Physiological and biochemical studies on the central and peripheral regulation of food intake in chicks

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博士論文内容の要旨

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論文題目（外国語の場合は，その和訳を併記すること。）

Physiological and biochemical studies on the central and peripheral regulation of food intake in chicks

（ニワトリヒナの中枢および末梢の摂食調節に関する生理生化学的研究）

指導教員　本田　和久

Over the last 80 years, chicken breeds have undergone intensive selection to optimize their productive performance. Rapid growth in meat-type chickens requires more feed consumption to cover the nutrient requirements. As a result, the intensive genetic selection in modern meat-type chickens has led to the development of hyperphagia. The rise in food consumption in broiler chickens has led to increased fat accretion, metabolic and health complications such as leg problems, and fatty liver syndrome. Feed restriction programs in broiler breeders has raised concerns regarding animal welfare due to the excessive feeling of hunger in birds. Therefore, identifying the regulatory mechanism of food intake in chickens is essential to finding solutions for health problems and improving animal welfare in the poultry industry.

Although the key genes involved in mammalian energy homeostasis were cloned and found to be conserved not only across mammals but also across all vertebrates, the anatomical and functional data on these genes varies among species from comparable to variable. For example, the adiposity signals leptin and insulin, which transmit the body fat levels to the brain, suppress food intake in mammals, whereas there is evidence that leptin and insulin may not function as adiposity hormones in chickens; the expression level of leptin was very low in adipose tissue, and there was no significant correlation between the plasma insulin levels and abdominal fat accumulation. The hunger signal ghrelin stimulates food intake in mammals but not in chickens. These findings clearly demonstrated that some aspects of the mechanisms of appetite regulation in chickens may differ from mammals.

Appetite-regulating neurons in the brain sense nutrient changes through satiety signals from peripheral hormones such as intestinal peptide YY and cholecystokinin (CCK) in mammals. Recent findings suggest that additional satiety signals, such as hepatic insulin-like growth factor-1 and pancreatic PYY, function in chickens. For example, central and peripheral administration of IGF-1 suppressed food intake in chicks. *PYY* mRNA levels were markedly higher in the pancreas than in the intestines, suggesting that the pancreas is the primary site of PYY production. In addition, intestinal receptors of gut hormones may also be involved in appetite regulation in chickens. CCK activates *CCK* receptor A (CCKAR) on gastrointestinal vagal afferents, causing suppression of the food intake in mammals. In chickens, there is evidene that the *CCKAR* expression levels in high growth haplotype chickens were lower than those in slow growth haplotype chickens, indicating an altered response to the CCK satiety signal in high growth haplotype chickens. These findings suggest that IGF-1, PYY, CCK, and their receptors are involved in the satiation of chickens.

The nucleus solitaries (NTS) in the brain stem receive satiety signals and convey these signals to the hypothalamus, the center of appetite regulation in mammals. Glucagon-like peptide *(GLP)-1* and 2, and *CCK* expressed in the NTS function as appetite suppressive neurotransmitters in mammals. The central administration of GLP-1 and 2 strongly suppressed food intake in chickens. The proglucagon mRNA levels in the chicken medulla oblongata were reduced by fasting. These findings raise the hypothesis that GLPs convey satiety signals to the hypothalamus in chickens.

In the present study, I investigated possible roles of satiety signals, such as pancreatic PYY, intestinal CCK, PYY, and their receptors, and hepatic IGF-related proteins. I also examined whether IGF-2 functions as a satiety signal in chicks like IGF-1. Finally, I investigated how GLP-1 and 2 influence appetite-regulating factors and signaling pathways in the hypothalamus in chicks. Our findings add new pieces, such as pancreatic PYY and IGF-related proteins in the circulation and GLPs in the brain, to the complex puzzle of the avian appetite-regulating system. This study gives a better understanding of avian-species-specific food intake regulation, which may provide potential targets for manipulating appetite regulation and solutions for metabolic-related problems in birds

In Chapter 1, I introduced the hyperphagia phenomena in modern meat-type chicken and how over-feed consumption contributed to health and metabolic problems in the poultry industry. I also reviewed how some appetite regulation aspects in birds are different than in mammals. I demonstrated the importance of satiety signals such as CCK, PYY, and IGF-1, the possibility that GLPs could deliver satiety signals to the hypothalamus in chickens. Finally, I explained the aim of this study.

In Chapter 2, I showed the effects of fasting and re-feeding on the expression of CCK, PYY, hypothalamic neuropeptides NPY and POMC, and hepatic IGF-related genes in layer and broiler chicks. In layer chicks, 12 h of fasting reduced the mRNA levels of intestinal CCK, PYY, Y2 receptor, and pancreatic PYY, and these changes were reversed by 12 h of re-feeding. On the other hand, in broiler chicks 12 h of fasting reduced the mRNA levels of intestinal PYY and Y2 receptor, but not intestinal CCK and pancreatic PYY, and these changes were reversed by 12 h of re-feeding. Hypothalamic NPY mRNA significantly increased by 12 h of fasting in both chicks, and these changes were reversed by re-feeding. Also, 12 h of fasting significantly increased

the mRNA levels of hypothalamic agouti-related protein and reduced the mRNA levels of hepatic IGF-1 only in broiler chicks, and 12 h of re-feeding did not change these. IGFBP-1 and -2 mRNA levels were markedly increased by 12 h of fasting in both chicks, and these changes were reversed by re-feeding. IGFBP-3 mRNA levels were increased by 12 h of fasting only in layer chicks, while re-feeding reduced the mRNA levels of IGFBP-3 in both types of chicks. These results suggest that several peripheral hormones, such as pancreatic PYY and intestinal CCK, may not play important roles in the regulation of food intake in broiler chicks.

In Chapter 3, I evaluated whether IGF-2 is involved in the regulation of food intake in chicks. I also examined the effects of fasting on the mRNA levels of IGF binding proteins (IGFBPs) in the liver and hypothalamus. Intracerebroventricular administration of IGF-2 significantly suppressed food intake in chicks. The mRNA levels of IGFBPs in the hypothalamus were not affected by six hours of fasting. On the other hand, six hours of fasting markedly increased the mRNA levels of hepatic IGFBP-1 and -2. The mRNA levels of IGFBP-3 were also significantly increased by six hours of fasting, whereas the mRNA levels of IGF-2, IGFBP-4, and -5 were unchanged. These findings suggest that circulating IGF-2 may be involved in satiety signals, but its physiological role may be regulated by IGFBPs production in the liver in chicks.

In Chapter 4, I showed effects of intracerebroventricular administration of glucagon-like peptides 1 and 2 on hypothalamic appetite regulating factors and sleep-like behavior in chicks. GLP1R mRNA levels in the brain stem and optic lobes were significantly higher than in other parts of the brain, whereas GLP2R mRNA was densely expressed in the telencephalon. Intracerebroventricular administration of either GLP-1 or GLP-2 significantly reduced the mRNA levels of corticotrophin releasing factor and AMP-kinase (AMPK) α1. The mRNA level of proopiomelanocortin was significantly increased, and those of AMPKα2 and GLP2R were significantly decreased by GLP-2, whereas the mRNA level of pyruvate dehydrogenase kinase 4 was significantly increased, and that of GLP1R was significantly decreased by GLP-1. Intracerebroventricular administration of either GLP-1 or GLP-2 induced sleep-like behavior in chicks. Our findings suggest that the anorexigenic peptides GLP-1 and GLP-2 induce similar behavioral changes in chicks, but the mechanism may differ between them.