Calcium-induced calcium release in astroglia—a view “from the inside”

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For over three decades, a detailed characterization of the transport mechanisms regulating global and local changes in the intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) has remained at the forefront of cellular physiology in general and glial physiology in particular [1, 11]. Many improvements to the properties of Ca^{2+} -sensitive indicators and to the methods of their delivery into cells have been sought and implemented over the years. The release of Ca^{2+} from intracellular stores, among which the endo/sarcoplasmic reticulum (E/SR) is probably the most important, plays a pivotal role in Ca^{2+} signaling in most, if not all, cells [2, 10]. Hence, a considerable effort has been spent to develop techniques for monitoring the E/SR intraluminal concentration of Ca^{2+} during the cellular responses to stimulation, either by using a low-affinity form of Fura-2 (mag-Fura-2, also known as Fura-2/AM) [4] or a recombinant low-affinity luminescent protein aequorin specifically targeted to the E/SR [5]. As a further development, the low-affinity Ca^{2+} indicators loaded into E/SR were successfully combined with high affinity cytoplasmic Ca^{2+} indicators to yield simultaneous recordings of the intraluminal ($[\text{Ca}^{2+}]_L$) and cytoplasmic $[\text{Ca}^{2+}]_c$ calcium concentration [7, 9]. Although the ability to record $[\text{Ca}^{2+}]_c$ simultaneously with $[\text{Ca}^{2+}]_L$ has provided some interesting insights into the intricacies of Ca^{2+} signaling in visceral smooth muscle, in cardiomyocytes, and in sensory neurones [3, 5, 8, 9], the technique is prone to potential artifacts, mainly because of unintended loading of other intracellular organelles and the risk of incomplete removal of the cytosolically located low affinity indicator.

A substantial progress in both the in vitro and in vivo measurements of $[\text{Ca}^{2+}]_L$ and $[\text{Ca}^{2+}]_c$ has been made by developing a genetically encoded low-affinity Ca^{2+} sensor targeted to the E/SR and combining this with conventional high-affinity fluorescent Ca^{2+} dye [6]. In this issue of *Pflügers Archiv EJP*, M. Rodriguez-Prados et al. use this technique to provide direct evidence for the existence of calcium-induced calcium release (CICR) in astrocytes in vitro as well as in-situ in organotypic slice cultures. The authors found that both spontaneous and depolarization-induced $[\text{Ca}^{2+}]_i$ transients are accompanied by the corresponding fast $[\text{Ca}^{2+}]_L$ decreases indicative of the E/SR Ca^{2+} release triggered by relatively small $[\text{Ca}^{2+}]_i$ rise induced by depolarization-activated Ca^{2+} entry from the outside. Indeed, inhibition of the SERCA pump that eventually eliminates the E/SR Ca^{2+} release due to uncompensated Ca^{2+} leak reveals these small depolarization-induced rises in $[\text{Ca}^{2+}]_c$. With this advanced approach, future experiments are expected to clarify whether the astroglial CICR phenomenon is afforded by the Ca^{2+} dependence of the InsP_3 -mediated $[\text{Ca}^{2+}]_L$ release or if it is due to the involvement of astroglial ryanodine receptors. Whichever scenario turns out to be the case, the findings presented in this skillfully executed study are as trustworthy as they are exciting, given the fact that propagating Ca^{2+} waves are the main manifestation of the astroglial excitability [11].

References

1. Carafoli E (2002) Calcium signaling: a tale for all seasons. PNAS 99:1115–1122. <https://doi.org/10.1073/pnas.032427999>
2. Clapham DE (2007) Calcium Signaling. Cell 131:1047–1058. <https://doi.org/10.1016/j.cell.2007.11.028>
3. Domeier TL, Blatter LA, Zima AV (2009) Alteration of sarcoplasmic reticulum Ca^{2+} release termination by ryanodine receptor sensitization and in heart failure. J Physiol 587:5197–5209. <https://doi.org/10.1113/jphysiol.2009.177576>
4. Hofer AM, Machen TE (1993) Technique for in situ measurement of calcium in intracellular inositol 1,4,5-trisphosphate-sensitive stores using the fluorescent indicator mag-fura-2. PNAS 90:2598–2602. <https://doi.org/10.1073/pnas.90.7.2598>

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5. Montero M, Alvarez J, Scheenen WJJ, Rizzuto R, Meldolesi J, Pozzan T (1997) Ca²⁺ homeostasis in the endoplasmic reticulum: coexistence of high and low [Ca²⁺] subcompartments in intact HeLa cells. *J Cell Biol* 139:601–611
6. Navas-Navarro P, Rojo-Ruiz J, Rodríguez-Prados M, Ganfomina MD, Looger LL, Alonso MT, García-Sancho J (2016) GFP-Aequorin protein sensor for ex vivo and in vivo imaging of Ca²⁺ dynamics in high-Ca²⁺ organelles. *Cell Chem Biol* 23:738–745. <https://doi.org/10.1016/j.chembiol.2016.05.010>
7. Shmigel AV, Eisner DA, Wray S (2001) Simultaneous measurements of changes in sarcoplasmic reticulum and cytosolic [Ca²⁺] in rat uterine smooth muscle cells. *J Physiol* 531:707–713. <https://doi.org/10.1111/j.1469-7793.2001.0707h.x>
8. Shmygol A, Wray S (2005) Modulation of agonist-induced Ca²⁺ release by SR Ca²⁺ load: direct SR and cytosolic Ca²⁺ measurements in rat uterine myocytes. *Cell Calcium* 37:215–223. <https://doi.org/10.1016/j.ceca.2004.10.002>
9. Solovyova N, Veselovsky N, Toescu EC, Verkhratsky A (2002) Ca²⁺ dynamics in the lumen of the endoplasmic reticulum in sensory neurons: direct visualization of Ca²⁺-induced Ca²⁺ release triggered by physiological Ca²⁺ entry. *EMBO J* 21:622–630. <https://doi.org/10.1093/emboj/21.4.622>
10. Verkhratsky A (2005) Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* 85:201–279. <https://doi.org/10.1152/physrev.00004.2004>
11. Verkhratsky A, Zorec R (2019) Astroglial signalling in health and disease. *Neurosci Lett* 689:1–4. <https://doi.org/10.1016/j.neulet.2018.07.026>

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