Chapter 7
Potential Cytoprotective Effects of Heat Shock Proteins to Skeletal Muscle

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Abstract Heat shock proteins (HSP) are chaperone molecules that are known to facilitate protein synthesis, protein assembly, provide cellular protection and regulate intracellular signaling. These cytoprotective effects have been linked to increases in HSP70 and HSP27p concentrations but there has been little progress in determining the specific role of HSP in human skeletal muscle adaptations. Short wave diathermy (SWD) and ultrasound are treatments commonly used to stimulate deep heat increases in skeletal muscle with limited research examining the effects of increased muscle temperature on muscle damage induced injury severity. Current research cannot definitively identify the mechanistic roles of HSP in mitigation of muscle damage even though they are commonly cited as mechanism of action for prevention of damage in heat-treated muscle. This article will examine the role of HSP induction in skeletal muscle as a therapeutic countermeasure for reduction of muscle atrophy during prolonged periods of immobilization as well as mechanisms for accelerated repair of injured muscle fibers through increased total protein concentrations.

Keywords Cytoprotection • Heat shock protein • Skeletal muscle • Cytokines • Signaling pathway • Therapeutic modalities • Heating

Abbreviations

HSF-1	Heat shock transcription factor-1
HSFs	Heat shock factors
HSP	Heat shock proteins
HSP70	70-kDa HSP
HSP72	70-kDa HSP
IL	Interleukin
SOL	Soleus

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7.1 Introduction

Early studies on muscle damage, and exercise-induced muscle damage in particular, suggested that the delayed onset of muscle soreness was due to micro tears in the muscle [1]. Though the hypothesis was later proven to be true [2], it does not fully explain the mechanisms of muscle damage. Proske et al. [3], showed that eccentric contractions and unaccustomed loading of skeletal muscle leads to severe disruptions of the sarcomeres, the sarcoplasmic reticulum, transverse tubules, and individual myofibrils, triggering an immediate, inflammatory immune response. Incurred damage to the sarcoplamic reticulum leads to an increased intracellular calcium concentration [4] that has been shown to activate calpains and further the degradation of cytoskeletal proteins [5]. Other consequences of muscle damage include swelling [6], disruption of contractile proteins [7–9], and extracellular matrix damage [10] with eventual apoptosis and cell death [3].

Many studies have focused on apoptosis activation by muscle damage and the role that apoptosis has in exacerbating muscle injury [11–13]. Following muscle damage there is an increase in local blood flow, plasma CK-8, α-actin [14], and HSP [15] along with an influx of neutrophils to the damaged area. Neutrophil invasion causes secondary injury through the release of free radicals and proteases, leading to pro-apoptotic signaling by way of increasing JNK [11, 13, 16], p53, [17] and caspase [18] activity. The levels of heat shock protein (HSP) expression appear to be positively related to the magnitude of damage to skeletal muscle [13, 19, 20]; however, there have been mixed results in experimental designs with some studies showing modest changes in HSP72 expression in the soleus (SOL) muscle [21, 22] and others unable to replicate these increases following a bout of downhill running [23]. The purpose of this chapter is to briefly discuss the cytoprotective effects of heat shock proteins and how they can be manipulated as part of therapeutic modalities with a primary focus on the role of HSP70 in skeletal muscle.

7.2 Induction of Heat Shock Proteins Following Skeletal Muscle Damage

The production of HSP in skeletal muscle is primarily stimulated by heat stress, oxidation and a high level of muscle contraction [24, 25]; however, the role these proteins play in attenuating damage to skeletal muscle is poorly understood. HSP70 is a family of stress proteins that are the most highly conserved and temperature sensitive of all the HSP [26]. It has been shown that the expression of HSP increases in response to muscle damage [19, 27–30]. Investigations involving humans have shown that single bouts of eccentric contractions can initiate a similar response in intramuscular (biceps brachi and vastus lateralis) HSP70 concentrations [19, 31]. Furthermore, eccentric exercise prior to unloading has been shown to attenuate muscle damage during subsequent reloading of skeletal muscle. HSP70 appears to

play a role in the repeated bout effect that is seen with adaptation to lengthening contractions. Thompson et al. [19] investigated the HSP response to a repeated eccentric stimulus. Upon reloading there were substantial decreases in the HSP70 response to the second bout of eccentric induced muscle damage. These authors also found changes in HSP70 concentrations were accompanied by a significant reduction in serum creatine kinase levels [19]. These data suggest that HSP70 not only mediates adaptation to exercise, but plays a role in preventing acute and chronic injury to myofilaments during bouts of unaccustomed loading.

The increase in HSP synthesis following muscle damage is thought to be triggered by two factors: (1) the proteolysis that occurs following eccentric contractions [19, 31] and (2) elevations in plasma IL-6 [32]. Ingalls et al. [33], reported that exercise induced muscle damage stimulated an increase in HSP70 expression in mice, which was thought to be related to a decline in actin and myosin heavy chain proteins as a result of muscle injury. These data support a role for HSP in the degradation process of damaged myofibrillar proteins but further research in the area is required to identify the particular mechanistic relationship of this process.

A recent study by Welc et al. [34] found that both heat shock factor-1 (HSF-1) and AP-1 play major roles in hyperthermic induction of IL-6. It is possible that HSF-1 may also be involved in the induction of IL-6 under other stress conditions. The data in this study suggests that HSF-1 regulates IL-6 activity even under physiologic conditions where HSF-1 is thought to be inactive. The regulatory link between the IL-6 and HSF-1 indicates that there may be a role for heat shock factors as mediators of the inflammatory response in skeletal muscle absent heat stress.

7.3 Attenuation of Skeletal Muscle Damage by Heat Shock Proteins

While a plethora of data is available exhorting the cytoprotective role HSP70 plays in a variety of other cell types [26], limited data exists in skeletal muscle. The available data does, however, suggest that HSP70 induction can attenuate the severity of muscle damage [12, 35, 36]. Most research has focused on the chaperoning functions of HSP70 and its ability to regulate protein folding and, subsequently, cellular repair processes in response to stress [37]. HSP70 has been implicated in protecting skeletal muscle from ischemia-reperfusion injury [38], and lengthening contractions [39]. Further, in a model using C2C12 skeletal muscle cells, brief exposure to heat shock treatment resulted in a significant increase in HSP expression and subsequent protection against exposure to the calcium ionophore, A23187 and the mitochondrial uncoupler, 2,4-dinitrophenol [12]. Similar results were seen in heat stressed rat skeletal muscle in the presence of a cardiotoxin. Induction of HSP70 stimulated not only satellite cell proliferation, but also protein synthesis during the regeneration of injured skeletal muscle [40]. HSP70 overexpression has also been shown to reduce histological evidence of muscle damage. A recent

investigation, cryolesioned the soleus and tibialis anterior muscles to induce injury, and analyzed these muscles up to 3 weeks following the bout of muscle damage [35]. Histological analysis showed that muscles from HSP70 expressing mice had reduced necrosis and preserved cross-sectional area, as compared to non-treated controls [35]. Collectively, these data imply that HSP70 is associated with reduced muscle damage that may be attributed to an increase in skeletal muscle proliferation.

Limited data is available concerning the effect of heat shock during unaccustomed loading. Interestingly, following 28 days of unloading, 7 days of reloading did not result in recovery of HSP70 protein levels and this continued impairment upon reloading is directly related to the continued suppression of HSF-1 [41]. It appears that longer periods of reloading (14–28 days) may be needed following unloading, to stimulate upregulation of HSP70 and recovery of muscle mass [42]. Exercise may accelerate this recovery. It was recently shown that intensive treadmill running significantly upregulated HSP expression in as little as 6 days following 4 weeks of unloading [15]. This rapid increase in HSP content stimulated by exercise during reloading may contribute to accelerated recovery from atrophy. Selsby et al. [43] has recently reported that heat shock used during reloading attenuated oxidative stress, and improved the rate of skeletal muscle re-growth. Significant muscle remodeling occurs during reloading, leading to muscle hypertrophy and the restoration of muscle function. Previous investigations have shown that a single bout of hyperthermia is capable of inducing increases in muscle hypertrophy and protein synthesis [44, 45]. Furthermore, Goto et al. [46] have shown an increase in muscle-to-body weight ratio following single bouts of heat stress.

The role of JNK appears to be pivotal [47] for the intrinsic pathway of apoptosis. We [23], and others [13] have shown increased JNK expression following muscle damage. JNK is a known regulator of Caspase-3 [48], which is significantly upregulated following muscle damage [49]. It is has been shown that this change in Caspase-3 activity is directly linked to the loss of actin filaments from the sarcolemma [50] and serves as an upstream regulatory factor for accelerating muscle proteolysis [50, 51].

HSP70 inhibits JNK and as a result reduces downstream signaling of apoptosis [47]. In support of this, HSP70 has been associated with inhibiting Caspase-3 activation and preventing the formation of the apoptosome [52]. However, it is not known if HSP70 mediates this process following muscle damage.

7.4 Clinical Modalities to Induce Heat Shock Proteins in Skeletal Muscle

Ultrasound and short wave diathermy (SWD) are common modalities for deep heating of skeletal muscle tissue. These modalities are most commonly used to treat large muscle areas and to target tissues from 2 to 5 cm. In rats, heat treatment (HT) has been shown to preserve muscle size during unloading experiments [53] and

improve the recovery of atrophied muscle [46]. We [23, 54], and others [55], have shown that various heat treatment modalities activate heat shock proteins in skeletal muscle.

Consistent with the current literature, our data suggests increases in HSP70 concentrations are associated with a need to maintain homeostasis and prevent future/further damage to the cell. For example, we saw that increasing HSP expression prior to muscle damage appears to protect skeletal muscle from injury. In addition, we suggest that heat shock prior to damaging exercise may facilitate recovery from exercise by increasing the total protein concentration and the expression of MHCneo in vivo. Heat treatment 48-h prior to damaging exercise enhanced muscle adaptation by increasing total protein content and MHCneo expression independent of Akt, p70s6k, and JNK signaling [23]. These findings are supportive of the majority of studies showing elevated HSP can have a positive effect on skeletal muscle and advance the idea that induced over expression of HSP prior to muscle damage may mitigate muscle fiber injury. That said, further research is required to identify the precise mechanism(s) by which HSP influence skeletal muscle regrowth and regeneration.

7.5 Pharmaceutical Induction of Heat Shock Proteins

The potential cytoprotective effects of the heat shock response are an attractive target for pharmacological therapies. This is particularly relevant for a number of neurodegenerative diseases associated with protein misfolding and subsequent aggregation [56] such as Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease. Hydroxylamine derivatives like bimoclomol and arimoclomol are co-inducers of the heat shock response by way of prolonging the activation of heat shock factor-1 (HSF1) [56–58]. Bimoclomol has been particularly effective in treatment of diabetes mellitus and cardiovascular diseases [59], but has shown few cytoprotective effects within skeletal muscle.

Arimoclomol has been shown to be effective in mouse models of motor neuron degeneration [60, 61] and, moreover, found to be well tolerated and safe in Phase II clinical trials of ALS patients [62]. Of particular interest for skeletal muscle applications, Kalmar et al. [60] found arimoclomol treatment improved muscle innervation in the periphery of $SOD1^{G93A}$ mice prior to central effects within the spinal cord. While this is of specific importance to treatment of ALS due to the different stages of disease progression, it also illuminates the ability of drug therapy to co-induce HSP expression within the skeletal musculature. An important note regarding the mechanism of the HSP co-induction through arimoclomol is the fact that the prolonged activation of HSF-1 only occurs in cells where HSF-1 is already activated [61] (i.e. only cells that are already stressed), providing for a very targeted response. Arimoclomol has exciting possibilities as a drug therapy targeting skeletal muscle but more research will be required to understand the positive and negative consequences of drug administration.

7.6 Conclusion

This chapter has covered the most relevant cytoprotective features of HSP, particularly HSP70, as it relates to human skeletal muscle. While the cytoprotective effects are observed in response to therapeutic modalities such as SWD and Microwave Diathermy, the specific mechanism underlying this phenomenon is unclear. This should not deter clinicians or other relevant practitioners from utilizing these modalities, but does identify the need to elucidate the exact role elevated HSP in human skeletal muscle in various conditions including muscle damage and exercise. Successful studies examining the mechanistic properties of HSP in skeletal muscle will further our current understanding of the role heat shock proteins play as chaperones and help identify other clinically relevant applications for use of heat therapies.

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