Central regulation of food intake in mammals and birds: a review

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Appetite regulates by a complex system of central and peripheral signals which interact in order to modulate ingestion response. A number of peptides comprise a complex network that regulates feeding behavior in vertebrates. This review is focused on the main neurotransmitters and peptides that influence feeding responses in mammals and birds. On the basis of literature review, there are several evidences that neurotransmitters have different effects on food intake between mammals and birds. Also, central regulation of food intake regulates via different mechanisms in animals. So, the aim of this review was to investigate comparative food-intake regulation mechanisms in mammals and birds.

Keywords: Food intake regulation; Mammals; Chicken


Introduction

Appetite regulates via a complicated of central and peripheral signals which interact with each other to regulate ingestion. Arcuate nucleus (ARC) is a portion of central nervous system (CNS) adjacent to the third ventricle is the principal hypothalamic area which regulates food intake. In mammals, two interconnected groups of neurons; neuropeptide Y (NPY) and agouti-related peptide (AgRP) are orexigenic while pro-opiomelanocortin (POMC) and cocaine- and amphetamine regulated transcript (CART) are anorexigenic [1]. On the other hand, in domestic chickens mechanisms that regulate food intake have relatively well-developed. Even though several aspects of central appetite control in poultry are similar to mammals, but there are several differences between them. For example, neurotransmitters like NPY, orexin-A, orexin-B, motilin, melanin-concentrating hormone (MCH), growth hormone releasing factor (GRF) and ghrelin stimulate food intake in mammals whereas except NPY and ghrelin, the other neurotransmitters had no effect on food intake in poultry [2, 3]. Therefore, it seems there are differences on food intake regulation between mammals and chickens. Thus, the aim of the current brief review was to investigate role of several neurotransmitters and neurological pathways that regulate food intake in vertebrates. Also, the possible differences between mammals and birds on feeding behavior will describe.

Ghrelin

Ghrelin passed 15-years from its discovery and because of different function in various types of animal its physiological role has not been fully investigated. Ghrelin is primarily
isolated from stomach of rat and human and is an endogenous ligand of growth hormone (GH) [4]. Accumulating evidences imply that ghrelin plays important role in mammals but a little known in non-mammalian vertebrates [5]. It is revealed that administration of ghrelin stimulates GH release and feeding in rat. Effect of ghrelin on food intake is completely dissimilar between chickens and mammals. Interestingly, in birds, either human or chicken’s ghrelin stimulates GH release but strongly inhibits food intake [4, 6]. In this regards, our previous research showed that intracerebroventricular (ICV) injection of ghrelin induces hypophagia in chicken [7, 8]. The mechanism underlying this phenomenon is unclear [4]. Ghrelin-induced Fos-positive neurons in nucleus tractus solitarius (NTS) and ARC express NPY and lead to impress orexigenic effects in rat [9]. The ARC plays undeniable role in regulation of peripheral ghrelin signals. However the direct mechanism of ghrelin induced hypophagia is still unclear in poultry. It is well documented that there are complex networks between ghrelin and other neurotransmitters on feeding behavior. Previous studies showed that there is an interaction between ghrelin and other neurotransmitters such as glutamate, adrenaline and serotonin in broiler chickens which will discuss later [7-10]. Such discrepancies between mammals and birds might relate to differences in species and/or the site of the brain which the neurotransmitters act. Saito et al. [11, 12] reported that ICV injection of ghrelin decreases food intake and increases serum corticosterone levels in avian. Likewise, a dose dependent decrease was observed on food intake after ICV injection of ghrelin (0.3, 1.1, 4.3 and 6.2 nMol) in 8 week old broilers [13]. Consistent with this hypothesis, a significant decrease was observed on food intake by ICV injection of 1 nMol ghrelin in Japanese quail [4].

Dopamine

Dopamine is one of the important neurotransmitters in mammalian CNS which have several of functions e.g. locomotor activity, cognition, emotion, positive reinforcement and food intake [14]. Frequent limbic nucleus such as nucleus accumbens (NAc), ventral tegmental area (VTA), amygdala, hippocampus, orbitofrontal cortex (OFC), cingulate gyrus (ACC), as well as hypothalamus along with dopamine which is associated with food intake regulation [15, 16]. Injection of D1 and D2 agonist decreases feeding behavior in both food deprived and non-deprived rats [17]. Recently, our research showed that ICV injection of dopamine decreases food intake in chicken and dopamine-induced hypophagia mediates by D1 receptors in chicken. Interestingly, there was no significant effect on food intake through D2, D3 and D4 receptors in broiler cockerels [18]. It seems, dopamine acts via similar pathway on feeding behavior in rodents and avian.

Serotonin

The serotoninergic system has a broad anatomical distribution in the CNS with widespread effects in the brain [19]. Serotonin (5-HT) is one of the major neurotransmitters that has crucial role on sleep-wake cycle, motor control, immune system, nociception, behavior and aggression regulation in species ranging from invertebrates to humans. In the CNS, 5-HT derives mainly from the midbrain raphe’ nuclei [20, 21]. Since years ago, it has been known that serotonin acts in mood regulation [22] but recently it is identified that the 5-HT has important role in the central control of feeding behavior in mammals and avian species. It is reported that administration of 5-HT or its analogue leads to a suppression on food intake in both human and rats [23]. In our previous study, we observed that ICV injection of 5-HT decreases food and water intake in chickens [24-25]. Therefore, effect of 5-HT on food intake is similar in both mammals and poultry. In this regard, it is well known that 5-HT mediates the anorexigenic effect via modify in activities of NPY/AgRP and POMC neurons [23, 26]. It is reported that there is a neurological interaction between serotonergic and dopaminergic systems [18]. Tryptophan is readily transformed into serotonin, consequently, serotonin levels increase in the brain. Co-administration of tryptophan and dopamine blocks ingestion behavior [27]. So it seems an interaction exist between 5-HT and other neurotransmitters in food intake regulation. For instance, 5-HT can modulate GABAergic and glutamatergic mechanisms involved on feeding in chicken which is fully described in the subsequent sections [28].

GABA

Gamma amino butyric acid (GABA) is the major inhibitory amino acid transmitter in the CNS [29]. Three isoform of GABA receptors have been recognized. GABA_A and GABA_C receptors are ligand-gated chloride (Cl^-) ionotropic receptors whereas GABA_B receptor is G protein coupled receptor [29, 30]. It is well documented that ICV injection of GABA_A receptor agonist increases food consumption [31-34]. Interestingly, it is revealed that ICV injection of GABA_B agonist, amplifies cumulative food intake in rat [35], layer- type hens [31] but not in meat-type chicken [31, 36]. As seen, GABA has controversial effects on appetite regulation in birds. On the basis of genetically differences between layer and broiler breeds, there is evidence claims that food intake regulatory mechanisms are differ between different breeds of chickens. For instance, comparative physiological studies on meat type chicken (broilers) and layer-type (hens) revealed that broiler compared to layers, is higher in feed consumption, basal metabolic rate and energy expenditure possibly due to a genetically altered feed intake control mechanisms [37, 38].
Genetic selection for growth in broiler chickens might alter their responsiveness to appetite regulation mechanisms [18, 37, 38]. As mentioned, there is a neurological interaction between GABA and 5-HT in the brain. ICV injection of 5-HT2 receptor agonist modulates post-synaptically GABA-mediated food intake. In fact, 5-HT2 receptors promote phosphorylation of GABA_A receptors by activation of protein kinase C (PKC) and probably attenuate GABA-induced food consumption. Likewise, GABA metabotropic receptor (GABA_B) was not able to modulate effect of 5-HT [28]. Recently, a neurological pathway identified between GABA and ghrelin. In a study, Jonaidi et al., [39] reported ICV injection of ghrelin significantly reduced GAD2 gene expression in neonatal chicken. So, ghrelin may decline feeding via reduction GABA synthesis and release in the CNS injection controlling centers.

**Histamine**

Histamine is a biogenic amine and has important function in the CNS and peripheral tissues (PNS). Four distinct G protein coupled receptors (GPCRs) are classified as H1, H2, H3 and H4 [40]. Central histaminergic system has been implicated in the modulation of numerous physiological aspects e.g. locomotor activity, thermo regulation and feeding behavior [41]. It is reported that endogenous histamine modulates feeding behavior via central H1 receptors in rat [42] and poultry [43]. In contrast, it is reported that ICV injection of chlorpheniramine (histamine H1 receptor antagonist) increases cumulative food intake in both rodents and birds [33, 43]. Additionally, ICV injection of α-fluoromethylhistidine (a histidine decarboxylase inhibitor) increases food intake in chickens [43]. Central histaminergic neuron cell bodies are localized in the posterior hypothalamus in tuberomamillary nucleus (TMN) and axons of these neurons project from the TMN to many areas of the brain [44]. It seems, food intake is regulated by H1 receptors whereas water consumption is not directly affected [43]. ICV injection of H1 receptor agonist predominantly provokes drinking but no effect on food consumption in rats [45]. Histamine perform its effect by increase in corticotropin releasing hormone (CRH) levels through stimulating proopiomelanocortin (POMC) and cocaine- and amphetamine regulated transcript (CART), as well as blocking NPY and AgRP neurons in the ARC [46, 47]. It seems, histamine decreases food intake both of avian and mammals via the same neurological pathways. Also, there is a neurological interaction between histaminergic and cholecystokinin (CCK) on feeding behavior, H3 receptor is involved in CCK-induced hypophagia in rats [48].

**Glutamate**

Glutamate is a major excitatory neurotransmitter in the CNS [34, 49]. Two major families of glutamate receptors have been identified. Ionotropic glutamate receptors (iGluR) include N-methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) and kainite receptors and metabotropic (mGluR) glutamate receptors (mGluRI, mGluRII, mGluRIII) [49]. It is well documented that ICV injection of glutamate or its agonists into the lateral hypothalamus diminished food intake in mammals [50-52]. In comparison, ICV injection of glutamate reduces feed intake and increases latency time to start feeding in cockerels. Also, pretreatment with ionotropic glutamate antagonist resulted in increase in feed intake [49]. Glutamatergic system has interaction with 5-HT ergic system in the CNS. Recently, it is reported that effect of glutamate on food intake modulates via NMDA and AMPA/Kainate receptors and cannot be modulated by metabotropic receptors [28]. Also, there is an interaction between ghrelin and glutamatergic system. It is suggested that ghrelin induced hypophagia amplified by pretreatment with glutamate receptor and this effect was attenuated through NMDA receptors [7]. It seems, effect of glutamate on food intake is similar in both of mammals and birds.

**Nociceptin/orphanin FQ**

Nociceptin/orphanin FQ (N/OFQ) is 17 amino acid neuropeptide and endogenous ligand for the opioid-like GPCR1 or nociceptin receptor (NOP), the fourth member of the opioid receptor family [53]. Literature review revealed that N/OFQ play crucial role in pain, anxiety and locomotion. Recently, NOP receptors are recognized in food controlling area in the rat brain. It is demonstrated that ICV injection of N/OFQ into the third ventricle and ARC amplifies food intake in rat [54-56] and avian [1, 37]. Central injection of N/OFQ induces feeding can be blocked by peripheral injection of opioid antagonist naloxone [58]. It is reported N/OFQ system is involves in GABA induced hypophagia via GABA_A receptors in mammals and birds [52]. Also, serotonergic system involves in N/OFQ induced food intake in chicken. In this regard, Zendehdel et al., [3] reported N/OFQ induced hyperphagia is mediated by 5-HT2C receptors in chickens.

**POMC**

Proopiomelanocortin (POMC) is a precursor for adrenocorticotropins, melanocortins and the β-endorphins [25]. α-MSH is derived from a multifunctional POMC and represents one of the main regulator of energy balance in this family. ICV injection of α-MSH or its agonist suppresses food intake in rodents [1]. Five receptors belonging to the MCR family have been recently cloned in avian [59]. Based on findings the anorexigenic effect of melanocortin mediates...
by MC3 and MC4 receptors [25]. These receptors highly represented in the ARC and it seems impress their effects through activation POMC and CART gene expression as well as NPY and AgRP downstream. NPY/AgRP and GABA terminals are in contact with nearby POMC neurons, thereby affecting POMC neuronal activity [1, 25]. There is a neurological interaction between serotonergic and melanocortin systems on feeding behavior. Our previous study showed that anorexic effect of serotonin is attenuated by ICV pretreatment of MC3 and MC4 receptors antagonists in chicken [25].

Noradrenaline

Few reports suggest that noradrenergic fibers penetrate into NTS. Presence of these fibers is essential for food intake regulation in rat. Noradrenaline excites approximately half of the neurons in the ARC, probably due to a direct postsynaptic response through α1 or β receptors [10]. It is well-documented that administration of β2-adrenergic receptor agonist decreases food intake in rats [60-62] and poultry [65, 64]. Intraperitoneal (IP) administration of β3 receptor agonist decreases food intake in rat [62]. It is suggested that ghrelin signals travel via vagus nerve to NTS and up regulates noradrenaline release via α1 and β2 receptors which increases food intake in rat. Effect of ICV injection of ghrelin on cumulative food intake mediates via β2 adrenergic receptors in cockerels [64].

Peptide YY

Peptide YY (PYY) is 36 amino acid residues peptide hormone and together with NPY, PYY is belongs to the pancreatic polypeptide (PP) family. Controversial reports exist about role of PYY in appetite regulation. Previous reports demonstrate that ICV administration of PYY stimulates feeding in rat [65]. Frequent, researches indicate that peripheral infusion of PYY reduces cumulative food consumption [66]. Also, involvement of serotonergic [67], adrenergic [68] and opioidergic systems [67, 69] in the development of PYY-induced hyperphagia has been reported in rats. It is described PYY-stimulated feeding behavior might need to action of endogenous opioids and serotonergic system [67]. Also, PYY-induced hyperphagia decreases by pretreatment with β2 agonist [68].

Orexin

The orexin-A (33-amino acid) and orexin-B (28-amino acid residues) are two peptides derived from the common precursor prepro-orexin [5]. They are related to GPCRs known as OX1 and OX2 [1]. Physiological studies revealed that orexins have several roles e.g. control of appetite, sleep-wake cycle and neuroendocrine secretion in the CNS of mammals [70]. Previously, it is demonstrated that ICV injection of orexin-A increases feeding in rat. Likewise, orexin-A antagonist reduces appetite in obese patients while peripheral injection of orexin A had no effect on feeding behavior in humans [1]. In non-mammalian vertebrates it is revealed that ICV administration of orexin-A amplifies arousal but not food intake in layer-type chicken. Interestingly, orexin-A had no effect on arousal in broiler chicks however they spent less time feeding. Additionally, orexin-B had no effect on arousal and food intake neither in layer nor broiler [71]. As seen, orexin has different effects in domestic birds. The differential responses to orexins in the two strains can related to variances in their receptors. Orexin-A is a ligand of both OX1R and OX2R whereas orexin-B activates only OX1R. Also, OX1R is associated with the Gq subclass of G proteins while OX2R is likely associated with the Gq and Gi/o [71]. In conclusion, presumably orexins induce feeding behavior acts via different neurological pathways in mammals and birds.

Leptin

Leptin is a hormone mainly produces in the adipose tissue [5]. This hormone penetrates into the brain in proportion to its plasma levels and has important role in food intake regulation [1]. ICV injection of leptin rapidly reduces food intake in rat and both broiler and leghorn chickens [43]. It seems, a neurological pathway exist between leptin and melanocortin system. Studies indicate that leptin stimulates α-MSH expression (the potent agonist of MCR3 and MCR4) and inhibit AgRP release (the antagonist of MCR3 and MCR4) [59].

Conclusion

On the basis of literature review, central regulation of food intake is performed via different mechanisms in mammals and birds; however, there are similar pathways in some neurotransmitters.

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Conflicts of interest

The authors report no conflicts of interest.

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