Chapter 6
Heat Shock Proteins, Exercise and Inflammation

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Abstract The heat shock response (HSR) plays a regulatory role in controlling inflammatory events within a cell. The activation/induction and interplay of heat shock factor 1 (HSF1) and heat shock proteins (HSP) have inhibitory effect on nuclear factor-kappa B (NFκB) inflammatory pathway, c-Jun N-terminal kinases (JNK) regulation, and preventing free radical damage. Exercise training induces the HSR and has the potential to reduce inflammation. The current chapter examines the regulatory impacts of the HSR on inflammation and the role of the HSR in chronic inflammatory disease states, such as skeletal muscle insulin resistance and ischemia/reperfusion injury of the myocardium. In addition, we discuss the inflammatory role of exercise training in activating the HSR, improving insulin signaling, reducing vasculature inflammation, and promoting cardioprotection against ischemia/reperfusion injury of the myocardium.

Keywords Cardioprotection · Cardiovascular disease · Free radical damage · Insulin resistance · Ischemia/reperfusion · Type 2 diabetes mellitus

Abbreviations

AKT	protein kinase B
AMPK	5′ adenosine monophosphate-activated protein kinase
AP-1	activation protein-1
ERK1/2	extracellular signal-regulated protein kinases 1 and 2
GLUT4	glucose transporter type 4
HIIT	high intensity interval training
HOMA	homeostasis model assessment index

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HSF-1	heat shock factor 1
HSP	heat shock proteins
HSP27	heat shock protein 27
HSP60	heat shock protein 60
HSP70 or HSPA	family of heat shock protein 70 kda
Hsp72 or HSPA1A	heat shock protein 72 kda
HSR	heat shock response
IKK	inhibitor of NF-κB kinase
IL-1β	interleukin-1 β
IMTG	intramuscular triglyceride
IR	insulin resistance
IRS-1	insulin receptor substrate 1
JNK	c-jun amino terminal kinase
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
NFκB	nuclear factor-kappa B
OGTT	oral glucose tolerance test
PBMC	peripheral blood mononuclear cell
RNS	reactive nitrogen species
ROS	reactive oxygen species
T2DM	type 2 diabetes mellitus
TNF-α	tumor necrosis factor-alpha
UCP-3	uncoupling protein 3
β-HAD	β-hydroxyacyl-CoA-dehydrogenase

6.1 Introduction

The heat shock response (HSR) is an intracellular chaperone mediated protein maintenance system involved in successful folding/re-folding of damaged proteins upon exposure to a wide range of stressors (e.g. heat, oxidative stress, bacteria, virus) (Feder and Hofmann 1999). The activation and induction of HSR components, namely the inducible heat shock protein 70 (HSP70 or HSPA) family, confer protection against subsequent exposure to a damaging stimuli; and support adaptations to the stressful environment (i.e. heat tolerance and heat acclimation). Further, overexpression of HSP70 from heat preconditioning or genetic engineering provides protection against lethal cellular insult such as lipopolysaccharide (LPS) exposure. A robust amount of literature exists examining the protective affects of the HSR chaperone system in various tissues (skeletal muscle, heart, brain, liver) under conditions of cellular insult (e.g. exercise, ischemia, heat stress). However, in the early 2000s, it was determined that the HSR may play a regulatory role in controlling inflammatory events within a cell (van Eden et al. 2005; Yoo et al. 2000). In this function, activation of the HSR controls pro-inflammatory signaling, such as cytokine production and release, that may lead to organismal injury or death.

The purpose of this chapter is to examine the regulatory impacts of the HSR on inflammatory pathways. In Sect. 6.1, we discuss the mechanism of how the HSR regulates inflammatory pathways. Section 6.2 highlights the role of the HSR in chronic inflammatory disease states. In addition, throughout the chapter, the role of exercise in activating the HSR is discussed.

6.1.1 Inflammatory Events Activating the HSR

A host of molecular events trigger cellular activation of the HSR. The wide range of signaling factors allows organisms to survive and adapt to an expanse number of environmental challenges. The obvious inducible factor is heat or hyperthermia; however, cold stress, oxidative, bacterial, and viral insults all activate the HSR (Hartl 1996). The HSR serves as a direct protective mechanism within the cell through re-folding of damage proteins to their native state, and prevention of apoptosis (Morimoto et al. 1997; Morimoto and Santoro 1998; Mosser et al. 2000; Yenari et al. 2005). This is demonstrated by greater cell survival in myocardial and brain tissue after ischemic (oxidative damage) insult among transgenic mice overexpressing HSP70. More recent, an anti-inflammatory role of the HSR has been identified, and has been referred to as the heat shock regulatory pathway (Yenari et al. 2005). This is most identifiable in a model of sepsis where invading pathogens promote the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) by leukocytes (neutrophils, monocytes, macrophages) leading to cellular destruction (Bruemmer-Smith et al. 2001). Global induction of HSP70 through heat pretreatment increases recovery from septic shock in animals (Hotchkiss et al. 1993). The regulatory effect of the HSR is mediated through suppression of inflammatory cytokine producing pathways and overall reduction in cellular damage. While the bacterial insult alone may activate heat shock factor 1 (HSF-1) leading to upregulation of multiple heat shock proteins (HSP) and cellular protection, evidence suggests that both HSF-1 and HSP70 have dual, and possibly separate roles, in controlling inflammation (Singh et al. 2004). An example of these binary roles was demonstrated in mouse macrophages where heat induced activation of HSF-1 DNA binding suppressed TNF-α production in the absence of HSP70 induction (Singh et al. 2004). In addition, overexpression of HSP70 in the absence of HSF-1 in human peripheral monocytes decreases TNF-α and interleukin-1 β (IL-1β) levels during LPS exposure (Ding et al. 1998, 2001). It is very difficult to differentiate the regulatory effects of HSF-1 and HSP70 on inflammation. Evidence suggests that HSF-1 may play a role in transcriptional control of inflammatory molecules (i.e. TNF- α, vascular adhesion molecules); while HSP70 may regulate upstream inflammatory pathways [i.e. Nuclear factor-kappa B (NFκB), c-jun amino terminal kinase (JNK)] (Mizushima 2010). This simplified model is diagrammed in Fig. 6.1. However, these conclusions are controversial and dependent upon cell/tissue type, experimental model (e.g. cell culture, rodent, human), and type of stressor (e.g. heat, oxidative, bacterial). Throughout Sect. 6.1 of this chapter we will detail the regulatory control

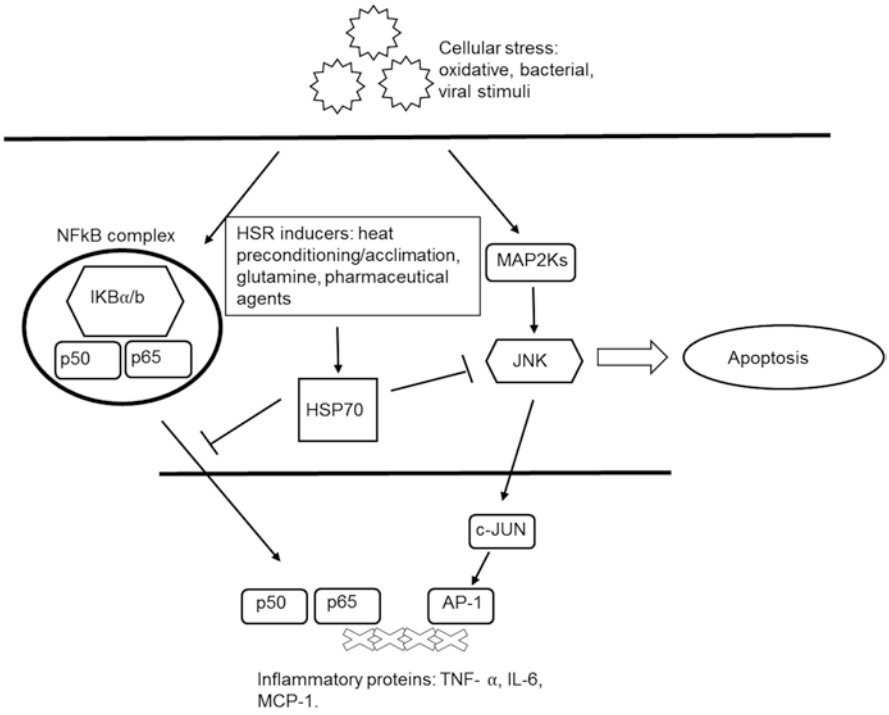

Fig. 6.1 The regulatory role of the HSR on NFκB and JNK pathways. Cellular stress activates both pathways (NFκB and JNK) leading to production of pro-inflammatory cytokines and apoptosis. Induction of the HSR through heat preconditioning and acclimation regulates inflammatory events though inhibition of NFκB and AP-1 transcriptional activity. *NFκB* nuclear factor enhancer of activated B cells, *IκBα/β* nuclear factor inhibitor, *p50* NFκB subunit, *p65* NFκB subunit, *MAP2K* MAP kinase kinases, *JNK* c-Jun N-terminal kinase, *AP-1* activator protein 1, *HSP70* heat shock protein 70, *TNF-α* tumor necrosis factor alpha, *IL-6* interluekin 6, *MCP-1* monocyte chemoattrant protein 1

of the HSR on both the NFκB and JNK inflammatory pathways. We will also briefly comment on the role of the HSR in modulating damage induced by free radicals. In each discussion, we will attempt to differentiate the roles of HSF-1 and HSP70 where appropriate. Lastly, HSR induction through exercise and nutritional supplements will be highlighted.

6.1.2 Regulation of NFκB Inflammatory Pathway

Transcriptional activity of pro-inflammatory cytokines is regulated by the NFκB inflammatory pathway, which is activated under conditions of cellular stress (heat, oxidative, sepsis, exercise) (Gloire et al. 2006; Selkirk et al. 2008). NFκB is

inactively bound in the cytosol to a complex of proteins (IκBα and IκBβ), and upon phosphorylation by inhibitor of NF-κB kinase (IKK), translocates to the nucleus to activate genes of inflammatory proteins (Liu and Malik 2006). The NFκB pathway is tightly controlled and important for innate immunity and cellular protection against bacterial insults; however it has been implicated in chronic low grade inflammatory conditions such as irritable bowel diseases, rheumatoid arthritis, and chronic obstructive pulmonary disease (Bektas et al. 2018; Holgate 2004). Robust activation of the NFκB in massive inflammatory events such as septic shock have resulted in cellular death, where inhibition in this situation improves survival (Li et al. 2009). For these reasons drugs targeting the NFκB pathway have been explored for treatment of various inflammatory states (Miller et al. 2010).

Utilizing various experimental models, researchers have shown that mild heat pretreatment prior to bacterial exposure resulted in suppression of NFκB activation, which correlated with increased HSP70 levels (Guzhova et al. 1997; Schell et al. 2005). This has been demonstrated in human lymphoma cells pretreated at 43 °C for 15 min prior to bacterial insult; brain tissue from rodents injected with LPS after whole body exposure to 41 °C for 20 min; and mouse macrophages immersed in a 42 °C water bath for 1 h before treatment with LPS (Guzhova et al. 1997; Heneka et al. 2003; Shi et al. 2006). In an interesting experiment, Brunt et al. (2017) exposed cultured endothelial cells to oxidative stress after supplementation with serum from heat treated humans who underwent 8-weeks of passive heat therapy by water immersion. NFκB activation and pro-inflammatory cytokine production were markedly reduced. HSP70 cellular inhibitory effects on NFκB may be through HSP70 physical protein binding with the **rel65** subunit of the NFκB complex preventing phosphorylation activity, and activation (Kizelsztein et al. 2009; Sun et al. 2005). In addition, HSP70 may have a regulatory role by preventing IKB degradation and nuclear translocation of NFκB, which appears to be independent of HSF-1 activation (Dokladny et al. 2010).

Acute, high intensity exercise and heat stress have been shown to activate NFκB in peripheral blood mononuclear cells (PBMCs) (Cuevas et al. 2005; Selkirk et al. 2008; Vider et al. 2001). Recently, we have demonstrated that overexpression of HSP70 in human PBMCs through glutamine supplementation suppresses NFκB activation in response to exertional heat stress (Dokladny et al. 2013; Zuhl et al. 2014, 2015). The PBMC overexpression of HSP70 further exhibited an inhibitory effect on interleukin 6 (IL-6) and TNF-α release and mRNA expression in response to a bacterial insult (Dokladny et al. 2010; Sun et al. 2005). In addition, work from our lab has shown that inhibiting PBMC HSP70 response to heat and exercise stress through anti-oxidant supplementation reduces the cytoprotective ability of the cells (Kuennen et al. 2011). In summary, activation of the HSR through heat pretreatment or glutamine supplementation has an inhibitory effect on the NFκB inflammatory pathway. Regulation is mediated through HSP70 control of NFkB by binding to rel65 unit, and preservation of IKBα inhibitory protein.

6.1.3 Regulation of JNK Pathway

The JNK pathway (sometimes referred to as stress activated protein kinase) is part of the mitogen activated protein kinase (MAPK) family and is responsible for inducing pro-apoptotic and inflammatory proteins (Dhanasekaran and Johnson 2007; Dhanasekaran and Reddy 2008). Ultraviolet irradiation, oxidative stress, heat, bacterial, cytokines, and ethanol exposure activate upstream MAP kinase kinases (MAP 2Ks) leading to phosphorylation and translocation of JNK to the nucleus. JNK phosphorylates and transactivates c-JUN ultimately forming activation protein-1 (AP-1), which is involved in transcription of a variety of proteins (Chang and Karin 2001; Dhanasekaran and Reddy 2008; Turjanski et al. 2007). Overexpression alone of JNK in human embryonic kidney cells causes profound cellular cytotoxicity and death (Chen et al. 1996). Drugs targeting the JNK pathway have become an emphasis for pharmaceutical researchers because overexpression of JNK has been linked to chronic inflammatory diseases such as diabetes, obesity, irritable bowel diseases, and atherosclerosis (Kaneto et al. 2004; Karin and Gallagher 2005; Ricci et al. 2004).

The HSR interferes with JNK signaling and improves cell survival upon exposure to damaging stimuli, and appears to be independent, or in the absence of protein damage repair (Gabai et al. 1998). In this model, the HSR inhibits the pro-apoptotic mechanisms of JNK activation under conditions of mild UV damage or TNF-α exposure, which does not induce protein damage (Gabai et al. 1998). HSP70 induced by both heat pre-treatment and transfection experiments drastically reduced apoptosis and inhibited JNK signaling in human lymphoid tumor cells (Gabai et al. 1997). This has been further demonstrated in rodent liver tissue, along with both animal and human skeletal muscle and macrophages (Adachi et al. 2010; Chung et al. 2008; Gupte et al. 2009). In both liver and skeletal muscle tissue, the inhibitory effect of HSP induction on JNK resulted in improved glucose uptake. In macrophages, HSP70 overexpression resulted in reduced pro-inflammatory cytokine release during LPS exposure, which was mediated by JNK inactivation (Wang et al. 2002). It appears that HSP70 has regulatory control by physically binding to JNK thus acting as a direct inhibitor (Park et al. 2001). In addition, HSP70 has been shown to have an indirect regulatory effect on JNK by decreasing release of TNF-α by tissue macrophages, which is a known activator of the JNK pathway (Liang et al. 2009).

Interestingly, in normal functioning skeletal muscle, JNK activation suppresses HSF-1 transcriptional activity and may serve as a controller of the cellular stress response (Park et al. 2001). However, continuous JNK induction as evident in chronic inflammatory states (e.g. insulin resistance), leads to HSR disruption which contributes to the progression of disease (Hooper and Hooper 2009). Mild heat therapy that activates HSP70 also inactivates JNK and improves glucose uptake in a rodent model of insulin resistance (Gupte et al. 2009; Hooper and Hooper 2009). This highlights the complexity of the interaction between the HSR and JNK signaling pathway. HSP70 overexpression protects cells from damaging stimuli by inhibiting JNK, and improves cell survival. However, JNK activation further suppresses HSF-1 function, possibly acting as a control mechanism in normal cellular function. In chronic inflammatory states, JNK overexpression may further inhibit the ability of an organism to fully activate the HSR.

Passive heat treatment mediates JNK levels through induction of HSR proteins, which confers protection against ischemic insult, along with improving glucose uptake in skeletal muscle (Chung et al. 2008; Yang et al. 2003). Short term passive heat acclimation (2 days) in rodents resulted in a threefold increase in HSR gene expression, which coincided with a twofold decrease in JNK genes in myocardial tissue (Horowitz et al. 2004). This was further demonstrated in rodent myocardial tissue after 30-days of passive heat acclimation (Horowitz et al. 2004). In addition, ischemia induced damage to both liver and myocardial tissue is reduced after heat preconditioning, which was mediated by HSP70 inhibition of JNK (Knight and Buxton 1996; Selzner et al. 2003). This demonstrates that inducing HSR through heat treatment may be a serviceable therapy to protect against myocardial injury such as infarction.

Any drug/supplement that upregulates components of the HSR should in theory inhibit the JNK pathway. This has been demonstrated using the pharmacological inhibitor geldanamycin, which prevented cell apoptosis induced by oxidative stress via inactivation of JNK (Choi et al. 2014). However, limited research exists exploring the effect of known nutritional HSR inducers (e.g. glutamine, zinc) on JNK activation in human models; especially under conditions of cellular stress (e.g. heat, bacterial, oxidative). Exercise induced HSR also appears to control JNK activity, but only in a pathological state such as metabolic or myocardial disease (Abubaker et al. 2013). The improvement in glucose uptake in insulin resistant tissue (skeletal muscle and liver) appears to be partially mediated by JNK inactivation, which may be due to HSR upregulation. The anti-inflammatory effects of exercise in chronic inflammatory diseases also appear to be manifested through JNK regulation; but this response is independent of HSR protein changes.

6.1.4 Prevention of Free Radical Damage

Excessive production of free radicals such as reactive oxygen species (ROS) or reactive nitrogen species (RNS) have been implicated in a host of pathological states such cardiovascular and neurological disease, along with cancer (Valko et al. 2007). The damaging stimulus induced by free radicals is commonly called oxidative stress and/or nitrosactive stress, and causes DNA, lipid, and protein damages. To remain concise, we will only discuss reactive oxygen species in the following section. Mitochondria are the main site for ROS production which occurs from partially reduced oxygen (superoxide anion) forming in the electron transport chain Complexes I and III (Muller et al. 2004). Additional sites of ROS production are peroxisomes and phagocytes (mainly neutrophils) during respiratory bursts (Decoursey and Ligeti 2005; Valko et al. 2007). Cellular damage can occur by excessive ROS production, a decrease in the activity of antioxidant defense systems, or both; and the balance between the two is the redox state of the cell. While excessive ROS production alone causes profound cellular damage, the change in the redox state has cellular signaling properties that further activate both inflammatory

and apoptosis pathways. For example, ROS have been shown to activate the NFκB pathway, along with AP-1 possibly though JNK activation (Ma et al. 1997; Pande and Ramos 2005; Valko et al. 2006). A major pathophysiology in the condition of heart failure is due to excessive ROS production, which mediates both chronic inflammation (through NFκB activation) and apoptosis (through AP-1 activation) (Moris et al. 2017). Damaging stimuli such as UV radiation, alcohol, smoking, asbestos, and ischemia are activators of the NFκB pathway through ROS production in various tissues (Valko et al. 2007).

Oxidative stress is a known activator of the HSR where mild repetitive ischemic/reperfusion insults of the heart resulted in burst activation of HSF-1 and led to an increase in HSP70 mRNA (Nishizawa et al. 1999). The upregulation of key heat shock proteins upon exposure to ROS is important for cellular adaptation to oxidative stress (Madamanchi et al. 2001). Ischemic/reperfusion preconditioning induction of HSP70 protects against subsequent lethal ischemia in rat hippocampus tissue, and profound cellular damage occurs when HSP70 is inhibited (Sun et al. 2010; Wang et al. 2011). Similar to preconditioning, in HSP70 overexpression experiments, cellular protection against reactive oxygen species is well established (Kalmar and Greensmith 2009; Wang et al. 2011). For these reasons, targeted therapy for HSR activation in ischemic injury disorders such as myocardial infarction and stroke have been explored; but the appropriate timing for administration is not well understood (Kalmar and Greensmith 2009). In summary, reactive oxygen species play an important role in disease pathology due to excessive oxidative stress. The HSR system is activated by ROS, and upregulation to these exposures is critical for cellular adaptation to chronic oxidative stress and confers protection against more severe exposure. In addition, overexpressing HSR proteins may be a preventive strategy against ischemic disease states.

6.2 Exercise Induce HSP and Reduce Inflammation

6.2.1 Insulin Resistance/Diabetes

Insulin resistance (IR) is characterized by a blunted effect of insulin on reducing circulating blood glucose at whole-body, or lower response of certain tissues to the action of this hormone, such as skeletal muscle, liver, and adipose tissue (Kasuga 2006). Skeletal muscle is responsible for about 70–80% of insulin-stimulated postprandial glucose uptake and plays a key role in the maintenance of whole-body insulin sensitivity and control of glycemic homeostasis (DeFronzo et al. 1981; Zierath et al. 2000). Additionally, IR in skeletal muscle is one of the earliest detectable defects preceding hyperglycemia even 10 years before type 2 diabetes mellitus (T2DM) is diagnosed (Di Meo et al. 2017). In the early stages of IR, an excessive release of insulin by the pancreas is needed to the cellular action of this hormone and no signs of impaired glucose disposal is present (no presence of fasting blood hyperglycemia). As it progresses, the pancreas produces extra insulin, but it can no

longer bring down sugar levels and a condition called pre-diabetes type 2 develops (fasting glucose of 100–125 mg/dl, hemoglobin A1C of >5.7–6.4% or glucose concentration after 2 h of oral glucose tolerance test (OGTT) between 140 and 199 mg/dl). In the late stages of IR, a pancreatic β cell dysfunction is present, and T2DM is diagnosed (fasting glucose of >126 mg/dl, hemoglobin A1C >6.5% or glucose concentration after 2 h OGTT >200 mg/dl). The Center of Disease Control estimates that 33.9% of United States adults aged 18 years or older (84.1 million people) had prediabetes in 2015. There is no current data reporting the prevalence of IR in the United States population, but it might be over 50% of the adult population.

A multitude of inflammatory molecules are involved in the disruption of the insulin signaling. Insulin signaling requires a cascade of protein phosphorylation that initiate with autophosphorylation of the insulin receptor tyrosine kinase followed by tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) and activation of downstream targets, including protein kinase B (AKT) and glucose transporter type 4 (GLUT4). The NF-κB pathway is directly involved in the pathogenesis of IR by upregulating genes that encode pro-inflammatory molecules such as IL-6, TNF-α and IL-1 β. For example, there is strong evidence that TNF-α is implicated in the etiology of insulin resistance and T2DM, primarily by reducing tyrosine phosphorylation of IRS-1. Uysal et al. (1997) demonstrated that TNF-α is a mediator of IR and that mutation of the gene encoding TNF-α and those encoding the two receptors for TNF-α in mice improves insulin sensitivity in the context of obesity. The authors concluded that TNF-α is an important mediator of insulin resistance in obesity through its effects on several important sites of insulin action. Other inflammatory serine/threonine kinases can also cause inhibitory phosphorylation on insulin-signaling molecules. The JNK, contributes to inflammation and IR possibly by the interplay between JNK and pro-inflammatory cytokines (Hirosumi et al. 2002).

The first evidence that there is an association between IR/T2DM and HSR was provided by Kurucz et al. (2002). The authors reported decreased expression of heat shock protein 72 kda (Hsp72 or HSPA1A) in skeletal muscle from patients with T2DM (tenfold lower than control individuals), and that the level of Hsp-72 mRNA correlated with the rate of insulin-stimulated glucose uptake and lipid turnover and glucose tolerance (Kurucz et al. 2002). Supporting evidences were also provided by Bruce et al. (2003) which also reported a reduction in the basal expression of Hsp72 mRNA in the skeletal muscle of patients with T2DM. The authors further demonstrated a significant correlation between the expression of Hsp72 mRNA and muscle oxidative capacity, as well as a moderate relationship between intramuscular triglyceride (IMTG) accumulation and Hsp72 mRNA (Bruce et al. 2003). Confirmatory data from Chung et al. (2008) latter demonstrated that insulin resistant humans have reduced Hsp72 protein expression and increased markers of inflammation (i.e. JNK phosphorylation) in skeletal muscle. We further reported that insulin sensitive obese individuals have lower HSP70 expression and higher JNK phosphorylation in skeletal muscle compared to non-obese individuals. The presence of IR resulted in a further increase in JNK phosphorylation and lower HSP70 expression (de Matos et al. 2014). Henstridge et al. (2010) also demonstrated in humans that Hsp72 protein expression in skeletal muscle is inversely correlated

with percentage body fat and positively correlated with insulin sensitivity in healthy individuals (Henstridge et al. 2010). Based on these initial studies, the intracellular concentration of Hsp72 (or HSR) is low in the skeletal muscle of individuals with insulin resistance and might be related to the inflammation observed in this condition.

Evidences exist between the potential therapeutic role of HSR in IR conditions. Chung et al. (2008) tested whether activation of Hsp72 through heat therapy (core temperature of 41 °C, once a week, for 16 weeks), transgenic overexpression ($Hsp72^{+/+}$), and pharmacologic means (BGP-15 drug, 15 mg/kg per day in 200 μl of saline for 15 days) either specifically in skeletal muscle or globally in mice would protect against the development of IR in the context of high fat diet and obesity. The authors reported that regardless of the means used to achieve an elevation in Hsp72 protein, protection against diet- or obesity-induced hyperglycemia, hyperinsulinemia, glucose intolerance, and IR was observed (Chung et al. 2008). This protection was tightly associated with the prevention of JNK phosphorylation. In this regard, Gupte et al. (2009) confirmed the findings by Chung et al. (2008) showing that heat therapy or overexpression of Hsp72 restored glucose uptake and improve insulin signaling in skeletal muscle from rats fed a high-fat diet. The authors indicated the underlying mechanism suggesting that Hsp72 and 25 may prevent an increase in JNK phosphorylation and IKK-β activation, possibly through direct interaction (Gupte et al. 2009). Also, heat treatment increased mitochondrial heat shock protein 60 (HSP60) and uncoupling protein 3 (UCP-3) expression and maintained mitochondrial enzyme activity in the presence of a high-fat diet. Moreover, Henstridge et al. (2014) showed that induction of HSP72 using BGP-15 drug or transgenic overexpression ($Hsp72^{+/+}$) in skeletal muscle can protect mice from high fat diet-induced insulin resistance and provided evidences that mechanisms other than blocking inflammation (JNK activation) is involved. It was shown that overexpression of Hsp72 in skeletal muscle enhanced muscle oxidative metabolism, thereby preventing ectopic lipid accumulation, increased mitochondrial number and oxidative metabolism, improved exercise performance and insulin action in mice fed a high-fat diet. The authors concluded that increased muscle Hsp72 promotes mitochondrial biogenesis and enhanced oxidative metabolism, likely via a mechanism involving increased 5′ adenosine monophosphate-activated protein kinase (AMPK) activity and sirtuin activation (Henstridge et al. 2014). Collectively, these findings suggest a potential therapeutic treatment for insulin resistance and identify an essential role for HSP blocking inflammation and/or improving maintaining oxidative metabolism in skeletal muscle in the context of high-fat diet-induced obesity.

Endurance exercise is a well-known non-pharmacological strategy for the prevention or treatment of IR and T2DM. In a meta-analysis conducted by Snowling and Hopkins (2006) using 27 studies evaluating the effect of aerobic, resistance, and combined training (aerobic + resistance) reported that all forms of exercise training result in small to moderate benefits in glucose control (measured by hemoglobin A1C). Also, the effects of exercise are similar to those of dietary, drug, and insulin treatments in type 2 diabetic patients (Snowling and Hopkins 2006). Although the

effect of exercise training on prevention and treatment of IR is well established, the mechanisms are less explored and known. An acute bout of exercise significantly enhances insulin's ability to stimulate glucose uptake in skeletal muscle and counteract insulin resistance. The effects of exercise in the skeletal muscle are mainly related to different cellular stressors including hyperthermia, hypoxia, mechanical and oxidative stress, energy depletion, acidosis, and increased calcium concentration (reviewed by Kregel 2002). In regard to exercise training, cellular adaptations occur to better cope with the acute stress of exercise, such as higher oxidant and oxidative capacity, and thermal tolerance. All of these stressors stimulate the HSR in skeletal muscle and may contribute directly or indirectly to enhance insulin action through a reduction in pro-inflammatory signaling.

Our group investigated the effects of a single session of aerobic exercise on the expression of HSP70, JNK, and IRS-1 serine residue phosphorylation in the skeletal muscle of obese and IR individuals. At rest, obese insulin sensitive individuals (determined by the Homeostasis Model Assessment index – HOMA >2.71) had higher levels of p-JNK and p-IRS-1 serine 612 and reduced HSP70 expression in the skeletal muscle than paired normal weight controls. In obese insulin resistant individuals (HOMA >2.71), we observed a further increase in JNK phosphorylation and decrease in HSP70 expression (de Matos et al. 2014). A significant positive correlation between plasma insulin concentration and JNK phosphorylation in the skeletal muscle was also observed. A single session of exercise reduced skeletal muscle JNK and p-IRS-1serine 612 phosphorylation levels in obese insulin resistant individuals. A main effect of exercise on HSP70 expression was also reported. JNK is an important negative feedback regulator for insulin signaling through inhibitory phosphorylation of IRS-1 in humans and a single exercise session is able to reduce JNK (Lee et al. 2003).

Exercise training adaptations result from the cumulative effect of acute stress of the exercise. The transient changes in mRNA and protein expression after each exercise session may restore skeletal muscle HSR of insulin resistant individuals reducing inflammation and enhancing insulin sensitivity. Atalay et al. (2004) showed that endurance training (8 weeks for 5 days/week) upregulates Hsp72 levels in skeletal muscle of diabetic rats induced by streptozotocin. However, this induction was several folds lower in diabetic animals than in nondiabetic control rats and HSF-1 activation occurred only in the control group (Atalay et al. 2004). Recently, we compared the effect of high intensity interval training (HIIT) on proteins involved in the insulin signaling pathway, MAPKs, and Hsp72 in the skeletal muscle of insulin-resistant and non-insulin-resistant obese individuals (de Matos et al. 2018). HIIT induced a significant reduction in fasting blood insulin concentration and insulin resistance measured by HOMA1-IR only in obese insulin resistant individuals. HIIT also increased phosphorylation of IRS-1 tyrosine 612 and Akt (Ser473), reduced extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylation, but did not change JNK1/2, Hsp72 and p38 phosphorylation. Also, HIIT promoted increased expression of β-hydroxyacyl-CoA-dehydrogenase (β-HAD) and cytochrome c oxidase subunit IV (COX-IV), possibly indicating an improvement in oxidative metabolism and, perhaps, this may have contributed to the improvement of insulin signaling. This result suggested that expression of

exercise-induced Hsp72 may not be necessary to obtain the beneficial effects of exercise on insulin resistance. However, Tsuzuki et al. (2017) reported that attenuation of exercise-induced Hsp72 expression in the skeletal muscle partially blunts the improvement in whole-body insulin resistance in type 2 diabetic rats. The authors trained diabetics rats (Otsuka Long-Evans Tokushima Fatty rats) 5 days/week for 10 weeks in two different environmental conditions: temperate (25 °C) or cold environment (4 °C) (Tsuzuki et al. 2017). The insulin levels during an intraperitoneal glucose tolerance test was higher in the cold than in the temperate environment group indicating a lower effect of the exercise training in the IR. Also, Hsp72 expression in the gastrocnemius muscle and liver was significantly lower in the cold than temperate environment group. Therefore, the role of Hsp72 induced by exercise training in reducing inflammation and improving insulin resistance in the skeletal muscle of humans remains unclear.

6.2.2 Cardiovascular Disease

Cardiovascular diseases are a group of disorders of the heart and blood vessels and the leading cause of death worldwide coronary (WHO 2017). An estimated 17.7 million people died from cardiovascular disease in 2015, representing 31% of all global deaths (WHO 2017). Inflammation has been linked, both experimentally and clinically, to cardiovascular disease (Pearson et al. 2003). It has been demonstrated that exercise training reduces cardiovascular risk factors and increase cardioprotection against ischemia followed by reperfusion injury through a direct effect on the myocardium (reviewed by Borges and Lessa 2015). The proposed mechanisms to explain the cardioprotective effects of exercise include induction of intracellular HSP. In the regard to the vasculature, exercise results in vascular stress through the increase in shear stress and mechanical stretch. Fluid shear stress induces the phosphorylation of heat shock protein 27 (Hsp27) in vascular endothelial cells (Li et al. 1996). Exercise pre-conditioning strengthens the endothelial barrier resulting in reduced brain injury by decreasing cerebral permeability and enhancing brain integrity after stroke (Ding et al. 2006). In fact, Silver et al. (2012) reported that a single bout of exercise in rats increased HSP70 mRNA in large intermyofibrillar blood vessels (Silver et al. 2012). Milne et al. (2012) suggested that the protection offered by exercise induce HSP70 against ischemia reperfusion injury may lie in its accumulation in the cardiac vasculature. The authors observed that the accumulation of HSP70 24 h after a single exercise bout (30 m/min for 60 min and 2% incline) or 5 days of training was predominantly located in large blood vessels and, in particular, colocalized with a marker of smooth muscle in rats (Milne et al. 2012). Furthermore, higher core temperatures attained during exercise led to more abundant accumulation in smaller vessels and the endothelium. In the context of vascular inflammation, HSP70 induced by a heat shock has been shown to inhibit TNF-α-induced expression of intercellular adhesion molecule-1 in human endothelial cells (Kohn et al. 2002). A popular prescribed drug class to lower serum cholesterol

concentrations and prevent arteriosclerosis increases HSP70 and nuclear translocation of HSF-1 (Uchiyama et al. 2006). Also, HSF-1 upregulation induces anticoagulation and eNOS expression and decreases endothelin-1 and plasminogen activator inhibitor-1 expression in vascular endothelial cells. Therefore, exercise may inhibit vascular inflammation via activation of HSR (Uchiyama et al. 2007). However, this association needs to be tested.

Disorders characterized by ischemia followed by reperfusion, such as myocardial infarction, stroke, and peripheral vascular disease, results in tissue damage and the accumulation of misfolded proteins. These misfolded proteins are toxic to cardiomyocytes and can cause cardiomyocyte death and heart failure (Pattison et al. 2008). ROS production increases dramatically with ischemia/reperfusion and is associated with tissue damage and accumulation of misfolded proteins. Exercise training (as few as five bouts of exercise on consecutive days) provides cardioprotection against ischemia/reperfusion injury of the myocardium (Powers et al. 2014). The mechanism of the exercise induced cardioprotection resistance against ischemia followed by reperfusion is complex and may involve the HSR. It is suggested that a HSR may protect the myocardium against ischemia/reperfusion injury by increasing myocardial antioxidant capacity, protecting mitochondria and cytosolic proteins against ischemia/reperfusion injury, and preventing apoptosis (Powers et al. 2014). Hsp72 upregulation through thermal preconditioning attenuates inflammation (measured by leukocyte-endothelial migration) induced by ischemia/reperfusion injury (McCormick et al. 2003). Preconditioning attenuated the effects of ischemia/reperfusion, and reduced the number of adherent and migrating leukocytes to control levels, at both the 30- and 60-min postischemia time points. Mice overexpressing HSP70 constitutively in the myocardium demonstrated enhanced recovery of high energy phosphate stores and correction of metabolic acidosis and greater myocardial preservation following brief periods of global ischemia (Radford et al. 1996). Locke et al. (1995) reported that both heat shock and exercise training improved post-ischemic recovery and suggested that Hsp72 was associated with ischemia/reperfusion injury prevention to rat hearts (Locke et al. 1995). The further involvement of HSP70 response to exercise conferred cardioprotection was investigated using a sexual dimorphism model. After exercising, male rats, compared with intact female rats, demonstrated a twofold greater cardiac HSP70 content. Removal of the ovaries, resulted in post-exercise HSP70 levels that were similar to those observed in male rats. The authors reported that the physiological importance of this sexual dimorphism is reflected in the finding that exercise improved post-ischemic cardiac function in male rats and ovariectomized female rats, which exhibited marked induction of HSP70 with exercise, but not in intact female rats (non-ovariectomized), which demonstrated relatively low post-exercise HSP70 expression (Paroo et al. 2002). Although many studies have shown an association between higher cardioprotection and Hsp72 with exercise training, Quindry et al. (2007) demonstrated that elevated cardiac levels of Hsp72 are not essential to achieve exercise-induced cardioprotection against ischemia/reperfusion -induced myocardial infarction or apoptotic cell death following ischemia/reperfusion in the rat. The authors observed that exercise in a cold environment inhibited an increase in body

temperature and prevented the increase in myocardial Hsp72. However, animals trained in the cold environment exhibited cardioprotection against ischemia/reperfusion-induced myocardial infarction and apoptosis similar to animals exercised in the warm environment (Quindry et al. 2007). Although exercise is cardioprotective against ischemia/reperfusion injury, its precise mechanisms offering protection have not been fully defined. The increase in Hsp72 expression promotes cardioprotection against ischemia/reperfusion injury of the myocardium, but it is not essential for exercise-induced cardioprotection.

6.3 Conclusions

The HSR plays a regulatory role in controlling inflammatory events within a cell that may lead to organismal injury or death. Although the exact mechanism still debatable, activation/induction and interplay of HSF1 and HSP have inhibitory effect on NFκB inflammatory pathway, JNK regulation and antioxidant capacity. These effects have potential to alter inflammatory related diseases, such as insulin resistance and cardiovascular diseases. Exercise training induces a HSR, improves insulin signaling, reduces vasculature inflammation, and protects myocardium against ischemia/reperfusion injury. Despite exercise induces a HSR and has anti-inflammatory effect, it cannot be confirmed that a HSR is essential for the anti-inflammatory effect of exercise.

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