Mechanisms of heat acclimation and tolerance induced by exercise training and heat exposure

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Abstract Most animals can adapt physiologically and biochemically when exposed to altered temperatures for prolonged periods. In humans, marked physiological adjustments are apparent following repeated bouts of core temperature elevation, either from exercise, or high ambient environmental temperatures, or both. In this review, the mechanisms for such adjustments, called “heat acclimation”, are discussed. First, the authors focus on thermoregulatory responses in the process of heat acclimation, i.e. how thermoregulation adapts to changes in temperature following repeated exposure to heat and exercise. Once heat acclimation is achieved, skin vasodilation and sweating are initiated at a lower core temperature threshold, and higher sweat rates can be sustained. Second, knowledge regarding the central and peripheral mechanisms for heat acclimation and tolerance is discussed. Recently, two advances - the implication that long-term accommodation to a changing environment involves functional neuronal remodeling associated with transcriptional reprogramming, and the understanding that there is neurogenesis in the hypothalamus - have introduced new concepts to the study of heat acclimation. Although it is still a developing issue, future study will bridge the gap between the classical physiological heat acclimation profile and molecular and cellular mechanisms.

Keywords: thermoregulation, body temperature, heat adaptation

Among various environmental stressors, “temperature is ecologically the most important, for it is a factor that is all pervasive, and in most environments lacks spatial or temporal constancy”¹. Most animals can adapt physiologically and biochemically when exposed to altered temperatures for prolonged periods. In humans, following repeated bouts of core temperature elevation, either from exercise, or high ambient environmental temperatures, or both, marked physiological adjustments are apparent². Humans have a greater ability for adaptation in thermoregulation compared with other animals; however, extreme heat stress impairs exercise performance and occasionally induces heat stroke. Thus, it is important to both adapt to a hot environment and improve heat tolerance in sports and outdoor activities. In this review, the mechanisms for the adjustments, called “heat acclimation”, are discussed. First, we focus on thermoregulatory responses in the process of heat acclimation, i.e. how thermoregulation adapts to heat following repeated exposure to heat and exercise. Second, our knowledge regarding the central and peripheral mechanisms for heat acclimation and tolerance is discussed, although it is still a developing issue.

The first reference to heat acclimation is from the 18th century, coinciding with emerging interests in tropical climate and diseases, but experimentation using humans and animals began in the 20th century. A large number of studies have demonstrated that heat acclimation induces significant physiological changes in humans as follows: enhanced sweating and cutaneous vasodilation, an increase in plasma volume, a decrease in core temperature at rest or during exercise, and reduced heart rate during exercise in a hot environment³. Improvements in exercise time to fatigue, where core temperatures reach about 40°C, have been attained by heat acclimation³. A recent study has demonstrated the effectiveness of heat acclimation for highly trained cyclists⁴. Although heat acclimation does not require daily exposure to heat and exercise, rapid adaptations are achieved more slowly with less frequent exposure. Heat acclimation can be achieved following 10 days of daily heat exposure, but requires 27 days when the frequency of exposure is reduced to every third day of experimentation⁵. Aerobically trained athletes retain heat acclimation benefits longer than unfit individu-
als because they are exposed to high body temperatures during training exercise. Höfler\(^6\) reported that heat acclimation induced a peripheral redistribution of sweating, such that the post-acclimation limb sweat rate appeared to be elevated more than at central body sites. This apparent peripheral shift in secretion could facilitate greater heat dissipation if the lower pre-acclimation limb sweat rate was also associated with less than optimal local evaporation rates. Because limbs have a relatively large surface area/mass ratio, an increase in sweating and evaporation could enhance thermal homeostasis. However, there is a contradicting report that a trunk-to-limb redistribution after heat acclimation is only applicable to the upper limbs, not the lower\(^7\).

After heat acclimation, skin vasodilation and sweating are initiated at a lower core temperature threshold, and higher sweat rates can be sustained without the sweat glands becoming “fatigued” (Fig. 1). Roberts et al.\(^8\) demonstrated that exercise training and successive exercise and heat exposure reduced the temperature threshold (Fig. 1). Prompt and accelerated responses improve heat dissipation and prevent hyperthermia in heat. Both central and peripheral mechanisms are involved in the overall mechanism for adaptation. Ogawa and Sugeno\(^ya\)\(^9\) observed that the number of sweat expulsions per minute, which may be indicative of sudomotor neural activity, increased after heat acclimation, suggesting that heat acclimation may alter central modulation of the sweating response. In contrast, several studies have supported the role of local changes in sweat gland function because of heat acclimation. For example, if regional temperature was maintained at a low temperature throughout a heat acclimation protocol, sweat responses of that region were not modified by heat acclimation\(^10\). Lorenzo and Minson\(^4\) investigated whether changes in maximal vasodilator capacity of the skin and in vascular responsiveness to a given level of stimulation are altered by heat acclimation in trained individuals. Although maximal forearm skin blood flow did not change following a period of heat acclimation, skin vascular responses to local acetylcholine (an endothelium-dependent vasodilator) administration were improved by heat acclimation. Autonomic thermoregulation in heat, i.e. sweating and skin vasodilation, is largely adapted to chronic heat exposure and exercise training. On the other hand, the way in which behavioral thermoregulation is affected by heat acclimation remains unclear.

Nadel et al.\(^11\) advocated two processes of adjustment in the sweating response due to heat acclimation (Fig. 2). In a peripheral component (a shift from line A to line B), sensitivity of the sweating response per unit change of central sweating drive increased; thus a peripheral mechanism accounts for the enhanced sweating response. This shift can provide for a given steady-state sweat rate at a lower core temperature. In addition, the central mechanism results in a further enhancement of the sweating response. The capability for sweating is increased by lowering the zero point of the central nervous system drive for sweating (a shift from line A or B to line C). Herein, there was no alteration in the sweating response per unit change of central sweating drive. Therefore, an individual acclimated to heat and exercise is able to dissipate a given thermal load at an even lower level of central drive than when merely exercise-acclimated. The lowering of the zero point may be caused by a reduction in resting core temperature after heat acclimation\(^12\). The hypothesis of Nadel et al.\(^11\) provides an ingenious explanation for the relationship between central and peripheral mechanisms and an operational definition for heat acclimation; however, the precise mechanisms for the enhancement of sweating and central shift remain unresolved.
There is a large body of evidence regarding heat acclimation-mediated shifts in temperature thresholds; however, most studies are at an integrative level, i.e. human model studies. There are a limited number of direct studies on central controller plasticity. In rats, Pierau et al. showed that heat acclimation led to a considerable decrease in the number of warm-sensitive neurons in the hypothalamus. A hypothalamus having a diminished number of these neurons has a very low temperature coefficient compared with matched populations of neurons in the hypothalamus of cold-acclimated rats. A clear effect of warm acclimation was the ability to convert a larger number of insensitive neurons to warm-sensitive neurons by mediators. Recently, two advances, the implication that long-term accommodation to a changing environment involves functional neuronal remodeling associated with transcriptional reprogramming, and the understanding that there is neurogenesis in the hypothalamus, have introduced new concepts to the study of heat acclimation.

Firstly, Horowitz’s group suggested, using transcriptome analysis, that the hypothalamus, the center of body temperature control, mediates cross-talk with peripheral organs. They focused on the time-course relationship between heat-dissipation responses and hypothalamic gene expression. At the onset of heat acclimation, a marked transient upregulation in transcription is predominantly confined to genes encoding voltage-gated ion channels, ion pumps, or transporters, as well as hormone or transmitter receptors and cellular messengers, and implicates enhanced membrane depolarization, leading to a release of transmitters and an increase in neuronal excitability. Furthermore, the transient downregulation of genes participating in intracellular protein trafficking, metabolism, or phosphorylation processes, implies a perturbation in cellular maintenance. During the following phase, there is a noteworthy decrease in the expression of specific initial-activated genes related to various metabolic activities, including mitochondrial energy metabolism and cellular maintenance processes, together with the resumption of pre-acclimation transcript levels of genes encoding proteins involved in ion movement and membrane or cellular signaling. Additional significant findings include the constitutive downregulation of genes associated with energy metabolism and food intake, and the marked upregulation of a large group of genes linked with immune response. These transcriptome analysis findings imply a framework of assumptions about the interaction between thermoregulatory responses and some specific genes; however, a more precise relationship will have to be elucidated by future studies.

The second recent advance is the finding that there is neurogenesis in the hypothalamus. Matsuzaki et al. showed that long-term heat acclimation generated a significant number of new mature neurons in the hypothalamus in rats. Proliferation started within the first 5 days of heat exposure. Differentiation to mature neurons was significantly augmented after 33 days of heat exposure. Therefore, heat exposure promoted proliferation of progenitor cells in the hypothalamus for the first 30 days and then accelerated neurogenesis. The cells were found in the preoptic area of anterior nuclei, ventromedial nuclei, dorsomedial nuclei, and the posterior hypothalamic area - central regions involved in thermoregulation. Although the time span differs from the 10-day heat acclimation protocol in humans, an adaptation of long-term heat acclimation may be linked with neurogenesis. How new mature neurons integrate in a neural network and relate to thermoregulatory responses remains to be clarified. Furthermore, how exercise training in heat promotes neurogenesis in the hypothalamus compared with only heat exposure is intriguing, because exercise training itself increases cell proliferation and neurogenesis in the dentate gyrus.

Apart from the peripheral and central mechanisms, a marked increase in the level of the inducible 70-kDa heat shock protein (HSP) may contribute to heat acclimation and tolerance. Heat shock response is a rapid, short-acting molecular process associated with the synthesis of some families of HSPs of different molecular weights for protecting cells from noxious stimuli and accelerating cell repair following heat injury. There have been several studies showing the upregulation of HSP70 during different types of exercise in normal or warm temperatures. A recent study showed the time course of serum HSP70 during a 15-day heat and exercise acclimation protocol that presented a biphasic pattern; an initial heat tolerance resulted in relatively large changes in HSP70, after heat exercise, and a second phase, heat acclimation, giving rise to elevated basal HSP70 levels and only a moderate increase after heat exercise. Although heat tolerance is not determined by simple factors, how HSPs function in hot environments remains to be clarified.

In this brief review, we provide possible mechanisms for heat acclimation. In peripheral mechanisms, some human experiments are revealing the precise adaptation in the skin after heat acclimation. Conversely, current knowledge regarding the central mechanism of heat acclimation is still poor. Moreover, how thermal sensation, pleasantness, and behavioral thermoregulation are altered during heat acclimation remains to be revealed. By using animal models that reasonably resemble human adaptations, we will begin to clarify these murky issues.

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References


