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Single-Molecule Discrimination within Dendritic Spines of Discrete Perisynaptic Sites of Actin Filament Assembly Driving Postsynaptic Reorganization

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In the brain, the strength of synaptic transmission between neurons is principally set by the organization of proteins within the receptive, postsynaptic cell. Synaptic strength at an individual site of contact can remain remarkably stable for months or years. However, it also can undergo diverse forms of plasticity which change the strength at that contact independent of changes to neighboring synapses. Such activity-triggered neural plasticity underlies memory storage and cognitive development, and is disrupted in pathological physiology such as addiction and schizophrenia. Much of the short-term regulation of synaptic plasticity occurs within the postsynaptic cell, in small subcompartments surrounding the synaptic contact. Biochemical subcompartmentalization necessary for synapse-specific plasticity is achieved in part by segregation of synapses to micron-sized protrusions from the cell called dendritic spines. Dendritic spines are heavily enriched in the actin cytoskeleton, and regulation of actin polymerization within dendritic spines controls both basal synaptic strength and many forms of synaptic plasticity. However, understanding the mechanism of this control has been difficult because the submicron dimensions of spines limit examination of actin dynamics in the spine interior by conventional confocal microscopy. To overcome this, we developed single-molecule tracking photoactivated localization microscopy (smtPALM) to measure the movement of individual actin molecules within living spines. This revealed inward actin flow from broad areas of the spine plasma membrane, as well as a dense central core of heterogeneous filament orientation. The velocity of single actin molecules along filaments was elevated in discrete regions within the spine, notably near the postsynaptic density but surprisingly not at the endocytic zone which is involved in some forms of plasticity. We conclude that actin polymerization is initiated at many well-separated foci within spines, an organization that may be necessary for the finely tuned adjustment of synaptic molecular content that underlies functional plasticity. Indeed, further single-molecule mapping studies confirm that actin polymerization drives reorganization of molecular organization at the synapse itself.