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BRIEF ARTICLES

Effect of 5-FU on modulation of disarrangement of immune-associated cytokines in experimental acute pancreatitis

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Abstract

AIM: To investigate the effects of 5-Fluorouracil (5-FU) on modulation of pro-inflammatory and anti-inflammatory cytokines in acute pancreatitis and the mechanism of it in the treatment of acute pancreatitis.

METHODS: Male Sprague Dawley rats were assigned to 3 Groups: Group A, sham operated rats as controls (n = 7); Group B, acute pancreatitis induced by ductal injection with 5% sodium cholate at a volume of 1.0 mL/kg without any other treatment; Group C, after the pancreatitis was induced as in Group B, the rats were injected intravenously with 5-FU 40 mg/kg. The animals in Groups B and C were killed at 2, 6 and 24 h after operation (n = 7), and blood samples were taken for measurement of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) (by bioassay), and interleukin-10 (IL-10), transforming growth factor-β (TGF-β) (by ELISA). The wet weight of pancreatic tissue, serum amylase levels and white blood cells were also measured.

RESULTS: Four rats in Group B and one in Group C died after pancreatitis was induced. Both pro-inflammatory cytokines (TNF-α, IL-1, IL-6) at the 2 and 6 h period and the anti-inflammatory cytokines (IL-10, TGF-β) at 24 h increased significantly (P < 0.05) in rats of Group B. After treatment with 5-FU, TNF-α, IL-1, and IL-6 in serum of rats of Group C were inhibited at 2 and 6 h after operation (P < 0.05), and IL-10, TGF-β were inhibited at 24 h compared to Group B (P < 0.05). Obvious improvements in the severity of the acute pancreatitis, including the amylase levels, wet weight of pancreatic tissue and neutrophil counts, were also observed after treatment with 5-FU.

CONCLUSION: 5-FU is an anti-metabolic and immunosuppressive agent which can minimize the abnormal immune cytokine response and relieve the pathophysiological disorders associated with experimental acute pancreatitis.

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Key words: Pancreatitis; Cytokines; Systemic inflammatory response syndrome; 5-Fluorouracil

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INTRODUCTION

5-Fluorouracil (5-FU) has been used in the treatment of acute pancreatitis both experimentally and clinically since 1970[1-3]. Several animal experiments of pancreatitis treated with 5-FU have shown very promising results, especially for a decrease in amylase and trypsin levels and improvement of survival rates[1,2]. It has been reported that prolongation of pancreatic allograft survival and protection from pancreatitis in dog pancreas allografts occur after pretreatment with 5-FU[4]. A prospective controlled clinical study was carried out in 1983, which showed that treatment with 5-FU was of some benefit in the modulation of clinical pancreatitis[5]. Clinical studies conducted in Russia documented that both the mortality and the length of hospital stay were reduced after treatment with 5-FU[6-8]. In China, administration of 5-FU

has been considered as an adjuvant therapy of acute pancreatitis. More than one thousand patients with acute pancreatitis have received the treatment of 5-FU each year in China, with many reports showing some beneficial results[9-12]. While there are many studies focusing on clinical observation of 5-FU treatment, research involving the mechanisms is sparse, but many investigators felt that the effect of 5-FU treatment for pancreatitis was derived from inhibiting the activities of pancreatic enzymes[1-3,5,9,10]. Recently, it has been increasingly clear that disarrangement of the immune system during acute pancreatitis is the determining factor in the pathophysiological process[13-19]. Considering that abnormal inflammation-associated cytokines (pro- and anti-inflammatory cytokines) present a primary index of disarrangement of immune function during acute pancreatitis[20-24], we designed this animal experiment to investigate the inhibiting effect of 5-FU on the inflammatory cytokines (TNF-α, IL-1, IL-6) and anti-inflammatory cytokines (IL-10, TGF-β) in acute pancreatitis and the relationship between the level of cytokines in serum and degree of acute pancreatitis.

MATERIALS AND METHODS

Materials

Sodium cholate was purchased from Sigma. Rat TGF-β and IL-10 EIA kits were purchased from R & D Co., USA. Reagents and instruments for measurement of TNF-α, IL-1, IL-6 were supplied by the Immunology Department, Medical Center, Sichuan University. Sprague Dawley (SD) rats were purchased from the Experimental Animal Center, Sichuan University, China.

Animals and pancreatitis model

SD rats (male, 10-12 wk-old, weighing 200-250 g) were fasted but allowed to drink water freely for 16 h before the experiment. They were allocated randomly into three Groups: Group A (n = 7), sham operation, with the same laparotomy under general anesthesia as Group B and sham intubation of the cholo-pancreatic duct but without any drug injection. These rats were killed 2 h later. In Group B, the acute pancreatitis Group, SD rats were injected with 5% sodium cholate into the cholo-pancreatic duct at a volume of 1.0 mL/kg using a midline laparotomy under general anesthesia and strict aseptic conditions to establish acute pancreatitis; Group C, acute pancreatitis with treatment of 5-FU. After pancreatitis was induced as in Group B, the rats were injected intravenously 40 min later with 5-FU 40 mg/kg. (This dosage is equal to 10-15 mg/kg in humans based on body surface). All the animals in Groups B and C were resuscitated post-operatively with 0.9% sodium chloride, subcutaneously at 6 mL/kg per hour. The surviving animals in Groups B and C were killed at 2, 6 and 24 h after operation (n = 7). Blood samples were taken for measurement of TNF-α, IL-1, IL-6, IL-10, and TGF-β. The wet weight of pancreatic tissue (the index of pancreatic edema), serum amylase levels and the total and differential count of leukocytes, were also measured and recorded.

All the measurements of cytokines were done in the Department of Immunology, Medical Center, Sichuan University. IL-1, IL-6 and TNF-α were measured by bioassay according to Lederer, Kimura and Heo's methods[25-27]. IL-10 and TGF-β1 were measured by EIA according to the manufacturer's instructions. Amylase and white blood cells levels were tested by the Clinical Laboratory, Medical Center, Sichuan University.

Statistical analysis

We used the analysis of variance for continuous variables to detect variation among Groups with the same time (version 9.0 SAS Institute, Inc, Cary, NC). Statistical significance was regarded as $P < 0.05$. All reported P values are 2 sided. Continuous variables were described as mean ± SD unless stated.

RESULTS

There were 4 deaths in Group B at the 4, 6, 8, 15 h time points after pancreatitis was induced, and one rat died in Group C at 12 h.

In Group A, TNF-α, IL-1, IL-6, IL-10, and TGF-β in the serum of rats were detected as basic concentrations because of tissue injury resulting from sham operation. After acute pancreatitis was induced in Group B, the concentrations of pre-inflammatory cytokines such as TNF-α, IL-1 and IL-6 in the serum of rats increased rapidly. At the 2, 6, and 24 h periods, TNF-α, IL-1, IL-6 in Group B and Group C were significantly higher than that of Group A ($P < 0.05$). After pancreatitis was treated with 5-FU, the concentrations of IL-1 and IL-6 in serum of rats in Group C were significantly lower than those of Group B at 2, 6 h periods after operation ($P < 0.05$). At 6 h after operation the concentration of TNF-α in serum of Group C was also lower than that of Group B ($P < 0.05$). But at the time point 24 h, TNF-α, IL-1, IL-6 in Groups B and C still maintained a higher level and there was no significant difference between these two Group (Table 1). We presume that this is due to 5-FU being quickly catabolised in the body so that its regulating action disappeared swiftly and was not maintained up to 24 h. Serum IL-10 and TGF-β were significant higher in Group B and Group C than in Group A at the 24 h period ($P < 0.05$). At 24 h after operation, compared to Group B, the concentrations of IL-10 and TGF-β in serum in rats of Group C were decreased significantly ($P < 0.05$) (Table 2). When we collected the samples of pancreas after rats were sacrificed, we found that samples of pancreas in Group C were more obviously swollen and congested than those of Groups A and C. Since some doctors have investigated histopathological change of pancreas in detail in similar animal experiments with 5-FU, here we only chose the wet weight of pancreas (index of pancreatic edema) and serum amylase as indexes of severity of acute pancreatitis. In the control Group, the weight of pancreatic tissue was 0.5 ± 0.09 g. At 2, 6, 24 h

Table 1 Change of level of pro-inflammatory cytokines in serum

Group	IL-1 (ng/mL)	IL-6 (IU/mL)	TNF (IU/mL)
A	0.28 ± 0.06	34.5 ± 6.40	11.82 ± 1.87
B (2 h)	1.02 ± 0.12[1]	98.83 ± 12.43[1]	43.67 ± 5.72[1]
(6 h)	1.13 ± 0.17[1]	101.0 ± 15.07[1]	48.67 ± 5.32[1]
(24 h)	1.15 ± 0.13[1]	127.17 ± 13.91[1]	55.33 ± 12.79[1]
C (2 h)	0.80 ± 0.07[1,2]	76.33 ± 7.42[1,2]	35.33 ± 4.50[1]
(6 h)	0.70 ± 0.06[1,2]	74.33 ± 11.02[1,2]	31.17 ± 4.54[1,2]
(24 h)	1.02 ± 0.18[1]	112.67 ± 20.06[1]	42.33 ± 11.64[1]

A: Sham operation Group without acute pancreatitis and drug injection; B: Acute pancreatitis Group; C: Acute pancreatitis with 5-FU group. 2 h, 6 h, 24 h: 2 h, 6 h, 24 h after operation. [1]Compared to sham operation Group (Group A), $P < 0.05$; [2]Compared to pancreatitis Group (Group B), $P < 0.05$.

Table 2 Change of level of anti-inflammatory cytokines in serum

Group	IL-10 (pg/mL)	TGFβ (pg/mL)
A	22.05 ± 14.87	66.40 ± 13.20
B (2 h)	36.52 ± 9.76	64.58 ± 10.56
(6 h)	37.75 ± 6.54	72.87 ± 18.34
(24 h)	68.13 ± 19.90[1]	103.77 ± 28.95[1]
C (2 h)	28.82 ± 6.63	61.15 ± 30.31
(6 h)	45.5 ± 4.72[1]	80.27 ± 19.83
(24 h)	24.0 ± 7.86[2]	68.52 ± 11.51[2]

[1]Compared to sham operation Group (Group A), $P < 0.05$; [2]Compared to pancreatitis Group (Group B), $P < 0.05$.

after acute pancreatitis being induced, the wet weights of pancreatic tissue in Group B were 1.63 ± 0.54 g, 1.85 ± 0.25 g and 1.53 ± 0.13 g, respectively; but at 2, 6, 24 h after treatment with 5-FU in Group C, the wet weights of pancreatic tissue were 0.87 ± 0.22 g, 0.58 ± 0.24 g and 0.88 ± 0.13 g, respectively. There was a significant difference between the acute pancreatitis Group (Group B) and the treatment with 5-FU Group (Group C) at all time periods ($P < 0.05$). In the control Group, the concentration of serum amylase was 374.2 ± 92.84 U/L. At 24 h after operation, the concentration of serum amylase was 1817.25 ± 459.35 U/L, but after treatment with 5-FU the concentration was 797.4 ± 225.9 U/L at the same time period. The concentration of serum amylase in the acute pancreatitis Group (Group B) was higher than that in the treatment with 5-FU Group (Group C), and it reached statistical significance ($P < 0.05$). In the control Group, leukocyte count in the peripheral blood of the rats was (6.59 ± 2.59) × 10^9/L. At 24 h after experiment, the leukocyte counts in the Groups A and B were (6.93 ± 0.67) × 10^9/L and (6.1 ± 1.44) × 10^9/L respectively and there was no significant difference between the two Groups. Percentage of neutrophils in rats in Group A was 0.35% ± 0.09%. In Group B, the percentage of neutrophils was increased significantly at each time period. After treatment of 5-FU, the percentage of neutrophils in Group C decreased compared to Group B, but it did not reach statistical significance until after the 2 h period (Table 3).

Table 3 Change of index of severity of acute pancreatitis

Group	Amylase (U/L)	W.Weight of P (g)	W.B.C (× 10^9/L)[2]	Neutrophils (%)
A	374.20 ± 92.84	0.51 ± 0.90	6.69 ± 2.59	0.35 ± 0.09
B (2 h)	371.25 ± 86.28	1.63 ± 0.54[1]	7.59 ± 2.25	0.74 ± 0.38[1]
(6 h)	508.83 ± 344.82	1.85 ± 0.25[1]	9.46 ± 2.16	0.75 ± 0.08[1]
(24 h)	1817.25 ± 459.35[1]	1.30 ± 0.13[1]	6.93 ± 0.67	0.62 ± 0.11[1]
C (2 h)	352.2 ± 118.15	0.87 ± 0.22[2]	7.90 ± 2.33	0.48 ± 0.09[2]
(6 h)	434.4 ± 138.35	0.68 ± 0.24[2]	10.72 ± 1.45	0.69 ± 0.06
(24 h)	794.40 ± 225.99[1,2]	0.88 ± 0.13[1,2]	6.10 ± 1.44	0.53 ± 0.10

W.Weight of P: wet weight of pancreatic tissue. [1]Compared to sham operation Group (Group A), $P < 0.05$; [2]Compared to pancreatitis Group (Group B), $P < 0.05$.

DISCUSSION

More and more studies have been reported to support the theory that the severity of acute pancreatitis largely depends on the degree of secondary disarrangement of inflammatory mediators[13-16]. Damage caused by trypsin at the initial stage of acute pancreatitis is an event that triggers the systemic inflammatory response syndrome (SIRS)[28]. The pathological process of SIRS results in the clinical manifestation and damage to other distant organs in acute pancreatitis[29,30]. If SIRS persists and anti-inflammatory cytokines are not adequate to suppress this response, SIRS may lead to clinical sepsis and the multiple organ dysfunction syndrome, which could account for one of the main causes of death in severe pancreatitis[31,32]. Along with the production and release of large amounts of pro-inflammatory cytokines in acute pancreatitis, anti-inflammatory cytokines (IL-10, TGF-β, IL-4, IL-13) and other immunosuppressive factors (PGE2, glucocorticosteroids) start to be synthesized and released. This process could be helpful to restrain SIRS and restore the balance between the inflammatory and anti-inflammatory responses. However, when the anti-inflammatory cytokines and other immunosuppressive factors became predominant in severe acute pancreatitis, these mediators will inhibit the immunity against pathogens, especially inhibiting the cellular immune function, and this will result in the so-called compensatory anti-inflammatory response syndrome (CARS), a secondary immunological deficiency syndrome[33-36]. CARS seems to be related to the systemic infection and pancreatic abscess which develop during severe acute pancreatitis[37-39]. In the present experiment, after pancreatitis was induced in animals in Group B, pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, increased promptly, and 24 h later, the anti-inflammatory cytokines IL-10 and TGF-β increased sequentially. These results indicate that there is a pro-inflammatory process (SIRS) followed by an anti-inflammatory process in acute pancreatitis. It is thus suggested that the strategy for acute pancreatitis should not only include modulation of SIRS, but also prevention of CARS.

With this knowledge, the mechanism of treatment of

acute pancreatitis with 5-FU should be evaluated further. Previously, it was thought that inhibition of exocrine secretion of the pancreas was a fundamental mechanism of treatment of acute pancreatitis with 5-FU[1,2,9]. 5-FU traditionally is classified as an anti-metabolic agent. 5-FU is a derivant of pyrimidine, and interferes with the synthesis of DNA and RNA both in normal cells and tumor cells. 5-FU also inhibits the synthesis of protein. Essentially, 5-FU can serve as a proteinase inhibitor and exert general action throughout the whole process of acute pancreatitis. 5-FU decreases the synthesis and secretion of pancreatic enzymes. Thus, it can alleviate the damage to pancreatic tissues by auto-digestion at the initial stage. This function has been confirmed previously[1-4]. Results from the present experiment provide evidence that 5-FU can reduce inflammation-associated cytokines. We also presume that 5-FU inhibits proteinases produced by leukocytes, which is thought a powerful factor in development of MODS. In this study, after the treatment of acute pancreatitis with 5-FU, the activity of inflammation-related cytokines was inhibited. Meanwhile, the level of serum amylase and the weight of pancreatic tissue, factors that reflect the severity of pancreatic injury and pathological lesions, were improved significantly. This indicated that 5-FU could improve the severity of acute pancreatitis by means of modulation of disarrangement of inflammation.

We cannot recommend that 5-FU could be a definite therapy for acute pancreatitis based only on the results of this experiment. We know that there is much difference between animal experiments and clinical practice with regard to results of medical research. Deterioration of acute pancreatitis is never due to simple inflammatory processes, many factors may be involved including secondary infection, derangement of blood circulation, even genetic predisposition so that clinical effects of 5-FU on acute pancreatitis need to be validated by large scale, prospective controlled studies. But we do think that 5-FU may be a candidate for treatment of SIRS based on results of this experiment. After the immunopathogenesis of sepsis following surgical disease was elucidated, many biological products were introduced for use against the pre-inflammatory cytokines[40-43] and the prevention of SIRS, such as anti-endotoxin antibodies[44], anti-TNF-α antibodies[45,46], IL-1 receptor antagonists[47-49] and monoclonal anti-interleukin 8 antibody[50]. None of these interventions have been shown to improve the prognosis of sepsis, possibly because many patients were already in a state in which anti-inflammatory responses dominated[51,52]. Because inflammation plays an important role in the defense against pathogenic microbes and reparation of injured tissue, there is a possibility of infection becoming lethal by excessive anti-inflammatory therapy. In our study, elevated TGF-β and IL-10 levels in an animal model of acute pancreatitis predicted the potential tendency of immunodepression. We think that the decrease of both pro-inflammatory cytokines in addition to the decrease of anti-inflammatory cytokines after treatment with 5-FU may offer a rational strategy for treatment of SIRS. As observed above, 5-FU has multiple actions and biphasic regulation for the disarrangement of immunity in acute pancreatitis. Compared with the effect of single inflammatory cytokine blockers, treatment with 5-FU for SIRS and CARS in surgical disease may be the more effective method. Moreover, immunoregulation with 5-FU displayed in this experiment opens a new possible pathway towards the search for therapy of surgical systemic inflammatory response syndrome.

COMMENTS

Background

5-Fluorouracil (5-FU) has been used in the treatment of acute pancreatitis both experimentally and clinically since 1970, but the mechanisms of the therapeutical effect of 5-FU are not clear, and it has been considered an adjuvant therapy of acute pancreatitis. Recently, it has been increasingly clear that disarrangement of the immune system during acute pancreatitis is the determining factor in the pathophysiologic process. Abnormal inflammation-associated cytokines (pro- and anti-inflammatory cytokines) present a primary index of disarrangement of immune function during acute pancreatitis and lead to sepsis. Sepsis revealed as self-destructive inflammatory reaction remains a puzzle worldwide with respect to its pathological mechanism and corresponding preventive and therapeutic strategies for the clinicians.

Research frontiers

The hotspots of sepsis therapy research have focused on the modification of the inflammatory factors existing in sepsis, ever since the basis of sepsis injuries were revealed as self-destructive inflammatory reactions. Although with some frustrations, research is still focused on the immune regulation.

Innovations and breakthroughs

The authors designed an acute pancreatitis animal model to investigate the inhibiting effect of 5-FU on the inflammatory cytokines (TNF-α, IL-1, IL-6) and anti-inflammatory cytokines (IL-10, TGF-β) in acute pancreatitis and the relationship between the level of cytokines in serum and degree of acute pancreatitis. The experiments obtained encouraging results that the 5-FU, as an immunosuppressive agent, could be effective because of its regulation of immunity. Previously it was thought that inhibition of exocrine secretion of pancreas was a fundamental mechanism of treatment of acute pancreatitis with 5-FU. This trial reveals the immunoregulatory effect of 5-FU in the therapy of acute pancreatitis. The majority of research in the last 20 years on sepsis focused on the blocking agents of inflammatory factors, which failed in clinical trials. According to their trial, 5-FU has multiple actions and biphasic regulation for disarrangement of immunity in acute pancreatitis. Compared with the effects of single inflammatory cytokine blockers, treatment with 5-FU for SIRS and CARS in surgical disease may be the more effective method.

Applications

This trial reveals the potential of 5-FU treatment against acute pancreatitis and sepsis in the clinic. 5-FU is cheaper and safer as a typical immunosuppressive agent, and has been a familiar therapy compared to new medicines.

Terminology

5-FU is one of the first pyrimidine antagonists to be synthesized as an antimetabolite; 5-FU *in vivo* is transformed enzymatically into 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which covalently binds and inhibits thymidylate synthase (TS) and interferes with the synthesis of nucleic acids and prevents the cell from making DNA. Another bio-transformed form of 5-FU, 5-fluorouridine-5'-triphosphate (FUTP), also incorporates itself into RNA and disrupts biological activity of RNA and protein. Systemic inflammatory response syndrome (SIRS) is the self-destructive, severe systemically inflammatory reaction of the body responding to invasion of pathogen, trauma or ischemia.

Peer review

This is an innovative study in which authors analyze the regulative effect of 5-FU on inflammatory reaction in rats. The results are encouraging and suggest that 5-FU is a potential therapeutic substance that could be used in acute pancreatitis, and sepsis caused by other etiological factor.

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