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REVIEW ARTICLE

Inducible heat shock protein 70 and its role in preconditioning and exercise

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Abstract Heat shock proteins (Hsp) are well known to be expressed in response to a range of cellular stresses. They are known to convey protection against protein denaturation and a subsequent immediate stress. Inducible heat shock protein 70 (Hsp70) is among the most studied of these stress proteins and its role and function are discussed here in terms of thermal and in particular exercise preconditioning. Preconditioning has been shown to confer cellular protection via expression Hsp, which may be of benefit in preventing protein damage following subsequent periods of exercise. Many studies have used animal models to gather data on Hsp70 and these and the most recent human studies are discussed.

Keywords Hsp70 · Thermal preconditioning · Exercise

Introduction

Cells undergo molecular changes when exposed to temperature above what would be considered normal. This is characterised by the production of heat shock proteins (Hsp), which are a ubiquitous family of highly inducible stress proteins. First reported by Ritossa (1962) as the effect of heat on Drosophila resulting in unusual chromosomal "puffs", the expression of these proteins have since been shown to be induced by a wide variety of stressors. Such stressors include hyper- (Slakey et al. 1993) and hypo-thermia (Yang et al. 1996), hypoxia (Patel et al. 1995), exercise (Locke and Noble 1995), viral infection (Collins and Hightower 1982), reactive oxygen species (Kukreja et al. 1994) and ischaemia (Richard et al. 1996) amongst others. Due to this variety of physiological stressors that induce Hsp expression, they are also commonly termed "stress proteins".

The role of Hsp is to protect the process of protein assembly and folding within a stressed cell and to act as molecular chaperones. The intracellular stimulus for Hsp induction is protein damage and rapid expression of Hsp can be seen soon after a sub-lethal exposure to a stressor (Perdrizet 1997). Hsp are grouped into families, which differ in molecular weight and location within the cell. Furthermore, they have been shown to translocate following stress (Snoeckx et al. 2001). The protective roles and associated Hsp are shown in Table 1. This review will cover synthesis, regulation and function of Hsp before focussing in particular on the expression and role of inducible heat-shock protein 70 (Hsp70) in conditioning and exercise.

Hsp70 protein synthesis and regulation

The Hsp70 family range in size from 70 to 78 kDa (Kiang and Tsokos 1998) and have been demonstrated to be the most inducible and abundant of all Hsp, accounting for 1–2% of cellular protein (Katschinski 2004).

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Table 1 Function of various heat shock proteins

HSP family (kDa)	Cellular location	Major function
HSP27	Cytosol and nucleus	Microfilament stabilization
HSP60	Mitochondria	Protein protection and repair
HSP70 Family		
HSP72 (HSP70)	Cytosol and nucleus	Protein folding and cytoprotection
HSP73 (HSC 70)	Cytosol and nucleus	Protein translocation
HSP75	Mitochondria	Protein translocation
HSP78	Endoplasmic reticulum	Cytoprotection and protein translocation
HSP90	Cytosol, nucleus, endoplasmic reticulum	Protein translocation and receptor regulation
HSP100–104	Cytosol	Protein folding

Hsp70 protein is coded for by a 2.44-kb sequence (Wu et al. 1986) containing no introns or intervening sequences thus allowing for rapid transcription and mRNA processing. Heat shock transcription factors (HSF) interact with regulatory elements within the sequence and the rapid expression of Hsp70 follows transcriptional activation and subsequent selective translation (Lindquist and Craig 1988). HSF are inactive in monomeric form, possessing no DNA binding capability and only become active once phosporylated and assembled as trimer (Rabindran et al. 1993). Trimerisation occurs as a response to stress and in this state HSF possess high DNA binding affinity. Human HSF are multizipper proteins and a carboxyl-terminus zipper may inhibit trimerisation through interactions with an N-terminus zipper (Rabindran et al. 1993), this interaction is thought to be heat-sensitive. HSF in trimeric from bind to specific sequences of DNA on the promoter region of the Hsp gene, which consist of inverted repeats (Fernandes 1994), and are known as heat shock elements (HSE). Binding of trimeric HSF to HSE is necessary for transcription of Hsp mRNA. Once initiated this results in detectable Hsp mRNA within a minute, and has been shown to increase 20-fold within 20 min (Perdrizet 1997).

Hsp70 function

Hsp70 has been shown to be involved in many protective functions within normal and stressed cells. Most are a result of protein denaturation by direct or indirect applied stresses. Demonstrable functions include involvement in protein folding within organelles, prevention of the formation of protein aggregates and degradation of damaged proteins (Bukau and Horwich 1998). Other functions include maintaining the higher structures and refolding misfolded proteins (Palleros et al. 1991) and protein translocation (Chirico et al. 1988). Hsp70 targets the exposed hydrophobic sites of proteins in the progress of denaturation due to a stress stimulus (Pelham 1986), although they can be found in unstressed cells bound to newly synthesised polypeptides, acting as chaperones.

Hsp also have an anti-apoptotic role, preventing or at least inhibiting programmed cell death (Garrido et al. 2001). The cellular concentrations of Hsp have been shown to be correlated closely to the activity of antioxidant enzymes suggesting that Hsp have a role in counteracting cellular damage caused by an increase in reactive oxygen species (Currie et al. 1988; Mocanu et al. 1993).

Thermal preconditioning

Thermal preconditioning aims to confer thermal tolerance to a subsequent thermal stress, affording cellular protection and increased survival. This is achieved by exposure to a sub-lethal thermal stress, which induces expression of Hsp, which then are available to counteract the effects of a subsequent exposure to thermal stress. Experimental evidence was provided using rat fibroblasts, where the severity of the initial heat stress was correlated to the duration and degree of thermal tolerance (Mizzen and Welch 1988). Other studies have also shown tolerance to a variety of stressors including hypoxia (Guttman et al. 1980), ATP depletion (Sciandra and Subjeck 1983) and ischaemia (Marber et al. 1995) after prior Hsp70 induction. Thermal tolerance, subsequent to applied heat stress, is conferred within hours and may last up to 5 days (Landry et al. 1982). The intrinsic role of Hsp in preconditioning has been confirmed using molecular techniques to block or increase Hsp70 synthesis (Johnston and Kucey 1988; Landry et al. 1989). Cells, which have been thermally preconditioned, produce less Hsp when exposed to a second stress (Li et al. 1983; Ryan et al. 1991), presumably due to the already elevated concentration of Hsp within the cell preventing further translation via negative feedback. It has also been shown that, following a period of exercise

resulting in an increase in core temperature to 40°C or above, the amount of Hsp70 produced in isolated human leukocytes was lowered in response to an immediate subsequent thermal challenge (Ryan et al. 1991). This suggests a degree of thermal tolerance was conveyed upon the leukocytes. It has been hypothesized that the heat acclimation is biphasic. Cells exposed to a sub-lethal heat shock develop an initial rapid thermo-tolerance that results in a desensitization of the Hsp70 response to a second heat shock. When acclimation has been achieved, an altered threshold for Hsp70 production results in an accelerated rate of Hsp70 transcription when exposed to acute heat shock (Horowitz et al. 1997; Maloyan et al. 1999; Arieli et al. 2003).

Exercise preconditioning

Exercise alone induces Hsp production (Noble 2002). Although an increase in core temperature due to the effects of exercise is an essential part of exercise preconditioning. This increase has been shown to cause a concurrent increase in myocardial Hsp70 (Taylor et al. 1999; Hamilton et al. 2001). This in turn attenuates myocardial stunning, infarction and ischaemia reperfusion injury (Locke et al. 1995; Powers et al. 1998; Hoshida et al. 2002). However, conflicting data exists which points to increased myocardial Hsp70 not being essential for protection against ischemia reperfusion injury (Taylor et al. 1999; Hamilton et al. 2001). Cellular stress caused by exercise can lead to ATP depletion, reactive oxygen species production and a decrease in intracellular pH, all potentially leading to protein denaturation and protein folding errors, as well as physical damage to muscle tissue itself (Noble 2002).

It was demonstrated, in a pioneering animal experiment, that a single bout of exhaustive treadmill running led to an increase Hsp70 synthesis in skeletal muscle, lymphocytes and spleen in rat (Locke et al. 1990). Acute exercise in animals produces increased Hsp70 levels in contracting skeletal muscle as well as organs such as the heart, kidney and liver (Salo et al. 1991; Locke et al. 1995; Kregel and Moseley 1996; Samelman 2000).

A single bout of exercise also accelerates the synthesis of Hsp70 in humans (Walsh et al. 2001; Thompson et al. 2002). Interestingly, a repeated bout of exercise has been shown to increase the level of endogenous Hsp70 as well as muscle Hsp70 but to a lesser extent than after the first bout of exercise. The basal level of extracellular and muscle Hsp70 was, before the second bout of exercise decreased compared to the pre-exercise samples (Thompson et al. 2002; Marshall et al. 2006). Furthermore, similar results were shown with the combination of exercise and heat (Mizzen and Welch 1988; Fehrenbach et al. 2001) indicating that there is an initial desensitisation of the heat shock response to exercise.

The magnitude of the heat shock response is dependent upon the intensity of the exercise bout, with higher exercise intensities yielding greater Hsp induction (Milne and Noble 2002). It has also been shown in human studies, for example, that prolonged exercise induced a more pronounced response of serum Hsp70 than shorter more intensive exercise (Fehrenbach et al. 2005). Moreover, studies have demonstrated that a single bout of exercise in non-trained subjects led to increased Hsp70 mRNA in skeletal muscle, but surprisingly (due to the mechanism of Hsp synthesis), no significant increase in Hsp70 protein was detected (Puntschart et al. 1996). A later study showed similar findings using quantitative (real-time) PCR and demonstrated that inducible Hsp70 mRNA was increased progressively within skeletal muscle tissue during prolonged (3 h) exercise (Febbraio and Koukoulas 2000). In agreement with the previous papers, Paulsen et al. (2007) showed that an increase in muscle mRNA was significantly increased 4 h after a single bout of eccentric exercise while muscle protein Hsp70 was not detectable until 24 h after the exercise. However, another recent study showed an increase in Hsp70 positive muscle type I fibres can be detected immediately after exercise (Tupling et al. 2007). In contrast to an earlier study (Walsh et al. 2001) both Tupling et al. (2007) and Paulsen et al. (2007) showed that the increase in muscle Hsp70 was sustained 6–7 days after exercise. The overall heat shock response also appears to depend on resting values of the protein. A correlation exists between pre-exercise values and the increase of Hsp70 post-exercise in human muscles biopsies measured over 5–8 weeks of exercise (Gjovaag and Dahl 2006). In a recent study, we (Sandström et al. 2007) showed the same correlation during a 15-day exercise heat acclimation period in an ultra-marathon runner. This indicates that the synthesised Hsp70 works as a negative feedback regulator in the inducible transcription of *Hsp70 genes*. Similarly, it was shown by McClung et al. (2007) that the Hsp70 response to acute heat shock in peripheral blood mononuclear cells was blunted after 10 days of heat exercise acclimatisation. Adaptation to regular exercise appears to lead to a lower basal Hsp70 concentration within peripheral blood mononuclear cells (Fehrenbach et al. 2000). At rest, aerobically trained athletes were shown to have the lower concentration when compared to non-trained individuals, although increases in Hsp were still observed post-exercise (Fehrenbach et al. 2000). It is interesting to speculate why athletes have lower basal Hsp70 in peripheral blood mononuclear cells, possibly an increased lung capacity and lowered heart rate contributes to a higher threshold required for Hsp synthesis due to availability of dissolved oxygen and therefore delay in ATP depletion. It has also

been suggested that this exercise-induced Hsp expression serves to cope with immediate myocardial and skeletal muscle damage, as well as protect against subsequent bout of potential damage to working muscles (Locke and Noble 1995; McArdle et al. 2001).

Paulsen et al. (2007) found a positive correlation between the reduced force-generating capacity after maximal eccentric exercise and increased Hsp70 levels. Indicating that the immediate increase in Hsp70 is important for refolding denatured proteins and folding of newly synthesised proteins. The long-term (up to 7 days) increase of Hsp70 indicates a potential role in longer-term protein assembly within cells of muscle tissue. It was further hypothesised that Hsp70 play a role in protecting against exercise-induced inflammation, which can cause increased muscle damage (Paulsen et al. 2007). Similarly, Hung et al. (2005) showed that long-term exercise in rats induces Hsp70 production and attenuates overproduction of tissue cytokines such as tumour necrosis factor-alpha. The production of Hsp70 has been shown to both attenuate and induce the production of cytokines after exercise (Asea et al. 2000; Hung et al. 2005; Paulsen et al. 2007), which illustrates the sensitivity and regulatory capacity of Hsp70. Training adaptations have recently been postulated to occur which allow for Hsp gene expression even in the presence of elevated levels of pathway inhibitors (Melling et al. 2007), which may be linked to HSF binding affinity.

Other beneficial effects of exercise preconditioning are, for example, the attenuation of myocardial stunning, infarction, ischemia reperfusion injury and its effect on increasing survival time during heatstroke in rats (Locke et al. 1995; Powers et al. 1998; Hoshida et al. 2002; Hung et al. 2005). However, conflicting data exists which points to increased myocardial Hsp70 not being essential for protection against ischemia reperfusion injury (Taylor et al. 1999; Hamilton et al. 2001).

Final considerations and perspectives

The combination of heat and exercise is known to induce elevated levels of Hsp70 (Mizzen and Welch 1988; Marshall et al. 2006) but they also induce similar response in Hsp70 to single bouts or conditioning of heat/exercise. It is not clear whether it is the change in temperature per se, which is responsible for the heat shock response during physical exercise. Current data is still mainly from animal studies and the findings using various tissue extracts are contradictive (Skidmore et al. 1995; Harris and Starnes 2001; Kim et al. 2004). Recently, there have been an increasing number of human studies approaching this problem (Morton et al. 2006; Lovell et al. 2007; Whitham et al. 2007). In a recent study it was shown that subjects who underwent exercise induced heating had significantly higher levels of Hsp70 compared to subjects who underwent passive heating, to the same rectal temperature as exercise subjects, or temperature clamped exercise (rectal temperature change 0°C) (Whitham et al. 2007). Although there was a significant increase in Hsp70 with passive heating, there appear to be other stimuli to heat to account for increases in Hsp70 seen during exercise. None of the studies mentioned above could pinpoint the factors responsible for the induction of Hsp70 during exercise. It is however, known that effectors such as increases in oxidative stress (Kukreja et al. 1994), hypoxia (Patel et al. 1995) and reduced energy availability (Kabakov 1997) effect the production of Hsp70 and could therefore be important regulatory factors of hsp70 during exercise.

At present, we can see an increasing number of published human studies investigating the relationship between exercise and Hsp70. However, when viewing the data from published studies on Hsp70 it is clear that there are problems measuring Hsp70. There are several different methods of measuring Hsp70; however, few are actually quantifiable. For example, flow cytometry measurement of intracellular Hsp70 yields semi-quantitative data; PCR can show a change in mRNA levels but a concomitant quantitative measurement of actual Hsp protein would prove more useful. Furthermore, when measuring serum/plasma Hsp70, the origin of the protein is unknown, and therefore it is a measurement of circulating Hsp70. Additionally, several published papers have failed to show any response to exercise (Liu et al. 2004; Watkins et al. 2007), and there is large variation between individuals (i.e. trained vs. untrained) (Walsh et al. 2001; Yamada et al. 2007). Finally, there is a continuous need for further research, to investigate the underlying mechanism for the difference in up-regulation of Hsp70 in individuals during exercise.

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