Neurodegenerative and psychiatric disorders affect hundreds of millions of people worldwide. Increasing evidence suggests that subtle alterations in signaling pathways involved in developmental and synaptic plasticity are central to the pathogenesis of many different neurological diseases. One example involves the excitatory neurotransmitter glutamate which normally regulates neurite outgrowth, synaptogenesis and synaptic plasticity. However, activation of glutamate receptors under conditions of reduced energy availability and increased oxidative stress, can result in cellular calcium overload and neuronal death in disorders such as stroke, Alzheimer's and Parkinson's diseases, and schizophrenia. A second example involves brain-derived neurotrophic factor (BDNF) which plays pivotal roles in neurogenesis and synaptic plasticity. Impaired BDNF signaling may contribute to neuronal dysfunction and/or degeneration in psychiatric disorders and Huntington's disease. A final example comes from recent findings concerning the involvement of Notch signaling in stroke and Alzheimer's disease. Notch, which is activated by ligand binding and cleavage of an intracellular domain by the gamma-secretase enzyme, plays important roles in neurogenesis and hippocampal synaptic plasticity. However, we have found that Notch signaling endangers neurons directly by perturbing calcium homeostasis, and indirectly by enhancing the activation of pro-inflammatory microglia and lymphocytes. Because signaling pathways involved in neuronal plasticity are sensitive to a range of environmental factors, they are attractive targets for preventive and therapeutic interventions. Indeed, exercise, cognitive stimulation and dietary energy restriction can both enhance plasticity and protect neurons against neurodegenerative and psychiatric disorders. The mechanism by which the latter factors protect neurons may involve activation of cellular stress signaling pathways and upregulation of the expression of genes that encode proteins that promote neuronal survival and plasticity including neurotrophic factors, protein chaperones, and mitochondrial and plasma membrane redox proteins. Emerging findings in this and other laboratories are revealing novel approaches to ensure that neural cell signaling does not cross to the dark side of fine line between brain health and psychiatric and neurodegenerative disorders.

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