Current Biology *18*, R880–R889, September 23, 2008 DOI 10.1016/j.cub.2008.07.063

TRPs in Our Senses

Review

Nils Damann[1], Thomas Voets[1], and Bernd Nilius[1,*]

In the last decade, studies of transient receptor potential (TRP) channels, a superfamily of cation-conducting membrane proteins, have significantly extended our knowledge about the molecular basis of sensory perception in animals. Due to their distinct activation mechanisms and biophysical properties, TRP channels are highly suited to function in receptor cells, either as receptors for environmental or endogenous stimuli or as molecular players in signal transduction cascades downstream of metabotropic receptors. As such, TRP channels play a crucial role in many mammalian senses, including touch, taste and smell. Starting with a brief survey of sensory TRP channels in invertebrate model systems, this review covers the current state of research on TRP channel function in the classical mammalian senses and summarizes how modulation of TRP channels can tune our sensations.

Introduction

In *De Anima*, book II, Aristotle for the first time defined five exteroceptive senses that allow humans to perceive the outside world: sight (visus); hearing (auditus); smell (olfactus); taste (gustus); and touch (contactus). Balance (or equilibrioreception) is now generally considered to be a sixth exteroceptive sense. These senses can be set apart from the so-called interoceptive senses, which provide information from within the body. For example, proprioception informs the brain about the relative position of muscles and joints.

An alternative way of classifying senses is based on the kind of stimulus that is measured, leading to the distinction between chemosensation, thermosensation, photosensation and mechanosensation. Whereas sight (photosensation), hearing and balance (mechanosensation) and smell (chemosensation) easily fit into these four functional categories, the situation is a little more complex for the two other exteroceptive senses. Taste can be primarily categorized under chemosensation, but has some clear thermo- and even mechanosensitive aspects; touch involves a mixture of thermo- and mechanosensation (Figure 1).

Probably more interesting than classification is the question of how the different sensory systems manage to translate the different kinds of stimulus into an electrical signal that can be interpreted by the central nervous system. In the last decade, our understanding of the molecular basis of sensory processes has made a large leap forward with the cloning of the superfamily of transient receptor potential (TRP) ion channels. In this review, we will summarize some of the recent knowledge on the function and role of TRP channels in the sensory system.

The advent of the family of TRP cation channels dates back to the observation of a spontaneous mutant of *Drosophila melanogaster*, in which the response to steady light appeared to be transient in contrast to the sustained response in wild-type flies. The mutant was therefore named 'transient receptor potential' (*trp*) [1]. The mutated gene was cloned 20 years later and the structural resemblance of the gene product to known channels was noted [2]. Based on detailed analysis of permeation properties of the light-activated channel in the *trp* mutant, it was proposed that the *trp*-encoded membrane protein was a light-sensitive channel [3]. These events started an exciting search for homologous channels, which has resulted so far in the description of seven subfamilies of TRP channel genes. Database searches in the six kingdoms of life have not (yet) revealed *trp*-related genes in the two prokaryotic kingdoms of the eubacteria and archaebacteria, or in the kingdom of protistas (e.g. green algae, flagellated or ciliated protozoans) or in plants. In fungi, a single *trp*-related gene has been found, which cannot be assigned to any of the known TRP subfamilies in animals. The first *trp* genes appear in the unicellular choanoflagellates (*Monosiga brevicollis*), which are considered to be the closest living relatives of the animals [4], and, in the animalia kingdom, a plethora of *trp*-related genes has now been identified from worms to humans (Table 1, adapted from [5]).

Sensing in Invertebrate Model Organisms

Before focusing on the role of TRP channels in the mammalian senses, we first provide a brief overview of sensory TRP channels in three lower organisms: yeast, *Caenorhabditis elegans* and *Drosophila melanogaster.*

Yeast TRPY1: An Ancient Mechanosensor and Chemosensor?

The only TRP channel in yeast is TRPY1 (previously known as *yvc1*), a large conductance cation channel located in the vacuolar membrane [6]. TRPY1 is activated by hyperosmotic stimuli, leading to calcium (Ca^{2+}) release from the vacuole into the yeast cytoplasm, which then initiates osmotic defense responses. TRPY1 is directly mechanosensitive and can also be activated by indole and other aromatic compounds. As such, TRPY1 may be considered to be an ancient mechanosensor and chemosensor.

Mechanosensation and Chemosensation in C. elegans*: TRPVs and More*

The nematode *C. elegans* was generally believed to be blind and lack phototaxis. Recently, however, cyclic-nucleotide-gated (CNG) channels activated by cyclic GMP (cGMP) have been identified, which are involved in phototaxis, indicating conservation of the basic principle of light reception between worms and vertebrates [7]. Although worms are probably deaf, they have primitive sensory systems that partly resemble the other classical senses defined by Aristotle: smell, taste and touch [8]. Genetic and behavioral results have provided strong evidence for the involvement of TRP channels in the different sensory modalities of *C. elegans*. An important advantage of the *C. elegans* model is that it contains a fixed amount of sensory neurons, which can be individually labeled and studied. A disadvantage is that most *C. elegans* TRP channels have not yet been functionally characterized in heterologous expression systems, which

[1]Laboratorium voor Fysiologie, Campus Gasthuisberg, Katholieke Universiteit Leuven, Herestraat 49, B-3000 Leuven, Belgium.
[*]E-mail: bernd.nilius@med.kuleuven.be

makes it difficult to conclude whether the channels function as primary sensors or rather as signal transducers/amplifiers.

Most studies on the role of TRP channels in *C. elegans* sensation have focused on OSM-9, a member of the TRPV subfamily, and the related OCR-1 to OCR-4 channels. OSM-9-deficient worms have deficits in the detection of olfactory and osmotic stimuli, as well as in mechanosensation in the nose. OSM-9 is expressed in several types of sensory neurons, including the olfactory AWA neurons and the polymodal ASH neurons that act as nociceptors. In general, soluble and volatile chemicals are detected by ~1,500 different G-protein coupled receptors (GPCRs) in *C. elegans*. In the AWA neurons, GPCR activation by volatile compounds is coupled to activation of OSM-9 and OCR-2 via production of polyunsaturated fatty acids (PUFAs). This mechanism contrasts with chemosensation in, for example, AWC neurons, where GPCR activity leads to activation of the CNG channels TAX-2 and TAX-4 via a receptor guanylate cyclase. Likewise, TRP-dependent and -independent mechanisms coexist for mechanosensation. The six sensory cells that respond to gentle touch contain a mechanoreceptor complex consisting of at least five proteins, including ion channels of the Deg/ENaC family, but apparently no TRPs. In contrast, other mechanosensory behavior, such as the withdrawal reflex from nose touch, harsh touch and responses to body stretch is dependent on TRP channels. For example, the ciliated nociceptive ASH neurons, which mediate avoidance of osmotic stimuli, hard touch, and various noxious chemicals, express the TRPV channels OSM-9, ORC-2 and ORC-4. OSM-9 mutants are almost fully deficient in their response to such noxious stimuli, whereas ORC-2-deficient worms display a similar but milder phenotype. Interestingly, mammalian TRPV4, which can be activated by osmotic cell swelling and mechanical stimuli, can restore the ASH-dependent behavioral responses to osmotic and mechanical stimuli in the OSM-9 mutant, whereas expression of mammalian TRPV1 in these neurons results in an artificial avoidance behavior for the TRPV1-agonist capsaicin [9,10].

In addition to OSM-9 and the related TRPV channels, a few other TRP channels from different subfamilies have been implicated in mechanosensation. TRPA-1, one of the two members of the TRPA subfamily in *C. elegans*, was recently found to be involved in responses to repetitive nose touch and in the typical *C. elegans* foraging behavior, which depend on the OLQ and IL1 neurons but not on the ASH nociceptors. It is worth noting that heterologously expressed TRPA-1 was found to be activated by mechanical stimuli, suggesting that it may be directly involved in the mechanosensory process. LOV-1 and PKD-2, the *C. elegans* orthologues of mammalian PKD1 (TRPP1) and PKD2 (TRPP2), respectively, are co-expressed in male-specific sensory neurons, and mutations in either of these TRPPs results in mechanosensitive deficits. TRP-4, the *C. elegans* homologue of the vertebrate TRPN channel, is a mechanosensitive channel involved in stretch-mediated proprioception [11]. Interestingly, *C. elegans* exhibits complex behavioral responses to nicotine, including locomotion effects (withdrawal), and these responses require the *C. elegans* vertebrate TRPC channel homologues TRP-1, TRP-2, and TRP-3 [12]. Finally, although *C. elegans* is clearly able to sense temperature, the TRP proteins involved in thermosensation have not yet been identified [13].

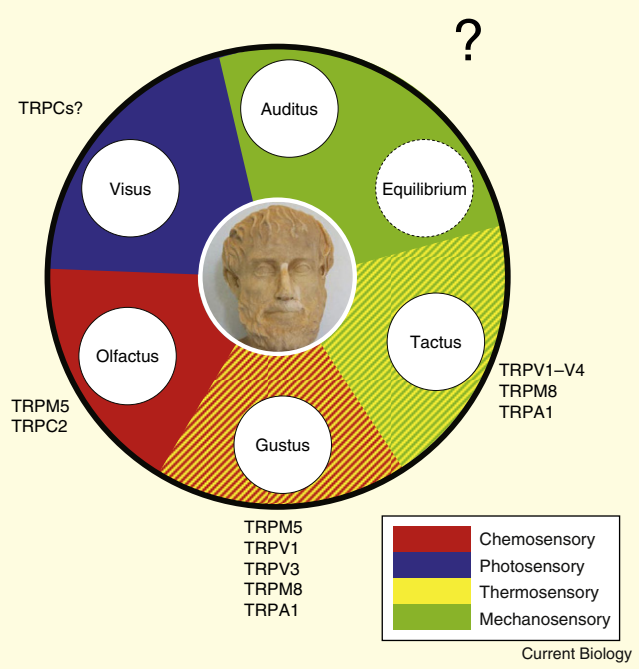

Figure 1. Aristotle's five senses + the sixth sense (equilibrium).
Colors and color combinations indicate the type of sensory receptors involved. TRP channels closely involved in the sensory process are also indicated.

As an important note, some TRP channels in *C. elegans* only function as heteromers or require at least physical protein–protein interaction. OSM-9 and OCR-2 mutually depend on each other and very likely form heteromers. Other examples concern the gene *thp-1* in chemosensory neurons which requires interaction with *orc-2*. *lov-1* and *pkd-2* interact in the same ciliary neurons and an interaction between *trp-1, trp-2* and *trp3* is probably required for nicotine-induced behavioral responses [9,12]. These important examples suggest that interactions between TRP channels in vertebrates are likely to be even more complex.

Senses in Drosophila

Drosophila has developed equivalents for Aristotle's five senses: it has well-developed eyes, can listen to the courtyard melodies, smell, taste, and exhibit mechanosensitivity and thermosensitivity comparable to touch. At least 30 genes have been identified that control light sensation in *Drosophila*, including at least TRP and TRPL. The light sensing cascade is triggered by light absorption via the GPCR rhodopsin, which is coupled to the phospholipase C (PLC) NORPA. Activation of NORPA leads to opening of TRP, a highly Ca^{2+}-selective cation channel, and TRPL, which is much less Ca^{2+} selective. Mutations or inactivation of *trp* lead to a transient response to light, a ~10-fold decrease in the Ca^{2+} response to light and severe defects in light responses. Disruption of TRPL alone results in a decreased response to light stimulation with a much milder phenotype, including defects in adaptation to dim backgrounds. Despite intensive research, the mechanism of TRP/TRPL activation following NORPA activation is still not completely understood: most likely, the channels are activated by diacylglycerol (DAG), which is formed upon phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis, or by a DAG metabolite

Table 1. The TRP channel families.

	Drosophila melanogaster	*Caenorhabditis elegans*	*Ciona intestinalis*	*Fugu rubripes*	*Danio rerio*	*Mus musculus*	*Homo sapiens*
TRPC	3	3	8	8	8	7	6
TRPV	2	5	2	4	4	6	6
TRPM	1	4	2	6	6	8	8
TRPA	4	2	4	1	2	1	1
TRPN	1	1	1	–	1	–	–
TRPML	1	1	9	2	2	3	3
TRPP	1	1	1	4	4	3	3
Total	13	17	27	25	27	28	27

TRP channels in *Drosophila melanogaster*, *Caenorhabditis elegans*, the sea squirt *Ciona intestinalis*, the puffer fish (*Fugu rubripes*), the zebrafish (*Danio rerio*), mouse and human. Other estimates report that there are nearly 60 TRPs in zebrafish, 30 in sea squirt, and 24 in nematodes [24,99]. The number of channels denoted in the table refers to those that have known functions.

(for excellent reviews, see [14,15]). Importantly, DAG lipase (encoded by the *inaE* gene) hydrolyzes DAG, and this hydrolysis is required for physiological light responses of *Drosophila* [16].

Drosophila contains several organs/structures involved in mechanosensation and sound-wave detection, including the sensory bristles, campaniform sensilla, chordotonal organs, and type II mechanoreceptors. The largest chordotonal organ in the fly is Johnston's organ, the adult fly's antennal ear, which senses, for instance, the vibrating wing of a courting male fly. The ciliated sensory neurons in Johnston's organ express two TRPV channels, *iav* and *nanchung* (*nan*), and mutants deficient in either of these channels completely lack sound-evoked potentials. There is evidence that IAV and NAN form heteromultimers, and both channels can be activated by hypotonic cell swelling *in vitro*, suggesting that they may exhibit some intrinsic mechanosensitivity. In addition, the founding member of the TRPN subfamily, NOMPC, is required for the mechanotransduction current in the sensory bristles and other mechanosensory organs. Detailed analysis of the auditory mechanics of antennal sound receivers has led to a model in which NAN and IAV are involved in propagation and mechanical amplification of the sound signal, whereas NOMPC may be part of the mechanotransduction channel itself. If so, the string of ~29 ankyrin domains of the amino terminus of NOMPC may form the gating spring of the mechanosensor [17].

Recent evidence also implies a role for TRP channels in the sensing of humidity. The TRPA channel encoded by *water witch* (*wtrw*) is required in hygrosensors that detect moist air, whereas NAN is involved in detecting dry air. Most likely, these channels do not directly sense air humidity, because channel function necessarily requires an electrolyte-containing solution on the extracellular side. Instead, altered humidity may be sensed as a mechanical stimulus or change in temperature [18].

The *Drosophila painless* mutant was identified on the basis of its strongly reduced response to heat stimuli, and was also found to be less sensitive to harsh mechanical stimuli and pungent isothiocyanates. Importantly, *painless* encodes one of the four TRPA channels. Two additional members of the TRPA subfamily, dTRPA1 and Pyrexia, have been shown to be heat activated, and mutants lacking these channels exhibit alterations in temperature-dependent behavior: dTRPA1-deficient larvae no longer avoid elevated temperatures along a thermal gradient, whereas *pyrexia* mutants become rapidly paralyzed upon exposure to a temperature of 40°C. TRP channels involved in cold sensation have not yet been identified in *Drosophila* (for a review, see [13]).

TRP Channels in the Mammalian Sensory System

The various roles played by TRP channels in the different invertebrate sensory modalities illustrate how the unique gating promiscuity of TRP channels can be employed to detect changes in the physical and chemical environment. Below we provide an overview of the known functions of TRP channels in the mammalian senses.

Vision and Photoreception

At first sight, the mechanisms for light perception in *Drosophila* seem of little relevance for human vision. Light perception in mammalian rods and cones occurs via a strikingly different mechanism involving rhodopsin and CNG channels but no TRPs. This does not imply that TRP channels play no role in human vision and photodetection, however. Apart from the rods and cones, the mammalian eye also contains another set of light-sensitive cells, the so-called intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells are involved in light-dependent processes, such as pupil constriction and brightness detection, coupled to circadian rhythms. The ipRGCs express melanopsin, a light-sensitive GPCR with a maximal sensitivity at the blue end of the spectrum. When melanopsin and mammalian TRPC3 were transfected into the HEK293 cell line, these cells attained a light-induced current similar to ipRGCs. Moreover, as in *Drosophila* phototransduction, activation of TRPC3 downstream of melanopsin required a G protein of the Gq family as well as PLC [19–21]. The exact contribution of particular TRP channels to the light-induced activation of ipRGCs has yet to be established, but pharmacological data and expression studies have put forward TRPC3, TRPC6 and TRPC7 as prime candidates.

Hearing and the Vestibular Sense

Hair cells in the cochlea and vestibular organ translate mechanical information originating from sound waves or head movement, respectively, into a neural signal that is conveyed to the central nervous system via the eighth cranial nerve. The principles of signal transduction in the inner hair cells of vertebrates are under intense investigation. A central aspect is the identification of the still enigmatic membrane molecule that transduces the deflection of the sensory hair bundles into a receptor potential — the mechano-electrical transduction (MET) channel. The identification of the crucial role for TRPN1 (NompC) in mechanosensation in flies and zebrafish [22] encouraged speculation about a potential role of TRP channels in mammalian hearing. TRPA1, the closest mammalian homologue of TRPN1, was put forward as a candidate for the MET channel, on the basis of its

specific localization in the apical region of inner hair cells [23] and the reduction of transducer current upon knockdown of TRPN1/TRPA1 expression in zebrafish and mouse hair cells. The molecular architecture of the TRPA1 amino terminus with its 16 ankyrin repeats suggested that it could form the elastic gating spring found in hair cells (for a review, see [24]). Recently, however, enthusiasm was dampened when TRPA1-deficient mice were shown to have normal auditory and vestibular behaviors and transduction was found to be normal in single mouse utricular hair cells isolated from these mice [25,26].

In contrast with the TRPA1-deficient animals, TRPV4-deficient mice exhibit diminished hearing [27]. TRPV4 is expressed in hair cells, stria vascularis, and spiral ganglion of the mouse cochlea and may be activated by mechanical stimuli (for a review, see [28]). It has been also shown that TRPV5 and TRPV6, by adapting the endolymphe Ca^{2+} concentration in the inner ear, are required for normal hearing, e.g. dysfunction of these channels causes deafness in the *Pendered syndrome* [29].

The *varitint-waddler* mouse is a spontaneous mutant characterized by tricolored fur, deafness and vestibular dysfunction. The gene mutated in these mice turned out to encode TRPML3, and recent evidence indicates that the *varitint-waddler* mutation actually results in a constitutively active TRPML3 channel, leading to Ca^{2+} overload and cell death [30]. TRPML3 is required for a maturation process that organizes the stereocilia in these cells in a correct staircase-like, V-shaped pattern [31]. Taken together, several TRP channels are expressed in the mammalian inner ear and vestibular organ, but it is questionable whether the MET channel belongs to the TRP superfamily.

The Chemical Senses: Taste, Smell and More

The perception of chemicals provides us with information about the edibility of food and its caloric content, can affect mood and behavior by way of smelling pleasant or unpleasant odors and can signal imminent danger e.g. smoke from a fire. Following Aristotle's senses, chemosensation would be subdivided into taste (perception of solid or fluid compounds in the mouth) and smell (perception of volatile compounds in the nose). In the context of sensory biology, however, such a classical subdivision is not unequivocal. Chemoreception is rather mediated by a variety of anatomical structures/sensory systems each being equipped with distinct types of receptor cells. For example, our perception of food originates from activation of taste receptors on the tongue (which detect sour, salty, bitter, sweet, and umami tastes), olfactory receptor neurons in the nose (which detect odorants), and trigeminal fibers in the mouth, throat and nose (which detect hot/spicy, cool/fresh, prickling, burning, stinging compounds and physico-chemical properties such as viscosity, texture, hardness or roughness).

In taste receptor cells of the tongue, receptor proteins for bitter, sweet and umami activate PLC via the G protein α subunit α-gustducin, leading to the production of inositol 1,4,5-trisphosphate (IP_3) and release of Ca^{2+} from intracellular stores. Recent findings have identified TRPM5, a Ca^{2+}- and voltage-activated Ca^{2+}-impermeable cation channel, as a critical player in the signal transduction cascade downstream of the activation of the sweet, bitter and umami receptors (for a review, see [32]). Current models propose that activation of TRPM5 by Ca^{2+} released from intracellular stores leads to receptor cell depolarization and subsequent release of ATP via connexin/pannexin hemichannels. Released ATP then stimulates afferent taste fibers, either directly or via another type of taste cell, the presynaptic cell, which releases a second transmitter, serotonin [33–36] (Figure 2). In this functional context, the inherent heat sensitivity of TRPM5 explains why, for example, sweet taste is perceived as being more intense when the temperature of the food is increased [37].

TRPP3 (PKD2L1) and the PKD1-related protein PKD1L3 have recently been implicated in sour taste. Both proteins are coexpressed in a subset of taste receptor cells, and elimination of the cells that express TRPP3 fully abolished sour taste responses in mice. Moreover, one study reported that heterologous co-expression of TRPP3 and PKD1L3 resulted in sour-activated current responses, suggesting that together these proteins may form a functional sour receptor [38]. Importantly, sour responses can only be found in so-called presynaptic taste bud cells, type III cells, which, unlike type II cells, do not express receptors for sweet, bitter and umami taste. Presynaptic type III cells specifically respond to acid taste stimulation and release serotonin. However, the stimulus for acid taste is the membrane-permeant, uncharged acetic acid moiety and not the free protons, indicating that the 'sour' receptor is activated by intracellular acidification [39]. Type III cells express the candidate sour receptor TRPP3 (PKD2L1) [40].

Recent evidence indicates that the olfactory system also utilizes a TRPM5-dependent mechanism for the detection of chemical signaling molecules, such as pheromones, that resembles the TRPM5 function in the taste receptor cells involved in tasting sweet, bitter and umami [41].

Apart from the taste receptor cells and olfactory receptor neurons, several other types of chemosensory cell have been described in the oral and nasal cavities of mammals, many of which utilize TRP channels. TRPC2 is found in the rodent vomeronasal organ (VNO), which is the primary system for pheromone detection in many mammalians (not in primates): male TRPC2-deficient mice have an impaired sex discrimination and show less male–male aggression, and female TRPC2-deficient mice show a reduction in female-specific behavior, such as maternal aggression and lactating behavior. TRPC2 is activated by DAG subsequent to stimulation of G-protein-coupled pheromone receptors (for a review, see [42,43]).

So-called solitary chemoreceptor cells have been found at the surface of the nasal epithelium, the airways and even within the gastrointestinal tract. Intriguingly, a large population of these chemoreceptor cells expresses all taste receptors, the taste-cell-specific G-protein α-gustducin and the taste-cell-specific cation channel TRPM5. Although their function in chemosensation is currently under discussion [44], TRPM5-expressing solitary chemoreceptor cells were shown to be responsive to odorous/bitter chemicals and were found in close proximity to trigeminal nerve fibers [45].

Finally, the tongue, palate and nose are intensely innervated with free nerve endings of trigeminal neurons, and several compounds that we use to spice up our food directly act on these sensory neurons. Several TRP channels have been identified as the key chemoreceptors in these neurons, including: TRPV1, the receptor for 'hot' compounds in different types of pepper; TRPM8, the receptor for 'cool' compounds, such as menthol and eucalyptol; and TRPA1, the receptor for pungent compounds, such as mustard oil and cinnamon. The functioning of these TRP channels in trigeminal neurons

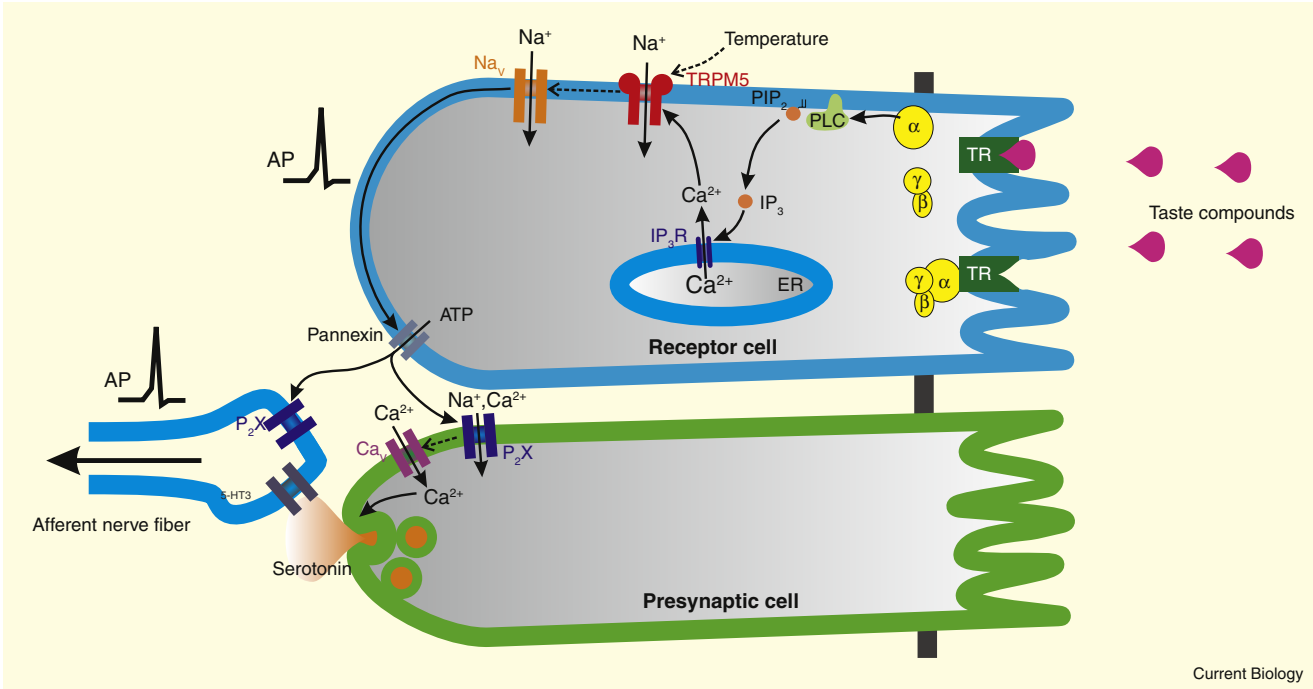

Figure 2. Model for the role of TRPM5 in the perception of sweet, bitter or umami taste.

In taste receptor cells of the tongue, taste compounds bind to G-protein-coupled taste receptor proteins (TRs), evoking bitter, sweet or umami taste sensation. These TRs include dimeric T1R2 + T1R3 for sweet taste and more than 36 T2Rs for bitter taste (for a review, see [36]). TRs activate phospholipase C (PLC) via the G protein α subunit α-gustducin, leading to the production of inositol 1,4,5-trisphosphate (IP_3) and release of Ca^{2+} from intracellular stores via the IP_3 receptor (IP_3R). The rise in intracellular Ca^{2+} opens TRPM5, leading to membrane depolarization, activation of voltage-gated Na^+ (Na_V) channels and generation of action potentials (AP). The depolarization results in the release of ATP, probably via pannexin-type hemichannels. The released ATP activates ionotropic purinergic (P_2X) receptors on neighboring presynaptic cells, leading to depolarization, activation of voltage-gated Ca^{2+} (Ca_V) channels and Ca^{2+}-dependent exocytosis of serotonin-containing vesicles. Afferent sensory fibers are depolarized by the serotonin release from the presynaptic cells (via ionotropic 5-HT3 receptors) and possibly by the ATP released from the taste receptor cells (via P_2X receptors).

is highly similar to that in dorsal root ganglion neurons whose endings terminate in the skin. Together, the trigeminal and dorsal root ganglion neurons constitute the primary sensory neurons of the somatosensory system, which will be discussed in more detail in the next section.

Touch and Somatosensation

The peripheral somatosensory system transmits information from sensory organs in the skin, muscles, joints, and viscera to the central nervous system. Herein, we only consider first-order neurons of the dorsal root and trigeminal nerves, which receive exteroceptive input. The term touch is commonly used in its broader somatosensory meaning and includes the submodalities mechanosensation, temperature sensation, chemosensation and nociception. The discovery that some members of the TRP channel superfamily function as receptor proteins in sensory neurons has initiated a re-evaluation of our understanding of molecular principles underlying somatosensation. Only the somatosensory system mediates such diverse physical stimuli and the involvement in several submodalities reflects the polymodal nature of individual TRP channels. Indeed, one type of receptor may be sensitive to several endogenous and exogenous stimuli, integrating these stimuli into a single signal that decides whether the membrane potential reaches the threshold for generation of patterns of electrical discharge. This stimulus integration is an outstanding example of signal processing at the level of the receptor protein, the site where sensation originates (Figure 3).

Skin mechanosensation is primarily mediated by diverse mechanosensors in the skin, such as Meissner's, Pacinian and Ruffini's corpuscles and Merkel receptors. Although TRP channels have been extensively discussed as candidate channels [24], an unequivocal mechanosensitive, depolarizing TRP channel has not yet been identified. By comparison, a role of TRP channels in nociception is well established. The cloning of the capsaicin receptor TRPV1 [46] has started a series of exciting discoveries that sharpened our understanding of excitatory mechanisms in sensory neurons. In dorsal root ganglion and trigeminal neurons TRPV1 was found to be a key player in the pain pathway. TRPV1 is mainly expressed in nociceptors, a subpopulation of small-diameter primary afferent neurons, in which it responds to several stimuli, such as capsaicin, temperatures in the noxious range (>43°C) or acidic pH, that evoke pain in psychophysical studies (for a review, see [47]). Activation of TRPV1 in peripheral nerve endings in the skin or mucous membranes promotes the influx of Na^+ and Ca^{2+}, depolarization and the release of neuropeptides like substance P and calcitonin gene-related peptide (CGRP) [48]. Some mediators of inflammation, such as arachidonic acid metabolites and endocannabinoids, can directly activate TRPV1, whereas other inflammatory components sensitize the channel, leading to thermal hyperalgesia (for a review, see [49]). Whereas TRPV1-deficient mice still show relatively normal sensitivity to acute heat stimuli, indicating that TRPV1 is not the sole heat receptor, these mice fail to develop thermal hyperalgesia after inflammation [50].

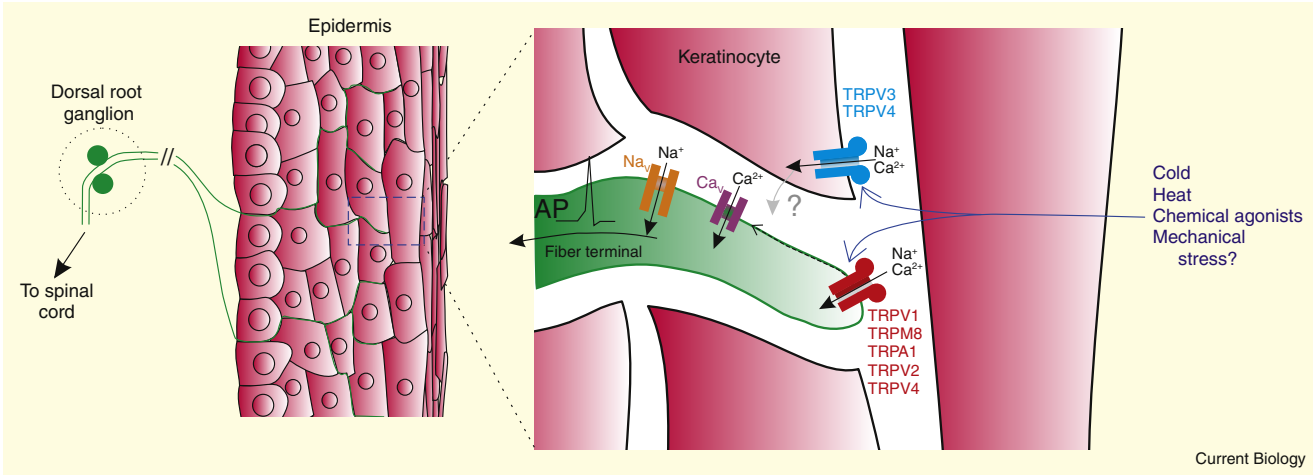

Figure 3. Model for the role of TRP channels detecting thermal, chemical and mechanical stimuli in the skin.

Free sensory nerve endings are located in the skin (left) and are coupled via the dorsal root sensory ganglia to the spinal cord for further information processing in the brain. An enlargement of the outer skin laminae is shown at the right. Physical and chemical stimuli can directly activate TRP channels in the free sensory nerve endings, causing depolarization of these fibers, activation of voltage-gated Na_V, Ca_V channels and generation of action potentials. In addition, TRPV3 and TRPV4 are expressed in keratinocytes, from which signal transduction to the DRG neurons may occur via a yet unresolved signal transduction pathway.

A second temperature-sensitive TRP channel, TRPM8, is now generally accepted to function as a cold sensor in the somatosensory system [51,52]. Like TRPV1, TRPM8 is a Ca^{2+}-permeable cation channel and provides excitatory input to primary afferent neurons that terminate in the skin and mucous membranes [51–54]. TRPM8 is activated by gentle cooling (<23°C), and several cooling compounds, such as menthol, icilin, eucalyptol, linalool, geraniol and hydroxycitronellal [51,52,55,56]. Low doses of menthol lower the threshold for cold activation [51,52,55], a principle humans experience when coming into contact with menthol, e.g. via candies or menthol cigarettes. TRPM8 seems to have a role in non-nociceptive perceptions but an additional input to the pain pathway is under current debate. Crosstalk between TRPM8-dependent sensory input and the pain pathway is very likely given that painful states can be perceived as being much milder when there is simultaneous TRPM8-dependent sensory input [57]. It is not clear on which level of the nervous system this crosstalk occurs; under normal conditions, TRPM8 is not coexpressed with TRPV1, ruling out receptor interference at the peripheral level.

Recent studies indicate that TRPM8 is not the sole menthol receptor, because TRPM8-deficient mice still have menthol-sensitive neurons [58,59]. Menthol may cause TRPM8-independent release of Ca^{2+} from intracellular stores [60], but TRPA1 was identified as an alternative molecular target for menthol [61]. TRPA1 is expressed in a subpopulation of TRPV1-expressing small-diameter nociceptors of the dorsal root, trigeminal, and nodose ganglia [62,63] and has attracted attention for its potential role in nociception and inflammatory pain. TRPA1 is a Ca^{2+}-permeable channel that acts downstream of receptors for inflammatory mediators (such as endocannabinoids and bradykinin) and serves as a detector of irritants, such as mustard oil, allicin, tear gas, α- and β-unsaturated aldehydes from cigarette smoke, and even of several general anesthetics used in surgery [64–69]. TRPA1 shows manifold modulatory mechanisms: thiol-reactive substances (allyl isothiocyanate from mustard and diallyl disulfide from garlic) and products of oxidative stress (e.g. hydrogen peroxide and endogenous alkenyl aldehydes) induce TRPA1 channel opening by covalent modification of cysteine residues of the channel protein [70]. In contrast, terpene alcohols, like menthol or thymol [61], are unlikely to modify proteins covalently and are capable of repeated activation of TRPA1. Interestingly, menthol and structurally related compounds were shown to have not only activatory but also inhibitory effects on TRPA1 channels [61,71]. TRPA1 activation substantially increases intracellular Ca^{2+} concentration [62,64] and thereby promotes neuronal excitation. Ca^{2+} was found to exert pronounced effects on the gating of TRPA1 [62,72] and might stimulate or sensitize TRPA1 and subsequently induce a desensitization process [62] that could be indispensable in preventing cellular Ca^{2+} overload. In addition to its role as a chemosensor, TRPA1 has also been proposed to act as a sensor for noxious cold. However, there are conflicting results with respect to both the intrinsic cold sensitivity of TRPA1 and its contribution to cold sensation *in vivo* [25,26]. Clearly, more research is required to determine whether TRPA1 contributes to thermosensation.

In addition to TRPV1, TRPM8 and TRPA1, three other channels of the TRPV family have been described to function in somatosensation, namely the heat-activated TRPV2, TRPV3 and TRPV4 channels. Interestingly, non-neuronal expression of these TRP channels also appears to play a role in environmental perception. For example, TRPV3 and TRPV4 are expressed in keratinocytes of the skin, where their activity might result in the stimulation of sensory neurons that contact these cells (Figure 3). TRPV3 is also expressed in sensory neurons, although the relevance of this expression is still under discussion and structures that promote excitatory contact between keratinocytes and sensory neurons remain elusive (for a recent review, see [73]).

Tuning the Senses by Modulating TRPs

Many sensory modalities can exhibit desensitization, a process whereby the response to a constant, invariant stimulus diminishes with time. For example, when stepping from

a darkened room into bright light, one is initially almost fully blinded, but gradually the eyes adapt to the new range of light intensities. In this case, an important mechanism leading to adaptation is the phosphorylation of rhodopsin and the subsequent binding of arrestin, leading to reduced light sensitivity of this light-sensitive GPCR [74]. Moreover, certain (patho)physiological conditions can lead to long-lasting increases in stimulus sensitivity, as exemplified by the well-known hypersensitivity of inflamed or injured tissue to mechanical and thermal stimuli [75].

Alterations in the perceived strength of an invariant stimulus can in principle be due to changes at the level of the receptor, or at the level of the downstream pathways or at the perceptual level in the CNS. It is becoming increasingly clear that several TRP channels are at the center of stimulus detection and that their modulation contributes significantly to the time- and stimulus-dependent alterations in sensory perception. Below we provide a brief overview of some more general mechanisms of TRP channel gating and modulation with potential relevance to sensory modulation.

Membrane Voltage

Although initially considered as rather insensitive to voltage, it is now well established that a significant subset of TRP channels exhibit intrinsic voltage dependence, including many channels involved in sensory perception [55,76,77]. Interestingly, the position of the voltage-dependent activation curve along the voltage axis is very flexible: ligands or changes in temperature can shift the midpoint of the activation curve by several hundreds of millivolts [55]. Recent evidence indicates that a region encompassing the fourth transmembrane segment is closely involved in the voltage sensing of TRPM8 [78], analogous to the well-studied voltage sensor region of voltage-gated K^+, Na^+ and Ca^{2+} channels. Interestingly, mutations in the region encompassing transmembrane (TM) domains 2–4 have been shown to alter the ligand affinity of different TRP channels, suggesting that these ligands act on the channel via a direct interaction with the voltage sensor [78]. It remains a matter of debate whether or not temperature-sensitive channels contain specific regions that endow them with steep thermosensitivity. (For a detailed survey of the mechanisms of voltage sensing and its relevance to TRP channels gating in response to thermal and chemical stimuli we refer the reader to recent reviews of this topic [73,79,80].) A physiological consequence of the voltage dependence of sensory TRP channels is that their sensitivity depends significantly on the resting membrane potential, such that a thermosensitive and/or chemosensitive TRP channel in a depolarized cell exhibits a higher stimulus sensitivity than the same TRP channel in a more hyperpolarized cell [55].

Membrane Phospholipids

Several recent studies have highlighted the involvement of membrane phospholipids in regulating TRP channel activity. In particular, many TRP channels appear to be highly sensitive to the cellular level of phosphatidylinositol 4,5-bisphosphate (PIP_2) [81]. PIP_2 is the most abundant acidic phospholipid and its concentration in the plasma membrane can change rapidly due to the action of different PLC isoforms and PI kinases/phosphatases, which can result in profound changes of the activity of TRP channels. Below, we briefly discuss how PIP_2 levels in sensory cells can tune their stimulus sensitivity. A more detailed overview of the TRP–PIP_2 connection can be found elsewhere [81,82].

The first evidence for PIP_2-dependent regulation of a TRP channel was obtained for TRPV1, which is sensitized by proalgesic agents such as nerve growth factor (NGF) or bradykinin. Evidence was presented that this sensitization was a result of these agents activating PLC and reducing plasma membrane PIP_2 levels, thereby relieving TRPV1 from tonic PIP_2-mediated inhibition. A carboxy-terminal region of TRPV1 rich in basic residues was found to be required for NGF-induced sensitization, which led to the suggestion that it functions as an inhibitory PIP_2-binding site [83]. However, more recent studies have challenged the view of an inhibitory effect of PIP_2 on TRPV1. First, it was found that, following TRPV1 activation, PIP_2 levels are strongly reduced and that the recovery from desensitization requires restoration of cellular PIP_2 levels [84]. Moreover, direct application of PIP_2 to the inner leaflet of TRPV1-expressing membranes leads to channel activation rather than inhibition, whereas sequestering PIP_2 using polylysine inhibits channel function [85]. Intriguingly, recent evidence suggests that PIP_2 may have a dual effect on TRPV1: inhibitory at low agonist concentrations and activatory in the presence of stronger TRPV1-activating stimuli [86]. On the basis of these newer data, it appears that changes in PIP_2 levels should no longer be considered to be the main mechanism of NGF-induced TRPV1 potentiation. An alternative mechanism has been proposed, whereby NGF receptor stimulation promotes the trafficking of TRPV1 to the plasma membrane via PI 3-kinase [85]. The effects of PIP_2 on TRPA1, which is co-expressed with TRPV1 in a subset of nociceptors, are also not yet fully understood. Activation of proteinase-activated receptor-2 (PAR2), a GPCR for proteinases such as trypsin and tryptase, was shown to sensitize TRPA1 in a PLC-dependent manner [87]. Similar increases in TRPA1 responses were obtained by sequestering PIP_2 with anti-PIP_2 antibody or polylysine, suggesting that receptor stimulation potentiates TRPA1 by relieving it from tonic PIP_2 inhibition [87], similar to what was initially proposed as a mechanism for NGF-induced sensitization of TRPV1 [88]. At this point, it is hard to provide a straightforward explanation for the conflicting data on PIP_2 modulation of TRPV1. It is important to note that many membrane-associated enzymes are sensitive to changes in membrane PIP_2 levels, several of which can directly or indirectly affect TRP channel function. For example, recent data show that the membrane protein Pirt interacts with both phosphoinositides and TRPV1, and that Pirt is required for the stimulatory effect of PIP_2 on TRPV1 activity [89]. Cell-specific variations in the level of such regulatory proteins may explain at least some of the discrepancies relating to the effects of PIP_2 on various TRP channels.

The effects of PIP_2 on the cold- and menthol-sensitive TRPM8 channel and on the taste-transducing TRPM5 channel are less controversial. In both channels, increased intracellular Ca^{2+} leads to channel desensitization, which can be attributed to activation of Ca^{2+}-dependent PLC (e.g. $PLC_{\delta 1}$), resulting in depletion of cellular PIP_2 and subsequent channel decay (for a detailed review, see [82]). PIP_2 depletion does not lead to full channel inactivity, but instead shifts the voltage dependence of channel activity to very positive potentials and reduces the sensitivity to ligands such as menthol (TRPM8) or Ca^{2+} (TRPM5) [90,91]. Evidence has been presented that positively charged residues in the TRP domain, which is located close to the carboxy-terminal end of TM6, may function as a stimulatory PIP_2-interacting site in these channels [91], although other clusters of positively

charged amino acids in the carboxyl terminus may also contribute [90]. Interestingly, ethanol was found to inhibit TRPM8 activity by directly interfering with the interaction between the channel and PIP_2 [92].

Phosphorylation

Activation of PLC not only results in breakdown of PIP_2 but also in the activation of protein kinase C (PKC). In the case of TRPV1, PKC activators can either activate TRPV1 or sensitize the channel for other stimuli such as heat or capsaicin, and a number of serine and threonine residues in the channel were identified as major PKC phosphorylation sites underlying these effects [93,94]. In contrast, TRPM8 is downregulated upon PKC activation, which, surprisingly, initiates the dephosphorylation of TRPM8 [95]. The identity of the kinases that mediate phosphorylation of TRPM8, and of the residues on the channel that are phosphorylated is currently unclear, as is the mechanism whereby PKC activity enhances dephosphorylation of TRPM8.

An additional pathway for the regulation of TRP channel activity following receptor stimulation occurs via protein kinase A (PKA). Activation of PKA, for example following stimulation with the inflammatory mediator prostaglandin E2, potentiates TRPV1 responses and counteracts channel desensitization, which could be attributed to the phosphorylation of a single amino-terminal serine residue [96]. The PKA-dependent modulation of TRPV1 requires anchoring of PKA to the channel via the A-kinase anchoring protein AKAP150 [97]. In contrast, PKA activation leads to desensitization of TRPM8 activity via an as yet unknown mechanism. It is interesting to note that both PKA- and PKC-dependent pathways have opposite effects on the heat-activated TRPV1 and the cold-activated TRPM8 [98].

Conclusions

TRP channels have revolutionized our understanding of sensory mechanisms. We must recognize, however, that TRP channels act in concert with other ion channels and in the context of a plethora of regulatory mechanisms. Obviously, some important sensory channels, including the mechanotransducing channels involved in hearing, balance or touch, have not been unequivocally identified, and it is currently questionable whether TRP channels are involved in these processes. The exact role of TRP channels in olfaction and vision remains to be investigated in depth. Our most advanced understanding of the sensory roles of TRP concerns nociception, temperature reception and taste. We certainly have to be careful not to overinterpret the role of TRP channels as global cell sensors, notwithstanding their unique properties as polymodal ion channels. Moreover, we have to face the difficulties in comparing data from expression systems with those from native sensory cells. In addition, investigations on sensory channels *in vivo* or *in vitro* often depend on knockout techniques or specific agonists, both of which are limited at this point. Ten years of sensory TRP channel research have brought some exciting answers to some thrilling questions. On the background of the few answers that we can already give, however, this review highlights that several crucial questions related to Aristotle's five senses remain to be solved.

References

1. Cosens, D.J., and Manning, A. (1969). Abnormal electroretinogram from a Drosophila mutant. Nature *224*, 285–287.
2. Montell, C., and Rubin, G.M. (1989). Molecular characterization of the Drosophila trp locus: a putative integral membrane protein required for phototransduction. Neuron *2*, 1313–1323.
3. Hardie, R.C., and Minke, B. (1992). The trp gene is essential for a light-activated Ca^{2+} channel in Drosophila photoreceptors. Neuron *8*, 643–651.
4. Cai, X. (2008). Unicellular Ca^{2+} signaling 'toolkit' at the origin of metazoa. Mol. Biol. Evol. *25*, 1357–1361.
5. Venkatachalam, K., and Montell, C. (2007). TRP channels. Annu. Rev. Biochem. *76*, 387–417.
6. Palmer, C.P., Zhou, X.L., Lin, J., Loukin, S.H., Kung, C., and Saimi, Y. (2001). A TRP homolog in Saccharomyces cerevisiae forms an intracellular Ca^{2+}-permeable channel in the yeast vacuolar membrane. Proc. Natl. Acad. Sci. USA *98*, 7801–7805.
7. Ward, A., Liu, J., Feng, Z., and Xu, X.Z. (2008). Light-sensitive neurons and channels mediate phototaxis in *C. elegans*. Nat. Neurosci., in press.
8. Sengupta, P. (2007). Generation and modulation of chemosensory behaviors in *C. elegans*. Pflugers. Arch. *454*, 721–734.
9. Kahn-Kirby, A.H., and Bargmann, C.I. (2006). TRP channels in *C. elegans*. Annu. Rev. Physiol. *68*, 719–736.
10. Brown, A.L., Ramot, D., and Goodman, M.B. (2008). Sensory transduction in Caenorhabditis elegans. In Sensing with Ion Channels, B. Martinac, ed. (Berlin-Heidelberg: Springer Verlag), pp. 201–219.
11. Li, W., Feng, Z., Sternberg, P.W., and Xu, X.Z. (2006). A *C. elegans* stretch receptor neuron revealed by a mechanosensitive TRP channel homologue. Nature *440*, 684–687.
12. Feng, Z., Li, W., Ward, A., Piggott, B.J., Larkspur, E.R., Sternberg, P.W., and Xu, X.Z. (2006). A *C. elegans* model of nicotine-dependent behavior: regulation by TRP-family channels. Cell *127*, 621–633.
13. McKemy, D.D. (2007). Temperature sensing across species. Pflugers. Arch. *454*, 777–791.
14. Hardie, R.C., and Postma, M. (2008). Phototransduction in Microvillar Photoreceptors of Drosophila and Other Invertebrates. In The Senses: A Comprehensive Reference, Vision I, Richard Masland and Thomas D. Albright, *vol. 1* (San Diego: Academic Press), pp. 77–130.
15. Wang, T., and Montell, C. (2007). Phototransduction and retinal degeneration in *Drosophila*. Pflugers. Arch. *454*, 821–847.
16. Leung, H.T., Tseng-Crank, J., Kim, E., Mahapatra, C., Shino, S., Zhou, Y., An, L., Doerge, R.W., and Pak, W.L. (2008). DAG lipase activity is necessary for TRP channel regulation in Drosophila photoreceptors. Neuron *58*, 884–896.
17. Kernan, M.J. (2007). Mechanotransduction and auditory transduction in Drosophila. Pflugers. Arch. *454*, 703–720.
18. Liu, L., Li, Y., Wang, R., Yin, C., Dong, Q., Hing, H., Kim, C., and Welsh, M.J. (2007). *Drosophila* hygrosensation requires the TRP channels water witch and nanchung. Nature *450*, 294–298.
19. Melyan, Z., Tarttelin, E.E., Bellingham, J., Lucas, R.J., and Hankins, M.W. (2005). Addition of human melanopsin renders mammalian cells photoresponsive. Nature *433*, 741–745.
20. Qiu, X., Kumbalasiri, T., Carlson, S.M., Wong, K.Y., Krishna, V., Provencio, I., and Berson, D.M. (2005). Induction of photosensitivity by heterologous expression of melanopsin. Nature *433*, 745–749.
21. Panda, S., Nayak, S.K., Campo, B., Walker, J.R., Hogenesch, J.B., and Jegla, T. (2005). Illumination of the melanopsin signaling pathway. Science *307*, 600–604.
22. Walker, R.G., Willingham, A.T., and Zuker, C.S. (2000). A Drosophila mechanosensory transduction channel. Science *287*, 2229–2234.
23. Corey, D.P., Garcia-Anoveros, J., Holt, J.R., Kwan, K.Y., Lin, S.Y., Vollrath, M.A., Amalfitano, A., Cheung, E.L., Derfler, B.H., and Duggan, A. (2004). TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. Nature *432*, 723–730.
24. Christensen, A.P., and Corey, D.P. (2007). TRP channels in mechanosensation: direct or indirect activation? Nat. Rev. Neurosci. *8*, 510–521.
25. Bautista, D.M., Jordt, S.E., Nikai, T., Tsuruda, P.R., Read, A.J., Poblete, J., Yamoah, E.N., Basbaum, A.I., and Julius, D. (2006). TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell *124*, 1269–1282.
26. Kwan, K.Y., Allchorne, A.J., Vollrath, M.A., Christensen, A.P., Zhang, D.S., Woolf, C.J., and Corey, D.P. (2006). TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. Neuron *50*, 277–289.
27. Tabuchi, K., Suzuki, M., Mizuno, A., and Hara, A. (2005). Hearing impairment in TRPV4 knockout mice. Neurosci. Lett. *382*, 304–308.
28. Nilius, B., Vriens, J., Prenen, J., Droogmans, G., and Voets, T. (2004). TRPV4 calcium entry channel: a paradigm for gating diversity. Am. J. Physiol. Cell Physiol. *286*, C195–C205.
29. Nakaya, K., Harbidge, D.G., Wangemann, P., Schultz, B.D., Green, E., Wall, S.M., and Marcus, D.C. (2007). Lack of pendrin HCO3- transport elevates vestibular endolymphatic [Ca^{2+}] by inhibition of acid-sensitive TRPV5 and TRPV6 channels. Am. J. Physiol. Renal. Physiol. *292*, F1314–F1321.
30. Cuajungco, M.P., and Samie, M.A. (2008). The varitint-waddler mouse phenotypes and the TRPML3 ion channel mutation: cause and consequence. Pflugers. Arch., in press.

31. Di Palma, F., Belyantseva, I., Kim, H., Vogt, T., Kachar, B., and Noben-Trauth, K. (2002). Mutations in Mcoln3 associated with deafness and pigmentation defects in varitint-waddler (Va) mice. Proc. Natl. Acad. Sci. USA *99*, 14994–14999.

32. Chandrashekar, J., Hoon, M.A., Ryba, N.J., and Zuker, C.S. (2006). The receptors and cells for mammalian taste. Nature *444*, 288–294.

33. Romanov, R.A., Rogachevskaja, O.A., Bystrova, M.F., Jiang, P., Margolskee, R.F., and Kolesnikov, S.S. (2007). Afferent neurotransmission mediated by hemichannels in mammalian taste cells. Embo. J. *26*, 657–667.

34. Huang, Y.J., Maruyama, Y., Dvoryanchikov, G., Pereira, E., Chaudhari, N., and Roper, S.D. (2007). The role of pannexin 1 hemichannels in ATP release and cell-cell communication in mouse taste buds. Proc. Natl. Acad. Sci. USA *104*, 6436–6441.

35. Zhang, Z., Zhao, Z., Margolskee, R., and Liman, E. (2007). The transduction channel TRPM5 is gated by intracellular calcium in taste cells. J. Neurosci. *27*, 5777–5786.

36. Roper, S.D. (2007). Signal transduction and information processing in mammalian taste buds. Pflugers Arch. *454*, 759–776.

37. Talavera, K., Yasumatsu, K., Voets, T., Droogmans, G., Shigemura, N., Ninomiya, Y., Margolskee, R.F., and Nilius, B. (2005). Heat activation of TRPM5 underlies thermal sensitivity of sweet taste. Nature *438*, 1022–1025.

38. Ishimaru, Y., Inada, H., Kubota, M., Zhuang, H., Tominaga, M., and Matsunami, H. (2006). Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. Proc. Natl. Acad. Sci. USA *103*, 12569–12574.

39. Huang, Y.A., Maruyama, Y., Stimac, R., and Roper, S.D. (2008). Presynaptic (Type III) cells in mouse taste buds sense sour (acid) taste. J. Physiol. (Lond) *586*, 2903–2912.

40. Kataoka, S., Yang, R., Ishimaru, Y., Matsunami, H., Sevigny, J., Kinnamon, J.C., and Finger, T.E. (2008). The candidate sour taste receptor, PKD2L1, is expressed by type III taste cells in the mouse. Chem. Senses. *33*, 243–254.

41. Lin, W., Margolskee, R., Donnert, G., Hell, S.W., and Restrepo, D. (2007). Olfactory neurons expressing transient receptor potential channel M5 (TRPM5) are involved in sensing semiochemicals. Proc. Natl. Acad. Sci. USA *104*, 2471–2476.

42. Zufall, F., Ukhanov, K., Lucas, P., Liman, E.R., and Leinders-Zufall, T. (2005). Neurobiology of TRPC2: from gene to behaviour. Pflugers Arch. *451*, 61–71.

43. Kimchi, T., Xu, J., and Dulac, C. (2007). A functional circuit underlying male sexual behaviour in the female mouse brain. Nature *448*, 1009–1014.

44. Gulbransen, B.D., Clapp, T.R., Finger, T.E., and Kinnamon, S.C. (2008). Nasal solitary chemoreceptor cell responses to bitter and trigeminal stimulants *in vitro*. J. Neurophysiol. *99*, 2929–2937.

45. Lin, W., Ogura, T., Margolskee, R.F., Finger, T.E., and Restrepo, D. (2007). TRPM5-expressing solitary chemosensory cells respond to odorous irritants. J. Neurophysiol. *98*, 1451–1460.

46. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature *389*, 816–824.

47. Tominaga, M., and Tominaga, T. (2005). Structure and function of TRPV1. Pflugers Arch. *451*, 143–150.

48. Zeilhofer, H.U., Kress, M., and Swandulla, D. (1997). Fractional Ca^{2+} currents through capsaicin- and proton-activated ion channels in rat dorsal root ganglion neurones. J. Physiol. *503*, 67–78.

49. Planells-Cases, R., Garcia-Sanz, N., Morenilla-Palao, C., and Ferrer-Montiel, A. (2005). Functional aspects and mechanisms of TRPV1 involvement in neurogenic inflammation that leads to thermal hyperalgesia. Pflugers Arch. *451*, 151–159.

50. Caterina, M.J., Leffler, A., Malmberg, A.B., Martin, W.J., Trafton, J., Petersen-Zeitz, K.R., Koltzenburg, M., Basbaum, A.I., and Julius, D. (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science *288*, 306–313.

51. Peier, A.M., Moqrich, A., Hergarden, A.C., Reeve, A.J., Andersson, D.A., Story, G.M., Earley, T.J., Dragoni, I., McIntyre, P., and Bevan, S. (2002). A TRP channel that senses cold stimuli and menthol. Cell *108*, 705–715.

52. McKemy, D.D., Neuhausser, W.M., and Julius, D. (2002). Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature *416*, 52–58.

53. Abe, J., Hosokawa, H., Okazawa, M., Kandachi, M., Sawada, Y., Yamanaka, K., Matsumura, K., and Kobayashi, S. (2005). TRPM8 protein localization in trigeminal ganglion and taste papillae. Brain. Res. Mol. Brain. Res. *136*, 91–98.

54. Nilius, B., and Voets, T. (2007). Neurophysiology: channelling cold reception. Nature *448*, 147–148.

55. Voets, T., Droogmans, G., Wissenbach, U., Janssens, A., Flockerzi, V., and Nilius, B. (2004). The principle of temperature-dependent gating in cold- and heat-sensitive TRP channels. Nature *430*, 748–754.

56. Chuang, H.H., Neuhausser, W.M., and Julius, D. (2004). The super-cooling agent icilin reveals a mechanism of coincidence detection by a temperature-sensitive TRP channel. Neuron *43*, 859–869.

57. Proudfoot, C.J., Garry, E.M., Cottrell, D.F., Rosie, R., Anderson, H., Robertson, D.C., Fleetwood-Walker, S.M., and Mitchell, R. (2006). Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. Curr. Biol. *16*, 1591–1605.

58. Colburn, R.W., Lubin, M.L., Stone, D.J., Jr., Wang, Y., Lawrence, D., D'Andrea, M.R., Brandt, M.R., Liu, Y., Flores, C.M., and Qin, N. (2007). Attenuated Cold Sensitivity in TRPM8 Null Mice. Neuron *54*, 379–386.

59. Dhaka, A., Murray, A.N., Mathur, J., Earley, T.J., Petrus, M.J., and Patapoutian, A. (2007). TRPM8 Is Required for Cold Sensation in Mice. Neuron *54*, 371–378.

60. Mahieu, F., Owsianik, G., Verbert, L., Janssens, A., De Smedt, H., Nilius, B., and Voets, T. (2007). TRPM8-independent menthol-induced Ca2+ release from endoplasmic reticulum and golgi. J. Biol. Chem. *282*, 3325–3336.

61. Karashima, Y., Damann, N., Prenen, J., Talavera, K., Segal, A., Voets, T., and Nilius, B. (2007). Bimodal action of menthol on the transient receptor potential channel TRPA1. J. Neurosci. *27*, 9874–9884.

62. Nagata, K., Duggan, A., Kumar, G., and Garcia-Anoveros, J. (2005). Nociceptor and hair cell transducer properties of TRPA1, a channel for pain and hearing. J. Neurosci. *25*, 4052–4061.

63. Story, G.M., Peier, A.M., Reeve, A.J., Eid, S.R., Mosbacher, J., Hricik, T.R., Earley, T.J., Hergarden, A.C., Andersson, D.A., Hwang, S.W., *et al*. (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell *112*, 819–829.

64. Jordt, S.E., Bautista, D.M., Chuang, H.H., McKemy, D.D., Zygmunt, P.M., Hogestatt, E.D., Meng, I.D., and Julius, D. (2004). Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature *427*, 260–265.

65. Bandell, M., Story, G.M., Hwang, S.W., Viswanath, V., Eid, S.R., Petrus, M.J., Earley, T.J., and Patapoutian, A. (2004). Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. Neuron *41*, 849–857.

66. Bautista, D.M., Movahed, P., Hinman, A., Axelsson, H.E., Sterner, O., Hogestatt, E.D., Julius, D., Jordt, S.E., and Zygmunt, P.M. (2005). Pungent products from garlic activate the sensory ion channel TRPA1. Proc. Natl. Acad. Sci. USA *102*, 12248–12252.

67. Macpherson, L.J., Geierstanger, B.H., Viswanath, V., Bandell, M., Eid, S.R., Hwang, S., and Patapoutian, A. (2005). The pungency of garlic: activation of TRPA1 and TRPV1 in response to allicin. Curr. Biol. *15*, 929–934.

68. Matta, J.A., Cornett, P.M., Miyares, R.L., Abe, K., Sahibzada, N., and Ahern, G.P. (2008). General anesthetics activate a nociceptive ion channel to enhance pain and inflammation. Proc. Natl. Acad. Sci. USA *105*, 8784–8789.

69. Andre, E., Campi, B., Materazzi, S., Trevisani, M., Amadesi, S., Massi, D., Creminon, C., Vaksman, N., Nassini, R., Civelli, M., *et al*. (2008). Cigarette smoke-induced neurogenic inflammation is mediated by alpha,beta-unsaturated aldehydes and the TRPA1 receptor in rodents. J. Clin. Invest., in press.

70. Hinman, A., Chuang, H.H., Bautista, D.M., and Julius, D. (2006). TRP channel activation by reversible covalent modification. Proc. Natl. Acad. Sci. USA *103*, 19564–19568.

71. Macpherson, L.J., Hwang, S.W., Miyamoto, T., Dubin, A.E., Patapoutian, A., and Story, G.M. (2006). More than cool: Promiscuous relationships of menthol and other sensory compounds. Mol. Cell Neurosci. *32*, 335–343.

72. Doerner, J.F., Gisselmann, G., Hatt, H., and Wetzel, C.H. (2007). Transient receptor potential channel A1 is directly gated by calcium ions. J. Biol. Chem. *282*, 13180–13189.

73. Talavera, K., Nilius, B., and Voets, T. (2008). Neuronal TRP channels: thermometers, pathfinders and life-savers. Trends Neurosci. *31*, 287–295.

74. Ridge, K.D., Abdulaev, N.G., Sousa, M., and Palczewski, K. (2003). Phototransduction: crystal clear. Trends. Biochem. Sci. *28*, 479–487.

75. Julius, D., and Basbaum, A.I. (2001). Molecular mechanisms of nociception. Nature *413*, 203–210.

76. Nilius, B., Talavera, K., Owsianik, G., Prenen, J., Droogmans, G., and Voets, T. (2005). Gating of TRP channels: a voltage connection? J. Physiol. *567*, 35–44.

77. Voets, T., Talavera, K., Owsianik, G., and Nilius, B. (2005). Sensing with TRP channels. Nat. Chem. Biol. *1*, 85–92.

78. Voets, T., Owsianik, G., Janssens, A., Talavera, K., and Nilius, B. (2007). TRPM8 voltage sensor mutants reveal a mechanism for integrating thermal and chemical stimuli. Nat. Chem. Biol. *3*, 174–182.

79. Nilius, B., Talavera, K., Owsianik, G., Prenen, J., Droogmans, G., and Voets, T. (2005). Gating of TRP channels: a voltage connection? J. Physiol. (Lond) *567*, 33–44.

80. Talavera, K., Voets, T., and Nilius, B. (2008). Mechanisms of thermosensation in TRP channels. In Sensing with Ion Channels, *vol.*, B. Martinac, ed. (Berlin-Heidelberg: Springer), pp. 101–120, Springers Series in Biophysics. pp. 101–120.

81. Voets, T., and Nilius, B. (2007). Modulation of TRPs by PIPs. J. Physiol. *582*, 939–944.

82. Rohacs, T., and Nilius, B. (2007). Regulation of transient receptor potential (trp) channels by phosphoinositides. Pflugers Archiv. *455*, 157–168.

83. Prescott, E.D., and Julius, D. (2003). A modular PIP_2 binding site as a determinant of capsaicin receptor sensitivity. Science *300*, 1284–1288.

84. Liu, B., Zhang, C., and Qin, F. (2005). Functional recovery from desensitization of vanilloid receptor TRPV1 requires resynthesis of phosphatidylinositol 4,5-bisphosphate. J. Neurosci. *25*, 4835–4843.

85. Stein, A.T., Ufret-Vincenty, C.A., Hua, L., Santana, L.F., and Gordon, S.E. (2006). Phosphoinositide 3-Kinase Binds to TRPV1 and Mediates NGF-stimulated TRPV1 Trafficking to the Plasma Membrane. J. Gen. Physiol. *128*, 509–522.

86. Lukacs, V., Thyagarajan, B., Varnai, P., Balla, A., Balla, T., and Rohacs, T. (2007). Dual regulation of TRPV1 by phosphoinositides. J. Neurosci. *27*, 7070–7080.

87. Dai, Y., Wang, S., Tominaga, M., Yamamoto, S., Fukuoka, T., Higashi, T., Kobayashi, K., Obata, K., Yamanaka, H., and Noguchi, K. (2007). Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. J. Clin. Invest. *117*, 1979–1987.

88. Chuang, H.H., Prescott, E.D., Kong, H., Shields, S., Jordt, S.E., Basbaum, A.I., Chao, M.V., and Julius, D. (2001). Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4,5)P2-mediated inhibition. Nature *411*, 957–962.

89. Kim, A.Y., Tang, Z., Liu, Q., Patel, K.N., Maag, D., Geng, Y., and Dong, X. (2008). Pirt, a phosphoinositide-binding protein, functions as a regulatory subunit of TRPV1. Cell *133*, 475–485.

90. Nilius, B., Mahieu, F., Prenen, J., Janssens, A., Owsianik, G., Vennekens, R., and Voets, T. (2006). The Ca2+-activated cation channel TRPM4 is regulated by phosphatidylinositol 4,5-biphosphate. EMBO J. *25*, 467–478.

91. Rohacs, T., Lopes, C.M., Michailidis, I., and Logothetis, D.E. (2005). PI(4,5)P2 regulates the activation and desensitization of TRPM8 channels through the TRP domain. Net. Neurosci. *8*, 626–634.

92. Benedikt, J., Teisinger, J., Vyklicky, L., and Vlachova, V. (2007). Ethanol inhibits cold-menthol receptor TRPM8 by modulating its interaction with membrane phosphatidylinositol 4,5-bisphosphate. J. Neurochem. *100*, 211–224.

93. Bhave, G., Hu, H.J., Glauner, K.S., Zhu, W., Wang, H., Brasier, D.J., Oxford, G.S., and Gereau, R.Wt. (2003). Protein kinase C phosphorylation sensitizes but does not activate the capsaicin receptor transient receptor potential vanilloid 1 (TRPV1). Proc. Natl. Acad. Sci. USA *100*, 12480–12485.

94. Premkumar, L.S., and Ahern, G.P. (2000). Induction of vanilloid receptor channel activity by protein kinase C. Nature *408*, 985–990.

95. Premkumar, L.S., Raisinghani, M., Pingle, S.C., Long, C., and Pimentel, F. (2005). Downregulation of transient receptor potential melastatin 8 by protein kinase C-mediated dephosphorylation. J. Neurosci. *25*, 11322–11329.

96. Bhave, G., Zhu, W., Wang, H., Brasier, D.J., Oxford, G.S., and Gereau. (2002). RWt: cAMP-dependent protein kinase regulates desensitization of the capsaicin receptor (VR1) by direct phosphorylation. Neuron *35*, 721–731.

97. Jeske, N.A., Diogenes, A., Ruparel, N.B., Fehrenbacher, J.C., Henry, M., Akopian, A.N., and Hargreaves, K.M. (2008). A-kinase anchoring protein mediates TRPV1 thermal hyperalgesia through PKA phosphorylation of TRPV1. Pain, epub ahead of print.

98. De Petrocellis, L., Starowicz, K., Moriello, A.S., Vivese, M., Orlando, P., and Di Marzo, V. (2007). Regulation of transient receptor potential channels of melastatin type 8 (TRPM8): effect of cAMP, cannabinoid CB(1) receptors and endovanilloids. Exp. Cell Res. *313*, 1911–1920.

99. Montell, C. (2005). The TRP superfamily of cation channels. Sci. STKE. *2005*, re3.