EDITORIAL

New insights into Ca^{2+} channel function in health and disease

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This issue of *The Journal of Physiology* contains reviews from a meeting held in Honolulu, sponsored in part by The Physiological Society and organized by Andrea Fleig, Anant Parekh and Reinhold Penner. The primary focus was on recent advances in our understanding of Ca^{2+}-permeable ion channels, how channel function can be hijacked in disease, and how this might be corrected therapeutically.

A rise in cytosolic Ca^{2+} is an evolutionarily conserved intracellular signal that regulates myriad responses over a wide temporal bandwidth. At one end of the spectrum is Ca^{2+}-dependent neurotransmitter release, which operates on a submillisecond time scale, and at the other is Ca^{2+}-dependent regulation of cell growth and differentiation, which can manifest hours to days after the Ca^{2+} signal has disappeared. Inherent to the use of the multifarious Ca^{2+} signal is the question of specificity: how are some Ca^{2+}-dependent responses activated and not others when all are gated by cytosolic Ca^{2+}? What is now becoming clear, and what emerged as a recurrent theme at the meeting, is that the location of the Ca^{2+} signal is critical for activating specific responses. Ca^{2+}-permeable channels differ in their selectivity profiles, unitary conductance and subcellular distribution. Hence Ca^{2+} flux through different channels produces distinct subcellular Ca^{2+} patterns, which can be decoded by different downstream targets to elicit discrete functional responses.

The first review, by Petersen *et al.* (2017), describes a mechanism for tunnelling Ca^{2+} from a site of Ca^{2+} uptake to a site of Ca^{2+} release by diffusion through the lumen of the endoplasmic reticulum (ER). Tunnelling is a three step process: it requires Ca^{2+} that has entered the cytoplasm through store-operated Ca^{2+} channels to be taken up by SERCA pumps on junctional ER located just below the plasma membrane; the Ca^{2+} diffuses through the ER and is then released into the cytosol at more distal sites by InsP_3 receptors. Ca^{2+} tunnelling is therefore an effective vehicle for transporting Ca^{2+} to release sites without the free ion diffusing through the intervening cytoplasm, obviating the risk of inappropriate activation of numerous Ca^{2+}-dependent pathways *en route*.

Specialized epithelial cells called ameloblasts are involved in the formation of enamel, which gives teeth its strength. A crucial element in the biomineralization of enamel is Ca^{2+}. The review by Nurbaeva *et al.* (2017) describes Ca^{2+} transport pathways in ameloblasts and how store-operated Ca^{2+} entry in particular plays a central role in the mineralization of dental enamel.

Ca^{2+} channels populating the ER and SR can be activated by cytosolic Ca^{2+}, resulting in Ca^{2+}-induced Ca^{2+} release. This is particularly important in the heart, where it enables the Ca^{2+} signal to spread quickly into the myocyte. The review by Santuli *et al.* (2017) describes new features of the release channels, how they influence other Ca^{2+} signalling organelles like mitochondria and why they are attractive therapeutic targets for a range of diseases.

Receptor stimulation often evokes oscillation in cytosolic Ca^{2+}, considered the physiological form of Ca^{2+} signalling (Parekh, 2011). Oscillations in non-excitable cells arise from InsP_3-dependent regenerative Ca^{2+} release with the ER refilling through store-operated Ca^{2+} entry. The review by Samanta and Parekh (2017) describes how Ca^{2+} microdomains near open InsP_3 receptors in the ER membrane are propagated rapidly into the mitochondria to regulate metabolism. Ca^{2+} microdomains generated by store-operated Ca^{2+} channels signal to the nucleus to activate gene transcription. Hence, in addition to amplitude and frequency of the Ca^{2+} oscillations, the subcellular spatial profile of the Ca^{2+} spikes provides additional means for extracting information.

Given the gamut of responses regulated by cytosolic Ca^{2+}, it comes as no surprise that aberrant Ca^{2+} signalling is linked to a range of human disease. Iamshanova *et al.* (2017) describe the multiple roles of cytosolic Ca^{2+} in the process of metastasis. Different Ca^{2+} channels elicit distinct subcellular Ca^{2+} signals that determine which underlying pathways will be activated and to what extent. Dissecting the role of the various Ca^{2+} channels in cancer cells opens up the possibility of rational therapeutic intervention. Another leading cause of death is stroke. The review by Sun *et al.* (2017) describes how silencing of TRPM7, a divalent cation-permeable channel, not only reduced neuronal cell death but maintained nerve cell activity following global cerebral ischaemia in adult rats. Targeting TRPM7 might therefore be of benefit in stroke. Although there are currently no inhibitors available for clinical use, studies on the organic extract of the soft coral *Sarcothelia edmondsoni* identified waixenicin A as potent, specific and intracellular Mg^{2+}-dependent inhibitor of the channels (IC_{50} of 16 nM for recombinant channels in a whole-cell patch clamp assay; Zierler *et al.* 2011).

Developing blockers of store-operated Ca^{2+} channels has proven challenging, but valuable insight into drug–channel interaction has come from the small molecule inhibitor 2-aminoethoxyodiphenyl borate (2-APB). Although it has been known for some time that low concentrations of 2-APB potentiate the size of the store-operated current, Ali *et al.* (2017) describe how this is accomplished. 2-APB dilates Orai1, the pore-forming subunit of the store-operated channel, from 3.8 to 4.6 Å, rendering the normally Ca^{2+}-selective channel permeable to Ca^{2+} and Na^{+}. Potentiation only occurs when Orai1 is in the open state, providing a possible starting point for the development of drugs that enhance the size of Ca^{2+} entry, although the change in ion selectivity would impact on Na^{+} transporters with complex consequences.

Much of our understanding of Ca^{2+} signalling has been extracted from isolated cells, but *in vivo* recordings are essential to place findings in a physiological context. The final review, by Tischbirek *et al.* (2017), describes the insights gleaned from a new red shifted fluorescent dye, Cal-590, which enables measurements as far as ~900 μm below the surface and from all six cortical layers. Dyes like Cal-590 with good signal

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to noise ratios and fast kinetics permit the detection of Ca^{2+} signals in neuronal circuits at depths that were previously inaccessible.

Although the meeting nicely highlighted the rapid progress being made in our understanding of the properties and functions of Ca^{2+}-permeable ion channels, it reinforced the need for the development of selective and potent inhibitors of non-voltage-activated Ca^{2+} channels as potential treatments for a range of diseases.

References

Ali S, Xu T & Xu X (2017). CRAC channel gating and its modulation by STIM1 and 2-aminoethoxydiphenyl borate. *J Physiol* **595**, 3085–3095.

Iamshanova O, Fiorio Pla A & Prevarskaya N (2017). Molecular mechanisms of tumour invasion: regulation by calcium signals. *J Physiol* **595**, 3063–3075.

Nurbaeva MK, Eckstein M, Feske S & Lacruz RS (2017). Ca^{2+} transport and signalling in enamel cells. *J Physiol* **595**, 3015–3039.

Parekh AB (2011). Decoding cytosolic Ca^{2+} oscillations. *Trends Biochem Sci* **36**, 78–87.

Petersen OH, Courjaret R & Machaca K (2017). Ca^{2+} tunnelling through the ER lumen as a mechanism for delivering Ca^{2+} entering via store-operated Ca^{2+} channels to specific target sites. *J Physiol* **595**, 2999–3014.

Samanta K & Parekh AB (2017). Spatial Ca^{2+} profiling: decrypting the universal cytosolic Ca^{2+} oscillation. *J Physiol* **595**, 3053–3062.

Santulli G, Nakashima R, Yuan Q & Marks AR (2017). Intracellular calcium release channels: an update. *J Physiol* **595**, 3041–3051.

Sun H-S (2017). Role of TRPM7 in cerebral ischaemia and hypoxia. *J Physiol* **595**, 3077–3083.

Tischbirek CH, Birkner A & Konnerth A (2017). *In vivo* deep two-photon imaging of neural circuits with the fluorescent Ca^{2+} indicator Cal-590. *J Physiol* **595**, 3097–3105.

Zierler S, Yao G, Zhang Z, Kuo WC, Pörzgen P, Penner R, Horgen FD & Fleig A (2011). Waixenicin A inhibits cell proliferation through magnesium-dependent block of transient receptor potential melastatin 7 (TRPM7) channels. *J Biol Chem* **286**, 39328–39335.

Additional information

Competing interests

None declared.