To not be hot when TRPV1 is not

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Induction of hyperthermia emerged as a major side effect impeding the development of antagonists of the transient receptor potential vanilloid-1 (TRPV1) nociceptor. New ligands are now exploiting the complicated pharmacology of TRPV1 to avoid hyperthermia while insights continue to grow regarding the mechanistic basis for the action of TRPV1 ligands on thermoregulation.

The identification of transient receptor potential vanilloid-1 (TRPV1) as the site of action of capsaicin, the pungent constituent in hot peppers, has led to an intense focus on this ion channel both for its role in thermoregulation and as a promising therapeutic target for treatment of pain and other conditions. The early excitement growing out of the identification of potent TRPV1 antagonists as potential non-narcotic analgesics has been tempered by their disruption of normal thermoregulation. Current developmental efforts are directed at the identification of candidate antagonists lacking such side effects. In the current issue, the review by Szolcsányi1 provides a definitive analysis of the current state of the literature regarding the regulation of thermoregulation by TRPV1 and the time dependent actions of TRPV1 ligands on thermoregulation. This affords the context for assessing strategies underlying the design of thermoneutral TRPV1 antagonists.

TRPV1 is a nociceptor, responsive to a triad of stimuli. The exogenous ligand capsaicin is the classic activator. Endogenous, functional analogs of capsaicin include anandamide, N-arachidonylethanolamine, and 5-(S)-hydroperoxyeicosatetraenoic acid. Additionally, TRPV1 is responsive to temperatures modestly elevated above physiological. The “hotness” of capsaicin reflects the function of TRPV1 as a thermoreceptor. Finally, low pH represents the third element in the stimulatory triad. Beyond these 3 elements, TRPV1 is exquisitely sensitive to the cellular environment in which it resides. It is regulated by multiple cellular signaling pathways, whose downstream effectors include protein kinase A, protein kinase C, and Ca2+-calmodulin-dependent kinase II. It is likewise influenced by the level of the lipid phosphatidylinositol 4,5-bisphosphate that links TRPV1 to those many receptors that regulate the metabolism and breakdown of this lipid. Typically, these various elements of the cellular environment shift the temperature dependence of TRPV1. Sensitization leads to physiological temperatures becoming activating.

The efforts to exploit TRPV1 as a therapeutic target have driven an appreciation of the complex pharmacology of this target. An initial breakthrough was the identification of the antagonist capsaicin, showing that antagonism represented an achievable objective. As more potent antagonists emerged, it was found that antagonism was not a quantal property. Rather, some compounds proved to be partial agonists/partial antagonists. The extents of partial activity depended, moreover, on the specific activating stimulus for TRPV1. Thus, a complete antagonist for capsaicin stimulation might show both a different extent of agonism/antagonism for heat or low pH as well as a different IC50. Moreover, this signature of relative agonism/antagonism was not inherent in the compound but also reflected the cellular environment in which the TRPV1 was found. Indeed, the TRPV1 response could be shifted from almost complete antagonism to almost complete agonism by modulating the cellular signaling environment.

The initial characterization of the TRPV1 knockout in mice had found no difference in body temperature under normal conditions. When the promising early, lead antagonists moved from cellular screening assays to the whole animal or to man, it was thus a surprise that the antagonists induced hyperthermia. As further antagonistic structures were evaluated, the extent of hyperthermia was found to depend on the specific antagonist, with separation of hyperthermia appearing to partially track with compounds that were full antagonists for capsaicin but not for low pH. The target for the hyperthermic response was suggested to be TRPV1 located in the visera. The two articles in the present issue bring us up-to-date on this important area.

Keywords: antagonist, capsaicin, drug development, pain, thermoregulation, TRPV1, vanilloid

Abbreviations: TRPV1, transient receptor potential vanilloid-1.

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The article by Gomtsyan et al.\textsuperscript{2} describes a series of chromanyl urea-based TRPV1 antagonists that elicit hyperthermia, hypothermia or normothermia, correlating with the ability of the compounds to inhibit acid-induced activation of TRPV1. Rat and human TRPV1 differed somewhat in their behavior, reflecting the substantial species differences, both in efficacy and potency, that further complicate for the field the extrapolation to the human of results in rodents. While emphasizing that “discovering a TRPV1 ligand with desired pharmacology remains more of an empirical than rational exercise,” the authors note that small structural differences within a structural class can have profound effects on ligand response and that the recent advances in the structural understanding of TRPV1 should yield future powerful insights. The prospects are very exciting.

Szolcsányi’s review\textsuperscript{1} brings up to the present the literature on the involvement of TRPV1 in thermoregulation, with a focus on studies at the level of the whole animal and nerve preparations thereof. An emphasis of the review is on the involvement of TRPV1 for mediating thermoregulation at physiological temperatures rather than its role for detecting noxious heat. New developments in the role of visceral thermoreceptors are highlighted and a critical issue is the extent to which TRPV1 in the viscera reflects thermal versus non-thermal mechanisms of activation. The development of TRPV1 knockout mice has provided a valuable complement to the earlier approach of defunctionalization by high dose capsaicin treatment for probing the physiological function of TRPV1. Differences between the behavior of TRPV1 in the physiological environment of the animal vs. that upon its exogenous expression in cell lines is a reminder of the important role of context on TRPV1 properties.

Long before the demonstration of specific capsaicin binding or the cloning of TRPV1, Szolcsányi had hypothesized the existence of the capsaicin receptor on the basis of structure activity studies. The term “capsaicin receptor” immediately suggests certain properties, such as ligand gating or heat responsiveness. As the complexity of TRPV1 regulation continues to emerge, the field is coming to recognize that the most neutral view of TRPV1 is that it is simply a channel, exquisitely poised to integrate and respond to its environment. The ongoing challenge in vanilloid drug development is to predict the outcome of this complex integration in the face of the further complexity contributed by the multiple roles of TRPV1 at the whole animal level. Breathtaking progress has been made but much remains to be learned.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

References
1. Szolcsányi J. Temperature 2015; 2:227-9; http://dx.doi.org/10.1080/23328940.2015.1048928
2. Gomtsyan A, et al. Temperature 2015; 2:297-301; http://dx.doi.org/10.1080/23328940.2015.1046013