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Serum Heat Shock Protein (HSP70) Changes In Horses After An Acute Exercise

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Abstract

Heat shock proteins (HSP) play critical roles in the body's self-defense under a variety of stresses. In particular, HSP70 is a key regulator of normal physiological processes including physical exercise. Exercise is associated with transient increases of HSP expression in rodents, humans and horses, but so far little is presently known about the effects of acute high-intensity exercise or training on the release of HSP70 in the blood of horses. The aim of the study was to investigate the effect of acute exercise as racehorse intensive training and gallop race on serum HSP70 levels. The research was carried out on 12 trained horses performing regularly training and gallop race. Serum HSP70 levels were analyzed by ELISA assay before and immediately after the end of both training and gallop race sessions. Results showed significant increased levels of serum HSP70, both after the end of the whole training session and gallop race, compared to basal values. A physiological stress associated with acute physical exercise seems to activate HSP70 pathway also in horses, suggesting the presence of an adaptation process to a stress of a novel homeostatic condition. Further investigations, at different times after the end of the exercise, could be useful to understand if HSP70 may be considered a new approach to monitoring exercise training and adaptive mechanisms in horses.

Keywords: HSP70; Horse; Race; Training

Introduction

Heat shock proteins (HSPs) are a group of highly evolutionally conserved proteins, which are found both inside and outside the cell (Moseley, 1998) of several mammalian species. They may interact with other proteins, hence they are highly inducible by a variety of pathological, physiological, and environmental stress. HSP regulate the conformation and functions of a large number of cellular proteins in order to protect the organism from stress (Feder and Hofmann, 1999), but are also critical in normal functioning of several cellular processes (Locke, 1997). In particular, HSP70 is a chaperone protein whose expression is induced upon exposure of the cell or tissues of the organism to stress conditions (Dimauro et al., 2016). It prevents protein aggregation and is able to promote the refolding of proteins that become damaged in response to environmental insults, pathogens, and diseases (Noble and Shen, 2012; Kültz, 2005; Hartl et al., 2011; Saibil, 2013). Its activity is essential for cellular survival and recovery under stress conditions, as well as

for the maintenance of normal cellular functions under non-stress conditions (Mayer and Bukau, 1998; 2005). HSP70 has been implicated in many diseases (Noble and Shen, 2012) and is also a key regulator of normal physiological processes including hyperthermia (Mosser and Bols, 1998), aging (Cobley et al., 2014; Ceci et al., 2014) and physical activity such as exercise (Noble and Shen, 2012). Exercise is associated with transient increases of HSP expression, together with body temperature, hormones and oxidative stress, which may reduce inflammatory mediators (Locke et al., 1990). As throughout the rest of the body, HSP likely play specific roles within the vasculature (Kim et al., 2004).

In addition, HSP70 can modulate the anti-inflammatory and inflammatory cytokine profile, reducing the presence of cell adhesion molecules and thereby leucocyte infiltration of the vascular wall (House et al., 2001; Nakabe et al., 2007). An acute, submaximal, physical activity was linked to the induction of HSP70 in rodents (Locke et al., 1990) and the alterations in rat striated muscle loading, resulting from changes in treadmill exercise intensity, were an important component of exercise-induced increases in HSP70 content (Milne and Noble, 2002). Always in rats, the increase of the expression of exercise-induced HSP70 was dependent on intensity and duration of exercise, and tissue muscle types (Shin et al., 2004).

In human athletes, after competition, an increase in blood levels of HSP70 (Banfi et al., 2006; Fehrenbach et al., 2000; Liu et al., 2000), but a decrease after training (Ziemann et al., 2013), was reported.

Up to date knowledge on the relationship between stress responses and physical exercise in horses is currently somewhat limited. In regularly trained Standardbred trotters, one bout of treadmill exercise at moderate intensity and duration (45 min) did not induce HSP (HSP70 and HSP90) responses despite the increased protein oxidation and tissue inflammation in equine muscle (Kinnunen et al., 2005). HSP72 and HSP70 expression was rapidly modulated in response to exercise-induced stress in the peripheral blood mononuclear cells (PBMC) of adult Jeju horses, but not in Thoroughbred horses (Khummuang et al., 2020). In whole blood of Standardbred horses, following acute submaximal exercise, an increased HSP70 expression, in both young and adult horses, with young horses exhibiting 3-fold greater HSP70 expression than aged mares at 2 hours post-exercise, was reported (Avenatti et al., 2018).

On this basis, we hypothesized that an acute exercise in horses would affect levels of HSP70 into the blood.

Materials and Methods

The animal care and use procedures were approved by the University of Messina Animal Committee and performed in accordance with the EU Directive 2010/63/EU for animal experiment. Informed consent from horse owners was provided.

Animals

Twelve healthy Thoroughbred horses (six females and six males), ranging in age from 3 to 6 years, mean body weight 480 ± 50 kg, housed at the Hippodrome of Syracuse, were used in the study. Horses were individually housed in 4 x 4 m box stalls and were feed according to the daily estimated energy requirements of 58 MJ NE (range 54 - 66) consisted of haylage and concentrate feed. Water and salt blocks were available ad libitum. All horses had a body conditional score 4 or 5 during the study (Henneke et al., 1983), which was measured by the same veterinarian who performed the blood sam pling.

All subjects, used for gallop races, underwent pre-race training sessions and then participated in a gallop race, according to the following protocol. The horses were trained regularly, by the same rider, on a 1,800 m sand track employing a traditional training schedule: two high-intensity training session per week (2 bouts of 5 minutes at an average speed of 10 m/s) completed by two low-intensity training sessions at mean speed 8.33 m/s. During the study, all horses performed both

training session (T) and gallop race on sand track (GR) session with an interval of 5 days between (T) and (GR) sessions. The weather conditions during both exercises were similar with temperatures between 16°C and 18°C and relative humidity between 49% and 50%. The training session included a warm-up of 3600 m slow trot (6.0-6.5 m/second), 1800 m trot (10.5-10.7 m/second), 10 minutes walk, and a gallop race of 1800 m (8.5-8.7 m/second). The gallop race on sand track (GR) included a warm-up of 3600 m slow trot (6.0-6.5 m/second), 1800 m trot (10.5-10.7 m/second), 10 minutes' walk, and a gallop race of 1800 m (10.2-10.5 m/second) (approximately 2 minutes).All the subjects, during the specific pre-race training sessions and gallop race, to which they were usually subjected, were carefully monitored by the same veterinarian who performed the blood sampling. Heart rate and plasma lactate concentrations (PLa) were also measured.

Sampling

Blood samples, at rest (baseline), and immediately after the end and at 30 minutes after of both training (T) and gallop race (GR) sessions, were taken from the jugular vein using evacuated tubes without anticoagulant and kept in ice water, by the same veterinary under quiet conditions. The resting sample was taken the day before to avoid the influence of emotional stress on the measured parameters. Moreover, horses were fasting at least at 3 hours after their last meal. After collection, the samples were immediately placed at 4°C temperature. Within 30 min, they were centrifuged at 1,000 g and 4°C for 15 min. Aliquots of serum were stored at -80°C. Prior to the HSP70 assay, frozen samples were slowly brought to 4°C and centrifuged to remove residual debris.

HSP70 Analysis

Serum HSP70 was evaluated using the ELISA assay kit "Elisa HSP70 high sensitivity EIA kit" (Enzo Life Sciences, Farmingdale, NY, USA). For each ELISA test performed, the standards provided by the kit were also processed, according to the reference protocol. The concentrations of HSP70 in the samples were calculated as follows: 1) calculating the Average Net OD (optical density) for each standard and sample by subtracting the average blank OD from the average OD for each standard and sample (Average Net OD = Average OD – Average Blank OD); 2) The OD values of the standards were used to construct a calibration curve and the concentration of each sample was determin ed by interpolation.

The sensitivity or the limit of detection of the assay was 0.09 ng mL-1 (90 pg/mL). The intra- and inter-assay coefficients of variability (CV) were 3.9% and 19.1 % respectively, on the basis of measurements performed in multiple assays.

Heart Rate

Heart rate was measured using a pulsimeter (Polar S710i, Polar Electro Oy, Kempele, Finland) continuously in both training (T) and simulated race on sand track (SR) sessions. The HRs at rest, after exercise, and at 30 minutes of recovery were recorded using a fonendoscope.

Lactate

For analysis of blood lactate concentrations, blood samples were collected at rest and after the end of both exercise sessions, T and GR, by making a small puncture with a lancet. Plasma lactate concentrations were measured immediately on a portable analyser (Accutrend lactate Roche Diagnostics GmbH, Mannheim, Germany).

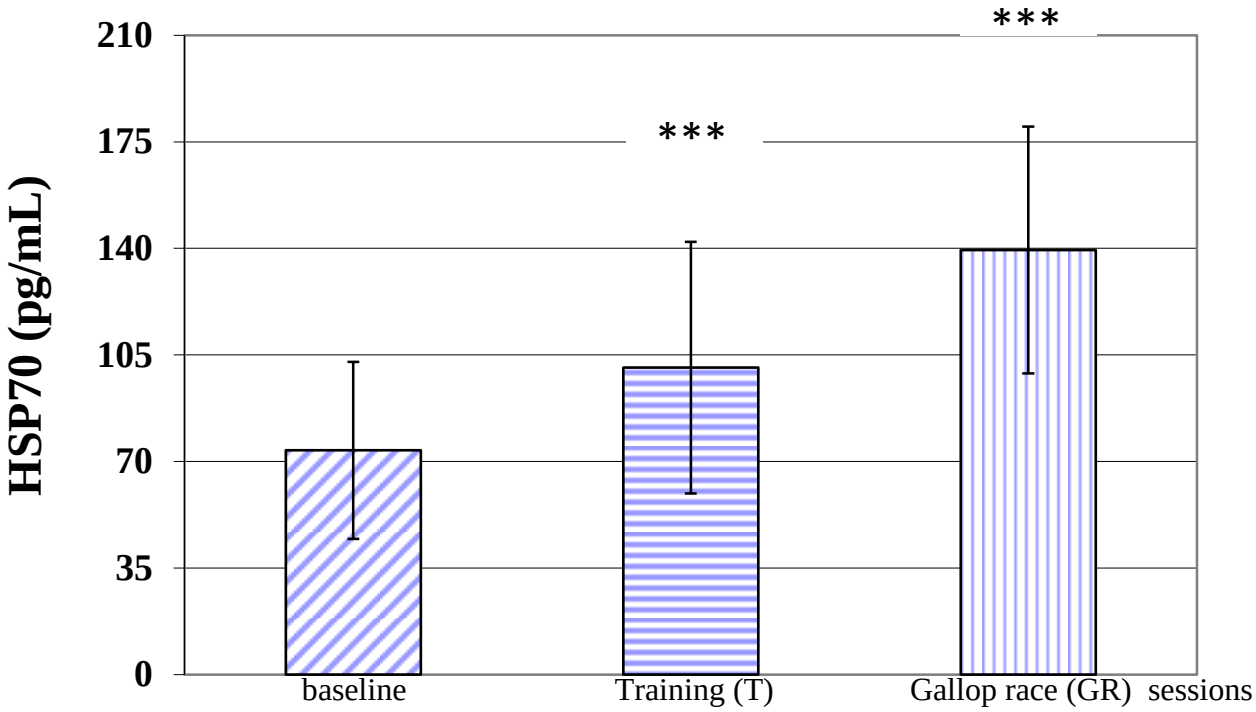
Statistical Analysis

All results are presented as means ± standard deviation. A 2-way analysis of variance with repeated measures (2-way RM ANOVA) was applied to test for the different type of sessions and sex, as well as for the interactions between them, on serum HSP70 changes. When the F statistic was significant, the difference between individual means was established using the Bonferroni test. The level of significance was set at $P \leq 0.05$. All calculations were performed using the PRISM software (GraphPad Software Inc, San Diego, CA).

Results

The mean and standard deviation (SD) values of HSP70 calculated for after training and racing horses, and control group are reported in (Figure 1).

Figure (1): Serum concentrations of heat shock protein 70 (HSP70) (mean ± SD) in horses (n= 12) during training and gallop race sessions (Baseline; immediately after training, and Gallop race).



Asterisks indicate significant differences versus Baseline (***P≤0.001). HSP70, heat shock protein 7

Statistical analysis showed significant higher levels of serum HSP70, both after the end of the whole training session (100.83 ± 41.36 pg/mL; P≤0.001) and gallop race (139.42 ± 40.53 pg/mL; P≤0.001), compared to basal values (73.67 ± 29.05 pg/mL). Two-way analysis of variance for repeated measures (2-way RM ANOVA) showed a significant effect of physical exercise on serum HSP70 levels (F= 34.54; P≤0.0001). No significant influence of sex on changes in HSP70 levels after training and gallop race was found.

Heart rate increased in both T and GR sessions and maximal HRs were 220 ± 8 beats/min in T and 200 ± 12 beats/min in GR. Heart rate was still elevated compared with basal values at 30 minutes of recovery for both GR and T. There was no difference in maximal HR or in HR during recovery in both sessions (Table 1). Both sessions determined an increase in PLa. The concentrations of blood lactate during exercise are presented in (Table 1).

Table (1): Mean ± S.D. for heart rate (HR) and plasma lactate concentration (PLa) in different sessions of exercises.

	Session	Baseline	Post-exercise	30 min Post-exercise
HR (beats/min)	T	39 ± 10	200 ± 18[a]	66 ± 4[a]
	GR	37 ± 11	186 ± 25[a]	72 ± 8[a]
PLa (mmol/L)	T	0.6 ± 0.2	17 ± 4	7 ± 2.3[a]
	GR	0.8 ± 0.2	21 ± 2.7[a*]	14 ±2.2[a*]

*Indicates a significant difference (P≤0.05) between different exercises.
[a]Indicates a significant difference from resting values.

Discussion

In line with what we are hypothesized, physical activity as training sessions and gallop race, induced an increase of serum HSP70 concentrations at short time after both the exercise.

Little information on HSP induction patterns in horses after exercise and sometimes contradictory is reported (Pösö et al., 2002). In fact, the dependence of the HSP70 induction on exercise intensity has already been demonstrated only in humans (Liu et al., 2000). Horses used in this study were all regularly trained but, differently from results reported in trotters, where a moderate intensity and duration of exercise did not induce the HSP defence system (Kinnunen et al., 2005), they were subjected to higher stress conditions, represented by an acute exercise, consisted of two high-intensity and two low-intensity training sessions, followed by a gallop race.

It is well known that physical exercise is related to many stressors, as hyperthermia, metabolic disturbances, changes of calcium homeostasis, increase of formation of reactive oxygen species (ROS), hormonal changes and tissue damages (Noble et al., 2008) and may also induce a limited inflammatory response (Sh ek and Shephard,1998).

It is also known an anti-inflammatory effect of HPS. Anti-inflammatory circumstances as exercise and heat shock increase the vascular content or alter the phosphorylation status of various HSP and both of these conditions are associated with anti-inflammatory states (Jones et al., 2011; Gleeson et al., 2011). Probably, the activation of the primary transcription factor involved in HSP induction, HSF1, may directly reduce general inflammation in vascular tissue (Xie et al., 2002).

The intensity of exercise-stress, acute or chronic, play an important role in inducing stress response. Generally, the more intense is the exercise, the greater the response (Milne and Noble, 2002; Fehrenbach et al., 2005).

HSP70 is the most abundant of all HSPs (Zylicz and Wawrzynow, 2001), accounting for 1–2% of cellular protein being highly represented in skeletal muscle. It is known that a single bout of exercise is sufficient to increase HSP70 in skeletal muscle at both mRNA and protein levels in an intensity dependent manner (Milne and Noble, 2002). Differently from other HSPs, baseline levels of HSP70 are increased by prolonged exercise training (Liu et al., 1999; Morton et al., 2008).

Several papers demonstrated that the increase in HSP70 gene expression in human muscles during or immediately after exhaustive exercises correlates with the degree of glycogen depletion (Tupling et al., 2007), while Ogawa et al. suggested that ATP level in plasma is a trigger of HSP70 release after exercise. In addition, redox-dependent induction of HSP70 protein by acute exercise is widely recognized (Khassaf et al., 2001; Khassaf et al., 2003; Fischer et al., 2006) and has been described also in blood cells (Dimauro et al., 2016).

A model that explains the activation of HSF1 with exercise and accompanying increases in vascular stress has been reported by Noble et al. (2008). According to this, the exercise initiates a number of factors, including elevations in temperature, reactive oxygen species (ROS), intracellular calcium (Ca2+), and decreased energy status, which may result in intracellular protein modification leading to dissociation of the heat shock transcription factor (HSF1) and heat shock proteins HSPs in the

cytoplasm. In addition, exercise activates adrenergic and shear stress intracellular signalling pathways. Consequently, HSF1 trimerizes and binds to heat shock elements (HSE) of nuclear DNA, where, upon specific phosphorylation/dephosphorylation events, lead to a heat shock response.

On the basis of these studies, the increase of serum HSP70 immediately after both training and gallop race could suggest the presence of an adaptation process to preserve redox balance. The exercise could promote a pro-reducing environment, leading to the down-regulation of the antioxidant enzymes, to facilitate the adaptation to a stress of a novel homeostatic condition. If so, it comes out that it would be very interesting to identify a proper training program, suitable for load and type of exercise, with different intensity and degree of duration, that is able to improve motor performance in adaptation and response to such homeostatic imbalanc e (Siciliano et al., 2020).

Any influence of sex on changes in HSP70 levels was observed in horses under study, in agreement with what is reported in humans, in response to a single bout of total body resistance exercise (Benini et al., 2015).

Further investigations, at different times after the end of the exercise, could be useful to understand if, once the muscle and peripheral systems recover from the acute stress, serum HSP70 returns to baseline levels (Morton et al., 2008).

Conclusion

In conclusion, a physiological stress associated with acute physical exercise seems to activate HSP pathway also in horses. The HSP response to exercise might well account for many health benefits associated with increased physical activity, therefore, exercise intervention may provide protection against protein-misfolding diseases or during aging, controlling of systemic inflammation and preserving muscle function. The knowledge about its changes on their serum levels may help in planning optimal training protocols. Among the subset of stress-responsive proteins, HSP70 may be considered a new approach to monitoring exercise training and adaptative mechanisms in horses, then, further investigations are needed to elucidate if the serum HSP70 measurement can be proposed as an useful and reliable indicator of muscle damage also in horses, in view of targeting possible focused therapeutic interventions.

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Conflict of Interest Statement

The authors declare no conflicts of interest and financial, personal, or other relationships with other people or organizations.

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