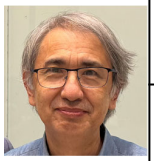
【Grant-in-Aid for Scientific Research (S)】

Cortical Spine Synaptic Mechanics and Synaptic Chemogenetics



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Project Information	Project Number : 25H00434　　Project Period (FY) : 2025-2029 Keywords : Mechanical transmission, synaptic chemogenetics, cognitive function, wakefulness

Purpose and Background of the Research

●Outline of the Research

We have discovered that when dendritic spines—tiny structures connecting neurons in the cerebral cortex—are prevented from enlarging, awake cognitive functions disappear. Our goal is to uncover how the enlargement drives both wakefulness and cognition.

●Dendritic spine in mental function

Most excitatory connections in the human brain occur on dendritic spines, which total around 100 trillion and vary greatly in shape (A). Although studies in 20th century linked abnormal spine shapes to mental disorders, the precise role of individual spines remained unclear.

We developed two-photon glutamate uncaging to show how spine structure relates to function (B,C), revealing that long-term shifts in spine function must match changes in spine shape. Notably, associative stimulation rapidly enlarges spines (D,E) and boosts their glutamate sensitivity (F)(***Nature*** 2004), indicating that spines serve as memory elements.

Furthermore, the rapid phase of spine enlargement mechanically pushes the presynaptic terminal, briefly enhancing its function (G)(***Nature*** 2021). This push exerts about 0.5 kgf/cm²—comparable to muscle force. Unlike artificial intelligence, our brain's "memory units" harness a living mechanical force. Our ongoing research suggests that such mechanical transmission underlies various cognitive processes in the awake brain.

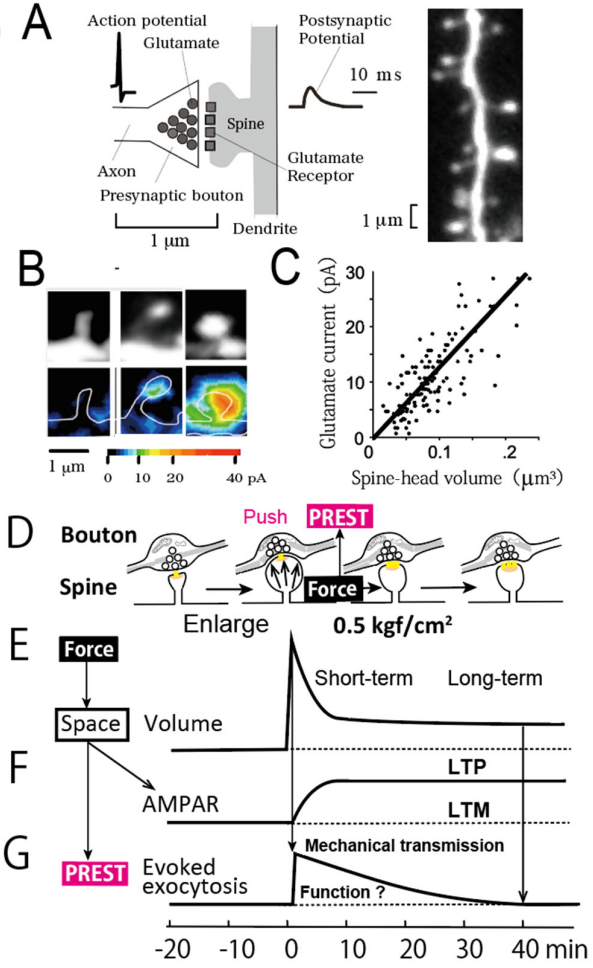

Figure 1. Dendritic spines in the brain function.

●Manipulation of spine enlargement

Knowing where spines enlarge is crucial for understanding cognition. We have successfully labeled these spines (***Nature*** 2015) and developed an improved labeling method called iAS (A).
We also devised a chemogenetic technique to alter spine structure. Unlike optogenetics, it avoids phototoxicity and reaches deeper into tissue (B)(***Science*** 2024). By combining iAS and chemogenetics, we can confirm the role of labeled spines in cognitive function. We can even enlarge specific spines to test whether we can reproduce certain cognitive functions.

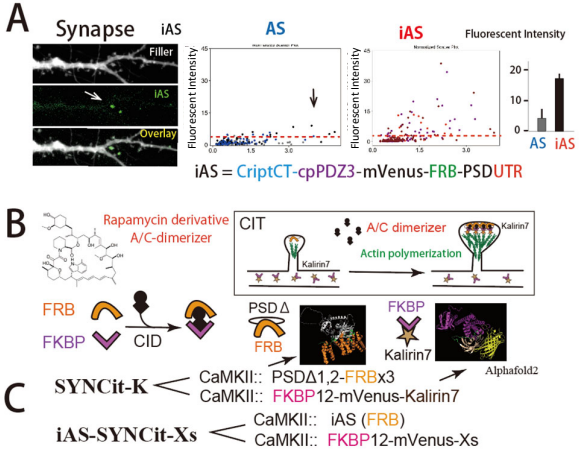

Figure 2. Labeling of spines and chemogenetics

Expected Research Achievements

●How spine enlargement underpins cognitive function

Dendritic spine chemogenetics shows that blocking spine enlargement in the brain prevents perception, executive function, and even wakefulness. Understanding this requires measuring the fast mechanical transmission (A), clarifying why cognitive impairments arise, and mapping where spine enlargement occurs in the cortex, even within single neurons. We will also examine the positive feedback loop between spine enlargement and circuit dynamics (B).

Rapid associative synaptic plasticity likely forms the basis of cognition, yet it has been difficult to demonstrate in the cortex. We have shown that spine enlargement can physically push the presynaptic terminal, enabling quick plasticity while increases in glutamate sensitivity happen more slowly (A). Despite technical difficulties, we will quantify the prodesses with the state-of-the art technology.

In mice, preventing spine enlargement abruptly halts behavior, yet this state is neither epileptic nor slow-wave sleep. It appears intermittently, with motive states. By analyzing these episodes, we hope to understand the mechanisms behind wakefulness.

Finally, labeling enlarged spines under different experimental conditions will deepen our understanding of brain function beyond traditional ideas of "functional localization."

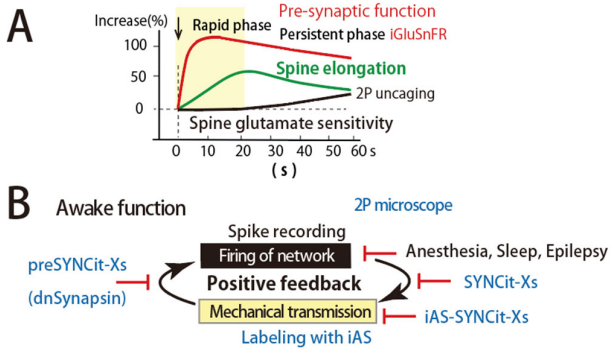

Figure 3. Underpinning of cognitive function

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