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Immunohistochemical Study on the Gastrin, Somatostatin and Serotonin Cells in the Gastric and Small Intestinal Mucosa of Rat during Development

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The developmental changes of three enteroendocrine cells, i.e. gastrin, somatostatin and serotonin, of gastric and small intestinal mucosa in pre- and postnatal rat were examined by peroxidase-antiperoxidase (PAP) method.

In the course of development, gastrin cells were observed in the pyloric gland region and the whole part of small intestine, while somatostatin and serotonin cells in the whole gastric gland region and small intestine. More entroendocrine cells were detected in the pyloric gland region and duodenum than in the other portion. In the stomach, gastrin, somatostatin and serotonin cells were first observed in the pyloric gland region on 17, 19 and 19 days of gestation respectively. The small intestinal gastrin and serotonin cells were first appeared in the duodenum and jejunum on 17 and 15 days of gestation respectively, and somatostatin cells in duodenum on 17 days of gestation. The number of cells examined from the stomach were increased from fetal to weanling period and showed a decrease during adult period; the notable increase was shown at the end of suckling period or at early weanling period. The cells of the small intestine increased from fetal to suckling period, especially, these cells markedly increased at the end of fetal period or at early suckling period, and decreased from weanling period.

The shape of these cells was oval or fusiform during fetal period. In the stomach, most of gastrin cells turned out to be oval and open-type from suckling period, while the remaining two types of cells were oval and open- or closed-type. In the small intestine, all types of cells examined were changed to fusiform and open-type from the end of fetal period.

Three types of cell were distributed over the stratified epithelium on 15 and 17 days of gestation. In the stomach, these cells were distributed lower gastric pit and gland from the following fetal period, and were detected mainly on the upper part of gland from suckling period, and then observed on the whole part of gland. In the small intestine, most of cells distributed over only between epithelium of villi on 19 days of gestation, increased in number on the crypt from following fetal period, and also observed abundantly in the crypt at adult period.

KEY WORDS: Immunohistochemistry, Gastrin cell, Somatostatin cell, Serotonin cell, Rat, Development

Recently, many of the different types of enteroendocrine cells, which operate an important physiological regulation in the process of digestion with the autonomic nerve system, have been distinguished in the gastrointestinal tract of various vertebrates (Larsson *et al.*, 1979; Yamada, 1987; Solcia *et al.*, 1987). It has been proposed that most of these cells produce either polypeptide hormones or biogenic amines.

With the physiological function in digestion, it has been suggested that enteroendocrine cells may also play an important role in cell proliferation, differentiation and morphogenesis of gastrointestinal tract, and so the distribution and quantity of these cells in fetal and immature tissue are quite different as compared with those of adult (Johnson, 1976; Larsson *et al.*, 1975, 1976, 1977; Larsson, 1977; Hughes *et al.*, 1978; Lehy *et al.*, 1979). The ontogeny of gastrin (Braaten *et al.*, 1976; Larsson *et al.*, 1976; Larsson, 1977; Stein and Morris, 1982; Marino *et al.*, 1985; Onolfo and Lehy, 1987), somatostatin (Alumets *et al.*, 1977; Larsson, 1977; Lehy *et al.*, 1979; Koshimizu, 1983; Dupouy *et al.*, 1983; Onolfo and Lehy, 1987) and serotonin (Park *et al.*, 1988) has been studied in fetus and immature rat employing immunohistochemical method. However, the relative importance of these cells in developing animals is incompletly known.

In the present study, we have investigated the developmental changes on the gastric and small intestinal gastrin, somatostatin and serotonin cells using immunohistochemical technique.

Materials and Methods

Female rats, virgin Sprague-Dawley (S/D) strain from 12 to 15 wks. of age, were placed overnight from 18:00 to 08:00 hr. with males and examined the following morning the presence of sperm in vaginal smear. The day which identified sperm in vaginal smear was designated as day 0 of gestation (McIntoch *et al.*, 1977; Dupouy, *et al.*, 1983). Rats were divided into four period-groups, such as fetal (15, 17, 19 and 21 days of gestation), suckling (1, 3, 5, 7 and 14 days old), weanling (21, 35 and 49 days old), and adult period (105 days old), in relation to pre- and postnatal development.

For the tissue preparation, rats of each period were anesthetized with ether and the stomach, duodenum, jejunum and ileum were immediately removed. The specimens were fixed Bouin's fluid for 24 hr. and embedded in paraplast melting at 56°C. Sections were cut in series at 5 μm.

Immunohistochemistry for demonstrating enteroendocrine cells was performed using the peroxidase-antiperoxidase (PAP) method (Sternberger, 1979). Deparaffinized and hydrated sections were treated with 0.5% H_2O_2 in methanol for 30 min. and rinsed in phosphate buffer saline (PBS: 0.01 M, pH 7.4). The sections were exposed for 30 min. to 3.3% goat normal serum at room temperature and then incubated for 24~48 hr. in moisture chamber at 4°C with rabbit anti-gastrin (DAKO Corp., A568), somatostatin (DAKO Corp., A566) and serotonin (Incstar Corp., 20080), as the primary antisera, at a dilution of 1:200, 1:300 and 1:500, respectively. The sections were rinced in PBS and then treated for 1 hr. at room temperature with horseradish peroxidase (HRP) conjugated anti-rabbit IgG (DAKO Corp., P448), as the secondary antisera, at a dilution of 1:200, and rinsed in Tris buffer (TB: 0.05 M, pH 7.6). The PAP complex treated in TB containing 3,3'-diaminobenzidine tetrahydrochloride (DAB) and 0.003% H_2O_2 to visualize, and lightly stained with Mayer's hematoxylin.

The frequency of cells was expressed as number of cells per 1 mm^2 of mucosa. Regional distribution and shape characteristic of cells were also observed.

Results

The frequency and distribution of three types of cells in the gastric and small intestinal mucosa of rat during development were shown in Tables 1~3.

Stomach

During development, gastrin cells were observed only in the pyloric gland region, however,

Table 1. The frequency (cell numbers/1 mm^2) and distribution of gastrin immunoreactive cells in the stomach and small intestine of rat during development

Regions	Days of gestation				Days after birth								
	Fetal rat				Suckling rat					Weanling rat			Adult rat
	15	17	19	21	1	3	5	7	14	21	35	49	105
FOR	0	0	0	0	0	0	0	0	0	0	0	0	0
ACG	0	0	0	0	0	0	0	0	0	0	0	0	0
AFG	0	0	0	0	0	0	0	0	0	0	0	0	0
APG	0	6.2	15.3	20.0	29.9	43.1	74.0	92.7	191.1	244.6	326.0	321.3	255.4
DUO	0	7.2	23.4	35.7	30.7	25.6	33.0	26.8	30.9	10.6	9.4	6.4	7.3
JEJ	0	*	*	*	10.3	6.0	12.0	9.3	14.1	16.9	10.7	16.4	9.6
ILI	0	0	0	0	*	*	*	*	*	*	*	*	*

Abbreviations: FOR, forestomach; ACG, area of cardiac gland; AFG, area of fundic gland; APG, area of pyloric gland; DUO, duodenum; JEJ, jejunum; ILI, ileum: *, rarely detected.

Table 2. The frequency (cell numbers/1 mm^2) and distribution of somatostatin immunoreactive cells in the stomach and small intestine of rat during development

Regions	Days of gestation				Days after birth								
	Fetal rat				Suckling rat					Weanling rat			Adult rat
	15	17	19	21	1	3	5	7	14	21	35	49	105
FOR	0	0	0	0	0	0	0	0	0	0	0	0	0
ACG	0	0	0	0	0	*	*	*	*	*	*	*	*
AFG	0	0	0	*	*	*	4.1	6.3	14.2	19.7	15.8	25.4	20.6
APG	0	0	*	*	*	6.2	11.7	18.7	46.9	72.2	94.2	133.1	96.6
DUO	0	*	*	8.5	9.1	22.8	13.8	21.7	19.9	15.3	4.3	6.2	3.9
JEJ	0	0	*	*	*	*	*	*	*	*	*	*	*
ILI	0	0	0	*	*	*	*	*	*	*	*	*	*

Abbreviations are the same as in the Table 1.

somatostatin and serotonin cells were seen in the whole gastric gland region. In the pyloric gland region, gastrin cells were first demonstrated in 17 day-old fetal rat, and somatostatin as well as serotonin cells in 19 day-old fetal rat. The somatostatin cells of the cardiac gland region and serotonin cells of the fundic gland region were first demonstrated in 3 day-old suckling rat, somatostatin cells of the fundic gland region in 21 day-old fetal rat, serotonin cells of the cardiac gland region in 1 day-old suckling rat. In the forestomach, however, no enteroendocrine cells were observed.

The number of gastrin cells in the pyloric gland region increased progressively from fetal to weanling period, the notable increase in number of these cells was shown in 19 day-old fetal and 14 day-old suckling rat. The somatostatin cell number in the glandular stomach with exception of cardiac gland region which were rarely demonstrated throughout all periods increased during suckling and weanling periods, and markedly increased in 14 day-old suckling rat. The serotonin cells were rarely detected from fetal to early suckling period, and then increased from late suckling period, the notable increase was shown in 3 and 14 day-old suckling rat and all weanling rat in the pylorus, in 7 day-old suckling and 35 day-

Table 3. The frequency (cell numbers/1 mm^2) and distribution of serotonin immunoreactive cells in the stomach and small intestine of rat during development

Regions	Days of gestation				Days after birth								
	Fetal rat				Suckling rat					Weanling rat			Adult rat
	15	17	19	21	1	3	5	7	14	21	35	49	105
FOR	0	0	0	0	0	0	0	0	0	0	0	0	0
ACG	0	0	0	0	*	*	*	14.0	10.0	8.0	48.0	32.0	10.7
AFG	0	0	0	0	0	*	4.0	9.2	13.3	8.4	3.8	6.0	6.3
APG	0	0	*	*	*	10.2	16.9	22.5	41.4	74.8	128.5	229.6	177.1
DUO	*	*	18.0	65.6	53.3	29.5	49.4	54.4	62.2	72.9	40.7	37.8	25.3
JEJ	*	*	15.3	21.3	20.5	25.0	16.6	16.8	17.0	16.8	18.9	14.3	13.4
ILI	0	0	7.4	12.4	10.4	6.0	5.4	7.7	11.0	7.6	10.8	8.3	10.3

Abbreviations are the same as in the Table 1.

old weanling rat in the cardiac gland region. And all types of cells examined showed a slight decrease in number in adult rat.

As for the distribution, enteroendocrine cells examined were distributed over the stratified epithelium in 17 day-old fetal rat, and during the following fetal period they were demonstrated on lower gastric pit and gastric gland. From the suckling period, these cells usually occurred on upper part of the gastric gland and only a few cells were detected in the gastric pit and lower part of gastric gland. From the weanling period, these cells were usually demonstrated in whole part of gland. However, in the fundic gland region, somatostatin cells were mainly demonstrated in the middle and lower part of gland, serotonin cells in the upper and middle part of gland.

The shape of cells was oval or fusiform displaying open- or closed-type during fetal period. From the suckling period, most of gastrin cells turned out to be oval and open-type, and the remaining cells oval and closed-type. Most of somatostatin and serotonin cells were oval and open- or closed-type throughout all periods.

Small intestine

Three types of cell were demonstrated in the whole part of small intestine in the course of development. The gastrin cells were first detected in duodenum and jejunum in 17 day-old fetal rat, in ileum in 1 day-old suckling rat. Somatostatin cells were first identified in duodenum, jejunum and ileum in 17, 19 and 21 day-old fetal rat respectively. The serotonin cells observed from 15 day-old fetal rat in the duodenum and jejunum, from 19 day-old fetal rat in ileum. The gastrin cells in the ileum and somatostatin cells in the jejunum and ileum were occasionally seen throughout all periods.

Gastrin cells increased from the fetal period, and the notable increase in number of duodenum and jejunum was shown at the end of fetal period and on 1 day-old suckling rat, respectively, and the following suckling period, these cells remained without variety in number. But from weanling period, gastrin cells in the duodenum markedly decreased in number. The somatostatin cells of duodenum markedly increased in number at the end of fetal and early suckling period and decreased from weanling period. The serotonin cells of the whole part of small intestine showed a notable increase at the end of fetal period, and then marked changes in number was not observed to weanling period, and slightly decreased in adult.

The gastrin, somatostatin and serotonin cells were distributed over the stratified epithelium in 15 and 17 day-old fetal rat, and only in epithelium of villi in 19 day-old fetal rat. From the following fetal period, the distribution of these cells increased on the crypt and also observed abundantly in the crypt. Most of cells were oval or fusiform during fetal period. From the end of fetal period, these cells were changed to fusiform and typical open-type that established contact to the

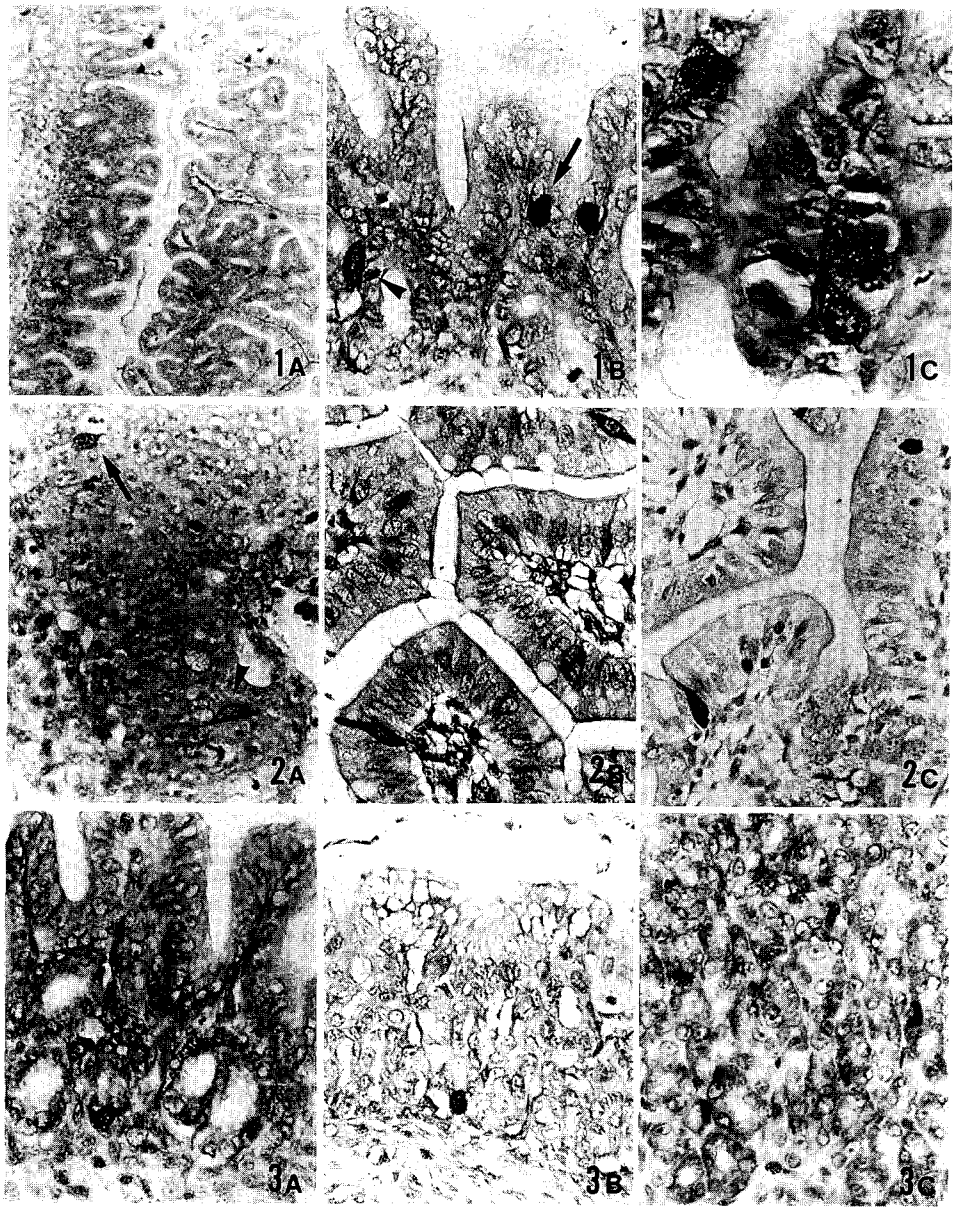

Fig. 1. The gastrin cells of the pyloric gland region in 1 day-old suckling rat (1A, ×100; 1B, ×400) and in 21 day-old weanling rat (1C, ×1,000). In the suckling rat, cells were found in the lower gastric pit and pyloric gland and showed oval and closed- (arrow) or open-type (arrowhead). At higher magnification of weanling rat, these cells exhibited as oval and open-type.

Fig. 2. The gastrin cells of the duodenum in 17 (2A, ×400) and in 21 day-old fetal rat (2B, ×400), and in 5 day-old suckling rat (2C, ×400). In 17 day-old fetal rat, cells noted in the stratified epithelium and showed as oval (arrow) or fusiform (arrowhead), but changed as fusiform and open-type in the villi of 21 day-old fetal and in those of suckling rat.

Fig. 3. The somatostatin cells of the pyloric gland region in 1 (3A, ×400) and in 7 day-old suckling rat (3B, ×400), and those of fundic gland region in 21 day-old weanling rat (3C, ×400). These cells in the gastric gland region were oval and open- or closed-type.

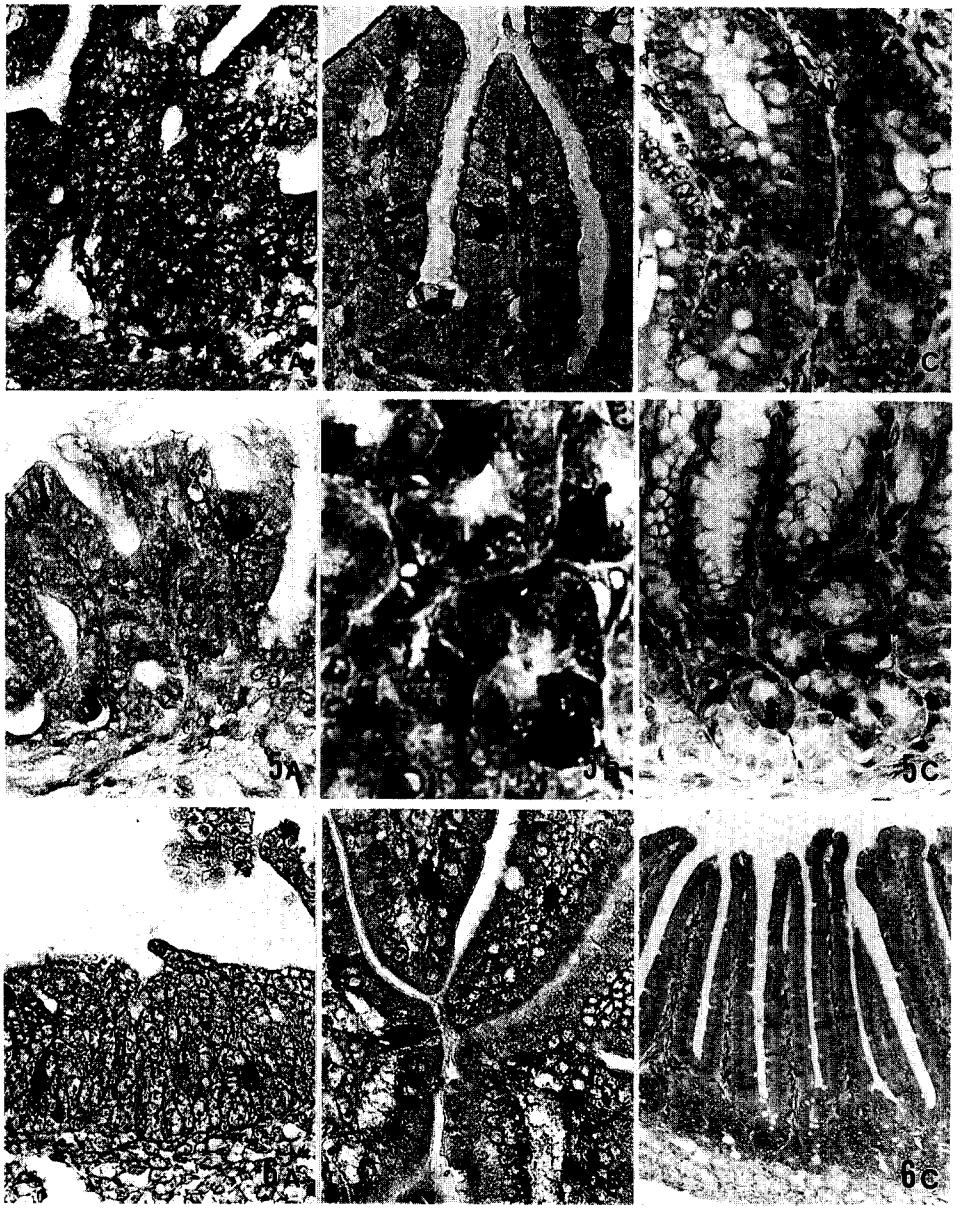

Fig. 4. The somatostatin cells of the duodenum in 19 day-old fetal (4A, ×400), and in 1 day-old suckling (4B, ×400) and in 49 day-old weanling rat (4C, ×400). In the fetal rat, these cells were exhibited in the lower part of villi as oval and closed-type and changed as fusiform in the villi and crypt from the suckling period.

Fig. 5. The serotonin cells of the pyloric gland region in 1 day-old suckling (5A, ×400), and in 21 (5B, ×1,000) and in 49 day-old weanling rat (5C, ×400). These cells were oval and closed-type in suckling rat, however, demonstrated as open- or closed-type in the weanling rat.

Fig. 6. The serotonin cells of the duodenum in 17 (6A, ×400) and in 21 day-old fetal rat (6B, ×400), and in 21 day-old weanling rat (6C, ×100). These cells were detected in the stratified epithelium in 17 day-old fetal rat and only villi in 21 day-old fetal rat. In 21 day-old weanling rat, these cells were distributed in villi and crypt as typical fusiform and open-type.

epithelial surface by apical cytoplasmic processes, and only a few oval and closed-type cells can be detected in the villi and crypt.

Discussion

During the fetal and neonatal life, many different enteroendocrine cells show a transitory increase or decrease in the cell population and have an appearance in restricted developmental period. The results on ontogeny of enteroendocrine cells suggest that these cells may have also important role in development of gastrointestinal tract (Johnson, 1976; Larsson *et al.*, 1975, 1976, 1977; Larsson, 1977). Although there was considerable evidence for cell proliferation effect including gastrin (Johnson, 1976; Larsson *et al.*, 1976; Goodlad and Wright, 1987) and serotonin (Lauder and Krebs, 1976) as a trophic factor, and somatostatin (Sagor *et al.*, 1985) as a reduction factor, it remained a shadow of dispute for it's multifactorial affair (Goodlad and Wright, 1987).

Regarding gastrin content in fetal stomach by radioimmunoassay, antral tissue gastrin has been detected on 14 (Marino *et al.*, 1985) and 16 days of gestation (Braaten *et al.*, 1976). Larsson *et al.* (1976), Larsson (1977) and Onolfo and Lehy (1987) reported that occasional gastrin cells were first identified between day 18 to 20 of gestation by immunohistochemistry. And gastrin cells gradually increased with age, a sharp increase was shown in antrum between day 1 to 15 (Braaten *et al.*, 1976) or between day 1 to 21 of neonatal life (Larsson *et al.*, 1976; Larsson, 1977) and reached to the maximal level in amount on 35 days after birth (Braaten *et al.*, 1976). In the duodenum, gastrin cells have been observed first on 18 days of gestation (Larsson, 1977), on pre-19 days of gestation (Onolfo and Lehy, 1987), and as early as the 15-16 days of gestation (Larsson and Mørche Jorgensen, 1978). And this type of cells increased in number untill a few days after birth, about 1-4 days after birth, and thereafter abruptly dropped (Larsson, 1977; Larsson and Mørche Jorgensen, 1978).

The results of present study were in disagreement with the study of Larsson (1977) who has reported that gastrin cells appear earlier in the duodenum than in the pylorus. However, these results were consistent with those found by other researchers (Larsson, 1977; Majumdar, 1984; Onolfo and Lehy, 1987) who mentioned that the number of duodenal gastrin cells were higher than those of gastric ones during fetal and early neonatal life.

Previous studies have reported that gastrin is subdivided 2 groups; G-17 and G-34 (Dockray *et al.*, 1978). The anti-gastrin antiserum used in the present study was G-17 nonsulfated form, reacts with nonsulfated and sulfated form of G-17 as well as G-34. Kataoka *et al.* (1985) has reported that G-17 first appeared in the pyloric mucosa on 14 days of gestation while G-34 appeared after birth coincides with the postnatal development of gastric mucosa and morphologically matured parietal cell. In line with Braaten *et al.* (1976) who demonstrated gastrin both in antrum and pancreas on 16 days of gestation, Garzon *et al.* (1982) found that immunoreactive gastrin is present in large amount in fetal blood from 16th day fetus, but these pentagastrin does not stimulate acid secretion until 20th day fetus. Although we know nothing as yet of this biological activity in fetal rat, as mentioned above, many of the previous studies deduced that it may play an important role as a trophic factor (Larsson *et al.*, 1976; Johnson, 1976; Braaten *et al.*, 1976).

Previous studies reported that gastric somatostatin cells were first seen in the antrum on 19-20th day of fetal life (Larsson, 1977) and in neonates (Alumets *et al.*, 1977; Lehy *et al.*, 1979; Onolfo and Lehy, 1987). After birth it immediately increased with age up to around 3 wks. old rat (Larsson, 1977; Alumets *et al.*, 1977; Lehy *et al.*, 1979; Onolfo and Lehy, 1987; Koshimizu, 1983). Duodenal somatostatin cells were present on pre-18 days (Larsson, 1977; Dupouy *et al.*, 1983) and on 16-17 days of gestation (Alumets *et al.*, 1977), and showed a progressive increase during late period of gestation and early suckling period and attained the maximum frequency, and following period a dramatical decrease in number began (Larsson, 1977; Alumets *et al.*, 1977; Dupouy *et al.*,

1983; Koshimizu, 1983).

In the present study, observed variation in number of somatostatin cells was in accordance with earlier studies (Larsson, 1977; Onolfo and Lehy, 1987; Koshimizu, 1983; Dupouy *et al.*, 1983). And a few studies have dealt with the development of the regulation of gastric function, results above mentioned and those from previous studies (Ducroc *et al.*, 1981; Garzon *et al.*, 1982) suggest that acidification at the end of gestation and diminution of gastric acid secretion after birth might be explained by the rapid increase of gastrin cells on fetal period and increase of somatostatin cells during neonatal life.

In the small intestine, Park *et al.* (1988) reported that serotonin cells were first detected in the intestinal epithelium as early as 10 days of gestation, even though it disappeared and reappeared on 17 days of gestation. Although there were some evidence on the serotonin as a trophic factor in differentiation and development of nervous system, the ontogeny of serotonin cells in gastrointestinal tract is not fully studied. But serotonin cells may participate as a trophic factor in the growth and morphogenesis of gastrointestinal tract besides their original function in the process of digestion (Park *et al.*, 1988).

Enteroendocrine cells are divided morphologically into two main groups, the so-called open- and closed-type, by Fujita and Kobayashi (1977). These types were related to their perception of stimulation. The open-type cells are chemically or mechanically stimulated at their apical cytoplasmic processes and the closed-type cells are reacted indirectly to mechanical and vegetative stimulation (Fujita and Kobayashi, 1977; Solcia *et al.*, 1987).

Kataoka *et al.* (1985) observed that a few open-type mouse gastrin cells showed in the pyloric mucosal epithelium. Dupouy *et al.* (1983) observed the open-type somatostatin cells to possess an elongated apical process in contact with the intestinal lumen in the duodenum of rat as the previous authors (Larsson *et al.*, 1979; Alumets *et al.*, 1977; Dupouy *et al.*, 1983). However, the cytoplasmic processes were not observed in this study. As for the distribution of these cells, mouse gastrin cells were mainly present in the lower part of foveola and pyloric gland and scattered in the villus and crypt epithelium of the duodenum (Kataoka *et al.*, 1985). Somatostatin cells demonstrated basally in the pyloric gland and scattered along the entire fundic gland (Alumets *et al.*, 1977) or middle and basal part in the fundic and cardiac gland, upper third in the pyloric gland (Weyrauch *et al.*, 1987).

Although these morphological changes of enteroendocrine cells were not fully studied, developmental changes of charateristics of shape and distribution are presumed to occur as a result of the difference of physiological function related to the process of digestion between fetus and adult.

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발생기 흰쥐 위와 소장점막의 gastrin, somatostatin 및 serotonin세포에 대한 면역조직화학적 연구

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태생기부터 성체기에 이르는 흰쥐 위와 소장점막의 gastrin, somatostatin 및 serotonin세포의 분포, 출현빈도 및 형태적 특징을 면역조직화학적으로 살펴보았다.

발생기동안 gastrin세포는 위의 유문선부와 소장의 모든 부위에서, somatostatin과 serotonin세포는 모든 위의 위선부와 소장부위에서 관찰되었으며 유문선부와 십이지장에 많이 분포하고 있었다. 위에서 유문선부의 gastrin세포가 임신 17일, somatostatin과 serotonin세포가 임신 19일에 가장 먼저 관찰되었다. 소장에서 십이지장과 공장의 gastrin 및 serotonin세포가 각각 임신 17 및 15일, 십이지장의 somatostatin세포가 임신 17일에 처음 관찰되었다. 발생단계별 출현빈도는 위에서 태생기부터 이유기까지 증가하는데 수유기말 또는 이유기초에 현저하였으며 성체기에는 감소하였다. 소장에서 태생기와 수유기에 증가하는데 특히 태생기말 또는 수유기초에 현저하며 이유기부터 감소하였다

세포의 형태는 태생기에 난원형 또는 방추형이나 위에서는 수유기부터 대부분의 세포가 난원형이었으며 gastrin세포는 개구형을, somatostatin과 serotonin세포는 개구형 또는 폐쇄형이었다. 소장에서는 태생기말부터 대부분의 세포가 방추형을 띤 개구형으로 변하였다. 세포의 분포는 15 및 17일 태자는 중층점막상피내에 분포하며 위에서 그후 태생기는 소와하부와 위선에, 수유기동안은 주로 위선상부에, 그후는 전 위선에서 관찰되었다. 소장에서 19일 태자는 융모에, 21일 태자부터는 융모와 은와에서 관찰되며 수유기와 이유기동안 은와의 분포수가 증가하여 성체에서 은와의 분포수가 더 많았다.