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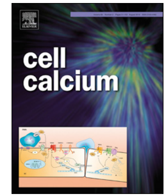
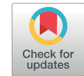


Neuronal calcium signaling *via* store-operated channels in health and disease



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ABSTRACT

Store-operated calcium entry (SOCE) is the flow of calcium ions (Ca^{2+}) into cells in response to the depletion of intracellular Ca^{2+} stores that reside predominantly in the endoplasmic reticulum (ER). The role of SOCE has been relatively well understood for non-excitable cells. It is mediated mostly by the ER Ca^{2+} sensor STIM1 and plasma membrane Ca^{2+} channel Orai1 and serves to sustain Ca^{2+} signaling and refill ER Ca^{2+} stores. In contrast, because of the complexity of Ca^{2+} influx mechanisms that are present in excitable cells, our knowledge about the function of neuronal SOCE (nSOCE) is still nascent. This review summarizes the available data on the molecular components of nSOCE and their relevance to neuronal signaling. We also present evidence of disturbances of nSOCE in neurodegenerative diseases (namely Alzheimer's disease, Huntington's disease, and Parkinson's disease) and traumatic brain injury. The emerging important role of nSOCE in neuronal physiology and pathology makes it a possible clinical target.

1. Introduction

Neurons depend on calcium ions (Ca^{2+}) for the regulation of such crucial processes as neurogenesis, neurotransmission, synaptic plasticity, and gene transcription. Compared with non-excitable cells, neurons possess a more diverse repertoire of Ca^{2+} handling proteins, many of which are specific to neurons [1]. Their task is to tightly control cellular Ca^{2+} levels in both space and time to enable the precise control of Ca^{2+} signaling effectors, such as the kinase CaMKII and phosphatase calcineurin (CaN). In all resting cells, Ca^{2+} levels are kept low in the cytosol (~100 nM), which is roughly four orders of magnitude lower than in the extracellular space [2]. Internally, Ca^{2+} is stored mostly in the endoplasmic reticulum (ER) where its concentration reaches hundreds of micromoles. The steep gradient between the cytosol and ER is maintained by sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) [2]. Upon cell stimulation, the Ca^{2+} that is stored is released from the ER *via* inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs) and ryanodine receptors (RyRs). These receptors are large channels with complex gating mechanisms that are both capable of mediating Ca^{2+}-induced Ca^{2+} release (CICR) from this organelle. Ca^{2+} can also leave the ER constitutively *via* poorly characterized Ca^{2+} leak channels [3]. In neurons, the ER forms an extensive continuous network that reaches axonal termini and most dendritic spines, especially larger ones, such as mushroom-type spines [4]. Thus, ER Ca^{2+} stores are present in all neuronal compartments that are crucial for neurotransmission. In resting neurons, ER Ca^{2+} levels are relatively low, but the ER can be quickly supercharged upon Ca^{2+} influx from the extracellular space upon cell depolarization [5–7]. Ca^{2+} influx in firing neurons is mediated by voltage-gated Ca^{2+} channels (VGCCs), which are abundant in the cell soma, dendrites, and nerve terminals [8], and receptor-operated channels (ROCs), such as ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs), which operate at synaptic and extrasynaptic sites [1]. Ca^{2+} entry *via* VGCCs and ROCs is complemented by store-operated Ca^{2+} entry (SOCE) that is mediated by store-operated channels (SOCs) in response to ER Ca^{2+} store depletion [1].

SOCE has been most thoroughly studied in non-excitable cells where it provides the major Ca^{2+} influx mechanism [9]. The search for a conducting component of SOCs took many years before it was identified in 2006 and named Orai1/CRACM1 [10–12]. The Orai1-based channel is also referred to as the Ca^{2+}-release activated Ca^{2+} (CRAC) channel because it is the molecular correlate of CRAC current (I_{CRAC}) that was well characterized in T lymphocytes and mast cells and exhibits high Ca^{2+} selectivity and low conductance [9]. The absence of Orai1 caused the abolishment of SOCE in MEF cells [13] and HeLa cells [14] and a substantial reduction in other cells, such as mast cells [15], T cells [13], and HEK293 cells [16]. In mammals, two additional closely related

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proteins, Orai2 and Orai3, can form similar SOCs upon their overexpression [17]. However, their physiological role remains uncertain. The *Drosophila* Orai channel is formed by six subunits [18], and mammalian SOCs can be composed of homomeric or heteromeric assemblies of Orai1-3 subunits [16]. The simultaneous deletion of *Orai1* and *Orai2* was recently reported to be required for the complete removal of SOCE in T cells [19]. Interestingly, the deletion of *Orai2* alone increased SOCE, which could be explained by the formation of channels composed entirely of Orai1 subunits that were more conductive for Ca^{2+} compared with Orai1/Orai2 heteromeric channels.

The activation of Orai1 is mediated by stromal interaction molecule 1 (STIM1), an ER integral membrane protein with an EF-hand motif on the luminal side [20,21]. A drop in ER Ca^{2+} levels (*e.g.*, upon Ca^{2+} release *via* IP_3Rs) causes the dissociation of Ca^{2+} from the EF hand motif, the oligomerization of STIM1 proteins, and their translocation toward ER-plasma membrane (PM) junctions where they bind and activate Orai1 channels by the so called STIM1-Orai1 Activating Region (SOAR)/CRAC activation domain (CAD)/CCb9 domain [22–24]. This results in Orai1-mediated SOCE. Orai1/STIM1 complexes can be observed under a microscope as distinct puncta. Orai1 can also be activated by another STIM protein, STIM2, albeit less efficiently [25]. Because STIM2 has a lower affinity for Ca^{2+} than STIM1 [26], its translocation to Orai1 channels is triggered by milder drops of ER Ca^{2+} [27]. STIM2 promoted the clustering of STIM1 at ER-PM junctions following partial Ca^{2+} store depletion [28]. It was also proposed to regulate resting ER and cytosolic Ca^{2+} levels [27]. Mutations of the human *ORAI1* and *STIM1* genes cause immunological disorders, muscle weakness, and ectodermal dysplasias, emphasizing their important physiological functions [29]. In contrast, no pathogenic mutations of *ORAI2*, *ORAI3*, or *STIM2* have been identified to date.

Another group of channels that is relevant for Ca^{2+} entry is the family of transient receptor potential (TRP) channels. These are numerous and widely expressed channels, but the most important for neuronal function are seven members of the canonical subfamily of TRP channels (TRPC1-7) [30]. TRP channels are formed by homo- or heterotetrameric arrangements of TRP proteins. TRPC channels are nonselective cation channels and for this reason they never fully met the requirements to be a constituent of CRAC channels [31]. Despite this, until the discovery of Orai1, they were frequently proposed to be SOCs, based on the results of Ca^{2+} imaging in gain-of-function and loss-of-function experimental setups. The current view is that TRPC channels, particularly TRPC1, contribute to SOCE in some types of cells in a way that depends on both STIM1 and Orai1 [31,32]. TRPC1-based channels are thought to mediate substantial SOCE in astrocytes [33]. TRPC1 was recruited to STIM1-Orai1 complexes upon Orai1-mediated Ca^{2+} influx [34]. TRPC1 is then activated by the polybasic domain in STIM1 that is distinct from SOAR/CAD/CCb9 [35]. Importantly, TRPCs, similar to other TRP channels, are able to open in response to various stimuli. TRPC3, TRPC6, and TRPC7 are directly activated by diacylglycerol, a product of phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis by phospholipase C, in a store-independent fashion [30,36]. As such, these channels can be regarded as ROCs. TRPC channels are now recognized to function as both STIM1-dependent and STIM1-independent channels, which is influenced by TRPC/Orai1 and TRPC/STIM1 ratios and the precise composition of TRPC channel subunits [36,37]. The combined current of STIM1-operated Orai and TRPC channels is referred to as store-operated current (I_{SOC}) to distinguish it from Ca^{2+}-selective I_{CRAC} that is driven exclusively by Orai channels [32].

The existence and physiological relevance of neuronal SOCE (nSOCE) was controversial before the identification of SOCE components [38] and continues to be debated more than a decade later [39]. Proving the store dependence of Ca^{2+} influx in neurons is challenging because the neuronal ER Ca^{2+} levels are unstable and appear to drop rapidly upon removal of extracellular Ca^{2+} even in the absence of SERCA inhibitors [40], such as thapsigargin (TG) or cyclopiazonic acid, which are commonly used to achieve ER Ca^{2+} store depletion in non-excitable cells. Therefore, "Ca^{2+} re-addition" assays of SOCE are difficult to control in neurons [39]. Furthermore, SOCE in neurons is relatively small in magnitude compared with SOCE in non-excitable cells and co-exists with other, much more efficient Ca^{2+} influx mechanisms that are typical of neuronal cells [39]. All this complicates the analysis of nSOCE. There is also little support from the clinic for an important role for nSOCE. Pathogenic mutations of the *ORAI1* and *STIM1* genes generally do not cause neurological symptoms. Among TRPC channels, only TRPC3 appears to be associated with a neurological condition. A point mutation of *TRPC3* was found in one patient with adult-onset ataxia, and the dominant *Moonwalker* gain-of-function mutation results in cerebellar ataxia in the mouse [41]. However, the gating mechanism of cerebellar TRPC3 remains unknown, and unclear is whether it involves a store-operated mode [41]. Nevertheless, accumulating evidence from research on animals that present defective STIM or Orai functions indicates an important physiological role for nSOCE in the mature brain and spinal cord. These data are summarized below. The emerging role of nSOCE in neurogenesis has been recently reviewed elsewhere [42] and will not be addressed in the present review. We also discuss various pathogenic conditions of the central nervous system that are associated with dysregulated nSOCE, such as neurodegenerative diseases (namely Alzheimer's disease, Huntington's disease, and Parkinson's disease) and traumatic injuries.

2. Distribution of major SOCE components in nervous tissue

SOCE is a common cellular Ca^{2+} influx mechanism and its molecular components are widely distributed in tissues. Inspection of the *Expression Atlas* (www.ebi.ac.uk/gxa) revealed prominent expression of the *ORAI1* gene in most human tissues, with particularly strong expression in the blood, spleen, lungs, and skin. The expression pattern of *ORAI3* is more uniform than *ORAI1*, without clear expression hotspots. Strikingly, *ORAI2* transcripts are enriched in the brain compared with other organs, and their levels are higher than *ORAI1* and *ORAI3* mRNA levels in various brain areas, such as the hippocampus, cerebellum, cerebral cortex, and hypothalamus. These findings are supported by expression data from the *Allen Brain Atlas*, showing the prominent expression of *Orai2* in the mouse hippocampus and to a lesser extent in the cerebellum, whereas *Orai1* is uniformly expressed in the brain at lower levels [43]. High levels of *Orai2* compared with *Orai1* and *Orai3* are found in cultured mouse hippocampal neurons [44] and Purkinje neurons (PNs) in the cerebellum [6]. In contrast, Orai1 dominates over Orai2 at both the mRNA and protein levels in mouse cortical neurons [45]. These data suggest that either Orai1 or Orai2 may be the major neuronal Orai isoform, depending on brain region. Among canonical TRP channels, *TRPC1* is by far the most abundant isoform in the whole human brain, with transcript levels comparable to *ORAI2* (data from *Expression Atlas*). In the mouse brain, *Trpc1* also has the strongest expression, except in the cerebellum, where *Trpc3* was equally abundant because of its very high expression levels in PNs [41].

Based on data from the *Expression Atlas*, *STIM1* and *STIM2* are both uniformly expressed in human tissues, with *STIM1* reaching higher average expression levels than *STIM2*. In the mouse brain, *Stim2* transcripts appear to dominate over *Stim1* transcripts [44,46]. The STIM2/STIM1 ratio was particularly high in the hippocampus at both the mRNA and protein levels [46]. This high ratio resulted from predominant *Stim2* expression in hippocampal neurons, demonstrated by the quantitative PCR (qPCR) analysis of laser-dissected hippocampal neurons of mouse [44] and rat [47] origin. *Stim2* mRNA levels were also higher than *Stim1* mRNA levels in rat cortical neurons [47]. Particularly high *Stim1* mRNA and STIM1 protein levels were found in the mouse cerebellum [48]. In this region, *Stim1* transcript levels can actually be higher than *Stim2*, especially in mouse PNs, in which *Stim1* transcripts were roughly 10-fold more abundant than *Stim2* transcripts [6].

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