PKCα integrates spatiotemporally distinct Ca2+ and autocrine BDNF signaling to facilitate synaptic plasticity

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Video Abstract

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Abstract

Our ability to form new memories is inextricably tied to synaptic plasticity – the structural and functional remodeling of brain tissue that allows us to adapt to an ever-changing environment. During plasticity, synapses must continually process and respond to ongoing fluctuations in biochemical information. Adding to the complexity of this arrangement is the fact that these signals occur under highly variable spatiotemporal scales. How do neurons perform such complex calculations? Researchers from the Max Planck Florida Institute for Neuroscience report that a specific isozyme of protein kinase C, known as PKCα, may be the key. The PKC family of enzymes has a long-established, critical role in synaptic plasticity. But which forms of PKC are activated and how activation occurs during this process has remained a mystery. To answer this question, the researchers developed highly specific biosensors to track the activity of classic PKC isozymes in brain tissue. This group of isozymes depend on calcium signaling to function, which is also of critical importance in neuronal communication. Two sensor designs were applied to each of the three classic PKC isozymes. The different designs enabled monitoring of two pivotal events in PKC activation: the translocation of the protein to the plasma membrane, and the subsequent docking of a substrate. Introducing the sensors into slices of mouse hippocampal brain tissue provided a controlled way to probe isozyme activity. This activity was investigated using a synaptic model of learning known as structural long-term potentiation, in which the patterned exposure of a single spine to the excitatory neurotransmitter glutamate can induce a long lasting increase in the strength and size of a synapse. Only PKCα exhibited strong activity under this condition, shown by its marked increases in membrane translocation and substrate docking compared to the other isozymes tested. Corroborating these results were the findings that mice lacking PKCα, but not PKCβ or PKCγ, were deficient in synaptic potentiation. The team next identified upstream activators of PKCα. By monitoring the isozyme while different signaling pathways were blocked during the induction of plasticity, they found that PKCα responds to two unique pathways. Remarkably, these pathways show order-of-magnitude differences in spatiotemporal signaling. The first transmits information on the submillisecond scale following the _local_ stimulation of a dendritic spine. The second develops over the course of minutes and can be initiated upon plasticity of _neighboring_ dendritic spines. These findings suggests that PKCα can integrate signals generated by recent, nearby synaptic activity with those produced by direct synaptic input to facilitate plasticity. Such integration appears to be an important factor in efficient learning, as mice lacking PKCα showed deficits in behavioral tests of learning. It may also be one mechanism through which synapse-specific plasticity and clustered plasticity are coordinated. These findings demonstrate that PKCα is a highly versatile molecule, capable of assimilating many disparate sources of information. Because of this adaptability, the protein is well poised as a mediator of the processes underlying synaptic plasticity and learning.