AMINES AND THE RAT EXOCRINE PANCREAS: (1)
EFFECTS OF RECEPTOR BLOCKERS ON TURNOVER OF L-DOPA

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Abstract—The acinar cells of the exocrine pancreas have the capacity of efficiently take
up and metabolize L-dopa. In the present study, the metabolism of L-dopa by the
exocrine pancreas of the rat and effects of receptor blockers on the metabolism were
studied by fluorescent histochemical and chemical methods. After i.v. administration
of L-dopa (50 mg/kg), a large amount of dopamine (DA) was detected in the exocrine
pancreas, and in the pancreatic juice large amounts of DA and its metabolites. DA-
blockers (haloperidol, sulpiride, and pimozide) and α-blockers (phenoxybenzamine,
and phentolamine) produced a significant increase in the accumulation of DA after
administration of L-dopa. On the other hand, β-blockers (propranolol, and oxprenolol)
were without effects. The excretion of DA into the pancreatic juice appeared to be
associated with the secretion of zymogen granules, thus DA serves as an indicator of
pancreatic secretory activity, especially of enzyme secretion. Because DA- and α-
blockers produced an increase in the accumulation of DA, dopaminergic and/or α-
adrenergic mechanisms probably exist in the exocrine pancreas of the rat and these
mechanisms modify the enzyme secretion.

The exocrine pancreas has a great capacity to take up amino acids and analogues of
amino acids (1–5) from the blood, presumably reflecting the high protein synthesizing
capacity of the organ. The exocrine pancreatic mechanism for the uptake and metabolism
of amino acids L-dopa and L-5HTP has been studied (6–13). These amino acids are de-
carboxylated in the exocrine cells, and the corresponding amines can subsequently be met-
abolized, probably mainly by oxidative deamination. These compounds are also taken up
and transiently stored in the zymogen granules where they seem to be protected from
enzymatic degradation. Reserpine, prenylamine, or desipramine prevented incorporation
of DA into the pancreatic zymogen granules (14). These findings suggest that there are
similarities, to some extent, between the exocrine pancreatic cells and the cells normally
synthesizing and storing biogenic monoamines (i.e. adrenergic nerves and certain endocrine
cell system).

In some fluorescent histochemical experiments on the gastro-intestinal organs, we gave
rats L-dopa and L-5HTP, and noticed that the fluorescence due to L-dopa and L-5HTP
injections was somewhat differently distributed in the exocrine pancreas. There is some
possibility that L-dopa and L-5HTP are metabolized in a different manner by the exocrine
pancreas, and a large amount of DA and 5-HT, accumulated intracellularly and
extracellularly, could modify the exocrine pancreatic function. In the present experiments,
we studied histochemically and chemically the L-dopa metabolism by the exocrine pancreas of the rat and the effect of receptor blockers on the metabolism.

**MATERIALS AND METHODS**

**Animals used:** Male Sprague-Dawley rats were used. Animals used for histochemical and chemical studies weighed 200–270 g while animals used for collection of the pancreatic juice weighed 350–400 g. The animals were given a standard diet and water *ad libitum* before experiments. In the experiments of starvation, animals were placed in individual cages and deprived of food for 3 or 5 days, but water was given freely.

**Histochemical and chemical studies:** Drugs were given i.v. or s.c. to rats, and after various times L-dopa was given i.v. Control animals were given vehicles instead of drugs. The animals were sacrificed by a blow on the neck 20 and 60 min after the injection of L-dopa, and the pancreas was excised for the histochemical and chemical analysis of DA and NA. Fluorescent histochemistry was performed according to the method of Falck and Hillarp (15). Assays of NA and DA were made fluorometrically according to the methods reported by Bertler et al. (16) and Atack (17), respectively.

**Chemical determinations of the L-dopa and metabolites in the pancreatic juice:** Under pentobarbital Na (30 mg/kg i.p.) anesthesia, bile free pancreatic juice was obtained according to the method of Grossman (18). A bypass for the bile to enter the duodenum was provided. After the operation the animals were kept in restraining cages of Bollman type with access to food and water. When the pancreatic secretion stabilized 14–16 hr after the operation, L-dopa 50 mg/kg was given i.v. The juice was collected in a test tube for 90 min. The test tube contained 1 ml of 0.4 N perchloric acid (PCA), to which EDTA (0.1 %) and ascorbic acid (0.4 mg/ml) had been added. The samples were stored frozen at −20 °C until assay. The chemical analysis of DA, DOPAC and HVA, and MTA were performed according to the methods of Atack (17), Murphy et al. (19), and Carlsson et al. (20), respectively.

**Fluorescence microscopy:** After injection of L-dopa, specific greenish fluorescence appeared in the exocrine pancreatic cells. As described by Alm et al. (12) the fluorescence could be divided into two types. Shortly after injection of L-dopa, the fluorescence due to DA was distributed diffusely all over the cytoplasm, and then gradually became confined to the zymogen granules appearing as coarse granular fluorescence. The former is referred to as diffuse fluorescence and the latter as granular fluorescence. Later, the granular fluorescence, being metabolized or excreted, gradually disappeared. The granular fluorescence seemed to be clearly contrasted to the specific diffuse fluorescence or background autofluorescence, and the change in fluorescence intensity and localization was more easily distinguished than the diffuse fluorescence. Therefore, the granular fluorescence served as a convenient indicator for the estimation of the turnover of L-dopa. Subjective estimation of the various treatments was made by assessing intensity and localization of the granular fluorescence over a wide range of acini. The changes of diffuse fluorescence were also recorded as reference data.

To clarify changes in the subjectively estimated observations, the use of grading method,
often applied in the subjective estimation, was avoided. Instead, two observers checked independently whether treated samples had (1) similar fluorescent pictures to those of control samples, or (2) wider distribution or higher density of DA than control samples, or (3) smaller distribution or lower density of DA than control samples. The data were adopted only when the two observers found similar results. The final estimates from 3–6 samples per group were expressed in Results by the signs of †, ‡, and ††, in the order described above. After injection of L-dopa alone, the fluorescence had an uneven or irregular distribution among the different acini. After application of certain drugs the distribution became regular. When the distribution patterns were uneven and even ones, they were denoted as U and E, respectively.

Substances used: L-dopa (Sigma) and D-dopa (Sigma) were dissolved in 0.9% saline with the aid of a minimal amount of 1N HCl and gentle warming. Polyethylene glycol (0.02 ml/ml) was then added to the warm solution and the pH carefully brought to between 4–5 with NaOH. Sulpiride (Delagrange) and haloperidol (Janssen) were dissolved in 0.9% saline with the aid of a minimum amount of 1N H2SO4 and 50%(v/v) acetic acid, respectively. Iproniazide phosphate (Aldrich), dopamine hydrochloride (Sigma), pyrogallol (Hayashi Chemicals), phenoxybenzamine hydrochloride (Tokyo Kasei), oxprenolol hydrochloride (CIBA-Geigy), pilocarpine hydrochloride (Nakarai Chemicals), desipramine hydrochloride (CIBA-Geigy) and secretin (Boots) were dissolved in 0.9% saline. Pimozide (Janssen) was suspended in 0.5% methylcellulose aqueous solution. Phentolamine mesylate (Regitin®, CIBA-Geigy) and propranolol hydrochloride (Inderal®, Sumitomo) were diluted with 0.9% saline. Reserpine (Serpasil®, CIBA-Geigy) was diluted with distilled water. The drugs were given in the following volumes: L- and D-dopa: 0.3 ml/100 g, iproniazide and pimozide: 0.5 ml/100 g, and all the other drugs: 0.2 ml/100 g.

Treatments with drugs: When effects of drugs on the L-dopa metabolism by the exocrine pancreas were studied, the drugs were given by respective schedules as following: pilocarpine (64 mg/kg) 4 hr, iproniazide (150 mg/kg) 3 hr, secretin (4 U/kg) 1–2 min, reserpine (4 mg/kg) 4 hr, pimozide (8 mg/kg) 30 min, desipramine (16 mg/kg) 10 min, pyrogallol (32 mg/kg) 10 min, haloperidol (2 mg/kg) 10 min, sulpiride (32 mg/kg) 10 min, phentolamine (8 mg/kg) 10 min, phenoxethazin hydrochloride (8 mg/kg) 10 min, propranolol (4 mg/kg) 10 min, and oxprenolol (0.5 mg/kg) 10 min before injection of L-dopa (50 mg/kg). Doses were expressed in terms of salts. Iproniazide and pilocarpine were given s.c., and all the other drugs were given into one of the lateral veins of the tail.

Abbreviations used: L-dopa; 3,4-dihydroxy-L-phenylalanine, D-dopa; 3,4-dihydroxy-D-phenylalanine, L-5HTP; 5-hydroxy-L-tryptophan, DA; dopamine, NA; noradrenaline, DOPAC; 3,4-dihydroxyphenylacetic acid, HVA; homovanillic acid, MTA; methoxytyramine, MAO; monoamine oxidase, and COMT; catechol-O-methyl transferase.

Statistical analysis: P values were calculated according to the Student's t-test or Cochran-Cox test with computer programs.
RESULTS

Histochemical study

Fluorescence pictures after injection of L-dopa alone: In the pancreas of normal rats, specific fluorescence was localized only in adrenergic nerves, chromaffin cells and small intensely fluorescent cells. The number of adrenergic nerves was sparse and almost exclusively followed the vessels. The exocrine parenchyma does not seem to be innervated by adrenergic nerves, nor has it normally any specific fluorescence (Fig. 1a). After injection of L-dopa, the pancreatic acinar cells attained strong specific fluorescence. In a pilot time-dose response study, L-dopa was given 20, 50, and 100 mg/kg, and the rats were sacrificed after 10, 20, 40, 60, 90, and 120 min. Up to 10 min after the injection, the intense specific fluorescence was observed to occur mainly in a diffuse manner throughout the acinar cells, but in the apical regions of the cells some coarse fluorescent granules were already observed. Little or no specific fluorescence occurred in the connective tissues. With passage of time, granular fluorescence in the apical regions predominated, although in the rats given a higher dose of L-dopa, diffuse fluorescence remained stronger for a longer period. The minimum dose that produced a clear and wide spread appearance of the granular fluorescence was 50 mg/kg.

From the results described above, the fluorescent pictures at 20 and 60 min after injection of L-dopa 50 mg/kg were considered to be suitable for the study of effects of drugs. Therefore, the fluorescent pictures under these conditions are described below in more detail. At 20 min after injection of L-dopa 50 mg/kg, the intense specific fluorescence was mainly confined to the apical regions of the acinar cells and the diffuse fluorescence outside the apical regions was weak (Fig. 1b). Granular fluorescence became weak to moderate after 60 min, and the diffuse fluorescence was apparently absent. After 120 min, granular fluorescence was seen only in some acini.

There were some individual variations as to the number of acini containing granular fluorescence. At the same time uneven distribution of the granular fluorescence among the different acini was observed in almost all the animals at all the doses used (Fig. 1c), although in a few animals such difference was not so remarkable. Two adjacent acini sometimes were different, but as a rule, the difference was greater between acini from different lobules. DA in a large dose (25 mg/kg) given over a period of 5–7 min, produced only a weak, initial diffuse fluorescence confined to the cytoplasm of some acini. After 60 min very weak apical fluorescent granules appeared in a few acini. Strong diffuse fluorescence but no granular fluorescence was observed at 20 and 60 min after injection of D-dopa (50 mg/kg). The fluorescence was distributed evenly.

Effects of various treatments

Results are summarized in Table 1.

Starvation: After starvation for 3 or 5 days, granular fluorescence was distributed evenly throughout a wide range of acini, and the fluorescent intensity was on the average slightly stronger than that of controls fed normally (Fig. 1d).

Secretagogues: Pilocarpine produced a slight decrease of granular fluorescence at
FIG. 1a. Pancreas of normal rat. Catecholamine fluorescence is observed only in the adrenergic nerves which follow arterioles of varying size. Langerhans' islands in normal rats do not show any specific fluorescence. ×160

FIG. 1b. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg). Specific granular and diffuse fluorescence is distributed unevenly among different acini. A small Langerhans' island with strong fluorescence is seen to the left. No specific fluorescence occurred in the connective tissue. ×100

FIG. 1c. Rat pancreas, 20 min after injection of a large amount of L-dopa (200 mg/kg). Stronger specific granular and diffuse fluorescence is distributed unevenly among different acini. ×100

FIG. 1d. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg) to the rat starved for three days. Granular fluorescence is distributed fairly evenly among different acini. A Langerhans' island is seen to the left. ×150
TABLE 1. Effects of drugs on the accumulation of DA in the exocrine pancreas of the rat after injection of L-dopa

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Dose mg/kg or U/kg</th>
<th>Time after L-dopa injection</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 min</td>
<td>60 min</td>
</tr>
<tr>
<td>L-dopa alone</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fasting</td>
<td></td>
<td>↑</td>
<td>-→</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>64</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Secretin</td>
<td>4</td>
<td>-→</td>
<td>→</td>
</tr>
<tr>
<td>Reserpine</td>
<td>4</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Desipramine</td>
<td>16</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Iproniazide</td>
<td>150</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pyrogallol</td>
<td>32</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>32</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Pimozide</td>
<td>8</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Phenotolamine</td>
<td>8</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>8</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Iproniazide</td>
<td>150</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>+ Sulpiride</td>
<td>32</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>32</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>+ Phenolamine</td>
<td>8</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>0.5</td>
<td>→</td>
<td>→</td>
</tr>
</tbody>
</table>

GF; granular fluorescence. DF; diffuse fluorescence. ⋮; the extent of distribution of DA is comparable to that of control. ↑; wider distribution or higher density of DA is observed. ↓; smaller distribution or lower density of DA was observed. Distribution pattern: DA fluorescence was evenly (E) distributed throughout a wide range of acini or unevenly (U).

60 min after injection of L-dopa. Secretin was without effect.

**Monoamine uptake inhibitor:** After administration of reserpine or desipramine, both diffuse and granular fluorescence became weak, and were distributed unevenly.

**Enzyme inhibitor:** Pretreatments with MAO inhibitor iproniaxide resulted in a wider distribution and stronger fluorescent intensity of both diffuse and granular fluorescence (Fig. 2a). However, the fluorescence was still distributed unevenly. Pretreatment with COMT inhibitor pyrogallol resulted in a very slight increase of diffuse and granular fluorescence only at 20 min.

**DA-blocker:** Haloperidol, sulpiride, and pimozide produced stronger granular fluorescence at 20 and 60 min after injection of L-dopa. In this respect, sulpiride was the most effective compound given. The most characteristic change was that granular fluorescence showed a more even distribution among acini than after MAO inhibitor (Fig. 2b). Moreover, diffuse fluorescence did not develop as after the MAO inhibitor pretreatment.

**α-blocker:** Pretreatment with phenoxybenzamine or phenolamine produced almost
FIG. 2a. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg) to the rat pretreated with iproniazide (150 mg/kg, 3 hr before injection of L-dopa). Intense granular and diffuse fluorescence developed, however, the unevenness in the distribution of fluorescence is noticeable. A Langerhans' island with strong fluorescence is seen to the upper left. ×100

FIG. 2b. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg) to the rat pretreated with sulpiride (32 mg/kg, 10 min before injection of L-dopa). Stronger granular fluorescence is evenly distributed throughout the acini. ×100

FIG. 2c. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg) to the rat pretreated with phentolamine (8 mg/kg, 10 min before L-dopa). Stronger granular fluorescence is evenly distributed throughout the acini. ×100

FIG. 2d. Rat pancreas, 20 min after injection of L-dopa (50 mg/kg) to the rat pretreated with propranolol (4 mg/kg, 10 min before injection of L-dopa). A wider distribution of diffuse fluorescence is evident. ×100
the same fluorescent pictures as after injection of sulpiride; even distribution of intense granular fluorescence with sparse diffuse fluorescence (Fig. 2c).

**β-Blocker:** Oxprenolol produced no remarkable change, whereas propranolol produced an intensification of granular fluorescence in some acini, especially around Langerhans’ islands and large arteries, and development of diffuse fluorescence (Fig. 2d).

**DA-blocker and MAO inhibitor:** After pretreatment with iproniazide and sulpiride, stronger diffuse and granular fluorescence developed. Diffuse fluorescence appeared widely all over the acini, and remained even 60 min after the L-dopa injection. Granular fluorescence was increased in intensity, however, slightly uneven distribution of the fluorescence between different acini remained.

**DA- and α-blocker:** After the combined treatment with sulpiride and phenoxybenzamine, slight intensification of granular fluorescence and almost completely even distribution of granular fluorescence were observed. Diffuse fluorescence (at 20 min only) did not develop to an extent as after the iproniazide plus sulpiride treatment.

**Chemical determinations of DA and NA**

Results are shown in Tables 2 and 3.

In the untreated pancreas, a larger amount of NA was found than DA. After L-dopa injection, the main catecholamine found in the pancreas was DA. In accordance with the histochemical observations, the pancreatic DA levels of the rats given DA- or α-blockers were significantly higher at 20 and 60 min after injection of L-dopa. NA levels did not show any remarkable changes. Despite the lack of universal appearance of granular fluorescence, the pancreas attained a high level of DA after pretreatment with propranolol, although it was not significant. This may be the chemical counterpart of the histochemical observation of the development of intense diffuse fluorescence and intensification of granular fluorescence in some acini after propranolol. On the other hand, no noticeable change in DA levels was observed after pretreatment with oxprenolol, and here no histochemical change was produced.

**Table 2.** Effects of drugs on the pancreatic DA contents (μg/g) after injection of L-dopa

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Dose mg/kg</th>
<th>Time after L-dopa injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 min</td>
</tr>
<tr>
<td>Saline</td>
<td>—</td>
<td>0.02 ± 0.01 (4)</td>
</tr>
<tr>
<td>L-dopa alone</td>
<td>50</td>
<td>10.50 ± 0.97 (10)</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>32</td>
<td>19.65 ± 2.80 (8)*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>16.80 ± 1.64 (10)**</td>
</tr>
<tr>
<td>Pimozide</td>
<td>8</td>
<td>15.18 ± 1.52 (5)*</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>8</td>
<td>22.29 ± 2.11 (5)**</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>8</td>
<td>22.64 ± 1.83 (10)**</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4</td>
<td>16.19 ± 3.10 (4)</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>0.5</td>
<td>8.38 ± 1.97 (6)</td>
</tr>
</tbody>
</table>

Values are mean ± S.E. Number of animals in parentheses. *: p<0.05 and **: p<0.01
Determinations of L-dopa metabolites in the pancreatic juice

Results are shown in Table 4. Metabolites of L-dopa such as DA, DOPAC, and HVA were found even in the juice from control animals. However, the individual difference was considerable. For example, while fairly high (0.88 and 0.95 µg/ml) DA levels were detected in 2 of 5 animals, in the remaining three rats no DA was found. After injection of L-dopa, large amounts of DA and DOPAC, and small amounts of HVA were found in the juice. VITA was not detected in either the control or test groups.

**DISCUSSION**

The present results with L-dopa, DA, D-dopa, MAO and COMT inhibitors, monoamine uptake inhibitors and pilocarpine confirmed the previous findings (12, 14, 21) that L-dopa is taken up and handled by the exocrine pancreas in a special way. To acquire additional information, effects of secretin and starvation were studied. Secretin, which increases the bicarbonate excretion, did not modify the turnover of L-dopa, in contrast to the finding (21) that pilocarpine, which increases the protein output, increased the turnover of L-dopa. Starvation of 24 hr gave no definite results (10). In the present study, however, longer starvation of 3 or 5 days produced clearly an increased accumulation of fluorescence. This result suggests that a depressed secretory activity of the pancreas produced the decreased
turnover of L-dopa. Thus, the metabolic processes of L-dopa may represent a specific mechanism for the metabolism of this amino acid, and at the same time it could also be a part of the general mechanism behind the protein synthesis.

A significantly higher accumulation of DA was observed after the pretreatment with DA- or α-blockers, but not after β-blockers, and at the same time the uneven distribution of fluorescence after injection of L-dopa alone was remedied. Malaisse-Lagae et al. (22) have reported a topographic partition of secretory function in the exocrine pancreas of rats; the pattern of enzymes contents found in pancreatic exocrine tissue surrounding the islets of Langerhans' differs from that of the rest of the pancreas. The uneven distribution of DA may imply that the pancreatic lobules or acini act asynchronously; each lobule or acinus takes up L-dopa and metabolizes it depending on the activity of each lobule or acinus. Some metabolic factors such as uptake, decarboxylation, enzymatic degradation, intracellular transport and subsequent excretion into the juice may affect the accumulation of DA in the pancreas, and the blockers might have acted directly or indirectly on any one or more of these metabolic processes.

From the present results, the enzymatic degradation of DA by MAO and COMT, and the excretion of DA and its metabolites into the pancreatic juice appear to be important in the metabolism of DA by the exocrine pancreas, although other factors cannot be neglected. The pancreas contains both MAO (23) and COMT (24). Several metabolites of DA by MAO and COMT were found in the pancreatic juice, and MAO and COMT inhibitors produced an increase in the accumulation of DA. However, it is not plausible that the DA- and α-blockers produced the increased accumulation of DA by inhibiting MAO and COMT: (1) MAO inhibitor, alone or in combination with DA-blocker, and COMT inhibitor always produced slight to strong diffuse fluorescence which was not apparent after DA- or α-blockers. (2) DA- and α-blockers produced an even distribution of DA throughout the lobules, whereas MAO and COMT inhibitors were not effective in this regard.

The pancreatic DA content was 10.50 μg/g at 20 min and diminished to 2.26 μg/g at 60 min after injection of L-dopa 50 mg/kg. In the juice collected for 90 min after injection of L-dopa 50 mg/kg, the concentrations of DA, DOPAC, and HVA were 5.32, 6.96, and 0.58 μg/ml, respectively. The pancreas weighed between 500–1,000 mg, and the volume of the juice secreted during 90 min after injection of L-dopa was between 0.6–1.2 ml. From these results it is obvious: (1) L-dopa was very rapidly metabolized by the normal exocrine pancreas, and (2) the majority of L-dopa metabolites were excreted into the juice. DA is reported to be rapidly metabolized by MAO, when not protected by binding to the zymogen granules (14). Thus, it is possible that a large proportion of the DA found in the juice was excreted together with zymogen granules. In this connection, the acinar cells, not the centroacinar and duct cells, are reported to be responsible for the L-dopa metabolism (25).

The results that DA- and α-blockers caused an increased accumulation of DA suggest that the blockers depressed directly or indirectly the pancreatic secretory activity. Two explanations are possible for this change. One is that the blockers themselves inhibited the
secretion of the zymogen granules, these granules apparently act as the carrier of DA. Another is that DA has a stimulatory effect on the secretion of zymogen granules, and these compounds blocked the action of DA. The DA formed from L-dopa in the organs other than pancreas may stimulate the pancreatic secretion. DA could also produce the stimulation intracellularly (26, 27). In the exocrine pancreas of dogs, a dopaminergic mechanism which induces a secretin-like response has been reported (28–31). In rats DA is reported to have only a weak stimulatory effect on the rate of flow (32, 33). However, there is the possibility that DA stimulate the enzyme secretion to a greater extent.

In this study, DA- and α-blockers produced the same changes. When these two blockers were combined, no particular change occurred. However, it is unlikely that these two kinds of blockers acted on the same receptors; phenoxybenzamine blocked peripheral and central NA receptors without affecting DA- and 5-HT receptors (34, 35).

David et al. (36) reported that when tissue levels of aromatic amino acids such as phenylalanine, tyrosine, and tryptophan are increased, decarboxylation to the corresponding amines becomes a major metabolic route. They suggested that this mechanism could explain the marked neurological effects in humans after administration of a monoamine oxidase inhibitor and relatively small amounts of tryptophan. Because the non-neuronal decarboxylase of liver and kidney comprises the bulk of the total aromatic amino acids decarboxylase activity of animals (36, 37), these two organs may be mainly responsible for the decarboxylation of the amino acids given in large doses. The decarboxylase of the pancreas and gastrointestinal mucosa (38) may also contribute to the excretion of the aromatic amino acids in excess amounts. L-dopa when given in a large dose can be similarly decarboxylated to dopamine by these organs. However, acinar cells of the pancreas have the characteristic ability to incorporate DA to the zymogen granules and excrete the DA with the zymogen granules. This ability has not been found in the structurally and functionally related cells such as zymogen cells of the gastric mucosa and acinar cells of the salivary gland, although Paneth cells, whose function has not been well defined, have been reported to handle L-dopa in a similar way. All these findings taken together indicate that the exocrine pancreas is a characteristic organ in the metabolism of L-dopa, however, the physiological significance remains uncertain.

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