Oddi sphincter function after canine auto-pancreas transplantation with bladder drainage

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AIM: Several neural and hormonal factors are known to affect motility of sphincter of Oddi (SO). The major roles of SO are to regulate the flow of bile and pancreatic juice into the duodenum and to prevent the reflux of duodenal contents into the biliary and pancreatic duct. After pancreas transplantation, SO function is affected by drugs and some drugs play important roles in the control of SO motility. SO motility is composed of tonic contraction and phasic contraction. Neural factors, hormones and some drugs play important roles in the control of SO motility. The major roles of SO are to regulate the flow of bile and pancreatic juice into the duodenum and to prevent the reflux of duodenal contents into the biliary and pancreatic duct. After transplantation, SO function is affected by drugs and some drugs play important roles in the control of SO motility. SO motility is composed of tonic contraction and phasic contraction. Neural factors, hormones and some drugs play important roles in the control of SO motility.

METHODS: Normal canine SO manometry and pancreas graft SO manometry after pancreas transplantation with bladder drainage were performed in seven dogs respectively before and after cholecystokinin (CCK) administration. Data of SO basal pressure, contraction frequency, amplitude and motility index after transplantation and CCK administration were compared with that in controls and before CCK administration.

RESULTS: SO showed regular contractions with a certain basal pressure in control dogs. After transplantation, the graft SO basal pressure and contraction frequency were higher than that in controls, but the amplitude decreased (P<0.01). There was no great difference in SO motility index. CCK administration could relax normal SO but stimulate graft SO after pancreas transplantation with bladder drainage. After CCK administration, SO basal pressure, frequency and motility index were increased significantly (P<0.05), in comparison with that before administration. The amplitude remained unchanged (P>0.05), in comparison with that before CCK administration.

CONCLUSION: After auto-pancreas transplantation with bladder drainage, SO motility was inhibited. Basal pressure and frequency increased but amplitude decreased. CCK administration after transplantation had an inhibitory effect on SO motility. After transplantation, SO motility was inhibited. Basal pressure and frequency increased but amplitude decreased. CCK administration after transplantation had an inhibitory effect on SO motility.
Pancreas graft SO manometry

The dogs were fasted and anesthetized the same as the control group. After a midline celiotomy with aseptic techniques, the tail of the pancreas was mobilized by division of the veins which drain the distal pancreas into the spleen vein. The head of the pancreas was then mobilized without cutting the pancreaticoduodenal vessels. After the common bile duct at its entry into the duodenum was ligated and divided, the lesser omentum was opened. At least 1 cm of gastroduodenal artery and vein were dissected from the bifurcation. The proximal duodenum was cut 1 cm distal to pylorus and closed. After inferior pancreaticoduodenal vessels were cut out, the distal duodenum was divided at the end of the second part of duodenum. Thus the donor was skeletonized with intact vascular connections. Finally, the gastroduodenal artery was ligated and divided as far as possible from the bifurcation of proper hepatic arteries, and the gastroduodenal vein was removed with a cuff of portal venous wall. The graft was immediately immersed in and flushed with cold Ringer solution while the portal vein wall was repaired. Reconstruction of vascular connections to the autograft was accomplished by an end-to-side anastomosis of the gastroduodenal vein to the right common iliac artery and end-to-end anastomosis of the accompanying artery to the internal iliac artery. After reperfusion, the distal pancreas was resected. Gastrointestinal continuity was restored by the Roux-en-Y technique with cholecystojejunostomy, gastrojejunostomy, and graft-duodenal-host bladder anastomosis. Average graft ischemia time was 30-40 min.

Fluid and antibiotics were given for 5 days. Oral alimentation was started on the second postoperative day. Serum and urine amylase, free blood sugar and insulin were determined on days 1, 3, 5 postoperatively. Five days after operation, the same manometry procedure from the residual bile duct before and after CCK injection was performed as for the control dogs.

Statistical analysis

All values were expressed as mean ±SD. Comparison of values between the two groups was made with analysis of variance and paired t tests. Differences were regarded as significant when P value was less than 0.5.

RESULTS

1. Changes of SO activity before and after transplantation are shown in Table 1.

Table 1 SO activity in control and transplanted dogs

| Basal pressure (mmHg) | Amplitude (mmHg) | Frequency (min⁻¹) | Motility index |
|-----------------------|------------------|-------------------|---------------|
| Control               | 18.5±2.8         | 47.1±5.5          | 9.7±1.5       | 235.6±56.1   |
| Transplant            | 27.8±2.8         | 7.2±1.4           | 13.1±1.9      | 211.3±33.2   |

SO showed regular contractions with a certain basal pressure in control dogs.

After transplantation, the graft SO basal pressure and contraction frequency increased as compared with that in controls, but the amplitude decreased (P<0.01). There was no great difference in SO motility index.

2. Changes of SO activity before and after administration of CCK in normal dogs are shown in Table 2.

Table 2 SO activity before and after CCK administration in normal dogs

| Basal pressure (mmHg) | Amplitude (mmHg) | Frequency (min⁻¹) | Motility index |
|-----------------------|------------------|-------------------|---------------|
| Before CCK            | 18.5±2.8         | 47.1±5.5          | 9.7±1.5       | 235.6±56.1   |
| After CCK             | 10.2±2.2         | 18.7±5.3          | 5.0±1.2       | 49.6±16.9    |

CCK administration could relax SO motility. SO basal pressure, contraction frequency and amplitude decreased significantly after CCK administration in comparison with controls (P<0.01).

3. SO activity of grafts before and after CCK administration is shown in Table 3.

Table 3 SO activity of grafts before and after CCK administration

| Basal pressure (mmHg) | Amplitude (mmHg) | Frequency (min⁻¹) | Motility index |
|-----------------------|------------------|-------------------|---------------|
| Before CCK            | 27.8±2.8         | 7.2±1.4           | 13.1±1.9      | 211.3±33.2   |
| After CCK             | 35.5±5.1         | 9.7±2.1           | 18.9±1.9      | 515.4±42.3   |

CCK administration stimulated graft SO motility. After CCK administration, SO basal pressure, frequency and motility index increased significantly in comparison with those before administration (P<0.05), while the amplitude remained unchanged (P>0.05).

4. After transplantation, there was no great difference in serum amylase, blood sugar and blood insulin as compared with those on day 0 (P>0.05). Urine amylase that reflects graft function increased significantly. These data showed a good pancreas graft function (Table 4).

Table 4 Pancreas graft function after transplantation

| Serum amylase (IU/L) | Urine amylase (IU/L) | Blood sugar (mmol/L) | Blood insulin (IU/L) |
|----------------------|----------------------|----------------------|----------------------|
| Day 0                | Day 1                | Day 3                | Day 5                |
| 22±5                 | 30±11                | 26±7                 | 24±4                 |
| 80±35               | 25 400±12 100        | 45 100±1 780         | 14 900±2 100         |
| 4.5±1.2             | 5.1±0.7              | 3.8±1.3              | 3.6±0.4              |
| 8.5±2.2             | 7.3±3.2              | 7.0±2.4              | 5.5±1.0              |

DISCUSSION

Canine segmental pancreatectomy and pancreas transplantation were often carried out in other studies. In order to investigate the SO motility after transplantation, we excluded the effect of rejection on the graft and also the graft must have intact SO. So, we established a canine auto-pancreaticoduodenal transplantation model. The results of serum and urine amylase, free blood sugar and insulin level after transplantation showed that the endocrine and exocrine functions of the pancreas graft were both good enough for SO manometry. The transplantation model was stable and suitable for SO manometry.

Canine SO plays an important role in controlling the flow of bile and pancreatic juice into the duodenum and acts as a variable resistive to prevent the reflux of duodenal contents[1-4]. SO is a complex neuromuscular structure located at the choledocho-pancreaticoduodenal junction. Canine SO exhibits regular phasic contractions superimposed on a low basal pressure under neurohormonal control. After pancreas transplantation with bladder drainage, the graft was denervated. Little was known about the SO motility after pancreas
transplantation. Several reports suggested that SO dysfunction played an important role in acute recurrent pancreatitis[13-15]. Graft pancreatitis was a serious complication after pancreas transplantation with bladder drainage. The late graft pancreatitis might be related to SO dysfunction caused by graft SO denervation. Our present study on canine SO motility after auto-pancreas transplantation with bladder drainage showed:

1. Canine SO exhibited regular contractions with a certain basal pressure. After transplantation, graft SO basal pressure and contraction frequency increased and amplitude decreased significantly. But there was no great difference in SO motility index.

2. CCK administration could relax normal canine SO, but stimulate graft SO after canine pancreas transplantation with bladder drainage. The denervated graft duodenum lost its normal migrating motor complex (MMC). These data suggested that the tonic contraction of SO remained and created a higher basal pressure than that before transplantation, and phasic contraction decreased significantly. This resulted in the obstruction of pancreatic juice flowing into the graft duodenum. Furthermore, when bladder pressure increased to a certain extent because of urine stasis, the urine would reflux into pancreatic duct and induce acute pancreatitis.

The role of extrinsic nerves in the control of SO motility has not been fully investigated. The SO was richly innervated by cholinergic, adrenergic and peptidergic neurons[8]. Direct neural pathways couple the duodenum with the gallbladder and SO, and the SO with the gallbladder. Several surgical procedures, such as gastrectomy[9], vagotomy[10] and cholecystectomy[11,12] have been known to alter SO motility by disrupting certain aspects of the innervations. Numerous reports described SO motility after transaction or electrical stimulation of extrinsic nerves, such as the vagal and splanchnic nerves[13-16]. Different effects of innervation on SO motility reflect the difference both in species and in experimental designs. Complete denervation using tetrodotoxin increased tonic pressure and amplitude of SO phasic contraction in the cats[10]. Ohkusu reported increased biliary sphincter basal pressure and amplitude after neural isolation of the pancreaticoduodenal region by surgical procedure in conscious dogs[17]. The present study showed that extrinsic innervation to the pancreaticoduodenal region had an inhibitory effect on SO motility. The main role of extrinsic nerves was to regulate phasic contraction and relax SO. Under normal condition, the relaxing effect of extrinsic nerve on canine SO motility was better than the stimulation effect. But the amplitude decreased significantly after transplantation instead of increasing observed in Ohkusu’s study. This is probably because the motility of graft SO was not affected by duodenum MMC. Furthermore, the effect of gastrointestinal hormone on SO motility may be different from that in normal canines because of its anastomosis to system vessels. Further investigations are needed to identify this guess.

CCK is the major physiological hormone regulating tone and motility of biliary system. It normally inhibited biliary sphincter motor activity in human and dogs but stimulated SO under various circumstances, which is known as a paradoxical response[18,19]. It is believed that these SO relaxant responses to CCK were induced via nonadrenergic, noncholinergic inhibitory neurons since cholinergic and adrenergic antagonists could not inhibit these relaxant responses[20]. Our present study showed that CCK could relax canine SO and lower SO basal pressure. But denervated SO after transplantation apparently produced paradoxical response of SO to CCK, which was likely caused by the direct effect of CCK on the smooth muscle of SO. Based on these data, we could consume that the paradoxical response of SO to CCK in SO dysfunctional patients might also be caused by the direct stimulation of CCK to SO smooth muscle because of injury of inhibitory nerves of SO.

Gancio reported that reflux pancreatitis was chemically induced by reflux of urine through SO into pancreatic duct during the voiding phase with high detrusor pressure (over 70 cmH2O)[21]. Others hypothesized that this could be caused by an incompleteness SO or by either pressure exerted on the pancreatic duct due to a large volume bladder or micturition narrowing the duodenocystotomy and obstructing it[22,23]. The current study showed that canine SO lost its normal contraction rhythm, increased basal pressure causing an obstruction of pancreatic juice into graft duodenum. When bladder pressure overrode the basal pressure, SO probably could not prevent the reflux of urine and duodenal contents into pancreatic duct. All these would contribute to graft pancreatitis.

In conclusion, after auto-pancreas transplantation with bladder drainage, canine SO motility was inhibited. Basal pressure and frequency increased but amplitude decreased. CCK administration after transplantation showed an inhibitory effect on canine SO instead of a relaxation effect to normal canine SO. This will increase the resistance of SO to the pancreatic juice flow and induce pancreatic juice stagnation and can not prevent reflux of urine and duodenal contents when the bladder pressure is increased to a certain extent, which may cause graft pancreatitis.

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