INTRODUCTION

In 1969, Cosens and Manning (1969) discovered that Drosophila with mutations in a peculiar gene was defective and displayed transient light-induced receptor potentials (TRPs) in response to continuous light exposure, causing visual impairment in photoreceptor cells. This phenomenon was explained by a deletion in ion channels, and led to the discovery of “TRP genes” that were named TRP channels. To date, the TRP channels superfamily contains 28 members in mammals and is subdivided into six subfamilies: TRPA, TRPC, TRPML, TRPM, TRPN, TRPV and TRPP, all of which permeate cations (Montell, 2005). The canonical transient receptor potential channels (TRPCs) are the first encoded TRP gene family in mammals and are the most dominating non-voltage-gated, Ca$^{2+}$-permeable cation channels in various cells (Zhu et al., 1995). TRPCs fall into four groups in terms of their amino acid homology and similarities in function: TRPC1, TRPC2 (as a pseudogene in humans), TRPC4/5, and TRPC3/6/7 (Table 1) (Nilius and Voets, 2005; Minke, 2006). The seven subtypes have an invariant sequence in common in the C-terminal tail called a TRP box (Philipp et al., 2000) and include three to four ankyrin-like repetitive sequences in the N-terminus (Montell et al., 2002). Many subunits of TRPCs are able to coassemble. There exist heteromultimeric channels that consist of heterologously expressed and endogenous TRPC monomers (Nilius et al., 2007). Indeed, TRPC1, TRPC4 and TRPC5 can form heteromers. Similarly, TRPC3, TRPC6, and TRPC7 form heteromers. In terms of activation mechanisms, members of the TRPC3, TRPC6 and TRPC7 subtypes can be stimulated by diacylglycerol (DAG) (Hofmann et al., 1999), which is the phospholipase C (PLC)-derived production regulating their physiological activation. In contrast, the TRPC1/4/5 subgroups are completely insensitive to DAG, which is still a controversial mechanism (Venkatachalam et al., 2003).

Most TRPCs are inserted in the plasma membrane (PM) and can be hindered by blockers (Zhang et al., 2013). Generally speaking, G protein-coupled receptors (GPCRs) have important roles in the regulation of TRPCs. In some cases, lipid signals can regulate the signals from GPCRs to TRPCs (Kukkonen, 2011).

A cytosolic Ca$^{2+}$ change may be induced by activation of specific GPCRs, including an initial transient increase resulting from release of calcium ions from the endoplasmic retic-
### Table 1. The properties of the TRPC family members

| Category | Tissue distribution | Structure | Activation mechanism | Proposed regulation | Reference |
|----------|---------------------|-----------|----------------------|---------------------|-----------|
| TRPC1    | Heart, Cartilage, Pituitary gland, Cerebellum, Caudate nucleus, Amygdala. | Six transmembrane spanning domains, TRP box in the C-terminus and three to four ankyrin-like repetitive sequences in the N-terminus | PKC-dependent phosphorylation | Store-operated, Store depletion | Riccio et al., 2002; Nilius and Voets, 2005; Minke, 2006; Xia et al., 2014 |
| TRPC3    | Pituitary gland, Cerebellum, Caudate nucleus, Putamen, Striatum. | Ibid ibidem | PKC-independent mechanism | DAG, Store-operated, Store depletion | Riccio et al., 2002; Welsh et al., 2002; Minke, 2006 |
| TRPC4    | Prostate, Bone, Parahippocampus. | Ibid ibidem | G-protein-coupled agonists | Store-operated, Store depletion? | Schaefer et al., 2000; Riccio et al., 2002; Plant and Schaefer, 2003 |
| TRPC5    | Cerebellum, Middle frontal gyrus, superior frontal gyrus | Ibid ibidem | G-protein-coupled agonists | Store-operated, Store depletion? | Schaefer et al., 2000; Riccio et al., 2002; Plant and Schaefer, 2003 |
| TRPC6    | Heart, Kidney, Adipose, Prostate, Cerebellum, Cingulate gyrus. | Ibid ibidem | PKC-independent mechanism | DAG, Receptor-operated | Winn et al., 2005; Xia et al., 2014 |
| TRPC7    | Pituitary gland, Kidney, Intestine, Prostate, Brain, Testis, Spleen, Cartilage. | Ibid ibidem | PKC-independent mechanism | DAG, Store depletion | Okada et al., 1999; Riccio et al., 2002 |
| TRPC2    | Only expressed in rodent, | Ibid ibidem | PLC-dependent mechanism | DAG, Store depletion? | Leybold et al., 2002; Stowers et al., 2002 |

"?" indicates that the proposed regulation is not completely confirmed.

### Table 2. TRPC channels may participate in most cardio/cerebro-vascular diseases

| Disease | Related TRPCs | Cells | Reference |
|---------|---------------|-------|-----------|
| Hypertension | TRPC1, TRPC3, TRPC6 | SMCs, Monocytes | Dietrich et al., 2006; Chen et al., 2010; Dietrich et al., 2010; Inoue et al., 2009; Fuchs et al., 2010; Eder and Molkentin, 2011; Gopal et al., 2015 |
| Pulmonary hypertension | TRPC1, TRPC3, TRPC6 | PASMCs | Liu et al., 2007a, 2009; Edwards et al., 2010; Iwasaki et al., 2011; Liu et al., 2012; Loga et al., 2013; Malczyk et al., 2013; Maier et al., 2015 |
| Cardiac hypertrophy | TRPC1, TRPC3, TRPC6, TRPC7 | Cardiomyocytes | Piper et al., 2004; Montell, 2005; Minke, 2006; Onohara et al., 2006; Nakashima and Kumagai, 2007; Ohba et al., 2007; Rosenbaum et al., 2015 |
| Atherosclerosis | TRPC1, TRPC3, TRPC4, TRPC5, TRPC6 | Platelets, VSMCs, Monocytes/ Macrophages, Endothelial cells | Short et al., 1993; Satoh et al., 2007; Shan et al., 2008; Smedlund and Vazquez, 2008; Smedlund et al., 2010 |
| Arrhythmia | TRPC3, TRPC6 | Myocardial cells, Fibroblast | Wang et al., 2006; Takahashi et al., 2007; Thilo et al., 2009; Tauseef et al., 2016 |
| Ischemia-reperfusion | TRPC3, TRPC6 | Myocardial cells | Xu and Beech, 2001; Wu et al., 2010; Zhang et al., 2014 |
Fig. 1. Molecular mechanism underlying cardiovascular diseases associated with the changing of intracellular Ca$^{2+}$ through TRPCs. GP-CRs, releasing DAG and IP3 via PIPL2 with the subsequent activation of PLC, were stimulated by Ang II and PE, which were hypertrophic stimuli. DAG stimulated ROCs, including TRPC3 and TRPC6, resulting in extracellular Ca$^{2+}$ influx. IP3 activated SOCE in response to depletion of intracellular Ca$^{2+}$ stores by Ca$^{2+}$ release in the SR/ER and subsequently activated TRPCs. The sustained TRPC-mediated Ca$^{2+}$ entry directly activated the calcineurin-NFAT pathway, subsequently resulting in the activation of hypertrophic gene expression, including TRPC1, TRPC3 and TRPC6. Simultaneously, after activating, NFAT might activate TRPC gene expression through a positive feedback mechanism. TRPCs interacted with the LTCC through membrane depolarization, playing a role in regulation of cardiac pacemaking, conduction, ventricular activity, and contractility. Mechanical stretch caused arrhythmia through the activation of SACs to elevate cytosolic Ca$^{2+}$ levels. Fibroblast regulated by Ca$^{2+}$-permeable TRPCs might be associated with AF, and fibroblast proliferation and differentiation are a central feature in AF-promoting remodeling. TRPCs maintained adherens junction plasticity and enabled EC-barrier destabilization by suppressing SPHK1 expression to induce endothelial hyperpermeability, leading to atherosclerosis. In addition, the omission of extracellular Ca$^{2+}$ with channel blockers (SKF96365, Pyr3) reduced monocyte adhesion and ATP-induced VCAM-1 and also relieved the progress of atherosclerosis. The rise of cytosolic [Ca$^{2+}$]i promoted SMC proliferation. TRPC channels associated with vascular remodeling caused hyperplasia of SMCs. Moreover, TRPCs participated in blood pressure regulation due to receptor-mediated and pressure-induced changes in VSMC cytosolic Ca$^{2+}$. Signaling via cGKI in vascular smooth muscle, by which endothelial NO regulated vascular tone, caused VSMC contraction. Activated TRPCs can activate downstream effectors and CREB proteins that have many physiological functions; TRPCs activated in neurons are linked to numerous stimuli, including growth factors, hormones, and neuronal activity through the Ras/MEK/ERK and CaM/CaMKIV pathways. GP-CR, G protein-coupled receptor; Ang II, Angiotensin II; PE, phenylephrine; ROCs, receptor-operated channels; SOCE, store-operated Ca$^{2+}$ entry; LTCC, L-type voltage-gated calcium channel; SACs, stretch-activated ion channels; AF, atrial fibrillation; SPHK1, sphingosine kinase 1; VCAM-1, Vascular cell adhesion molecule-1; SMCs, smooth muscle cells; VSMC, vascular smooth muscle cells; cGKI, cGMP-dependent protein kinase I; CREB, cAMP/Ca$^{2+}$- response element-binding.

Role of TRPCs in hypertension

Hypertension is a chronic cardiovascular disease characterized by persistently elevated blood pressure and is a major risk factor for coronary artery disease, stroke, heart failure, and peripheral vascular disease. In recent years, numerous studies have focused on the relationship between primary hypertension and TRPCs (Fuchs et al., 2010). In pathological states, some signaling factors are involved in the transition of SMCs into the proliferative phenotype, leading to an excessive growth of SMCs (Beamish et al., 2010). Abnormal overgrowth of SMCs is implicated in various vascular diseases,
Role of TRPCs in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is characterized by a thickening of the pulmonary arterial walls, which can cause right heart failure (Yu et al., 2004). Increased pulmonary vascular resistance is a primary factor in the progression of PAH. Ca\(^{2+}\) entry from the extracellular space, acting as a crucial mediator, is implicated in vasoconstriction (through its pivotal effect on pulmonary artery smooth muscle cells (PASMCs) contraction) and vascular remodeling (through its stimulatory effect on PASMC proliferation) (Kuhr et al., 2012; Weber et al., 2015). The most frequently expressed isoforms of TRPC in VSMCs are TRPC1, TRPC4, and TRPC6; TRPC3, TRPC5, and TRPC7 are less frequently detected (Inoue et al., 2006; Maier et al., 2015). Studies showed that Ca\(^{2+}\) entry improved the level of cytosolic Ca\(^{2+}\) through SOCs and ROCs (which is formed by TRPCs), and sufficient Ca\(^{2+}\) in the SR induced VSMC proliferation (Bimbaumer et al., 1996; Golovina et al., 2001; Bergdahl et al., 2003; Satoh et al., 2007; Seo et al., 2014).

TRPC1, TRPC4 and TRPC6 are involved in hypoxic pulmonary vasoconstriction, which is related to increased SOCE. Additionally, SOCE contributes to basal intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) and the proliferation and migration of PASMCs in rat (Lu et al., 2008). Malczyk et al. (2013) demonstrated that TRPC1 played an important role in hypoxia-induced PAH, as hypoxia-induced PAH is alleviated in Trpc1\(^{-/-}\) mice. Xia et al. (2014) found that TRPC1/6 are crucial for the regulation of neo-muscularization, vasoreactivity, and vaso-motor tone of pulmonary vasculatures; the combined actions of the two channels have a distinctly larger influence using Trpc1\(^{-/-}\), Trpc6\(^{-/-}\) and Trpc1\(^{-/-}\)/Trpc6\(^{-/-}\) mice. Significantly, another study confirmed the upregulation of TRPC1/6 expression in murine chronic hypoxia PAH models (Wang et al., 2006). Silence of TRPC1 and TRPC6 specifically attenuated thapsigargin- and 1-oleoyl-2-acetyl-sn-glycerol (OAG)-induced cation entries, respectively, indicating that TRPC1-mediated SOCE and TRPC6-mediated ROCO are upregulated by chronic hypoxia (Lin et al., 2004). TRPC4 is also involved in PAH. In monocrotaline-induced PAH rats, TRPC1 and TRPC4 protein levels were both increased significantly, resulting in enhanced vasoconstriction to endothelin-1 (ET-1) (Liu et al., 2012). In addition, siRNA specifically targeting TRPC4 reduced increases in TRPC4 expression and capacitative calcium entry (CCE) amplitude and inhibited ATP-induced PASMC proliferation (Zhang et al., 2004).

The expression and function of TRPCs are variously regulated by molecules in PAH. Wang et al. (2015) implied that both bone morphogenetic protein-4 (BMP4) and hypoxia inducible factor-1\(\alpha\) (HIF-1\(\alpha\)) upregulated TRPC1 and TRPC6, leading to elevated basal [Ca\(^{2+}\)]\(_i\) in PASMCs, driving the development of chronic hypoxia-induced PAH (Wang et al., 2015). Another study found that TRPC expression was found absent in mice partially deficient for HIF-1\(\alpha\) (Wang et al., 2006). In human PASMCs, siRNA of the HIF-1\(\alpha\) reduced hypoxia-induced BMP4 expression and knockout of either HIF-1\(\alpha\) or BMP4 abrogated hypoxia-induced basal cytosolic Ca\(^{2+}\) increase and TRPC expression (Zhang et al., 2014; Wang et al., 2015). Also, TRPCs have been recognized as reactive oxygen species (ROS)-activated channels and it is suggested that they are critical for hypoxia associated with vascular regulatory procedures in lung tissue.

TRPCs could be regulated by pharmacological intervention.
during PAH. The treatment of experimental PAH with sildenafil and sodium tanshinone IIA sulfonate suppresses TRPC1/6 expression (Lu et al., 2010; Wang et al., 2013a). SAR7334, an inhibitor of TRPC6, suppresses native TRPC6 activity in vivo (Maier et al., 2015) and opens new opportunities for the investigation of TRPC function. In the lung and PASMC from idiopathic PAH patients, the mRNA and protein expression levels of TRPC6 were much higher than that from normotensive or secondary PAH patients. Also, inhibition of TRPC6 expression markedly attenuated idiopathic PAH-PASMC proliferation (Yu et al., 2004). As a consequence, the participation of TRPC1/4/6 are crucial for PAH.

These results suggest that overexpression of TRPC may partially contribute to the increased PASMC proliferation, hinting at a promising therapeutic strategy for PAH patients.

Role of TRPCs in cardiac hypertrophy

Cardiac hypertrophy serves as a common pathway in cardiovascular diseases. It is the most important pathological foundation resulting in cardiogenic death. Although one study showed that the knockout of some TRPC genes did not result in abnormality in normal mice hearts (Yue et al., 2015), TRPCs have been demonstrated to play an important role in the pathological progress of cardiac hypertrophy through the mediation of ion channel activities and downstream signaling. Dysregulation of TRPCs may lead to maladaptive cardiac hypertrophy.

Numerous studies have shown that TRPC expression and activity are up-regulated in pathological cardiac hypertrophy (Bush et al., 2006; Kuwahara et al., 2006; Ohba et al., 2007; Seth et al., 2009). Cardiac hypertrophy induced by transverse aortic constriction (TAC) was improved in Trpc1-/- mice. Meanwhile, downregulation of TRPC1 reduced SOCE and prevented ET-1-, Ang II-, and phenylephrine (PE)-induced cardiac hypertrophy, indicating that deletion of TRPC1 avoided harmful influences in response to increased cardiac stresses in Trpc1-/- mice (Ohba et al., 2007). Also verified that TRPC1-mediated Ca2+ entry stimulated hypertrophic signaling in cardiomyocytes (Seth et al., 2009). Similarly, cardiac pathological hypertrophy could be caused by stimulation of pressure overload or overexpression of the TRPC3 gene in cardiomyocytes from TRPC3 transgenic mice, and could be selectively inhibited by Pyr3 (Nakayama et al., 2006; Kiyonaka et al., 2009). Also, TRPC6 has been proposed as a critical target of anti-hypertrophic effects elicited via the cardiac ANP/BNP-GC-A pathway (Kinoshita et al., 2010). However, a recent study showed Trpc6-/- mice resulted in an obvious augment in the cardiac mass/tibia length (CM/TL) ratio after Ang II, while the Trpc3-/- mice showed no alteration after Ang II injection. However, the protective effect against hypertrophy of pressure overload was detected in Trpc3-/-/Trpc6-/- mice rather than in Trpc3-/- or Trpc6-/- mice alone (Seo et al., 2014). Similarly, the newly developed selective TRPC3/6 dual blocker showed an obvious inhibition to myocyte hypertrophy signaling activated by Ang II, ET-1 and PE in a dose-dependent manner in HEK293T cells as well as in neonatal and adult cardiomyocytes (Seo et al., 2014).

Although the TRPCs role in myocardial hypertrophy is controversial, it is generally believed that calcineurin-nuclear factor of activated T-cells (Cn/NFAT) is a critical factor of microdomain signaling in the heart to control pathological hypertrophy. Studies found that transgenic mice that express dominant-negative myocyte-specific TRPC3, TRPC6 or TRPC4 attenuated the reactivity following either neuroendocrine-like or pressure overload-induced pathologic cardiac hypertrophy through Cn/NFAT stimulation in vivo, demonstrating that blockades of TRPCs are necessary adjusters of hypertrophy (Dietrich et al., 2006; Wu et al., 2010; Eder and Molkentin, 2011). Undoubtedly, TRPCs play an important role in cardiac hypertrophy and can be regarded as new therapeutic target in the development of new drugs.

Role of TRPCs in atherosclerosis

Atherosclerosis is commonly considered a chronic disease with dominant accumulation of lipids and inflammatory cells of the arterial wall throughout all stages of the disease (Tabas et al., 2010). Several types of cells such as VSMCs, ECs, monocytes/macrophages, and platelets are involved in the pathological mechanisms of atherosclerosis. It has been reported that the participation of proliferative phenotype of VSMCs is a consequential part in atherosclerosis. Cytoplasmic Ca2+ dysregulation via TRPC1 can mediate VSMC proliferation (Edwards et al., 2010). Studies have established that TRPC1 is implicated in coronary artery disease (CAD), during which the expression of TRPC1 mRNA and protein are elevated (Cheng et al., 2008; Edwards et al., 2010). Kumar et al. (2006) showed the upregulated TRPC1 in hyperplastic VSMCs was related to cell cycle activity and enhanced Ca2+ entry using a model of vascular injury in pigs and rats. In addition, the inhibition of TRPC1 effectively attenuates neointimal growth in veins (Kumar et al., 2006). These results indicate that upregulation of TRPC1 in VSMCs is a general feature of atherosclerosis.

The vascular endothelium is a polyfunctional organ, and ECs can generate extensive factors to mediate cellular adhesion, smooth muscle cell proliferation, thromboreistance, and vessel wall inflammation. Vascular endothelial dysfunction is the earliest detectable manifestation of atherosclerosis, which is associated with the malfunction of multiple TRPCs (Poteser et al., 2006). Tauseef et al. (2016) showed that TRPC1 maintained adherens junction plasticity and enabled EC-barrier destabilization by suppressing sphingosine kinase 1 (SPHK1) expression to induce endothelial hyperpermeability. Also, Poteser et al. (2006) demonstrated that porcine aorta endothelial cells, which co-expressed a redox-sensitive TRPC3 and TRPC4 complex, could give rise to cation channel activity. Furthermore, mice transfected with TRPC3 showed increased size and cellularity of advanced atherosclerotic lesions (Smedlund et al., 2015). In addition, studies further supported the relevance of EC migration to the healing of arterial injuries, suggesting TRPC5 and TRPC6 were activated by hypercholesterolemia, which impairs endothelial healing in vitro and in vivo (Rosenbaum et al., 2015; Chaudhuri et al., 2016).

Monocyte activation, adhesion to the endothelium, and transmigration into the sub-endothelial space are critical for early pathogenesis of atherosclerosis. The roles of TRPCs have been identified in the macrophage effecrofusis and survival, two crucial events in atherosclerosis lesion development (Tano et al., 2012). It has been shown that high D-glucose or peroxynitrite-induced oxidative stress significantly increased the expression of TRPC5 human monocytes (Wuensch et al., 2010). Vascular cell adhesion molecule-1 (VCAM-1) is important in monocyte recruitment to the endothelium as a critical factor in the development of atherosclerotic lesions. Smedlund et al. suggested that inhibition of TRPC3 expression
could significantly attenuate ATP-induced VCAM-1 and monocyte adhesion (Smedlund and Vazquez, 2008; Smedlund et al., 2010), indicating TRPC3 is involved in atherosclerosis lesion development. The platelet also plays important roles in cardiovascular diseases, especially in atherosclerosis, by participating in the formation of thrombosis and the induction of inflammation (Wang et al., 2016). Liu et al. (2008) investigated platelets in type II diabetes mellitus (DM) patients and found a time-dependent and concentration-dependent amplification of TRPC6 expression on the platelet membrane after challenge with high glucose. These results indicate that the incremental expression and activation of TRPC6 in platelets of DM patients may result in the risk of increasing atherosclerosis.

In summary, the pathophysiological relevance of TRPCs in several critical progresses has been linked to atherosclerosis.

**Role of TRPCs in arrhythmia**

Arrhythmia is a group of conditions in which the electrical activity of the heart is irregular, either too fast (above 100 beats per minute, called tachycardia) or too slow (below 60 beats per minute, called bradycardia). Several experiments have shed light on TRPC-regulated Ca\(^{2+}\) entry in arrhythmia. Sabourin et al. (2011) found that the existence of TRPC1,3,4,5,6 and 7 in the atria and ventricle, via association with the L-type voltage-gated calcium channel (LTCC), plays a role in the modulation of cardiac pacemaking, conduction, ventricular activity, and contractility during cardiology. Mechanical stretch is one of the causes of cardiac arrhythmia. It has been demonstrated that mechanical transformation of ventricular myocytes can modulate TRPC6. The process can be inhibited by GsMTx-4, which is a peptide isolated from tarantula venom and a specific inhibitor of stretch-activated channels (SAC) (Dyachenko et al., 2009; Anderson et al., 2013; Gopal et al., 2015).

One of the most common arrhythmias is atrial fibrillation (AF) (Nattel, 2011; Watkili et al., 2011). By researching fibroblast regulation by Ca\(^{2+}\)-permeable TRPC3, Harada et al. (2012) found that AF increased expression of TRPC3 by activating NFAT-mediated downregulation of microRNA-26. Further, they found that AF induced TRPC3-dependent increase of fibroblast proliferation and differentiation, likely by mediating the Ca\(^{2+}\) entry that stimulates extracellular signal-regulated kinase signaling. TRPC3 blockade prevented AF substrate development in a dog model of electrically maintained AF in vivo (Harada et al., 2012). In conclusion, by promoting fibroblast pathophysiology, TRPC3 is likely to play an important role in AF.

**Role of TRPCs in ischemia reperfusion injury**

Tissue injury led by ischemia reperfusion is the main cause of cell apoptosis and necrosis leading to myocardial infarction, stroke, and other deadly diseases. After focal cerebral ischemia, brain injury results from a suite of pathological progresses, including inflammation, excitotoxicity, and apoptosis. Researchers have indicated that an increase in cytosolic Ca\(^{2+}\) is a critical step in initiating myocardial cell apoptosis and necrosis responding to ischemia reperfusion (Carafoli, 2002; Brookes et al., 2004). Several Ca\(^{2+}\) entry pathways, including the CCE and the Na\(^+/Ca\(^{2+}\) exchanger channel, have been implicated in mediating myocardial cell Ca\(^{2+}\) overload (Carafoli, 2002; Brookes et al., 2004; Piper et al., 2004). An increasing number of studies show that members of the TRPC proteins are involved in regulating CCE. Given this growing evidence linking TRPC proteins to CCE in myocardial cells subjected to ischemia reperfusion injury, Liu et al. (2016) tested the assumption that increased expression of TRPC3 in myocardial cells results in increased sensitivity to the injury after ischemia reperfusion, and found that the treatment of CCE inhibitor SKF96365 markedly improved cardiomyocytes viability in response to overexpressed TRPC3. In contrast, the LTCC inhibitor verapamil had no effect (Shan et al., 2008; Liu et al., 2016). These data strongly indicate that CCE mediated through TRPCs may lead to Ca\(^{2+}\)-induced cardiomyocyte apoptosis caused by ischemia reperfusion injury.

Intracellular Ca\(^{2+}\) overload is also the major reason of neuronal death after cerebral ischemia. TRPC6 protein is hydrolyzed by the activation of calpain induced by intracellular Ca\(^{2+}\) overload in the neurons after ischemia, which precedes ischemic neuronal cell death. The inhibition of proteolytic degeneration of TRPC6 protein by blocking calpain prevented ischemic neuronal death in an animal model of stroke (Du et al., 2010). Studies found that the upregulated TRPC6 could activate downstream effectors cAMP/Ca\(^{2+}\)-response element binding (CREB) proteins, which are activated in neurons linked to a number of stimuli including growth factors, hormones, and neuronal activity through the Ras/MEK/ERK and CaM/CalMIVK pathways (Shaywitz and Greenberg, 1999; Tai et al., 2008; Du et al., 2010). It was also demonstrated that enhanced CREB activation activated neurogenesis, avoided myocardial infarct expansion, and reduced the penumbra region of cerebral ischemia and infarct volumes (Zhu et al., 2004). Thus, TRPC6 neuroprotection relied on CREB activation. Similarly, Lin et al. (2013) demonstrated that resveratrol prevented cerebral ischemia/reperfusion injury through the TRPC6-MEK-CREB and TRPC6-CaMIV-K CREB pathway.

The aforementioned results provide further evidence that TRPC3 and TRPC6 play roles in the mediation of cardiomyocyte function and suggest that TRPC3 and TRPC6 may contribute to increased tolerance to ischemia reperfusion injury.

**DISCUSSION**

Mechanisms including elevated activation or expression of TRPCs that partake in mediating Ca\(^{2+}\) influx activated by GPCRs offer the chance to interfere with Ca\(^{2+}\)-dependent signaling processes, thus playing a significant role in cardiovascular diseases. The primary regulatory paradigm for most of these activities takes charge of total cytosolic Ca\(^{2+}\) or the propagation of intracellular Ca\(^{2+}\) signaling events that regulate cellular activity. Strong evidence indicates that TRPCs conduct to mechanical and agonist-induced SMC or fibroblast proliferation, cardiomyocytes apoptosis, and endothelium dysfunction. TRPCs were also present in Ang II-induced endothelium-dependent vasodilation and elevated contractility, regulation of vascular angiogenesis to participate in hypertension, pulmonary arterial hypertension, cardiac hypertrophy, atherosclerosis, arrhythmia, and ischemia reperfusion injury. These new findings permit a more comprehensive assessment of the molecular and cellular importance of TRPCs in physiology and pathophysiology.

Many questions remain to be elucidated. Therefore, researchers should keep a watchful eye on how the novel effects of TRPCs can be committed to human cardio/cerebrovascular diseases and clarify the clinical relevance of TRPC.
| Inhibitor  | Chemical structure | Targeting channels | Predicted effects                                                                 | Action mechanism                                                                 | Reference                |
|-----------|--------------------|--------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------|
| SKF96365  | ![chemical structure](image1) | TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6, TRPC7 | Selectively decrease receptor-mediated calcium entry (RMCE) in human platelets, neutrophils and endothelial cells | Inhibit receptor-mediated Ca\(^{2+}\) entry and voltage-gated Ca\(^{2+}\) entry | Merritt et al., 1990; Farooqi et al., 2013 |
| Pyrazole-3 (Pyr3) | ![chemical structure](image2) | TRPC3 | Prevent stent-induced arterial remodeling and inhibit SMC proliferation | Inhibit TRPC3 by binding to the extracellular side of the receptor | Rowell et al., 2010; Christian and Maik, 2011; Koenig et al., 2013 |
| SAR7334   | ![chemical structure](image3) | TRPC3, TRPC6, TRPC7 | Effect on acute hypoxic pulmonary vasoconstriction and systemic blood pressure | Inhibit TRPC3, TRPC6, TRPC7-mediated Ca\(^{2+}\) influx into cells | Maier et al., 2015 |
| GsMTx-4   | ![chemical structure](image4) | Stretch-activated ion channels and NaV1.7 Na\(^{+}\) channels and TRPC1, TRPC6 | Potential therapeutic targets for cardiac arrhythmias | Inhibit Na\(^{+}\) voltage-gated channels and cation-selective mechanosensitive channels | Franz and Bode, 2003; Bowman et al., 2007; Rowell et al., 2010 |
| BTP2      | ![chemical structure](image5) | TRPCs and Store-operated Ca\(^{2+}\) influx and Ca\(^{2+}\) release-activated Ca\(^{2+}\) channels | Suppresses cytokine production (IL-2, IL-4, IL-5, IFN-\(\gamma\), etc.) and proliferation in T cells in vitro | Inhibit anti-CD3 antibody-induced sustained Ca\(^{2+}\) influx | Ohga et al., 2008; Rowell et al., 2010 |
activities. An improved understanding of the underlying mechanisms of cardiovascular and cerebrovascular diseases may assist in the design of new therapies and the identification of more selective pharmacological agonists and antagonists (Table 3) for TRPCs or interdependent channels as well as promote exciting chances to develop new therapies that prevent or treat cardio/cerebro-vascular diseases.

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