D-1 Dopamine Receptors Mediate Dopamine-Induced Pancreatic Exocrine Secretion in Anesthetized Dogs

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Characterization of dopamine (DA) receptor subtypes was examined on the canine exocrine pancreas using selective DA receptor agonists and antagonists in anesthetized dogs. Each drug was injected i.a. in a single bolus fashion. Graded doses of DA (0.01-3 μmol) produced dose-dependent increases in the secretory rate of pancreatic juice, with a maximum effect at approximately 1 μmol. SCH23390 (3-30 nmol), a selective D-1 DA receptor antagonist, caused a progressive parallel shift to the right in the dose-response curve for DA-induced pancreatic secretion without changes in the maximal response. However, domperidone (3 μmol), a selective D-2 DA receptor antagonist, did not antagonize the DA-induced pancreatic exocrine secretion. A Schild analysis of the data indicates that the inhibitory constant value for SCH23390 to inhibit DA-stimulated secretion was 6.9 nmol. In addition, the stimulatory effects of SKF38393 (0.1-10 μmol) and YM435 (0.3-30 nmol), selective D-1 DA receptor agonists, and LY171555 (1-10 μmol), a selective D-2 DA receptor agonist, on pancreatic secretion were demonstrated. The rank order of agonist potency was YM435 > DA > SKF38393 > LY171555. These results suggest that DA-induced pancreatic exocrine secretion is mediated by activation of D-1 DA receptors. (Hypertens Res 1995; 18 Suppl. I: S173-S174)

Key Words: pancreas (dog), exocrine secretion, dopamine D-1 receptors

It has been demonstrated that exogenous DA stimulates pancreatic secretion of water and bicarbonate in anesthetized dogs and that there are specific DA receptors related to the pancreatic exocrine secretion (1,2). Recently, the novel drugs discriminating between D-1 and D-2 receptors have been developed. However, the specific receptor subtype through which selective DA agonists and antagonists elicit their effects on pancreatic exocrine secretion has not been determined. The present study was undertaken to evaluate the inhibitory effects of SCH23390 (a selective D-1 receptor antagonist) and domperidone (a selective D-2 receptor antagonist) on dopamine-induced exocrine secretion and the stimulatory effects of YM435 and SKF38393 (selective D-1 receptor agonists), and LY171555 (a selective D-2 receptor agonist) on exocrine secretion to determine the specific DA receptor subtype in dog pancreas.

Materials and Methods

The abdomen of the dog was opened after pentobarbital anesthesia. A polyethylene tube was inserted into the main pancreatic duct, and the drops of the pancreatic juice flowing out of the tube were counted by a drop counter. The pancreas was hemodynamically isolated and perfused at a constant blood flow rate (3). In brief, polyethylene cannulae were inserted into the gastroduodenal and splenic arteries, through which the pancreas was perfused with the animal’s own heparinized blood conducted from the left femoral artery using a peristaltic pump. Drugs were injected into a rubber tube connected to the shank of the arterial cannula leading to the pancreas with a syringe as a single bolus. Drugs used in this study were dopamine hydrochloride (Sigma Chemical Co., St. Louis, MO, USA), YM435 (kindly donated by Yamanouchi Co., Tokyo, Japan), SKF38393 hydrochloride (kindly donated by Smith Kline and French Lab., Philadelphia, PA, USA), LY171555 (kindly donated by Eli Lilly Res. Lab., Indianapolis, IN, USA), SCH23390 (kindly donated by Schering Co., Bloomfield, NJ, USA) and domperidone (Janssen Pharmaceutica, Beerse, Belgium). An unpaired Student’s t test was used for the comparison of two means.

Results

Effects of YM435, DA and SKF38393 on Pancreatic Exocrine Secretion

The basal rate of pancreatic secretion during the course of the experiment was 12.2 ± 0.7 μl/min per 100 g of pancreas (n = 28). The time course of pancreatic juice secretion in response to i.a. injections of YM435 (0.1, 1 and 10 nmol) and DA (0.01, 0.1 and 1 μmol) is shown in Fig. 1. and the summarized dose-response curves for YM435, DA and
SKF38393 are shown in Fig. 2. An i.a. injection of YM435 (0.3-30 nmol) and DA (0.03-3 μmol) produced a dose-dependent increase in the rate of pancreatic juice, with a maximum effect at approximately 10 nmol and 1 μmol, respectively. SKF38393 (0.3-10 μmol) also caused a dose-dependent increase in the rate of pancreatic juice in almost the same fashion. However, even a high dose of LY171555 (10 μmol) slightly increase pancreatic exocrine secretion.

**Effects of DA Receptor Antagonists on YM435-, DA- and SKF38393-Stimulated Pancreatic Exocrine Secretion**

As shown in Fig. 2, SCH23390 at doses of 3, 10 and 30 nmol caused a parallel rightward shift of the dose-response curves for the effect of YM435, DA and SKF38393 on pancreatic exocrine secretion. However, even a high dose of domperidone (10 μmol) failed to modify YM435-, DA- and SKF38393-stimulated pancreatic exocrine secretion. A Schild analysis of the data indicates that the inhibitory constant values for SCH23390 to inhibit YM435- and DA-stimulated secretion were 2.9 nmol and 6.9 nmol, respectively. The slopes of the Schild regression lines were 0.93 and 1.01, and were not significantly from 1.

**Discussion**

The present study demonstrated that YM435, DA and SKF38393, injected i.a., dose dependently increased the secretion of pancreatic juice. The secretory activity of 3 nmol of YM435 corresponded roughly to that of 0.16 μmol of DA and 5 μmol of SKF38393, respectively. Thus, YM435 was about 53 times and 1600 times more potent than DA and SKF38393 in stimulation pancreatic secretion, respectively. Pancreatic secretion stimulated by YM435, DA and SKF38393 was inhibited by pretreatment with SCH23390 (a DA D-1 receptor antagonist), but not by domperidone (a DA D-2 receptor antagonist). Therefore, YM435, DA and SKF38393 may stimulate pancreatic exocrine secretion by acting on DA D-1 receptors of the pancreas. SCH23390 caused a progressive parallel rightward shift in the dose-response curves for the effect of YM435 and DA on pancreatic secretion. The slope of the Schild regression line was not different from 1, suggesting that SCH23390 competitively inhibited YM435- and DA-stimulated pancreatic secretion.

**References**