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BDNF AND CONTROL OF SYNAPTIC PLASTICITY IN THE ADULT BRAIN

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Experience-dependent changes in synaptic connectivity are thought to play a vital role not only in memory formation, but also in long-term adaptive responses involved in mood regulation, reward behavior, and pain control. The neurotrophin, brain-derived neurotrophic factor (BDNF), which has recently been implicated in memory formation and aspects of major depression, is also an important regulator of long-term synaptic plasticity in the adult mammalian brain. We have investigated BDNF function in the dentate gyrus, a brain region implicated in depression and the action of antidepressant drugs. Local infusion of BDNF into the dentate gyrus generated a long-term potentiation (LTP) of synaptic efficacy at medial perforant path-granule cell synapses. This LTP is associated with expression of the immediate early gene, Arc, in postsynaptic granule cells and transport of Arc mRNA to synaptic regions on dendrites. Using local infusion of antisense oligodeoxynucleotides to block Arc synthesis, we show that Arc is required for the induction and time-dependent consolidation of BDNF-induced LTP. The sustained synthesis of Arc during a critical time-window is required for local expansion of the actin cytoskeletal network in dendritic spines. These results identify Arc as a critical mediator of BDNF in long-term synaptic plasticity in the adult brain. Microarray expression profiling has further revealed a panel of genes that, like Arc, are strongly upregulated following acute BDNF infusion or chronic treatment with the antidepressant fluoxetine.

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