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Feeling hot, feeling cold: TRP channels—a great story unfolds

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This editorial is about the roles that TRP channels play in heat and cold sensation and body temperature regulation. These roles may be exploited for therapeutic purposes (indeed, drugs targeting TRPV1, TRPA1 and TRPM8 channels are currently undergoing clinical trials for indications that range from pain through chronic cough and overactive bladder to cancer) or, conversely, may limit drug development (for example, several TRPV1 antagonists were withdrawn from clinical trials due to the hyperthermic reaction that they caused). In the future, modulation of thermosensitive TRP channels may ultimately find application in the treatment not only of pain, but also itch, stroke, asthma, and metabolic disorders. Of the multitude of targets involved in temperature sensation and body temperature regulation, why TRP channels? And why now?

Some physiological sensations have clear origins and unfold in predictable ways, but thermosensation is not one of them. Despite legions of studies since the molecular cloning of TRPV1, the archetypal temperature-sensitive Transient Receptor Potential (TRP) channel ("thermoTRP") in 1997,[1] the role of TRP channels in heat and cold sensation and body temperature regulation remains a riddle.[2]

This thematic issue contains 9 review articles (along with 3 discovery papers, one symposium report and a research paper), covering recent advances in our understanding of the potential roles that different TRP channels are now believed to play in thermosensation and regulation under physiological and pathophysiological conditions. In addition, we pay homage to the late Nicholas (Miklós) Jancsó, whose pioneering studies with capsaicin, the pungent principle in hot pepper, paved the way to the cloning of TRPV1, the founding member of the subfamily of "thermoTRPs," and to Davis Julius, whose laboratory accomplished this scientific breakthrough[1] almost 50 years after Jancsó's first description of capsaicin desensitization.[3] Of note, an estimated one quarter of the World's population consumes capsaicin on a daily basis. Somewhat paradoxically, Mother Nature developed capsaicin in her laboratory to protect the pepper pod from herbivores. It is still a mystery why human beings enjoy eating a pungent compound which (if sprayed on red cedar) repels deer from browsing the forest.[4]

As detailed in this thematic issue, some of the TRP channel functions may be exploited for therapeutic purposes whereas others, by contrast, can clearly hamper drug development. TRPV1 provides good examples for both phenomena. For example, as discussed by Feketa and Morelli,[5] activation by agonists of TRPV1 lowers body temperature and this hypothermia may help patients with stroke and other diseases. Conversely, Gomtsyan and colleagues remind us that TRPV1 antagonists may evoke a hyperthermic reaction as a dose-limiting adverse effect that limits therapeutic utility.[6] In fact, despite many years of research in the pharmaceutical sector targeted at delivering TRPV1 antagonists for the treatment of chronic pain,[2] the only proven effect of TRPV1 antagonists in humans has been the role of this target in thermoregulation. Although the effect of capsaicin (the prototypical TRPV1 agonist) on thermoregulation is common knowledge (connoisseurs of hot spicy food know gustatory sweating from personal experience), its mechanism of action is still unclear (discussed by János Szolcsányi[7]). Another heat (warm) sensitive channel is TRPM3 (Held et al.[8]), though its role in physiological warm sensation and regulation remains unclear.

By contrast, there can be little doubt that TRPM8 is involved in cold sensation. Indeed, TRPM8 is activated by cold temperatures (8–25°C) and cooling agents such as menthol and icilin.[2] Several studies with TRPM8 knockout mice demonstrated significant deficiencies to cold responses including cold allodynia. Additionally, it was recently reported that in clinical trials, the TRPM8 antagonist PF-05105679 did not significantly change body temperature, but caused hot sensations localized in mouth.[9] In most species (including humans) TRPA1 mainly functions as a chemosensor as it can be activated by variety of chemicals found in spices (such as allicin in garlic or isothiocyanates in horseradish, wasabi, and mustard oil), as well as environmental irritants in cigarette smoke and exhaust fumes.[2] TRPA1 seems to play various roles in temperature detection in different species: for example, it detects heat in insects, it responds to noxious cold in rodents, and it is temperature-insensitive in nematodes.[10,11] This diversity hinders the extrapolation of animal studies to humans. Because TRPA1 is expressed in

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Abbreviations: TRP, transient receptor potential; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8.

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both neuronal and non-neuronal tissues, the therapeutic potential of the receptor was studied in a number of disease models. Three papers in this issue (Chen,[10] Laursen et al.,[11] and Bellemer[12]) describe different aspects of TRPA1 role in thermoregulation.

Far from disappointing the hope to find effective analgesics, the diverse roles of thermosensitive TRP channels in the pathophysiology of thermosensing, thermoregulation and other cellular functions including proliferation and cell migration suggest that modulation of thermosensitive TRP channels may ultimately find application in the treatment not only of pain, but also itch, stroke, asthma, and cancer.

We are giving this special issue to the hands of the reader in the sincere hope that it will facilitate the translation of current findings in basic TRP channel research into clinical applications.

Disclosure of Potential Conflicts of Interest

Philip R Kym is an employee of AbbVie, a pharmaceutical company with an interest in TRP channels. Irina Vetter and Arpad Szallasi have nothing to declare.

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