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FRONT MATTER: COMMENT

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HSP72 Up-regulation with heat acclimation

Comment on: Amorim FT, et al. Insights into the role of heat shock proteins 72 to whole-body heat acclimation in humans. Temperature 2015; 2:499-505; http://dx.doi.org/10.1080/23328940.2015.1110655

In a companion paper in this journal, Amorim and coworkers[1] reviewed recent human studies which show that Heat Shock Proteins (HSP72 and possibly HSP90) are elevated during heat acclimation. They suggest that these cellular changes result in both cellular and whole body thermotolerance.

Thermotolerance after an initial sub-lethal heat exposure, has been shown repeatedly in cell studies, and has been linked with elevated intracellular HSP72 levels. Animal species that live in hot desert climates have been shown to have greater ability to synthesize HSPs. However, it is nearly impossible to prove if a similar induced heat tolerance occurs humans. Specifically, can previously heat exposed humans tolerate higher core body temperatures without ill effects? Amorim et al.,[1] suggest this may be the case and HSP72 upregulation may be the cause.

Amorim and coworkers[1] go further and suggest HSP72 is involved in inducing at least some of the classic signs of heat acclimation, such as increased sweating and skin blood flow and lower body temperatures. This suggestion is based on a study in which HSP up-regulation during heat acclimation was blocked by the ingestion of an HSP blocker, quercetin, and the thermoregulatory benefits also were blocked.[2] A second human study also supports this idea. With a limited number of subjects, Kresfelder and coworkers[3] identified a subset of heat intolerant individuals who possessed a modified allele of HSP72. The authors attributed the inability of these subjects to heat acclimate to their modified form of HSP72.

Although Amorim and coworkers[1] mostly limited their discussion to human studies, Tetievsky and coworkers[4] studying rats have identified a variety of molecular pathways that are activated or deactivated during heat acclimation/de-acclimation/re-acclimation, including the HSP pathway. Heat exposures were found to turn-on or turn-off specific genes and to induce epigenetic alterations that persist for long periods, resulting in a "molecular memory" which allows more rapid re-acclimation. Taylor, in a review of ethnic differences in heat tolerance[5] suggests that such phenotypic changes (from molecular memory) after a single heat acclimation most likely are responsible for the improved heat tolerance previously attributed to ethnic differences in heat tolerance.

From cell studies it is known that upon heat exposure, heat shock factor-1 (HSF-1) is released from the HSP-HSF-1 complex. The HSF-1 trimerizes in the cytoplasm, becomes phosphorylated and then migrates into the nucleus where it binds with the heat shock element (HSE) in the promotors of the heat shock genes, stimulating translation and transcription of new HSP molecules. The freed and newly synthesized HSP have a multitude of beneficial effects, to both repair and minimize cellular damage (an initial response to short-term heat exposures), and later (with long-term heat acclimation) to up-regulate the cellular pathways to allow a more rapid synthesis of HSP72 and possibly interacting with other pathways (HIF, anti-oxidant, anti-inflammatory, anti-apoptosis) to develop thermotolerance against further environmental insult. Thus, a molecular response to heat acclimation, also seen in human leucocytes, is an intracellular accumulation of HSP72. Due to an increased HSP72 reserve after heat acclimation, there is less need to further augment HSP72 in response to an acute heat exposure.

Paradoxically, following heat acclimation in humans while intracellular HSP72 is increased, basal extracellular HSP72 is reduced. Indeed Kresfelder et al.[3] suggest that this reduced serum HSP72 can be used as an indicator that an individual has been heat acclimated. Extracellular HSP72 is involved in activation of pro-inflammatory protective responses involving TNF-α and IL-6. The protective effects of up-regulated cellular HSP72 after heat acclimation may thus reduce immune provocation during exercise in the heat, and minimize circulating HSP72.

Amorim et al.[1] also discuss the role of intracellular HSP72 in regulation of the pro-inflammatory transcriptional factor NFκB. HSP72 over-expression in rat renal tissue through heat preconditioning suppressed the activation of the IκB kinase complex and NFκB translocation. This may result in lower production of pro-inflammatory cytokines such as TNF-α, IL-12, and IL-18. Interestingly, non-steroidal anti-inflammatory drugs have been shown to induce HSP70 in human monocytes and reduce expression of pro-inflammatory cytokines indicating the anti-inflammatory benefits of HSP upregulation. Combined, this demonstrates that HSP serve a repair function to improve cell survival, and also serve a regulatory role by influencing protein transcriptional activity.

Amorim et al.[1] also reviewed the proposed effects of HSP on gut permeability. Studies in human intestinal cells have shown that heat stress increases gut permeability, but this effect can be blocked by an up-regulation of the heat shock protein pathway. The activation of HSF-1 is thought to initiate a series of cellular changes that increase the levels of the tight junctional membrane protein occludin, which decreases paracellular permeability. Recent human studies have confirmed that heat acclimation prevents the increase in gut permeability normally seen during severe exercise in the heat. However, this protective effect did not occur when individuals ingested quercetin, a blocker of heat shock protein synthesis.[2] By stabilizing tight junctional proteins and gut permeability, HSF-1 reduces endotoxin translocation from the gut, and minimizes any ensuing inflammatory reaction. In this way, heat shock proteins may be providing not only a cellular thermotolerance, but also a protective effect for the whole body. Such work raises the interesting possibility that dietary modifications could prevent (quercetin) or enhance (glutamine) acquisition of heat tolerance.

Although Amorim and coworkers[1] limited their review to the role of HSP72 in thermotolerance, recent studies suggest that many other pathways may be involved in heat acclimation adaptations. In gene mapping studies, Horowitz and coworkers[6] have demonstrated that heat acclimation alters the production of several mitochondrial enzymes involved in glycolysis, mitochondrial biosynthesis and electron transport. These changes may be responsible for a more efficient metabolism and thereby lower heat production. Other genes activated following heat acclimation include some involved red cell production, microvascular remodeling, and fluid and electrolyte exchanges across cell membranes. These are systems that could improve vascular perfusion and protect against hypoxia and ischemic tissue injuries. Other genes activated, including the HSP pathway, may alter immune function and apoptosis. The actions of all of these pathways are likely involved in not only thermotolerance, but when upregulated may also provide resistance against other forms of environmental stressors such as hypoxia, hypoglycemia, ischemic reperfusion injury, ROS, and brain injury. Such cross tolerances have been verified in animal studies.[6]

One specific area of cross adaptation/cross tolerance mentioned by Amorim and coworkers[1] is the positive benefit shown following heat acclimation in tolerance against hypoxia. Recent authors have suggested that the upregulation of HSP72 is involved in increased tolerance of human subjects to hypoxia.[6-7] However, from cardiac cell studies an increased tolerance to ischemic hypoxia must include both the heat shock and the hypoxia-inducible pathway (HIF-1).[6] Heat/hypoxic cross tolerance may also involve an up-regulation of HSP90.[7]

The field of thermoregulation has been revitalized with recent new discoveries involving molecular responses to heat and heat acclimation. These findings are especially exciting since they suggest that the positive adaptations to heat acclimation may translate to an improved tolerance against a variety of stressors, and may even provide resistance against some disease states. However, there is still a huge gap between what has been shown in cells and animals and what can be confirmed in humans. The non-human findings provide a useful blueprint for new human studies, especially as new non-invasive methodologies arrive.

References

[1] Amorim FT, Fonseca IT, Machado-Moreira CA, Magalhaes F. Insights into the role of heat shock proteins 72 to whole-body heat acclimation in humans. Temperature 2015; 2:499-505; http://dx.doi.org/10.1080/23328940.2015.1110655

[2] Kuennen M, Gilliam T, Dokladny K, Bedrick E, Schneider S, Moseley L. Thermotolerance and heat acclimation may share a common mechanism in humans. Am J Physiol Regul Integr Comp Physiol 2011; 301:R524-33; PMID:21613575; http://dx.doi.org/10.1152/ajpregu.00039.2011

[3] Kresfelder TL CN, MJ Cronje. HSP70 induction and hsp70 gene polymorphisms as indicators of acclimatization and hyperthermic conditions. J Thermal Biol 2006; 31:406-15; http://dx.doi.org/10.1016/j.jtherbio.2006.02.001

[4] Tetievsky A, Assayag M, Ben-Hamo R, Efroni S, Cohen G, Abbas A, Horowitz M. Heat acclimation memory: do the kinetics of the de-acclimated transcriptome predispose to rapid re-acclimation and cytoprotection? J Appl Physiol 2014; 117:1262-77; PMID:25237184; http://dx.doi.org/10.1152/japplphysiol.00422.2014

[5] Taylor NAS. Ethnic differences in thermoregulation: genotypic versus phenotypic heat adaptation. J Thermal Biol 2006; 31:90-104; http://dx.doi.org/10.1016/j.jtherbio.2005.11.007

[6] Horowitz M. Heat acclimation, epigenetics, and cytoprotection memory. Comprehensive Physiology 2014; 4:199-230; PMID:24692139; http://dx.doi.org/10.1002/cphy.c130025

[7] Salgado R, White A, Schneider S, Mermier C. A novel mechanism for cross-adaptation between heat and altitude acclimation: the role of heat shock protein 90. Physiol J 2014; 2014:1-12; http://dx.doi.org/10.1155/2014/121402

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