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The TRPM2 channel in temperature detection and thermoregulation*

Comment on: Song K, Wang H, Kamm GB, Pohle J, Reis FC, Heppenstall P, Wende H, Siemens J. The TRPM2 channel is a hypothalamic heat sensor that limits fever and can drive hypothermia. Science 2016; 353:1393-1398; http://dx.doi.org/10.1126/science.aaf7537

Detecting and interpreting changes in temperature is essential for our well-being. Somatosensory neurons that innervate the skin mediate the detection of external ambient temperatures that are ultimately interpreted as "cold," "warm" or "hot." However, several other tissues and organs harbor internal temperature sensors, albeit we are not consciously aware of their continuous thermal monitoring.

Nearly hundred years ago it was demonstrated for the first time that the brain itself has the ability to detect changes in local temperature. Within the brain, the preoptic area (POA), a region located in the most anterior part of the hypothalamus, is central for regulating core body temperature homeostasis. A multitude of studies have shown that the POA not merely integrates thermal information from peripheral sensors but also detects temperature changes itself. Neurons that are exquisitely tuned to respond to warming by increasing their action potential firing rates have been described in the POA. It has been proposed that these neurons monitor deep-brain temperature to regulate the body's core temperature.[1] However, both the identity and role of these warm-sensitive neurons (WSN) within thermoregulatory circuits have remained elusive. Similarly, the molecular repertoire that mediates their temperature sensitivity has remained unknown. We now have identified an ion channel that mediates heat sensitivity in a subset of POA neurons.[2]

In contrast to preoptic thermo-responsiveness, considerable progress has been made in elucidating the molecular mechanisms of peripheral, somatosensory thermoreceptors. These efforts have led to the identification of a number of temperature-sensitive ion channels. Most prominently among these are members of the Transient Receptor Potential (TRP) ion channel family, several of which have emerged as bona fide temperature detectors. Both, in the cool to cold range and in the warm to hot range different members of the TRP channel family equip somatosensory neurons with thermosensitive properties necessary for peripheral temperature detection.[3]

Many of these discoveries were made possible by combining primary cultures of rodent sensory neurons and the use of *in vitro* calcium-imaging. This relatively simple cellular approach allows tight control over the experimental conditions – temperature stimulation and drug application – while at the same time it enables monitoring the activity of hundreds of sensory neurons simultaneously. The latter is important for effective analysis because sensory neurons are a very heterogeneous population of cells and only relatively small subsets of neurons are dedicated to respond to specific sensory modalities such as cold or warm temperatures or other non-thermal (chemical or physical) stimuli.

A similar scenario is encountered in the preoptic area of the hypothalamus: vastly diverse neuroendocrine cell types are intermingled with only a subfraction of them responding to warmth stimuli. Together with the lack of marker genes, the sprinkled "salt-and-pepper" distribution of warm-sensitive neurons in the POA has hampered the characterization of these cells by classical electrophysiological means.

The discovery of a role for TRP channels in peripheral thermoreception has led to the hypothesis that these molecules may also serve as temperature sensors of preoptic deep-brain temperature. Thus, in order to shed light onto the molecules involved in deep-brain thermoreception in mammals, we took advantage of calcium-imaging

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as a means to monitor temperature sensitivity in a heterogeneous population of neurons. We found that approximately 15% of POA neurons were heat sensitive,[2] a percentage that is in good agreement with the fraction of temperature sensitive neurons identified via electrophysiological recordings of similarly cultured POA neurons. Surprisingly, the heat responses were effectively blocked by application of 2-aminoethoxydiphenylborate (2-APB), a molecule that modulates the activity of several ion channels and that inhibits the heat-activated TRPM2 channel. Immunohistochemistry and *in situ* hybridizations demonstrated that TRPM2 is expressed in the mouse POA, and electrophysiological recordings confirmed functional expression of TRPM2 in preoptic neurons. Most importantly, heat responses were significantly reduced in cultured POA neurons and acute slice preparations obtained from TRPM2-deficient ($TRPM2^{-/-}$) mice when compare with preparations obtained from their wild-type littermate controls. While other molecular mechanisms are likely contributing to temperature sensitivity of POA neurons in the normothermic range around 37°C, our results demonstrate that TRPM2 is a hypothalamic heat sensor that mediates responses to temperatures above 37°C.

Next to hyperthermia, fever is a condition at which the body temperature (including that of the brain) exceeds 37°C. Interestingly, in addition to its thermoregulatory function at normothermic conditions, the POA also mediates different thermo-effector responses that lead to the increase of body temperature during fever. With this in mind, we therefore asked if the preoptic heat sensor TRPM2 might modulate fever temperature. Indeed, we found that $TRPM2^{-/-}$ mice developed significantly larger fever responses compare with littermate $TRPM2^{+/+}$ mice when challenged with high doses of pyrogens directly infused into the POA. These findings suggest that preoptic TRPM2 may work as a heat sensor that protects against severe forms of body temperature elevation, potentially preventing tissue damage. In 1997 Basta et al. have previously proposed that corresponding "temperature guardian" neurons reside in the POA.

Intriguingly, TRPM2 has also been found to be a sensor for reactive oxygen species (ROS). Although not well established, it is likely that ROS levels are elevated under fever conditions. Thus it is tempting to speculate that high brain temperatures and ROS synergize to activate a TRPM2-regulated pathway that prevents overheating by mediating body cooling. In this regard it is noteworthy that high concentrations of Acetaminophen (also known as Paracetamol), one of the most widely used antipyretic drugs, has been reported to activate TRPM2 in liver cells. Based on our results, it is feasible that Acetaminophen's antipyretic effect, whose mechanism is not fully understood, could – in part – be mediated via activation of preoptic TRPM2. Such an antipyretic mechanism may putatively be mediated via the drug's capacity to generate ROS.

Individual heat sensitive TRP channels only contribute marginally to overall heat sensation in peripheral sensory neurons. As such, mice deficient for TRPV1 only display modest impairments in noxious-heat detection. However, animals *depleted* of sensory neurons expressing TRPV1 completely lack the ability to detect noxious-heat.[3]

Based on these results found in peripheral sensory neurons, we examined if preoptic TRPM2-expressing neurons might also play a more prominent role in thermoregulation than the TRPM2 molecule itself. Using a chemogenetic strategy we indeed observed that activation of TRPM2-expressing preoptic neurons resulted in long-lasting hypothermia, reaching body temperatures as low as 27°C. Oppositely, when the same population of preoptic neurons was inhibited, mice developed a marked hyperthermia. These results confirm that preoptic TRPM2, as expected for an interoceptive heat sensor, is expressed in a population of neurons constituting an integral part of the circuitry that bidirectionally regulates core body temperature *in vivo*.

Interestingly, TRPM2 has recently also been implicated in detecting innocuous heat in peripheral sensory neurons.[4] The authors of this study found that TRPM2 drives mice away from environments that are uncomfortably hot. It is thus tempting to speculate that TRPM2 serves roles in both, behavioral and autonomic thermoregulation via its expression in sensory neurons and preoptic neurons, respectively.

For the thermoregulatory system to function efficiently, it appears imperative to monitor temperature information at multiple sites to allow precise body temperature regulation. Next to temperature sensors in the POA and in peripheral fibers innervating the skin, temperature sensors have also been located in the spinal cord and presumably also reside in deep-body cavities (Fig. 1). A future challenge will be to uncover the logic of the central circuitry for thermoregulation and determine how different thermal (and non-thermal) information is weighted to compute a homeostatic output. According to the current model of thermoregulation, different warm-sensitive neuron populations autonomously control distinct thermoregulatory effector pathways.[1] However, our work

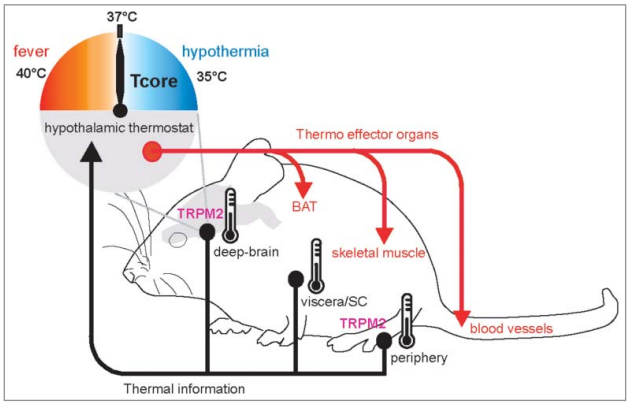

Figure 1. Thermoregulatory Pathways. The cartoon depicts afferent pathways that provide temperature feedback information (black) and efferent regulatory pathways (red). The hypothalamus serves as an integration site for thermal (and non thermal) information to generate output signals to thermal effector organs that establish thermal homeostasis. The TRPM2 channel has been identified as a heat sensor in POA neurons,[2] and - among several other heat-sensitive ion channels - in peripheral sensory neurons.[4] Among the main thermal effector organs are the brown adipose tissue (BAT) that directly generates heat, skeletal muscles that mediate thermogenesis by shivering and cutaneous blood vessels that regulate heat dissipation to the environment. The colored temperature scale and dial indicate the thermal processor function of the hypothalamus. Note that although the core body temperature of mice and men is usually maintained close to 37°C, this temperature is not a fixed value and can change context dependently under physiological and pathological conditions. (SC, spinal cord).

suggests that a defined genetic population of preoptic WSNs can control at least 2 such pathways, one regulating brown adipose tissue and another one that regulates cutaneous blood flow and heat dissipation.[2] Similarly, another recent study also emphasizes the control of several thermal effector pathways by a molecularly-defined preoptic neuron population that responds to peripheral warmth stimulation.[5]

Using these and other genetic markers may allow to ascertain how diverse preoptic WSNs truly are and whether different types of preoptic WSNs operate as autonomous units that control parallel effector pathways independently. Alternatively, according to a more classic view of hypothalamic physiology, it is also possible that WSNs orchestrate downstream thermoregulatory responses in a hierarchical fashion by simultaneously recruiting multiple interconnected thermal effector pathways.

Temperature not only affects all aspects of life (down to every enzymatic reaction), but the reverse is also true and all vital functions – in particular energy consumption and metabolism, muscle activity, cardiovascular status etc. – directly affect body temperature. How all these vital parameters are integrated to allow precise regulation of the body's core temperature close to 37°C is truly amazing.

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