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Review

Heat shock proteins as an aid in the treatment and diagnosis of heat stroke

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ABSTRACT

It is now well established that induction of heat shock protein 72 (HSP72) protects the cell or tissue against a second otherwise lethal exposure to heat, a phenomenon known as thermotolerance. Because of this protective role, HSP72 is potentially useful in the treatment of heat illnesses, which range from relatively benign disorders such as heat cramps to heat stroke, which can be life threatening. This review discusses various ways in which HSP72 might be used in the diagnosis and treatment of the heat illnesses. This includes methods to induce HSP72, analysis of HSP72 in the cells and tissues of heat stroke patients, and screening methods to detect individuals who may be heat intolerant.

Contents

1. Introduction

Heat shock proteins are found widely in nature, and belong to several families with molecular weights ranging from 8 to 150 kDa. Heat shock protein 72 (HSP72) is the most studied member of this group of proteins and is strongly induced by exposure to heat. Such upregulation of HSP72 confers protection not only against a second hyperthermic episode, but also against other stressors such as hypoxia and oxidative stress. In rodent models of heat stroke, prior induction of HSP72 has been found to aid survival. This review discusses ways in which the beneficial properties of HSP72 might be utilized to diagnose and treat or prevent future episodes of heat stroke.

2. Types of heat illness

The International Classification of Diseases contains 10 categories of heat disorders (Armstrong, 2003). These include

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Table 1
Different features of classic and exertional heat stroke

Feature	Classic	Exertional
Age	Older	Younger
Activity before onset	Sedentary	Strenuous
Acid base disturbance	Respiratory alkalosis	Lactic acidosis
Temperature (°C)	>41	May be <41 or >41
Occurrence	Epidemic	Isolated

heat oedema, heat fatigue and heat syncope, disorders resulting from water or salt depletion including heat exhaustion and heat cramps, and the most serious disorder, heat stroke, which is classified as either classic or exertional (Table 1) (Parsons, 2003). While this classification is based on the activity level immediately prior to the onset of the illness, there are marked differences in the two groups of patients affected. Classic heat stroke typically affects the very old or young in hot environments. The elderly who are socially isolated without access to air conditioning are particularly vulnerable. With higher ambient temperatures experienced in normally temperate environments in recent years, there have been more heat-related deaths recorded, notably in France in 2003 (Davido et al., 2006). Biochemical abnormalities including rhabdomyolysis, disseminated intravascular coagulation and acute renal failure are often a feature of exertional heat stroke, but rare in the classic form of the disorder (Hart et al., 1982).

Exertional heat stroke typically affects fit, young men, although women can be affected. In a study of Marine Corps recruits the rate of heat illness was similar in males and females while the severity varied, with 11% of males and no females requiring hospitalization (Kark et al., 1996). It is not clear why serious exertional heat stroke is rare in women. This could be due to hormonal factors, the fact that men generate more heat because of their larger muscle mass, or psychological factors (Knochel, 1996). There are numerous instances of people collapsing during exercise dating back to antiquity, with an example documented in the Old Testament (II Kings 4: 18–20) (Shibolet et al., 1976). Collapse of soldiers participating in military training is often the basis for reports of exertional heat stroke in the literature. In 1943, a soldier was admitted to hospital with a temperature of 109°F (42.8 °C) and coma soon set in. Despite cooling with ice packs, cold enemas and fanning, death occurred approximately 2 h after collapse (Malamud et al., 1946). The course of the illness can be more protracted. Another man aged 25 collapsed while on a march, and was admitted to hospital with a T_{rec} of 110 °F (43.3 °C). The patient's temperature remained elevated for 4 days, after which he appeared to improve; however, on the 12th day he developed pneumonia and died (Malamud et al., 1946). These examples demonstrate the serious nature of heat stroke, which has a mortality rate of around 10% even with vigorous treatment (Simon, 1993). More recently, athletes are better educated as to the dangers of heat stroke, but cases still occur. In 1988 in Australia, a 28-year-old man collapsed with heat stroke after competing in an 8 km fun-run in hot conditions, and spent 5 months in intensive care, suffering severe rhabdomyolysis, neurological deficit and the loss of one leg (Lee et al., 1990). Immediate cooling is the most important treatment objective, with ice water immersion the most effective method (Casa et al., 2005). The length of time the patient is hyperthermic can have an impact on recovery, hence speed of cooling is important. There are currently no medications that are effective in treating heat stroke (Bouchama and Knochel, 2002).

3. Physiology

Last century, Adolph (1947) published studies in animals demonstrating that there is a threshold rectal temperature (T_{rec}) that is always lethal when exceeded. While there are some species differences, 100% of dogs, rabbits and guinea pigs died at a T_{rec} of 44.0 °C. At temperatures just below this level, there is some variation within species, however, "the variations in lethal rectal temperatures within any one species are not related to any known factor" (Adolph, 1947). Even today we do not know why some humans can tolerate a core temperature of 41 °C without incident, while others find temperatures 1–2 °C lower fatal. It is now known that mammals such as man tightly regulate body core temperature by a variety of methods to around 37 °C at rest (Gisolfi and Mora, 2000). The hypothalamus acts as the body's thermostat, responding to temperature sensors located throughout the body, and initiating physiological mechanisms to either increase heat gain or loss to the body. Physiological effector responses for heat dissipation include sweating and increased skin blood flow, while cold exposure leads to shivering and cutaneous vasoconstriction.

4. Mechanism of HSP72 in preventing heat stroke

Heat shock proteins have different functions, and are located in various cellular compartments. Most studies to date have examined HSP72 because it is the most inducible heat shock protein, and its upregulation correlates with thermotolerance and protection against the deleterious effects of thermal exposure at the cellular and whole organism level. This characteristic of HSP72 led to the hypothesis that induction of HSP72 may be protective in cases of heat stroke.

It is not yet clear how HSP72 mediates its protective role in the cell. At the molecular level, the role of HSP72 as a molecular chaperone appears to be an important part of the cytoprotective function. HSP72 is able to refold damaged proteins, prevent protein aggregation and move proteins between cellular compartments (Kregel, 2002).

HSP72 transcription is controlled by HSF1, the heat shock factor which normally exists in the monomeric state bound to HSP72 (Kiang and Tsokos, 1998). Following heat shock, the HSF dissociates from HSP72, forms a trimer which becomes phosphorylated at serine residues, moves into the nucleus and binds to the heat shock element resulting in transcription (Fig. 1). The newly synthesised HSP72 molecules bind to HSFs to prevent further transcription.

At the organ level, intestinal permeability is increased with higher core temperatures in human and animal models, leading to endotoxaemia in the splanchnic circulation and initiation of the release of inflammatory mediators (Moseley and Gisolfi, 1993). Accumulation of heat shock proteins reverses the increase in intestinal permeability preventing the pathological changes associated with endotoxin release. In addition to an effect of HSP72 on epithelial barrier integrity, HSPs may be associated with endotoxin tolerance (Hotchkiss et al., 1993; Ryan et al., 1992) and an attenuated cytokine secretion due to upregulated HSPs. While HSP72 expression has no effect on IL-6 levels, IL-1 and tumour necrosis factor were reduced following heat shock treatment in human and rat cultured cells (Leon, 2007). HSP72 may also act directly in the bilateral nucleus tractus solitarii, thereby potentiating the baroceptor reflex response, and conferring cardiovascular protection during heat stroke (Li et al., 2001). While HSP72 is protective inside the cell, in the extracellular environment it acts as a danger signal, resulting in release of proinflammatory cytokines (Fig. 2) (Asea et al., 2002).