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Effect of dopamine on pancreatic secretion in the dog

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Summary

1. Effects of L-dopa and dopamine on the secretion of pancreatic juice were investigated in preparations of the isolated blood-perfused canine pancreas.

2. Dopamine (1–10 μg) given intra-arterially caused a profuse flow of juice.

3. The secretory activity of dopamine (3 μg) was approximately equal to that of secretin (0·1 unit).

4. L-Dopa (10–100 μg) given by a single intra-arterial injection was ineffective, but infusion at 100 μg/min for 10 min caused a marked increase of secretion after a delay of a few minutes.

5. Intravenous administration of either L-dopa (3 mg/kg) or dopamine (10–100 μg/kg) elicited a marked increase of pancreatic secretion, but was definitely less effective than intra-arterial injection.

6. Dopamine-induced secretion was not modified by atropine, phentolamine, propranolol, guanethidine or tetrodotoxin.

7. It is concluded that dopamine acts directly on the exocrine cells in the pancreas.

Introduction

Blaschko (1957) suggested that dopamine, a precursor of adrenaline and noradrenaline, might have a humoral function of its own. The actions of several sympathomimetic amines on the exocrine secretion from the pancreas was studied by Greengard, Roback & Ivy (1942) who observed a secretogogue effect with a few compounds, including dopamine and dopa.

In this study the secretogogue effects of L-dopa and dopamine were investigated on an isolated canine pancreas preparation with intact autonomic innervation.

Methods

Twenty-nine adult mongrel dogs of either sex, weighing 10–18 kg were used. Food was withdrawn for 24 h before experiments, but water was given *ad libitum*.

Animals were anaesthetized with sodium pentobarbitone (30 mg/kg, i.v.) and additional intramuscular doses of 10 mg/kg every hour. A tracheal tube was inserted and animals were ventilated artificially with air. The main pancreatic duct was carefully isolated close to the duodenum. The minor papilla was found after longitudinal incision of duodenal wall, and a polyethylene tube (I.D. 0·8 mm O.D. 1·35 mm) was inserted through the papilla into the main pancreatic duct. The tube was ligated tightly and connected to a drop counter. The accessory pancreatic duct was ligated and cut.

The isolation of the pancreatic circulation as illustrated in Fig. 1 was performed as follows. The gastroduodenal artery was isolated, preserving perivascular nerves as far as possible. The right gastric and the right gastroepiploic arteries arising from the gastroduodenal artery were ligated. The duodenum was divided about 1 cm distal from the pylorus. The gastric branches of the splenic artery were successively ligated, having only the pancreatic branches, and then splenectomy was performed. Finally, vascular connexions between the pancreas and the duodenum were carefully ligated and cut. Bile was drained off through a tube inserted into the bile duct. An initial dose of heparin (300 units/kg) was given and a maintenance dose of 100 units/kg was given hourly. An arterial cannula was inserted into the gastroduodenal artery which was perfused with the arterial blood pumped from the left femoral artery. The inferior pancreaticoduodenal artery was then ligated. The splenic artery was also cannulated and perfused retrogradely with blood from the femoral artery. Finally, the splenic artery was ligated at its point of origin, care being taken not to injure the perivascular nerves and to preserve the left gastric artery. With these procedures, the whole pancreas was perfused by the two arterial cannulae without any interruption of the blood supply to the pancreas during the operation. The blood supply to the liver and stomach was not affected.

Figure 2 shows a schematic diagram of the experimental arrangement. The arterial blood led from the left femoral artery was pumped into both cannulated arteries of the pancreas with a variable speed peristaltic pump (Harvard Apparatus, Model 1215). The perfusion pressure was maintained at 100 mmHg (1 mmHg≡1·333 mbar) by means of a Starling pneumatic resistance draining to the femoral vein. The blood flow to the pancreas was measured by an electromagnetic flowmeter (Nihon Kohden, MF-2) and the flow of pancreatic juice was measured by a drop counter. The systemic blood pressure and the perfusion pressure were measured by electromanometers (Nihon Kohden, MP-24T), and the heart rate by a tachograph (Nihon Kohden, RT-2). The perivascular nerves of the gastroduodenal artery were stimu-

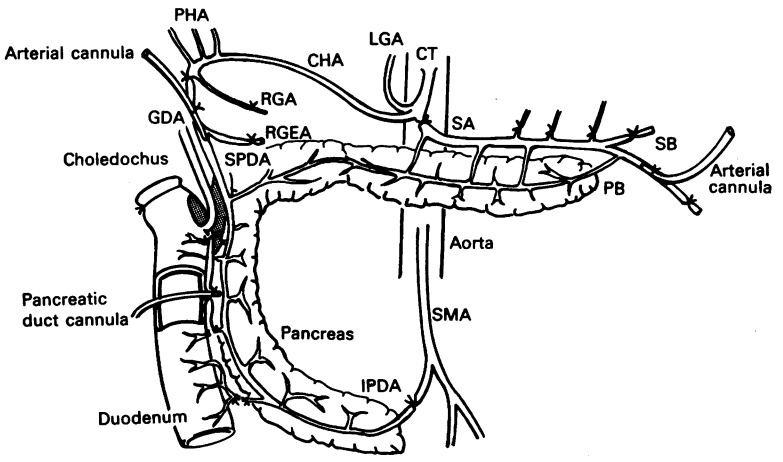

FIG. 1. Vascular supply to the canine pancreas. Arterial cannulae are inserted into the gastroduodenal and splenic arteries. CHA, common hepatic artery; CT, coeliac trunk; GDA, gastroduodenal artery; IPDA, inferior pancreaticoduodenal artery; LGA, left gastric artery; PB, pancreatic branches; PHA, proper hepatic arteries; RGA, right gastric artery; RGEA, right gastroepiploic artery; SA, splenic artery; SB, splenic branches; SMA, superior mesenteric artery; SPDA, superior pancreaticoduodenal artery.

lated through a pair of silver electrodes. The stimuli were of 10 V amplitude, 1 ms duration, and were delivered in 60 s trains at 10 Hz.

The incised abdomen was covered with vinyl sheet and warmed by an electric lamp so that the exposed pancreas was kept moist and the rectal temperature maintained at 38–39° C. The pancreas responded well to repeated doses of secretin during an experiment lasting for more than 4 hours.

Drug solutions were injected into the tubing which led to both arterial cannulae. A microsyringe was used to inject 10 μl (in 4 s) or 100 μl (in 20 s) of drug solution.

Drugs used in this study were L-dopa (Sankyo Cent. Res. Labs.), dopamine hydrochloride (ICN), L-noradrenaline (Fluka AG), L-adrenaline (Merck), L-isoprenaline hydrochloride (Nikken Kagaku), phentolamine methansulfonate (Ciba), propranolol hydrochloride (Sumitomo), atropine sulphate (Torii), guanethidine sulphate (Ciba), tetrodotoxin (Sankyo Cent. Res. Labs.), acetylcholine chloride (Daiichi), and secretin (Boots). They were dissolved in 0·9% NaCl solution immediately before use. L-Noradrenaline and L-adrenaline were dissolved in 1/100 N HCl. Doses of secretin are given in units (Crick, Harper & Raper, 1950).

Results

Perfusion flow rate and pancreatic secretory rate under resting conditions

In twenty-five experiments, the pancreatic blood flow was $12{\cdot}3 \pm 0{\cdot}9$ ml/min (mean $\pm$ S.E.). A sparse flow of pancreatic juice was observed in most preparations under resting conditions, the mean rate being $11{\cdot}8 \pm 1{\cdot}2$ μl/minute. The average weight of the pancreas measured at the end of each experiment was $63{\cdot}0 \pm 2{\cdot}7$ g. Thus, the perfusion flow rate was 0·20 (ml/min)/g gland.

Comparison of the effect of dopamine and secretin

Vascular and secretory responses to dopamine and secretin were examined in seven experiments. Dopamine (1–10 μg), caused a profuse flow of pancreatic juice which increased with the dose given. The increased flow of juice appeared within 10–20 s and reached a maximum 1–2 min later. The increased secretion caused

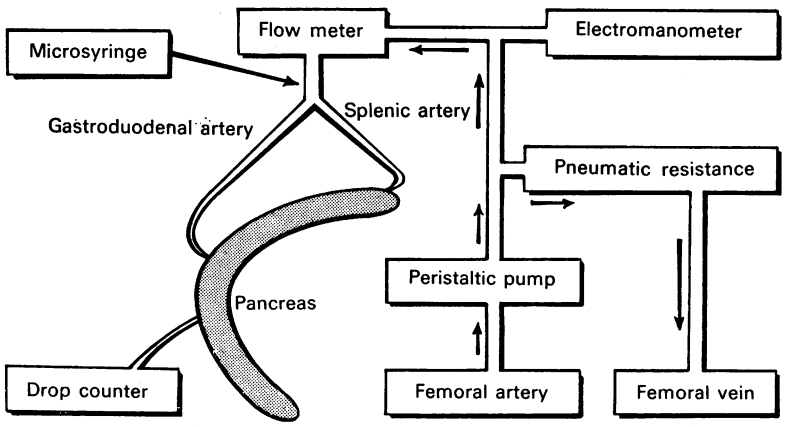

FIG. 2.—Diagram of circuit for constant pressure perfusion of the gastroduodenal and splenic arteries with blood from the femoral artery.

by dopamine (10 μg) subsided after 5–10 min (Fig. 3). Secretin (0·1–1 unit) produced an effect with a similar time course (Fig. 3). Dopamine decreased the blood flow slightly while secretin increased it.

Table 1 shows the secretory responses produced by dopamine and secretin. The effect of dopamine (3 μg) corresponded roughly to that of secretin (0·1 unit).

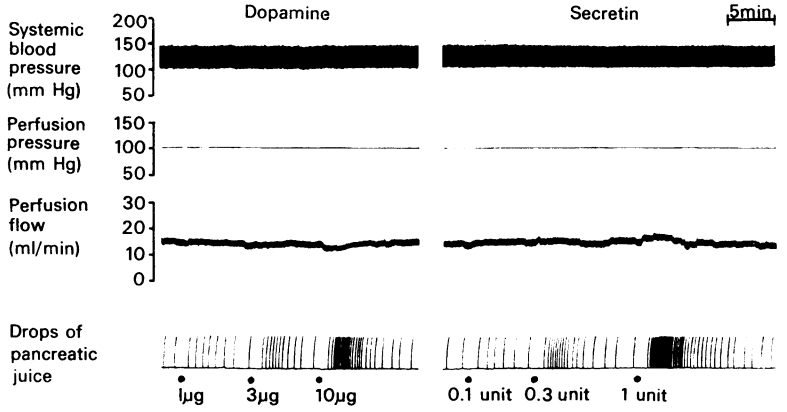

FIG. 3. Comparison of the vascular and secretory effects of dopamine and secretin. Drugs are injected intra-arterially. Note that dopamine decreases the blood flow slightly while secretin increases it.

TABLE 1. *Comparison of the volume of pancreatic juice induced by intra-arterial administration of dopamine and secretin*

Compound	Dose	Volume of juice (mean ± S.E.)	No. of animals
Dopamine	1 μg	59 ± 14 μl	7
	3 μg	290 ± 44 μl	7
	10 μg	630 ± 134 μl	7
Secretin	0·1 unit	245 ± 47 μl	7

The effect of dopamine (3 μg) corresponds to that of secretin (0·1 unit).

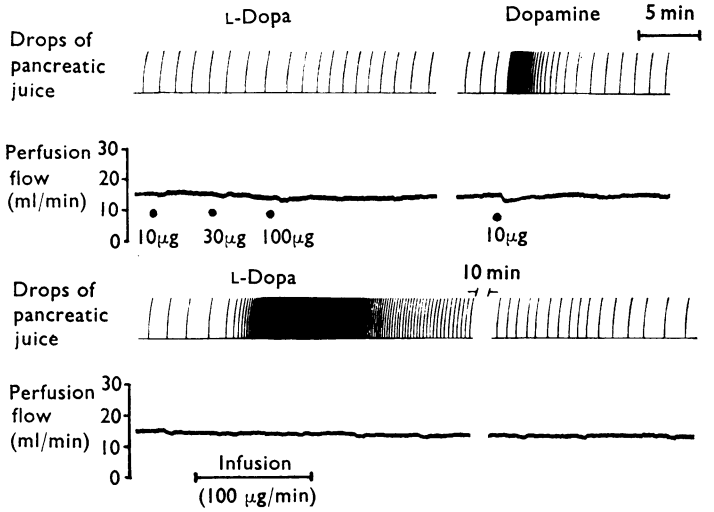

FIG. 4. Effect of L-dopa intra-arterially on the pancreatic secretion. A single injection of L-dopa (10–100 μg) has no effect on pancreatic secretion but infusion at 100 μg/min for 10 min causes a marked increase of secretion after a delay of a few minutes.

Effect of L-*dopa on the pancreatic secretion*

In three experiments, the effect of L-dopa on pancreatic secretion was examined. A single injection of L-dopa up to 100 μg was ineffective but an infusion of L-dopa at a rate of 100 μg/min for 10 min caused a marked increase of secretion after a delay of 3 minutes. The increased secretion reached a maximum in about 5 min, and persisted for about 1 h even after the infusion was stopped (Fig. 4). Infusion of L-dopa had no effect on the pancreatic blood flow.

Effect of intravenous administration of L-*dopa and dopamine on pancreatic secretion*

In four experiments, L-dopa and dopamine were given intravenously, and the effect was compared with that of secretin. A single injection of L-dopa (3 mg/kg) caused a profuse flow of juice with a delay of 1 min which reached a maximum about 6 min later and lasted for about 35 min as shown in Fig. 5. Dopamine also elicited a profuse flow of juice but with a much shorter time course. Thirty microgrammes per kilogramme of dopamine roughly corresponded to 0·3 units/kg of secretin. In comparison with secretin, intravenous administration of dopamine was definitely less effective than intra-arterial administration. Dopamine was roughly 100 times more potent than L-dopa, though the time course of its action was different.

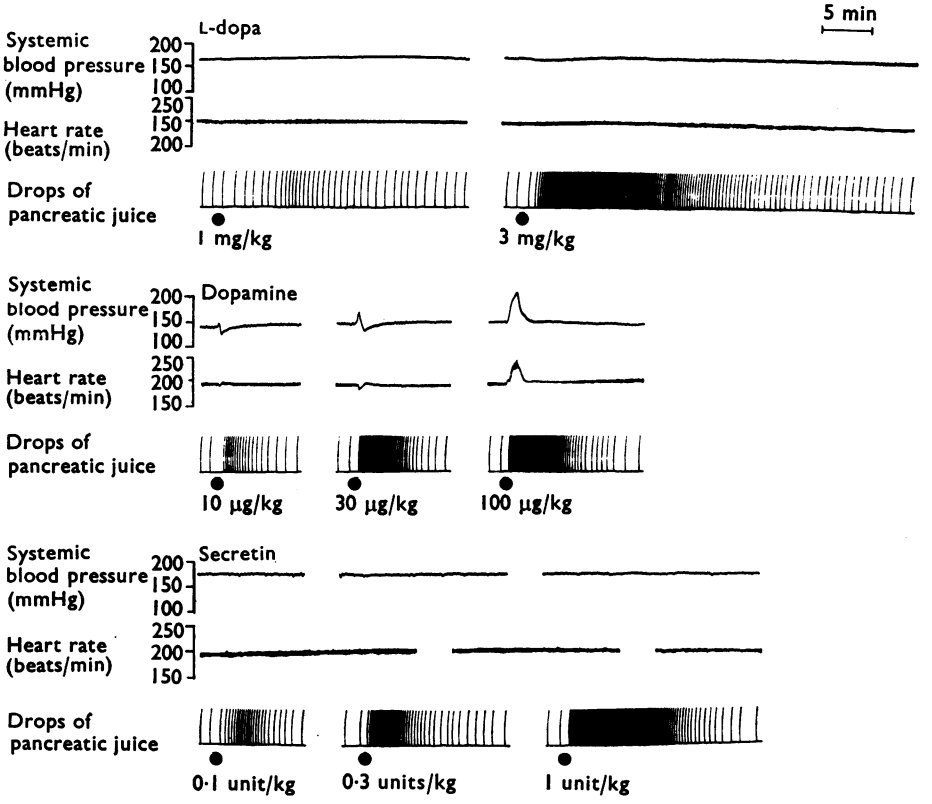

FIG. 5. Effects of intravenous administration of L-dopa, dopamine and secretin on pancreatic secretion.

Effect of catecholamines on pancreatic blood flow and secretion

The effects of intra-arterial noradrenaline, adrenaline and isoprenaline were compared with those of L-dopa and dopamine in three animals. Typical responses are illustrated in Fig. 6. Noradrenaline and adrenaline (1 μg) caused a significant vasoconstriction with a transient inhibition of pancreatic secretion. Isoprenaline caused an increase of pancreatic blood flow with no marked effect on secretion. Thus the pronounced stimulation of secretion with dopamine was not obtained with any other catecholamine tested.

Absence of effect of autonomic blocking agents on the secretion produced by dopamine

The blocking agents were given intra-arterially a few minutes before testing the effect of dopamine. The doses tested were: phentolamine (30–100 μg), propranolol (10–300 μg), atropine (30–300 μg), guanethidine (30–100 μg), tetrodotoxin (3–10 μg).

None of these agents appreciably altered the secretory response of the pancreas to dopamine (Figs. 7 & 8). Both guanethidine and tetrodotoxin abolished the vasoconstriction produced by stimulation of the periarterial nerves. The vascular actions of dopamine were modified by the phentolamine and propranolol (Fig. 7), phentolamine converting the vasoconstriction to a small dilatation, and propranolol enhancing the vasoconstriction.

Discussion

The observation of Greengard *et al.* (1942) that of several sympathomimetic amines tested dopa and dopamine alone caused an increase in pancreatic secretion has been confirmed in this study. The secretory activity of dopamine (3 μg) was approximately equivalent to that of secretin (0·1 unit).

When L-dopa was given intra-arterially by a single injection, it was ineffective in causing pancreatic secretion, whereas an intra-arterial infusion caused a long-lasting increase of secretion with a marked latent period. According to the observation of Alm, Ehinger & Falck (1969), the granular fluorescence of rat and mouse exocrine cells appeared 10 min after the injection of dopamine, but L-dopa took 40 min to produce the effect. Dopa decarboxylase has been demonstrated in the pancreas of several species (Holz, Credner & Strübing, 1942), and inhibition of this enzyme

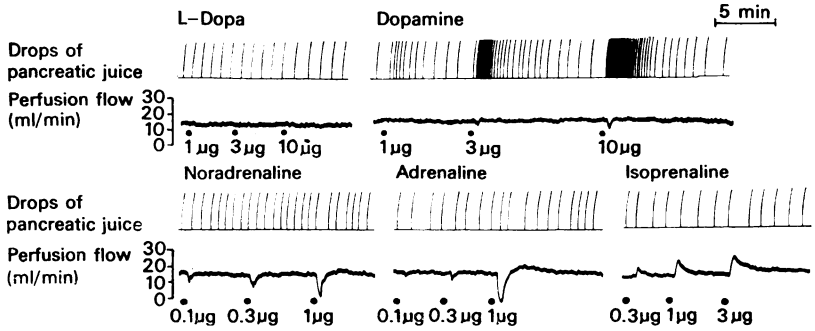

FIG. 6. Effects of catecholamines on pancreatic blood flow and secretion. Drugs are injected intra-arterially. Note that dopamine increases the pancreatic secretion while noradrenaline, adrenaline and isoprenaline have almost no effect.

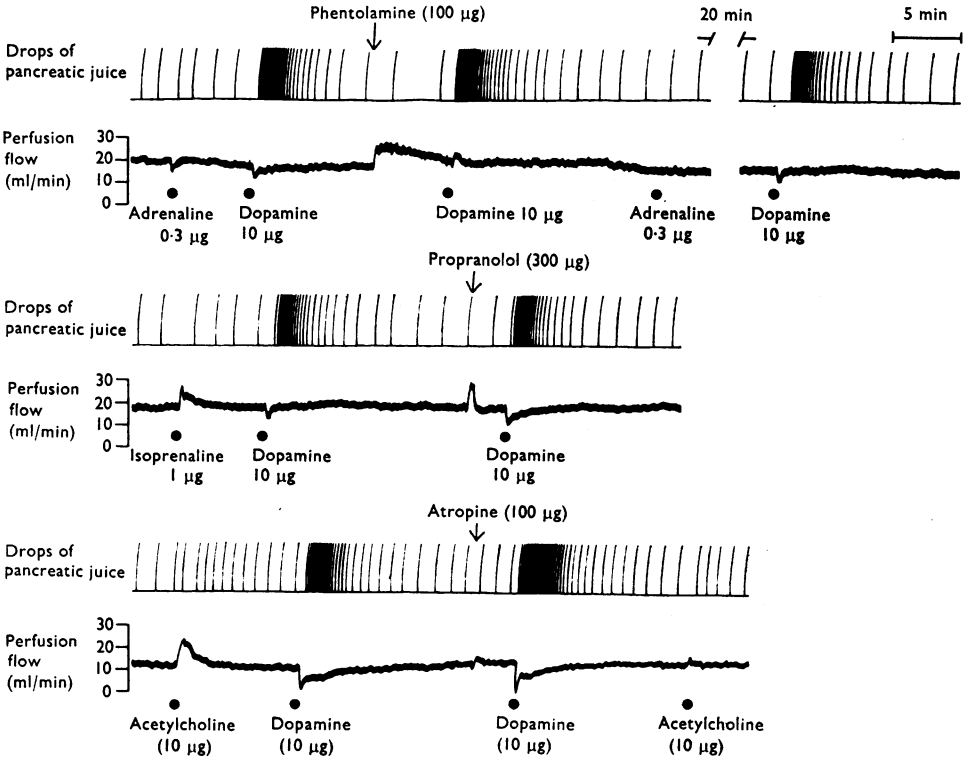

FIG. 7. Absence of effect of phentolamine, propranolol and atropine on dopamine-induced secretion. Drugs are injected intra-arterially.

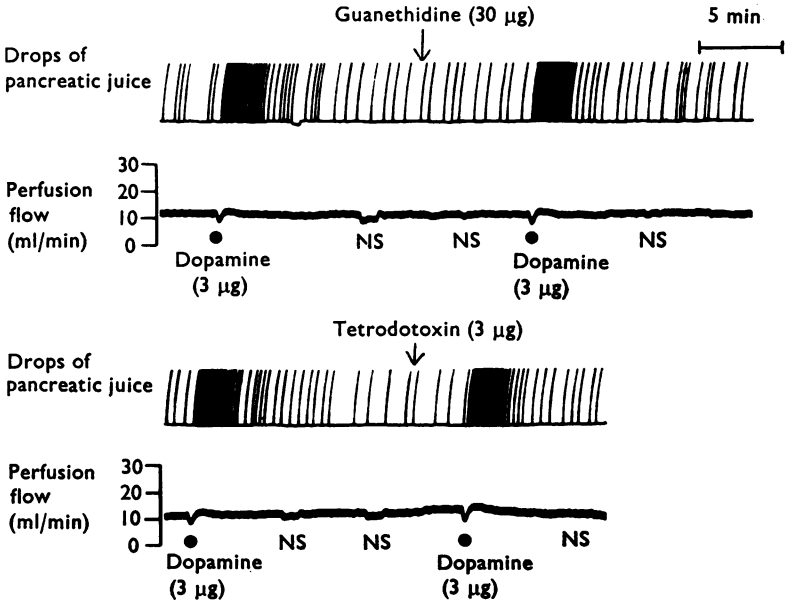

FIG. 8. Absence of effect of guanethidine and tetrodotoxin on dopamine-induced secretion. Drugs are injected intra-arterially. NS, perivascular nerve stimulation at the gastroduodenal artery (10 Hz for 60 s). Guanethidine and tetrodotoxin do not change either secretory or vascular responses to dopamine, but abolish the effect of perivascular nerve stimulation.

prevented the appearance of granular fluorescence after treatment with L-dopa (Alm, Ehinger & Falck, 1969), suggesting that L-dopa is converted to dopamine after being taken up by exocrine cells. The slow time course of the secretory action of L-dopa may therefore indicate that the formation of dopamine may be necessary for this effect.

Dopamine-induced secretion was not modified appreciably by atropine, phentolamine or propranolol, which suggests that the mechanism does not involve muscarinic receptors or either type of catecholamine receptor. The involvement of adrenergic or cholinergic nerves in the response to dopamine is excluded by the lack of effect of guanethidine or tetrodotoxin on the response. From these observations, it is therefore likely that dopamine acts directly on the exocrine cells in the pancreas.

Whether or not dopamine has a physiological role in pancreatic exocrine function is not clear. Schümann & Heller (1959) demonstrated that dopamine in the pancreas comprised more than 50% of the total catecholamines and suggested that dopamine was not only the precursor of noradrenaline but also an active substance in its own right, possibly a local hormone. Our experimental results are consistent with this possibility.

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