Development of a fluorescent sensor for real-time recording of oxytocin dynamics in the brain

Department of Pharmacology, Graduate School of Medicine

Specially Appointed Lecturer Daisuke Ino Researchmap https://researchmap.jp/daisukeino?lang=en

Professor Hiroshi Hibino Researchmap https://researchmap.jp/hiroshi_hibino?lang=en

Abstract

Oxytocin (OT), a neuromodulator also known as the 'happiness hormone,' plays a key role in our rich emotional experiences and overall mental and physical health. However, spatio-temporal dynamics of OT in the brain remains elusive, largely due to the lack of the suitable method for measuring OT with a high sensitivity in the living brain. Hence, we have developed MTRIA$_{OT}$, an ultra-sensitive fluorescent sensor for measuring the extracellular OT level with precision. By using this innovative tool, we have achieved real-time measurements of OT dynamics in the living brain, unraveling the enigma surrounding its functions.

Background & Results

OT plays a crucial role in a wide range of physiological functions such as mitigation of anxiety and stress, regulation of appetite, and control of metabolism, thereby profoundly influencing our rich daily lives. Moreover, abnormalities in OT have been linked to refractory mental disorders, adding to its significance as a pivotal molecule in therapeutic development. However, previous methods to detect and monitor OT have been limited in their ability to accurately reflect dynamic changes in extracellular OT levels over time. Therefore, fundamental questions such as 'when,' 'where,' and 'how' OT functions in the brain have remained unresolved.

To address this problem, we developed a fluorescent sensor that detects the change in the extracellular OT concentration as a fluorescence readout. By introducing sequential mutations to a chimera protein comprising OT receptors and green fluorescent proteins, we successfully developed MTRIA$_{OT}$, an ultra-sensitive fluorescent OT sensor exhibiting approximately eightfold increase in fluorescence intensity upon OT binding (Figure 1). By using MTRIA$_{OT}$, we conducted in vivo measurements of OT dynamics in mouse brain under various experimental conditions. Interestingly, our analysis revealed that the temporal profiles of OT dynamics in the brain are highly variable depending on the behavioral context of the animal (Figure 2).

Significance of the research and Future perspective

The development of MTRIA$_{OT}$, an ultra-sensitive fluorescent OT sensor engineered by our team, has empowered us to engage in real-time monitoring of OT dynamics within the living brain. While we conducted several proof-of-concept studies in the mouse brain utilizing MTRIA$_{OT}$, a multitude of biological phenomena linked to OT signaling remain untouched. Given a key role of OT as a molecule of interest in the treatment of complex mental disorders like autism spectrum disorders and schizophrenia, our tool holds the potential to illuminate the underlying causes and propel drug development for these intractable conditions.

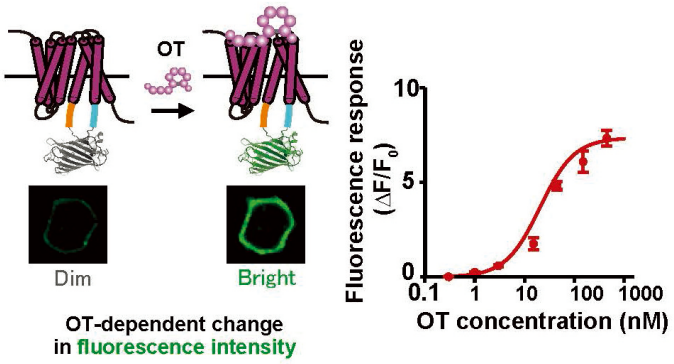

Fig.1 Development of an ultra-sensitive fluorescent OT sensor MTRIA$_{OT}$. Schematic illustrating how MTRIA$_{OT}$ works (left). Dose-response curve of MTRIA$_{OT}$ (right).

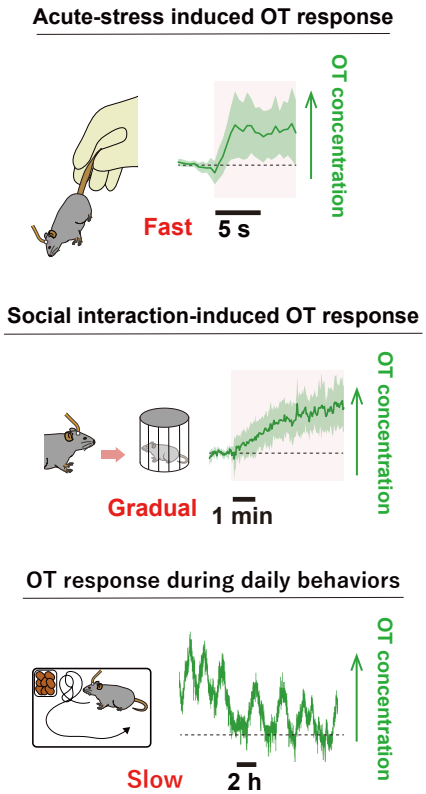

Fig.2 Measurement of brain OT dynamics with MTRIA$_{OT}$.
Brain OT responses induced by acute-stress stimulus (left), by social interaction (center), and during daily behaviors (right). Our measurements revealed that the temporal profiles of OT signals were highly variable and depended on the behavioral context of the mouse.

Patent

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