The Mechanisms of Antidepressant Action

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Given the centrality of cyclic nucleotide signaling in many aspects of neuronal signaling and brain function, it is not surprising that alterations in cAMP and cGMP signaling are implicated in a variety of neuropsychiatric disorders and in the actions of numerous medications that influence the central nervous system.

For example, increasing evidence suggests that upregulation of cAMP-mediated signaling is central to the mechanism of action of many antidepressant drugs (Pittenger et al, 2008). Most conventional antidepressants act by increasing levels of the monoaminergic neurotransmitters serotonin (5-HT), norepinephrine (NE) and dopamine (DA) at synapses in the brain, most commonly by blocking their reuptake into neurons. Among the downstream effects is an enhancement of cAMP signaling in the hippocampus through increased activation of G protein–coupled receptors and membrane-bound adenylyl cyclase activity. This leads to an increase in cAMP, PKA levels, and activation of downstream targets such as the transcription factor CREB (Pittenger et al., 2008). These changes are likely to be important for antidepressant efficacy: enhancement of CREB function in transgenic mice leads to an antidepressant response in animals, independent of any pharmacological treatment (reviewed in Pittenger et al., 2008).

Because of the association of this signal transduction cascade with antidepressant response, there has been significant interest in the potential antidepressant efficacy of pharmacologically inhibiting phosphodiesterases. These efforts have focused primarily on the type 4 phosphodiesterase, which is highly expressed in hippocampus and other limbic brain regions implicated in depression. Rolipram, an inhibitor of the PDE4, has been found to have some antidepressant efficacy in a controlled clinical trial (Fleischhacker et al., 1992).

Unfortunately, rolipram produced significant side effects—chiefly nausea—that have limited its potential as an antidepressant treatment. Ongoing pharmacological studies are seeking to identify more specific inhibitors of PDE4 isozymes in an effort to identify a pharmacological strategy that will produce a novel antidepressant that is better tolerated by patients.