International Journal of Peptide Research and Therapeutics (2021) 27:2349–2370
https://doi.org/10.1007/s10989-021-10257-1

The Crosstalk Between Brain Mediators Regulating Food Intake Behavior in Birds: A Review

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Accepted: 8 July 2021 / Published online: 22 July 2021

Abstract

Appetite is controlled by a complex system of central and peripheral signals interacting to modulate the ingestion response. Several brain mediators with complex networks adjust food intake in birds. Based on the available literature, these mediators have interactions with a number of other neurotransmitters (NT_S) involved in feed intake. It means that, NT_S regulate feeding behavior through mediating other peptide and NTs activity. In birds, insulin known as a hypophagic hormone that is interplaying with neuropeptide Y (NPY), pro-opiomelanocortin (POMC), and corticotropin-releasing factor (CRF) in brain. Another hormone ghrelin, inhibits food intake in birds and other mediators, such as glutamate, endocannabinoid system (ECS), serotonin (5-hydroxytryptamine, 5-HT), and norepinephrine (NE), which play a key role in ghrelin-induced hypophagia. Another involved peptide on feeding behavior in chickens called nociceptin/orphanin FQ (N/OFQ) is modulated by histamine, glutamate, dopamine (DA), gamma-aminobutyric acid (GABA), agouti-related protein (AgRP), and cocaine and amphetamine-regulated transcript (CART). Some of the NT_S such as opioid have both orexigenic and anorexigenic effects in birds while has interaction with NE, glutamate, histamine, DA, and cannabinoids (CBs). Thus, interaction among mediators is a prominent process needs to be considered in order to understanding the mechanisms underlying feed intake regulation in birds. This review aims to investigate the role of major regulators and their mediatory interactions with one another in poultry feeding behavior. According to mentioned interactions, it seems that dopamine, serotonin, and glutamate have the most interactions with other NT systems. Therefore, they play an axial role in the central regulation of food intake in CNS.

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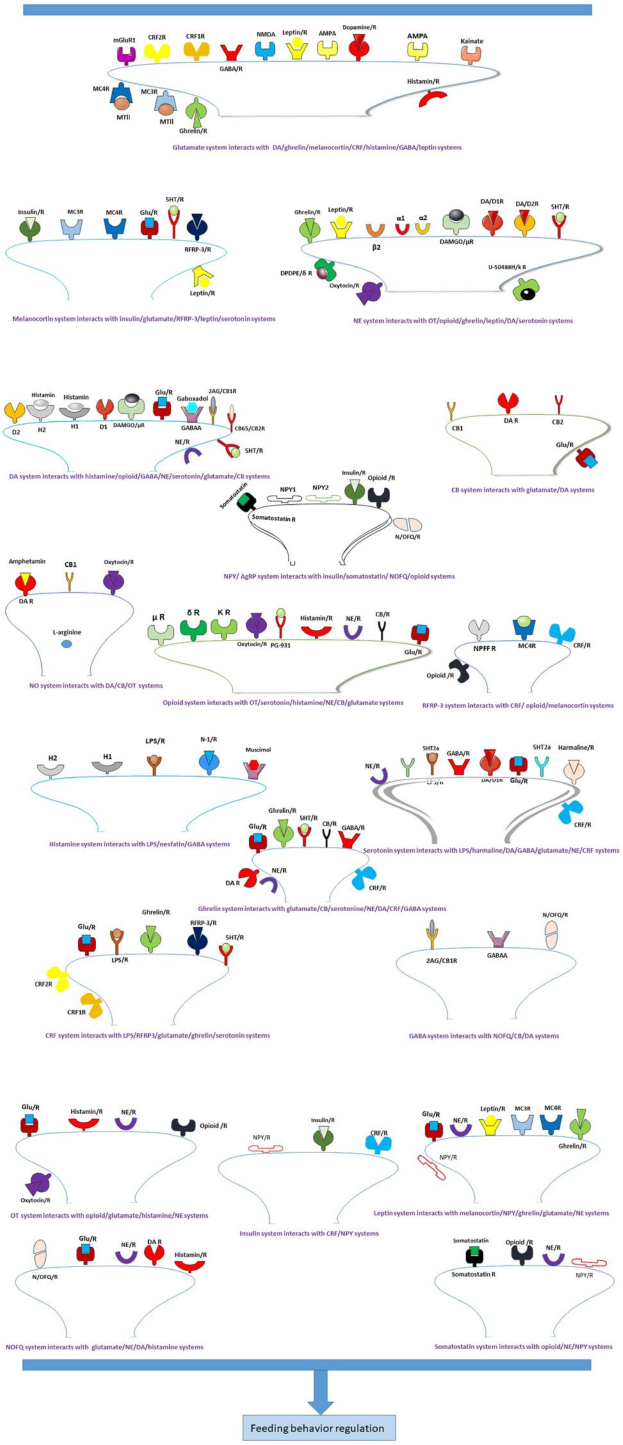
Graphic Abstract



Keywords Mediator · Interaction · Central feed intake regulation · Birds

Introduction

Appetite modulation is a complicated physiologic phenomenon that is made of various central and peripheral signal integration at the CNS. Different CNS compartments such as hypothalamus, nucleus accumbens (NAcc), amygdala, ventral tegmental area (VTA), and nucleus of the tractus solitaries have effect on appetite modulation (Barnes et al. 2006). In this view, the hypothalamic subregions the arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), and lateral hypothalamic area (LHA) have underpinning role in regulate food consumption (Fig. 1) (Wynne et al. 2005; Yousefvand and Hamidi 2021). Cerebral mechanisms by neural mediators control food intake in the hypothalamus (Zendehdel et al. 2014). It has been demonstrated that the mediators in the CNS, have different stimulatory, inhibitory, and modulatory roles in order to regulate various physiologic behaviors, such as perception, pleasure, excitement, memory, and learning.

It is worth mentioning that appetite is adjusted by a vast scattered network of neurons via different NT$_S$ (Alizadeh et al. 2015; Hassanpour et al. 2015). NT$_S$ are kinds of mediators secreted by neuronal terminals, influencing pre-/postsynaptically. Some of them, such as DA, 5-HT, and ghrelin, decrease food intake in birds, while N/OFQ, CBs, and GABA increase it (Denbow et al. 2000; Bungo et al. 2009; Zendehdel et al. 2014a, 2017c, 2020, 2013c, 2019, 2017a, 2008). Among the NT$_S$ involved with the food intake regulation, epinephrine, NE, DA, 5-HT, and histamine belong to the subgroup of biogenic amines; however, GABA and glutamate are amino acids, NPY and opioids are recognized as neuropeptides. Given the importance of food consumption in several physiological processes, such as growth, immunity, and production, realizing the NTS effect on ingestion behavior has been one of the interesting fields of study over the last decades. On this line, the interaction between NT$_S$ is a noticeable research field in which different investigations have revealed its significant effect on the modulation of food intake. For instance, the previous studies have shown that the hypophagic effect induced by the melanocortin receptors (MCRs) is modulated by the serotonin and glutamate in the chicken's brain (Khodadadi et al. 2017; Zendehdel et al. 2016; Shiraishi et al. 2008). In this aspect of view, the crosstalk between above-mentioned NT$_S$ and the other mediators such as leptin and insulin is a remarkable subject which is under evaluation. Considering the importance of interactions regulating feed intake, this review intends to study the role of mediators and the interactions between them in the central regulation of food intake in birds.

Study Methodology

In this review, various valid papers from electronic sources have been used in order to investigate the crosstalk between brain mediators regulating food intake behavior in birds. Authentic articles were indexed in the Web of Science, Scopus, PubMed, SID, Google scholar, and ISI databases by using of the key words: Central regulation of food intake, Brain neurotransmitters, Bird food intake, and Feeding behavior studied.

Biogenic Amines

Dopamine (DA)

DA is the primary catecholamine neurotransmitter in the central nervous system (CNS), controlling several physiological operations, such as emotion, locomotor activity, cognition, and food intake. DA is an important anorexigenic neurotransmitter regulating reward function through its projections from VTA into NAcc and ARC (Volkow et al. 2011). Nowadays, five different subtypes of DA receptors are recognized (D$_{1–5}$), appertain to G protein-coupled receptor subtypes (GPCRs). D$_1$, like receptor subtypes D$_1$ and D$_5$, connects to the stimulatory G protein (Gs) by adenylyl

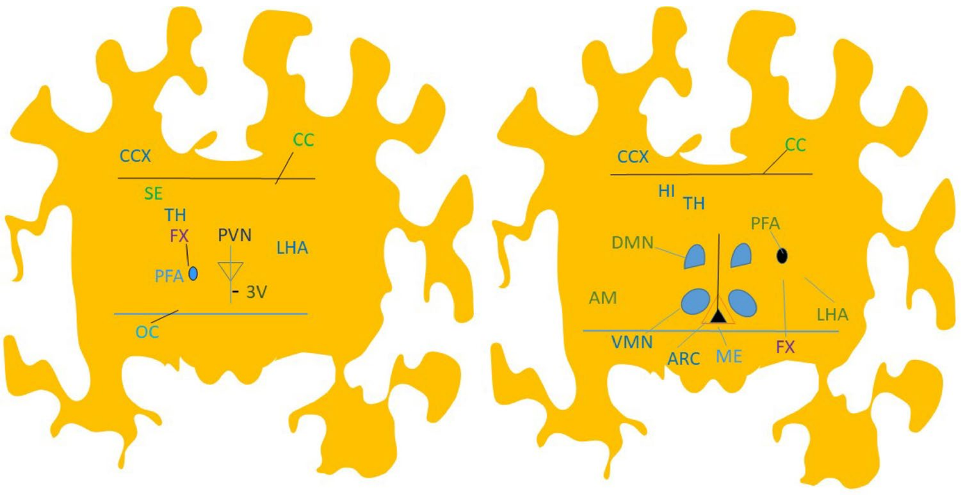


Fig. 1 Schematic figure containing the special nuclei which regulate appetite. AM amygdala, ARC arcuate nucleus, CCX cerebral cortex, DMN dorsomedial nucleus, FX fornix, CC corpus callosum, HI hippocampus, LHA lateral hypothalamic area, ME median eminence, PFA perifornical area, OC optic chiasm, PVN paraventricular nucleus, 3 V third ventricle, TH thalamus, VMN ventromedial nucleus, SE septum (Yu and Kim 2012)

cyclase pathway, whereas D_2, like subfamily D_2, D_3, and D_4, performs via inhibiting adenylyl cyclase and activating K channels (Ikemoto 2007). D_1 and D_2 receptors are ampler than the other DA receptors in the brain areas (Cadet et al. 2010). It has been revealed that DA decreases food intake via the D_1 receptor (Bungo et al. 2010; Zendehdel et al. 2014a). Also, it has been reported that D2 has a mediatory role in appetite regulation (Khodadadi et al. 2017). The mediatory function of D1 and D2 receptors in food desire, induced by other central systems, has been confirmed (Mahzouni et al. 2016). Previous studies have shown DA interaction with other brain mediators. In this regard, Taherian et al. (2016) have reported that DA-induced hypophagia is mediated via NMDA and $mGlu_1$ receptors in chicken. Also, Zendehdel et al. (2014a) have shown that DA performs its effect through the 5-HT receptor, $5\text{-}HT_{2c}$. Based on recent studies, yohimbine (α_2 receptor antagonist) and ICI 118,551 (β_2 adrenergic receptor antagonist) amplify and inhibit DA-induced hypophagia, respectively (Zanganeh et al. 2020). The anorexigenic effect of DA agonists is enhanced by the precursor of Nitric oxide (NO), showing a connection between them (Zendehdel et al. 2017a). Besides, there is a neurological interplay between μ and D_1 receptors in appetite regulation (Zendehdel et al. 2016). Pretreatment with the cannabinoid receptor agonist increases feed consumption mediated through the DA receptor antagonist (Khodadadi et al. 2017). Moreover, the interplay between GABA and DAergic systems in feeding behavior has been demonstrated. Accordingly, research on birds has shown that the $GABA_A$ receptor agonist-hyperphagic effect amplifies by D_1 receptor antagonization (Hashemzadeh et al. 2018). In addition, GhandForoushan et al. (2017) have indicated that H_1 and H_2 receptors antagonist respectively attenuates and amplifies the DA hypophagic effect on food intake. All above-mentioned results accentuate the interconnection between DA and the glutamate, 5-HT, NE, NO, opioid, CBs, GABA and histamine systems in regulation of food intake behavior in birds.

Serotonin (5-Hydroxytryptamine, 5-HT)

5-HT acts as a mediator in many processes in both the peripheral and central nervous systems and has various effects on food desire, general metabolism, and sleep (Caliendo et al. 2005). Based on our knowledge, 5-HT receptors can be categorized into seven subtypes ($5\text{-}HT_1$-$5\text{-}HT_7$), considering amino acid sequence, pharmacological property, signal transduction, and molecular cloning (Hoyer et al. 2002). Almost all 5-HT receptors, except for the $5\text{-}HT_3$ subtype as a ligand-gated ion channel, form a subset of G protein-coupled receptors (GPCRs) (Bikker et al. 1998). In CNS, 5-HT originates mainly from the midbrain raphe' nuclei (Ciranna 2006; Takahashi et al. 2010). Further, 5-HT is known to regulate mood, although 5-HT affects the central regulation of feeding behavior in mammals and avian species (Bechtholt et al. 2007; Fang et al. 2013). Reduction effect and mediatory contribution of 5-HT in food intake have been reported through different researches; 5-HT reduces food desire by connecting to POMC neurons (Zendehdel et al. 2012a). Also, an interplay has been observed between DA and 5-HT; hypophagic effect of D_1 was attenuated by $5\text{-}HT_{2C}$ antagonist (Zendehdel et al. 2014a). Besides, anorexigenic effect of this ligand is amplified by $GABA_A$ receptor antagonist and α_2 receptor antagonist whereas attenuated by NMDA, AMPA/Kainate receptor antagonist, and β_2 receptor antagonist (Zendehdel et al. 2017c; Mortezaei et al. 2013). Additionally, some receptors of 5-HT ($5\text{-}HT_{2a}$ and $5\text{-}HT_{2c}$) can decrease the anorexigenic effect of harmaline on food desire (Zendehdel et al. 2013b). The receptors of 5-HT ($5\text{-}HT_{2c}$) and glutamate (NMDA) diminished the hypophagic effect of lipopolysaccharides (LPS) regulated via CRF (Zendehdel et al. 2012b; Jonaidi et al. 2019).

Norepinephrine (NE)

Norepinephrine (NE), as a catecholamine, plays a significant role in response to the stressful stimuli in chicken. Based on the studies, catecholamines have a regulatory role by adjusting appetite in birds' production. Also, the regulatory activity of NE in the brain-gut-microbiome axis has been emphasized in chicken (Dennis et al. 2016). In overall, it has been well documented that this ligand intracranioventricularly changes food desire in birds similar to mammals (Denbow and Sheppard 1993). Although the ICV injection of this catecholamine increases food intake in chicken (Denbow 1983), the same treatment in turkey shows controversial results; interestingly, the same study in leghorn does not show any effect on appetite in this strain (Denbow et al. 1983). NE has also a mediatory role in food intake in relation with the other brain mediators. For example, the effect of ghrelin and leptin is adjusted by this ligand receptor. In this respect, the significant attenuating effect of β_2 antagonist on hypophagia induced by ghrelin and leptin has been detected in broiler chickens (Zendehdel and Hassanpour 2014a, b; Zendehdel et al. 2020). Moreover, as mentioned earlier, NE interacts with opioid, 5-HT, oxytocin (OT), and DA (Nayebzadeh et al. 2020; Zendehdel et al. 2017c; Mirnaghizadeh et al. 2017; Zanganeh et al. 2020).

Histamine

Histamine is a biogenic amine with a central function in the Nervous System. Its receptors include H_1, H_2, H_3, and H_4 (Masaki et al. 2005). The central histaminergic system is implicated in adjusting several physiological aspects, e.g., food consumption, thermos-regulation, and locomotor activity (Swiergiel et al. 1999). According to studies, histamine diminished food desire in birds and also it has regulatory effect in feeding (Zendehdel et al. 2008); the anorexigenic effect of LPS is lessened by the H_1 receptor of this amine (Zendehdel et al. 2015a). Further, the effect of nesfatin-1, an endogenous anorectic peptide, and GABA is attenuated by H_1 and H_3 receptors antagonist (Heidarzadeh et al. 2018; Morteza et al. 2013).

Amino Acids

Glutamate

One of the major stimulative NTs in the CNS, playing an important role in reward processes and hypothalamic centers, is glutamate (McFadden et al. 2014). According to pharmacological properties of the glutamate receptors, they can be divided into two categories, including the ionotropic and metabotropic receptors (mGluRs). Main glutamate receptors called N-methyl-D-aspartate (NMDA), Kainate, AMPA, and the metabotropic receptors (mGluRs) with different subtypes (Charles et al. 2014). Glutamate has hypophagic effect, as well as many interactions with other mediators, showing its significant role in food intake regulation in birds. Based on studies, feed intake in pigeon is affected by the injection of NMDA and AMPA-kainite receptor antagonists (Da Silva et al. 2003). It has been well documented that the receptor antagonist of NMDA increases food intake (Taati et al. 2011). In chickens, DA performs its effect via some receptors of glutamate (Taherian et al. 2016). Also, the glutamate hypophagic effect is mediated through melanocortin system, CRF, GABA, and histamine. As reported, receptor antagonist of MCR_S and CRF_S adjust the effect of glutamate on feed desire in a manner that the administration of the receptors $MC_{3,4}$ antagonists, similar to that of in $CRF_{1,2}$ receptors, attenuated the hypophagic effect of glutamate. These results suggested that the hypophagic effect of glutamate mediates via $CRF_{1,2}$ and $MC_{3,4}$ receptors in chickens (Ahmadi et al. 2019). Moreover, it has been shown that the effect of glutamate on feeding behavior is enhanced through the $GABA_A$ receptor antagonist (Zendehdel et al. 2009). Recently, an interplay between glutamate and receptors of histamine $H_{1,3}$ has been observed. Accordingly, in contrary to H_3 antagonist, H_1 antagonist can reduce the hypophagic influence of glutamate in layer chicken (Mobarhan et al. 2020). In addition, previous studies have demonstrated that the anorexigenic properties of ghrelin and leptin is modulated through the glutamic system (Taati et al. 2011; Adeli et al. 2020).

Gamma-Aminobutyric Acid (GABA)

GABA is an important neurotransmitter with many physiological roles such as respiration and appetite control, anti-convulsion, memory and sleep regulation beside the pain modulation (Chen et al. 2015). $GABA_A$, $GABA_B$, and $GABA_C$ are three receptors that the GABAergic system acts through (Stratford and Wirtshafter 2013). $GABA_A$ and $GABA_C$ belong to a macromolecular complex coupled to a Cl-ionophore, whereas $GABA_B$, a metabotropic receptor, is a member of G-protein-coupled receptors (GPCRs). Feeding behavior by proposed receptors is the subject of many studies. Based on previous studies, feeding is enhanced by $GABA_A$ and $GABA_B$ agonists (Zendehdel et al. 2017c; Bungo et al. 2003). However, $GABA_B$ agonist does not affect broiler food desire (Zendehdel and Hassanpour 2014a, b). In addition, GABA stimulates food intake in the turkey (Denbow 1991). It has been shown that $GABA_A$ has orexigenic effect on appetite in birds and this effect is adjusted by Nitrol-arginine methyl ester (L-NAME) and N/OFQ (Mokhtarpouriani et al. 2016a, b; Tajalli et al. 2006); orexigenic effect of $GABA_A$ decreased by CB_1 receptor antagonist and amplified by D_1 receptor antagonist (Hashemzadeh et al. 2018; Zendehdel et al. 2017c).

Glycine

Glycine is an inhibitory neuronal mediator in the CNS where several functions are accomplished by this ligand such as synaptic transmission (Colin et al. 1998; Scain et al. 2010), important role in motor control (Rees et al. 2003), pain perception (Harvey et al. 2004), and food intake (Rahimi et al. 2021; Reidelberger et al. 2011; Sorrels and Bostock 1992). Research on chicken has revealed that glycine decreases food intake and this effect is amplified by DA. Also, recently, it has been reported that this interaction is exerted through D_1 receptors (Rahimi et al. 2021).

Peptides

In the bellow chapters, the effects of well-known peptides and their interactions with different NTs systems on regulation of feeding behavior will be described. According to the fact that these peptides may have anorexigenic and/or orexigenic effects in avian and other species, the following classification is considered in which the peptides with hypophagic, hyperphagic, and both hypo- and hyperphagic properties have been categorized in anorexigenic, orexigenic, and orexigenic/anorexigenic subtypes respectively.

Anorexigenic Peptides

Corticotropin-Releasing Factor (CRF)

CRF is a 41 amino acid neurotransmitter which acts on the anterior pituitary to stimulate the secretion of corticotropin and regulates the synthetic/secretory activity of the adrenal cortex (Vale et al. 1981). This peptide in the central nervous system and in the periphery, has various actions such as regulating anxiety, mood, feeding, inflammation, gastric emptying, and blood pressure (Dautzenberg and Hauger 2002). Regarding its effect on feeding, feed intake in mammals and chickens is affected and decreased by ICV injection of CRF (Contarino and Gold 2002; Furuse et al. 1997; Denbow et al. 1999; Zhang et al. 2001). From the interactional perspective, it has been documented that CRF has interplay with LPS, ghrelin, RFamide-related peptide-3 (RFRP-3), and glutamate and adjusts their effects on feeding in chicken. As a result of these interactions, anorexigenic effect of LPS, ghrelin, RFRP-3, and glutamate is attenuated by central injection of CRF receptors antagonist. Moreover, as mentioned earlier, there is an interplay between 5-HT (5-HT2c) and CRF (Kooshki et al. 2019; Saito et al. 2005; Moosadoost et al. 2020; Ahmadi et al. 2019).

Melanocortins

The melanocortins include adrenocorticotropic hormone (ACTH), and α-, β-, and γ-melanocyte-stimulating hormones (α-, β-, γ-MSHs) which are derived from the cleavage of the precursor POMC (Wang et. al. 2019). ACTH is an important component of the hypothalamic–pituitary–adrenal axis and is often produced in response to biological stress. It has shown that this peptide changes food intake and can induce anorexia in animals (Stevenson et al. 1970; Van Putten et al. 1953; Schulz et al. 2010; Deviche and Delius 1981). α-MSH performs a similar role to ACTH in feeding behavior and energy homeostasis (Kawakami et al. 2000; Zendehdel et al. 2012a); in avian, α-MSH has five subtypes of MCR expressed throughout the body which are a family of G protein-coupled receptors (Dores et al. 2013). In this relevant, MCR subtypes 3 and 4 ($MC_{3,4}$) are presented more abundant in the brain (Shojaei et. al. 2020) and perform a hypophagic effect in chicken (Zendehdel et al. 2012a). In terms of the studying the role of brain mediators interaction in poultry food intake behavior, several lines of studies have revealed the interplay between melanocortin receptors and various mediators such as 5-HT, glutamate, insulin, leptin, RFRP-3, and Neuropeptide FF (NPFF). In this view, there is a neurological interaction between serotoninergic and melanocortin systems, affecting the feeding behavior. It is further reported that the 5-HT anorexigenic effect is mediated by receptors of melanocortin (Zendehdel et al. 2012a). Moreover, the hypophagic effect of glutamate is decreased through $MC_{3,4}$ receptors antagonist (Ahmadi et al. 2019; Shiraishi et al. 2008). Besides, it has been depicted that, central injection of insulin in chicks significantly increased expression of POMC mRNA which leads to diminish food intake (Shiraishi et al. 2008). Also, previous research on broiler chickens has demonstrated that the expression of hypothalamic gene of MCR subtypes 4 and 5 was significantly reduced by the infusion of leptin (Dridi et al. 2005). This, in turn, postulated that the crosstalk between melanocortin system and leptin can regulate food intake in birds through inducing hypophagia. In addition, it has been proved that the anorexic neuropeptide RFRP-3, which belongs to arginine-phenylalanine-amide (RFamide) peptide family, decreases food intake in chicken, and its effect is mediated via MC_4 and CRF_2 receptors. Also, authors have suggested a modulatory role for receptors of the Neuropeptide FF (NPFF), a member of RFamide family, in food intake induced by RFRP-3 in chickens brain (Moosadoost et al. 2019, 2020).

Oxytocin (OT)

OT is synthesized in supraoptic and PVN nuclei, as well as hypothalamic magnocellular accessory neurons (Adan et al. 1995). Receptors of OT are located in the PVN and VMH nucleus, the stria terminals, and the dorsal part of the supraoptic nucleus (Adan et al. 1995). The OT injection declines food desire in mammals and birds (Jonaidi et al. 2003; Arletti et al. 1990). Further, OT performs its effect through receptors of opioid (μ and κ opioidergic receptors) and glutamate (NMDA and AMPA receptors) (Jalali et al. 2019; Raji-Dahmardeh et al. 2019). Finally, its effect on food consumption is adjusted via receptors of histamine (H_1 and H_3 receptors) and NE (β_2 receptors) in birds (Mirnaghizadeh et al. 2017).

Leptin

Leptin, known as an obesity gene product, is a small (16 kDa) peptide hormone secreted from adipose tissue. Its central injection reduces food intake and enhances energy expenditure. In CNS, leptin has a significant role in food desire (Valassi et al. 2008). Chicken's leptin cDNA (CLEP) (Genebank AF 012727, AF082500) is cloned and sequenced in birds. Sequencing the leptin gene in chicken has confirmed 145 amino acids instead of 146 in mammals. It is noted that leptin is in chicken even before its sequencing in this species (Ashwell et al. 1999). Farkašová et al. (2016) confirm the presence of the LEP gene in birds after long-term debates on the absence (Lovell et al., 2015) or the presence of CLEP sequence in the chicken genome. Similar to mammals, the leptin reduction effect on feed intake in avian is reported (Denbow et al. 2000). As mentioned above, previous research on feeding regulation demonstrated the crosstalk between leptin and the melanocortin system. In this view, under stimulation of leptin, hypothalamic gene expression of MC4/MC5 has significantly become downregulated (Dridi et al. 2005). Remarkably, the recombinant chicken leptin has also decreased the gene expression of the orexigenic neuroprptides NPY, orexin and orexin receptor in broiler chicken hypothalamus (Dridi et al. 2005). This latter demonstrates the leptin interaction with NPY and orexin system. Interestingly, leptin and ghrelin in a wild bird decrease hoarding behavior (Henderson et al. 2018). In addition, it has been well documented that the anorexigenic effect of leptin is attenuated by β_2-selective adrenoceptor antagonist displaying the interaction between leptin and NE system (Zendehdel et al. 2020). Furthermore, in terms of the interplay between leptin and other brain mediator systems, recently the receptors of glutamate (NMDA and AMPA) have been shown to modulate the effect of leptin (Adeli et al. 2020).

Insulin

Insulin is a hormone secreted from Beta cells of the pancreas that controls blood sugar. In the brain, it affects the central regulation of food desire and energy consumption (Plum et al. 2005). A number of studies have shown the effect of insulin on appetite adjustment. In general, insulin mainly has anorexigenic properties through having interaction with different peptides with orexigenic or anorexigenic effects. In this view, it is stated that mRNA levels of POMC, CART, and CRF are upregulated by insulin. To have more explanation, it has been reported that α-MSH known as an anorexigenic peptide, forms from the post-translational cleavage of POMC at the hypothalamus, CART and CRF have hypophagic effect on ingestion behavior in birds (Honda et al. 2007). Interestingly, it has been demonstrated that the antagonization of melanocortin receptors can prohibit the hopophagia induced by insulin in chicks (Shiraishi et al. 2008). Therefore, as in mammals, the central melanocortin system mediates insulin-induced hypophagia in birds (Fig. 2). In another aspect, the central injection of this hormone, namely insulin, in chicks decreases NPY mRNA (Shiraishi et al. 2008). Also, its ICV injection affecting food intake is mediated via the interaction with the receptors of NPY (Yousefvand et al. 2018, 2019). NPY_1 receptor antagonist potentiates decreasing effect of insulin on food consumption; while, this decreasing effect of insulin is prevented by antagonizing NPY_2 receptor (Yousefvand et al. 2020).

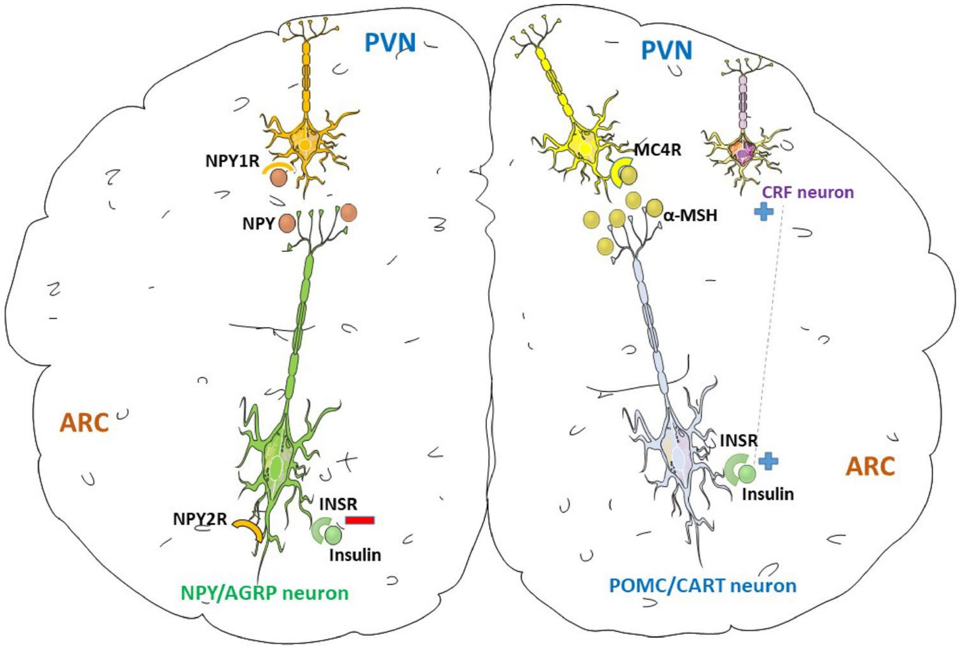


Fig. 2 The POMC and NPY neurons situated in ARC nucleus as well as receptors of insulin found on these neurons. Also, CRF, receptors of POMC ($MC_{3,4}$) and NPY_1 are located on the PVN. The ICV administration of insulin stimulated neurons of CART and POMC along with suppressing NPY neurons. Consequently, increased level of α-MSH resulted from POMC neurons stimulated the melanocortin receptors and resulted hypophagia. In another aspect, insulin-induced decreased level of NPY in synaptic space caused reduction activity of NPY_1 receptor. Besides, there is an interaction between insulin and CRF neuron in PVN. Consequently, anorexigenic output is exported by PVN, and caused a hypophagic effect on food consumption in bird under effect of insulin and mentioned interactions (Honda et al. 2007; Shiraishi et al. 2008; Yousefvand et al. 2018 and 2019)

Orexigenic Peptides

Agouti-Related Peptide (AgRP)

AgRP is a peptide which is made up of 112 amino acids and synthesized in the ARC, projects to other key hypothalamic nuclei and sites involved in feeding (Bagnol et al. 1999; Haskell-Luevano et al. 1999; Lu et al. 1994). AgRP potentiates food intake behavior and this orexigenic effect of AgRP has documented in birds and mice (Boswell and Dunn 2017; Takahashi and Cone 2005). Functionally, AgRP binds to the melanocortin receptors $MC_{3,4}$ and therefore is considered as a member of central melanocortin system (Boswell and Dunn 2017). Research on mammals has revealed that AgRP exerts its effect through agonizing Gi protein- coupled MC_4 which results in inversing the effect of Gs protein- coupled MC4 agonists (i.e., α-MSH); subsequently, decreasing the levels of cAMP and the synthesis of CRF and Thyroid releasing hormone (TRH) in hypothalamus (Baldini and Phelan 2019; Sarkar et al. 2002). This inverse agonistic effect of AgRP leads to increase in food intake behavior (Baldini and Phelan 2019). The biased agonism of AgRP is also reported toward MC_3 (Yang and Tao 2017). Beside of the decreasing effect of CRF on feeding, which was mentioned before, the similar effect is also produced by subcutaneous and ICV administration of TRH in rodents (Choi et al. 2002; Vijayan and McCann 1977). It has been proposed that this effect is independent of hypothalamus-pituitary-thyroid, HPT, axis and is exerted via central mechanisms (Yoo et al. 2021). In this respect, TRH increases the histamine turnover in tuberomammillary, PVN, VMH nuclei, and activates GABAergic neurons in lateral hypothalamic area resulting melanin-concentrating hormone, an orexigenic peptide, expressing neurons suppression (Zhang et al. 2012; Gotoh et al. 2007). Interestingly, in another aspects of view, it has been shown that AgRP neurons in ARC can be excited by glutamatergic projections originated from TRH expressing neurons in PVN introducing TRH orexigenic effects (Krashes et al. 2014). Reciprocally, NPY/AgRP neurons along with POMC neurons in ARC develop synaptic inputs to PVN TRH neurons (Yoo et al. 2021). Since the most of TRH neurons in PVN express MC_4, and in consideration of the agonistic effect of α-MSH on Gs protein- coupled MC_4 along with agonistic effect of AgRP on Gi protein- coupled MC_4, the regulatory role of central melanocortin system consists of AgRP and α-MSH through MC_4 on TRH neurons is plausible. These mechanisms remain to be determined in the future studies on birds.

Moreover, there is interaction between AgRP and other mediators which have key role in food intake such as opioids and N/OFQ. For instance, the concentration of AgRP mRNA in the diencephalon increased after central injection of N/OFQ (Hagan et al. 2001; Bungo et al. 2009).

Neuropeptide Y (NPY)

NPY is one of the amplest peptides in the nervous system affecting food intake. Structurally, it consists of 36 amino acids with a single different residue between avian and mammalian amino acid sequences. NPY gene regulates food consumption and reproductive activity (Fraley and Kuenzel 1993). NPY is the most potent orexigenic peptide functioning through NPY_1 and NPY_2 receptors. The ARC is well presented as the major center for controlling appetite at the hypothalamus in mammalian. Further, it is shown to be almost permeable to NPY and able to receive peripheral inputs from lateral ventricle fluid. It has been indicated that the first-order orexigenic neurons located in the Arc are responsible for NPY secretion. NPY has been reported to have the orexigenic effect in broiler and Leghorn (Denbow et al. 1988; Cline and Furuse 2013). It increases food intake in chicken, while the injection of anti-chicken NPY antibody reduces it in early hatched chickens (Chen et al. 2016). Research on rodents has unraveled that the stimulation of the NPY receptor subtype 1 potentiates feeding activity; in contrary, agonizing the NPY_2 receptor presents hypophagic behavior. For sake of clarity, NPY_2 receptor exerts its action as an autoreceptor resulting the inhibition of NPY biosynthesis and release (Ortiz et al. 2007). Likewise, the extracted data of further studies on chickens are in agreement with mentioned results (Yousefvand et al. 2019). The mediatory role of NPY and related receptors in adjusting food desire in birds has been documented. NPY has interaction with insulin so that the hypophagic effect of insulin are regulated by the receptors of NPY, NPY_1 and NPY_2 (Yousefvand et al. 2018, 2019). In another aspect, insulin can reduce the mRNA expression of NPY highlighting the interplay between NPY system and insulin (Shiraishi et al. 2008). Moreover, research work on chickens has shown that somatostatin has orexigenic properties. Interestingly, on this line, somatostatin has interaction with the receptor NPY_1 (Yousefvand et al. 2018).

Nociceptin/Orphanin FQ (N/OFQ)

N/OFQ is an endogenous ligand for the opioid-like $GPCR_1$ or nociceptin receptor (NOP) (Alt et al. 2012). As reported in earlier researches, food desire is increased under effect of N/OFQ (Zendehdel et al. 2013a; Abbasnejad et al. 2005). This ligand involves GABA-induced hyperphagia through receptors of GABAA in birds (Tajalli et al. 2006). 5-HT amplifies the influence of this neuropeptide in chicken by receptors of $5HT_{2C}$ (Zendehdel et al. 2013a). Also, based on findings, the orexigenic effect of N/OFQ is mediated through CART, AgRP, glutamate, NE, DA, and histamine in chicken. It is stated that this ligand increases the concentration of AgRP mRNA while declines CART mRNA. α-MSH blocks this neuropeptide effect, indicating that the AgRP and the CART neurons may mediate such a hyperphagic effect, as in mammals (Bungo et al. 2009). The receptor of NE (β_2) and glutamate (NMDA and AMPA) can increase the hyperphagic effect of N/OFQ (Zendehdel et al. 2017b; Abolghasempour et al. 2019); the N/OFQ effect is enhanced by receptors of DA (D1 and D2) and histamine (H_1), but it is attenuated by H_3 (Zendehdel et al. 2019, 2015b).

Somatostatin

Another peptide which consists of 14 amino acids and was isolated from the ovine hypothalamus in 1973 for the first time, is somatostatin (Stengel et al. 2015). It acts as an inhibitory neurotransmitter, distributed in the brain especially in the ARC and the PVN nuclei (Stengel et al. 2015), plays an important role in stimulating food intake in animal (Schneeberger et al. 2014; Stengel et al. 2010b, 2010a; Karasawa et al. 2014). It has shown that this peptide has interplay with other madiators. For instance, somatostatin, in chickens through opioidergic-μ and adrenergic α-$_2$-receptors, stimulates food intake (Tachibana et al. 2009). Also, the somatostatin- induced hyperphagia is significantly declined by NPY_1 antagonist in chicken (Yousefvand et al. 2019).

Anorexigenic/Orexigenic Peptides

Ghrelin

As an endogenous ligand for growth hormone (GH), ghrelin was isolated from rat and human's stomach about 15 years ago. It, as one of the most important appetite-regulating peptides, has shown a stimulatory effect on food intake and GH release in the brain. Gene expression of ghrelin and its receptor GHS-R1a in the hypothalamus, liver, and abdominal fat of chicken's body has been measured recently. Although ghrelin is a stimulant factor for the secretion of human and avian GH in the brain, it prevents food intake in avian (Kaiya et al. 2011). In addition, it is confirmed that ghrelin has a reduction effect in avian (Taati et al. 2011; Zendehdel et al. 2013c). According to previous research, ghrelin-induced hypophagia is mediated via glutamate, CBs, 5-HT, NE, DA, CRF, and GABA. When it comes to the mediatory role of glutamate, NMDA receptor antagonist enhances the anorexigenic effect of ghrelin (Taati et al. 2011). Concerning the ghrelin interaction with CBs, the receptor antagonist of CBs can modulate its anorexigenic effect (Taherian et al. 2019). In mediation with 5-HT receptors, it has been demonstrated that the $5\text{-}HT_{2C}$ receptor antagonist attenuates the effect of ghrelin (Zendehdel et al. 2013c). Besides, ghrelin performs its effect by interacting with the receptor of NE, namely β_2 (Zendehdel and Hassanpour 2014a, b). Based on recent studies, cannabinoid receptor antagonists enhance the influence of ghrelin on appetite, and its impact is mediated by the DA receptor (Farrokhi et al. 2020). Ghrelin may diminish food desire in chicks by declining GABA synthesis due to its reduction effect on glutamate decarboxylase 2 (GAD2) gene expression (Jonaidi et al. 2012). Also, the effect of ghrelin is modulated via CRF, which has anorexic effect (Saito et al. 2005). In this regard, it has been concluded that the ICV administration of ghrelin in chickens accentuates the release of CRF; subsequently, HPA axis and corticosterone release (Saito et al. 2005). This illustrated the interplay between the anorexigenic peptides ghrelin and CRF in birds.

Opioids

Opioids form a well-known subgroup of inhibitory NTs. Its receptors consist of μ, δ, and k, being homologous to GPCRs (Fichna et al. 2007; Erbs et al. 2015). There is a plethora of endogenous opioid peptides in CNS, playing a key role in controlling respiration, pain mechanism, and the immune system (Le Merrer et al. 2009; Bodnar and Klein 2006). According to studies, the endogenous opioidergic system contributes to food intake regulation in birds. For example, the ICV injections of DAMGO (μ-opioid receptors agonist) reduce appetite, whereas DPDPE (δ-opioid receptors agonist) and U-50488H (κ-opioid receptor agonist) boost feeding behavior in chicks (Bungo et al. 2004, 2005). The μ receptor of opioid declines food consumption in chicken; however, other receptors enhance food desire (Zendehdel et al. 2016). There are some interactions between opioids and other brain mediators such as 5-HT (Shojaei et al. 2015), histamine (Jaefari et al. 2018), NE (Nayebzadeh et al. 2020), CBs (Zendehdel et al. 2015c), glutamate (Torkzaban et al. 2018), nitric oxide (NO) (Alimohammadi et al. 2015), and OT (Raji-Dahmardeh); given this, the reduction effect of DAMGO (μ-opioid receptor agonist) is amplified by CB_1 and CB_2 receptors antagonist, H_3 receptor antagonist, and L-arginine (the precursor of NO) whereas that is diminished by NMDA and mGlu1 receptors antagonist, OT antagonist, β_2 receptor antagonist, H_1 receptors antagonist, and $5\text{-}HT_{2c}$ receptor antagonist. Also, DPDPE (δ-opioid receptors agonist) induced hyperphagia is decreased by α_1 receptor antagonist, while that is increased by AMPA glutamate receptors antagonist. In addition, orexigenic effect of U-50488H (κ-opioid receptor agonist) is attenuated by α_2 receptor antagonist and has no interaction with the other drugs mentioned above (Raji-Dahmardeh et al. 2019).

RFamide Peptides

RFamide-related peptide-1 (RFRP-1) and RFamide-related peptide-3 (RFRP-3) belong to the arginine-phenylalanine-amide (RF amide) family and 5 peptide groups of this family such as Neuropeptide FF, (PQRFa) PrRP, LPXRFamides

(RFRPs), Kisspeptin and QFRP (26RFa) have been recognized yet, playing a crucial role in food intake, puberty, and reproduction activity (Tsutsui et al. 2010). These peptides have hyperphagic and hypophagic effects in animals; it has been reported that an increasing trend in food intake occurs in mice after administration of 26RFamide (Chartrel et al. 2003) whereas NPFF and PRrP decrease feeding (Murase et al. 1996; Lawrence et al. 2000). Also, RFRP-3 increases food intake in mammals (Johnson et al. 2007; Murakami et al. 2008; Dockray 2004), but has hypophagic effect in chicken (Moosadoost et al. 2020). Some interactions between this family members and other mediators have been shown. For example, NPFF has crosstalk with DAMGO (μ-opioid receptor agonist), which regulates anorexigenic effect of this ligand in rats (Murase et al.1996; Nicklous and Simansky 2003). Also, in chicken, RFRP-3 induced hypophagia is mediated via corticotropin (CRF_2) and melanocortin receptors (MC_4) (Moosadoost et al. 2020).

Cocaine and Amphetamine-Regulated Transcript (CART)

CART is a neuropeptide distributed in the central nervous system including hypothalamus nuclei, PVN and ARC (Douglass and Daoud 1996; Gautvik et al. 1996; Couceyro et al. 1997). Previous studies documented that CART not only plays a significant role in feeding, but also it has different effects on it; ICV administration of CART reduces appetite (Kristensen et al. 1998; Larsen et al. 2000) while its administration directly into the PVN increases food intake (Smith et al. 2008; Yousefvand and Hamidi 2020). Also, in chickens, ICV injection of CART peptide is reported to inhibit food intake (Tachibana et al. 2003; Honda et al. 2007; Cai et al. 2015). Studies have also reported that this peptide has a mediatory role in food intake (Kristensen et al. 1998; Lambert et al. 1998; Vrang et al. 1999); in chicken, CART interacts with NPY in the central nervous system which leads to regulate feeding through the attenuation of NPY hyperphagic effects (Tachibana et al. 2003). Also, increasing CART/TRH through injection of CCK and leptin decreases food intake (Akieda-Asai et al. 2014).

Endocannabinoid System (ECS)

Marijuana (9-tetrahydrocannabinol, THC) or psychoactive ingredients of the Cannabis sativa plant is called CBs (Novoseletsky et al. 2011). It has been confirmed that glucose homeostasis, eating behaviors, lipogenesis, and energy balance all are controlled by the ECS in humans, rodents, and poultry (KEYSHAMS et al. 2016; Alizadeh et al. 2015). Two cannabinoid receptor proteins, i.e., CB_1 and CB_2, belong to the G-protein-coupled family of receptors. Generally, in mammals and birds, CB_1 receptors are situated in presynaptic terminals of the inhibitory and excitatory nerves in the CNS (Sharkey et al. 2014a, b; Novoseletsky et al. 2011). In contrast, CB_2 receptors are mainly related to the immune cell function located in the brain (Sharkey et al. 2014a, b). Risen food intake via the CB_2 receptor has been reported in layer-type chickens (Alizadeh et al. 2015). In addition, both mentioned receptors have shown increased food intake in mammals and layer-type chickens (Alizadeh et al. 2015; Pertwee 2005). In broilers, CB_1 has shown a different trend since its injection has no effect, while CB_2 remains increasing as in previous cases (Emadi et al. 2011). The CBs interact with glutamate and DA in chicken; CB_1 agonist- induced hyperphagia is increased by NMDA antagonist whereas is decreased by D_2 antagonist. Also, orexigenic effect of CB_2 is amplified through the antagonization of D_2 and AMPA/kainate receptors (Keyshams et al. 2016; Khodadadi et al. 2017).

Nitric Oxide (NO)

NO which has important physiological functions in the CNS, is produced from L-arginine by NO synthase (NOS). It has been reported that the central inhibition and stimulation of NO synthesis change feeding behavior in both meat- and layer-type chicken in different manners (Zendehdel et al 2015a, 2015b, 2015c; Khan et al. 2007; Choi et al. 1994; Clonidine Choi et al. 1995). In comparison with layers, the broiler chicks have genetically higher food consumption and energy expenditure in which the decremental alteration in feeding behavior has been observed through ICV injection of L-NNA but not L-NAME, the inhibitors of NO synthesis (Khan et al. 2007; Choi, et al. 1994). This effect was attenuated by the precursor of NO, namely L-arginine (Choi et al. 1994). Interestingly, ICV administration of L-NAME in layer chicks, has induced hyperphagia in dose dependent fashion. On this line, the hypophagic properties of L-arginine have been detected in layers (Alimohammadi et al. 2015). These controversial results extracted from different avian species can be ascribed to the effect of genetic diversity on the responsiveness of feeding regulatory pathways (Denbow, 1994). In this way, the precise mechanisms need to be elucidated in the future studies.

The interaction of NO with several brain mediators and neuronal pathways have been discussed in different literatures. Choi et al., have been shown that increased appetite induced by α_2-receptor agonist, has been weakened by inhibition of NO synthesis in neonatal broiler chicks (Choi et al. 1995). In addition, an interplay between NO and cannabinoidergic systems has been accompanied by an increasing effect of L-NAME on CB_1 agonist- induced hyperphagia in layer-type chickens (Hassanpour et al. 2015). Also, during several studies on layers, hypophagia- induced by OT, amphetamine

Table 1 Various studies conducted on interactions between brain mediators in central regulation of food intake in birds

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Zendehdel et al. (2017c)	Layer chicken	Amphetamine (Indirect DA agonist	Hypophagia	ICV	L-NAME (NG-nitro-L-arginine methyl ester)	Decreasing effect
Choi et al. (1995)	Broiler chickens	Clonidine (α_2-receptor agonist)	Hyperphagia	ICV	L-NNA (NO synthesis inhibitor)	Decreasing effect
Zendehdel et al. (2020)	Broiler chickens	Leptin	Hypophagia	ICV	ICI118, 551 (Selective β_2 adrenergic receptor antagonist)	Decreasing effect
Ahmadi et al (2019)	Broiler chickens	Glutamate	Hypophagia	ICV	astressin-B (CRF_1/CRF_2 receptors antagonist) SHU9119 ($MC_{3,4}$ receptor antagonist)	Decreasing effect
Shojaei et al. (2015)	Layer chicken	DAMGO (μ-opioid receptor agonist)	Hypophagia	ICV	SB2420 ($5HT_{2C}$ Selective antagonist)	Decreasing effect
Abolghasempour et al (2019)	Broiler chickens	N/OFQ	Hyperphagia	ICV	MK-801 (NMDA receptor antagonist) CNQX (AMPA receptor Antagonist)	Increasing effect
Adeli et al. (2020)	Broiler chickens	Leptin	Hypophagia	ICV	MK-801 (NMDA receptor antagonist) CNQX (AMPA receptor Antagonist)	Decreasing effect
Ahmadi et al. (2019)	Broiler chickens	MTII ($MC_{3,4}$ receptors agonist)	Hypophagia	ICV	MK-801 (NMDA receptor antagonist)	Decreasing effect
Alimohammadi et al. (2015)	Layer chicken	DAMGO (μ-opioid receptor agonist)	Hypophagia	ICV	L-arginine	Increasing effect
Zanganeh et al. (2020)	Layer chicken	NA	Hypophagia	ICV	AMI-193 (D_2 dopaminergic receptor antagonist) SCH23390 (D_1 dopaminergic receptor antagonist)	Decreasing effect
Taati et al (2011)	Broiler chickens	Ghrelin	Hypophagia	ICV	DL-AP5 (NMDA receptor antagonist)	Decreasing effect
Zendehdel et al. (2016)	Layer chicken	DAMGO (μ-opioid receptor agonist)	Hypophagia	ICV	SCH23390 (D_1 dopaminergic receptor antagonist)	Decreasing effect
Taherian et al. (2016)	Broiler chickens	DA	Hypophagia	ICV	MK-801 (NMDA glutamate receptors antagonist) AIDA (mGLUR1 glutamate receptors antagonist)	Decreasing/Increasing effect

Table 1 (continued)

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Hashemzadeh et al. (2018)	Layer chicken	Gaboxadol (GABAA receptor agonist)	Hyperphagia	ICV	SCH23390 (D_1 dopaminergic receptor antagonist)	Increasing effect
Zendehdel et al. (2014)	Broiler chickens	DA	Hypophagia	ICV	SB242084 ($5HT_{2C}$ Selective antagonist)	Decreasing effect
Zendehdel et al. (2019)	Broiler chickens	N/OFQ	Hyperphagia	ICV	SCH23390 (D_1 receptors antagonist) AMI-193 (D_2 receptors antagonist)	Increasing effect
Zendehdel et al. (2017a, b, c)	Layer chicken	2-AG (selective CB_1 receptors Agonist)	Hyperphagia	ICV	picrotoxin ($GABA_A$ antagonist)	Decreasing effect
Hassanpour et al. (2015)	Layer chicken	2-AG) (a CB_1 receptor Agonist)	Hyperphagia	ICV	L-NAME (a nitric oxide synthesis inhibitor)	Increasing effect
Heidarzadeh et al. (2018)	Broiler chicken	nesfatin-1	Hypophagia	ICV	Astressin-B (CRF_1/ CRF_2 receptors antagonist) α-FMH (inhibitor of histidine decarboxylase) Chlorpheniramine (histamine H_1 receptors antagonist)	Decreasing effect
GhandForoushan et al. (2017)	Broiler chicken	Histamine	Hypophagia	ICV	SCH23390 (D_1 dopaminergic receptor antagonist)	Decreasing effect
Taherian et al. (2019)	Layer chicken	Ghrelin	Hypophagia	ICV	SR141716A (selective CB_1 receptors antagonist) AM630 (selective CB_2 receptors antagonist)	Increasing effect
Zendehdel et al. (2013b)	Broiler chicken	Harmaline	Hypophagia	ICV	SB242084($5\text{-}HT_{2c}$ receptor antagonist) Ketanserin ($5HT_{2a}$ receptor antagonist)	Decreasing effect
Jaefari-Anari et al. (2018)	Broiler chicken	DAMGO	Hypophagia	ICV	Chlorpheniramine (histamine H_1 receptors antagonist) Thioperamide (histamine H_3 receptors antagonist)	Decreasing/Increasing effect

Table 1 (continued)

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Jalali et al (2019)	Broiler chicken	OT	Hypophagia	ICV	MK-801 (NMDA receptor antagonist) CNQX (AMPA glutamate receptor antagonist)	Decreasing
Keyshams et al. (2016)	Layer chicken	2-AG (CB_1 receptors agonist) CB65 (CB_2 receptor agonist)	Hyperphagia	ICV	MK-801(NMDA receptor antagonist) CNQX (AMPA/kainate receptor antagonist)	Increasing effect
Khodadadi et al. (2017)	Layer chicken	2-AG (CB_1 receptors agonist) CB65 (CB_2 receptor agonist)	Hyperphagia	ICV	AMI-193 (D_2 receptor antagonist)	Increasing/Decreasing effect
Mahzouni et al. (2016)	Broiler chicken	Methylamine	Hypophagia	ICV	AMI-193 (D_2 receptor antagonist) SCH23390 (D_1 receptor antagonist)	Decreasing effect
Mirnaghizadeh et al. (2017)	Broiler chicken	OT	Hypophagia	ICV	Chlorpheniramine (histamine H_1 receptors antagonist) Thioperamide (histamine H_3 receptors antagonist) ICI 118,551 (β_2 adrenergic receptor antagonist) α-FMH (histidine decarboxylase inhibitor)	Decreasing/Increasing effect
Mokhtarpouriani et al. (2016a, b)	Layer chicken	L-arginine	Hypophagia	ICV	gaboxadol ($GABA_A$ Agonist)	Decreasing effect
Mortezaei et al. (2013)	Cockerel	5-HT	Hypophagia	ICV	MK- 801 (NMDA receptor antagonist) CNQX (AMPA/kainate receptor antagonist) picrotoxin ($GABA_A$ receptor antagonist)	Decreasing/increasing effect

Table 1 (continued)

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Nayebzadeh et al. (2020)	Layer chickens	DAMGO (μ-opioid receptors agonist) DPDPE (δ -opioid receptors agonist) U-50488H (κ opioid receptors agonist)	Hypophagia/Hyperphagia	ICV	ICI 118,551 (β_2 receptor antagonist) parazosin (α_1 receptor antagonist) yohimbine (α_2 receptor antagonist)	Decreasing effect
Moosadoost et al. (2019)	Broiler Chicken	PG-931 (MC4R agonist)	Hypophagia	ICV	RF9 (NPFF receptor antagonist)	Decreasing effect
Raji-Dahmardeh et al. (2019)	Layer chicks	OT	Hypophagia	ICV	U-50488H (κ receptor agonist) DAMGO (μ receptor agonist)	Decreasing/increasing effect
Zendehdel et al. (2012b)	Chicken	LPS	Hypophagia	ICV	SB 242084 (5-HT$_{2c}$ receptor Antagonist) DL-AP5 (NMDA receptor Antagonist)	Decreasing effect
Zendehdel et al. (2017b)	Layer chicken	5-HT	Hypophagia	ICV	ICI 118.551 (β_2 receptor antagonist) Yohimbine (α_2 receptor antagonist)	Decreasing/Increasing effect
Torkzaban et al. (2018)	Broiler Chicken	DAMGO (μ-opioid receptor agonist) DPDPE (δ-opioid receptor agonist)	Hypophagia/ Hyperphagia	ICV	AIDA (mGLU1 receptors antagonist) MK-801 (NMDA glutamate receptors antagonist) CNQX (AMPA glutamate receptors antagonist)	Decreasing/Increasing effect
Yousefvand et al. (2019)	Broiler Chicken	Somatostatin	Hyperphagia	ICV	B5063 (selective NPY$_1$ receptor antagonist)	Decreasing effect
Yousefvand et al. (2018)	Broiler cockerel	Insulin	Hypophagia	ICV	B5063 (selective NPY$_1$ receptor antagonist) SF22 (selective NPY$_2$ receptor antagonist)	Decreasing/Increasing effect
Zendehdel et al. (2012a)	Broiler cockerel	5-HT	Hypophagia	ICV	SHU9119 (a nonselective melanocortin receptor (McR) antagonist) MCL0020 (a selective McR antagonist)	Decreasing effect

Table 1 (continued)

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Zendehdel et al. (2009)	Broiler cockerel	Glutamate	Hypophagia	ICV	bicuculline (GABA$_A$ receptor antagonist) muscimol (GABA$_A$ receptor agonist)	Increasing/Decreasing effect
Zendehdel et al. (2013c)	Chicken	Ghrelin	Hypophagia	ICV	PCPA (a brain's 5-HT depletion) SB242084 (selective antagonist for the 5-HT$_{2C}$ receptor) fluoxetine (selective 5-HTreuptake inhibitor–SSRI)	Decreasing / Increasing effect
Zendehdel et al. (2013a)	Broiler cockerel	N/OFQ	Hyperphagia	ICV	para-chlorophenylalanine (PCPA) (cerebral serotonin depletive) SB 242,084 (5-HT$_{2c}$ receptor antagonist)	Increasing effect
Zendehdel et al. (2015b)	Broiler Chicken	N/OFQ	Hyperphagia	ICV	a-Fluoromethylhistidine (a-FMH; histidine decarboxylase inhibitor) Chlorpheniramine (histamine H$_1$ receptor antagonist) Thioperamide (histamine H$_3$ receptor antagonist)	Increasing / Decreasing effect
Zendehdel et al. (2015c)	Chicken	DAMGO (μ-opioid receptors agonist) DPDPE (δ -opioid receptors agonist)	Hyperphagia/ Hypophagia	ICV	SR141716A (CB$_1$ receptors antagonist) AM630 (CB$_2$ receptors Antagonist)	Decreasing / Increasing effect
Zendehdel et al. (2015d)	Broiler chicken	LPS	Hypophagia	ICV	Chlorpheniramine (histamine H$_1$ receptor antagonist)	Decreasing effect
Zendehdel et al. (2017c)	Broiler chicken	N/OFQ	Hyperphagia	ICV	ICI 118,551 (β$_2$ adrenergic receptor antagonist)	Increasing effect
Zendehdel and Hassanpour. (2014a, b)	Cockerel	Ghrelin	Hypophagia	ICV	ICI 118,551 (β$_2$ adrenergic receptor antagonist)	Decreasing effect
Yousefvand et al. (2020)	5-day-old chicken	Insulin	Hypophagia	ICV	NPY$_1$/NPY$_2$	Decreaing /Increasing effect
Zendehdel et al (2008)	Broiler cockerel	Muscimol (BABA$_A$ agonist)	Hyperphagia	ICV	Chlorpheniramine (histamine H$_1$ receptor antagonist)	Decreasing effect

Table 1 (continued)

Reference	Animal	Modulation of neuronal activity by	Feed intake behavior	Route of administration	Interaction with	Outcome
Mobarhan et al. (2020)	Layer chicken	Glutamate	Hypophagia	ICV	a-Fluoromethylhistidine (a-FMH; histidine decarboxylase inhibitor) chlorpheniramine (histamine H_1 receptors antagonist) thioperamide (histamine H_3 receptors antagonist)	Decreasing / Increasing effect
Moosadoost et al. (2020)	Broiler chicken	RFRP-3	Hypophagia	ICV	Astressin-B (CRF_1/ CRF_2 receptors antagonist) SHU9119 (melanocortin antagonist) MCL0020 (a selective McR antagonist)	Decreasing effect
Tajalli et al. (2006)	Broiler chicken	N/OFQ	Hyperphagia	ICV	bicuculline ($GABA_A$ receptor antagonist)	Decreasing effect
Bungo et al. (2009)	Layer chicks	N/OFQ	Hyperphagia	ICV	α- MSH	Decreasing effect
Shiraishi et al. (2008)	Layer chicks	Insulin	Hypophagia	ICV	SHU9119 (melanocortin antagonist)	Decreasing effect
Farrokhi et al. (2020)	Broiler chicken	Ghrelin	Hypophagia	ICV	D1 receptor antagonist CB1 receptore antagonist	Decreasing / Increasing effect
Saito et al (2005)	chicks	Ghrelin	Hypophagia	ICV	Astressin (CRF receptor antagonist)	Decreasing effect
Rahimi et al (2021)	Broiler chicken	Glycine	Hypophagia	ICV	SCH23,390 (D_1 antagonist)	Inccreasing effect
Zendehdel et al (2021)	Layer- chicken	OT	Hypophagia	ICV	L-NAME (NOS inhibitor)	Decreasing effect
Jonaidi et al. (2019)	chicks	LPS	Hypophagia	ICV	Astressin (CRF receptor antagonist)	Decreasing effect

(an indirect agonist of DA), and DAMGO (μ-opioid receptor agonist) significantly decreased by the central inhibition of NO synthesis which highlighted the crosstalk between central nitrergic system with OT, DA, and opioidergic systems (Zendehdel et al. 2021, 2017a; Alimohammadi et al. 2015).

Conclusion

Central interaction between mediators is a process which has underpinning role in regulation of appetite and feeding behavior. In above- mentioned chapters the interaction between different mediators in brain modulating food intake behavior in birds has been described. In this respect, the interplay between the most important mediators in different classes including biogenic amines, aminoacids, peptides, ECS, nitrergic systems and different relevant subclasses were under debate. In terms of peptides, according to the fact that the well-known peptides and the relevant subtypes have anorexigenic and/or orexigenic effects in avian and other species, the mentioned classification is considered in this review. In conclusion, the interactions between NTs involved in food intake regulation in birds have been documented; among them the biogenic amines dopamine and serotonin, and also the amino acid glutamate have more notable mediatory role due to the further interactions they have with other NT systems.

In consideration of developing global food demands, poultry industry and chicks breeding is one of the most important processing to fulfill of food requirements. Increasing food intake behavior in chickens can improve the poultry industry; understanding the neuronal pathways and related crosstalk affecting chicks appetite leads to have a better outline of feeding behavior in birds which is effective factor to progress poultry industry.

During studying the interplay of neuronal pathways in the control of food consumption, several variations have been demonstrated not only among different animal species but also within different strains of birds (Table 1). It seems that these noticeable differences detected among different bird strains are dependent on genetical diversity resulted in variations in central neuronal pathways and their dominancy in appetite and feeding regulation. The exact molecular mechanisms underlying the relevant variations remains to be elucidated in the future studies.

In the field of surveying the interactions between neuronal pathways intervening poultry food intake, most research works have employed the ICV administration of different drugs in order to inducing the alterations in feeding behavior. In consideration of the rout of drug administration in these studies, the identification of the regions in CNS and the neuron locations, which have role in feeding regulation, is not possible. To fix this issue, the use of intranuclear drug injection is being recommended to be applied as a research method in the future studies in this field. Moreover, the most of conducted models have induced the alterations in neuronal activity via pharmalogical agonizing and antagonizing procedures (Table 1). Although, the useful and applicable data has been extracted out of pharmacological methods, it is suggested that the new neurological techniques such as chemogenetics and optogenetics be widely employed to control the firing of specific neuronal pathway more precisely. Undoubtedly, these precise methods are capable of simulating the research models closer to the physiological status in more controlled condition.

Author Contributions All authors have agreed to be named as authors on this manuscript. Any work (data, text, or theories) of others besides the authors has been properly acknowledged. The work is original and not previously published. All data are true and accurate to the knowledge of the authors.

Declarations

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

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