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EDITORIAL

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Manipulating transient receptor potential vanilloid 1 antagonists: How to cool down a hot molecule?

See related article: Garami, A., Pakai, E., McDonald, H. A., Reilly, R. M., Gomtsyan, A., Corrigan, J. J., Pinter, E., Zhu, D. X. D., Lehto, S. G., Gavva, N. R., Kym, P. R., Romanovsky, A. A. 2018. TRPV1 antagonists that cause hypothermia, instead of hyperthermia, in rodents: Compounds' pharmacological profiles, in vivo targets, thermoeffectors recruited and implications for drug development. *Acta Physiol* **223**, e13038.

Transient receptor potential, vanilloid 1 (TRPV1) is a promising pain target.[1] Although a number of small molecule TRPV1 antagonists have been advanced into clinical trials, thus far, none has progressed beyond Phase II due to on-target side effects such as a febrile reaction.[1] In this issue of *Acta Physiologica*, Romanovsky et al report two TRPV1 antagonists that paradoxically induce hypothermia in experimental animals, potentially opening a new avenue for drug development.[2]

Connoisseurs of hot, spicy food are intimately familiar with the predominant pharmacological actions of capsaicin from personal experience. They know that capsaicin induces a strong sensation of pungency, accompanied by the perception of heat and profuse perspiration during and after the meal, the latter known as "gustatory sweating." To explain the popularity of spicy food in tropical climates, it has been speculated that this gustatory sweating provides a cooling effect: "capsaicin as air-conditioner." Indeed, as discovered over a century ago, capsaicin reduces rectal temperature in experimental animals. This effect is so characteristic that it was used by pharmacologists for decades as a biomarker to detect capsaicin-like activity.[3]

Despite decades of research, the mechanisms by which capsaicin lowers the body temperature are essentially unknown. The target that mediates the effect of capsaicin on body temperature regulation was first localized to the brain by microinjection studies, and its molecular substrate was later recognized to be the TRPV1 ion channel (reviewed in ref. 3). Therefore, it was quite unexpected that TRPV1 antagonists that do and do not cross the blood-brain barrier both caused a similar hyperthermic response.[4] What is unequivocal is that capsaicin-treated rats have red ears due to dilated blood vessels and they seek cool surfaces. Furthermore, capsaicin-treated dogs pant. Thus, one may argue that capsaicin tricks animals (and maybe also humans) into feeling hot and thereby activates counter-regulatory mechanisms to lose heat. To try to explain these observations, it was speculated that the capsaicin receptor TRPV1 functions as a polymodal sensor with endogenous tone set by temperature.[5] Activation of TRPV1 by capsaicin would signal an apparent increase in body temperature which, in turn, could centrally trigger thermoregulatory responses to lose heat, thereby producing hypothermia. Yet, TRPV1 null mice have normal body temperature although the hypothermic response induced by capsaicin is greatly reduced.[6] Thus, the exact role of TRPV1 as a thermosensor in physiologic body temperature regulation, if any, remains to be determined.

If capsaicin, the archetypal TRPV1 agonist, causes hypothermia, TRPV1 antagonists are expected to cause the opposite effect. Indeed, a major adverse effect of TRPV1 antagonists is a transient increase in body temperature (febrile reaction), the duration and magnitude of which varied significantly among the compounds tested (reviewed in ref. 1). For example, AstraZeneca reported only a modest increase in body temperature (~0.4°C in average) in most patients after an oral dose of their compound, AZD-1386 (55 mg). By contrast, Amgen terminated its Phase 1b dental pain study with its clinical candidate molecule, AMG517, prematurely due to the lasting (1–4 days) and marked febrile response (up to 40.2°C) that it caused in human volunteers.

To rid the TRPV1 antagonists of the undesirable effects on body temperature, many groups pursued modality-specific inhibitors (reviewed in ref. 1). Briefly, TRPV1 has three major means of activation: heat, protons, and capsaicin. Interestingly, TRPV1 antagonists that do not interfere with proton activation of the receptor do not induce hyperthermia in rats even if heat activation is blocked. Using one such antagonist, JYL1421, it was possible to eliminate hyperthermia in the rat while preserving the analgesic activity. Unfortunately, this effect was highly species-dependent: JYL1421, a compound that did not cause hyperthermia in the rat, still elevated body temperature both in dogs and monkeys.

Recently, several companies have reported second generation TRPV1 antagonists that did not raise body temperature (reviewed in ref. 1). NeoMed is developing NEO6860 for osteoarthritic pain. According to the company, this compound does not affect body temperature in humans.[7]

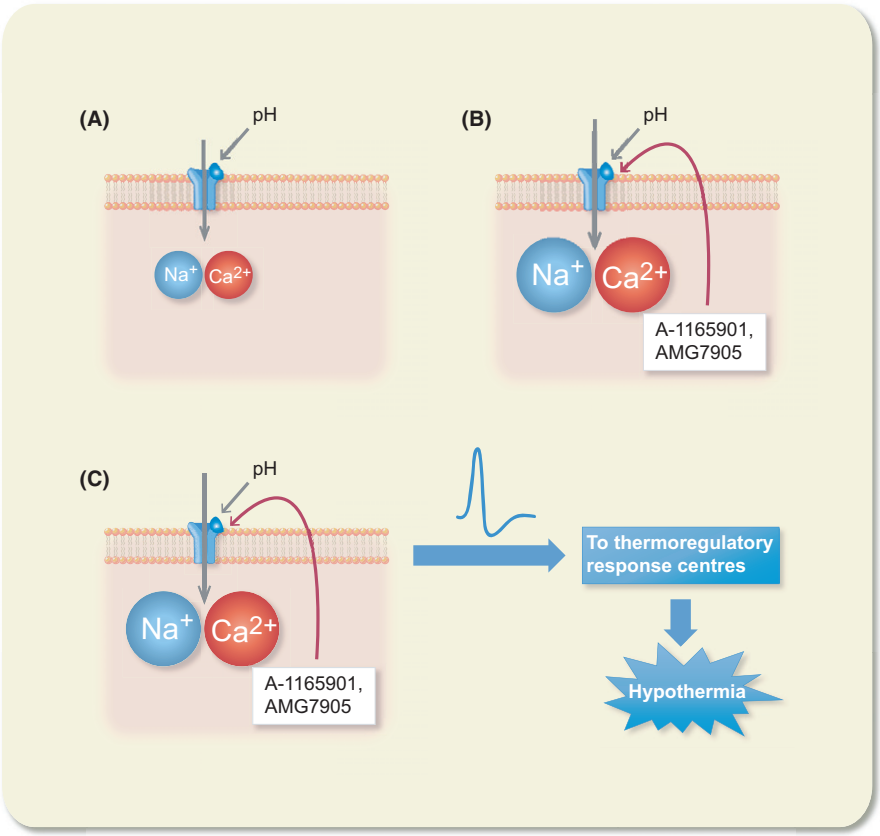

FIGURE 1 Concept: The TRPV1-expressing visceral sensory neurone functions as a pH sensor that also provides important input for thermoregulation. The mildly acidic environment maintains the endogenous tone of TRPV1. TRPV1 antagonists (such as A-1165901 and AMG7905) that potentiate the pH activation of TRPV1 send a signal to the thermoregulatory response centres to activate mechanisms of heat loss

In this issue of *Acta Physiologica*, Romanovsky et al report two TRPV1 antagonists that paradoxically induce hypothermia.[2] When administered peripherally, the newly synthetized compound, A-1165901, and the previously reported molecule, AMG7905, both triggered vasodilatation, an effect similar to that of application of capsaicin. Moreover, it blocked thermogenesis when the animal was placed in a cold environment. Their overall effect is an almost 2°C reduction in body temperature. This unexpected effect was clearly on-target because it was absent both in TRPV1 null mice and in animals whose TRPV1 receptor was desensitized by intra-abdominal resiniferatoxin administration. A key finding of this study is that these hypothermic TRPV1 antagonists blocked activation by capsaicin but potentiated (and did not block) channel activation by protons. It has been previously shown that the proton mode of TRPV1 activation correlates with the effect of the antagonist on body temperature: compounds that block proton activation increase body temperature; compounds with no effect on proton activation have no effect on body temperature either; and, finally, compounds that potentiate proton activation lower the body temperature.

The results presented in this study also shed light on the physiological role of TRPV1 in thermoregulation. The authors propose that TRPV1 channels do not act as visceral heat sensors, but instead would be tonically activated by extracellular protons present in the slightly acidic environment in the abdomen. Potentiation of this tonic activation by the compounds characterized in this study (and capsaicin!) would lead to TRPV1 activation and signalling to reduce thermogenesis and increase heat loss by vasodilation (Figure 1). This scenario reinforces the notion that viscerally expressed TRPV1 channels do not act as a thermosensors but as pH sensors.

If these observations hold true in humans, they might pave the way for the synthesis of analgesic TRPV1 antagonists that do not alter body temperature. Such compounds may have clinical value in patients with pain conditions without the undesirable side effects that limited the use of TRPV1 antagonist in the past.

CONFLICT OF INTEREST

Neither author has any conflict of interest to disclose.

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