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• BRIEF REPORTS •

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

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Abstract

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, graft SO was denervated and graft pancreatitis might have relations to SO motility. The motility of SO after canine pancreas transplantation with bladder drainage was investigated.

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, canine SO motility was inhibited. Basal pressure and frequency increased but amplitude decreased. CCK administration after transplantation had an inhibitory effect on canine SO instead of a relaxation effect observed in 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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INTRODUCTION

The major roles of the sphincter of Oddi (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. 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. SO motility is related to migrating motor complex (MMC) of the duodenum. Graft pancreatitis is one of the factors for graft dysfunction with bladder drainage. Reflux of urine and pancreatic juice can cause graft pancreatitis. After transplantation, the graft was denervated and graft duodenum lost its MMC. Little is known about the function of SO and its effect on the graft function after pancreas transplantation with bladder drainage. The aim of this paper was to study canine SO function after pancreas transplantation with bladder drainage and its effect on the graft.

MATERIALS AND METHODS

Preparation of animal

Fourteen healthy adult mongrel dogs, weighing 13-18 kg were anesthetized with 35 mg/kg intravenous pentobarbital sodium, and maintained under adequate anesthesia with 15 mg/kg intravenous pentobarbital sodium as required. System blood pressure was monitored through a catheter placed into the femoral artery. The femoral vein was cannulated and used for systemic administration of solutions and drugs.

Normal canine SO manometry

After an upper medium laparotomy using aseptic technique, the biliary tree was identified. A small longitudinal incision was made in the common bile duct. A triple lumen catheter was cannulated and tied in the bile duct to avoid any leakage and occlusion of the orifice of the catheters. The triple lumen catheter, measuring 1.7 mm of outer diameter and 0.5 mm of inner diameter, with three holes at 2-mm intervals, was perfused with sterile water at a rate of 0.25 ml/min per channel by means of a low-compliance pneumohydraulic pump, and connected via transducers to a computerized recording system. The catheter was sent into the duodenum. Intraduodenal pressure was taken as zero reference. By 1-mm station pull through technique, the catheter was placed just at the site of SO. After a stable basal recording for at least 2 min was obtained at the level of SO high pressure zone, 20 mg/kg cholecystokinin (CCK) diluted in 5 ml saline was injected intravenously and registration continued for a few more minutes until 2 min of stable recording was obtained during drug infusion. SO basal pressure above duodenal zero, amplitude above basal pressure, and frequency of phasic contractions before and after CCK

injection were calculated as well as the motility (amplitude per frequency).

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 lessen omentum was opened. At least I 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 cholecystojejunal, gastrojejunal and graft-duodenal-host bladder anastomosis. Average graft ischemia time was 30-40 min. The bile duct residual of graft was placed under the skin. Fluid and antibiotics were given for 5 days. Oral alimentation was started on the second postoperative day. Serum and urinary 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 CCKadministration 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

	Day 0	Day 1	Day 3	Day 5
Serum amylase (IU/L)	22±5	30±11	26±7	24±4
Urine amylase (IU/L)	80±38	25 400±12 100	45 100±1 780	14 900±2 100
Blood sugar (mmol/L)	4.5±1.2	5.1±0.7	3.8±1.3	3.6±0.4
Blood insulin (IU/L)	8.5±2.2	7.3±3.2	7.0±2.4	5.5±1.0

DISCUSSION

Canine segmental pancreas auto-transplantation and pancreaticoduodenal allotransplantation were often carried out in other studies. In order to investigate the SO motility after pancreas 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 resister 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[5-7]. 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. Furthemore, 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 innervatd by cholinergic, adrenergic and peptidegic 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 transection 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 tetrodoxtoxin increased tonic pressure and amplitude of SO phasic contraction in the cats[10]. Ohtsuke reported increased biliary sphincter basal pressure and amplitude after neural isolation of the pancreatoduodenal region by surgical procedure in conscious dogs[17]. The present study showed that extrinsic innervation to the pancreatoduodenal 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 Ohtsuke' 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 cholenergic 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 cmH_2O)[21]. Others hypothesized that this could be caused by an incompletent SO or by either pressure exerted on the pancreatic duct due to a large volume bladder or micturition narrowing the duodenocystostomy 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 overrided 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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