LETTER

Reply to Voets et al.: Constellation pharmacology is poised to answer scientific questions

Voets, Talavera, and Nilius (VTN) offer an alternative interpretation (1) of our data (2) that focuses on menthol responses in neurons sensitive to allyl isothiocyanate (AITC), a functional marker for transient receptor potential (TRP) A1 expression. They argue that such responses are mediated by TRPA1, not TRPM8. There is an ongoing controversy surrounding the relative roles of TRPA1 and TRPM8 in cold sensation. VTN argue that TRPA1 plays a primary role (ref. 1 and references therein), whereas others argue that TRPA1 is not a cold sensor or is only a minor contributor to cold sensation (3, 4). We did not intend to step into the middle of that controversy. The focus of our article (2) was to illustrate the utility of constellation pharmacology with specific physiologically relevant examples.

We agree with VTN that more selective TRP channel ligands are needed. However, we continue to favor our original interpretation of our data for multiple reasons. First, VTN cite their own article to argue that menthol is an agonist of TRPA1 (5). However, they fail to mention that only submicromolar to low-micromolar menthol concentrations activated TRPA1, whereas their own study, among others, demonstrated that high menthol concentrations (≥250 μM) did not activate TRPA1 but actually blocked it (5). Because our experiments were conducted with 250–500 μM menthol (2), the responses were likely mediated by TRPM8. Second, we and VTN (5) have observed that only a minority of AITC-sensitive neurons are menthol sensitive, which is difficult to explain if 250–500 μM menthol activates TRPA1. Third, VTN state that their reinterpretation is consistent with the observation that TRPM8 antagonists blocked menthol responses in AITC-insensitive neurons but not in AITC-sensitive neurons (6). However, their own article demonstrated that the TRPM8 antagonist clotrimazole is also a TRPA1 agonist (6). Clotrimazole’s failure to block menthol responses in AITC-sensitive neurons may be explained by the activation of TRPA1 counteracting block of TRPM8. Thus, VTN’s own published data seem to argue against their reinterpretation.

Although we favor our original interpretation, we assert that VTN have overstated our scientific claims. In fact, we did not claim that “…TRPM8 is the sole functional cold and menthol sensor…” or that menthol is a “…specific TRPM8 agonist” (emphasis added). Nor did we claim that the difference in cold and menthol sensitivity between M+A+ (menthol, ATP, and AITC positive) neurons and M+A− (menthol positive but ATP and AITC negative) neurons “…is mainly due to differences in the constellation of voltage-gated Ca2+, K+, and Na+ channels.” We stated explicitly that “…the magnitude of the response is mainly a function of differences in the constellations of ion channels expressed….” Because TRPA1 is part of the constellation in M+A+ neurons, our statement is open to a TRPA1 contribution to cold and menthol sensitivity. We also stated, “The M+A+ neurons may be nociceptors that detect extreme cold with a sensation of burning pain, consistent with the coexpression of TRPM8 and TRPA1 in the same neuron” (2), thus acknowledging the potential role of TRPA1 in the sensation of noxious cold.

Russell W. Teichert1 and Baldomero M. Olivera
Department of Biology, University of Utah, Salt Lake City, UT 84112

1To whom correspondence should be addressed. E-mail: Russ.Teichert@utah.edu.

Author contributions: R.W.T. designed research; R.W.T. performed research; R.W.T. and B.M.O. analyzed data; and R.W.T. and B.M.O. wrote the paper.

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