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TRP ion channels in the nervous system

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The transient receptor potential (TRP) superfamily comprises a group of non-selective cation channels that sense and respond to changes in their local environments. TRP channels are found in many eukaryotes, from yeast to mammals. They are a diverse group of proteins organized into six families: classical (TRPC), vanilloid (TRPV), melastatin (TRPM), muclopins (TRPML), polycystin (TRPP), and ANKTM1 (TRPA). In the peripheral nervous system, stimuli including temperature, pressure, inflammatory agents, and receptor activation effect TRP-mediated responses. In the central nervous system, TRPs participate in neurite outgrowth, receptor signalling and excitotoxic cell death resulting from anoxia. TRP channels are emerging as essential cellular switches that allow animals to respond to their environments.

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Abbreviations

DAG	diacylglycerol
PLC	phospholipase C
PIP_2	phosphatidylinositol 4,5-biphosphate
mGluR	metabotropic glutamate receptor
TRP	transient receptor potential
TRPC	classical TRPs
TRPM	melastatin TRPs
TRPP	polycystin TRPs
TRPV	vanilloid receptor TRPs

Introduction

Living things must sense and respond to environmental changes. Some ion channels act as the cellular sensors that translate fluctuations in the external milieu into changes in membrane excitability and second messenger signals, particularly Ca^{2+}. The channel family most intimately involved in this process is the transient receptor potential (TRP) family. A spontaneous *Drosophila* phototransduction mutant identified in 1977 displayed transient receptor potentials (*trp*) in response to continuous light [1]. Identification of the gene product underlying that mutation [2] and recognition of its function as an ion channel [3] gave rise to our awareness of a new class of cation channels that differed significantly from the canonical voltage-dependent channels. TRP channels are one of the largest groups of ion channels, but were only recently uncovered in full through the elucidation of complete genomes. In humans, at least 28 genes in six families can be classified as TRP channels. They are weakly voltage-sensitive, largely nonselective, cation channels. Unlike other cation-selective channel families, the TRPs are classified by primary amino acid sequence rather than selectivity or ligand function because their properties are so varied and their regulation so complex. With the exception of capsaicin for TRPV1, there are no currently available pharmacological agents or toxins that can be used to separate their physiological functions.

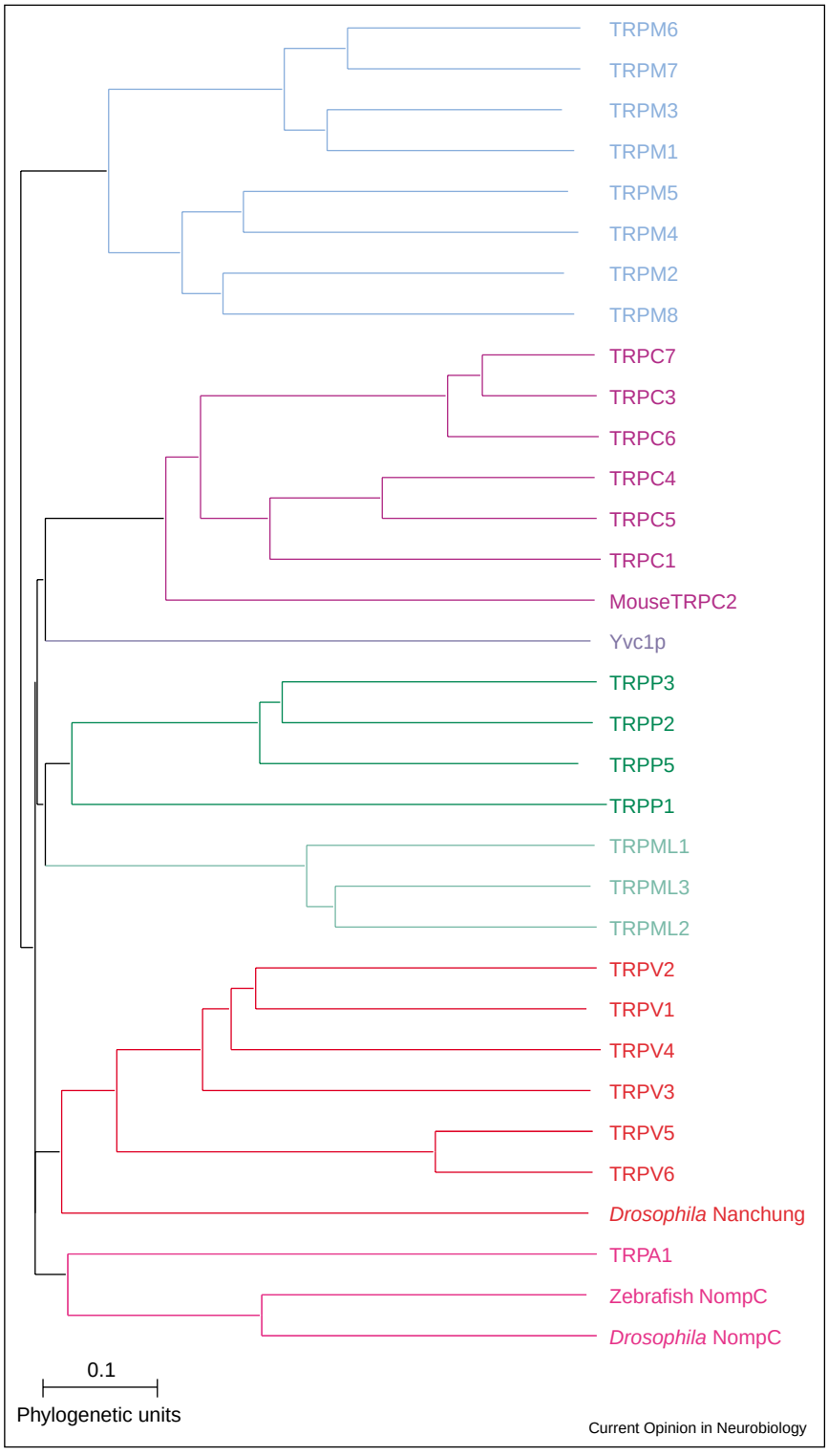
Six protein families comprise the mammalian TRP superfamily: the classical TRPs (TRPCs), the vanilloid receptor TRPs (TRPVs), the melastatin or long TRPs (TRPMs), the mucolipins (TRPMLs), the polycystins (TRPPs) and ankyrin transmembrane protein 1 (ANKTM1) (TRPA1; Figure 1, [4,5]). With the exception of some polycystins, all are predicted to have six transmembrane domains. Despite the topographic similarities between the TRPs and the voltage-gated potassium channels or sperm cation channels (CatSpers), the TRPs are actually only distantly related to these channels (Figure 2). TRPs are found in eukaryotes from yeast to mammals, often functionally associated with G protein-coupled and growth factor (tyrosine kinase) receptors and phospholipase C (PLC) (Figure 3). Here, we summarize the biophysical properties and various modes of activation of these TRPs. We discuss their potential biological functions such as thermo-, mechano-, gustatory and pheromone sensation. Possible functions of TRPs in the brain will also be highlighted.

TRPs in sensation

Temperature

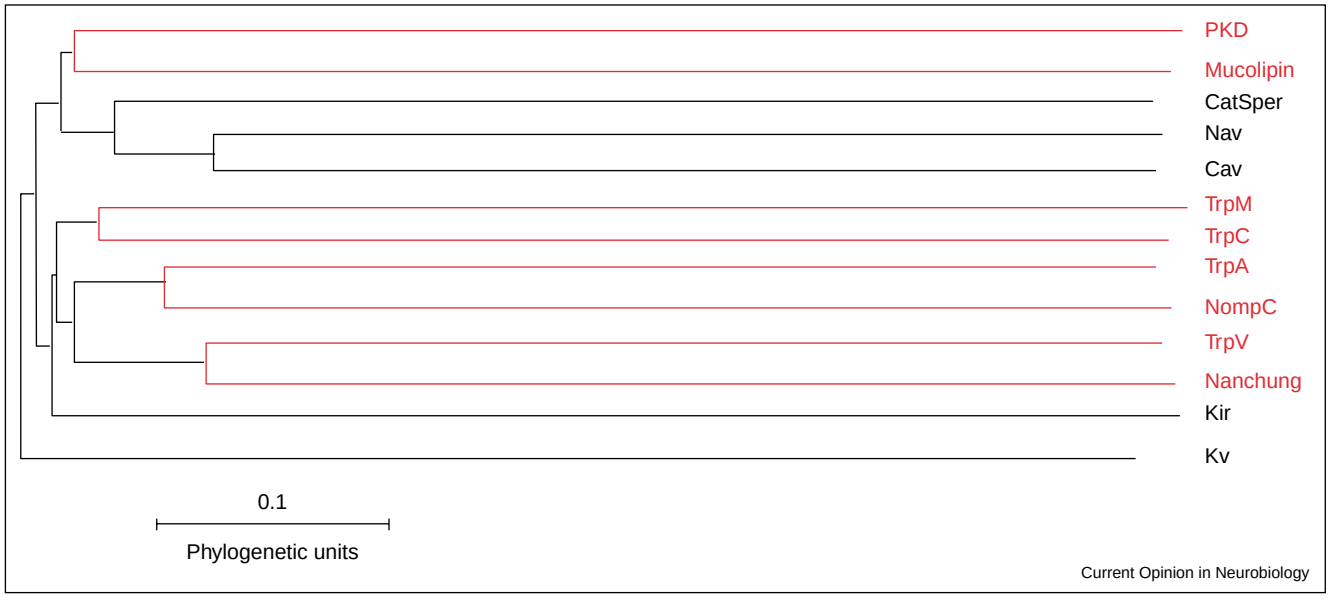
Organisms sense and react to temperature fluctuations. All ion channels and, indeed, all proteins are temperature-sensitive. But several TRP channels have unusually high temperature sensitivity (Q_{10}>10; where Q_{10} is a 10 degree temperature coefficient, defined as [rate(T+10)/rate(T)]) and are present in known pain and temperature-sensing neurons. TRPV1 is the most established of the temperature-sensing channels. Capsaicin, acid, and decreased membrane phosphatidylinositol 4,5-biphosphate (PIP_2) levels alter TRPV1's temperature-sensing range [6].

Figure 1



A phylogeny tree to show how the human TRP channels are related. As TRPC2 is a pseudogene in humans, the mouse is represented. Zebrafish, *Drosophila* and yeast TRPs discussed are also shown. Scale is in phylogenetic units, where 0.1 represents approximately 10% difference.

Figure 2

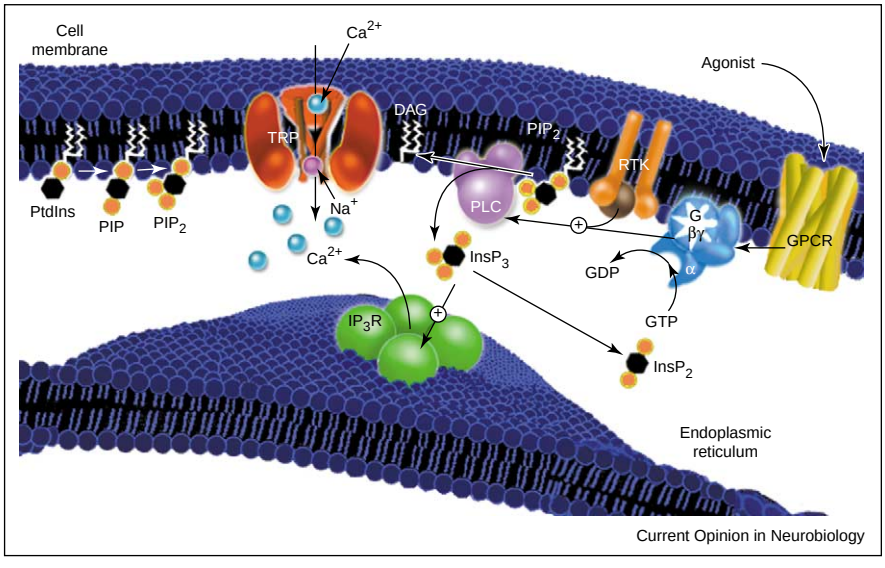


A phylogeny tree to show the relation of the TRP families to other ion channel families. CatSpers are a new family of six transmembrane sperm ion channels. Cav represents the voltage-gated calcium channels. Nav represents the voltage-gated sodium channels, whereas Kv shows the voltage dependent potassium channels. Kir represents the inward rectifier potassium channels.

TRPV1 knockout mice show impaired responses to noxious heat and vanilloid-induced pain [7].

The case for temperature sensing by TRPV2–4 is based largely on observed changes in heterologously expressed channel gating over various temperature ranges. Deletion of these genes in mice and the study of temperature sensing neurons and behaviors would help to clarify their roles. Initial studies of TRPV2 [8] suggest that it is sensitive to noxious heat (>50°C), whereas TRPV3 and

Figure 3



The PLC pathway is a principal activator of TRP channels. Ligand binding of a G-protein coupled receptor (GPCR; i.e. acetylcholine binding to the M1 receptor) results in the conversion of GTP to GDP and the activation of the Gα and Gβγ subunits. The subunits in turn stimulate PLCβ activity. Similarly, growth factors, such as NGF, activate receptor tyrosine kinases that trigger PLCγ activity. PLC hydrolyses PIP2 into membrane-bound DAG and soluble inositol triphosphate (IP_3). Generation of IP_3 results in inositol triphosphate receptor (IP_3R) mediated release of calcium from intracellular stores. Intracellular calcium and DAG both activate members of the TRP family.

TRPV4 are activated by temperatures between 22 and 40°C [9,10,11•,12]. TRPV3's high temperature coefficient [11•] and its robust expression in skin and sensory neurons [9,11•] make it an ideal candidate for involvement in thermoregulation [9,10,11•]. Repeated exposure to warmth sensitizes TRPV3 responses and increases both the magnitude and the speed of the response [11•]. TRPV1–4 might heteromultimerize to form distinct temperature sensitive channels, but genetic disruption, RNAi, or dominant negative subunits will probably be required to determine their effects on complex thermal and spatial responses.

Cooling below 22°C activates heterologously expressed TRPM8. Menthol, the compound responsible for the refreshing quality of mint, and icilin, the supercooling agent, shift the activation threshold of the channel to room temperature [13,14•]. Whole cell patch clamp recordings indicate little selectivity among monovalent cations, but high Ca^{2+} permeability. Repeated exposure to either stimulus resulted in a marked desensitization of the current in a $[Ca^{2+}]_O$-dependent manner (square brackets indicate concentration) [14•].

The tissue distributions of TRPM8 and TRPV1–4 and TRPV4's osmotic sensitivity suggest that these channels might be more than temperature sensors. Indeed, TRPV4 deletion in mice alters central nervous system control of antidiuretic hormone (ADH) secretion and diminishes their sensitivity to tail pressure and acid nociception [15–18]. Expression of TRPV4 in heterologous systems results in a Ca^{2+}-permeable non-selective current that is elicited by decreases in extracellular osmolarity. Temperature [12], intracellular and extracellular $[Ca^{2+}]$ [19,20], and phorbol esters [20] all modulate TRPV4 activation. PIP_2 hydrolysis after PLC activation [21] sensitizes TRPV1 [22], but inactivates TRPM7 [23]. This additional modulation by PLC might explain the proalgesic effects of nerve growth factor (NGF) and bradykinin mediated by TRPV1. TRPM8 was originally identified as a gene upregulated during prostate cancer and other malignancies [24] and its expression is currently one of the best markers for advanced disease [25]. These findings suggest a role for TRPM8 outside the realm of thermosensation, as the prostate is not subject to pronounced temperature fluctuations. Similarly, TRPV1–4 mRNAs are present in several tissues that have tight temperature regulation, including the brain [8,11•,12,26].

TRPA1 (ANKTM1) is the sole member of a distinct TRP family that was initially reported to sense noxious cold temperatures (<15°C) [27]. Although the existence of another cold receptor would explain the presence of cold-induced currents in neurons that do not respond to menthol [27], more recent work failed to show any cold activation of TRPA1 [28•]. Julius and co-workers argue that it senses mustard oils and the cannabinoid compound, Δ9-tetrahydrocannabinol (THC). The characteristics of the heterologously expressed channel resemble the properties of currents activated by mustard oils in trigeminal neurons. In addition to being activated by these inflammatory agents, the TRPA1 current is also triggered by the PLC-coupled M1 muscarinic acetylcholine receptor [28•], which suggests a receptor-operated mechanism of activation. The ability of THC to induce current in TRPA1-expressing cells, combined with the sensitivity of TRPV1 to the endogenous cannabinoid anandamide [29], suggests that the TRP superfamily might contain a family of ionotropic cannabinoid receptors [28•].

Mechanical forces

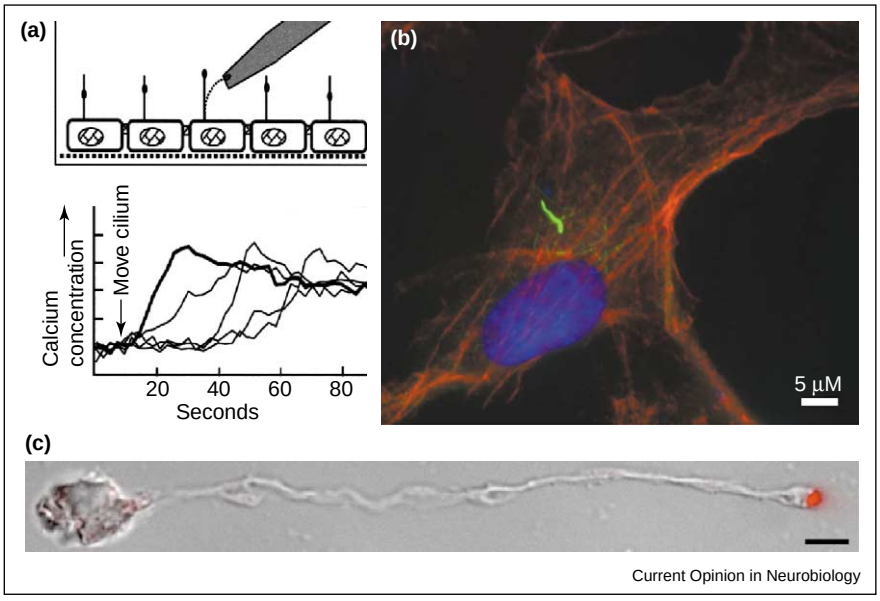
Ciliated structures multiply mechanical forces [30]. The presence of TRPs in cilia is consistent with a generalized role for TRPs as transducers of mechanical force (Figure 4). Nanchung, a member of the *Drosophila* TRPV family that is activated by stretch, localizes to the cilia of mechanosensory chordotonal neurons that respond to sound and pressure. Despite normal chordotonal organ morphology, mutants are deaf [31]. NompC, a second member of the *Drosophila* TRP family is required for the generation of pressure-induced currents in sensory bristles [32], and might also be a mechanosensitive channel. Morpholino antisense oligonucleotide-mediated reduction of NompC's zebrafish homolog impaired hair cell signal transduction, producing deafness, raising the possibility that its homolog, TRPA1, serves as a hearing mechanotransducer in mammalian systems [33]. *Caenorhabditis elegans* TRPV family members osmosensory-9 (OSM-9) and *osm-9*/capsaicin receptor related-2 (OCR-2) localize to the cilia, and are required for mechanosensation, olfaction, and osmosensation [34,35]. As these two proteins affect one another's function and targeting [35] it seems likely that these TRPV family members heteromultimerize.

TRPP1 and TRPP2 localize to the primary renal cilia [36,37] in adult mice where they sense fluid flow [36]. In the developing embryo TRPP2 is an integral part of the flow-sensing nodal cilia. Perturbation of TRPP2 causes a randomization of heart looping and embryonic turning [38], perhaps due to aberrations in the asymmetric Ca^{2+} transients that normally coincide with nodal flow [39•]. As many TRPs are expressed in ciliated cells, it will be important to determine which of these are actually present in the cilia itself. It will also be crucial to ascertain if movement of the cilia activates TRP channels and how force is translated into channel opening (Figure 3).

Taste

Differential screening of individual taste receptor cells identified TRPM5 as a candidate protein involved in the transduction of taste. Northern blots and *in situ* hybridizations confirmed that TRPM5 is expressed at high levels in

Figure 4



Mechanosensing by cilia. **(a)** Movement of a single cilia induces a rise in $[Ca^{2+}]I$ (from [63]). **(b)** Primary cilium (green) on an epithelial cell in culture (human telomerase reverse transcriptase immortalized retinal pigment epithelial line [hTERT-RPE], from [64]). **(c)** TRPC2 (red)-stained sensory microvilli in an isolated rat vomeronasal organ neuron (from [65]).

taste sensing tissue and colocalizes with other known elements of the gustatory signaling pathway, including α-gustducin [40]. In $TRPM5^{-/-}$ mice, bitter, sweet and savory (monosodium glutamate; umami) tastes are disrupted, whereas salty and sour remain intact [41••]. This finding indicates that TRPM5 is a common taste transduction element involved in relaying information from a subset of different taste receptors. Studies that focus exclusively on heterologously expressed TRPM5 indicate that the current is a voltage modulated, monovalent-selective cation conductance that is activated by micromolar levels of intracellular Ca^{2+} [42•,43,44]. These current properties resemble those of the highly homologous TRPM4b channel [45]. Rapid desensitization of the TRPM5 current is reversed by PIP_2 [42•]. Receptor stimulation upstream of PLC-β2 (which colocalizes with TRPM5) [40], could generate 1,4,5-inositol triphosphate (IP_3) and thereby increase intracellular $[Ca^{2+}]$ to a level that triggers ion flux through TRPM5. Understanding the regulation of TRPM5 should facilitate future studies of its role in tissues such as the stomach, small intestine [40], and pancreas [44] where TRPM5 mRNA is also found.

Pheromone sensation

Just as TRPM5 is required for normal taste transduction, murine TRPC2 is essential for the transmission of many pheromone-mediated signals. Male mice that lack TRPC2 do not display stereotypical male–male aggression responses and they mate indiscriminately with male or female mice [46••]. This atypical behavior is likely to result from a lack of pheromone-evoked neuronal activity in their vomeronasal organs (VNO) [46••]. Subsequent studies of currents in isolated VNO sensory neurons indicated that the absence of TRPC2 correlated with the reduction of a diacylglycerol (DAG)-activated current [47]. This observation suggests that like TRPC3, 6 and 7 [48], TRPC2 might be activated by PLC-mediated generation of DAG. As human TRPC2 is a pseudogene, it is possible that one of these other DAG-sensitive channels participates in human pheromone transduction.

TRPs in the brain

TRPs are widely distributed in the brain, with almost every TRP subunit being represented. Most have not been studied in any detail yet. TRPC1, TRPC4, and TRPC5 are present in the cerebral cortex, hippocampus, cerebellum, and amygdala [49–51]. TRPC1 forms hetero-multimeric channels with TRPC4 or TRPC5 [52], and in neonatal brain with TRPC3 [53]. TRPC1 does not appear to be expressed as a homomer [52]. TRPC1/5 heteromers appear to be confined to the cell body and proximal processes, whereas TRPC5 is transported to growth cones to form homomeric channels [54]. Receptor-coupled PLCs activate both TRPC1/5 heteromers and TRPC5 homomers [52], and each of these channels has distinct current-voltage relationships. Expression of a dominant-negative version of TRPC5 in these cells results in the formation of abnormally long growth cones and filopodia [54]. These findings are consistent with a role for TRPs in regulating some aspects of neurite outgrowth and axonal pathfinding in the immature hippocampus.

TRPCs might also underlie metabotropic glutamate receptor (mGluR) dependent conductances in rat CA3 pyramidal neurons [55], midbrain dopaminergic neurons [56,57], and cerebellar Purkinje neurons [58]. The mGluR dependent currents in CA3 pyramidal neurons [55] particularly resemble currents from heterologously expressed TRPC1/TRPC5 heteromultimers [52]. G protein alpha q (G_q)-activation also stimulates TRPC1/TRPC5 and this current shows a region of negative slope conductance similar to the mGluR dependent current observed in slice recordings. As both TRPC1 and TRPC5 are present in hippocampal [53] and dopaminergic neurons [56], genetic disruption or RNAi mediated decrease of TRPC1 or TRPC5 will be required for more detailed separation of their roles.

TRPs might respond to pathological stimuli as well as normal signaling cues. Recent work indicates a function for TRPM7 in reaction to excitotoxicity and anoxic cell death. Recordings from cortical neurons after oxygen and glucose deprivation revealed a non-selective cation current that was blocked by gadolinium (Gd^{3+}, a trivalent cation, blocks many non-selective cationic conductances), with a current-voltage relation somewhat consistent with TRPM6 [59] or TRPM7 channels [60,61]. Blocking the current permitted the survival of anoxic neurons [62••]. Addition of PIP_2 to the patch pipette resulted in an enhancement of the current [62••], which is again consistent with TRPM7 being part of the pore forming unit [23]. Expression of TRPM7 in human embryonic kidney cells (HEK) cells revealed additional similarities between the heterologously expressed TRPM7 current and the current seen in dying cortical neurons, including an augmentation in the presence of reactive oxygen species [62••]. To confirm the involvement of TRPM7, the authors reduced its expression with small interfering RNAs (siRNAs). Neurons depleted of TRPM7 lacked much of the current normally induced by anoxia and were resistant to cell death. Interestingly, multiple siRNAs directed against TRPM7 also significantly decreased levels of TRPM2, indicating that the two transcripts might be coordinately regulated. This observation raises the possibility that some portion of the anoxia-induced current is actually carried by TRPM2 or TRPM7 heteromultimers [62••].

Conclusions

Recent work has demonstrated that TRP channels play crucial parts in both interoception and exteroception. TRPs are sometimes called 'store operated' channels (SOC) based on the observation that calcium entry following intracellular calcium release from stores (probably endoplasmic reticulum) is potentiated in cells transfected with some types of TRP channels. This is a definition based on an experimental condition rather than a mechanism. Our interpretation is that few, if any, TRPs are SOCs in any direct sense; the link between store depletion and TRP-mediated enhancement of calcium entry could be quite indirect. The more substantiated hypothesis is that TRPs are receptor-activated through phospholipase C and unknown downstream messengers. Other perturbations of the cell, such as temperature changes and alteration of the lipid bilayer, might intersect with these pathways. Given the broad range of sensory processes that involve TRPs, the future of this diverse channel family should be exciting, but is likely to be difficult given the large number of channels, their similar electrophysiological properties, wide distribution, potential heteromeric combinations, and obscure gating mechanisms. Nonetheless, TRP channels have the potential to fill in large gaps in our understanding of the nervous system.

Update

Recently, the Patapoutian group [66] verified the activation of TRPA1 by compounds that elicit sensory responses, including cinnamaldehyde and mustard oils. The group again reported that noxious cold activates both the human and the mouse versions of the channel, though this activation is not as robust as that observed with cinnamaldehyde.

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