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RAPID COMMUNICATION

Ligustrazine alleviates acute renal injury in a rat model of acute necrotizing pancreatitis

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Abstract

AIM: To evaluate the effect of ligustrazine, a traditional Chinese medicine, on renal injury in a rat model of acute necrotizing pancreatitis (ANP).

METHODS: A total of 192 rats were randomly divided into three groups: control (C group), ANP without treatment (P group), and ANP treated with ligustrazine (T group). Each group was further divided into 0.5, 2, 6, 12 h subgroups. All rats were anesthetized with an intraperitoneal injection of sodium pentobarbital. Sodium taurocholate was infused through the pancreatic membrane to induce ANP. T group was infused sodium taurocholate as above, and 0.6% ligustrazine was then administered *via* the femoral vein. Serum urea nitrogen (BUN) and creatinine (Cr) concentrations were measured for the evaluation of renal function. The effects of ligustrazine on the severity of renal injury were assessed by renal function, TXA_2/PGI_2 and histopathological changes. Renal blood flow was determined by the radioactive microsphere technique (RMT).

RESULTS: Compared with control group, the renal blood flow in P group was decreased significantly. Serious renal and pancreatic damages were found in P group, the BUN and Cr levels were elevated significantly, and the ratio of TXA_2 to PGI_2 was increased at 2, 6 and 12 h. Compared with P group, the blood flow of kidney was elevated significantly at 6 and 12 h after induction of ANP, the renal and pancreatic damages were attenuated, and the BUN and Cr levels were decreased significantly, and the ratio of TXA_2 to PGI_2 was decreased at 6 and 12 h in T group.

CONCLUSION: Microcirculatory disorder (MCD) is an important factor for renal injury in ANP. Ligustrazine can ameliorate the condition of MCD and the damage of pancreas and kidney.

INTRODUCTION

Acute pancreatitis complicated by multiple organ dysfunctions is still a life-threatening disease[1,2], although the precise mechanism by which such local inflammation in the pancreas progresses to systemic illness is still unclear. Recently, this systemic inflammatory response syndrome (SIRS) has become a widely accepted disease state[3], which could lead to the failure of distant organ systems, such as the lungs, intestine, stomach and kidneys[4-6].

Acute pancreatitis (AP) is often complicated by renal injury. However, its pathogenesis remains unclear. Recent studies indicate that during the pathogenesis of acute necrotizing pancreatitis (ANP), the change of microcirculation plays an important role in the worsening of pancreatitis[7].

Pharmacologic studies have demonstrated that ligustrazine, an intravenous drug made from traditional Chinese herbs, is able to inhibit release of intracellular calcium and to scavenge oxygen free radicals[8,9]. Ligustrazine has been widely applied in the treatment of vascular diseases in China due to its significant efficacy on cerebral ischemia and reperfusion injury. However, its role and mechanism in treatment of renal injury have not been extensively studied. The effect of ligustrazine on renal injury was observed in this study based on the established model of ANP.

MATERIALS AND METHODS

Animals

One hundred and ninety-two adult Sprague-Dawley rats (250-300 g) were provided by the Laboratory Animal Center of Jiangsu University, China. The animals were kept in rooms at 21 ± 1℃ in a 12 h light/dark cycle for 1 wk to acclimate to the surrounding with free access to water and standard laboratory chow. Prior to experiment, the rats

were fasted overnight with access to water.

Experimental design

The animals were randomly divided into three groups: control (n = 64, C group), ANP without treatment (n = 64, P group), and ANP treated with ligustrazine (n = 64, T group). Each group was further divided into 0.5, 2, 6, 12 h subgroups. All rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mL/kg). Sodium taurocholate (50 g/L, 4 mL/kg, Ward Blen Kinsop CO., UK) was infused through the pancreatic membrane to induce ANP as previously described[10]. After 5-10 min, pancreatic edema and dotted bleeding occurred. T group was infused sodium taurocholate as above, 6 g/L ligustrazine (Seventh Pharmaceutical Factory, Wuxi, China; batch number: 0008241) was then administered *via* the femoral vein (10 mL/kg) as previously described[11,12]. C group received isovolumetric infusion of 9 g/L physiological saline solution using the same method. The abdominal wounds were closed and all the rats were sent back to their cages. Half of the animals in each subgroup were sacrificed at 0.5, 2, 6 and 12 h after infusion for further examination. Left kindeys were removed immediately and fixed in paraformaldehyde solution for 12-24 h and paraffin-embedded for routine histopathologic analysis. The histopathologist was blinded to routine histopathologic analysis. The blood was obtained from eight rats in each group *via* superior mesenteric vein for determination of serum blood urea nitrogen (BUN), creatinine (Cr), TXA_2 and PGI_2. The remaining rats in each group were used for kidney blood flow determination by the radioactive microsphere technique (RMT). The left kidney was also removed and weighed at 0.5, 2, 6 and 12 h after infusion for subsequent radioactive measurement.

Blood flow measurements

At 0.5, 2, 6 and 12 h after the infusion, renal blood perfusion values were determined by RMT as previously described[10]. $^{99}Tc^m$-labeled microspheres (^{99}Mo-$^{99}Tc^m$ generator preparation was provided by Chinese Institute of Nuclear Power) with a specific activity of 74 MBq/Ml were used for measurement of blood flow. The right carotid artery was catheterized with placement of the tip of the tubing in the left ventricle for infusion of $^{99}Tc^m$-labeled microspheres. One milliliter $^{99}Tc^m$ radioactive microspheres (approximately 500 000 microspheres) was injected for 10 s *via* the catheter with its tip in the aortic ventricle of the heart. A reference blood sample was obtained from the femoral artery catheter for 60 s at a constant rate of 1 mL/min with a continuous-withdrawal pump. The animals injected microspheres were killed by intra-arterial injection of 2 mL 100 g/L KCL. The whole left kidney was removed, weighed, cut into small pieces and placed in a γ-counter (GC-1200 Gamma Radioimmunoassay Counter, USTC Chuangxin CO. Ltd., China) to determine the radioactivity (cpm).

The blood flow values were calculated according to the following formula:

$$Q_{org}\ [mL/(min \cdot g)] = \frac{Q_{ref}\ (mL/min) \times N_{org}\ (cpm)}{N_{ref}\ (cpm) \times weighing\ (g)}$$

Where Q_{org} denotes organ blood flow (mL/min.g), Q_{ref} is withdrawal rate of the reference sample (mL/min), N_{org} is the number of microspheres in the organ (count/min) and N_{ref} is the number of microspheres in the reference sample.

Table 1 Grading of histological injury using microscopic injury score

Score	Findings
O	Normal
I	Notable cloudy swelling of tubular epithelial cells
II	Swelling denaturation of renal tubular epithelial cells, interstitial congestion, edema and infiltration of inflammatory cells
III	Diffuse coagulation necrosis in tubular epithelial cells

Detection of serum BUN, Cr, TXA_2 and PGI_2

The blood from the superior mesenteric vein was collected into a tube. The tube was immediately centrifuged at 3500 r/min for 15 min. Collected plasma was stored at -40℃ until use. BUN and Cr levels were assayed using an automatic biochemistry analyzer (CL-7300; SHIMADZU Corporation, Kyoto, Japan) with assay kits. The level of TXA_2 and PGI_2 was detected according to the manufacturer's instructions (Science and Technology Development Center, General Hospital of PLA, Beijing, China).

Histological examination

Renal and pancreas specimens were harvested and fixed in 10 g/L formalin for histological examination. The tissues were dehydrated, embedded in paraffin wax, cut into 5-μm sections, and mounted. After removed from the paraffin, the tissues were stained with hematoxylin and eosin. The severities of renal injury were quantified using a histological scoring system as previously described[13]. Histopathologic analysis of renal specimens was performed and scored as 0-Ⅲ (Table 1). Twenty fields per kidney were examined, a mean of the total score was compared between the groups. The renal sections were also analyzed with a HPIAS-1000 multimedia color analysis system (Huahai Co., Shanghai). Five fields (0.265 mm × 0.2 mm) of each section were read. Average values of neutrophil infiltration were calculated and recorded. All examinations were performed in a blind fashion by an experienced pathologist.

Statistical analysis

All data were analyzed by the SPSS 11.0 software. The results were expressed as mean ± SD except for data on the grading of renal lesions. Differences in grading of renal lesion were determined using the non-parametric Mann-Whitney test. Statistical analysis was performed with post-hoc test. $P < 0.05$ was considered statistically significant.

RESULTS

Renal blood flow

Blood flow in the P group was significantly lower than that in the C group. It began to decrease at 0.5 h and became

Table 2 Renal blood flow in groups C, P and T [mL/(min•g)] (mean ± SD, *n* = 8)

Group	0.5 h	2 h	6 h	12 h
C	7.33 ± 0.35	7.63 ± 0.43	7.46 ± 0.67	7.55 ± 0.67
P	5.67 ± 0.51[b]	6.64 ± 0.68[b]	5.81 ± 0.67[b]	5.16 ± 0.72[b]
T	7.17 ± 0.72	7.22 ± 0.82	7.22 ± 0.73[d]	7.31 ± 1.12[d]

[b]$P < 0.01$ *vs* C group; [d]$P < 0.01$ *vs* P group.

Table 3 Serum BUN level in groups C, P and T (mean ± SD, mmol/L)

Group	0.5 h	2 h	6 h	12 h
C	9.80 ± 1.36	10.31 ± 1.50	10.05 ± 0.87	10.21 ± 1.33
P	11.99 ± 2.08[a]	12.73 ± 1.72[a]	14.71 ± 2.08[b]	15.16 ± 2.73[b]
T	10.12 ± 1.23[c]	10.53 ± 2.25[c]	11.52 ± 2.21[d]	11.71 ± 1.31[d]

[a]$P < 0.05$, [b]$P < 0.01$ *vs* C group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* P group.

Table 4 Serum Cr level in groups C, P and T (mean ± SD, mmol/L)

Group	0.5 h	2 h	6 h	12 h
C	21.12 ± 1.67	21.06 ± 1.58	21.50 ± 1.78	21.62 ± 1.75
P	24.97 ± 3.40[a]	25.36 ± 3.11[b]	30.40 ± 1.93[b]	30.60 ± 2.04[b]
T	22.13 ± 1.57[c]	23.5 ± 2.61[a,c]	23.58 ± 2.61[a,d]	24.73 ± 1.01[b,d]

[a]$P < 0.05$, [b]$P < 0.01$ *vs* C group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* P group.

Table 5 Serum level of TXA_2/PGI_2 in groups C, P and T (mean ± SD)

Group	0.5 h	2 h	6 h	12 h
C	1.18 ± 0.15	1.22 ± 0.11	1.24 ± 0.15	1.23 ± 0.16
P	1.23 ± 0.16	1.50 ± 0.21[b]	1.61 ± 0.19[b]	1.86 ± 0.28[b]
T	1.19 ± 0.14	1.31 ± 0.14	1.31 ± 0.17[a,c]	1.45 ± 0.24[a,d]

[a]$P < 0.05$, [b]$P < 0.01$ *vs* C group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* P group.

Table 6 Renal tissue injury in groups C, P and T

Group	0.5 h				2 h				6 h				12 h			
	0	I	II	III	0	I	II	III	0	I	II	III	0	I	II	III
C	8	0	0	0	8	0	0	0	8	0	0	0	8	0	0	0
P	0	1	3	4[b]	0	0	4	4[b]	0	0	3	5[b]	0	0	0	8[b]
T	4	4	0	0[d]	0	3	5	0[d]	1	2	2	3[d]	0	1	3	4[c]

[b]$P < 0.01$ *vs* C group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* P group.

Table 7 Renal tissue neutrophil infiltration in groups C, P and T (mean ± SD)

Group	0.5 h	2 h	6 h	12 h
C	5.5 ± 1.2	6.5 ± 1.2	6.7 ± 1.3	6.9 ± 1.4
P	13.0 ± 1.6[b]	15.0 ± 1.9[b]	18.0 ± 1.7[b]	21.1 ± 3.0[b]
T	6.9 ± 1.4	10.8 ± 1.4[b,d]	13.0 ± 1.6[b,d]	15.0 ± 2.0[b,d]

[b]$P < 0.01$ *vs* C group; [d]$P < 0.01$ *vs* P group.

the lowest at 12 h. However, the blood flow in the T group was significantly higher than that in the P group at 6 and 12 h, showing no significant difference from the C group (Table 2).

Serum levels of BUN, Cr, TXA_2 and PGI_2

Compared with the control group, the BUN and Cr levels in the P group were elevated significantly ($P < 0.01$ or $P < 0.05$), and the ratio of TXA_2 to PGI_2 was increased at 2, 6 and 12 h ($P < 0.01$). Compared with the P group, the BUN and Cr levels were decreased significantly ($P < 0.01$ or $P < 0.05$), and the ratio of TXA_2 to PGI_2 was decreased at 6 and 12 h in the T group ($P < 0.01$ or $P < 0.05$) (Table 3, Table 4, Table 5).

Pathological examination

After induction of ANP model, the pancreas showed mild edema and congestion. At 0.5 h, typical pathological changes of ANP were found, such as a large number of inflammatory cells, necrosis of the adjacent fat tissues, interstitial edema, parenchyma hemorrhage and necrosis, large amount of ascites. The changes became severer with the prolongation of time. The renal pathological changes were aggravated significantly in the P group. Histopathologic scores were higher in the P group than in the C group throughout the experiment ($P < 0.01$) and lower in the T group than in the P group (Table 6). Under the light microscope, different swelling denaturation and necrosis of renal tubular epithelial cells were observed. Simultaneously, interstitial congestion, edema and infiltration of inflammatory cells were also observed. While in the ligustrazine-treated group, the outward appearance of the kidney was normal. The mean number of neutrophils infiltrated in × 400 field increased from 0.5 h in the T group, while decreased significantly from 2 h in the P group (Table 7).

Correlated analysis

Correlated analysis showed that there was a negative correlation between renal blood flow and serum Cr ($r = -0.931$, $P < 0.01$) and TXA_2/PGI_2 ($r = -0.977$, $P < 0.05$), as well as between renal blood flow and pathologic score($r = -0.948$, $P < 0.05$).

DISCUSSION

Acute renal injury is a major cause of morbidity in ANP. Our experimental study in rats demonstrated that microcirculatory disorder (MCD) of rats resulted in a sequence of events that ultimately caused renal injury. Although the renal injury occurring in ANP has been well described, the underlying mechanism remains unclear. The rat model of renal injury in this study resulted in a dramatic decrease in renal blood flow as evidenced by

RMT and renal histological changes.

Microcirculatory disturbances are important early pathophysiological events in various organs during AP[14-18]. Microcirculatory change is an important factor during the development of ANP. It can damage the pancreas and extrapancreatic vital organs[19,20]. The possible contributory mechanisms involved in the development of this disease include increased vascular permeability, reduced blood flow, leukocyte-endothelia interactions and development of intravascular thrombi[21,22]. The radioactive microsphere technique can efficiently estimate blood flow to various organs in the body. With the availability of different radioactive labeled microspheres, it is possible to measure regional blood flow repeatedly[23]. In our study, at the early stage of ANP, the renal blood flow began to decrease significantly at 0.5, 2, 6 and 12 h after infusion as compared with the C group. The renal injury was possibly due to ANP and the release of inflammatory mediators. A series of changes in the nerve endocrine system led to the redistribution of visceral blood flow, thus producing a sharp decrease of renal blood flow, suggesting that microcirculation disturbances may contribute to renal injury under conditions such as ischemia/reperfusion at the early stage of ANP. Therapeutic agents that improve pancreatic blood flow might be valuable in the treatment of acute pancreatitis[24]. In this study, ligustrazine improved microcirculation and reduced acute renal injury in rats with ANP.

In the present study, the protective effect of ligustrazine against renal injury was investigated in rats with ANP. Scrum levels of BUN and Cr were used as indicators of renal protection. TXA_2 is both a vasoconstrictor and a potent stimulus for platelet aggregation. Its effect is antagonized by prostacylin, which is released from vascular endothelial cells. Prostacylin exerts a variety of effects on the cardiovascular system, including a decrease in blood pressure associated with a decrease in systemic vascular resistance. Feng *et al*[25] demonstrated that TXA_2 may be involved in the pathogenesis of acute pancreatitis at its early stage. The ratio of TXA_2 to PGI_2 was significantly lower after reperfusion than before reperfusion, indicating that the disorder of TXA_2 and PGI_2 might also be involved in the circulation disorders during ANP. Although the precise mechanism remains unknown, they may play a role in the pathobiology of ANP.

The second prominent feature in this experimental model is the development of granulocytosis and accumulation of neutrophils in the microvasculature of renal capillaries. Because neutrophils are known to be required for the development of renal injury in ANP, interventional studies were undertaken to assess whether intravenous administration of ligustrazine would result in decreased neutrophil accumulation in renal tissues. Our results showed that neutrophil accumulation was markedly elevated after induction of pancreatitis, which was significantly reduced by ligustrazine.

Ligustrazine is widely used in traditional Chinese medicine, often in combination with other herbs. It was used traditionally to treat a diversity of ailments, particularly cardiac (heart) and vascular disorders such as atherosclerosis or blood clotting abnormalities. Ligustrazine could intervene in hemorheological events, such as blood flow, erythrocyte deformation, leukocyte adhesion, platelet aggregation and thrombolysis[26]. It was reported that ligustrazine could inhibit pulmonary hypertension by decreasing the mRNA expression of endothelin-1, oxygen free radical level, lipid peroxidation and adjusting TXA_2/PGI_2 imbalance in pulmonary arterioles[27,28].

To investigate the protective effects of ligustrazine against renal injury, the influence of ligustrazine injection on BUN, Cr and TXA_2/PGI_2, as well as changes of morphology of renal tubules, were studied in a rat kidney model during ANP. Ligustrazine improved renal microcirculation, suggesting that the protective effects of ligustrazine against renal injury may be attributable to improving microcirculation and further preventing accumulation of neutrophils.

In conclusion, MCD plays an important role in the development of renal injury. The early use of ligustrazine seems to be effective. This provides further evidence for ligustrazine as a therapeutic strategy against renal injury during ANP.

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COMMENTS

Background

Acute pancreatitis (AP) is often complicated by renal injury. However, its pathogenesis remains unclear. The significant efficacy of ligustrazine on cerebral ischemia and reperfusion injury was confirmed in this study. However, the role and mechanisms of ligustrazine in treatment of renal injury have not been extensively studied.

Research frontiers

To investigate the protective effects of ligustrazine against renal injury, the influence of ligustrazine injection on BUN, Cr, and TXA_2/PGI_2, as well as changes of morphology of renal tubules, were studied in a rat kidney model during ANP.

Innovations and breakthroughs

The effect of ligustrazine on renal injury was observed in this study based on the established model of ANP. The radioactive microsphere technique was used to analyze the blood flow. Although it is not commonly used and has major disadvantages, it can analyze the blood flow in the pancreas and extrapancreatic vital organs simultaneously.

Applications

In the present study, ligustrazine improved renal microcirculation, suggesting that ligustrazine can protect against renal injury by improving microcirculation and further preventing accumulation of neutrophils. The early use of ligustrazine seems to be effective. This provides further evidence for ligustrazine as a therapeutic strategy against renal injury during ANP.

Terminology

Radioactive microsphere technique (RMT): Microspheres containing radioactive substances are infused into the circulatory system to measure perfusion rates in tumors and normal tissues, cerebral blood flow, tissue oxygenation, cardiovascular function, regional vascular resistance, and the effect of various drugs on these parameters. In the present study, $^{99}Tc^{m}$-labeled microspheres were used for measurement of blood flow.

Peer review

This is a very interesting study demonstrating the effects of ligustrzineon on the pathophysiology of acute pancreatitis. However, some limitations and additional data should be provided.

S- Editor Wang GP **L- Editor** Wang XL **E- Editor** Bi L