Perioperative Precision Medicine
ISSN: 2957-5443

Zentime

Review Article https://doi.org/10.61189/313377zqjuff

Progress in heatstroke-induced multiple organ damage

Ruilong Li[1,2*], Dezhi Guo[1,2*], Tianying Li[1,2], Panpan Hu[1,3], Tianying Xu[1]

[1]Department of Anesthetic Pharmacology, School of Anesthesiology, Second Military Medical University/Naval Medical University, Shanghai 200433, China. [2]College of Basic Medicine, Second Military Medical University/Naval Medical University, Shanghai 200433, China. [3]National Key Laboratory of Immunity & Inflammation, Second Military Medical University/Naval Medical University, Shanghai 200433, China.
[*]The authors contribute equally.

Corresponding authors: Tianying Xu and Panpan Hu.

Acknowledgement: This work was supported by the Basic Medical Research Fund of Naval Medical University (2023QN034). The authors would like to thank all the guest editors and anonymous reviewers for their constructive comments.

Received January 23, 2024; Accepted April 29, 2024; Published September 30, 2024

Highlights

- Patients with heatstroke often suffer from multiple organ dysfunction and have a high fatality rate.
- The molecular mechanisms underlying multiple organ damage in heatstroke are complex.
- This review outlines the manifestations of multiple organ dysfunction caused by heatstroke and explores the possible molecular mechanisms involved.

Abstract

Heatstroke is a life-threatening acute condition characterized by dysregulated temperature control, resulting in high core temperature and multi-organ dysfunction. Despite extensive research, the molecular mechanisms underlying heatstroke-induced organ damage have not been fully elucidated. This review aims to summarize recent advancements in the field of heatstroke, focusing on etiological factors, organ damage, and molecular mechanisms. By exploring the intricate interplay between heat-related cytotoxicity, inflammatory response, and tissue dysfunction, this review offers insights for future research and clinical practice in managing heatstroke patients. Further investigations are warranted to elucidate the specific mechanisms of organ damage and improve treatment strategies for heatstroke.

Keywords: Heatstroke, organ damage, molecular mechanisms

Introduction

Heatstroke is a heat-related disease characterized by hyperthermia (core body temperature greater than 40 °C) and delirium [1]. It can be classified into exertional heatstroke (EHS), caused by excessive heat production during physical activity in hot and humid environments, and classic heatstroke, more prevalent in the elderly or those with underlying health conditions affecting heat dissipation [2]. Heatstroke often leads to multiple organ dysfunction, initially impacting the cardiovascular system, followed by the central nervous, digestive, urinary, and respiratory systems [3]. To maintain a relatively stable body temperature and prevent heatstroke, the human body primarily relies on the hypothalamus, which receives heat information from sensors in the skin, spinal cord, and internal organs. The hypothalamus regulates heat production and dissipation accordingly. Additionally, it is crucial to avoid excessively high environmental temperatures, as they can directly damage cells, induce oxidative stress, and compromise cell membrane stability, ultimately contributing to multiple organ dysfunction. Epidemiological data indicate an increasing incidence of heatstroke, exacerbated by extreme heatwaves and climate change [4, 5]. In short, heatstroke can occur when the body's temperature regulation function is im-

Address correspondence to: Tianying Xu, Department of Anesthetic Pharmacology, School of Anesthesiology, Second Military Medical University/Naval Medical University, 800 Xiangyin Road, Shanghai 200433, China. Tel: +86 021 81872029, E-mail: xutianying@smmu.edu.cn; **Panpan Hu**, Department of Anesthetic Pharmacology, School of Anesthesiology, National Key Laboratory of Immunity & Inflammation, Second Military Medical University/Naval Medical University, 800 Xiangyin Road, Shanghai 200433, China. Tel: +86 021 81872029, E-mail: hpp510@smmu.edu.cn.

paired or when environmental temperatures are excessively high, affecting various bodily systems.

Etiological and risk factors for the occurrence of heatstroke

Heat imbalance

Heat imbalance is a key pathogenic mechanism of heatstroke, characterized by excessive heat production and limited heat dissipation in the body. Risk factors include high ambient temperatures, food intake, fever elevate metabolic heat production in a resting state, etc. Additionally, increased heart rate and pulmonary ventilation raise energy demands, further augmenting metabolic heat production. Skeletal muscles primarily contribute to the elevated basal metabolic rate [6]. During intense physical activity, skeletal muscle excitation-contraction coupling sharply increases the rate of metabolic heat production, reaching levels up to 15-20 times higher than at rest [7].

The excitation-contraction coupling mechanism of skeletal muscles proceeds as follows: Action potentials propagate along the sarcolemma and T-tubules, activating L-type calcium channels on the sarcolemma [8]. This activation induces a conformational change, opening calcium release channels in the sarcoplasmic reticulum, allowing calcium ions to be released into the cytoplasm along the concentration gradient [8]. The increased cytoplasmic calcium concentration initiates muscle contraction through binding to muscle calcium-binding protein C [9]. Subsequently, the majority of cytoplasmic calcium ions are recaptured into the sarcoplasmic reticulum via the activated calcium pump in the sarcolemma [10]. Both muscle contraction and calcium reuptake by the pump require ATP for energy supply. Skeletal muscle contraction consumes approximately 20% of metabolic energy, with the remaining 80% released as heat, contributing to excessive heat production. Elevated heat from excessive production can promote the leakage of calcium ions from the sarcoplasmic reticulum, further enhancing skeletal muscle metabolic heat production and potentially triggering heatstroke [11].

When body temperature rises, a cascade of pathophysiological responses occurs to maintain normothermia. This includes an increase in heart rate and cardiac output. Simultaneously, there is a redistribution of circulatory blood volume, with decreased flow to internal organs like the intestines and kidneys, and increased flow to the skin, reaching up to 50% of cardiac output. Heat carried by the bloodstream to the skin prompts vasodilation of skin blood vessels, while sweat glands actively secrete sweat to facilitate heat dissipation [12]. Dysregulation in sweat gland function can reduce overall sweat rate, significantly impairing the body's ability to dissipate heat.

When skin temperature exceeds ambient temperature, the body can still dissipate heat effectively through dry mechanisms like conduction and convection. However, when ambient temperature equals or exceeds skin temperature, evaporation becomes the primary heat loss avenue. In humans, evaporative heat dissipation occurs primarily through the conversion of sweat, secreted by skin sweat glands, into a gaseous state. Approximately 580 kcal of heat can be carried away per liter of evaporated sweat. Excessive evaporation leading to significant sweat loss may reduce blood volume, particularly organ blood flow, diminishing heat transport to the skin via circulation. This can rapidly elevate core body temperature, ultimately culminating in heatstroke. Moreover, in humid environments that hinder evaporation, sweat may accumulate on the skin surface, compromising the evaporative heat dissipation pathway and increasing heatstroke risk.

Heat adaptation disorder

Heat adaptation is a physiological phenomenon widely observed in mammals [13]. It refers to the adaptive response of individuals residing in hot environments for extended periods to heat exposure. Compared to individuals exposed to high temperatures for shorter durations, those living in such environments long-term typically exhibit increased heat tolerance. For instance, protein-carbohydrate supplementation during a 5-day training period enhanced plasma volume expansion and thermoregulatory adaptation, thereby reducing heat and cardiovascular strain in young men [14]. It is indicated that heat adaptation is closely associated with genetic factors, potentially involving enhanced physiological functions facilitated by heat-tolerant genes or their products [15]. These functions play a significant role in maintaining cell membrane stability under conditions of elevated temperatures [15].

Under normal physiological conditions, the interaction between environmental temperature and signals transmitted from effector organs to the hypothalamic temperature regulation center, along with changes in the number and excitation levels of thermo-sensitive neurons, lowers the threshold for heat dissipation by or-

gans and raises the threshold for heat damage. This broadens the adaptive range of dynamic body temperature regulation [15]. Clinical signs of heat adaptation include a lower core temperature, decreased heart rate, and increased sweating responses during activities in high temperatures. While repeated elevation of core temperature is recognized as a primary stimulus for promoting heat adaptation, recent years have brought debate over the optimal method to induce such adaptation [16]. It is important to note that individuals lacking heat adaptation capability are more susceptible to heatstroke, thus facing an increased risk of heat stress.

Preexisting diseases diminish heat tolerance

The "multiple hit hypothesis" suggests that the immune system, once "primed" by initial stimuli such as mild diseases, infections, skin allergies, or blisters, becomes more susceptible to subsequent impacts of exercise-induced heat stress [17]. There is substantial evidence supporting this hypothesis. For example, an experiment with rats injected with lipopolysaccharide from Salmonella enteritidis, a gram-negative bacterial cell wall product triggering a reaction similar to that induced by live bacteria, showed a rapid increase in body temperature at a lower heat exposure temperature compared to rats injected with isosmotic saline without a heat source [18]. This suggests that concurrent or pre-existing inflammation or infection may increase the risk of heatstroke. In addition, these preexisting conditions can exacerbate the progression of heatstroke, leading to increased mortality. An in vitro experiment demonstrated that pretreatment with tumor necrosis factor (TNF) and interferon (IFN) can enhance the heat stress-induced death of microvascular endothelial cells [19].

In a study where participants engaged in brisk walking in high temperatures for four consecutive days and developed mild cellulitis due to foot blisters on the third day, their core temperature was higher despite maintaining the same exercise intensity and duration as on the other days [20]. Moreover, the research indicates that mild diseases or inflammation can increase susceptibility to heat injury or hyperthermia in both soldiers and volunteers [20]. Animal studies further support this, suggesting that mice with a prior history of disease, even if showing no overt clinical symptoms during heat exposure, experience increased severity of heatstroke [21].

Genetics and epigenetics alterations

Current research highlights EHS as a potentially life-threatening condition with long-term epigenetic implications observed in female mice. These studies suggest that EHS can induce epigenetic changes in monocytes, enhancing the production of robust immune cells characterized by altered heat shock protein (HSP) responses and immunosuppression [22].

Additionally, epigenetics plays a critical role in regulating cellular heat adaptation, involving chromatin remodeling, particularly through post-transcriptional modifications of histones H3 and H4, such as phosphorylation and acetylation. During the consolidation phase of heat adaptation "memory," short-term heat stress triggers phosphorylation of histone H3, crucial for heat shock factor (HSF)1 binding to heat shock elements and subsequent transcription of HSPs like HSP70, irrespective of H3 acetylation status. The heat adaptation phenotype is characterized by abundant reserves of HSP72 and HSP90, with HSP90 playing a pivotal role in regulating various proteins, including facilitating HIF-1α nuclear translocation. Studies have indicated involvement of histone expression changes in the H1 cluster, multiple microRNAs, and other epigenetic markers in this process [15].

The susceptible gene ryanodine receptor (RyR) may play a role in the pathogenesis of heatstroke. Type 1 RyR (RyR1) serves as a calcium release channel in skeletal muscle, and mutations in RyR1 can lead to channel overactivation, triggering malignant hyperthermia (MH). RyR1 selective inhibitors, such as the oxyquinoline acid derivative (Compound 1), have shown potential in rescuing animals from EHS-induced heat stress [23]. Moreover, MH-related mutations in the RyR1 gene have been reported in some cases of heatstroke [24]. Research indicates that at high temperatures (41 °C), calsequestrin-1 undergoes oligomerization, reducing its interaction with RyR1/2 and increasing RyR2 activity in ventricular muscle [25]. This regulation affects calcium release from ventricular muscle cells, influencing MH and arrhythmias induced by environmental heatstroke [25]. Therefore, variations in RyR genes may contribute to heatstroke pathogenesis.

EHS has been linked to specific gene mutations, particularly those at the g.31829044 locus of the HSPA1B gene. HSPA1B, a subtype of HSP72, is highly induced and promotes positive heat adaptation and cellular responses during exercise [26]. Participants with a history of EHS and heat tolerance often possess the AG genotype at the HSPA1B single nucleotide

polymorphism g.31829044 locus, suggesting it may serve as a protective marker against heat stress [27]. Animal studies have shown a positive correlation between HSPA1B expression and primate heat stress severity [28]. Additionally, HSPA1B expression is upregulated in individuals with a history of EHS [29]. However, due to limited current evidence, further research is necessary to elucidate the functional role of the HSPA1B single nucleotide polymorphism in the HSPA1B gene and its impact on heatstroke.

Manifestations of organic injury in heatstroke

Central nervous system injury

Neurological injury is a frequent and serious outcome of heatstroke, especially in cases of sudden exposure to high temperatures. Cooling interventions typically result in substantial neurological improvement in 70% to 90% of heatstroke patients. However, those who do not regain consciousness after cooling or initial treatment often develop seizures or focal motor disorders. Histological examinations of the central nervous system in heatstroke patients reveal notable injuries such as white matter demyelination, significant reduction in Purkinje cells, and progressive degeneration of cortical neurons [30]. Autopsy findings commonly show congestion, edema, and microhemorrhages alongside these histopathological changes [31].

Animal models of heatstroke demonstrate increased intracranial pressure and decreased arterial blood pressure, leading to reduced cerebral perfusion pressure [32]. Heatstroke-induced intracranial hypertension may be attributed to cerebral edema, and lowering cerebral perfusion pressure below the self-regulating threshold can result in cerebral ischemia and neuronal damage in affected animals. Studies have investigated the survival of cortical and hippocampal neurons under high temperature conditions, as well as their effects on DNA degradation and nuclear morphology, highlighting the critical role of cell culture duration in heat stress-induced necrosis or apoptosis [33]. Neuronal damage due to high temperatures involves endoplasmic reticulum stress, nuclear damage, and cytoskeletal damage from protein denaturation [34]. Neurons show significant activation within 24 hours of heat stress, leading to apoptosis, indicating that the impact of high temperatures is not only irreversible but also persists beyond the cessation of heat stress.

Clinically, some patients develop trunk ataxia, orientation disorders, and weakness following heatstroke. Brain diffusion-weighted magnetic resonance imaging reveals high signal intensity and decreased apparent diffusion coefficient values in the bilateral cerebellar hemispheres and globus pallidus [35]. Dysfunction in the globus pallidus contributes to disorientation and malaise, while dysfunction in the cerebellar hemispheres leads to trunk ataxia [36, 37]. Elevated temperatures can damage the anterior and lateral horns of the spinal cord, resulting in quadriplegia and degeneration of Purkinje cells in the cerebellum. During heatstroke, increased release of catecholamines, particularly dopamine, serotonin, and interleukin-1β (IL-1β), contributes to neuronal degeneration and necrosis, accompanied by significant down-regulation of γ-aminobutyric acid B receptors and inhibition of the high-affinity γ-aminobutyric acid uptake system [38]. Studies have shown that high temperatures adversely affect the autonomic nervous system, impacting axonal conduction and synaptic transmission velocity, particularly in laryngeal reflexes and sudden infant death [34].

Rhabdomyolysis (RM)

RM is characterized by the breakdown of muscle fibers, often triggered by high temperatures. The incidence of RM due to hyperthermia ranges from 4% to 8%. Evidence suggests that individuals with a predominance of type II muscle fibers are not only at higher risk of RM but also more prone to EHS [39].

Following RM, activated neutrophils are the first responders to the site of muscle damage, where they clear cellular debris. Subsequently, monocytes migrate to the inflamed area and differentiate into macrophages, which possess superior phagocytic capabilities compared to neutrophils within days or weeks, becoming the primary phagocytes. Both neutrophils and macrophages contribute to tissue degradation by releasing reactive oxygen and nitrogen species, exacerbating injury, increasing membrane permeability, and facilitating the release of intracellular proteins (such as myoglobin and creatine kinase) into the systemic circulation. Additionally, damaged muscle fibers, leukocytes, and other resident inflammatory cells contribute to cytokine production at the injury site. The substantial release of free radicals and intracellular toxic substances is a crucial factor contributing to the systemic inflammatory response (**Figure 1**).

Myoglobin released from RM can be cleaved into myosin, which plays a critical role in the coagulation cascade, including factors involved in both coagulation and fibrinolysis [40]. Post-RM,

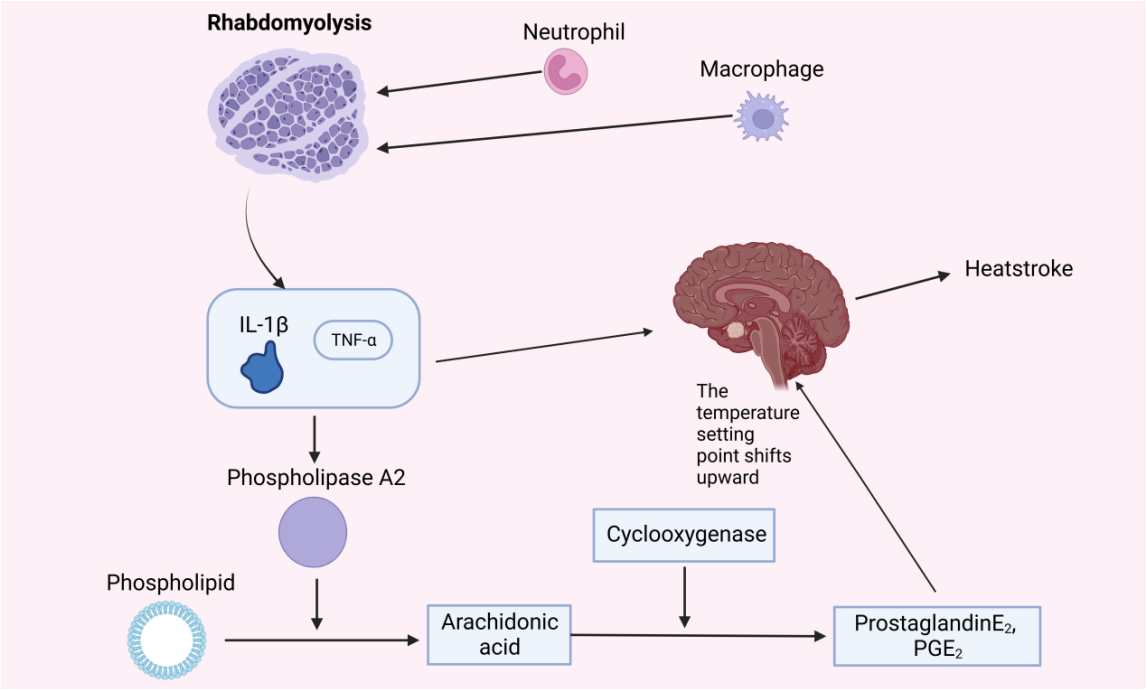

Figure 1. Rhabdomyolysis exacerbates the occurrence of heatstroke. After rhabdomyolysis, neutrophils and macrophages will sequentially reach the damaged area, exacerbating the damage, and helping the production of pro-inflammatory cytokines at the damaged site, including interleukin-1β and tumor necrosis factor-α. These inflammatory factors can directly act on the hypothalamic temperature regulation center to produce a fever response after entering the blood, or promote the release of phospholipase A2. Phospholipase A2 can cleave membrane phospholipids, release arachidonic acid, and generate PGE_2 under the action of cyclooxygenase. PGE_2 can increase the set point of body temperature, thus exacerbating the development of heatstroke. IL-1β, interleukin 1β; TNF-α, tumor necrosis factor α; PGE_2, Prostaglandin E_2.

there is a significant influx of sodium and potassium ions, leading to blood hyperconcentration and an increased thrombotic risk. Furthermore, the release of nuclear proteins (such as histone 3 and high-mobility group protein B1) from damaged muscle cells activates platelets, contributing to disseminated intravascular coagulation. Pro-inflammatory cytokines like IL-1β, TNF-α, and IFN-α enter the bloodstream, mediating the febrile response via the hypothalamic temperature regulation center. These cytokines also stimulate phospholipase A2, which cleaves membrane phospholipids to release arachidonic acid. Arachidonic acid is converted to prostaglandin E_2 (PGE_2) by cyclooxygenase, increasing the body's temperature set point and leading to fever, ultimately contributing to heatstroke [41].

Several studies have investigated ultrastructural changes in muscle tissue following EHS [42]. Imaging has shown rupture of the outer mitochondrial membrane, loss of cristae, and an increase in markers of cell ferroptosis, such as malondialdehyde, 12-hydroxyeicosatetraenoic acid, and prostaglandin endoperoxide synthase 2. Ferroptosis, characterized by iron-dependent lipid peroxidation and specific mitochondrial alterations, is considered a crucial pathway of cell death in RM post-EHS [43]. The mechanism involves EHS-induced Yes-associated protein upregulating ACSL4 through TEAD1/TEAD4, promoting lipid peroxidation and subsequent ferroptosis of skeletal muscle cells, contributing to muscle cell loss and subsequent RM [43].

Intestinal barrier dysfunction

Studies indicate that, while high temperatures can induce heatstroke, the primary driving force for the progression of heatstroke is the systemic inflammatory response mediated by various cytokines [44]. The gut is recognized as the body's largest reservoir of bacteria and toxins. When enteric microbial products, such as endotoxin, flagellin, and bacterial DNA, enter the bloodstream, they trigger the production of numerous cytokines, including PGE_2, TNF-α, IL-1β, IL-6, and IFN-γ [45]. This cascade of events ultimately results in a systemic inflammatory response, leading to disseminated intravascular coagulation, multiple organ failure, and other critical conditions. In scenarios where high temperatures lead to a sustained elevation in core body temperature, blood flow is redirected to the skin and active skeletal muscles, consequently diminishing blood flow to internal organs. This redirection reduces the transfer of heat from internal organs to the skin, allowing

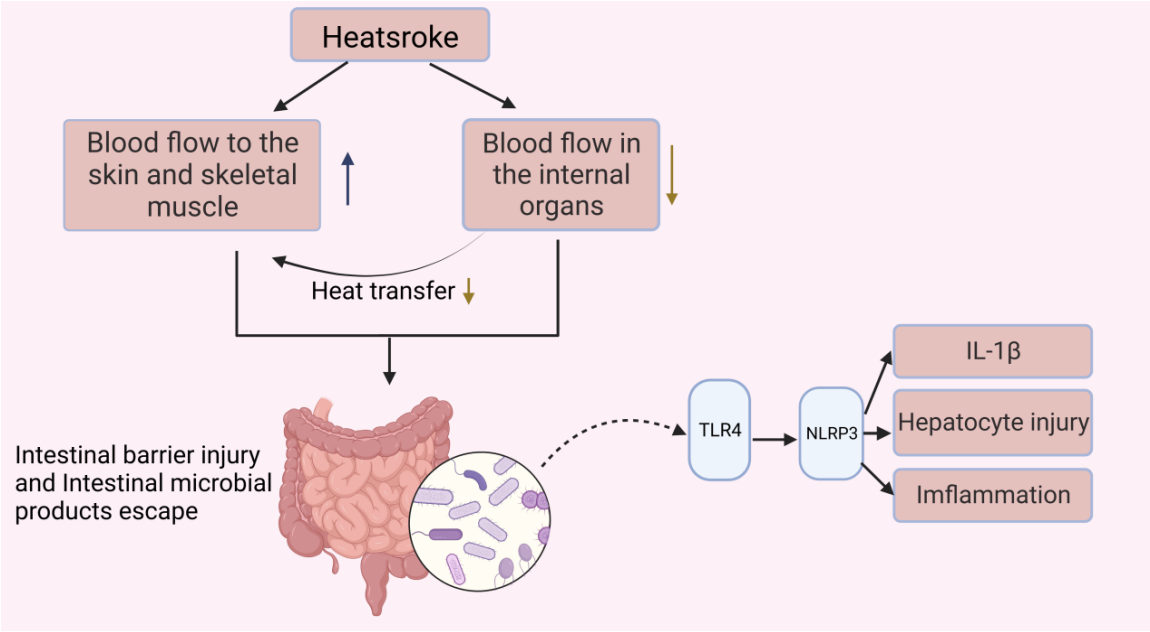

Figure 2. The impact of high temperature on intestinal barrier dysfunction. In cases of a continuous rise in core temperature due to elevated external temperatures, blood preferentially flows to the skin and active skeletal muscles, consequently diminishing blood flow to internal organs. As a result, the heat transferred from internal organs to the skin is also reduced, triggering a rapid increase in core temperature and leading to organ dysfunction, including intestinal ischemia. This sequence of events results in tissue hypoxia, acidosis, and damage to the intestinal barrier, facilitating the escape of microbial products from the intestine. These products then interact with Toll-like receptor 4, activating the inflammasome and further promoting the release of IL-1β, liver cell apoptosis, and sterile inflammation. TLR4, Toll-like receptor 4; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, interleukin 1β.

for a rapid increase in core temperature. Such an escalation may result in dysfunction of vital organs, including intestinal ischemia and liver cell injury. Intestinal ischemia fosters tissue hypoxia, acidosis, and a sequence of alterations disrupting the structure and function of the intestinal mucosa, ultimately increasing intestinal permeability [46]. Additionally, cell culture experiments have demonstrated that even a slight elevation in ambient temperature (1.3 °C) can swiftly and transiently alter the integrity of the intestinal epithelial barrier, a change that persists for up to 24 hours [47].

The gut barrier serves as both a physical and biochemical defense, crucial for preventing commensals and pathogens from crossing into the bloodstream [48]. High temperatures can compromise this barrier, allowing intestinal microbial products to escape and bind to Toll-like receptors (TLRs). TLRs play a key role in immune signaling by recognizing pathogen-associated molecular patterns. Interaction between TLR4 and advanced glycation end products activates the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, triggering the release of IL-1β, liver cell apoptosis, and sterile inflammation (**Figure 2**) [49]. This cascade leads to functional liver cell loss, impairing the liver's ability to clear endotoxins from the body [50]. Consequently, inhibiting gut microbial translocation becomes challenging, perpetuating elevated body temperature.

The liver's reticuloendothelial system, comprising monocytes, macrophages, and Kupffer cells, monitors pathogens, activates the complement cascade, locally produces PGE_2, and transmits this signal to the hypothalamic ventral preoptic area via the vagus nerve. This process induces norepinephrine production, alters preoptic PGE_2 levels, and reduces the firing rate of temperature-sensitive neurons, disrupting temperature regulation, heat dissipation, and further elevating core body temperature [51]. Research exploring bovine colostrum, rich in growth factors, suggests it may modulate these responses. Studies indicate colostrum can mitigate temperature-induced increases in Baxα and decreases in Bcl-2 levels, potentially enhancing exercise performance and reducing heatstroke risk [52].

Recent research has highlighted the pivotal role of CCAAT enhancer binding protein homologous protein (CHOP) in mediating heatstroke-induced cell apoptosis and barrier dysfunction in intestinal epithelial cells by regulating the expression of Bcl-2 and Bax [53]. Studies indicate that 4-phenylbutyrate can effectively modulate this process by inhibiting the PERK-CHOP pathway, thereby decreasing the levels of pro-apoptotic

Bax and increasing anti-apoptotic Bcl-2 proteins [53]. This intervention has shown promise in reducing cellular morphological changes and apoptosis induced by heatstroke, suggesting potential utility for 4-phenylbutyrate as a therapeutic approach in managing heatstroke [53]. Furthermore, recent findings suggest that intestinal microbes can bypass the liver and enter the systemic circulation through the mesenteric lymph nodes [54]. Once in circulation, microbial products encounter various host defense mechanisms, including binding by natural antibodies such as immunoglobulin G and M, leukocyte granule proteins like lactoferrin and lysozyme, and interactions with high-density lipoproteins [55]. These pathways help neutralize microbial products, mitigate excessive cytokine production, and potentially delay the progression of heatstroke.

In summary, the liver's detoxification function and the presence of immune antibodies in the systemic circulation are two crucial mechanisms for detoxifying gastrointestinal microbial products in humans. However, these mechanisms become impaired at core body temperatures exceeding 41-42 °C, exacerbated by strenuous exercise. Consequently, excessive heat production during exercise compromises both detoxification processes, allowing pathogen-associated molecular patterns in the gastrointestinal tract to bind to TLRs on cell membranes, triggering the transcription of activator protein-1 and nuclear factor kappa-B (NF-κB) [12, 56]. This leads to heightened production of pro-inflammatory mediators including PGE_2, TNF-α, IL-1β, IL-6, IFN-γ, and acute-phase C-reactive protein [45]. This inflammatory cascade perpetuates a positive feedback loop, driving continuous microbial product and cytokine production, which activates systemic inflammation. This inflammatory response is a key driver of disseminated coagulation, tissue necrosis, and organ failure, ultimately precipitating conditions conducive to sepsis and potentially fatal shock.

Cardiovascular system disorders

Cardiovascular diseases remain the leading cause of morbidity and mortality in the developed world, accounting for over 30% of deaths in the United States. Several studies have demonstrated a significant correlation between high temperatures and cardiovascular mortality, arrhythmias, sudden cardiac arrest, and the incidence of coronary heart disease [57]. High temperatures can increase myocardial oxygen consumption, potentially leading to fatal arrhythmias, with sinus tachycardia being the most common [57]. Sinus tachycardia promotes heat dissipation by increasing cardiac output. Additionally, high adrenaline stress due to elevated temperatures can trigger myocardiopathy and even result in circulatory failure or death [58]. High temperatures can also induce microcirculatory disorders, primarily due to increased expression of endothelial damage biomarkers (such as von Willebrand Factor and thrombomodulin), elevated release of cell adhesion molecules (such as ICAM-1), and an imbalance in the release of vasoactive substances involved in regulating local vascular relaxation and contraction (such as NO and endothelin). These changes can lead to tissue edema, damage to organ vascular endothelial cells, microthrombosis, extensive hemorrhage, and necrosis, causing heatstroke and multiple organ damage [59]. Specifically, patients with EHS exhibit a higher incidence of cardiovascular disease, myocardial infarction, ischemic heart disease, and acute ischemic stroke as early as 14 years following the initial heatstroke event [60].

Calcium Calsequestrins are expressed in the heart and regulate heart rate by controlling Ca^{2+} release from the sarcoplasmic reticulum. Heat stress can induce arrhythmias in rats by causing calsequestrin-1 oligomerization, which alleviates its inhibitory effect on RyR -2-mediated Ca^{2+} release. Additionally, calsequestrin-1 deficiency can independently lead to MH and EHS-like ventricular arrhythmias, revealing a new genetic mechanism for arrhythmias and MH/EHS arrhythmic occurrences [25].

Platelet damage

Heatstroke is often accompanied by coagulation disorders, with the incidence of disseminated intravascular coagulation reported to be as high as 48% [61]. The mechanisms of platelet damage caused by heatstroke may include the following:

1. Apoptosis mechanism triggered by high fever: High temperatures can directly damage platelets by inducing their apoptosis.

2. Inflammatory mediators causing platelet damage: Different inflammatory mediators can damage platelets through various pathways, primarily by activating platelets to release proteins and small molecules, inducing platelet apoptosis and necrosis.

3. Damage by reactive oxygen species (ROS): Due to ischemia and hypoxia in heatstroke patients, neutrophils are activated, leading to a respiratory burst and the production of a large

amount of ROS under the catalysis of reduced nicotinamide adenine dinucleotide.

4. Effects of vascular endothelial damage on platelets: Substances released by vascular endothelial cells can cause platelet aggregation and adhesion [62].

5. Direct activation of platelets by heat: Heat can directly promote platelet aggregation. Excessive aggregation caused by high temperatures can lead to platelet damage [63]. The specific pathway may involve elevated extracellular high mobility group box protein 1 (HMGB1) inducing high levels of ROS through platelet TLR4 and receptor for advanced glycation end product (RAGE), thereby participating in the activation of the NLRP3 inflammasome, resulting in platelet reduction during heatstroke [64].

The reduction in platelets and the release of inflammatory mediators and cytokines further damage vascular endothelial cells, promote coagulation reactions, form thrombi, block organ perfusion, and create a vicious cycle, leading to multiple organ dysfunction syndrome.

Liver function failure

The liver is the main organ involved in the production and response to cytokines during inflammation. In recent years, examinations of heatstroke patients have revealed that widened liver lymphocyte gap, thinner or spherical microvilli liver cells, and increased levels of enzymes such as glutamic pyruvic transaminase and lactate dehydrogenase, which are indicators of liver function [38]. Additionally, due to hypoxia, ischemia, and metabolic acidosis, there is local neutrophil infiltration in the liver, formation of local microthrombosis in the liver sinusoids, rupture of the liver cell membrane, balloon-like lesions, and even necrosis of liver cells, resulting in liver function failure [38, 65]. Some reports have indicated that heatstroke patients present with severe hypophosphatemia at the time of admission [66]. Hypophosphatemia may be related to respiratory alkalosis induced by hyperthermia, which causes phosphorus to shift from the extracellular to the intracellular compartment, resulting in reduced ATP synthesis and 2,3-diphosphoglycerate in red blood cells. This reduction diminishes the oxygenation function of the liver, impairs liver perfusion, and ultimately leads to acute liver failure [67].

Studies have shown that after heatstroke, the expression level of PINK1 in mitochondria increases, and the translocation of Parkin from the cytoplasm to the mitochondria also increases [68]. This indicates that heatstroke stabilizes PINK1 at the outer mitochondrial membrane, thereby recruiting more Parkin to eliminate damaged mitochondria. In heatstroke-induced acute liver injury (HS-ALI), the upregulation of p53 is involved in triggering HS-induced cell apoptosis [69]. Cytoplasmic p53 inhibits the translocation of Parkin to damaged mitochondria, preventing the removal of these damaged mitochondria. The lack of mitophagy subsequently increases cell apoptosis and oxidative stress response in HS-ALI [68]. In summary, cytoplasmic p53 binds to Parkin and inhibits mitophagy by preventing Parkin's translocation from the cytoplasm to the mitochondria, thereby reducing mitophagy activation and causing liver cell apoptosis in HS-ALI. Therefore, pharmacological inhibition of p53 to induce mitophagy may be a novel therapeutic approach for HS-ALI treatment. Additionally, research has found that angiotensin II-induced ROS activation leads to liver injury after heatstroke [44]. The angiotensin-(1-7) receptor agonist AVE 0991 can alleviate liver injury by inhibiting the ROS-NLRP3 inflammatory signaling pathway, indicating that the angiotensin-(1-7) receptor may be a potential target for treating liver injury following heatstroke [70].

Kidney injury

An increased death toll from chronic kidney disease among agricultural workers in Africa, India, the Middle East, and Central America has been reported, which is related to heat exposure and dehydration [71]. Heatstroke is often accompanied by acute kidney injury (AKI), characterized by renal tubular cell degeneration and apoptosis, resulting in symptoms such as hematuria and proteinuria, which may rapidly progress to acute renal failure with high mortality [72]. The pathogenesis of heatstroke-induced AKI involves multiple mechanisms, including renal ischemia, RM, and heat damage [73]. Hyperthermia can lead to disorders of the human anticoagulation system. Studies have shown that under hyperthermic conditions, there is glomerular swelling, inflammatory cell infiltration, vacuolar degeneration of endothelial cells, and renal tubular erythrocytes, which are characteristic signs of congestion, indicating a high risk of hemorrhage [74]. As a coagulation-related marker, the risk of AKI increases by 5.4 times with every 1 mg/L increase in D-dimer levels [75]. Other studies have shown that enhanced mitochondrial uncoupling protein 2 expression can improve mitochondrial dynamics in AKI [76].

Heatstroke-induced AKI is not only due to de-

hydration or reduced renal blood flow but also related to tubular injury caused by heat stress itself and the inflammatory immune response [77]. Some studies have shown that neutrophil infiltration in the kidney increases immediately after heat exposure and significantly increases 24 hours after heat stress [78]. A retrospective study on EHS patients in intensive care units also showed that increased neutrophils and decreased lymphocytes were risk factors for AKI [79]. Other studies have also shown that a decreased lymphocyte count is associated with an increased 90-day mortality rate and AKI incidence in heatstroke patients [80]. A reduction of macrophages in the kidney can inhibit renal recovery from AKI and exacerbate renal fibrosis. Additionally, due to heat damage, the release of myoglobin from RM in EHS gradually increases. Trials have revealed that muscle damage induced by exercise prior to high-temperature running can result in a more pronounced inflammatory response and increased renal stress compared to exercises without muscle damage [81]. Consequently, muscle damage should be recognized as a potential risk factor for AKI during physical activity in hot conditions [81]. Experimental models have shown that myoglobin may be a pathogenic factor for human renal proximal tubular cells after heat stress, exacerbating cell ferroptosis and endoplasmic reticulum stress response [82].

Lung Injury

The respiratory system is often affected during the initial attack of heatstroke. Acute lung injury (ALI) is a common complication in heatstroke patients, clinically characterized by acute pulmonary congestion and edema. Severe cases can develop into acute respiratory distress syndrome [83]. Microscopically, ALI is manifested by interstitial vasodilation and congestion caused by increased capillary permeability, widening of the interstitial spaces, blurred alveolar structure, injured epithelial cells, and pulmonary injury due to tissue infiltration of inflammatory cells [84].

The malignant cycle of ALI induced by heatstroke and the role of aldehyde dehydrogenase 2 (ALDH2) in breaking this vicious cycle can be attributed to several factors. Heat stress induces inflammation and cell apoptosis through the production of ROS and endogenous active aldehydes. Heat stress activates p38 and NF-κB, leading to the upregulation of NADPH oxidase-1 (NOX-1) overexpression in endothelial cells through NF-κB and p38 activation [85]. ROS produced by NOX causes a decrease in intracellular potential ($\Delta\Psi m$), leading to an increase in ROS produced by mitochondria, which further activates NOX, forming a vicious cycle [86]. Research has found that mitochondrial ALDH2, combined with the ALDH2 activator Alda-1, can inhibit this process, reduce ROS accumulation, and prevent heatstroke-induced ALI [87]. Therefore, Alda-1 can be used as an adjuvant therapy for heatstroke-induced ALI.

Heatstroke may cause ferroptosis in pulmonary tissue. This process involves divalent iron or lipoxygenase catalyzing the high expression of unsaturated fatty acids on the cell membrane, leading to lipid peroxidation and subsequent cell death [88]. Additionally, studies have found that increased acetylation levels of p53 can promote ferroptosis of pulmonary epithelial cells in heatstroke-induced ALI [89]. Research has shown that overexpressing the plasmid of silent information regulator 1 (SIRT1) can reduce the acetylation level of p53 and inhibit ferroptosis in heatstroke-induced mouse lung epithelial-2 cells, indicating that SIRT1-mediated deacetylation of p53 can reverse this process to alleviate ferroptosis [83]. Furthermore, heat stress can induce receptor-interacting protein kinase-dependent necroptosis in pulmonary vascular endothelial cells, which may lead to or exacerbate heatstroke-induced ALI.

Skin damages

The impact of ultraviolet radiation on skin health is a significant area of research. Numerous studies have demonstrated that exposure to ultraviolet radiation accelerates skin aging and carcinogenesis. The specific mechanisms include the formation of ROS, DNA damage, and chronic photodamage [90]. Additionally, while keratinocytes and fibroblasts do not predominantly contribute to the production of cytokines and prostaglandins in cases of heatstroke (< 44 ℃), they may play a significant role in evaporative cooling failure, focal hotspots, or systemic reactions [91].

Endocrine damages

Ischemic, hypoxic, and oxidative damage to the hypothalamus during heatstroke can lead to multi-organ dysfunction or failure via a hypothalamic–pituitary–adrenal axis mechanism. Rodents subjected to heatstroke exhibited elevated hypothalamic cell ischemia values and markers of injury, including pro-oxidant enzymes, pro-inflammatory cytokines, inducible nitric oxide synthase-dependent nitric oxide, and polymorphonuclear leukocyte accumulation [92]. Furthermore, these animals demonstrated neuronal injury post-heatstroke compared to

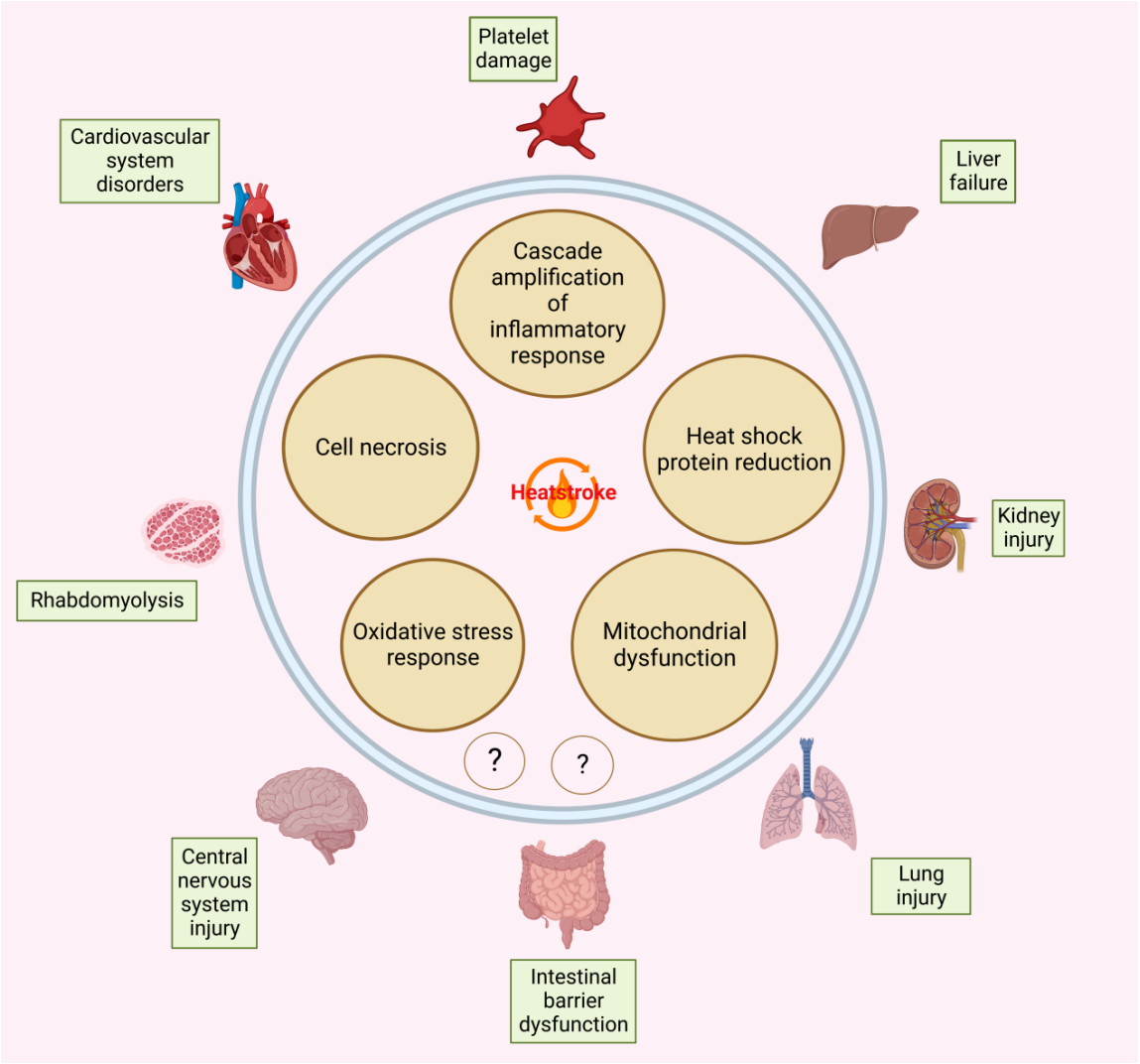

Figure 3. Heatstroke patients suffer from multiple organ injuries involving various molecular mechanisms. The molecular mechanisms of heatstroke include: elevated body temperature inducing oxidative stress, culminating in the generation of reactive oxygen species and subsequent tissue damage; hyperthermia facilitating the penetration of cell cytochrome C through the mitochondrial membrane, resulting in decreased mitochondrial cytochrome C levels, heightened reactive oxygen production, and disruption of mitochondrial membrane integrity; hyperthermia diminishing the permeability of the intestinal wall, enabling the escape of a significant amount of endotoxin, which activates Toll-like receptors, triggering the production of inflammatory factors and subsequently activating Kupffer cells, leading to a "sepsis-like response"; hyperthermia inducing misfolding of cytoplasmic proteins, reducing heat shock proteins, and attenuating the inhibition of the pro-inflammatory pathway; heat stress inducing MLKL and Caspase-8-dependent RIPK3-induced necroptosis through ZBP1. The consequential impact of heatstroke includes a spectrum of symptoms, encompassing liver, kidney, and lung damage, along with compromised intestinal barrier function. MLKL, mixed lineage kinase domain-like pseudokinase; RIPK3, receptor-interacting protein kinase 3; ZBP1, Z-DNA binding protein 1.

their normothermic counterparts. EHS-induced erectile dysfunction was observed in these rats. Additionally, testicular temperature disturbances were noted, along with poor seminiferous tubule differentiation, impaired sperm quality, and atrophy of various testicular tissue cells, such as interstitial mesenchymal cells, supporting cells, and peritubular cells. This was accompanied by spermatozoa azotemia, ruptured spermatozoa, and prostatic inflammation [93].

Molecular mechanisms of organ damage due to heatstroke

Heatstroke, a critical illness characterized by elevated body temperature and neurological manifestations, poses a significant threat to multiorgan function [2]. The pathophysiology of heatstroke involves a cascade of intricate molecular mechanisms, including oxidative stress response, mitochondrial dysfunction, inflammatory amplification, HSP insufficiency, and induction of cell necrosis. These interconnected pathways collectively contribute to the

progression of organ damage and dysfunction during heatstroke, highlighting the need for a comprehensive understanding of the underlying molecular processes for effective therapeutic interventions (**Figure 3**).

Oxidative stress response

Oxidative stress is a type of cellular damage and death that can promote the development and progression of heatstroke through various pathways, such as upregulating the function and expression of the antioxidant system, inducing lipid peroxidation, and activating cell apoptosis [94]. High temperatures can induce the body to produce a large amount of ROS [95]. Several mechanisms may be involved in this process:

1. After entering the irreversible stage, the decrease in cardiac output causes local hypoxia, which induces the production of ROS [67, 94, 95].

2. High heat can adversely affect the integrity of the mitochondrial membrane and its electron transport chain, resulting in the production of ROS. Additionally, high heat can stimulate the production of ROS by inducing mitochondrial fission or inhibiting the activity of mitochondrial complex I [96, 97].

3. Heat stress can induce the production of ROS by upregulating angiotensin II and its receptor (angiotensin receptor 1) [95].

4. Heat stress can promote the activation of the p38-MK2 signaling pathway, which promotes cell apoptosis by regulating the accumulation of ROS [98].

5. Heat stress can activate the Z-DNA binding protein 1 (ZBP1)- receptor-interacting protein kinase 3 (RIPK3) signaling pathway, which may be related to the production of ROS [99].

The high reactivity of ROS can modify several large cellular molecules, such as nucleic acids, proteins, and lipids. Heat stress is an effective inducer of ROS production. Once the cellular redox defense system, which consists of glutathione, glutathione peroxidase, superoxide dismutase, and heme oxygenase 1, is depleted, it can induce cell apoptosis by promoting ERK and Bcl-2 signaling and the release of apoptotic factors, eventually leading to tissue damage [100, 101].

Mitochondrial dysfunction

About ten years ago, the "lysosome-mitochondria axis" cell apoptosis signaling pathway was proposed, revealing the interaction between lysosomes and mitochondria in cell apoptosis. In this process, lysosomal membrane permeabilization is considered a key step, as tissue cysteine cathepsin is released from the lysosome into the cytoplasm and found to be involved in cell apoptosis. Specifically, tissue cysteine cathepsin B cleaves Bid and degrades the anti-apoptotic Bcl-2 protein in the cytoplasm, leading to the activation of caspases and subsequent mitochondrial depolarization, thereby triggering the mitochondrial pathway of cell apoptosis [102]. Recent studies have shown that when SW480 cells and intestinal tissues are exposed to heat stress, lysosomal membrane permeabilization occurs, releasing tissue cysteine cathepsin B into the cytoplasm [4]. This mediates the downstream lysosome-mitochondria apoptosis pathway in intestinal tissues and cultured epithelial cells [4]. Additionally, ROS induced by heat stress acts as an upstream signal in the cell's lysosomal damage and mitochondrial apoptosis pathways through various stimuli. It regulates the lysosome-mitochondria pathway and promotes cell apoptosis induced by heat stress in intestinal tissues and epithelial cells [4, 103].

Furthermore, some studies suggest that heat stress causes a sharp decrease in glutathione levels [104]. The combination of glutathione depletion and increased ROS production is considered an early event in heat-induced cell apoptosis. Due to the heat sensitivity of the respiratory chain, the energy activity of mitochondria changes under heat shock. Heat stress causes the inactivation of complex I in the respiratory chain and its degradation into smaller components, thereby reducing the flow rate of electrons in the electron transfer chain, leading to increased ROS production. Subsequently, ROS may cause the accumulation of secondary mtDNA mutations, leading to increased ROS leakage in the electron transfer chain, further exacerbating mitochondrial respiratory defects and increasing mitochondrial ROS production and lipid peroxidation [105].

High temperatures cause heatstroke, leading to an increase in the expression of the Bcl protein family in liver cells, making it easier for cytochrome C (Cyt-c) to be released from the mitochondrial membrane into the cytoplasm [68]. Once Cyt-c is released into the cytoplasm, it produces two main effects. First, it can activate enzymes of the Caspase family, thereby initiating apoptosis signal pathways and inducing liver cell apoptosis. Secondly, due to the inhibi-

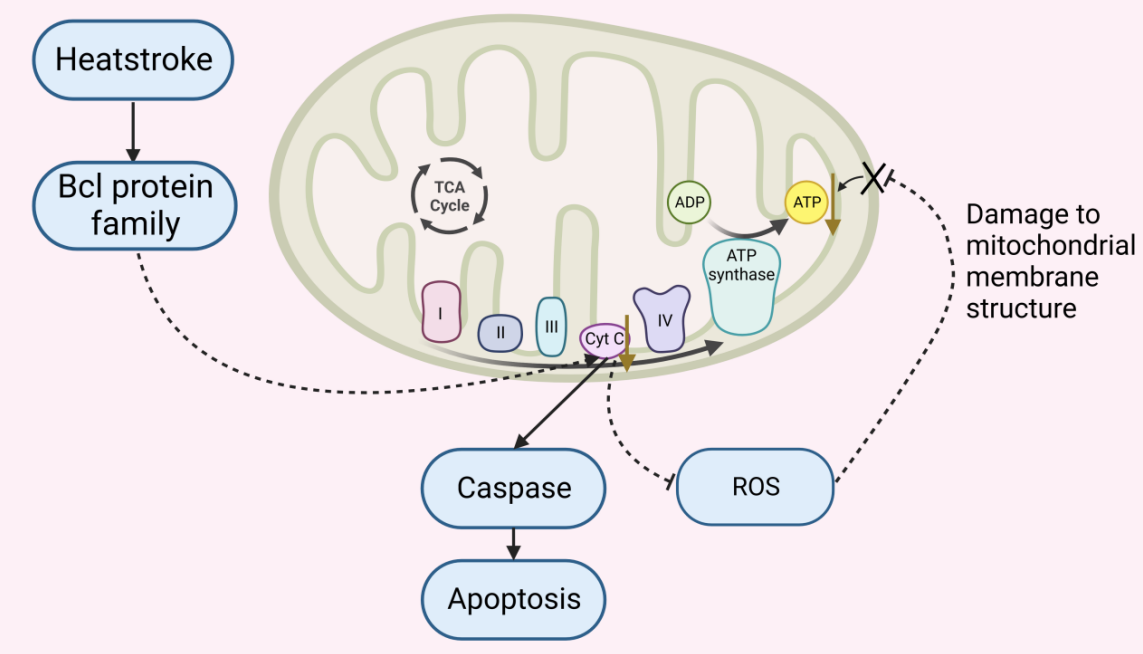

Figure 4. Heat stress leads to mitochondrial dysfunction. Heat stress triggers the expression of the Bcl protein family in mitochondria, facilitating the movement of Cyt-c through the mitochondrial membrane. This dual effect involves Cyt-c entering the cytosol, initiating the apoptosis signaling pathway, and inducing hepatocyte apoptosis. Simultaneously, the reduction of mitochondrial Cyt-c inhibits the electron transport in the oxidative respiratory chain, leading to an accumulation of reactive oxygen species. Elevated ROS levels further compromise the mitochondrial membrane structure, resulting in decreased ATP production and subsequent release of Cyt-c into the cytosol. Cyt-c, cytochrome C; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle.

tion of electron transfer in the oxidative respiratory chain by the decrease of mitochondrial Cyt-c, ROS production increases. Excessive ROS further disrupts the mitochondrial membrane structure, leading to ATP depletion and more Cyt-c release into the cytoplasm (**Figure 4**).

Cascading amplification of inflammatory response

When heatstroke occurs, a large number of endotoxins enter the liver through the portal vein and activate the TLR signaling pathway. These endotoxins bind to lipopolysaccharide binding protein in the blood. Subsequently, they are recognized and bound to TLR4 on the Kupffer cell membrane, forming a complex that interacts with CD14 and MD2 subunits on the membrane. This complex activates intracellular signal transduction through MyD88-dependent and MyD88-independent pathways, leading to the activation of NF-κB. Consequently, this upregulates the expression and release of inflammatory factors such as TNF-α and IL-1β [106]. This process activates Kupffer cells, resulting in a "sepsis-like response."

Insufficient HSP

Heat sickness induces the misfolding and aggregation of proteins within the cytoplasm. This triggers the release of HSPs from inactive monomeric HSF1, initiating the heat shock response. Activated transcription factors then enter the nucleus, forming trimers that activate the gene expression of inducible HSPs. Inducible HSPs, in turn, activate more HSF, triggering the unfolded protein response. This pathway enhances the protein's ability to fold correctly and, in extreme cases, reduces the synthesis of new proteins or induces apoptosis [107]. Additionally, inducible HSPs can bind to misfolded proteins, facilitating their refolding or degradation by proteases to inhibit apoptosis.

The duration and magnitude of the heat shock response are influenced by individual age, genetic and epigenetic regulation, and the degree of adaptation to heat. HSPs, particularly HSP70, play a crucial role in mitigating the onset and development of heat stress disorders. Acting as a molecular chaperone, HSP70 forms protein aggregates and degrades damaged proteins while aiding in the correct refolding of newly synthesized proteins. Furthermore, HSP70 exhibits a potent anti-inflammatory function within cells. In summary, HSPs exert cytoprotective and anti-inflammatory effects by inhibiting multiple pro-inflammatory pathways. Most stress adaptation responses require increased HSP levels, and a reduction or insufficiency in HSP expression may heighten sensi-

tivity to stress.

Cell necrosis induced by heat stress

ZBP1, initially identified as an IFN-induced tumor-associated protein, has been implicated in the pathogenesis of heatstroke. Research indicates that heat stress elevates ZBP1 expression by enhancing the activation and occupancy of HSF1 binding sites in the ZBP1 promoter [108]. ZBP1 activation occurs through a nucleic acid sensing-independent mechanism. Positioned upstream of mixed lineage kinase domain-like pseudokinase (MLKL) and Caspase-8, ZBP1, upon activation, triggers the phosphorylation-dependent activation of MLKL by RIPK3, leading to programmed necrosis [99]. Furthermore, ZBP1 and RIPK3 activation may instigate thrombin activation, fibrosis deposition, and platelet adhesion in microvessels. In summary, heat stress, by mediating MLKL and Caspase-8-dependent RIPK3-induced necroptosis through ZBP1, may contribute to circulatory failure, organ damage, and, in severe cases, heatstroke-related fatalities [108].

Conclusion

This review provides a comprehensive overview of recent advancements in understanding multiple organ damage and the molecular mechanisms of heatstroke. Although existing research indicates that the intricate interplay between heat-related cytotoxicity, inflammatory response, coagulopathy, RM, and gastrointestinal disruption contributes to multiple organ damage in heatstroke patients, the specific mechanisms remain incompletely elucidated. Future investigations should explore high-temperature-induced metabolic changes, tissue cell dysfunction during the cooling process, and the utilization of animal models to delve deeper into the pathophysiological processes and the development and progression mechanisms of heatstroke. Such endeavors will aid clinicians in more accurately assessing the severity and prognosis of patients, facilitating the development and implementation of improved treatment plans.

Authors contributions: Ruilong Li, Dezhi Guo, and Tianying Li wrote the main manuscript text. Tianying Xu and Panpan Hu revised and edited the manuscript. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

References

[1] Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346(25):1978-1988.

[2] Yeo TP. Heat stroke: a comprehensive review. AACN Clin Issues 2004;15(2):280-293.

[3] Argaud L, Ferry T, Le QH, et al. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. Arch Intern Med 2007;167(20):2177-2183.

[4] Yi G, Li L, Luo M, et al. Heat stress induces intestinal injury through lysosome- and mitochondria-dependent pathway in vivo and in vitro. Oncotarget 2017;8(25):40741-40755.

[5] Lucas RA, Epstein Y, Kjellstrom T. Excessive occupational heat exposure: a significant ergonomic challenge and health risk for current and future workers. Extrem Physiol Med 2014;3:14.

[6] Periasamy M, Herrera JL, Reis FCG. Skeletal Muscle Thermogenesis and Its Role in Whole Body Energy Metabolism. Diabetes Metab J 2017;41(5):327-336.

[7] Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43(8):1575-1581.

[8] Marty I, Fauré J. Excitation-Contraction Coupling Alterations in Myopathies. J Neuromuscul Dis 2016;3(4):443-453.

[9] Lin BL, Li A, Mun JY, et al. Skeletal myosin binding protein-C isoforms regulate thin filament activity in a Ca(2+)-dependent manner. Sci Rep 2018;8(1):2604.

[10] Calderón JC, Bolaños P, Caputo C. The excitation-contraction coupling mechanism in skeletal muscle. Biophys Rev 2014;6(1):133-160.

[11] van der Poel C, Stephenson DG. Effects of elevated physiological temperatures on sarcoplasmic reticulum function in mechanically skinned muscle fibers of the rat. Am J Physiol Cell Physiol 2007;293(1):C133-C141.

[12] Smith CJ, Johnson JM. Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: Neural control of skin blood flow and sweating in humans. Auton Neurosci 2016;196:25-36.

[13] Angilletta MJ, Jr., Cooper BS, Schuler MS, et al. The evolution of thermal physiology in endotherms. Front Biosci (Elite Ed) 2010;2(3):861-881.

[14] Goto M, Okazaki K, Kamijo Y, et al. Protein and carbohydrate supplementation during 5-day aerobic training enhanced plasma volume expansion and thermoregulatory adaptation in young men. J Appl Physiol (1985) 2010;109(4):1247-1255.

[15] Horowitz M. Heat acclimation, epigenetics, and cytoprotection memory. Compr Physiol 2014;4(1):199-230.

[16] Taylor NAS, Notley SR, Lindinger MI. Heat

adaptation in humans: extrapolating from basic to applied science. Eur J Appl Physiol 2021;121(4):1237-1238.
[17] Laitano O, Leon LR, Roberts WO, et al. Controversies in exertional heat stroke diagnosis, prevention, and treatment. J Appl Physiol (1985) 2019;127(5):1338-1348.
[18] Lin XJ, Li YJ, Li ZL, et al. Pre-existing lipopolysaccharide may increase the risk of heatstroke in rats. Am J Med Sci 2009;337(4):265-270.
[19] Abello PA, Buchman TG. Heat shock-induced cell death in murine microvascular endothelial cells depends on priming with tumor necrosis factor-alpha or interferon-gamma. Shock 1994;2(5):320-323.
[20] Carter R 3rd, Cheuvront SN, Sawka MN. A case report of idiosyncratic hyperthermia and review of U.S. Army heat stroke hospitalizations. J Sport Rehabil 2007;16(3):238-243.
[21] Dineen SM, Ward JA, Leon LR. Prior viral illness increases heat stroke severity in mice. Exp Physiol 2021;106(1):244-257.
[22] Murray KO, Brant JO, Iwaniec JD, et al. Exertional heat stroke leads to concurrent long-term epigenetic memory, immunosuppression and altered heat shock response in female mice. J Physiol 2021;599(1):119-141.
[23] Yamazawa T, Kobayashi T, Kurebayashi N, et al. A novel RyR1-selective inhibitor prevents and rescues sudden death in mouse models of malignant hyperthermia and heat stroke. Nat Commun 2021;12(1):4293.
[24] Poussel M, Guerci P, Kaminsky P, et al. Exertional Heat Stroke and Susceptibility to Malignant Hyperthermia in an Athlete: Evidence for a Link? J Athl Train 2015;50(11):1212-1214.
[25] Sun Z, Wang L, Han L, et al. Functional Calsequestrin-1 Is Expressed in the Heart and Its Deficiency Is Causally Related to Malignant Hyperthermia-Like Arrhythmia. Circulation 2021;144(10):788-804.
[26] Gibson OR, Tuttle JA, Watt PW, et al. Hsp72 and Hsp90α mRNA transcription is characterised by large, sustained changes in core temperature during heat acclimation. Cell Stress Chaperones 2016;21(6):1021-1035.
[27] Alele FO, Otto JR, Malau-Aduli BS, et al. Next Generation Sequencing of Genotype Variants and Genetic Association between Heat Shock Proteins HSPA1B Single Nucleotide Polymorphism at the g.31829044 Locus and Heat Tolerance: A Pilot Quasi-Experimental Study. Biomolecules 2022;12(10):1465.
[28] Dehbi M, Baturcam E, Eldali A, et al. Hsp-72, a candidate prognostic indicator of heatstroke. Cell Stress Chaperones 2010;15(5):593-603.
[29] Sonna LA, Wenger CB, Flinn S, et al. Exertional heat injury and gene expression changes: a DNA microarray analysis study. J Appl Physiol (1985) 2004;96(5):1943-1953.
[30] Bazille C, Megarbane B, Bensimhon D, et al. Brain damage after heat stroke. J Neuropathol Exp Neurol 2005;64(11):970-975.
[31] Leon LR, Bouchama A. Heat stroke. Compr Physiol 2015;5(2):611-647.
[32] Kao TY, Lin MT. Brain serotonin depletion attenuates heatstroke-induced cerebral ischemia and cell death in rats. J Appl Physiol (1985) 1996;80(2):680-684.
[33] Wang L, Deng Z, Zhao Y, et al. Mesenchymal stem cells regulate activation of microglia cells to improve hippocampal injury of heat stroke rats. J Therm Biol 2021;101:103081.
[34] Burke S, Hanani M. The actions of hyperthermia on the autonomic nervous system: central and peripheral mechanisms and clinical implications. Auton Neurosci 2012;168(1-2):4-13.
[35] Hirayama I, Inokuchi R, Ueda Y, et al. Heat Stroke Lesions in the Globus Pallidus. Intern Med 2020;59(7):1015-1016.
[36] Siegel JS, Snyder AZ, Metcalf NV, et al. The circuitry of abulia: insights from functional connectivity MRI. Neuroimage Clin 2014;6:320-326.
[37] Nelson S, Toma H, LaMonica H, et al. Major Cognitive Changes and Micrographia following Globus Pallidus Infarct. Case Rep Neurol Med 2014;2014:252486.
[38] Knapik JJ, Epstein Y. Exertional Heat Stroke: Pathophysiology, Epidemiology, Diagnosis, Treatment, and Prevention. J Spec Oper Med 2019;19(2):108-116.
[39] Hsu YD, Lee WH, Chang MK, et al. Blood lactate threshold and type II fibre predominance in patients with exertional heatstroke. J Neurol Neurosurg Psychiatry 1997;62(2):182-187.
[40] Deguchi H, Morla S, Griffin JH. Novel blood coagulation molecules: Skeletal muscle myosin and cardiac myosin. J Thromb Haemost 2021;19(1):7-19.
[41] Keuter M, Dharmana E, Kullberg BJ, et al. Phospholipase A2 is a circulating mediator in typhoid fever. J Infect Dis 1995;172(1):305-308.
[42] Schlader ZJ, Davis MS, Bouchama A. Biomarkers of heatstroke-induced organ injury and repair. Exp Physiol 2022;107(10):1159-1171.
[43] He S, Li R, Peng Y, et al. ACSL4 contributes to ferroptosis-mediated rhabdomyolysis in exertional heat stroke. J Cachexia Sarcopenia Muscle 2022;13(3):1717-1730.
[44] Leon LR, Helwig BG. Heat stroke: role of

the systemic inflammatory response. J Appl Physiol (1985) 2010;109(6):1980-1988.
[45] Neves AL, Coelho J, Couto L, et al. Metabolic endotoxemia: a molecular link between obesity and cardiovascular risk. J Mol Endocrinol 2013;51(2):R51-R64.
[46] Hall DM, Buettner GR, Oberley LW, et al. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am J Physiol Heart Circ Physiol 2001;280(2):H509-H521.
[47] Lambert GP, Gisolfi CV, Berg DJ, et al. Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. J Appl Physiol (1985) 2002;92(4):1750-1761;discussion 1749.
[48] Wells JM, Brummer RJ, Derrien M, et al. Homeostasis of the gut barrier and potential biomarkers. Am J Physiol Gastrointest Liver Physiol 2017;312(3):G171-G193.
[49] Zhang ZT, Gu XL, Zhao X, et al. NLRP3 ablation enhances tolerance in heat stroke pathology by inhibiting IL-1β-mediated neuroinflammation. J Neuroinflammation 2021;18(1):128.
[50] Kawasaki T, Okamoto K, Kawasaki C, et al. Thrombomodulin improved liver injury, coagulopathy, and mortality in an experimental heatstroke model in mice. Anesth Analg 2014;118(5):956-963.
[51] Blatteis CM. The onset of fever: new insights into its mechanism. Prog Brain Res 2007;162:3-14.
[52] Marchbank T, Davison G, Oakes JR, et al. The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. Am J Physiol Gastrointest Liver Physiol 2011;300(3):G477-G484.
[53] Cao Y, Fan M, Pei Y, et al. CCAAT/Enhancer-Binding Protein Homologous Protein (CHOP) Deficiency Attenuates Heatstroke-Induced Intestinal Injury. Inflammation 2022;45(2):695-711.
[54] Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon 2012;10(6):350-356.
[55] Munford RS. Detoxifying endotoxin: time, place and person. J Endotoxin Res 2005;11(2):69-84.
[56] Fukui H. Endotoxin and Other Microbial Translocation Markers in the Blood: A Clue to Understand Leaky Gut Syndrome. Cell Mol Med 2016;2:3.
[57] Liu J, Varghese BM, Hansen A, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. Lancet Planet Health 2022;6(6):e484-e495.
[58] Marchand M, Gin K. The Cardiovascular System in Heat Stroke. CJC Open 2022;4(2):158-163.
[59] Chen F, Li H, Zhu G, et al. Sodium tanshinone IIA sulfonate improves inflammation, aortic endothelial cell apoptosis, disseminated intravascular coagulation and multiple organ damage in a rat heat stroke model. Mol Med Rep 2017;16(1):87-94.
[60] Wang JC, Chien WC, Chu P, et al. The association between heat stroke and subsequent cardiovascular diseases. PLoS One 2019;14(2):e0211386.
[61] Huisse MG, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: the link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. Crit Care Med 2008;36(8):2288-2295.
[62] Proctor EA, Dineen SM, Van Nostrand SC, et al. Coagulopathy signature precedes and predicts severity of end-organ heat stroke pathology in a mouse model. J Thromb Haemost 2020;18(8):1900-1910.
[63] Majeed EN. Effects of heat on camel platelet structure and function--a comparative study with humans. Platelets 2009;20(7):528.
[64] Yin H, Wu M, Lu Y, et al. HMGB1-activatied NLRP3 inflammasome induces thrombocytopenia in heatstroke rat. PeerJ 2022;10:e13799.
[65] Wang F, Zhang Y, Li J, et al. The pathogenesis and therapeutic strategies of heat stroke-induced liver injury. Crit Care 2022;26(1):391.
[66] Salathé C, Pellaton C, Carron PN, et al. Acute liver failure complicating exertional heat stroke: possible role of hypophosphatemia. Curr Sports Med Rep 2015;14(1):49-50.
[67] Lian P, Braber S, Garssen J, et al. Beyond Heat Stress: Intestinal Integrity Disruption and Mechanism-Based Intervention Strategies. Nutrients 2020;12(3):734.
[68] Huang W, Xie W, Zhong H, Cai S, Huang Q, Liu Y, Zeng Z and Liu Y. Cytosolic p53 Inhibits Parkin-Mediated Mitophagy and Promotes Acute Liver Injury Induced by Heat Stroke. Front Immunol 2022;13:859231.
[69] Chen Y, Yu T. Involvement of p53 in the Responses of Cardiac Muscle Cells to Heat Shock Exposure and Heat Acclimation. J Cardiovasc Transl Res 2020;13(6):928-937.
[70] Zhang M, Zhu X, Tong H, et al. AVE 0991 Attenuates Pyroptosis and Liver Damage after Heatstroke by Inhibiting the ROS-NLRP3 Inflammatory Signalling Pathway. Biomed Res Int 2019;2019:1806234.
[71] Sorensen C, Garcia-Trabanino R. A New Era of Climate Medicine - Addressing Heat-Triggered Renal Disease. N Engl J Med 2019;381(8):693-696.
[72] Wu M, Wang C, Zhong L, et al. Serum myoglobin as predictor of acute kidney injury and 90-day mortality in patients with rhabdomyolysis after exertional heatstroke:

an over 10-year intensive care survey. Int J Hyperthermia 2022;39(1):446-454.
[73] Thongprayoon C, Qureshi F, Petnak T, et al. Impact of Acute Kidney Injury on Outcomes of Hospitalizations for Heat Stroke in the United States. Diseases 2020;8(3):28.
[74] Mozzini C, Xotta G, Garbin U, et al. Non-Exertional Heatstroke: A Case Report and Review of the Literature. Am J Case Rep 2017;18:1058-1065.
[75] Wang C, Yu B, Chen R, et al. Association of D-dimer and acute kidney injury associated with rhabdomyolysis in patients with exertional heatstroke: an over 10-year intensive care survey. Ren Fail 2021;43(1):1561-1568.
[76] Qin N, Cai T, Ke Q, et al. UCP2-dependent improvement of mitochondrial dynamics protects against acute kidney injury. J Pathol 2019;247(3):392-405.
[77] Goto H, Kinoshita M, Oshima N. Heatstroke-induced acute kidney injury and the innate immune system. Front Med (Lausanne) 2023;10:1250457.
[78] Hu J, Kang H, Liu C, et al. Acute immune responses are involved in liver and kidney injury in heat stroke. Eur J Inflamm 2019;17(9):2058739219838709.
[79] Wu M, Wang C, Liu Z, et al. Clinical Characteristics and Risk Factors Associated With Acute Kidney Injury Inpatient With Exertional Heatstroke: An Over 10-Year Intensive Care Survey. Front Med (Lausanne) 2021;8:678434.
[80] Ji J, Su P, Lin W, et al. Immune Cells Characteristics and Their Prognostic Effects in Exertional Heatstroke Patients: A Retrospective Cohort Study. Front Med (Lausanne) 2022;9:867774.
[81] Junglee NA, Di Felice U, Dolci A, et al. Exercising in a hot environment with muscle damage: effects on acute kidney injury biomarkers and kidney function. Am J Physiol Renal Physiol 2013;305(6):F813-F820.
[82] Luan Y, Huang E, Huang J, et al. Serum myoglobin modulates kidney injury via inducing ferroptosis after exertional heatstroke. J Transl Int Med 2023;11(2):178-188.
[83] Chen H, Lin X, Yi X, et al. SIRT1-mediated p53 deacetylation inhibits ferroptosis and alleviates heat stress-induced lung epithelial cells injury. Int J Hyperthermia 2022;39(1):977-986.
[84] Mokrá D. Acute lung injury - from pathophysiology to treatment. Physiol Res 2020;69(Suppl 3):S353-S366.
[85] Song W, Wei L, Du Y, et al. Protective effect of ginsenoside metabolite compound K against diabetic nephropathy by inhibiting NLRP3 inflammasome activation and NF-κB/p38 signaling pathway in high-fat diet/streptozotocin-induced diabetic mice. Int Immunopharmacol 2018;63:227-238.
[86] Masselli E, Pozzi G, Vaccarezza M, et al. ROS in Platelet Biology: Functional Aspects and Methodological Insights. Int J Mol Sci 2020;21(14):4866.
[87] Tsai HY, Hsu YJ, Lu CY, et al. Pharmacological Activation Of Aldehyde Dehydrogenase 2 Protects Against Heatstroke-Induced Acute Lung Injury by Modulating Oxidative Stress and Endothelial Dysfunction. Front Immunol 2021;12:740562.
[88] Yu T, Sun S. Role and mechanism of ferroptosis in acute lung injury. Cell Cycle 2023;22(19):2119-2129.
[89] Chen H, Xie W, Peng Z, et al. Nobiletin ameliorates heatstroke-induced acute lung injury by inhibiting ferroptosis via p53/slc7a11 pathway. Shock 2024;61(1):105-111.
[90] Mohania D, Chandel S, Kumar P, et al. Ultraviolet Radiations: Skin Defense-Damage Mechanism. Adv Exp Med Biol 2017;996:71-87.
[91] Bowers W, Blaha M, Alkhyyat A, et al. Artificial human skin: cytokine, prostaglandin, Hsp70 and histological responses to heat exposure. J Dermatol Sci 1999;20(3):172-182.
[92] Chen SH, Lin MT, Chang CP. Ischemic and oxidative damage to the hypothalamus may be responsible for heat stroke. Curr Neuropharmacol 2013;11(2):129-140.
[93] Lin PH, Huang KH, Tian YF, et al. Exertional heat stroke on fertility, erectile function, and testicular morphology in male rats. Sci Rep 2021;11(1):3539.
[94] Ni XX, Nie J, Xie QY, et al. Protective Effects of Hyperbaric Oxygen Therapy on Brain Injury by Regulating the Phosphorylation of Drp1 Through ROS/PKC Pathway in Heatstroke Rats. Cell Mol Neurobiol 2020;40(8):1253-1269.
[95] Wang X, Yuan B, Dong W, et al. Humid heat exposure induced oxidative stress and apoptosis in cardiomyocytes through the angiotensin II signaling pathway. Heart Vessels 2015;30(3):396-405.
[96] Yu T, Ferdjallah I, Elenberg F, et al. Mitochondrial fission contributes to heat-induced oxidative stress in skeletal muscle but not hyperthermia in mice. Life Sci 2018;200:6-14.
[97] Huang C, Jiao H, Song Z, et al. Heat stress impairs mitochondria functions and induces oxidative injury in broiler chickens. J Anim Sci 2015;93(5):2144-2153.
[98] Li H, Liu Y, Gu Z, et al. p38 MAPK-MK2 pathway regulates the heat-stress-induced accumulation of reactive oxygen species that

mediates apoptotic cell death in glial cells. Oncol Lett 2018;15(1):775-782.
[99] Li F, Deng J, He Q, et al. ZBP1 and heatstroke. Front Immunol 2023;14:1091766.
[100] Li L, Tan H, Yang H, et al. Reactive oxygen species mediate heat stress-induced apoptosis via ERK dephosphorylation and Bcl-2 ubiquitination in human umbilical vein endothelial cells. Oncotarget 2017;8(8):12902-12916.
[101] Tajeddine N. How do reactive oxygen species and calcium trigger mitochondrial membrane permeabilisation? Biochim Biophys Acta 2016;1860(6):1079-1088.
[102] Chen F, Deng Z, Xiong Z, et al. A ROS-mediated lysosomal-mitochondrial pathway is induced by ginsenoside Rh2 in hepatoma HepG2 cells. Food Funct 2015;6(12):3828-3837.
[103] Ding Y, Wang H, Niu J, et al. Induction of ROS Overload by Alantolactone Prompts Oxidative DNA Damage and Apoptosis in Colorectal Cancer Cells. Int J Mol Sci 2016;17(4):558.
[104] Ohtsuka Y, Yabunaka N, Fujisawa H, et al. Effect of thermal stress on glutathione metabolism in human erythrocytes. Eur J Appl Physiol Occup Physiol 1994;68(1):87-91.
[105] Kirkinezos IG, Moraes CT. Reactive oxygen species and mitochondrial diseases. Semin Cell Dev Biol 2001;12(6):449-457.
[106] Chen XJ, Tang ZZ, Zhu GG, et al JNK signaling is required for the MIP-1α-associated regulation of Kupffer cells in the heat stroke response. Mol Med Rep 2017;16(3):2389-2396.
[107] Morimoto RI. The heat shock response: systems biology of proteotoxic stress in aging and disease. Cold Spring Harb Symp Quant Biol 2011;76:91-99.
[108] Yuan F, Cai J, Wu J, et al. Z-DNA binding protein 1 promotes heatstroke-induced cell death. Science 2022;376(6593):609-615.