Imaging of extracellular Ca^{2+} in the hippocampus by a novel CMOS ion image sensor

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Intracellular calcium ion (Ca^{2+}_i) is one of the most important cation that controls several cellular functions, and thus there were already huge number of literature about Ca^{2+}_i imaging in various cells. Although it is believed that Ca^{2+}_i increase is accompanied by extracellular Ca^{2+} (Ca^{2+}_o) decrease, the kinetics of Ca^{2+}_o decrease remain unknown because of the limited imaging options. To overcome this limitation, we developed a Ca^{2+} image sensor (CIS) that is highly selective to Ca^{2+} but not to other cations within wide dynamic range (from 100 nM to 100 mM). We used CIS for the imaging of Ca^{2+}_o in acute hippocampal slices. Stimulation with glutamate (Glu) decreased Ca^{2+}_o to around 200 nM within 3 s, which returned to the baseline level (2 mM) with slow kinetics (5 min). Glu stimulates both neurons and glial cells to evoke Ca^{2+}_i elevation, thereby reducing Ca^{2+}_o . Thus, we tested NMDA to selectively stimulate NMDA receptor in neurons. NMDA mimicked Glu-evoked Ca^{2+}_o decrease. Interestingly, Ca^{2+}_o decrease was initiated at hippocampal CA1-2, before spreading along the pyramidal layers. Glutamate- and NMDA-evoked Ca^{2+}_o decreases were inhibited by a NMDA receptor antagonist D-APV, suggesting involvement of neuronal NMDA receptors in decrease in Ca^{2+}_o . So far, many scientists neglected Ca^{2+}_o , but the CIS would tell us its importance for understanding brain functions.