REVIEW

Intracellular Ca^{2+} waves in mammalian cells

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Abstract

Intracellular calcium waves refer to the coordinated propagation of increased free calcium ion (Ca^{2+}) concentration in the cytoplasm. Ca^{2+} is one of the major intracellular second messengers which coordinates many cells function including gene transcription, division, and cell apoptosis. The spread of the ions in the cytoplasm is not the same in all cell types. Experiments indicate the strength of the stimuli, the site of the first Ca^{2+} entry and the localization of the organelles influence the Ca^{2+} propagation and may lead to functional compartmentalization. Polarized cells with complex anatomy already have anatomical subparts (like processes) which elevate the probability of the functional separation between the cell parts. Cells are stimulated at special parts where the receptors/channels are located. Ca^{2+} enters the cell via ligand or voltage gated calcium channels, connexin channels from the neighboring cells or with the activation of G-protein coupled receptors which activate Ca^{2+} release from the cytosolic Ca^{2+} stores. The emptying stores may activate store-operated Ca^{2+} channels, too. These local signals could globalize and elevate free Ca^{2+} concentration in the cells. Smaller, more compact cells form a uniformly activated cell, however, in polarized cells this cannot happen in each time, leads to spatiotemporally different subpart activation. In this review, we discuss the main mechanisms of the cells which involved in Ca^{2+} signaling and the possible methods how a single event (a Ca^{2+} spike) can form slow intracellular Ca^{2+} wave and globalized signal. Intracellular Ca^{2+} waves were found in multiple cell types starting with simple egg cells. Here, we bring examples to anatomically more complex polarized cells with processes, but without excitability: the radial glia, astrocytes, Müller glia and osteocytes as a cell does not connect strongly to sensory-neural structures.

Keywords Intracellular Ca^{2+} waves · CICR · Mitochondrial CICR · Egg cells · Radial glia · Astrocyte · Müller cell · Osteocytes

Introduction

Intracellular calcium ion (Ca^{2+}) concentration ([Ca^{2+}]$_i$) is one of the major signals in every cell: it controls activity of enzymes, gene transcription, exocytosis, cell division and death (for reviews see (Berridge 2009, 2016; Clapham 2007; Lohse et al. 2024)). Because of its widespread function, the [Ca^{2+}]$_i$ is highly regulated by the cells. Characteristics of the elevating concentration (like the rise time, duration, amplitude, decay time or the frequency of the oscillation if oscillation is detected) can control different outcomes, e.g., short elevation leads to channel phosphorylation, but prolonged high concentration activate apoptosis in most of the cells (Pihán et al. 2021; Taheri et al. 2017; Takeuchi et al. 2020; Yang et al. 2022). The characteristics of the response depend on the number and the type of the channels which let Ca^{2+} inside (in addition, pore formation was hypothesized in case of mechanical stimuli (Li et al. 2018; Zhou et al. 2024)), the intracellular Ca^{2+} stores, the buffer and the extruder mechanisms (Fig. 1).

[Ca^{2+}]$_i$ is widely investigated by different Ca^{2+} imaging technics which are continuously developed. During the imaging experiments, fluorescent Ca^{2+} chelator dyes introduced to cytoplasm which emit different wavelength in Ca^{2+} bound and unbound forms. These indicators detect reliably the [Ca^{2+}]$_i$. Ca^{2+} dyes with different affinity to Ca^{2+} (K_d values) are available for answer the different questions: higher K_d value dyes are for detecting more globalized responses

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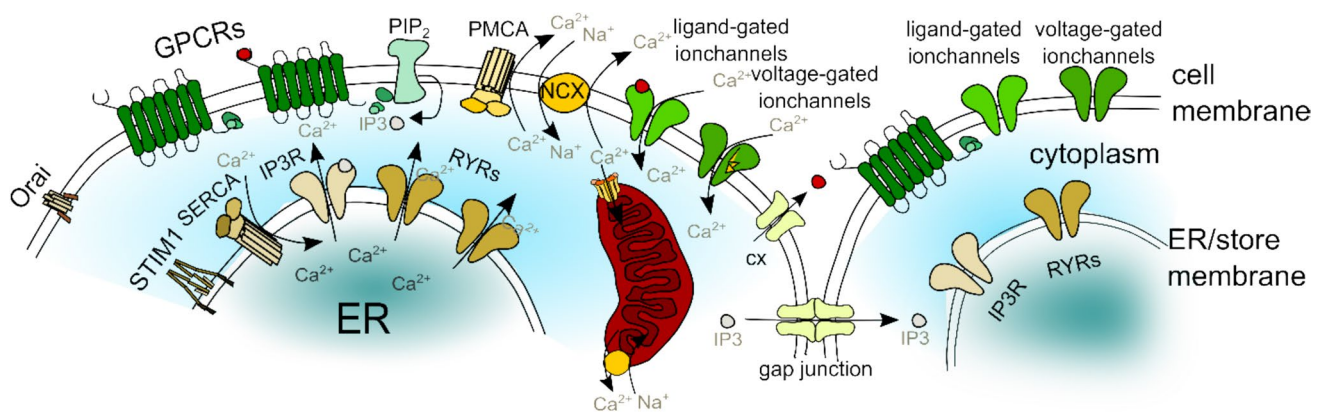
Fig. 1 Ca^{2+} handling mechanism in cells. $[Ca^{2+}]_i$ could be elevated by several mechanisms: release from the intracellular stores (like ER) induced by the G protein coupled receptors (GPCRs). Morphological changes activated by their ligands leads to the dissociation of the coupled G protein. The α subunit induces the membrane bounded phospholipase C which catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2). The formation of inositol-1,4,5-trisphosphate, and its diffusion to the ER located receptors leads to the release from the ER because of the concentration gradient. IP3R is also sensitized by the elevated Ca^{2+} at some point (and inhibited above it). The Ca^{2+} also activates the other internal store receptors: ryanodine receptors (RYRs). The cluster formation of the IP3Rs and RYRs could be the basis of the intracellular Ca^{2+} waves as the Ca^{2+} induces the release of more Ca^{2+} (CICR). Additionally, IP3 could move between cells via gap junctions, which could lead to intercellular waves. The source of $[Ca^{2+}]_i$ can be the extracellular space through ligand-gated cation channels and voltage-gated Ca^{2+} channels. In some cells, elevated $[Ca^{2+}]_i$ leads to the release of molecules (such as ATP) via connexin hemichannels, which can also activate the neighboring cells and cause intercellular Ca^{2+} waves. Resting $[Ca^{2+}]_i$ is restored by the Ca^{2+}/ATPases located on the ER (SERCA) and on the plasma membrane (PMCA). The Na^+/Ca^{2+} exchangers (NCX) on the plasma membrane help to decrease $[Ca^{2+}]_i$, whereas mitochondrial NCXs elevate the $[Ca^{2+}]_i$. Mitochondrial uniporters take up Ca^{2+} during the cytoplasmic elevation then release it by NCX. Cytoplasmic proteins also help in the buffering processes. In case of store depletion, STIM1 molecules change their morphology, connect to the membrane Orai proteins and refill the stores. Mitochondria and proteins (not shown) are involved in buffering the increased $[Ca^{2+}]_i$

involved more ions while indicators with lower value are better to find local Ca^{2+} elevations (for review see (Grienberger et al. 2022; Tang et al. 2020; Zhang et al. 2023a, b)). Most of the imaging studies are focused on the whole cell $[Ca^{2+}]_i$. First chemical indicators appeared around 1980 ($K_d \sim 1.1$ μM). Nowadays used chemical indicator K_d values are mostly between 300 and 400 nM. A widespread exception is Fura-2 which has 145 nM affinity to Ca^{2+} and sense lower concentrations, but Fura-2 has been showed to tend compartmentalize in the cell. In addition it Fura-2 needs to be activated by shorter, ultraviolet wavelength which can be harmful to the cells (Blatter and Wier 1990).

Next to the chemical synthetic indicators, since the 1997 genetically encoded Ca^{2+} indicators (GECIs) are on the market, but for their usage the genetic code of the cells are needed to be known (Chalfie et al. 1994; Miyawaki et al. 1997). In addition, the first GECIs K_d values were higher compared to the used synthetic ones (typically > 400 nM). The sixth generation of GECIs (from the GCaMP6 family) have 100–200 nM affinity which let more precise subcellular imaging (Akerboom et al. 2013; Inoue et al. 2019)). Next to the better affinity organellar GECIs are also available, but, as organelle Ca^{2+} concentration usually 30–300 μM, K_d values are higher (Suzuki et al. 2016). Nowadays the seventh and eighth generations of the indicators are developed and mostly neural Ca^{2+} signals investigated with the help of them—GCaMP7s present higher affinity compared to GCaMP6s (Dana et al. 2019) which is good for examine short $[Ca^{2+}]_i$ elevations (but has higher decay time and not suitable to investigate extrusion mechanisms). The GCaMP7c provide higher sensitivity (c stands for contrast) and promises to be a good choice for investigate small concentration changes, hence small compartment investigations (Dana et al. 2019). GCaMP8s provide faster decay times and involved in the research for small and transient elevation in $[Ca^{2+}]_i$ (Zhang et al. 2023a, b).

Ca^{2+} enters to the cytoplasm at a specific location in the cell and this local phenomenon could, but not always, globalize (Bootman, et al. 2001a; Denizot et al. 2019, 2022; Nakamura et al. 2012). Globalization can happen rapidly (for instance, the velocity of the intracellular Ca^{2+} propagation in neurons 106 μm/s (Breit and Queisser 2018)). However, some cells show slowly propagated intracellular Ca^{2+} waves which need more seconds to reach the other parts of the cell but still form globalized signals. In our review, we discuss the basic Ca^{2+} handling mechanisms of the cells and investigate how these slowly propagated Ca^{2+} signals could be formed and what function it could be (for faster Ca^{2+} waves review see: (Jaffe 2010)). We classify slow Ca^{2+} waves which propagation velocity is slower than 10 μm/s which is the lower third regime of the fast waves in Jaffe's review (3–30 μm/s). We decided to redefine his previous

class, because in case of Ca^{2+} waves slower than 3 μm/s rarely cause globalized signals in the cell, and Jaffe classification focused on the wave phenomena not specifically Ca^{2+} waves. Waves with slower propagation can be found during the smooth muscle contractions (contractile waves—in intestines or vessel walls).

Ca^{2+} handling mechanisms

The $[Ca^{2+}]_i$ of the cells depends on the cells molecular apparatus which let the Ca^{2+} enter to the cytoplasm, buffer it and then extrude it. The balance of these mechanisms influence the cell activation or not activation to a stimulus. Intracellular $[Ca^{2+}]_i$ in cells are usually maintained low (100 nM) (Chun and Santella 2013) and changes only in very narrow range, while the extracellular concentration is in millimolar range (Atchison and Beierwaltes 2013; Berridge 2016; Suzuki et al. 2014; Toman et al. 2020)—influx to the cytoplasm is always passive. Extrusion is ATP dependent or molecular carriers use other ion-gradients to cover their energy needs. Take a short look at each Ca^{2+} handling step which could be involved in a Ca^{2+} transient of a cell.

Influx

The $[Ca^{2+}]_i$ of the cells could elevate by 3 different, but connecting manner: with receptor regulated, capacitance regulated, and store-operated Ca^{2+} entry.

Receptor regulated Ca^{2+} entry

Receptor regulated Ca^{2+} entry refers to the ligand gated Ca^{2+} (or not selective cation) channels, inositol-1,4,5-triphosphate (IP3) receptors (IP3R) and ryanodine receptors (RYR). The two lasts are located on the surface of the endoplasmic reticulum (ER) and initialize the internal Ca^{2+} store release (Fig. 1). In addition to these 2 classical receptor groups, the transient receptor potential (TRP) channel family could be added, which are regulated by various internal stimuli, such as pH changes, heat, mechanical stimuli and several endogenous ligands (Fallah et al. 2022; Koivisto et al. 2022; Zhang et al. 2023a, b). Piezo channels, a freshly described, evolutionally conserved mechanically activated channel group also could let Ca^{2+} into the cytoplasm from the extracellular space. Piezo channels' influence on the hemichannels was demonstrated in osteocytes (Zeng et al. 2022) which could be involved in Ca^{2+} homeostasis of the cell (Coste et al. 2010; Delmas et al. 2022; Qin et al. 2021) (Table 1).

The cell surface located receptors/channels (like P2X purinoreceptor), opened by their stimulus (e.g., ATP), let the Ca^{2+} enter the cytoplasm. The possible uneven distribution of these receptors/channels could lead to local $[Ca^{2+}]_i$

elevation, which activates other intracellular mechanism to globalize the signal (e.g., depolarize the cell by ions entering to the cytoplasm and activate the capacitive Ca^{2+} inflow from the extracellular space). Polarized cells (epithelial cells, neurons, glia or cells with processed morphology) show higher inequality in receptors/channels distribution of their surface. A well-known example is the receptor localization of neural synapses: synaptic membrane surfaces are rich in not only receptors/channels where the cations could enter and may cause to further depolarization of the cell, but also in extruder molecules, pumps are localized in high numbers. Theoretically proofed the uneven distribution of these molecules is evolutionary more adaptive if the signal location has a distinct origin (Wang and Thomson 2022). Not only neurons, but epithelial, glandular cells or cells which connect two different compartments with their soma (e.g., Müller cells which bind the inner and outer part of the retina) classically show receptor/channel rich and poor parts (Brass et al. 2012; Ghose et al. 2022; Lohmann et al. 2005).

The intracellularly localized Ca^{2+} channels are found in the surface of membrane compartments, like ER, which functions as the biggest internal Ca^{2+} store (Berridge 2016; Daverkausen-Fischer and Pröls 2022). ER normal Ca^{2+} concentration ($[Ca^{2+}]_{ER}$) is between 100 and 1000 μM which is three magnitudes higher than the cytoplasmic concentration. Besides the ER, mitochondria, endosomes and lysosomes could be important internal stores in signalization, however, Golgi apparatus and autophagosomes also contains 100–10 000-fold higher Ca^{2+} concentrations in their lumen compared to the cytoplasm (Hu et al. 2024a, b, c).

IP3 receptors are the main non-selective cation channels on the surface of the ER. There are 3 isoforms (Alexander et al. 2023; Choi 2018; Schmitz et al. 2022), which could form homo- or heterotetrametric receptors with high Ca^{2+} conductivity (Prole and Taylor 2019; Schmitz et al. 2022). IP3Rs tend to form clusters on specific parts of the ER (Hu et al. 2024a, b, c; Prole and Taylor 2019). The receptor is activated by IP3 (Fig. 1). Ca^{2+} in lower concentrations works as a cofactor in the activation of IP3R1 (Alexander et al. 2023; Prole and Taylor 2019; Schmitz et al. 2022). In higher concentrations Ca^{2+} tend to inhibit all three subtypes (Alexander et al. 2023). Also, ATP could be a pre-activator of the channels (Schmitz et al. 2022). Interestingly, high Ca^{2+} concentration both in the cytoplasm and in the lumen of the ER (sensed by annexin1 Ca^{2+} binding protein) inhibit the channel activity (Vais et al. 2020).

Ryanodine receptors (RYRs) are the other widespread channels located on the ER surface. These receptors are sensitive to small $[Ca^{2+}]_i$ elevation and inhibited by higher concentrations (other ligands are the Mg^{2+} and ATP) (Choi 2018; Hu et al. 2024a, b, c). RYRs magnifies the signal in many cells via Ca^{2+} induced Ca^{2+} release (CICR) (Hu et al. 2024a, b, c). RYRs are also activated by the luminal

Table 1 List of Ca^{2+} permeable, ligand-gated ion, TRP and mechanically activated piezo channels which let extracellular Ca^{2+} enter to the cytoplasm of the cells

Name	Selectivity	Notes	Reference
Location on the surface membrane			
5-HT$_3$ receptors	Non-selective	6 subtypes 5-HT$_{3A}$ additional ligands: Ca^{2+}, Zn^{2+} and Mg^{2+}	Alexander et al. (2023), Barnes et al. (2023)
ASIC	Mostly selective to Na^+ but have low Ca^{2+} permeability detected	3 subtypes	Alexander et al. (2023), Kellenberger and Rash (2023)
Ionotropic Glu receptors	Non-selective; NMDA subtypes have higher permeability to Ca^{2+} than other subtypes	18 subtypes (classified in 4 groups: AMPA, kainite, delta, NMDA receptors)	Alexander et al. (2023) and Bettler et al. (2023), Pankratov and Lalo (2014)
nACh receptors	Non-selective; only some subunit combinations are Ca^{2+} permeable (for instance α9 (Matsunobu et al. 2001))	16 Mammalian subunit (+1 avian), each receptor builds up from 5 subunits	Alexander et al. (2023), Gotti et al. (2023), Pankratov and Lalo (2014)
P2X receptors	Non-selective	7 subunits; 3 subunits form a receptor	Alexander et al. (2023), Di Virgilio et al. (2023), Pankratov and Lalo (2014)
TRP channels	Usually non-selective, but: TRPV5 and TRPV6 are selective to Ca^{2+}; TRPM3 is selective to Ca^{2+} and Mn^{2+};	28 Mammalian proteins (classified in 6 subfamilies in 2 groups: group 1: TRPA, TRPC, TRPM, TRPV; group 2: TRPP, TRPML) + TRPN (not found in Mammalians)	Alexander et al. (2023), Blair et al. (2023), Fallah et al. (2022)
Piezo channels	Non-selective	2 subtypes	Alexander et al. (2023), Coste et al. (2010), Delmas et al. (2022)
Location on the membrane of the internal vesicular system			
IP3 receptors	Modest selectivity to Ca^{2+} over K^+	3 subtypes	Alexander et al. (2023), Hu et al. (2024a, b, c), Pankratov and Lalo (2014)
RY receptors	Non-selective	3 isoforms	Alexander et al. (2023); Takeshima et al. (2015)
TRP channels	Non-selective (+ TRPP1-2 shows localization dependent selectivity)	In endomembranous TRPVs, TRPP1-2, TRPM1-3, TRPML1-3 were demonstrated	Blair et al. (2023), Garrity et al. (2016), Kilpatrick et al. (2016), Li et al. (2019), Márquez-Nogueras et al. (2023), Tian et al. (2022)
P2X$_4$	Non-selective		Huang et al. (2014), Zhong et al. (2016)
TMBIM	Non-selective		Carrara et al. (2017), Guo et al. (2019), Kim et al. (2021), Pihán et al. (2021)
PTP	Non-selective	Strictly in the mitochondrial membrane	Bernardi et al. (2023), Bernardi and Di Lisa (2015), Ichas et al. (1997), Szabo and Szewczyk (2023)

5-HT, 5-hydroxytriptamide; ASIC, acid sensing ion channels; Glu, glutamate; nACh, nicotinic acetylcholine; TRP, transient receptor potential; IP3, inositol-1, 4, 5-triphosphate; RY, ryanodine; TMBIM, transmembrane BAX inhibitor motif; PTP, permeability transition pore

Ca^{2+} and hypothesized to prevent the overload of the internal store via the activation of the store overload-induced Ca^{2+} release (SOICR) (Takeshima et al. 2015). SOICR can induce apoptosis in the cell, which phenomenon seems to be promising in cancer therapies (Dong et al. 2023).

Next to the IP3Rs and RYRs, the TRP channels are expressed on the endomembrane (mostly on ER) system. TRPP2 channels are found to be activated by intracellular Ca^{2+} with high conductivity and fast release from the internal stores (Koulen et al. 2002; Márquez-Nogueras et al. 2023; P. fei Tian et al. 2022). The channel's ability to go four different state subconductant and reactivate fast seem to make it a good candidate to cause Ca^{2+} oscillations and rhythmicity in cell functions (Velázquez et al. 2023). TRPM1-3 and TRPML1-3 channels were found in late endosomes and lysosomes coordinating the Ca^{2+} efflux from these organelles and influencing exocytosis and membrane formation (Cheng et al. 2014; Garrett et al. 2024; Hirschi et al. 2017; Hu et al. 2024a, b, c; Kilpatrick et al. 2016; Matamala et al. 2021; McVeigh et al. 2024; Miao et al. 2015).

Special ion channels of the acidic membrane compartments (ER, Golgi apparatus, lysosomes, and inner mitochondrial membrane) are the transmembrane BAX inhibitor motif (TMBIM) proteins (Carrara et al. 2017; Group and Seitaj 2021; Kim et al. 2021). These proteins are activated by H^{+} and cause Ca^{2+} influx to cytoplasm, directly affect the cell proliferation and mitochondrial cristae morphology (Carrara et al. 2017; Guo et al. 2019; Pihán et al. 2021). Purinoreceptors, in addition to cell membrane, are also present on endomembrane system (Huang et al. 2014; Kroemer and Verkhratsky 2021; Santos et al. 2022). The activation of this receptors is involved in lysosomal fusion, ATP formation and elevation of lysosomal permeability (in immune cells) (Huang et al. 2014; Zhong et al. 2016).

Mitochondria play role in the Ca^{2+} dynamics of the cell. Mitochondrial Ca^{2+} concentration ([Ca^{2+}]$_{MT}$) is in the range of 0.05–300 µM (Jouaville et al. 1998; Suzuki et al. 2014, 2016). In case of elevated [Ca^{2+}]$_{i}$, the external membrane Ca^{2+} uniporter starts to take up the Ca^{2+} from the cytoplasm, with a facilitated diffusion into the mitochondria. The uniporter activity depends on a protein complex (VDAC—voltage dependent anion channel) thus the mitochondrial potential (Belosludtsev et al. 2019; Boyman et al. 2021; Raffaello et al. 2016; Toescu 2000; Wacquier et al. 2016; Zhao and Pan 2021). After the [Ca^{2+}]$_{i}$ decreased, the mitochondrial sodium-calcium exchanger (NCX) releases the elevated [Ca^{2+}]$_{MT}$. All in all, mitochondria have a buffering role in cell Ca^{2+} dynamics. However, in Ca^{2+} buffering mitochondria showed high cell-to-cell variations in HeLa cells and differences in subpopulation of mitochondria was also detected (Suzuki et al. 2014). The variability of the Ca^{2+} buffering activity

is independent from the mitochondrial pH and electricity (Suzuki et al. 2014).

It should be noted that there are many contact sites between the members of the internal membrane system. These contact sites allow each member to influence the others' function via the Ca^{2+} concentration (Atakpa et al. 2018; Ichas et al. 1997; Li et al. 2019; Peng et al. 2020; Raffaello et al. 2016). In some cases, this is necessary for the proper functioning of the organelle—for example, mitochondria or lysosomes need the Ca^{2+} which is released by the IP3R of the ER (Atakpa et al. 2018; Cárdenas et al. 2010; Garrity et al. 2016; Peng et al. 2020; Raffaello et al. 2016). The tight connection between the organelles helps to prevent Ca^{2+} globalization and only short Ca^{2+} spikes or puffs can be measured instead of global signs (Erustes et al. 2021).

Voltage-gated Ca^{2+} entry

The ion fluxes that are followed by the activation of the receptors shift the resting potential and may lead to opening of voltage-gated Ca^{2+} channels (Fig. 1). Voltage-gated channels are activated by changes in the ion balance between the intra-and extracellular compartments. Previously, these channels were thought to be present only on excitable cell (Catterall et al. 2023), however, several non-excitable cells were demonstrated to express them (e.g., adipocytes, fibroblasts, chondrocytes, hepatic cells, immune cells, glia and glia-like cells) (Pitt et al. 2021). The conductivity of the voltage-gated channels is higher than the ligand-gated channels and their activation leads easier to the globalization of the Ca^{2+} signals. The localization and number of these channels influence the intracellular Ca^{2+} wave velocity.

In addition to the membrane localized voltage-gated channels, the endomembrane system also expresses some voltage-dependent channels: on late endosomes and lysosome systems Na^{+} selective voltage-gated two pore channels (TPCs) were demonstrated (She et al. 2018; Zajac et al. 2024). These channels and their activation are still controversial: the voltage dependence and ion selectivity could be different depending on the activating cues of the channel (Gerndt et al. 2020; Hu et al. 2024a, b, c). The ER also seems to be depolarized, mostly because of the activation of RYRs (Campbell et al. 2023; Rad et al. 2018). The Ca^{2+} efflux from ER changes the membrane voltage of the organelle (which is normally considered to be 0 mV (Hu et al. 2024a, b, c)) leads to opening trimeric intracellular cation channels (TRICs). TRICs are impermeable to Ca^{2+} but let K^{+} enter to the ER to (possibly) balance the missing Ca^{2+} (Shrestha et al. 2020; Takeshima et al. 2015; Zhou et al. 2014).

Capacitive Ca²⁺ entry/Store-operated Ca²⁺ entry

Capacitive or store-operated Ca^{2+} entry (SOCE) happens when the internal Ca^{2+} stores are depleted and need to be recharged. Up to our knowledge, the only SOCE pathway is initiated by the stromal interaction molecule (STIM) activation (Ahmad et al. 2022; Shen et al. 2021; Shrestha et al. 2020) (Fig. 1). This molecule is located in the ER lumen and, due to the decreasing Ca^{2+} concentration, Ca^{2+} dissociates its N-terminal EF-hand (Bakowski et al. 2021; Shrestha et al. 2020). STIM1 morphology changes and binds to the membrane located Orai1 molecule, forming the STIM1/Orai1 complex responsible for ER refilling (Bakowski et al. 2021; Chakraborty et al. 2023; Shrestha et al. 2020). The formation of STIM1/Orai1 complexes starts only, when the $[Ca^{2+}]_{ER}$ decreases to 600 µM (Suzuki et al. 2014). Other STIM isoforms with Orai indicated to activate the TRPC1 non selective cation channels which also induce Ca^{2+} influx and activate the store refilling by SERCA (Moccia et al. 2023; Sanchez-Collado et al. 2022; Shalygin et al. 2021). In some cells (like HeLa), SOCE is fast enough not to elevate the cytoplasmic Ca^{2+} concentration. However, other cell types—like Jurkat T-cells, which have lower SERCA activity—have a considerable change in the $[Ca^{2+}]_i$ (Suzuki et al. 2014). SOCE mechanisms are also good candidates for coordinating intracellular oscillations in T-cells and glia cells (Schulte et al. 2022).

Connexin channels

Besides organelle contact sites, cell–cell contact sites and cell–cell communication are also important for Ca^{2+} signaling. In intercellular communication, gap junctions are one of the most important contributors. These channels are built up of connexins, a protein family with 21 protein isoforms in humans. Connexin monomers can oligomerize into hexameric structures forming the connexin hemichannels (HCs), through which ions (e.g., Ca^{2+} and K^+) and molecules with a molecular mass of up to 1 kDa (e.g., ATP, glutamate, IP3, Fig. 1) are able to pass (Van Campenhout, et al. 2021a, b; Zeng et al. 2022). The HCs of two adjacent cells can dock end-to-end to form gap junctions, therefore the HCs assist in the communication between the cell and the extracellular milieu while gap junctions contribute to the intercellular communication e.g., in the form of intercellular Ca^{2+} waves. HCs could also coordinate intercellular Ca^{2+} wave propagation through the release of ATP which induces neighboring cells (Cotrina et al. 1998; Stout et al. 2002). As HCs and gap junctions are important in intercellular Ca^{2+} signaling, they will not be discussed in a more detailed manner in this review. Those interested in further information on this topic can find additional information in these reviews: (Bayraktar

et al. 2024; Jagielnicki et al. 2024; Lucaciu et al. 2023; Van Campenhout et al. 2021a, b).

Buffering

For investigating the intracellular Ca^{2+} waves, it is not enough to check the influx mechanisms. Free Ca^{2+} rarely diffuses freely because more than 70 different cytoplasmic proteins have Ca^{2+} binding domains and Ca^{2+} is chelated rapidly (Elíes et al. 2020). When Ca^{2+} enters, 2 things can happen: a protein binds it, or leaves the cytoplasm with the help of an ATPase pump or a carrier.

As previously mentioned, mitochondria could buffer the elevated $[Ca^{2+}]_i$ with the help of Ca^{2+} uniporter, permeability transition pore (PTP) and NCX (Fig. 1). After the uptake of the excess $[Ca^{2+}]_i$, the mitochondria are only re-activated (Naryzhnaya et al. 2019) when the cytoplasmic Ca^{2+} begins to fall, and they slowly release the excess using an NCX (Dupont and Combettes 2016; Jackson and Robinson 2015; Mann et al. 2009). In short term $[Ca^{2+}]_i$ remains in physiological range. However, massive Ca^{2+} overload can cause mitochondrial malfunction (Krstic et al. 2022; Strubbe-Rivera et al. 2021). This buffering mitochondrial mechanism is not the only one to moderate the unexpectedly high $[Ca^{2+}]_i$: proteins of the cytoplasm could also bind the free Ca^{2+}. Depending on their respond to Ca^{2+} binding, they fall into 2 main groups: the buffer proteins, which simply bind Ca^{2+} until $[Ca^{2+}]_i$ decreases to a level that is not harmful to the cell, then release it; and the effector proteins which become activated by Ca^{2+} binding and have enzymatic functions in the cell (Chin and Means 2000; Elíes et al. 2020). The Ca^{2+} affinity of the protein depends on the domain that binds the Ca^{2+} which is the basis of their classification: EF-hand domains; EGF-like domains; γ-carboxyl glutamic acid-rich domains; cadherin domains; Ca^{2+}-dependent (C)-type lectin-like domains; Ca^{2+}-binding pockets of family C G-protein-coupled receptors. This review does not want to discuss all the Ca^{2+} binding proteins here, but some important ones must be mentioned. The most famous effector proteins, involved in several intracellular pathways, are the calmodulins belong to the group of EF-hand domain proteins (Andrews et al. 2021). Calmodulins are involved in the interactions of gap junction opening/closing processes (Peracchia and Peracchia 2021; Zou et al. 2014), activation of Ca^{2+} pumps, channels and Ca^{2+} activated K^+ channels (Ames 2021; Bohush et al. 2021; Mantilla et al. 2023; Vydra Bousova et al. 2023; Zou et al. 2014). Calmodulins are the inbuilt part of many GECIs: found in the Camgaroos, GCaMPs, Cameleons, pericams, RCaMPs and GECOs (Akerboom et al. 2013; Day-Cooney et al. 2023; Kotlikoff 2007; Tian et al. 2012).

Other than calmodulins, troponins should be mentioned as a Ca^{2+} binding part of GECIs. Troponins also belong to

the EF-hand domain proteins and usually have 4 binding parts (Vinogradova et al. 2005). These molecules are part of the TN family of GECIs (e.g.,: TN-L15, TN-XL) and Twich's (Heim and Griesbeck 2004; Mank et al. 2006; Thestrup et al. 2014). Their physiological function is the block the myosin binding sites on the actin filaments is muscle cells in a complex with tropomyosin (Tobacman 2021).

One big Ca^{2+} binding effector protein family is the C2 domain containing family, which includes protein kinase C and synaptotagmins (Bowers and Reist 2020; Elíes et al. 2020; Gruget et al. 2020; Kohout et al. 2002). The buffering proteins in neurons are used for classification of interneurons: parvalbumin, calbindin, calretinin and cholecystokinin are the most well-known ones (Capsoni et al. 2021; Jung et al. 2020; Ruden et al. 2021; Schwaller 2009).

Efflux

The Ca^{2+} extrusion from the cytoplasm is necessary for the survival of the cell (Hu et al. 2024a, b, c; Xiao et al. 2023). Most of the efflux-mechanism are induced by the elevated $[Ca^{2+}]_i$. Molecules involved in the phenomenon contain Ca^{2+} binding sites that determine which $[Ca^{2+}]_i$ activate the mechanism. The Ca^{2+} removal from the cytoplasm can be directed toward the extracellular space, the lumen of the endoplasmic reticulum, mitochondria, and other inner membrane structures.

Ca^{2+}/ATPases

Ca^{2+}/ATPases are energy (ATP) requiring pumps located on membrane surfaces (Fig. 1). The most effective pump involved in the decrease of the $[Ca^{2+}]_i$ is the sarcoplasmic/endoplasmic reticulum Ca^{2+}/ATPase (SERCA), which refills the ER. ER can refill other organelles with their membrane-membrane connections (Aguayo-Ortiz and Michel Espinoza-Fonseca 2020; Alexander et al. 2023; Stroik et al. 2018; Tedeschi et al. 2021; Wuytack et al. 2002; Xu and Remmen 2021). SERCA has 3 isoforms (SERCA1-3) and many splice variants (Wuytack et al. 2002). SERCA3 isoform has five-fold lower affinity for cytosolic Ca^{2+} (Wuytack et al. 2002). This indicates that SERCA3 is mostly active only at high $[Ca^{2+}]_i$ during transients, while other SERCA types help to maintain basal Ca^{2+} levels. The velocity of SERCA can directly influence the Ca^{2+} signals globalization and wave formation—in slower pumping back speed let the signs to globalize, but faster activity disrupts the intracellular waves and elevate the probability of short spikes (Sato et al. 2021). The $[Ca^{2+}]_{ER}$ is not only important for the fine folding of the freshly expressed proteins, but it influences the Ca^{2+} levels of other organelles (e.g., lysosomes) via contact sites (Garrity et al. 2016; Tedeschi et al. 2021; Yang et al. 2019).

Ca^{2+}/ATPases are also located on the plasma membrane (PMCA1-4). The stoichiometry of PMCA is lower: it only takes out 1 Ca^{2+} per ATP (whereas SERCA takes out 2 Ca^{2+}/ATP). However, PMCA Ca^{2+} affinity is high and helps maintain the basal $[Ca^{2+}]_i$ (Bomfim et al. 2023; Brini and Carafoli 2011). This seems to be supported by the data that acidic phospholipids also activate the PMCA, which are constantly active at about 50% of their maximal activity (Bomfim et al. 2023; Niggli et al. 1981). Some studies investigate the 4 isoforms and splice variants (> 30) of the PMCA found that some variants could be activated by higher Ca^{2+} concentrations (in the μM range). This suggests that these pumps may also play a role in the reduction of $[Ca^{2+}]_i$ during transients, perhaps in cooperation with the Na^+/Ca^{2+} exchanger (Alves and Oliveira 2024; Brini 2013; Brini and Carafoli 2009, 2011) or other proteins like neuroplastin in neurons (Constantin et al. 2021).

A third type of pump, the secretory pathway Ca^{2+}/Mn^{2+}/ATPases (SPCA1-2) which found in the Golgi apparatus and mitochondria (Chen et al. 2023; Makena et al. 2022). These pumps can upload the lumen of the organelles without the help of the ER (store independent Ca^{2+} uptake from the cytoplasm) (Makena et al. 2022; Wu et al. 2023).

Other type of transporter proteins

In addition to the pump proteins, the Ca^{2+}/cation exchangers also help carrying the Ca^{2+} through membranes (Khananshvili 2023). This big antiporter group uses Na^+, K^+, H^+, Li^+, or Mg^{2+} and their concentration gradients to transport the Ca^{2+} (Khananshvili 2023). The most important family in this group is the Na^+/Ca^{2+} exchanger (Fig. 1). NCX1 is found in all cells, while NCX2 and NCX3 are mostly expressed in the brain and in muscle cells (Brini and Carafoli 2011; Giladi et al. 2024; On et al. 2008). NCXs use the extracellular Na^+ to facilitate the extrusion of Ca^{2+} from the cell after a Ca^{2+} transient, although it could switch to reverse mode and extrude the elevated Na^+ from the cytoplasm, e.g., after an action potential in neurons (Alexander et al. 2023; Hancox 2021; Xue et al. 2023). NCXs have low affinity for Ca^{2+} but high capacity (Brini and Carafoli 2011; Xue et al. 2023). In addition to the plasma membrane, NCXs were also found on the mitochondria to release Ca^{2+} that was taken up during the buffering process (Magi et al. 2020; Zhang and Morad 2025). However, some studies indicate that it is not the NCX but another family, the $Na^+/Ca^{2+}/Li^+$ exchangers (NCLXs), are more important for mitochondrial buffering (Rysted et al. 2021; A. Takeuchi and Matsuoka 2021). NCLX transports Li^+ with the Na^+. The third Ca^{2+}/cation transporter family is the potassium transporter NCKX (Al-Khannaq and Lytton 2022; Hancox 2021; Hassan and Lytton 2020) which is also hypothesized to be localized in the mitochondria (Takeuchi and Matsuoka 2021).

Ca^{2+} could enter to the lysosomes, which have a pH-dependent Ca^{2+} uptake mechanism and a Ca^{2+}/H$^+$ exchange mechanism (Christensen et al. 2002; Meng et al. 2023; Zajac et al. 2024), but another type of ATPase, the ATP13A2, also seems to facilitate the Ca^{2+} uptake in this organelle (Zajac et al. 2024).

Ca^{2+} induced Ca^{2+} release

Ca^{2+} induced Ca^{2+} release (CICR) refers to the mechanism by which Ca^{2+} is released from the internal stores, especially from the ER, under the control of Ca^{2+}. This mechanism is present in both excitable and non-excitable cell types and is thought to be the most important enhancer mechanism with positive feedback in the cell Ca^{2+} signaling. As mentioned above, the two main receptors of this signaling are the IP3Rs, dominant in non-excitable cells, and the RYRs, characteristic of excitable cells (Brini et al. 2014; Hund et al. 2008; Kochkina et al. 2024; Nikolaienko et al. 2024; Rossi et al. 2021; Tagirova et al. 2022; Zhang et al. 2022). As a ligand binds to GPCRs of a non-excitable cell, it activates the phospholipase C enzyme, which leads to the hydrolysis of phosphatidylinositol-4,5-bisphosphat (PIP2), producing IP3 (Fig. 1.) and diacylglycerol (DAG) (Avila-Medina et al. 2018; Bootman et al. 2001a, b, c; Sanchez-Collado et al. 2022; Sukkar et al. 2023). IP3 then binds to the IP3Rs, thereby activating Ca^{2+} release from the ER. The released Ca^{2+} also binds to IP3Rs and can enhance further Ca^{2+} efflux via increasing the open probability of the IP3Rs (Fig.) (Ivanova et al. 2024; Siekmann et al. 2019; Tambeaux et al. 2023). The positive feedback loop continues until the increasing [Ca^{2+}]$_i$ reaches a point, where Ca^{2+} becomes an inhibitory factor for the receptor (Barbara 2002; Schmitz et al. 2022; Siekmann et al. 2019).

In excitable cells, RYRs are activated by the Ca^{2+} that enters the cytosol during an action potential. Interestingly, the RYR agonist caffein was able to elevate the speed of fast neuronal Ca^{2+} waves by 87% (Barbara 2002; Egger et al. 2024; Reber and Schindelholz 1996). The open probability of the RYRs is increased by low [Ca^{2+}]$_i$, leading to earlier and bigger Ca^{2+} efflux from the ER/SR (Egger et al. 2024; Siekmann et al. 2019).

There are other modulators of this mechanism, such as the Ca^{2+} binding proteins in the ER lumen: calsequestrin connects to the RYRs through transmembrane proteins, and lectin chaperons (calreticulin and calnexin) in the case of IP3Rs (Elíes et al. 2020). Jaffe found a similar, ER involved mechanism, which could be linked to the Ca^{2+} waves (Fig. 3C) (Jaffe 2004). His mechanism is based on the proton amount of ER which was found to be elevated during the cytoplasmic Ca^{2+} elevation. The protons modify calsequestrin to unbind Ca^{2+} and Ca^{2+} released more effectively (Jaffe 2004).

Mitochondrial Ca^{2+} induced Ca^{2+} release

Mitochondrial buffering (uptake of Ca^{2+} in case of elevated [Ca^{2+}]$_i$ and the release of Ca^{2+} after the cytoplasmic concentration decreases) has an effect on the CICR because it removes Ca^{2+} which could sensitize IP3Rs and RYRs (Ichas et al. 1997; Mann et al. 2009; Suzuki et al. 2014). On the other hand, the elevated [Ca^{2+}]$_{MT}$ affect the permeability transition pore (PTP). This inner membrane localized protein complex allows molecules up to 1.5 kDa to diffuse between the matrix and the outer membrane (Bernardi et al. 2022, 2023; Bernardi and Di Lisa 2015). If the [Ca^{2+}]$_i$ is elevated for longer period and the PTP is open continuously, mitochondria rupture, which leads to cell death (Bernardi et al. 2022, 2023; Bernardi and Di Lisa 2015; Mnatsakanyan et al. 2022; Zhivotovsky and Orrenius 2011). However, opening of the PTP in a so-called low conductance mode releases Ca^{2+} from the matrix and leads to mitochondrial Ca^{2+} induced Ca^{2+} release (mCICR) (Ichas et al. 1997; Oster et al. 2011, 2008; Selivanov et al. 1998). The PTP opening rearranges the Ca^{2+}, K$^+$ and H$^+$ concentrations and causing a potential change. This leads to a mitochondrial spike which propagates to the neighboring mitochondria via Ca^{2+} diffusion (Ichas et al. 1997; Krstic et al. 2022; Oster et al. 2011, 2008; Selivanov et al. 1998).

Diffusion

Most of the phenomena mentioned above are based on the diffusion of the molecules and of Ca^{2+} in the cytoplasm and in the internal stores. The movement of a molecule or ion is modified by the concentration gradients, the size of the molecule, the openness of the space and the non-specific interaction with other molecules and ions. Diffusion rate and velocity could be different depending on the cell cytoplasm and the number and type of proteins in the cytoplasm (Huang et al. 2024, 2022; Trovato and Tozzini 2014). Free Ca^{2+} rarely diffuses, because of the numerous Ca^{2+} binding proteins, however, if it binds to a motile protein, they could diffuse together. It should be noted that during imaging experiments it is the bond Ca^{2+} that is detected—more precisely, the diffusion of the dye-Ca^{2+} complex could be seen as an intracellular Ca^{2+} wave (Fig. 2). The regulation of Ca^{2+} activated protein movement is important in every cell but not studied well enough. At this point, we know that viscosity and the diffusion are homeostaticly regulated in yeast cells (Huang et al. 2022; Persson et al. 2020), but more studies are needed regard this topic.

Slow intracellular waves in specific cells

Why intracellular Ca^{2+} waves could be interesting? It is clear, that the free Ca^{2+} in the cytoplasm cannot simply jump up from the basal level and the elevation cannot be balanced
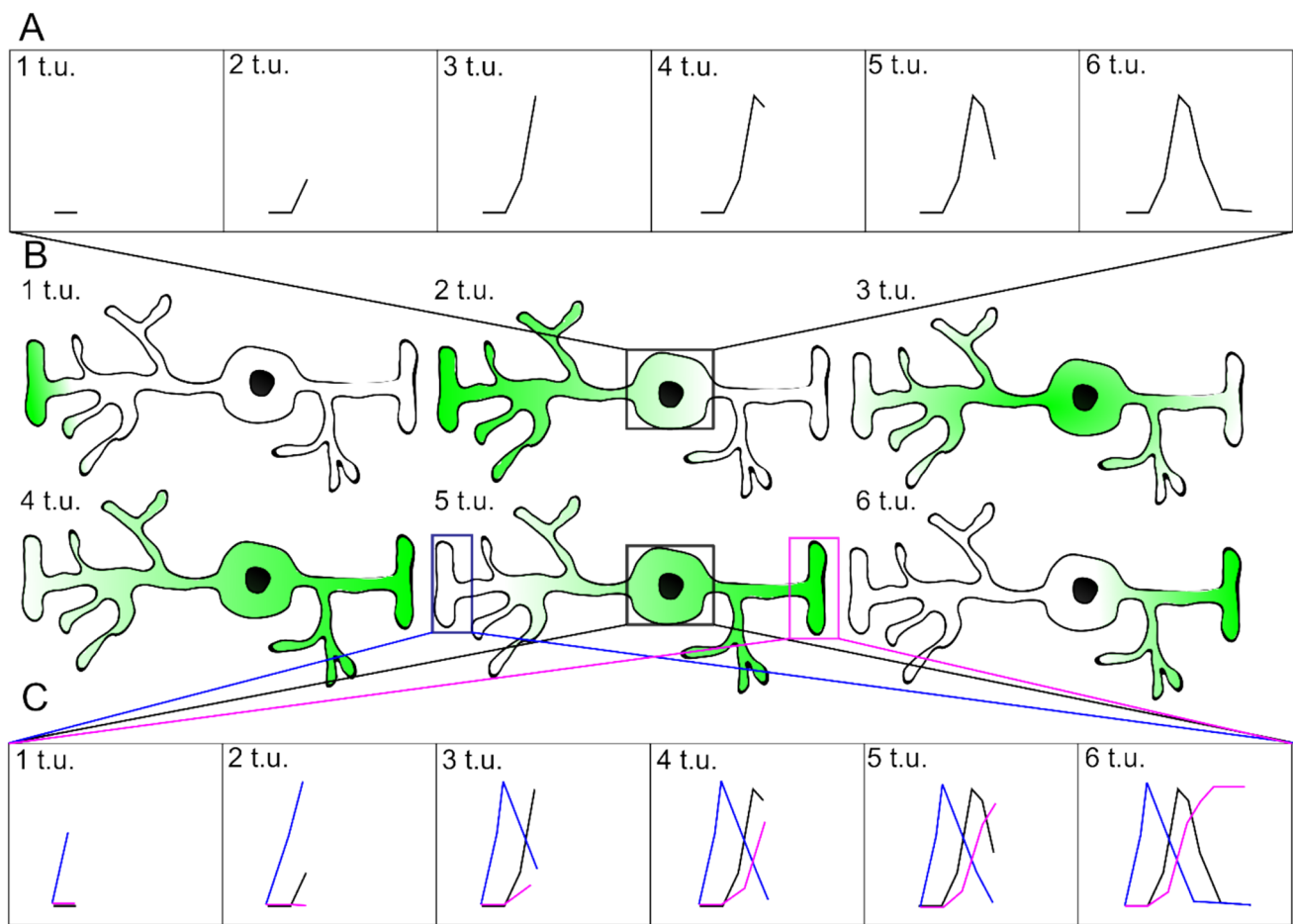
Fig. 2 Intracellular Ca^{2+} waves transiently makes different microenvironment in the cell can be followed by intensity changes of the fluorescent indicators. Intracellular waves investigation is challenging: in tissue preparations cell processes cannot be seen and region of interests (ROIs) are placed on the more visible cell body which makes the wave invisible (**A**: intensity changes followed during 6 time-units (t.u.) of a schematic cell's soma). To investigate the waves more ROIs should be located on the same cell, required unique indicator fill, or separated cells (**C**: 3 ROIs placed on a schematic processed cell, and the followed their intensity for 6 t.u.—the dynamics of the intensity change is different in the ROIs located on the left end of the cell (blue), the soma (black) and the right end of the cell (pink)). **B** an imaginary processed cell (like retinal Müller cell) schematic intracellular Ca^{2+} wave response indicated by the change of the indicator intensity (green) to a stimulus arrived on a special part of the cell

in the whole cell, as there will be Ca^{2+} influx and efflux sites which coordinate the whole spatiotemporal distribution of the signal. However, the smaller or bigger Ca^{2+} signals have distinct functions. The spread of the signal, and the velocity of it will cause intracellular differences and functional compartmentalization (Fig. 2). In most of the cells we cannot see real differences, because the Ca^{2+} could spread in high speed (~ 60 µm/s) (Gelens et al. 2014; Rash et al. 2016). However, we know of some cells, in which this speed is a magnitude lower (~ 5–6 µm/s) (Gelens et al. 2014). In this review, we will focus on these slower Ca^{2+} waves and only some examples of the faster ones will be mentioned to help in the comparison.

Previous studies showed that damage-induced intercellular Ca^{2+} waves induced cell protective enzyme upregulation (e.g., extracellular signal induced kinases (ERK1/2)) (Ghilardi et al. 2020); the radius of wave depend on the distance from the damage and can influence the response strength. However, it is still not clear, what are (if there any) function of the intracellular Ca^{2+} waves.

One of the reasons of the numerous opened questions that intracellular waves are difficult to examine (Fig. 2). In tissue preparations the cell compartments are overlapping, therefore smaller compartments cannot be seen, and only bigger parts (soma of the cells) are recorded, where (depending on the time units of the sampling) waves are not visible (Fig. 2). Separated or individually labeled cells are needed for the investigation of the intracellular Ca^{2+} waves which slows down and makes more difficult the investigations.
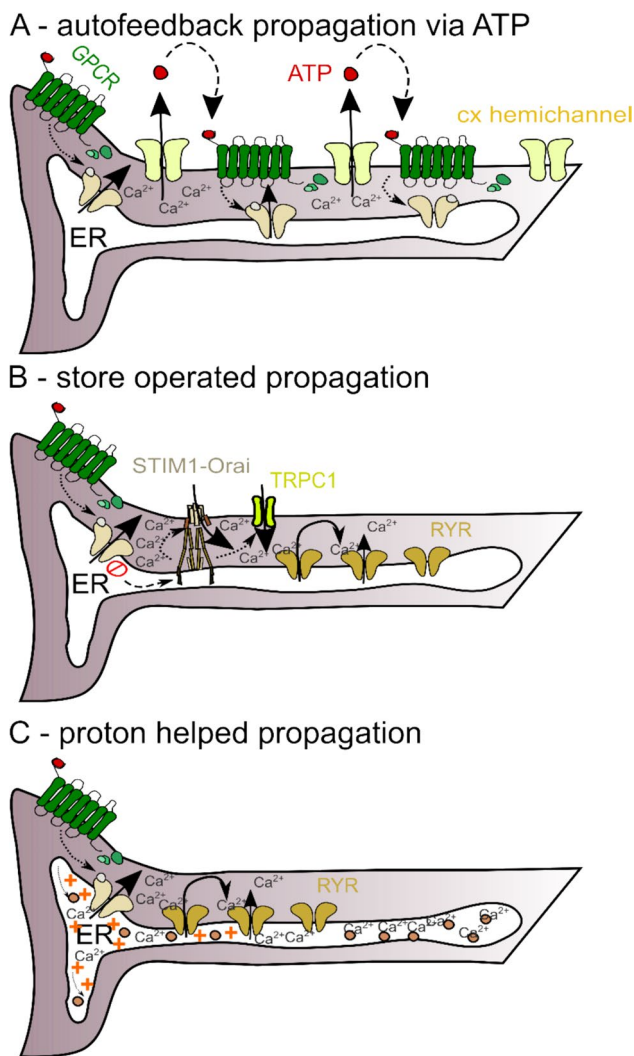
Fig. 3 Ca^{2+} wave propagation in Müller glia end-feet. **A panel** shows the autofeedback hypothesis: A ligand of GPCR activate the receptor and the IP3 pathway which leads to Ca^{2+} release from the internal stores (S. S. Wang & Thompson 1995). The elevated [Ca^{2+}]$_i$ results in opening of the cell surface hemichannels and ATP released is from the cells, which activates the self-expressed P2Y receptors and the IP3 pathway again. **B panel** shows the store-operated propagation hypothesis: some ligand activates the GPCRs which activate the IP3 pathway. Ca^{2+} from the internal store is released and the store depletion is sensed by the STIM1 molecules. STIM1 induces the Orai and TRPC1 on the cell surface and let extracellular Ca^{2+} enter the cell. The elevated [Ca^{2+}]$_i$ activates the RYRs and all in all this leads to CICR, too. **C panel** shows Jaffe theory (Jaffe 2004). This theory says that the Ca^{2+} release from the stores leads to proton concentration elevation in the ER lumen. The pH change affects the Ca^{2+} buffering protein, calsequestrin, which unbinds the Ca^{2+}, allowing it to leave the ER

Egg cells

During the fertilization, egg cells of several species produce Ca^{2+} waves, known as the fertilization waves (Bock and Ackrill 1995; Jaffe 2010; Toperzer et al. 2023).

Xenopus laevis, sea urchin and Ascidian eggs are the most used deuterostome models to study these mechanisms. The Ca^{2+} wave is generated by the diffusion of sperm specific phospholipase ζ1 which can activate the formation of IP$_3$ and CICR (Swann 2023). Fertilization waves are fast: 50–100 µm/s (Puls et al. 2024; Swann 2023). After fertilization, each mitosis generates similar, but slow Ca^{2+} waves through the cytoplasm of the cells, with dynamically changing velocity, reaching slower rate of about 5–9 µm/s or even beneath 1 µm/s (found in *Drosophila*) (McDougall and Sardet 1995; Puls et al. 2024). Modeling studies showed there is no spatial difference in the cell during the faster waves, but slower waves transmit information through the cells. Next to this function, the mechanism of induction also seems to be different: slower waves maintained by diffusion of proteins forming more stable waves compared to the fast ones, which indicated by the activation of the neighboring position of the cells and involves extracellular sources (Huang et al. 2024; Puls et al. 2024). The origin of the Ca^{2+} waves are ER domains, as the dislocation of the mitochondria by centrifugation did not affect the origin of the waves, and the waves appear to start 1–2 µm below the plasma membrane (McDougall and Sardet 1995; Speksnijder 1992). However, mitochondria-ER contact sites seem to be formed and mitochondria Ca^{2+} uptake is enhanced in mitosis (Zhao et al. 2024). Most probably the CICR is the main controlling mechanism, as the IP3 pathway manipulators elevated the latencies (McDougall and Sardet 1995). We must mention that it is still not clear whether or not RYRs are also involved in the fertilization waves, and further research is needed on this topic (Stricker 1999). Ascidian eggs seem to express the RYRs (Albrieux et al. 1997, 2000) but in sea urchin it appears to be only a secondary, redundant way to generate waves (Galione et al. 1993; Lee et al. 1993; Stein et al. 2020).

Radial glia

Glia cells are good models for investigating the intracellular Ca^{2+} waves as their shape is usually elongated with several branches. The stimuli from the environment often trigger only one specific part of these cells, and the escalation of local stimuli can travel through the cell and globalize (Bootman, et al. 2001b; Nakamura et al. 2012).

Radial glial cells are a transient type of glial cells, involved in the development of the neural cortex (Miranda-Negrón and García-Arrarás, 2022). These cells were monitored by GCaMP5 and Ca^{2+} waves with average velocity of 10.6 ± 1.4 µm/s were detected (Rash et al. 2016), but in the cerebellum, measured by GCaMP6 these progenitors have 40–60 µm/s speed, which can be decreased with heptanol to 15–25 µm/s (Pereida-Jaramillo et al. 2021). This result suggests faster Ca^{2+} waves involve gap junction channels in

the cerebellar cells and supports the idea of diversity of the radial glia (Pereida-Jaramillo et al. 2021). In slower cortical cells the propagation of the wavefront often spread to both direction of the cells and the pattern did not change in the radial process in Ca^{2+} free extracellular environment or in the presence of IP3 receptor inhibitor (2-aminoethoxydiphenylborate, 100 μM). However, these manipulations decreased the amplitude and frequency in the apical process (Rash et al. 2016). In this study, another Ca^{2+} signaling mechanism was hypothesized: Notch inhibition of Ca^{2+} signaling downstream. FGF2, a Notch down regulator, increased the amplitudes, durations, propagation distances and frequencies (Rash et al. 2016). The direct mechanism remains unclear, but Notch thought to be an enhancer of the Ca^{2+} entry from the extracellular space, affecting STIM2 aggregation in HEK293 cells (Song et al. 2020) and its role was indicated in endothel phenotype formation during angiogenesis connected to Ca^{2+} oscillations with the help of gap junction molecules (Debir et al. 2021). The strict morphology of radial glia is maintained by cytoskeletal elements with non-muscle myosin types (D'Arcy et al. 2023). The subcellular end feet part of the radial glia is less than 10 μm in diameters, full of the cytoskeletal elements. These make diffusion more difficult for the molecules which could cause the slower intracellular Ca^{2+} wave (Novak et al. 2009; Trovato and Tozzini 2014).

Along with the intracellular waves, intercellular waves also present in radial glia. The cell–cell propagation involves CICR mechanisms induced by P2Y receptors and connexin coordinated molecular movement between cells. Intercellular waves propagated at a speed of 6 ± 0.07 μm/s (Weissman et al. 2004; Yuryev et al. 2016). Connexin hypothesized to form hemichannels and extracellular ATP diffusion activates the neighboring cells (Weissman et al. 2004). The intracellular waves seem to be faster than the intercellular ones, particularly in cells where both wave types were detected, possibly because of the distance which molecules have to travel (Jaffe 2010).

Astrocytes

Astrocytes, the first described glial cells, have a characteristic shape with many processes around the soma. These are localized in the central nervous system and, contrast the previously thought supporting role, indicated to have essential functions e.g., recovery after damage involves gliosis and scar formation, perisynaptic processes contribute to the stability of synapses and regulate them by releasing gliotransmitters, with both excitatory and inhibitory effects. The most known gliotransmitters are glutamate, D-serine, ATP and GABA (Cho and Huh 2020). Being non-excitable cells, astrocytes use chemical signals, such

as Ca^{2+} elevations. Although there are voltage-gated channels on the cell membrane, they help to synchronize the astrocytic response rather than triggering action potentials (Dragić et al. 2021; McNeill et al. 2021; Pappalardo et al. 2016). However, the primary mechanism of Ca^{2+} elevation is induced is through G_q protein coupled IP3 production (Sherwood et al. 2021). IP3 then activates the CICR mechanism as discussed earlier. Ca^{2+} can enter the cytoplasm also from the mitochondria through the mitochondrial PTP. From the extracellular space, Ca^{2+} influx is mediated, for example, by TPR channels and store-operated Orai channels (Novakovic et al. 2023; Semyanov 2019; B. Zhou et al. 2019).

Most studies regarding astrocytic Ca^{2+} signaling concentrate on either microdomain Ca^{2+} elevations (which are never globalized) or intercellular Ca^{2+} waves, e.g., (Denizot et al. 2021, 2022; Lawal et al. 2022; Mellor et al. 2022; Spennato et al. 2024; Tóth et al. 2021). It seems that intercellular Ca^{2+} waves travel by extracellularly via releasing ATP or with the help of gap junctions transmitting Ca^{2+} and/or IP3 (Fujii et al. 2017; Karadayi et al. 2022; Pereida-Jaramillo et al. 2021; Zhou et al. 2020). These waves are rather characteristic of injury and pathological conditions than they are of physiological conditions (Cho and Huh 2020; Crowe et al. 2010). After injuries these carry information about the site, increase the proliferation and self-renewal of neural stem cells and activate microglia migration (Kraft et al. 2017). Propagation velocities are between 10 and 30 μm/s. This is relatively slow compared to neuronal propagation (neuronal propagation is three orders of magnitude faster), but faster than in radial glial cells (Novakovic et al. 2023; Tóth et al. 2021).

Despite the number of studies on intercellular waves, there are only a few studies investigating intracellular Ca^{2+} waves. Cultured astrocytes produced intracellular Ca^{2+} waves even in Ca^{2+} free environment, which indicate the stores importance in the propagation. This is supported by the disruption of waves after ER depletion (Forcaia et al. 2021). Computational models were set up to investigate intracellular Ca^{2+} waves in astrocytes (Polykretis et al. 2018; Shoemaker and Bekkouche 2025). The Polykretis model features a single cell with several processes, with seven synapses on each. They found that different combinations of active synapses can produce different Ca^{2+} elevations from local waves with decreasing amplitude to global Ca^{2+} waves accumulating in the cell body. A newer, Schoemaker model, emphasize the importance of RYRs which had impact on wave speeds and amplitudes. In their simulations receptor densities and the diffusion coefficient for cytoplasmic Ca^{2+} seems to be the most important factors in the propagation of intracellular Ca^{2+} waves.

Müller glia

The Müller glia is one of the glial cells of the retina. It plays a significant role in the structure and forms the membrana limitans externa and interna which are the two borders of the retina. In between these layers are the nuclei of the retina cells which are connected with the Müller cells through processes (Reichenbach and Bringmann 2020). The morphology of Müller cells is very characteristic with their elongated form, a basal and an apical process originating from the perikaryon and ends with a bulbous end-foot. (Molnár et al. 2016). The outer process contains high number of mitochondria and many bundles of intermediate filaments, while the end-foot is filled with ER (Molnár et al. 2016; Salman et al. 2021; J. Wang et al. 2017).

Müller cells take part in the homeostasis of the retina, such as the ion concentration regulation and the maintenance of the blood-retinal barrier (Reichenbach and Bringmann 2020), including the in- and outflux of Ca^{2+}, mostly via purinergic receptors. Positive expression was found to P2Y1, P2Y2, P2Y4, P2Y6, P2X7 (Fries et al. 2005; Saltzberg et al. 2003) and various types of TRP channels (Hu et al. 2024a, b, c; Jo et al. 2022). Connexin 43 forms gap junction channels, and have been shown to augment cytosolic Ca^{2+} via influx of extracellular Ca^{2+} in response to ATP, coordinate intercellular coupling of Ca^{2+} transients (Caminos et al. 2023; Karadayi et al. 2022; Tworig et al. 2021; Yu et al. 2009).

Ca^{2+} signaling in Müller cells contributes to pathological conditions such as retinal detachment or proliferative vitreoretinopathy (Bringmann et al. 2007; Iandiev et al. 2006; Uckermann et al. 2003). Mutations in the Cacna1f gene (codes L-type voltage gated Ca^{2+} channel) disrupt Ca^{2+} signaling and cellular organization in the mouse retina (Mansergh et al. 2005). The overactivation of P2X7 receptor leads to Ca^{2+} overload and neuronal and microvascular cell death and has role in other age-related retinopathies (Reichenbach and Bringmann 2016).

The Ca^{2+} waves of Müller cells are slower than in other cell types caused the absent of autocrine/paracrine purinergic signaling. SOCE is hypothesized to have a role to trigger I_{CRAC} (store depletion triggered Ca^{2+} current) initiated transcellular Ca^{2+} waves that propagated from apical and end-foot processes toward the soma (Molnár et al. 2016) (Fig. 3). These SOCE-induced Ca^{2+} waves were initiated at the end-foot in 58% of cells with propagation speeds of 4.3 ± 0.77 μm/s. In cases, where the apical processes initiated the response, the speed was similar (Molnár et al. 2016). Originally the mechanisms were suggested to involve ATP release from neurons and autocrine activation of metabotropic receptors. However, purinergic autofeedback is not required for the propagation of Ca^{2+} waves in Müller cells as PPADS (a non-selective purinergic receptor inhibitor) could not decrease the velocity of the intracellular waves in either

direction (Phuong et al. 2016) (Fig. 3). The wave initiation is suggested to start with the synergic activation of TRPC and Orai channels that control the SOCE mechanisms (Molnár et al. 2016). Inhibition of altered Orai1 channels in Müller cells protects photoreceptors in retinal degeneration. Müller cells of TRPC1$^{-/-}$ and TRPC3$^{-/-}$ mice shows smaller amplitudes during the Ca^{2+} waves.

Müller cells have many ER cisternae (Chernorudskiy and Zito 2017; Lee et al. 2023; Marchese et al. 2022) in the end-foot from where Ca^{2+} waves could be initiated in most cases, however, the exact localization of ER in the end-foot is not well studied. Still, it is not clear yet how these cisternae start waves, but it is thought that SOCE-induced Ca^{2+} waves reflect rapid, SERCA-mediated refilling of internal ER stores associated with regenerative activation of Ca^{2+}-sensitive RYRs. The intracellular wave propagation was decreased by store depletion and carbachol (a muscarinic receptor agonist) supporting the roles of the internal stores in the intracellular Ca^{2+} waves (Ryskamp et al. 2014).

Osteocytes

Osteocytes, bone cells, are like glial cells in terms of branched processes and gap junctions between them. However, we found some studies that were promising for the relevance of intracellular waves in osteocytes (Guo et al. 2006). Most studies investigate the cell to cell Ca^{2+} propagation (with the velocity of 3.7 ± 2.8 and 3.3 ± 2.3 μm/s depending on the distance between the cells) and provides no information about the molecular mechanism (Guo et al. 2006). The osteocytes express P2X7 receptors, voltage gated Ca^{2+} channels and hemichannels in their membranes which complex called mechanosomes as with Ca^{2+} influx through this complex connected to mechanical stimuli of the processes of the cells. The intracellular waves formed after the mechanical activation and propagate to the body of the cells (Lewis et al. 2021). Other studies focus Ca^{2+} oscillations which are also the indicator of intracellular waves (Hu et al. 2020; Ishihara et al. 2012; Lewis 2021).

Conclusions for future biology

Intracellular Ca^{2+} waves are most probably present in each cell as the Ca^{2+} is one of the main signaling molecules and cells get information/stimulus in one special part in an exact moment. To generalize the cell reaction, these local $[Ca^{2+}]_i$ elevations should become global phenomena that could be realized via Ca^{2+} waves. In many cells, these are fast mechanisms and cannot be hypothesized to have a function or have any other side effects. However, some distinct cells (like most of the glia cells) produce slower intracellular Ca^{2+} waves. The propagation speed in these cases could cause

huge differences between the cells distinct parts and may have some functional aspects, but this has not yet been investigated. The causes of the differences in propagation speed are still unknown. Both fast and slower waves are described with the help of CICR. Other diffusion–reaction hypotheses are not well accepted in the scope. Glial cells are excellent models for the investigation of these Ca^{2+} waves as most of them have process-rich, branched and elongated structure, which provides enough time to see the waves moving through the cells. Their morphology is stabilized by several cytoskeletal elements which could decrease the diffusion rate and explain their slower waves—however, it should be noted that the huge amount of the intracellular protein is not enough to explain this feature, as the neurons, which also have a large quantity of proteins and cytoskeletal elements produce fast and ultrafast waves (Jaffe 2010). Overall, slow intracellular Ca^{2+} waves are still an open question and may lead to some astonishing results in the future.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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