L-DOPA AND PANCREATIC SECRETION

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GREENGARD, ROBACK and IVY (1942) first observed that epinine (*N*-methyldopamine), dopamine (dihydroxyphenylethylamine) and few phenylethylamine derivatives given intravenously stimulated the canine pancreatic secretion, while the majority of sympathomimetic amines tested inhibited it. Although this observation appeared strikingly important, no particular attention had been given until ALM, EHINGER and FALCK (1967) when FALCK and his collaborators reported on the L-dopa turnover to dopamine in the mouse pancreas using fluorescense method. "After L-dopa i.v. first the whole of the pancreatic acinar cells displayed a specific diffuse fluorescence within few minutes and then most of the fluorescence was situated in zymogen granules as the second pattern of fluorescence after 40–60 min". Thus, they assumed that L-dopa was decarboxylated to dopamine in the cytoplasm and then incorporated in granules. On the other hand, HOLZ, CREDNER and STRÜBING (1942) demonstrated the existence of dopa decarboxylase in the pancreas, and SCHÜMANN and HELLER (1959) detected a relatively large amount of dopamine in the pancreas of the ox and the sheep.

THE SPECIFICITY OF THE DOPAMINE-INDUCED PANCREATIC SECRETION

In the course of comparative studies on the vascular and the functional responses of the isolated blood-perfused organs to various pharmacological agents, we observed that dopamine stimulated strikingly the exocrine pancreas (TAKEUCHI *et al.*, 1971). Such striking response to dopamine was not observed in any other organ. Since the canine pancreas had its spontaneous secretion even in the fasting state, either stimulation or inhibition could be readily observed when substances were injected intra-arterially. The specificity of dopamine as a secretagogue of the exocrine pancreas was confirmed when effects of various biogenic and foreign substances were compared on the pancreatic secretion in the resting state (TAKEUCHI *et al.*, 1973). Among sympathomimetic amines tested, i.e., dopamine, noradrenaline, adrenaline, isoprenaline, phenylephrine, methoxamine, ephedrine, tyramine, epinine, α-methyldopamine and 6-hydroxydopamine, only dopamine (1–10 μg) and 6-hydroxydopamine (100 μg), one of metabolites of dopamine (SENOH *et al.*, 1959) stimulated the secretion, but the latter was far less active than the former. Others had either no effect, or rather an inhibitory effect, on the secretion. We could not find any stimulation of the pancreatic secretion with epinine given intra-arterially, although GREENGARD *et al.* described a striking stimulation by an intravenous injection. The contradictory results may be due to impurity of epinine used in their experiments. The intra-arterial administration has the merit of excluding an indirect effect. Among amino acids tested, L-dopa induced a profuse and long-lasting secretion by the intra-arterial infusion at a rate of 100 μg/min for 10 min with a delay up to 5 min for the induction of secretion. Tyrosine and phenylalanine had no stimulatory effect on the pancreatic

secretion. Among endogenous substances tested, acetylcholine, histamine, gastrin and glucagon were effective to induce the secretion, and foreign substances such as dibutyryl cyclic AMP, cholinergic drugs, ganglion stimulants, methylxanthines, nitroglycerin, apomorphine and fusaric acid were found to be effective. The stimulation caused by these substances, however, were far less than that induced by L-dopa or dopamine. It was interesting that bradykinin, kallikrein and vasopressin inhibited the spontaneous secretion while angiotensin had no effect. Nucleotides, nucleosides, 5-HT, various vasodilators and cocaine had no effect. The secretory effects of these drugs did not relate with their vascular ones.

MECHANISM OF THE STIMULATION OF THE PANCREATIC SECRETION INDUCED BY L-DOPA OR DOPAMINE

The mode of action of dopamine intra-arterially was quite similar to that of secretin, causing a larger volume of juice with higher concentrations of bicarbonate and protein (FURUTA *et al.*, 1972). The secretion was promptly induced and its volume increased in a dose-related manner without any tachyphylaxis. The higher dose was given, the higher concentrations of bicarbonate and protein were measured in a larger volume of juice. The potency of dopamine (10 μg) intra-arterially was approximately equal to that of secretin (Boots) (0·3 units) or secretin (Jorpes) (0·03 units) (HASHIMOTO *et al.*, 1971). The pancreatic juice stimulated by the infusion of L-dopa contained naturally a high concentration of bicarbonate ions.

The increased secretion induced by the intra-arterial infusion of L-dopa (100 μg/min) was antagonised by Ro 4-4602 (300 μg), a dopa decarboxylase inhibitor, while the secretagogue effect of dopamine (1–10 μg) intra-arterially was not affected by Ro 4-4602. The effect of dopamine was enhanced by the infusion of fusaric acid (100 μg/min), a dopamine-β-hydroxylase inhibitor and also enhanced by treatment with nialamide (100 mg/kg), a monoamine oxidase inhibitor (FURUTA *et al.*, 1973). The effect of α-methyl dopa was further investigated, which showed an effective antagonism between L-dopa and α-methyldopa but not between dopamine and the latter, suggesting the inhibition of dopa decarboxylase induced by α-methyldopa (Fig. 1). α-Methyldopa might be converted to α-methyldopamine which did not

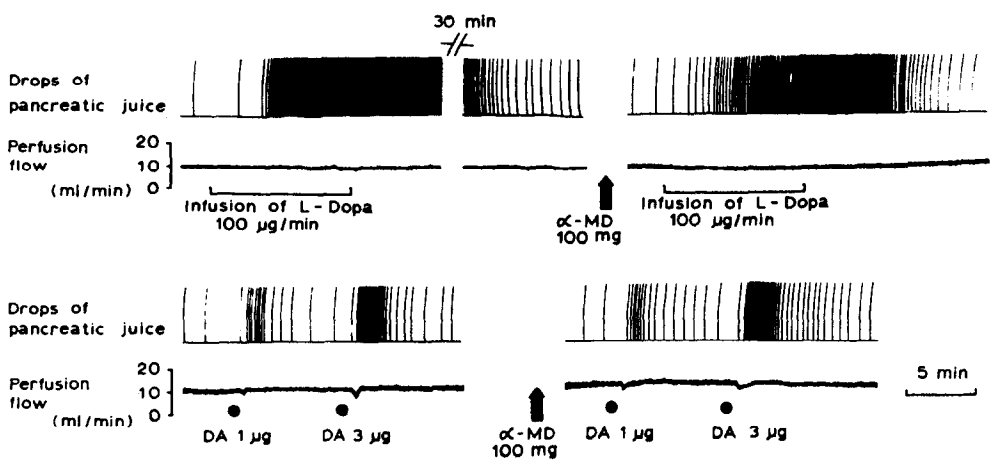

FIG 1

stimulate the exocrine pancreas. We assume that L-dopa will not be a secretagogue but it is converted to dopamine in the exocrine pancreas cells which induced the dopaminergic effect of the stimulation of the secretion. The intracellular level of dopamine may be controlled by enzymatic equilibrium.

CONTENT OF CATECHOLAMINES IN THE PANCREATIC TISSUE

The canine pancreas was quickly removed under anesthesia with sodium pentobarbitone and immediately frozen. The duodenal portion was used for the assay (SHELLENBERGER and GORDON, 1971). Reserpine (0·1 mg/kg s.c. for 5 days) led to selective depletion of noradrenaline while the L-dopa infusion increased selectively the dopamine content in the pancreatic tissue. It is worthy to note that various treatments produced an apparent differentiation between the noradrenaline and the dopamine contents in the pancreatic tissue (Table 1).

TABLE 1. THE DOPAMINE AND THE NORADRENALINE CONTENTS IN THE CANINE PANCREAS

Treatment	Number of animals	Dopamine (ng/g)	Noradrenaline (ng/g)
None	13	139 ± 6	375 ± 40
L-DOPA (5 mg/kg i.v.)	5	818 ± 204*	563 ± 109
Reserpine (0·1 mg/kg s.c., 5 days)	5	135 ± 8	14 ± 5*

* $P < 0.01$

EFFECT OF HALOPERIDOL AND APOMORPHINE

The dopamine-induced secretion was not modified by atropine, phentolamine, propranolol, guanethidine or tetrodotoxin (HASHIMOTO *et al.*, 1971) while haloperidol (1 mg) intra-arterially attenuated the dopamine-induced pancreatic secretion (FURUTA *et al.*, 1973). The vasoconstriction induced by dopamine was completely blocked by phentolamine and that by perivascular stimulation was blocked by tetrodotoxin. The vasodilation induced by dopamine after α-adrenoceptor blockade was also completely blocked by haloperidol. Apomorphine (1 mg) intra-arterially stimulated markedly the exocrine pancreas. Its effect was long-lasting. After the stimulated secretion returned to the initial level, the dopamine-induced stimulation was significantly blocked but the secretin-induced one was not blocked. This characteristic effect may suggest some similarity to the depression of the vomiting center by subsequent doses of apomorphine (GOODMAN and GILMAN, 1970). Such specific antagonism was previously observed by GOLDBERG and MUSGRAVE (1971) in the renal circulation.

EFFECTS OF COCAINE AND DESMETHYLIMIPRAMINE ON THE DOPAMINE-INDUCED SECRETION OF THE EXOCRINE PANCREAS

Cocaine 1 mg intra-arterially enhanced the L-dopa- or the dopamine-induced pancreatic secretion but not the secretin-induced one (Fig. 2). Desmethylimipramine had a similar effect. These phenomena can be understood as follows: The transport of dopamine across the membrane of zymogen granules is blocked with cocaine and

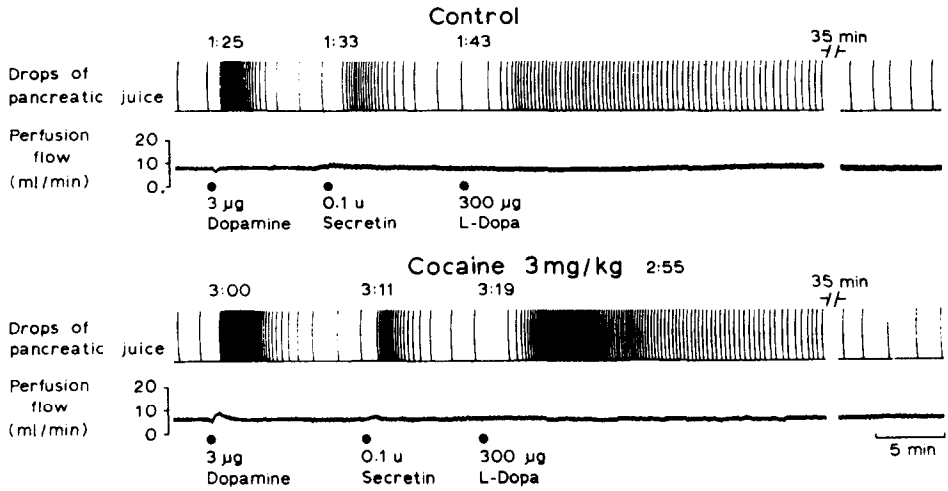

FIG. 2

consequently dopamine acts longer at the receptor sites. Previously ALM and his collaborators observed first diffuse cytoplasmic and later incorporated fluorescence in zymogen granules after L-dopa i.v. The similar phenomenon was observed also with dopamine injection but only a weak fluorescence even in larger doses. Thus they suggested the highly efficient mechanism for the uptake of L-dopa presumably through some active mechanism in the cell membrane (ALM *et al.*, 1967). Their assumption will be natural, because the active transport of amino acids prevails in the pancreas for the protein synthesis.

ABSENCE OF INTERACTION BETWEEN DOPAMINE AND SECRETIN

The stimulation of exocrine pancreas by secretin and that by dopamine were additive and they neither inhibited nor potentiated each other, although both substances had a quite similar mode of action to increase the volume of pancreatic juice and the excretion of bicarbonate ions and protein. By lowering Ca ions concentration in the circulating blood by GEDTA infusion, the stimulation of secretion induced by either secretin or dopamine was profoundly reduced (IWATSUKI *et al.*, 1973b). On the other hand, the difference between secretin and dopamine existed at the receptor site: (1) Prostaglandin $F_{2\alpha}$ (100 μg) inhibited the secretin-induced secretion but it did not modify the dopamine-induced one (IWATSUKI *et al.*, 1973a). (2) On the other hand haloperidol (FURUTA *et al.*, 1973) and apomorphine antagonised the dopamine-induced secretion but not the secretin-induced one. (3) Either cocaine or desmethylimipramine enhanced the dopamine-induced secretion but not the secretin-induced one.

THE CONTROL MECHANISM OF THE PANCREATIC SECRETION INDUCED BY L-DOPA OR DOPAMINE AT THE CELLULAR LEVEL

The incorporation of dopamine in zymogen granules may be probably understood as one of inactivation process, because dopamine will be quickly degradated in the alkaline medium of the pancreatic juice when granules are extruded into the pancreatic ducts. Furthermore dopamine in the cytoplasm is broken down with

monoamine oxidase. Kallikrein inhibited the spontaneous secretion of the pancreas and also the dopamine-induced secretion. Thus we can not neglect some possibility of control mechanism of spontaneous pancreatic secretion by natural constituents in the pancreatic tissue.

CONCLUSION

Although the results obtained in the organ level must be confirmed in the cellular and the subcellular levels, we assume that L-dopa is taken up across the membrane of the exocrine pancreas cell and is converted to dopamine by dopa decarboxylase in the cytoplasm. Dopamine interacts with the specific receptor sites of the acinar, centroacinar and ductule cells and stimulates the pancreatic secretion, meanwhile the excess of dopamine is incorporated in the zymogen granules or broken down by monoamine oxidase. When dopamine is stored in the zymogen granules and no excess of dopamine remains in the cytoplasm, the L-dopa-induced secretion will cease. Recently, NG, COLBURN and KOPIN (1972) reported that incorporated dopamine in particles of rat brain homogenates was released by addition of dopamine in the suspending medium. The incorporation in zymogen granules could be understood as an exchangable storage of dopamine. ALM, EHINGER and FALCK pointed out that "L-dopa readily accumulates in the pancreas but is not taken up to significant extent into the adrenergic nerves or into the other monoaminergic cell systems as the endocrine pancreas". It may be given as a conclusion of these studies that the dopaminergic system exists in the pancreas independently of the adrenergic system.

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