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The role of synaptic and cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder

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Mood disorders are common, chronic, recurrent mental illness that affect the lives and functioning of millions of individuals worldwide. A growing number of recent studies indicate that for a majority of these individuals, outcome is quite poor. High rates of relapse, chronicity, lingering residual symptoms, subsyndromes, cognitive and functional impairment, psychosocial disability, and diminished well-being are unfortunately common. Furthermore, mood disorders are frequently associated with a wide range of physiological perturbations and medical problems, including cardiovascular disease, diabetes mellitus, obesity, and thyroid disease.

Neurobiological studies of mood disorders over the last 40 years have primarily focused on abnormalities of the monoaminergic neurotransmitter systems, on characterizing alterations of individual neurotransmitters in disease states, and on assessing response to mood stabilizers and antidepressant medications. The monoaminergic systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders. Unfortunately, these studies have not yet greatly advanced our understanding of the underlying biology of recurrent mood disorders, which must include an explanation for the predilection to episodic and often profound mood disturbance that can become progressive over time.

Research on the biological underpinnings of mood disorders has therefore moved away from focusing on absolute changes in neurochemicals such as monoamines and neuropeptides, and instead has begun highlighting the role of neural circuits and synapses, and the plastic processes controlling their function. Thus, these illnesses can best be conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters. The integration of knowledge derived from different physiological and phenomenological levels continues to help move us towards a more conceptual understanding of the etiology and pathophysiology of mood disorders. A growing body of data supports the contention that mood disorders arise from abnormalities in cellular plasticity cascades, leading to aberrant information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative function. Indeed, in a recent whole genome association study of bipolar disorder (BPD), all of the highly significant associations implicated signaling cascades.

Evidence suggests that alterations in critical signaling pathways play an important role in the pathophysiology and treatment of mood disorders. Supporting evidence comes from many areas, including the finding that the most efficacious medications used to treat these disorders have immediate, acute, and/or long-term effects on signaling pathways. Thus, signaling pathway components are direct targets for some psychotropic medications. For example, the most well established treatment for BPD, lithium, is believed to exert its initial biochemical effects by inhibiting the activity (through competition for magnesium) of a select group of enzymes including inositol monophosphatase (IMPase) and glycogen synthase kinase-3 (GSK-3). Another common mood stabilizer, valproic acid, likewise inhibits the activity of some enzymes and may act in a similar manner to lithium.

Furthermore, because the vast majority of psychotropic medications (with the exception of acutely acting sedatives and anxiolytics) only exert their primary therapeutic actions following at least week(s) of treatment, the long-term action of psychotropic medications is believed to involve a cascade of changes both initiated and maintained by critical intracellular signaling pathways. An important consideration is - how do changes in intracellular molecules bring about complex behavioral changes? These signaling cascades undoubtedly converge to regulate synaptic plasticity, and, thus, information processing in critical circuits mediating the affective, cognitive, motoric, and somatic manifestations of mood disorders.

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In this context, it is now clear (see presentation by Malenka) that modification of the levels of synaptic AMPA and NMDA receptors, in particular by receptor subunit trafficking, insertion, and internalization, is a critically important mechanism for regulating various forms of synaptic plasticity. Thus, through phosphorylation of specific sites on AMPA receptor subunit GluR1, GluR1 trafficking is regulated by protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC). Phosphorylation/dephosphorylation of the receptor subunits regulates both the intrinsic channel properties of the receptor and the interaction of the receptor with associated proteins that modulate the membrane trafficking and synaptic targeting of the receptor. NMDA receptor subunits are regulated by similar mechanisms.

A growing body of data shows that many of the effects of mood stabilizers/antidepressants on signaling cascades ultimately converge to regulate AMPA and NMDA synaptic transmission. The regulation of transmission at the synapse may be mediated by changes in neurotransmitter levels, receptor subunit phosphorylation, surface/cellular levels or receptors, and conductance changes, among others. Building upon these preclinical data, recent clinical trials have investigated the clinical effects of direct NMDA modulators in subjects with mood disorders. Indeed, NMDA antagonists have demonstrated remarkably rapid antidepressant effects in treatment-refractory depressed patients. These findings are leading to a reconceptualization of the necessity to accept a prolonged lag period in onset of action for the effective treatment of depression. This several week long delay in onset of action has been one of the major limitations of existing therapeutics, but emerging data is suggesting therapeutic strategies to markedly impact of the temporal course of antidepressant action.

The mood stabilizers lithium and valproate are both effective in the treatment of bipolar disorder; however, their therapeutic mechanisms remain unclear. Because of the delayed onset of clinical efficacy (days to weeks), it has been proposed that adaptive changes in gene expression, rather than their initial pharmacological actions, may be directly responsible. In order to investigate this possibility further, we have used mRNA differential display and cDNA microarrays to profile gene expression changes in response to treatment with lithium and valproate. Of particular interest is a subset of genes regulated in like fashion by both drugs. Alterations in the expression of five genes were selected for validation by real-time RT-PCR. Manual and automated investigation of categorical trends suggest the involvement of hitherto unexpected classes of gene targets, including those related to cell survival, mitochondrial function, cytoskeletal dynamics, and metabolism. Chronic administration of both agents at therapeutic doses increased the expression of BAG-1 (bcl-2 associated athanogene) in the hippocampus. Furthermore, these findings were validated at the protein level; bag-1 is an important chaperone of bcl-2, and enhances bcl-2's anti-apoptotic functions; furthermore, through interaction with raf, bag-1 is able to activate ERK MAP kinases. Consistent with this, we found that lithium and valproate activate ERK MAP kinases and exert anti-apoptotic effects. Bag-1 also inhibits GR activation, which may counteract the deleterious effects of hypercortisolemia seen in BD. Small inhibitory RNA (siRNA) studies have shown that BAG-1 siRNA attenuates the effects of mood stabilizers on GR-mediated nuclear translocation and gene expression. Complementary human studies have shown that chronic lithium significantly increases gray matter content in a regionally selective manner, suggesting a reversal of illness-related atrophy and an increase in the volume of the neuropil. Interestingly, the gray matter changes are seen in a regionally-specific manner, and are only observed in treatment-responders. The growing body of preclinical/clinical data suggests that for many refractory patients, optimal treatment may only be attained by providing both trophic and neurochemical support; the trophic support would be envisioned as enhancing and maintaining normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. There are a number of pharmacologic «plasticity enhancing» strategies being investigated which may be of considerable utility in the treatment of mood disorders; this research hold much promise for the development of novel therapeutics for the treatment of severe mood disorders.

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