



Imaging serotonin dynamics with designed genetically encoded indicators

Dong CE, Unger EK, Altermatt M, Hon OJ, Keller JP, Liang R, Yao Z, Jaffe DA, Sun J, Underhill S, Sinning S, Borden PM, Carlin J, Marvin JS, Temple Lang D, Prescher J, Lavis LD, Kash TL, Yarov-Yarovoy V, Grdinaru V, Looger LL, Tian L.

Abstract

The neurotransmitter serotonin is involved in numerous biological and cognitive processes in both health and disease. A deeper understanding of serotonergic circuitry and signaling, and the function of drugs such as SSRIs, is hindered by the inability to readily and reliably measure serotonin dynamics with high spatial and temporal resolution. We exploited two scaffolds to engineer different genetically-encoded, single-wavelength intensiometric fluorescent sensors for serotonin from circularly permuted GFP with a bacterial periplasmic binding protein (PBP) or serotonin receptor. However, there is no known PBP that binds serotonin. To produce the PBP-based sensor (i5HTSnFR), we developed a machine learning-guided binding pocket redesign strategy and applied it to an acetylcholine sensor scaffold. To produce the serotonin receptor-based sensor (sLight), we applied the module strategy used in designing our published dopamine sensor dLight. We characterized and validated both sensors' performance, whereby we can detect serotonin transients in mammalian cells, dissociated neuronal cultures, acute slices and freely behaving mice.

