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Review Article

Research progress of ulinastatin in the treatment of liver diseases

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Abstract: Ulinastatin (UTI) is a trypsin inhibitor observed in urine. UTI can treat some diseases by inhibiting the broad-spectrum hydrolysis activity of various enzymes and other pharmacological effects. UTI can widely treat pancreatitis, systemic multiple organ dysfunction syndrome, circulatory failure, and toxic shock clinically. The liver is a major metabolic organ of the human body. Various biological metabolic reactions require the liver's participation. When various physical and chemical factors drive the body, it will damage the liver to varying degrees. As a clinically effective drug, UTI is also known to treat some liver diseases. This article mainly describes UTI's research progress in treating septic liver injury, hepatitis, liver fibrosis, autoimmune liver disease with liver failure, and liver ischemia-reperfusion injury.

Keywords: Ulinastatin, septic liver injury, hepatitis, hepatic fibrosis, an autoimmune liver disease with liver failure, hepatic ischemia-reperfusion injury

Introduction

Ulinastatin (UTI) is a type of hydrolase protein inhibitor obtained by extracting from human urine. UTI includes 143 amino acid molecules with a relative molecular mass of about 67 kda. UTI is the main protein binding inhibitor of various trypsin, chymotrypsin, and various pancreatic proteases [1]. UTI can inhibit the production and release of inflammatory factors through mediating inflammatory pathways [2], anti-apoptosis [3], regulation of multiple enzyme activities, regulation of blood coagulation [4], and control of immune regulation [5]. UTI can prevent and control various diseases such as acute and chronic pancreatitis, cerebral edema, acute respiratory distress, acute circulatory failure, sepsis, and systemic inflammatory response syndrome [6].

The liver is an endocrine organ with powerful detoxification, metabolism, immunity, and other vital functions [7]. The way of biotransformation of different substances in the liver is different. Urinary and bile are water-soluble substances [8]. In comparison, fat-soluble substances are not difficult to accumulate in the body and affect cell metabolism, which must be inactivated by a series of enzyme systems in the liver or excreted after being converted into water-soluble substances [9]. UTI can prevent and control septic liver injury [10], hepatic ischemia-reperfusion injury [11], hepatitis [12], hepatic fibrosis, autoimmune liver disease with liver failure, and other liver system diseases [13].

Pharmacological effects of ulinastatin

Reduce the production and release of inflammatory factors

When the body tissue is injured, infected, and ischemia-reperfusion injury, many inflammatory response factors may enter the body and release them. When the inflammatory factors expand to a certain degree, it will directly cause the body's systemic inflammatory response syndrome, multiple organ dysfunction response syndrome, and acute sepsis [14]. Through studying the UTI mechanism on the treatment of the LPS induced sepsis model, Cao, et al. found that under the action of UTI, the protein expression of TLR4 and NF-κB proteins

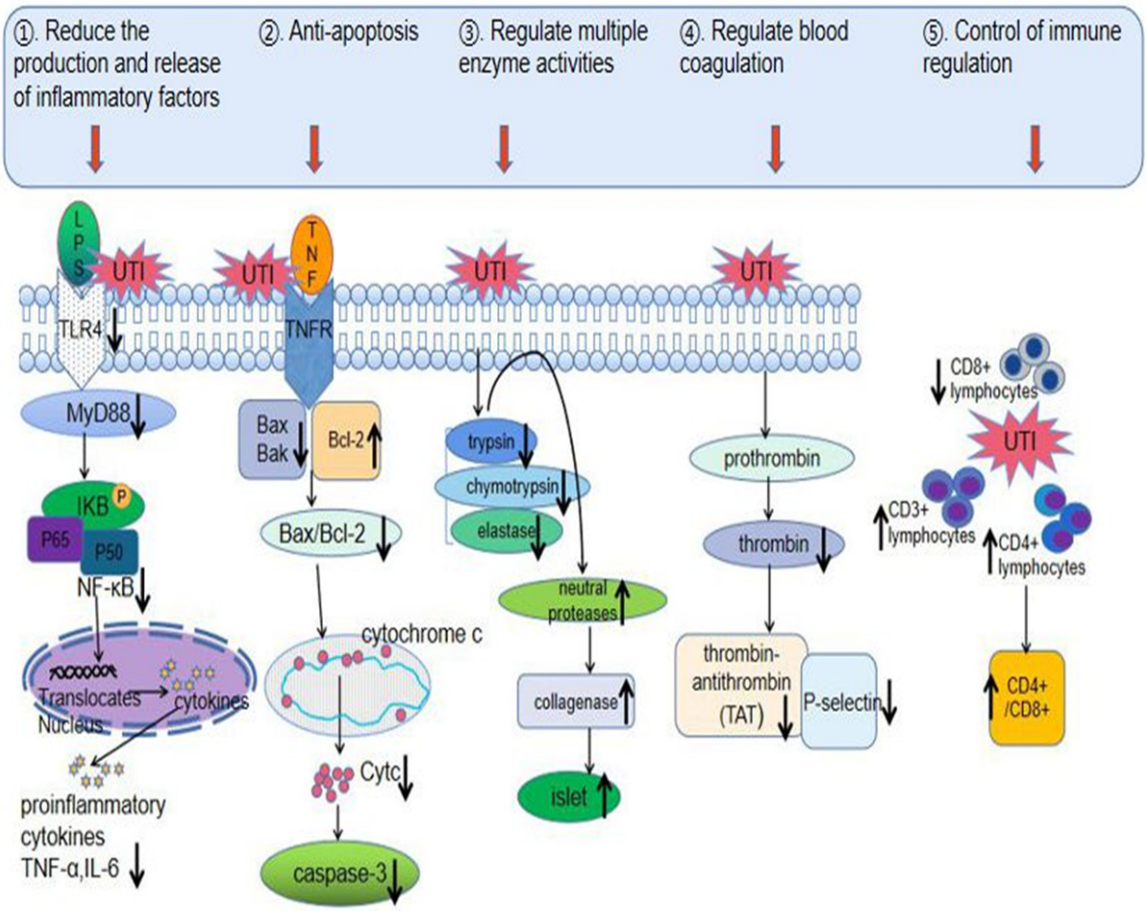

Figure 1. The figure shows the pharmacological effects of ulinastatin. UTI: ulinastatin; LPS: lipopolysaccharide; MyD88: myeloid differentiation primary response gene 88; IκB: inhibitor of nuclear factor kappa-B kinase; NF-κB: nuclear factor kappa-B kinase; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2 associated x; Cytc: cytochrome-c; ①. UTI can reduce the release of inflammatory mediators TNF-α and IL-6 by inhibiting the protein expression of TLR4, MyD88, and NF-κB, thereby attenuating the acute lung injury induced by LPS. ②. For the apoptosis pathway stimulated by TNF. UTI can up-regulate Bcl-2 and down-regulate Bax, leading to down-regulation of the ratio of Bax/Bcl-2, decreased cytochrome c release, decreased caspase3 activation, and decreased apoptosis response. ③. UTI can inhibit endogenous proteases (trypsin, chymotrypsin, and elastase) and increase neutral protease activity. The activation of the neutral protease can significantly enhance collagenase activity and thus increase the islet yield. ④. UTI can inhibit the excessive conversion of prothrombin into thrombin and reduce thrombin-antithrombin complex (TAT) and P-selectin production to regulate blood coagulation function effectively. ⑤. UTI can prevent immunosuppression by increasing the ratio of CD3+ and CD4+ lymphocytes, reducing CD8+ lymphocytes' rate, thereby increasing the proportion of CD4+/CD8+.

decreased, and inflammatory mediators such as TNF-α and IL-6 decreased accordingly. It showed that UTI could attenuate the TLR4/NF-κB inflammatory pathway and reduce inflammatory factors [15]. In a study of UTI's therapeutic effect on pulmonary fibrosis, Li, et al. found that UTI could down-regulate the gene expression of TGF-β, TNF-α, and NF-κB, resulting in the weakening of inflammation and inhibition of the development of pulmonary fibrosis [16] (see **Figure 1**).

Anti-apoptosis

Apoptosis is the primary mechanism of regulating programmed cell death controlled by various genes and is affected by numerous factors. Apoptosis is related to the development of multiple diseases [17]. The mitochondrial apoptosis pathway is an essential pathway that mediates apoptosis [18]. The various pathways interact and connect to jointly regulate the process of apoptosis. DNA damage [19]

and growth factor deficiency can directly turn on the mitochondrial apoptosis pathway [20]. Cell surface stimulating signals TNF can also indirectly activate the mitochondrial apoptosis pathway [21]. Cytochrome-c is essential to the mitochondrial apoptosis pathway [22]. Wang, Lu, and other researchers found that in diabetes-induced cardiac dysfunction ulinastatin (UTI) could significantly reduce the expression level of caspase-3 and the ratio of Bax/Bcl-2 in diabetic patients. Thus significantly reducing the percentage of apoptotic cardiomyocytes. UTI downregulated TNF-α and IL-6, suggesting that UTI could protect heart dysfunction caused by diabetes by anti-apoptosis and anti-inflammation [23]. Similarly, Li studied UTI treatment on acute paraquat poisoning in rats and found that UTI can reduce the expression of caspase-3 and the number of apoptosis cells. These test results indicated that UTI can effectively inhibit cell apoptosis, thereby exerting neuroprotective effects [24] (see **Figure 1**).

Regulate multiple enzyme activities

Ulinastatin (UTI) is a variety of collagenase inhibitors and protein combined inhibitors. It can treat diseases caused by lysosomal cell membrane rupture and hydrolase overflow [25]. UTI can inhibit endogenous proteases (trypsin, chymotrypsin, and elastase) and increase neutral protease activity. Activation of neutral protease can significantly enhance collagenase activity and thus increase the islet yield [26]. Wang studied the protective effect of UTI on ARDS. UTI can reduce endothelial glycocalyx destruction, heparan sulfate (HS) production, and heparanase activity. At the same time, the activity of heparanase is also reduced [27]. In the process of islet cell transplantation, maintaining the normal viability of organs after the acquisition of pancreatic collagenase is very important for the function of islet transplantation and the habitual survival of the body [28]. Current research results show that UTI can play an active role in early clinical islet cell transplantation through its inhibitory effect on trypsin and less collagenase protein inhibition [29] (see **Figure 1**).

Regulate blood coagulation

Ulinastatin (UTI) can effectively inhibit the synthesis and activation of coagulation factors, narrow the excessive transformation of prothrombin into thrombin, effectively improve the hypercoagulable process, and reduce the formation of thrombus [30]. The results of a joint study by Yao and Fang showed that under UTI treatment it can effectively reduce postoperative bleeding, reduce blood transfusion, and inhibit excessive dissolution of fibrous collagen [31]. The results of the joint study of Liu and Wu showed that the application of high-dose UTI could improve the symptoms of sepsis in mice and inhibit blood coagulation in young mice by reducing the thrombin-antithrombin (TAT) complex and P-selectin [32] (see **Figure 1**).

Control of immune regulation

The study found that treatment with ulinastatin (UTI) can reduce the percentage of CD4 (+) CD25 (+) regulatory T lymphocytes (Tregs), improve the immune function of T lymphocytes, and increase the expression of human leukocyte antigen (HLA-DR) on CD14 (+) monocytes [33]. Zhang, et al. studied the preventive mechanism of UTI on immunosuppression in patients with esophagectomy. They have found that UTI can prevent immunosuppression by increasing the ratio of CD3+ and CD4+ lymphocytes, reducing CD8+ lymphocytes' ratio, thereby increasing the percentage of CD4+/CD8+. Simultaneously, the proportion of postoperative complications and recurrences has also decreased, effectively improving the recovery [34] (see **Figure 1**).

Study of ulinastatin in liver diseases

Septic liver injury

Sepsis can harm the liver and other organs in many parts of the body. The role of the liver includes metabolism, detoxification, and immunity. Sepsis quickly invades the liver and causes great damage. Liver dysfunction is also an essential factor affecting sepsis prognosis [35]. UTI can effectively alleviate septic liver injury by inhibiting the inflammatory response pathway, inhibiting the production and release of leukocyte inflammatory response factors, anti-apoptosis [36], immune regulation, and anti-oxidation [37]. Chen, et al. studied the effect of UTI in sepsis. The study results showed that TNF-α content decreased, and IL-10 content increased under the action of UTI. It indicates that UTI can inhibit inflammation by down-regulating

the content of TNF-α and up-regulating the content of IL-10. Thereby alleviating septic injury [38]. Song, Miao, et al. studied UTI's therapeutic effect in mice with sepsis. After UTI treatment, it reduced 4-hydroxynonanal, nitrotyrosine, and activated caspase-3 in liver tissues, and inhibited the activation of mitogen-activated protein kinase pathways, thereby alleviating septic liver injury [39]. Cao, et al. have shown in clinical studies that UTI can effectively regulate the number and function of regulatory T cells (Tregs) by inhibiting the TLR4/NF-κB inflammatory response pathway. Thus effectively reducing septic injury caused by excessive production and release of inflammatory factors [40].

Hepatic ischemia-reperfusion injury

Primary liver cancer, liver transplantation, and surgical resection of liver cell perfusion may cause liver ischemia-reperfusion injury [41]. The results of studies showed that ulinastatin (UTI) can effectively inhibit the release of inflammatory response factors, anti-apoptosis [42], anti-oxidative stress [43], and inhibit hydrolase activity [44]. UTI can effectively inhibit the continuous development of systemic inflammatory response through these pharmacological effects, thereby effectively alleviating systemic liver ischemia-reperfusion injury. Wang, Li, et al. studied the effect of UTI combined with dexmedetomidine on the liver ischemia-reperfusion injury. The results showed that UTI increased the activity of SOD, but decreased the concentration of malondialdehyde (MDA) and tumor necrosis factor-α (TNF-α). It proves that UTI can inhibit the progress of inflammation and oxidative stress, thereby protecting liver ischemia-reperfusion injury [45]. Guan, et al. conducted experiments by adding UTI to the liver soaked in lactated Ringer's solution (LR). The experiment concluded that UTI's addition could inhibit the activation of pro-apoptotic genes BAX and caspase-3, and promote the activation of the anti-apoptotic gene Bcl-2, thereby effectively inhibiting the occurrence of cell apoptosis and alleviating hepatic ischemia-reperfusion injury [46].

Hepatitis

The results show that ulinastatin (UTI) can effectively inhibit the production and release of liver inflammatory response factors, improve liver coagulation system function, immune regulation, and protect liver function. Lin, et al. found that UTI levels in the plasma and urine of patients with acute hepatitis B in the middle and late stages decreased [47]. The changes of UTI were consistent with the changes in prothrombin activity time (PT) and plasminogen (PLG), but after the recovery of liver function, the level of UTI increased. Okubo, et al. researched alcoholic hepatitis. The results show that the patients with alcoholic hepatitis have extremely high white blood cell (WBC) count, high serum bilirubin, and low prothrombin time (PT). After five times of granulocytapheresis and UTI treatment, the serum IL-6, IL-8, and WBC count increased gradually, and the total bilirubin and prothrombin activity time (PT) improved. It is possible to conclude that granulocytapheresis and UTI therapy can effectively reduce cytokines and neutrophil elastase and improve patients' overall condition with alcoholic hepatitis [48].

Hepatic fibrosis

The possibility of liver fibrosis is between liver cirrhosis and primary liver cancer. Chemical factors such as cytokines and oxidative stress metabolites can directly cause hepatic fibrosis by stimulating hepatic stellate epithelial cells [49]. Some researchers have carried out the study of ulinastatin (UTI) on liver fibrosis in mice. The concentrations of hyaluronic acid (HA) and transforming growth factor-β (TGF-β) in homozygous UTI-knockout (KO) mice were significantly higher than those in heterozygous UTI-KO mice. After 20 weeks, histology confirmed that liver fibrosis of homozygous UTI-knockout (KO) mice was more serious. It shows that UTI's presence can reduce the production of HA and TGF-β and slow down the process of liver fibrosis [50].

Autoimmune liver disease with liver failure

There are three main types of autoimmune liver disease: primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis [51]. There are two types of liver failure, chronic liver failure or acute liver failure, both of which may be accompanied by apparent chronic systemic nervous system inflammation [52]. The study results of Cui, et al. showed that ulinastatin (UTI) can effectively decrease the content of inflammatory mediators such as

IL-6 and IL-8, improve the chemical reaction to inflammation, and protect immune liver disease complicated with chronic or acute liver failure [53]. Lu and Chen conducted a study of UTI on acute liver failure. The experimental results showed that UTI reduced AST, ALT, MDA, inducible nitric oxide synthase (iNOS), TNF-α, and caspase-3. In contrast, SOD and glutathione peroxidase (GSH-Px) levels increased. It shows that UTI has anti-inflammatory, anti-apoptotic, anti-oxidant, and other effects, and can treat acute liver failure [54].

Adverse reactions or limitations of ulinastatin

UTI also has some limitations. In rare cases, intravenous injection of high-doses of UTI may cause adverse reactions such as dizziness, pain at the injection site, decreased number of white blood cells, nausea, vomiting, and even allergic reactions. However, these adverse reactions are short-lived in most cases, and severe reactions are present in a few instances. UTI is usually tolerable and safe for most patients at a reasonable dose [55]. After UTI treatment, it can narrow the patient's mechanical ventilation time, ICU hospitalization time, and mortality rate [56, 57]. All in all, although UTI has some adverse reactions in a few cases, it still plays a useful role in treating liver diseases.

Conclusion

In summary, ulinastatin (UTI) can inhibit the production and release of inflammatory factors through mediating inflammatory pathways, anti-apoptosis, regulate multiple enzyme activities, regulate blood coagulation, and control of immune regulation. UTI can be used through these pharmacological effects to treat liver diseases such as septic liver injury, hepatic ischemia-reperfusion injury, hepatitis, hepatic fibrosis, autoimmune liver disease, and liver failure. At present, researchers are gradually discovering the mechanism of UTI. They can study the effects of UTI on other liver diseases and multiple organs in the future.

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Disclosure of conflict of interest

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