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Experimental Studies on the Interrelationship between Organs Mediated by Peptide YY: Effect on Splanchnic Circulation and Exocrine Pancreas in Dogs

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Abstract

Peptide YY (PYY) which is most likely to mediate colonic inhibition on digestive organs is also a potent vasoconstrictor. However, very little is known about the effect of circulating PYY on splanchnic blood flow. This study examined the effect of systemic administration of peptide YY on splanchnic circulation and exocrine pancreas in dogs. Under secretin stimulation, intravenous administration of PYY (0.1, 0.5, 1 and 2 μg/kg) significantly decreased pancreatic secretion volume and blood flows in the pancreatic tissue, the superior mesenteric artery and the celiac artery in a dose-related manner. At the same time, PYY increased mean blood pressure. Under secretin plus cholecystokinin stimulation, PYY (1 μg/kg) significantly inhibited pancreatic secretion volume and protein output. This study first shows that PYY potently reduces celiac arterial blood flow as well as intestinal blood flow at such doses that PYY inhibits exocrine pancreatic secretion.

Introduction

Peptide YY (PYY) which consists of a linear chain of 36 amino acids was isolated and characterized from the extract of porcine upper intestinal tissue[51,52]. Because the primary structure of PYY is homologous to those of pancreatic polypeptide (PP)[25,30] and neuropeptide Y (NPY)[53], these peptides are considered to make a family of regulatory peptides[36,46,53]. PYY has been found to distribute in mammalian digestive organs and most of them have been localized in the endocrine cells of the mucosa in lower part of the ileum, in the colon and in the rectum[3,13,34,54]. Several stimulations including meal ingestion have been shown to increase plasma PYY levels[2,3,4,5,41,42,54].

Intravenous infusion of PYY has been shown to inhibit several digestive functions including pancreatic exocrine secretion[1,19,21,31,33,40,41,52], gastric acid secretion[1,14,41] and cholecystokinin (CCK) release[19,32]. Vasoconstrictor effect of PYY has been also shown in the submandibular salivary gland [35,36] and the superior mesenteric artery (SMA)[34] by local intra-arterial administration and in the

Key words: Peptide YY (PYY), Superior mesenteric arterial blood flow, Celiac arterial blood flow, pancreatic tissue blood flow, Exocrine pancreatic secretion.
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pancreas by systemic administration[21]. From these findings, some authors[19,41,46] have suggested that PYY may actually be pancreatone[16,17] or one of its constituents. Namely, it is very likely that PYY is, at least, one of the humoral factors which mediate colonic inhibition on sevral digestive organs[10,15,16,20,24,28,39,43].

Abnormal plasma levels of PYY have been reported in several clinical states. Elevated basal and/or postprandial PYY levels have been reported in patients with dumping syndrome[2], symptomatic Crohn's disease[26], untreated coeliac disease[45], hepatic cirrhosis[26], previous partial ileal resection[4,26] and previous pancreatectomy[4]. On the other hand, low basal and postprandial PYY levels have been reported in patients who have undergone colonic resection or ileostomy[4]. However, the pathophysiological significancies of these abnormalities still remain to be determined.

Although it is clear that PYY has a vasoconstrictor effect[21,34,35,36], the effect of systemic administration of PYY on splanchnic circulation remains still uncertain. The responses of splanchnic vascular beds to PYY may be substaintially different according to their relative responsibilities. In fact, we have observed that vasoactive intestinal polypeptide which is a potent vasodilator is less effective to SMA than portal vein[22,48] and that gastric inhibitory peptide which potently increases SMA blood flow has very little effect on celiac artery (CA)[27]. Therefore, this study was conducted to examine the effect of synthetic PYY[38] on the blood flows in SMA and CA with simultaneous observation of exocrine secretion and tissue blood flow of the pancreas.

Material and Method

Experimental preparation

Five mongrel dogs of either sex weighing between 7 and 14 kg were used after 18-hour fast. Rearing of these dogs and the experiments were carried out at the Institute of Laboratory Animals, Faculty of Medicine, Kyoto University. Each dog was anesthetized by intravenous sodium pentobarbital (25 mg/kg body wt) and mechanically ventilated via an intratracheal tube through the study. Right femoral vein was catheterized and used for drip infusion of 0.9% saline and administration of agents. Left femoral vein was catheterized for continuous infusion of secretin alone or secretin and cholecystokinin (CCK). Left femoral artery was catheterized and used for continuous monitoring of systemic arterial pressure by pressure transducer (MPUO 5A, Nihon Koden, Tokyo, Japan).

After midline laparotomy, the main pancreatic duct was cannulated with a # 3 French-sized polyethylene tube through duodenotomy while the accessory pancreatic duct was ligated. The duodenotomy was then closed by suture. Pancreatic juice was collected every 10 minutes through the study. After volume measurement, the samples were stored at $-20°C$ for later protein assay by Bradford's method[9]. The common bile duct and the pylorus were ligated. Bile and gastric juice were drained extracorporeally by catheters, respectively.

In order to measure the both blood flows in the superior mesenteric artery (SMA) and the celiac artery (CA) simultaneously, we used an ultrasonic transit-time volume flow meter (TRANSONIC T-201, Transonic System Inc., Ithaca, NY, USA)[12]. This flow meter can continuously measure blood flows of two vessels with sufficient stability and reproducibility[11,27,48,49]. Two probes of this flow meter were placed at the root of SMA and CA, respectively.

In order to monitor pancreatic tissue blood flow continuously, we used a laser Doppler flow meter[47] (LD5000, Medpacific Corp., Seattle, WA, USA)[18,21,48,49]. This flow meter sensitively

measures relative changes in microcirculatory blood flow of various tissues and put them out as changes in voltage. A probe of this flow meter was attached to the dorsal surface of the right lobe of the pancreas with an double sided adhesive tape. After these preparations, the laparotomy was roughly closed.

Experimental protocol

Pancreatic exocrine secretion was stimulated by continuous intravenous infusion of secretin (Peptide Institute, Osaka, Japan) at a dose of 0.25 μg/kg/hr. After blood flow measurement and pancreatic secretion became stabilized, synthetic porcine PYY[38] dissolved in 0.9% saline containing 2% bovine serum albumin (Sigma Chemicals, St. Louis, MO, USA) was intravenously injected as a bolus at doses of 0 (vehicle alone), 0.1, 0.5, 1 and 2 μg/kg body wt in this order. The intervals between these injections were 40 to 80 minutes except for vehicle alone. In this series, effects of PYY on the blood flows, blood pressure and pancreatic secretion volume were mainly observed and analysed.

Consequently, pancreatic secretion was stimulated by continuous infusion of secretin (0.25 μg/kg body wt) plus CCK-8 (Peptide Institute, Osaka, Japan) (0.1 μg/kg body wt). Under this stimulation, PYY was administered at doses of 0.1 and 1 μg/kg body wt as a bolus with a interval of 40 minutes in three dogs. In two dogs, either 0.1 or 1 μg/kg body wt of PYY was administered, respectively. In this series, effect of PYY on volume and protein output of the pancreatic secretion was mainly examined.

Data analysis

Effects of PYY on the blood flows and blood pressure were estimated by the percentage of the maximal response after injection with each pre-injection value as 100%. Changes in the pancreatic secretion volume under secretin stimulation was also estimated by the percentage of the 10-minute volume immediately after the injectin with each pre-injection value as 100%. Statistical analysis was performed by two-way analysis of variance for repeated measurements. In addition, the time course of the secretion volume was analysed by paired t-test between pre- and post-injection values. The effect of PYY on the pancreatic secretion under secretin plus CCK-8 stimulation was analysed by paired t-test because protein output under this condition normally decreases with time. Significance was accepted when p-value was less than 0.05. Values are expressed as the mean±SEM.

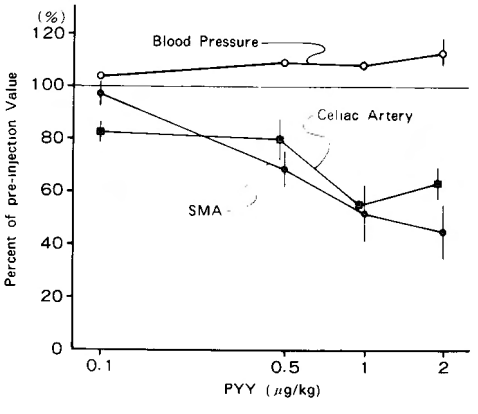

Fig. 1 Percent changes in the superior mesenteric arterial blood flow (closed circle, n=4), the celiac arterial blood flow (closed square, n=4) and mean blood pressure (open circle, n=4). Each vertical bar represents SEM.

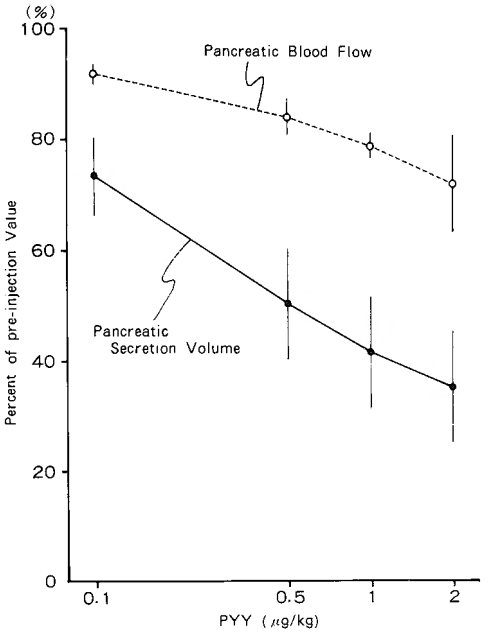

Fig. 2 Percent changes in the pancreatic secretion volume (closed circle, n=4) and the pancreatic tissue blood flow (open circle, n=3) under secretin stimulation. Each vertical bar represents SEM.

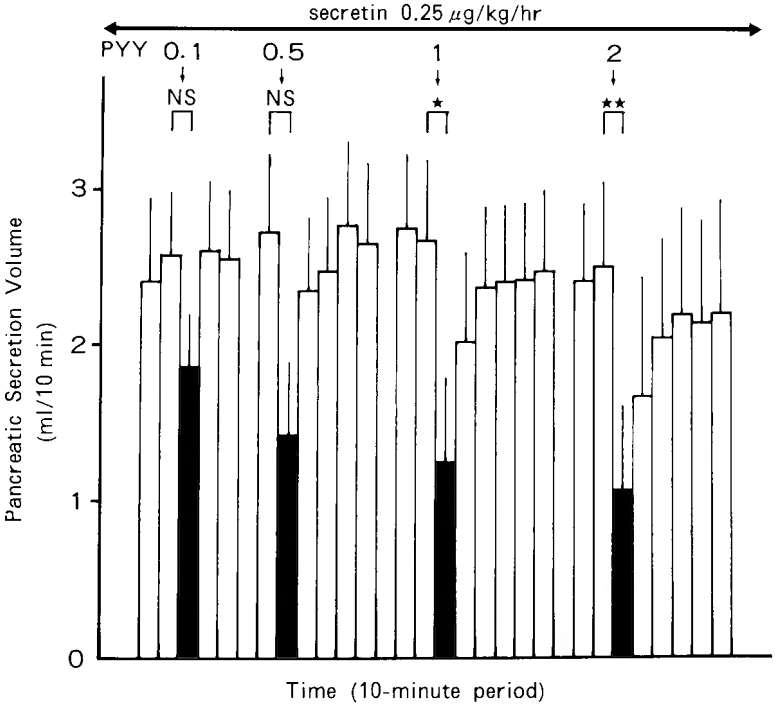

Fig. 3 Changes in the pancreatic secretion volume with time under secretin stimulation. Each vertical bar represents SEM. Each arrow indicates the time of PYY injection. NS: not significant, *: $p<0.02$, **: $p<0.01$.

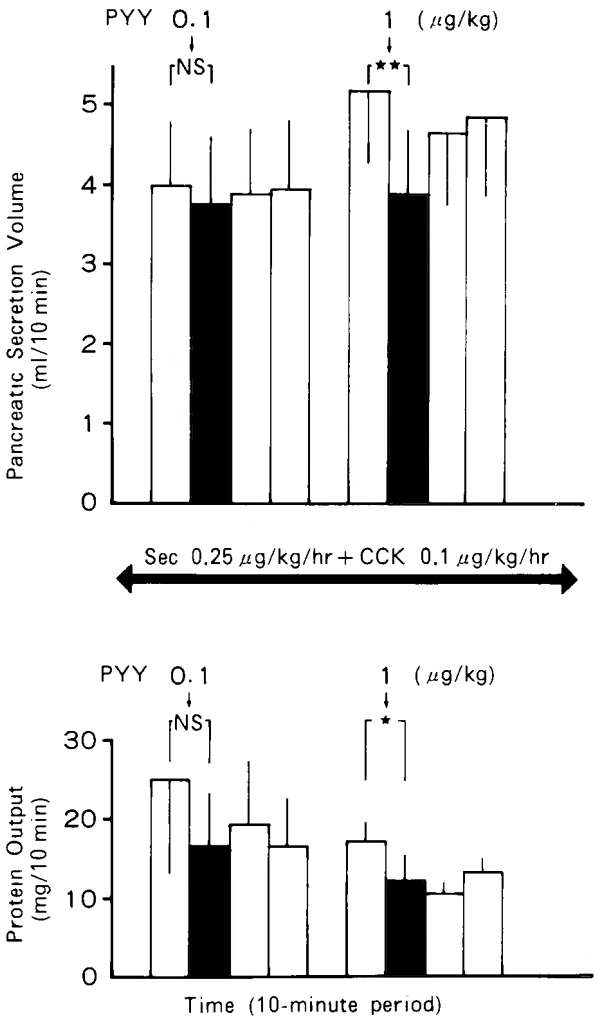

Fig. 4 Changes in the pancreatic secretion volume (top) and in the protein output (bottom) with time under secretin plus CCK stimulation. Each vertical bar represents SEM. Each arrow indicates the time of PYY injection. NS: not significant, *: $p<0.05$, **: $p<0.01$.

Results

Before the first dose of PYY under secretin stimulation, mean blood pressure, SMA blood flow and CA blood flow were 118.3 ± 3.5 mmHg, 92.8 ± 19.5 ml/min and 84 ± 10.9 ml/min, respectively. At the same time, the output of the laser Doppler flow meter was 240 ± 18 mV and secretion volume was 2.8 ± 0.4 ml/10 min.

Under secretin stimulation, injection of vehicle alone did not evoke any changes in any measurements of circulation. The doses of PYY significantly decreased blood flows in SMA ($p<0.01$, $F(4, 12)=23.4$) and CA ($p<0.01$, $F(4, 12)=12.1$), in a dose-related manner (Fig. 1), respectively. On the other hand, mean blood pressure was increased dose-dependently by PYY

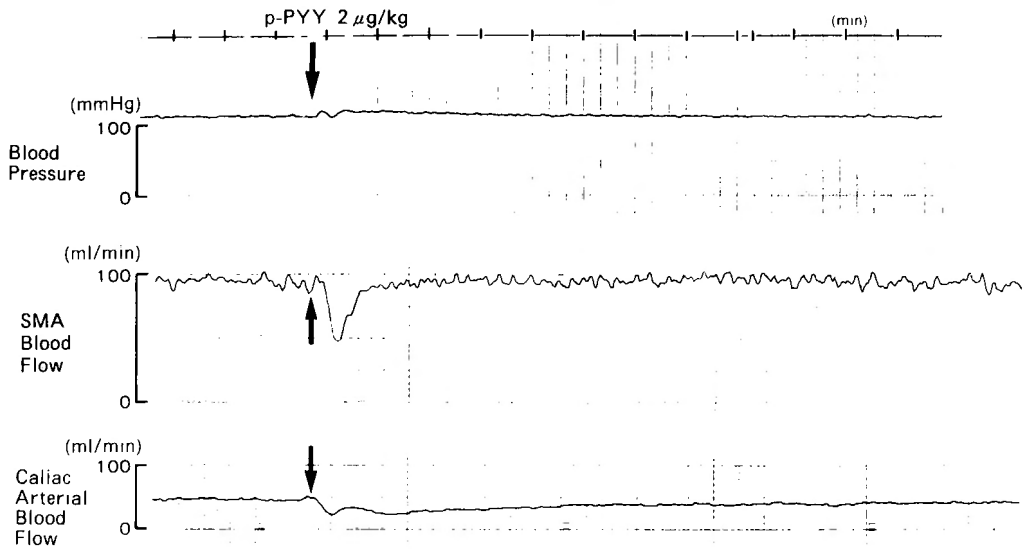

Fig. 5 A typical recording of the effect of PYY (arrow) on mean blood pressure (upper), superior mesenteric arterial (SMA) blood flow (middle) and celiac arterial blood flow (lower) in a dog. These measurements were performed simultaneously.

($p<0.025$, F (4, 12)=4.2) (Fig. 1). These doses of PYY also significantly decreased secretin-stimulated pancreatic secretion volume ($p<0.01$, F (3, 9)=30.3) and pancreatic tissue blood flow ($p<0.05$, F (4, 8)=4.7), respectively in a dose related manner (Fig. 2). The changes in secretion volume with time are shown in Fig. 3. The greater dose of PYY excerted more potent and long-acting inhibition on the pancreatic secretion volume (Fig. 3).

Under secretin plus CCK stimulation, both pancreatic secretion volume and protein output were significantly (volume: $p<0.01$, protein output: $p<0.05$) decreased by 1 μg/kg body wt of PYY, respectively (Fig. 4).

In response to intravenous administration of PYY, blood flows in SMA and CA rapidly decreased and gradually increased to the pre-injection levels (Fig. 5). The response was more persistent in CA than in SMA (Fig. 5). In CA, the decrease appeared to be biphasic, namely a intial rapid decrease with the bottom within about 1 minute after injection and a slow decrease with the broad bottom in about 2 minutes after the injection. Mean blood pressure showed a increase of long duration at the same time (Fig. 5).

Discussion

This study first showed that intravenous administration of PYY causes reduction in blood flows in CA and SMA. However, the duration of the decrease persisted longer in CA than in SMA. Further, the decrease in CA appeared to be biphasic whereas the decrease in SMA had only one bottom. These findings lead us to speculate that PYY may decrease blood flow in CA in two different mechanisms, one of which is the same as in SMA and the other is different. According to Lundberg JM et al., in perfused cat pacreas, NPY which is a structually related peptide of PYY causes persistent increase in perfusion pressure lasting up to 10 minute and a moderate reduction in volume of the spleen[37]. On the other hand, some binding assay suggest that no binding sites distinguish between

PYY and NPY[23,44]. Therefore, the different response appeared in CA blood flow may represent the response of the splenic blood flow.

We have studied the effect of NPY on blood flows in the pancreatic tissue, SMA and the portal vein and exocrine pancreatic secretion in dogs[50]. In this study, NPY decreased SMA blood flow, pancreatic tissue blood flow and exocrine pancreatic secretion in a similar manner as PYY did in the present study. Although it is difficult to compare them directly, the relative potencies of PYY and NPY appeared to be the following. The hemodynamic effect of PYY was approximately three times as potent as NPY. On the other hand, the inhibitory effect of PYY on exocrine pancreatic secretion appeared to be five to ten times as potent as NPY.

Inoue K et al. have studied the effect of natural porcine PYY on the pancreatic tissue blood flow, exocrine pancreatic secretion and blood pressure in dogs and have found that PYY reduces pancreatic tissue blood flow as well as inhibits secretin- or secretin plus CCK-stimulated exocrine pancreatic secretion at doses of 0.1, 0.5 and 1 μg/kg body wt[21]. The dose-response relationships of these effects in the present study is comparable to those in the previous study by Inoue et al., thereby suggesting that the synthetic PYY used in the present study[38] has the identical biological effects of the natural peptide.

In this study, PYY reduced blood flows in CA, SMA and the pancreatic tissue and inhibited pancreatic exocrine function at the same doses. Therefore, the reducing effect on these blood flows could be physiological as well as the inhibiting effect on the exocrine pancreas[40,41].

As to the mechanism of the inhibition on exocrine pancreatic secretion by PYY, Louie DS et al. have shown the absence of an effect of PYY in isolated pancreatic acini or pancreatic lobules in vitro, thereby suggesting that the effect is mediated by indirect mechanisms[33]. Konturek SJ et al. have suggested that the inhibitory effect of PYY on exocrine pancreas is, at least in part, mediated by the adrenergic pathway[29]. On the other hand, sevral reports indicate the relationship between pancreatic blood flow and exocrine function[6,7,8,55]. According to these reports, reduction in blood flow can be a cause of reduction in exocrine pancreatic secretion. Therefore, we may well speculate that the decrease in pancreatic tissue blood flow by PYY is one of the possible mechanisms in which PYY inhibits exocrine pancreatic secretion. However, the mechanism awaits further elucidation.

In conclusion, this study showed that intravenous injection of PYY potently decreased blood flows in CA and SMA and inhibits secretin- and secretin plus CCK-stimulated exocrine pancreatic secretion with reduction in pancreatic tissue blood flow in anesthetized dogs. These observation suggests that PYY may have a physiological role in modulating splanchnic circulation as well as inhibiting sevral digestive functions as a humoral factor which mediates colonic inhibition.

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和文抄録

Peptide YY を介する臓器相関に関する実験的研究
——イヌ腹部臓器血流と膵外分泌に対する作用——

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消化器諸臓器に対する大腸由来の抑制作用は Peptide YY (PYY) を介するものと考えられているが，PYY はまた強力な血管収縮作用を有している．しかし，循環血液中 PYY の腹部血流に対する作用はほとんど知られていない．本研究では腹部循環と膵外分泌に対する PYY 全身投与の効果を検討した．セクレチン刺激下で，PYY の静脈内投与 (0.1, 0.5, 1, 2 μg/kg) は，膵液分泌量，膵組織血流，上腸間膜動脈血流，腹腔動脈血流を用量反応性に有意に低下させ，同時に平均動脈圧を上昇させた．セレクチンとコレシストキニンの同時刺激下では，PYY (1 μg/kg) は膵液分泌量と膵液中蛋白分泌量を有意に減少させた．本研究は，PYY が膵外分泌を抑制する用量で腸管血流と同様に腹腔動脈血流を減少させることを初めて示した．