Gut Hormones and Regulation of Food Intake in Birds

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Gut hormones act as appetite regulatory hormones in mammals. For example, the hunger hormone ghrelin, which is released from the stomach before food intake, stimulates appetite. In contrast, satiety hormones such as cholecystokinin (CCK), glucagon-like peptide (GLP)-1, and peptide YY (PYY), which are released from the intestines after food intake, suppress appetite. The effects of these peptides on food intake have been shown to be similar in both mammals and fishes. However, evidence suggests that the physiological roles of these gut hormones may be different between birds and other vertebrates. This review summarizes the current information on the roles of gut hormones in the regulation of food intake in birds, especially in chickens.

Key words: brain, chicken, gut hormones, hypothalamus, intestine

Introduction

The appetite regulatory system has been a focus of research for more than half a century (Woods, 2013). The brain integrates information from peripheral hormones, such as leptin, insulin and gut hormones, and consequently regulates food intake: adiposity hormones such as leptin and insulin are secreted in proportion to body fat and suppress food intake, whereas gut hormones are secreted before or after meals and regulate food intake (Woods, 2009; Sam et al., 2012; Williams and Elmquist, 2012). In chickens, central administration of leptin (Denbow et al., 2000) and insulin (Honda et al., 2007; Shiraishi et al., 2008) suppresses food intake. However, there is much debate on the physiological significance of leptin and insulin as adiposity hormones in birds. For example, the mRNA levels of leptin in adipose tissue were extremely low in chickens (Seroussi et al., 2016), zebra finches (Huang et al., 2014), and rock doves (Friedman-Einat et al., 2014) and relatively low in Japanese quail (Seroussi et al., 2016). Plasma insulin levels were not correlated with either abdominal fat mass or the mRNA levels of appetite-regulating neuropeptides in the hypothalamus in layer chickens (Honda et al., 2015a). Therefore, leptin and insulin may not be primarily involved as adiposity hormones in the regulation of food intake in chickens. Birds need to fly. Therefore, birds may have developed so as not to increase their body fat mass for flying. The physiological roles of adiposity signals in the appetite regulatory system might be lost in birds or developed subsequently in mammals. In other words, the appetite-regulating role of gut hormones in birds might be physiologically more important than that in mammals.

Many studies on the regulatory mechanism of food intake have revealed that gut hormones, such as ghrelin, cholecystokinin (CCK), glucagon-like peptide (GLP)-1, and peptide YY (PYY) play critical roles in the regulation of food intake in mammals. Ghrelin is released from the stomach and transmits the hunger signal to the brain before food intake, resulting in the stimulation of appetite. CCK, GLP-1, and PYY are released from the intestines and transmit satiety signals to the brain after food intake, resulting in the suppression of appetite (Woods, 2009; Sam et al., 2012; Williams and Elmquist, 2012). Recent studies on various species of fish have demonstrated the orexigenic effect of ghrelin (Riley et al., 2005; Matsuda et al., 2006a, 2006b; Penney and Volkoff, 2014) and anorexigenic effects of CCK (Himick and Peter, 1994; Volkoff et al., 2003; Penney and Volkoff, 2014; White et al., 2016), GLP-1 (Silverstain et al., 2001; White et al., 2016), and PYY (Gonzalez and Unniappan, 2010, 2016; Chen et al., 2013, 2015). These findings suggest that the appetite-regulating roles of the gut hormones may have been conserved among vertebrates. All the gut hormone genes are expressed in the gastrointestinal tract of chickens (Fig. 1): ghrelin mRNA is densely expressed in the proventriculus, the glandular stomach of chickens, whereas mRNAs of CCK, PYY, and proglucagon (the precursor of GLP-1) are expressed in the small intestine. These gut hormones might provide information about gastrointestinal transit and emptying to the brain. However, an increasing amount of evidence suggests the hypothesis that the physiological roles of these gut hormones in birds...
somewhat differ from those of other vertebrates. In this review, we summarize the current information on the possible role of gut hormones in the regulation of food intake in birds.

**Ghrelin**

Ghrelin is a peptide that was purified and identified in the stomach of rats as an endogenous ligand specific for the growth-hormone secretagogue receptor (Kojima et al., 1999). Wren et al. (2000) first reported that intraperitoneal (IP) administration of ghrelin stimulated food intake in freely feeding rats. They also demonstrated that ghrelin is the first circulating hormone to stimulate food intake in humans (Wren et al., 2000). However, a number of studies on ghrelin suggest that ghrelin functions as an anorexigenic peptide in birds (Table 1). For example, peripheral administration of ghrelin suppressed food intake in broiler chicks (Buyse et al., 2009; Geelissen et al., 2006; Ocłon, 2011). These findings suggest that ghrelin does not function as a peripheral hunger hormone in chickens.

Ghrelin mRNA is densely expressed in the proventriculus of chickens (Kaiya et al., 2002) and ducks (Shao et al., 2010). Ghrelin mRNA and immunopositive cells have been detected in both the proventriculus and small intestine of the ostrich (Wang et al., 2009, 2011). In layer chicks and Japanese quail, plasma ghrelin levels were elevated after fasting, and the elevation of plasma ghrelin was reversed by refeeding (Shousha et al., 2005a; Kaiya et al., 2007). Avian ghrelin receptors have been identified in chickens (Tanaka et al., 2003), Japanese quail (Kitazawa et al., 2009), and ducks (Nie et al., 2009) and are widely distributed in the brain (Geelissen et al., 2003; Tanaka et al., 2003; Nie et al., 2009) and peripheral tissues (Geelissen et al., 2003; Tanaka et al., 2003; Kitazawa et al., 2009; Nie et al., 2009). Shousha et al. (2005a) reported that IP administration of low doses (0.5–1 nmol/bird) of ghrelin stimulated food intake in Japanese quail, although the highest dose (3 nmol/bird) of ghrelin suppressed food intake. These results are similar to the results of mammalian studies, although the effect of ghrelin on food intake in chickens differed from that in mammals. Chickens might not feel hungry, even when there are no digesta in their stomachs. However, the physiological roles of ghrelin might be different between bird species. Further studies are required to evaluate whether ghrelin suppresses food intake in other avian species.

**Cholecystokinin**

CCK is produced in the small intestines of chickens and ostrich (Jonsen et al., 2000) and both small and large intestines of ducks (Castaldo and Lucini, 1991, 1994). Dietary protein, amino acids, and fat stimulate CCK release in chickens (Furuse, 1999). Peripheral administration of CCK suppressed food intake in chickens (Table 1) (Savory and Gentle, 1983; Covasa and Forbes, 1994; Rodriguez-Sinovas et al., 1997; Tachibana et al., 2012), and the satiety effect of CCK has been suggested to be mediated by the vagus nervous system in broiler chickens (Covasa and Forbes, 1994) as well as mammals (Ritter and Ladenheim, 1985; Smith et al., 1985; Moran et al., 1997). Administration of type A CCK receptor antagonist, but not type B receptor antagonist, increases the meal size in mammals (Moran et al., 1993; Beglinger et al., 2001; Reidelberger et al., 2003). Chicken CCK receptors have been cloned and widely expressed in the brain and peripheral tissues (Nilsson et al., 2003; Ohkubo et al., 2007). Dunn et al. (2013) reported that chickens with the high-growth type A CCK receptor haplotype are resistant to the anorectic effect of exogenously administered CCK. They suggested that the satiety set point was altered, and decreased expression of the type A CCK receptor was responsible for increased growth and body weight during the domestication of chickens.

### Table 1. Effects of peripheral administration of gut hormones on food intake in birds

| Hormone                | Food intake   | Bird       | Dose                | Rout    | Reference                  |
|------------------------|---------------|------------|---------------------|---------|----------------------------|
| **Orexigenic hormone in mammals** |
| Ghrelin                | Decreased     | Broiler chicken | 1 nmol/bird   | IV      | Buyse et al., 2009         |
|                        | Decreased     | Broiler chicken | 10 nmol/kg BW  | IV      | Geelissen et al., 2006     |
|                        | Decreased     | Broiler chicken | 5–20 nmol/kg BW | IP      | Ocłon, 2011                |
|                        | No change     | Layer chicken | 500 pmol/bird     | IV      | Kaiya et al., 2007         |
|                        | Decreased     | Japanese quail | 3 nmol/bird      | IP      | Shousha et al., 2005a      |
|                        | Increased     | Japanese quail | 0.5–1 nmol/bird  | IP      | Shousha et al., 2005a      |
| **Anorexigenic hormones in mammals** |
| Cholecystokinin        | Decreased     | Layer chicken | 2–8 μg/kg BW     | IV      | Savory and Gentle, 1983    |
|                        | Decreased     | Broiler chicken | 3.5–28 μg/kg BW | IP      | Covasa and Forbes, 1994    |
|                        | Decreased     | Layer chicken | 10 nmol/kg BW    | IV      | Rodriguez-Sinovas et al., 1997 |
|                        | Decreased     | Layer chicken | 60–300 nmol/kg BW| IP      | Tachibana et al., 2012     |
| Glucagon-like peptide-1| Decreased     | Japanese quail | 0.5–1 nmol/bird  | IP      | Shousha et al., 2007       |
|                        | No change     | Layer chicken | 0.12–3 nmol/bird | IP      | Tachibana et al., 2003     |
| Glucagon-like peptide-2| Decreased     | Broiler chicken | 1.5 nmol/kg BW  | IV      | Honda et al., 2015d        |
| Peptide YY             | Decreased     | Broiler chicken | 3–6 nmol/kg BW  | IV      | Aoki et al., 2017          |

Abbreviations used: BW, body weight; IV, intravascular administration; IP, intraperitoneal administration
However, the physiological importance of CCK in chickens as a satiety hormone has not yet been elucidated. For example, potent stimulators of CCK release did not alter the food intake of chickens (Furuse, 1999). Devazepide, a cholecystokinin-A receptor antagonist, did not increase the food intake of chickens (Choi et al., 1994). Further studies are required to evaluate the physiological importance of CCK among various gut hormones in chickens.

**Glucagon-like peptide-1**

GLP-1 is released from the intestine in response to food ingestion in mammals (Tolhurst et al., 2009). A metaanalysis revealed that intravascular administration of GLP-1 reduces energy intake in humans (Verdich et al., 2001). GLP-1 can directly stimulate anorectic pathways in the brain or indirectly stimulate them through the vagus nervous system (Abbott et al., 2005a; Van Bloemendaal et al., 2014). In chickens, frequencies of occurrence of GLP-1-immunoreactive cells were influenced by food deprivation (Monir et al., 2014a), dietary protein levels (Monir et al., 2014b), and dietary amino acids (Nishimura et al., 2015). GLP-1 immunoreactive cells were detected in the small intestine of ducks (Ding et al., 2013). GLP-1 receptor mRNA is widely distributed in both the brain and gastrointestinal tract of chickens (Huang et al., 2012). IP administration of GLP-1 significantly suppressed the food intake of Japanese quail (Shousha et al., 2007). However, the physiological importance of GLP-1 in birds as a satiety hormone has not yet been elucidated. For example, IP administration of GLP-1 did not influence food intake and crop emptying in layer chicks (Tachibana et al., 2003). In contrast, IP administration of GLP-1 suppresses food intake in Japanese quail (Shousha et al., 2007). Richards and McMurtry (2008) reported that plasma GLP-1 levels were not influenced by fasting and refueling in broiler chickens. Further studies are required to evaluate the physiological importance of GLP-1 among various gut hormones in birds.

**Glucagon-like peptide-2**

GLP-2 is produced from the same precursor of GLP-1 in mammals (Janssen et al., 2013) and chickens (Honda, 2016). Immunohistochemical and morphometric studies of chickens suggest that GLP-2 colocalizes with GLP-1 in the same secretory granules of L cells in the small intestine of chickens (Monir et al., 2014c; Nishimura et al., 2013). Intravascular administration of GLP-2 suppressed the food intake of chicks (Honda et al., 2015d). GLP-2 receptor mRNA is expressed in the brain and gastrointestinal tract of chickens (Richards & McMurtry, 2008; Mo et al., 2014). Therefore, it is possible that GLP-2 acts as a postprandial satiety hormone in chickens. Studies on humans have not reported the satiety effect of peripheral GLP-2 (Schmidt et al., 2003; Sorensen et al., 2003). The most apparent role for GLP-2 is its promotion of growth and function of the intestinal mucosa in mammals (Janssen et al., 2013). Thus, the physiological role of GLP-2 may be different between mammals and chickens.

**Peptide YY**

In 1992, PYY was isolated from the small intestine of adult layer chickens (Conlon and O’Harte, 1992). Amino acid sequence analysis revealed the presence of an additional N-terminal alanine residue, and an extract of the chicken intestine did not contain PYY3-36, the major form of PYY in mammals (Conlon and O’Harte, 1992). PYY-immunoreactive cells were detected in the duodenum and jejunum of chickens (El-Salhy et al., 1982). In contrast, PYY was abundantly expressed in the large intestine rather than the small intestine of mammals (Ekblad and Sundler, 2002; Zhou et al., 2006; Ueno et al., 2008). Recently, we identified the full-length cDNA sequence for chicken PYY and found that the PYY mRNA was densely expressed in the small intestine but not in the large intestines of chicks (Aoki et al., 2017). These findings clearly demonstrate that the N-terminal sequence of PYY and the production sites of PYY in the gastrointestinal tract are different between mammals and chickens.

The plasma concentration of PYY is elevated after feeding (Zwirski-Korczała et al., 2007; Stadlbauer et al., 2013) and after the intraintestinal administration of nutrients in mammals (Fu-Cheng et al., 1995). Peripheral administration of PYY3-36 reduces food intake in humans and rodents (Batterham et al., 2002; Martin et al., 2004; Degen et al., 2005; Scott et al., 2005; Chelikani et al., 2007). Peripheral PYY3-36 transmits satiety signals to the brain via the neuropeptide Y receptor Y2 (Y2R) in the hypothalamus and/or gastric vagal afferent nerves in mammals (McGowan and Bloom, 2004; Abbott et al., 2005b; Ueno et al., 2008). In chickens, PYY mRNA levels were significantly higher under ad libitum feeding conditions than under 12-h-fasting conditions (Aoki et al., 2017). An in vitro binding assay demonstrated that chicken PYY preferentially binds to Y2R (Salanek et al., 2000). Y2R mRNA was expressed in the brain and peripheral tissues of chickens (Bromée et al., 2006). We recently found that the intravascular administration of chicken PYY significantly decreased the food intake of chicks in a dose-dependent manner (Aoki et al., 2017). These findings suggest that PYY may function as a satiety hormone in chickens as well as mammals.

**Conclusions and Future Research**

The appetite regulatory system of chickens has been a focus of research in recent decades. Increasing evidence has raised the hypothesis that the physiological roles of CCK, GLP-1, and PYY as satiety hormones have been conserved during the evolutional process in chickens. In addition, the anorexigenic action of other peptides expressed in the gastrointestinal tract, such as GLP-2 (Honda et al., 2015c), oxyntomodulin (Honda et al., 2014), growth hormone releasing hormone (Tachibana et al., 2015), and neuregulin U (Shousha et al., 2005b; Kamisoyama et al., 2007; Honda et al., 2015b), has been reported in birds. Birds need to fly. Therefore, birds may have developed not to increase intestinal content as much as possible. The satiety system
regulated by gut hormones in birds may be more complex than we thought. The combinational effect of gut hormones, routes that mediate the satiety signals to the brain, and the mechanism underlying the integration of peripheral satiety signals in the brain need to be clarified. However, it is possible that unknown adipokines function as appetite-regulating hormones and/or influence the appetite-regulating effect of gut hormones in birds. Further studies might also be needed to clarify the relationship between adipokines and gut hormones in the appetite regulatory system in birds. Recent technical advances in avian transgenesis allow efficient extensions of experimental protocols and research areas (Park et al., 2013; Naito 2015), and therefore, in the future, highly developed genome editing technology will contribute to understanding the physiological importance of each gut hormone in birds.

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