TRPV1 IN THERMOREGULATION: A THERMOSENSOR IT IS NOT

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The ongoing development of antagonists of the transient receptor potential vanilloid-1 (TRPV1) channel as pain therapeutics has revealed that these compounds cause dangerous hyperthermia in humans. This undesirable on-target side effect has triggered a surge of interest in the role of TRPV1 in thermoregulation and revived the hypothesis that TRPV1 channels serve as thermosensors. We review literature data on the distribution of TRPV1 channels in the body and on thermoregulatory responses to TRPV1 agonists and antagonists. We propose that there are two principal populations of TRPV1-expressing cells that have connections with efferent thermoeffector pathways: (1) first-order sensory (polymodal), glutamatergic dorsal-root (and possibly nodose) ganglia neurons that innervate the abdominal viscera and (2) higher-order sensory, glutamatergic neurons in the median preoptic hypothalamic nucleus. We further hypothesize that all thermoregulatory responses to TRPV1 agonists and antagonists and all thermoregulatory manifestations of TRPV1 desensitization stem from primary actions on TRPV1 channels in these two neuronal populations. We then analyze what roles TRPV1 may play in thermoregulation and conclude that this channel does not serve as a thermosensor, at least not under physiological conditions. In the hypothalamus, TRPV1 channels are inactive at common brain temperatures. In the abdomen, TRPV1 channels are tonically activated, but not by temperature. Yet, tonic activation of visceral TRPV1 by non-thermal factors suppresses autonomic cold-defense effectors and, consequently, body temperature. Blockade of this activation by TRPV1 antagonists disinhibits thermoeffectors and causes hyperthermia. The potential physiological and pathological significance of TRPV1-mediated thermoregulatory effects is discussed.