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TRP CHANNELS AS BIOLOGICAL SENSORS.

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INTRODUCTION.

TRP is the most recently discovered family of ion channels and display the largest structure and function diversity among ion channels. Most TRP channels are key elements in sensory cells, where they are involved in the response to a broad range of external stimuli such as light, sound, chemicals, temperature and touch. In addition, cells detect changes in their local environment, like osmolarity and oxidative stress, by means of TRP channels. They have been found in eukaryotes like yeasts, worms, insects, fishes, birds, and mammals. In mammals, they are present in a wide range of organs and cells including central and peripheral nervous system.

TRP channels were discovered in *Drosophila* photoreceptors, in a mutant that elicits a transient rather than maintained receptor potential in response to a sustained light stimulus. For this reason, this gene was termed transient receptor potential or trp. This mutation causes a ~10-fold reduction in the light induced Ca^{2+} influx to the photoreceptor (3, 6).

TRP structural features.

It is thought that TRP channels form tetrameric assemblies with different subunit composition (homo and heterotetramers). Although the members of this family generally share low sequence identity, they display a predicted topology of six transmembrane segments (S1-S6), a pore forming loop between S5 and S6 and intracellularly located NH_2 and COOH termini domains. The charged residues present in the fourth segment (S4) of voltage-gated channels that normally participate in voltage sensing, are replaced by non-charged amino acids in TRP channels. Therefore, TRP channels are not voltage-gated, although some of them acquire voltage dependence through pore blocking by divalent cations like Ca^{2+} and Mg^{2+}, whereas others display voltage regulation. In any case, voltage dependence of TRP channels is a matter of intense ongoing discussions. Most functionally characterized TRP channels are unselective for monovalent and divalent cations, although some (TRPV5 and TRPV6) present a high relative permeability for Ca^{2+} over monovalent cations and a few (TRPM4 and TRPM5) are only permeable to monovalent cations (7, 10).

One important restriction for the study of TRP channels is that no specific blockers have feen found for them. And since they have never been crystallized, the design of specific inhibitors remains poorly developed. To date, the only crystallized structure of TRP channels is the ankyrin repeat domain of the TRPV1, TRPV2 and TRPV6 channels (8, 19) and the atypical serine/threonine kinase domain of TRPM7 (28). This domain has raised

high interest for the enzymatic activity of 279 of its amino acids, extending from residue 1549 to 1828, in the COOH terminal.

Classes of TRP channels.

TRP channels have been divided into two major groups according to their topological similarities, and into seven subfamilies by sequence homology **(Figure 1)**. Group 1 is formed by TRPC (canonical), TRPV (vanilloid), TRPM (melastatine), TRPN (NOMP or no mechanoreceptor potential) and TRPA (ankyrin). Group 1 TRP channels share significant sequence identity in their transmembrane domains. TRPC, TRPM and TRPN (except for *Drosophila* NOMPC) present a TRP domain, which consists of a highly conserved sequence of 23-25 amino acids, located C-terminal to the sixth transmembrane domain. No role has been ascribed to the TRP domain. Group 1 channels (except for TRPM) have in common the presence of at least three ankyrin repeats in the N-terminal domain (21). Ankyrin repeats are 33 amino acid sequences that participate in protein-protein interactions and cytoskeleton anchorage (14). A remarkable feature of some TRPM channels is a functional intracellular enzymatic domain in the C-terminal. Such is the case of TRPM2, which contains a pyrophosphatase domain, and TRPM6 and TRPM7, which exhibit a kinase domain. Another TRP channels feature is the presence of phosphorylation sites involved in the regulation of the channel and in functional interactions with other proteins.

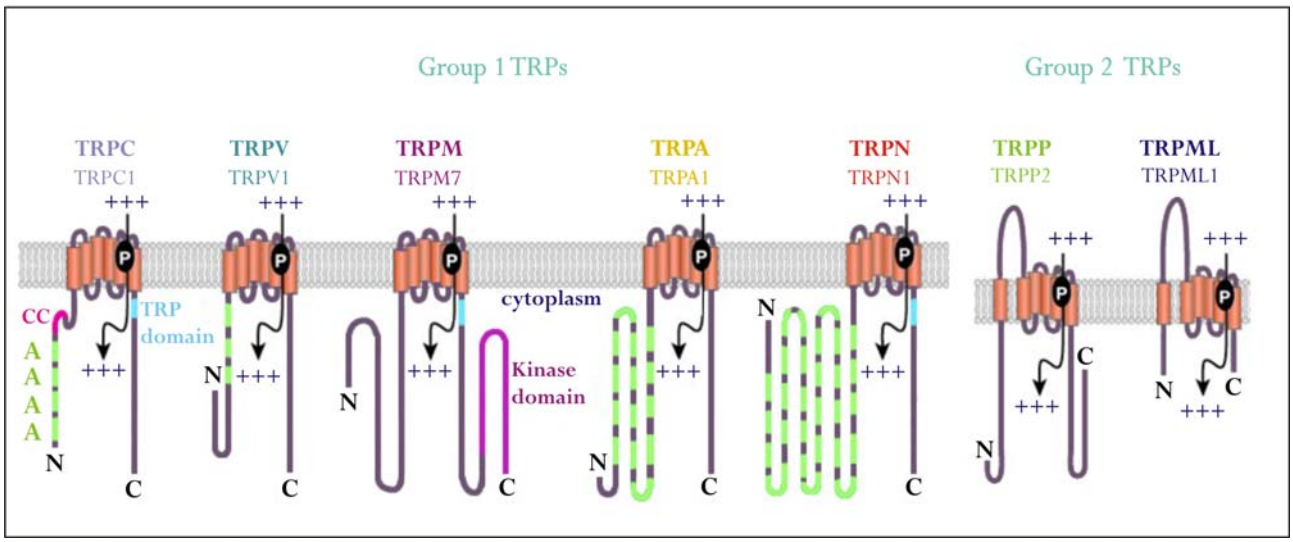

Figure 1. *Diversity of TRP channels structures. (a) Subfamilies of Group 1 TRPs. (b) Subfamilies of Group 2 TRPs . The following domains are indicated: A, ankyrin repeats; CC, coiled-coil domain; protein kinase domain; TRP domain. Also shown are transmembrane segments (vertical rectangles) and pore loop (P), allowing cations influx (+++).* ***Adapted from Kartik Venkatachalam and Craig Montell, Annu. Rev. Biochem. 2007. 76:387–417.***

Interestingly, Group I channels TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1 are expressed in sensory neurons of the dorsal root ganglia and play important roles in nociception. For this reason, these channels are promising targets for the design of novel analgesic drugs. The contribution of TRP channels to pain sensation and disease makes them very attractive targets for medical research.

Group 2 is formed by TRPP (polycystin) and TRPML (mucolipin) subfamilies. They have been poorly characterized and were included in a separate group due to their low sequence and topological similarities with the channels of Group 1. Their most striking feature is the presence of a long extracellular loop between the first and second transmembrane domains, which is missing in Group 1 members. TRPP channels are divided in TRPP1-like and TRPP2-like. TRPP1 proteins are strikingly different to other TRP channels in that they display 11 membrane-spanning segments (15) and a long extracellular domain (3,000 amino acids) containing conserved polycystin motifs of unknown function. TRPP2-like proteins have, like other TRPs, intracellular NH_2 and COOH termini and a predicted topology of six transmembrane domains. They possess a coiled-coil structure in their COOH terminus which mediates interactions with TRPP1-like channels and other proteins (15). The three members of TRPML subfamily are poorly characterized, but TRPML1 is thought to be localized in late endosomes and lysosomes.

I. GROUP 1 TRP CHANNELS.

TRPC.

TRPC channels comprise nine members, TRPC1-7, plus *Drosophila* TRP and TRPL. TRPC are found in worms, flies and mammals. In mammals, it is found in brain, heart, testis, ovaries, lung, retina, endothelia and adrenal glands. They partake in multiple physiological functions such as neuronal excitability in Purkinje cells, acrosome reaction in sperm cells, pheromone response, vasorelaxation and neurotransmitter release. They represent an important Ca^{2+} source for cells and have also been associated with Ca^{2+} oscillations. Their gating mechanism is related to phospholipase C (PLC) activity, which releases the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG) from the membrane phospholipid, phosphatidyl inositol biphosphate (PIP_2). There is a big controversy concerning the activation mechanism of these and other TRP channels, because it is still unclear whether DAG or its metabolic products, the polyunsaturated fatty acids (PUFAs), are the direct activators, or if the change in the lipid composition of the membrane surrounding these channels triggers their opening (25). More investigation is needed for determining their activation mechanism. There are other identified factors that also participate in TRPC channel opening **(Figure 2)**. Some of these channels are coupled to the endoplasmic reticulum (ER) membrane such that their gating is linked to Ca^{2+} depletion of this Ca^{2+} store, for which they are known as store operated channels (SOCs). Other TRPC channels are activated by plasma membrane insertion from intracellular vesicular compartments (TRPC3, TRPC4 and TRPC5).

TRPV.

The TRPV subfamily consists of six members found in worms, flies and mammals. Nanchung and OSM-9 have only been found in D. *melanogaster* and *C. elegans*, respectively. In mammals, they are expressed in sensory neurons of trigeminal and dorsal root ganglia (also known as nociceptors), urinary bladder, spleen, liver, intestine, placenta, kidney, lung and testis (25). Like TRPC channels, their gating is related to PLC activity. TRPV1-4 sense high temperatures, in the range from heat (>39ºC) to noxious heat (>43ºC). TRPV1 behaves as an intriguingly multi-signal integrator in its physiological

environment, as the binding of different ligands can modulate its affinity for other ligands. In addition to heat, it is activated by organic compounds like capsaicin, camphor, piperine, anandamide, among other compounds, and can be modulated by pH **(Figure 2)**. Protons (pH ≤5.9) reduce TRPV1 temperature threshold and enable it to be active at room temperature (24). Another modulator of TRPV1 is PIP_2. Depletion of this lipid potentiates the capsaicin-evoked response and decreases the temperature threshold (20). It is noteworthy that heat and irritant compounds like capsaicin and low pH act synergistically, increasing the maximal TRPV1-dependent membrane conductance. This is also significant because TRPV1 gating can be modulated by physiological conditions during inflammatory pain processes (24), resulting in the release of substance P and calcitonine gene-related peptide, which in turn increases blood flow and induces edema. Another example of multiple signal integration is TRPV4, where each activation mode involves different mechanisms, since a point mutation in the third transmembrane domain inhibits its activation by heat, but not by cell swelling or arachidonic acid (27). TRPV5 and TRPV6 represent two highly homologous members within this family. Together with *Drosophila* photoreceptors TRP, these two channels exhibit the highest Ca^{2+} permeability of all TRP channels ($pCa^{2}+/pNa^{+}>100$), and are constitutively active at physiological membrane potentials (26). They participate in Ca^{2+} homeostasis in the duodenum, jejunum, placenta, pancreas and prostate, and are responsible for Ca^{2+} reabsorption in the kidneys.

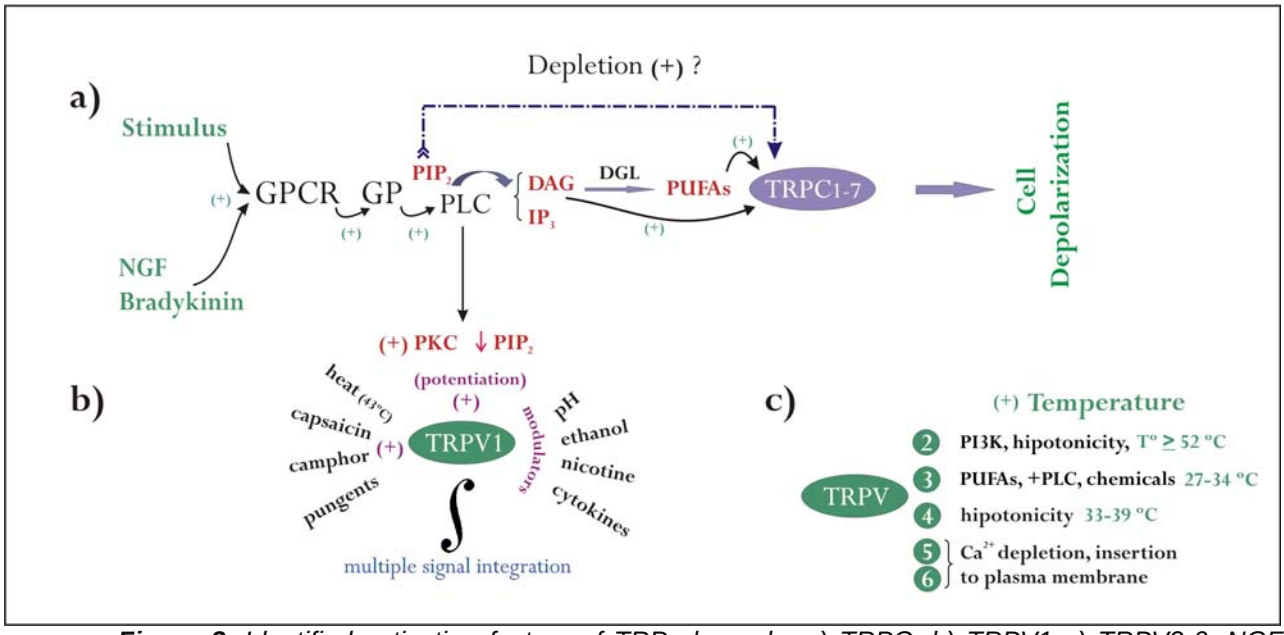

Figure 2. *Identified activating factors of TRP channels. a) TRPC, b) TRPV1 c) TRPV2-6. NGF, Nerve Growth Factor; GPCR, G Protein Coupled Receptor; GP, G-Protein; PLC, Phospholipase C; DAG, Diacylglycerol; IP_3, Inositol 1,4,5-trisphosphate; PIP_2, Phosphoinositide-4,5-bisphosphate; DGL, Diacylglycerol Lipase; PUFAs, Polyunsaturated Fatty Acids; PKC, Protein Kinase C; Phosphoinositide 3-kinase.*

TRPM.

TRPM, the most recently identified TRP subfamily, is comprised of eight members in mammals, where they are expressed in brain, kidney, heart, prostate, intestine, liver and lung. They are also found in *Drosophila* and *C. elegans*. The first one to be discovered was TRPM1, which gave the name melastatine to this subfamily because its expression

level inversely correlates with the metastatic potential of some melanomic cell lines (4). TRPM2 is a channel presenting enzymatic properties (chanzyme) in its C-terminal domain. This is an ADP-ribose pyrophosphatase domain (18) which has been implicated in oxidative and nitrosative stress. These channels operate as cellular redox sensors, being activated by peroxide and other agents **(Figure 3)** that generate reactive oxygen or nitrogen species (5). TRPM4 (16) and TRPM5 (7) are unusual among TRPs in that they are voltage-modulated, Ca^{2+}-activated, monovalent cation-selective channels (VCAM). TRPM4 and TRPM5 are also activated by PIP_2, which can reverse the Ca^{2+} dependent desensitization of these channels (11, 29). TRPM5 is a temperature sensor, but unlike TRPV channels, it responds to low and moderate temperatures (15-35ºC) (23). It is highly abundant in rodent chemosensory organs including taste buds, olfactory epithelium and vomeronasal organ (9).

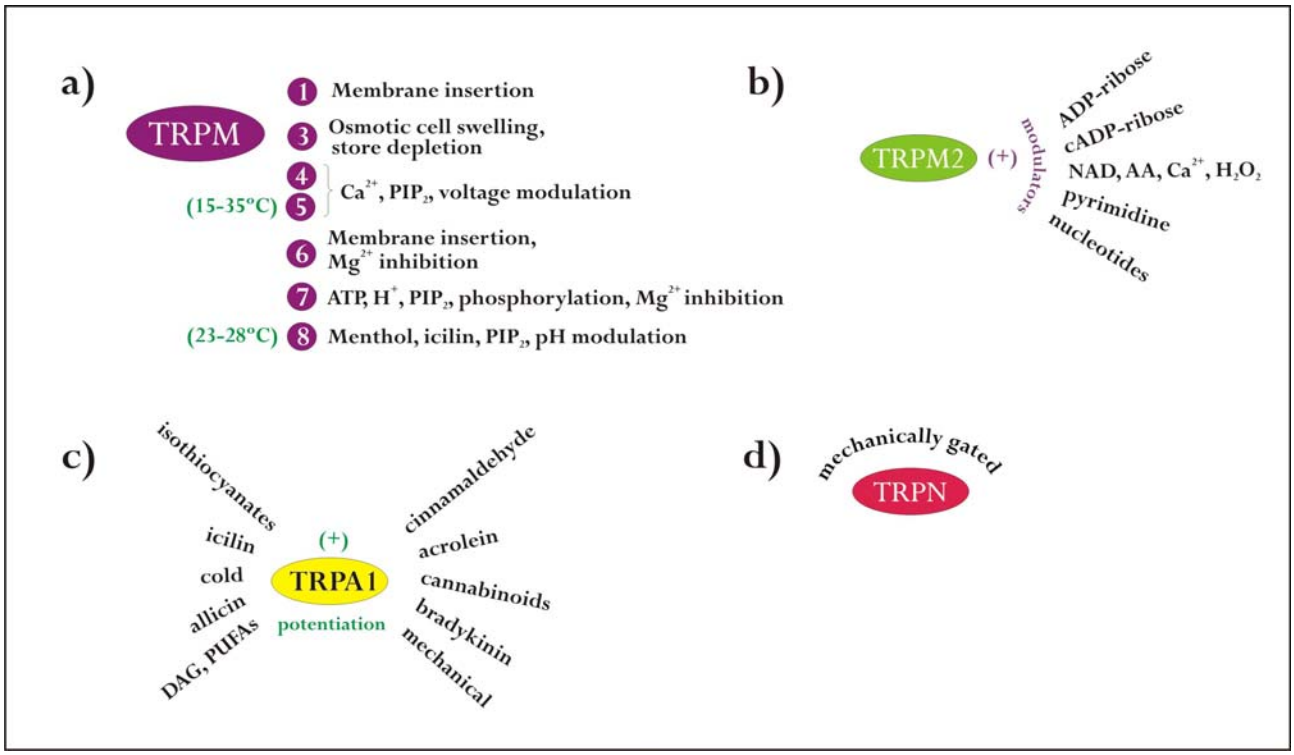

Figure 3. *Identified activating factors of TRP channels. a) TRPM1,3-8, b) TRPM2, c) TRPA1 and d) TRPN channels. PIP_2, Phosphoinositide-4,5-bisphosphate; DAG, Diacylglycerol; PUFAs, Polyunsaturated Fatty Acids; AA, arachidonic acid; NAD, Nicotinamide adenine dinucleotide.*

TRPM6 and TRPM7 bear atypical kinase domains in their C-terminal. Both channels are permeant to a wide range of divalent cations, including trace metals, and hence, they are very important for Mg^{2+} epithelial reabsorption and homeostasis. TRPM7 is a polymodal regulated channel, whose activity is increased by low pH, ATP, lipids and insertion of trafficking vesicles in the plasma membrane. Like TRPV1, TRPM8 exhibits multiple signal integration mechanisms. This channel responds to moderate temperatures (<23-28ºC) and intriguingly, also to compounds that evoke a cool sensation, like menthol, eucalyptol and icilin (13, 17). As determined by point mutations, temperature acts in a different domain than menthol, as one effect persists independently of the other (1). Low pH, capsaicin and high temperature shift the G-V curve of TRPV1 to more negative voltages. The same behaviour is exhibited by TRPM8 to low temperatures and menthol, as low temperatures increase the maximal TRPM8-dependent membrane conductance and shifts the voltage dependence towards negative potentials (2). An allosteric model has

been proposed to explain this interesting gating mechanism (2). According to this model, temperature and voltage act independently on TRPM8 gating, yet they have mutual allosteric effects. The same model has been successfully applied to TRPV1 to account for pH, temperature and capsaicin dependence (12). Altogether, these data suggest that polymodal TRPs may be equipped with multiple independent sensors that act concertedly to gate the channels .

TRPA.

The TRPA subfamily has only one member in mammals, two in *C. elegans* and zebrafish, and four in *Drosophila*. Like TRPN channels, TRPAs have several intracellular ankyrin repeats in their NH2 terminal domain that may be anchoring the protein to other signalling proteins. Their activation depends on the DAG branch of the PLC pathway. They respond to irritants, pungent compounds like horseradish, wasabi active ingredients, mustard, garlic, cinnamon and cannabinoids **(Figure 3)**. It is expressed in hair cells and sensory DRG neurons in mammals. Their temperature sensitivity is still not completely resolved, although it is established that *Drosophila* homologs are thermosensors.

TRPN.

The TRPN subfamily has not been detected in mammals, but is present in *Drosophila*, zebrafish and worm. It has been proposed to be sensitive to mechanical stimuli and is expressed in mechanosensory neurons of the ear and eye (22).

II. GROUP 2 TRP CHANNELS.

TRPP and TRPML.

TRPP and TRPML subfamilies include three mammalian members and one in *Drosophila* and *C. elegans.* TRPP channels may be the most primitive members of the TRP family, as they are also found in sea urchins and yeast. They are widely expressed, even though their highest expression is found in kidney and heart. Their activity is modulated by insertion in the plasma membrane and mechanical stimuli (25).

In mammals, TRPML channels are expressed in brain, heart and skeletal muscle. TRPML1 and TRPML2 are found in lysosome membranes, where they permeate protons out of the organelle, preventing it from over-acidification. TRPML1 has a lipase domain with unknown function between its S1 and S2 segments. TRPML3 is found in ER membranes when heterologously expressed in cultured cells.

TRPP and TRPML channels are attracting increasing interest because of their involvement in several human diseases (15). This plethora of disorders includes cardiovascular diseases, sensory deficits, abnormal sensitivity to pain, gastrointestinal diseases, renal and neurodegenerative diseases, certain types of cancer, asthma and even psychiatric diseases.

Concluding Remarks.

TRP channels are specialized polymodal molecular sensors that function as multiple signal integrators of external and internal signals, as well as important signalling elements for cell physiology and homeostasis. In order to achieve such physiological functions, their responses should be transient, spatially confined and highly specific, greatly amplified and in some cases their activation must occur extremely fast. TRP channels may integrate in one single protein several characteristics of signalling systems, including a plasma membrane ion channel that can be directly or indirectly gated by a sensory stimulus, an enzyme with a catalytic domain and an effector of a signal-G protein coupled pathway which can in turn stimulate other target proteins (enzymes or ion channels).

What makes TRPs so special in comparison to other channels? Perhaps the answer relies on their structural versatility within a common general scheme **(Figure 1)**, their expression in organelles specialized in sensory transduction in a variety of receptor cells, the presence of multiple ligand sites within the same channel molecule and on their arrangement in heteromultimeric protein complexes. In contrast, other ion channel family members usually exhibit rather constrained structural features and more restricted properties, such as a common ionic selectivity and gating mechanism. Members of the TRP family possess ankyrin, regulatory and enzymatic domains of which other plasma membrane channels are devoid. Ankyrin repeats may be relevant for TRP function, because they can enable the channel to interact with the molecular components present in the different cell systems, often confined to specific specialized regions within the cell. This is noteworthy because when some TRP channels are heterologously expressed, they show a different gating mechanism and function than in their native cells. This ability is a reflection of the remarkable plasticity allowed by TRP channels structure. Moreover, this high flexibility may have conferred them evolutionary advantages, since they can partake in a wide diversity of functions.

Regarding their gating mechanisms, physiological functions and involvement in diseases, TRP channels may be only beginning to surprise us.

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