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Review

Store-operated calcium channels: Potential target for the therapy of hypertension

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Effective therapy of hypertension represents a key strategy for reducing the burden of cardiovascular disease and its associated mortality. The significance of voltage dependent L-type Ca^{2+} channels to Ca^{2+} influx, and of their regulatory mechanisms in the development of heart disease, is well established. A wide variety of L-type Ca^{2+} channel inhibitors and Ca^{2+} antagonists have been found to be beneficial not only in the treatment of hypertension, but also in myocardial infarction and heart failure. Over the past two decades, another class of Ca^{2+} channel – the voltage independent store-operated Ca^{2+} channel – has been implicated in the regulation and fine tuning of Ca^{2+} entry in both cardiac and smooth muscle cells. Store-operated Ca^{2+} channels are activated by the depletion of Ca^{2+} stores within the endoplasmic/sarcoplasmic reticulum, or by low levels of cytosolic Ca^{2+}, thereby facilitating agonist-induced Ca^{2+} influx. Store-operated Ca^{2+} entry through this pivotal pathway involves both stromal interaction molecule (STIM) and Orai channels. Different degrees of changes in these proteins are considered to promote Ca^{2+} entry and hence contribute to the pathogenesis of cardiovascular dysfunction. Several blockers of store-operated Ca^{2+} channels acting at the level of both STIM and Orai channels have been shown to depress Ca^{2+} influx and lower blood pressure. However, their specificity, safety, and clinical significance remain to be established. Thus, there is an ongoing challenge in the development of selective inhibitors of store-operated Ca^{2+} channels that act in vascular smooth muscles for the improved treatment of hypertension.

Keywords

Store-operated Ca^{2+}-channels; endoplasmic/sarcoplasmic Ca^{2+} stores; stromal interaction molecule; orai channels; hypertension therapy

1. Introduction

Although significant improvements in the management and treatment of coronary heart disease and stroke have reduced overall cardiovascular mortality in recent decades, it remains the number one killer worldwide (Forouzanfar et al., 2017; Lawes et al., 2008; Wellman et al., 2001). As hypertension is the most salient risk factor for cardiovascular disease, contributing to approximately 54% of all strokes and 47% of ischemic heart disease occurrences worldwide (Chaturvedi, 2003; Forouzanfar et al., 2017; Stanaway et al., 2018), this review is focused upon its pathophysiology and treatment. In particular, in view of the critical role of Ca^{2+} in determining the status of cardiovascular function (Barlow et al., 2006; Bers, 2008; Berridge et al., 2000; Carafoli, 2003; Cortes et al., 1997; Dhalla et al., 1977, 1982), we also describe the roles of various types of Ca^{2+} channels in health and disease, as well as therapeutic interventions that inhibit the vascular contractile response via blockage of Ca^{2+} entry into vascular smooth muscle. In doing so, we highlight recent discoveries in types of Ca^{2+} channels and the development of their inhibitors for the therapy of hypertension.

2. Cardiovascular Abnormalities and Ca^{2+}-channel Antagonists

According to Global Health Observatory data, 1.13 billion people globally are affected with elevated blood pressure (BP), which increases morbidity of conditions such as left ventricular hypertrophy, coronary heart disease, heart failure, atrial fibrillation, and peripheral artery disease (Lewington et al., 2002; Manolis et al., 2015; Mrowka, 2019; Wei et al., 2017). Hypertension itself, however, may not be associated with symptoms (Dorans et al., 2018; Khoury and Ratchford, 2018; Whelton et al., 2018). Many pathophysiological factors are known to be involved in the pathogenesis of hypertension, including structural and functional abnormalities as well as molecular and cellular mechanisms underlying cardiovascular alterations (e.g. cardiac output, peripheral resistance, the renin-angiotensin-aldosterone system, the sympathetic nervous system, endothelial dysfunction, and loss of nitric oxide (NO) bioavailability) (Bartekova et al., 2015; Beevers et al., 2001; Bhatt et al., 2014; Cain and Khalil, 2002; Chiong et al., 2008; Eid et al., 2018; Oparil et al., 2003). Furthermore, impaired vasodilation, impaired Ca^{2+}signaling, oxidative stress, and the production of pro-inflammatory cytokines and pro-fibrotic growth factors are thought to play a role (Beevers et al., 2001; Carretero and Oparil, 2000; Fritze et al., 2012; Gates et al., 2009; Green et al., 2010; Van den et al., 2012). Several clinical trials have demon-

strated that antihypertensive therapy reduces cardiovascular disease events and all-cause mortality (Dorans et al., 2018; Tocci et al., 2015). Treatments for hypertension include diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, vasodilators, and calcium channel antagonists (Bhatt et al., 2014; Chobanian et al., 2003; Fleckenstein, 1977; Godfraind, 2017; Gong et al., 1996; Kuramoto, 1999; Liu et al., 1998; Ozawa et al., 2006; Staessen et al., 1997; Tocci et al., 2015).

Since Ca^{2+} is known to play a critical role in transforming extracellular stimuli into intracellular signalling, its entry is controlled by the presence of different types of Ca^{2+} channels within the cell plasma membrane (Bers, 2008; Bean and McDonough, 2010; Carafoli, 2003). The concept of Ca^{2+} entry blockade by drugs in hypertension was developed in the 1960s in pharmacological screening studies of coronary dilators; these agents were later called Ca^{2+} channel blockers or Ca^{2+} antagonists (Dhalla et al., 1982; Fleckenstein, 1977; Godfraind, 2017). The classification of numerous Ca^{2+} -channel antagonists used therapeutically is given in Table 1 (Bangalore et al., 1994; ?; Dilmac et al., 2003; Hockerman et al., 1997; Hofmann et al., 1999; Kurokawa et al., 1997; Remuzzi et al., 2002; Scultety and Tamaskovits, 1991; Wang et al., 1994). Ca^{2+} antagonists are most frequently used in the treatment of cardiovascular disease and have been demonstrated to work by blocking Ca^{2+} entry through voltage dependent L-type calcium channels (Abernethy and Schwartz, 1999). The use of N-type and T-type calcium channel blockers has also been associated with reductions in cardiovascular events and renal injury, as well as the alleviation of hypertension (Ozawa et al., 2006). According to existing evidence, Ca^{2+} antagonists exert vasodilatory action on vascular smooth muscle cells by inhibiting Ca^{2+} entry through L-type calcium channels, whereas the blockade of N-type or T-type calcium channels in cardiac pacemaker cells may suppress heart rate and thus reduce cardiac events and improve survival (Harada et al., 2003; Takahara et al., 2004). Several L-type Ca^{2+} channel antagonists including verapamil, nifedipine, and diltiazem are now known for their beneficial effects in reducing BP and in the treatment of hypertension (Table 1). However a major side effect of Ca^{2+} channel antagonists, namely the depression of cardiac function, limits their clinical use in hypertension. As such,efforts are being made to discover other types of Ca^{2+}entry blockers acting upon voltage independent Ca^{2+}-channels, which may confer fewer side effects (Collins et al., 2013; Colovina, 1999; Guibert et al., 2008; Leung et al., 2008; Xu et al., 2015).

3. Store-operated Calcium Channels in Health and Disease

To date, knowledge is incomplete regarding the role of store-operated calcium channels (SOCC) in the pathogenesis of cardiovascular disease. A recently conducted cursory PubMed search found 143 research articles (of which 35 were reviews) for their role in cardiovascular diseases, including 123 research articles and 21 reviews for their role in hypertension. Although some investigators (Avila-Medina et al., 2018; Bolotina, 2008; Godfraind, 2017; Ozawa et al., 2006; Parekh and Putney, 2005; Tanwar et al., 2017) have attempted to analyze the existing data on SOCC, the mechanisms of the store-operated Ca^{2+} entry (SOCE) and the components of this pathway remain to be fully elucidated. It should be noted that SOCC are activated by depletion of Ca^{2+}stores within the endoplasmic/sarcoplasmic reticulum (ER/S R) or by low levels of cytosolic Ca^{2+} ($[Ca^{2+}]_i$) (Lambert et al., 2018; McFadzean and Gibson, 2002). These channels co-exist with voltage dependent Ca^{2+} channels within the plasma membrane of excitable tissues including cardiomyocytes, neurons, vascular myocytes and skeletal muscle cells (Arakawa et al., 2000; Collins et al., 2013; Pang et al., 2002; Trepakova et al., 2000) and are involved in Ca^{2+} entry from the extracellular space (Putney, 2018). The main feature differentiating voltage independent Ca^{2+} channels from all other types of Ca^{2+} channels is their activation, which occurs by the depletion of Ca^{2+} stores from the lumen of ER/SR (Lewis, 2011). SOCE was first conceptualized in the early 1980s (during which period it was known as 'capacitative Ca^{2+} entry'), describing direct Ca^{2+} entry from the extracellular space to refill ER/SR Ca^{2+} stores (Putney, 1986, 1990, 2009). It was shown that Ca^{2+} is released form the intracellular inositol-1, 4, 5-trisphosphate (IP3)- or ryanodine (RyR)-sensitive SR stores in response to physiological stimuli (Lewis, 2011). This Ca^{2+} efflux and consequent depletion of intracellular Ca^{2+}stores thus demands the influx of extracellular Ca^{2+} into the cytosol in order for stores to be replenished (Bose, 2017; Parekh and Putney, 2005; Prakriya and Lewis, 2015; Putney, 2011). The accumulated evidence supporting the notion of sensing of ER/SR Ca^{2+} stores for the control of Ca^{2+} influx represents the nascence of the SOCC model (Putney, 1986, 1990).

3.1 Physiological and Pathophysiological role of SOCC

SOCC are notable particularly with regard to their activation via retrograde signalling mechanisms, as well as their imperative role under both physiological and pathophysiological conditions (Leung and Kwan, 1999). The replenishment of intracellular Ca^{2+} stores following their depletion during intracellular Ca^{2+} signaling has long been thought as the main function of SOCC; however, they have recently been found to carry out other tasks, which may offer direct Ca^{2+} signals to locations near Ca^{2+} entry sites to recruit particular pathways. A growing number of studies have supported the role of SOCC in biological processes including endothelial cell proliferation (Abdullaev et al., 2008), breast cancer cell migration and metastasis (Yang et al., 2009), skeletal muscle contraction (Stiber et al., 2008), and smooth muscle migration and proliferation (Berra-Romani et al., 2008; Potier et al., 2009). SOCC have also been implicated in a number of human disorders including cardiovascular diseases, immunodeficiency, acute pancreatitis, Alzheimer's disease, Duchenne muscular dystrophy, and vascular disorders, positioning them amongst the important therapeutic targets in these diseases (Karlstad et al., 2012; Leung et al., 2008; Putney, 2011; Ruhle and Trebak, 2013; Spinelli and Trebak, 2016; Tian et al., 2016; Xu et al., 2015; Zhang and Trebak, 2011). In both cardiac and vascular myocytes, SOCCs exhibit sensitivity to an array of deleterious factors including redox stress, hyperglycemia, hypoxia, and acidosis which modify and/or disrupt SOCE pathways as an early event in diseases such as diabetic angiopathy, atherosclerosis and hypertension (Freichel et al., 2001; Groschner et al., 2017; Nakayama et al., 2006; Spinelli and Trebak, 2016). Investigations into the molecular regulation of SOCC has provided support for their role in cardiomyocyte function and for their pathophysiological role in cardiac hypertrophy, as well as in ischemia reperfusion-induced Ca^{2+} overload (Collins et al., 2013;

Table 1. Classification and Effects of Different Types of Ca^{2+}-antagonists

Classification	Antagonists	Effects	References
A. Dihydropyridines	Amlodipine, Aranidipine, Azelnidipine, Barnidipine, Benidipine, Cilnidipine, Clevidipine, Efonidipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Pranidipine	Reduce systemic vascular resistance and arterial pressure.	Bangalore et al., 1994; Kurokawa et al., 1997; Remuzzi et al., 2002
B. Non-Dihydropyridines			
a. Benzothiazepines	Clenazem, Diltiazem	Reduce arterial pressure	Hofmann et al., 1999
b. Phenylalkylamines	Gallopamil, Verapamil, Fendiline	Reduce myocardial oxygen demand, reverse coronary vasospasm	Dilmac et al., 2003; Hockerman et al., 1997
C. Non-selective	Bepridil, Flunarizine, Fluspirilene, Fendiline, Mibefradil,	Treat epilepsy and neuropathic pain.	Scultety and Tamaskovits, 1991
D. Non-medical	Ethanol	Induce muscle relaxation	Wang et al., 1994

Hulot et al., 2011; Luo et al., 2012). The involvement of SOCC in cardiovascular biology has also been explored and the potential for the development of therapy associated with these channels in apoptosis, hypertrophy, and arrhythmias has been suggested (Inoue et al., 2006; Watanabe et al., 2008). It has also been documented that disturbance in cardiovascular SOCC is of pathological significance, and thus therapeutic targeting of these channels has emerged as a favourable strategy for the treatment of cardiovascular diseases (Spinelli and Trebak, 2016).

3.2 Store-operated Ca^{2+} entry pathways

Two major functional molecular components of SOCC have been identified, namely: (i) Stromal interaction molecule (STIM), which serves as the ER/SR Ca^{2+} sensor; and (ii) Orai protein, which acts as a pore-forming channelin the plasma membrane (Cahalan, 2009; Fahrner et al., 2013; Liou et al., 2005; Putney, 2011; Shaw and Feske, 2012). There are three human Orai proteins-Orai 1, Orai 2 and Orai 3-as well as two human STIM proteins-STIM1 and STIM 2 (Hogan and Rao, 2015). The ER/SR Ca^{2+}sensors, STIM 1 and 2, differentially regulate and control the gating of plasma membrane Ca^{2+} release-activated Ca^{2+} channels (CRAC) in many cells (Hogan and Rao, 2015). STIM1 and STIM2 are identical in their overall structure, with a N-terminal domain in the ER/SR lumen, a single transmembrane segment anchoring the protein in ER, and a C-terminal cytoplasmic domain (Soboloff et al., 2012). The functional regions of this protein in the ER/SR lumen are: (i) the Ca^{2+}-sensing sterile α motif domain; (ii) the cytoplasmic region that both stabilizes inactive STIM and, upon Ca^{2+}store depletion, transmits the activating conformational change; (iii) the STIM-Orai activated region and CRAC activation region domain that recruits and gates Orai channels; (iv) the polybasic tail that interacts with plasma membrane phosphoinositides; and (v) a full length dimer in unstimulated cell (Hogan and Rao, 2015; Muik et al., 2011; Yang et al., 2012; Yuan et al., 2009; Zhou et al., 2010). Sensing Ca^{2+}in the ER/SR lumen and networking store depletion to other proteins (including Orai channels) are the key functions of STIM. Upon depletion of IP3- or RyR- sensitive Ca^{2+}stores, the localized sensor in STIM directly couples with plasma membrane Orai channels mediating Ca^{2+} influx (Bose, 2017; Lur et al., 2009). This is considered to be the basis STIM-Orai signaling. The overall underlying mechanism for this SOCC activation and inactivation cycle is shown in Fig. 1. It should be noted that it is upon ER/SR Ca^{2+} depletion that STIM proteins oligomerize into multiple punctae and relocate to the proximity of the plasma membrane and form ER/SR-plasma membrane junctions.

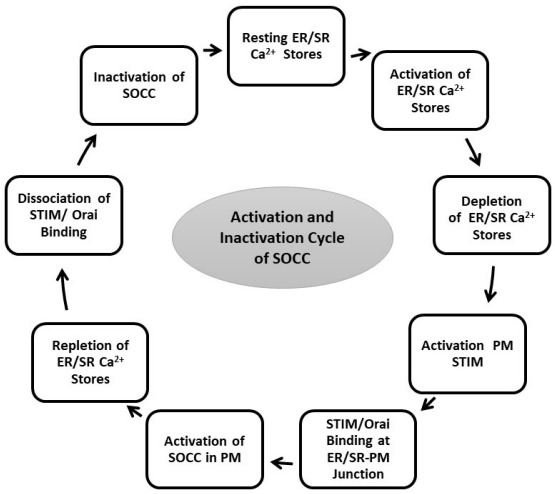

Figure 1. Schematic mechanism of store-operated Ca^{2+} entry pathways. ER-endoplasmic reticulum; SR-sarcoplasmic reticulum; PM-plasma membrane; SOCC-store-operated Ca^{2+} channel; STIM-Stromal interaction molecule.

Diminution of Ca^{2+} stores also enhances binding of microtubule and end-binding protein to STIM oligomers, which provides guidance toward the plasma membrane (Chen et al., 2013;

Honnappa et al., 2009; Tsai et al., 2014). The SOCC Orai proteins translocate to the STIM-containing ER/SR plasma membrane junctions following Ca^{2+} store depletion and open to mediate Ca^{2+} entry by direct physical interaction between the cytoplasmic C-terminal coiled-coil domain of Orai 1 and the cytoplasmic C-terminal CRAC domain/STIM-Orai activating region of STIM (Chen et al., 2016; Fahrner et al., 2014; Frischauf et al., 2009; Wu et al., 2006). On the other hand, the STIM1 binding proteins, SARAF, golli and ORMDL3, play an important regulatory role in modulating Ca^{2+}entry as well as in the inactivation of Ca^{2+}entry to prevent Ca^{2+} overload (Albarran et al., 2016a; Carreras-Sureda et al., 2013; Lopez et al., 2016; Palty et al., 2012; Walsh et al., 2010). Two types of SOCC pore-forming subunits including Ca^{2+} release-activated Ca^{2+} modulator (CRACM1), Orai 1/2, and transient receptor potential canonical (TRPC) channels have been identified (Desai et al., 2015; Lopez et al., 2016; Smani et al., 2016; Vaeth et al., 2017). However, it has been revealed that the depolarization-induced opening of L-type voltage dependent Ca^{2+} channels is inhibited by Ca^{2+} store depletion in a STIM1-dependent pathway (Berridge, 2002; Park et al., 2010; Wang et al., 2010). It may be noted that Orai 1 participate by co-localizing with STIM1 and L-type Ca^{2+} channels in ER/SR plasma membrane junctions after Ca^{2+} store depletion (Wang et al., 2010). While Orai, as well as TRPC channels, are opened, L-type Ca^{2+} channels are inhibited by the ER/SR Ca^{2+} store depletion by the same signaling mechanism acting as a switch between these two routes of Ca^{2+} entry. Thus, the STIM protein interacts directly with both SOCC and store-inhibited Ca^{2+}channels, whereas the Orai protein plays a crucial role in functioning as a SOCC itself (Berridge, 2002; Lee et al., 2010).

3.3 Store-operated Ca^{2+}channel activators

Any procedure that depletes the ER/SR Ca^{2+}stores can activate SOCC. Store emptying can be achieved by an increase of IP3 or other Ca^{2+} releasing signals, resulting in Ca^{2+} release from these stores. A growing number of studies has supported several such mechanisms, including: IP3 production in the cytosol or the stimulation of IP3 receptors; blockade of the SR Ca^{2+}-ATPase pump (SERCA) using thapsigargin; increase of SR membrane permeability with Ca^{2+} ionophore (ionomycin); and dialyzation of the cytoplasm with Ca^{2+} chelators (EGTA or BAPTA) (DeHaven et al., 2009; Gordon et al., 2000; Lemonnier et al., 2006; Parekh and Putney, 2005; Putney, 2010). Mostly known as an inhibitor of SOCC at high concentrations, 2-aminoethyldiphenyl borinate (2-APB) in the 1-20 μM range has been shown to act as an activator of SOCC and enhance the SOCE (Ma et al., 2002; Prakriya and Lewis, 2001). Ionomycin and SERCA pump blockers, which usually cause a rise in cytoplasmic Ca^{2+} concentration due to Ca^{2+} store depletion, could also open Ca^{2+}-activated cation channels (Parekh and Putney, 2005). However, accumulating evidence suggests that two direct activators of SOCC - a peptide representing the Orai interacting domain of STIM1 (Kawasaki et al., 2009; Muik et al., 2009; Park et al., 2009; Yuan et al., 2009) and the Ca^{2+} influx factor (Bolotina and Csutora, 2005) isolated from Ca^{2+} store-depleted cells-are capable of activating SOCC in the absence of store depletion, acting independently of STIM1 (Bolotina, 2008).

Recognizing their involvement in SOCC mechanism, both STIM and Orai proteins, which sense and respond to Ca^{2+} store depletion, can be modulated. Several agents have been identified to modify STIM-Orai signaling in SOCC (Hogan and Rao, 2015). These include: the ER/SR resident protein STIM-activating enhancer (STIMATE) and the cytosolic protein CRAC regulator 2A (CRACR2A), which stabilize the STIM1-Orai1 signalplex; and septins, which support recruitment and translocation of STIM1 in ER/SR plasma membrane junctions (Albarran et al., 2016b; Jing et al., 2015; Lopez et al., 2016; Sharma et al., 2013; Srikanth et al., 2010; Wilson et al., 2015). In addition, lysophospholipid products of Ca^{2+} independent phospholipase A2 (iPLA2) has been suggested as an auxiliary component that co-activates and mediates STIM1-Orai 1 interaction (Bolotina, 2008). However, it has been shown that STIM1, through its Orai-activating domain, interacts with and gates Orai channels through a direct protein-protein interaction (Avila-Medina et al., 2018). Also, STIM1, independently of its essential role in SOCC activation, is altered by diverse stimuli such as oxidation, temperature, hypoxia, and acidification (Hooper et al., 2013).

3.4 Store-operated Ca^{2+} channel antagonists

The discovery of several molecular components of SOCC (Fig. 2) has created the opportunity to develop drugs to, for example, block the pore of the Orai channel or modulate the activity of STIM1 (Putney, 2010). A number of agents that block SOCC have been suggested, either direct channel inhibitors or mechanism-based inhibitors (Table 2) (Chen et al., 2013; Chung et al., 1994; Clementi and Meldolesi, 1996; DeHaven et al., 2008; Franzius et al., 1994; Gregory et al., 2001; Holowka et al., 2014; Hoth and Penner, 1993; Irvine, 1990; Iwasaki et al., 2001; Ohana et al., 2009; Peinelt et al., 2008; Putney, 2001, 2010; Rodland et al., 1997; Smyth et al., 2008; Sweeney et al., 2009; Tian et al., 2016; Xu et al., 2015). Traditionally, ianthanides Gd^{3+} (gadolinium) and La^{3+} (lanthanum) were utilized extensively for blocking SOCC (Bird et al., 2008; Broad et al., 1999; Putney, 2001; Xu et al., 2015). STIM1 fails to activate SOCC when microtubule cytoskeleton disconnects from the ER/SR to form the mitotic spindle during mitosis; this mitotic destruction of STIM1 function is linked to specific phosphorylation sites in the C terminus (Smyth et al., 2008). Due to the association of STIM1 with microtubules within the ER/SR, microtubule reorganization with drugs such as nocodazole or colchicine has been proposed for STIM1-induced SOCE blockade.

For inhibition of the development of STIM1 into puncta as well as ER/SR-plasma membrane translocation, the myosin light chain kinase inhibitor (ML-9) has been suggested (Smyth et al., 2008). 2-aminoethyldiphenyl borinate (2-APB), in the 25-100 μM range transiently blocks the activation of Orai 1-mediated Ca^{2+}entry (DeHaven et al., 2008; Lis et al., 2007; Schindl et al., 2008; Zhang et al., 2008), as well as the ER/SR-plasma membrane translocation of STIM1 into puncta (DeHaven et al., 2008; Peinelt et al., 2008). This may further slow down the kinetic for Orai 2 blockade (DeHaven et al., 2008; Lis et al., 2007). Series analogs of 2-APB, DPB162-AE and DPB163-AE, have similarly shown their effectiveness as SOCC blockers (Goto et al., 2010). In addition, 3, 5-bis-trifluoromethyl pyrazole derivatives (BTP1, BTP2 and BTP3) in T-cells (Ishikawa et al., 2003; Zitt et al., 2004), SKF-96365 inhibited thapsigargin-induced SOCE in Jurkat T cells (Chung et

al., 1994; Tian et al., 2016), and carboxyamidotriazole (CAI) in HEK293 cells (Hussain et al., 2003; Kohn et al., 2001), have been shown to exert SOCC blockade. Recently, linoleic acid, an 18-C polyunsaturated fatty acid (PUFA) commonly known as omega-6 has been reported to inhibit antigen- or thapsigargin-mediated SOCE in mast cells by affecting STIM1 oligomerization and subsequent STIM1/Orai 1 coupling (Holowka et al., 2014). Another

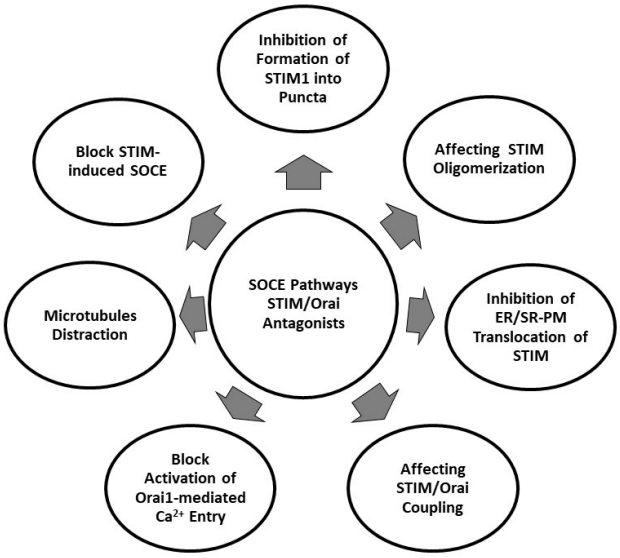

Figure 2. Effects of store-operated Ca^{2+} entry antagonists. ER-endoplasmic reticulum; SR-sarcoplasmic reticulum; PM - Plasma membrane; STIM-Stromal interaction molecule.

important selective Orai 1 inhibitor RO2959 has been suggested to potently inhibit human T-cell receptors (TCR)-mediated SOCE, T-cell proliferation, cytokine production, and gene expression (Chen et al., 2013). SOCC blockers such as 2-APB and SKF-96365 have also been shown to inhibit lysophosphatidic acid-induced increase in intracellular Ca^{2+} and protein synthesis in vascular smooth muscle (Xu et al., 2005, 2015). Although various SOCC inhibitors (Table 2) including lanthanides and 2-APB have been demonstrated to block transient receptor Ca^{2+} channels and IP_3 receptors, these inhibitors have a limited clinical use due either to their toxic effect or poor specificity (Johnson and Trebak, 2019; Tian et al., 2016).

4. Store-operated Ca^{2+} Channels in Cardiovascular Function

It is evident that Ca^{2+}entry through SOCC plays a critical role in regulating cardiovascular function in both health and disease. Since cardiovascular function is mainly determined by the coordinated interaction of cardiac muscle, vascular smooth muscle, and endothelium, this section is focused on the role of SOCC in the function of cardiomyocytes, vascular myocytes, and endothelial cells.

4.1 Role of SOCC in cardiomyocyte function

Several investigators have shown the presence of SOCC and their different components, such as STIM and Orai proteins, in cardiomyocytes, as well as demonstrating their role in Ca^{2+}entry and the augmentation of ventricular contractility (Bootman and Rietdorf, 2017; Mohl et al., 2011; Rosenberg et al., 2019). Not only are these channels involved in refilling SR Ca^{2+} stores, but they have also been shown to maintain resting levels of Ca^{2+} in car-

Table 2. Pharmacological inhibitors of Store-operated Ca^{2+} Entry (SOCE)

SOCE Inhibitors	Blockade Site	References
A. Lanthanides: La^{3+} (lanthanum); Gd^{3+} (gadolinium)	SOCC Orai	Hoth and Penner, 1993; Tian et al., 2016; Xu et al., 2015
B. Imidazole compounds: SKF-96365; SKF 96465; econazole; miconazole	Thapsigargin mediated SOCC	Chung et al., 1994; Franzius et al., 1994; Hoth and Penner, 1993
C. Diphenylboronate compounds: 2-Aminoethyldiphenyl borate (2-APB): 2-APB analogs- DPB162-AE and DPB163-AE (2-APB derivatives)	Translocation of STIM puncta and STIM/Orai binding; Partially Orai channel	DeHaven et al., 2008; Gregory et al., 2001; Iwasaki et al., 2001; Peinelt et al., 2008
D. Pyrazole compounds: Bis(trifluoromethyl) (BTP1, BTP2 and BTP3)	SOCE	Sweeney et al., 2009
E. ML-9 Myosin light chain kinase (MLCK)	Coalescence of STIM1 into puncta	Smyth et al., 2008
F. Diethylstilbestrol (DES 18) -a synthetic estrogen agonist	SOCE in mast cells and vascular smooth muscle cells	Hoth and Penner, 1993; Ohana et al., 2009
G. Carboxyamidotriazole (CAI)	Ca^{2+} dependent inactivation CRAC	Rodland et al., 1997
H. RO2959	Human TCR mediated SOCE	Chen et al., 2013
I. Linoleic acid: 18-C polyunsaturated fatty acid (PUFA)	SOCE by affecting STIM1 oligomerization and subsequent STIM1/ORAI1 coupling	Holowka et al., 2014

diomyocytes (Huang et al., 2006; Touchberry et al., 2011). Different molecules of SOCC including Orai 1, Orai 3 and STIM1 were found to regulate normal and hypertrophic growth in cardiomyocytes (Ohba et al., 2009; Saliba et al., 2015; Voelkers et al., 2010). While Orai protein deficiency has been shown to lead the development of heart failure (Volkers et al., 2012), the elevation of STIM1 protein in the heart was associated with Ca^{2+} handling abnormalities and cardiomyopathy (Correll et al., 2015). These observations provide evidence that SOCE affects cardiomyocyte function in both health and disease.

4.2 Role of SOCC in vascular smooth muscle cell function

As in other striated muscles, the presence of SOCC and its components such as STIM and Orai proteins has been observed in different types of smooth muscle cells (Feldman et al., 2017; Golovina et al., 2001; Shibata et al., 2019; Sweeney et al., 2002; Yan et al., 2019). These channels not only promote SOCE but also increase the level of intracellular Ca^{2+} and refill SR/ER Ca^{2+} stores in the smooth muscle cells. Hypoxia was found to upregulate SOCC in pulmonary artery smooth muscle cells by increasing the protein expression of STIM1/STIM2 and Orai 1/Orai 2, as well as inducing pulmonary vascular remodeling and vasoconstriction (He et al., 2018; Jernigan et al., 2012). Silencing of STIM1 attenuated the hypoxia-induced pulmonary artery smooth muscle cell proliferation through depression in the SOCE, and accordingly STIM1 was suggested to play an important role in pulmonary hypertension (Hou et al., 2013). On the other hand, an increased level of STIM2 and Orai 2 proteins was shown to contribute in the transition of pulmonary arterial smooth cells from contractile to proliferative phenotypes (Fernandez et al., 2015). Thus, upregulation of SOCC in different types of smooth muscle cells is thought to play a critical role in the development of hypertension.

4.3 Role of SOCC in endothelial cell function

By virtue of its ability to produce endothelin-1 (ET-1), a potent vasoconstrictor, and nitric oxide (NO), a potent vasodilator, defects in endothelial cell function are known to play an important role in the development of hypertension. Since the formation and release of ET-1 and NO are dependent upon the entry of Ca^{2+} in the endothelium, various investigators have demonstrated the participation of SOCC and its components in the function of endothelial cells (Giachini et al., 2009; Molnar et al., 2016; Peng et al., 2010; Wilson et al., 2015; Zhou et al., 2016). Hypoxia has been shown to increase SOCE by stimulating SOCC in pulmonary artery endothelial cells, and is known to be involvedin vascular remodeling and hypertension (Fantozzi et al., 2003; Paffett et al., 2007). In fact, reduced SOCE in pulmonary endothelial cells due to chronic hypoxia was found to be due to reduced membrane cholesterol (Zhang et al., 2018a), known to exert a tight control of endothelial cell function (Zhang et al., 2018b). Different interventions have also been demonstrated to profoundly impact upon SOCC in endothelial cells with respect to the production and release of both NO and ET-1 (Adapala et al., 2011; Boittin et al., 2008; Graier et al., 1990; Kaczara et al., 2018; Qu et al., 2017). Both NO and ET-1 have been shown to affect SOCE in smooth muscle cells and are known to be intimately involved in the control of blood pressure (Ansari et al., 2004; Chuang et al., 2012; Clementi, 1998; Jernigan et al., 2006).

5. Store-operated Ca^{2+} Channels in Hypertension

The physiological and pathophysiological significance of SOCC-associated mechanisms, as well as molecular and cellular pathways for their regulation, are considered to form the basis of SOCE inhibitors as a potential therapy for several human diseases, including hypertension (Avila-Medina et al., 2018; Collins et al., 2013). There is growing evidence to suggest that Ca^{2+} enters through SOCC in VSMC (Barlow et al., 2006; Dominguez-Rodriguez et al., 2012; Park et al., 2008; Rodriguez-Moyano et al., 2013) and that disorder of these channels are associated with the development of hypertension (Tanwar et al., 2017). The activation of SOCC in VSMC (either by vasoactive agonists or by SERCA inhibition) maintains Ca^{2+} homeostasis for proper Ca^{2+} signaling, it is the defective regulation of intracellular Ca^{2+}that plays a crucial role in the genesis of hypertension (Albert and Large, 2002; Jackson, 2000; Manjarres et al., 2010). It has been suggested that SOCC inhibitors (e.g. rapamycin) may serve as promising drugs for the treatment of hypertension (Houssaini et al., 2013). The beneficial actions of SKF 96365 (SK) on changes in blood pressure, cell proliferation and intracellular Ca^{2+} have been shown, and the use of a SOCC inhibitor SK in combination with Ca^{2+} channel antagonist verapamil has been shown to exert additive effects on BP as well as on intracellular Ca^{2+} (Xu et al., 2005, 2015).

5.1 Store-operated Ca^{2+}pathways - STIM1/Orai 1 in Hypertension Treatment

Essential regulators of intracellular Ca^{2+} homeostasis, including STIM and Orai proteins, are key contributors to Ca^{2+} signaling mechanisms that support their role in cardiovascular disease (Ruhle and Trebak, 2013). The increase in cytosolic Ca^{2+} via SOCC mediated by STIM and Orai proteins activates a variety of signaling cascades to regulate several cellular functions. Conversely, their dysregulation promotes several pathophysiologies, including atherosclerosis, arterial stenosis, thrombosis, and hypertension (Ruhle and Trebak, 2013; Tanwar et al., 2017). There is a strong correlation between hypertension and enhanced STIM and/or Orai protein expression (Kassan et al., 2016; Pulina et al., 2013; Spinelli and Trebak, 2016; Zhang and Trebak, 2011). It has been proposed that augmented Ca^{2+} influx through SOCE pathways, STIM1/Orai 1, may contribute in potentiating vascular reactivity (Giachini et al., 2009, 2012) and vascular tone and force generation (Goulopoulou and Webb, 2014; Kitazono et al., 2002; Tanwar et al., 2017) (Fig. 3). The treatment of aortic rings in male spontaneously hypertensive rats with high concentrations of SOCC blockers (either 2-APB and Gd^{3+}, or with STIM1 and Orai1 antibodies) was found to result in a reduction of spontaneous tone and force generation to levels found in normotensive rats. However, it has been observed that higher concentrations of SOCC inhibitors are likely to affect other ion channels, such as ER/SR Ca^{2+} release channels and pumps, which in turn can result in SOCE inhibition (Cortes et al., 1997; Giachini et al., 2009). A similar study using aortic tissue from rats undergoing chronic ethanol consumption for 30 days showed increases in SOCE, systolic blood pressure, and STIM1 protein expression (Souza Bomfim et al., 2017). Since STIM1 is a key regulator of Ca^{2+} homeostasis for supporting communications between the ER/SR and the plasma membrane, its upregulation could lead to direct or indirect

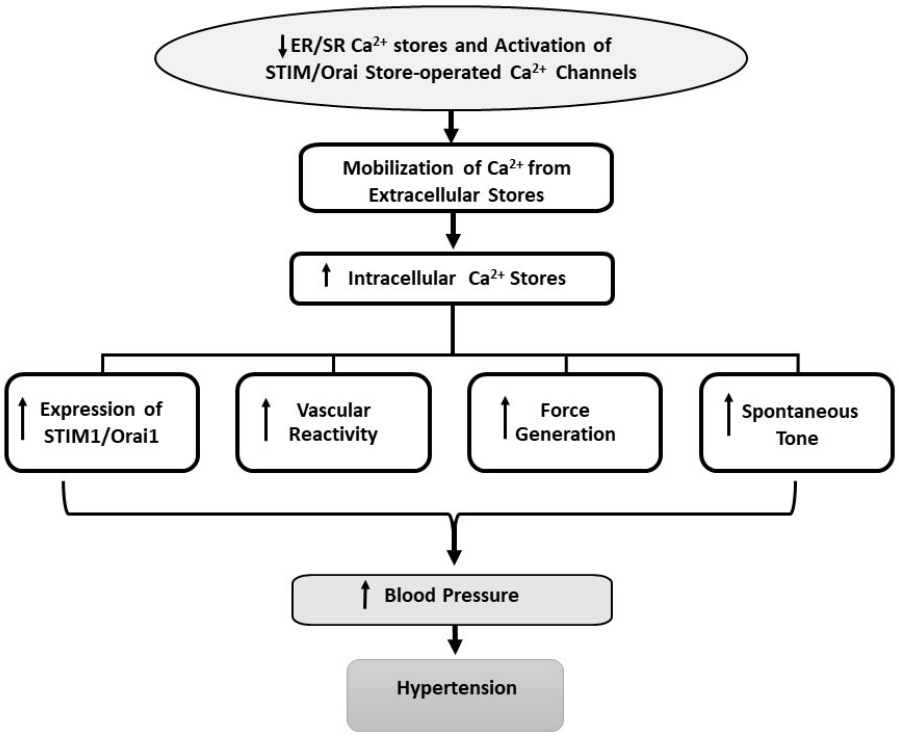

Figure 3. Involvement of Store-operated Ca^{2+} entry in the development of hypertension. STIM-Stromal interaction molecule; ER-endoplasmic reticulum; SR-sarcoplasmic reticulum.

ER/SR stress, as well as dictating the development of cardiovascular complications in hypertensive conditions. Wild-type mice infused with angiotensin II have been shown to develop hypertension, cardiac hypertrophy, perivascular fibrosis and endothelial dysfunction associated with enhanced STIM1 expression in heart and blood vessels, in study by Kassan et al. (2016). The same authors reported that STIM1 up-regulation during angiotensin II-induced hypertension was associated with enhanced ER/SR stress through TGF-β and NADPH oxidase-dependent pathways. Accordingly, it has been suggested that smooth muscle STIM1 not only plays a vital role in the pathogenesis of hypertension and associated cardiovascular pathologies, but also signifies a promising therapeutic target in these diseases (Kassan et al., 2016). This is also supported by studies targeting STIM- and/or Orai-mediated SOCE by different inhibitors for the treatment of hypertension (Ruhle and Trebak, 2013).

6. Conclusion

Hypertension is a prevalent risk factor of cardiovascular diseases and thus a major cause of mortality worldwide. It is treatable with medications as well as lifestyle changes. Most of the classical antihypertensive agents, including Ca^{2+} channel antagonists, ameliorate hypertension by lowering intracellular Ca^{2+} within vascular smooth muscle cells. Although existing medications for hypertension are generally well tolerated, they are known to have side effects. It has been observed that β-blockers may aggravate asthma and decrease heart rate, ACE inhibitors may lead to dry cough, L-type Ca^{2+} channel antagonists may cause leg swelling, and diuretics may increase urination and leg cramps. Thus, efforts are being made to improve drug therapy for hypertension. A new class of antihypertensive agent for the prevention of Ca^{2+} entry through SOCC is being developed, but some SOCC inhibitors, including lanthanides, are limited in their clinical use due to either toxicity or poor specificity. The ongoing challenge of developing specific inhibitors of SOCC involving STIM and Orai proteins as targets is to be met only by further developing our understanding of STIM/Orai mechanisms, interactions, and channel gating, with the overarching goal of improving upon currently available drug treatments.

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Conflict of Interest

The authors declare no conflict of interest.

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