

Abstract

Modification of synapses in response to particular patterns of brain activity is a key mechanism underlying synaptic plasticity, which, in turn, is thought to underlie our ability to learn and form memories. Activity-dependent functional modifications of synapses are accompanied by structural changes. Both structural and functional synaptic changes contribute to synaptic plasticity and are at the centre of experience-dependent brain plasticity. However the mechanisms that coordinate structural and functional synaptic change are almost unknown. Here we show that PSD-95, a scaffolding multidomain protein present in the postsynaptic density of excitatory synapses, regulate separately spine structure and synaptic activity. Our findings show that a mutant of PSD-95 that lacks its GK domain clusters along the dendritic shaft and dramatically decreases the spine density without affecting the frequency of miniature excitatory postsynaptic currents (mEPSCs). In addition, the removal of the GK domain leads to a decrease in the frequency of the miniature inhibitory postsynaptic currents (mIPSCs). Finally the inhibition of the action potential mediated activity by TTX decreases the amplitudes of mIPSCs in neurons expressing PSD-95. These results demonstrate that the GK domain is required for spine morphogenesis but does not affect the functional properties of excitatory synapses. In addition, they suggest that excitatory synapses are relocalized along the dendritic shaft and that may reduce the number of inhibitory synapses. PSD-95 is thus an attractive synaptic molecule candidate that could integrate different independent signaling pathways and regulates spatially and temporally synaptic structural and functional plasticity.