ENHANCEMENT OF DOPAMINE-INDUCED STIMULATION OF PANCREATIC SECRETION BY 5-DIMETHYLDITHIO- CARBAMYLPICOLINIC ACID (YP-279), A DOPAMINE β -HYDROXYLASE INHIBITOR

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Abstract—Effect of 5-dimethyldithiocarbamylpicolinic acid (YP-279), a dopamine β -hydroxylase inhibitor, on the secretion of pancreatic juice induced by dopamine was investigated in preparations of the isolated blood-perfused canine pancreas. Either a single injection (300 μ g) or an infusion (100 μ g/min) of YP-279 intra-arterially (i.a.) caused no change in the outflow of the pancreatic juice, but the secretagogue effect of dopamine (1–10 μ g, i.a.) was enhanced by the infusion of YP-279 (100 μ g/min, i.a.) for 60 min. The previous conclusion obtained with fusaric acid was confirmed as follows; the dopamine β -hydroxylase activity controls the dopaminergic mechanism of the pancreatic secretion.

Dopamine β -hydroxylase inhibitors such as disulfiram (1), fusaric acid (2) and 5-(n-butyl)-picolinamide (3) have been proved to decrease norepinephrine level while dopamine level was increased not only in the brain but also in various peripheral organs. Recently, 5-dimethyldithiocarbamylpicolinic acid (YP-279) has been synthesized and it was proved that YP-279 was a selective dopamine β -hydroxylase inhibitor and equipotent to fusaric acid in an *in vitro* study (4).

Previously we reported that dopamine caused an increase in the secretion of pancreatic juice in dogs but norepinephrine showed entirely no effect on the pancreatic secretion (5) and the secretagogue effect of dopamine was enhanced by the treatment of fusaric acid (6), which suggested that there were specific receptors to secrete the pancreatic juice by dopamine. Facilitation with the treatment of fusaric acid, however, raised a question since fusaric acid itself stimulated the pancreatic stimulation.

In the present study, previous results were reinvestigated by use of YP-279, a peripheral dopamine β -hydroxylase inhibitor and the role of dopamine β -hydroxylase on the pancreatic secretion was discussed.

MATERIALS AND METHODS

Six mongrel dogs of either sex, weighing 11 to 15 kg, were anesthetized with 30 mg/kg of sodium pentobarbital given i.v. A polyethylene tube was inserted into the main pancreatic duct for collection of the pancreatic juice. Polyethylene cannulae were inserted into the

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gastroduodenal and splenic arteries through which the pancreas was perfused with the animal's own blood from the left femoral artery by mean of a Harvard peristaltic pump (Model 500-1200). All experiments were performed under constant pressure at 100 mmHg. Details of the preparation were described in previous papers (5, 6). A dose of 300 U/kg of sodium heparin was given at the beginning of the perfusion and a supplementary dose of 2,000 units was given i.v. Drugs used were dopamine hydrochloride (ICN) and 5-dimethyldithiocarbamylpicolinic acid (YP-279, kindly provided by Prof. H. Hidaka, Mie University Medical School). Drugs were dissolved in 0.9% saline solution and were injected or infused into a rubber tube connected to the arterial cannula. Statistical analysis was made by means of Student's *t*-test.

RESULTS

Either a single injection (300 μ g) or an infusion (100 μ g/min) of YP-279 i.a. produced no change in the outflow of the pancreatic juice. Dopamine (1, 3 or 10 μ g) i.a. caused an increase in the secretion of the pancreatic juice as reported previously (5). The dopamine-induced pancreatic secretion was significantly enhanced by treatment with YP-279 (100 μ g/min) for 60 min. Table 1 shows the results obtained in 6 dogs.

TABLE 1. Effect of YP-279 infusion on the secretion of pancreatic juice induced by dopamine

Dose of dopamine	No. of experiments	Volume of pancreatic secretion (μ l)	
		Control	YP-279 infusion for 60 min
1 μ g	6	76 $\pm$ 13	113 $\pm$ 14*
3 μ g	6	310 $\pm$ 52	483 $\pm$ 35*
10 μ g	6	961 $\pm$ 65	1240 $\pm$ 56*

YP-279 was infused at a rate of 100 μ g/min and dopamine (1, 3 and 10 μ g) was injected intra-arterially. Each value represents the mean $\pm$ s.e.m. Significance of difference $P < 0.05$ (*)

DISCUSSION

Previously we observed similar results that dopamine-induced pancreatic secretion was enhanced by fusaric acid, although fusaric acid itself stimulated pancreatic secretion (6). The enhancement caused by fusaric acid (100 μ g/min) was significant 30 min after the infusion ($p < 0.05$) and highly significant 60 min after the infusion ($p < 0.01$). The potency of YP-279 required to enhance dopamine-induced secretion *in vivo* was less than that of fusaric acid. Hidaka et al. (4) have reported that YP-279 is equipotent with fusaric acid as an inhibition of dopamine β -hydroxylase *in vitro*, but its *in vivo* inhibitory activity is less potent than that of fusaric acid. The potency of these drugs for enhancement of the pancreatic secretion may then be correlated with the potency of dopamine β -hydroxylase inhibition *in vivo*.

There is much evidence supporting the role of dopamine β -hydroxylase in the biosynthesis of catecholamine at the adrenergic nerve terminals, and such was also confirmed by Symchowicz et al. (7) in the pancreas. On the other hand, Alm et al. (8) observed by use of

a specific fluorometric method that L-dopa and dopamine were taken up in the acinar cells of the rat pancreas and once accumulated in the granules in these cells, the characteristic fluorescence faded gradually and finally disappeared. They did not report the effect on the exocrine pancreas of L-dopa and dopamine. We examined the effects of various pharmacodynamic agents on the exocrine secretion of the canine pancreas (9) and further analysed the specific stimulatory effect of dopamine and L-dopa (10). We obtained the following results: 1) L-dopa and dopamine stimulated the secretion of pancreatic juice, while norepinephrine and epinephrine did not. 2) Ro 4-4602 (benserazide), an L-aromatic amino acid decarboxylase inhibitor, blocked the stimulatory effect of L-dopa while dopamine was not modified by this treatment. 3) The effect of either L-dopa or dopamine was significantly attenuated by haloperidol, a dopamine receptor antagonist. 4) The content of bicarbonate was high in the dopamine-induced pancreatic juice while the protein content was low, this response being similar to that seen with secretin. This observation confirmed the site of dopaminergic receptors at the ductal cells. 5) Stimulation of the secretion of pancreatic juice induced by L-dopa showed a definite delay in initiation of the response, thus suggesting the conversion of L-dopa to dopamine in the ductal cells. It is interesting to speculate whether or not dopamine is converted to norepinephrine in the ductal cell which may control the secretagogue effect of dopamine. Fusaric acid enhanced the stimulatory effect of dopamine, while fusaric acid itself had a definite stimulatory effect on the pancreatic secretion. YP-279, a selective inhibitor of peripheral dopamine β -hydroxylase, had no stimulatory effect on the pancreatic secretion but definitely enhanced the dopamine-induced pancreatic secretion, in this study. These results suggest that the dopamine β -hydroxylase activity in the pancreas controls the dopaminergic mechanism of the pancreatic secretion in dogs.

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