POTENTIATING EFFECTS OF DIPYRIDAMOLE ON THE SECRETION OF PANCREATIC JUICE INDUCED BY SECRETIN IN THE BLOOD-PERFUSED DOG PANCREAS

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In 1971, Hashimoto et al. (1) developed a preparation of the isolated, blood-perfused dog pancreas. This preparation is convenient as a tool for studying the direct actions of drugs on the pancreas (2). Recently, we reported that a potent vasodilator, papaverine, caused a secretion of pancreatic juice in dogs (3). Dipyridamole has many pharmacologic properties qualitatively similar to those of papaverine (4). However, its effect on pancreatic secretion has received little attention. In the present study, we have examined the effects of dipyridamole on pancreatic secretion using an isolated, blood-perfused dog pancreas preparation.

Seven mongrel dogs, weighing 12-15 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. The accessory pancreatic duct was ligated. Isolation of the pancreatic circulation was done by the method of Hashimoto et al. (1) with some modifications. The gastroduodenal artery was isolated. The gastric branches of the splenic artery were successively ligated, leaving only pancreatic branches. Vascular connections between the pancreas and the duodenum were carefully ligated. An initial dose of heparin (500 units/kg) was given i.v., and a maintenance dose of 200 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 pancreatico-duodenal artery was then ligated. The splenic artery was also cannulated and perfused retrogradely with blood from the femoral artery. The splenic artery was then ligated at its point of the origin, care being taken not to injure the perivascular nerves and to preserve the left gastric artery. Arterial blood, led from the left femoral artery, was pumped into both the cannulated arteries of the pancreas. All experiments were performed under a constant perfusion pressure of 100 mmHg. Drugs used in this study were dipyridamole (Tanabe) and secretin (Eisai). Drugs were dissolved in saline solution and were injected or infused into the rubber tube connected to the arterial cannulae. Statistical analysis was carried out by means of the Student's t-test.

Dipyridamole in doses from 100 μg to 3 mg given intra-arterially has no secretory effect, although it caused a transient increase in the flow rate of perfusion. In contrast, secretin (0.03-0.3 units) promptly caused an apparent increase in the pancreatic juice in a dose-dependent manner. Then, rates of pancreatic secretion induced by secretin were examined before and during the infusion
of dipyridamole. When dipyridamole was infused at a dose of 10 μg/min, dipyridamole did not cause any effect on the resting secretion of pancreatic juice nor did it modify the secretin-induced pancreatic secretion. The perfusion flow rate also did not change. However, with the infusion of 50 μg/min of dipyridamole, the perfusion flow rate was increased transiently. After the perfusion flow rate returned to the control level, secretin (0.03, 0.1 and 0.3 units) was injected. The secretin-induced secretion was usually potentiated by this injection, and this potentiation was more apparent at high doses of secretin. Resting secretion of pancreatic juice was not modified by the infusion of 50 μg/min of dipyridamole. Typical responses to secretin during the infusion of dipyridamole are shown in Fig. 1 and summarized data obtained from 5 dogs are given in Table 1.

Dipyridamole has been classified as a vasodilator and used in the treatment of angina pectoris (4). The actions of dipyridamole seem to be linked, at least in part, to the metabolism and transport of adenosine and adenine nucleotides; in particular, dipyridamole inhibits the uptake of adenosine by erythrocytes and other cells (5, 6) and inhibits the deamination of adenosine (5). This could result in an accumulation of adenosine in specific organs. However, it can be ruled out that increased adenosine causes the pancreatic secretion since adenosine and adenine nucleotides did not have any effect on pancreatic secretion (2). Dipyridamole inhibits phosphodiesterase, thereby increasing the intracellular concentration of cyclic AMP (7). Adenylate cyclase and phosphodiesterase are present in a significant concentration in the pancreas (8, 9). Case and Scratcherd (10) reported that the secretory response to secretin was accompanied by an increase in the cytoplasmic levels of cyclic AMP. Dibutyryl cyclic AMP given intra-arterially

![Fig. 1. Typical secretory responses of the dog pancreas to secretin before and during the infusion of dipyridamole given intra-arterially.](image)

**Table 1.** Effect of dipyridamole infusion on the secretion of pancreatic juice induced by secretin

<table>
<thead>
<tr>
<th>Dose of secretin (units)</th>
<th>Volume of pancreatic secretion (μl)</th>
<th>(B)/(A) (%)</th>
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<tr>
<td></td>
<td>(A) Control (B) During infusion of dipyridamole</td>
<td></td>
</tr>
<tr>
<td>0.03</td>
<td>105±21 114±33</td>
<td>108.6</td>
</tr>
<tr>
<td>0.1</td>
<td>375±26 486±28*</td>
<td>129.6</td>
</tr>
<tr>
<td>0.3</td>
<td>846±38 1020±40*</td>
<td>120.6</td>
</tr>
</tbody>
</table>

Dipyridamole was infused at a rate of 50 μg/min, and secretin (0.03, 0.1 and 0.3 units) was injected intra-arterially. Each value represents the mean±S.E.M. *P<0.05 as compared to the control.
also caused the secretion of pancreatic juice (2). These results suggest that cyclic AMP acts as a second messenger or a mediator of secretin. Recently, it was reported that papaverine and methylxanthine potentiated the secretin-induced pancreatic secretion (3, 10). From these results, it is suggested that dipyridamole potentiates the secretin-induced pancreatic secretion which may be mediated through an increase of the intracellular cyclic AMP. The potentiating effect of dipyridamole on pancreatic secretion is similar to that of papaverine; however, papaverine itself caused the pancreatic secretion (3), but dipyridamole did not. The discrepancy might be due in part, to the difference in potency as a phosphodiesterase inhibitor because the inhibitory activity of papaverine has been reported to be 3.7 times more potent than that of dipyridamole (7).

REFERENCES


