REVIEW ARTICLE

Experimental treatments for mitochondrial dysfunction in sepsis: A narrative review

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Sepsis is a systemic inflammatory response to infection. Sepsis, which can lead to severe sepsis, septic shock, and multiple organ dysfunction syndrome, is an important cause of mortality. Pathogenesis is extremely complex. In recent years, cell hypoxia caused by mitochondrial dysfunction has become a hot research field. Sepsis damages the structure and function of mitochondria, conversely, mitochondrial dysfunction aggravated sepsis. The treatment of sepsis lacks effective specific drugs. The aim of this paper is to undertake a narrative review of the current experimental treatment for mitochondrial dysfunction in sepsis. The search was conducted in PubMed databases and Web of Science databases from 1950 to January 2014. A total of 1,090 references were retrieved by the search, of which 121 researches met all the inclusion criteria were included. Articles on the relationship between sepsis and mitochondria, and drugs used for mitochondrial dysfunction in sepsis were reviewed retrospectively. The drugs were divided into four categories: (1) Drug related to mitochondrial matrix and respiratory chain, (2) drugs of mitochondrial antioxidant and free radical scavengers, (3) drugs related to mitochondrial membrane stability, (4) hormone therapy for septic mitochondria. In animal experiments, many drugs show good results. However, clinical research lacks. In future studies, the urgent need is to develop promising drugs in clinical trials.

Key words: Mitochondria, mitochondrial dysfunction, sepsis, drug

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INTRODUCTION

Sepsis is a systemic inflammatory response to infection. Its high morbidity and high mortality cost a lot of medical resources. According to statistics,[1] about 750,000 patients are diagnosed to have severe sepsis in the United States each year. And the incidence is considered to increase by 1.5%/year, rising to millions of cases annually by 2020. Sepsis, which can lead to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation), is an important cause of mortality. It also reduces the quality of life of many survivors.

The pathogenesis of sepsis is very complicated. It involves a complex process of cellular activation resulting in the activation of neutrophils, monocytes, and microvascular endothelial cells; the triggering of neuroendocrine mechanisms; and cytokine storm, inflammatory mediators falls, bacterial translocation and intestinal endotoxemia, the interaction between the coagulation system and inflammatory systems, micro-circulation and mitochondrial dysfunction,[2] and so on. In recent years, the cellular hypoxia induced by mitochondrial dysfunction has become a hot field of research. Sepsis damages the structure and functions of mitochondrion, whereas the dysfunction of mitochondrion also aggravate sepsis. The effect of sepsis treatment improved significantly with the recent therapy of early goal-directed fluid resuscitation, appropriate antibiotic therapy, and supportive care for vital organs. However, the high mortality of sepsis makes it another hot academic research field.

Many scholars have conducted experimental studies to dysfunction of mitochondria in sepsis. And they have achieved gratifying results. Their empirical studies of mitochondrial drugs accumulated a solid foundation for clinical therapy of septic patients. In this paper, the recent articles about the experimental treatment against mitochondrial dysfunction in sepsis will be systematically reviewed. And the relevant drugs related to mitochondrial damage will be summarized.

MATERIALS AND METHODS

Search strategy

The literature research was conducted in PubMed databases and Web of Science databases from 1950

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to January 2014. The following groups of terms were searched:

1. "Mitochondria OR mitochondrial dysfunction OR mitochondrial function OR mitochondrial therapy,"
2. "sepsis OR septic shock OR severe sepsis OR systemic inflammatory response syndrome OR septicemia OR septicemia,"
3. the combination of the terms listed in (1) and (2). There were no language restrictions.

Only published studies available up to January 2014 were included, without contacting authors of the relevant studies for any unpublished work.

Inclusion criteria

Titles and abstracts of all the studies were reviewed to identify relevant studies for inclusion. Full texts of potentially relevant studies were assessed to decide whether they met the inclusion criteria. Full text articles were included in the review when the title and/or abstract reported the use of a mitochondrial therapy in sepsis. Any disagreement about the criteria was resolved by discussion or by consultation with a third reviewer.

Exclusion criteria

Studies whose mitochondrial therapy was given in combination with another therapy were excluded. Any articles not related to the therapy for septic mitochondria were excluded. The review articles without primary research were excluded.

Data extraction

Author, publications, date of publication, treatment programs, mechanism of effect, specific mitochondrial target, model, reported primary and secondary outcomes were extracted from each original article and were tabulated. After initial data extraction, treatments were grouped according to the drug's effect on different aspects of mitochondria.

RESULTS AND DISCUSSION

A total of 1,090 references were retrieved by the search, within which 121 researches meet all the inclusion criteria. The role for the mitochondrial therapy in the prevention or amelioration of mitochondrial dysfunction and its sequelae during sepsis were investigated. According to the drug's effect on different aspects of mitochondria, the drugs were divided into four categories [Figure 1]:

1. Drugs related to mitochondrial matrix and respiratory chain,[3]
2. drugs of mitochondrial antioxidant and free radical scavengers,
3. drugs related to mitochondrial membrane stability,
4. hormone therapy for septic mitochondria.

Drug related to mitochondrial matrix and respiratory chain

Mitochondrion is famous as "cell power plant". In the cytoplasm, nutrients such as carbohydrates and fat are broken down to produce pyruvate and fatty acids which will be taken into the mitochondrial matrix. Then through a series of processes they are turned into acetyl coenzyme A. The acetyl-CoA feeds into the tricarboxylic acid (TCA) cycle, which further provides the electron transport chain (ETC) substrates NADH and FADH2. Electrons produced from substrates are passed from complexes I and II of the ETC through complexes III and IV to oxygen, forming water eventually. The protons from TCA are pumped across the mitochondrial inner membrane. And then, proton pump drives protons back through the adenosine triphosphate (ATP) synthase in the inner membrane, forming ATP from ADP and phosphate. ATP is the "energy currency" of the body which provides energy for various life activities. The normal function of mitochondria could be injured by the change of mitochondrial matrix components and structure of the respiratory chain, as well as variation of some cofactors.

Succinate, including in oxidative phosphorylation, is the important intermediates of TCA cycle. By binding to cell surface receptor SUCNR1 (GPR91), it affects cellular immune function, which is associated with hyperglycemia and hypertension. Succinate fuels complex II of the ETC. During sepsis, function of complex I is commonly inhibited while complex II is relatively preserved. Because complex I and complex II feed electrons in parallel into complex III, succinate may increase electron flow and oxygen utilization,

Figure 1: Drugs for mithchondrial dysfunction in sepsis

Drug categories	Reference	Drug categories	Reference
Drugs related to mitochondrial matrix and respiratory chain		Drugs of mitochondrial antioxidant and free radical scavengers	
Succinate	[4,5]	MitoQ	[27-29]
Glutamine	[6-10]	Szeto–Schiller peptides	[3,30]
ATP-$MgCl_2$	[11,12]	Mn(III) porphyrin	[30]
Carnitine	[13-15]	GSH	[31-33]
Coenzyme Q	[16,17]	N-acetylcysteine	[34,35]
Cytochrome C	[18-20]	NOS inhibitors	[36-41]
Caffeine	[21,22]	Tempol	[42-49]
Thioctic acid	[23,24]	Pyruvate	[3,50-54]
rhTFAM/NaHS	[25,26]	HO inducer	[55-57]
Drugs related to mitochondrial membrane stability		Hormone therapy for septic mitochondria	
		Glucocorticoid	[66,67]
Cyclosporin A/NIM811	[58-64]	Insulin	[66,68-70]
Tetramethylpyrazine	[65]	Melatonin	[71,72]

NOS = Nitric oxide synthase; rhTFAM = Recombinant human transcription factor; NaHS = Sodium hydrosulfide; HO = Heme oxygenase; GSH = Glutathione; ATP = Adenosine triphosphate

and improve mitochondrial phosphorylation capacity.[3] In animal models of sepsis, succinate can increase ATP levels in liver tissue, and promote lactic acid removal. Additionally, in the presence of glutamate (GLN) plus malate, mitochondrial oxygen consumption was abnormally low. In addition to succinate, mitochondrial respiration was augmented. The experiment indicated that succinate increases mitochondrial oxygen consumption in septic animals through bypassing the predominant inhibition occurring at complex I.[4] During tissue hypoxia or sepsis, extracellular succinate may play a co-stimulatory role in platelet aggregation by binding SUCNR1 (GPR91), which is present in human platelets and, by (partially) antagonizing the effects of platelet inhibitors.[5]

Glutamate is the most abundant amino acids in plasma and human muscles. It is nonessential amino acids in the traditional view. But during sepsis or injury, more and more scholars are now more likely to regard it as conditionally essential amino acids. Clinically, Endogenous production of GLN may become insufficient during critical illness. Therefore, with high safety, GLN has been widely used as nutrients in sepsis, blood diseases, and tumors.[6] However, some scholars believe that GLN can't reduce mortality of preterm children and children sepsis.[7] Therefore, clinical routine use is not advocated. Could GLN benefit septic patients? And how it affects the mitochondria during sepsis? To answer these questions, many scholars have conducted lots of deep researches. Sepsis resulted in large consumption of GLN, leading to a sharp drop in blood pressure. GLN sudden decline increases the mortality of sepsis.[7] Meanwhile, the conversion of pyruvate to acetyl coenzyme A can be blocked because of inhibition of pyruvate dehydrogenase, which leads to the damage of the TCA, eventually inhibiting the process of oxidative phosphorylation. In cecal ligation and double puncture (CLP) model, GLN restores cytochrome oxidase (COX) activity, significantly increases myocardial oxygen extraction and consumption, and increases LVP. The beneficial effects of GLN therapy during sepsis may partly be the restoration of oxidative phosphorylation and abrogation of sepsis-associated myocardial depression.[8] In 11-day rat pups, GLN administration partially prevents the sepsis-induced fall in plasma glutamine levels and reduces the concentration of both proinflammatory and antiinflammatory cytokines.[9] It may be unrelated with the generation of nitric oxide (NO) and lipid peroxidation. However, during the experiment of interleukin-1β (IL-1β)-activated rat hepatocytes intervented with GLN,[10] the inducible nitric oxide synthase (iNOS) protein and mRNA levels significantly decreased in liver cells. And it has dose-dependent relationship with the GLN. This cell research induced that GLN is related to NO and has a protective effect on mitochondria during the inflammation stress.

Nucleotide triphosphate (ATP), directly supply about 95% of the body energy, is the body's energy currency. ATP, usually combined with calcium or magnesium ions, primarily comes from the generation of mitochondrial oxidative phosphorylation. ATP can add energy to the respiratory chain and can be reversed by exogenous ATP when cells are under hypoxia in sepsis. Many experiments[3] claimed that ATP-$MgCl_2$ is much better than the simple use of ATP. Because of the interaction with Mg ions, the single use of ATP may affect the hemodynamic stability. In animal models of ischemia-reperfusion injury and sepsis,[3] ATP-$MgCl_2$ elevated organ blood flow and micro-circulation, promoted energy balance, improved cellular and mitochondrial function, and increased survival and cardiopulmonary function. At the cellular level, administration of ATP-$MgCl_2$ after a septic insult raised ATP levels, increased ileal mucosal cell oxygen tension, and improved hepatic lactate clearance and gluconeogenesis. ATP-$MgCl_2$ also had salutary effects on immune function-improving RES function and lymphocyte proliferation during sepsis. However, the clinical use of ATP-$MgCl_2$ to rescue shock is few. Because, there is a possibility of causing hypotension and third-degree atrioventricular block induced by the rapid injection of ATP-$MgCl_2$. There were occasional reports about the experimental treatment of ATP-$MgCl_2$ for pulmonary hypertension patients and multiple organ dysfunction syndrome (MODS) in the clinic.[11] Some scholars believed that the elevated mitochondrial F0F1-ATPase activity is concomitant with the decline of intramitochondrial ATP concentration in late septic liver. In addition, the mRNA and the mitochondrial content of IF1 decreased in late sepsis. ATPase inhibitors[12] and upregulating IF1 may increase sepsis mitochondrial ATP levels and protect liver cells. However, studies of mitochondrial ATPase inhibitor in experimental sepsis were so few that it is difficult to evaluate its clinical effects.

Carnitine, an important quasi-vitamin, relates to fat metabolism and is an essential coenzyme in animal tissue. Carnitine plays an important role in fat metabolism and energy production in mammals, whose insufficiency can affect the liver and kidney function. L-carnitine is a form of carnitine bearing biological activity.[13] More and more mitochondrial oxidative stress model are used to study the therapeutic effect. Additionally, many experiments investigate its effect in sepsis and multiple organ dysfunctions. L-carnitine plays an important role in the transport of fatty acids into the mitochondria. In addition, as a free radical scavenging antioxidant, it may be associated with mitochondrial lipid membrane stability and mitochondrial biogenesis. Carnitine deficiency may lead to systemic inflammation. Studies have shown that the use of L-carnitine reduces the release of pro-inflammatory mediators such as IL-1, IL-6, and tumor necrosis factor

(TNF)[3] in animal models of sepsis. Clinically, trauma and surgical anesthesia often causes the body to produce excessive reactive oxygen species (ROS), which may lead to sepsis, myocardial damage, and eventually increase mortality. Intravenous L-carnitine to abdominal surgery patients can regulate oxidative stress, reduce platelet activation, and benefit the patients finally.[14] In addition, the clinical phase II study to investigate the role of L-carnitine in septic shock has been completed, laying a solid foundation for the phase III trials.[15]

Coenzyme Q, which plays an important role in proton translocation and electron transfer in the respiratory chain, is a fat-soluble quinone compounds *in vivo*. Coenzyme Q, an important antioxidant, is an activator of cell respiration and metabolism. Offering coenzyme Q in the animal model of sepsis induced by lipopolysaccharide (LPS) pretreatment could improve ATP levels, protect liver cells, inhibit lipid peroxidation and improve survival rate finally. In a similar animal experiments, researcher also found that coenzyme Q could reduce pro-oxidative markers and increase glutathione (GSH) levels in cells.[16] Coenzyme Q content was insufficient in patients with septic shock in the large prospective clinical trials,[17] and the lack of coenzyme Q was associated with the inflammatory cascade.[73] Therefore, coenzyme Q could have potential therapeutic value in patients with septic shock.

Cytochrome C (Cytc) is conserved nuclear encoded mitochondrial protein composed of 104 amino acids. Cytc, an intracellular multifunctional enzyme and involved in proton transport, is mobile proton carrier. It can translocate proton from the respiratory chain complex III to complex IV. Cytc is an important component of mitochondrial ETC. And it is essential in mitochondrial electron transport and intrinsic type II apoptosis. Mammalian Cytc also sweeps ROS under healthy conditions, produces ROS with the co-factor p66Shc, and oxidizes cardiolipin during apoptosis.[18] In animal models of sepsis, the loss of mitochondrial Cytc caused dysfunction of respiratory chain complex IV, leading to decreased synthesis of ATP. And the leakage of Cytc from mitochondrial promoted apoptosis. Intravenous Cytc on septic rats can reverse cellular hypoxia and myocardial dysfunction caused by sepsis. Cytc can also enhance left ventricular pressure, improve heart function and improve survival rate finally. The protective effect may be related to improved capacity of myocardial mitochondrial matrix and activity of Cytc dioxygenase.[19] Interestingly, the leakage of mitochondria Cytc could cause cell apoptosis, while exogenous administration Cytc doesn't activate apoptotic program. Possible explanation is that only oxidation state of Cytc can trigger apoptosis. Exogenous Cytc can increase activity of cytochrome oxygenase, which is considered as a magical effect in improving cellular hypoxia.[20]

Caffeine, also known as three methylxanthine (1,3,7-trimethylxanthine), is a xanthine alkaloid compounds. Caffeine, a central nervous system stimulant, is the world's most widely used psychoactive drug that can temporarily drive away drowsiness and restore energy. Caffeine can increase cyclic adenosine monophosphate (cAMP) levels of mitochondria and is the potential therapeutic agents for mitochondrial dysfunction in sepsis. cAMP, which comes from the conversion of ATP, is an important intracellular second messenger involved in signal transduction in cells. cAMP-dependent phosphorylation of Cytc oxidase, the terminal oxidase of the ETC, is known to stimulate and optimize the oxidative phosphorylation efficiency.[3] Phosphodiesterase is needed in the process of cAMP decomposition into AMP, in which caffeine is an inhibitor of the enzyme. Caffeine can inhibit cAMP decomposition, raise the level of cAMP, thereby enhancing the COX activity by inhibiting phosphodiesterase. Giving caffeine after abdominal surgery in a rat model of CLP, scholars found that caffeine can repair COX activity, increase left cardiac ventricular pressure and improve heart function.[21,22]

Thioctic acid (α-lipoic acid), as an enzyme in the mitochondria, can eliminate pathogenic accelerating aging and free radicals. It is a water-soluble and fat-soluble antioxidant. α-Lipoic acid an important coenzyme take part in two critical oxidative decarboxylation. For example, it is capable of catalyzing the generation and transfer of acyl in the pyruvate dehydrogenase complex and the α-ketoglutarate dehydrogenase complex. α-Lipoic acid can accept acyl and acetyl of pyruvic acid, and then form a thioester bond, ultimately transferred the acetyl coenzyme A to the sulfur atom of the molecule. Dihydrolipoamide of auxiliary group can be re-converted into oxidized lipoic acid by dihydrolipoamide dehydrogenase (requires NAD^+). In rats' models of sepsis, LPS can strengthen oxidative stress in the diaphragm and cardiac muscle cells, increase NO level, and eventually damage mitochondrial function. But the mitochondrial function can be prevented by given α-lipoic acid treatment to inhibit oxidative stress.[23] Subsequent studies[24] found that α-lipoic acid can protect myocardial cellular functions by activating the PI3K/Akt signaling pathway. Liver and yeast cells are particularly rich in content of α-Lipoic acid that is widely distributed in nature. α-Lipoic acid and Vitamin B1 often coexist in foods. Human α-lipoic acid deficiency has not been reported. However, is α-lipoic acid inadequate in patients with sepsis? And can it improve mitochondrial function by giving α-lipoic acid to assist septic patients? Up to now, there are few reports for these questions.

In addition, recombinant human transcription factor A (rhTFAM) and sodium hydrosulfide (NaHS) can also protect sepsis mitochondria. rhTFAM[25] can increase the number

of copies of mitochondrial DNA in rats with sepsis, raise the level of respiratory chain complex I, and increase ATP synthesis in mitochondrial. NaHS[26] reduces organ injury in pneumosepsis, possibly via preservation of oxidative phosphorylation and thereby ATP synthesis as well as by promoting mitochondrial biogenesis.

Drugs of mitochondrial antioxidant and free radical scavengers

A series of mitochondrial oxidative phosphorylation inlaid enzyme synthesized ATP using oxygen. Electrons transfer between the enzyme complexes of the respiratory chain. Electron flow and proton transfer contributed to the formation of the mitochondrial membrane potential. ROS is a byproduct of the oxidative phosphorylation process, and about 1% of the oxygen is converted to ROS[3] under physiological conditions. ROS contains an unpaired electron named radicals, such as superoxide anion, hydrogen peroxide. It has a strong activity and can react with the surrounding molecules. ROS is likely to cause cell damage when there is no corresponding balanced system. Mitochondrial ETC is the main place of the body to produce ROS. A small amount of ROS has important significance for maintaining the body's stability. Under pathological conditions, such as ischemia and hypoxia, infection, injury, a large number of ROS will be generated, which damages DNA, membrane structure and some important enzymes, thereby affecting the normal function of cells, organs and even the body.[74]

Oxidative stress itself is closely related to mitochondrial dysfunction. Free radical can damage mitochondrial membrane permeability, thus reducing the generation of ATP. Impaired mitochondrial respiratory chains produce ROS excessively, which damage the mitochondria in reverse, thus forming a vicious cycle. Mitochondrial damage often occurs in septic patients, and sepsis increased mitochondrial damage, leading to the occurrence of MODS. Mitochondrial dysfunction in sepsis leads to cell oxygen utilization disorders, decrease energy production and promotes apoptosis. Many experimental research evidences support the fact that mitochondrial dysfunction mediated the tissue and organ damage caused by sepsis and MODS. Many scholars focus on the antioxidant therapy for sepsis mitochondrial. Many antioxidant treatments were evaluated clinically, but the effects were unsatisfactory. However, until recently, mitochondrial specific antioxidant seems to bring new hope to the academic community because the mitochondrial specific antioxidant appeared. Through mitochondrial transmembrane transport, antioxidants gathered themselves together in the area of mitochondrial, which plays an powerful antioxidant effect.

MitoQ, lipophilic TPP group together with a coenzyme Q, is exogenous antioxidants. It can rapidly pass through the blood circulation across the inner mitochondrial membrane, and accumulate in the mitochondria. The concentration in the mitochondrion can be up to several hundred times of plasma concentrations. In the mitochondrial matrix, MitoQ is attached to the inner mitochondrial membrane and exert a strong antioxidant effect by repeatedly activating the respiratory chain of coenzyme Q.[27] With the protection against ischemia-reperfusion in cardiac and protection of mitochondria function, MitoQ is widely used in various animal models. *In vitro*, MitoQ can reduce ROS, protect mitochondria; in animals sepsis models, MitoQ can reduce liver damage, kidney damage, and mitochondrial membrane potential.[27] Some studies have shown that it has mitochondrial antioxidant function and can improve heart function.[28] High concentration of MitoQ is prone to cause poisoning, resulting in mitochondrial depolarization, which limited its clinical applications. Clinically, MitoQ was used to treat hepatitis C during Phase II clinical trials,[27] suggesting that MitoQ, as mitochondria-specific antioxidant, has potential applications to repair mitochondrial function in sepsis. Furthermore, mitochondrial specific phenyl-naphthylamine (MitoPBN), another cationic antioxidant, can protect against ischemia-reperfusion injury and prevent damage to the body in septic shock in animal models.[3]

Szeto–Schiller peptides (SS peptide), small fragments of recent synthetic amino acid chain, is a specific mitochondrial antioxidant. It contains a serine analogs, which can bind with H_2O_2, OH- and ONOO-, and inhibit lipid peroxidation.[3] SS peptide does not depend on energy, turns into the mitochondria independently, and accumulate in the mitochondrial inner membrane where the ROS produce is without saturation. By reducing the generation of ROS, SS peptides can inhibit mitochondrial swelling and protect the mitochondrial respiratory chain complexes. In ischemia-reperfusion injury and neurodegenerative disease animal models, SS peptides have been extensively studied, but so far rarely reflected in sepsis research.[3] Additionally, synthetic antioxidant Mn (III) porphyrin[29] can also reduce oxidative stress in sepsis, and protect mitochondrial function in diaphragm.

Glutathione is a combination of glutamic acid, cysteine, and glycine. With a tripeptide containing mercapto group, it has antioxidant effects. Oxidized GSH is another form of GSH, and the majority of which is under physiological conditions. The specific structure of GSH, containing a thiol reactive, which is easily oxidative dehydrogenation, makes it a major free radical scavenger. It is able to scavenge free radicals, protect many proteins, enzymes, and other molecules. *In vitro* experiments, although inhibited by the GSH enzymes activity, lymphocytes would produce much ROS, causing DNA damage, and increase the cell apoptosis. This suggested that the GSH system play an

important role in maintaining the integrity of DNA and protecting against apoptosis in lymphocytes.[30] GSH, the most abundant mitochondrial antioxidant system, plays an important role in protecting mitochondrial function and mitochondrial membrane stability. Mitochondrial takes in GSH by cytoplasmic and thus increases the concentration of GSH in the mitochondrial. GSH choline ester was an early researched drug to protect mitochondrial function.[31] In LPS septic models, GSH can reduce rat plasma TNF and IL-1, protect against acute lung injury caused by sepsis.[32] However, the report that GSH used in septic patients is rare. Little is known about the value of GSH for sepsis in clinic.

N-acetyl cysteine (NAC), a GSH precursor, is N-terminal acetyl L-cysteine derivatives. NAC contains mercapto antioxidant and is often used as antioxidants in the animal model of sepsis. How can NAC treatment in systemic inflammatory respond to sepsis? Visvanathan group[33] conducted a literature review. The analysis contained 37 clinical studies, including 2768 patients with SIRS and sepsis. They found that there was no significant difference between NAC and placebo group on length of Intensive Care Unit stay, duration of mechanical ventilation, incidence of organ failure, and duration of inotropic support. It shows that the current data do not prove NAC could benefit the patients. But because of limited number of patients included, more clinical randomized controlled trial trials are needed to find the difference that has not been found but may actually exist.[3] At the presence of iron ions, NAC may promote oxidation effect, which limits its application. That NAC and Fe can chelate to form deferasirox (DFX) has recently been given attention in animal models of sepsis. The combination therapy[34] of NAC and DFX, work together as antioxidant in CLP septic rats, can reduce the production of inflammatory mediators, the release of Cytc and the mitochondrial permeability transition (MPT). It also can protect liver cells through the promotion of Krebs cycle.

Nitric oxide synthase catalyze L-arginine to produce NO, a simple structure molecule with an unpaired electron. It is a highly reactive free radical. Under physiological conditions, only a small amount of NO can be generated. Excessive NO can interact with superoxide anion to form peroxynitrite compounds that are potentially harmful to nucleotides, lipids, and proteins. It can impair mitochondrial respiratory function, inhibit electron transport and reduce ATP generation.[3] Sepsis, which could enhance cellular stress and activate iNOS, caused large amounts of NO production.[35] NOS inhibitors can reduce NO production, which has become the new treatment strategy for sepsis. L-NAME as a nonspecific NOS inhibitor, can regulate immune function in rats with peritonitis, and reduce pro-inflammatory mediator release in a dose-dependent manner.[36] Oxidative stress could be strengthened, NO and other free radical generations were found to be excessive in Septic rats muscle tissue. Excessive NO damages the function of the mitochondrial ETC complex that can be partially prevented by L-NAME.[37] But there are also reports in the CLP model, using L-NAME and specific NOS inhibitor aminoguanidine treatment.[38] Although GSH concentrations can be stabilized, the concentration of TBARS was exactly the opposite. The experiment indicated that the appropriate concentration of NO is required in the brain tissue of sepsis. But the controversy still exists. There were studies suggested that, L-NAME did not reverse the high oxidative stress in rats with sepsis, and cannot reverse the swelling of mitochondria, as well as the activity of respiratory chain complexes.[38] It was also confirmed that L-NAME and other nonselective NOS inhibitors did not reduce mortality of sepsis and septic shock during Phase III clinical trials.[39] The pathophysiology of NOS and NO in the sepsis specific mitochondria remains unclear. And how to intervene, reduce or reverse the damage of sepsis mithchondrial dysfunction still needs further research.

Tetramethylpiperidine (tempol), an efficient oxidation catalyst, is capable of turning primary and secondary alcohol into carbonyl compounds. It can capture the free radicals, singlet oxygen quencher and selective oxidation. Tempol, a low molecular weight ROS scavenger, accumulates in mitochondria through blood circulation and across the inner mitochondrial membrane. It can scavenge free radical[40] in the mitochondria that ROS produced. Liver and kidney were damaged, circulation function failed, oxidative stress was too strong, the activation of PMN infiltrated into the lung and liver in CLP septic rats. After tempol treatment, it can not only improve blood circulation, reduce PMN exudation, improve liver and kidney function, but also reduce the levels of plasma NO, IL-1 and organ superoxide anion.[41] The mechanism may be related to that tempol inhibit the formation of ROS. In addition, tempol can improve hemodynamics in septic pigs by improving metabolic state, partly correcting coagulation disorders, and inhibiting oxidative stress.[42] Tempol can increase mesenteric blood supply in septic rats, reduce the activity of PARP in glomeruli and lungs.[43] Tempol can also reduce the incidence of organ failure and improve survival.[41,44] 4NH2-Tempo can also specifically gather in the mitochondria. 4NH2-Tempo, which have a similar function as antioxidant and free radical scavenger, can reduce lipid peroxidation and improve survival in septic rats models.[45,46] However, they were seldom applied in clinical studies. Whether they could be used in septic patients to lower oxidative stress and protect, mitochondrial functions needs further studies.

Pyruvate, energy metabolism intermediates, is very promising endogenous ROS scavenger with high research

value. Exogenous pyruvate can reduce oxidative stress in an animal model of sepsis, therefore, reduce the incidence of organ failure.[47,48] However, pyruvate solution is unstable and easy to be concentrated to 2-hydroxy-2-methyl-4-two valproic acid, which can inhibit citric acid cycle. So its clinical application is limited.[3] Ethyl pyruvate, a derivative of pyruvate solution mixed with potassium and sodium calcium, is similar to Ringer's lactate solution and is used[49] in the experimental study recently. *In vitro*[48] experiment, it was found that ethyl pyruvate can reduce TNF-α, inhibit TNF-α mRNA, block nuclear factor-κB transcription factor and other pro-inflammatory signaling pathways. In the rat model of sepsis, Ethyl pyruvate can raise blood pressure, reduce IL-6, elevated IL-10, inhibit oxidative stress,[75] lower blood circulating NOS markers nitrate and nitrite, and prolong the survival time of mice in sepsis.[76] In the pig model of sepsis, Ethyl pyruvate could reduce lipid peroxidation, lower blood nitrite,[50] and improve the function of liver and kidney. Some researchers believed that the protective effect was related to the inhibition of HMGB1.[48] In a multi-center, double-blind, controlled clinical trial II research, Ethyl pyruvate treatment was used in postoperative high-risk cardiac patients. Unfortunately, compared with placebo, Ethyl pyruvate can't bring any benefits to postoperative cardiac patients but may benefit septic patients.[51] However, the effect of ethyl pyruvate on septic patients in the clinic has rarely been reported.

Heme oxygenase (HO), a ubiquitous antioxidant defense enzyme, is a member of heat shock protein family. It is the rate-limiting enzyme during the heme catabolism process which can promote heme generate CO, bilirubin, and free iron. CO, bilirubin, and transferrin, as HO metabolites, have antioxidant function. They are the major effector of HO for anti-inflammatory, anti-apoptotic and anti-proliferative functions. Hemin is HO inducer that can reduce the rat plasma levels of nitrate and nitrite, inhibit LPS-induced free radical generation, and reduce mitochondrial dysfunction caused by sepsis.[52] In addition, there are also considered Hemin mitigated intestinal obstruction in sepsis by inducing HO.[53] Quercetin, a natural antioxidant, can promote biological repair mechanisms of mitochondria through HO1/CO system both *in vivo* and *in vitro*.[54]

Drugs related to mitochondrial membrane stability

Mitochondrial inner membrane damage and mitochondrial swelling are performance of mitochondrial dysfunction that is related to the damage of mitochondrial membrane potential. The respiratory chain complex V oxidative phosphorylation can be driven by mitochondrial membrane potential, which is dependent on MPT function. The increase of MPT,[3] would lead to swelling of the mitochondrial matrix, uncoupling of oxidative phosphorylation, efflux of Ca^{2+} ion, and release Cytc. Eventually, it would trigger apoptosis. MPT dysfunction occurred in the course of sepsis and MODS. Although the mechanism of the open channel is not clear, many compounds were used to inhibit its opening for protecting mitochondria. Curbing MPT and maintaining mitochondrial membrane stability have become the new direction for mitochondrial treatment in sepsis.

Cyclosporin A (CsA), a cyclic polypeptide consisting of 11 amino acids, is a potent immunosuppressants that is used for the treatment of autoimmune diseases, as well as liver, kidney and heart transplant rejection clinically. CsA can inhibit MPT by combining with cyclophilin D, a component of MPT.[55] In animal models of sepsis and organ failure, CsA can inhibit apoptosis, restore the function of mitochondrial ETC.[56] In cats, CsA can protect the functions of left ventricular and mitochondria caused by sepsis.[57] The mechanism may be related to NOS inhibition and regulation of TLR4 receptor-mediated signaling pathways.[58,59] Fatal secondary ischemia-reperfusion injury often occur after myocardial revascularization because of excessive open of MPT.[60] But with the CsA treatment, the infarct size was reduced, which may be related to the suppression of mitochondrial MPT. Apoptosis increased and immune cells reduced in patients with sepsis, which is associated with mitochondrial damage and Cytc leakage. CsA can inhibit excessive openness of MPT, being beneficial possibly in the treatment of sepsis. But CsA suppresses immune function, which limited its application in the clinic. NIM811 (N-methyl-4-isoleucine CsA), a derivative of CsA, has no immunosuppressive effect but retained the MPT and cyclophilin D binding function. It is similar to CsA in the protection of cell function in sepsis model.[61] In addition, melatonin has antioxidant function of removing ROS, acting directly on the MPT. These characters of affecting ion in and out of the mitochondria make it likely to become anti-apoptotic drugs.[62]

Aquaporin (AQP) is a passage of water molecules, enjoying a high selectivity and high specific transport function for water molecules on the cell membrane. AQP8, expressed in the mitochondrial membrane, can mediate rapid water and solute transport to the cytoplasm. Dysfunction of AQP8 could cause mitochondria swelling, energy metabolism disorders, and affect ATP generation finally. It also can cause rupture of the outer mitochondrial membrane, leading to release of Cytc and a number of pro-apoptotic substance.[63] Recently, studies have found that tetramethylpyrazine[64] can upregulate the expression of AQP8, reduce mitochondria swelling and protect liver cells under septic conditions.

Hormone therapy for septic mitochondria

There are lots of controversies for glucocorticoids (GCs) use in sepsis. But now the widely accepted academic view is that intravenous hydrocortisone as a treatment of adult septic shock patients should be avoided if

adequate fluid resuscitation and vasopressor therapy can restore hemodynamic stability. If this cannot be achieved, intravenous hydrocortisone alone should be used at a dose of 200 mg/day. Timely hydrocortisone therapy should be used in children with the fluid refractory, catecholamine resistant shock and suspected or proven absolute adrenal insufficiency.[77] These pragmatic treatments were partly related to that GC therapy that can improve mitochondrial function of septic patients. Dexamethasone treatment attenuated renal dysfunction,[78] but it was not associated with improvement of hemodynamic parameters. Dexamethasone-induced organ protective effect was associated with reduced mitochondrial injury with preserved Cytc oxidase and suppression of proapoptotic proteins as well as reduced cytokine release.

Insulin, a protein hormone secreted by pancreatic β cells, is the only hormone that lowers blood sugar in the body. It can also promote glycogen, fat and protein synthesis metabolism. Blood glucose should be strictly controlled in patients with sepsis. A consensus has been formed to ensure the stability of blood glucose.[77] Newborns, children and adult patients with sepsis are all required to control blood glucose under 180 mg/dL. This is because using insulin and blood glucose control in critically ill patients can significantly reduce mortality and severe complications,[65] such as severe infections, and the incidence of DIC and MODS. To investigate the protective effects of continuing insulin infusion on liver mitochondrion and its mechanism, continuous insulin infusion in the septic rats during the early stage of sepsis was investigated. And it was found[66] that in the early stage of septic rats, reversible liver mitochondrion injury can be observed. Continue insulin infusion can protect liver mitochondrion through attenuating inflammatory reaction and reducing the blood glucose level in septic rats. The inspection of the body of death in septic patients found that the strict insulin therapy can improve liver mitochondrial ultrastructure.[67]

Melatonin is an amine hormone secreted by the pineal gland. It is the component of antioxidant system with the function to prevent oxidative damage. Melatonin can directly scavenge a variety of toxic oxygen and nitrogen-based reactants, stimulate antioxidative enzymes and increase the efficiency of the ETC, thereby limiting electron leakage and freeing radical generation, and promoting ATP synthesis.[68] Via these actions, melatonin preserves the integrity of the mitochondria and helps to maintain cell functions and survival. During sepsis, there is a significant increase in the expression and activity of mitochondrial iNOS (i-mtNOS), which parallels the changes in cytosolic iNOS. The overexpression of iNOS/i-mtNOS can inhibit the respiratory chain activate.[69] Melatonin administration inhibits iNOS/i-mtNOS induction, restores mitochondrial homeostasis in septic mice, and preserves the activity of nNOS/c-mtNOS.[69,70] Many studies discussed the role of melatonin in animal models of sepsis. Exogenous melatonin inhibited mitochondrial dysfunction caused by sepsis and protected organ function,[79] repaired the ability of oxidative phosphorylation.[79,71] This may result from the function of melatonin, which is capable of removing NO, reducing lipid peroxidation, inhibiting oxidative stress,[72] and repairing GSH system.[80] In some countries, melatonin was sold in the market as health care or food additives. In addition, it is often used to treat insomnia, circadian adjustment. Due to its powerful antioxidant effects, doctors began to carry out more studies on its therapeutic effect.[81] Some studies have shown that melatonin was beneficial to the treatment of respiratory distress syndrome in premature children and septic shock.[82] And it is effective to treat bacterial infections and viral infections.[83,84] A volume of 20 mg oral melatonin (p.o. 10 mg, 1-h intervals) can improve the treatment efficacy for neonatal sepsis.[85] However, whether melatonin is really beneficial to children with sepsis or septic shock needs further observation in the clinic.[86]

CONCLUSION

Sepsis leads to cellular hypoxia and detriment of mitochondrial respiratory chain, resulting in energy generation disorders and excessive free radical production, promote septic shock and MODS. But the treatment of sepsis lack of effective specific drugs. Luckily, the emergence of mitochondria-specific antioxidants for the treatment brought new hope for septic patients in recent years. Drugs for the treatment of mitochondrial dysfunction could be divided into four categories:

1. Drugs related to mitochondrial matrix and respiratory chain,
2. drugs of mitochondrial antioxidant and free radical scavengers,
3. drugs related to mitochondrial membrane stability,
4. hormone therapy for septic mitochondria.

Due to the lack of clinical studies, it is now difficult to evaluate their clinical value of many drugs. It is urgent to do more experiments on some promising drugs in clinical trials for exploring new therapeutic options to sepsis.

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AUTHOR'S CONTRIBUTION

GZ contributed in the conception of the work, conducting the study, revising the draft, approval of the final version

of the manuscript, and agreed for all aspects of the work. QZ contributed in the conception of the work, approval of the final version of the manuscript, and agreed for all aspects of the work. JL contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. JH contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. DX contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MX contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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