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Neuropeptide Y: an undisputed central stimulator of avian appetite

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ABSTRACT

During the last few decades, identifying the physiological pathways involved in appetite regulation has become popular among researchers. Although studying feeding regulation in birds, especially in poultry (for breeding purposes) and ornamental birds (for therapeutic purposes), is extremely important, limited experiments have been conducted on these animal models. Until today, more than 50 neurotransmitters affecting birds' appetite have been identified. In the current study, we overviewed the role of one of the most important neural mediators, neuropeptide Y (NPY), in regulating avian appetite. Based on the findings, the presence of this neuropeptide and its receptors in the key areas of food intake regulation, especially the hypothalamus's arcuate nucleus (ARC), has been proven. Numerous studies on birds have repeatedly shown the hyperphagic effects of NPY. Among the different NPY receptors, type 1, 2, and 5 receptors play the most important role in appetite regulation. It has also been observed that the interaction of NPY with neurotransmitters such as glucagon-like peptide-1 (GLP-1), vasotocin, bombesin, opioids, alpha-melanocyte-stimulating hormone (α-MSH), cocaine- and amphetamine-regulated transcript (CART) and gamma aminobutyric acid (GABA) is effective in NPY-induced hyperphagia. In addition, the NPY system is also involved in the effects of various mediators such as adiponectin, neuropeptide W (NPW), phoenixin-14, visfatin, adrenomedullin, spexin, kisspeptin, insulin, and somatostatin on appetite regulation. Finally, NPY seems to be one of the most important appetite-stimulating factors in birds and also plays an undeniable role in the effects of other neurotransmitters on appetite regulation.

Keywords: *Appetite, Bird, Hypothalamus, Neuropeptide Y, Neurotransmitter*

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1 Introduction

Appetite regulation involves a complex interplay of hormones and neural signals influencing hunger and satiety (1, 2). Although the participation and efficient functioning of both the central and peripheral nervous systems are required to balance the regulation of food intake, the hypothalamus is undoubtedly the primary center for processing appetite-related information (3). The nuclei of the hypothalamus are composed of different nerve bundles, the connections between which ultimately regulate the amount of food received (4). Today, appetite regulation is a critical research area due to the global obesity epidemic, which emphasizes the importance of investigating gut hormones and central nervous system (CNS) interactions for potential anti-obesity interventions (5). In addition to humans, it is very important to know the processes involved in controlling appetite in animals, mainly farmed species. Despite the limited studies conducted on birds, more than 50 neural mediators involved in controlling food intake have been identified in these species (6, 7). A detailed study on the effect path of each of these mediators and their interactions, while providing basic data to compare with mammalian and human species, can be fruitful in the field of eugenics and breeding species with higher productivity (8).

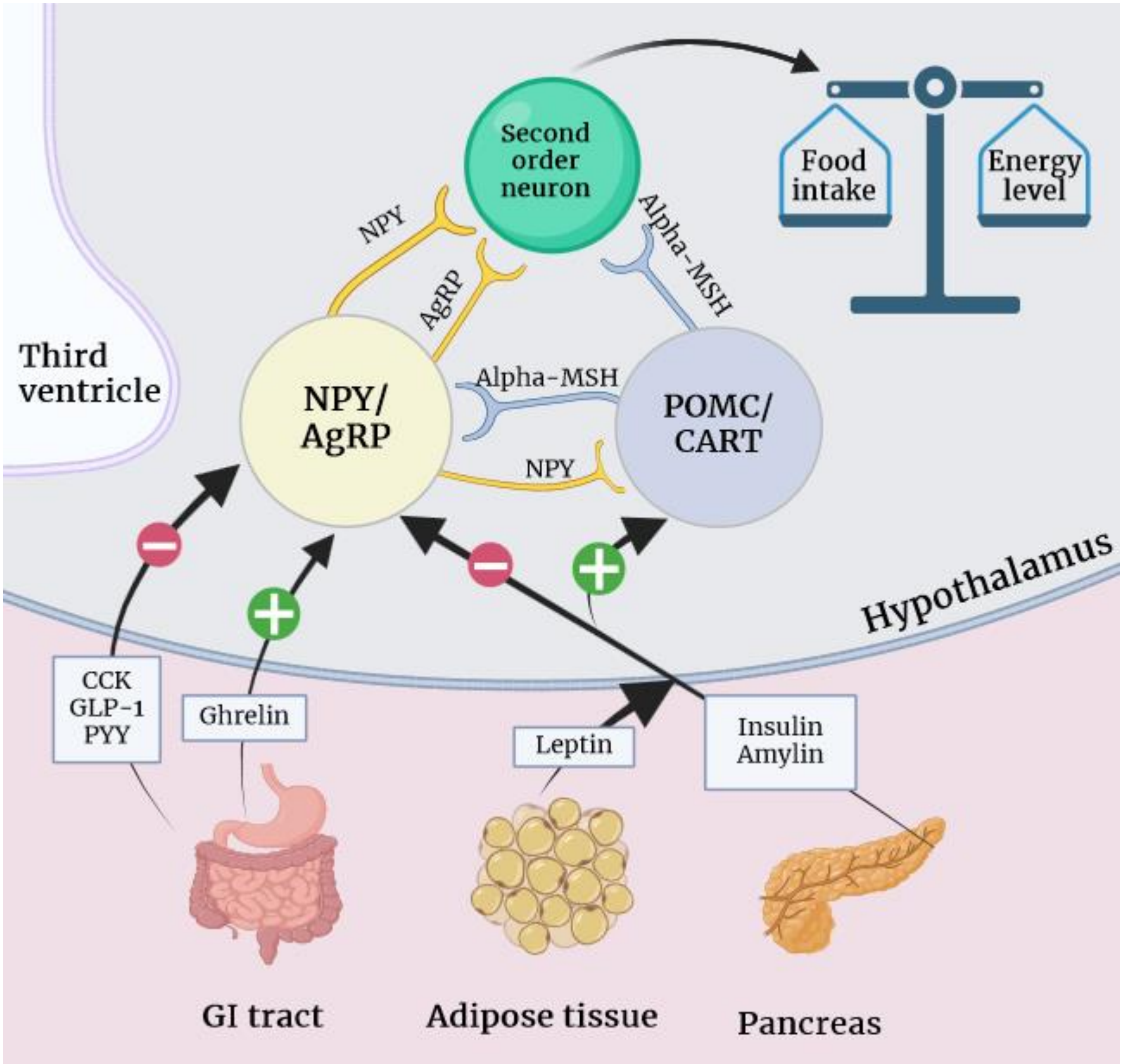

Figure 1. Interaction between NPY/AgRP and POMC/CART neurons in the central control of food intake.

The research on nervous systems led to identifying neuropeptide Y (NPY) as one of the most important neurotransmitters; subsequently, extensive studies have been carried out on its physiological functions in mammals and birds (9). This neurotransmitter is a member of the NPY family, which also includes peptide YY (PYY) and pancreatic polypeptide (PP) (10). The structure of NPY is characterized by its 36 amino acids, which allow it to interact with its receptors and modulate various physiological functions related to appetite regulation, stress modulation, anxiety levels, circadian rhythm, and pain perception in the CNS (11). Regarding the role of NPY in regulating food intake, it has been shown that stimulation of NPY/agouti-related protein (AgRP) neurons in hypothalamic nuclei leads to increased food consumption. In contrast, stimulation of pro-opiomelanocortin (POMC) neurons and cocaine/amphetamine-regulated transcript (CART) decreases appetite (12) (Figure 1). Studies have shown that NPY and its receptors are expressed in birds' central and peripheral tissues, confirming its widespread influence on physiological processes beyond appetite control (13). The structure of NPY is highly conserved across species, with over 90% identity in the amino acid sequence among mammalian species and greater than 80% identity between chicken and other species (14). Therefore, the study of the physiological effects of this neuropeptide, especially in the field of appetite regulation, can provide interesting results compared to the studies conducted on mammalian models.

Considering the importance of knowing the factors affecting the food intake of birds and the outstanding role of NPY in regulating appetite, in the present review, we will have a general insight into the role of NPY in feeding and regulating birds. In this regard, while examining the receptors' types of this system and its anatomical distribution, we will look at the function of this neuropeptide in birds' food intake. In this regard, while reviewing the studies conducted on NPY, we will discuss its interaction with other neurotransmitters involved in appetite regulation.

2 NPY receptors

NPY receptors are a family of receptors that belong to class A G-protein coupled receptors (GPCRs). There are five known mammalian NPY receptors (NPY1, NPY2, NPY4, NPY5, and NPY6) (15). Furthermore, Y7 is found in fish, chicken, and other avian species, ., and Y8a and Y8b receptors may also be present in frogs and teleost fish, respectively (16). The NPY receptors are involved in post-synaptic transmission activity, while the Y2 receptor also plays a role in pre-synaptic processing (17). These receptors are activated by NPY, PYY, and PP, playing a role in controlling various behavioral processes such as appetite, circadian rhythm, and anxiety (18). NPY system receptors have a long evolutionary history and are divided into three separate families based on their amino acid sequence similarity (Figure 2) (15):

- The Y1 family: The Y1 family of NPY receptors includes receptors such as Y1, Y4, Y6, and Y8 (only in teleost fish and frogs). These receptors are part of the NPY system and are characterized by their ability to bind NPY. The Y1 type of binding site, as characterized in human neuroblastoma and rat pheochromocytoma cell lines, binds to NPY and plays a role in modulating different biological actions, including food intake, circadian rhythm, pain transmission, and hormone release (19, 20).

- The Y2 family: The Y2 family includes Y2 and Y7 receptors. Human studies have shown that the NPY2R gene encodes the Y2 receptor. This receptor is essential in various physiological processes, including food intake, bone formation, and mood regulation. The Y2 receptor has been identified as an important drug target for conditions such as obesity and anxiety (19, 21).

- The Y5 family: The Y5 family of NPY receptors includes only the Y5 receptor. The Y5 receptor is known for its role in regulating meal consumption and body weight. Several studies have shown that the stimulatory effect of NPY on feeding behavior is transduced by the NPY5 receptor (Y5R). In mice, the inactivation of the Y5R gene has been associated with late-onset obesity characterized by increased feed intake, body weight, and adiposity. Interestingly, younger Y5R-null mice initially feed and grow normally but develop mild obesity later on. These findings highlight the significance of the Y5 receptor in meal consumption and body weight regulation (19, 22).

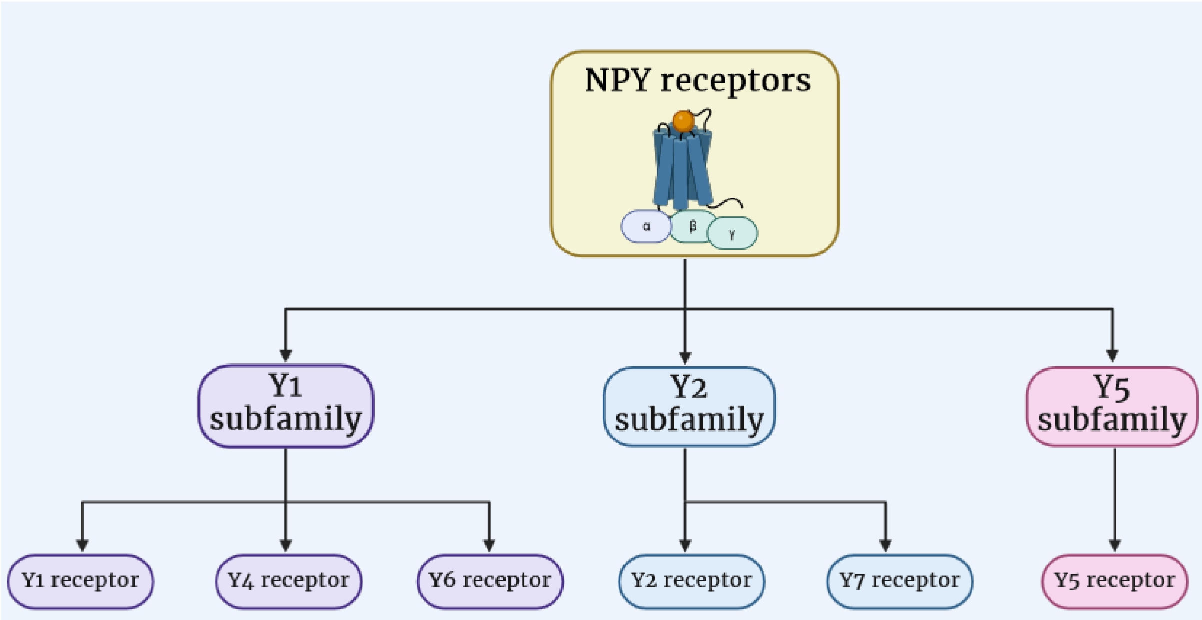

Figure 2. Classification of avian NPY receptors.

3 Anatomical distribution

The anatomical distribution of NPY in the CNS of mammalian models was investigated using various techniques. These studies revealed that NPY has a widespread distribution in the brain, with the highest concentrations found in specific regions such as the hypothalamic paraventricular nucleus (PVN) and arcuate nucleus (ARC) (23). These regions contained the highest density of immunoreactive fibers and the number of perikarya, indicating a significant presence of NPY in these areas (24). Additionally, moderate concentrations and densities of NPY were observed in regions like the dorsomedial hypothalamic nucleus, paraventricular thalamic nucleus, and bed nucleus of the stria terminalis (25). These findings highlighted the extensive distribution of NPY in the CNS, suggesting its involvement in various physiological functions. Studies conducted on bird models, specifically on chickens, reveal a widespread presence of NPY-immunoreactive neurons and fibers in the brain. In avian species like chickens, NPY is also highly expressed in regions such as the hypothalamic infundibulum and hippocampus (26). The distribution of NPY in birds mirrors its presence in mammalian brains, highlighting its conserved role across species in regulating neural processes and behaviors.

4 Role in regulating food intake

Environmental, genetic, hormonal, and nutritional factors influence the regulation of NPY expression (27). Several studies have shown that conditions such as food restriction and deprivation increase the expression of NPY mRNA in the brain and the activity of neurons (28). The results of a study showed increased NPY content in the inferior hypothalamic nucleus (IN) and PVN but not in the lateral hypothalamic area (LHA) in chicks deprived of food for three days (29). One day after feeding, the level of this neuropeptide in the PVN returned to its normal level, which indicates the effect of nutritional status on the concentration of NPY in the brain. Also, in another experiment, an enhancement in the expression of NPY following a reduction in feed intake was observed in three-week-old male chickens, which again indicates the relationship between nutritional status and NPY level (30).

In long-term selected chickens, researchers found that hypothalamic NPY expression was higher in fat compared to lean bird lines in both fed and fasted conditions for the ratio of abdominal fat to live weight. The same group found hypothalamic NPY expression was lower in low-fed versus low-fed efficient male quail but remained unchanged between female lines, suggesting potential sex-dependent effects (31).

Based on the study of Saneyasu et al. (2011) on broiler and layer chickens, it has been observed that the central administration of NPY in both species increases food intake. It was also observed that despite consuming more food in broiler chickens, the expression of NPY mRNA and its receptors in meat-type chickens is lower than in egg-type chickens. These results show that the increase in appetite caused by NPY in broilers is probably unrelated to the change in the expression of NPY mRNA and its receptors (32). In another study on broiler chickens, the hyperphagic effects of NPY were again observed, as intracerebroventricular (ICV) injection of 5 micrograms of NPY doubled food consumption in chickens (33). The researchers showed that ICV administration of chicken NPY did not affect food intake in low body weight (LWS) chickens at any time (up to 3 hours post-injection). However, in high body weight (HWS) chickens, all three doses of NPY tested were associated with similar increases in food intake at all study times. Also, that study found that NPY was associated with increased c-Fos immunoreactivity in both LWS and HWS chickens. However, in any case, there was no therapeutic interaction (34). Although most studies on avian food intake have focused on broiler and egg-laying chicken models, the role of neuropeptide Y in appetite regulation in other bird species has also been investigated. It was found that injecting NPY into the brain of white-crowned sparrows causes increased food consumption (35). Hence, NPY appears to have appetite-enhancing effects in birds, similar to those in mammals.

5 Interferences with other systems

In addition to the studies conducted on the role of NPY in feeding regulation and proving its hyperphagic effects, various experiments have been done to identify the mediation role of other neural systems in the occurrence of NPY's appetite-enhancing effects, some of which are listed in Table 1.

Table 1. The mediating effects of different neurotransmitters on NPY-induced hyperphagia in birds

Animal model	Interaction with	Outcome	Reference
Broiler	Glucagon-like peptide-1	Decrease	(36)
Broiler	SR-49059 (vasotocin four receptor antagonist)	Increase	(37)
Broiler	Bombesin	Decrease	(38)
Broiler	Picrotoxin (GABAA receptor antagonist)	Decrease	(39)
Broiler	α-melanocyte-stimulating hormone	Decrease	(40)
Broiler	β-Funaltrexamine (µ opioid receptor antagonist) Naloxonazine (µ1 opioid receptor antagonist)	Decrease	(41)
Broiler	Glycyl-l-glutamine (a non-opioid peptide derived from β-endorphin)	Decrease	(42)
Broiler & Layer	Cocaine- and amphetamine-regulated transcript	Decrease	(43)

Also, the presence of NPY and its receptors in the main areas involved in food intake has caused the receptors of this system to play an important role in mediating the effects of other neurotransmitters on food consumption. Table 2 shows the results of a number of studies conducted in this regard.

Table 2. The mediating role of NPY receptors in appetite changes induced by other neurotransmitters in birds

Neurotransmitter	Animal model	Changes in feeding	Interaction with	Outcome	Reference
Adiponectin	Layer	Hyperphagia	B5063 (NPY1 receptor antagonist)	Decrease	(44)
Neuropeptide W	Broiler	Hyperphagia	BMS193885 (NPY1 receptor antagonist)	Decrease	(45)
Phoenixin-14	Layer	Hyperphagia	B5063 (NPY1 receptor antagonist)	Decrease	(46)
			SML0891 (NPY5 receptor antagonist)	Increase	
Visfatin	Broiler	Hyperphagia	B5063 (NPY1 receptor antagonist)	Decrease	(47)
Adrenomedullin	Layer	Hypophagia	B5063 (NPY1 receptor antagonist)	Increase	(48)
Spexin	Broiler	Hypophagia	B5063 (NPY1 receptor antagonist)	Increase	(49)
Kisspeptin	Layer	Hyperphagia	BIBP-3226 (NPY1 receptor antagonist)	Decrease	(50)
Insulin	Broiler	Hypophagia	B5063 (NPY1 receptor antagonist) SF22 (NPY2 receptor antagonist)	Increase Decrease	(51)
Somatostatin	Broiler	Hyperphagia	B5063 (NPY1 receptor antagonist) SF22 (NPY2 receptor antagonist) SML0891 (NPY5 receptor antagonist)	Decrease Increase Decrease	(52)

6 Conclusion

Based on the presented findings, NPY acts as a potent appetite stimulant in birds, similar to its role in mammals. In addition, type 1, 2, and 5 receptors of the NPY system have the most significant role in the process of feeding regulation. Although the interaction effect between NPY and other systems has been studied to some extent, considering the important role of this system in appetite control and its anatomical distribution in the key areas of appetite regulation, wider and more diverse studies can be conducted on the interactions of NPY and other neurotransmitters and hormones. In addition, considering that most of the studies were conducted on broilers and egg-laying chickens, designing experiments on other bird species can provide helpful information.

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Conflict of Interest

The authors declared no conflicts of interest.

Author Contributions

All authors wrote the main review text, and Prof. Morteza Zendehdel read and approved the final version.

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Data are available from the corresponding author upon reasonable request.

Ethical Considerations

None.

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