Protein kinase C delta activity triggered by plasticity of synapses regulates cell-wide changes in gene transcription

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When you learn, synaptic compartments on your neurons grow and strengthen, represented abstractly as buds opening into full bloom. New research has discovered that during this process, signaling enzymes named PKCd, drawn above as fluttering butterflies, are activated to support the strengthening and growth of synapses while also sending signals that spread, like the pollen from the flowers, from the synapses to the nucleus of the neuron to regulate cell wide

gene expression. Credit: Helena Pinheiro

When you interact with the world around you, your experiences are recorded as changes in the connection strengths between neurons in your brain. This process, called synaptic plasticity, alters how information flows through your brain and is critical for learning, memory, and even injury recovery.

New research guided by MPFI Scientific Director Dr. Ryohei Yasuda and published this week in the *Journal of Neuroscience* has identified a critical role for a signaling enzyme called protein kinase C delta (PKCd) in this process.

The team of scientists developed biosensors to track the activity of PKCd during plasticity, overcoming long-standing challenges in studying its function. Through this new approach, they found that PKCd created a "butterfly effect" transmitting local signals from a few of the thousands of synapses in a neuron to regulate cell-wide changes in gene expression.

Synaptic plasticity consists of hundreds of coordinated biochemical reactions that alter the structure and function of individual synapses, the tiny compartments where information is transferred between neurons. These biochemical reactions are the work of enzymes, specialized proteins in your cells that function together during plasticity to physically grow or shrink your synapses and make them stronger or weaker.

Interestingly, when just a few synapses of the thousands in a neuron undergo plasticity, these reactions extend beyond individual synaptic compartments and spread throughout the neuron to the nucleus, where neuron-wide changes in gene-expression occur.

The coordination of local plasticity at the synapses with changes in the nucleus enables lasting changes in information transfer in the brain during learning. However, the enzymes and reactions coordinating synapse-to-nucleus signaling were not fully understood. By developing new approaches to studying old questions, scientists at MPFI were able to identify that PKCd is essential for this critical process.

PKCd is part of the PKC family, a group of 12 closely related enzymes, that has been known to be necessary for synaptic plasticity. However, the role of individual enzymes in the PKC family in synaptic plasticity was not clear. This uncertainty was due primarily to scientists lacking tools that would allow them to distinguish the unique roles of these closely related family members.

To overcome this limitation, the scientists developed biosensors to visualize the activity of the specific members of the PKC family of enzymes. The team found that one of these enzymes, PKCd, was indispensable for synaptic plasticity. Blocking its function prevented the increase in the strength and size of synaptic connections.

Most notably, the study revealed that the activity of PKCd varied depending on the nature of the plasticity stimulus. PKCd was activated to a greater degree and for a longer time when several synapses were being strengthened. Moreover, its activity spread throughout the neuron, regulating biochemical reactions from the synapses throughout the neuron to the nucleus, where they activated gene transcription.

"This work provides new tools, which overcome long-standing limitations in studying the functions of individual PKC enzymes and provides greater understanding of synaptic plasticity, a critical process in brain function," describes Dr. Lesley Colgan, the study's lead researcher.

"Through this approach, we discovered an efficient mechanism for

information exchange between synapses and gene transcription within the nucleus, converting short-term plasticity into longer lasting forms of plasticity that likely underly memory formation."

Like the spreading of PKCd activity from a few synapses throughout the neuron, the scientists hope that the development of new biosensors for the PKC family of enzymes will have an impact beyond the field of synaptic plasticity.

As Dr. Colgan remarked, "The PKC family of enzymes is involved in many cellular functions and has been implicated in many diseases, including Alzheimer's disease, cancer, and heart disease. We hope the tools developed in this paper will be used by others in the scientific community to address many different questions and make an impact in these important scientific fields."

More information: Lesley A. Colgan et al, Dual Regulation of Spine-Specific and Synapse-to-Nucleus Signaling by PKCδ during Plasticity, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.0208-22.2023

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