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PDF issue: 2025-12-05

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(Citation)
World's Poultry Science Journal,77(2):301-312

(Issue Date)
2021-04-03

(Resource Type)
journal article

(Version)
Accepted Manuscript

(Rights)
This is an Accepted Manuscript of an article published by Taylor & Francis in [World's Poultry Science Journal on 2021] available online:
http://www.tandfonline.com/10.1080/00439339.2021.1898296

(URL)
https://hdl.handle.net/20.500.14094/90008491

Peripheral regulation of food intake in chickens -adiposity signals, satiety signals, and others-

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Abbreviated Title: Food intake in chickens

Summary

Broiler chickens eat more food and grow faster than layer chickens. However, hyperphagia-induced excessive accumulation of body fat in broiler chickens has become a serious problem in the modern poultry industry. Species specificity in terms of the physiological role of appetite-regulating hormones and neuropeptides can make it difficult to understand the mechanisms underlying the central regulation of food intake in chickens. Therefore, although the appetite regulatory system of chickens has been a focus of research in recent decades, the mechanisms underlying the hyperphagia of broiler chickens is not fully understood. Our previous studies demonstrated that peripheral hormones significantly suppress food intake in chicks. These findings suggest that postprandial elevation of peripheral anorexigenic hormones play important roles in appetite regulation in chickens. This review provides an overview of recent findings on the role of peripheral hormones in the regulation of food intake in chickens and propose the new insight of avian-species specific system of peripheral regulation of food intake and promising strategies for reducing body fat mass in broiler chickens.

Key words: adiposity, appetite, gut hormones, satiety

Introduction

Modern broiler chickens, which are bred for rapid growth and high meat yield, develop hyperphagia. Consequently, their overconsumption of food can lead to excessive accumulation of visceral fat, which is regarded as an animal by-product or as waste. In addition, excessive fat accumulation may lead to metabolic diseases, which are serious

problems for the poultry industry (Julian 2005). Thus, the appetite regulatory system of chickens has been a focus of research in recent decades (Denbow 1994; Richards and Proszkowiec-Weglarz, 2007; Boswell and Dunn 2017). In mammals, appetite is regulated in response to the energy demands of the body. For example, adiposity signals, such as leptin and insulin, provide information about body fat mass to the brain, and thereby suppress appetite (Schwartz et al. 2000). Satiety signals, such as cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), provide information about meal intake to the brain, and thereby suppress appetite (Sam et al. 2012; Woods 2009). However, lines of evidence suggest that the physiological roles of these signals are different between mammals and chickens. The role of adiposity signals, satiety signals, and other signals in chickens is summarized herein, and new insight and future perspectives are provided.

Adiposity signals

Leptin

The hyperphagic and obese phenotypes of ob/ob mice are a result of a lack of gene encoding leptin, a hormone secreted by adipocytes (Zhang et al. 1994). Lines of evidence revealed that leptin plays an important role as an adiposity signal in mammals (Schwartz et al. 2000). In chickens, central administration of mammalian leptin suppressed food intake in broiler and layer chickens (Denbow et al. 2000). However, avian orthologs of leptin are densely expressed in the brain, but not in the adipose tissue, in chickens (Seroussi et al. 2016; Farkašová et al. 2016) and zebra finches (Huang et al. 2014). Miller (2014) concluded that the

orthologs are not compatible with an adipocyte signaler to appetite centers in the hypothalamus in mammals. Leptin receptors are densely expressed in the pituitary in chickens (Seroussi et al. 2016), rock doves (Friedman-Einat et al. 2014), zebra finches (Huang et al. 2014), and Japanese quails (Wang et al. 2016). All these findings suggest that leptin does not function as an adiposity signal in chickens, although it may play other physiological roles in in the brain.

Insulin

In mammals, the pancreatic hormone insulin is known to be an adiposity signal (Schwartz et al. 2000). An orexigenic peptide neuropeptide Y (NPY) and an anorexigenic peptide α-melanocyte stimulating hormone (α-MSH) are involved in the appetite suppressive pathway of insulin in the central nervous system (Schwartz et al. 2000; Woods 2009). There is evidence that central administration of insulin suppresses food intake in chicks (Honda et al. 2007; Shiraishi et al. 2008). Shiraishi et al. (2011) demonstrated co-localization of the insulin receptor and α-MSH or NPY in the infundibular nucleus of the chick hypothalamus. We also showed that hypothalamic Akt-mediated signaling is involved in the anorexigenic action of insulin, the same as in mammals (Saneyasu et al. 2018). All these findings suggest that insulin plays an important role in appetite regulation in chickens. However, blood insulin levels were not correlated with abdominal fat mass in chickens (Honda et al. 2015a). It is therefore possible that insulin does not function as an adiposity signal in chickens. On the other hand, lines of evidence clearly demonstrated that plasma levels of insulin are elevated after refeeding in chickens (Bigot et al. 2003; Richards and McMurtry 2008). It seems likely that

insulin functions as a satiety signal in chickens. Further study is required to clarify the physiological importance of insulin in the regulation of food intake in chickens.

Adipokines

Adipokines play a pivotal role in the metabolic homeostasis of healthy subjects (Cao 2014). Daković et al. (2014) suggested a loss of adipokine genes in the chicken genome. Thus, the physiological roles of adiposity signals in the appetite regulatory system could be lost in birds and may have developed subsequently in mammals. However, Resnyk et al. (2013) reported that chicken abdominal fat serves a dual function as both an endocrine organ and an active metabolic tissue. Nesfatin-1, an adipokine in mammals, was detected in the serum of chickens (Morton et al. 2018) and has an anorectic effect in broiler chicks (Heidarzadeh et al. 2018). Tumor necrosis factor-like ligand 1A was expressed in adipose tissue in chickens (Takimoto et al. 2005) and its central administration suppressed food intake in layer chicks (Tachibana et al. 2018). Expression of adiponectin and its receptors in avian species have been well investigated (Ramachandran et al. 2013), but there is no evidence indicating that adiponectin regulates food intake in chickens. Further study is required to clarify the physiological role of adipokines in the regulation of food intake in chickens.

Satiety signals

Cholecystokinin

CCK has long been known as a satiety signal in mammals (Woods 2013). In chickens,

both central and peripheral administration of CCK suppressed food intake (Tachibana et al. 2012). Dunn et al. (2013) reported that decreased expression of the satiety signal receptor CCKAR was responsible for increased growth and body weight following the domestication of chickens. These findings suggest that CCK plays a physiological role in chickens. However, potent stimulators of CCK release did not alter the food intake in chickens (Furuse, 1999). Devazepide, a cholecystokinin-A receptor antagonist, did not increase the food intake in chickens (Choi et al. 1994). CCK mRNA was densely expressed in the distal small intestine in chickens (Honda et al. 2017), although the proximal small intestine is the CCK production area in mammals (CÔTÉ et al. 2012). Therefore, the physiological importance of CCK in the regulation of food intake in chickens has not yet been clarified.

Glucagon-like peptides

GLP-1 and GLP-2 are brain gut peptides resulting from cleavage of the precursor preproglucagon in mammals and chickens (Janssen et al. 2013; Richards and McMurtry 2008). GLP-1 functions as a satiety signal, and GLP-2 plays a physiological role as an intestinal growth factor in mammals (Janssen et al. 2013; Sam et al. 2012). In chickens, central administration of GLP-1 strongly suppressed food intake (Honda et al. 2015b). Intestinal L cells secrete GLP-1 in response to food ingestion in chickens, and proteins and amino acids such as lysine and methionine in the diet triggered GLP-1 secretion from the chicken intestinal L cells (Hiramatsu 2019). However, plasma levels of GLP-1 were not changed by 24 h of fasting or refeeding in chickens (Richards MP, McMurtry 2008). On the other hand, we found that central and peripheral administration of GLP-2 significantly

111 suppressed food intake in chicks (Honda et al. 2015b, 2015c). There is evidence that GLP-2
112 colocalized with GLP-1 in the same secretory granules in the ileum (Nishimura et al. 2013).
113 These findings suggest that GLP-2 plays an important role as a satiety signal in chickens.
114
115 Peptide YY
116 PYY was regarded as an orexigenic peptide in mammals (Hagan 2002). However,
117 Baterham et al. (2002) clearly demonstrated that PYY physiologically suppresses food intake
118 via the NPY Y2 receptor (Y2R) in mammals. Therefore, PYY is regarded as a satiety signal in
119 mammals. In chickens, PYY mRNA levels were significantly higher under ad libitum feeding
120 conditions than under a 12-h-fasting condition (Aoki et al. 2017). An in vitro binding assay
121 demonstrated that chicken PYY preferentially binds to Y2R (Salaneck et al. 2000). Y2R
122 mRNA was expressed in the brain and peripheral tissues of chickens (Bromée et al. 2006). We
123 recently found that the intravascular administration of chicken PYY significantly decreased
124 the food intake of chicks in a dose-dependent manner (Aoki et al. 2017). These findings
125 suggest that PYY functions as a satiety signal in chickens as well as in mammals.
126 PYY-immunoreactive cells were detected in the duodenum and jejunum of chickens (El-
127 Salhy et al. 1982). We recently found that chicken PYY mRNA was densely expressed in the
128 small intestine but not in the large intestine (Aoki et al. 2017). Reid et al. (2017) found that
129 the pancreas is the major site of PYY transcription and that the major site of gastrointestinal
130 PYY expression is around the distal jejunum in broiler chickens. In contrast, PYY was
131 abundantly expressed in the large intestine rather than the small intestine in mammals (Ekblad
132 and Sundler 2002; Zhou et al. 2006; Ueno et al. 2008). These findings suggest a species-

133 specific difference in the physiological roles of PYY between mammals and chickens.

134

135 **Other signals**

136 Ghrelin

137 Ghrelin functions as an orexigenic hormone in mammals; it suppresses food intake and
138 ghrelin plasma levels of it decrease after meals (Sam et al. 2012). However, the role of ghrelin
139 in appetite regulatory systems seems to be different between mammals and chickens. For
140 example, central and peripheral administration of ghrelin significantly suppressed food intake
141 in chickens (Kaiya et al. 2013), while plasma ghrelin levels were elevated after fasting, and
142 the elevation of plasma ghrelin was reversed by refeeding in chicks and Japanese quail
143 (Shousha *et al*., 2005a; Kaiya *et al*., 2007). Ghrelin had an anorexigenic action in amphibians
144 and fish (Jönsson 2013; Shimizu et al. 2014). All these findings suggest that the physiological
145 role of ghrelin as a hunger signal may be lost in birds. Insulin and glucocorticoid stimulate
146 ghrelin secretion in chickens, in contrast to mammals (Song et al. 2018). The abundant
147 expression of ghrelin and its receptor in the liver and abdominal fat pad may be associated
148 with energy balance (Song et al. 2019). Therefore, the role of ghrelin on the appetite and fat
149 metabolism in chickens would be different from that of ghrelin in mammals.

150

151 Insulin-like growth factor-1

152 Duclos et al. (1999) suggested that the insulin-like growth factor (IGF) system in birds
153 exhibits the same general characteristics as in mammals. Recent findings also suggested that
154 IGF-1 upregulates the protein synthetic pathway and downregulates the protein degradative

155 pathway in chicken myotube cultures (Nakashima and Ishida 2017; Nakashima et al. 2017).
156 In mammals, the anorexigenic effect of IGF-1 has been observed only in diabetic rats (Lu et
157 al. 2001). Birds maintain higher plasma glucose concentrations than other vertebrates of
158 similar body mass (Braun and Sweazea 2008). However, the effect of IGF-1 on food intake in
159 chickens has not been investigated. We recently found that central and peripheral
160 administration of IGF-1 significantly suppressed food intake in chicks (Fujita et al. 2017).
161 There is evidence that plasma levels of IGF-1 are elevated by refeeding in chickens (Kita et
162 al. 1998). We also showed that hypothalamic Akt-mediated signaling is involved in the
163 anorexigenic action in IGF-1 (Fujita et al. 2019). These findings suggest that IGF-1 functions
164 as a satiety signal in chickens. The hepatic mRNA levels of insulin-like growth factor binding
165 protein (IGFBP)-1 and 2 decreased after refeeding in chicks (Fujita et al. 2018), suggesting
166 that IGFBP-1 and 2 may negatively regulate the anorexigenic function of IGF-1 in chickens.
167 Further study is needed clarify the physiological importance of IGF-1 and IGFBPs in the
168 regulation of food intake in chickens.
169
170 Myokines
171 Birds need to have adequate breast muscles for wing flapping. However, too much breast
172 muscle increases body weight and can interfere with the ability to fly. It is therefore possible
173 that birds have evolved to maintain an optimum weight of skeletal muscles for flying. Skeletal
174 muscles produce and secrete myokines including irisin, interleukin 6 (IL6), interleukin 8
175 (IL8), and brain-derived neurotrophic factor (BDNF), which exert auto-, para- and/or
176 endocrine effects (Schnyder and Handschin 2015). Central administration of irisin suppressed

177 food intake in diabetic rodents (Duan et al. 2016). Therefore, some myokines act as appetite-
178 regulating hormones in mammals. In chickens, Byerly et al. (2009) concluded that BDNF
179 may constitute a homeostatic mechanism that links hypothalamic energy regulation to control
180 body composition, but the appetite-suppressive action of BDNF has not been investigated.
181 Visfatin, an adipokine in mammals, is highly expressed in the skeletal muscles in chickens
182 (Krzysik-Walker et al. 2008; Li et al. 2017). Plasma visfatin levels determined by enzyme
183 immunoassay were significantly higher in 8-wk-old compared with 4-wk-old broiler chickens
184 (Krzysik-Walker et al. 2008). Central administration of visfatin significantly increased food
185 intake in broiler (Cline et al. 2008) and layer chicks (Li et al. 2018). Li et al. (2018) concluded
186 that visfatin causes hyperphagia via the proopiomelanocortin/corticotropin-releasing hormone
187 (CRH) and NPY/agouti-related protein (AgRP) signaling pathways in layer chicks. Tachibana
188 et al. (2017) showed that intracerebroventricular injection of IL6 and IL8 did not influence
189 food intake in chicks. Further study is required to clarify the physiological role of myokines
190 as an appetite regulating hormone in chickens.
191

192 **Conclusion and future perspectives**

193 Peripheral signals from circulating hormones released from the adipose tissue, pancreas,
194 and gastrointestinal tract are integrated in the brain, which in turn regulates food intake in
195 mammals (Schwartz et al. 2000; Morton et al. 2006; Woods and D'Alessio 2008; Woods
196 2009). However, physiological roles of peripheral hormones are different between mammals
197 and chickens as described below.

198 Adiposity signals including leptin and insulin are involved in the long-term regulation of

199 food intake, whereas satiety signals including gut hormones are involved in the short-term
200 regulation of food intake in mammals. In addition, satiety signal CCK appears to interact with
201 long-term signal leptin in rodents (Barrachina et al. 1997; Emond et al. 1999). On the other
202 hand, a peripheral hormone that is involved in the long-term regulation of food intake in
203 chickens have not been identified. In particular, identification of avian leptin genes (Huang et
204 al. 2014; Seroussi et al. 2016; Farkašová et al. 2016) would be enough to change our belief
205 described in the previous review articles (Richards and Proszkowiec-Weglarz 2007). In this
206 review, myokines emerge as candidates of peripheral hormones involved in the long-term
207 regulation of food intake in chickens. Further study will be required not only to identify the
208 physiologically important myokine but also to evaluate the relationships with other signals
209 including short-term satiety signals.

210 In contrast to the long-term signals, satiety signals would play more important roles in the
211 short-term regulation of food intake in chickens when compared with mammals. For example,
212 GLP-2 and IGF-1, which are not regarded as appetite regulating hormones in mammals, seem
213 to play important roles as a satiety signal in chickens. Birds need to fly. Therefore, birds may
214 have developed not to increase intestinal content as much as possible. However, the effects of
215 coadministration of satiety signals have not been examined, although these molecules
216 coordinately elevated in the bloodstream after food intake. In addition, the elevation of portal
217 vein nutrients such as glucose and amino acids suppressed food intake in chickens (Shurlock
218 and Forbes 1984). Gut fullness might also influence appetite in birds (Boswell and Dunn
219 2017). There is evidence that a satiation threshold is composed of not only hormones, but also
220 nutrients and other factors in mammals (Woods 2009). Taken together, further study will be

221 required to evaluate the relationships with satiety factors such as hormones, gut fullness, and
222 nutrients.

223 In mammals, the brain integrates incoming information in the form of hormonal and
224 neural signals via hypothalamus and brainstem (Schwartz et al. 2000; Morton et al. 2006;
225 Woods and D'Alessio 2008; Woods 2009). For example, insulin and leptin are sensed by
226 neurons in the hypothalamic arcuate nucleus, which contains two functionally different
227 neurons: (a) neurons that suppress food intake by releasing α-MSH; and (b) neurons that
228 stimulate food intake by releasing NPY and/or AgRP (Schwartz et al. 2000; Morton et al.
229 2006; Woods and D'Alessio 2008). The actions of α-MSH, NPY, and AgRP are mediated by
230 downstream neuropeptides, such as CRF in the paraventricular nucleus and MCH and orexin
231 in the lateral hypothalamic area (Schwartz et al. 2000). There is evidence that CCK and
232 proglucagon in the nucleus of the solitary tract are involved in the anorexigenic pathway of
233 leptin (Garfield et al. 2012). CCK-mediated suppression of feeding involves brainstem
234 melanocortin system (Fan et al. 2004). Similar model in poultry was proposed in birds
235 (Richards and Proszkowiec-Weglarz 2007; Bungo et al. 2011; Boswell and Dunn 2017).
236 However, it is presently uncertain how the regulation of the central melanocortin system in
237 birds is brought about in the situation of the apparently reduced importance of leptin and
238 ghrelin compared to mammals (Boswell and Dunn 2017). Also, interaction and cascades of
239 appetite-regulating neuropeptides between hypothalamic and brainstem have not been
240 identified in chickens. Furthermore, Song et al. (2013) proposed the model of AMPK actions
241 on hypothalamic gene expressions of chickens as well as in mammals (Woods 2009). Our
242 recent findings suggest that hypothalamic Akt-mediated signaling regulates food intake in

243 chicks (Saneyasu et al. 2018; Fujita et al. 2019). Further studies is needed to investigate the
244 effects of peripheral hormones on signaling molecules and neurotransmitters including
245 neuropeptides in the brainstem and clarify the detailed mechanism underlying the integration
246 of peripheral signals in the brain of chickens.

247 Supplementation of gut hormone secretagogues in feed to adequately suppress feed intake
248 may be effective for reducing body fat mass in broiler chickens. Also, if myokines provide
249 information about changes in the skeletal muscle mass to the brain, and thereby suppress
250 appetite, an increase in skeletal muscle mass could be a reasonable approach to reduce body
251 fat mass in broiler chickens. In conclusion, understanding the physiological roles of peripheral
252 hormones in the regulation in chickens will provide new strategies for reducing body fat mass
253 in broiler chickens.

254

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