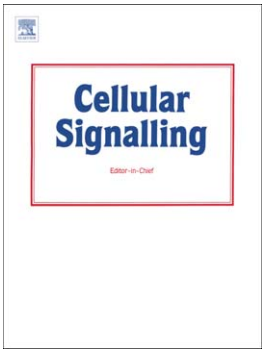

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Calmidazolium evokes high calcium fluctuations in *Plasmodium falciparum*

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ABSTRACT

Calcium and calmodulin (CaM) are important players in eukaryote cell signaling. In the present study, by using a knockin approach, we demonstrated the expression and localization of CaM in all erythrocytic stages of *Plasmodium falciparum*. Under extracellular Ca^{2+}-free conditions, calmidazolium (CZ), a potent CaM inhibitor, promoted a transient cytosolic calcium ($[Ca^{2+}]_{cyt}$) increase in isolated trophozoites, indicating that CZ mobilizes intracellular sources of calcium. In the same extracellular Ca^{2+}-free conditions, the $[Ca^{2+}]_{cyt}$ rise elicited by CZ treatment was ~3.5 fold higher when the endoplasmic reticulum (ER) calcium store was previously depleted ruling out the mobilization of calcium from the ER by CZ. The effects of the Ca^{2+}/H^+ ionophore ionomycin (ION) and the Na^+/H^+ ionophore monensin (MON) suggest that the $[Ca^{2+}]_{cyt}$-increasing effect of CZ is driven by the removal of Ca^{2+} from at least one Ca^{2+}-CaM-related (CaMR) protein as well as by mobilization of Ca^{2+} from intracellular acidic calcium stores. Moreover, we showed that the mitochondrion participates in the sequestration of the cytosolic Ca^{2+} elicited by CZ. Finally, the modulation of membrane Ca^{2+} channels by CZ and thapsigargin (THG) was demonstrated. The opened channels were blocked by the unspecific calcium channel blocker Co^{2+} but not by 2-APB (capacitative calcium entry inhibitor) or nifedipine (L-type Ca^{2+} channel inhibitor). Taken together, the results suggested that one CaMR protein is an important modulator of calcium signaling and homeostasis during the *Plasmodium* intraerythrocytic cell cycle, working as a relevant intracellular Ca^{2+} reservoir in the parasite.