Molecular mechanisms of therapeutic effects of Saiko-keishi-to on spontaneous chronic pancreatitis in the WBN/Kob rat

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Abstract

Saiko-keishi-to (TJ-10) has been clinically used as an oral therapeutic drug for chronic pancreatitis. In this review, we present our data on molecular action mechanisms of TJ-10 on spontaneous chronic pancreatitis in the WBN/Kob rats. Anti-inflammatory effects of TJ-10 were suggested by the suppression of the gene expressions of pancreatitis-associated protein (PAP), cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 by reverse transcription-polymerase chain reaction (RT-PCR) analysis. Anti-fibrotic effects were confirmed by the observations on the amelioration of pancreatic fibrosis assessed with AZAN staining and the analysis of expressions of fibrosis-related factors such as transforming growth factor (TGF)-β, α-smooth muscle actin, type III collagen and fibronectin. Anti-apoptotic effect was examined with the TUNEL method and the analysis of apoptosis-related factors such as Fas and Fas ligand. Anti-oxidant effect was suggested by the findings of TJ-10-induced enhancement of the expression of superoxide dismutase and the suppression of the expression of inducible nitric oxide synthase. These results suggest that TJ-10 is effective for chronic pancreatitis by the major four action mechanisms: anti-inflammatory, anti-fibrotic, anti-apoptotic, and anti-oxidant effects.

Key words Saiko-keishi-to (Chai-Hu-Gui-Zhi-Tang, 柴胡桂枝湯), chronic pancreatitis, pancreatitis-associated protein, apoptosis, pancreatic fibrosis, cytokine.

Background

Clinical definition of chronic pancreatitis is a disease of the pancreas with permanent alteration of the anatomical organ structure and/or with functional damage to the pancreas due to progressive inflammation.[1] Pathologically, chronic pancreatitis is characterized by inflammatory change, fibrosis, and acinar destruction.[1] A specific serum marker of pancreatic fibrosis is not available.[2] There are only a few oral therapeutic drugs such as camostat mesilate.[3]

Saiko-keishi-to (Chai-Hu-Gui-Zhi-Tang in Chinese, TJ-10 by Tsumura & Co.) has been used for chronic pancreatitis in Japan. However, action mechanisms of TJ-10 on pancreatitis is yet to be elucidated. It is difficult to examine serial changes of the pancreas histologically in humans. In this review, we present our experimental results on the effects of TJ-10 on rat spontaneous chronic pancreatitis.

Clinical use of TJ-10 for chronic pancreatitis

There are several reports on the clinical effect of TJ-10 on chronic pancreatitis in terms of abdominal and/or back pain, serum amylase and exocrine pancreatic function.[4,5] Nakata *et al.*[4] reported that the effective rate of Kampo medicines was 39% in 62 cases of chronic pancreatitis. They used 52 kinds of Kampo formulas, and TJ-10 was most prescribed, followed by Saiko-sokan-to (Chai-Hu-Shu-Gan-Tang), Ennen-hange-to (Yan-Nian-Ban-Xia-Tang), Anchu-san-ka-bukuryo (An-Zhong-San-Jia-Hu-Ling), and Rikkunshi-to (Liu-Jun-Zi-Tang). Since camostat mesilate is the only oral agent in the treatment of chronic pancreatitis, it would be of great importance to investigate action mechanisms of traditional herbal medicines.

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Spontaneous chronic pancreatitis in the WBN/Kob rat

The WBN/Kob rat is a novel *in vivo* model for chronic pancreatitis.[6] It does not need any specific drugs or stress. Chronic pancreatitis develops in the WBN/Kob rats spontaneously around at 24 weeks of age when fed an ordinary diet. However, chronic pancreatitis appears at 12 weeks when fed a special breeding diet MB-3, which is a protein-rich, fat-rich pellet diet.[7] In addition, normal Wistar rats do not develop chronic pancreatitis when fed the MB-3 diet. Pancreatitis occurs only in male WBN/Kob rats. Histopathologically, there are typical features of chronic pancreatitis such as inflammatory cell infiltration, acinar destruction, fibrosis, and ductular proliferation. Pancreatic fibrosis improves after the peak at 16 weeks, and there is acinar regeneration at 20 weeks.[8] Pathogenesis of chronic pancreatitis in this model includes pancreatic juice stasis, pancreatic ischemia, and estrogen deficiency.[7] Recently, there is a molecular approach for a disease-causing gene.[9]

We analyzed the gene expressions of various cytokines,[10,11] chemokines,[12] and pancreatitis-associated proteins[8,13] in the pancreatic tissues of the WBN/Kob rats at every 4 weeks by reverse transcription-polymerase chain reaction (RT-PCR). The expression of tumor necrosis factor (TNF) -α precedes the onset of pancreatitis, showing its peak at 8 weeks.[10] The expression of pancreatitis-associated protein (PAP) mRNA was detected also at 8 weeks.[8] Then, at 12 weeks, PAP[8] and several other factors such as interleukin (IL)-6,[10] IL-8,[11] transforming growth factor (TGF)-β,[10] p8,[13] reached their peaks in gene expression. Furthermore, interferon (IFN)-γ[10] and insulin-like growth factor (IGF)-I[14] showed their peaks at 16 weeks and 24 weeks, respectively. Thus, we showed a cytokine network in the pancreas of WBN/Kob rats. These factors are possibly involved in the onset and progression of spontaneous chronic pancreatitis in this model, interacting with each other like a cascade.

Action mechanisms of TJ-10

TJ-10 consists of 9 medicinal herbs (Table I). As expected from their actions, TJ-10 has been used for the treatment of peptic ulcer, chronic pancreatitis, subacute phase of acute infections. We focused on the effects of TJ-10 on chronic pancreatitis.

TJ-10 was mixed in the MB-3 diet at 3.4% concentration, which is 10 times higher than that for human use. TJ-10 was administered from 4 weeks old continuously until 24 weeks old. Six rats were sacrificed by exsanguinations via heart puncture under anesthesia with diethyl ether at every 4 weeks. After macroscopic observation, pancreata were fixed in 4% paraformaldehyde at 4℃ overnight and stained with hematoxylin and eosin. Histological alteration of the pancreas was scored according to the grade of interstitial edema, inflammatory cell infiltration, hemorrhage, hyperplasia of the ductular epithelia, acinar degeneration, and fibrosis as follows: 0: 0%; 1: < 25%; 2: 25-50%; and 3: >50% of the total area of the specimen.

1) Pathological findings

Macroscopically, there was hemorrhage and edema

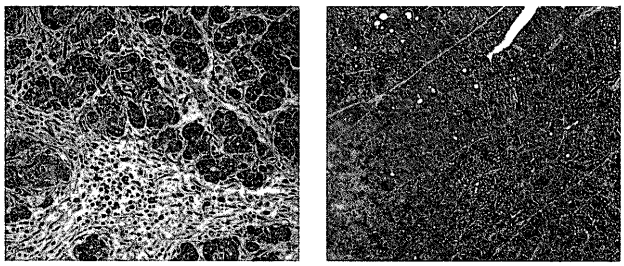
Table I Constituents of TJ-10 and their pharmaceutical actions

Herb	Japanese name	Weight in gram	pharmaceutical action
Bupleuri Radix	Saiko	5	anti-inflammation, anti-stress, antacid
Pinelliae Tuber	Hange	4	anti-stress, anti-ulcer
Glycyrrhizae Radix	Kanzo	2	stimulation of secretin secretion, antacid
Ginseng Radix	Ninjin	2	improvement of microcirculation, free radical scavenger
Scutellariae Radix	Ogon	2	anti-inflammatory, increase in prostaglandin E_1
Cinnamomi Cortex	Keihi	2	vasodilatation, amylase activity inhibition, anti-oxidant
Paeoniae Radix	Shakuyaku	2	analgesic, vasodilatation, antacid
Zizyphi Fructus	Taiso	2	anti-stress, anti-ulcer
Zingiberis Rhizoma	Shokyo	1	analgesic, increase in gastric motility , antacid

TJ-10 (normal human dose: 7.5 g/day) contains 4.5g of dried extracts of herbal constituents mixed in the proportions as shown in the above Table.

A B

Fig. 1. Macroscopic findings of the pancreas from untreated WBN/Kob rat (Fig.1A) and from TJ-10-treated WBN/Kob rat (Fig. 1B) at 12 weeks of age.



A B

Fig.2. Histopathological findings of the pancreas from untreated WBN/Kob rat (Fig.2A) and from TJ-10-treated WBN/Kob rat (Fig.2B) at 12 weeks of age. Original magnification X100.

Table II Effect of TJ-10 on the pancreatic histopathology of the WBN/Kob rats

Age (weeks)	interstitial edema	inflammatory change	hemorrhage	acinar degeneration	fibrosis	ductal hyperplasia
TJ-10 (-)						
4 (n=6)	0	0	0	0	0	0
8 (n=6)	0	0	0	0	0	0
12 (n=6)	1.50±0.22	2.50±0.22	1.50±0.22	1.67±0.33	0.83±0.48	0.83±0.48
16 (n=6)	1.33±0.21	2.17±0.31	1.33±0.21	2.50±0.22	2.50±0.22	1.83±0.40
20 (n=6)	1.33±0.52	1.67±0.33	1.17±0.17	2.17±0.17	1.50±0.34	1.17±0.17
24 (n=3)	1.33±0.58	1.33±0.58	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00
TJ-10 (+)						
8 (n=6)	0	0	0	0	0	0
12 (n=6)	0*	0*	0*	0*	0*	0*
16 (n=6)	0.83±0.17**	0.67±0.21*	0.50±0.22*	0.83±0.40*	0.67±0.33*	0.50±0.22*
20 (n=6)	1.17±0.17#	1.67±0.21#	0.67±0.21**	1.83±0.31*#	1.33±0.21#	1.08±0.20#
24 (n=5)	1.00±0.00	1.20±0.20	0.20±0.20	1.00±0.00	0.80±0.20	0.80±0.20

*$p < 0.001$, **$p < 0.05$ vs. untreated group; #$p < 0.05$ vs. untreated group at 12 weeks; ##$p < 0.01$ vs. untreated group at 16 weeks. TJ-10 (-): untreated group; TJ-10 (+): TJ-10-treated group. Data represent the mean ± S.E.M. of histological scores. Student's *t* test.

in the pancreas from untreated WBN/Kob rat (Fig.1A), whereas macroscopic findings of the pancreas from TJ-10-treated WBN/Kob rat were normal (Fig. 1B). Histopathologically, chronic pancreatitis developed in the pancreas from untreated WBN/Kob rat (Fig.2A), whereas the pancreas of TJ-10-treated WBN/Kob rats was normal (Fig.2B). Even in TJ-10-treated WBN/Kob rats, there were pathological findings of chronic pancreatitis at 16, 20, and 24 weeks, but inflammatory changes and fibrosis were significantly decreased in these time points, compared to those at the pancreas of WBN/Kob rats at 12 weeks (Table II).

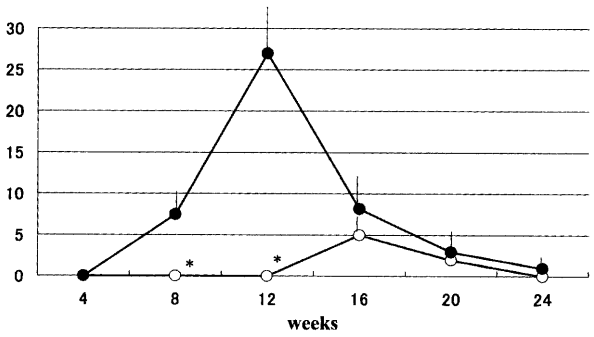


Fig.3. Effect of TJ-10 on the expression of pancreatitis-associated protein (PAP) mRNA in the pancreas of WBN/Kob rats (semi-quantitative RT-PCR analysis). Closed circles: untreated control; open circles: TJ-10-treated. Mean + S.E.M., n=6. *p<0.05 vs. untreated control.

2) Effects of TJ-10 on the expressions of pancreatitis-associated proteins and cytokines

TJ-10 suppressed the peak expression of TNF- at 8 weeks, PAP (Fig. 3) and IL-6 at 12 weeks. On the other hand, anti-inflammatory cytokine such as IL-10 was not expressed in the pancreas of WBN/Kob rats at 12 weeks, and TJ-10 did not induce IL-10. Thus, it is suggested that TJ-10 shows its anti-inflammatory effects by suppressing inflammatory cytokines and related proteins.

Table III Effect of TJ-10 on the pancreatic fibrosis of the WBN/Kob rats

	Fibrotic rate (%) of the pancreas		Staining rate (%) of -SMA		Staining rate (%) of type III collagen	
Age (weeks)	TJ-10 (-)	TJ-10 (+)	TJ-10 (-)	TJ-10 (+)	TJ-10 (-)	TJ-10 (+)
8	2.90±0.13	2.53±0.45	0.25±0.03	0.27±0.07	0.54±0.20	0.53±0.04
12	15.60±2.12	2.46±0.32*	2.37±0.14	0.56±0.17*	2.31±0.72	0.72±0.07*
16	30.40±2.18	5.43±0.82*	6.65±0.39	1.63±0.47*	7.15±1.15	1.53±0.27*
20	21.72±1.80	20.56±1.28#	3.19±0.95	2.57±0.41#	4.50±0.36	3.85±0.87#
24	12.75±1.15	11.24±1.48	1.83±0.03	2.02±0.42	2.80±0.96	2.53±0.18

*$p < 0.001$ vs. untreated group; #$p < 0.001$ vs. untreated group at 16 weeks. TJ-10 (-): untreated group, n=6; TJ-10 (+): TJ-10-treated group, n=6. Data represent the mean ± S.E.M. Student's t test.

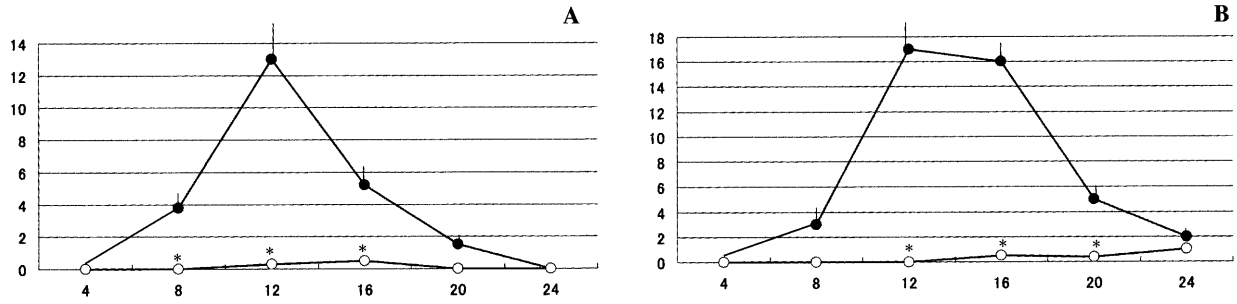


Fig. 4. Effect of TJ-10 on the mRNA expression of TGF-β (4A) and fibronectin (4B) in the pancreas of WBN/Kob rats (semi-quantitative RT-PCR analysis). Mean + S.E.M., n=6. *p <0.05 vs. untreated control.

3) Anti-fibrotic effect of TJ-10

Sho-saiko-to (Xiao-Chai-Hu-Tang in Chinese, TJ-9 by Tsumura & Co.) is reported to suppress "hepatic" fibrosis.[15,16] TJ-10, which is a combination of TJ-9 and Keishi-to (Gui-Zhi-Tang, TJ-45), is expected to show a similar anti-fibrotic effect. However, there has been no report on the effect of TJ-10 on "pancreatic" fibrosis. We showed an anti-fibrotic effect of TJ-10 using the WBN/Kob rats.[17] In untreated WBN/Kob rats, pancreatic fibrosis appeared at 12 weeks, and peaked at 16 weeks, whereas in TJ-10-treated WBN/Kob rats, there was no fibrosis at 12 weeks, and fibrosis peaked at 20 weeks. The peak scores of TJ-10-treated group were significantly lower than those of untreated group. Furthermore, we found significant decrease in the pancreatic fibrosis rate (assessed by AZAN stain and an image analyzer), the expressions of type III collagen, α-smooth muscle actin (Table III), TGF-β, and fibronectin in TJ-10-treated group (Figure 4). Thus, we showed, for the first time, the anti-fibrotic effect of TJ-10 on chronic pancreatitis.

4) Anti-apoptotic effect of TJ-10

Body weight and pancreatic wet weight of WBN/Kob rats were significantly lower than those of normal Wistar rats.[18] It is feasible that acinar cell apoptosis is deeply involved in the process of pancreatic atrophy due to perpetual inflammation and fibrosis. We showed that acinar cell apoptosis peaked at 12 and 20 weeks. TJ-10 ameliorated the decrease in body weight and pancreatic wet weight.[17] At a cellular level, TJ-10 inhibited acinar cell apoptosis assessed by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) method and by RT-PCR analysis on the gene expressions of Fas and Fas ligand.

5) Anti-oxidant effect of TJ-10

TJ-10 enhanced the gene expression of manganese

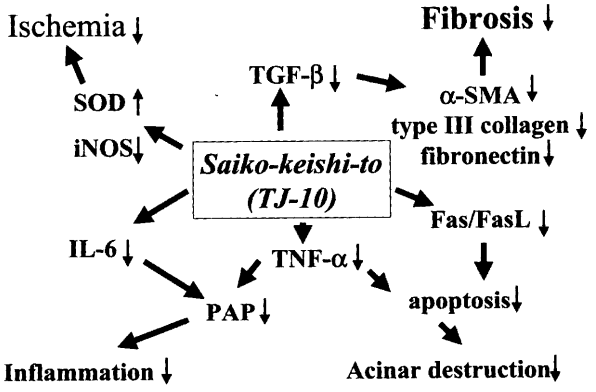


Fig. 5. Possible action mechanisms of TJ-10 on chronic pancreatitis.

Table IV Effect of various herbal medicines on the pancreatic histopathology of the WBN/Kob rats

Drugs	Age (weeks)	inflammatory change	hemorrhage	acinar degeneration	fibrosis	ductal hyperplasia
untreated	12 (n=4)	1.67±0.33	1.17±0.17	1.67±0.33	0.83±0.48	0.83±0.48
	20 (n=4)	2.67±0.34	1.00±0.00	2.67±0.34	2.67±0.34	1.67±0.33
TJ-10	12 (n=4)	0*	0*	0*	0*	0*
	20 (n=4)	1.67±0.33*	0.67±0.33	2.00±0.41	1.17±0.17*	1.00±0.00*
TJ-14	12 (n=4)	0.75±0.25*	0.50±0.29*	0.25±0.25*	0.25±0.25	0*
	20 (n=4)	2.50±0.29	1.25±0.25	2.50±0.29	2.50±0.29	1.50±0.29
TJ-24	12 (n=4)	1.25±0.25	1.00±0.00	0.88±0.32	0.88±0.32	0.75±0.25
	20 (n=4)	2.50±0.29	1.00±0.00	2.25±0.48	2.25±0.48	1.50±0.29
TJ-43	12 (n=4)	0.50±0.50*	0.63±0.48*	0.38±0.38*	0.25±0.25	0.25±0.25
	20 (n=4)	2.50±0.29	1.00±0.00	2.50±0.29	2.50±0.29	1.50±0.29
TJ-102	12 (n=4)	1.00±0.00*	0.75±0.15*	0.50±0.29*	0.50±0.29	0.50±0.29
	20 (n=4)	2.50±0.29	1.00±0.00	2.50±0.29	2.50±0.29	1.50±0.29
TJ-107	12 (n=4)	1.13±0.13*	0.88±0.13*	0.50±0.29*	0.50±0.29	0.50±0.29
	20 (n=4)	2.38±0.24	1.00±0.00	2.25±0.25	2.13±0.32	1.74±0.48
camostat	12 (n=4)	0.38±0.29*	0.33±0.29*	0.33±0.29*	0*	0*
mesilate	20 (n=4)	1.50±0.29*	1.00±0.00	1.50±0.29*	1.50±0.29*	1.00±0.00*

Data represent the mean ± S.E.M. *$p < 0.05$ vs. untreated group. The Mann-Whitney U test.
TJ-10: Saiko-keishi-to, TJ-14: Hange-shashin-to, TJ-24: Kami-shoyo-san, TJ-43: Rikkunshi-to, TJ-102: Touki-to, TJ-107: Gosha-jinki-gan.

superoxide dismutase (MnSOD) in the pancreas of the WBN/Kob rats, which indicates the improvement of pancreatic ischemia. Thus, the action mechanisms of TJ-10 on chronic pancreatitis could be schematically summarized in Figure 5. We have shown anti-inflammatory, anti-fibrotic, anti-apoptotic, and anti-ischemic actions and related mediators in this review.

Comparison of TJ-10 with other herbal medicines

We compared the efficacy of TJ-10 with other herbal medicines which had been clinically used for chronic pancreatitis. TJ-10 was administered as either a prophylactic (from 4 to 12 weeks) or a therapeutic (from 12 to 20 weeks) purpose. The pancreas was removed either at 12 weeks or at 20 weeks, and pathological and molecular analyses were done.

In the analysis on prophylactic effects of herbal medicines at 12 weeks, there was no evidence of pancreatitis in the TJ-10 group, and pathological findings of chronic pancreatitis were significantly decreased in Hange-shashin-to (Ban-Xia-Xie-Xin-Tang in Chinese, TJ-14 by Tsumura & Co.), Rikkunshi-to (Liu-Jun-Zi-Tang , TJ-43), and Touki-to (Dang-Gui-Tang, TJ-102). Kami-shoyo-san (Jia-Wei-Xiao-Yao-San, TJ-24) tended to show milder pancreatitis (Table IV). As for PAP

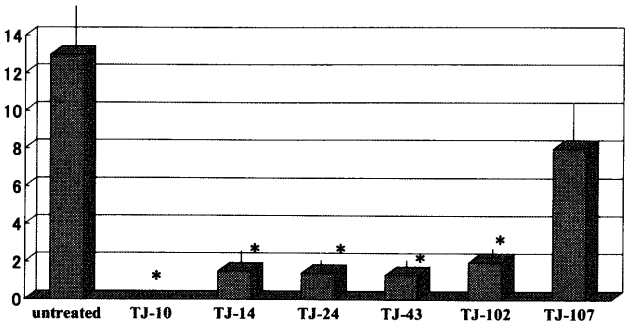


Fig.6. Effects of various herbal medicines on the expression of pancreatitis-associated protein (PAP) mRNA in the pancreas of the WBN/Kob rats at 12 weeks. Mean + S.E.M., n=4. *p <0.05 vs. untreated control.

mRNA expression, TJ-10 completely suppressed PAP mRNA expression at 12 weeks, and PAP mRNA expression was significantly decreased in the WBN/Kob rats treated with other herbal medicines except for Gosha-jinki-gan (Niu-Che-Shen-Qi-Wan, TJ-107), compared to the untreated group (Fig.6). In the analysis on therapeutic effects of herbal medicines at 20 weeks, there was pathological improvement only in TJ-10 group. PAP mRNA expression was significantly suppressed in all the groups of herbal medicines tested (data not shown). Thus, TJ-10 showed the strongest therapeutic effect on this chronic pancreatitis model among the herbal medicines in this study. In addition, from these results, it is speculated that other herbal medicines, which have been

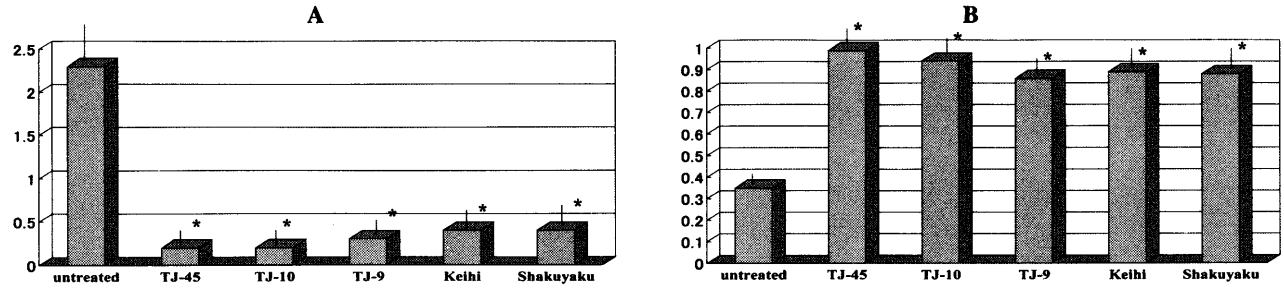


Fig.7. Effects of TJ-10, TJ-9, TJ-45 and their components on the gene expressions of PAP (Fig.7A) and MnSOD (Fig.7B) in arginine-treated AR4-2J cells. Mean + S.E.M., n=6. *p <0.05 vs. untreated control.

clinically used, have anti-pancreatitic effects.[19]

TJ-10 as a combination of TJ-9 and TJ-45

Since TJ-10 is a combination of TJ-9 and TJ-45, anti-pancreatitic effect of TJ-10 was speculated to derive from an anti-inflammatory action of TJ-9, which action mechanisms have been extensively studied in liver diseases. However, to our surprise, TJ-45 showed almost the same therapeutic effects as TJ-10 on chronic pancreatitis in the WBN/Kob rats, whereas TJ-9 did not prevent the onset of pancreatitis.[20]

We analyzed the expressions of PAP mRNA and MnSOD mRNA in the pancreas of WBN/Kob rats treated with TJ-9, TJ-10 or TJ-45. PAP mRNA was significantly suppressed in all the 3 groups, compared to untreated control at 12 and 16 weeks, whereas MnSOD mRNA tended to increase at 16 weeks in each group. Furthermore, we tested the effects of herbal medicinal components on arginine-induced pancreatic acinar cell injury in rat pancreatic AR4-2J cells *in vitro*.[20] We selected *Cinnamomi Cortex* (Keihi) and *Paeoniae Radix* (Shakuyaku) because only these two components were included in TJ-45 and TJ-10, and not in TJ-9. We added herbal medicines and the 2 components into the culture media of the AR4-2J cells which were injured by L-arginine (5 mg/ml).[21] Total RNA was extracted from the cells at 6 hrs after the addition of the herbal medicines. All the herbal medicines and the 2 components significantly suppressed PAP mRNA expression (Fig.7A) and enhanced MnSOD mRNA expression, compared to untreated controls (Fig. 7B). Furthermore, inducible nitric oxide synthase (iNOS) mRNA is induced in AR4-2J cells when injured by arginine, but such an increase was significantly suppressed by TJ-45 and TJ-9 (data not shown). Among other herbs of TJ-10, *Bupleuri Radix* (Saiko) and *Scutellariae Radix* (Ogon), next to *Cinnamomi Cortex* and *Paeoniae Radix*, and among other herbal components, paeoniflorin of *Paeoniae Radix*, cinnamaldehyde of *Cinnamomi Cortex* and glycirrhizin of *Glycyrrhizae Radix* (Kanzo) suppressed PAP and iNOS mRNA expressions. *Bupleuri Radix, Scutellariae Radix, Zingiberis Rhizoma* (Shokyo), *Ginseng Radix* (Ninjin), *Zizyphi Fructus* (Taiso), *Pinelliae Tuber* (Hange), *Glycyrrhizae Radix,* and ginsenoside of *Ginseng Radix* enhanced MnSOD mRNA expression (data not shown). These results suggested the usefulness of TJ-10 as a free radical scavenger. Herbal medicines such as Orengedoku-to (Huang-Lian-Jie-Du-Tang) and its components such as *Coptidis Rhizoma* (Oren) and *Scutellariae Radix* are reported to inhibit nitric oxide production in macrophages induced by inflammatory stimuli.[21]

Conclusions

We showed our experimental results on the action mechanisms of TJ-10 in chronic pancreatitis. From the viewpoints that pathophysiology of chronic pancreatitis consists of inflammation, fibrosis, apoptosis, and pancreatic ischemia, the efficacy of TJ-10 on all the above items indicates that our results provide some basic evidence when TJ-10 is used as an oral drug for chronic pancreatitis.

和文抄録

柴胡桂枝湯（TJ-10）は慢性膵炎の経口治療薬として臨床的に使用されてきた。本総説ではWBN/Kobラットにおける自然発症慢性膵炎に対するTJ-10の治療効果の分子機構について我々の実験結果を中心に述べた。RT-PCR解析によるpancreatitis-associated protein（PAP）やサイトカイン（TNF-α, IL-6など）の発現抑制から

TJ-10の抗炎症作用が示唆された。アザン染色からみた膵線維化改善やTGF-β，α平滑筋アクチン，III型コラーゲン，ファイブロネクチンなどの線維化関連因子の発現抑制によりTJ-10の抗線維化作用を確認した。TUNEL法やFas, Fasリガンドなどのアポトーシス関連因子の発現抑制より膵腺房細胞に対するTJ-10の抗アポトーシス作用が示唆された。最後にSODの発現増加とiNOS発現抑制によりTJ-10の抗酸化作用を確認した。以上より，TJ-10は抗炎症・抗線維化・抗アポトーシス・抗酸化の4つの作用機序により慢性膵炎に有効であると考えられた。

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