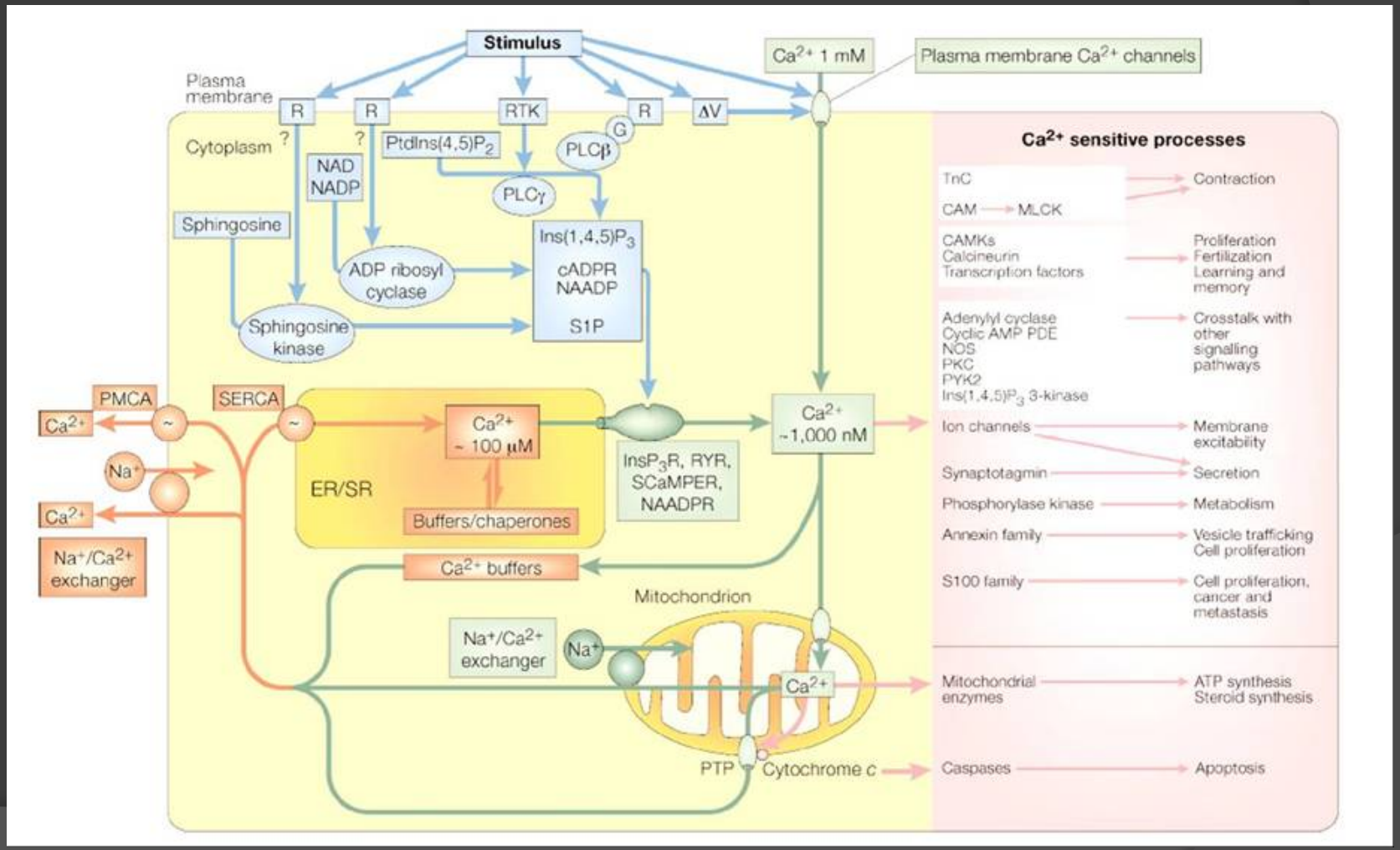
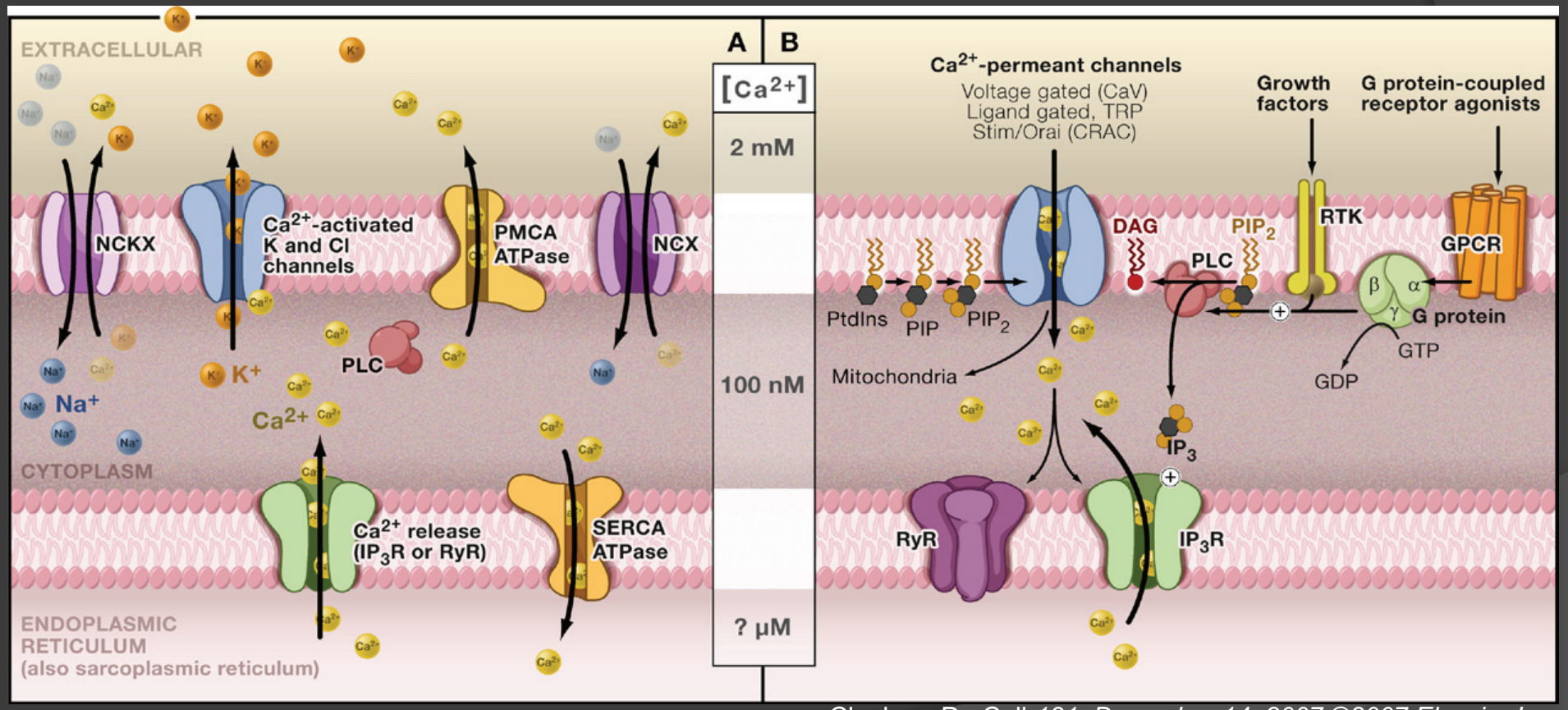
THE VERSATILITY AND UNIVERSALITY OF CALCIUM SIGNALLING

Michael J. Berridge, Peter Lipp and Martin D. Bootman

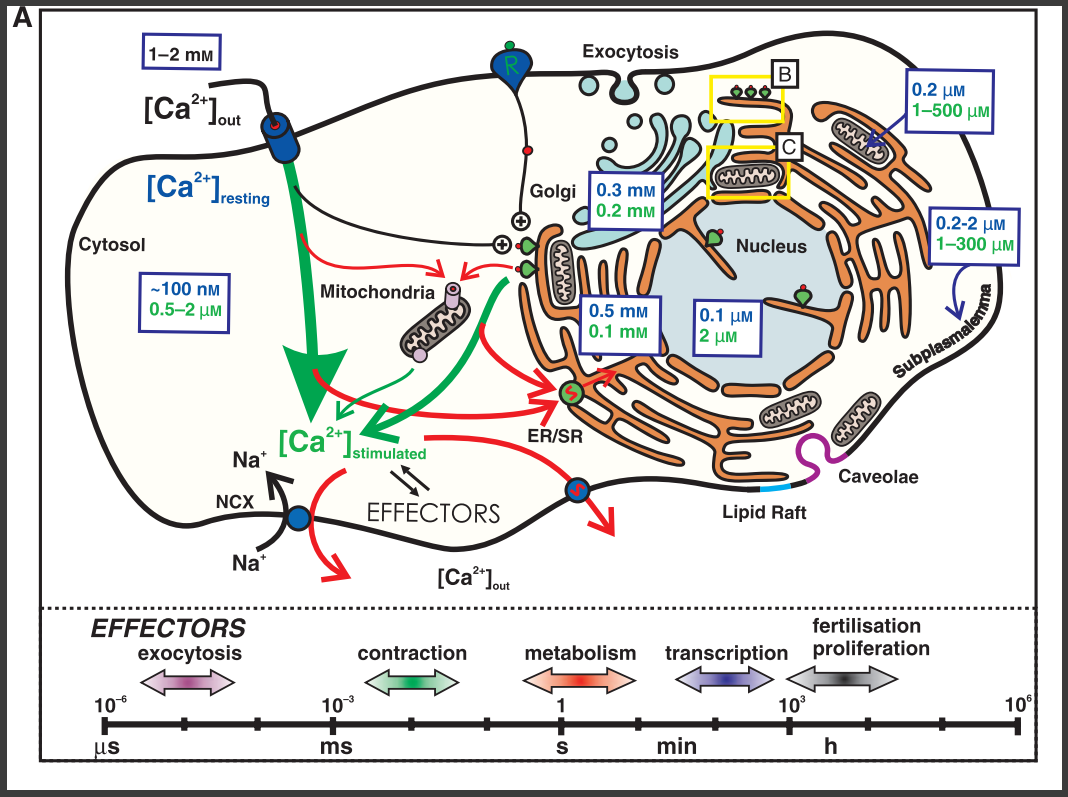


Maintaining and Using Ca2+ Gradients for Signaling



Clapham D., Cell *131, December 14, 2007 ©2007 Elsevier Inc.*

Segnali di Ca2+: dai singoli eventi alla risposta cellulare

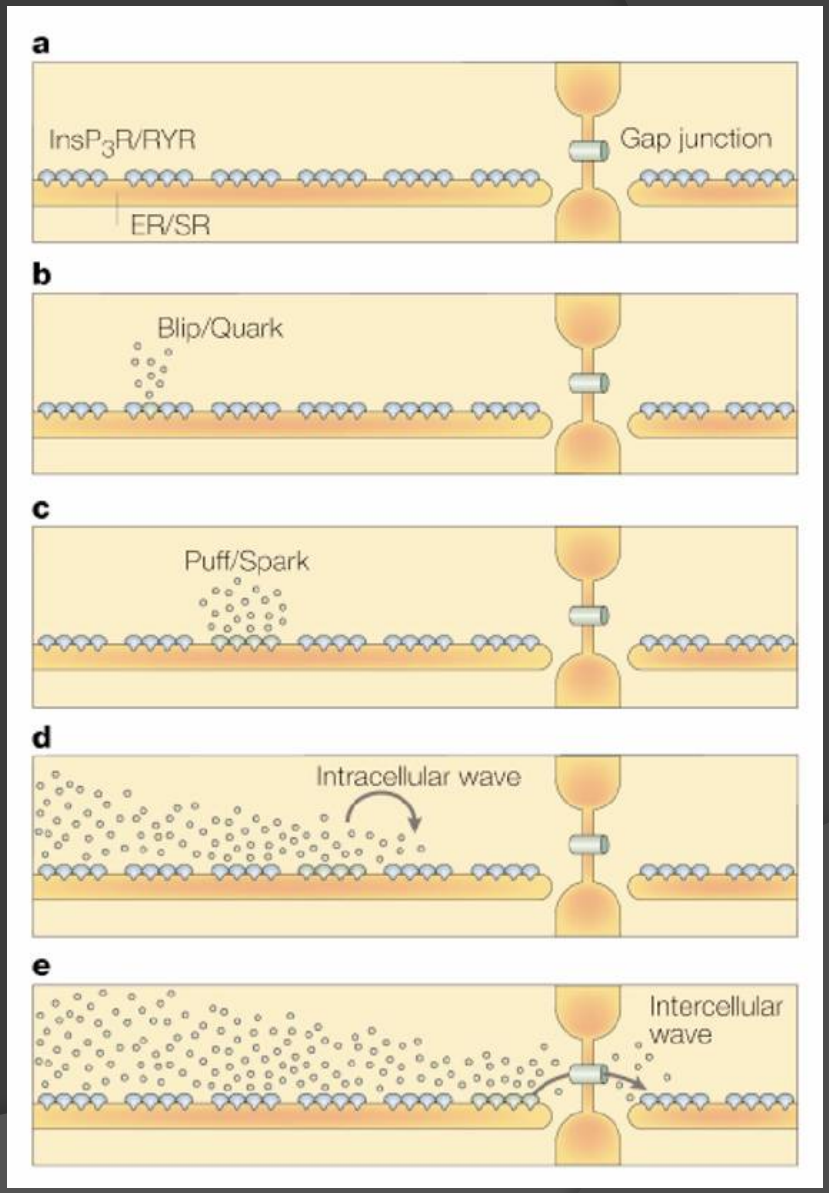


Generation of Ca2+ signals that can be small or large in amplitude, restricted to a small microdomain or global across the cell. Ca2+ signals can be of variable duration lasting from a few milliseconds to many hours

Elementary calcium events (blips, puffs…)

Two main types:

- those involving IP3 receptors (IP3Rs), which are responsible for Ca2+ ‘blips’ and ‘puffs’ in non-excitable cells;
- and Ca2+ ‘quarks’ and ‘sparks’ in muscle, which primarily involve ryanodine receptors (RYRs).



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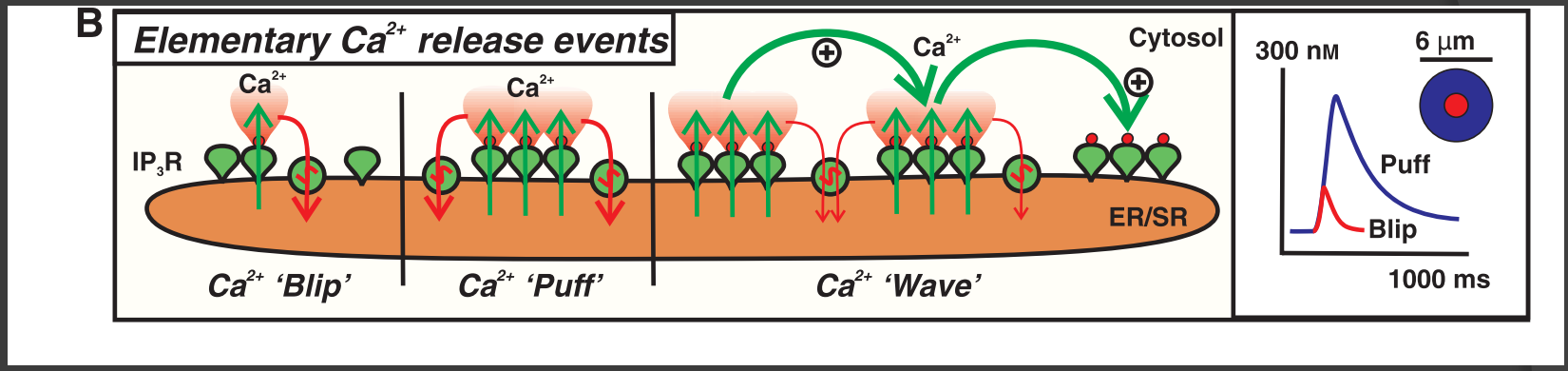

- Stimulation of cell-surface receptors leads to the activation of phospholipase C, hydrolysis of phosphatidylinositol bisphosphate and the formation of IP3. IP3 binds to IP3Rs on the ER, depending upon the IP3R state, the number of IP3 molecules and bound Ca2+ ions, the IP3R–Ca2+ channel opens and Ca2+ enters the cytoplasm to form a so-called ‘elementary release event’.

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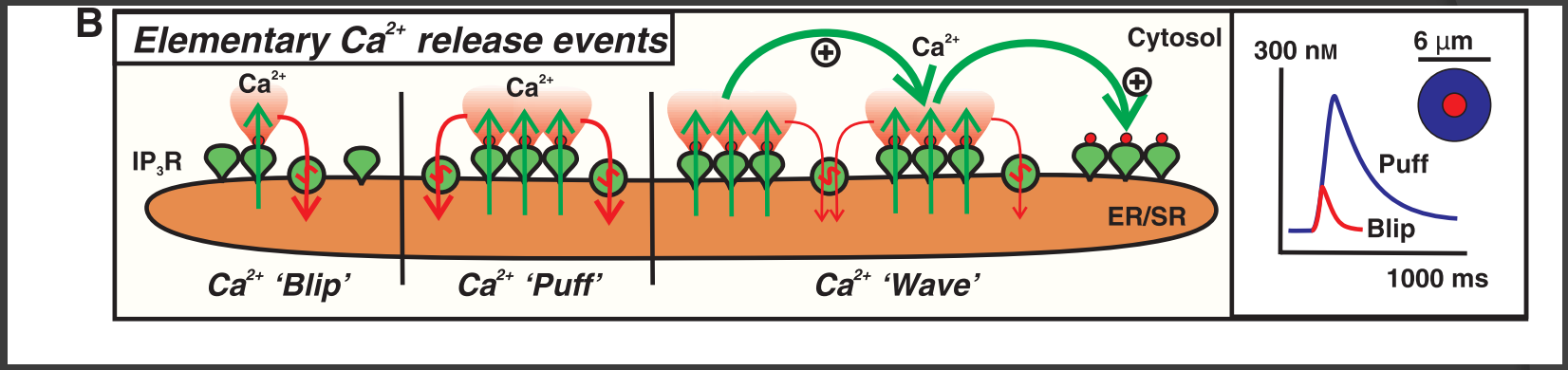

the most simple event:

- 'Ca2+blip' (or 'quark' for RYRs), which arises from the opening of single IP3Rs (or RYRs). They last for 200 ms, have an amplitude < 30 nM and depending upon the cytosolic environment, spread for no more than a couple of micrometres

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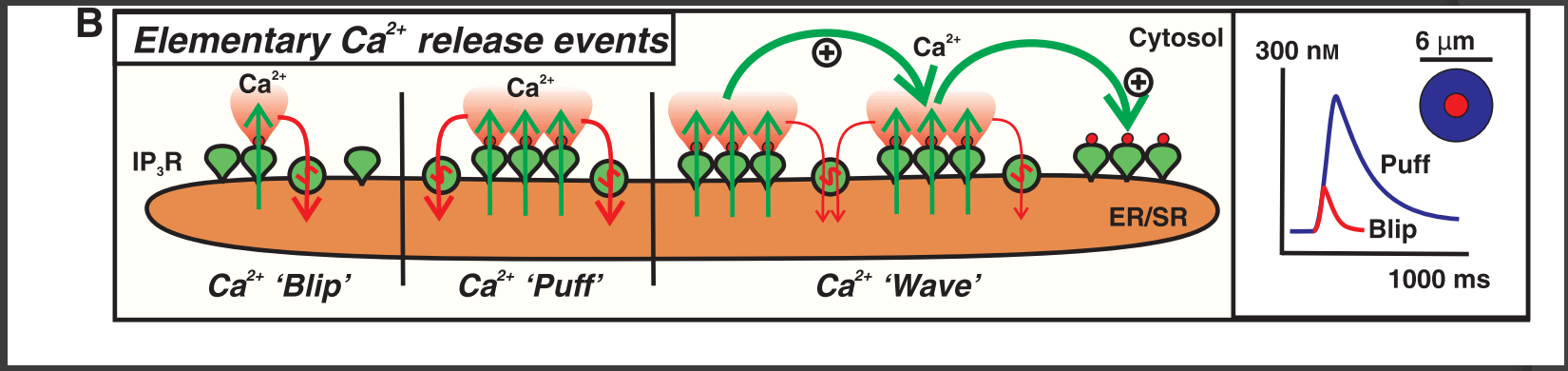

- The second event:
- Ca2+ 'puff', forms from the coordinated Ca2+ release from a population or cluster of IP3Rs and is analogous to the Ca2+ 'sparks' observed as a result of RYR stimulation by Ca2+ in cardiomyocytes. 'Puff' events spread no more than 6 um, have typical amplitudes of 200 nM and last for 500 ms. Modelling has suggested that clustering of 40–70 IP3Rs may underlie a puff event

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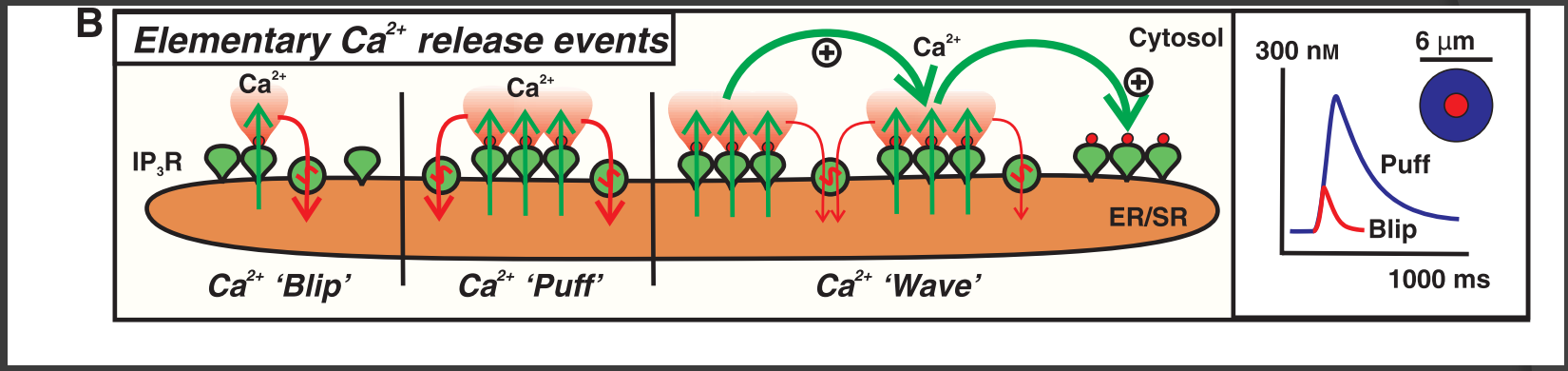

The third event is:

- regenerative Ca2+ 'wave' resulting from the spatiotemporal summation of Ca2+ puffs which can spread rapidly throughout the cell. The combination of cytoplasmic Ca2+ buffering and reuptake mechanisms act to restrict the Ca2+ signals. Only when these sinks are overcome does a Ca2+ signal spread. Subsequently, the diffusion rate of Ca2+ through the cytosol is relatively slow (10–50 um2/s) and organelles can profoundly modify a spreading Ca2+ wave.

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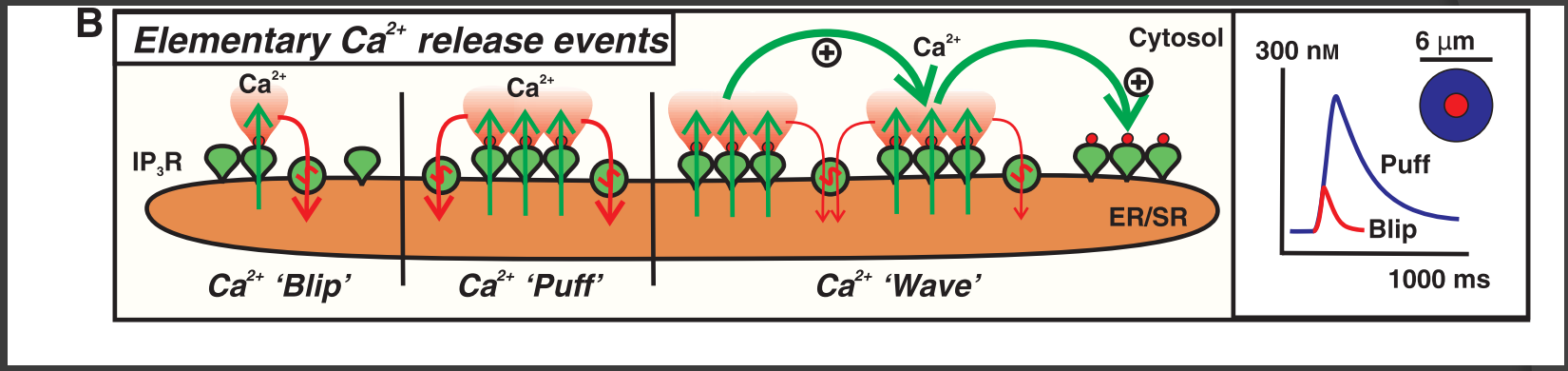

- Ca2+ release from RYRs is generally brought by Ca2+-induced Ca2+-release (CICR), that is activated when 1–10 uM Ca2+ is adjacent to the receptor and is inhibited when Ca2+ is 1–10 mM, the exact effects depending upon the RYR isoform.
- Ca2+ release from RYRs can also be triggered or enhanced by cyclic ADP-ribose (cADPr) although the effect of cADPr on specific RYR isoforms is debatable and its precise mode of action remains unclear.

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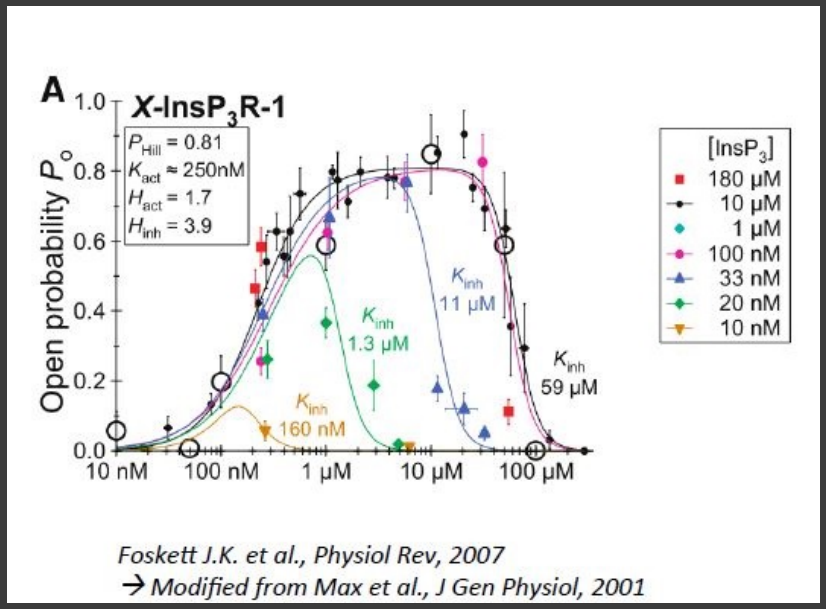
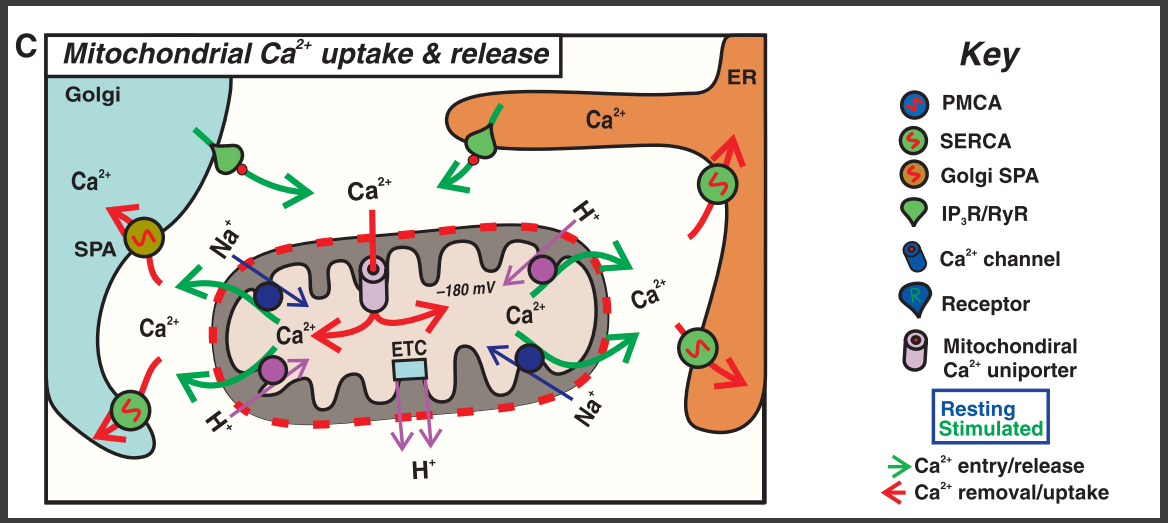


Foskett J.K. et al., Physiol Rev, 2007
→ Modified from Max et al., J Gen Physiol, 2001

- Detailed studies on the relations between IP3 and Ca2+ indicate that, like the RYR, the IP3R can also be considered to act via CICR. The IP3R cannot release Ca2+ even in saturating IP3 if the surrounding Ca2+ is < 50 nM. Like RYRs, IP3Rs are inhibited by elevated [Ca2+]c (10–100 um). This CICR-like behaviour is crucial in the initiation and propagation of Ca2+ signals across the cytoplasm and can lead to Ca2+ oscillations as seen in hepatocytes, endothelial cells and pancreatic acinar cells.

Physical Ca2+ compartments



As with [Ca2+]c, organellar Ca2+ is dynamic and through a diverse array of uptake and release mechanisms organelles play a major role in generating, modulating and decoding Ca2+ signals. Of the many compartments present within a cell, early attention was focused on the roles of the sarco-endoplasmic reticulum and the mitochondria.

However, Ca2+ also accumulates in acidic organelles and secretory granules. Within the nucleus, the pattern of Ca2+ signals can differ from those seen within the cytoplasm.

Callular compartimentalization of Ca2+ signals

Dense packing of the cell with organelles, Ca2+ buffers and sinks means that Ca2+ does not diffuse easily across the cell. Rather, Ca2+ signals that spread throughout the cell do so by propagation. This enables Ca2+ signals to be restricted to particular cytosolic domains unless they reach a threshold to allow propagation.