy balance signals with the NPY system.

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