Journal of Poultry Sciences and Avian Diseases

Journal homepage: www.jpsad.com

Central regulation of appetite in birds: Recent advances and future perspective

Kimia Mahdavi[1], Morteza Zendehdel[1*], Hamed Zarei[2]

[1] Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
[2] Department of Biology, Faculty of Basic Science, Central Tehran Branch, Islamic Azad University, Tehran, Iran

*** Corresponding author email address**: zendedel@ut.ac.ir

A r t i c l e I n f o

Article type:
Review Article

How to cite this article:
Mahdavi, K., Zendehdel, M., & Zarei, H. (2023). Central regulation of appetite in birds: Recent advances and future perspective. *Journal of Poultry Sciences and Avian Diseases, 1*(3), 42-50.
http://dx.doi.org/10.61838/kman.jpsad.1.3.4

A B S T R A C T

Understanding the mechanism of food intake is important for comprehending energy balance, obesity, and the body weight regulation. In particular, examining birds' appetite is critical for conservation efforts, managing human-bird interactions, and understanding the environmental implications of bird feeding practices. In this systematic review, using the PRISMA guideline, we investigated the mediators that were identified as factors affecting the birds' appetite in 2022 and 2023. In order to obtain the appropriate studies, suitable keywords were searched in the relevant electronic databases and an anthology of the desired articles was done. According to the findings, the central administration of adrenomedullin, apelin-13, lipopolysaccharide, neuromedins and spexin causes hypophagia in chickens, while the injection of adiponectin, neuropeptide W (NPW) and phonexin-14 increased the food intake of birds. Also, regarding the members of RF-amide peptide family, neuropeptide VF (NPVF) and neuropeptide FF (NPFF) weakened the food consumption of birds, while kisspeptin and prolactin-releasing peptide (PrRP) strengthened it. The effects observed in birds were similar to mammals in most cases, indicating the structural and general similarities in the regulatory mechanisms of these strains, on the other hand, the contradictory effects between the two species were probably caused by genetic differences. Finally, despite the progress made in identifying the factors and mechanisms involved in regulating the appetite of birds, it is recommended to conduct future studies using modern laboratory methods, especially cellular-molecular methods.

Keywords: *Appetite, Food intake, Neurotransmitters, Birds*

Article history:
Received 13 June 2023
Revised 04 August 2023
Accepted 09 August 2023
Published online 01 September 2023

1 Introduction

The process of food consumption and regulating appetite is a crucial physiological function for the survival of animals and humans. It involves various regulatory processes that ensure the receipt of energy and nutrients necessary to sustain life. The body regulates appetite through various mechanisms involving the central nervous system (CNS) and peripheral signals (1). The hypothalamus, a critical center in the CNS, plays a main role in monitoring, processing, and aggregation of peripheral messages, including hormones, to regulate food consumption and energy expenditure. Indeed, different neurons and synaptic connections within the hypothalamus, are involved in the management of nutritional processes and the appetite regulation. The arcuate nucleus (ARC) in the hypothalamus contains subpopulations of neurons that produce anorexigenic neuropeptides, pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) and orexinergic neuropeptides, neuropeptide Y (NPY)/agouti-related peptide (AgRP) (2). In addition, research has shown the possible role of microRNAs in feeding regulation and body mass accumulation, emphasizing the intricate molecular mechanisms involved in the physiological adjustment of energy balance and appetite (3).

Until today, extensive studies have been conducted around the identification of factors and functions involved in the food consumption regulation, most of which have been focused on mammals. By introducing experimental models of birds in appetite research, at the same time as identifying different neurotransmitters, the role of each one in feeding behavior has been determined. In table 1, the influence type of these mediators on birds' food intake is mentioned separately. These findings, while confirming the existence of similarity in the function of factors involved in appetite control between birds and mammals, indicate the existence of differences in the effectiveness of some of these mediators between the two species (4).

These differences in the role of mediators in food acquisition highlight the need for independent research on birds. On the other hand, it should be noted that regulating food intake in broiler and laying poultry is essential for sustaining egg production, ensuring optimal growth performance, maintaining overall health, and well-being. Understanding the nutritional demands and regulatory mechanisms involved in food intake is crucial for optimizing poultry nutrition and productivity. Considering the mentioned points and the importance of understanding the precise processes of appetite regulation in birds, in the current review study, while referring to the latest achievements in order to identify the factors involved in the feeding behavior, we provide a perspective of future research in this field.

Table 1. Effects of central neurotransmitters on food intake of birds

Neurotransmitter		Effect on food intake	Reference
Norepinephrine		Decrease/ Increase	(5, 6)
Dopamine		Decrease	(7, 8)
Serotonin		Decrease/ No effect	(9, 10)
Nociceptin/Orphanin FQ (N/OFQ)		Increase	(11)
Histamine		Decrease	(12)
Glutamate		Decrease	(13, 14)
Gamma-Aminobutyric Acid (GABA)		Increase	(15, 16)
Glycine		Decrease	(17)
Corticotropin-Releasing Factor		Decrease	(18)
Oxytocin		Decrease	(19)
Melanocortins		Decrease	(20)
Neuropeptide Y (NPY)		Increase	(21)
Somatostatin		Increase	(22)
Opioids	mu-opioid receptor	Decrease	(23, 24)
	delta-opioid receptor	Increase	
	kappa-opioid receptor	Increase	
Cocaine and Amphetamine-Regulated Transcript (CART)		Decrease	(25)
Galanin		Increase	(26)
Orexin		No effect	(27)

2 Methodology

The current systematic review was conducted based on PRISMA guidelines, which includes sections of introduction, study methodology, findings, discussion, and conclusion. The method of finding articles and sources was to use a targeted search of appropriate keywords in reliable electronic databases including Google Scholar, PubMed, Scopus, Science Direct, Web of Science, Elsevier, and Springer. The references of the selected papers were also reviewed to find more research. It should be noted that in the current review, the latest findings, studies conducted in 2022 and 2023, regarding the mediators' role in the feed consumption regulation of birds have been examined.

3 Findings

3.1 Adrenomedullin

Adrenomedullin is a peptide hormone that is involved in various biological actions, including blood pressure regulation, vascular tone, and inflammation (28). It is produced by a number of different body tissues such as the adrenal gland, heart, lungs, and kidneys (29). The adrenomedullin's mechanism of action is not fully understood, but it is thought to act via a variety of receptors, including the receptor activity-modifying proteins (RAMPs) and the calcitonin receptor-like receptor (CLR) (30). Several experiments have investigated the effects of adrenomedullin on feed consumption in animals, particularly mammals. According to a research, adrenomedullin has decreasing effects on food consumption and causes browning of fat tissue and reduction of obesity caused by insulin resistance and high-fat diet in mice (31, 32). The Zahed et al.'s research (2023) showed that this hypophagic effect of adrenomedullin following intracerebroventricular (ICV) administration is also observed in layers. The findings of this experiment indicated the mediatory role of NPY1 and CCK8s receptors in the occurrence of this effect (33).

3.2 Adiponectin

Adiponectin is a protein-based hormone secreted by adipose tissue and is involved in different physiological functions such as insulin sensitivity, lipid metabolism, energy balance, inflammation, and immune response (34). Adiponectin receptors, AdipoR1 and AdipoR2, mediate the antidiabetic metabolic functions of adiponectin and reduce obesity-related insulin resistance (35). It has been shown that the concentration of adiponectin has a negative correlation with cancer, cardiovascular diseases and diabetes, and it can be increased with proper and healthy nutrition (34). Adiponectin has been studied as a potential biomarker to diagnose and monitor the effectiveness of therapeutic and preventive interventions for these diseases (34). It can increase fatty acid oxidation and glucose consumption through activating AMP-activated protein kinase (AMPK), a key regulator of energy levels (34). Hypoadiponectinemia, resulting from the interaction of genetic and environmental factors that cause overweight, appears to play a remarkable role in insulin resistance, metabolic syndrome, and type 2 diabetes (35). Regarding the effects of this hormone on meal consumption in mammals, it has been determined that adiponectin stimulates AMPK activity in the ARC through the AdipoR1 receptor to enhance meal consumption (36). Recently, in Madadi et al.'s (2023) study on layers, the increasing effects of adiponectin on food intake following its administration were observed. It also seems that GABAA and NPY1 receptors were involved in this effect (37).

3.3 Arginine-phenylalanine-amide (RFamide)-related peptides

RFamide-related peptides are a family of neuropeptides that play an impressive role in organizing various biological functions of the body, including reproduction, stress responses, energy metabolism, and pain modulation (38). The distribution of RFRPs in the CNS varies depending on the animal model, but they are generally localized in the brain regions involved in reproductive and metabolic functions, and specifically in the hypothalamus (39). RFRPs have been studied in relation to metabolic disorders such as overweight and diabetes, and may represent a potential therapeutic target for these conditions (40). In vertebrates, five groups of RFamides have been identified, each of them has a distinct precursor protein: Gonadotropin-inhibitory hormone (GnIH) or Neuropeptide VF (NPVF), Neuropeptide FF (NPFF), Pyroglutamated RFamide peptide (QRFP), Prolactin-releasing peptide (PrRP), and Kisspeptin. The role of each of these peptides has been studied separately in mammals. The experiments of Moosadoost et al. (2022) and Hamidi et al. (2021) have shown the hypophagic effects of NPVF on meal consumption of chickens. Also, the mediating role of NMDA/ AMPA, CRF2, MC4, and μ opioid receptors in the occurrence of these effects has been proven (41, 42). Studies have also shown the reducing role of NPFF on the meal intake of chickens and its role in the occurrence of appetite-decreasing

effects of melanocortins (43). It has been observed that ICV administration of PrRP enhance chow down in chickens (44). Also, Kord et al. (2022) showed the increasing effects of Kisspeptin on the meal consumption of layers and the mediatory role of NPY1 and GABAA receptors in the occurrence of this effect (45).

3.4 Apelin-13

Apelin-13 is a neuropeptide that binds to the apelin receptor (APJ), a G protein-coupled receptor (GPCR) that is involved in the regulation of diverse biological functions such as hemodynamic response, heart failure, uterine contractility, and cardiomyocyte hypertrophy (46). Investigating the effects of apelin on the feeding regulation in mammals has brought conflicting results in terms of animal model, dose and period of administration. According to the findings of an experiment, apelin-13 appears to increase food intake in male rats, possibly through activation of leptin and ghrelin levels (47). In confirmation of previous findings, it was observed in another study that chronic (10 days) central injection of apelin-13 in mice stimulated meal consumption, locomotor activity, body weight, and temperature (48). Contrary to these studies, injection of apelin-13 has been shown to reduce rats' appetite (49). Also, subsequent experiments showed that this suppressing effect is probably mediated through the corticotropin-releasing factor (CRF) receptors in mice (50). Limited experiments have been done with the aim of investigating the role of this neuropeptide in regulating avian feed intake. According to the Aminizadeh et al.'s (2023) research, central administration of apelin-13 has been shown to reduce feeding in neonatal meat-type chickens (51). While confirming the suppressive role of apelin on appetite, the experiments of Safi Khani et al. (2023) showed the involvement of melanocortinergic and corticotropinergic receptors in the occurrence of this effect (52).

3.5 Lipopolysaccharide (LPS)

LPS is a large molecule that is found in the outer membrane of Gram-negative bacteria. It is recognized by the innate immune system through the Toll-like receptor 4 (TLR4) and myeloid differentiation factor 2 (MD-2) complex, and has been implicated in the feeding behavior and various disorders (53). LPS has been studied in relation to various diseases, including sepsis, inflammatory bowel disease, and Alzheimer's disease, and may represent a potential therapeutic target for these conditions (54). LPS is involved in the meal intake regulation in mammals, as it has been demonstrated to activate neurons of RFRPs, which control energy metabolism and stress responses (55). LPS also plays a role in inhibiting ghrelin-stimulated neurons in the brain and reduce feeding via central nitric oxide signaling in rats (56). On the other hand, LPS after peripheral injection seems to activate dorsal medullary and pontine structures, which reduces food intake in rats (57). Studies conducted on broilers have shown the hypophagic effects caused by LPS and the involvement of 5-HT2c, NMDA, and H1 receptors in it (4, 58). Subsequent findings showed that decreased gene expression of NPY and AgRP was responsible for LPS-induced hypophagia at a dose that did not affect body temperature (59). In another study, peripheral administration of LPS remarkably reduced meal consumption and increased interleukin-1β (IL1β) and interleukin-8 (IL8) mRNA expression in the brain (60). Recently, the research of Ghiasi et al. (2023) showed that the preference of chickens to various types of diets is affected by central or peripheral injection of LPS (61).

3.6 Neuromedins (NM)

Neuromedins are a family of neuropeptides that are involved in the different biological actions such as immune responses, feed intake, energy balance, stress responses, and inflammation (62). In the following, we introduce each member of this family and mention their role in regulating avian feed consumption:

Neuromedin U (NMU): This neuropeptide ubiquitously distributed, with highest levels found in the gastrointestinal (GI) tract and brain. Two GPCRs for NMU have recently been identified. NMU is involved in the smooth muscle contraction, ion transport in the gut, stress responses, cancer, cardiovascular function, gastric acid secretion, pronunciation, and appetite (63). It has been proven that the central injection of NMU reduces chow down in chickens and Japanese quails (64, 65). It has also been found that NMU-induced anorexia is probably mediated via D1/D2, GABAA, and 5-HT2c receptors in 5-day-old chickens (66).

Neuromedin S (NMS): a neuropeptide that is involved in the feed consumption regulation, energy metabolism, and stress responses. The ICV injection of NMS has caused anorexia in chickens under both ad libitum and food deprivation-induced feeding conditions. It also seems that D1/D2, and β2 receptors are involved in the NMS-induced hypophagia (67, 68).

Neuromedin B (NMB): NMB is one member of a family of bombesin-like peptides, which exerts a variety of biological actions through its receptor (NMBR). Decreasing effects on feed intake have been reported following central injection of NMB in laying chickens (69).

Neuromedin C (NMC): The fragment of gastrin-releasing peptide is called NMS. Central administration of this bombesin-like peptides reduces meal consumption in neonatal chickens (69).

Neuromedin K (NMK), Neuromedin L (NML), and Neuromedin N (NMN): According to the authors' review, there has been no study on the role of these neuromedins in birds' meal intake behavior.

3.7 Neuropeptide W (NPW)

NPW is a 23-amino acid peptide that was first isolated from the porcine brain in 2002 (70)**.** It has been shown to activate two GPCRs, NPW1R and NPW2R, which are widely expressed in the CNS and peripheral tissues (70). NPW has been studied in relation to various diseases, including obesity, diabetes, and anxiety disorders, and may be a potential therapeutic target for these conditions (70, 71). NPW has also been shown to play a role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is involved in the stress response (70). Several studies showed that NPBWR1 knockout mice are obese and hyperphagic (72). It also seems that central administration of NPW in mice causes hyperphagia and increased water drinking (73). In another test, administration of this compound into the lateral hypothalamus (LH) or paraventricular nucleus (PVN) led to enhance in meal consumption in rats (74). It should be noted that both the mentioned experiments were conducted in the light phase. In the dark phase, central injection of NPW resulted in attenuation of meal consumption and weight loss in Wistar rats (75). Mahdavi et al.'s (2023) experiments on broiler chickens showed that central injection of this neuropeptide significantly increases food consumption up to two hours after administration. Also, according to the findings, it seems that NPW-induced hyperphagia can be mediated via NPY1, CRF1, and CRF2 receptors (76).

3.8 Phoenixin-14 (PNX-14)

PNX-14 is a neuropeptide that is generated from the larger precursor protein pre-pro-apelin. It is a ligand for the GPR173 and has been isolated from central and peripheral tissues of zebrafish, rats, human, mice, and bovine. PNX-14 has been studied in relation to various physiological functions in the body, including feeding behavior, anxiety, microglial function, memory, inflammation, energy balance, cardiovascular function, and endocrine activity (77, 78). It was reported that ICV administration of PNX-14 during the light phase induced an increase in meal consumption of rats in a dose-dependent manner. In particular, an in-depth assessment of appetite showed that central administration of PNX-14 induced an increase in meal size, meal intake duration, and food intake rate, while the interval between meals and the satiety ratio decreased (79). However, when PNX-14 was ICV injected in dark or injected intraperitoneally under light, it did not affect feeding behavior (77). Until now, not many experiments have been done to investigate the role of PNX-14 on the birds' appetite. In a recent research conducted by Rajaee et al. (2022), the appetite-increasing effects of central administration of PNX-14 were observed in egg-type chickens. Also based on these observations, the possibility of the mediation of NPY1, NPY5, and CRF1/CRF2 receptors in the occurrence of this effect was raised (80).

3.9 Spexin (SPX) or Neuropeptide Q (NPQ)

SPX is a neuropeptide involved in organizing various body processes including food intake, energy metabolism and reproduction. It was first identified in 2007 as a novel neuropeptide that is highly conserved across vertebrates (81). SPX has been shown to activate the galanin receptor 2 (GALR2) and galanin receptor 3 (GALR3) in various tissues such as the brain, GI tract, and adipose tissue, and may represent a potential therapeutic target for metabolic disorders such as hyperglycemia and insulin resistance (82). The findings of a study demonstrated that acute peripheral injection of SPX inhibits meal consumption in rats. It appears that this hypophagic effect may be mediated via GALR3 and inhibition of NPY through p-CaMK2 and c-Fos in the brain (83). The results of another research show the role of SPX in the leptin's action on POMC gene expression in the hypothalamus which affects the hypophagic effects of leptin (84). Despite the limitations of experiments conducted on birds, Farzin et al.'s (2022, 2023) studies showed that SPX-induced anorexia could be mediated via nitric oxide (NO), 5-HT2C, NPY1, GalR3, CRF1, and CRF2 receptors in meat-type chickens (85, 86).

4 Future perspective

The studies conducted on the CNS have recently been associated with impressive developments, including the production of transgenic strains of laboratory animals that, in combination with previous genetic methods, allow the mapping, control and monitoring of the activity of neuronal populations or specific receptors using opto-genetic methods, chemo-genetics and neuronal imaging. Therefore, the study of the systems involved in the food consumption regulation using these new methods can bring interesting data. On the other hand, creating diversity in the species of laboratory animals, especially creating induction models of diseases such as diabetes and epilepsy can also help to better understand the effectiveness of these systems. Finally, it is suggested that along with the more precise identification of the systems and mediators involved in appetite regulation, the identification of the interactions of neurotransmitters with other nervous and peptide systems and the use of cellular-molecular methods can be considered in future studies.

5 Conclusion

Understanding the processes and factors involved in the meal intake regulation has been one of the hot research topics in recent decades. In this review study, we introduced and investigated the effects of the latest neural factors involved in the meal consumption regulation, which are mentioned in Table 2, and according to the finding presented, despite the lack of research on bird animal models, good progress has been made in this area. Finally, it seems that in addition to focusing on the identification of new factors and interactions between systems involved in feeding behavior regulation, the use of modern laboratory methods and diversity in laboratory models can bring beneficial results.

Table 2. Recently identified neural mediators involved in feeding regulation of birds, their effects and interactions

Neurotransmitter		Effect	Interactions	Reference
Adrenomedullin		Hypophagia	NPY1 and CCK8s receptors	(33)
Adiponectin		Hyperphagia	GABAA and NPY1 receptors	(37)
RFamide-related peptides	NPVF	Hypophagia	CRF2, MC4, NMDA/ AMPA, and μ opioid receptors	(41, 42)
	NPFF	Hypophagia	MC4 receptors	(43)
	PrRP	Hyperphagia	CRF and NPY receptor	(44)
	Kisspeptin	Hyperphagia	NPY1 and GABAA receptors	(45)
Apelin-13		Hypophagia	CRF1/CRF2 and MC3/MC4 receptors	(52)
Lipopolysaccharide		Hypophagia	5-HT2c, NMDA, and H1 receptors	(4, 58)
Neuromedins	NMU	Hypophagia	D1/D2, 5-HT2c, and GABAA receptors	(66)
	NMS	Hypophagia	D1/D2 and β2 receptors	(67, 68)
	NMB	Hypophagia	No Report	(69)
	NMC	Hypophagia	No Report	(69)
Neuropeptide W		Hyperphagia	CRF1, CRF2 and NPY1 receptors	(76)
Phoenixin-14		Hyperphagia	NPY1, NPY5, and CRF1/CRF2 receptors	(80)
Spexin		Hypophagia	NO, 5-HT2C, CRF1, CRF2, NPY1, and GalR3 receptors	(85, 86)

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.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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