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Clinical Review

INTESTINAL INJURY IN HEAT STROKE

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☐ **Abstract—Background: Heat stroke is a life-threatening syndrome that is characterized by its severe clinical symptoms, rapid progression, and high rate of mortality. Recently, research has indicated that a dysfunctional intestinal epithelia barrier plays an important role in the pathophysiology of heat stroke. Protecting the intestines from heat stress had been identified as a potentially effective treatment for patients with heat stroke and may reduce the innate immune response caused by endotoxins in circulation. Objectives: The aim of this review is to discuss this key event in heat stroke and to describe the mechanism during progression. Discussion: Direct injuries and secondary impairments of the intestine induced by heat stress are discussed; recent studies that refer to intestine-specific prevention and treatment in heat stroke and heat stress-induced injuries are also summarized. Conclusions: A more detailed pathogenesis of heat stroke needs to be elucidated so that potentially effective means of treatment and prevention of heat stroke can be developed and studied.** © 2019 Elsevier Inc. All rights reserved.

☐ **Keywords—heat stroke; intestinal injury; intestinal mucosal barrier**

INTRODUCTION

Heat stroke is a life-threatening syndrome. When it occurs, it is generally a consequence of ≥1 intense thermal loads. The intense thermal load that precipitates heat stroke can be a consequence of environmental factors or metabolic factors. Environmental factors include exposure to a hot environment, exposure to a high-humidity environment in which evaporative cooling is compromised, or both. The thermal load that causes heat stroke can also be a consequence of a high metabolic rate, as during intense physical activity. In many patients, when heat stroke occurs, both environmental and metabolic factors have exerted their combined effects (1). Heat stroke begins with a series of pathophysiologic changes, including an elevation of the body core temperature, dehydration, and electrolyte disturbances (2). As failure of dissipation of the intense thermal load from the external environment and from metabolic heat production ensues over time, dysfunctional thermoregulation occurs. This causes heat-induced hypothalamic damage, then severe hyperthermia. Debilitating central nervous system dysfunction may subsequently rapidly develop (3). Individuals who have suffered from heat stroke should be treated as soon as possible to mitigate the severity of critical complications, such as systemic inflammatory response syndrome (SIRS), characterized by early endogenous expression of interleukins, disseminated intravascular coagulation (DIC) triggered by heat stress, and multiple organ dysfunction syndrome (MODS), which may result in a high mortality, and irreversible denaturation of proteins, which can begin at body temperatures in excess of approximately 41°C or 42°C (4,5).

Although heat stroke has been studied for hundreds of years, the precise pathogenesis remains unclear (6). As currently known, heat stroke relates to a complex set of

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processes, comprised of dehydration, electrolyte disturbances, protein denaturation, and injuries of endothelial cells. Heat stroke causes damage to important organs via nitrosative stress, oxidative stress, and endotoxemia (7). At the onset of heat stroke, development of pathological lesions depends largely upon the magnitude of increased proinflammatory factors and prolonged inflammatory immune response, caused by reductions in blood flow.

In this review we discuss the pivotal role of the intestines in heat stroke and summarize the potential intestine-specific targeting and treatments known to date. This review can help researchers uncover the explicit pathogenesis of and explore novel therapeutic strategies for heat stroke.

Heat Stress and the Gut

The intestines act as important digestive and immune organs. However, they also contain many intraluminal bacteria and can produce numerous endotoxins (8). Gut-derived endotoxin translocation that ensues after dysfunction of the intestinal mucosal barrier has been identified as an important causative factor of mortality in recent years; many studies have also suggested that preventing injury to the intestinal mucosal barrier could be an effective therapeutic modality in patients with heat stroke and in animal models of heat stroke (9,10). The diagnosis of heat stroke is a clinical one, characterized by hyperthermia accompanied by an altered mental status. However, the multiple organ injuries that ensue with heat stroke are difficult to reverse. The pathologic processes, the potential therapeutic time window, and better treatment strategies remain to be fully explored.

Direct Injury of the Intestine Caused by Heat Stress

Integrity of the intestinal barrier is necessary to prevent bacteria in the intestine from translocating into the intestinal capillary beds. Also, the dysfunctional intestinal mucosal barrier that results from heat stroke often results in a gut-derived endotoxinemia, which may significantly promote the progression of SIRS and MODS (11). Many studies have indicated that increased intestinal epithelial permeability and endotoxin translocation into the circulatory system is closely associated with the injury of organs caused by continuous heat stress (12,13).

Intestinal Barrier Injury in the Intestine

The tight junctions between intestinal epithelial cells present a robust barrier to invasion by bacteria and their toxins (14). Both epithelial cells and the tight junctions between them play a pivotal role (14,15). Defective tight junctions are also the primary reason for heat stroke–related alterations in intestinal permeability. The tight junction consists of transmembrane proteins (occludin, claudins, and junction adhesion molecules), intracellular plaque zonula occludens (ZO-1, ZO-2, and ZO-3), and others (16–18). In a thermal environment, the need for heat dissipation requires increasing skin blood flow. This causes redistribution of blood flow away from visceral vascular beds and toward the cutaneous vasculature. Ischemic and hypoxic injuries, together with heat stress, causes the damage to intestinal epithelial cells (7,19).

Oxidative stress influences both the survival of intestinal epithelial cells and the function of intercellular tight junctions (20). ZO-1 is an important component of tight junctions. A recent study has detected a reduction of expression of ZO-1 and an increase of paracellular permeability under sustained heat stress (21). As one of the most important structural proteins of tight junctions, occludin shows a reactive increase to maintain the function of tight junctions in the early stages of heat strain. However, a high level of heat shock protein is necessary to maintain the expression of occludin, which indicates that heat stress may also harm occludin secretion (21). Furthermore, trypsin in the small intestine also exacerbates the injury of intestinal epithelial cells and intercellular tight junctions, leading to impairment of intact intestinal barrier function (22).

Other Functional Injuries of the Intestine

Heat stress also influences the functions of the intestines in other ways. It is known that there are a vast number of lymphoid tissues and immune cells in the intestines that can prevent pathogens from invading the internal environment under normal conditions. Cytotoxicity of ischemia and heat stress not only increases the permeability, oxidative stress, and inflammatory responses in the gut but also results in a dysfunction of immune cells directly. In such a condition, pathogens in the intestines may not be restrained by protective mucosal immune responses in time (23).

In addition, other intestinal changes that accompany heat stroke may be easily ignored. The mucous membrane of the small intestine, which is essential in maintaining the balance of body fluids and electrolytes, plays an important role in the absorption of liquids and the transport of solutes (24,25). In the early stages of heat stroke, water–electrolyte imbalance often occurs, secondary to profuse sweating. The normal expression of aquaporins in the small intestine has been identified as an important part of water absorption by mediating transcellular water movement. With the absorptive

function of the small intestine being adversely affected by heat stress, water shortage and electrolyte disturbances in the body will further aggravate heat stroke. In an in vivo and in vitro study, the expression of aquaporins 1, 3, 5, 7, 8, and 11 in the small intestine were proven to be up-regulated and down-regulated at different time phases after heat stroke, which indicates that dysfunctional water absorption may also influence the clinical state of patients with heat stroke (26). In light of this, it may be necessary in some patients with only mild symptoms to assess whether oral rehydration therapy is effective.

Secondary Impairments of the Intestine in Heat Stress

Aside from the direct injuries mentioned above, there are various secondary impairments after intestinal barrier function has been impaired. As the dysfunctional intestinal barrier fails to separate intestinal epithelia cells from lipopolysaccharide (LPS) in the intestinal tract, endotoxins may induce a breakdown of proteins in tight junctions by direct contact and damage intercellular tight junctions by affecting the process of phosphorylation/dephosphorylation (27). Digestive enzymes in the small intestine cause additional damage to the intestinal barrier and intestinal wall by autodigestion in severe heat stress as a result of the dysfunctional intestinal barrier. Many studies showed a significant protective effect in the intestine of animal models of hemorrhagic shock and sepsis by blocking the activity of trypsin in the lumen of the intestine, indicating that trypsin is one of the most critical factors in the secondary injury in intestine (28).

Endotoxin Translocation in Heat Stroke

Many studies have shown that endotoxins appearing in the blood of patients with heat stroke are derived from gut lumen. The important role of the intestinal mucosal barrier has been confirmed in the progression of heat stroke in vivo and vitro (29–31). Endotoxemia in heat stroke has been accepted as the initial link of SIRS and MODS and the major cause of mortality in patients with heat stroke (32,33). In the early stage of heat stroke, organs and the intestinal barrier have been damaged by heat stress to a degree.

After endotoxin leakage into the bloodstream, strong innate and adaptive immune systems sense and respond to endotoxins through Toll-like receptors (34). Excessive immune response in the internal environment results in further aggravated activation of neutrophil-dominated inflammatory cells, followed by the secretion of various inflammatory cytokines, such as tumor necrosis factor–α (TNF-α), interferon gamma (IFN-γ), and interleukins (ILs)-1, -6, and -8. A rapid increase of proinflammatory cytokines in the blood results in more severe multiple organ injuries and cellular apoptosis.

More mechanisms of injury and related signal pathways have recently been uncovered (35,36). TNF-α can affect the expression and distribution of tight junction proteins. It also cooperates with IFN-γ to influence the regulatory proteins of tight junction proteins, such as myosin light chain kinase, which may cause a further increase of intestinal permeability (37). IFN-γ also has a direct influence on expression of claudin-2 and occludin and results in more serious damage to the intestinal mucosal barrier (38). During this stage, a strong inflammatory response induced by LPS in the circulation promotes damage of the intestine, which in turn accelerated the entrance of more and more pathogens and LPS into the circulatory system.

The interactions among various cytokines in the circulatory system also result in an increasing level of systemic inflammatory response. Accordingly, the vicious cycle mentioned above has been identified as the critical factor of severe damage of organs in the body and the main cause of high mortality in patients with heat stroke (39). On the other hand, intestine-derived endotoxins in the circulatory system and cytokines activate vascular endothelial cells and coagulation factor XII to amplify the coagulation cascade. With the hypercoagulable state caused by excessive water loss, large amounts of microthromboses form easily as a result of the damage to vascular endothelial cells and recruitment of platelets (40). Overall, damage to the intestine and intestine-derived endotoxin translocation might be the decisive components during the pathologic process of heat stroke.

Intestine-Specific Treatment in Heat Stroke

The main treatments for heat stroke include cooling, rehydration, and other related supportive treatments (41). With numerous studies defining intestine-derived endotoxin translocation as the key event in heat stroke, intestine-specific prevention and treatment has logically become a focus of research.

Although a few studies have indicated that pretreatment with an antiendotoxin agent is effective in protecting organs from severe injury, a large number of clinical trials have shown that there was no obvious effect from the treatment of using anti-LPS antibodies, anti-inflammatory drugs, platelet-activating factor receptor antagonists, or human TNF-α monoclonal antibodies after intestine-derived endotoxin translocation into the circulatory system has occurred because of heat stroke (34,42–44). This may be because of the rapid expansion of the inflammation response and the mutual promotion effect once the endotoxin translocation has ensued after the dysfunction of intestinal barrier function has begun.

Therefore, it is reasonable to suspect that in the future, intestine-specific treatments may be developed that will have a salutatory role, once they become available and if they are administered as soon as possible.

Recent findings may herald new treatments for alleviating intestinal injuries caused by heat stroke. Propofol had been shown to be protective in the intestines of patients with heat stroke. The mechanism is associated with its inhibitory effect on the production of nitric oxide and proinflammatory cytokines. A related study indicated that propofol may act by regulating the recruitment of platelets (45). Moreover, propofol can inhibit the release of high mobility group box 1 (HMGB1) among intestinal epithelial cells, which reduces the damage to the intestine caused by LPS (46–48).

Somatostatin can minimize the damage to intestinal epithelial cells caused by trypsin, and up-regulate the expression of occludin and ZO-1, by inhibiting the secretion of trypsin (49). Somatostatin has also been shown to regulate the extracellular signal related kinase/mitogen-activated protein kinase signaling pathway by inhibiting the activation of extracellular signal related kinase 1 and 2 caused by LPS and inhibiting the activation of nuclear factor kappaB in intestinal epithelial cells in heat stroke (50).

A traditional Chinese medicine called Xuebijing has shown to be protective in animal models of heat stroke. Although related studies have indicated that Xuebijing can protect the small intestinal barrier by regulating the expression of intercellular adhesion molecule, a more detailed mechanism and the main effective components of this compound preparation has yet to be investigated (51–53).

Potential Intestine-Specific Prevention in Heat Stroke

Because of the rapid progression and high mortality of heat stroke, preventative strategies are more clinically effective than any current therapeutic strategies. Many studies have focused on the prevention of heat stroke. Proliferation and repair of intestinal epithelial cells are crucial for the rebuilding of the intestinal barrier once heat stroke has begun. Adding tributyrin to the diet helps the repair of intestinal epithelia cells during heat stress, whereas other studies show that supplementing an individual's diet with various amino acids helps prevent damage of the intestine caused by heat stress (54). Glutamine is an important substrate of the intestine mucosa that also acts to impair protein damage and improve the permeability of the intestine in an adverse environment. Replacement of an appropriate quantity of glutamine helps to inhibit the production of nitric oxide synthase and prevent the down-regulation of ZO-1 messenger RNA caused by hyperthermia (55,56). In addition, the protective effect of glutamine may be related to the epidermal growth factor receptor and related signaling pathways, such as activated extracellular kinase 1/2 and reduced p38 mitogen–activated protein kinase (57,58). However, antioxidative stress against injury in heat stroke is as important as repairing the intestinal epithelium (59,60). A cohort study indicated that the concentration of malondialdehyde and endotoxin in the circulatory system of soldiers under heat stress after military training with the pretreatment of glutamine and vitamin C was significantly lower than that of soldiers in another group that was pretreated only with glutamine (61).

Adding an appropriate quantity of selenium and vitamin E to the diet of experimental animals helped reduce oxidative stress injury and maintain the integrity of the intestinal mucosa barrier under heat stress (62). Ferulic acid is conductive to the integrity of the intestinal mucosal barrier under heat stress, preventing the reduction and redistribution of occludin, ZO-1, and E-cadherin (63). Pretreatment with 17-dimethylaminoethylamino-17-demethoxygeldanamycin helps reduce the damage to the intestine in rats with heat stroke. This protective effect may relate to the activation of heat shock factor-1 and the up-regulation of HSP-70 (64).

Zinc carnosine is a health-promoting food that has been shown to be protective in small intestine injury in vivo and in vitro (65). A recent cohort study carried out in healthy volunteers indicated that ingestion of zinc carnosine plus colostrum significantly attenuated the increase of intestinal permeability caused by heat stress. The mechanism of action includes reducing temperature-induced apoptosis and modulating the expression and phosphorylation of tight junction proteins (66).

CONCLUSION

Heat stroke is the most severe form of heat illness and it endangers or ends many lives every year. Intestine-derived endotoxin translocation has been identified as the key event in the clinical progression of heat stroke. Potential risk of SIRS, DIC, MODS, and high mortality could theoretically be reversed if the dysfunction of intestine barrier caused by heat stress is alleviated in a timely fashion. As mentioned above, preventative strategies are more effective than any current therapeutic strategies. Heat acclimation, adequate nutrition, and fluid intake are necessary for individuals who may need to be exposed to high temperature environments with and without strenuous exercise. To prevent and mitigate intestinal injury also could be considered a potential clinical strategy to minimize the incidence of heat stroke.

Although cooling therapy is always effective to mitigate apparent hyperthermia, critical complications are the main causes of death in patients with heat stroke. We reviewed effective pretreatment strategies primarily because these factors may inform the development of useful therapeutic strategies. However, pretreatments may not be clinically practical, because most patients with heat stroke develop their disease in clinical settings in which pretreatments may be impossible to accomplish. Although some studies have indicated that survival of heat stroke patients may increase with the treatment of cold hemodialysis and continuous hemodiafiltration, most reports are of small sample size (67,68). In addition, timely and effective cure is necessary because of the rapidly progressing course of heat stroke; hemodialysis treatment requires medical equipment that may not be available in all medical institutions. However, a more detailed pathogenesis of heat stroke needs to be discovered so that effective treatment and prevention of heat stroke may be carried out more easily.

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ARTICLE SUMMARY

1. Why is this topic important?

Heat stroke is an acute, life-threatening syndrome, as has been known for hundreds of years. However, the pathophysiologic mechanisms of heat stroke remain to be fully elucidated and the high risk of mortality caused by heat stroke has not yet been meaningfully impacted by current treatments.

2. What does this review attempt to show?

During recent years, gut-derived endotoxin translocation that ensues after the dysfunction of the intestinal mucosal barrier had been identified as the most important causative factor of mortality in heat stroke; a growing body of studies have also suggested that preventing injury of the intestinal mucosal barrier could be an effective treatment in patients with heat stroke and animal models of heat stroke. This review focuses on the mechanisms of intestinal injury in heat stroke and the progress in intestine-specific preventions and treatments.

3. What are the key findings?

This review discusses the pivotal role of the intestine and of intestine-specific preventative and therapeutic modalities in heat stroke. However, because of its rapid progression and high mortality, heat stroke remains a disease for which prevention is more effective than any current treatment.

4. How is patient care impacted?

Patient care was not mentioned in this review. Currently, most severe heat stroke patients need to be monitored in the intensive care unit for several days. If more effective treatment strategies can be discovered, improved patient care paradigms may ensue.