Synapse-specific and size-dependent mechanisms of spine structural plasticity accompanying synaptic weakening

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AUTHOR SUMMARY

As neural circuits are established during development and modified during learning, their optimization and fine-tuning involves the weakening and loss of superfluous synaptic connections. In the mammalian cerebral cortex, these functional changes in circuits are supported by structural changes in dendritic spines, the microscopic protrusions (volumes of ~0.001–1 μm^3) from neuronal dendrites that serve as the primary postsynaptic sites for excitatory synaptic connections (1). Here, we used focal photolysis of caged glutamate (2) at individual dendritic spines on hippocampal neurons to define the neural activity patterns and signaling mechanisms that drive the shrinkage and loss of spiny synapses during circuit remodeling. We found that low-frequency glutamatergic activity causes weakening and shrinkage of spiny synapses in an input-specific and size-dependent manner. These results further our understanding of the mechanisms that underlie circuit plasticity in the hippocampus, a region of the brain involved in learning and memory.

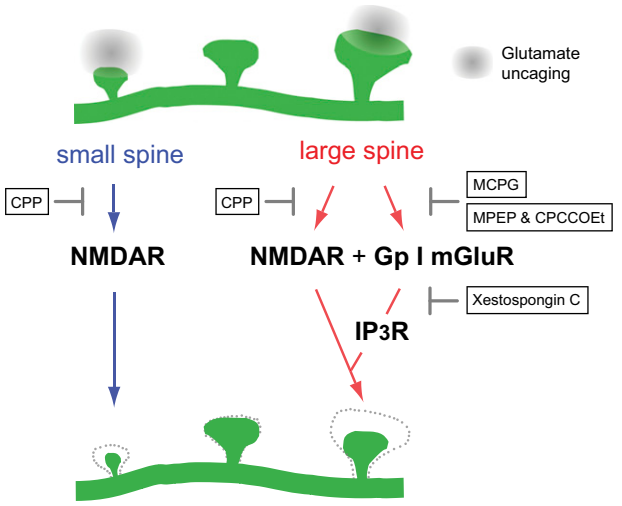

Fig. P1. Size-dependent mechanisms of synapse-specific spine shrinkage in response to glutamatergic activity at individual dendritic spines. Activity-dependent shrinkage of individual spines in response to low-frequency glutamate uncaging (LFU) is input specific and requires NMDA receptor activation. Shrinkage of large spines additionally requires signaling through group I mGlu and IP_3 receptors. Inhibitors: CPP, NMDAR inhibitor; MCPG, mGluR inhibitor; MPEP and CPCCOEt, Group I mGluR inhibitors; Xestospongin C, IP_3R inhibitor.

One of the most remarkable properties of the brain is its ability to undergo adaptive modifications in response to changing environments. This property, known as "experience-dependent plasticity," is essential not only for the fine-tuning of developing circuits but also for behavioral changes, such as learning and memory, in adults. Over the past decade, advances in fluorescent labeling and imaging techniques have enabled direct visualization of the structural reorganization of neuronal circuits during experience-dependent circuit plasticity. Dendritic spines have been a major focus of these studies; the gain or loss of spines is thought to represent the establishment or elimination of neural circuit connections, respectively (1). Indeed, newly gained spines are rapidly functional (3), suggesting that they can incorporate rapidly into functioning neural circuits. Furthermore, because spine size is directly proportional to synaptic strength (2), the enlargement or shrinkage of spines is considered to represent an increase or decrease in the strength of synaptic connections. Despite tremendous recent progress, key questions remain unanswered concerning the precise neural activity patterns and signaling mechanisms that selectively drive the destabilization and loss of individual dendritic spines that are no longer useful for brain circuits.

Several studies have established that low-frequency synaptic stimulation leads to spine shrinkage in populations of spines located proximal to the stimulating electrode (4, 5). However, in these studies, neuronal plasticity could not be resolved at the single-spine level and therefore the input- and synapse-specific mechanisms that drive the shrinkage and loss of individual dendritic spines during circuit plasticity could not be addressed. Here, we examined the role of neural activity in the selective shrinkage and loss of individual dendritic spines using two-photon microscopy, which allows high-resolution imaging of living neurons in deep tissue, combined with two-photon photolysis of an inactive caged glutamate, which releases active glutamate in a very small volume that enables reliable stimulation of visually identified single spines with defined patterns that mimic neural activity (2). We found that prolonged low-frequency uncaging of glutamate at individual spines on hippocampal CA1 pyramidal neurons leads to input- and synapse-specific synaptic weakening and spine shrinkage (Fig. P1). Importantly, we observed that shrunken spines were functionally intact and still able to undergo repotentiation at the end of the imaging session.

How does low-frequency glutamatergic activation lead to spine shrinkage? To answer this question, we performed pharmacological manipulations in combination with two-photon glutamate uncaging. Surprisingly, we found that the mechanisms initiating spine shrinkage were dependent on spine size. Whereas shrinkage at all spines requires activation of NMDA-type glutamate receptors (NMDARs), we found that shrinkage of large spines additionally requires signaling through metabotropic glutamate receptors (mGluRs) and inositol 1,4,5-trisphosphate

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The authors declare no conflict of interest.

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receptors (IP_3Rs) (Fig. P1). Supporting these results, we observed higher mGluR-mediated signaling activity in large spines, which could be caused by higher expression levels of mGluRs and/or by elevated activity-state or levels of key signaling molecules downstream of mGluRs. These results support an essential role for mGluRs in modulating the structure and function of large, mature spines during neuronal plasticity.

Our studies provide fundamental insights into the cellular and molecular mechanisms that support the activity-dependent and synapse-specific modification of spiny synapses, which are critical for adaptive plasticity. Moreover, many neurological disorders, including fragile X syndrome and Alzheimer's disease, have been associated with abnormal spine shrinkage and loss. By addressing long-unresolved questions regarding the mechanisms of synapse-specific structural plasticity, this study has deepened our understanding of how the brain fine-tunes neural circuits in response to various environmental stimuli and suggests avenues for future research that may shed light on neurological and cognitive disorders.

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