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Thermal physiology in a changing thermal world

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This editorial focuses on articles submitted to the Temperature call "Thermal Physiology in a Changing Thermal World." It highlights an array of topics related to thermoregulatory and metabolic functions in adverse environments, and the complexity and adaptability of the systems to changing climatic conditions, at various levels of body organization.

In a joint effort, the organizing committee of Physiology and Pharmacology of Temperature Regulation (PPTR2014)[1] and the journal *Temperature (Landes)* issued a special call for papers on the topic "**Thermal Physiology in a Changing Thermal World**." Submissions received in response to this call included reviews and original research articles, published in the first 2 issues of *Temperature* (1.1; 1.2 2014) and in the current (2.1 2015) one. This editorial overviews the topics presented in these submissions, which include an evaluation of the evolutionary adaptation to adverse environments on one end of the spectrum, to the roles of central and peripheral modulators of thermoregulatory function, as well as the influence of factors of nonthermal origin on thermal homeostasis, on the other. Additionally, we highlight how survival in a changing adverse environment can be influenced by one's capacity to perceive thermal changes in the environment, and how performance in adverse environments can be mediated by our capacity to harness thermoregulatory adaptations. Finally, we outline the discussion of new ideas on old concepts presented in a number of reviews on thermoregulatory function and control.

Delegates at PPTR 2014 experienced the vast landscapes of the Kruger National Park and the spectacular wildlife, which includes some of Africa's largest terrestrial mammals known as the 'Big Five': Elephant, Lion, Rhino, Leopard and Buffalo. In the past few decades, the survival of these mammals has been increasingly threatened by climate change. In a series of papers, the evolutionary adaptations to climate change are examined. Hetem and colleagues[2] discuss the challenges faced by the large terrestrial mammals and highlight our lack of knowledge pertaining to our understanding of the adaptive responses and the inherent risks large terrestrial mammals face in adjusting to their rapidly changing environment. Using criteria that have been established for small ectotherms and even endotherms, which use multiple mechanisms of adaptive plasticity (if the species did not exhaust their adaptive responses, e.g.[3]), the authors conclude that the rate of climate change is too fast for genetic adaptation to occur in mammals with longevities of decades, typical of large mammals, and that landscape fragmentation and human barriers to movement further threaten the survival of these large mammals. They surmise that the only mechanism remaining to counter effects of climate change is the expression of latent phenotypic plasticity. Future research in climate change biology requires measurement of physiological characteristics of many free-living individual animals for long periods, probably decades, to discover whether expression of phenotypic plasticity will be sufficient to cope with climate change.

The paper by Cooper and Withers[4] examines how changes in metabolic activity induced by different environmental conditions can influence survival in small mammals like the mountain pygmy possum (Burramys parvus). The pygmy possum is the Australian mammal most threatened by global warming. This endangered marsupial is restricted to high altitude boulder fields of the Australian Alps, where it hibernates under the snow during winter. Overwinter survival is a key factor in demographic and population size of this species. In these small mammals, a loss of water equivalent to 5% loss of body mass, appears to be a critical limit requires arousal from torpor (the state of decreased physiological activity in an animal, usually associated with reduced body temperature and metabolic rate). To define this physiological limit the authors modeled the energetic cost of the pygmy possums (for 5% loss of body mass before arousing to rehydrate) while consuming either snow or water.[4] Their model indicates that the potential hibernation period is reduced by 30 d for animals consuming snow compared with 8.6 d for those drinking water. Altogether, their findings indicate that habitats with subnivean

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Abbreviations: ATP, adenosine-5′-trphosphate; CIVD, cold-Induced vasodilatation; Prdm16, PR domain containing 16; POA, preoptic area; TNZ, thermoneutral zone.

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access to liquid water during winter, such as those with subterranean streams running under boulder fields may be of particular value for energy conservation and overwinter survival of this species. The physiological significance of this adaptive response is discussed further in a commentary by Kronfeld-Schor.[5]

Extending on this theme of factors affecting species survival is the review by Flouris and Piantoni,[6] which discusses the relationship between thermoregulatory function and the aging process in endotherms and ectotherms. They argue that, contrary to conventional beliefs, low body temperature may in fact be beneficial for life span in endotherms and ectotherms. However, as the authors note, '*finding the key to temperature regulation remains the problem*'. In support of this relationship, the authors highlight the fact that reducing body temperature through genetic manipulation in mice resulted in a 20% increase in life span. Additionally, in endotherms, the role of the uncoupling protein (UCP) pathways has been substantiated. Further, prolonged exposure to low ambient temperatures in ectotherms such as fish, butterflies, and *Caenorhabditis elegans* (soil nematode) has been shown to increase lifespan. Studies on the soil nematode suggest that thermosensory neurons have evolved that, when activated, trigger neuro-humoral signals which may affect lifespan. Despite our current knowledge, the link between thermoregulation and longevity in ectotherm vertebrates remains limited. What is abundantly evident is that both endotherms and ectotherms have a specific temperature zone at which they function optimally. This zone is defended by both physiological and behavioral responses and is important for organismal senescence. Notably, the recent discoveries of the role of environmental impacts on aging and of long term epigenetic influences are widely discussed by various authors (e.g.,[7]). Evidence presented in this review reveals the existence of a myriad of factors in thermoregulation and longevity and highlights the need to further explore the thermoregulatory mechanisms that are implicated in the aging process, especially given its potential relationship to lowering disease and mortality risk.

The second cluster of contributions includes research papers and reviews on central and peripheral thermoregulatory mechanisms and non-thermoregulatory signals that are involved in body temperature homeostasis.

McAllen, a neurophysiologist with an interest in the central nervous regulation of cardiovascular and autonomic functions, and his team, present 2 papers.[7,8] The first investigated whether human preoptic neurons, similarly to those in animals, are involved in thermogenic sweating. In the second, they evaluated the role of intra-abdominal temperature sensors in the reflex control of vasoconstriction in rats. The first paper is among recently published papers on fMRI (functional magnetic resonance imaging) studies aiming to correlate the activity of certain neuron clusters and homeostatic mechanisms.[8] The role of the preoptic area (POA) in human thermoregulation has not been previously reported using imaging techniques, most likely for technical reasons. Here, the authors overcame the technical difficulties and used blood oxygen level-dependent (BOLD) signals to reveal activated neuronal clusters. A cluster in the POA showed peaks of activation that were time-locked to thermogenic sweating events. Using that locus as a 'seed', the authors then found increased 'functional connectivity' (correlated activity) between the POA cluster and other brain areas including the limbic cortices (and others): those correlations were present during periods when subjects were heated (and sweating) but not during unheated periods. This study suggests that a network of interactions within the central nervous system is engaged during thermoregulation, and this warrants further investigation. In the second paper,[9] post-ganglionic activity was recorded from sympathetic nerves supplying the tail vasculature (TSNA) in anesthetized rats. Trunk skin and intra-abdominal temperatures were independently manipulated while brain temperature was measured concurrently The experiments showed that increases in temperature induced by a heat exchanger in the abdominal cavity inhibited TSNA independently of any change in skin or brain temperatures. Though highly significant, the reflex effect of intra-abdominal warming on TSNA was relatively modest compared with the influences of skin or brain temperatures. However, the relative impact of intra-abdominal warming was probably underestimated because the distribution of intra-abdominal thermoreceptors is uncertain and the abdominal heat exchanger was smaller than that applied to the skin.

Transitioning to the evaluation of factors modulating heat exchange during cold stress, Kozyreva et al.[10] addressed the question of whether ATP - adenosine-5'-trphosphate (ATP) modulates the thermoregulatory response to a cold stress. Additionally, they examined whether co-transmitters of sympathetic nervous system, ATP and norepinephrine, differentially modulate thermoregulatory responses during cooling. Using a rat model, separate and combined iontophoretic administration of ATP and norepinephrine were applied to the abdominal skin while it was cooled at a rate of 0.1°C/sec, until a decrease of rectal temperature by 3–4°C was achieved. The authors surmised from their observations that ATP and norepinephrine behave as co-transmitters, acting on different components of cold-induced thermogenesis (ATP on shivering and norepinephrine on non-shivering thermogenesis, respectively), and that this response occurs in a hierarchal manner. The study by Solymár et al.[11] aimed to advance our understanding of the interplay between daily torpor and body weight during exposure to a cool environment and the state of fasting. Specifically, they compared obese mice (fed a high fat diet) and those on a conventional rodent diet. Mice were examined in a cool ambient temperature that was just below thermoneutrality for adult mice. Control mice developed progressive daytime hypothermia within 3 d of total fasting. Obese mice could tolerate total fasting for almost one month, with progressive hypothermia developing only during the last fasting week. The authors found that diet-induced obesity in mice did not seem to influence the body mass threshold for the thermoregulatory response to fasting: this was the same as before they developed obesity. Further studies using other small mammals would

add insight into this interesting new finding.

In a paper that received the *Temperature* award for the best paper, Kingma et al.[12] focuses on what combinations of core and skin temperature satisfy the biophysical requirements of being in the thermoneutral zone (TNZ) for humans. Kingma et al., developed a biophysical model that calculates heat transport within a body, taking into account metabolic heat production, tissue insulation, and heat distribution by blood flow and equates that to heat loss to the environment, considering skin temperature, ambient temperature and other physical parameters. The authors showed that ambient temperature by itself is not a sufficient criterion to ensure heat balance in the TNZ. Rather, they argue that core and skin temperature responses must be an integral component defining the TNZ. Additional, their model identifies a significant relationship between the integration of the TNZ and thermal comfort zone in maintaining thermal balance, and highlights the importance of this association with respect to metabolic research and the built environment. Further emphasis on the importance of this model is discussed in a commentary by Schlader.[13]

Reviews by Cheung[14] and Filingeri and Havenith[15] examine our state of knowledge on the human physiological response to thermal stressors. The review by Cheung[14] examines the mechanisms underlying cold-Induced vasodilatation (CIVD) in the hands and feet during cold exposure. Rapid changes in skin blood flow occur in the extremities of the body upon exposure to cold. With prolonged exposure to cold, attenuations in skin blood flow are paralleled by reductions in tactile sensitivity, manual dexterity, and gross motor function such as occurs in the hands. Ultimately, these responses can have a detrimental impact on an individual's functional ability and performance which is of particular concern to military personnel and workers in many occupational settings. After a brief period of diminished skin perfusion paralleled by reduced surface temperature, a seemingly paradoxical and temporary increase in blood flow and rewarming occurs – a process termed cold-induced vasodilation (CIVD). As a consequence, skin temperature can rise by as much as 10°C in a cyclical manner. Increasing evidence suggests that this response may play an important role in preserving or improving performance during cold exposure. Notably, the concomitant measurements of heart rate variability and finger blood flow during cold immersion suggested that CIVD is associated with a vasoconstricting sympathetic drive followed by vasodilation due to withdrawal of sympathetic tone. Moreover, this response appears to be strongly related to a core temperature threshold, whereby the response remains intact so long as core temperature remains at or above this threshold temperature. Local reflexes may play also an important role in the response. Increasing evidence indicates that bioavailability of nitric oxide may play an important role in the CIVD response, such that cold-induced reductions in nitric oxide may delay vasodilation. However, a role for endothelin (a modulator of skin blood flow) has not been observed. The review does highlight important advances in our understanding of the neuromechanisms and mediators involved in CIVD, but because of the obvious methodological and ethical limitations associated with exposing human subjects to a prolonged cold stress, the physiological mechanisms underpinning CIVD remain unresolved.

The review by Filingeri and Havenith[15] reveals how skin wetness sensation can play an important role in modulating behavioral and autonomic adaptations of the human thermoregulatory response. Further, their paper provides an overview of the current knowledge on human hygrosensation, along with potential directions for future research, and they discuss our current state of knowledge on the psychophysical and neurophysiological basis of human skin wetness perception. They surmise that potential neurophysiological cues, linked to wetness sensation (i.e. thermal and tactile) occur via a specific human hygrosensation strategy, primarily defined by perceptual learning from sensory experiences. They note that repeated exposure to thermal, tactile and neurophysiological inputs contributes a neural representation of a typical wet stimulus via a learning mechanism. If this coded learnt combination is presented, wetness will be sensed.

An important emerging topic highlighted in this special call for papers is the phenomenon of cross-tolerance between heat acclimation and novel (namely, a stress that the animal was never exposed to) environmental stressors. Heat acclimation confers protection to a variety of environmental stressors. At the cellular and the molecular level, cross-tolerance emerges from an enhanced capacity or responsiveness of shared universal molecular signaling between the acclimating (primary stress) and the secondary (novel) stress, as well as organ-specific acclimatory pathways. In a second paper that received the *Temperature* award for a young scientist, Yacobi et al.[16] showed that in both the frontal cortex and the hippocampus regions of the brain, heat acclimation induces changes in subunits of the NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoazole-propionic-acid) receptors. Both receptors are involved with Ca^{2+} influx via the glutamate-gated ion channels, and the changes could be interpreted as causing a decrease in Ca^{2+} influx. Following exposure to hypoxia, cell death is mainly caused by calcium influx via glutamate-gated ion channels. The detected NMDA receptor subunit ratio, underpinning decreased Ca^{2+} influx, was positively correlated with behavioral neuroprotection, defined by motor functional test. Given our understanding that cross-tolerance depends on global and organ specific components, in brain hypoxia, altered features of the NMDA-receptors may be essential to cross-tolerance. Further emphasis on the importance of this model is discussed in a commentary presented by Ely et al.[17]

The link between cellular cross-tolerance and systemic responses is less well understood than is the molecular/cytoprotective impact. A topical review by Ely et al.[18] translates the molecular and cellular mechanisms of cross-tolerance from human heat acclimation and hypoxia to global systemic responses. Specifically the authors attempted to bridge the gap between adapted responses of heat shock proteins (HSPs; 70Kd, 90 K_d) and Hypoxia-inducible factor 1-α (HIF-1α), that are shared by acclimation to hypoxia and

heat, with the systemic responses to elevations in environmental heat load and metabolic rate during exercise. The authors hypothesized that systemic responses with potential benefits occur through the oxy-hemoglobin dissociation curve, namely enhanced O_2 saturation of hemoglobin for a given PO_2. Based on downstream HIF-1α targets (mitochondrial, glycolytic enzymes), an improved lactate threshold during exercise is also expected. In addition to the above described adaptation, attenuation of the splanchnic vasoconstriction reflex during an environmental and/or exercise-induced heat load (nitric oxide-HIF-1 mediated[19]) and decreased intestine permeability (HSP mediated[20]) are additional options for systemic cross-tolerance. There are possible dangers and challenges in the adaptive response to multiple stressors. Described as cross-interference, stressors can have conflicting outcomes on human adaptive responses (e.g., heat-induced acclimation resulting in plasma expansion versus diuresis-induced plasma volume contraction associated with hypoxia). Translational studies on the link between cellular cross-tolerance and systemic responses are still in their infancy.

Within this call, a number of papers examined potential mechanisms associated with the heat stress responses and the disturbances in physiological function caused by prolonged heat stress. For example, Montilla et al.[21] evaluated the extent to which heat stress disrupts redox balance and initiates an inflammatory response in oxidative and glycolytic skeletal muscle of pigs subjected to 3 d of heat stress of 35°C and 20–35% relative humidity. The authors showed that there is a transient increase in free radicals on the first day of exposure, which is later compensated by increased levels of antioxidants. Following the 3 d of heat stress, a return of the free radical production to that of thermoneutral conditions is likely to indicate a significant shift in cellular physiology. Their data suggest that oxidative muscles are more susceptible to heat-induced changes in redox balance than are glycolytic muscles, perhaps as a result of heat-induced effects on the mitochondria. A study by Miko et al.[22] further highlighted in a commentary by Roth,[23] assessed whether alarin, a new member of the galanin peptide family (GALP) may have both an orexogenic (i.e., increasing or stimulating appetite) and a thermoregulatory effect. They showed that alarin appears to elicit a slow hypermetabolic hyperthermic response in rats, which characterizes a role of a catabolic peptide mediator. Further investigations are still needed to clarify the role of alarin in energy homeostasis. A second paper by Sanz-Fernandez et al.[24] attempted to evaluate whether bovine whey peptide or colostral whey peptide protect intestine permeability in heat stressed (32°C, 26% humidity) pigs, as assessed during a 24 hour exposure period. Their data showed that dietary milk whey protein and colostral whey protein do not mitigate intestinal integrity dysfunction during heat stress.

Finally, the study by Ketko et al.[25] introduced a new heat tolerance index: thermal-circulatory ratio (TCR), which integrates responses from both the thermoregulatory and cardiovascular systems. The results of 104 tolerance tests were reanalyzed to assess this relationship. The authors reported that a ratio of 0.320 (°C/heart bpm), calculated after a 60 minute heat tolerance test (HTT), could be used to determine tolerance with 100% sensitivity and 60% specificity. Ultimately, this methodological approach could be used to distinguish between heat tolerance and intolerance of individuals who may, as a function of their jobs or daily activities (e.g., workers, athletes, military personnel), be exposed to high heat stress conditions. Since the current heat tolerance test lasts 120 min., the suggested index may enable shortening of the HTT.

A growing area of interest is the thermogenic effects of adipose tissues. As a result of the discovery of functional brown adipose tissue in adult humans in recent years, there has been an increasing number of studies examining the physiological role of brown adipose tissue.[26,27] Several recent studies have evaluated the role and extent to which different modifiers affect brown adipocyte metabolism, and as a consequence, body core temperature homeostasis. For example, the role of PR domain containing 16 (PRDM16), which acts as a transcription co-regulator controlling the development of brown adipocytes in brown adipose tissue, in this context was discussed in a review presented by Ishibashi and Seale.[28] In this review the authors highlight our current state of knowledge on the structure and function of this transcription factor during embryogenesis, its cross-talk with additional genes from the PRDM family of factors, and euchromatic histone-lysine-N-methyltransferase 1 (Ehmt1), which can interact with several Prdm family factors. The involvement of Prdm16 in the genetic program of fat development and in the function of thermogenic adipose tissue is discussed. The authors report that mouse models have confirmed that this type of fat tissue provides substantial metabolic protection against the harmful effects of high fat or high energy-intake diets. The authors speculate that activation of Prdm16 holds promise for stimulating thermogenesis in fat cells to reduce human obesity and its complications.

Summary

The studies and reviews highlighted in this special call cover a vast array of topics related to thermoregulatory function and heat balance in adverse environments and the adaptability of the system to changing climates. These papers reveal the complexity of factors that can play pivotal roles in modulating and/or regulating how the different physiological systems respond to these environmental stressors. While it is evident that significant advances have been made in our understanding of thermoregulatory control, there is still much to learn and understand about how different species can adapt to our rapidly changing thermal world.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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