ature changes with 20th century observations, Esper *et al.* scale their series by matching the magnitude of its multidecadal trends to those in Northern Hemisphere mean (land and marine) annual temperatures from 1900 to 1977. After smoothing to remove year-to-year fluctuations, the records can be matched closely with either the annual or summer mean temperatures, because their trends over this period are very similar.

For the early 17th century, annual temperature estimates from Esper *et al.* differ by about 0.7°C from those of Mann *et al.* [see figure 3 of (*1*)]. However, when we regressed the record of Esper *et al.* against nonsmoothed data (see the figure), this difference was reduced to about 0.4°C. Recalibrating both curves against year-by-year warm season temperatures (*10*) reduces this difference further to about 0.35°C.

The results of calibrating any proxy data depend on whether raw or smoothed records are used and on the chosen seasonal temperature predictand. Reconstructions of annual temperature records with predictors that are strongly influenced by summer conditions, assume stationary relationships between proxy and summer climate and between annual and summer climates (and hence between summer and winter). The relationship was stationary over the Esper *et al.* calibration period, but over other periods it may vary: summer warming of extratropical land has progressed at a slower rate than winter warming in the Northern Hemisphere (by about 0.6°C since 1860, see dotted line in the figure) and this is predicted, on the basis of climate model experiments, to continue over the next century at least.

Whatever the true degree of cold in the 17th century, a surprising aspect of the results of Esper *et al.* is the indication of equally cold conditions throughout the 12th, 13th, and 14th centuries, where their reconstructed temperatures are consistently well below those indicated by all other records. On the evidence of this new series, the last millennium was much cooler than previously interpreted. The warming of the 20th century is seen more clearly as a continuation of a trend that began at the start of the 19th century, not the early 20th, and an early period of warmth in the late 10th and early 11th centuries is more pronounced than in previous large-scale reconstructions. This warmth also peaks slightly earlier than could be captured in the shorter Mann *et al.* record and is warmer than in any previous reconstruction.

Even accepting the knotty issue of reconstruction uncertainty, the curve of Esper *et al.* provides evidence for greater climate swings in the last 1000 years than has yet been generally accepted. We need more independent reconstructions like this, based on improved proxy records, and we need to know why it was once so warm and then so cool, before we can say whether 21st-century warming is likely to be nearer to the top or the bottom of the latest IPCC range of 1.4° to 5.8°C (*2*).

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11. T.O. was supported by the UK Met Office (PB/B3539).

PERSPECTIVES: SIGNAL TRANSDUCTION

Hot *and* Cold TRP Ion Channels

David E. Clapham

Sipping a cold mint julep on a hot summer's day evokes several different pleasurable sensations in the nervous system. Recent papers from McKemy *et al.* (*1*) and Peier *et al.* (*2*) lift some of the mystery surrounding these sensations. These two groups identify an ion channel that is opened (gated) by both cold temperature and menthol, a cooling agent from the mint plant. This ion channel belongs to the transient receptor potential (TRP) superfamily first identified in the photoreceptor cells of the fly. The new channel opens in response to mildly cold temperatures (15° to 25°C), admitting Na^+ and Ca^{2+} ions into sensory neurons, which then become depolarized. The sensory neurons that express the new channel are in the mouth, projecting to the brain's trigeminal ganglia, and in the skin, projecting to the dorsal root ganglia of the spinal cord (see the figure). Turn on the hot or cold tap, and out pours hot or cold water. Turn on the TRP channels in nerve cells with heat or cold, and Ca^{2+} ions dribble into the neurons.

The two papers take very different routes to arrive at the same conclusion. McKemy and colleagues have previously identified and extensively characterized the "hot" pepper (capsaicin)/heat (>43°C) sensor, called TRPV1 [VR1 (*3*)], and a related channel TRPV2 [VRL1 (*4*)], which responds to burning heat (>52°C) (*5*). On the basis of published data, and their own experiments on trigeminal ganglia, they hypothesized that an unidentified protein sensed both cold and menthol. Expression cloning has been the key to identifying receptors that mediate other senses such as smell and taste. Although laborious, the method is robust in that it correctly identifies the protein performing a known function. Using this method, McKemy *et al.* discovered that a protein previously identified in prostate cancer cells—and variously called TRPM8, CMR1 (for cold and menthol receptor 1) or Trp-p8 (*6*)—was also present in dorsal root ganglia and trigeminal ganglia of mice, and responded to both cold and menthol.

Realizing that a cold sensor exists in dorsal root ganglia, Peier *et al.* identified a known gene with domains that have homology to the fourth and sixth transmembrane domains of the hot pepper/heat receptor TRPV1. These transmembrane domains were closely associated with gating the channel. Using reverse transcriptase–polymerase chain reaction, they identified the TRPM8 channel in dorsal root ganglia and showed that it was activated by cooling in the 15° to 22°C temperature range, and by menthol. Both studies showed that menthol slightly raises the temperature threshold for TRPM8 activation. McKemy *et al.* also extensively characterized the pharmacological response of trigeminal sensory neurons to menthol and its more potent relative icilin.

The mammalian TRP channel family is defined primarily by structural homology within the transmembrane-spanning domains, but overall sequence identities between members can be quite low. The TRP family were initially classified by Harteneck *et al.* (*7*) into short (TRPC), osm-9–related (TRPV, vanilloid), and long (melanostatin-related, TRPM) channels (*8*, *9*). A 25–amino acid "TRP domain" of unknown function and containing a TRP box (Glu-Trp-Lys-Phe-Ala-Arg) is present in the carboxyl terminus of all TRPC channels, but not in all TRP channels. The amino-terminal cytoplasmic domains of TRPC and TRPV channels contain ankyrin repeats, whereas the TRPC and TRPM carboxyl termini contain proline-rich regions.

Like most of the characterized TRPs that express measurable currents, TRPM8 is relatively nonselective for cations and allows a smaller inward than outward current (*8*). Interestingly, the TRPM8 cold sensor, 1104

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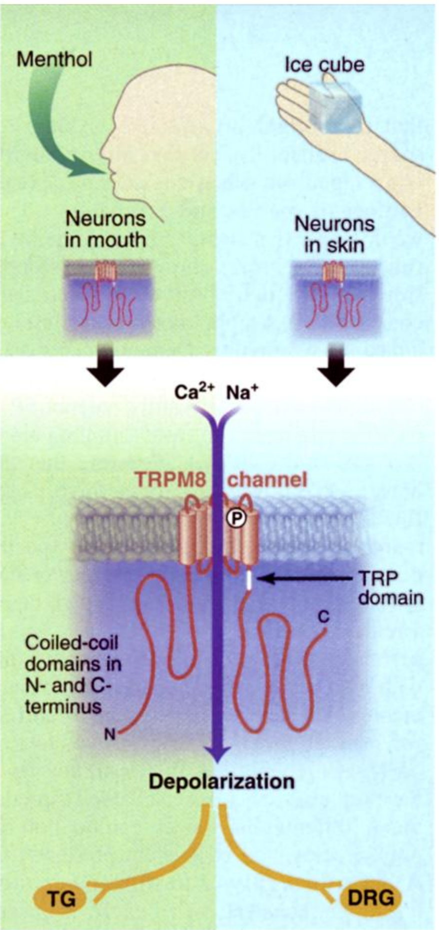

Cool mint. Mildly cool temperatures (25° to 15°C) and the cooling agent menthol activate the TRPM8 ion channel. This channel is expressed by sensory neurons in the mouth that project to the trigeminal ganglia (TG) in the brain, and by sensory neurons in the skin that project to the dorsal root ganglia (DRG) of the spinal cord. When activated, TRPM8 channels open, allowing Ca^{2+} and Na^+ ions into neurons, which then become depolarized. TRPM8, like other TRPM channels, is a tetramer with each subunit containing six transmembrane domains and unusually long amino and carboxyl termini.

amino acids in length, is in the class of TRP channels that has extremely long amino and carboxyl termini rather than in the vanilloid class of temperature-sensing TRPs containing ankyrin repeat domains. This class of long or melanostatin-related TRPs was thought to be involved in cell division, although the best-characterized TRP channels are all sensory: The *Drosophila* TRP channel is involved in vision, and the vanilloid TRPs sense temperature or osmotic changes.

It is intriguing that although TRPM8 was already identified, its sensitivity to temperature and menthol remained undiscovered. First, the classification of TRPM8 in the TRPM family may have been somewhat misleading because it does not bear close homology to TRPM class members. Also, presumably due to low levels of mRNA, TRPM8 did not show up in commercially available Northern blots of nervous tissue. Finally, because most cells in patch-clamp recordings are equilibrated at ~22°C, the TRPM8 current would have been only weakly activated.

The two studies are in reasonable agreement about the threshold for activation of TRPM8 (22° to 26°C), and the ~5°C shift induced by subactivating concentrations of menthol. Also, both studies agree that the channel is expressed in small-diameter neurons, consistent with the known sensitivity to temperature of unmyelinated C and thinly myelinated $A\delta$ primary afferent sensory neurons. However, the papers do come to some different conclusions. In cultures of mouse trigeminal sensory neurons, McKemy *et al.* found that ~50% of neurons expressing TRPM8 also expressed TRPV1 (VR1). This suggests that some neurons are both heat and cold sensors, potentially explaining the confusing sensations that we humans can have with hot and cold stimuli. As McKemy *et al.* point out, simultaneous contact with warm and cool surfaces (such as a thermal grill) evokes a sensation of burning pain. Also, mild cold can induce a feeling of burning pain after elimination of large nerve fibers by nerve block or injury. Using in situ hybridization in trigeminal ganglia from adult mice, Peier *et al.* found that TRPM8 was not expressed in TRPV1 (VR-1)–containing neurons, suggesting that there exist distinct subpopulations of neurons expressing either TRPM8 or TRPV1. Peier *et al.* also propose that the TRPM8 channel is uniquely associated with neurons that express the TrkA growth factor receptor; indeed, TRPM8 mRNA was not present in newborn mice lacking TrkA. The issue of whether heat and cold sensors are in the same neurons could be efficiently resolved in further studies of freshly isolated human and mouse nerve tissue.

Besides the complex road ahead for determining how neurons recognize and evaluate temperature, another set of interesting mysteries remains to be solved. The thermosensors TRPV1, TRPV2, and TRPM8 are expressed not only in neurons but also in nonneuronal cells. What could these receptors be doing in such tissues as the prostate? Finally, it will be intriguing to learn the native chemical messengers in neurons that open these channels.

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PERSPECTIVES: ECOLOGY

Of Predators, Prey, and Power Laws

Pablo A. Marquet

Power laws, in which one quantity can be expressed as some power of another, are ubiquitous in physical and social systems. They have been used to describe phenomena as diverse as the frequency of earthquakes of different magnitudes (the Gutenberg-Richter law), the distribution of income among individuals (Pareto's law), and the rank-frequency distribution of city sizes, or words in natural languages (Zipf's law) (*1*, *2*). Power laws in the form of scaling or allometric relationships are used by biologists to express how physiological, ecological, and life-history attributes relate to body size (W) raised to a power, usually a multiple of 1/4 (*3*). Among the vast number of biological power laws, those related to energy acquisition, transformation, and delivery are of fundamental importance, because energy sustains life. Thanks to the work of Max Kleiber in the 1930s, we know that the amount of energy organisms need to extract from their environments to sustain themselves, metabolism (M), scales with body mass according to $M \propto W^{3/4}$ (Kleiber's law) (*4*). This simple power law represents a fundamental first principle whose consequences for the structure and operation of ecological systems we are just beginning to appreciate. On page 2273 of this issue, Carbone and Gittleman (*5*) demonstrate that the interaction between metabolic requirements and locally available energy can account for the observed power law relation between carnivore population density and body size. Their approach illustrates the importance of incorporating local ecological information if we are to understand large-scale patterns in biodiversity.

It follows from Kleiber's law that a lim-

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