

Editorial

Calcium signaling in physiology and pathophysiology

He-ping CHENG^{1,4}, Sheng WEI¹, Li-ping WEI², Alexei VERKHRATSKY^{3,4}

¹Institute of Molecular Medicine and State Key Laboratory of Biomembrane and Membrane Biotechnology, College of Life Science, Peking University, Beijing 100871, China; ²Center for Bioinformatics, College of Life Science, Peking University, Beijing 100871, China;

³Faculty of Life Sciences, the University of Manchester, Manchester M13 9PT, UK

⁴Correspondence to Prof He-ping CHENG.
Phn/Fax 86-10-6276-5957.
E-mail chengp@pku.edu.cn
and Prof Alexei VERKHRATSKY.
Phn 44-161-275-5414.
Fax 44-161-275-5948.
E-mail alex.verkhratsky@manchester.ac.uk

Received 2006-05-22
Accepted 2006-05-22

doi: 10.1111/j.1745-7254.2006.00399.x

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 signalling 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

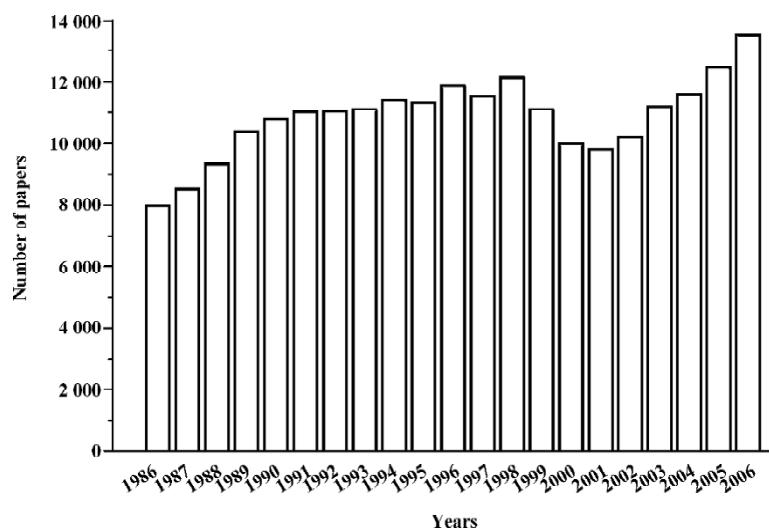


Figure 1. Publication of papers, dedicated to calcium signalling, according to the PubMed.

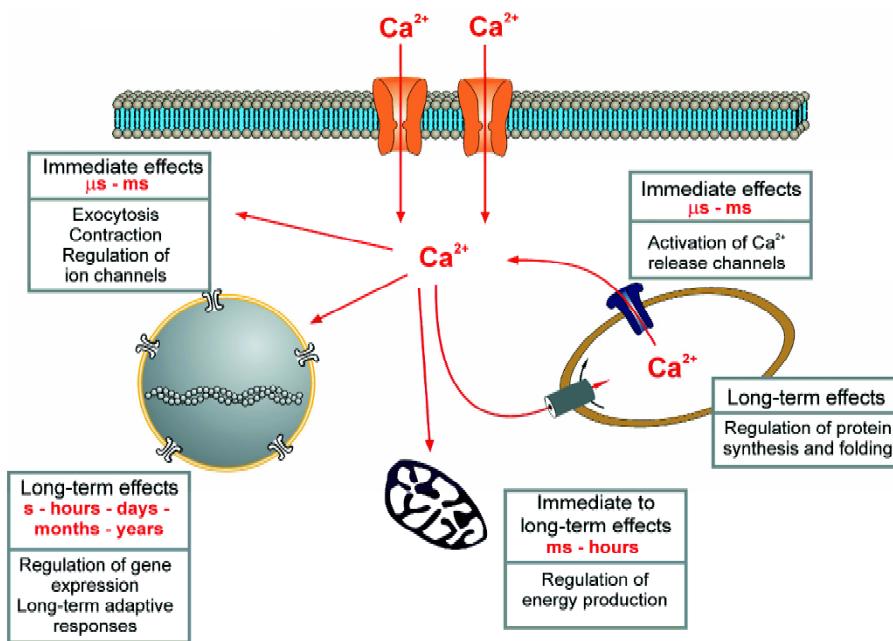


Figure 2. Temporal domains of calcium signalling.

changes in the environment, and therefore the combinations of calcium signalling molecules (or “Ca²⁺ 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 Ca²⁺ sensors, is represented by thousands of proteins, which have different affinity to Ca²⁺ ions, with the dissociate constant spanning seven orders of magnitude (Figure 4), and different cellular location. This host of Ca²⁺ sensors

determines the ubiquity and promiscuity of Ca²⁺ signaling: expression of specific Ca²⁺ sensors commands specific Ca²⁺-regulatory function (eg, expression of Ca²⁺-sensitive contractile in muscle cells determines the excitation contraction coupling), whereas different affinity/localization of Ca²⁺ 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

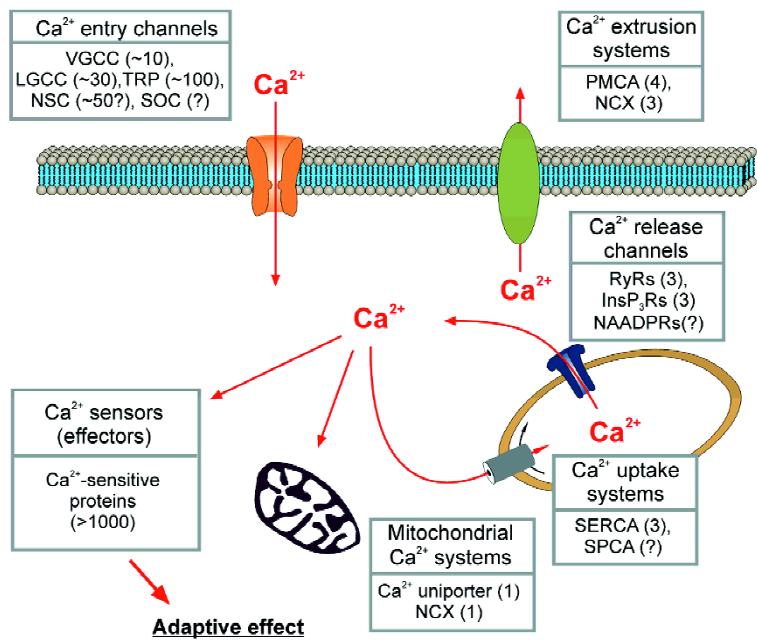


Figure 3. Simplicity and complexity of calcium signalling. Calcium signals are controlled by a relatively limited quantity of molecules (approximate number of these molecules is indicated in the parentheses), which include Ca^{2+} channels [voltage-gated Ca^{2+} channels (VGCC), ligand-gated Ca^{2+} 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); $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger (NCX)]; intracellular Ca^{2+} release channels [ryanodine receptors (RyRs); InsP_3 receptors (InsP_3 Rs); 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 $\text{Na}^{+}/\text{Ca}^{2+}$ 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.

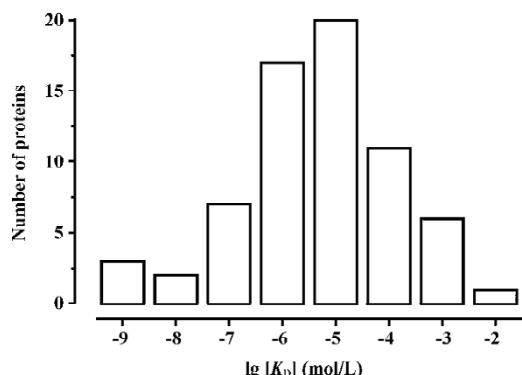


Figure 4. Diversity of calcium binding affinity of Ca^{2+} -sensors. The dissociation constants (K_d) of Ca^{2+} binding proteins (68 K_d values obtained by text search and manual curation from the literature) vary over 7 logarithmic units, ranging from nmol/L to 10 mmol/L with a broad mode around 10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

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+} ($[\text{Ca}^{2+}]_i$) 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 $[\text{Ca}^{2+}]_i$, 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 ($[\text{Ca}^{2+}]_L$), is set at a rather high level, 100–800 $\mu\text{mol/L}$ ^[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 $\mu\text{mol/L}$) $[\text{Ca}^{2+}]_L$ 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 $[\text{Ca}^{2+}]_i$ ^[43–45], while the balance between Ca^{2+} release and Ca^{2+} uptake is regulated by $[\text{Ca}^{2+}]_L$ and $[\text{Ca}^{2+}]_i$ 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 $\text{Na}^+/\text{Ca}^{2+}$ exchanger) Ca^{2+} ^[13]. Mitochondrial Ca^{2+} signalling links cellular activity to ATP production and ROS metabolism; in addition mitochondria can participate in $[\text{Ca}^{2+}]_i$ 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.

References

- 1 Ringer S. A further contribution regarding the influence of different constituents of the blood on the contractions of the heart. *J Physiol (Lond)* 1883; 4: 29–43.
- 2 Ringer S. The influence of saline media on fishes. *J Physiol (Lond)* 1883; 4: vi–viii.
- 3 Ringer S. Further experiments regarding the influence of small quantities of lime, potassium and other salts on muscular tissue. *J Physiol (Lond)* 1886; 7: 291–308.
- 4 Ringer S. Concerning experiments to test the influence of lime, sodium and potassium salts on the development of ova and growth of tadpoles. *J Physiol (Lond)* 1890; 11: 79–84.
- 5 Ringer S Sainsbury H. The action of potassium, sodium and calcium salts on *Tubifex rivulorum*. *J Physiol (Lond)* 1894; 16: 1–9.
- 6 Locke FS. Notiz über den Einfluss, physiologischer Kochsalzlösung auf die Eregbarkeit von Muskel und Nerve. *Zentralb Physiol* 1894; 8: 166–7.
- 7 Overton E. Beiträge zur allgemeinen Muskel- und Nervenphysiologie. III. Mittheilung. Studien über die Wirkung der Alkali-und Erdalkali-salze auf Skeletalmuskeln und Nerven. *Pflugers Arch* 1904; 105: 176–290.
- 8 Heilbrunn LV. An outline of general physiology. Philadelphia: Saunders; 1943.
- 9 Petersen OH, Michalak M, Verkhratsky A. Calcium signalling: past, present and future. *Cell Calcium* 2005; 38: 161–9.
- 10 Wuytack F, Raeymaekers L Missiaen L. PMR1/SPCA Ca^{2+} pumps and the role of the Golgi apparatus as a Ca^{2+} store. *Pflugers Arch* 2003; 446: 148–53.
- 11 Vanoevelen J, Dode L, Van Baelen K, Fairclough RJ, Missiaen L, Raeymaekers L, et al. The secretory pathway $\text{Ca}^{2+}/\text{Mn}^{2+}$ -ATPase 2 is a Golgi-localized pump with high affinity for Ca^{2+} ions. *J Biol Chem* 2005; 280: 22800–8.
- 12 Vangheluwe P, Raeymaekers L, Dode L, Wuytack F. Modulating sarco(endo)plasmic reticulum Ca^{2+} ATPase 2 (SERCA2) activity: cell biological implications. *Cell Calcium* 2005; 38: 291–302.
- 13 Nicholls DG. Mitochondria and calcium signaling. *Cell Calcium* 2005; 38: 311–7.
- 14 Guerini D, Coletto L, Carafoli E. Exporting calcium from cells. *Cell Calcium* 2005; 38: 281–9.
- 15 Triggle DJ. L-type calcium channels. *Curr Pharm Des* 2006; 12: 443–57.
- 16 Parekh AB, Putney JW Jr. Store-operated calcium channels. *Physiol Rev* 2005; 85: 757–810.
- 17 Perez-Reyes E. Molecular physiology of low-voltage-activated t-type calcium channels. *Physiol Rev* 2003; 83: 117–61.
- 18 Pedersen SF, Owsianik G Nilius B. TRP channels: an overview.

- Cell Calcium 2005; 38: 233–52.
- 19 Bezprozvanny I. The inositol 1,4,5-trisphosphate receptors. Cell Calcium 2005; 38: 261–72.
- 20 Galione A, Ruas M. NAADP receptors. Cell Calcium 2005; 38: 273–80.
- 21 Hamilton SL. Ryanodine receptors. Cell Calcium 2005; 38: 253–60.
- 22 Morad M, Soldatov N. Calcium channel inactivation: possible role in signal transduction and Ca^{2+} signaling. Cell Calcium 2005; 38: 223–31.
- 23 Burdakov D, Verkhratsky A. Biophysical re-equilibration of Ca^{2+} fluxes as a simple biologically plausible explanation for complex intracellular Ca^{2+} release patterns. FEBS Lett 2006; 380: 463–8.
- 24 Burdakov D, Petersen OH, Verkhratsky A. Intraluminal calcium as a primary regulator of endoplasmic reticulum function. Cell Calcium 2005; 38: 303–10.
- 25 Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol 2003; 4: 517–29.
- 26 Petersen OH, Petersen CC, Kasai H. Calcium and hormone action. Annu Rev Physiol 1994; 56: 297–319.
- 27 Burnashev N, Rozov A. Presynaptic Ca^{2+} dynamics, Ca^{2+} buffers and synaptic efficacy. Cell Calcium 2005; 37: 489–95.
- 28 Barclay JW, Morgan A, Burgoyne RD. Calcium-dependent regulation of exocytosis. Cell Calcium 2005; 38: 343–53.
- 29 Jarvis SE, Zamponi GW. Masters or slaves? Vesicle release machinery and the regulation of presynaptic calcium channels. Cell Calcium 2005; 37: 483–8.
- 30 Alonso MT, Barrero MJ, Michelena P, Carnicer E, Cuchillo I, Garcia AG, et al. Ca^{2+} -induced Ca^{2+} release in chromaffin cells seen from inside the ER with targeted aequorin. J Cell Biol 1999; 144: 241–54.
- 31 Alvarez J, Montero M. Measuring $[\text{Ca}^{2+}]$ in the endoplasmic reticulum with aequorin. Cell Calcium 2002; 32: 251–60.
- 32 Mogami H, Tepikin AV, Petersen OH. Termination of cytosolic Ca^{2+} signals: Ca^{2+} reuptake into intracellular stores is regulated by the free Ca^{2+} concentration in the store lumen. EMBO J 1998; 17: 435–42.
- 33 Solovyova N, Verkhratsky A. Neuronal endoplasmic reticulum acts as a single functional Ca^{2+} store shared by ryanodine and inositol-1,4,5-trisphosphate receptors as revealed by intra-ER $[\text{Ca}^{2+}]$ recordings in single rat sensory neurones. Pflugers Arch 2003; 446: 447–54.
- 34 Solovyova N, Veselovsky N, Toescu EC, Verkhratsky A. Ca^{2+} dynamics in the lumen of the endoplasmic reticulum in sensory neurons: direct visualization of Ca^{2+} -induced Ca^{2+} release triggered by physiological Ca^{2+} entry. EMBO J 2002; 21: 622–30.
- 35 Tse FW, Tse A, Hille B. Cyclic Ca^{2+} changes in intracellular stores of gonadotropes during gonadotropin-releasing hormone-stimulated Ca^{2+} oscillations. Proc Natl Acad Sci USA 1994; 91: 9750–4.
- 36 Verkhratsky A. Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. Physiol Rev 2005; 85: 201–79.
- 37 Mogami H, Nakano K, Tepikin AV, Petersen OH. Ca^{2+} flow via tunnels in polarized cells: recharging of apical Ca^{2+} stores by focal Ca^{2+} entry through basal membrane patch. Cell 1997; 88: 49–55.
- 38 Mogami H, Gardner J, Gerasimenko OV, Camello P, Petersen OH, Tepikin AV. Calcium binding capacity of the cytosol and endoplasmic reticulum of mouse pancreatic acinar cells. J Physiol 1999; 518: 463–7.
- 39 Petersen OH, Tepikin A, Park MK. The endoplasmic reticulum: one continuous or several separate Ca^{2+} stores? Trends Neurosci 2001; 24: 271–6.
- 40 Verkhratsky A. The endoplasmic reticulum and neuronal calcium signalling. Cell Calcium 2002; 32: 393–404.
- 41 Michalak M, Robert Parker JM, Opas M. Ca^{2+} signaling and calcium binding chaperones of the endoplasmic reticulum. Cell Calcium 2002; 32: 269–78.
- 42 Verkhratsky A, Toescu EC. Endoplasmic reticulum Ca^{2+} homeostasis and neuronal death. J Cell Mol Med 2003; 7: 351–61.
- 43 Friel DD, Tsien RW. A caffeine- and ryanodine-sensitive Ca^{2+} store in bullfrog sympathetic neurones modulates effects of Ca^{2+} entry on $[\text{Ca}^{2+}]_i$. J Physiol 1992; 450: 217–46.
- 44 Shmigol A, Kostyuk P, Verkhratsky A. Role of caffeine-sensitive Ca^{2+} stores in Ca^{2+} signal termination in adult mouse DRG neurones. Neuroreport 1994; 5: 2073–6.
- 45 Usachev Y, Shmigol A, Pronchuk N, Kostyuk P, Verkhratsky A. Caffeine-induced calcium release from internal stores in cultured rat sensory neurons. Neuroscience 1993; 57: 845–59.
- 46 Hongpaisan J, Pivovarova NB, Colegrave SL, Leapman RD, Friel DD, Andrews SB. Multiple modes of calcium-induced calcium release in sympathetic neurons II: a $[\text{Ca}^{2+}]_i$ - and location-dependent transition from endoplasmic reticulum Ca accumulation to net Ca release. J Gen Physiol 2001; 118: 101–12.
- 47 Albrecht MA, Colegrave SL, Hongpaisan J, Pivovarova NB, Andrews SB, Friel DD. Multiple modes of calcium-induced calcium release in sympathetic neurons I: attenuation of endoplasmic reticulum Ca^{2+} accumulation at low $[\text{Ca}^{2+}]_i$ during weak depolarization. J Gen Physiol 2001; 118: 83–100.
- 48 Toescu EC, Verkhratsky A. Neuronal ageing from an intraneuronal perspective: roles of endoplasmic reticulum and mitochondria. Cell Calcium 2003; 34: 311–23.
- 49 Toescu EC. Hypoxia sensing and pathways of cytosolic Ca^{2+} increases. Cell Calcium 2004; 36: 187–99.
- 50 Toescu EC. Hypoxia response elements. Cell Calcium 2004; 36: 181–5.
- 51 Nelson MT, Cheng H, Rubart M, Santana LF, Bonev AD, Knot HJ, et al. Relaxation of arterial smooth muscle by calcium sparks. Science 1995; 270: 633–7.
- 52 Wellman GC, Nathan DJ, Saundry CM, Perez G, Bonev AD, Penar PL, et al. Ca^{2+} sparks and their function in human cerebral arteries. Stroke 2002; 33: 802–8.
- 53 Wellman GC, Nelson MT. Signaling between SR and plasmalemma in smooth muscle: sparks and the activation of Ca^{2+} -sensitive ion channels. Cell Calcium 2003; 34: 211–29.
- 54 Paschen W, Mengesdorf T. Endoplasmic reticulum stress response and neurodegeneration. Cell Calcium 2005; 38: 409–15.
- 55 Berliocchi L, Bano D, Nicotera P. Ca^{2+} signals and death programmes in neurons. Philos Trans R Soc Lond B Biol Sci 2005; 360: 2255–8.
- 56 Leist M, Nicotera P. Apoptosis versus necrosis: the shape of neuronal cell death. Results Probl Cell Differ 1998; 24: 105–35.
- 57 Kristian T. Metabolic stages, mitochondria and calcium in hypoxic/ischemic brain damage. Cell Calcium 2004; 36: 221–33.

- 58 Pringle AK. In, out, shake it all about: elevation of $[Ca^{2+}]_i$ during acute cerebral ischaemia. *Cell Calcium* 2004; 36: 235–45.
- 59 Yao H, Haddad GG. Calcium and pH homeostasis in neurons during hypoxia and ischemia. *Cell Calcium* 2004; 36: 247–55.
- 60 Starkov AA, Chinopoulos C, Fiskum G. Mitochondrial calcium and oxidative stress as mediators of ischemic brain injury. *Cell Calcium* 2004; 36: 257–64.
- 61 Pisani A, Bonsi P, Calabresi P. Calcium signaling and neuronal vulnerability to ischemia in the striatum. *Cell Calcium* 2004; 36: 277–84.
- 62 Yamashima T. Ca^{2+} -dependent proteases in ischemic neuronal death: a conserved ‘calpain-cathepsin cascade’ from nematodes to primates. *Cell Calcium* 2004; 36: 285–93.
- 63 Kahlert S, Reiser G. Glial perspectives of metabolic states during cerebral hypoxia-calcium regulation and metabolic energy. *Cell Calcium* 2004; 36: 295–302.
- 64 Mattson MP, Chan SL. Neuronal and glial calcium signaling in Alzheimer’s disease. *Cell Calcium* 2003; 34: 385–97.
- 65 Scoote M, Williams AJ. Myocardial calcium signalling and arrhythmia pathogenesis. *Biochem Biophys Res Commun* 2004; 322: 1286–309.
- 66 Sipido KR, Eisner D. Something old, something new: changing views on the cellular mechanisms of heart failure. *Cardiovasc Res* 2005; 68: 167–74.
- 67 Toescu EC, Verkhratsky A. Ca^{2+} and mitochondria as substrates for deficits in synaptic plasticity in normal brain ageing. *J Cell Mol Med* 2004; 8: 181–90.
- 68 Verkhratsky A, Toescu EC. Calcium and neuronal ageing. *Trends Neurosci* 1998; 21: 2–7.
- 69 Toescu EC, Verkhratsky A, Landfield PW. Ca^{2+} regulation and gene expression in normal brain aging. *Trends Neurosci* 2004; 27: 614–20.

The 7th Chinese Symposium on Calcium Signalling (The 7th CSCS Meeting)

October/November 2008, Wuhan, China

Info: Prof Zong-jie CUI, PhD
Institute of Cell Biology
Beijing Normal University
Beijing 100875, China
Phn/Fax 86-10-5880-9162
E-mail zjcui@bnu.edu.cn