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Pharmacology of TRPC Channels and Its Potential in Cardiovascular and Metabolic Medicine

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Abstract

Transient receptor potential canonical (TRPC) proteins assemble to form homo- or heterotetrameric, nonselective cation channels permeable to K^+, Na^+, and Ca^{2+}. TRPC channels are thought to act as complex integrators of physical and chemical environmental stimuli. Although the understanding of essential physiological roles of TRPC channels is incomplete, their implication in various pathological mechanisms and conditions of the nervous system, kidneys, and cardiovascular system in combination with the lack of major adverse effects of TRPC knockout or TRPC channel inhibition is driving the search of TRPC channel modulators as potential therapeutics. Here, we review the most promising small-molecule TRPC channel modulators, the understanding of their mode of action, and their potential in the study and treatment of cardiovascular and metabolic disease.

INTRODUCTION

Following identification of the gene underlying the photoreceptor transient receptor potential (TRP) phenotype of mutant *Drosophila melanogaster*, related genes were identified in mammals and first reported in the literature a quarter of a century ago (1, 2). The first mammalian TRPs to be recognized were those with the closest sequence similarity to *D. melanogaster* TRP, which became known as transient receptor potential canonicals (TRPCs) (3, 4). There are seven genes encoding such proteins in mammals. In *Homo sapiens* and closely related primates, *TRPC2* is a pseudogene (5), so there are considered to be six human TRPC proteins (TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7) (3, 4, 6). In some instances, there are splice variants, notably for TRPC4, further increasing complexity (7).

As with *D. melanogaster* TRP, the TRPCs assemble as tetramers around a single central ion pore that is gated and nonselectively permeable to cations. When the gate is closed (i.e., the channel is not activated), the tetramers are nonpermeable. Activation stimuli lead to opening of the gate. In physiology, the gated permeability results in influx of Na^+ and Ca^{2+} across the plasma membrane and efflux of K^+. The entry of Ca^{2+}, the special signaling ion, usually leads to an elevated cytoplasmic Ca^{2+} concentration, which stimulates normal cellular activity unless the Ca^{2+} elevation is too high, which may be detrimental to cell survival (8). The nonselective flux of cations has a depolarizing influence on the membrane potential, driving it from a negative value toward zero. In cells that fire action potentials, such as neurons, depolarization usually increases action potential firing and excitability; in cells that do not, such as endothelial cells (ECs), quiescence may be promoted because of decreased electrical driving force on Ca^{2+} entry. Na^+ entry can be important in its own right by elevating the intracellular Na^+ concentration: stimulating Na^+/K^+-ATPase activity, driving Na^+ entry into mitochondria, and reducing the transmembrane Na^+ gradient, thereby decreasing the energy available for Ca^{2+} extrusion by Na^+-Ca^{2+} exchangers (9).

Voltage Sensitivity of TRPC Channels

TRPC channels are broadly similar in structure to voltage-gated K^+ channels such as those of the K_V1 type. However, TRPC channels are not K^+-selective and not considered to be voltage gated. The activation mechanisms for TRPC channels are not as clear-cut as they are for many other types of ion channel. The K_V1s, for example, are activated by depolarizations of specific magnitude, without which they do not usually open; ligand-gated ion channels such as P2X receptors are activated specifically by exposure to one chemical or a related set of chemicals. The concepts are vaguer and often multifactorial for TRPCs (4, 9, 10). Although not considered to be voltage gated, these channels exhibit variable voltage dependence, especially when overexpressed in cell lines. Their activity may increase substantially as membrane voltage becomes positive and conversely decrease in activity or conductance as voltage becomes negative; hence the channels show signature double-rectifying current-voltage relationships in voltage-clamp experiments (11–14). Such voltage dependence may occur on a background of constitutive activity or chemically stimulated activity (3, 15). The physiological significance of the voltage dependence is unclear. Instead, direct and indirect chemical activation mechanisms are thought to be most important (4, 9, 13).

Physiological Activation of TRPC Channels

The chemical activators of TRPC channels are numerous, and there are reasonable cases to be made for the channels being coincidence detectors of multiple chemical signals, sensors of cocktails of chemicals, and perhaps broad sensors of the chemical melees of the extracellular and intracellular environments (4, 9, 16). A common theme of TRPCs is their association with

G protein–coupled receptors (GPCRs) and their downstream signaling pathways (4, 11, 17). There is ample evidence for activation by agonists (e.g., acetylcholine, ATP, histamine, sphingosine-1-phosphate) that act via GPCRs and downstream Gαq/11 or Gαi proteins to stimulate TRPC channel activity (4, 11, 17, 18). The channels are associated with receptors and G proteins linked to phospholipase C activation and the lipid substrates and products of phospholipase Cs (4, 10, 19). Such activity usually promotes channel opening but may also drive subsequent channel desensitization (20). Elevation of the intracellular Ca^{2+} concentration is often associated with these mechanisms, for example, via inositol trisphosphate–evoked Ca^{2+} release, which can be a powerful enhancer of TRPC channel activity in conjunction with other stimulators. The channels are probably not simply Ca^{2+} activated (contrasting, for example, with the Ca^{2+}-activated K^+ channels) because Ca^{2+} elevation alone does not activate or is a poor activator; it seems that cofactors are needed, and so the channels might best be considered as Ca^{2+} facilitated (10, 11, 21, 22). There are also lipid and redox stimulators of the channels, some of which may act directly, such as diacylglycerol (23–25), oxidized phospholipids (26), and reduced thioredoxin (13). Other factors to consider are protons (27, 28) and temperature (29). The latter is an important regulator of other mammalian TRP channels such as TRPV1 and TRPM8 (30). However, while there is evidence for TRPC5 channels being activated by noxious cold (29, 31), temperature change is not generally considered to be a major stimulant for TRPCs.

TRPC Heteromerization

TRPC1 stands out among the TRPCs because it generates little or no channel activity when expressed alone in a host cell line and does not usually reach the surface membrane (18, 32, 33). In contrast, when coexpressed with TRPC4 or TRPC5, it readily forms heteromers with them, impacting the overall voltage dependence, pore conductance, and ion selectivity (12, 13, 33, 34). TRPC1 is in some ways comparable to electrically silent K_v channel subunits (35): a γ subunit that is similar in structure to α subunits, such as TRPC4, and unable to function on its own yet able to incorporate with α subunits and function with them as an assembly (32, 33). The other TRPCs are all capable of forming functional homomers when expressed in cell lines, and some of them may do so natively in physiology—particularly TRPC3 and TRPC6. TRPC4 and TRPC5 seem more likely to exist physiologically as functional heteromers with TRPC1, which is widely expressed. In general, native TRPC channel compositions are technically difficult to determine and so remain uncertain in most situations (36). The biophysical characteristics and activation mechanisms of the channels often make it challenging to convincingly distinguish TRPC channel activity from other channel activity or background signals in native cells. Advances in TRPC channel pharmacology, as we describe in this review, increasingly enable better delineation of native activation mechanisms and determination of the relative importance of these channels in physiology and disease.

Expression of TRPC Channels

D. melanogaster TRP is specifically associated with the fly's phototransduction, but in mammals, phototransduction occurs via other mechanisms involving different ion channels. TRPC expression, at least at the messenger RNA level, is broadly detected across many, if not all, mammalian cell types, and there may be no mammalian cell type that completely lacks TRPC expression (4, 37). However, TRPC proteins and functional TRPC channels may not be expressed and important in all cell types. Instead, there seems to be differential expression and functional importance in different cell types and contexts, depending, for example, on whether the system is stressed by inflammation or disease. Perhaps unsurprisingly—because TRPCs form ion channels with

potentially a major impact on cell function—their abundance is quite low and often at the limits of reliable detection by biochemical or functional assays.

TRPC Channels in Physiology and Disease

Genetic knockouts of TRPCs, either alone or in combination, are not lethal for mice (38). This suggests that TRPCs are not critical for life, or at least the life of laboratory mice. This does not mean that TRPCs lack importance. Experiments on animal models of disease and studies of cells and tissues from humans with disease suggest TRPC channels or their excessive activation may cause or exacerbate disease; proposed functions of TRPCs are often linked to disease or a model of disease (37), including central nervous system disorders, kidney disease, cancer, and cardiovascular and metabolic disease. Such findings support the idea that inhibitors of TRPCs may be beneficial against certain types of disease and have relatively mild or no adverse effects.

Here we provide an overview of the most promising chemical TRPC channel modulators that can be used to investigate TRPC channels in cells, tissues, and animals. We also discuss recent progress with structural studies of TRPC channels that are starting to unveil the modes of action of chemical modulators, and we present key findings of the role of TRPC channels in cardiovascular and metabolic physiology and pathology.

SMALL-MOLECULE TRPC MODULATORS

Unraveling the roles of TRPC channels in physiology and pathology benefits from carefully designed combinations of genetic and pharmacological approaches. Since our last review of the field in 2013 (37), academic and industrial groups have reported many high-quality small-molecule TRPC channel modulators, some of which have been used to discover new biological functions of TRPC channels. Wang et al. (39) recently published a comprehensive review of the TRPC channels and their small-molecule modulators, and several recent, more focused reviews are available (36, 40–42). Here, we focus on TRPC modulators that (*a*) are the most promising for use as potent and selective chemical probes, (*b*) have been used to discover biological functions of specific TRPC channels, and (*c*) provide new insights into TRPC channel regulation (for example, through structural studies). We advise on TRPC1/4/5 pharmacology from direct experience. For TRPC3/6/7 pharmacology, we describe observations reported by other groups.

TRPC Channel Activators

Supplemental Material >

Structures and properties of TRPC channel activators discussed in this section are listed in **Supplemental Table 1**.

TRPC1/4/5 channel activators. The most potent, efficacious, and selective TRPC1/4/5 activator is the natural product (−)-englerin A (EA) (43–45). It activates TRPC1/4/5 currents at low nanomolar concentrations; so far, no other targets have been found that are modulated at such concentrations. The toxicity of EA to certain human cancer cells correlates with the expression of TRPC4 and/or TRPC5, and its cytotoxic effect on A498 renal cancer cells and SW982 synovial sarcoma cells has been demonstrated to result from increased Na^+ influx mediated by heteromeric TRPC1:C4 channels (44, 46). EA has been used to activate endogenous TRPC1/4/5 channels in cells (43, 44, 46), tissues (47), and animals (48). However, its (on-target) toxicity (45, 49) and instability in (rodent) plasma (45) need to be considered when using EA for in vivo studies.

The xanthine AM237, a close analog of Pico145 (see below), is a potent partial agonist of homomeric TRPC5:C5 channels that inhibits TRPC4:C4 channels and heteromeric TRPC1/4/5

channels (50). AM237 activation of TRPC5:C5 is apparently competitively inhibited by Pico145. AM237 is selective with respect to TRPC3, TRPC6, TRPV4, and TRPM2 channels. The xanthine-based photoaffinity probes Pico145-DA and Pico145-DAAlk mimic the functional effects of AM237 on TRPC1/4/5 channels and have been used to demonstrate direct interactions between xanthine-based TRPC1/4/5 modulators and TRPC5 protein in cells (51). These studies highlight AM237 as a potentially useful tool in distinguishing TRPC5:C5 channels from other TRPC1/4/5 tetramers and provide insights into the mode of action of xanthines as TRPC1/4/5 modulators (see below).

The marketed drug riluzole has been reported to activate TRPC5:C5 (EC_{50} 9.2 μM) and TRPC1:C5 channels but not TRPC4 channels (52). Its suitability for oral dosing has led to the use of riluzole as a TRPC5 activator for in vivo studies (53). Although its activity is thought to be relatively direct, based on activities in excised patch recordings and reversibility on washout, riluzole modulates a large number of targets, including many ion channels (54). This needs to be considered when using riluzole in functional studies, for example, by including controls in which riluzole's effect on TRPC5 channels is inhibited using a selective TRPC5 inhibitor.

TRPC3/6/7 channel activators. A high-throughput screen followed by structure-activity relationship studies resulted in the discovery of pyrazolopyrimidines (including the highly potent pyrazolopyrimidine 4n) as TRPC3/6/7 channel activators that do not activate TRPC4, TRPC5, or several other TRP channels (55). Close analogs were subsequently reported as potent TRPC6 inhibitors (56).

Researchers at GlaxoSmithKline developed the potent and selective TRPC3/6 activator GSK1702934A, which was used in studies with murine Langendorff hearts, in which it enhanced contractility and evoked arrhythmia (57, 58). Tiapko et al. (59) developed a photoswitchable analog of GSK1702934A called OptoBI-1, which displayed faster kinetics than the previously developed OptoDArG (60) and allowed optical control of endothelial and neuronal TRPC3 channels.

Recently, researchers at Amgen reported the discovery of the potent TRPC6 channel activator AM-0883 and the identification of its binding site by cryogenic electron microscopy (cryo-EM) (see below) (61).

TRPC Channel Inhibitors

Structures and properties of TRPC channel inhibitors discussed in this section are listed in **Supplemental Table 2**. The potency and efficacy of TRPC channel inhibitors can be activator dependent. The choice of activator used for inhibitor discovery can be pragmatic and may depend on the assay type and cell lines used. For example, EA (for TRPC1/4/5) and 1-oleoyl-2-acetyl-*sn*-glycerol (for TRPC3/6/7) give robust responses in both fluorometric assays and electrophysiology, while responses to specific GPCR activation may be more relevant to physiology but can be more difficult to distinguish from background signals. Therefore, we recommend (where possible) profiling new TRPC inhibitors against multiple activators and considering activity against specific activators when combining activators and inhibitors in functional studies.

Supplemental Material >

TRPC1/4/5 channel inhibitors. Xanthine derivatives were claimed as TRPC5 channel inhibitors in a patent by Hydra Biosciences describing over 600 examples (62). One of these xanthines, Pico145 (also called HC-608), is the most potent TRPC1/4/5 inhibitor reported to date (63, 64), with picomolar potencies against heteromeric channels. Bauer et al. (65) used a competitive photoaffinity labeling approach to demonstrate that the effect of xanthines such as Pico145

on TRPC5 channels is mediated by a direct binding interaction, and subsequent cryo-EM studies revealed the TRPC5 binding site and mode of Pico145 (see below) (66). In addition, Yu et al. (67, 68) reported the development of Pico145-based ^{11}C and ^{125}I radiotracers. Just et al. (64) reported the anxiolytic and antidepressant effects in mice of a close analog of Pico145, named HC-070. They confirmed HC-070 and Pico145 as potent inhibitors of human, mouse, and rat TRPC1/4/5 channels. In addition, both compounds were more than 400-fold selective against a large set of ion channels, receptors, enzymes, kinases, and transporters (>2,000-fold for most) and were orally bioavailable. HC-070 has been reported to bind to the same site of TRPC5:C5 as Pico145 (69). Overall, Pico145 and HC-070 are considered valuable chemical probes for functional studies of TRPC1/4/5 channels, with demonstrated use for inhibition of endogenous TRPC1/4/5 channels in cells (46, 63, 70–72), tissues (71, 73, 74), and animals (49, 62, 64, 74, 75).

A team at Goldfinch Bio discovered GFB-8438 as a potent inhibitor of rat and human TRPC4:C4 and TRPC5:C5 channels, with favorable physicochemical properties and good selectivity against TRPC3/6/7, other TRP channels, and cardiac channels (76). So far, its activities against heteromeric TRPC1/4/5 channels have not been reported. The TRPC4 binding site and mode of GFB8438 were recently determined by cryo-EM (see below) (77).

In 2011, Miller et al. (78) reported ML204 as a low micromolar inhibitor of TRPC4:C4 and TRPC5:C5 channels with high selectivity with respect to other channels, receptors, and transporters. ML204 has been used for in vivo studies of TRPC5 (53). It should be noted that its activity on heteromeric TRPC1/4/5 channels may be activator dependent (53, 79).

TRPC3/6/7 channel inhibitors. One of the first submicromolar TRPC3 channel inhibitors was Pyr3, which showed selectivity with respect to TRPC5 channels and was suggested to bind directly to TRPC3 based on photoaffinity labeling (80). The compound suppressed cardiac hypertrophy in mice. Although Pyr3 also targets calcium release–activated calcium channel 1 (ORAI1) activity with similar potency, further analogs have been developed that show different selectivities between TRPC and ORAI channels (81).

GSK2833503 is a member of a class of potent, selective TRPC3/6 inhibitors based on a 2-aminothiazole core, some of which were used to inhibit pathological cardiac hypertrophy in mice (82, 83). The enantiomer of GSK2833503 is tenfold less potent against TRPC3 and 100-fold less potent against TRPC6, providing a potential control compound with well-matched physicochemical properties. The analog BTDM was used to determine the location of a small-molecule binding site of the TRPC6:C6 channel by cryo-EM (see below) (84).

The TRPC3/6/7 channel inhibitor BI749327 is most potent against TRPC6 and does not inhibit TRPC5, other TRP channels, or cardiac channels. The compound is suitable for oral dosing and was used for studies in mouse models of heart and kidney disease (85).

Derivatives of the natural product (+)-larixol have been described as inhibitors of TRPC3/6/7 channels (86, 87), with the methyl carbamate derivative SH045 being the most potent one (87). SH045 is selective with respect to TRPC4, TRPC5, and other TRP channels and was shown to decrease edema in explanted mouse lungs.

The indane derivative SAR7334 was reported as a nanomolar TRPC3/6/7 inhibitor with selectivity against TRPC4/5 and TRPC5 channels. SAR7334 is orally bioavailable and suppresses acute pulmonary vasoconstriction in mice (88). The most potent TRPC6 inhibitor reported so far is its close analog, AM-1473, which was used to determine the location of an indane binding site of the TRPC6:C6 channel by cryo-EM (see below) (61). DS88790512 is another analog that, while lacking the aromatic indane core, retains high potency against TRPC6 channels as well as oral bioavailability (89).

Table 1 Overview of sub-4-Å TRPC channel structures

Channel (construct[a])	PDB ID (EMDB)	Resolution (Å)	Bound molecules (site)	Reference
hTRPC3 (full length)	6CUD (7820)	3.30	Two unidentified lipids, modelled as a PE (lipid 1) and a diglyceride (lipid 2)	92
mTRPC4 (1–758 of 974)	5Z96 (6901)	3.28	CHS (lipid 1), PA or C1P (lipid 2)	94
drTRPC4 (full length)	6G1K (4339)	3.60	CHS (lipid 1), PA or C1P (lipid 2)	93
drTRPC4 (full length)	7B0S (11970)	3.60	CHS (lipid 1), PA or C1P (lipid 2), GFB-8438 (VSLD/cation)	77
drTRPC4 (full length)	7B05 (11957)	3.80	CHS (lipid 1), PA or C1P (lipid 2), GFB-8749 (VSLD/cation)	77
drTRPC4 (full length)	7B16 (11979)	3.15	CHS (lipid 1), PA or C1P (lipid 2), GFB-9289 (VSLD/cation)	77
mTRPC5 (1–765 of 975)	6AEI (9515)	2.80	CHS (lipid 1), PA or C1P (lipid 2)	95
hTRPC5 (1–765 of 973)	6YSN (10903)	3.00	Unmodelled density (lipid 1), Pico145/HC-608 (lipid 2)	66
hTRPC6 (full length)	5YX9 (6856)	3.80	BTDM (between VSLD and pore), weak density for lipids (lipid 1, lipid 2)	84
hTRPC6 (73–end)	6UZA (20954)	3.08	AM-1473 (VSLD/cation); CHS (lipid 1); PC (lipid 2); CHS (outer leaflet), PC (inner leaflet)	61
hTRPC6 (73–end; V867T/L868T)	6UZ8 (20953)	2.84	CHS (lipid 1); AM-0883 (lipid 2); CHS (outer leaflet), PC (inner leaflet)	61
hTRPC5 (1–764)	7D4P (30576)	2.70	CHS (lipid 1), POPC (lipid 2), clemizole (Ca^{2+} binding site)	69
hTRPC5 (1–764)	7D4Q (30576)	2.70	CHS (lipid 1), HC-070 (lipid 2)	69

[a]Note that not all residues and domains of the used constructs could be observed/modelled.

Abbreviations: C1P, ceramide-1-phosphate; CHS, cholesteryl hemisuccinate; EMDB, Electron Microscopy Data Bank; PA, phosphatidic acid; PC, phosphatidyl choline; PDB, Protein Data Bank; PE, phosphatidylethanolamine; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; VSLD, voltage sensor–like domain.

STRUCTURAL INSIGHT INTO TRPC CHANNEL PHARMACOLOGY

Determination of 3-dimensional structures of proteins can aid the understanding of their molecular interactions and function. TRPC proteins form large, membrane-spanning, flexible, and structurally heterogeneous channels, which may explain why, so far, crystallographic approaches have been unsuccessful. However, cryo-EM structures of multiple TRPC channels have been determined to resolutions sufficient to observe amino acid side chains as well as bound small molecules and lipids (39, 90, 91).

TRPC Channel Structures

Sub-4-Å structures have been reported for several homomeric TRPC channels, including human TRPC3:C3 (84, 92), human TRPC6:C6 (61, 84), zebrafish (77, 93) and mouse (94) TRPC4:C4, mouse TRPC5:C5 (95), and human TRPC5:C5 (66) (**Table 1**). Each structure shows the same overall fold consisting of a homotetramer with each monomer providing six transmembrane helices (**Figure 1**). The first four transmembrane helices (S1–S4) of each monomer

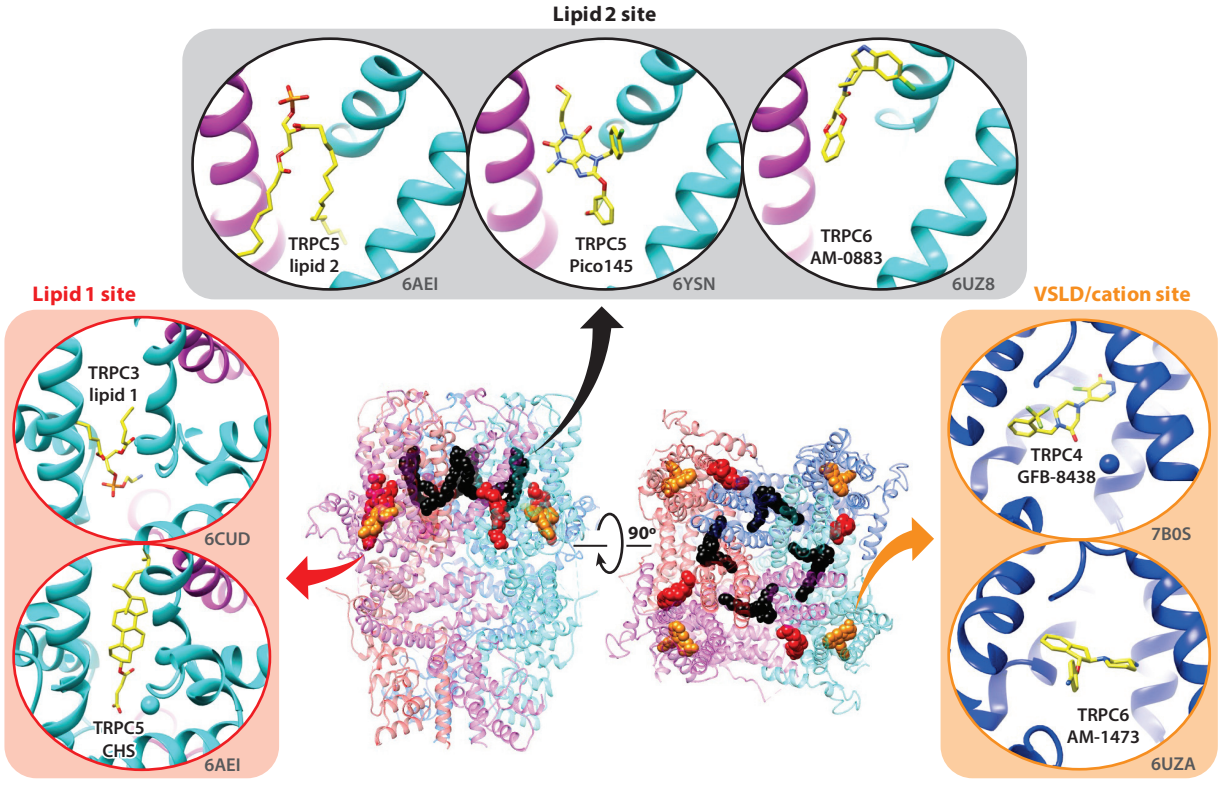

Figure 1

Transient receptor potential canonical (TRPC) channel cryogenic electron microscopy (cryo-EM) structures revealing bound lipids and small-molecule modulators. In the center, the structure of mTRPC5:C5 [Protein Data Bank (PDB) ID 6AEI] is shown, side and top views, including the four TRPC5 subunits (*magenta*, *blue*, *cyan*, and *salmon*) and the binding sites of lipid 1 [cholesteryl hemisuccinate (CHS), *red*] and lipid 2 (modelled as phosphatidic acid; *black*). In addition, a molecule of GFB-8438 (from the drTRPC4:C4 structure, PDB ID 7B0S; *orange*) is superposed onto the voltage sensor–like domain (VSLD)/cation binding site. Surrounding the mTRPC5:C5 structure are examples of lipid and small-molecule binding sites from different TRPC cryo-EM structures (PDB IDs shown in *gray*), with colors of the surrounding ring matching the binding sites displayed on the full mTRPC5:C5 structure. For a full overview of sub-4-Å TRPC channel structures, see **Table 1**.

independently fold into a voltage sensor–like domain (VSLD) followed by two transmembrane helices (S5 and S6) with a reentrant P loop in-between that forms the ion pore of the channels. The channels have internal N and C termini that fold into a large intracellular domain and several relatively short external (E) loops. Although the overall structures of TRPC channels are similar, TRPC1/4/5 channels contain additional residues in the E3 loop, which have been implicated in their differential response to lanthanides when compared to TRPC3/6/7 channels (96). In contrast, TRPC3/6/7 channels contain additional residues in the E1 and E2 loops, further from the central pore. It should be noted that the largest differences between TRPC proteins are in the intracellular N- and C-terminal domains of TRPC channels, which contain intrinsically disordered regions. In structural studies, these domains are often truncated or not modelled (97).

Lipid Binding Sites of TRPC Channels

Membrane proteins often have essential and specific interactions with membrane lipids, which can have stabilizing or regulatory roles. Because lipids play a role in the regulation of TRPC

channel activity, the observation of lipids in some of the TRPC cryo-EM structures is of interest. Although several lipid-like groups are usually visible in EM maps, there are two main sites with well-defined lipids or lipid-like molecules (**Figure 1**). Lipid site 1 is found in the inner leaflet in the VSLD, whereas lipid 2 is observed in the outer leaflet bound to the P loop and S6 helix of adjacent subunits. In the absence of small-molecule modulators, the TRPC5:C5 (66, 95) and TRPC4:C4 (93, 94) structures contain in site 2 a well-defined lipid (thought to be ceramide-1-phosphate or phosphatidic acid), which interacts with phenylalanine and tryptophan residues conserved within the leucine-phenylalanine-tryptophan (LFW) motif of the TRPC family. In addition, density was observed in site 1, which was attributed to cholesterol hemisuccinate (CHS; added during purification). The 3.3-Å TRPC3:C3 structure and 3.1-Å structures of TRPC6:C6 also show two additional nonprotein densities in these sites (61, 92). The density observed in site 1 in these TRPC6:C6 structures [Protein Data Bank (PDB) ID 6UZA and PDB ID 6UZ8] is also modelled as CHS. In TRPC3:C3, this density was modelled as a phospholipid, as it is not CHS shaped and no CHS was added during purification. This suggests that lipid site 1 might bind endogenous lipid in all TRPC channels. The TRPC6:C6 structures also contain additional modelled lipids in the inner [phosphatidylethanolamine (PE)] and outer (CHS) leaflets of the membrane. Lipid 2 in TRPC6:C6 occupies an overlapping site with the lipid observed in TRPC4:C4 and TRPC5:C5, again making interactions with phenylalanine and tryptophan residues of the LFW motif. However, the lipid is shifted toward the extracellular side and rotated close to perpendicular compared to lipid 2 in TRPC4/5 structures.

Small-Molecule Binding Sites of TRPC Channels

Recently, structures of TRPC4, TRPC5, and TRPC6 channels have unambiguously revealed binding sites and binding modes of small-molecule modulators (**Figure 1**). Structures of hTRPC5:C5 in the presence of the potent inhibitor Pico145 showed that Pico145 binds to lipid site 2 and replaces the phospholipid observed in this site in TRPC4/5 structures determined in the absence of small-molecule modulators (66). The structural analog HC-070 has been reported to bind to the same site of TRPC5:C5 (69). A similar replacement of lipid 2 was observed in the structure of TRPC6:C6 in the presence of the TRPC6 agonist AM-0883 (61). Structures of drTRPC4:C4 in the presence of the closely related inhibitors GFB-8438, GFB-8749, and GFB-9289 show that these molecules bind to a region close to the modelled cation in the VSLD (77). This binding site is also observed in the structure of TRPC6:C6 in the presence of the inhibitor AM-1473 (61), suggesting that this is a common site for modulation of TRPC channels. The structure of TRPC6:C6 was also determined in the presence of the inhibitor BTDM (84), which showed additional unmodelled density between the VSLD and the pore (an interaction between S4, the S4–S5 linker, and S5) in a distinct site, at an equivalent position to resiniferatoxin in the structure of TRPV1:V1 (98).

Although structures have been solved in the presence of activators and inhibitors, structures of TRPC channels in the open state have remained elusive. Additionally, the native state of many TRPC channels may not be a homotetramer; various heteromeric states (of unknown stoichiometries) may be present in many tissues, especially for TRPC1/4/5 channels.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Most TRPC channels are ubiquitously expressed in cardiovascular cells, including vascular smooth muscle cells (VSMCs), ECs, and cardiac pacemaker cells and myocytes. Significant evidence exists for roles of TRPCs in cardiac electrical activity, excitation-contraction coupling, and vascular tone (99–101). TRPC1-, TRPC3-, and TRPC4-mediated Ca^{2+} influx in VSMCs and ECs can

regulate vasoreactivity and thus vascular tone (102). Although a role for TRPC5 was suggested in baroreceptor mechanosensors (103), this finding has been challenged (104–106). TRPC1/3/4/5 channels have also been shown to regulate angiogenesis by controlling different endothelial functions such as proliferation, migration, and tube formation (107). Recently, Zhu et al. (108) showed that pharmacological activation of endothelial TRPC5 improves recovery from hypoxic injury through the NFATc3-ANGPT1 signaling pathway using a hind limb ischemia model. While the physiological contributions of TRPC channels to cardiovascular cellular function are still debatable, unequivocal evidence exists for their involvement in models of cardiovascular disease (for reviews, see 100, 102, 109–113). By and large, inhibiting channel activity or decreasing expression reduces such cardiovascular disease–like pathologies. Here, we summarize current evidence on the participation of TRPC channels in the major cardiac, vascular, and metabolic pathologies.

Cardiac Disorders

TRPC-mediated Ca^{2+} influx and downstream events involving calcineurin and NFAT are implicated in murine models of cardiac hypertrophy induced by neurohormonal agents such as angiotensin II (82, 114) and by ischemia/reperfusion (I/R) injury (115, 116), aortic constriction (82, 114), and pulmonary hypertension (112). TRPC channels may act as receptor- and store-operated Ca^{2+} entry channels in cardiac cells, and there is some evidence for their role in stretch-activated Ca^{2+} entry, too (109, 117). Gene knockout and dominant-negative expression studies showed that TRPC1/4 and TRPC3/6 are involved in hypertrophic remodeling (113, 118). Both in vitro and murine data suggest that stimulation of GPCRs by hypertrophic agents and mechanical stress leads to TRPC3/6/7 activation and thus cardiac hypertrophy (119). Camacho Londoño et al. (114) showed that reduction of background Ca^{2+} entry into cardiac myocytes (through constitutively active TRPC1/4) in TRPC1/4 double-knockout mice ameliorated cardiac hypertrophy induced by neurohormonal and mechanical stimulation and suggested no role for TRPC3/6. However, the TRPC3 inhibitor Pyr3 inhibited hypertrophic growth in rat neonatal cardiomyocytes and in pressure overload–induced cardiac hypertrophy in mice (80). Moreover, using genetic and chemical approaches, Seo et al. (82) showed that TRPC3/6 inhibition reduces cardiac hypertrophy. Such discrepancy may be explained by different genetic background (C57Bl/6J versus mixed) or compensatory changes in the expression of other TRPCs or related genes/pathways. The TRPC3/6/7 inhibitor BI749327 improved left heart function by reducing interstitial fibrosis in a pressure overload mouse model (85). Upregulation of TRPC channels in myocytes of murine and human hypertrophic hearts has been observed, which may indicate that their overexpression could be part of the pathogenesis (113, 120). Activation of the mineralocorticoid pathway has been suggested as the molecular mechanism of this upregulation (121). In addition, TRPC1/3/4/6 were upregulated in post–myocardial infarction heart, while knockout of TRPC3/6/7 reduced the infarct size and tissue damage (115). Triple knockout of TRPC3/6/7 reduced I/R injury, and thus these channels were proposed as specific targets for I/R injury. Interestingly, a well-known cardioprotective action of urocortin-2 in I/R injury was suggested to act through reduced expression of ORAI1 and TRPC5 (116). Notably TRPC3/6 channels can physically interact with and activate reactive oxygen species (ROS)-producing NADPH oxidase (Nox) enzymes and thus induce oxidative stress in cardiomyocytes and cardiac fibroblast, leading to cardiac remodeling and fibrosis (122–124). Given the central role of ROS in cardiac failure, these findings suggest that TRPC channels are a potential target for heart failure. In support of this, increased expression of TRPC5 and TRPC6 was observed in failing human hearts (125, 126). Because sarcoplasmic reticulum Ca^{2+} is a key regulator of action potential generation/propagation and cardiac contraction, and roles of TRPC channels have been suggested, it is not surprising that investigators have proposed that dysregulation of TRPC expression and function can lead to arrhythmia (127). TRPC1/4/5 channels

[upregulated by aldosterone-induced mineralocorticoid signaling (128)] and TRPC3/6 channels [activated by angiotensin II (129) or the TRPC3/6 agonist GSK1702934A (58)] have been associated with arrhythmias that are sensitive to the nonselective TRPC channel inhibitor SKF-96365 (128, 129). TRPC channels may play key roles in electromechanical conduction in developing hearts (99). Stretch-dependent modulation of TRPC6 expression in atrial endocardium has been suggested to regulate endothelin-1 (ET-1) production and thus play a key role in the development of myocardial calcium transients and arrhythmia (130). For detailed reviews of these topics, see References 109 and 131.

Vascular Disorders

While physiological functions of TRPC channels in the vasculature remain underexplored, we and others have conducted extensive work elucidating their roles in vascular pathophysiological processes and disorders, including angiogenesis, atherosclerosis, neointimal hyperplasia, inflammation, and systemic and pulmonary hypertension. Phenotypic transition of contractile VSMCs to a synthetic type is one of the key pathological processes regulated by TRPC channels and underlies many of these vascular diseases (132–134). A summary of salient findings on the role of TRPC channels in major vascular disorders is given below.

Atherosclerosis and vascular inflammation. Intracellular Ca^{2+} is well established as a key signaling ion in fundamental pathophysiological processes—including endothelial dysfunction (135), leukocyte extravasation and adhesion (136), smooth muscle migration and proliferation (137), and oxidative stress (138)—that contribute and lead to vascular inflammation and atherosclerosis (139). Hence Ca^{2+} channel inhibitors have long been advocated for treating atherosclerosis (140). TRPC1 induces smooth muscle migration and proliferation, and its expression was enhanced in pig models of vascular injury and in vitro human vein culture models (134). Importantly, inhibition of TRPC1 reduced neointima formation in those models. Vazquez and colleagues (141, 142) found that Ca^{2+} influx through TRPC3 channels is essential for cell adhesion–molecule expression and activity in ECs and that the TRPC3 inhibitor Pyr10 (81) reduced endoplasmic reticulum stress–induced apoptosis in ECs. These findings suggest TRPC3 as a potential target for atherosclerosis management. Moreover, activity of TRPC3 in macrophages can protect them from apoptosis, which can enhance atherosclerotic lesion progression (143). TRPC1/5 and TRPC3/4 are redox sensitive (13, 144). As described in cardiac disorders, TRPC3 interacts with Nox enzymes and contributes to ROS generation in ECs as well (141). Knockout studies showed that TRPC5 and TRPC6 activity impairs endothelial healing in vitro and in vivo after endothelial injury (145, 146).

Systemic and pulmonary hypertension. Given the significant role of TRPC1/3/6 in VSMC phenotypic switching and proliferation, nitric oxide (NO) signaling, and regulation of vascular tone, it is not surprising that multiple studies have shown a link between TRPC channels and primary systemic hypertension (100, 112). Defective Ca^{2+} homeostasis and increased expression of TRPC1, TRPC3, and TRPC5 have been described in the vasculature and peripheral blood cells of hypertensive humans and animals (100). In contrast, TRPC6 knockout mice exhibited hypertension, which could—at least partly—be explained by a compensatory increase in TRPC3 expression (147). However, mesenteric vessels of 11-deoxycorticosterone acetate–treated hypertensive rats showed increased TRPC6 expression and activity (148). These studies suggest that the role of specific TRPC channels in contraction and resultant blood pressure regulation is complex and dependent on both the partner channels and the pathophysiological context. Increased pulmonary vascular contractility and resistance led to pulmonary remodeling, resulting in pulmonary arterial hypertension (PAH) (149). TRPC1/4/6 are commonly implicated in pulmonary

artery smooth muscle cell and EC Ca^{2+} influx and proliferation, hypoxic vasoconstriction, and subsequent vascular remodeling and PAH (150, 151). Importantly, treatment with a β-carboline derivative or larixyl acetate, probably through inhibition of TRPC6-containing channels, can reduce the hypoxic pulmonary vasoconstriction, suggesting TRPC channels as promising targets for the treatment of PAH (86, 152, 153). Similarly the TRPC3/6/7 inhibitor SAR7334 suppressed acute hypoxic pulmonary vasoconstriction in mice, but mean arterial pressure was unaltered in spontaneously hypertensive rats (88).

Cardiovascular complications of diabetes. Physiologically, TRPC3 channels in hypothalamic neurons are essential for sensing glucose and thus insulin secretion and glucose regulation (154). Leptin-induced TRPC4 activation leads to trafficking of ATP-sensitive potassium (K_{ATP}) channels to the plasma membrane of pancreatic β cells during fasting and thus dampens insulin secretion (155). While expression of TRPCs has been described in the islet cells, their roles remain largely unknown. However, TRPC channels have been implicated in the development of diabetic complications such as nephropathy (156), neuropathy (157, 158), retinopathy (159), and vasculopathy (160, 161). Diabetes upregulates the expression of various TRPC channels in ECs and VSMCs, and thus it is conceivable that TRPC-mediated pathological signaling leading to vascular disorders could be exacerbated in diabetes (160). Involvement of TRPC5 and TRPC6 has been extensively studied in kidney disease (for a review, see 162). Recent knockout studies have shown that TRPC6 signaling may have mixed effects on diabetic nephropathy, which highlights the complex roles of TRPC channels in different tissues and conditions (163). Quadruple-knockout (TRPC1/4/5/6) mice were protected from hyperglycemia-induced retinal changes through the preservation of Muller and microglial functions (159). Involvement of TRPC6 has been described in peripheral neuropathy using a streptozotocin-induced rat model of diabetes (158).

Adipose tissue and obesity. Major functions of adipocytes, including metabolism, insulin signaling, and adipokine secretion, require Ca^{2+}-mediated signals. The physiological functions of TRPC channels in adipose tissue and their pathophysiological importance in obesity-associated metabolic diseases are not yet completely understood. In an in vitro adipocyte model cell line, 3T3-L1, adipocyte differentiation induced the expression of TRPC1 and TRPC5 (15). In addition, murine and human adipocytes expressed constitutively active TRPC1 and TRPC5 channels that sense ω-3 fatty acids; inhibiting the channels led to increased secretion of the cardioprotective adipokine adiponectin both in vitro and in vivo (15). In agreement with this study, a transgenic mouse model with TRPC5 pore mutation that prevents ion permeation through the channels showed reduced weight gain and favorable adipose phenotype upon high-fat feeding (164). Using global TRPC1 knockout mice, it was shown that TRPC1 channels have a significant role in the regulation of cellular energy metabolism and that loss of TRPC1 results in increased fat mass and insulin resistance upon high-fat feeding compared to wild-type litter mates (165). It has also been reported that TRPC1 regulation of adiposity is through its contrasting effects on autophagy and apoptosis of adipocytes (165). These studies suggest that inhibition of TRPC1:C5 channels could be a potential therapeutic strategy in metabolic disorders and may improve the beneficial effects of exercise. In contrast, disruption of *Trpc1* increased weight gain and adversely affected the metabolic profile by downregulating thermogenic gene expression in brown adipose tissue (166). Furthermore, a study using a neuronal and proopiomelanocortin-specific *Trpc5* knockout model showed increased weight gain in knockout animals, leading to the hypothesis that TRPC5 is essential for leptin regulation of hunger/satiety and energy homeostasis (167). Further work is needed to clearly elucidate the roles of TRPC channels in adipose tissue and obesity.

CONCLUSIONS

TRPC channels remain a fascinating class of ion channels, especially because of their ability to assemble as various distinct tetramers and integrate a wide range of physical and chemical signals. Essential physiological roles of TRPC channels are still incompletely understood. However, involvement of TRPCs in diverse cardiovascular and metabolic diseases, in combination with the lack of major adverse effects of TRPC knockout or TRPC channel inhibition, renders TRPC channels attractive therapeutic targets. For many cardiovascular and metabolic diseases, neither the exact composition of the relevant TRPC channels nor the implication of potential redundancy and compensatory upregulation of other channels is known. In addition, in only very few studies of TRPC channels in the cardiovascular system were specific TRPC channel modulators used. Recent advances in the development of potent and selective chemical probes of specific TRPC channel subtypes will enable the design of studies that carefully combine targeted genetic approaches (e.g., conditional/site-specific knockouts or gene editing) with high-quality pharmacological approaches. In addition, rapidly developing insights into the mode of action of small-molecule modulators, through structural biology and detailed pharmacological studies, will underpin the design of the next generation of chemical probes and drug candidates.

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