Effects of transmitters and interleukin-10 on rat hepatic fibrosis induced by CCl₄

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Supported by Natural Science Foundation of Fujian Province, No. C96042

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Abstract

AIM: To study the effects of transmitters ET, AgII, PGI₂, CGRP and GG on experimental rat hepatic fibrosis and the antifibrogenic effects of IL-10.

METHODS: One hundred clean SD rats weighing 140-180 g were randomly divided into 3 groups: control group (N): intraperitoneal injection with saline 2 ml·kg⁻¹ twice a week; the fibrogenesis group (C): intraperitoneal injection with 50 % CCl₄ 2 ml·kg⁻¹ twice a week; IL-10 treated group (E): besides same dosage of CCl₄ given, intraperitoneal injection with IL-10 4 ug·kg⁻¹ 2 ml·kg⁻¹ twice a week, to drink tap water and eat in any time when they needed, animals were breeding in the routine condition (room temperature 22±2 °C, humidity 55±5 %, lighting 12 hrs per day, to drink tap water and eat in any time when they needed, animals was fed by BK company in shanghai.).

RESULTS: The hepatic fibrosis was developed with the increase of injection frequency of CCl₄. The ET, AgII, PGI₂, CGRP and GG levels in serum of group N were 71.84±33.62, 102.2±99.9 ng·L⁻¹, 313.0±101.7 ng·L⁻¹, 61.97±21.4 ng·L⁻¹ and 33.62±14.37 ng·L⁻¹, respectively; the levels of them in serum of group C were 523.30±129.3 ng·L⁻¹, 127.24±50.0 ng·L⁻¹, 648.91±357.29 ng·L⁻¹, 127.15±62.0 ng·L⁻¹ and 85.26±51.83 ng·L⁻¹, respectively; the levels of them in serum of group E were 452.52±99.5 ng·L⁻¹, 90.60±44.7 ng·L⁻¹, 475.57±179.70 ng·L⁻¹, 102.2±29.7 ng·L⁻¹ and 38.05±19.94 ng·L⁻¹, respectively. The histological examination showed that the degrees of the rats liver fibrosis in group E were lower than those in group C.

CONCLUSION: The transmitters ET, AgII, PGI₂, CGRP and GG play a significant role in the rat hepatic fibrosis induced by CCl₄. IL-10 has the antagonistic action on these transmitters and can relieve the degree of the liver fibrosis.

Wang XZ, Zhang LJ, Li D, Huang YH, Chen ZX, Li B. Effects of transmitters and interleukin-10 on rat hepatic fibrosis induced by CCl₄. World J Gastroenterol 2003; 9(3): 539-543

http://www.wjgnet.com/1007-9327/9/539.htm

INTRODUCTION

Hepatic fibrosis is a disease which is characterized by an increase of type I and type III collagens, proteoglycans fibronectin and hyaluronic acid in extracellular matrix (ECM) deposition[1,9]. It is an inevitable phase during the formation of liver cirrhosis, which is an irreversible stage of several liver pathological changes[10-12]. So it is important for how to prevent and cure hepatic fibrosis, i.e. antifibrogenetic treatment. Transmitters play an important role in the portal hypertension which is associated with the fibrosis[13,14]. In our study, the transmitters endothelin (ET), angiotensin II (Ag II), prostacyclin (PGI₂), calcitonin-gene related peptide (CGRP) and glucagon (GG) were selected to explore their effects on hepatic fibrosis induced by CCl₄ and the antifibrogenesis effect of interleukin-10 (IL-10) was explored as well.

MATERIALS AND METHODS

Animals

One hundred clean SD rats weighing 140-180 g were randomly divided into 3 groups. The control group (group N) included 24 rats; the fibrogenesis group (group C) included 40 rats and the IL-10 treated group (group E) included 36 rats, respectively. All the rats were breeding in the routine condition (room temperature 22±2 °C, humidity 55±5 %, lighting 12 hrs per day, to drink tap water and eat in any time when they needed, animal food was provided by BK company in shanghai.).

Establishment of the fibrosis model

Rats in group N were injected intraperitoneally with saline 2 ml·kg⁻¹ twice a week. Rats in group C and group E were injected intraperitoneally with 50 % CCl₄ 2 ml·kg⁻¹ twice a week[15]. From the third week, rats in group E were injected intraperitoneally with IL-10 4 ug·kg⁻¹ (dissolved in saline)[16] 20 minutes before they were injected with CCl₄. All injections were performed in Monday and Thursday, rats’ body weight was recorded before the injection. In the fifth week, 3 rats in group C and 2 rats in group E died, in the seventh week, total 8 rats in group C and 4 rats in group E died, in the ninth week, total 10 rats in group C, 6 rats in group E and 3 rats in group N died. In 5.7-9 weeks, 10 rats of group C and E and 7 rats in the control group were selected randomly to collect their plasma and liver tissue samples.

Assessment of samples

The blood samples were added into the tubes with 30 µl 10 % EDTA and 40 µl trislyol in ice bath, the tubes were centrifuged at 3 000 rpm for 10 minutes at 4 °C, then the plasma was frozen for the assessment. The plasma levels of ET, Ag II, PGI₂, CGRP and GG were assayed by radioimmunoassay (RIA, kits provided by EastAsia Immune-technology Institute, Beijing). Each plasma sample was taken 100 µl into the tube, then 200 µl buffer and 100 µl antiserum were added into each sample, they were agitated and incubated for 24 hour at 4 °C; then 100 µl 125I-marked serum was added, agitated and incubated for 24 hour at 4 °C; also 500 µl precipitation was added, after incubation for 20 min at room temperature, the tubes were centrifuged at 3 500 rpm for 25 min at 4 °C, the upper layer was carefully removed, the cpm account was measured using γ
radioimmunocounter. The blank control and the standard control was measured respectively at the same time. The liver tissue was made of paraffin section with silver staining.

Statistical analysis
All data were expressed as ±, t test was used for comparison between groups.

RESULTS
Plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG
The plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG in group C were higher than those in the control ($P<0.05$). After the intervention of IL-10, the levels of them were decreased, and had no difference with group N ($P>0.05$). Furthermore, their levels were increased with the development of hepatic fibrosis.

Table 1 Plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG in fibrosis and normal rats (ng·L$^{-1}$)

|     | n   | ET  | AgII | 6-K-PGF$_{1α}$ | CGRP | GG  |
|-----|-----|-----|------|----------------|------|-----|
| N   | 21  | 71.84±60.2 | 76.21±33.3 | 313.03±101.71 | 61.97±21.4 | 33.62±14.37 |
| C   | 30  | 523.30±129.3 | 127.24±50.0 | 648.91±357.29 | 127.15±62.0 | 85.26±51.83 |
| E   | 30  | 452.52±99.5 | 90.60±44.7 | 475.57±179.70 | 102.2±29.7 | 38.05±19.94 |

$^*$ <0.05 vs group N, $^{aP}$ <0.05 vs group N.

Figure 1 Plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG in fibrosis and normal rats.

Table 1 and Figure 1 showed that after the treatment of CCl$_4$, the plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG were increased, their levels were significantly higher than those in the normal controls ($P<0.05$). After treated with IL-10, their levels were obviously decreased, and there was no significant difference with those in the normal controls. It was showed that when the effective treatment was applied in the fibrosis rats, the levels of these transmitters showed the descending trend. It suggested that the levels of those transmitters were increased in liver fibrosis and they might play important pathogenic roles during the development of liver fibrosis.

Pathological assay
The histological feature showed that liver of control rats had no appreciable alterations (Figure 3). The degree of liver fibrosis in group C was up-going with the incres of the treatment frequency of CCl$_4$. In the fifth week, few reticular fiber deposited in the perportal tissue space. In the seventh week, the reticular fiber extended with hepatic plate but the full delimitation was not formed, while in the ninth week the integrity fibrous septum was developed in the interlobular septum, sometimes pseudolobular could be seen (Figure 4,5,6). The degrees of inflammation of hepatocytes were decreased evidently in the seventh week after the treatment of IL-10, in the ninth week, the reticular fiber in the interlobular septum was limited remarkably, no pseudolobular could be seen (Figure 7).

Figure 2 Plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG in fibrosis rats.

Table 2 and Figure 2 showed that the levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG were gradually increased and associated with the increase of CCl$_4$-treated frequency, especially in the ninth week ($P<0.05$). It suggested that there was close relation between the levels of the transmitters and the degrees of liver fibrosis.

Table 2 Plasma levels of ET, AgII, 6-K-PGF$_{1α}$, CGRP and GG in fibrosis rats (ng·L$^{-1}$)

| Week | n   | ET  | AgII | 6-K-PGF$_{1α}$ | CGRP | GG  |
|------|-----|-----|------|----------------|------|-----|
| No.5 | 10  | 421.48±52.3 | 105.73±36.3 | 323.15±76.2 | 88.68±23.2 | 54.48±18.9 |
| No.7 | 10  | 489.30±87.7 | 131.42±18.9 | 684.98±214.0 | 118.14±24.3 | 55.77±19.2 |
| No.9 | 10  | 658.6±102.3 | 144.58±72.2 | 1081.6±294.3 | 174.65±87.7 | 141.66±50.8 |

Figure 3 The liver of normal rat (silver staining, ×100).

Figure 4 The liver of the rat in group C (the fifth week, silver staining, ×100).
activation and is independent of the absolute number of ET\textsubscript{A} binding sites if a threshold level of expression is maintained. It has been shown that ET-1 could act as a cell growth promoter via the ET\textsubscript{A} receptor to promote the proliferation of smooth muscle cell. Also, ET-1 is able to elicit MAPK (mitogen-activated protein kinase) activity in human HSCs with time-course and dose-response kinetics similar to those reported in mesangial cells through the ET\textsubscript{A} receptor. Recent studies have shown that the ETR antagonist modifies the development of portal hypertension in carbon tetrachloride treated rats\cite{27,28}. Some studies suggest that ET has two effects on HSC\textsubscript{B}\textsuperscript{29}. ET can inhibit the contraction and collagen synthesis in cells that have more ET\textsubscript{B} receptors than ET\textsubscript{A} receptors; it indicates that ET could restrict the development of liver fibrosis. The difference is linked to the active, contractile HSC phenotype. The cellular sites of action of AgII within the hepatic vasculature are incompletely defined; recent studies have shown that HSCs may be a potential cell target for the AgII actions in the hepatic vasculature\cite{30}. Two different types of AgII receptors have been described. The AT1 receptors are present in most mesenchymal cells and mediate most of the biological effects of AgII. The AT2 receptors are mainly found in fetal cells, but their physiological role is not completely understood. AgII receptors (AT1 subtype) exist in many cells, including the human HSC\textsubscript{B}\textsuperscript{31}, the activated HSCs may be an important target of the AgII in the hepatic vasculature\cite{27}. The binding of AgII to AT1 receptor induces contraction and proliferation\cite{33,34}. AgII causes a marked increase in [Ca\textsuperscript{2+}], and cell contraction, which largely depends on the entrance of Ca\textsuperscript{2+} through L-type Ca\textsuperscript{2+} channels. In recent years, much attention has been focused on the growth-promoting effects of AgII and it has been found that AgII is also a mitogenic factor for activated HSCs through an MAPK-dependent pathway. So we could hypothesis that AgII plays a role in the proliferation of HSCs and in the progression of liver fibrosis. The inflammation may be the initial fibrogenic event. PGI\textsubscript{2} is a potent vasodilator produced by the splanchnic endothelium, would account for much of the observed hyperemia\cite{35}. Cyclooxygenase blockade reverses the splanchnic hyperemia\cite{36}. The mechanism for the increase of portal PGI\textsubscript{2} remains unknown. Some have suggested of increase that blood pressure alone will increase the production of PGI\textsubscript{2}. Theoretically, damage to any type of liver cell membrane can serve as a source of AA metabolites that initiate fibrosis. In the intact liver, the most probable target cells are the nonparenchymal cells such as endothelial cells. The inflammation may be the initial fibrogenic event. The inflammation involving the release of arachidonic acid (AA) from phospholipids by activation of phospholipase A\textsubscript{2} in damaged cell membranes and formation of bioactive AA metabolites (prostaglandins, thromboxane A\textsubscript{2} and leukotrienes) by way of 5\textsuperscript{th} lipoxygenase pathway is one of the earliest biochemical events in hepatic fibrosis. The concentration of 5\textsuperscript{th}-lipoxygenase products (PGG\textsubscript{2} and PGG\textsubscript{2}), the stable metabolite of PGI\textsubscript{2}, represents the plasma level of PGI\textsubscript{2}. The enhanced production of 6-keto-PGF\textsubscript{1\alpha} increases the TGF-β\textsubscript{1} gene expression by way of enhancing degradation of platelets and inflammatory cells which are rich source of the fibrotic cytokine TGF-β\textsubscript{1}\cite{37}. As we all know, TGF-β\textsubscript{1} can promote the synthesis and deposition of ECM and inhibit the degradation of ECM\cite{38,39}. CGRP is a highly potent vasodilator and is widely distributed in nerve fibers with relation to vascular structures\cite{40}. The circulating CGRP is elevated in liver cirrhosis\cite{41,42}, but little information is known about CGRP in these patients\cite{43}. Some authors have reported that CGRP could inhibit the lipid peroxidation on the liver, which antagonists the effects of ET\textsubscript{A}\cite{44}. So it is a protector in the liver fibrosis. Whether the CGRP has effects on the activation of HSC and the synthesis of collagen is not clarified. GG is a stress hormone whose release is stimulated by

**Figure 5** The liver of the rat in group C (the seventh week, silver staining, ×100).

**Figure 6** The liver of the rat in group C (the ninth week, silver staining, ×100).

**Figure 7** The liver of the rat in group E (the ninth week, silver staining, ×100).

**DISCUSSION**

Endothelins are a family of polypeptides consisting of 21-amino acids\cite{17-19}. ET-1 is initially noted for its powerful vasoconstrictor properties\cite{20-24}. It is markedly overexpressed in different cellular elements in cirrhotic liver tissue, and particularly in sinusoidal endothelial cells and hepatic stellate cells (HSCs) in their activated phenotype located in the sinusoids of the regenerating nodules and at the edges of fibrous septa\cite{25}. It plays an important role in the regulation of hepatic vascular tone. They elicit biological responses via the ET\textsubscript{A} and ET\textsubscript{B} receptors. ET-1 induces contraction, proliferation, and collagen synthesis of HSCs in vitro, which may be mediated via the ET\textsubscript{A} receptors\cite{26}. ET-1 is able to increase [Ca\textsuperscript{2+}], in a dose-dependent fashion in HSCs, which results from both intracellular release of Ca\textsuperscript{2+} and extracellular Ca\textsuperscript{2+} influx via a dihydropyridine-insensitive pathway. ET-1-induced contractility of HSCs is maintained through all stages of

![Figure 5](image5.png)

![Figure 6](image6.png)

![Figure 7](image7.png)
catecholamines, cortisol, and growth hormone[45]. GG plays an important role in the formation of portal hypertension[46]. The present studies show that plasma GG levels are elevated in cirrhotic patients with portal hypertension. It is also clearly demonstrated that plasma GG levels is increased with the progression of cirrhosis. In addition, positive correlations has been found between plasma GG levels and Pugh’s score or liver functions. In our study the increase of GG was associated with the failure of GG’s degradation in liver and the hyperexcretion of pancreas. IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of pro-inflammatory cytokines by T helper type 1 cells. It is produced locally in the liver and acts in an autocrine or paracrine way. IL-10 can inhibit a range of macrophage effector functions, including nitric oxide and reactive oxygen intermediate production, MHC class II antigen expression, and eicosanoid synthesis. IL-10 can down-regulate expression of adhesion molecules, ICAM-1 and B7, on human monocytes, and also the nuclear transcription factor, nuclear factor kB. It is able to inhibit chemokine synthesis in T cells, neutrophils, and fibroblasts. Moreover, proinflammatory cytokines synthesis by a wide range of cells, particularly monocytes and macrophages, is profoundly inhibited by IL-10[47]. Previous reports indicated that IL-10 had a role in the remodeling of the extracellular matrix[48]. In vitro, IL-10 down regulates collagen type I while up regulates metalloproteinase gene expression. It also has antifibrogenic properties by down regulating profibrogenic cytokines, like TGF-β1 and TNF-α[49,50]. Nelson et al treated 24 patients with chronic hepatitis C with IL-10, they found that IL-10 normalized serum ALT levels, decreased hepatic inflammation, with chronic hepatitis C with IL-10, they found that IL-10 down regulates collagen type I while up regulates metalloproteinase gene expression. It also has antifibrogenic properties by down regulating profibrogenic cytokines, like TGF-β1 and TNF-α[49,50]. Nelson et al treated 24 patients with chronic hepatitis C with IL-10, they found that IL-10 normalized serum ALT levels, decreased hepatic inflammation, reduced liver fibrosis and was well tolerated in patients[47].

After that treatment of IL-10, all of the transmitters decreased. Therefore, transmitters play important roles in rat hepatic fibrosis induced by CCl4. IL-10 decreases the levels of these transmitters so it has antifibrogenesis effect.

REFERENCES

1 Nie QH, Cheng QY, Xie YM, Zhou YX, Bai XG, Cao YZ. Methodologic research on TIMP-1, TIMP-2 detection as a new diagnostic index for hepatic fibrosis and its significance. World J Gastroenterol 2002; 8: 282-287
2 Nie QH, Cheng QY, Xie YM, Zhou YX, Cao YZ. Inhibiting effect of antisense oligonucleotides phosphothioate on gene expres-
3 Wang HL, Cai WM, Liu RH. Animal experiment and clinical study of effect of gamma-interferon on hepatic fibrosis. World J Gastroenterol 2003; 7: 42-48
4 Sun DL, Sun SQ, Li TZ, Lu XL. Serologic study on extracellular matrix metabolism in patients with viral liver cirrhosis. Shijie Huanren Xiaohua Zazhi 1999; 7: 55-56
5 Chen PS, Zhai WR, Zhang YE, Zhang JS. The effects of hypoxia on hepatic stellate cell generate collagen and matrix metalloproteinase. Shijie Huanren Xiaohua Zazhi 2000; 8: 586-587
6 Liu SR, Gu HD, Li DG, Lu HM. A comparative study of fat stor-
ing cells and hepatocytes in collagen synthesis and collagen gene expression. X in Xiaohua Bingxue Zazhi 1997; 15: 761-762
7 Wu J, Zern MA. Hepatic stellate cells: a target for the treatment of liver fibrosis. J Gastroenterol 2000: 665-672
8 Jiang HQ, Zhang XL. Mechanism of liver fibrosis. Shijie Huanren Xiaohua Zazhi 2000; 8: 687-689
9 Wang YJ, Sun QZ, Quan QZ, Yu JJ. Fat-storing cells and liver fibrosis. Chin J New Gastroenterol 1996; 2: 58-60
10 Missale G, Ferrari C, Fiaccadori F. Cytokine mediators in acute inflammation and chronic course of viral hepatitis. Ann Ital Med Int 1996; 10: 14-19
11 Wang YJ, Sun QZ. The cytology and molecular biology investi-
gate advance in liver fibrosis. X in Xiaohua Bingxue Zazhi 1994; 2: 244-246
12 Wang FS, Wu ZZ. Current situation in studies of gene therapy for liver cirrhosis and liver fibrosis. Shijie Huanren Xiaohua Zazhi 2000; 8: 371-373
13 Zhang LJ, Wang XZ. Liquid substance and portal hypertension. Shijie Huanren Xiaohua Zazhi 2000; 8: 1280-1281
14 Zhang LJ, Wang XZ, Huang YH, Chen ZX. The effects of CGRP, Agli and ET on the liver fibrosis rats. Shijie Huanren Xiaohua Zazhi 2003; 9: 457-459
15 Takahara T, Kojima T, Miyabayashi C, Inoue K, Sasaki H, Muragaki Y, Ooshima A. Collagen production in fat-storing cells after carbon tetrachloride intoxication in the rat. Immunolocalization microscopic observation of type I, type III collagens and prolyl hydroxylase. Lab Invest 1988; 59: 509-521
16 Nelson DR, Lauwers GY, Lau JY, Davis GL. Interleukin 10 treat-
ment reduces fibrosis in patients with chronic hepatitis C: a pilot trial of interferon nonresponders. Gastroenterology 2000; 118: 655-660
17 Zhang Y, Ren XL. Endothelin, nitric oxide and liver cirrhosis. Chin J New Gastroenterol 1996: 4: 40-41
18 Cheng RC, Jin XL. The changes of plasma endothelin level in the patient with discompensation liver cirrhosis. X in Xiaohua Bingxue Zazhi 1995; 3: 110-111
19 Li XR, Wu JS, He ZS, Ma QJ. The contents of endothelin in portal vein and peripheral blood of patients with portal hypertension of liver cirrhosis. Shijie Huanren Xiaohua Zazhi 1998; 6: 827
20 Liu F, Li JX, Li CM, Leng XS. Plasma endothelin in patients with endotoxemia and dynamic comparison between vasoconstrictor and vasodilator in cirrhotic patients. World J Gastroenterol 2003; 7: 126-127
21 Liu BH, Chen HS, Zhou JH, Xiao N. Effects of endotoxin on endothelin receptor in hepatic and intestinal tissues after endotoxemia in rats. World J Gastroenterol 2000; 6: 298-300
22 Zhang ZY, Ren XL, Yao XX. Effects of endothelin and nitric oxide in hemodynamics disturbance of cirrhosis. Shijie Huanren Xiaohua Zazhi 1998; 6: 598-590
23 Chen S, Liu B, Cai XM, Gu CH. Clinical significance of changes of endothelin and nitric oxide levels in peripheral blood of patients with severe hepatitis. Shijie Huanren Xiaohua Zazhi 1999; 7: 122-124
24 Chen YK. The significance of changes of endothelin in patients with severe hepatitis. Shijie Huanren Xiaohua Zazhi 1998; 6: 157
25 Pinzani M, Milani S, De Franco R, Grappone C, Caligiuri A, Gentilini A, Tosi-Guerra C, Maggi M, Faiili P, Ruocco C, Gentilini P. Endothelin-1 is overexpressed in human cirrhotic liver and exerts multiple effects on activated hepatic stellate cells. Gastroenterology 1996; 110: 534-548
26 Reinehr RM, Kubitz R, Peters-Regehr T, Bode JG, Haussinger D. Activation of rat hepatic stellate cells in culture is associated with increased sensitivity to endothelin-1. Hepatology 1998; 28: 1566-1577
27 Sogni P, Moreau R, Gomola A, Gadano A, Calmiail S, Calmus Y, Clozel M, Lebrer D. Beneficial hemodynamic effects of bosentan, a mixed ET, and ET receptor antagonist, in portal hypertensive rats. Hepatology 1998; 28: 655-659
28 Cho JJ, Hoeben B, Herbst H, Jia JD, Ruelh M, Hahn EG, Riecken EO, Schuppan D. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. Gastroenterology 2000; 118: 1169-1176
29 Rockey D. Endothelin in hepatic fibrosis - friend or foe? Hepatology 1996; 23: 1698-1700
30 Schneider AW, Kald F, Klein CP. Effect of Losartan, an Angio-
tensin II receptor antagonist, on portal pressure in cirrhosis. Hepatology 1999; 29: 334-339
31 Wei HS, Lu HM, Li DG, Zhan YT, Wang ZR, Huang X, Cheng JL, Xu QF. The regulatory role of AT1 receptor on activated HSCs in hepatic fibrogenesis: effects of RAS inhibitors on hepatic fibrosis induced by CCL4. World J Gastroenterol 2000; 6: 824-828
32 Wei HS, Li DG, Lu HM, Zhan YT, Wang ZR, Huang X, Zhang J, Cheng JL, Xu QF. Effects of AT1 receptor antagonist, losartan, on rat hepatic fibrosis induced by CCL4. World J Gastroenterol 2000; 6: 540-545
33 Balatier R, Gines P, Nicolas JM, Gorbi MG, Garcia-Ramallo E, Gasull X, Bosch J, Arroyo V, Rodes J. Angiotensin II induces con traction and proliferation of human hepatic stellate cells. Gastro-
Gorbig MN, Gines P, Bataller R, Nicolas JM, Garcia-Ramalli E, Tobias E, Titos E, Rey MJ, Claria J, Arroyo V, Rodes J. Artial norepinephrine peptides antagonizes endothelin-induced calcium increased and cell contraction in culture human hepatic stellate cells. Hepatology 1999; 30: 501-509

Garcia-Pagan JC, Bosch J, Rodes J. The role of vasoactive mediators in portal hypertension. Semin Gastrointest Dis 1995; 6: 140-147

Yue QL, Zhang XK, Zhang XR. The changes of contents of nitric oxide and prostaglandine in gastric mucosa and plasma of rats with portal hypertensive gastropathy. Shijie Huan Xiaohua Zazhi 1999; 7: 547

Geraci JP, Mariano MS. Radiation hepatopathy of the rat: association of the production of prostacyclin with radiation-induced hepatic fibrosis. Radiat Res 1996; 145: 93-97

de Bleser PJ, Niki T, Rogiers V, Geerts A. Transforming growth factor-beta gene expression in normal and fibrotic rat liver. J Hepatol 1997; 26: 886-893

Sun ZQ, Wang YJ. The regulate effect of soluble cytokines on liver fibrosis. Xin Huan Xiaohua Bingxue Zazhi 1994; 2: 163-164

Schiffer S. Expression of the calcitonin gene family in medullary thyroid carcinoma. Peptides 1997; 18: 307-317

Wang X, Wen QS, Huang YX, Zhong YX, Chu YQ, Wang QL. The effects of calcitonin gene-related peptide on portal vein pressure of rats with liver cirrhosis. Shijie Huan Xiaohua Zazhi 1998; 6: 933

Liu CQ, Pu J, Li ZX, Liu XF, Zhao YT. The changes of plasma peptides in the patients with liver cirrhosis. Shijie Huan Xiaohua Zazhi 1999; 7: 1089

Henriksen JH, Schifter S, Moller S, Bendtsen F. Increased circulating calcitonin in cirrhosis. Relation to severity of disease and calcitonin gene-related peptide. Metabolism 2000; 49: 47-52

Moller S, Bendtsen F, Schifter S, Henriksen JH. Relation of calcitonin gene-related peptide to systemic vasodilatation and central hypovolemia in cirrhosis. Scand J Gastroenterol 1996; 31: 929-933

Johnson TJ, Quigley EM, Adrian TE, Jin G, Rikkers L. Glucagon, stress, and portal hypertension. Plasma glucagon levels and portal hypertension in relation to anesthesia and surgical stress. Dig Dis Sci 1995; 40: 1816-1823

Greco AV, Crucitti F, Ghirlanda G, Manna R, Altomonte L, Rebulli AG, Bertoli A. Insulin and glucagon concentrations in portal and peripheral veins in patients with hepatic cirrhosis. Diabetologia 1979; 17: 23-28

Kovalovich K, DeAngelis RA, Li W, Furth EE, Ciliberto G, Taub R. Increased toxin-induced liver injury and fibrosis in interleukin-6-deficient mice. Hepatology 2000; 31: 149-159

Thompson K, Maltby J, Fallowfield J, McAlay M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. Hepatology 1998; 28: 1597-1606

Louis H, Laethem JL, Wu W, Quentinmont E, Degraef C, Van Den Berg K, Domals A, Goldman M, Moine OL, Geerts A, Deviere J. Interleukin-10 controls neutrophilic infiltration, hepatocyte proliferation, and liver fibrosis induced by carbon tetrachloride in mice. Hepatology 1998; 28: 1607-1615

Edited by Xu XQ