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Mechanosensitive Channels in Striated Muscle and the Cardiovascular System: Not Quite a Stretch Anymore

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Abstract

Stretch-activated or mechanosensitive channels transduce mechanical forces into ion fluxes across the cell membrane. These channels have been implicated in several aspects of cardiovascular physiology including regulation of blood pressure, vasoreactivity, and cardiac arrhythmias as well as the adverse remodeling associated with cardiac hypertrophy and heart failure. This review discusses mechanosensitive channels in skeletal muscle and the cardiovascular system and their role in disease pathogenesis. We describe the regulation of gating of mechanosensitive channels including direct mechanisms and indirect activation by signaling pathways, as well as the influence on activation of these channels by the underlying cytoskeleton and scaffolding proteins. We then focus on the role of transient receptor potential channels, several of which have been implicated as mechanosensitive channels, in the pathogenesis of adverse cardiac remodeling and as potential therapeutic targets in the treatment of heart failure.

Introduction

All cell types, from bacteria and yeast cells to the most specialized human cells, possess a mechanism to detect and respond to changes in mechanical stresses in their environment (25). While this response likely reflects a homeostatic mechanism to regulate cell volume, a number of disease processes are thought to reflect altered mechanotransduction including tumor metastasis, hypertension and certainly myocardial hypertrophy and failure (7, 26, 37, 75). Cellular adaptation to mechanical forces may take the form of an immediate response to resist mechanical demands imposed by transient forces or a long term response needed to strengthen the adhesive properties of the cell in order to resist stretch induced damage imposed by persistent forces. Failure of the short and long term responses can then lead to diseases associated with altered mechanotransduction. Understanding the mechanism of these systems will likely provide novel therapeutic strategies for disease processes such as cardiac hypertrophy and failure.

Three basic principles should be met in order to consider a molecule as mechanosensitive (8, 24, 42). First, the relevant molecules should reside in regions of the cell that are subjected to mechanical forces. In striated muscles these regions include the Z-disc, focal adhesion complex, and costamere (20, 51). Mechanosensors localize to these regions in order to sense

the local changes in mechanical forces imposed by the hemodynamic load. In these local environments, physical forces may post-translationally modify a subset of molecules to evoke a specific response without influencing the entire pool of molecules in the cell. The second principle is that the function of the molecule should be titrated to the level of mechanical force applied to it. All cells are subjected to a wide range of physical forces to which mechanosensors must respond in varying degrees (8). Finally a mechanosensor should then participate in a cascade of events known to be mechanically relevant (8). Mechanosensitive ion channels (MSCs) are an excellent example of such mechanosensors as they fulfill all three principles. MSCs localize to specific regions of the cell where physical forces are applied. Mechanical forces can then change channel pore configuration and therefore alter the gating properties of these channels (42). As a consequence, these channels then influence the electrical properties of the cell or participate in signaling cascades that are known to be influenced by mechanical stretch.

MSCs have been observed in almost all tissues including the cardiovascular system where they have been shown to play important roles in regulating diverse physiologic processes (43). Mechanosensitive ion channels in aortic baroreceptors respond to stretch of the arterial wall forming an integral part of a feedback loop involved in blood pressure regulation (65). The molecular identities of these channels have been largely unknown but recently hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and the KCNQ family of voltage-dependent potassium channels have been shown to play important roles (40, 81). Mechanosensitive channels have also been shown to exert an effect on pacemaking in the sino-atrial node and in the triggering of arrhythmias (12). Isolated sino-atrial node preparations have been shown to respond to distension with changes in their spontaneous beating rate (35). The expression of TRPM4, previously shown to be activated by stretch, has been demonstrated in mouse sinoatrial node cells (15), and TRPM4 has also implicated in the triggering of arrhythmias by delayed after-depolarizations observed under conditions of calcium overload (75). TREK channels which belong to the superfamily of two-pore-domain K^+ channels and are activated by membrane stretch and heat have been shown to contribute to the resting membrane potential in embryonic atrial myocytes (88).

Several mechanosensitive currents have been recorded in various cardiomyocyte preparations of different species and in different developmental timeframes (embryonic, neonatal or adult)(10, 41, 55, 68, 87). Using single-channel patch-clamp recordings, Ruknudin et. al. were able to describe five distinct types of mechanosensitive currents in cultured chick ventricular cardiomyocytes (55). With 140 mM K^+ in the pipette, four separate channels with linear conductances of 25, 50, 100, and 200 pS were observed with the fifth channel noted to be an inward rectifier with a conductance of 25 pS at 0 mV membrane potential. The 100 and 200 pS channels were K^+ selective, while the others passed Cs^+ and Ca^{2+} . Channel density was approximately $0.3/\mu m^2$ for the linear conductances and $0.1/\mu m^2$ for the inward rectifier (55). Subsequent details of the K^+ selective currents identify TREK and TWIK channels as mediators of the K^+ selective mechanosensitive currents (83).

Clemo and Baumgarten used the perforated patch voltage-clamp technique and video microscopy to simultaneously determine the whole-cell ionic currents and relative cell

volume of rabbit ventricular myocytes in the presence of osmotic swelling (9). Osmotic swelling induced a graded, inwardly rectifying, Gd^{3+} -sensitive cation current as well as an outwardly rectifying Cl^- current that was absent after Cl^- replacement and blocked by 1mM 9-antracene carboxylic acid. In hypotonic bathing solution (178 mOsm/liter) the Gd^{3+} -sensitive current density was -1.34 ± 0.05 pA/pF at -80 mV and $+0.09 \pm 0.01$ pA/pF at 0 mV, with a reversal potential of -57 mV. Block of the inwardly rectifying cation current by Gd^{3+} reduced the volume of osmotically swollen cells in a swelling and voltage dependent manner (9). Sorota used the whole-cell patch clamp technique to identify a swelling-induced Cl^- current in canine atrial cells (59), and subsequently Clemons et. al. found that this swelling-induced Cl^- current was persistently activated in ventricular myocytes from a canine pacing-induced dilated cardiomyopathy model (10).

Importantly, several groups have observed very low levels of current density indicating little contribution to the larger, more prominent voltage gated currents for Na^+ , Ca^{2+} and K^+ (48). Mechanosensitive channels influence background or resting currents. These currents are therefore only likely to influence high impedance portions of the action potential such as the plateau phase and pacemaker potential (87). In fact, mechanosensitive currents are recorded in cultured cardiomyocytes where calcium oscillations are frequently observed in neonatal cardiomyocytes and sino-atrial nodal cells (87).

This review will focus on the regulation of gating of mechanosensitive channels in striated muscle and the cardiovascular system including direct mechanisms and indirect activation by signaling pathways, as well as the influence on activation of these channels by the underlying cytoskeleton and scaffolding proteins. We then discuss the role of transient receptor potential channels, several of which have been implicated as MSCs, as potential therapeutic targets in preventing the adverse cardiac remodeling that occurs during the pathogenesis of cardiac hypertrophy and heart failure.

Regulation of Mechanosensitive Channels

Direct Gating

Classical mechanosensitive channels are gated directly by tension that is developed purely in the lipid bilayer. Criteria for establishing direct mechanical activation of ion channels were recently proposed by Christensen et. al. (8). The latency of activation would be expected to be less than 5 milliseconds with direct activation, faster than known second-messenger systems, and the kinetics of channel activation should depend on the amplitude of the stimulus with a larger mechanical force resulting in faster channel opening. Finally, some part of the channel or an associated subunit that is closely coupled to the gating has to show detectable movement in response to force (8). Maroto et. al. used a strategy to identify the molecular identity of the MSC based on detergent solubilization of frog oocyte membrane proteins, followed by liposome reconstitution and evaluation by the patch-clamp technique (43). A membrane-protein fraction was identified that reconstituted MSC activity and showed abundance of a protein that was identified by immunological techniques as TRPC1. The finding that the MSC retained its mechanosensitivity even after detergent solubilization and reconstitution in liposomes free of cytoskeletal elements suggested that TRPC1 formed a directly-gated mechanosensitive channel (43). Subsequently work reported that TRPC6

was also activated by mechanical or osmotic membrane stretch which was independent of phospholipase C (60). However, a recent study has shed doubt on whether TRPC1 or TRPC6 serve as directly-gated mechanosensitive channels (24). Heterologous expression of TRPC1 or TRPC6 in either COS or CHO cells failed to significantly alter the amplitude of the mechanosensitive current in these cells (24), and data from TRPC1 and TRPC6 knockout mice has raised further questions over whether these TRP channels serve as direct mechanosensors (17, 18). This may indicate that regulatory or interacting proteins (e.g. heteromeric TRP assembly) may be required for proper trafficking and functioning of this class of ion channels.

Indirect Activation

As members of the transient receptor potential (TRP) family of non-selective cation channels have been implicated as sensors of membrane stretch (i.e. TRPC1 and TRPC6), there has been considerable interest in the potential role of these channels in vascular reactivity. TRPC1, TRPC3, and TRPC6 expression has been described in the rat aorta (21), and TRPC6 has been implicated in receptor-operated Ca^{2+} influx in smooth muscle cells (SMCs) (58). Surprisingly, however, SMCs from TRPC6 $-/-$ mice showed increased basal cation entry and more depolarized membrane potentials. This increased basal cation influx was associated with upregulation of constitutively active TRPC3 channels in TRPC6 $-/-$ SMCs and was abolished by expression of siRNAs designed for silencing of TRPC3 (18). TRPC6 is also expressed in the pulmonary vasculature where it has been shown to play an essential role in hypoxic pulmonary vasoconstriction (76). Regional hypoventilation resulted in severe hypoxemia in TRPC6 $-/-$ but not WT mice and was associated with a lack of hypoxia-induced cation influx in SMCs from precapillary pulmonary arteries of TRPC6 $-/-$ mice (76). In addition to their role in the pulmonary and systemic vasoreactivity, TRP channels have also been implicated in the arterial response to injury as well as cerebral arterial vasospasm after subarachnoid hemorrhage (2, 36, 84).

Despite descriptions of TRPC1 as a mechanosensitive channel, data from TRPC1 $-/-$ mice has failed to demonstrate a physiologic role for TRPC1 in transducing membrane stretch in the vasculature, however (17). Cerebral arteries from TRPC1 $-/-$ mice failed to show any impairment in pressure-induced constriction and SMCs from TRPC1 $-/-$ mice showed no significant differences in cation currents in response to hypo-osmotic swelling and positive pipette pressure compared to WT cells (17). Similarly, pressure-induced constriction was unaltered in cerebral arteries from TRPC6 $-/-$ mice. Although TRPC6 channels do not appear to act as classical mechanosensors, membrane stretch can activate a TRPC6 current in a G protein- and phospholipase C (PLC)-dependent manner (16, 17). Agonist-independent activation of the G (q/11)-coupled receptor, the angiotensin II AT1 receptor, activates TRPC6-mediated cation influx in a PLC-dependent manner. Mechanically activated receptors recruit beta-arrestin and can be blocked by specific antagonists and inverse agonists. Thus while TRPC6 does not appear to be a classic mechanosensitive channel in SMCs, it can be activated indirectly by stretch via G-protein coupled receptor signaling through PLC (16, 17). Similar agonist-independent activation of the angiotensin II AT1 receptor has been described in cardiomyocytes as well (47, 73, 85).

Role of the Cytoskeleton and Scaffolding Proteins

Because the transverse mechanical properties of the plasma membrane are dependent on the cytoskeleton, as the pre-stress, or intrinsic stress, present in cells in the absence of applied loads depends on microtubules and actin (11), it is likely that MSCs would be influenced by the underlying cytoskeleton. Further, several MSCs have been shown to interact with the cytoskeleton via motifs at their amino or carboxyl termini. TRPC1 contains multiple ankyrin-like repeats at its amino terminal cytoplasmic loop which may mediate an interaction with the cytoskeleton as well as a domain at its carboxyl terminus which bears significant homology to dystrophin (43). Disruption of the dystrophin-glycoprotein complex (DGC), which links the cytoskeleton to the plasma membrane, is a hallmark of multiple forms of muscular dystrophy and has been associated with abnormal MSC activity leading to increased calcium influx (32). Streptomycin, an inhibitor of MSCs has been shown to prevent the rise of resting intracellular Ca^{2+} and partially prevented the decline of tetanic intracellular Ca^{2+} and force seen after stretched eccentric contractions in *mdx* muscle fibers which lack dystrophin (86). *Mdx* mice treated with streptomycin systemically also showed a significant decrease in frequency of central nuclei compared to controls. Vandebrouck et. al. have shown a physical association between TRPC1 and dystrophin as well as alpha1-syntrophin (69, 80), both components of the DGC, and repression of TRPC1 expression with antisense oligonucleotides has been shown to decrease single-channel activity in *mdx* myofibers (70).

The prevalence of cardiac involvement, namely left ventricular dysfunction, in patients with Duchenne's muscular dystrophy (DMD) increases with age (45). Although there appears to be no direct correlation between the degree of skeletal and cardiac involvement, the mechanism of cardiac involvement is postulated to be similar to that of skeletal muscle with a deficiency of dystrophin leading to loss of sarcolemmal integrity and myocardial necrosis (13). In a series of approximately 300 patients with DMD studied by Nigro et. al., 50% of patients showed evidence of a cardiomyopathy on echocardiogram by age 14 of which 36% were symptomatic, and by age 18 almost all patients exhibited some form of cardiomyopathy of which 57% were symptomatic (45). *Mdx* mice which lack dystrophin exhibit more benign skeletal muscle pathology than patients with muscular dystrophy due to muscle regeneration by satellite cells. *Mdx* mice show no evidence of left ventricular dysfunction at 8 weeks of age, but older *mdx* mice do show evidence of a dilated cardiomyopathy by 42 weeks of age (52). Increased levels of basal cytosolic calcium have also been measured in isolated ventricular myocytes from older *mdx* mice (80). These increases in basal calcium were blocked by GsMTx-4 peptide and streptomycin, two blockers of stretch-activated channel activity, suggesting that abnormal stretch-activated channel activity plays a role in the cardiomyopathy seen in DMD as well (80).

Using measurements of patch capacitance and geometry, Suchyna et. al. showed that the higher levels of MSC activity in *mdx* mice, compared to wild-type mice, are linked to cortical membrane mechanics rather than to differences in channel gating (63). Patches from *mdx* mice were found to be strongly curved towards the pipette tip by actin pulling normal to the membrane, producing substantial tension that can activate MSCs in the absence of overt stimulation. The inward curvature of patches from *mdx* mice was eliminated by actin

inhibitors (63). Hayakawa et. al. recently demonstrated that direct mechanical stretching of an actin stress fiber using optical tweezers can activate MSCs in cultured human umbilical vein endothelial cells (29). Then by using high-speed total internal reflection microscopy, spots of Ca^{2+} influx were visualized across individual MSCs distributed near focal adhesions providing direct evidence that the cytoskeleton works as a force-transmitter to activate MSCs (29).

Because the scaffolding protein Homer 1 has been implicated in TRP channel regulation, we hypothesized that Homer proteins play a significant role in skeletal muscle function. Mice lacking Homer 1 exhibited a myopathy characterized by decreased muscle fiber cross-sectional area and decreased skeletal muscle force generation (61). Homer 1 knockout myotubes displayed increased basal current density which was blocked by GsMTx-4 peptide, and spontaneous cation influx. This spontaneous cation influx in Homer 1 knockout myotubes was blocked by re-expression of Homer 1b, but not Homer 1a, and by gene silencing of TRPC1. Moreover, diminished Homer 1 expression in mouse models of Duchenne's muscular dystrophy suggests that loss of Homer 1 scaffolding of TRP channels may contribute to the increased MSC activity observed in *mdx* myofibers. These findings provide direct evidence that Homer 1 functions as an important scaffold for TRP channels and regulates mechanotransduction in skeletal muscle (61).

TRP Channels in Mechanotransduction

It is clear from a number of studies that TRP channels are involved in anchorage dependent processes, e.g. cell migration, growth cone turning, oncogenesis and stretch activation (3, 39, 72, 77). In striated muscle, myocytes establish specialized membrane domains called costameres that are similar to focal adhesions (20). Costameres serve to anchor the sarcolemma at Z-disc regions during contraction-relaxation cycles and are thus important in preventing membrane tearing associated with augmented stress. Costameres respond to increased mechanical forces through the stretch-induced strengthening response (23, 89). Here stretch results in increased expression of mechanically sensitive proteins which enhances the adhesive properties of the costamere to resist increased mechanical forces (19, 54). This counterbalancing force is fundamental to the adhesiveness of cardiomyocytes that is conferred by cytoskeleton, extracellular matrix and the surface receptors (e.g. integrins) (19). Changes in the cytoskeleton influence the stiffness of the cell which may be an immediate response to pressure overload but chronic stiffness may activate adverse remodeling (56, 78). Recent studies using a murine skeletal muscle line, as well as our own unpublished work, support the hypothesis that calcium entry through TRP channels influences adhesiveness, and the possibility that with too much TRP channel activity there is too little adhesion leading to a myopathy (89). TRPC1 currents, based on our own unpublished data, may influence the material properties of the costamere even under physiologic conditions indicating that costameres are not simply static structures. TRPC channels may sense changes in isometric tension through contacts with scaffolding proteins (e.g. Homer 1). Then calcium entry through TRPC1 channels reduces the stretch-induced strengthening response either by a mechanism involving calpain proteolysis of cytoskeletal elements or through calcineurin dependent dephosphorylation of cofilin (74, 77, 89). When considered in this context TRP channels may govern adhesiveness of the load bearing

regions of the cell. In this way, these channels may fulfill criteria as mechanically sensitive channels, providing a basis for the function of these channels in cardiomyocytes.

Role of Stretch-Activated Channels in Maladaptive Hypertrophy and the Progression to Heart Failure

Several members of the TRP channel family have been implicated in the mechanotransduction of the cardiomyocyte including TRPM, TRPV, TRPP and TRPC channels. Upregulation of TRPM4 protein in cardiomyocytes from spontaneously hypertensive rats correlates with the development of left ventricular hypertrophy, and TRPM4 currents may participate in some features of cardiac arrhythmias, such as delayed after depolarizations (DADs) or early after-depolarizations (EADs) associated with hypertrophy (27, 28). TRPP1 and TRPP2 are polycystins that are mutated in polycystic kidney disease (PKD)(14). TRPP channels play a significant role in ciliary mechanotransduction of the proximal tubules of the kidney. Many of the cardiac manifestations of PKD, such as left ventricular hypertrophy and reduced aortic distensibility, are felt to be secondary to the hypertension that develops in the disease in the setting of renal impairment; although for other cardiovascular manifestations such as mitral valve prolapse and intracranial aneurysms, the relationship is less clear (14, 33). A broader role for these channels, including a direct effect on cardiac phenotype, has been suggested by studies of mice lacking TRPP channels. Cardiomyocytes lacking TRPP2 (PKD2) exhibited defects in RYR2 regulation such as a higher frequency of spontaneous Ca^{2+} oscillations, reduced Ca^{2+} release from the sarcoplasmic reticulum stores, and reduced Ca^{2+} content compared with TRPP2+/+ cardiomyocytes (1). TRPP2-/- (Pkd2-/-) mice exhibit embryonic lethality after E13.5 and manifest structural defects in cardiac septation and cyst formation in maturing nephrons and pancreatic ducts (82). In addition, mice with a homozygous targeted deletion of TRPP1 (del17-21) die at embryonic days 13.5-14.5 from a primary cardiovascular defect that includes double outflow right ventricle, disorganized myocardium, abnormal atrio-ventricular septation, and severe defects in skeletal muscle development (5).

TRPV family members are found in skin fibroblasts, peripheral neurons and cardiac and skeletal muscle (46). These are non-selective channels that are activated by environmental heat and in the case of TRPV1 by capsaicin (38). Increased sarcolemmal expression of TRPV2 channels was observed in the skeletal muscle of patients with muscular dystrophy as well as in dystrophic heart and skeletal muscle of BIO14.6 hamsters which lack delta-sarcoglycan (34). No change in total expression of TRPV2 between normal and dystrophic muscle was noted, suggesting a spatial redistribution. TRPV2 is known to be activated by osmotic stress and hydrostatic stretch. In fact, vesicles containing TRPV2 in the cytosol traffic to the membrane in response to membrane stretch where TRPV2 may act as a mechanosensitive channel causing increased Ca^{2+} influx (34). Consistent with this pathological role, transgenic mice expressing TRPV2 in the heart display features consistent with cardiomyopathy including left ventricular dilation, decreased systolic performance, disorganized myocyte arrangement, interstitial fibrosis, and early lethality (34).

Recent findings that TRPC channels may act directly or indirectly as mechanosensitive channels raise the interesting possibility that TRPC channels may be operative during

cardiac hypertrophy in response to mechanical stimuli such as stretch. In fact, several groups have found a correlation between TRPC channel activity and calcineurin signaling in models of cardiac hypertrophy and failure. TRPC1, TRPC3 and TRPC6 have been found to be upregulated in the heart in response to pressure overload (7, 26, 37, 44). Onohara et. al. reported that the activities of TRPC3 and TRPC6 channels were essential for angiotensin II-induced NFAT activation and hypertrophic responses (50), while Bush et. al. showed that TRPC3 expression is upregulated in multiple rodent models of pathological cardiac hypertrophy, whereas TRPC5 expression is induced in failing human hearts (7). Cardiac-specific overexpression of TRPC3 in mice was associated with increased calcineurin/NFAT activation, cardiomyopathy, and increased hypertrophy after neuroendocrine agonist or pressure overload stimulation (44). These adverse effects on cardiac remodeling after pressure overload stimulation associated with TRPC3 overexpression were blocked by targeted disruption of the calcineurin A beta gene.

TRPC6 expression was found to be increased in mouse models of cardiomyopathy due to constitutive calcineurin activity or pressure overload. Cardiac specific overexpression of TRPC6 in transgenic mice was associated with increased NFAT-dependent gene expression, heightened sensitivity to pressure overload, a propensity for heart failure, and increased lethality in a dose dependent manner (37). The promoter of the TRPC6 gene contains two conserved NFAT sites which were required its activation in response to calcineurin/NFAT signaling, and TRPC6 overexpression in cardiomyocytes activated the calcineurin/NFAT dependent *RCAN1* gene *in vivo*. Thus TRPC6 appears to form a positive regulatory circuit in the calcineurin/NFAT pathway facilitating the transition to cardiomyopathy (37).

Stretch-Activated Channels as Therapeutic Targets in Heart failure

TRP channels represent a potential therapeutic target in blocking abnormal calcineurin/NFAT signaling that occurs during pathologic hypertrophy. 3,5-bistrifluoromethyl pyrazole (BTP) derivatives which have been shown to potently block store operated calcium influx, NFAT activation, and cytokine production in T cells, have also been shown to block activation of TRPC3 and TRPC5, but not TRPV6, in heterologous cells (30, 67). One limitation of the study of TRP channels is the current lack of specific inhibitors of these channels. In addition, although there is tissue specificity among TRP channels, in general, there is not unique tissue specificity. Most TRP channels are expressed to varying degrees in a few different types of tissues raising the possibility of off-target effects of TRP channel blockade (75). Because TRPC family members can form heteromultimers with distinct electrophysiological properties, it will be important to assess the relative importance of individual TRPC members in adverse cardiac remodeling (7). In addition, downregulation of one TRP channel may lead to unexpected results due to compensatory upregulation of another. There may also be important species differences (i.e. human vs. mouse) in the relative importance of different TRP channels in the heart and vasculature (7).

While an emerging body of evidence has linked TRP channels, several of which may be directly or indirectly activated by stretch, in the pathogenesis of pressure-overload hypertrophy and adverse cardiac remodeling, whether stretch-activated channels represent a therapeutic target in human heart failure remains unknown. Although the potential etiologies

of heart failure are many and include ischemic heart disease, hypertensive heart disease, valvular heart disease, and idiopathic cardiomyopathy, abnormal mechanical stress is a hallmark of the hemodynamic derangements that occur with decompensated heart failure regardless of etiology. Thus stretch-activated channels represent an interesting potential target for the treatment of this devastating disease. Blockade of stretch activated channels has already shown promise in rodent models of mechanical pain, muscular dystrophy, and atrial fibrillation (4, 25, 79, 86).

GsMTx4, a 4 kDa peptide isolated from the venom of the tarantula, *Grammostola spatulata*, was identified and isolated from a screen of invertebrate venoms looking for blockers of MSCs and has been shown to block cationic MSCs in a variety of cell types including cardiomyocytes (6). GsMTx4 is an amphipathic peptide with a hydrophobic surface surrounded by mostly positive charges (6). Suchyna et. al. showed that both GsMTx4 and its enantiomer blocked inhibited cationic MSCs suggesting that its mechanism of action does not fit the traditional lock-and-key model of ligand-channel interactions but suggested that GsMTx4 could function as a gating modifier by altering bilayer properties (64). By examining its effects on gramicidin A channel gating in a planar lipid bilayer, they also showed that GsMTx4 modulates channel activity by altering lipid packing at the interface of the channel and the membrane (64). Because a stoichiometric, sterically well-defined interaction between GsMTx4 and any known channel protein does not exist, mechanistic inferences from studies using GsMTx4 should be evaluated with caution. Although its effects on membrane partitioning suggest the possibility of non-specific effects on channel activity, thus far the known effects of GsMTx4 have been limited to inhibition of cationic MSCs. GsMTx4 has not been shown to have any effect on voltage-gated channels in rat astrocytes or rabbit cardiomyocytes and has no effect on the action potential of resting rabbit atrial cells (6, 62). The observation that both enantiomers of GsMTx4 are equally active has positive implications for the use of this peptide in drug development. Because typically only one of the two enantiomers of a given peptide is susceptible to hydrolysis in the body by endogenous proteases, this suggests that the alternate form may be stable in the circulation (22).

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Table 1

List of TRP channels involved in cardiovascular physiology, their tissue distribution(71), and proposed cardiovascular function. When the evidence for the role of a particular TRP channel includes a transgenic, knock-in of a targeted mutation, or knock-out model, this is indicated in parentheses.

TRP Channel	Tissue Distribution	Proposed CV Role
TRPC1	Heart, brain, testis, ovary, liver, vascular SMC	Cardiac hypertrophy (49), mechanosensor (43), response to vascular injury (2, 36)
TRPC3	Brain, skeletal muscle, heart, lung, peripheral nervous system, vascular SMC	Cardiac hypertrophy (transgenic) (7, 44), ischemia-reperfusion injury (57), vascular reactivity (18)
TRPC5	Brain, testis, kidney, uterus, heart	Dilated cardiomyopathy (7)
TRPC6	Lung, brain, kidney, heart, skeletal muscle	Cardiac hypertrophy (transgenic) (37, 50), vascular reactivity(18), mechanosensor(60)
TRPV2	Peripheral nervous system, brain, lung, spleen, intestine, heart, skeletal muscle	Myocyte degeneration, cardiomyopathy (transgenic) (34)
TRPP1	Kidney, pancreas, heart, skeletal muscle, testis, ovary, intestine	Cardiac and skeletal muscle development (knock-in) (5)
TRPP2	Kidney, liver, heart, skeletal muscle, grain, spleen, testis	Cardiac development (knock-out) (82)
TRPM4	Prostate, colon, heart, kidney, testis, vascular smooth muscle	Vascular reactivity(53), arrhythmias(15, 28)
TRPM7	Kidney, heart, pituitary, bone, adipose, vascular smooth muscle	Vascular reactivity(31, 66)