

Systemic Inflammation Mediates the Effects of Endotoxemia in the Mechanisms of Heat Stroke

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Received date: November 30, 2016; Accepted date: December 24, 2016; Published date: December 31, 2016

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Abstract

Heat stroke is triggered by heat, but is driven by endotoxemia and the downstream effects of systemic inflammation, acute phase response and the pyrogenic response. Whereas heat stroke and its related fatality commonly occur at core temperature (Tc) >40°C, healthy individuals have tolerated Tc 40°C-42°C without symptoms of heat stroke, suggesting that besides hyperthermia, there are other factors that can also cause heat stroke. The “dual-pathway model (DPM)” suggests that heat stroke is triggered by the endotoxemia pathway at Tc up to ~42°C and independently, by heat toxicity at Tc >42°C. The second pathway in the DPM is based on evidence showing that cytoskeletal structures start to disintegrate at ambient temperature >41.5°C. Since most exertional stroke cases occur at Tc <42°C, the endotoxemia pathway, and not heat, might be the primary cause of heat stroke in the active population. Current evidence suggests that exercising under a poor state of health and a compromised immune system may also cause heat stroke, independent from the effects of hyperthermia. Strategies to prevent heat stroke should put equal emphasis on maintaining a good state of health and immune function. The current practice of focusing primarily on heat strain and hydration to prevent heat stroke may not have comprehensively addressed the pathophysiology of heat stroke and may explain why heat stroke continues to occur after more than 2000 years.

Keywords: Heat stress; Exercise; Endotoxemia; Leakage of gram-negative bacteria (bacterial translocation); Lipopolysaccharides (LPS); Gut barrier; Inflammatory cytokines

Introduction

Heat stroke is the fatal form of heat injury that is often presented with hyperthermia and symptoms of central nervous system (CNS) dysfunction and can lead to coma and death [1,2]. Heat stroke is also an ancient illness dating back more than two thousand years and its pathology has been attributed to the effects of hyperthermia and heat toxicity [3-5]. The roles of hyperthermia and heat toxicity in causing heat stroke have not been proven empirically, but form the basis for the current understanding, prevention and treatment of heat stroke [5,6]. However, evidence presented in the last two decades suggests that heat- and exercise-induced endotoxemia and the downstream consequences of systemic inflammation may play important roles in triggering and driving the mechanisms of heat stroke [2,7-9]. Therefore, this short review aims to summarize and discuss the evidence supporting the roles of endotoxemia and systemic inflammation in triggering and driving the mechanisms of heat stroke, independent from the effects of heat.

“Dual-Pathway Model (DPM)” of Heat Stroke

The earlier proponents of endotoxemia in the mechanisms of heat stroke advocated that heat stroke is triggered by heat but is driven by endotoxemia and the downstream effects of systemic inflammation, acute phase response and the pyrogenic response [2,9,10]. However, whereas heat stroke and its related fatality commonly occur at core temperature (Tc) >40°C [11], healthy individuals have tolerated Tc

40°C-42°C without symptoms of heat stroke [12,13]. This evidence suggests that besides hyperthermia, there are other factors that can also cause heat stroke, which supports the notion that heat and endotoxemia may activate the mechanisms of heat stroke through independent pathways [8].

The “dual-pathway model (DPM)” of heat stroke suggests that heat stroke is triggered by the endotoxemia pathway at Tc up to ~42°C and independently, by heat toxicity at Tc >42°C [8]. The second pathway in the DPM is based on *in vitro* evidence showing that cytoskeletal structures start to disintegrate at ambient temperature >41.5°C [14]. Since most exertional stroke cases occur at Tc <42°C [8,11], the endotoxemia pathway, and not heat, might be the primary cause of heat stroke in the active population.

Gut Barrier Response to Exercise and Heat Stresses

Proponents of the endotoxemia pathway agree that the pathophysiology of heat stroke originates from the gut, which houses hundreds of millions of bacteria [9,15]. The gut epithelium functions as a physical barrier that separates the septic condition in the gut space from the aseptic condition in circulating blood. However, the permeability of the gut-epithelium is increased during intense exercise and heat stress exposure, which promotes the leakage of gram-negative bacteria (endotoxins, a.k.a. lipopolysaccharides, LPS) from the gut space into the portal circulation [16,17]. From the portal circulation, LPS is transported to the liver, where LPS is scavenged and removed from the body by Kupffer cells (hepatic macrophages) [9,10]. During prolonged intense exercise, LPS influx may overwhelm LPS clearance in the liver [9,15,18], leading to the leakage of LPS from the liver into the central circulation, where LPS can be removed by high density

lipoprotein, LPS-specific antibodies and the innate immune system [19].

Pro-inflammatory Cytokine Response to Endotoxemia

A sub-lethal increase in the circulating concentration of LPS can induce the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6, which have both inflammatory and pyrogenic functions [2,10]. In a healthy state, the anti-LPS mechanisms can scavenge and remove LPS from the body through the reticuloendothelial system in the liver [8]. However, under conditions of immune suppression, LPS concentration in the blood can increase to the threshold of triggering the systemic inflammatory response [8]. The downstream effects of this "shock" response include disseminated intravascular coagulation (DIC), multi-organ failure (MOF), haemorrhage and CNS disturbances, which are commonly reported in heat stroke victims [20-22]. Therefore, the endotoxemia pathway implies that during exposure to heat and exercise stresses, the integrity of the gut barrier may play important "gatekeeping" roles in blocking the cascade of events that can lead to the occurrence of heat stroke. Under conditions where the immune system is compromised and is unable to cope with the influx of LPS from the gut, endotoxemia can progress to activate the mechanisms of heat stroke through the downstream effects of septicaemia and systemic inflammation.

Evidence Derived from Studies on Healthy Athletes

The roles of immune disturbances as an independent trigger of heat stroke are supported by evidence derived from healthy individuals, heat stroke victims and from animals that were exposed to lethal heat stress. Healthy runners have increased blood concentration of LPS during endurance races [23-25] and gut permeability changes during exercise were positively associated with exercise intensity [26]. Moreover, the increase in gut permeability during intense exercise resulted in endotoxemia only when running in warm, but not in cool conditions [15] and aerobic training can modulate the increase in circulating concentration of LPS during exercise in the heat [27]. However, four weeks of daily probiotic supplementation (45 billion CFU) did not have significant effects on serum LPS concentration and gut permeability during an acute bout of intense exercise in the heat [28]. This evidence demonstrates the occurrence of mild endotoxemia and the associated increase in gut permeability during intense exercise and supports the possible roles of gut-related LPS translocation in the mechanisms of heat stroke.

Evidence Derived from Heat Stroke Victims and Animal Studies

In heat stroke victims, blood samples collected at the emergency department had increased concentrations of endotoxin and pro-inflammatory cytokines [29,30]. These immune changes are consistent with common pathological findings in deceased heat stroke victims, which include systemic inflammation, DIC, MOF, necrosis, hemorrhage, and symptoms of CNS failure [19,20,31,32]. Except for hyperthermia, these clinical symptoms in heat stroke victims are similar to those reported in patients with sepsis (endotoxemia) [9]. Epidemiological evidence from a military hospital in Thailand also supports the notion that exercising with a suboptimal immune system can increase the risk of having heat stroke [33]. Twelve years of medical record showed that more than 95% of heat stroke patients treated in the military hospital had mild fever, upper respiratory tract

infection or diarrhea prior to the heat stroke event [33]. This evidence further supports the central role of a compromised immune system in triggering the mechanisms of heat stroke, possibly through endotoxemia-induced systemic inflammation. In animal studies, inhibiting endotoxemia through gut cleansing and injection of steroids, anti-LPS antibody or antibiotic drugs protected 100% of dogs [34], rabbits [35], monkeys [36-38] and rats [39] from lethal heat stress, when almost all animals in the control group died under the same conditions. Taken together, the evidence presented suggests that the occurrence of endotoxemia or having an infection before and during prolonged intense exercise and heat exposure may progress to trigger the systemic inflammatory response, which may function as the switch that triggers or inhibits the mechanisms of heat stroke. Protecting the health of the individuals, and the immune system in particular, during prolonged periods of intense physical training and heat exposure may play critical roles in protecting against heat stroke due to the endotoxemia pathway.

Conclusion and Future Directions

The current evidence suggests that exercising under a poor state of health and a compromised immune system may cause heat stroke, independent from the effects of hyperthermia. The evidence also suggests that healthy active individuals can tolerate a higher degree of heat stress (up to $T_c \sim 42^\circ\text{C}$) without triggering heat stroke. Strategies to prevent heat stroke, especially in the active population, should put equal emphasis on maintaining a good state of health and immune function. The current practice of focusing primarily on controlling heat strain and on promoting hydration to prevent heat stroke may not address the pathophysiology of heat stroke comprehensively [7] and may explain why heat stroke continues to occur after more than 2000 years. Although preventing hyperthermia [40] and ensuring fluid ingestion [41,42] can attenuate the systemic inflammatory response during exhaustive exercise [22,43-46], the other countermeasures to improve general and specific health conditions, such as functional food [45-50] to promote gut barrier protection and the appropriate immune surveillance, should be examined in the future studies.

Acknowledgements

This work was partly supported by a Grant-in-Aid for the Scientific Research (A) and Strategic Research Foundation at Private Universities from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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