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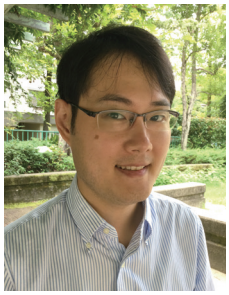

研 究 課 題： 記憶の長期的な保存機構の理解と応用
（Understanding and applying long-term memory storage mechanisms）
専 門 分 野： 神経科学（Neuroscience）
受 入 先 部 局： 医学研究科（Graduate School of Medicine）
前職の機関名： 京都大学医学研究科（Graduate School of Medicine, Kyoto University）

私の専門は神経科学で、「記憶」の研究をしています。記憶が脳内の神経細胞でいつ、どのようなメカニズムで作られるかを、マウスを用いた生物学的なアプローチから研究しています。例えば神経細胞のスパインと呼ばれる微小構造物上で記憶ができる瞬間を 2 光子顕微鏡によって撮影したり、学習中のマウスの脳内の数百個の神経活動をリアルタイムで観察することで記憶を担う神経活動を解析したり、光によって記憶を操作することで記憶が誘導される時間枠を調べたりしています。

白眉プロジェクトの研究では、記憶が長期保存される過程に着目して研究します。例えば我々は子供の頃の出来事など、数十年まえの記憶を持つことができますが、このような長期記憶が脳のいつどこでどのようにして作られるかを、上記のイメージングと光操作技術を用いて明らかにしていきます。また光による記憶操作技術を様々な精神疾患の治療法に応用することも目指します。

I study memory in the field of neuroscience, focusing on when and how memories are formed in neurons in the brain using a biological approach in mice. For example, I capture the moment when memories are formed on microstructures called neuronal spines using two-photon microscopy. I also record hundreds of neuronal activities in real-time in the brain of a learning mouse to analyze the neuronal activity responsible for memory, and I investigate the time frame in which memories are induced by manipulating them with light.

In the Hakubi Project, I will focus on the processes by which memories are stored over time. For example, we can recall memories of events from our childhood that are several decades old. I will use imaging and optogenetics to clarify when, where, and how such long-term memories are formed in the brain. I also aim to develop treatments for various mental disorders using optical memory manipulation techniques.

Development of optical technology to detect memory encoding cells

Memories are initially formed in the hippocampus, but over time, they are transferred to other brain regions and stored stably over the long term. This process is known as 'memory consolidation,' and understanding its cellular mechanisms is important for understanding long-term memory storage (Goto 2022, Neurosci. Res.). I have recently succeeded in developing an original optical technique to detect synaptic long-term potentiation (LTP), a cellular-level memory phenomenon (Goto et al., 2021, Science). LTP is formed by the enlargement of microstructures on neurons called spines. Inactivation of LTP-related proteins by light irradiation using the CALI technique suppressed spine enlargement and erased memories within 20 minutes of LTP induction. Therefore, by examining whether light irradiation erases memories, it is possible to identify the brain regions and time frames in which memories are formed by LTP. This optogenetics technique has shown that long-term memories are formed in the cortex during sleep on the day after learning (Fig. 1).

Optogenetics is further combined with Ca^{2+} imaging (observation of neural activity) and FRET imaging (observation of

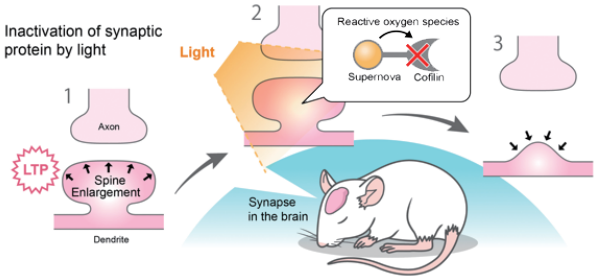

Fig. 1 Optogenetics to detect memory formation during sleep. A method to cancel LTP (spine enlargement) by irradiating light has been developed, which reveals that long-term memories are formed during sleep.

LTP). FRET imaging can detect cells involved in memory by observing the activity of nuclear ERK, which is highly correlated with LTP. To enable simultaneous and long-term LTP manipulation, as well as Ca^{2+} and FRET imaging by optogenetics, fiber endomicroscopy will be developed. In fiber endomicroscopy, one end of a fiber bundle consisting of thousands of optical fibers, each about 2 microns in diameter, is inserted into different regions of the brain, while the other end is scanned with a confocal microscope, allowing multiple optical systems to be assembled (Goto et al., 2015, PNAS). The use of multiple fiber bundles also allows simultaneous observation of memory dynamics in multiple regions.

Elucidating the cellular mechanisms of memory consolidation

After developing the optical technology, I will first use optogenetics to clarify the time frame of LTP in brain regions involved in long-term memory formation. The time frame of LTP in the hippocampus and anterior cingulate cortex has already been revealed (Goto et al., 2021, Science.). Thus, experiments will be conducted in other brain regions involved in memory, such as the amygdala, to identify the specific brain regions and time frames in which long-term memories are formed. Next, Ca^{2+} and FRET imaging will be performed to analyze the cells responsible for memory in more detail. Long-term Ca^{2+} and FRET imaging will be performed simultaneously within multiple regions in mice brain before and after learning, revealing long-term memory at the cellular level by detecting cells in which LTP is induced and which are responsible for memory.

Investigation of PTSD treatment using light-based memory manipulation

Long-term storage of memories is essential in modern society, where ageing and associated dementia are significant social problems. On the other hand, post-traumatic stress disorder (PTSD), insomnia, and withdrawal from the past are also major social issues, and no method has yet been established for treating PTSD by removing specific memories. Therefore, I will investigate whether my optogenetics method can be used to treat PTSD in mice. I will explore optimal conditions for treating PTSD by specifically erasing distressing memories with light.

I will also design a system to enhance memories with light. In the light-induced memory-erasing system, light inactivated proteins important for memory in the spine. Therefore, I will construct a light irradiation system that can specifically enhance memory with light by inactivating the proteins that inhibit memory formation.

References

- Goto, Synaptic plasticity during systems memory consolidation. ***Neurosci Res*** 189 29-36, 2022.
- Goto et al., Stepwise synaptic plasticity events drive the early phase of memory consolidation. ***Science*** 374, 857-863.
- Goto et al., Circuit-dependent striatal PKA and ERK signaling underlies rapid behavioral shift in mating reaction of male mice. ***Proc Natl Acad Sci U S A***. 112 (21) 6718-6723, 2015.