HIGHLIGHTED TOPIC | Molecular Adaptations to Exercise, Heat Acclimation, and Thermotolerance

Common mechanisms for the adaptive responses to exercise and heat stress

Lisa R. Leon

U.S. Army Research Institute of Environmental Medicine, Thermal and Mountain Medicine Division, Natick, Massachusetts

In this highlighted topic we present five reviews that explore the molecular mechanisms mediating adaptive and maladaptive responses to exercise and environmental heat stress. Energetic stress, including changes in metabolic status, production of reactive oxygen species, and increased temperature can all present significant challenges to cellular homeostasis that evoke cytoprotective mechanisms (6). Transcriptional changes form the basis for many adaptations, with recent evidence suggesting epigenetics improves tolerance to a multitude of dissimilar stressors (9).

Adaptation to exercise requires expansion of the mitochondrial pool to match changing metabolic demands of the tissue. Mitochondrial synthesis and degradation is regulated by an evolutionary conserved mechanism known as autophagy (7). In “The regulation of autophagy during exercise in skeletal muscle”, Drs. Vainshtein and Hood (13) present an overview of the mitochondrial life cycle in the context of adaptations to both acute and chronic exercise. They first provide perspective on basal autophagy that aids in cellular homeostasis and how perturbations of this function are thought to contribute to degenerative disease, aging, and skeletal muscle dysfunction. The cellular machinery and transcriptional modifications mediating nuclear- and lysosomal-autophagy responses to both acute and chronic exercise are discussed in detail. The neuroprotective effects of chronic exercise illustrate how adaptation extends beyond the skeletal muscle to include the brain (and other organs). Interestingly, aging is associated with the suppression of autophagy, suggesting a link between these responses, although it becomes the age-old “chicken vs. egg” question of whether autophagy dysfunction contributes to aging or vice versa. Clearly, additional research is required in this important area of exercise adaptation, which may impart valuable health benefits to our aging, obese, and increasingly sedentary population.

The review “Sexual dimorphism in skeletal muscle protein turnover” by Drs. Smith and Mittendorfer (12) provides a more detailed discussion of muscle function changes by focusing on the challenges facing men and women as they transition into the golden years of aging. Aging is associated with declines in muscle mass even for those individuals that continue to engage in regular exercise programs. However, recent evidence indicates that older women show greater basal muscle protein synthesis than older men, which may explain the slower rate of muscle loss as women age compared with their male counterparts. On the other hand, the anabolic response is diminished in older women compared with men, suggesting that men and women may require different intervention strategies for muscle mass preservation. A critical role for estradiol on muscle growth after atrophy may explain why older women experience a blunted anabolic response to exercise.

Heat shock proteins (HSPs) are the most recognized class of cytoprotective proteins, with an extensive body of literature demonstrating adaptive responses from bacteria to man (8). Drs. Henstridge, Febbraio, and Hargreaves (4), in their review entitled “Heat shock proteins and exercise adaptations. Our knowledge thus far and the road still ahead” provide detailed commentary and thought-provoking questions on what is known and what has yet to be elucidated with respect to the role of the HSP72 response in exercise adaptations. The significance of circulating extracellular HSP (eHSP), the mechanism(s) by which this occurs, and the organs that may be contributing continues to be investigated. The question remains as to whether eHSP72 is simply a consequence of cellular spillover or a signal for metabolic “cross-talk” among multiple organs. If, as postulated, eHSP72 participates in central nervous system sensation of fatigue, activators of this response may be leveraged as a therapeutic approach to improve motivation, enhance performance, or compensate for lack of exercise in frail, obese, or diseased individuals.

One of the primary consequences of severe exercise or heat strain is breakdown of tight junction (TJ) proteins that leads to a “leaky” gut epithelial membrane barrier. A cause and effect relationship between TJ barrier breakdown and leakage of luminal endotoxin has been well-established (1, 10). Drs. Dokladny, Zuhl, and Moseley (2) describe in “Intestinal epithelial barrier function and tight junction proteins with heat and exercise” the changes in occludin and ZO-1 protein expression that mediate TJ breakdown and how this response differs under exertional and passive heat exposure conditions. Additional factors implicated in TJ barrier breakdown include dehydration, hypoperfusion, increased temperature, as well as direct and indirect effects of LPS through a feed-forward pathway. The therapeutic implication of HSPs and nutritional interventions to improve intestinal barrier health are discussed with the caveat that much research still needs to be conducted in these areas.

Heat acclimation has been shown to induce reversible phenotype changes that confer protection against multiple stressors within an individual’s lifetime. Dr. Horowitz (5) discusses in “Epigenetics and cytoprotection with heat acclimation” the transcriptional networks controlling the rate, magnitude, timing, and function of protein responses that mediate short- and long-term heat acclimation. A fascinating outcome of heat...
acclimation is “cross tolerance” in which cellular protection against a novel stressor is attained without prior exposure. This review provides a deeper understanding of the upstream epigenetic processes controlling HSP cytoprotective reserves and how these changes facilitate rapid reacclimation after a deacclimation period.

The increased prevalence of sedentary lifestyles is becoming a public health concern because it often progresses to obesity, Type 2 diabetes, and other disease conditions. Chronic exercise is well recognized for its beneficial effects on metabolic status, cardiovascular health, and cognition (3). Unfortunately, compliance with a regular exercise program is often low because of frailty, lack of motivation, or disease states that compromise movement. Heat stress remains a pervasive environmental threat that is particularly dangerous for individuals with compromised health status (11). As these reviews demonstrate, there are commonalities in the transcriptional pathways that mediate adaptive and maladaptive responses to exercise and heat stress. The challenge is in identifying novel therapeutics that can stimulate HSPs and other signaling pathways for protection against exercise, heat, and multitude of other environmental stressors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: L.R.L. drafted manuscript.

REFERENCES