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Editorial

Calcium signaling in physiology and pathophysiology

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Abstract

Calcium ions are the most ubiquitous and pluripotent cellular signaling molecules that control a wide variety of cellular processes. The calcium signaling system is represented by a relatively limited number of highly conserved transporters and channels, which execute Ca^{2+} movements across biological membranes and by many thousands of Ca^{2+}-sensitive effectors. Molecular cascades, responsible for the generation of calcium signals, are tightly controlled by Ca^{2+} ions themselves and by genetic factors, which tune the expression of different Ca^{2+}-handling molecules according to adaptational requirements. Ca^{2+} ions determine normal physiological reactions and the development of many pathological processes.

Ja, Kalzium das ist alles...
Otto Loewi
(1936 Nobel Laureate)

Experimental indications, demonstrating the role of calcium as a universal signalling molecule, controlling a huge variety of very different physiological functions appeared at the end of 19th century. First, Sydney Ringer showed that calcium ions were indispensable for fish survival, muscle contraction, the development of fertilized eggs and tadpole and for cells adhesion[1–5]. Several years later, Locke[6] and Overton[7] demonstrated the critical importance of Ca^{2+} for signal transduction between nerve and muscle. The general theory of calcium as a universal second messenger, however, appeared half a century later, when Lewis Victor Heilbrunn concluded that "the reaction of this calcium with the protoplasm inside the cell is the most basic of all protoplasmic reactions"[8]. This theory, although almost completely ignored at the time of its appearance, brilliantly withstood the test of time and experimental efforts (Figure 1), and today, the calcium signalling is generally regarded as the most ubiquitous and the most pluripotent system, involved in regulation of almost all known cellular processes[9].

The universality of calcium as a signaling molecule is manifested on many levels. First, Ca^{2+} ions act as intracellular messengers throughout phylogenetic history, from early prokaryotes to eukaryotic cells.

Second, within every cell, Ca^{2+} exerts its action through several very different levels, which are executed in different spatial and temporal domains. Indeed, Ca^{2+} ions control localized processes, (eg, exocytosis) and global responses (eg, myocyte contraction) with equivalent efficacy and ease (Figure 2). Similarly, Ca^{2+}-dependent cellular responses occur in an amazingly wide time scale, from microseconds (eg, activation of ion channels) to many hours, weeks, months or even years (eg, synaptic plasticity, memory, long-term adaptation or neuronal ageing).

Third, the Ca^{2+} signaling system is constructed with an incredible intrinsic versatility. The actual molecular cascades controlling Ca^{2+} movements through cellular membranes (Figure 3) are limited to several families of relatively similar pumps (plasmalemmal and intracellular PMCA, SERCA or SPCA[10–12]), sodium-calcium exchangers (NCX, residing in plasmalemma or in mitochondria[13,14]) and plasmalemmal[15–18] and intracellular[13,19–21] Ca^{2+} channels. Yet these cascades are very tightly regulated, which determines their great adaptability and versatility. Importantly, calcium signalling molecules are subject to a control by Ca^{2+} ions themselves: changes in Ca^{2+} gradients or local concentration control the availability of Ca^{2+} channels and regulate the activity of Ca^{2+} pumps[22–24]. On a different level, the expression of various molecules, controlling Ca^{2+} movements is responsive to the

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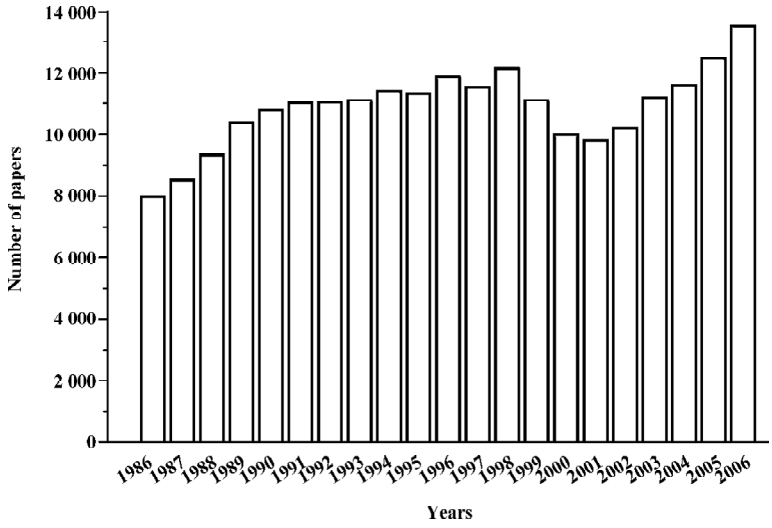

Figure 1. Publication of papers, dedicated to calcium signalling, according to the PubMed.

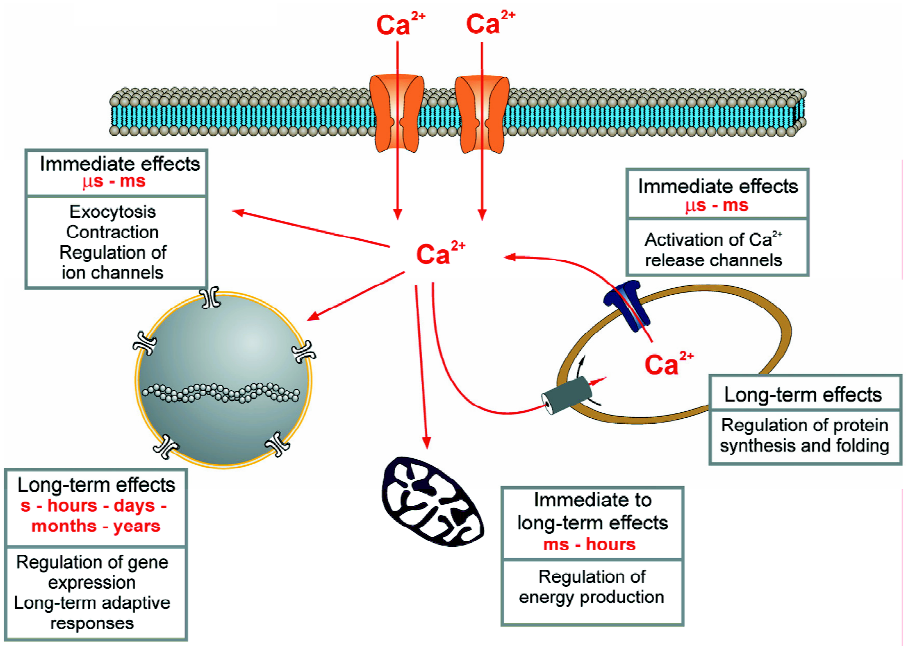

Figure 2. Temporal domains of calcium signalling.

changes in the environment, and therefore the combinations of calcium signaling molecules (or "Ca^{2+} signalling toolkits"[25]) can be rapidly modified, thus adapting the system to the external demands.

Fourth, the effector part of the calcium signalling system, the Ca^{2+} sensors, is represented by thousands of proteins, which have different affinity to Ca^{2+} ions, with the dissociate constant spanning seven orders of magnitude (Figure 4), and different cellular location. This host of Ca^{2+} sensors determines the ubiquity and promiscuity of Ca^{2+} signaling: expression of specific Ca^{2+} sensors commands specific Ca^{2+}-regulatory function (eg, expression of Ca^{2+}-sensitive contractile in muscle cells determines the excitation contraction coupling), whereas different affinity/localization of Ca^{2+} sensors will allow precise regulation of very different processes within a single cell.

The specificity and precise localization of calcium signalling machinery is also supported by an existence of

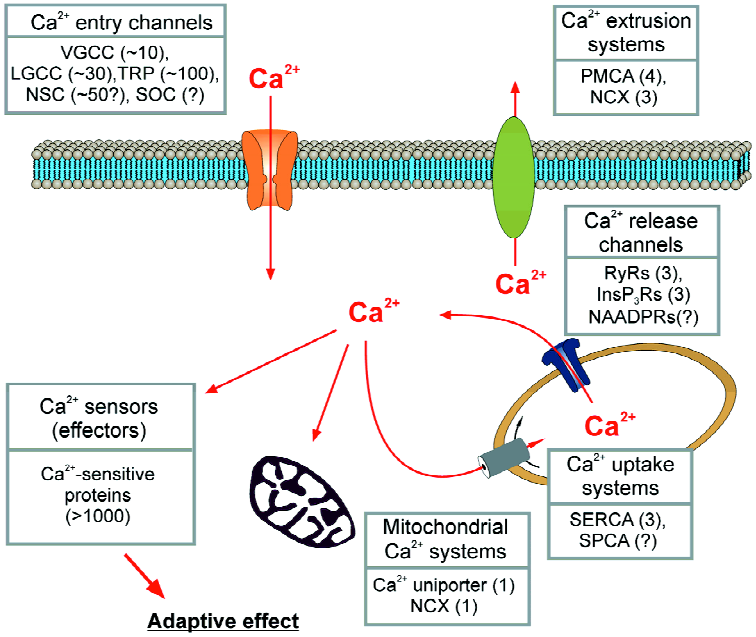

Figure 3. Simplicity and complexity of calcium signalling. Calcium signals are controlled by a relatively limited quantity of molecules (approximate number of these molecules is indicated in the parentheses), which include Ca^{2+} channels [voltage-gated Ca^{2+} channels (VGCC), ligand-gated Ca^{2+} channels (LGCC); transient receptor potential Ca^{2+} permeable channels (TRP); non-selective channels; SOC-store-operated Ca^{2+} channels (NSC)]; plasmalemmal Ca^{2+} extrusion systems [plasmalemmal Ca^{2+} ATPase (PMCA); Na^{+}/Ca^{2+} exchanger (NCX)); intracellular Ca^{2+} release channels [ryanodine receptors (RyRs); $InsP_3$ receptors ($InsP_3Rs$); NAADP receptors (NAADPRs)]; intracellular Ca^{2+} pumps [sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA); Ca^{2+} ATPases of Golgi complex (SPCA)] and mitochondrial Ca^{2+} transporting systems (Ca^{2+} uniporter; and mitochondrial Na^{+}/Ca^{2+} exchanger). The calcium signalling system exerts physiological effects through Ca^{2+} sensors (effectors), which are represented by approximate thousands of enzymes and Ca^{2+}-binding proteins.

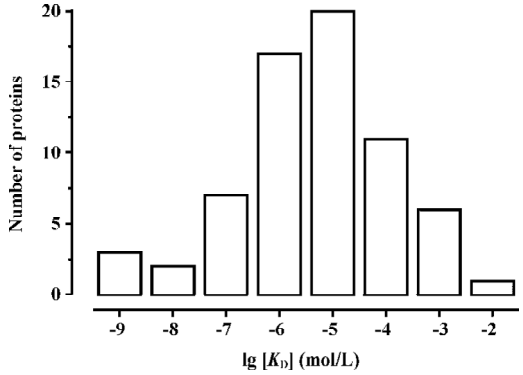

Figure 4. Diversity of calcium binding affinity of Ca^{2+}-sensors. The dissociation constants (K_d) of Ca^{2+} binding proteins (68 K_d values obtained by text search and manual curation from the literature) vary over 7 logarithmic units, ranging from nmol/L to 10 mmol/L with a broad mode around 10 μmol/L.

several intracellular compartments, characterized by a clearly distinct Ca^{2+} homeostasis. These compartments are represented by the cytosol, by endoplasmic reticulum (ER) and mitochondria. In the cytosol the concentration of free Ca^{2+} ($[Ca^{2+}]_i$) is very low, approximately 50–100 nmol/L, which is achieved by continuous activity of Ca^{2+} extruding systems and by high-affinity cytosolic calcium buffers[14,26,27]. As a consequence, activation of Ca^{2+} entry channels results in rapid elevation of $[Ca^{2+}]_i$, yet the strong Ca^{2+} buffering favours localisation of Ca^{2+} signals and the creation of Ca^{2+} microdomains. This is very important for regulation of focal cellular responses, such as exocytosis[28,29].

The ER, in contrast, provides for a very different Ca^{2+} handling environment. The intra-ER, or intraluminal free Ca^{2+} concentration ($[Ca^{2+}]_L$), is set at a rather high level, 100–800 μmol/L[30–36], which is achieved by a continuous activity of SERCA pumps. In addition, the affinity of intra-ER Ca^{2+} buffers is rather low, being in the range of 0.5–1.0 mmol/L, which favours Ca^{2+} diffusion through the continuous ER lumen. The latter therefore forms a nanoscopic "Ca^{2+} tunnel", which allows long-range Ca^{2+} transport in polarised cells[37–40]. Importantly, numerous intra-ER Ca^{2+}-dependent enzymatic systems require high (>50 μmol/L) $[Ca^{2+}]_L$ for normal functioning[41,42]. The ER acts as a very powerful intracellular signalling organelle, which integrates various incoming signals with cellular biochemistry (through regulation of protein synthesis and posttranslational folding). Furthermore, the ER produces numerous output signals, which regulate cell function and determine adaptive responses. Particularly important is the role of ER in the generation of cytoplasmic Ca^{2+} signals because the ER acts as a dynamic Ca^{2+} store able to rapidly release Ca^{2+} through intracellular Ca^{2+} channels[19,21] and to terminate Ca^{2+} signals through SERCA-dependent Ca^{2+} pumping. As a consequence, the ER appears simultaneously as a source and sink for $[Ca^{2+}]_i$[43–45], while the balance between Ca^{2+} release and Ca^{2+} uptake is regulated by $[Ca^{2+}]_L$ and $[Ca^{2+}]_i$ dynamics in a vicinity of Ca^{2+} release channels[46,47].

The third intracellular compartment with specific Ca^{2+} homeostasis is represented by mitochondria, which are able

to accumulate (via Ca^{2+} uniporter) and release (via Na^+/Ca^{2+} exchanger) Ca^{2+} [13]. Mitochondrial Ca^{2+} signalling links cellular activity to ATP production and ROS metabolism; in addition mitochondria can participate in $[Ca^{2+}]_i$ regulation, especially in pathological conditions[48–50].

Finally, the signalling system mediated by Ca^{2+} ions operates in two modes: the digital and analogue. The digital mode is determined by a discrete character of Ca^{2+} entry through the membrane, which is controlled by opening and closing of Ca^{2+} permeable channels. Yet, when inside the intracellular compartments, Ca^{2+} ions diffuse, and they diffuse with a different velocity and anisotropy, thus creating a complex concentration gradients, which represents an analogue signalling, coded in amplitude, space and time.

All these features make the Ca^{2+} signaling system absolutely unique among other cellular signaling pathways. Ca^{2+} ions are fundamentally different from other signalling molecules in a sense that they are subjected to neither catabolism nor anabolism; they can be merely bound to calcium buffers or accumulated into Ca^{2+} stores, yet they remain readily available for mobilisation. This makes the signalling system quite economical. Huge Ca^{2+} gradients, existing between extracellular space, intracellular organelles and the cytoplasm contribute to an exceedingly high signal-to-noise ratio of the whole signalling system. Further, the promiscuity of Ca^{2+} ions as intracellular messengers provides for a remarkable versatility; the variety of Ca^{2+} sensor proteins together with temporal and spatial heterogeneity of Ca^{2+} fluctuations, make the signalling system both context and history-specific. As a consequence, Ca^{2+} ions often play very opposite effects even within the same cell. One of the best examples of such a dualism exists in arterial smooth muscle cells, where subsurface calcium sparks relax the myocyte by activating Ca^{2+}-dependent K^+ channels[51–53], whereas global calcium signals trigger cell contraction.

Not surprisingly, the omnipotence of Ca^{2+} signaling makes it an important player not only in normal conditions but also in pathological cellular reactions. Here the dualism of Ca^{2+} ions transpires even more illustriously, as indeed Ca^{2+} ions are the ions of life and death. Depriving the cells from Ca^{2+} ions by the removal of extracellular Ca^{2+}, or artificial chelating of intracellular Ca^{2+}, or depletion of cellular free Ca^{2+}, all of these interventions result in rapid and inevitable cell death[42,54]. At the same time excess of Ca^{2+} is absolutely toxic, and cell death from Ca^{2+} overload represents probably the most general mechanism of cell demise[55,56]. Similarly, chronic disruptions of Ca^{2+} homeostatic machinery may cause development of various diseases, such as ischemic-induced cell death[57–63], neurodegeneration[42,54,64], heart failure[65,66] or underlying cognitive deficits in senescence[67–69].

When compiling this special issue we tried to cover all of the important parts of calcium signaling machinery and its role in physiology and disease. We hope that this collection of articles will spark further interest in various aspects of Ca^{2+} and inspire further developments into the functions and importance of this truly magnificent ion of life.

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