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

Molecular, cellular and circuit interrogation of Arc-dependent memory stabilization

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Purpose and Background of the Research

●Outline of the Research

The brain is an organ that defines human nature. The foundation of various higher-order brain functions, including memory and learning, lies in neural circuits that maintain specific input-output relationships. These functional neural circuits exhibit two universal characteristics.

First, there exists a "circuit blueprint" in which 10^{11} neurons are interconnected to form functional systems, alongside a strict "grammar" that ensures the accurate reading of this blueprint. Second, there is "synaptic plasticity," which allows 10^{14} synapses to flexibly adapt and respond to internal and external environmental changes on an individual basis, as well as an intrinsic "learning ability" that modifies and refines plastic responses based on past experiences.

What, then, is the foundation of the Neural Code—the information representation rule—that enables the coexistence of these seemingly contradictory properties: the rigidity of the "circuit blueprint" and the flexibility of "synaptic plasticity"?

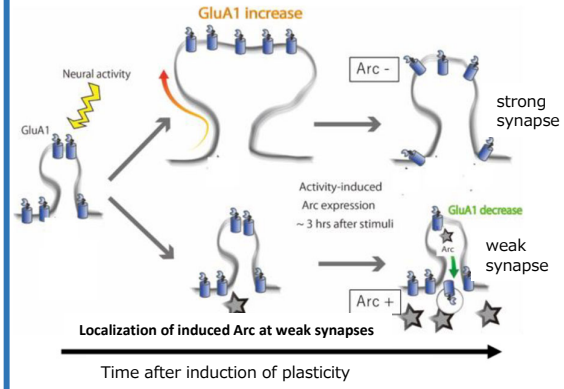

Fig1. Depression of weak synapses via inverse synaptic tagging

We discovered that immediately following the induction of neural plasticity, when the synaptic strength ratio undergoes significant changes, the "inverse synaptic tagging" rule is activated. This process is mediated by Ca^{2+}-CREB-Arc signaling, leading to the retention of strong synapses while weaker synapses gradually weaken, thereby stabilizing the synaptic strength ratio (Fig1).Furthermore, we elucidated that the cellular-level representation of long-term memory (enhancement of strong neurons) and the synaptic-level representation (suppression of weak synapses within strong neurons) are directly linked through the synaptic localization of the Arc molecule.

Fig2. Measurement and manipulation via multiplex Ca^{2+} imaging

To address this challenge, we have pioneered the development of a multicolor simultaneous visualization technique for monitoring the neural activity dynamics of excitatory and inhibitory neurons, as well as axonal and dendritic processes.

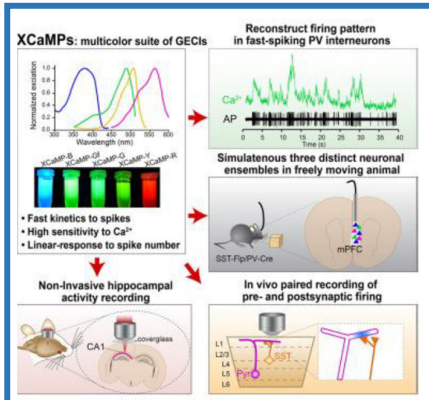

Fig3. Rational design of XCaMP, a high-res Ca^{2+} sensor

Building on these prior research findings, this study aims to elucidate the mechanisms underlying synaptic plasticity and circuit remodeling that govern the long-term stabilization of memory. As a breakthrough approach, we leverage the inverse synaptic tagging rule, which our research group was the first in the world to uncover, along with related molecular and cellular neuroscience insights. Furthermore, we employ recently developed advanced imaging technologies and probes capable of simultaneously capturing the activity of multiple cell types and numerous synapses, forming the core of our research strategy.

Expected Research Achievements

In this study, we aim to investigate the hypothesis that Arc, a synaptic regulatory molecule dependent on neural plasticity, functions to "link the information representation of long-term memory between the cellular and synaptic levels, thereby governing the long-term stability of associative memory." Specifically, we seek to elucidate the multi-scale interaction mechanisms between synaptic plasticity and circuit connectivity remodeling by focusing on three levels of interaction: (1) between synapses and cells, (2) between cells and circuits, and (3) between circuits and pathological conditions.

Aim 1: Elucidating the Molecular Mechanisms Underlying the Persistence of Inverse Synaptic Tagging in Strengthened Neurons

The discovery of the inverse synaptic tagging mechanism has, for the first time, revealed a potential mechanism linking two distinct hierarchical levels of information representation that define long-term memory—namely, information representation at the cellular level and at the synaptic level. In this study, we aim to further elucidate the details of this mechanism in the adult brain in vivo. Additionally, we will investigate the synaptic information representation that underlies long-term retention of associative memory using a novel approach that combines glutamate receptor fluorescent probes with multiplexed two-photon excitation microscopy imaging of activity sensors. This will provide insights into both the physiological and pathological bases of memory stabilization.

Aim 2: Investigating the Stabilization of Synaptic Strength Ratios in Memory-Engram Cells and Identifying the Strengthened Cortical and Subcortical Circuits and Their Regulatory Mechanisms

The neuronal populations that are both necessary and sufficient for remote memory traces are localized in the mouse prefrontal cortex. However, little is known about their activity dynamics and regulatory mechanisms. In this study, we will leverage next-generation memory-trace labeling techniques to analyze the activity patterns exhibited by memory-trace cells during the stepwise formation of remote memory. Furthermore, we will elucidate how these dynamics are controlled through interactions between cortical and subcortical circuits.

Aim 3: Validating an Intervention Strategy Targeting Normal Aging and Cognitive Pathology by Manipulating the Mechanisms Underlying Remote Memory Stabilization and Persistence

Building upon the findings from Objectives 1 and 2, we will develop and validate an intervention strategy aimed at enhancing the storage mechanisms of remote memory traces. Specifically, we will evaluate whether this strategy can prevent memory decline in aging and dementia models by targeting the mechanisms underlying remote memory retention.

Homepage Address, etc.	https://researchmap.jp/Bito?lang=en http://neurosci.umin.jp/e/neurochemistry.html