Minireview

Store-operated calcium entry and diabetic complications

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Abstract

Store-operated Ca^{2+} entry (SOCE) is mediated by the store-operated Ca^{2+} channel (SOC) that opens upon depletion of internal Ca^{2+} stores following activation of G protein-coupled receptors or receptor tyrosine kinases. Over the past two decades, the physiological and pathological relevance of SOCE has been extensively studied. Recently, accumulating evidence suggests associations of altered SOCE with diabetic complications. This review focuses on the implication of SOCE as it pertains to various complications resulting from diabetes. We summarize recent findings by us and others on the involvement of abnormal SOCE in the development of diabetic complications, such as diabetic nephropathy and diabetic vasculopathy. The underlying mechanisms that mediate the diabetes-associated alterations of SOCE are also discussed. The SOCE pathway may be considered as a potential therapeutic target for diabetes-associated diseases.

Keywords: Store-operated Ca^{2+} channel, store-operated Ca^{2+} entry, calcium, diabetes, diabetic complications

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Introduction

Store-operated Ca^{2+} entry (SOCE), previously known as Ca^{2+} release activated Ca^{2+} influx[1,2] or capacitative calcium entry[3], is an essential Ca^{2+} entry mechanism in both excitable and non-excitable cells. This Ca^{2+} entry is mediated by store-operated Ca^{2+} channel (SOC) which is activated by depletion of internal Ca^{2+} stores i.e. endoplasmic reticulum (ER)/sarcoplasmic reticulum (SR).[4] Therefore, circulating or locally produced hormones that activate either G protein-coupled receptors or receptor tyrosine kinases can open SOC through activation of the phospholipase C/inositol 1, 4, 5-triphosphate (IP_3) pathway.[5] It is important to note that any channel that exhibits Ca^{2+} store-dependent activity can be referred to as a SOC. Electrophysiological studies of cells with depleted ER stores have shown membrane currents with diverse properties, indicating that different classes of cells express distinct SOC.[4] The most studied and best-characterized SOC is the Ca^{2+} release-activated Ca^{2+} channel (CRAC) that is mainly expressed in the immune cells.[1,2] In this review, we do not specify Ca^{2+} entry mediated by different types of SOC (CRAC or general SOC). Instead, we use SOCE to refer Ca^{2+} entry through any type of SOC.

Although SOCE was discovered about 30 years ago, its molecular players were not identified with certainty until recently. By high throughput RNAi screening, two protein families, stromal interaction molecule (STIM)[6,7] and Orai,[8–10] were identified as required components of SOCE. STIM1 is a single-pass transmembrane protein located primarily in the ER membrane and functions as an ER Ca^{2+} sensor to sense ER luminal Ca^{2+} concentration. Orai1 is a small plasma membrane protein, which constitutes the pore-forming unit of SOC. Upon depletion of ER Ca^{2+}, STIM1 aggregates and translocates to ER-plasma membrane junctions, where it physically associates and subsequently activates Orai1 causing Ca^{2+} entry into the cytosol.[11,12] In addition to STIM1 and Orai1, STIM2 (a mammalian homolog of STIM1), and Orai2 and 3 (two mammalian homologs of Orai1) may also constitute/regulate SOC, but with distinct functional properties.[13–18] The Orai/STIM family-constituted SOCE pathway has become more complicated with the recent identification of splicing variants of Orai1 (Orai1α and Orai1β)[19,20] and STIM1 (STIM1L),[21–24] which generate SOC with distinct signaling and regulatory properties. Furthermore, several isoforms of canonical transient receptor potential (TRPC) proteins, which had been proposed as the molecular components of SOC prior to the discovery of Orai1 and STIM1, may also contribute to SOCE by interacting with STIM1 and/or Orai1.[25–33] Readers are referred to recent outstanding reviews for more information on the molecular components and gating/regulatory mechanisms of SOC.[34–39]

SOCE was initially considered as a major mechanism of Ca^{2+} entry in non-excitable cells, such as immune cells, platelets, and endothelial cells.[4,40] Later, this Ca^{2+} entry pathway was also found in many excitable cells, such as neurons,[17] cardiac myocytes,[41] skeletal muscle cells,[42] and vascular smooth muscle cells.[43] It is now widely accepted that SOCE is a ubiquitous Ca^{2+} signaling pathway that

regulates diverse cellular functions in a variety of tissues and organ systems.[44–51] Therefore, it is not surprising that dysfunction of SOC can lead to a series of disorders, such as immunodeficiency, myopathy, and vascular diseases.[44,51–60] Over the past decade, accumulating evidence has demonstrated that many diabetic complications involve alterations of SOCE and its signaling pathways.[60–64] Since diabetes and its complications are becoming epidemic worldwide and there is no curative therapy currently available for diabetic complications,[65–67] continued exploration of the basic pathophysiology of diabetic complications and of new therapeutic approaches is in need. This review summarizes the published studies on the associations of abnormal SOCE with the pathology of diabetic complications. The aim of this review is to provide information that the SOCE pathway may be a potential therapeutic target for various organ and system disorders associated with diabetes.

SOCE and the development of diabetic complications

SOCE and diabetic nephropathy

Diabetic nephropathy, one of the most common complications of diabetes mellitus, is a major cause of end stage renal disease.[68,69] Early features of diabetic nephropathy include glomerular hypertrophy with thickening of the glomerular basement membrane and expansion of the glomerular mesangium, which eventually develop into glomerulosclerosis and renal insufficiency.[70–74] Glomerular mesangial cells are the major contributor to these structural changes in diabetic kidney.[75–77] Mesangial cell function is controlled by intracellular Ca^{2+} signaling which involves several types of Ca^{2+} channels, including SOC.[78] The SOC in mesangial cells was first reported by Menè et al.[79] and later was electrophysiologically and pharmacologically characterized by Ma et al.[50] Several protein components, such as TRPC1, TRPC4, Orai1, and STIM1, which are required for SOCE were identified in human mesangial cells.[62,80,81] Furthermore, studies demonstrated that SOC participated in hormone-stimulated Ca^{2+} responses in mesangial cells.[82–85]

Alterations of SOC function in mesangial cells under conditions of diabetes have been extensively studied in both *in vitro* and *in vivo* settings. In earlier studies conducted in cultured rat and human mesangial cells, Mene et al. demonstrated that arginine vasopressin- and angiotensin II-induced SOCE was attenuated by high glucose treatment (30 mM for five days).[84,86] However, both vasopressin and angiotensin II not only activate SOC, but activate the receptor-operated Ca^{2+} channel as well.[87,88] Therefore, the attenuation of the Ca^{2+} response by high glucose in that study might be due to impairment of the receptor-operated Ca^{2+} channel. Nutt and coworkers examined the effects of high glucose on endothelin-1- (activates both SOC and receptor-operated Ca^{2+} channel) and thapsigargin- (selectively activates SOC)-induced Ca^{2+} response in cultured rat mesangial cells. They revealed that high glucose treatment at 30 mM for 5–7 days significantly reduced endothelin 1-induced Ca^{2+} entry, but had no effect on thapsigargin induced Ca^{2+} response.[85] Their study suggests that in a time period of five days, high glucose treatment did not impair SOCE, but significantly inhibited the Ca^{2+} entry through the receptor-operated channel. Because diabetic nephropathy is a progressive disease and biological processes in kidney cells are altered along with the disease development,[70,73,89] we recently examined the time course effect of high glucose treatment on SOC activity in cultured human mesangial cells. Prolonged treatment with high glucose (25 mM for >7 days) significantly enhanced cyclopiazonic acid-induced SOCE and IP_3-induced SOC current while a short-term treatment (<3 days) had a tendency to reduce SOC activity.[62] Although the mechanism for the initial suppression of SOC by high glucose was not clear, the augmentation of SOCE in a later phase was attributed to upregulation of STIM1 and Orai1.[62] Importantly, the abundance of STIM1 and Orai1 proteins was also significantly increased in the renal glomeruli/cortices of 4-week, but not 2-week streptozotocin (STZ)-treated rats (type 1 diabetes) and of high fat diet diabetic rats (type 2 diabetes) which manifested overt diabetic nephropathy.[62] Taken together, studies from different groups suggest that high glucose/diabetes effects on SOCE in mesangial cells are time course dependent. Although the mechanism and significance of the changes are not known at present, these studies have at least established an association of abnormal SOCE with diabetic kidney disease.

It is well known that over-production of extracellular matrix proteins by mesangial cells contributes to glomerular damage in diabetic nephropathy.[75–77] In general, SOCE promotes protein synthesis and cell growth, for instance contributing to cardiac hypertrophy.[51,90] However, a recent study revealed that the SOC-mediated Ca^{2+} influx suppressed cell growth in mouse embryonic fibroblasts and rat uterine leiomyoma cells through inhibition of AKT1.[91] Thus, the effect of SOC on protein production is cell type specific and/or cell context-dependent. We recently found that activation of SOC abrogated high glucose- and TGF-β1-induced fibronectin protein expression in cultured human mesangial cells.[92] Consistently, downregulation of SOC function in mesangial cells significantly increased extracellular matrix protein expression in cultured mesangial cells or in glomeruli/renal cortices in animals.[92] Thus, SOC in mesangial cells is an anti-fibrotic mechanism in kidney. It is possible that the early attenuation of SOCE in mesangial cells caused by high glucose described above[62] contributes to the early pathological changes in diabetic glomerulus (deposition of extracellular matrix proteins and mesangial expansion), but the later enhancement of SOCE is a compensatory response to counteract detrimental pathways in diabetic kidneys.

It should be noted that in addition to mesangial cells, several other types of kidney cells are also involved in the development of diabetic nephropathy, such as podocytes,[93–95] tubular epithelial cells,[70,71,96,97] and smooth muscle cells in the renal arterioles.[98–101] Studies have shown that SOC is present in some of those cells.[102–106] However, an association of SOC in those cells with the development of diabetic kidney disease has not been established.

SOCE and diabetic vasculopathy

An early indicator for the development of microvascular and macrovascular complications of diabetes is endothelial dysfunction, defined as a reduction in the vasodilatation response to an endothelium-dependent vasodilator (such as acetylcholine) or to flow-mediated vasodilatation.[107–110] Studies have linked the diabetes-associated dysfunction of the vascular endothelium to disturbances in Ca^{2+} homeostasis.[61,111] Prolonged exposure (4 days) of human umbilical vein endothelial cells to high glucose medium (30 mM) resulted in a significant increase in apoptosis, which was associated with increased SOC activity (assessed by whole cell patch clamp).[112] Furthermore, blockade of SOC with 2-aminoethoxydiphenyl borate (2-APB) and La^{3+} reversed the hyperglycemia-induced apoptosis. Similarly, in bovine aortic endothelial cells, Bishara and Ding showed that high glucose treatment at 25 mM for 24 and 72 h resulted in a sustained increase in SOCE following activation of the P_2Y receptor by ATP.[113] They proposed that the TRPC1 protein contributed to the enhanced SOCE because TRPC1 protein expression was elevated after 72-h high glucose treatment, and antisense TRPC1 treatment attenuated the ATP-induced Ca^{2+} response. However, it is not clear whether the TRPC1 protein functions as an SOC itself or as a regulator/modulator of SOC in that study. Recently, Daskoulidou et al. provided a molecular basis for high glucose-enhanced SOCE in vascular endothelial cells. They demonstrated that hyperglycemia (25 mM for three days) augmented SOCE which was accompanied by increased abundance of Orai1-3 and STIM1-2 proteins.[63] Expression levels of the Orai1-3 and STIM1-2 mRNAs were significantly increased in the abdominal aortae of Akita diabetic mice and STZ-diabetic mice.[63] Furthermore, expression levels of Orai1-2 and STIM1-2 mRNAs were also significantly higher in the aortae in type 2 diabetic patients.[63] However, an intriguing question which was not addressed in that study is whether the increases in SOCE and Orais/STIMs are the consequence of diabetes or the cause of diabetic vascular disease. Contrary to the Daskoulidou study, Estrada et al. recently reported that STIM1 protein expression was significantly reduced in coronary endothelial cells from STZ-diabetic mice.[114] The decrease in STIM1 protein abundance impaired ER Ca^{2+} refilling by disrupting the interaction between STIM1 and the ER/SR Ca^{2+}-ATPase, and consequently attenuated endothelium-dependent relaxation in diabetic coronary arteries.[114] Importantly, the endothelial dysfunction could be rescued by restoring the expression level of STIM1 in diabetic coronary endothelial cells.[114] Surprisingly, SOCE was not significantly different between control and diabetic endothelial cells in that study.[114] The discrepancies between the Daskoulidou and Estrada studies in the same diabetic model (STZ mouse) at similar stages of diabetes (6-8 weeks after STZ injection) may be derived from differences in the segments of vessels prepared (aortae vs. coronary artery), the samples studied (entire vesicular tissues vs. endothelial cells), and the molecular levels analyzed (mRNA vs. protein). Furthermore, the Estrada study did not examine the expression level of STIM2 which is also present in the coronary endothelial cells and may play a major role in regulating resting Ca^{2+} level in the ER (refilling).[17]

It is known that vascular complications of diabetes are produced, at least in part, by increased contraction of vascular smooth muscle cells due to elevated intracellular Ca^{2+} concentration.[115–117] Store-operated Ca^{2+} influx was substantially reduced in retinal microvascular smooth muscle from STZ diabetic rats. The attenuated SOCE was reversed by insulin treatment (to normalize blood glucose level).[118] Using the same diabetic model, Ma et al. also found an attenuated SOCE in aortic smooth muscle cells of STZ rats.[119] Importantly, the contractile response of the vessel was significantly reduced in the diabetic rats compared to that in control rats.[119] Similar results were also reported in type 2 diabetic animals. Mita and colleagues demonstrated that SOCE (activated by cyclopiazonic acid)-induced contraction of caudal artery smooth muscle strips isolated from Goto-Kakizaki rats (a type 2 diabetes model) was compromised. Interestingly, the expression levels of TRPC1 and TRPC6 were about two-fold greater in the vascular myocytes from Goto-Kakizaki rats than in those from non-diabetic rats.[120] In addition, the vascular smooth muscle from the diabetic rats expressed the TRPC4 protein, which was not present in the muscle cells from control rats.[120] The authors proposed that these contradictory findings of increased TRPCs with decreased SOC activity were due to changes in TRPC protein expression in Goto-Kakizaki rats. Increase in some TRPC proteins may specifically affect the assembly of the homo- and heterotetramers building the TRPC channels, resulting in channels with different electrophysiological activity.[120] On the contrary, the saphenous veins from patients with type 2 diabetes showed exaggerated cyclopiazonic acid-induced SOCE and contraction compared to the vessels from subjects without diabetes.[60] Apparently, the diabetes/high glucose effect on SOCE in vascular smooth muscle cells is complex and may be dependent on the species (human vs. rat/mouse), the stage of diabetes/duration of high glucose treatment, and the segments of the vessels. If SOCE in vascular smooth muscle cells is attenuated in diabetes as demonstrated by most studies discussed above, it is difficult to interpret the enhanced contractile response of vascular myocytes, a characteristic of diabetic vasculopathy.[115–117] One possible explanation is that a decrease in SOCE is a compensatory response, which protects vascular smooth muscle from over-reactive contraction in diabetes.

SOCE and platelet disorder in diabetes

Diabetes mellitus is a well-known risk factor for atherosclerotic disorders. In diabetes, exaggerated aggregation of platelets is one of the key factors for the initiation and progression of atherosclerosis.[121,122] Abnormality of Ca^{2+} mobilization was observed in platelets from diabetic patients.[123,124] Platelets have two separate agonist-sensitive Ca^{2+} stores and SOCE is the major mechanism of Ca^{2+} entry in platelets. Earlier studies revealed that SOCE stimulated by thrombin, thapsigargin or ionomycin was significantly greater in platelets from type 2 diabetic patients than in those from healthy controls.[125,126] Treatment with catalase

and trolox almost completely abolished the increased SOCE response, suggesting a reactive oxygen species (ROS)/reactive nitrogen species-mediated mechanism.[125] A later study from the same group provided molecular evidence for the diabetes-induced enhancement of SOCE in platelets. They found that the STIM1 and Orai1 proteins were significantly increased in platelets from patients with type 2 diabetes mellitus.[127] Interestingly, in a recent study this group used Mn^{2+} entry as an indication of SOC activity and found that SOCE in platelets from type II diabetic patients was actually reduced even though the overall Ca^{2+} entry was increased.[128] The authors reasoned that the enhanced SOCE observed previously might be derived from other Ca^{2+} entry mechanisms secondary to store depletion, such as reverse Na^+/Ca^{2+} exchange, secretion of autocrine signaling molecules, and TRPC channels. Nevertheless, their studies provided evidence that SOCE in platelets is altered in diabetes and the abnormality of SOCE could contribute to increased adhesiveness and aggregation of platelets, a prothrombotic state leading to micro and macroangiopathy in diabetes. Apparently, further study is needed to establish a cause–effect relationship between an abnormal SOCE in platelets and diabetic cardiovascular complications.

SOCE and diabetic cardiomyopathy

Diabetic cardiomyopathy is characterized by hypertrophy and it often deteriorates into a loss of cardiac mass.[129] In cardiomyocytes, SOCE has been shown to play an important role in regulating hypertrophic signaling pathways.[51,90] An increased amount of STIM1 protein as well as its variant STIM1L, in cardiomyocytes contributed to pathological cardiac hypertrophy by enhancing SOCE.[22] However, studies on the role of SOCE in diabetes-derived cardiac hypertrophy are scarce. In a study of cultured neonatal rat ventricular myocytes, Pang et al. demonstrated that short-term hyperglycemia (30 mM for 20 h) significantly decreased SOCE stimulated by angiotensin II or thapsigargin.[130] Hyperglycemia also significantly blunted the Ca^{2+}-dependent hypertrophic response as well as the Ca^{2+}-sensitive nuclear translocation of nuclear factor of activated T-cells (NFAT),[130] a well-known signaling pathway for cardiac hypertrophy.[131] However, it is uncertain whether this short-term hyperglycemia effect is beneficial or detrimental for the heart in diabetes. Although a prolonged hypertrophy may eventually lead to chronic cardiac failure, an initial cardiac hypertrophy may be an adaptive mechanism to hemodynamic stress at the early stage of diabetes. Further study is needed to clarify the significance and pathological relevance of altered SOCE in the development of diabetic cardiomyopathy.

Mechanisms for altered SOCE in diabetes

Because of the ubiquitous distribution and diverse functions of SOC and the sophisticated molecular and biological processes of diabetes, it is impossible to delineate a common mechanism for abnormal SOCE in different organs/tissues in diabetes. However, several factors, as described below, have been proposed to mediate the diabetes-associated alterations of SOCE.

Impairment of interactions among the molecular components of SOCE pathway

Shortly after the discovery of SOCE, the ''conformational coupling model'' was proposed to delineate how SOC was activated. In this model, depletion of the internal Ca^{2+} stores induces a conformational change of a particular protein on the ER membrane (an IP_3 receptor in the original hypothesis), and consequently elicits the opening of SOC through a direct physical coupling between the ER protein and the channel proteins in the plasma membrane.[132–136] With the recent breakthrough findings about the STIM1 and Orai1 proteins,[6–10] this protein–protein interaction model has been modified to a currently widely accepted model in which STIM1 protein on the ER membrane aggregates and translocates to ER-plasma membrane junctions upon depletion of ER Ca^{2+}, where it physically associates and subsequently activates Orai1/TRPCs, resulting in SOCE.[11,12,25–33] Therefore, interactions between STIM1 and Orai1/TRPCs are required for the initiation of SOCE, and impairment of those interactions is expected to attenuate SOCE. Diabetes may influence SOCE by disrupting the physical interactions among these essential protein components of the SOCE pathway. In a recent study by Jardin et al., SOCE was reduced in platelets from type II diabetic subjects.[128] However, the expression levels of several proteins in the SOCE pathway were increased (STIM1 and Orai1) or not altered (TRPC1).[127] A further study demonstrated that associations between STIM1 and Orai1/TRPC1 were attenuated in platelets from diabetic donors.[128] Therefore, the attenuation of SOCE in diabetic platelets is due to impairment of functional coupling between the gating protein (STIM1) and the channel proteins (Orai1/TRPCs). An interesting question is whether the diabetes-induced alteration of protein coupling is specific to platelets or is a common mechanism for other cell types. If it is platelet specific, what is the underlying mechanism for this cell context-dependent pathway?

ROS

ROS is a critical pathogenic factor in the development of diabetic complications.[77,137–139] Accumulating evidence has indicated that ROS contributes to the abnormality of SOCE in diabetes. In cultured human umbilical vein endothelial cells, high glucose treatment (30 mM for 4 days) enhanced SOCE, and consequently resulted in apoptosis.[112] Both responses were significantly inhibited by catalase, an enzyme that activates the decomposition of H_2O_2 into water and oxygen.[140] Thus, H_2O_2 is a mediator of high glucose-enhanced SOCE. Redondo et al. also reported an association of H_2O_2 with increased SOCE and aggregation in platelets from type 2 diabetic patients.[125] As discussed above,[130] short-term hyperglycemia (30 mM for 20 hours) reduced SOCE and hypertrophy in cardiomyocytes.[130] This heart-protective effect of hyperglycemia was partially restored by inhibition of

superoxide production with thenoyltrifluoroacetone (an inhibitor of electron transport complex II) and aminooxyacetic acid (an inhibitor of the malate-aspartate shuttle), suggesting a ROS-mediated response.[130] Therefore, ROS can increase SOCE (in endothelial cells and platelets), which is detrimental, and decrease SOCE (cardiomyocytes), which is beneficial, in diabetes depending on the tissues/organs. The dual effects of ROS on SOCE may reflect the complicated roles of ROS in cell signaling, i.e. being both an intracellular secondary messenger in many cellular signal transduction pathways and a major contributor to a variety of diseases.[77,137–139,141–145]

pp60^{src}

In an earlier study, King et al. found that the activity of tyrosine kinase pp60^{src} was elevated in STZ-induced diabetic rats.[146] Recent studies have shown that activation of this enzyme might contribute to diabetes/high glucose-induced augmentation of SOCE.[112,126] In cultured human umbilical vein endothelial cells, inhibition of pp60^{src} with PP1 significantly attenuated high glucose (30 mM for 4 days)-induced increase in SOCE.[112] In platelets from patients with type 2 diabetes, SOCE was exaggerated, which was accompanied by a greater activity of pp60^{src} upon depletion of the internal Ca^{2+} stores.[126] However, neither study determined how diabetes/high glucose activates pp60^{src}. It is known that pp60^{src} is a redox sensitive tyrosine kinase and mediates H_2O_2-induced responses in a variety of cells.[147–149] Therefore, it is possible that this enzyme is a downstream component of ROS in the regulation of SOCE in states of diabetes mellitus.

Protein kinase C

Hyperactivation of isoforms of protein kinase C (PKC) has been implicated in multiple complications associated with diabetes.[150] In glomerular mesangial cells cultured in medium containing normal glucose, PKC mediated store depletion-induced SOC activation.[151] However, when mesangial cells were cultured in high glucose medium (30 mM for five days), PKC suppressed SOCE.[84] This glucose concentration-dependent effect may be due to distinct isoforms of PKC which are activated under different conditions. For instance, under normal glucose conditions, it is the α isoform of PKC (PKCα) that is predominantly activated and is responsible for SOC activation.[152] However, under high glucose conditions, another isoform of PKC, such as PKCβ, which could be inhibitory to SOC, may play a predominant role. It has been firmly established that PKCβ is associated with the development of diabetic nephropathy.[153–156] Curtis et al. also proposed a PKC-mediated pathway for the reduction of SOCE in the smooth muscle cells of retinal microvessels from STZ diabetic rats.[118] In their study, the PKC antagonist staurosporine completely restored the reduced SOCE in the diabetic vascular myocytes.[118] Further study suggested that the β isoform of PKC was responsible for the inhibition because PKCβII was specifically upregulated in diabetic retina, and an inhibitor of PKCβ partially reversed the attenuated SOCE in the vascular smooth muscle cells from these diabetic rats.[118]

O-GlcNAcylation

Dynamic cycling of N-acetylglucosamine (termed *O*-GlcNAcylation) on nuclear and cytoplasmic proteins serves as a nutrient sensor to regulate cellular metabolism and physiology in response to nutrients, such as glucose.[157] *O*-GlcNAcylation regulates cellular process both independently and also via cross-talking with protein phosphorylation and other post-translational modifications.[158] Recently, emerging evidence has shown that *O*-GlcNAcylation of proteins is a major molecular player in the development of complications associated with diabetes, such as vasculopathy,[159,160] retinopathy,[161,162] cardiopathy,[163,164] and nephropathy.[165] Although multiple mechanisms which may be tissue-specific are responsible for contributions of abnormal *O*-GlcNAcylation to diabetic complications,[158–165] modulation of SOCE may play a role. As in a study discussed earlier, SOCE was attenuated by hyperglycemia (30 mM for 20 h) in cardiomyocytes.[130] This inhibitory effect was prevented by azaserine, an inhibitor of hexosamine biosynthetic pathway.[130] The hexosamine biosynthetic pathway is crucial in providing the substrate in formation of *O*-linked β-N-acetylglucosamine, which is needed for *O*-GlcNAcylation of proteins. Thus, modification of key components of SOCE pathway by *O*-GlcNAcylation may contribute to the impairment of SOCE in diabetes. Indeed, it has been reported that modification of STIM1 by *O*-GlcNAcylation attenuates SOCE in neonatal cardiomyocytes.[64]

Calcineurin/NFAT

It is known that the calcineurin/NFAT pathway is activated and contributes to the development of diabetic complications.[76,166] In cardiomyocytes and vascular endothelial cells, this pathway has been shown to reside downstream of SOCE and to mediate SOCE-induced hypertrophy [51,130] and apoptosis.[112] However, Daskoulidou et al. found that high glucose (25 mM for three days)-promoted SOCE in vascular endothelial cells and smooth muscle cells was mediated by the activation of calcineurin/NFAT signaling which upregulated the expression of Orai/STIM proteins.[63] Therefore, it is possible that diabetes triggers a positive feedback loop between SOCE and the calcineurin/NFAT pathway. In this loop, an initial increase in SOCE activates calcineurin/NFAT signaling which subsequently stimulates Orai1/STIM1 protein expression and consequently enhances SOCE, amplifying the cascade.

Closing remarks

It is clear that diabetes is associated with global changes in the SOCE pathway. However, the alterations of SOCE vary among different cell types and tissues with increased activity in some cells/tissues and decreased in others. Even in the same cell type and tissue, results from different groups appear to contradict each other. Although the reason for the discrepancies is not known with certainty, it is worth noting

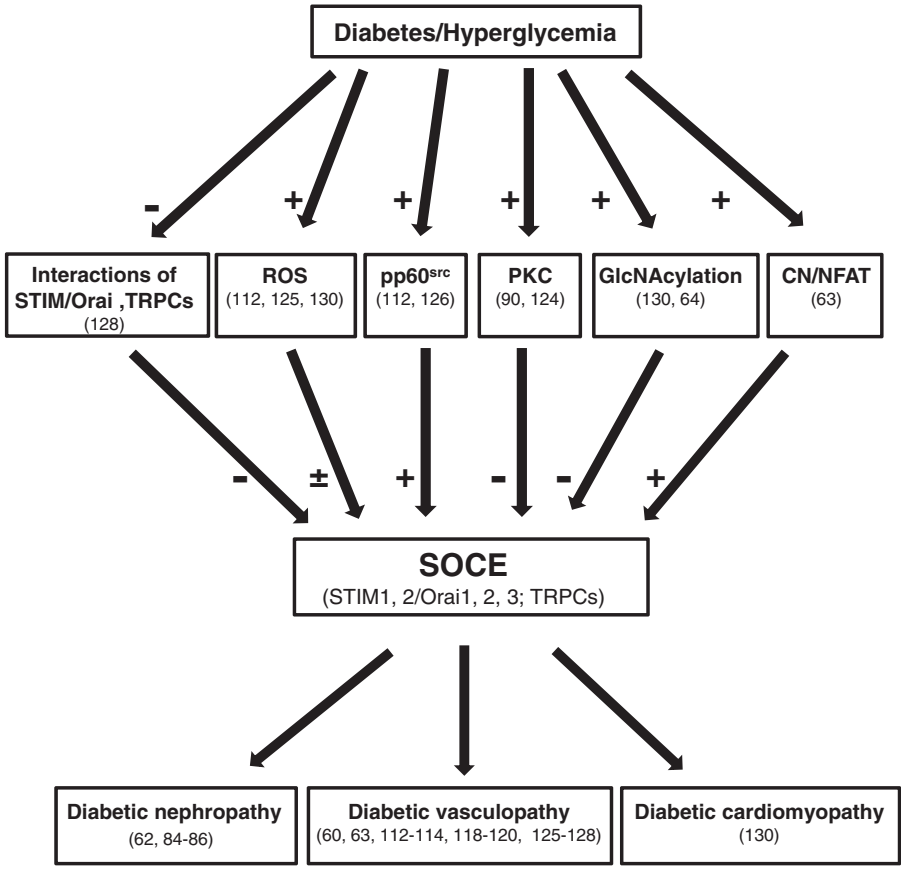

Figure 1 Illustration of involvement of abnormal SOCE in diabetic complications and possible underlying mechanisms. VSMCs: vascular smooth muscle cells; ROS: reactive oxygen species; PKC: protein kinase C; CN: calcineurin; NFAT: nuclear factor of activated T cell. ''+'': denotes promotion; ''-'': denotes inhibition; ±: denotes either promotion or inhibition, depending on tissues and cell types. The numbers in parenthesis indicate citations

that in many instances the animal species, cell/tissue types, stages and severity of diabetes, approaches for testing SOC activity, and glucose concentrations differ between sets of experiments. In addition, there are likely several different pathways mediating the diabetes-associated SOC dysfunction. These intracellular pathways may be cell type specific and therefore contribute to the varying SOCE responses to high glucose or diabetes in different type of cells. Furthermore, the mechanism of diabetes-associated SOCE dysregulation is currently unclear. Although several molecules, such as ROS and PKC, have been proposed to be mediators in this pathological process, how they upregulate or downregulate SOCE in diabetes is unknown. Moreover, whether the alteration of SOCE is the cause or the effect of diabetic diseases has yet to be determined. Figure 1 summarizes what is presently known regarding diabetes-associated changes in SOCE in different tissues and the possible underlying mechanisms for those changes. As a result of more information becoming known regarding abnormal SOCE and the development of diabetic complications, the development of specific regulators of SOCE could be a strategic option for various diabetic complications. Given the global pandemic of diabetes, searching for additional therapeutic agents is essential to reduce the immense burden of the disease. SOCE and its molecular components (STIM1/Orai1) may be a novel therapeutic target for patients with diabetic complications.

Authors' contributions: SC and RM equally contributed to this manuscript preparation.

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