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Research Progress on the Mechanism of Sivelestat Sodium in Sepsis-Related Organ Dysfunction

Weiquan Chen, Lihua Zhou*

Department of Critical Care Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010000, Inner Mongolia Autonomous Region, China
Corresponding author

Abstrac: ***Sepsis is a life-threatening organ dysfunction caused by the host 's dysfunctional response to infection, which seriously threatens life and health. The pathogenesis of sepsis is very complicated. Neutrophil elastase is closely related to the occurrence and development of sepsis. It promotes the migration of immune cells and induces the release of pro-inflammatory mediators by degrading extracellular matrix, thus causing organ dysfunction. Sivelestat sodium has received continuous attention in recent years due to its specific inhibition of neutrophil elastase and its possible role in sepsis-related organs through multiple pathways. This article reviews the research progress of the mechanism of sivelestat sodium in sepsis-related organ dysfunction.***

Keywords: Sivelestat; Sepsis; Organ dysfunction syndrome; Neutrophil elastase.

1. INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. epsis is one of the leading causes of death in patients in intensive care units worldwide, accounting for nearly 20 % of all deaths in the world each year, with more than 20 deaths per minute [2]. Its pathogenesis is very complex, in which inflammation and immune response play a key role [3-4]. In sepsis, pathogen-associated molecular patterns (PAMPs) or damage associated olecular patterns (DAMPs) activate pattern recognition receptors (PRRs) in neutrophils, induce cytokine storms and activate the immune system [5]. The immune cells of the innate immune system are mobilized to participate in the process of sepsis. Neutrophils migrate to the site of inflammation, resist infection and eliminate pathogens [6]. Neutrophils play a key role in sepsis-induced inflammatory pathophysiology and immune disorders, and are the first line of defense in the innate immune defense [7]. Neutrophil elastase (NE), as a biomarker of neutrophils, is the most important proteolytic enzyme, which is related to the occurrence and development of sepsis [8]. Sivelestat sodium is a specific NE inhibitor that can reduce systemic inflammatory response. Recently, more and more literatures have reported that sivelestat sodium not only specifically inhibits NE, but also may act on sepsis-related organs through various pathways. The research progress of the mechanism of sivelestat sodium in sepsis-related organ dysfunction is reviewed below.

2. THE MECHANISM OF NE IN SEPSIS

The pathogenesis of sepsis is very complex, mainly due to the invasion of various pathogenic microorganisms into the host, causing systemic inflammatory response, microcirculation disorder and immune dysfunction, resulting in the destruction of homeostasis, insufficient tissue perfusion and organ dysfunction [9]. Neutrophils play an important role in the pathogenesis of sepsis through three ways: phagocytosis, degranulation and release of neutrophil extracellular traps (NET) [10-12]. NET is a kind of extracellular network structure released by neutrophils stimulated by pathogens, inflammatory factors, etc. It is mainly composed of DNA, histones and granular proteins, among which granular proteins NE, myeloperoxidase (MPO) and cathepsin G, etc. NET can neutralize and kill bacteria, fungi and viruses, and inhibit their spread [13]. However, large-scale production or ineffective clearance of NET leads to the progression of sepsis and related organ dysfunction [14-16].

NE is a serine protease, mainly released by neutrophils elastase, stored in polymorphonuclear neutrophils azurophilic granules or expressed on the surface of cells initially activated by cytokines [17]. NE accounts for about 80 % of the total protease hydrolysis activity in the human body. It can degrade elastin, a variety of extracellular matrix and plasma proteins, including collagen (type I-IV), fibronectin, laminin and proteoglycan. Its level and activity reflect the state and severity of the disease [18-19]. NE is one of the main effectors of immune

defense and inflammatory response regulation. It is involved in the inflammatory response of extracellular matrix remodeling, producing neutrophil and monocyte chemotaxis by hydrolyzing extracellular matrix fragments, attracting additional anti-inflammatory factors and shortening the infection process. In addition, the damaged basement membrane releases laminin fragments, promotes neutrophil migration and antioxidant factor recruitment, and also accelerates the inflammatory process [20]. In addition, NE is involved in the formation of NET and plays an important role in its release process. Studies have shown that NE knockout mice can reduce NET formation [21].

There is a protease-antiprotease system in the body. Proteases include serine protease, matrix metalloproteinase and cysteine protease. Protease inhibitors include: α1-antitrypsin, anti-white protease superfamily, etc. Under physiological conditions, the activity of NE is regulated by endogenous elastase inhibitors, and the protease-antiprotease system is in equilibrium. In sepsis, a large increase in NE and activated neutrophils produce reactive oxygen species (ROS) to inactivate endogenous elastase inhibitors, which makes the protease-antiprotease system in an unbalanced state. NE maintains its active state and the lack of endogenous elastase inhibitors, leading to inflammatory response and organ dysfunction [22-23]. When the body 's endogenous neutrophil elastase inhibitors are consumed, exogenous supplementation of neutrophil elastase inhibitors can antagonize the damage of NE to sepsis-related organs [24-26].

3. EXOGENOUS NE INHIBITORS

Exogenous NE inhibitors include: sivelestat (ONO-5046), ONO-6818, AZD9668, EPI-hNE-4, KRP-109, etc [27-28]. Sivelestat sodium is a specific NE inhibitor, which directly binds to the active center of NE and plays a role through hydrogen bonding, van der Waals force and hydrophobic interaction. It inhibits the function of NE and reduces systemic inflammatory response. It not only selectively, competitively and reversibly inhibits NE, but also is not sensitive to ROS and has a smaller relative molecular weight compared with endogenous protease inhibitors. It can effectively penetrate into cells and tissues, but has no significant inhibition on other proteases [29]. ONO-6818 is a specific, reversible, non-peptide NE inhibitor, which can inhibit NE-induced acute lung injury in rats, reduce pulmonary hemorrhage and neutrophil accumulation in the lung [28]. AZD9668 is an oral NE inhibitor with high selectivity to NE, and the interaction between AZD9668 and NE is fast and reversible [30]. EPI-HNE-4 is a quick-acting specific NE inhibitor, which can play a protective role in vitro and in vivo. Compared with endogenous protease inhibitors, it is resistant to oxidants and is stable under acidic or high temperature conditions [31]. KRP-109 is a small molecule NE inhibitor that can reduce NE-driven mucin degradation in vitro [32]. In addition, NE inhibitors have also been found in different organisms. NSPs from Musca domestica (MDSPI 16) and Araneus ventricosus (AvCI) showed NE inhibitory activity.Triterpenoids found in Ganoderma lucidum in some Asian countries have inhibitory effects on the release of NE and the production of superoxide anions [33].

4. APPLICATION OF SIVELESTAT SODIUM IN SEPSIS-RELATED ORGAN DYSFUNCTION

Sivelestat sodium is mainly used to improve acute lung injury / acute respiratory distress syndrome (ALI/ARDS) of systemic inflammatory response syndrome [34]. At present, the application of exogenous neutrophil elastase inhibitors in sepsis-related organ dysfunction is mainly based on sivelestat sodium. More and more literatures have reported that sivelestat sodium not only specifically inhibits NE, but also may act on sepsis-related organs through various pathways.

4.1 Sepsis-associated acute lung injury / acute respiratory distress syndrome

Sepsis acute lung injury / acute respiratory distress syndrome (ALI/ARDS) is the earliest and most common, which is one of the main factors leading to poor prognosis in patients with sepsis, and the mortality rate is as high as 30 % ~ 50 % [35]. Okekeke [36] and other experiments showed that sivelestat sodium significantly inhibited LPS-induced neutrophil production of NE, inflammatory factors and chemokines (TNF-α, IL-6 and G-CFS, etc.), and targeted delivery of sivelestat sodium to neutrophils through interbilayer-crosslinked multilamellar vesicles (ICMVs). ICMV-Sive can reduce lung bleeding, inflammatory cell infiltration and interstitial edema in LPS mice. Sivelestat sodium can not only inhibit the production of NE, inflammatory factors and chemokines, but also may play a role by inhibiting inflammatory pathways.Yuan et al [37] showed that sivelestat sodium may reduce ALI in LPS rats by inhibiting the NF-κB signaling pathway. Compared with the LPS group, the lung tissue injury in the LPS + sivelestat sodium group was lighter. The W/D ratio, the expression of intercellular cell adhesion molecule-1

(ICAM-1) in vascular endothelial tissue, the expression of ICAM-1 mRNA and NF-κB-p65 in lung tissue were significantly decreased. In addition, sivelestat sodium may also regulate the Mer signaling pathway. Lee et al [38] found that sivelestat sodium can reduce pulmonary edema in rats, inhibit the expression of inflammatory factors IL-6 and TNF-α mediated by TLR4 and NF-κB induced by LPS, reduce the expression of ICAM-1 and NF-κB-p65, increase the expression of MerTK protein, and up-regulate the Mer signaling pathway by treating LPS-induced ALI rats during the recovery of neutropenia with cyclophosphamide.In addition, sivelestat sodium also alleviates LPS-induced ALI by regulating endoplasmic reticulum stress to improve lung tissue damage, lung function, reduce inflammatory response, oxidative stress and apoptosis [39]. In summary, sivelestat sodium may play a protective role in sepsis ALI / ARDS by inhibiting inflammatory pathways, regulating endoplasmic reticulum stress, reducing the levels of inflammation and chemokines, and reducing lung tissue damage.

4.2 Sepsis-induced myocardial injury

The heart is one of the most vulnerable target organs of sepsis, and about 60 % of sepsis patients will be involved in the myocardium [40]. Studies have found that sivelestat sodium reduces myocardial injury in sepsis by inhibiting vascular endothelial cell glycocalyx damage [41]. The pathophysiological mechanism of myocardial injury in sepsis is complex and affected by many ways. Studies have shown that ERK1/2 phosphorylation can inhibit endoplasmic reticulum stress during myocardial ischemia-reperfusion, reduce myocardial cell apoptosis, and protect the heart [42]. Studies have shown that sivelestat sodium can reduce myocardial cell swelling, inflammatory cell infiltration and apoptosis in septic rats, effectively reduce the expression of inflammatory factors IL-1β, IL-6 and TNF-α, reduce the levels of CTnT, CK-MB and BNP, increase left ventricular systolic pressure (LVSP) and left ventricular systolic maximum rate (+dp/dtmax), reduce left ventricular end-diastolic pressure (LVEDP) and left ventricular diastolic maximum rate (-dp/dtmax), reduce the expression of pro-apoptotic gene Bax protein, and inhibit the expression of apoptotic gene Bcl-2 protein. Increase the expression of ERK1/2 protein [43].

4.3 Sepsis-associated acute kidney injury

Acute kidney injury (AKI) is one of the most serious complications of sepsis. Up to 60 % of sepsis patients are complicated with AKI, and the mortality rate is 3 ~ 5 times higher than that of sepsis patients without AKI [44]. High mobility group protein B1 (HMGB1) is a late pro-inflammatory cytokine released by monocytes and / or apoptotic cells in sepsis, which can further aggravate the inflammatory response [45]. During sepsis, the activation of inducible nitric oxide synthase (iNOS) leads to the increase of NO level, which leads to renal tubular injury by local production of active nitrogen. Inhibition of iNOS is considered to be a potential therapy for sepsis AKI [46]. Studies have shown that sivelestat sodium can restore the damage of mean arterial pressure and glomerular filtration rate in septic rats, activate the serine/threonine kinase (Akt) pathway, reduce the levels of BUN and NGAL, inhibit the infiltration of macrophages, reduce the levels of inflammatory mediators TNF-α, IL-1β, HMGB1 and iNOS, and reduce AKI in septic rats [47].

4.4 Sepsis-induced intestinal injury

Intestinal tract plays a central role in the occurrence and development of systemic stress response and multiple organ dysfunction during sepsis.During sepsis or septic shock, intestinal microvascular endothelial cells are susceptible to excessive inflammation and ischemia - reperfusion injury. At the same time, a large number of opportunistic pathogens and endotoxin can be transferred to the circulation through damaged vascular endothelial cells, leading to distant organ infection, systemic inflammatory response, and multiple organ dysfunction [48]. Intestinal epithelium is an important barrier for the body to resist potentially harmful microorganisms and pathogens.The intestinal barrier is damaged during sepsis, causing intestinal inflammation, decreased expression of tight junction proteins between epithelial cells, and increased intestinal permeability. Neutrophil recruitment is directly related to changes in the intestinal microbiota during infection, leading to degradation of intestinal epithelial ligand proteins, changes in intestinal barrier permeability, and intestinal flora imbalance by releasing NE [49]. Pathogens in the intestinal flora enter the blood through the intestinal epithelium, which is the main cause of intestinal flora translocation in sepsis, and will further lead to multiple organ dysfunction and even death [50-51]. Animal experiments have shown that inhibition of NE can reduce the intestinal colonization of Salmonella and other pathogens, and can prevent the occurrence of gastroenteritis [52]. Studies have confirmed that sivelestat sodium can significantly reduce the activity of intestinal NE [53]. Gammaproteobacteria is a kind of Gram-negative bacteria, which contains a variety of common pathogens and can interact with the host 's immune cells, resulting in the production of pro-inflammatory mediators [54]. The experiment found that the composition

of intestinal microbiota in septic rats was significantly disturbed, potential pathogens such as Shigella and Gammaproteobacteria were dominant, and the beneficial microbiota represented by lactic acid bacteria was reduced. After treatment with sivelestat sodium, it was reversed and the microbial state was restored to a state similar to that of healthy rats.It mainly changes the abundance of metabolites such as Lactobacillus and some amino acids by affecting the intestinal microbiome, regulates the biosynthesis of phenylalanine, tyrosine, tryptophan and tyrosine metabolism, and plays a protective role in intestinal injury of sepsis [55]. The study of the effect of sivelestat sodium on intestinal microbiome and metabolic profile in septic rats can provide new therapeutic ideas for the treatment of intestinal injury in sepsis.

5. SUMMARY

Sepsis has the characteristics of high morbidity and high mortality. It is one of the main causes of death in patients in intensive care units around the world.Its treatment plan has always been concerned. At present, the treatment plan is mainly symptomatic and supportive treatment, including early fluid resuscitation, infection control, organ and nutritional support. The pathogenesis of sepsis is very complicated.NE is closely related to the occurrence and development of sepsis.It induces organ dysfunction by degrading extracellular matrix, promoting immune cell migration, and inducing the release of pro-inflammatory mediators. Sivelestat sodium is an exogenous NE inhibitor, which not only specifically inhibits NE,but also may protect sepsis-related organs by regulating multiple signaling pathways, regulating endoplasmic reticulum stress, reducing inflammatory factors, regulating amino acid metabolism and regulating intestinal flora.It has a positive impact on the prognosis of patients with sepsis.It is expected that more safety and efficacy trials will be carried out in the future to explore the effect of sivelestat sodium on sepsis and related mechanisms, so as to provide more evidence for the treatment of sepsis.

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Author Profile

Zhou Lihuaprofessor, master tutor, Department of Critical Care Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot,Inner Mongolia Autonomous Region.Research direction:The etiology, pathogenesis, prevention and treatment of various acute and severe diseases.

Chen Weiquan Department of Critical Care Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot,Inner Mongolia Autonomous Region.Research direction:Study on the etiology, pathogenesis, prevention and treatment of acute kidney injury.