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Importance of Liver tissue as an Endocrine Organ in Ruminant

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Abstract

The liver plays a crucial role as a secondary endocrine organ in controlling homeostasis. In ruminant, hepatic function changes dramatically during weaning and parturition through the signaling of hormones and blood metabolites. The management systems, feed composition, and feeding program greatly affect the pathological processes of energy metabolism disorders in the liver. The endocrine system and liver are codependent, and both can alter the quantity and quality of animal production. In this review, we will provide our data on the physiological roles of chemerin and ANGPTL8 (angiopoietin Like 8) as hepatic hormones, and the regulatory factors controlling their production, to better understand hepato-endocrine interplay.

Physiological characteristic function in the liver of ruminant

The liver is an important organ that adjusts metabolism according to the nutrients it takes in, leading to its own biological maintenance and growth. The primary functions of the liver include glucose metabolism, protein metabolism, lipid metabolism, regulation and detoxification of ion gradients, and bile production and secretion; these functions are so diverse that they are often compared to those in chemical factories.

Endocrine research in livestock has significantly contributed to the elucidation of the molecular mechanisms of livestock production traits such as lactation, meat production, and reproduction, which are based on nutrient metabolism. Recent studies have revealed that various organs and tissues other than the classical endocrine glands secrete peptides and cytokines. Therefore, current endocrinology is undergoing a paradigm shift from being a simple model of regulation of metabolic organs by endocrine glands to a metabolic regulation network through hormone secretion by various tissues throughout the body, including the endocrine glands, and this complex network.

In ruminant, shortly after birth, the rumen is physically and functionally underdeveloped (Warner, 1956; Tamate *et al.*, 1962). Like monogastric animals, ruminant take nutrients from milk after birth, but after weaning they take in nutrients produced from solid diets in the rumen. Roughage contributes to rumen development by providing physical stimulation; consequently, short-chain fatty acids (SCFA), which are fermented rumen products, contribute to this development by chemical stimulation.

Hepatokines

The liver has a wide range of functions, and it can be referred to as the largest nutrient-metabolizing organ in the body. Although ruminant livestock such as cattle have metabolic characteristics that differ from those of monogastric animals, they still have functionally important organs wherein nutrients absorbed from the rumen and small intestine are first metabolized. However, recent studies have revealed that the liver also plays a role as an endocrine organ. IGF-1 (Insulin-like growth factor 1) is well known as an endocrine factor derived from the liver (Roberts *et al.*, 1990), but new liver-derived hepatokines such as Fetuin-A, FGF-21 (Fibroblast growth factor-21), Selenoprotein-P, and ANGPTLs have been discovered. Hepatokine has been reported to regulate systemic glucose metabolism, lipid metabolism, and insulin signals, and it is thought that the liver regulates systemic metabolism by issuing endocrine signals according to its own nutritional metabolism status.

It has been suggested that endocrine factors such as insulin and IGF-1 may also be involved in rumen development (Gerrits *et al.*, 1998; Shen *et al.*, 2004). Before weaning, glucose, long chain fatty acids (LCFA, long chain fatty acid), and amino acids are obtained from milk; however, after weaning, short chain fatty acids produced by rumen microorganisms are absorbed in the rumen. Before weaning,

the liver is the main tissue for glycolysis via glucose and ketone body production from LCFA. However, after weaning, gluconeogenesis via propionate becomes more important, and ketone body production decreases due to the decrease in carbohydrate supply from feed and the influence of decomposition by rumen microorganisms. In this paper, I will discuss the physiological roles of chemerin and ANGPTL8 in relation to metabolic regulation in ruminant.

Chemerin

Chemerin is a chemokine-type secretory protein encoded by TIG2 (Tazarotene-induced gene 2), also known as RARRES2 (retinoic acid receptor responder) (Nagpal *et al.*, 1997). To date, three types of chemerin receptors have been identified: CMKLR1 (chemokine like receptor 1), GPR1 (G-protein receptor 1), and CCRL2 (chemokine (C-C motif) receptor-like 2) (Wittamer *et al.*, 2003; Zabel *et al.*, 2005; Barnea *et al.*, 2008). The major gene expression sites of chemerin in mice and humans are the heart, lung, liver, spleen, kidney, pancreas, white adipose tissue, brown adipose tissue, placenta, and uterus; these sites are highly expressed, especially in the liver and white adipose tissue. CMKLR1 is highly expressed in the heart, lung, skeletal muscle, and adipose tissue. In addition, CCRL2 is highly expressed in the spleen and lymph nodes, and GPR1 is highly expressed in skeletal muscle, adipose tissue, and the brain (Fan *et al.*, 1998; Rourke *et al.*, 2014).

The physiological actions of chemerin in relation to the immune system, glucose metabolism, and lipid metabolism are well known. The immune system attracts dendritic cells, macrophages, and NK cells to the site of inflammation. As a metabolic system, insulin sensitivity of peripheral tissues, regulation of glucose uptake, differentiation of mature adipocytes from adipose progenitor cells, and regulation of insulin secretion have been reported (Goralski *et al.*, 2007; Roh *et al.*, 2007; Sell *et al.*, 2009; Ernst *et al.*, 2010; Takahashi *et al.*, 2011).

Chemerin mRNA is highly expressed in adipose tissue, liver, kidney, adrenal gland, spleen, and small intestine, especially in the liver (Suzuki *et al.*, 2016). The chemerin receptors (CMKLR1 and CCRL2) were expressed in various tissues; however, CMKLR1 was highly expressed in the liver, adrenal gland, spleen, and lung, and CCRL2 was highly expressed in adipose tissue, adrenal gland, spleen, large intestine, and lung. In addition, expression of GPR1 was observed only in adipose tissue, liver, lung, and rumen, and its expression was particularly high in the liver. Chemerin was localized in the cytoplasm of bovine hepatocytes. A previous report confirmed that the expression of chemerin was higher in adipocytes than in vascular stromal cells, but the results were consistent (Song *et al.*, 2010). Compared to the expression level in other tissues, it is believed that the liver is the main endocrine organ that produces chemerin in cattle.

Chemerin has been shown to have an insulin secretagogue effect in sheep (Suzuki *et al.*, 2012). Administration of a chemerin analog led to an acute rise in the plasma insulin levels and decreased glucose levels. Plasma NEFA (non-esterified fatty acids) levels were elevated from 60 to 180 min after administration. Chemerin analog administration also transiently elevated the levels of plasma triglyceride and total cholesterol, suggesting increased VLDL (very low-density lipoprotein) secretion from the liver. Plasma HDL (high-density lipoprotein) levels declined after administration. A previous study by our group showed five SNPs in the coding region of the bovine chemerin gene in Japanese Black cattle (Yamauchi *et al.*, 2015). The c.276C>T SNP of the chemerin gene potentially regulates meat quality by affecting the composition of intramuscular fatty acids.

Since the expression of chemerin in the liver during the lactation period was decreased, it is expected that the concentration of chemerin in the blood during this period was decreased. It is possible that the decrease in the expression level of chemerin is involved in the decrease in insulin secretion during lactation. Throughout the lactation and dry stages, the cellular composition within the mammary gland changes significantly. Increased expression of chemerin receptors during the dry period may be caused by immune cells infiltrating the mammary gland tissue during the dry period. The chemerin receptors are expressed in bovine mammary epithelial cells, and chemerin activates the ERK pathway and increases the expression of milk synthesis-related genes. Therefore, it is believed that chemerin may have a lactogenic action or a growth factor-like action in mammary epithelial cells. However, increased expression of the chemerin receptor was found in mammary glands during the dry period. Chemerin is considered to regulate the immune system and metabolic system as hepatokines that are highly expressed in the liver and affect productivity of cattle.

ANGPTL8

ANGPTL8 is a liver-derived secretory protein that is also known as TD26, RIFL, Lipasin, or betatrophin. The expression sites of ANGPTL8 in humans and mice are liver, white adipose tissue, and brown adipose tissue, and its expression in other tissues is extremely low (Zhang, 2012). It has been reported that the physiological effects of ANGPTL8 are involved in the regulation of blood TG (triglyceride) levels, although the receptor for ANGPTL8 has yet to be identified. ANGPTL8 expression in mouse liver decreases with fasting and increases after feeding (Ren *et al.*, 2012). The overexpression of ANGPTL8 resulted in dyslipidemia (elevated blood TG), and knockout mice showed low TG levels (Quagliarini *et al.*, 2012; Wang *et al.*, 2013). In ANGPTL8 KO mice, adipose tissue development is delayed and VDL (very low density) release from the liver is also reduced.

Lipid metabolism in cattle is closely related to growth, energy storage, and supply during lactation in cattle. ANGPTL8 mRNA was highly expressed in liver and adipose tissue and was either slightly or not detected in other tissues of cattle (Nakano *et al.*, 2018). ANGPTL8 protein was detected only in the liver. As a result, the expression of ANGPTL8 in the liver showed no significant change throughout the lactation period or the dry period. The expression of ANGPTL8 in the liver during parturition was examined in the biopsied liver tissue, which showed that the expression of ANGPTL8 in the liver before calving was not changed; however, it was significantly reduced after parturition. The blood TG concentration was observed to be lower one week before calving and it reached its lowest value on parturition; subsequently, it decreased during the first four weeks post-parturition, while the blood NEFA concentration was higher

four weeks after parturition. In dairy cattle, with the start of lactation, NEFA released from adipose tissue is converted to VLDL in its original state or in the liver and subsequently mobilized to the mammary gland (Drackley *et al.*, 2001). Because ANGPTL8 inhibits LPL (Lipoprotein lipase) activity and increases blood TG concentration, it is considered that the changes in ANGPTL8 expression coincide with blood TG concentration during the parturition. Since the regulation of hepatic ANGPTL8 expression by insulin and fasting has been reported, it is considered that the decrease in ANGPTL8 expression after parturition is due to a decrease in blood insulin concentration and a negative energy balance. When the lactation period and the dry period were compared, there was no difference in the expression level of ANGPTL8 in the liver; it is possible that cows used in the dry period were not pregnant. As described above, it was suggested that ANGPTL8 is a factor that regulates lipid mobilization during lactation in dairy cows.

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