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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].

3. Function of SOCE in nervous tissue

In non-excitable cells, such as white blood cells, the role of SOCE is relatively well understood. SOCE enables a sustained Ca^{2+} response that leads to CaN-mediated dephosphorylation of the transcription factor NFAT and its translocation into the nucleus [49]. This response is required for the transcription of a new set of genes and the subsequent activation of T cells. Ca^{2+} that enters cells *via* SOCs can also be transported by SERCA into the ER to refill Ca^{2+} stores. SOCE in non-excitable cells is predominantly mediated by STIM1 and Orai1, whereas the contribution of other STIM and Orai isoforms to SOCE is only beginning to be understood [50]. Furthermore, STIM1 and Orai1 were shown to reconstitute SOCE *in vitro* [51]. We found that the overproduction of Orai1 and STIM1 potentiated TG-induced SOCE in rat cortical neurons, whereas the overproduction of Orai1 and STIM2 increased constitutive Ca^{2+} entry [47]. The stronger interaction between endogenous Orai1 and STIM2 was subsequently demonstrated in cortical neurons that were exposed to a Ca^{2+}-free medium [52]. These findings suggested that STIM1 regulates SOCE, whereas STIM2 interacts with Orai1 to regulate resting Ca^{2+} levels in cortical neurons, akin to what was previously found in HeLa cells [27].

Many studies confirmed the existence of SOCE in neurons by applying pharmacological inhibitors of SOCE or by knocking down key components of SOCE machinery. nSOCE elicited by SERCA inhibition was blocked by ML-9 [47], an inhibitor of STIM1 translocation, and SOC inhibitors (*e.g.*, 2-APB, YM-58483, and SKF96365) [7,53–56]. The study by Berna-Erro et al. was one of the earliest attempts to investigate nSOCE in knockout (KO) mice that were devoid of SOC machinery components [44]. SOCE elicited by SERCA inhibition was absent in primary cortical neurons that were isolated from *Stim2* KO mice but not in neurons that were isolated from *Stim1* KO or *Orai1* KO mice. These results were consistent with high neuronal levels of *Stim2* mRNA and low detectable levels of *Orai1* and *Stim1* mRNA (notably, however, these authors provided qPCR data for hippocampal and not cortical neurons). *Stim2* KO mice developed normally but suffered from sudden death beginning 8 weeks after birth. Despite this, *Stim2* KO mice were better protected against cerebral ischemia compared with control mice, suggesting that the lack of STIM2 reduces Ca^{2+} overload during ischemic challenge [44]. A more detailed discussion of the role of STIM and Orai proteins in ischemic damage and stroke can be found in a recent review [57].

An additional line of evidence of an important role for STIM2 in nSOCE and neuronal physiology was provided by Bezprozvanny and coworkers. Genetic ablation of the *Stim2* gene diminished SOCE in the soma of hippocampal neurons and almost completely abolished SOCE in dendritic spines [58]. Neurons that lacked STIM2 had fewer mushroom spines, which are essential for memory storage [58–60]. STIM2 and nSOCE were also required for proper levels of phosphorylated CaMKII, and STIM2 co-localized with CaMKII in mushroom spines [58]. The results suggested that STIM2-regulated Ca^{2+} influx is necessary for the persistent activation of CaMKII and the maintenance of mushroom spines. STIM2-regulated SOCs in hippocampal synapses consisted of Orai2 subunits [43]. Interestingly, ER Ca^{2+} store depletion led to the assembly of a mature SOC complex that also contained TRPC6. All three proteins were enriched in the mouse hippocampus, and all three were required for maintaining normal numbers of mushroom spines (Fig. 1A). Orai1, although present in hippocampal neurons, was not required for nSOCE or the maintenance of mushroom spines. In contrast, Korkotian et al. found that Orai1 plays a crucial role in the formation of new synapses in rat hippocampal neurons [56]. The authors demonstrated that the presence of Orai1 facilitated the formation of new spines and that Orai1-positive spines had substantially higher Ca^{2+} influx than Orai1-negative spines. The knockdown of *Orai1* resulted in fewer mushroom spines and less frequent miniature excitatory postsynaptic currents (EPSCs). Orai1 strongly co-localized with STIM2 in dendritic spines upon extracellular Ca^{2+} depletion, whereas STIM1 was clearly less mobile and depended on STIM2 for its colocalization with Orai1. The reasons for the reported discrepancies in the requirement for Orai1 remain unknown. They may reflect species-dependent differences (*e.g.*, mouse *vs.* rat) or temporal differences (*e.g.*, Orai1 is required at earlier stages of spine formation than Orai2). Altogether, the aforementioned studies demonstrate a crucial role for nSOCE in the formation and maintenance of mature mushroom spines and suggest its role in synaptic plasticity. In fact, nSOCE was shown to be required for both the long-term potentiation (LTP) [53] and long-term depression (LTD) [45] of excitatory synaptic inputs. LTP and LTD reflect the activity-dependent strengthening and weakening, respectively, of synaptic connections and are widely believed to underlie learning. Additionally, STIM proteins were shown to affect synaptic plasticity in a way that appears to be nSOCE-independent (see also below) [59–62].

In cerebellar PNs, synaptic transmission from parallel fibers results in EPSCs that can be split into an AMPA-dependent fast component and metabotropic glutamate receptor 1 (mGluR1)-dependent slow component. Slow EPSCs were shown to result from the activity of TRPC3, the most abundant TRPC in these neurons [6,41] (Fig. 1B). The specific ablation of *Stim1* expression in mouse PNs led to the absence of IP_3-mediated ER Ca^{2+} release and TRPC3-mediated slow EPSCs through the exhaustion of ER Ca^{2+} stores. TRPC3-mediated currents could only be restored after the electrical stimulation of PNs that caused the supercharging of ER Ca^{2+} stores *via* VGCC activity. Therefore, STIM1 was proposed to regulate the refilling of dendritic Ca^{2+} stores in resting neurons (Fig. 1C). The idea that nSOCE is required to maintain steady-state Ca^{2+} levels was supported by direct measurements of both ER and cytosolic Ca^{2+} levels in hippocampal neurons. The removal of extracellular Ca^{2+} led not only to the rapid depletion of ER Ca^{2+} but also to a decrease in cytosolic Ca^{2+} levels [40]. The latter effect was also observed by others and suggests the existence of efficient Ca^{2+} extrusion mechanisms in neurons, which at a steady-state must be counteracted by continuous Ca^{2+} influx [54]. Importantly, the blockade of SOCE with two different inhibitors led to the fast decline of ER Ca^{2+} levels, suggesting that SOCE-like continuous activity is required for the maintenance of ER Ca^{2+} stores [40]. Another line of evidence of an important role for STIM1 and SOCE in resting neurons was provided by Lalonde et al. [7]. SOCE appeared to be constantly active in hyperpolarized cerebellar granule neurons. Under these conditions, STIM1 localized in puncta, and Ca^{2+} influx *via* SOCs led to rapid ubiquitination and degradation of the transcription factor Sp4 (Fig. 1D). Membrane depolarization, *Stim1* knockdown, and the pharmacological inhibition of SOCE all prevented the degradation of Sp4. The studies described above suggest an important homeostatic function of SOCE that provides resting neurons with Ca^{2+} when ROCs and VGCCs are not conducting [63].

A novel role for SOCE in nociception was suggested by Gao et al., who found that a SOCE inhibitor attenuated chronic pain [64]. A more recent study found that *Orai1* KO mice exhibited less nociceptive behavior after intraplantar injections of formalin or carrageenan [65]. At the molecular level, these noxious stimuli led to PKC-mediated ERK phosphorylation in dorsal horn neurons of the spine, which was not observed in *Orai1* KO mice. Orai1 deficiency also abrogated TG-induced SOCE and lowered the neuronal excitability of dorsal horn neurons, measured as spiking frequency in current-clamp experiments. The greater neuronal excitability in the presence of Orai1 was explained by a reduction of A-type potassium currents upon ERK activation (Fig. 1E). Furthermore, greater spiking after SOC stimulation following TG treatment was observed in sensory neurons of the dorsal root ganglia [66]. In this case, the suppression of this effect required the simultaneous knockdown of *Orai1* and *Orai3*, which were also both required for SOCE. In contrast, *Orai2* was not essential for SOCE despite its higher mRNA levels compared with *Orai1* and *Orai3* mRNA. In astrocytes of the spinal cord, TG-elicited Ca^{2+} influx was inhibited by 2-APB and YM-58483 treatment [67]. It was also almost completely inhibited by *Orai1* knockdown and partially by *Stim1* and *Stim2* knockdown. In

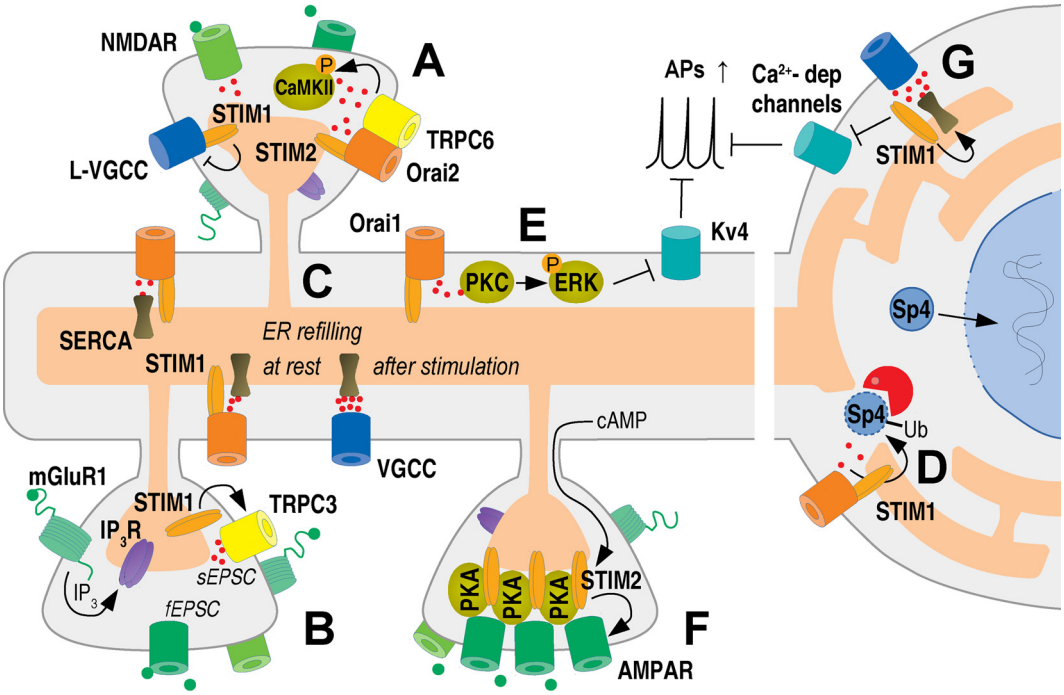

Fig. 1. Dendritic and somatic functions of SOCE and STIM proteins. (A) Structural plasticity of hippocampal dendritic spines. STIM2 drives neuronal SOCE (nSOCE) mediated by Orai2 and TRPC6 to activate CaMKII and stabilize mushroom spines [43,58,95]. STIM1 inhibits L-type VGCCs upon membrane depolarization as a negative-feedback response in order to enlarge the spinal ER compartment [70]. (B) Excitatory transmission in Purkinje neurons (PNs). AMPARs mediate fast EPSC (fEPSC), whereas STIM1 is required for TRPC3-mediated slow EPSC (sEPSC) in a store-dependent fashion [6]. (C) nSOCE maintains ER Ca^{2+} levels at rest, whereas VGCCs supercharge ER Ca^{2+} stores after membrane depolarization [6]. (D) nSOCE at rest leads to ubiquitination (Ub) and degradation of the transcription factor Sp4 in cerebellar granule cells [7]. (E) nSOCE enhances the excitability of dorsal horn neurons by the ERK-mediated inactivation of A-type currents through Kv4 channels [65]. (F) STIM2 enhances the phosphorylation and insertion of AMPARs into plasma membrane following ER Ca^{2+} store depletion or higher cAMP levels [59,72]. (G) STIM1 enhances the intrinsic excitability of PNs by facilitating the clearance of cytosolic Ca^{2+} in the soma through SERCA [73]. Depicted are the following classes of proteins: Orai channels (dark orange), STIMs (light orange), TRPCs (yellow), NMDARs (lime), AMPARs (dark green), mGluR1/5 (light green), VGCCs (dark blue), Cl^- and K^+ channels (light blue), IP_3Rs (purple), and SERCA (brown). Glutamate is shown as green circles, and Ca^{2+} is shown as red circles (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

contrast, the knockdown of *Orai2* and *Orai3* had no effect. This strongly suggests the existence of Orai1-mediated SOCE in these cells. Importantly, the pharmacological inhibition of SOCE or downregulation of *Orai1* or *Stim2* (but not *Stim1*) blocked LPS-induced production of the proinflammatory cytokines TNF-α and IL-6, suggesting that SOCE in spinal astrocytes may contribute to the development of chronic pain by stimulating cytokine production [67]. In summary, SOCE mediated by Orai1 may stimulate neuronal excitability and cytokine production and thus play an important role in the central and peripheral sensitization of nociception.

In addition to activating Orai channels to trigger SOCE in response to ER Ca^{2+} store depletion, STIM proteins have been shown to regulate other channels and processes that are relevant to neurophysiology. STIM1 was shown to inhibit Cav1.2, a widely expressed L-type VGCC [68,69]. Interestingly, the inhibition was mediated by the same STIM1 C-terminal domain that is employed to activate Orai1. The inhibitory action of STIM1 on L-type VGCCs in hippocampal neurons was validated in another study [70]. The inhibition occurred as a consequence of CICR that was triggered by activated NMDARs and L-type VGCCs and was necessary for ER enlargement inside dendritic spines [70] (Fig. 1A). STIM1 also exerts an inhibitory action on non-L-type VGCC-mediated Ca^{2+} influx at nerve terminals as part of a feedback loop that links ER Ca^{2+} content and neurotransmitter release [71]. However, the mechanistic details of this inhibition remain unknown. Using rat cortical neurons, we recently showed that STIM1 and STIM2 interacted with GluA1 and GluA2 subunits of AMPARs to regulate AMPAR-mediated Ca^{2+} influx in a store-dependent fashion [72]. Interestingly, Garcia-Alvarez et al. reported that STIM2 enhanced the phosphorylation and plasma membrane localization of GluA1 in response to cAMP [59]. Although these two studies differed with regard to the mechanism underlying the translocation of STIM2 toward ER-PM junctions, they both implicated STIM proteins in the dynamics of AMPARs (Fig. 1F). To investigate the role of STIM1 in hippocampal synaptic plasticity, transgenic mice that overexpressed *STIM1* under the Thy1.2 promoter were generated in our laboratory [61]. The transgenic mice exhibited significant impairments of mGluR-dependent LTD that was induced either by 5 Hz electrical stimulation or application of the mGluR1/5 receptor agonist DHPG. No changes in Ca^{2+} dynamics were observed in *STIM1*-overexpressing hippocampal neurons, raising the possibility that the STIM1-induced reduction of LTD was Ca^{2+}-independent. Finally, a novel Orai-independent role for STIM1 in the soma of PNs was reported by Ryu et al. [73]. STIM1 was shown to facilitate the SERCA-mediated uptake of Ca^{2+} that entered the cytosol *via* VGCCs (Fig. 1G). The lack of STIM1 caused the accumulation of cytosolic Ca^{2+} and reduced the intrinsic firing activity of PNs.

4. Disturbances of SOCE in Alzheimer's disease

Alzheimer's disease (AD) is the most frequent neurodegenerative disorder affecting 5 million people worldwide each year [74]. AD patients suffer from cognitive impairment and memory loss. Most cases are sporadic, with an onset after 65 years of age, but 1–6% of cases have an earlier onset (30–65 years of age) and are usually caused by mutations of the genes that encode presenilin-1 (PS1), presenilin-2 (PS2), and amyloid precursor protein (APP). This inherited form of AD is referred to as familial AD (FAD). Presenilins are enzymatic components of γ-secretase, which process integral membrane proteins, including APP. The amyloidogenic processing of APP results in the formation of β-

amyloid (Aβ) peptides, which can accumulate as extracellular plaques in AD patients. The prevalent amyloid cascade hypothesis of the pathogenesis of AD states that the deposition of Aβ leads to neuronal death mostly in the cerebral cortex and hippocampus and dementia. However, all attempts to date to reduce Aβ aggregates have failed to halt the progression of AD [75]. Currently, soluble Aβ oligomers are considered to be toxic species. Accumulating evidence suggests that neuronal death is preceded by the aberrant hyperactivation of neuronal networks by Aβ oligomers [76]. This can also lead to an increase in intracellular Ca^{2+} levels. Transgenic AD model mice exhibited Ca^{2+} overload in neurons that were close to Aβ plaques [77] and a global increase in astrocytic Ca^{2+} levels [78]. Aβ was proposed to enhance multiple Ca^{2+} entry pathways [79] and RyR-mediated ER Ca^{2+} leakage [80]. In addition to generating toxic Aβ, PS1 and PS2 FAD mutants affect ER Ca^{2+} signaling in a γ-secretase-independent manner (*i.e.*, precluding the involvement of Aβ), although the underlying mechanism is still a matter of debate [81–84]. PS1 and PS2 FAD mutations were also shown to reduce SOCE [5,55,58,85–88], whereas the depletion of PSs or inhibition of γ-secretase activity enhanced SOCE [86–90]. However, the possibility that these alterations of SOCE may simply be a consequence of the effects of PSs on ER Ca^{2+} cannot be excluded [5,85,91]. The effects of APP and APP FAD mutations on Ca^{2+} signaling have been less explored and appear to be less striking than the effects exerted by PSs. The knockdown of *App* diminished SOCE in cortical astrocytes, most likely due to concomitant reduction of Orai1 and TRPC1 levels [92], but not in neurons or HeLa cells, suggesting that the effect of APP on SOCE is cell type-dependent [14,55]. Direct measurements of ER Ca^{2+} content revealed higher resting levels of ER Ca^{2+} in cells devoid of APP [93] and lower loading of the ER with Ca^{2+} in cells overproducing the APP FAD mutant [94]. Therefore, similar to PSs, APP can regulate ER Ca^{2+} content, which may consequently also affect SOCE in some cells or experimental settings.

Recent work has provided mechanistic insights into the way in which SOCE is altered in FAD models (Fig. 2). The first hint came from the observation of a decrease in STIM2 levels in B lymphocytes isolated from FAD patients [87]. The reduction of STIM2 levels was subsequently confirmed in hippocampal neurons in two different knock-in mouse models of AD and proposed to be a compensatory response to higher ER Ca^{2+} levels [58,95]. As a result of STIM2 depletion, Orai2/TRPC6-mediated SOCE in the cell soma and especially in spines was substantially attenuated [43,58,95]. A functional consequence was a lower number of mature (mushroom-type) spines that was attributable to insufficient CaMKII phosphorylation. The authors proposed that disruption of the STIM2-nSOC-CaMKII pathway contributes to the loss of synapses and cognitive decline in AD patients [58]. The proximal effect (*i.e.*, higher ER Ca^{2+} levels) was explained by slower leakage of Ca^{2+} in the ER or the hyperactivation of mGluR5 by Aβ [58,95]. In contrast to these findings, the prolonged treatment of hippocampal astrocytes with Aβ augmented SOCE *via* the transcriptional upregulation of several genes, including *mGluR5*, *Trpc1*, and *Orai2* [96]. Thus, Aβ appears to lead to differential effects on SOCE in hippocampal neurons and astrocytes. A different mechanistic explanation for the attenuation of SOCE and fewer mushroom spines in hippocampal neurons was provided by Tong et al. [88]. These authors found that STIM1 was a substrate for γ-secretase, and its cleavage could lead to fewer functional STIM molecules in FAD cells. Unfortunately, the possible cleavage of STIM2 by γ-secretase was not investigated.

Most of our knowledge about changes in Ca^{2+} handling in AD comes from multiple cell and animal FAD models, in which one or more FAD-linked proteins are overproduced [97]. However, these models may not fully recapitulate changes in Ca^{2+} that occur in the much more frequent, sporadic form of Alzheimer's disease (SAD). To shed light on this issue, we analyzed Ca^{2+} dynamics in freshly isolated B lymphocytes from human subjects [98]. SOCE was significantly enhanced in cells from subjects with mild-cognitive impairment, a condition that frequently precedes the diagnosis of AD. However, no changes in SOCE were observed in cells from SAD patients compared with people without dementia. These results suggest that the overactivation of SOCE may be a transient feature of peripheral cells during the progression of cognitive decline.

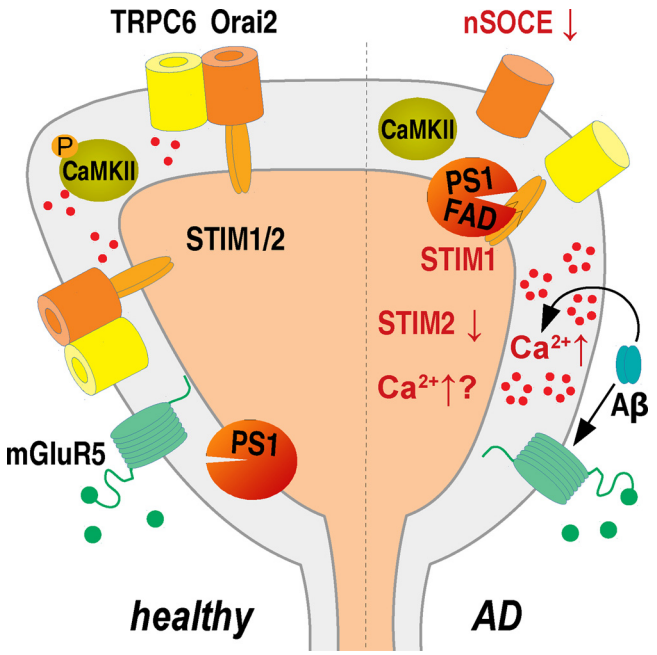

Fig. 2. nSOCE is diminished in AD hippocampal spines because of lower levels of functional STIM proteins. STIM2 levels are reduced in FAD cells [58,87], and STIM1 is inactivated by cleavage by FAD PS1-containing γ-secretase [88]. At the same time, Aβ causes intracellular Ca^{2+} overload *via* multiple mechanisms [79], including the hyperactivation of mGluR5 [95]. Whether there is concomitant Ca^{2+} overload in the ER is a matter of debate [81–84]. A decrease in nSOCE *via* Orai2 and TRPC6 leads to the insufficient activation of CaMKII and causes the destabilization of mature spines [43,58,95].

5. Disturbances of SOCE and ER Ca^{2+} release in Huntington's disease

Huntington's disease (HD) is a demential, inheritable neurodegenerative disease that is induced by the expansion of a CAG trinucleotide repeat in exon 1 of the huntingtin (*HTT*) gene. The repeat is translated into a polyglutamine tract in Huntingtin protein. When bearing more than 35 glutamine repeats, the polyglutamine tract becomes preferentially toxic to medium spiny neurons (MSNs) in the striatum [99,100]. To identify the mechanisms underlying HD neurodegeneration, several models have been developed. One of these models is transgenic YAC128 mice that overproduce full-length Huntingtin with 128 CAG repeats [101]. This HD model exhibits an age-dependent loss of striatal neurons, similar to human HD patients [101]. Other models for studying HD are R6/1 and R6/2 mice that overexpress exon 1 of the human *HTT* gene that encodes around 115 and 150 CAG repeats, respectively. These mice are characterized by a more pronounced HD phenotype [102]. Neural cultures of HD patient-derived induced pluripotent stem cells are also a convincing model to study neurodegeneration in HD [103,104]. Among the dysregulated genes, identified by RNA-seq analysis in HD patient-derived induced pluripotent stem cells, are genes that encode proteins involved in glutamate and GABA signaling, axonal guidance, the regulation of neuronal development and maturation, and Ca^{2+} influx [105]. The genes that encode TRPC6 and IP_3R1 were upregulated, whereas most other genes involved in Ca^{2+} signaling were downregulated. Changes in Ca^{2+} toolkit gene expression profiles were also found by other groups. For example, the higher expression of genes that encode Huntingtin-associated protein 1 (HAP1),

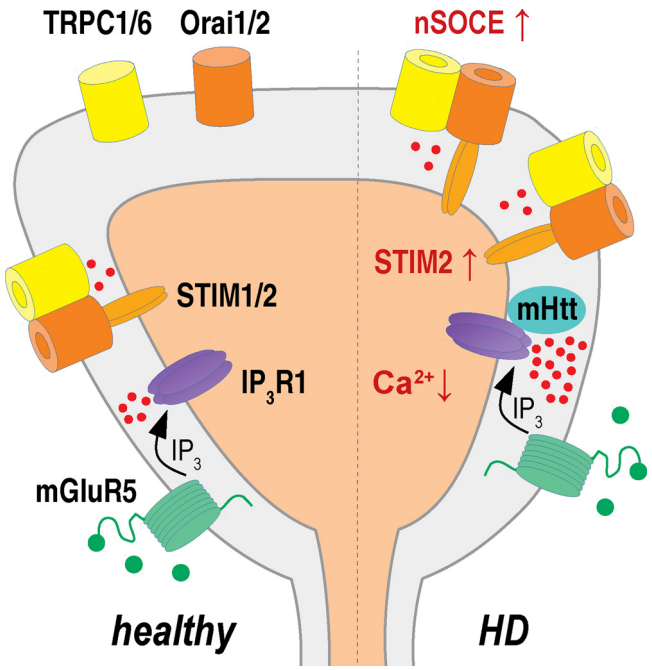

Fig. 3. nSOCE is upregulated in HD striatal MSN spines as a consequence of greater ER Ca^{2+} release. The binding of glutamate to mGluR5 initiates the IP_3 signaling cascade. The binding of mHtt to IP_3R1 facilitates ER Ca^{2+} release [113], which leads to an elevation of nSOCE through channels composed of TRPC1, TRPC6, Orai1, and Orai2 [118,119]. STIM2 levels are increased in YAC128 MSNs, which can further enhance nSOCE [117]. The upregulation of nSOCE results in the loss of spines in MSNs.

CacyBP/SIP, Calretinin (Calb2), CIB1, and CIB2 in the striatum in YAC128 mice were reported [106]. The list of 67 genes that were downregulated (*e.g.*, genes that encode VGCCs, TRP channels, STIM1, and Calb2) and 32 genes that were upregulated in models of HD are described in a review [99]. Disturbances in Ca^{2+} homeostasis and signaling were observed in most, if not all, HD models [99,106–109]. Mutant Huntingtin (mHtt) enhanced NMDAR function [110–112]. Furthermore, in the presence of HAP1, mHtt interacted with and facilitated the activation of IP_3R1 [113,114] (Fig. 3). This ternary interaction increased Ca^{2+} release *via* IP_3R1 upon the stimulation of mGluR5 [113]. The resulting reduction of ER Ca^{2+} content caused the upregulation of SOCE in YAC128 MSNs [115–118]. The levels of STIM2 were elevated in cultured YAC128 MSNs and YAC128 mouse striatum, which may further explain the observed enhancement of TG-induced nSOCE [117]. Importantly, the hyperactivation of SOCE led to striatal synaptic loss in YAC128 mice [117]. The normalization of SOCE by the downregulation of IP_3R1 or STIM2 levels led to the rescue of spine loss in YAC128 MSNs [117].

Using the same HD model, we found a 40% increase in DHPG-induced SOCE and an almost 20% increase in TG-induced SOCE in YAC128 MSNs compared with control cells [115]. All changes in Ca^{2+} signaling were specific to MSNs — no such changes were found in glial cells. The upregulation of SOCE in MSNs from YAC128 mice could be reversed by a tetrahydrocarbazole compound. The molecular target of this drug remains unknown, but it could involve changes in the cytoskeleton or posttranslational modifications of SOC machinery because of the short time required for treatment (*i.e.*, 5 min) [115]. Other drugs that normalized nSOCE and exhibited neuroprotective activity against glutamate excitotoxicity in YAC128 MSNs, such as EVP4593, were found to inhibit current flow through TRPC1-based channels [116]. The authors suggested that EVP4593 and other inhibitors of the STIM2-dependent nSOCE pathway are promising leading structures for the development of anti-HD drugs.

The identity of Ca^{2+} channels responsible for the increased SOCE in HD MSNs and their validation as potential therapeutic targets for HD were systematically analyzed by Bezprozvanny's group [119]. They found that the RNAi-mediated knockdown of *Trpc1*, *Trpc6*, *Orai1*, or *Orai2* rescued YAC128 MSN spines and suppressed hyperactive SOCE in these spines. In contrast, the knockdown of other *Trpc* genes or *Orai3* did not rescue spine loss in YAC128 MSNs. Based on *in vitro* and *in vivo* experiments, the authors postulated that TRPC1 may be a drug target in HD. The normalization of nSOCE and rescue of spines were also observed after *Stim1* knockdown. Together with previous findings from the same group [117], both STIM isoforms appear to be involved in nSOCE in HD MSNs.

Another potential drug target is the sigma-1 receptor (S1R). The S1R is an ER transmembrane protein that plays a role in regulating Ca^{2+} signaling between the ER and mitochondria. The S1R has high-affinity for pridopidine, which has been shown to improve motor symptoms of HD in clinical trials [120]. Pridopidine also prevented spine loss in aging YAC128 MSNs [121]. Its synaptoprotective effects may be attributable to the suppression of excessive ER Ca^{2+} release and nSOCE in MSN spines.

SERCA2 mRNA levels were significantly reduced in peripheral cells that were isolated from subjects carrying an HD causative mutation, regardless of disease status, compared with aged-matched controls [122]. The authors suggested that *SERCA2* mRNA is a potential molecular biomarker of the onset and progression of HD. It remains to be determined whether SERCA2 levels are reduced in the striatum in HD patients. If so, then this could likely lead to the same condition that is observed in HD models, namely a decrease in ER Ca^{2+} content and the upregulation of nSOCE.

One unresolved issue is whether the dysregulated Ca^{2+} homeostasis is a cause or a compensatory mechanism of HD? This is an important issue when developing potential treatments. It was suggested that compensatory processes likely develop to mitigate the harmful effects of mHtt [100]. Some of them can lessen disruptive effects of mHtt, but others may contribute to pathogenesis. The enhancement of IP_3R1 activity and upregulation of SOCE represent crucial targets for anti-HD treatments [100]. Compounds that block the downstream effects of greater IP_3R1 activity, such as the elevated SOC response, might be useful HD treatments, but more preclinical work is needed to validate this treatment approach [115,117].

6. Disturbances of SOCE in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease. It is caused by the loss of midbrain substantia nigra (SN) dopaminergic (DA) neurons, but its etiology remains unclear. Many mechanisms are thought to be involved in the death of these neurons, such as mitochondrial dysfunction, oxidative stress, impairment of the autophagy-lysosome pathway, and changes in intracellular Ca^{2+} homeostasis [123]. In fact, almost all factors that lead to PD are directly or indirectly related to Ca^{2+} signaling [123]. ER stress and perturbations in the ubiquitin proteasome system are also considered to contribute to the pathogenesis of PD [123–125]. Lower SERCA activity has been identified as a major cause of ER stress and neuron loss in PD. A small-molecule activator of SERCA that increases ER Ca^{2+} content rescued neurons from ER stress-induced cell death *in vitro* and had significant efficacy in the rat 6-hydroxydopamine model of PD [126].

MPTP is a drug that specifically kills DA neurons, so it is often used to generate PD models. The knockdown of *Stim1* increased the viability of PC12 cells that were injured with MPTP [127]. A similar protective effect against MPTP was observed with SOCE inhibitors. Both *Stim1*-targeting siRNA and SOC antagonists decreased Ca^{2+} influx in PC12 cells, thus linking the MPTP vulnerability to SOCE. The molecular mechanism by which SOCE inhibition exerts protective effects appears to involve the upregulation of *Homer1a* expression [127].

SN DA neurons engage Cav1.3 subunits as L-type VGCCs for their rhythmic activity. This may explain the higher vulnerability of SN DA

neurons in the development of PD compared with other neurons [128]. The identity of other Ca^{2+} channels involved in PD has not been established, but members of the TRPC family are likely candidates [129]. One of them is the TRPC1 channel, which was shown to protect PC12 cells from MPTP-induced apoptosis [130]. In a recent study, the pacemaking activity of SN DA neurons was found to increase in *Trpc1* KO mice [131]. Store depletion decreased rhythmic activity in wildtype mice, whereas no such decrease was observed in *Trpc1* KO mice. The addition of 2-APB or knockout of *Trpc1* inhibited TG-induced currents, suggesting that I_{SOC} in DA neurons is mediated by TRPC1. Furthermore, MPTP attenuated TRPC1 expression, which led to an abnormal increase in Cav1.3 activity and the subsequent degeneration of DA neurons. In contrast, the expression of STIM1 and Orai1 in neurotoxin-treated samples was unaltered. The results of this study indicated that TRPC1 provides a scaffold for STIM1 to bind and inhibit Cav1.3, thereby preventing the development of PD [131]. To reconcile these findings with the apparently contrasting data that were reported by Li et al. above [127], STIM1 appears to contribute to MPTP-induced toxicity in cultured neuron-like cells by activating detrimental SOCE, but in SN DA neurons, STIM1 appears to play a protective role by inhibiting L-type Ca^{2+} currents in a store- and TRPC1-dependent fashion.

New evidence suggests that Orai1-mediated SOCE may in fact be beneficial to DA neurons [132]. SOCE was markedly reduced in skin fibroblasts derived from both idiopathic PD (idPD) patients and a PD patient carrying a mutation in the PLA2g6 gene (*PARK14*) that encodes Ca^{2+}-independent phospholipase A2 (iPLA2β). The familial *PARK14* mutation prevented the proper activation of iPLA2β, and the plasma membrane-associated iPLA2β levels were reduced in idPD cells. To investigate the role of iPLA2β-dependent Ca^{2+} signaling in PD a new mouse model defective for store-dependent iPLA2β activation was established (PLA2g6 $ex2^{KO}$). The DA neurons from PLA2g6 $ex2^{KO}$ mice had reduced SOCE and low ER Ca^{2+} levels, and they also showed a marked deficiency in autophagy, which is one of the hallmarks of PD. Importantly, PLA2g6 $ex2^{KO}$ mice exhibited age-dependent loss of DA neurons. The data suggest that iPLA2β- and Orai1-dependent SOCE is required for the maintenance of ER Ca^{2+} stores and provide a link between Ca^{2+} signaling and autophagic flux in DA neurons [132].

7. SOCE in traumatic brain injury

Traumatic brain injury (TBI) occurs as a result of an external force to the head (*e.g.*, from vehicle collisions, sports, falls, and violence) and is a frequent cause of death and disability, especially among young people. The initial damage occurs at the moment of brain impact. Secondary damage occurs after the initial trauma and can last for a few hours or even months. During this period, there is a large release of excitatory neurotransmitters and ion influx. Cell damage associated with TBI is induced by the influx of Ca^{2+} into neurons and astrocytes. Mechanical stress that occurs in TBI also leads to disruption of the blood-brain barrier.

Our current understanding of the dysregulation of Ca^{2+} homeostasis and signaling in TBI is derived mostly from *in vitro* studies. The effects of stretch-induced traumatic injury on Ca^{2+} homeostasis were examined in cortical neurons cultured on silastic membranes [133]. After the stretch, intracellular Ca^{2+} was rapidly but transiently elevated. In the majority of cells, neuronal Ca^{2+} returned to basal levels within 3 h after injury. However, persistent alterations of Ca^{2+} signaling were observed, such as a greater elevation of intracellular Ca^{2+} in response to glutamate or NMDA, alterations of the responsiveness to mGluR agonists, and no response of Ca^{2+} stores to a stimulus shortly after injury, indicating that the ER was either empty or unable to release Ca^{2+}. The size of Ca^{2+} stores and ability to sequester Ca^{2+} appeared to recover within 3 h after injury [133]. The recovery was likely driven by the upregulated SOCE [134]. In 2001, this Ca^{2+} influx through SOCs was proposed to be mediated by both “conformational coupling and a diffusible messenger” [134]. Now, the mechanism can be referred to as the interaction between STIM and Orai during SOCE.

mGluR1 receptors have been shown to be involved in TBI by altering signaling and Ca^{2+} regulatory mechanisms in both immediate and delayed stages of TBI [135]. The initial release of Ca^{2+} from the ER after the stretch injury of axons was followed by higher Ca^{2+} transients, the number of which was greater compared with uninjured controls and persisted for many hours [136]. The ER was the initial source of Ca^{2+}, and the second peak appeared to depend on extracellular Ca^{2+}. It was suggested that the release of Ca^{2+} from intracellular stores is responsible for secondary Ca^{2+} influx *via* SOCs [136].

Two recent studies investigated the role of STIM proteins in TBI. The expression of *Stim2* was upregulated by TBI, whereas the level of *Stim1* was unaffected [137]. The downregulation of *Stim2* but not *Stim1* by shRNA technology improved neuronal survival in both *in vitro* and *in vivo* models of TBI, decreasing neuronal apoptosis and preserving neurological function. This neuroprotection was associated with a decrease in Ca^{2+} overload. The downregulation of *Stim*2 inhibited Ca^{2+} release from the ER, reduced SOCE, and decreased mitochondrial Ca^{2+}. STIM2 was suggested to promote secondary brain injury and might be a good target for TBI treatment [137]. In contrast to the aforementioned findings, another group showed the upregulation of *Stim1* expression in response to neuronal injury [138]. As a model of TBI, they used cultures of cortical neurons that were cut by 28 parallel blades using a punch device. In this traumatic neuronal injury (TNI) model, they observed effects of immediate death under the blades and secondary insults outside the cuts. They confirmed a role for mGluR1 activation after TNI in Ca^{2+} release from the ER. They found that *Stim1* knockdown using siRNA improved neuronal survival and reduced neuronal apoptosis after TNI. The mechanism involved a decrease in mGluR1-dependent Ca^{2+} overload. The knockdown of *Stim1* was suggested to prevent the release of Ca^{2+} from the ER by both IP_3Rs and RyRs after TNI [138].

However, searches for an effective pharmacological agent for TBI treatment have failed to date. In an *in vitro* model of traumatic cortical neuron injury, the TRPM7 channel inhibitor carvacrol reduced lactate dehydrogenase release, apoptosis, and caspase-3 activation. These neuroprotective effects were accompanied by a decrease in intracellular Ca^{2+} levels, but TG-induced SOCE and the expression of SOCE components were unaltered. Thus, carvacrol protected against TNI through a store-independent mechanism that possibly involves TRPM7 inhibition [139].

8. Concluding remarks

Substantial data demonstrate important functions of SOCE in nervous tissue, in both neurons and astrocytes. nSOCE is required for the maintenance of spines, neuronal excitability, and gene transcription. At the cellular level, Ca^{2+} flow through SOCs regulates kinases and phosphatases and affects the levels of transcription factors. Neuronal ER Ca^{2+} levels are relatively low, and Ca^{2+} easily escapes the ER and cytosol [40], thus demonstrating that constant SOC activity is required to maintain proper ER Ca^{2+} levels in resting neurons. Therefore, nSOCE plays an important homeostatic role [63]. Depending on brain region, Orai1 or Orai2 is the dominant Orai isoform, whereas Orai3 appears to play a less important role. The reason for the high abundance of Orai2 in the hippocampus and cerebellum is unknown, but it might be related to different characteristics of its Ca^{2+} currents compared with Orai1 [19,140] or possibly different binding partners (*e.g.*, TRPC6 in hippocampal neurons [43]). Evidence exists that functional neuronal SOCs can be formed by physically and functionally interacting Orai and TRPC channels [43]. In such arrangements, Orai subunits provide regulation by STIM proteins and high Ca^{2+} selectivity, whereas TRPC channels provide high conductance. Slightly surprising is the emerging important role of STIM2 in the brain, especially in the hippocampus. STIM2 is abundant in hippocampal neurons, localizes in dendritic spines, and is required for their maintenance [56,58]. STIM2 also exhibits striking changes in expression under pathophysiological conditions. Its levels in

the mouse hippocampus decrease with age [58] and are also reduced in mouse models of AD [58], human AD patients (including cerebral cortex samples [58] and peripheral cells [87]) and the mouse cortex following TBI [137]. In turn, STIM2 levels are elevated in the striatum in the mouse model of HD [117]. The changes in STIM2 levels appear to be the cause rather than consequence of a pathological condition because the normalization of STIM2 levels typically rescues the phenotype that is associated with this condition. Changes in STIM2 levels are positively correlated with neuronal SOC activity in hippocampal and MSN spines [58,117]. Notably, however, not all STIM functions in the brain are directly linked to nSOCE activation because STIM isoforms may target not only SOCs but also other channels, such as VGCCs and AMPARs.

Changes in nSOCE may be opposite under different pathological conditions. nSOCE is downregulated in hippocampal spines in mouse models of AD [58,95], but the opposite is observed in MSN spines in the YAC128 mouse model of HD [117]. In both disease models, dendritic spines are lost, which likely explains synaptic dysfunction and eventual neuronal death in AD and HD. The restoration of normal nSOCE levels by pharmacological treatment or correcting the levels of SOC components rescues the loss of dendritic spines [43,58,95,117,119]. Therefore, nSOCE has become a possible target for therapeutic interventions in neurodegenerative diseases. However, one important implication from the findings from animal models of AD, HD, and PD is that the pharmacological normalization of nSOCE in the affected brain region might have unwanted side effects in other brain regions. *Trpc1* knockout rescued spine loss and motor deficits in YAC128 mice [119], but it was shown to be detrimental to SN DA neurons [131]. Thus, potential drugs targeting neuronal SOC components, such as TRPC1, will most likely have to fit a narrow therapeutic window.

9. Disclosure statement

The authors declare no conflict of interest.

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