Heat acclimation induces hypothalamic temperature sensitivity that promotes heat tolerance

After long-term heat exposure, a discrete group of hypothalamic neurons in the anterior ventromedial preoptic area become hyperactive and acquire temperature sensitivity. This reversible plasticity mechanism renders mice heat tolerant, meaning they can keep their body temperature within physiological limits when ambient temperatures are high.

This is a summary of:
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The problem

Heat acclimation is an important adaptive process that enables organisms to adapt to long-lasting increases in ambient temperature and become heat tolerant[1,2]. Owing to increasing environmental temperatures worldwide, insights into heat acclimation mechanisms and their relevance for physiology and disease, as well as exploration of the limits of heat adaptability, are timely and pressing topics. Changes in the central nervous system (CNS) that occur during heat acclimation are not well understood, and their role in driving heat tolerance is largely unknown. Neuronal networks are adaptable, a property known as plasticity; it is unclear how long-term heat exposure triggers specific plasticity alterations in the CNS, or whether such alterations would modulate peripheral organ systems to promote heat tolerance.

The discovery

We based our hypothesis on the assumption that sustained and strong sensory stimuli trigger neuronal plasticity in brain regions relevant to the respective sensory modality. We reasoned that long-lasting heat stimuli might trigger some form of neuronal plasticity along the thermo-afferent sensory axis (the pathway that delivers thermal information to the brain). If such plasticity exists, it might influence thermoregulatory capacity and thereby thermotolerance (the ability to cope with prolonged high temperatures). Because the hypothalamic preoptic area is considered to be the CNS thermoregulatory center that receives thermo-afferent signals, we focused our search for putative heat-induced neuronal plasticity on known thermoregulatory neurons in the anterior ventromedial preoptic area (VMPO) that mediate body cooling[3–5]. Given that such plasticity would probably be stable (at least in the short-term), we performed electrophysiological analysis of these VMPO neurons, which express the leptin receptor (LepR), in ex vivo brain slices from heat-acclimated mice.

Although we found little evidence for synaptic plasticity, we unexpectedly found that after heat acclimation, thermoregulatory neurons transformed to become tonically (continuously) active pacemaker neurons (that is, they spontaneously and rhythmically fire) as a result of altered sodium channel functionality. Moreover, these cells gained intrinsic temperature sensitivity and became intrinsically warm-sensitive neurons (WSN, Fig. 1a). Inhibiting this warm-sensitive activity resulted in blunted heat tolerance in a physiological heat endurance assay (Fig. 1b), whereas artificially inducing the tonic activity gained by VMPO neurons in the heat-acclimated state rendered mice heat tolerant without prior heat exposure. Collectively, these results show that the plastic conversion of these neurons is important for mice to gain heat tolerance.

The implications

Long-term heat exposure affects many aspects of physiology, and individuals with cardiovascular diseases or metabolic disorders are among the most vulnerable during heat waves. Understanding the body's mechanisms for coping with heat might shed light on possible medically relevant opportunities to increase heat adaptation and resilience. Such insights might provide opportunities beyond a purely thermo-adaptive perspective; for example, long-term heat exposure can lead to reduced food intake and body weight. Thus, understanding the underlying CNS plasticity mechanisms might provide new entry points for treating obesity.

Our study shows that the plastic transformation of VMPO^{LepR} neurons is important to activate heat tolerance mechanisms after heat acclimation is accomplished. Our gain-of-function experiments suggest that the neurons also participate in (slowly) developing heat tolerance mechanisms over time. However, because blocking the neurons permanently abrogates acute heat defense mechanisms, segregating the acute thermoregulatory functions of VMPO^{LepR} neurons from their potential role in slowly driving peripheral heat adaptations is a challenge — and a limitation of this study. Additionally, we used a heat endurance assay that assesses body temperature as a key parameter for survival at high ambient temperatures. Our study does not provide insights into which peripheral organ system(s) are modulated by the acclimation-induced VMPO plasticity to achieve the gained heat tolerance.

It will be important to elucidate the signal(s) that trigger VMPO neuron plasticity and the efferent pathways and specific organ system(s) that are modulated to increase heat tolerance. Additionally, it will be interesting to further investigate the ionic conductance-based mechanism that mediates warm-sensitivity of neurons in the hypothalamic preoptic area, a cellular phenomenon known for decades but for which mechanistic insights are largely absent.

Jan Siemens
Institute of Pharmacology, Heidelberg University, Heidelberg, Germany.

EXPERT OPINION

"This study investigates the neural mechanisms that allow animals to adapt to prolonged exposure to heat. It is a fascinating study that reveals unexpected plasticity in the thermoregulatory system. The use of a heat acclimation model combined with circuit manipulations is novel, and the correlation between VMPO^{LepR} neuron activity in slice and heat resilience in vivo is striking." **Zachary Knight, University of California San Francisco, San Francisco, CA, USA.**

FIGURE

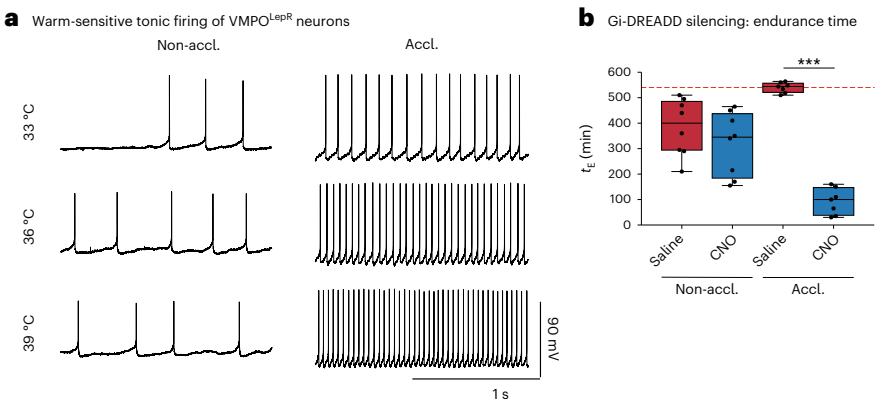

Fig. 1 | Heat acclimation transforms VMPO neurons into warm-sensitive neurons promoting heat tolerance. a, In heat-acclimated (accl.) mice, leptin receptor-expressing neurons in the hypothalamic ventromedial preoptic area (VMPO^{LepR} neurons) become warm-sensitive and show tonic firing of action potentials. **b**, VMPO^{LepR} neurons were modified to express the inhibitory Gi-DREADD receptor; application of clozapine *N*-oxide (CNO) activates the receptor, thereby silencing the neurons and abolishing the gained heat tolerance in acclimated mice, as assessed in a heat endurance assay. Boxplots show median and interquartile range of endurance time (t_E); ***$P < 0.0001$.

BEHIND THE PAPER

It has been suggested that heat stimuli can be detected by WSN in the preoptic area, but whether such deep-brain temperature detection is physiologically relevant has remained unclear and is a matter of debate. Our initial hypothesis was that long-term heat stimuli would induce synaptic plasticity in the preoptic area. We were surprised to discover that long-term heat exposure converts thermoregulatory neurons into WSNs! This was a 'eureka!' moment because our findings not only identify a slowly evolving plasticity mechanism relevant for heat tolerance mechanism(s), but they also provide a provocative idea as to the physiological relevance of WSNs: they are important when ambient temperatures are permanently high and life-threatening but are much less so in response to short, acute heat exposure. Peripheral thermosensory neurons seem to be better poised for such acute heat defense. **J.S.**

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FROM THE EDITOR

"The identification of a mechanism, triggered by prolonged heat exposure, that increases heat tolerance in mice has obvious relevance in this era of global warming and might pave the way for further research into such mechanisms in other species, including humans." **Leonie Welberg, Senior Editor, *Nature Neuroscience*.**