A Light Microscopic Study of the Gastro-Entero-Pancreatic Endocrine Cells of the Mink

(Mustela vison)

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Summary. Endocrine cells in the stomach, intestine and pancreas of the mink were investigated, using silver impregnation and immunohistochemical methods, and the following results were obtained.

1. The stomach of the mink possesses a well-developed acid-secreting region which occupies about 70% of the gastric mucosa.

2. Half of Brunner’s glands whose excretory duct empties in the most proximal duodenum are located in the duodenal submucosa with the remainder in the pyloric submucosa. The area covered by the glands is 7.5 mm long in rostrocaudal direction.

3. Endocrine cells are numerous in Brunner’s glands, in the pyloric gland region and in the duodenum, while they are few in the colorectum.

4. Somatostatin-immunoreactive cells are distributed throughout the whole GEP system, while gastrin-immunoreactive cells are located mainly in the pyloric gland region. Secretin-, motilin- and neurotensin-immunoreactive cells are found in the duodenum, jejunum and lower jejunum, respectively.

5. Glucagon-immunoreactive cells are located mainly in the pancreatic islet and are distributed scarcely in the fundic gland region. A few glucagon-immunoreactive cells are also found in the middle portion of the jejunum.

6. In addition to the somatostatin-immunoreactive cells, argentaffin, glucagon- and glicentin-immunoreactive cells in the fundic gland region and argentaffin and gastrin-immunoreactive cells in the pyloric gland region extend cytoplasmic processes along the basement membrane. This suggests a paracrine secretion of these cell types.

7. A few open type cells which are stained with Hellerström-Hellman’s or Sevier-Munger’s method or are reactive to the somatostatin antiserum are found in the fundic gland region.

A possible relation between the present observation of the endocrine cells and the eating habits of the mink is discussed.

Studies on the gastro-entero-pancreatic (GEP) endocrine system have recently made a remarkable advance by the use of the immunohistochemical methods (Solcia et al., 1978a, b, 1981; GrUBE and FORSSMANN, 1979). Thus far, however, reports have dealt

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with either a certain cell type in the system or various cell types in a particular digestive region; there has been little research conducted on the overall occurrence and distribution of different cell types in the entire GEP system.

In this histological and immunohistochemical study, we have aimed at describing the occurrence and distribution of several endocrine cell types in the GEP system of the mink.

Among carnivores, the mink retains its carnivorous nature unlike the dog and cat, which should actually be regarded as omnivorous now. In gross anatomical terms, the digestive tract of the mink is highly consistent with the descriptions given by Kainer (1954a, b). It is characterized by some salient features including a wide acid secreting region in the stomach, lack of the caecum, and an extremely short colorectum.

The results obtained are discussed with regard to the relationship between the morphological features of the endocrine cells and the digestive functions characteristic of the mink.

**MATERIALS AND METHODS**

Fourteen minks (*Mustela vison*) of either sex were used. Tissues were dissected out from the stomach, small and large intestines and pancreas (Fig. 1a, b). Tissue blocks were fixed by immersion in Bouin’s or 10% buffered neutral formalin solution and embedded in paraffin. Sections were cut at a 3–5 μm thickness and examined by the following methods:

![Diagram](image_url)

**Fig. 1.** a. Sampling portions. S1–5* stomach along the greater curvature, S6–9* stomach along the lesser curvature, S10–12* stomach midway between the greater and lesser curvatures (*S5, 9 and 12 contain the juxta-pyloric duodenum), I1 first portion of the duodenum, I2 cranial portion of the jejunileum, I3 middle portion of the jejunileum, I4 caudal portion of the jejunileum, I5 last portion of the jejunileum, I6 distal portion of the colorectum, P1 pancreatic body, P2 distal portion of the left limb of the pancreas, P3 distal portion of the right limb of the pancreas. b. Details of the sampling portions of the intestine. The whole intestine was stretched and dissected at an equal distance except for I5 which was the middle locus between I4 and 6.
Histological methods

1) Hematoxylin-eosin staining. 2) Silver impregnation methods: For the argyrophil cells, Grimmelius' method (GRIEMELIUS, 1968), Hellerström-Hellman's method (HELLERSTRÖM and HELLMAN, 1960) and the ammonical silver nitrate solution method of SEVIER and MUNGER (1965) were used. To detect the argentaffin cells, Masson-Hamperl's method (SINGH, 1964) was applied.

Immunohistochemical methods

Antisera against guinea pig anti-synthetic human gastrin (GP-1304, recognizing the C-terminus, diluted 1:5,000), rabbit anti-synthetic porcine glicentin (R-4804, recognizing the C-terminus, 1:2,000), rabbit anti-synthetic porcine secretin (R-3501, recognizing the C-terminus, 1:1,000), rabbit anti-synthetic porcine motilin (R-1104, recognizing the C-terminus, 1:2,000), rabbit anti-synthetic porcine vasoactive intestinal polypeptide (VIP) (R-502, raised against whole molecule, 1:4,000) and rabbit anti-porcine substance P (R-2404, 1:2,000) were kindly donated by Prof. N. YANAIHARA, Shizuoka, Japan. Antisera against rabbit anti-porcine somatostatin (JG-1, 1:2,000) and rabbit anti-porcine pancreatic gluacagon (JK-20, 1:1,000) were purchased from Japan Immunoresearch Laboratories Co. Ltd., Takasaki, Japan. For the detection of the gastrin-immunoreactivity and of the immunoreactivity for the rest of the peptides, the bridge method (MASON et al., 1969) and the peroxidase-antiperoxidase (PAP) method (STERNBERGER, 1974) were applied, respectively. It was confirmed that no antisera used cross-reacted with other GEP peptide hormones. For control sections, phosphate buffered saline was applied instead of the first or second layer, or inactivated antiserum, which was preincubated with a proper quantity of specific antigen, was applied instead of the first layer.

The mean number of the endocrine cells per 0.25 mm² was determined and shown in Figures 2a, b.

RESULTS

The gastric mucosa of the mink consisted of cardiac, fundic, transitional and pyloric gland regions. The cardiac gland region was narrow (about 1 mm in width) and was composed of gland cells lightly stained by hematoxylin-eosin. The fundic gland region, occupying 36% of the gastric mucosal surface, was found to contain chief, mucous neck and parietal cells. In the region transitional between the fundic and pyloric gland regions, which occupied 33% of the gastric surface, chief cells were either very few in number or absent altogether. The pyloric gland region, covering about 30% of the gastric surface, contained lightly staining gland cells.

Half of Brunner's glands were situated in the proximal portion of the duodenal submucosa and the rest extended over the pyloric submucosa (Fig. 7). The excretory duct emptied in the most proximal duodenum. Brunner's glands occupied an area measuring 7.5 mm on the average along the rostro-caudal axis of the gastrointestinal tract.

Endocrine cells demonstrated by either of the methods applied were widely distributed in the whole GEP system (Fig. 2a, b). In the stomach, no significant difference was observed between the populations of the cells along the greater and
lesser curvatures, and the same was true when either was compared with that observed along the midway between the two.

Grimelius' method demonstrated many argyrophil cells. Their frequency was moderate in Brunner's glands, higher in the fundic (Fig. 3) and pyloric gland regions and highest (22.5/0.25 mm²) in the duodenum. From there on the frequency declined towards the caudal portions of the intestine, though a slight increase was observed in the lower jejunoileum. Distally, the frequency dropped abruptly to the colorectum.

The number of the argyrophil cells detectable by Hellerström-Hellman's method

Fig. 2. Frequency of the endocrine cells reacting with each silver impregnation method (a) and immunohistochemical method (b) per unit area (0.25 mm²) in different portions of the gastrointestinal tract of the mink. Abscissa: portions, ordinate: cell number. a. □ Grimelius, ○ Hellerström-Hellman, △ Sevier-Munger, ● Masson-Hamperl. b. ● Gastrin, ○ Somatostatin, ○ Glucagon, △ Glicentin, ■ Secretin, ▲ Motilin, ♦ Neurotensin. Portions: 1 Fundic gland region, 2 Transitional region between the fundic and pyloric gland regions, 3 Pyloric gland region, 4 Brunner's glands, 5 Duodenum just caudal to the pyloric gland region, 6 First portion of the duodenum (11), 7 Cranial portion of the jejunoileum (12), 8 Middle portion of the jejunoileum (13), 9 Caudal portion of the jejunoileum (14), 10 Last portion of the jejunoileum (15), 11 Distal portion of the colorectum (16).

Fig. 3. Many argyrophil cells using Grimelius' method in the fundic gland region of the mink. Cells are distributed throughout the glands. ×330

Fig. 4. Sevier-Munger-positive cells in the pyloric gland region. They are present throughout the glands, although a tendency to gather around the cell proliferation zone is observed. ×330

Fig. 5. Argentaffin cells reacting to Masson-Hamperl's method in Brunner's glands. ×300

Fig. 6. Somatostatin-immunoreactive cells in the duodenum (D) and Brunner's glands (B). The cells are numerous in Brunner's glands. PAP method, diluted 1: 2,000. ×330

Fig. 7. Many gastrin-immunoreactive cells in the pyloric gland region (P) and a few immunoreactive cells in the duodenum (D) and Brunner's glands (B) (arrows). In the duodenum, the frequency suddenly becomes low. Bridge method, 1: 5,000. ×330
Fig. 3-7. Legends on the opposite page.
were smaller than those detectable by Grimelius' method. The Hellerström-Hellman-sensitive argyrophil cells were most numerous (18.5/0.25 mm²) in the pyloric gland region followed by the region of Brunner's glands. Their frequency decreased towards the distal portions, but slightly increased in the colorectum.

The argyrophil cells demonstrated by Sevier-Munger's method was larger in number than those demonstrated by Hellerström-Hellman's but smaller in number than those detected by Grimelius' method. The cell frequency was moderate in the fundic gland region and highest (16.4/0.25 mm²) in the pyloric gland region (Fig. 4); it decreased towards the caudal portions of the intestine.

With Masson-Hamperl's method, argentaffin or enterochromaffin cells were shown to be widely distributed. The highest frequency (12.4/0.25 mm²) was found in Brunner's glands (Fig. 5). The number of the cells diminished towards the caudal portions of the intestine except in the last portion of the jejunum, where it showed a slight increase.

By application of Grimelius', Hellerström-Hellman's and Masson-Hamperl's methods, it was demonstrated that the reactive cells were distributed over any given part of the glands throughout the fundic and transitional gland regions (Fig. 3), around the cell proliferation zone of the pyloric gland region and in the basal part of the crypts of the small and large intestines, whereas they were very few in number in the epithelia of the villi of the small intestine. Using Sevier-Munger's method, on the other hand, the reactive cells were detected in the middle part of the glands of the fundic and transitional gland regions, and throughout the glands of the pyloric gland region with a tendency to gather around the cell proliferation zone (Fig. 4). In addition, they were widely observed in the epithelium covering the crypts and villi of the small intestine, and also throughout the crypts of large intestine.

Seven types of immunoreactive cells were identified with the antisera against somatostatin, gastrin, glucagon, glicentin, secretin, motilin and neurotensin (Fig. 2b).

Somatostatin-immunoreactive cells were scattered in the whole GEP system (Fig. 6), with a peak density (18.0/0.25 mm²) in the pyloric gland region. Their occurrence...
and distribution patterns closely resembled those revealed by Hellerström-Hellman’s method.

Gastrin-immunoreactive cells were most frequently observed (32.7/0.25 mm²) in the pyloric gland region (Fig. 7). They then decreased in number in the intestine and disappeared in the last portion of the jejunoileum. In Brunner’s glands, very few gastrin-immunoreactive cells were detected (Fig. 7). Those detected were distributed around the cell proliferation zone of the pyloric gland region and mainly in the basal part of the crypts.

In the stomach were found a small number of glucagon-immunoreactive cells (0.3/0.25 mm²) with a restrictive distribution only in the middle part of the glands of the fundic gland region (Fig. 8a). These cells were also present in the crypts and less frequently in the villous epithelia in the middle portion of the jejunoileum (Fig. 9a).

A few glicentin-immunoreactive cells were found in the middle part of the fundic glands (Fig. 8b), and also detected in moderate number (4.7/0.25 mm²) in the jejunoileum (Fig. 9b) and colorectum. Examination in serial sections revealed that all cells in the fundic gland region and some in the jejunoileum were immunoreactive to both glucagon and glicentin antisera, whereas the rest of the cells in the jejunoileum were immunoreactive only to glicentin antiserum (Fig. 8a, b, 9a, b).

Secretin-immunoreactive cells were observed in moderate numbers throughout the crypts and villi of the duodenum (Fig. 10a) and the cranial portion of the jejunoileum, with a peak density (5.7/0.25 mm²) in the portion just caudal to the pyloric gland region.

Motilin-immunoreactive cells appeared in the cryptal and villous epithelia of the jejunoileum (3.3/0.25 mm²) (Fig. 10b) down to the caudal portion of the jejunoileum. Motilin-immunoreactivity was never observed in the enterochromaffin cells identified in the serial sections.

Neurotensin-immunoreactive cells were seen only in the basal part of the crypts of the lower jejunoileum (1.3/0.25 mm²) (Fig. 11).

All the silver impregnation methods used in this study demonstrated that many
Fig. 10. Duodenal mucosa stained by secretin (a) and motilin (b) antisera. In both figures, an open type cell is seen. PAP method, 1:1,000 (a) and 1:2,000 (b). ×330

endocrine cells in the fundic, transitional and pyloric gland regions extended cytoplasmic processes along the basement membrane (Fig. 12a–e), which, however, never reached the luminal surface. In addition, some other cells also possessed such processes along the basement membrane: those immunoreactive to somatostatin (Fig. 12f), and those immunoreactive to glucagon or glicentin (Fig. 8a, b) in the fundic gland region; and some gastrin- or somatostatin-immunoreactive cells in the pyloric gland region. Many of these processes were characterized by a terminal swelling like a synaptic button, which was associated with chief, parietal, mucous or other endocrine cells. The processes often seemed to embrace adjacent cells. A few cells with such processes were also demonstrated by Grimelius’ method in the villi and basal part of the duodenum.

Almost all cells in the pyloric gland region and small and large intestines, and some cells in the cardiac gland region and Brunner’s glands reached the luminal surface, i.e., they were open in type. Furthermore, in the fundic gland region, a few cells which were positive to Hellerström-Hellman’s method, Sevier-Munger’s method, or somatostatin antiserum were also open in type (Fig. 13a, b).

In the pancreas, Grimelius’ and Hellerström-Hellman’s methods revealed argyrophil cells, and the antisera against somatostatin, glucagon and glicentin demonstrated immunoreactive cells. In the islet, the Grimelius-positive cells were distributed peripherally (Fig. 14a) and the Hellerström-Hellman-positive cells more centrally. Cells

Fig. 11. Neurotensin-immunoreactive cells in the jejunum. They are distributed predominantly in the basal part of the crypts. PAP method, 1:1,000. ×330
reactive to both glucagon and glicentin antisera were distributed peripherally (Fig. 14b, c), corresponding to the distribution pattern of the Grimelius-positive cells. Somatostatin-immunoreactive cells had nearly the same distribution pattern as the Hellerstrom-Hellman-positive cells. Furthermore, Grimelius-positive, Hellerstrom-Hellman-positive or somatostatin-immunoreactive cells also occurred in the pancreatic duct (Fig. 14d). Grimelius' or Hellerstrom-Hellman's method revealed endocrine cell aggregations directly adjacent to nerve cells, forming a neuroinsular complex (Fig. 15).

No endocrine cells were immunoreactive to the antisera against substance P or VIP, but the nerve fibers in the lamina propria and in Meissner's and Auerbach's plexuses (Fig. 16a, b) were immunoreactive to both antisera. Furthermore, nerve cell bodies in the intramural plexuses and intrapancreatic ganglia were stained by VIP antiserum (Fig. 17a, b). The nerve elements positive to these peptides were predominant in Auerbach's plexuses in the small intestine.

In the control sections, no immunoreactivity was observed.

**DISCUSSION**

The occurrence and distribution of the GEP endocrine cells in the mink as demonstrated...
by silver impregnation and immunohistochemical methods are in a close parallel with previous descriptions in other species (Funk et al., 1966; Sato et al., 1976; Oomori et al., 1980; Kitamura et al., 1982), in that the endocrine cells are concentrated in the pylorus, fundus and duodenum. The mink, however, is further characterized by its Brunner’s glands containing almost as numerous endocrine cells as the pyloric gland region does. Although there have been few studies dealing with the endocrine cells in Brunner’s glands, what has been reported tells us that the frequency of the endocrine cells in this region is low in the cat (Vassallo et al., 1969; Kitamura et al., 1982), dog and human (Solcia et al., 1975). Brunner’s glands are known to secrete alkaline mucus in order to neutralize acid from the stomach thereby preventing duodenal epithelia from injury by the acidity. Since the gastric acid-secreting region of the mink is extremely large (about 70% of the gastric surface), the activity of Brunner’s glands in this animal

Fig. 14. The pancreatic islet reactive to Grimelius’ method (a) and to the antisera against glucagon (b) and glicentin (c). In adjacent sections, cells positive to both antisera are observed (b, c arrows). Some somatostatin-immunoreactive cells in the pancreatic duct are shown (d). PAP method, 1:1,000 (b) and 1:2,000 (c, d). a: ×540, b and c: ×1,000, d: ×1,200.
seems to be conspicuously high. Support for this suggestion is given by the unusual location of Brunner's glands in the mink, resembling that in the monotremes in which these glands are present only in the distal portion of the stomach (KRAUSE, 1971). That the mink has large numbers of the endocrine cells in Brunner's glands suggests the purposefully regulated activity of the glands in this animal. It is reasonable to assume that in response to the chemical information from the lumina of the glands some types of endocrine cells stimulate secretion by the glands while others inhibit it. It was reported recently that the secretory function of Brunner's glands may be stimulated by VIP, a large number of which has been demonstrated in nerve fibers and cell bodies in these glands of the rat (KIRKEGAARD et al., 1981). In the present study, however, VIP-immunoreactive nerve elements could not be observed in Brunner's glands in the mink. The somatostatin-immunoreactive cells which were very numerous in Brunner's glands of the mink are presumed to inhibit the secretory function of these glands.

Gastric acid secretion is stimulated by gastrin, and it is suppressed by somatostatin and glucagon. Somatostatin-immunoreactive cells have been assumed to suppress the secretion of the parietal cells in the fundic gland region and also of gastrin-immunoreactive cells in the pyloric gland region, the suppression being induced by paracrine secretion with their cytoplasmic processes which are attached to these cells (KUSUMOTO

Fig. 15. Aggregation of Grimelius-positive cells in the pancreas. They are seen adjacent to a large nerve cell (arrow). ×1,600

Fig. 16. Substance P-immunoreactivity in the duodenum. Immunoreactive nerve fibers in the lamina propria (a) and in Auerbach's plexus (b) are found. PAP method, 1:2,000. a: ×330, b: ×460
et al., 1979; ALUMETS et al., 1979; LARSSON et al., 1979). In the present study, short processes of gastrin-immunoreactive cells and long processes of enterochromaffin and glucagon-immunoreactive cells have been detected in addition to the processes of somatostatin-immunoreactive cells. These processes seem to present morphological evidence for the paracrine secretion by any of these cell types.

It has been pointed out that no endocrine cells in the fundus are open to the lumen in the human (FUJITA and KOBOYASHI, 1973). However, a few open type endocrine cells have been observed in this region in our study of the mink, and we presume that these cells are sensitive to the luminal information and, in response to it, release their hormones.

Endocrine cells are numerous in the rectum of the cat (KITAMURA et al., 1982), of the same order, Carnivora, as in the case of the mink, and the same is true in the rectum of the horse (SATO et al., 1976) and sheep (Oomori et al., 1980), animals of the order Herbivora. In contrast, the mink does not exhibit such an elevation in cell number in this region. This, together with the absence of the caecum and the shortness of the large intestine, is likely to suggest a digestive function oriented primarily to protein-rich foods, its minor role being the absorption of water.

Radioimmunological and immunohistochemical studies have established that there are two types of glucagon: the pancreatic-type and the gut-type (LARSSON et al., 1975). The pancreatic-type glucagon-immunoreactive cells are demonstrated only in the pancreatic islet and, depending on the species, in the gastric fundus (LARSSON et al., 1975; ITO and KOBAYASHI, 1976; GARAUD et al., 1980). Cells of this type have been reported in the human colon (KNUDSEN et al., 1975; COLONY et al., 1982). In our study of the mink, cells which were immunoreactive to the antisemur specific to the pancreatic-type glucagon have also been found in the jejunileum. All such glucagon-immunoreactive cells were positive to the anti-glicentin serum in the serial sections, although not all glicentin-immunoreactive cells were stained by the anti-glucagon serum.

There have been some reports concerning the distribution pattern of the cell types in the pancreatic islet of several species. In the horse (FUJITA, 1973; Ito et al., 1978), A or glucagon-containing cells are distributed centrally, B or insulin-containing cells

![Fig. 17. VIP-immunoreactivity observed in some nerve cells in Auerbach's plexus of the transitional region (a) and in a ganglion of the pancreas (b). PAP method, 1:4,000. ×600](image-url)
GEP Endocrine Cells of the Mink

peripherally, and D or somatostatin-containing cells between the two. The reverse pattern with insulin-containing cells in the center and glucagon-containing cells in the periphery is known in the rat (ITO et al., 1978) and mouse (LUNDQVIST et al., 1979). In the present study, glucagon- and glicentin-immunoreactive cells are distributed peripherally and somatostatin-immunoreactive cells more centrally. The B cells were believed to be located in the center of islets, although insulin-immunoreactivity was not examined in this study. This pattern of islet cell distribution resembles that in the rat and mouse.

The VIP- and substance P-immunoreactive nerve elements that have been observed in this study are consistent with reported descriptions that these hormones are neural peptides and are especially abundant in Auerbach’s plexuses in the small intestine (PEARSE and POLAK, 1975; SCHULTZBERG et al., 1978; LUNDQVIST et al., 1979; MALMFORS et al., 1981; LEANDER et al., 1981).

A structure in which nerve cells, and often fibers, and endocrine cells occur mingled in the pancreas is called the “neuroinsular complex” and has been observed in some species including the mink (FUJITA, 1959; FUJITA et al., 1981). The existence of the similar structure is confirmed in the pancreas by Grimelius’ or Hellerström-Hellman’s method in the present study.

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