Press Release

Keio University Sanyo-Onoda City University

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Discovery of a New Intracellular Signal that Facilitates Early Stage Neural Network Formation

—New Intracellular Transducer : Magnesium Ion—

A joint research group consisting of Professor Kotaro Oka and other members of the Keio University Faculty of Science and Technology, Department of Biosciences and Informatics and Assistant Professor Ryu Yamanaka of the Sanyo-Onoda City University Faculty of Pharmaceutical Science has shown that the fluctuations in intracellular magnesium ion concentration is a new signal transducer that facilitates the maturation of neuronal networks. The research group used an intracellular magnesium ion fluorescent probe that they developed for their ongoing research to analyze magnesium ion dynamics in hippocampal neurons. This led to the very first discovery that GABA, which is a type of neurotransmitter, induces the release of magnesium ions from the mitochondria into the cytoplasm. Furthermore, it has been clarified that the released magnesium ions facilitate the maturation of neural networks by simultaneously controlling the activities of multiple intracellular signaling molecules. Until now, it had been thought that the intracellular magnesium ion concentration remained constant and that there was no connection to the dynamic changes of the cells. However, the results of this study showed that the intracellular magnesium ion is a new signal transducer that integrates extracellular signals and regulates numerous downstream molecules. The role of the magnesium ion as a new transducer has become fundamental knowledge in biology and medicine, and there are expectations that this will contribute to the development of medications in the future.

The findings of this research were published in the December 17, 2018 (Mon.; Japan time) issue of the American scientific journal “Current Biology.”

1. Main Points of Research

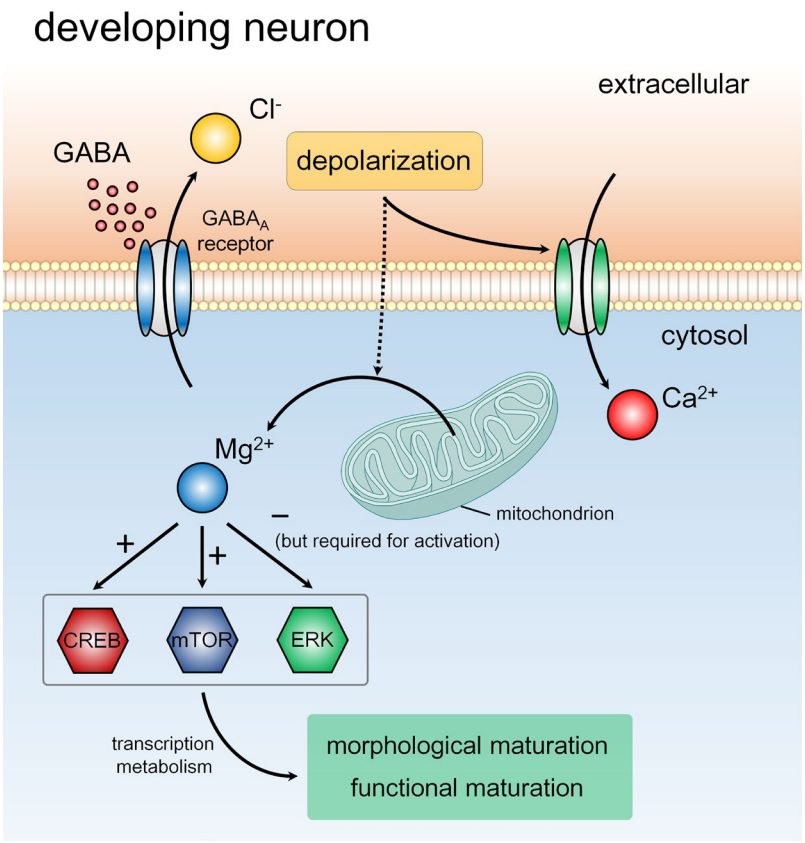
- Discovery that the GABA neurotransmitter induces the release of magnesium ions from mitochondria using live cell imaging
- Proof that the released magnesium ions regulate downstream intracellular activities
- First-time proof that the released magnesium ions are essential for the maturation of neural networks
- Proof that the magnesium ion is a new intracellular signal transducer within cells

2. Background of Research

Within its developmental process, the neurons that make up the brain form neural networks through neurite elongation and by connecting with other neurons and synapses that are formed. It is known that complex neural networks are successfully formed within this process because each neuron senses and responds to its surrounding environment in various ways. For this, the neurons have various intracellular signal transduction systems that transmit extracellular environmental signals into the neurons. It has been known for a long time from the results of in vitro experiments that magnesium ions ※1 influence various chemical reactions. However, it had been thought that the intracellular magnesium ion concentration remained constant and that there was no connection to the dynamic changes of the neurons. Therefore, magnesium ions were not considered to be molecules responsible for intracellular signal transduction ※2.

3. Content of Research and Results

First, the research group used an intracellular magnesium ion probe that was developed for their ongoing research to search for physiological stimuli that bring about changes in intracellular magnesium ion concentration while neural network formations take place. This led to the discovery that GABA ※3, which is a type of neurotransmitter, induces the release of magnesium ions from the mitochondria into the cytoplasm at the early stages of neurogenesis. It was found that the released magnesium ions inhibit the activities of the ERK ※4 intracellular signal and facilitate the activities of both CREB ※5 and mTOR ※6. In particular, in the case of the mTOR signals, it was shown that the magnesium ion plays the role of a switch that turns its activities on and off. Furthermore, it was revealed that the magnesium ion signal increases the thickness of the neurites and strengthens the synaptic connections between the neurons to facilitate the functional connection of them in the neuronal network. It was found that the magnesium ions released by the GABA-induced mitochondria facilitate the maturation of neural networks by regulating numerous intracellular signals. These experimental outcomes show that intracellular magnesium ions are a new intracellular signal transducer. It has been well known for a long time that in intracellular signal transduction, signal molecules have high specificity, and it was generally accepted that a single downstream molecule was the target for the activation of a specific signal molecule. However, this study showed that the magnesium ion is a “multitarget” intracellular transducer that regulates numerous downstream signals. This shows that magnesium ions carry out transduction by regulating numerous downstream signals at the same time during the developmental stages before the acquisition of sophisticated signal transduction systems such as calcium signals. The outcomes of this research have led to a new perspective on the acquisition process of cell signaling systems while cell differentiation is taking place.



Overview of findings of this research

4. Future Developments

The role of the intracellular magnesium ion as a new signal transducer has become fundamental knowledge in biology and medicine, and there are expectations that this will be targeted for drug development for nervous system diseases.

＜Details of Original Paper ＞

Title: GABA-induced intracellular Mg2+ mobilization integrates and coordinates cellular information for maturation of neural network

Authors: Ryu Yamanaka, Yutaka Shindo, Kohji Hotta, Koji Suzuki, and Kotaro Oka

Journal: Current Biology

DOI: https://doi.org/10.1016/j.cub.2018.10.044

＜Glossary＞

※1 Magnesium ion: A divalent cation essential for living organisms. It bonds with numerous intracellular proteins and helps them function.

※2 Intracellular signal transduction: Senses environmental changes of extracellular neurotransmitters and hormones, growth factors, nutrients, etc., and transmits signals within the cells to induce cellular responses. Intracellular signal transduction is generally organized as a chain of biochemical reaction networks made up of a large number of molecules.

※3 GABA (gamma-aminobutyric acid): Induces the penetration of chlorine ions through the GABAA receptor, which is an ion channel type GABA receptor. It functions as an inhibitory

neurotransmitter in mature neurons and as an excitatory neurotransmitter in immature neurons.

※4 ERK (extracellular signal-regulated kinase): One of the intracellular signal transduction proteins. When a cell is stimulated by a growth factor, etc., it is phosphorylated by an upstream signal molecule. ERK itself also functions as a phosphoenzyme, and by phosphorylating various substrates, including transcription factors, it controls cellular functions such as cell proliferation and differentiation, cell survival, and cell death.

※5 CREB (cAMP response element-binding protein): A transcription factor that binds to the cAMP response element (CRE) on the promoter and controls the transcription. It is generally activated downstream of intracellular signals such as calcium and cAMP.

※6 mTOR (mechanistic target of rapamycin): An enzyme that regulates various functions of the cell such as growth, proliferation, survival, and differentiation. It is generally thought that its activity changes depending on the extracellular nutritional state and intracellular energy state.

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※Please direct any requests or inquires to the contact information provided below.

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