EFFECT OF GASTRIN ON THE CELL KINETICS OF
RAT GASTRIC MUCOSA

BY
Masao Okamoto

ABSTRACT

The effects of gastrin on the cell kinetics of the gastric mucosa were studied in the rats. The labelling index by tritiated thymidine of the cell in the mucous neck zone began to rise 14 hours after a single dose of tetragastrin at 100 or 1,000 μg/kg or synthetic human gastrin at 1,000 μg/kg and reached the peak at 18 hours. With tetragastrin 100 μg/kg administered subcutaneously together with a depot for 35 days, observations were made on the change in the turnover rate of the gastric epithelium by means of labelling index. The turnover rate was delayed in the surface epithelium and accelerated in the cells at the lower part of the foveolae in the gastrin-administered group. The cell suspension prepared from the rat gastric mucosa by trypsin digestion was cultivated with 5 per cent of CO₂ in air for 48 hours. The group which was added with 10 μg/ml of tetragastrin showed fluctuations in the labelling index almost similar to the groups administered 100 and 1,000 μg/kg in vivo.

It might be possible to support the hypothesis that gastrin not only has a trophic effect on the mucous neck zone but it also might be concerned with the turnover of the mature stage of gastric mucosa.

INTRODUCTION

In 1955 Zollinger and Ellison⁴ reported on the mode of illness which showed a marked increase in the secretion of the gastric juice in the pancreas tumor, suggesting that humoral substances might be concerned.

In 1964 Gregory and Tracy found a new substance which was named “gastrin”. Pollacek (1966)⁶ reported that the Zollinger-Ellison syndrome showing hypergastrinemia was often accompanied by parietal cell hyperplasia. Then there came the report by Crean et al. (1969)⁷ on parietal cell hyperplasia following the chronic administration of pentagastrin in the rats and the experiments by Martin et al. (1970)⁸ on hypoplasia of the fundic mucosa resulting from antrectomy; thus, it was suggested that endogenous as well as exogenous gastrin might exert a trophic effect on the gastric mucosa.

However, although it is known now that gastrin is shown to have the action of secreting insulin, of accelerating the movement of the intestinal tract and of increasing the blood flow of the gastric mucosa, there still remains some questions as to the mechanism by which the trophic action of gastrin on the gastric mucosa manifests itself.

In 1973 Miller et al.⁹ cultivated the gastric mucosa of the rat and man in vitro and observed that gastrin had a direct effect on the gastric mucosa.

Today, the gastrin-like peptide is used

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clinically as gastric juice stimulants and is said to exert a trophic effect on the cell of gastric mucosa like the gastrin$^{6,8}$.

The present studies were designed to elucidate the relationship between the trophic effect and the concentration of gastrin-like peptide in the rat gastric mucosa by means of labelling index (L.I.) by tritiated-thymidine (H-TdR) in vivo and in vitro. The difference in the trophic effect between the synthetic human gastrin (S.H.G.) and gastrin-like peptide, tetragastrin, was also studied in vivo. Furthermore, the author discusses about the change in the turnover rate of the gastric mucosal cells in continuous hypergastrinemia.

**Materials and Methods**

Experimental animals used were Wister male rats weighing 162 g (150–200 g) on the average.

1) Method for measurement of acidity of gastric juice by tetragastrin stimulation

The abdomen of the rat fasting for 24 hours was opened under anesthesia with sodium pentobarbital 5 mg/kg. A silicone tube 2 mm in diameter was passed through the pyloric ring into the stomach and then a ligature was made. Likewise a similar tube was passed from the mouth and fixed at a place where the tip passes through the cardiac orifice. A constant volume of physiological saline solution was poured into the stomach through the tube from the side of the mouth, perfusing the stomach, and the saline solution was collected in fractions every five minutes from the tube from the side of the pylorus. Adjustment was made so that the amount collected is 5 ml per 5 minutes; the pH of the solution collected was measured at the time when the amount poured and the amount discharged became constant, and this was made the value before stimulation.

Then tetragastrin in doses of 1, 10, 100 and 1,000 μg/kg was injected via the tail vein to the group of three rats; the perfusate was collected every five minutes for 60 minutes and its pH was measured. The tetragastrin used is a product of the benzylxoy-carbonyl group (Sana Pharmaceutical Co.).

2) Observations on the cell kinetics of gastric mucosa (in vivo)

One hundred and eight rats were divided into six groups. Synthetic human gastrin (S.H.G.) (ICl) 1,000 μg/kg dissolved in physiological saline solution and distilled water equivalent to 1, 10, 100 and 1,000 μg/kg of tetragastrin was administered intraperitoneally to all animals, or 18 rats to each.

Thereafter, the animals were sacrificed on a time-course basis, that is, at the 5th, 12th, 14th, 16th, 18th and 24th hour. One hour before sacrificing, 1 μC/g of H-TdR was administered intraperitoneally. After sacrificing, the stomach was extirpated; a tissue specimen was prepared from a certain part of the anterior wall of the corpus and a autoradiograph was performed. Two weeks later, the films were developed and fixed; hematoxylin-eosin staining was done and the labelling index (L.I.) was measured on the labelled cells in % per 1,000 epithelial cells of the entire mucosa while at the same time optical microscopic observations were made.

3) Observations on cell kinetics of gastric mucosa after long-term administration of tetragastrin (in vivo)

Forty-eight rats were divided into two groups in the present experiment. According to the method of Cox et al.$^{7}$ with the necessary modification, tetragastrin 1 mg was mixed with the depot of 1 ml in which liquid paraffin and beeswax were mixed at the ratio of 4 to 1; the mixture of a dose
of 0.1 ml was administered subcutaneously to the rats once a day for 35 consecutive days. The group administered depot alone was used as the control. The site of the injection was changed every day, but many of the sites were palpable as subcutaneous nodules. On the 5th, 6th and 7th day after the initiation of injection, 1 μg/g of ³H-TdR was injected intraperitoneally. One hour after the third injection of ³H-TdR, three rats each of both groups were sacrificed. This was designated as the date of the initiation of the experiment (zero day).

Thereafter, the animals were sacrificed on the time-course basis, that is, on 7th, 14th, 18th, 21th, 25th and 28th; autoradiograph was performed as in the short-term experiment, observations were made on the distribution of labelled cells and the L.I. was computed.

4) Method for preparation of suspensions of cells of gastric mucosa

The stomach was extirpated from the 30 rats fasting for 24 hours, washed throughly with physiological saline solution and allowed to stand in the Minimum Essential Medium (MEM) (GIBCO) supplemented with 10,000 U/ml penicillin and 10 mg/ml streptomycin. After washing with Hank's BSS solution containing 0.125% trypsin (GIBCO) for 15 minutes at 37°C with a magnetic stirrer and then filtrated off with a nylon mesh. This filtrate was centrifuged at 800 r.p.m. for five minutes and the supernatant was discarded and the residue was suspended in 80 ml of medium for tissue culture, which was used as the suspension of the cells of the gastric mucosa.

The medium was composed of 60% L-15 Medium (GIBCO), 20% NCTC 109 (DIFCO), 10% fetal calf serum (GIBCO), 100 U/ml penicillin and 100 μg/ml streptomycin. All procedures described above including the extirpation of the stomach were performed aseptically and as quickly as possible.

The suspension of the cells of the gastric mucosa obtained by the method mentioned above showed a cell count of 1.02 x 10⁶/ml and a viability of 56.9%.

5) In vitro cultivation and method of observation

One-ml portions of the suspension of the cells of the gastric mucosa were placed in the chamber slide of Lab-Tek and cultivated at 37°C with 5% CO₂ in air.

It was replaced by a medium of the same composition 24 hours after, whereupon the cells were suspended in the medium. Theoretically, 3.3 x 10⁸/ml of the cells were considered as being alive and adhering to the bottom of the chamber. The viability of all the cells in the chamber at this time stood at 26.3 percent. When the cells were observed with H.E. staining done after fixation with solution, the adhering cells retained the nucleus and protoplasm well and were easily distinguishable from the parietal cells.

After the replacement of the medium, all of the chambers were divided into four groups, and tetragastrin diluted with physiological saline solution was added so that the medium contained 0.1, 1.0 and 10.0 μg per 1 ml. The amount added was made constant at 0.06 ml, while the one with only physiological saline solution added was used as the control.

For 24 hours thereafter, it was partially replaced by a medium supplemented with 80% MEM, 20% fetal calf serum and 10 μg/ml of ³H-TdR; after incubation for 60 minutes, fixation was done with Carnoy solution and autoradiograph performed. As for the L.I., 200 cells within a fixed range were counted and the labelled cells were expressed in %.
Results

1) Effects of tetragastrin on pH of rat gastric juice

The effects of stimulation by tetragastrin of varying concentrations, 1, 10, 100 and 1,000 µg/kg, on the pH of the rat gastric juice are shown in Table 1.

The pH of the perfusate before stimulation by tetragastrin averaged 3.3±0.21. The 1-µg/kg group showed little change in the pH for 60 minutes after stimulation. In the 10-µg/kg group, gastrin was shown to have the effect of acid secretion, mild as it was. In the 100-µg/kg group, the pH began to drop from five minutes after intravenous injection, dropped to 2.6±0.20 20 minutes after, rose gradually thereafter and returned to the prestimulation values 60 minutes after. In the 1,000-µg/kg group, the highest

![Graph showing pH changes over time for different concentrations of tetragastrin.](image)

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(mean±SD)

Fig. 1. Time-course Changes of Cell Kinetics of Gastric Mucosa Following Single Administration of Tetragastrin
Table 1. Effect of Tetragastrin in Various Concentrations on pH of Rat Gastric Juice

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<td>3.1 ± 0.20</td>
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<td>2.5 ± 0.31</td>
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</table>

(mean±SD)

Fig. 2. Labelled cells Immediately After Administration of ³H-Thymidine appearing as a Belt Circumscribing Mainly the Mucous Neck Zone (×1000)

acidity of pH 2.4±0.23 showed a tendency almost similar to that in the 100-µg/kg group.

2) Changes with time of cell kinetics of gastric mucosa following single ad-

ministration of tetragastrin (Fig. 1)

The labelled cells immediately after the administration of ³H-TdR appeared as a belt, circumscribing mainly the mucous neck zone (Fig. 2).

The labelling index (L.I.) for the non-treated group was 16.7±0.88%. The L.I. for the 1-µg, 10-µg/kg groups showed a tendency to rise slightly 18 hours after, but it was not regarded as a significant variation. In the 100-µg/kg group, the L.I. began to rise from the 14th hour after the administration of tetragastrin, reaching the maximum value of 46.0±9.09% 18 hours after and dropped 24 hours later.

In the 1,000-µg/kg group too, the fluctuations in the L.I. showed the same pattern as in the 100-µg/kg group. That is to say, the L.I. rose gradually becoming 22.0±1.63% 5 hours after the administration of tetragastrin, 24.7±2.46% 12 hours after, 37.7±4.74% 14 hours after and 47.3±6.62% 16 hours after, reaching the maximum value of 52.7±5.70% 18 hours after and dropping to 32.0±4.32% 24 hours after.

3) Time-course change in cell kinetics of gastric mucosa after single administration of S.H.G.

As in the experiment with tetragastrin, studies were made on the L.I. of the mucous neck zone after the administration of
S.H.G. 1,000 μg/kg.

The L.I. rose gradually to 19.3±6.19% 5 hours after the administration of S.H.G. 1,000 μg/kg, to 28.7±4.09% 12 hours after, to 38.7±4.96% 14 hours after and to 43.3±6.21% 16 hours after, forming a peak at 46.7±2.43% 18 hours after and dropping to 30.7±6.78%.

Fig. 3 shows the comparison of these results with the group administered 1,000 μg/kg of tetragastrin. It was obvious that both groups showed almost the same numerical values for L.I. at each point of time, that there was no difference in the L.I. between the two groups and that the L.I. reached the highest value at the 18th hour after administration and showed almost similar fluctuations in both groups.

4) Changes in cell kinetics of gastric mucosa after long-term administration of tetragastrin

a) Time-course changes in the L.I.: Since it was obvious that both tetragastrin and S.H.G. exerted an accelerating effect on the cell kinetics of the mucous neck zone after a single administration, the cell kinetics of the gastric mucosa was measured after prolonged stimulation with tetragastrin (Fig. 4).

The L.I. on the zero day of the initiation
of the experiment was 46.0±2.83‰ in the tetragastrin-administered group and 42.0±2.45‰ in the control group. There was no difference between them. Thereafter, the L.I. dropped gradually to 40.0±3.74‰ and 39.5±4.95‰ respectively, in the tetragastrin-administered group and the control group 3 days after, 34.0±4.24‰ and 24.0±2.45‰ respectively, 7 days after and 22.5±2.60‰ and 16.5±1.65‰ respectively, 14 days after. The decrease of the L.I. became somewhat slow thereafter, becoming 21.0±1.00‰ and 19.0±2.24‰ 18 days after and 19.5±2.60‰ and 9.0±1.73‰, respectively, 28 days after, respectively.

That is to say, the variations in the L.I. followed almost the same course in both the tetragastrin-administered group and the control group. Yet, the tetragastrin-administered group showed high values at all times and particularly the results obtained 7 days and 14 days after were judged to be significant (p<0.01).

b) Distribution of labelled cells: Cells labelled with ³H-TdR appeared as a belt centering around the mucous neck zone on the zero day, but they were seen distributed more widely above and below the foveolae as compared with the experiments after a single administration. Three days after, they spread further upward and downward, some of them reaching the upper end of the
foveolae. Seven days after, labelled parietal cells were also observed (Fig. 5). After fourteen days the labelled cells were found in the mucous neck zone and surface epithelium, but they decreased distinctively in number compared with that in the early days of the experiment.

As the dropping of L.I. became relatively slow thereafter, the labelled cells were seen moving downward gradually. The difference in the rate of the decrease of L.I. with the 14th day as a borderline was clearly noticeable in both the tetragastrin-administered group and the control group. From

Fig. 5. Labelled Parietal Cells Observed Seven Days After Last Administration of 3H-Thymidine (×1000)

due to the fluctuations in the distribution of the labelled cells, it is supposed that the rate of the decrease of L.I. reflects the change in the L.I. in the surface epithelium up to the 14th day and that in the cells in the lower part of the foveolae, including the parietal cells thereafter.

When the changes in the L.I. in both groups were observed before and after the 14th day, they could be expressed as a primary function (Fig. 6). That is, they were expressed as $Y = 45.6 - 1.7 \times (p<0.01)$ up to the 14th day and $Y = 33.3 - 0.8 \times (p<0.01)$ thereafter in the tetragastrin-administered group, while in the control group they could be expressed as $Y = 43.8 - 2.6 \times (p<0.01)$ up to the 14th day and $Y = 22.2 - 0.4 \times (p<0.01)$ thereafter.

Comparison of the straight lines indicated clearly that the decrease in the L.I. was slow up to the 14th day in the tetragastrin-administered group compared with the control group ($p<0.01$). By contrast, there was a tendency thereafter for such a decrease to be somewhat fast in the former.

Judging from the fluctuations in the labelled cells with time, the straight lines were considered as indicating the turnover in the surface epithelium before the 14th day and that in the cells in the lower part of foveolae, thereafter. The turnover rate ($T1/2$) was calculated to be 13 days and 21 days, respectively, in the tetragastrin group and 8 days and 28 days, respectively, in the
control group.

5) Time-courses changes in kinetics of suspended cells of gastric mucosa by addition of tetragastrin

With the cells of the gastric mucosa in a liberated state, incubation was done for 24 to 48 hours and observations were made on the change in the rate of \(^{3}\)H-TdR ingested following the addition to tetragastrin.

Fig. 6. Time-course Changes in Labelling Index in Both Groups Expressed as a Primary Function

Fig. 7. Cells With H.E. Staining Following Fixation With Carnoy Solution After 24-Hour Cultivation at 37°C With 5% CO\(_2\) in Air (×400)
Fig. 7 shows the cells with H.E. staining, done following fixation with the carnoty solution 24 hours after.

Fig. 8 indicates the cell labelled with \(^3\)H-TdR. From their morphological properties, it seems likely that it is a cell of the mucous neck zone.

The L.I. before the addition of tetragastrin was 9.2±11.87\%o. Observations were made on the fluctuations in the L.I. of the groups supplemented with 0.1, 1.0 and 16 \(\mu\)g/ml of tetragastrin and of the control group (Fig. 9).

No obvious tendency was observed in the 0.1 \(\mu\)g/ml-added group and in the control group. In the 1.0 \(\mu\)g/ml-added group, the L.I. rose to 26.7±12.47\%o 16 hours after, but it was not judged to be a significant change.

The L.I. in the 10 \(\mu\)g/ml-added group rose gradually, slight as it was, to 16.3±16.54\%o 5 hours after the administration of tetragastrin, to 16.7±9.42\%o 12 hours after, to 26.7±16.99\%o 14 hours after, the highest value being 49.0±15.12\%o 16 hours after. Thereafter, it tended to drop slightly while showing a high value of 46.7±4.58\%o 18 hours after.

**Discussion**

At the beginning of this century, the humoral component in the serum was supposed to take part in the exocrine accommodation mechanism of the digestive tract. Since gastrin was discovered by Gregory and Tracy in 1964, a remarkable progress in gastrointestinal hormones have been made.

Today, it is well known that gastrin has a gastric juice-stimulating effect. With tetragastrin, a dose of 4 \(\mu\)g/kg shows the maximum stimulation in man. In the rat, however, the dose which yields the maximum stimulation is far larger; a dose of 100 \(\mu\)g/kg is not sufficient but 1,000 \(\mu\)g/kg is sufficient.

The author first made an observation on the gastric juice-stimulating effect of tetragastrin in doses of 1, 10, 100 and 1,000 \(\mu\)g/kg in the rat and then made a comparative
study on the trophic effect of tetragastrin at various concentrations on the cell kinetics of the gastric mucosa.

When the L.I. by $^3$H-TdR for the cells of the gastric mucosa after a single administration of tetragastrin 1, 10, 100, and 1,000 μg/kg in vivo was examined, the maximum value of L.I. was observed 18 hours after the administration of tetragastrin at all concentrations and the administration of a dose of 1,000 μg/kg gave a value of more than three times.

A similar experiment was also performed by Willems et al. They infused gastrin at the rate of 2 μg/kg/hr continuously for 4 hours in the dogs and subsequently observed the fluctuations in the L.I. by $^3$H-TdR on the time-course basis; the value of the L.I. began to rise 12 hours after the initiation of the drip infusion and reached the maximum 16 hours after. Johnson et al. (1974) injected 250 μg/kg of pentagastrin to the rats and sacrificed them at various times after the injection. Then, they determined the rate of DNA synthesis in the gastric mucosa after incubation in the tissue culture medium containing $^3$H-TdR and observed that the incorporation of thymidine in the pentagastrin-injected rats was 275 percent of the control in the
stomach 16 hours after. Though differences existed among the experimental animals used and in according to the kind and amount of gastrin, these results showed a tendency similar to the results obtained by the author.

While the gastric juice-stimulating effect to tetragastrin was observed obviously with 10 μg/kg, the trophic effect on the cell kinetics of the gastric mucosa was not necessarily clear with 10 μg/kg. This result, natural as it is, means that the target cell on which gastrin acts is different and indicates that the effect of gastrin on the cell kinetics of the gastric mucosa is observed only at concentrations higher than those showing the gastric juice-stimulating effect.

It has been obvious that tetragastrin has the effect of promoting the cell kinetics of the gastric mucosa, but reports are few on the difference in the effects because of the difference in the composition of various kinds of gastrin. Then the author observed the trophic effect of 1,000 μg/kg of S.H.G. on the cell kinetics of the rat gastric mucosa. As a result, a change in L.I. was found almost to be similar to that found after the administration of the same dose of tetragastrin. The gastric juice-stimulating effect of S.H.G. is said to be almost the same as that of tetragastrin\(^\text{9}\). Regarding the effect of promoting the cell kinetics of gastric mucosa, it is also possible to say that the effect of S.H.G. is regarded to be almost equal to that of tetragastrin.

The results obtained from this observation could not be applied in the case of the human being when considering the difference in sensibility and other factors. However, the fasting serum gastrin value of normal persons is less than 100 pg/ml and it is said to increase two-fold by the diet stimulus\(^\text{14}\). Thus, it may be said that the gastric secretion is influenced by the varia-

In the Zollinger-Ellison syndrome which is known to show endogenous hypergastrinemia and parietal cell hyperplasia, the serum gastrin level increase to 250 ng/ml\(^\text{15}\).

With regard to the action of endogenous gastrin, therefore, it may be possible to say that there is a difference between the threshold of gastrin showing the gastric juice-stimulating effect and that showing the cell kinetics-accelerating effect.

Cells of the gastric mucosa labelled with \(^3\)H-TdR are almost limited to the undifferentiated cells located in the mucous neck zone immediately after labelling\(^\text{16}\). These cells differentiate to mature cells and migrate gradually to the superficial or deep layer of the mucosa; the former diverses into the cells of the surface epithelium and the latter into the cells in the lower part of the foveolae, both of which disappear subsequently\(^\text{17,18}\). Therefore, the time-course changes in the L.I. may be considered as suggesting the turnover rate of the gastric epithelium.

The time-course changes in the L.I. could be expressed as the primary function before and after the 14th day. Judging from the movement of the labelled cells, the former was presumed to indicate the turnover rate of the surface epithelium and the latter that of the cells in the lower part of the foveolae.

The half-life computed from these straight lines was calculated to be 8 days before the 14th day and 28 days thereafter. This assumption the author made would not much wrong from the report that the surface epithelium of the stomach is replaced in four or six days\(^\text{18,19}\).

Then, observations were made on the change in L.I. with time by administrating tetragastrin in the form of depot. As a result, the L.I. was high in the tetragastrin-administered group at all times. The half-
life computed from the attenuated straight lines before and after the 14th day was calculated to be 13 days and 21 days, respectively. These values show that the turnover is slow in the former and fast in the latter compared with the 8 days and 28 days in the control group. Then, it follows that the addition of tetragastrin results in the slow turnover of the surface epithelium and fast turnover of the cells in the lower part of the foveolae.

Meanwhile, the tissue picture of the gastric mucosa 28 days after tetragastrin administration did not show any changes such as hyperplasia and hypoplasia. This result differs from the report of Crean et al.\(^5\) and Willems\(^6\) that there was observed hyperplasia of the parietal cells following the administration of pentagastrin. This might be attributable to the difference in the blood gastrin level caused by the differences in the dosage of gastrin and method of administration. That is, Crean et al. administered 2 mg of pentagastrin in the form of depot twice a day and Willems et al. 10 \(\mu\)g of porcine gastrin dissolved in saline every eight hours. By the author's method there is the possibility that the blood level of tetragastrin did not rise as expected due to the insufficient liberation of gastrin.

Therefore, it appears reasonable to postulate that gastrin has an effect on the differentiation of the cells of the gastric mucosa. That is, gastrin can be considered as having the effect of accelerating the splitting of the mucous neck cells, delaying the differentiation to the surface epithelium and accelerating the differentiation to the cells in the lower part of the foveolae. Sufficient concentrations of gastrin result in parietal cell hyperplasia and, in the case of low concentrations of gastrin, there is observed no marked change histologically.

However, the turnover rate is observed to be delayed in the surface epithelium and accelerated in the cells in the lower part of the foveolae even in the case of low concentrations.

Obviously, gastrin acts on the cell kinetics of the gastric mucosa in vivo. Regarding the mechanism of its action, many workers consider it as being the direct effect on the cells of the gastric mucosa from the experiments by Miller et al.\(^5\) in which the addition of pentagastrin to the cultured cells of the gastric mucosa caused the mitotic index to increase two-fold. However, the experiments by Miller et al. are not without problems. That is, it is known that the cells lose their intrinsic nature by cultivation\(^2\). Therefore, the possibility cannot be ruled out that the cells cultured by Miller et al. will not reflect the intrinsic nature of the cells of the gastric mucosa.

The author isolated the cells of the gastric mucosa, added tetragastrin during the primary culture and observed the trophic effect of tetragastrin. As a result, the addition of 10 \(\mu\)g/ml had the effect of accelerating the cell kinetics of the gastric mucosa as in the in vivo experiments.

This result was slightly different from that of the in vivo experiments in that the maximum value was reached earlier, that is, 16 hours after the addition of tetragastrin and that the L.I. still showed high values even 24 hours after; however, they are considered natural if the conditions between the in vivo and in vitro experiments are taken into account. It may be all right to draw the conclusion that the effect of tetragastrin of accelerating the cell kinetics of the gastric mucosa is a direct action on the cells of the gastric mucosa.

Yet, the method of experiments conducted by the author also has some problems. Suspended cells of gastric mucosa
prepared by the author, natural as it is, are unavoidably mixed with mesenchymal cells such as fibroblasts. Thus it may be pointed out that the effect of tetragastrin on these nonepithelial cells is included in the overall evaluation. However, judging from the results that gastrin has no effect of accelerating the splitting the fibroblast\(^5\), there appears to be no need to be concerned about the mixture of nonepithelial cells.

**Conclusion**

Using Wister male rats, studies were made on the effect of gastrin on the cell kinetics of the gastric mucosa as follows:

1) After the intraperitoneal administration of various concentrations of tetragastrin, the labelling index (L.I.) for the mucous neck cells was calculated on the basis of time-course by \(^3\)H-TdR. The L.I. of the groups administered 100 and 1,000 \(\mu\)g/kg of tetragastrin began to rise 14 hours after administration and reached the maximum 18 hours after.

2) In the group administered 10 \(\mu\)g/kg of tetragastrin, the effect of gastric juice-stimulation was shown clearly but its effect on the cell kinetics was not necessarily so.

3) The L.I. of the group administered 1,000 \(\mu\)g/kg of synthetic human gastrin was observed by the same method. The change is almost equal to that observed by the administration of 1,000 \(\mu\)g/kg of tetragastrin.

4) When 100 \(\mu\)g of tetragastrin were injected subcutaneously together with depot daily, fluctuations in the gastric mucosal cells labelled with \(^3\)H-TdR was observed, but no remarked changes were observed histologically. The turnover rate was presumed to be delayed in the surface epithelium and accelerated in the cells in the lower part of the foveolae including the parietal cells in the tetragastrin-administered group.

5) The cell suspensions of gastric mucosa prepared by trypsin digestion were cultured with tetragastrin in vitro. The L.I. of the group administered 10 \(\mu\)g/ml showed fluctuations almost equal to those in vivo.

From these findings it was obvious that gastrin exerts a trophic effect directly on the mucous neck cells and that there is a difference between the threshold value of gastrin showing the gastric juice-stimulating effect and that of gastrin showing the cell kinetics-accelerating effect.

Tetragastrin and synthetic human gastrin are considered to have almost equal effectiveness at the concentration of 1,000 \(\mu\)g/kg in vivo. Furthermore, the possibility was suggested that gastrin exerts its influence on the entire life-span of the gastric epithelial cells, in which are included differentiation, maturation and migration of the cells.

**References**


