

《Review》

Chicken Intestinal L Cells and Glucagon-like Peptide-1 Secretion

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Many types of endocrine cells have been identified in the gastroenteropancreatic system of vertebrates, which have subsequently been named with alphabet(s). L cells which secrete the glucagon-like peptide (GLP)-1 are scattered in the intestinal epithelium. This review discusses the morphological features of chicken L cells and GLP-1 secretion from intestinal L cells. L cells, identified using GLP-1 immunohistochemistry, are open-type endocrine cells that are distributed in the jejunum and ileum of chickens. GLP-1 co-localizes with GLP-2 and neurotensin in the same cells of the chicken ileum. Intestinal L cells secrete GLP-1 in response to food ingestion. Proteins and amino acids, such as lysine and methionine, in the diet trigger GLP-1 secretion from the chicken intestinal L cells. The receptor that specifically binds chicken GLP-1 is expressed in pancreatic D cells, implying that the physiological functions of chicken GLP-1 differ from its functions as an incretin in mammals.

Key words: chicken, glucagon-like peptide-1, intestine, L cell

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Introduction

The vertebrate gastroenteropancreatic (GEP) system plays important roles in the digestion of ingested foods and subsequent absorption of nutrients. The GEP system organizes the intrinsic nervous system, called the enteric nervous system (ENS). The gastrointestinal tract is innervated by the ENS, which controls the motility of the stomach and gut, local blood flow, and movement of fluid between the intestinal lumen and body fluid compartment, and within passages of the central nervous system (Furness *et al.*, 2014). The secretion of digestive juices from accessory glands, the liver and pancreas, is also regulated by the nervous system. Furthermore, the GEP system contains many endocrine cells and regulates important physiological functions, similar to the endocrine system (Dockray and Walsh, 1994). Pancreatic islets, which participate in the control of glucose level in the bloodstream, are the typical endocrine tissues in the GEP system. Endocrine cells in the gastrointestinal tract act as the primary sensors of ingested nutrients (Psichas *et al.*,

2015) and enable a cross talk with the ENS. Motility of the gastrointestinal tract is modulated by a complex neural and hormonal network (Wu *et al.*, 2013).

Gastrointestinal endocrine cells are scattered as single cells in the epithelium of the alimentary tract and are named as “basal granulated cells”, owing to the secretory granules that are accumulated in their basal cytoplasm. Heidenhain (1870) was the first to identify chromaffin cells that secrete 5-hydroxytryptamine (5-HT) in the mammalian alimentary tract. Kull (1913) later described non-chromaffin cells that contain acidophilic granules. Since his discovery, many types of endocrine cells have been identified in the mammalian GEP system. The endocrine cells in the GEP system had been originally classified based on dye-affinity and the morphological features of cells; however, this has changed with the advent of improved techniques. Silver impregnation using the Grimelius method (Grimelius, 1968), is one of the most useful methods of detecting endocrine cells in the GEP system. This method divides endocrine cells into argentaffin and argyrophil cells. The former is relevant to enterochromaffin (EC) cells that secrete serotonin, and the latter secretes peptides. Gastrointestinal endocrine cells can also be classified into closed- and open-type cells based on morphology. Open-type cells make contact with the gastrointestinal lumen with their long cytoplasmic process and respond to chemical signals in the lumen such as pH and amino acids. Closed-type cells extend their cytoplasmic processes under the basal side of adjacent cells and respond to physical signals such as expansion of the stomach. The electron microscope, invented by Max Knoll and Ernst August Frie-

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drich Ruska in 1931, enabled the classification of gastrointestinal endocrine cells on the basis of their ultrastructural features, especially the morphology of secretory granules present in the endocrine cells (Ferreira, 1971; Kubeš *et al.*, 1974; Larssen and Jørgensen, 1978; Peranzi and Lehy, 1984; Usellini *et al.*, 1984c). The diameter and electron density of the core of the secretory granules are important for the classification of endocrine cells.

Immunohistochemistry was developed in the 1970's (Sternberger *et al.*, 1970), and used for the detection of hormones in endocrine tissues, including the GEP system. Using immunohistochemistry coupled with light and electron microscopy, many researchers have demonstrated that regulatory peptides, gastrin, cholecystokinin, secretin, and motilin, are secreted from gastrointestinal endocrine cells (Polak *et al.*, 1975; Robinson and Dawson, 1975; Buffa *et al.*, 1978; Alumets *et al.*, 1983; Usellini *et al.*, 1984a, 1984b). The first classification of endocrine cells of the GEP system was presented in Bologna, Italy in 1973. In 1977, a meeting was organized in Lausanne, Switzerland by eighteen endocrinologists of the GEP system, where the above-mentioned international classification was accepted (Buchan and Polak, 1980; Solcia *et al.*, 1980). According to this classification, more than ten types of endocrine cells were recognized on the basis of their location, morphological features of secretory granules, and hormone content, and designated with letter(s), such as A, D, and S. This nomenclature has been accepted ever since.

Glucagon-like peptide (GLP)-1 is a regulatory peptide secreted from intestinal endocrine cells named L cells (Eissele *et al.*, 1992). The present review summarizes the morphological features of L cells in the chicken intestine and the secretion of GLP-1 from these cells.

Endocrine cells of the avian gastrointestinal tract

The anatomical features of the poultry GEP system differ from those of mammals in several aspects. For example, the stomach consists of glandular (proventriculus) and non-glandular (gizzard) parts, an extremely short large intestine called the colorectum, and a pair of relatively long ceca. However, many types of regulatory peptides identified in mammalian species have also been detected in the endocrine cells of the poultry gastrointestinal tract. Reviews by Rawdon and Andrew guide us to a better understanding of avian GEP endocrinology (Rawdon, 1984; Rawdon and Andrew, 1999).

Recent studies have revealed the distribution and morphology of endocrine cells containing regulatory peptides in the GEP system of several avian species, including chickens. The distribution and ontogeny of peptides belonging to the gastrin-cholecystokinin (CCK) family have been shown in the chicken gastrointestinal tract (Salvi *et al.*, 1996; Aksoy and Cinar, 2009; Reid and Dunn, 2018). Ghrelin, which stimulates growth hormone secretion, and orexin, which influences feeding behavior, have been detected in the endocrine cells of the chicken gastrointestinal tract (Neglia *et al.*, 2005; Eidaroos *et al.*, 2008; Arcamone *et al.*, 2014).

Pirone *et al.* (2011) determined the distribution of the gastric inhibitory polypeptide (GIP), a mammalian incretin hormone, and the gastrin-releasing peptide (GRP), which has regulatory functions in the central nervous system and gastrointestinal tract of mammals. Distribution of various endocrine cells has also been investigated in the gastrointestinal tract of birds such as Passeriformes (Mendes *et al.*, 2009), pheasant (Pirone *et al.*, 2012), and ostrich (Durities *et al.*, 2013).

Morphology of L cells in the chicken small intestine

Immunohistochemistry for GLP-1 revealed that chicken L cells are scattered as single cells in the epithelium of the jejunum and ileum, although rarely in the duodenum, cecum, and colorectum (Hiramatsu *et al.*, 2003, 2005). Their frequency in the small intestine gradually increases from the proximal part to the distal part, and is the maximum in the distal ileum. L cells have comma-like or wedge-like shape in crypts (Fig. 1b) but flask-like shape with long cytoplasmic processes reaching the intestinal lumen in the villous epithelium (open-type, Fig. 1a) (Hiramatsu *et al.*, 2003, 2005). Electron microscopy shows microvilli at the tip of the cytoplasmic process (Fig. 1c) (Nishimura *et al.*, 2013). Electron microscopy shows accumulation of many round-shaped secretory granules in the basal cytoplasm of L cells (Fig. 1c). The average diameter of these granules is approximately 300 nm, with a core of intermediate electron density (Fig. 1d). The cores are homogeneous and closely attached to the limiting membrane of the secretory granules.

L cells, with immunoreactivity for GLP-1, are located in the area from crypts to the middle part of villi in each intestinal segment. However, L cells expressing proglucagon, the precursor of GLP-1, are located in the crypts and villi bottom in the chicken ileum. Immunocytochemistry using gold particle as a marker showed that GLP-1 content in the secretory granules of L cells is significantly low between the crypts and villous epithelium, indicating that L cells in the chicken ileum mature and complete their GLP-1 production in the crypts (Nishimura *et al.*, 2016).

Colocalization of GLP-1 with other hormones has been reported not only in the mammalian intestine (Mortensen *et al.*, 2003; Theodorakis *et al.*, 2006; Pyarokhil *et al.*, 2012; Svendsen *et al.*, 2015), but also in the chicken intestine. GLP-2 is co-encoded with GLP-1 by the gene encoding proglucagon, which generates a single mRNA transcript in the intestinal L cells (Baggio and Drucker, 2004). Immunocytochemistry has demonstrated that GLP-1 is co-stored with GLP-2 within the same secretory granule of L cells in the chicken ileum (Nishimura *et al.*, 2013). Nevertheless, the distribution and frequency of occurrence of GLP-2-immunoreactive cells differs from those of GLP-1-immunoreactive cells in the chicken small intestine. GLP-2-immunoreactive cells are mainly located in crypts and their frequency of occurrence is lower than that of GLP-1-immunoreactive cells (Monir *et al.*, 2014b).

Neurotensin, a 13-amino acid peptide originally isolated from bovine hypothalamus, also co-localized with GLP-1 in

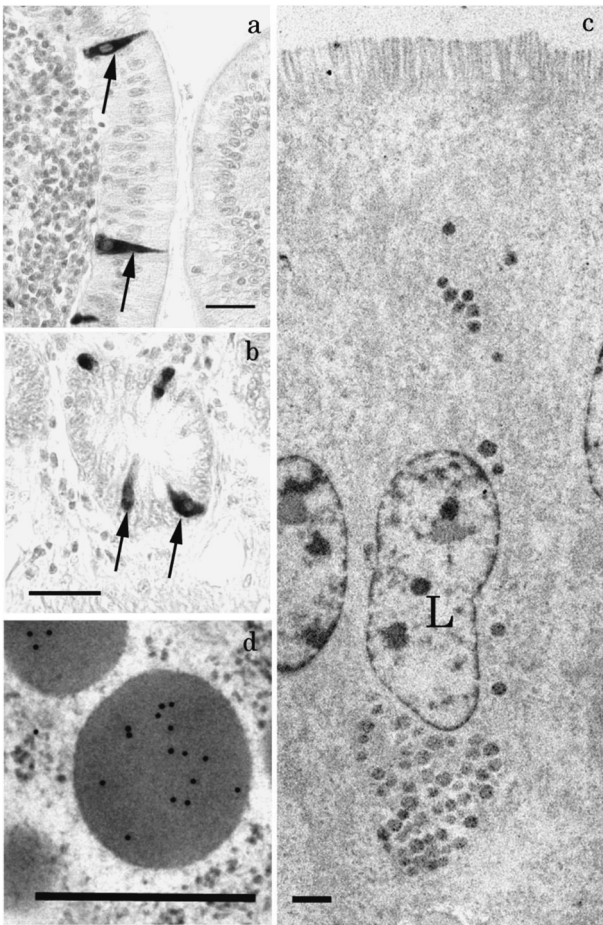


Fig. 1. Light (a, b) and electron (c, d) microscopic views of the chicken L cells identified using immunohistochemistry for glucagon-like peptide (GLP)-1. GLP-1-immunoreactive cells (arrows) are located in the villous epithelium (a) and crypt (b) of chicken distal ileum. Bars=20 μ m. Low magnification view of L cell (L) that shows GLP-1-immunoreactivity and is located in the villous epithelium (c). Note that its apical surface is covered with microvilli. Bar=1 μ m. High magnification view of a secretory granule from L cells (d). Particles of colloidal gold (12 nm in diameter) are diffusely arranged on a secretory granule. Bar=0.5 μ m. c, d: Cited from Nishimura *et al.* (2013).

the same enteroendocrine cells of the chicken ileum. Using double immunofluorescence, three types of enteroendocrine cells were detected in the chicken ileum (Nishimura *et al.*, 2017). The first type contains both GLP-1 and neurotensin, and is the most abundant in the ileum (Fig. 2). The second one contains only GLP-1, and the third one only neurotensin. Neurotensin is released from enteroendocrine cells, named N cells, in mammalian (Sundler *et al.*, 1982) and avian species (Atoji *et al.*, 1994). These findings add to the confusion regarding the nomenclature of endocrine cells in the GEP system. Therefore, Cho *et al.* (2015) proposed revising the traditional classification using alphabets in their article on K and L cells. Helander and Fändriks (2012) proposed to

rename GEP endocrine cells for the avian species.

GLP-1 secretion from chicken L cells

The chicken L cell is an open-type endocrine cell and is presumed to respond to ingested feed or nutrients in the intestinal lumen. In fact, restricted feeding increases the frequency of occurrence of GLP-1-immunoreactive cells in the chicken small intestine (Monir *et al.*, 2014c), thereby indicating that L cells secrete GLP-1 in response to food ingestion in the chicken small intestine. Many investigators have shown that nutrients in the intestinal lumen stimulate GLP-1 secretion from L cells in the mammalian intestine (Eissele *et al.*, 1992; Burcelin, 2005; Deacon, 2005). Proteins and amino acids, such as lysine and methionine, are the triggers that induce GLP-1 secretion from chicken ileal L cells (Monir *et al.*, 2014a; Nishimura *et al.*, 2015). Significant correlation has been observed between dietary protein ingestion and frequency of occurrence of GLP-1-immunoreactive cells in the chicken ileum (Monir *et al.*, 2014a).

The physiological importance of GLP-1 in mammals has been reviewed extensively (Stanley *et al.*, 2004; Baggio and Drucker, 2004; Drucker, 2006; Holst *et al.*, 2011; Wu *et al.*, 2013; Yabe and Seino, 2013; Bodnaruc *et al.*, 2016). GLP-1 released from intestinal L cells exerts multiple effects on the central nervous system and gastrointestinal tract in mammalian species (Balkan, 2000; Brubaker, 2006; Holst, 2007; Trapp and Hisadome, 2011). In chickens, GLP-1 regulates emptying of the crop (Tachibana *et al.*, 2003) and food intake (Furuse *et al.*, 1997; Honda *et al.*, 2017). However, this hormone mainly acts as an incretin hormone (Drucker, 2006); the receptor that specifically binds to GLP-1 is located on the pancreatic B cell, which is known to secrete insulin in mammals (Hörsch *et al.*, 1997; Tornehave *et al.*, 2008; Pyke *et al.*, 2014). Our research group generated a specific antibody against the chicken GLP-1 receptor (cGLP1R) and demonstrated its location in the chicken pancreas using immunohistochemistry. According to our observations, cGLP1R is expressed in pancreatic D cells that secrete somatostatin (Fig. 3) (Watanabe *et al.*, 2014). Similar localization of cGLP1R has been observed in the pancreatic islets of other avian species, northern bobwhites, and common ostriches (Watanabe *et al.*, 2018). Hall *et al.* (1986) demonstrated a rapid increase in plasma glucose concentration after the intravenous injection of anti-somatostatin serum in domestic fowls. Overall, these observations suggest that GLP-1 in avian species may exert its physiological action on the regulation of plasma glucose concentration via somatostatin from pancreatic D cells.

In conclusion, morphological features of chicken intestinal L cells are similar to those of mammals. However, the mechanism underlying the secretion of GLP-1 from L cells and its physiological role in chicken may differ from those in mammals.

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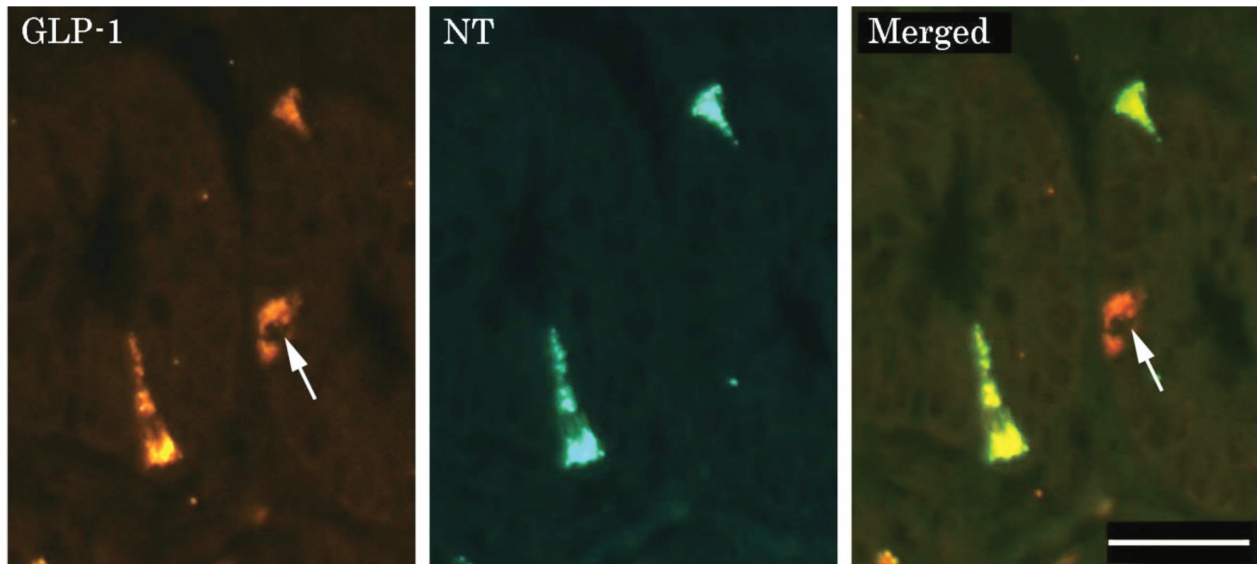


Fig. 2. Double fluorescent immunohistochemistry shows the colocalization of glucagon-like peptide (GLP)-1 with neurotensin (NT) in the same L cells of the chicken ileum. Arrow indicates L cell expressing GLP-1 immunoreactivity only. Bar=20 μ m.

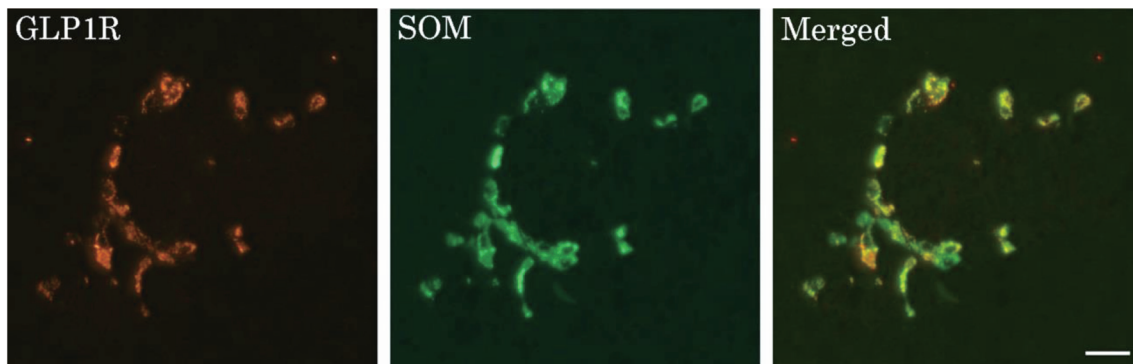


Fig. 3. Double fluorescent immunohistochemistry shows that glucagon-like peptide (GLP)-1 receptor (GLP1R) is expressed on somatostatin (SOM)-immunoreactive cells in the chicken pancreas. Bar=20 μ m.

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