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Studies on the True Nature of FUJIE's Gastric Hormone 'Productin', from the Point of View of Actional Inhibition by Enzymes.

I. Studies on the Stimulants which Promote the Discharge of 'Productin'.

酵素による作用阻害の面から見た胃壁ホルモン「プロダクチン(藤江)」
の本態について.

I. 'プロダクチン' 分泌促進剤について.

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FUJIE (1953) has previously demonstrated that the gastric hormone *productin* so named by him is similar to histamine, because the effects of a histamine injection are almost identical with those of *productin* secreted into the blood and also because the action of *productin* was controlled by the injection of anti-histaminic substance or of histaminase. SHIMIZU (1958) has recently observed that the mixture of histamine and histaminase (refined by TABOR's method from hog kidneys) had the same effects on the gastric peptic cells as FUJIE's *productin*, and he consequently deduced that *productin* and histamine were similar.

In the most recent research on the true nature of *productin*, FUJIE et al. (1957) have histochemically found an imidazol group in the subnuclear portion of the gastric surface cells, in which *productin* vacuoles are seen. It is worthy to notice that not only actional similarity but also component similarity was observed.

The author, here, attempted to prove if the chemical component of *productin* was connected to the imidazol group. The first way to prove this will be to prove that *productin* is similar either to histamine or to histidine, applying the inhibitory effects of enzyme (histaminase and histidase) to *productin* secreted into the blood. On the secretion of *productin*, it was proved by Prof. KUROTSU and his collaborators (1953) that the electric stimulation of the sympathetic centrum brings about an accumulation of *productin* vacuoles in the gastric surface cells and that the stimulation of the parasympathetic centrum brings about a remarkable discharge of *productin* vacuoles from the surface cells. The author, therefore, investigated here how to discharge *productin* in vivo artificially, as discharged in cases where diet was administered.

I. Materials and Methods.

Adult and male rats, weighting 100—110 g, were fed Mc COLLUM's artificial

diet. 24 hrs. after the administration of the last diet, various stimulants of the parasympathetic nerve — which will promote the discharge of the gastric hormone *productin* from the gastric surface cells — were injected subcutaneously, as follows. Then the animals were killed and the materials were taken at periods of 1/3, 2/3, 1, 2 and 3 hrs. after the injection.

1. Acetylcholin 30mg per 1 kg of body weight was injected.
2. Pilocarpin 30mg/kg was injected.
3. Eserin (Physostigminum) 0.1mg/kg was injected.
4. The mixture of Acetylcholin 30 mg/kg and Eserin 0.1 mg/kg was injected.
5. Atropin (0.5 mg) was injected, 10 min. later, a mixture of the above 4 was injected.

To take materials, LUNA's liquid was injected from the left heart ventricle for the vital fixation, and small pieces were taken from the stomach (glandular portion) and the pancreas, then they were placed in KOLSTER's liquid for the post fixation. Paraffin sections of 4μ were made and they were stained by HEIDENHAIN's iron haematoxylin. The gastric peptic cells, the pancreatic cells, in which the action of *productin* are plainly recognizable, and the gastric surface cells from which *productin* is secreted into the blood, were observed.

II. Observations.

a) *The gastric peptic cells.*

The observations were based on the quantity of secretion granules, of secretion vacuoles, on the form of plastosomes (pls.) and on the aspect of the gland lumen, and they were tabulated as in Tables 1—6. The quantity of secretion granules and vacuoles was determined by the method which was frequently used in FUJIE's laboratory, i. e. such diagrams as shown in Fig. 1.

Fig. 1. The standard diagrams to determine the quantity of secretion granules and vacuoles in the peptic cell.

Table 1. Control. Administration of the artificial diet.

Hrs. after the feeding	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Granules	Vacuoles		Granules	Vacuoles	
Before	— ~ ±	— ~ ±	long or short rod, filament	— ~ ±	— ~ ±	narrow
$\frac{1}{2}$	± ~ + + irregular	± ~ +	short rod, supra-short rod, long rod	++	+	a little wide, narrow
1	± ~ + + + irregular	± ~ + + +	short rod, granule, supra-short rod, long rod,	+ + + ++ ±	± ++ + + +	wide, a little wide
$1\frac{1}{2}$	± ~ + + +	+ ~ + + +	supra-short rod, granule, short rod	+	+ + ~ + + +	wide, a little wide
2	± ~ + + +	+ ~ + + +	short rod, guitar form, long rod	+	++	a little wide, wide
3	± ~ +	± ~ + +	short rod, long rod	+	+	a little wide, narrow

Table 2. Acetylcholin 30mg/kg.

Hrs. after the injection	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Gronules	Vacuoles		Granules	Vacuoles	
$\frac{1}{3}$	— ~ ±	± ~ ++ unclear	supra-short rod, guitar form, short rod	±	+	a little wide, narrow
$\frac{2}{3}$	— ~ ±	± ~ + unclear	short rod, guitar form, long rod	— ~ ±	± ~ +	a little wide, narrow
1	— ~ +	± ~ +	short rod, supra-short rod, long rod	— ~ ±	± ~ +	a little wide, narrow
2	± ~ ++ irregular	± ~ +	short rod, long rod, supra-short rod	+	±	narrow, a little wide
3	± ~ ++ irregular, straggling	± ~ ++	short rod, rosary form, long rod	+	+	narrow

Table 3. Pilocarpin 30 mg/kg.

Hrs. after the injection	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Granules	Vacuoles		Granules	Vacuoles	
$\frac{1}{3}$	+ ~ + + + irregular	$\pm \sim +$	short rod, supra-short rod, long rod	+ ~ + +	$\pm \sim +$	narrow, a little wide
$\frac{2}{3}$	- ~ + + irregular	- ~ +	short rod, long rod	- ~ +	- ~ +	narrow, (a little wide)
1	- ~ +	- ~ +	short rod, long rod	- ~ $\pm$	- ~ $\pm$	narrow
2	- ~ $\pm$	$\pm \sim +$	long rod, short rod,	-	$\pm$	narrow
3	- ~ + +	$\pm \sim + +$	short rod, long rod	$\pm$ + + +	+ + + $\pm$	narrow, a little wide

Table 4. Eserin 0.1 mg/kg.

Hrs. after the injection	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Granules	Vacuoles		Granules	Vacuoles	
$\frac{1}{3}$	- ~ + +	$\pm \sim + +$	short rod, long rod, guitar form	+ + + -	$\pm$ + + +	a little wide
$\frac{2}{3}$	- ~ +	$\pm \sim + + +$	short rod, guitar form, long rod	- ~ $\pm$ - ~ +	+ + ~ + + + + $\pm \sim +$	a little wide, narrow
1	- ~ $\pm$	$\pm \sim + +$	short rod, guitar form, long rod	- ~ $\pm$	$\pm \sim + +$	narrow, a little wide
2	- ~ $\pm$	$\pm \sim +$	long or short rod	- ~ $\pm$	$\pm \sim +$	narrow
3	- ~ +	- ~ +	long or short rod, guitar form	- ~ +	- ~ +	narrow, a little wide

Table 5. The mixture of Acetylcholin and Eserin.

Hrs. after the injection	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Granules	Vacuoles		Granules	Vacuoles	
$\frac{1}{4}$	+ ~ + + + irregular	$\pm \sim +$	short rod, supra-short rod, granule, long rod	+ + ~ + + +	+	wide, very wide
$\frac{2}{4}$	$\pm \sim + + +$ irregular	- ~ + + +	short rod, supra-short rod, granule	+ + + $\pm$ $\pm$ (+ +	- + + + - + +)	wide, a little wide
1	+ ~ + + + irregular	- ~ + +	short rod, granule, supra-short rod, long rod	+ + ~ + + +	- ~ $\pm$	wide, (very wide)
2	- ~ + + small	+ ~ + +	short rod, long rod, granule	+	+	a little wide, narrow
3	$\pm \sim + +$ small	$\pm \sim +$	long rod, short rod	+ ~ + +	$\pm \sim +$	narrow

Table 6. Atropin (0.5mg) then the mixture of Acetylcholin and Eserin*.

Hrs. after the injection	Total results			Representative result		Gland lumen
	Quantity of the intracel- lular secretory substance		Form of pls.			
	Granules	Vacuoles		Granules	Vacuoles	
$\frac{1}{4}$	- ~ + + + irregular	- ~ + + +	short rod, supra-short rod, long rod, granule	+ + + + + - ~ $\pm$	- ~ $\pm$ + + + + +	narrow, a little wide
$\frac{2}{4}$	$\pm$ ~ + + + irregular	- ~ + + +	short rod, long rod, granule	+ + + + + $\pm$	- ~ $\pm$ + + + ~ + + +	a little wide, narrow
1	- ~ + + + irregular	$\pm$ ~ + + +	short rod, long rod, guitar form	- + + ~ + + + - ~ $\pm$	$\pm$ $\pm$ + + +	narrow
2	$\pm$ ~ + + + irregular	$\pm$ ~ + + +	short rod, long rod	+ + ~ + + + ($\pm$	$\pm$ + + + +)	narrow, a little wide
3	- ~ + + + irregular	$\pm$ ~ + + +	long or short rod	+ + ~ + + + -	$\pm$ + + +	narrow

* Atropin 0.5 mg was injected, then 10 min. later, the mixture of Acetylcholin and Eserin was injected. Atropin is, as is well known, a peripheral paralytica of the parasympathetic nerve, and it will inhibit the discharge of *productin* vacuoles from the gastric surface cell.

b) The *productin* vacuoles in the gastric surface cells.

The quantity of the *productin* vacuoles in the cell was observed. To determine the quantity, the method shown in diagram (Fig. 2) was used.

Fig. 2. The standard diagrams represented the quantity of *productin* vacuoles in the gastric surface cell.

Table 7. Quantity of the 'productin' vacuoles in the surface cells.

Exp.	Hrs.	Total result	Representative result	Exp.	Hrs.	Total result	Representative result
Control. Administ- ration of the diet	Before	± ~ + + + +	+ + ~ + + + +	Eserin	$\frac{1}{3}$	± ~ + + +	± ~ + +
	$\frac{1}{2}$	- ~ + +	- ~ + +		$\frac{2}{3}$	± ~ + + +	± ~ + + +
	1	- ~ + +	- ~ +		1	± ~ + + +	± ~ + +
	$1\frac{1}{2}$	± ~ + +	± ~ + +		2	± ~ + + +	± ~ + + +
	2	± ~ + +	± ~ + +		3	+ ~ + + +	+ ~ + + +
	3	± ~ + + +	+ ~ + + +	Acetylcholin and Eserin	$\frac{1}{3}$	- ~ + + +	± ~ + +
	$\frac{1}{3}$	± ~ + + +	± ~ + + +		$\frac{2}{3}$	- ~ +	- ~ +
Acetylcholin	$\frac{2}{3}$	- ~ + + +	± ~ + + +		1	- ~ + + +	- ~ + +
	1	± ~ + + + +	+ ~ + + +		2	- ~ + + +	+ ~ + +
	2	+ ~ + + +	+ ~ + + +		3	± ~ + + +	+ + ~ + + +
	3	± ~ + + +	+ ~ + + +	Atropin then Acetylcholin and Eserin	$\frac{1}{3}$	- ~ + + + +	± ~ + +
Pilocarpin	$\frac{1}{3}$	- ~ + + +	± ~ + +		$\frac{2}{3}$	± ~ + + +	+ ~ + + +
	$\frac{2}{3}$	± ~ + + +	+ ~ + + +		1	± ~ + + + +	+ ~ + + +
	1	+ ~ + + +	+ ~ + + +		2	+ ~ + + + +	+ ~ + + +
	2	+ ~ + + +	+ ~ + + +		3	± ~ + + +	+ ~ + + +
	3	+ ~ + + + +	+ + ~ + + +				

c) The pancreatic cells.

These observations are described in tables (8—13) according to the methods

which were previously used by FUJIE (Arch. hist. jap. 10 1956, p 315). The methods of determining the quantity of zymogen granules in the cell and of observing the gland lumen are shown in the diagrams (Fig. 3 and Fig. 4).

Fig. 3. Diagram on the content of zymogen granules in the pancreatic cell.

Fig. 4. Standard figures on the content of the pancreatic gland lumen.

Table 8. Control. Administration of the artificial diet.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
Before	++~+++	loose	little	long rod, short rod	weakest weak	empty, (massive)	weakest weak
1/2	+++	dense	large	short rod, granule, long rod	middle	empty, straggling	weakest weak
1	+~+++		large	granule, guitar form, short rod	strong very strong	darkly stained, massive, straggling	strong middle
1 1/2	±~++	loose	large	granule, short rod	strong	darkly stained, massive	strong
2	+~+++	a little dense	large	short rod, granule, rosary form	middle	straggling, massive, darkly stained	middle strong
3	++~+++	a little dense	a little	short rod, long rod, granule	weak middle	straggling, empty, massive	middle

Table 9. Acetylcholin 30 mg/kg.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
$\frac{1}{3}$	++~+++	a little dense	a little	granule, guitar form, short rod, long rod	weak	empty, straggling	weak weakest
$\frac{2}{3}$	+++	a little dense	a little	short rod, long rod, supra-short rod	weak	empty, straggling	weak weakest
1	++~+++	a little dense	little	long or short rod, supra-short rod	weakest weak	empty, straggling	weak weakest
2	++~+++	loose	little	long or short rod, (supra-short rod)	weakest weak	empty, straggling, massive	weak middle
3	++(~+++)	very loose	little	long rod, short rod	weakest weak	empty, straggling, darkly stained	middle

Table 10. Pilocarpin 30 mg/kg.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
$\frac{1}{3}$	+~+++	a little dense	a little	short rod, long rod, guitar form	weak	empty, straggling	weak
$\frac{2}{3}$	$\pm$ ~+++ (~+++)	dense	large	granule, short rod, guitar form, (long rod)	middle	empty, massive	middle
1	++~+++	dense, a little dense	large	short rod, guitar form, granule, long rod	weak middle	empty, straggling, massive	weak middle
2	$\pm$ ~+++	loose	little	long or short rod, (guitar form)	weakest weak	straggling, empty, massive	middle
3	$\pm$ ~+++	dense	very large	supra-short rod, rosary form, short rod, long rod	weak middle	empty, straggling, (massive)	weakest weak

Table 11. Eserin 0.1 mg/kg.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
$\frac{1}{3}$	+++~++++	loose	a little	short rod, supra-short rod, guitar form, long rod	weak middle	empty, straggling, massive	weak
$\frac{2}{3}$	+++~++++	dense	large	short rod, supra-short rod, rosary form	middle	straggling, massive, empty	middle
1	+~++++	loose	a little	short rod, rosary form, long rod	weak	massive, straggling, empty, darkly stained	middle strong
2	$\pm$ ~+++ (Vacuolization)	loose	little	long or short rod, rosary form	weakest weak	straggling, empty, massive	weak middle
3	$\pm$ ~+++		a little	long or short rod, guitar form, supra-short rod	weak	empty, straggling, massive	weak

Table 12. The mixture of Acetylcholin and Eserin.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
$\frac{1}{3}$	++++~+++++	a little dense	a little	short rod, supra-short rod, granule	middle strong	empty, straggling, massive	weak
$\frac{2}{3}$	++++~+++++	dense	large	short rod, supra-short rod, long rod (a few)	strong	empty, straggling	weak weakest
1	++++~+++++	a little dense	a little	short rod, long rod, granule (a few)	middle	staggling, empty	weak
2	++~++++	dense	a little	long rod, short rod, granule	weakest weak	straggling, empty, massive	weak
3	+~++++	a little dense	a little	long rod, short rod, supra-short rod	weakest weak	straggling, empty	weak

Table 13. Atropin (0.5mg) then the mixture of Acetylcholin and Eserin.

Hrs.	Zymogen granules			Form of pls.	Production to be considered	Gland lumen	Discharge to be considered
	Quantity	Distribution	Irregularity in size				
$\frac{1}{3}$	+ ~ + + +	a little dense	little	long or short rod	weakest weak	empty, straggling, massive	weak
$\frac{2}{3}$	+ ~ + + +	loose, a little dense	little	long or short rod, guitar form, rosary form	weak	empty, straggling, massive, darkly stained	weak middle
1	+ + ~ + + +	a little dense	little	long or short rod, guitar form, granule	weak	empty, straggling	weakest weak
2	+ + ~ + + +	a little dense	little	long or short rod, supra-short rod	weakest weak	empty, straggling	weakest weak
3	+ + ~ + + +	loose, a little dense	little	long rod, short rod	weakest weak	empty, straggling	weakest weak

III. Discussion.

The author described the average quantity of secretion granules, and vacuoles in the peptic cells and of *productin* vacuoles in the surface cells into the same figure, so that the observations manifested in the tables might be easily understood (Fig. 5 and 6).

In case of Acetylcholin injection (Fig. 5), secretion granules do not increase in the cell until 1 hr. after the injection, secretion vacuoles increase a little 20 min. after the injection.

Each of these vacuoles, however, are unclear and cloudy on the whole. The same kind of vacuoles were previously observed by FUJIE (Arch. hist. jap. 3. 1952), and are probably peculiar to the case of Acetylcholin. *Productin* vacuoles decrease only a little after the injection. This latter observation explains the non increase of secretion granules and the inactive transformation of plastosomes in the peptic cells. These results will be due to the fact that an action of Acetylcholin, as a stimulant of the parasympathetic nerve, is inhibited by cholinesterase in vivo, so that the injection of Acetylcholin alone can not attain the object.

In case of Pilocarpin injection (Fig. 5), secretion granules increase temporarily after the injection, secretion vacuoles are few during all periods until 2 hrs. after the injection. *Productin* vacuoles decrease more than in the former case, but this is also temporary.

In case of Eserin injection (Fig. 6), it is observed that while secretion vacuoles in the peptic cells increase positively, *productin* vacuoles in the surface cells decrease considerably but secretion granules in the peptic cells are few. The fewness of secretion granules and plentifulness of secretion vacuoles in the peptic cells seems to be inconsistent with the decrease of *productin* vacuoles (the secretion of *productin* into

Fig. 5.

Fig. 6.

● Secretion granules in the peptic cell, ○ Secretion vacuoles in the peptic cell, --x-- Productin vacuoles in the surface cell.

the blood), according to FUJIE's *productin* theory. It may be presumed, I think, that the injection of Eserin alone may effect the action which may promote a decomposition of *productin* in vivo. At any rate, above results are considerably different from those of the normal case in which artificial diet was administered.

It is well known that Eserin is not only a stimulant of the parasympathetic nerve but an inhibitor of an activity of cholinesterase in vivo and that, accordingly, the action of acetylcholin injected can be encouraged by eserine. When acetylcholin

is used for the experiment, it is usual to add eserin. Here the author injected the mixture of Acetylcholin and Eserin. In this case (Fig. 6), secretion granules are produced copiously in the peptic cells and *productin* vacuoles are discharged positively from the surface cells and they are quite similar to those of the normal case (Fig. 5). Secretion vacuoles, however, are fewer than in the normal case. This is natural because of the copious secretion of *productin* and of the lesser secretion of saliva as a result of non-feeding of the diet (anti-histamic action theory of saliva by FUJIE).

If the peripheral end of the parasympathetic nerve is paralysed by Atropin before the injection of Acetylcholin and Eserin (Fig. 6), secretion granules in the peptic cells are less, secretion vacuoles are relatively more numerous and *productin* vacuoles are discharged temporarily after the injection, and the functional figures of the cells, which were observed 20 min. after the injection, continue for a long period. These will be due to the fact that the discharge of *productin* is prevented by Atropin, and the secretory function of the peptic cells is, accordingly, stopped at the same time.

Surveying the above results, it is noticed that the injection of parasympathetic stimulants brings about usually the production of secretion granules in the peptic cells. It will be wrong to connect the cause and the effect in these observations, because it is recognized by many investigators that the stimulation of the parasympathetic nerve causes the discharge of the secretory substance from the gland cells. It is noticed, on the other hand, that when the production of secretion granules in the peptic cells seems to be very copious, the decrease of *productin* vacuoles in the surface cells is also remarkable. That the *productin* vacuoles are discharged from the surface cells according to the stimulation of the parasympathetic nerve will be so natural that the production of secretion granules must be considered as due to the *productin* which was thus discharged. It is also noted, in cases of Pilocarpin (Fig. 5) and of Acetylcholin and Eserin (Fig. 6), that while secretion granules in the peptic cells are produced positively, there is only a few secretion vacuoles (discharging stage of secretory substance). This will be proof of the fact that the secretory function of the gastric peptic cells is effected by *productin* more than by the autonomic nerves, as was previously pointed out by FUJIE (Arch. hist. jap. 5, 1953, p. 185).

Therefore, the effects of the parasympathetic stimulants will be determined by the decrease of *productin* vacuoles in the surface cells and the decrease of *productin* vacuoles will be indorsed by the increase of secretion granules in the peptic cells. And the best method for the natural discharge of *productin* is to inject a mixture of Acetylcholin and Eserin.

On the other hand, it was previously demonstrated that the production of zymogen granules in the pancreatic cells is promoted by *productin*, and that their discharge is promoted by *secretin* which is secreted into the blood from the duodenal mucosa. In the present experiments, the discharge of *productin* vacuoles from the gastric surface cells and the production of zymogen granules in the pancreatic cells are so coincident, and the observations in case of Acetylcholin and Eserin are so similar to those of normal case, that the author reached the same conclusion as in

the case of the peptic cells.

IV. Summary.

The author attempted to inquire into the effects of enzymes injections on the action of *productin*, so that the true nature of *productin* might be made more clear. For this purpose, the author, at the first, investigated the best method by which *productin* could be discharged into the blood from the gastric surface cells in as natural a manner as possible. Various stimulants of the parasympathetic nerve were tested on rats by subcutaneous injection, then after the injection, a fluctuation of *productin* vacuoles in the gastric surface cells and the action of *productin*, which effected to the secretory function of the gastric peptic cells and of the pancreatic cells were observed.

The respective application of Acetylcholin (30 mg/kg), Pilocarpin (30 mg/kg) or Eserin (0.1 mg/kg) can not attain the above object, but the mixture of Acetylcholin and Eserin induces the most natural and ideal result, similar to those of the case in which the diet was administered.

内 容 自 抄.

胃壁ホルモン Productin (藤江) の本態を究明する一助として生体内に放出された Productin の作用と酵素の相互関係を知りたいと企図した著者は、食餌摂取の場合と同様の Productin 分泌を人工的に行わしめる手段を先ず研究し、副交感神経末梢刺激剤の注射を試み、胃粘膜表在細胞の Productin 空胞の消長、胃腺主細胞及び膵細胞の分泌機能に現われる Productin の作用を追究した。その結果 acetylcholin, pilocarpin, eserine の各個使用では満足すべき結果は得られないが、acetylcholin (30 mg/kg) と eserine (0.1 mg/kg) を混合使用すると、あらゆる点で理想的な結果が得られ、今後の研究に使用出来ることが知られた。

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