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Editorial

Neural mechanisms of thermoregulation

Life as we know it can exist in a relatively narrow temperature range. Over the course of biological evolution, animals have acquired the ability to detect thermal fluctuations to avoid tissue damage and occupy specific ecological niches. Thermosensitivity is a primordial sense that enables organisms to tell hot and cold from optimal, and which has been serving as a major contributor to the spread of animals across a wide range of ecological habitats. The appearance of endotherms, who can generate their own heat to maintain stable body temperature, further facilitated the spread of life, which now occupies virtually every latitude on the planet. Thermal signals, whether coming from within the body or from the environment, need to be detected by specialized receptors and processed by the nervous system to generate adaptive response via effector organs. Understanding such multi-tiered system is hampered by its inherent complexity, requiring a cross-disciplinary approach and advanced experimental techniques. The general understanding of the logic and function of the effector organ response, such as heat preservation or loss via vasoconstriction, vasodilation and sweating, or heat generation via shivering or non-shivering thermogenesis, have been known for many decades. Many molecular and cellular aspects of thermosensitivity and thermoregulation have only started to become clear with the advent of sophisticated molecular biological and biochemical techniques. This enabled the cloning and characterization of molecular receptors for heat and cold in the peripheral nervous system [1,2], revealed the molecular machinery for electrical signal transduction [3–5], and sparked experimental approaches to interrogate the principles sensory processing in the central nervous system, which transforms sensory information into adaptive responses [6,7]. Technological advances in biophysics and bioinformatics paved the way to studies in non-standard animal models at the molecular level, including animals with labile thermosensory and thermoregulatory systems, such as hibernating mammals. Arguably, hibernators provide a unique perspective on the subject, unachievable using the standard models [8–10]. This Special Issue of Neuroscience Letters collects an exciting set of reviews that delivers a slice of this fascinating field to the attention of scholars.

In preparing this issue, we chose to solicit contributions from experts from a diverse set of disciplines that pertain to thermosensation and thermoregulation rather than to give a comprehensive and detailed overview on a single topic. We also strived to present a broad physiological and evolutionary perspective on the subject by including reviews that detail some of the exciting developments in ectothermic species and non-standard animal models in addition to more standard animals. Solinski and Hoon give broad overviews of the molecular and cellular pathways for thermosensory detection and processing of external and internal temperatures, including the molecular sensors of heat and cold in peripheral thermoreceptors, neurons in the spinal cord, and regions in the central nervous system that define the sensory output [11]. Madden and Morrison describe how sensory information from thermal afferents is integrated by the preoptic area of hypothalamus to trigger adaptive thermoregulatory reflex in the effector organs via brown adipose tissue thermogenesis, shivering, vasoconstriction or sweating [12]. Chang delves into the role of the vagal afferents and efferents in mediating the cross-talk between visceral organs and the brain in control of internal thermosensation, immune response, inflammation, energy homeostasis, body metabolic status under normal and pathological conditions. The review provides a tantalizing perspective on experimental approaches to understand functional specialization of vagal neurons [13].

A major part of the thermoregulatory system in mammals is the ability to generate heat. Non-shivering thermogenesis is achieved, in part, through energy expenditure via dissipation of the electrochemical gradient in mitochondria by the uncoupling protein 1 (UCP1). Though UCP1 was thought for a long time to be a prerogative of eutherian mammals only, recent discoveries revealed that the *UCP1* gene is present in fishes, suggesting a role for the protein in processes other than non-shivering thermogenesis. It is therefore interesting to explore the transformation of UCP1 function to better understand the evolution of thermoregulation at the molecular level. A review by Gaudry and Jastroch touches upon the contribution of UCP1 to non-shivering thermogenesis in brown adipose tissues, while the bulk of their work presents a stimulating discussion on the role of UCP1 and its paralogs UCP2 and UCP3 in neurons of vertebrates, where these proteins are thought to contribute to processes unrelated to thermoregulation [14].

Hibernation in mammals involves a cycling reprogramming of thermosensory and thermoregulatory phenotypes, which enables the normally warm-blooded animals to drop their core body temperature to near freezing to survive harsh environmental conditions. Studying hibernators permits an unprecedented viewpoint from which to interrogate basic principles of these general physiological processes. In this Special Issue, Oliver et al describe the current understanding of thermoregulation in hibernating mammals, focusing on the role of skeletal muscles and brown adipose issues in the regulation of body temperature during the entry into torpor as well as rewarming upon arousal, and detail the role of the micro-peptide sarcolipin in non-shivering thermogenesis during hibernation [15].

Thermosensation is an ancient process pertinent to endotherms, including invertebrates. Here, Angilletta et al provide a comparative analysis of the neural pathways that confer adaptive plasticity to the processes of thermotolerance and thermoregulation in response to changing environmental contexts, using the perspectives gleaned from studies of worms, flies and mammals [16]. Bryant and Hallem review molecular and neuronal pathways that subserve thermosensory behavior in a diverse group of helminths that target mammals and insects, providing a comprehensive picture of how thermal cues drive host

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seeking and host invasion in invertebrates [17].

This Special Issue of Neuroscience Letters demonstrates an enormous progress that has been made in recent years to gain insight into the mechanisms of thermosensitivity and thermoregulation. A deeper mechanistic understanding of how animals detect internal and external temperature and maintain thermal homeostasis is essential for understanding how organisms adapt to the continuously changing environment. The recent progress in the development of powerful tools for efficient and targeted modification of the genome, super-resolution imaging, deep sequencing, bioinformatics and other techniques should further facilitate our understanding of these basic biological processes. We anticipate that the chapters in this issue will spark new ideas in the field and facilitate the exploration of molecules and pathways that pertain to thermosensation and thermoregulation in various species, beyond of the traditional set of standard model organisms.

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