Hypothalamic Melanocortin System on Feeding Regulation in Birds: A Review

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Regulation of feed intake in chickens represents a complex homeostatic mechanism involving multiple levels of control. Understanding the regulation of feeding behavior can be a very important theme in animal production. Recently, a close evolutionary relationship between the peripheral and hypothalamic neuropeptides has become apparent. In the infundibular nucleus (the avian equivalent of the mammalian arcuate nucleus), the melanocortin system, which contains neuroendocrine neurons that regulate endocrine secretions by releasing substances, is an essential site in the brain for signals about the status of peripheral energy balance. The structure and function of many hypothalamic neuropeptides, melanocortins, neuropeptide-Y (NPY) and agouti-related protein (AGRP) have been characterized. This review provides an overview of the various effects and interrelationship of these central and peripheral neuropeptides, and summarizes the role of the melanocortin system on feeding regulation in chicks.

Key words: agouti-related protein (AGRP), chick, feed intake, melanocortin system, neuropeptide-Y (NPY), pro-opio-melanocortin (POMC)

Introduction

Feeding behavior in domestic chickens is one of the greatest concerns of animal scientists and producers because it not only establishes a healthy life but also holds the key to improvements in productive efficacy for meat and eggs. Thus, understanding the regulation of feeding behavior can be a very important theme in poultry production. There are various factors which affect feeding behavior and the information-processing network of those factors should operate accurately. In particular, there is a vast amount of research on brain function because the central nervous system (CNS) is thought to be a critical center of behavioral motivations. From the initial findings, it is well known that the lateral hypothalamic area is the feeding center that accelerates feed intake, and the ventromedial nucleus of the hypothalamus is the satiety center that decelerates feed intake. The hypothalamic arcuate nucleus (ARC) has become the focus of much attention in recent years because of its critical brain site, which is conveniently located at the floor of the third ventricle in an area without the blood brain barrier. This facilitates signaling from the peripheral organs/tissues to reach the relevant nuclei via the ARC.

To regulate feeding, caloric intake must equal caloric expenditure over time. Such an intricate process relies on the interactions of a number of physiological systems. There is considerable evidence that the regulatory system signals from the peripheries (e.g., intestines, pancreas and adipose tissue) inform the ARC about the status of peripheral energy balance. Several observations suggest that the ARC contains neuroendocrine neurons, the so called melanocortin system which is an essential mediator for the peripheral signals such as leptin and insulin action in the CNS (Schwartz et al., 2000; Benoit et al., 2002). In an expanded sense, the melanocortin system consists of pro-opiomelanocortin (POMC) neurons inhibiting feeding, and neuropeptide-Y (NPY) and/or agouti-related protein (AGRP) neurons stimulating feeding.

Previous reviews of the relevant neuropeptides and their comparative functions in mammals on feeding regulation have discussed the role of the CNS in chicks (Furuse, 2002; Furuse et al., 2007). This review provides an overview of and discusses the role of the melanocortin system on feeding regulation in birds, especially in chickens.

1. Characteristics of Feeding Regulation in the Melanocortin System

1.1. POMC

POMC is a precursor for the melanocortin peptides, α-,
β- and γ-melanocyte stimulating hormone (MSH) and the endogenous opioid, β-endorphin. To date, five melanocortin receptors (MC1R to MC5R) have been identified (Mountjoy et al., 1992; Adan and Gispen, 2000). MC3R and MC4R are highly expressed in the CNS, and α-MSH released by POMC neurons in the ARC plays a key role in the control of feed intake by acting on these receptors in mammals (Mountjoy et al., 1992, 1994; Roselli-Rehfuss et al., 1993). Central injection of α-MSH or MTII (a synthetic melanocortin agonist for MC3R and MC4R) inhibits feed intake in rodents, as well as in primates (Poggioli et al., 1986; Fan et al., 1997; Rossi et al., 1998; Murphy et al., 2000; Wirth et al., 2001), and the intracerebroventricular (ICV) administration of melanocortin antagonists, SHU9119 (both MC3R and MC4R antagonists) and HS014 (a selective MC4R antagonist), stimulates feeding behavior in rats (Seeley et al., 1997; Fan et al., 1997; Kask et al., 1998b). α-MSH can also increase energy expenditure (Poggioli et al., 1986; Brown et al., 1998; Hillebrand et al., 2005). Genetic rodent models indicate the importance of the melanocortin system in the maintenance of body weight (Huszar et al., 1997; Yaswen et al., 1999; Butler et al., 2000).

The chicken POMC gene was found to be a single copy gene and shows the same structural organization as that of other species of different classes, suggesting that melanocortins in chickens act in a paracrine and/or autocrine manner to control a variety of functions in the central and peripheral tissues (Takeuchi et al., 1999). Additionally, Phillip-Singh et al. (2003) revealed the presence of α-MSH-expressing neurons in the infundibular nucleus (IN), the avian equivalent of the mammalian ARC (Fig. 1). As for the control of feeding behavior, the central injection of α- and β-MSH, which non-specifically binds both MC3R and MC4R, suppresses feed intake in chicks (Kawakami et al., 2000; Smith et al., 2008; Kamisoyama et al., 2009), and HS014 stimulates feed consumption in doves (Strader et al., 2003) and chicks (Bungo et al., unpublished data). Although MC3R and MC4R, which have potential roles in the control of feed intake and body weight in mammals, are highly expressed in mammalian brains (Grantz et al., 1993; Mountjoy et al., 1994), MC3 R expression is not detected by RT-PCR in the chicken brain (Takeuchi and Takahashi, 1999). However, γ-MSH that is highly selective for MC3R versus MC4R in chickens (Ling et al., 2004), reduces feed intake in chicks (Smith et al., 2009). Thus, similar to mammals, the anorexigenic action of melanocortins by POMC neurons in birds seems to be mediated by MC3R and/or MC4R.

1.2. AGRP

AGRP is a 132 amino acid peptide with 25% homology to agouti (Fong et al., 1997), and is produced in the ARC as a biologically active fragment of the endogenous antagonist of α-MSH at the MC3R and MC4R (Ollmann et al., 1997). In rodents, central injection of AGRP potently increases feed intake (Hagan et al., 2000; Kim et al., 2000; Lu et al., 2001), and the anorexigenic effects of α-MSH and MTII can be blocked by co-administration of AGRP (Rossi et al., 1998). In good agreement with these pharmacological findings, genetic manipulations resulting in over expression of AGRP lead to hyperphagia and obesity in mammals (Ollmann et al., 1997; Marks and Cone, 2001). Marsh et al. (1988) reported that a targeted disruption of the MC4R gene in mice eliminates the anorexigenic effects of MTII, suggesting that the anorexigenic effect of α-MSH and the orexigenic effect of AGRP are integrated by MC4R. Taken together, this system is unique in neuroendocrinology in having both agonistic and antagonistic endogenous ligands that regulate stimulation and inhibition of feed intake depending on the state of energy balance.

The chicken AGRP gene was found to encode a 154 or 165 amino acid protein with its C-terminal region showing high homology to mammalian counterparts, and PT-PCR analysis detected the AGRP mRNA in the brain, liver and so on (Takeuchi et al., 2000). Administration of AGRP into the lateral ventricle of chicks enhances feeding behavior and inhibits the anorexigenic action of α-MSH (Tachibana et al., 2001). Collectively, α-MSH and AGRP produce opposing effects on feeding behavior in chicks, comparable to those in mammals. In mammals, several pharmacological studies have suggested a role for the central melanocortin system in the regulation of the activity of the hypothalamo-pituitary-adrenal (HPA) axis (Calogero et al., 1988; Ludwig et al., 1998; Dhillo et al., 2002). In avians, ICV injection of α-MSH increases the level of plasma corticosterone in chicks but the effect is not blocked by co-administration of AGRP (Tachibana et al., 2007), suggesting that MCs related to the feeding regulation or HPA axis might be different in the chick CNS.
AGRP gene expression in avians closely resembles that in mammals both in its exclusive localization in the IN and also in the fact that the majority of neurons that express AGRP also co-express NPY, a potent appetite neuropeptide as mentioned below (Boswell et al., 2002; Phillips-Singh et al., 2003).

1.3. NPY

NPY contains 36 amino acid residues belonging to the pancreatic polypeptide family (Tatemoto, 1982), and is one of the most abundant peptides in the brain of rats (Allen et al., 1983). In mammals, NPY is the most potent stimulator of feed intake (Edwards et al., 1999) and NPY producing neurons are present in the hypothalamus and brainstem (Gray and Morley, 1986). The ARC is the major site of expression for NPY within neurons in the hypothalamus that projects to the paraventricular nucleus, the ventromedial nucleus and other sites, facilitating the interaction of NPY with other orexigenic and anorexigenic signals in the hypothalamus (Sahu et al., 1988). For example, NPY and AGRP co-express in the ARC neurons and simultaneously repress anorexigenic melanocortin signaling in the ARC (Kalra and Kalra, 2004).

ICV injection of NPY produces a powerful and prolonged increase in feed intake in rats (Clark et al., 1984), while long-term administration results in decreased thermo genesis and obesity (Stanley et al., 1986). The NPY stimulation of feeding is in a dose-dependent manner, although at higher doses feeding stimulation is less marked (Clark et al., 1987). As for the receptors for NPY, fasting increases NPY Y1 receptor mRNA expression in the rat hypothalamus (Wyss et al., 1998), and Y1 receptor deficient mice show significant reduction of daily, fasting- and NPY-induced feed intake (Pedrazzini et al., 1998; Kanatani et al., 2000). Mice lacking the Y5 receptor eat normally with normal responses to exogenous NPY but demonstrate late onset of weight gain (Marsh et al., 1988). Consistent with these findings, pharmacological studies prove that appetite stimulation by NPY in mammals is mediated by receptors Y1 and Y5 (Kask et al., 1998a; Lecklin et al., 2002, 2003). In addition to Y1 and Y5, Y2 is also an important receptor in the melanocortin system: POMC neurons in the ARC are inhibited by the administration of the Y2 receptor agonist PYY3-36 (Ghamari-Langroudi et al., 2005), and mice without Y2 receptors in the NPY neurons show increased NPY and decreased POMC mRNA expression in the ARC (Shi et al., 2010).

The presence of NPY in the CNS of chickens was first demonstrated by the NPY-like immunohistochemical study using antibodies against porcine NPY and avian pancreatic polypeptide (Kuenzel and McMurtry, 1988). Thereafter, the chicken NPY gene was cloned (Blomqvist et al., 1992), and NPY was found to be synthesized within the avian brain by in situ hybridization studies (Boswell et al., 1998; Wang et al., 2001; Boswell et al., 2002). Similar to mammals, central administration of NPY robustly stimulates feeding behavior in chickens and chicks in a dose-dependent manner (Kuenzel et al., 1987; Kuenzel and McMurry, 1988; Furuse et al., 1997; Bungo et al., 2000).

Fasting leads to increased NPY mRNA levels in the IN hypothalamus of birds (Boswell et al., 2002). Six NPY receptors (Y1, Y2, Y4, Y5, Y6 and Y7) have been identified in chickens and their binding characteristics have been investigated (Salanek et al., 2000; Holmberg et al., 2002; Lundell et al., 2002; Bromée et al., 2006). Although these reports demonstrate that the Y1 and Y5 receptors are expressed in the hypothalamus containing the IN (Holmberg et al., 2002), in vivo pharmacological studies have shown contradictory results: the Y1 receptor antagonist did not prevent fasting- and NPY-induced feeding (Kawakami et al., 2001), while [Leu31, Pro34]-NPY, with a high affinity to the chicken NPY Y2 and Y4 receptors (Salanek et al., 2000; Lundell et al., 2002), increased feed intake, comparable to NPY (Ando et al., 2001). Because there are conflicting data between the receptor expressions and pharmacological effects, further studies will be needed to understand the role of NPY and its receptor subtypes in the melanocortin system.

1.4. Simplified Correlation between the Components on the Feeding Behavior

Based on the above-mentioned mammalian results, a schematic illustration of the hypothalamic melanocortin system for regulating feed intake is shown in Fig. 2. Briefly, increased signals of a fasting condition (negative energy balance) from the peripheries (intestines, pancreas and adipose tissue) to the ARC inhibits the POMC anabolic pathway and stimulates the NPY/AGRP anabolic pathway, resulting in accelerated feed intake (left diagram in Fig. 2), while increased satiety signals inhibit the NPY/AGRP pathway and stimulate the POMC pathway, resulting in decelerated feed intake (right diagram in Fig. 2). As described above, the melanocortin system in the IN of chickens resembles that in mammals, and the system has been neuroanatomically and functionally conserved during long periods of vertebrate evolution (Lin et al., 2000; Phillips-Singh et al., 2003; Boswell, 2005).

2. Factors Affecting the Melanocortin System

Increasing evidence suggests that peripheral signals from adipose tissue, the pancreas and the intestines may communicate with the centers of feeding regulation in the CNS through the melanocortin pathway. There have been a number of reviews regarding the network in the mammalian melanocortin system (e.g., Schwartz et al., 2000; Seeley et al., 2004; Cone, 2005; Garfield et al., 2009). However, it should be noted that the network in the avian melanocortin system remains to be fully explored. This section is a summary of the characteristics of major factors, which regulate the network in the hypothalamus of chicks, compared with the results in mammals.

2.1. Hypothalamic Signals

2.1.1. Cocaine- and Amphetamine-Regulated Transcript (CART)

CART was first identified as a major brain mRNA upregulated by cocaine and amphetamine and found to be
co-localized with POMC, and expressed in the hypothalamus (Douglass et al., 1995; Kuhar and Dall Vechia, 1999). In rodents, ICV injection of CART fragments has been shown to suppress both normal and fasting-induced feeding, and completely blocks the feeding response induced by NPY (Kristensen et al., 1998; Lambert et al., 1998). While CART antiserum administration increases nighttime feeding, suggesting the role of CART as an endogenous satiety factor (Lambert et al., 1998). There is a decrease in the ARC CART mRNA following feed deprivation, demonstrating that CART mRNA regulation is related to the fuel availability and peripheral hormone status (Li et al., 2002).

Like mammals, central infusion of human CART induces anorexia in chicks (Tachibana et al., 2003), and the CART mRNA expressions are changed by anorexigenic and orexigenic peptide treatments (Honda et al., 2007; Bungo et al., 2009). Although the chicken CART gene has not yet been fully identified, it can be predicted that POMC neurons in the IN also resemble their mammalian counterparts in co-expressing CART mRNA. Studies are therefore required to clone and characterize the chicken CART gene.

2. 1. 2.  μ-Opioid Receptor Agonists and β-Endorphin Fragments

The opioid system, β-endorphin, dynorphin and enkephalins are the three biologically active peptides described in the hypothalamus (Levine and Billington, 1989). Opioid peptides mediate the hunger component in the control of feed intake (Baile et al., 1986), but in contrast to NPY-induced feeding, their effect is relatively modest and short-lived. Among opioid peptides, β-endorphin (and its receptor) is one of the essential modulators in the melanocortin system because it is derived from β-lipotropin, which in turn is derived from POMC (Mains et al., 1977). β-Endorphin has affinity for both the μ- and δ-opioid receptors (MOR and DOR) in rats (Raynor et al., 1994), but opioid antagonist analyses of β-endorphin feeding have shown reductions induced by MOR, but not by DOR antagonists in mammals (Silva et al., 2001). It has been recognized that β-endorphin acts in an auto-receptor manner to the MOR on POMC neurons, diminishing the ARC POMC neuronal activity in response to elevated POMC-derived melanocortin peptides that inhibit feed intake in mammals (Cowley et al., 2001). NPY stimulates β-endorphin release in the hypothalamus (Horvath et al., 1992), indicating a functional link between NPY and β-endorphin in mammals. These results suggest that NPY may induce feeding directly on its own and also by stimulating β-endorphin. The immediate actions of AGRP are blocked by non-specific opioid receptor antagonists but not the long-term effects (Hagan et al., 2001). These findings suggest that the endogenous MOR ligands are an important “system” modulator which may regulate not only the POMC but also NPY/AGRP neuron activities.

Similar to that in mammals, central infusion of MOR agonist enhances feeding behavior in chicks (Bungo et al., 2004, 2005, 2007), and the orexigenic effect is abolished by MOR, but not by DOR antagonists (Yanagita et al., 2008a). Co-injection of MOR antagonists are effective in reducing NPY-induced feeding, whereas DOR antagonists had little effect, suggesting NPY stimulates β-endorphin release in the hypothalamus in chicks (Dodo et al., 2005). Central MOR agonist infusion with insulin prevents insulin-induced hypophagia, and attenuates increasing POMC mRNA expression in the brain of chicks (refer to “2.2.2 Insulin” below). β-endorphin is processed into
N-terminal fragment peptides by enzyme, and its fragments having low potency, attenuate β-endorphin-induced action in mammals (Hammonds et al., 1984; Suh et al., 1987; Plum et al., 2009). In chicks, the fragment abolishes β-endorphin-induced feeding (Yanagita et al., 2008 b), and accelerates insulin-induced anorexia (Shiraishi et al., 2010). These findings imply that β-endorphin acts in an autoreceptor manner to the MOR on POMC neurons in the IN of chicks, as in mammals. Further histochemical studies will be needed to understand the role of MOR and MOR ligands in the melanocortin system of chicks.

2.1.3. Nociceptin/orphanin FQ (N/OFQ)
Nociceptin/orphanin FQ (N/OFQ) is an opioid-related heptadecapeptide identified as the endogenous ligand for the orphan Gαi/o-coupled opioid receptor-like 1 receptor (NOP1) (Meunier et al., 1995; Reinscheid et al., 1995). N/OFQ and NOP1 are widely distributed in the brain (Mollerreau and Mouledous, 2000; Reinscheid et al., 2000), consistent with involvement in the control of a variety of biological functions including feeding regulation: N/OFQ has been shown to stimulate feeding behavior in rats following ICV administration (Ponomis et al., 1996; Polidori et al., 2000; Economidou et al., 2006). The ARC has been shown to be the most sensitive brain site of action for N/OFQ in rats (Polidori et al., 2000). The orexigenic effects of N/OFQ in the CNS are associated with changes in the hypothalamic AGRP, CART, catecholamines and excitatory and inhibitory amino acids (Murphy et al., 1996; Murphy and Maidment, 1999; Marti et al., 2004; Bewick et al., 2005).

As in mammals, ICV injection of N/OFQ increases feed intake in chickens (Abbasnejad et al., 2005; Tajalli et al., 2006). It also induces the increased AGRP and decreased CART mRNA expression in the CNS of chicks, and simultaneous administration of α-MSH completely blocks its orexigenic effect (Bungo et al., 2009), suggesting that N/OFQ functions in chickens as one of the modulators in the melanocortin system, as in mammals.

2.1.4. Gamma-Aminobutyric Acid (GABA)
It should be emphasized that in the hypothalamus, the key chemical mode of communication between neurons is via GABA. GABA, the most widely distributed inhibitory neurotransmitter in the vertebrate central nervous system (Sivilotti and Nistri, 1991), is found in high concentrations in brain areas known to be involved in the control of ingestive behavior (Decavel and Van den Pol, 1990). Hence, rather than functioning as a directly acting facilitatory orexigenic agent, it is possible that GABA may exert an inhibitory effect on an existing anorexigenic tone in the CNS, thus indirectly facilitating feeding behavior. This might be mediated by decreasing α-MSH release (Jegou et al., 1993) or by rendering crucial target sites highly responsive to NPY. Concerning the melanocortin system, histochemical studies suggest that NPY neurons in the ARC largely contain GABA (Horvath et al., 1997), and NPY/AGRP neurons contact and inhibit adjacent POMC neurons by releasing the inhibitory neurotransmitter GABA (Acuna-Goycolea et al., 2005).

In chicks, GABA has been shown to exist in various regions of the brain (Csilag et al., 1987; Stewart et al., 1988; Granda and Grossland, 1989), as it does in mammals. Although there is considerable evidence that GABA in the CNS directly and indirectly induces hyperphagia in chickens (Jonaïdi et al., 2002; Takagi et al., 2003; Bungo et al., 2003), little is known concerning the relationship with the components in the hypothalamic melanocortin system. Further histochemical and mRNA expression studies will be needed to understand the role of GABA in the melanocortin system.

2.1.5. Fatty Acid Synthase (FAS)
FAS, a critical enzyme in de novo lipogenesis, catalyzes the seven steps in the conversion of malonyl-CoA and acetyl-CoA to palmitate in the cytoplasm. FAS inhibition has been shown to facilitate weight loss through increased peripheral utilization of fat as well as reduction of feed intake in mammals (Ronnett et al., 2005). Additionally, FAS is expressed in various sites of the brain, and co-localized with NPY in neurons in the ARC. Inhibitor experiments revealed that 3-carboxy-4-alkyl-2-methylene-butyrolactone (C75), a specific inhibitor of FAS, alters feed intake via interactions within the ARC-PVN pathway mediated by NPY in mice. (Kim et al., 2002). C75 also prevents the hypophagia-induced increases in mRNA for AGRP in the ARC of rodents (Aja et al., 2006), suggesting that FAS may be involved in the mammalian melanocortin system.

Similar to mammals, FAS is found in a number of brain regions, including the IN, and peripheral administration of FAS inhibitor significantly reduces feed intake in chickens (Dridi et al., 2006). Dridi et al. (2006) also revealed that the inhibitor decreased gene expressions of the MC1, MC4 and MC5 receptors, but not NPY, AGRP and POMC in the brain of chickens. These results suggest that the central FAS in chickens may participate in the regulation of feeding behavior through the melanocortin system. Although experiments aimed at determining the role of FAS in the melanocortin system of neonatal chicks have not been performed, our recent research shows that ICV injection of C75 reduces feed intake in chicks (Bungo et al., unpublished data), suggesting the central FAS in neonatal chicks may also be involved in the melanocortin system, comparable to mammals.

2.1. Peripheral Signals to the CNS
2.2.1. Leptin
The discovery of leptin, the adipocyte-derived protein hormone providing this signal (Zhang et al., 1994), plays an important role in defining the neuronal circuitry in the hypothalamic controlling feed intake in mammals (Schwartz et al., 2000). Peripheral leptin administration results in activation of hypothalamic neurons expressing the leptin receptor (Håkansson et al., 1998), suggesting a hypothalamic mediation of leptin effects on satiety. In the hypothalamic ARC, leptin facilitates satiety through inhibition of the NPY/AGRP neurons while stimulating POMC
neurons (Sahu, 2003) and CART (Kristensen et al., 1998). Leptin acutely suppresses NPY-induced feeding and on a long term basis in rats (Xu et al., 1998). NPY-deficient mice demonstrated leptin-induced suppression of feeding, suggesting the importance of other pathways in the action of leptin (Erickson et al., 1996). Blockade of MC4R reduces the ability of leptin to inhibit feed intake, suggesting that the melanocortin pathway has a major role in mediating leptin effects (Seeley et al., 1997).

The chicken leptin cDNA sequence that shares 95% and 97% sequence identity with mouse leptin at the nucleotide and amino acid level, was cloned (Taouis et al., 1998; Ashwell et al., 1999). The effect of central administration of mammalian or recombinant chicken leptin is consistent with an inhibitory influence of the hormone on feed intake in chickens (Denbow et al., 2000; Dridi et al., 2000). Continuous infusion of chicken leptin down-regulates the expression of the MC4R, MC5R, leptin and NPY receptors but does not affect POMC or AGRP mRNA expression in the hypothalamus (Dridi et al., 2005). There is evidence that the cloned chicken leptin receptor shows conservation of the key motifs in the long form (Horev et al., 1999; Ohkubo et al., 2000) and short form (Liu et al., 2007), and a leptin-like signaling system is present (Adachi et al., 2008). On the other hand, several independent laboratories have been unable to amplify the reported sequence by PCR (Friedman-Einat et al., 1999; Petel et al., 2000; Amills et al., 2003), and infusion of mouse leptin is ineffective in feeding behavior in chicks (Bungo et al., 1999). Thus, the existence of a natural chicken leptin gene and its encoded protein should be unequivocally established before progress can be made in understanding the effects of leptin on energy balance in birds (Sharp et al., 2008).

2.2.2 Insulin

Insulin is well recognized as the key glucostatic regulator. Recent data show that in addition to the control of glucose uptake in peripheral areas, this role also encompasses powerful central effects, in synergy with leptin. Insulin receptors and components of the insulin-signaling pathway are also widely distributed in the CNS, and regulate vital physiological processes in mammals (Pagotto, 2009). Recently, it has been suggested that impairment in brain insulin availability or signaling results in serious problems such as metabolic, mental or reproductive disorders (Saltiel and Kahn, 2001; Obici et al., 2002; Gerozissis, 2004). Tschritter et al. (2006) reported that CNS insulin resistance contributes to human obesity. It has been proposed that insulin resistance may not only be a consequence of, but also involved in the etiology of obesity in humans (Pagotto, 2009). Insulin has been suggested to have anorexic effects centrally (Woods et al., 1979), and notably, the ARC is one of the prominent sites of insulin receptor expression in mammals (Corp et al., 1986; Marks et al., 1990). Insulin down-regulates NPY and AGRP gene expression and increases POMC gene expression in the mammalian ARC (Schwartz et al., 1992; Benoit et al., 2002), suggesting that the anorexigenic effects of insulin are associated with the melanocortin system.

Like mammals, the insulin receptor is present in the CNS of chickens (Simon and Leroith, 1986). Injection of insulin into the lateral ventricle of chicks inhibits feed intake, and increases expression of POMC mRNA and decreases that of NPY mRNA (Shiraishi et al., 2008a, b, 2009). Also, the melanocortin antagonists prevent the anorexic effect of insulin. Recently, we found that the expression of chicken insulin receptors in the CNS by nutrient conditions, to be localized in the IN (Shiraishi et al., unpublished data). These findings suggest that the central melanocortin system mediates the anorexia by central insulin, as in mammals. Further studies are therefore required for the insulin receptor to be co-localized with the POMC or NPY neurons in the chicken IN.

2.2.3 Ghrelin

Ghrelin, identified from rat stomach as an endogenous ligand for the growth hormone secretagogue receptor, is unique as the first gut hormone (Kojima et al., 1999), and is shown to stimulate feeding behavior (Strader and Woods, 2005). It further stimulates feeding by its action on NPY/AGRP neurons and inhibition on POMC neurons in the CNS (Cowley et al., 2003a; Greenman et al., 2004), suggesting the role of the melanocortin pathway in transmitting gut hunger signals to the mammalian brain. Ghrelin increases c-fos activity in the NPY/AGRP neurons but not in the POMC neurons (Wang et al., 2002), and the hyperpolarization of POMC neurons thus induced by ghrelin might be mediated through GABA release by NPY/AGRP neuron depolarization (Cowley et al., 2003b). While leptin might transmit energy balance signals over a long term, the gut hormones might mediate short term signaling due to rapid fluctuation with meals.

Chicken ghrelin, containing a 26 amino acid peptide, has been cloned and identified (Kaiya et al., 2002), and has a variety of physiological functions, as in mammals (see Review, Kaiya et al., 2007a). The levels of ghrelin and its mRNA in chicks are changed by nutritional condition, like in mammals (Kaiya et al., 2007b). However, dissimilar to mammalian results, central administration of ghrelin or its agonist has the opposite effect on feeding: it prevents fasting- and NPY-induced hyperphagia (Saito et al., 2002, 2005; Khan et al., 2006). Also the expression of NPY mRNA in the CNS is not altered by ghrelin infusion (Saito et al., 2005). Interestingly, recent data show that peripheral injection of chicken ghrelin has a short acting orexigenic effect, and acutely up-regulated hypothalamic FAS mRNA levels in chicks (Buyse et al., 2009). This finding indicates that the effects of ghrelin in the melanocortin system in chicks remain to be fully explored.

3. Conclusions

Figure 3 shows a schematic diagram for the predicted melanocortin system in the IN of chickens. Population of first-order NPY/AGRP and POMC neurons, which are mutually connected with synapses, are regulated by pe-
Fig. 3. Schematic diagram depicting the predicted hypothalamic infundibular nucleus (IN) neuronal network. See text for details. NPY, neuropeptide Y; AGRP, agouti-related protein; POMC, pro-opiomelanocortin.

Peripheral signals

Second-order and downstream neurons

POMC

NPY/AGRP

IN

3rd ventricle

rhythmic hormonal and nutrient/metabolic signals, and project to second-order hypothalamic neuropeptide neurons involved in the regulation of feed intake. Although details for the receptors are not indicated, some receptors for the numbers of hormones, neuropeptides and neurotransmitters (e.g., MOR, NPY Y1, and GABA receptors) known to regulate the network are assumed to exist in the hypothalamic melanocortin system, as in mammals. Furthermore, detailed second-order hypothalamic neuropeptide neurons (e.g., corticotropin-releasing hormone, galanin, melanin-concentrating hormone and so on) are not described in this review due to lack of space. Some of the studies described in the present review are only initial studies, and more work remains to be carried out with regard to the precise mapping in the CNS of the synthesis and release of neuropeptides related to their feeding regulatory activities, and the innervation and localization of their receptors in the CNS. A better understanding of feeding regulation may aid the selection of chickens for production and animal welfare.

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