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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, glucagon-like peptide-1, and peptide YY, 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

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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

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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; Ocłoń, 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 (Jønson *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; Rodríguez-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	Rodríguez-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 meta analysis 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 refeeding 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 PYY_{3-36}, 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 (Zwirska-Korczala *et al*., 2007; Stadlbauer *et al*., 2013) and after the intraintestinal administration of nutrients in mammals (Fu-Cheng *et al*., 1995). Peripheral administration of PYY_{3-36} 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 PYY_{3-36} 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 (Salaneck *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 neuromedin 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

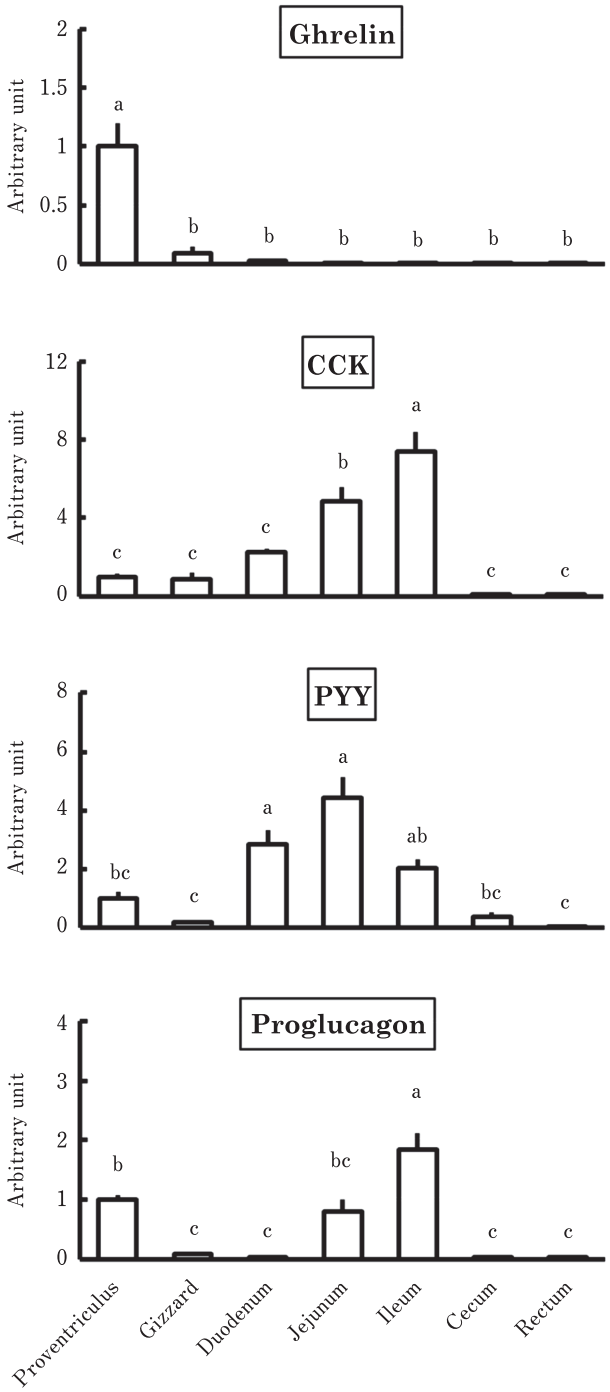

Fig. 1. **Comparison of the mRNA levels of ghrelin, cholecystokinin (CCK), peptide YY (PYY) and proglucagon in the gastrointestinal tract of 8-day-old broiler chicks.** Real-time PCR analysis was performed to quantify the mRNA levels of the gut hormones. The mRNA levels of ribosomal protein S17 (RPS17) were also analyzed as the internal standard. Values represent the mean±SEM of four birds. Different letters above each bar denote statistical significance ($P<0.05$, Tukey-Kramer test). Complementary DNAs of ghrelin and CCK were amplified with the primers as follows: ghrelin sense, 5′-CCC ACA TAT AAA AAC ATA CAG CAA CA-3′; ghrelin antisense, 5′-GCC TCG GCG ATG TAA TCT TG-3′; CCK sense, 5′-GCG CTG CTG GCC AAG TA-3′; and CCK antisense, 5′-GAC AGA GAA CCT CCC AGT GGA A-3′. Complementary DNAs of PYY, proglucagon, and RPS17 were amplified with the primers described previously (Honda *et al*., 2015d, Aoki *et al*., 2017). This experiment was approved by the Institutional Animal Care and Use Committee (Permission number: 25-08-01) and carried out according to the Kobe University Animal Experimental Regulation.

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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