Applying Ca^{2+} Image Sensor to visualize extracellular Ca^{2+} dynamics in hippocampus.

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Unlike intracellular Ca^{2+} , extracellular Ca^{2+} ($[\text{Ca}^{2+}]_o$) has received only limited attention. $[\text{Ca}^{2+}]_o$ has profound effects on neuronal membrane potential and synaptic transmission. Physiological conditions like sensory stimulation, sleep-wake transitions and pathological conditions like seizures, ischemia are reported to decrease $[\text{Ca}^{2+}]_o$. However, these data are obtained from a single point analysis using a Ca^{2+} electrode and lack spatiotemporal information of $[\text{Ca}^{2+}]_o$ changes. To understand processes shaping local and global $[\text{Ca}^{2+}]_o$ change involved in regulating physiological and pathological neuronal activity, we need an imaging technique that provides higher spatiotemporal resolution. Thus, we developed a label-free $[\text{Ca}^{2+}]_o$ image sensor (CIS) with a time resolution of a few tens of milliseconds at 23.55 μm pitch of 128 x 128 pixel. The CIS is highly selective to Ca^{2+} but not to other cations within wide dynamic range (from 100 μM to 100 mM). We used CIS for the imaging of $[\text{Ca}^{2+}]_o$ in acute hippocampal slices. Stimulation with neurotransmitter glutamate (Glu), decreased $[\text{Ca}^{2+}]_o$ to around 800 μM within 10 s, which gradually returned to the baseline level (2 mM) with slow kinetics (5 min). The Glu-evoked $[\text{Ca}^{2+}]_o$ decrease was higher in CA1 and DG compared to CA3, and was inhibited by a NMDA receptor antagonist D-APV but not AMPA receptor antagonist CNQX. NMDA mimicked the Glu-evoked $[\text{Ca}^{2+}]_o$ decrease and, again was inhibited by D-APV. These findings suggest that Glu acts on neuronal NMDA receptors to reduce $[\text{Ca}^{2+}]_o$ with different spatiotemporal patterns, reflecting differences in NMDA receptors distribution. Our study demonstrates that a CIS can detect $[\text{Ca}^{2+}]_o$ changes associated with biological events and have broad applicability in future biological studies.