Cellular Plasticity Cascades: Genes-To-Behavior Pathways in Animal Models of Bipolar Disorder

Haim Einat and Hussein K. Manji

Background: Despite extensive research, the molecular/cellular underpinnings of bipolar disorder (BD) remain to be fully elucidated. Recent data has demonstrated that mood stabilizers exert major effects on signaling that regulate cellular plasticity; however, a direct extrapolation to mechanisms of disease demands proof that manipulation of candidate genes, proteins, or pathways result in relevant behavioral changes.

Methods: We critique and evaluate the behavioral changes induced by manipulation of cellular plasticity cascades implicated in BD.

Results: Not surprisingly, the behavioral data suggest that several important signaling molecules might play important roles in mediating facets of the complex symptomatology of BD. Notably, the protein kinase C and extracellular signal-regulated kinase cascades might play important roles in the antimanic effects of mood stabilizers, whereas glycogen synthase kinase (GSK)-3 might mediate facets of lithium's antimanic/antidepressant actions. Glucocorticoid receptor (GR) modulation also seems to be capable to inducing affective-like changes observed in mood disorders. And Bcl-2, amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors, and inositol homeostasis represent important pharmacological targets for mood stabilizers, but additional behavioral research is needed to more fully delineate their behavioral effects.

Conclusions: Behavioral data support the notion that regulation of cellular plasticity is involved in affective-like behavioral changes observed in BD. These findings are leading to the development of novel therapeutics for this devastating illness.

Key Words: Mania, underlying mechanisms, cellular plasticity

Bipolar disorder (BD) is a common, severe, chronic, and life-threatening illness where patients alternate between episodes of depression and mania. Although previously believed to have a relatively good prognosis, new studies show that outcome is quite poor, with high rates of relapse, chronicity, residual symptoms, cognitive and functional impairment, and psychosocial disability (Judd and Akiskal 2003; Kupfer 2005; Tohen et al 2003). Furthermore, suicide and many other deleterious health-related effects are increasingly being recognized (Kupfer 2005).

The monoaminergic neurotransmitter systems have received the greatest attention in neurobiological studies of mood disorders (Drevets 2001; Manji et al 2001; Nestler et al 2002a). A growing appreciation that investigations have excessively focused on monoaminergic systems with lack of significant advances led to investigation of the roles of intracellular signaling cascades and synaptic plasticity. Recent evidence demonstrating that antidepressants and mood stabilizers exert major effects on pathways that regulate cellular plasticity generated considerable excitement (D'Sa and Duman 2002; Manji et al 2001; Nestler et al 2002a; Young 2002; Figure 1); however, a direct extrapolation from biochemical and molecular data to mechanisms of disease demands proof that direct manipulation of candidate genes, proteins, or pathways result in behavioral changes that resemble the disease or its treatment (Ikonomov and Manji 1999; Nestler et al 2002b). This type of evidence is strongest when human experimentation data are available, but well-designed animal model studies can be very useful for guiding research towards the ultimate clinical studies.

Animal Models for BD: An Endophenotypic Approach

Ideal animal models for BD are not available, but a variety of behaviors in animals might represent certain facets of the disease. Beyond the longstanding debate regarding the value of models that are not a comprehensive reflection of a disorder or its underlying pathophysiology (Kilts 2001; Machado-Vieira et al 2004), it is accepted that partial models are helpful (McKinney 2001). Furthermore, there is a growing appreciation that BD might represent a heterogeneous group of disorders that might be more amenable to study with an endophenotypic approach (Lenox et al 2002). Thus, the diagnosis of BD is on the basis of clusters of symptoms that do not necessarily describe homogeneous disorders but rather reflect final common pathways of different pathophysiological processes (Charney et al 2002; Hasler et al 2004). The term “endophenotype” was described as an internal, intermediate phenotype between genes and distal diseases (Gottesman and Shields 1973). This notion supports the exploration of specific behavioral changes in animals that model specific facets of the disorder (Cryan and Mombereau 2004; Einat, in press).

Accordingly, changes in behavior that are related to any facet of the depression-mania continuum might be relevant as models of these components of BD. Behavioral tests for many such components are available and used in different contexts. Animals are tested for activity, response to drugs, hedonistic properties, resilience and despair, anxiety and risk taking behaviors, judgment, sexual behavior, distractibility, sleep patterns, and more, all behaviors that might be relevant to BD. Not all these models might be valid for components of BD, and the process of validating models requires significant work (Einat et al 2003a; Willner 1991), however, experimentation done in different contexts might still help gain insight into possible mechanisms involved in BD (brief explanation of some common models is presented in Table 1).

This report discusses behavioral changes induced by manipulation of cellular plasticity cascades implicated in BD. Most of the presented behavioral work was done while studying other disorders or normal brain and behavior. Therefore, the original

From the College of Pharmacy (HE), Duluth, University of Minnesota; and the Mood and Anxiety Disorders Program (HKM), National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services.

Address reprint requests to Haim Einat, Ph.D., College of Pharmacy, Duluth, University of Minnesota, 376 Kirby Plaza, 1208 Kirby Drive, Duluth, MN 55812; E-mail: heinat@d.umn.edu.

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The Phosphoinositide Cycle/Protein Kinase C Signaling Cascade

The phosphoinositide cycle was first implicated in BD with the unreplicated finding of changes in inositol levels in affective disorder patients’ plasma (Barkai et al 1978). Later findings that lithium inhibits inositol monophosphatase and results in reduced inositol levels led to the inositol depletion hypothesis of lithium action (Berridge 1989) with further support from imaging studies indicating reduced inositol in brains of lithium-treated bipolar patients (Davanzo et al 2001; Moore et al 1999). Animal findings supported the hypothesis, whereas inositol supplementation attenuated lithium enhancement of pilocarpine-induced seizures (Patishi et al 1996a). This action seems to be inositol-dependent and can be reversed by inositol treatment (Kofman and Belmaker 1993; Kofman et al 1993) and augmented by inositol reuptake inhibitors (Einat et al 1998b; Wolfson et al 2000).

Interestingly, chronic inositol augmentation has effects in animal models of depression (Einat et al 1999, 2002) and anxiety (with and without prior stress) (Cohen et al 1997; Einat et al 1998b; Kofman et al 2000) as well as in preliminary clinical studies of depressed (Levine et al 1995) and anxious (Benjamin et al 1995; Fux et al 1996) patients. Altogether, the behavioral data indicate that the phosphoinositide signaling might be involved in affective disorders, albeit in a more complex manner than was initially hypothesized (Table 2).

Protein Kinase C

Protein kinase C (PKC) is highly enriched in brain and plays a major role in regulating both pre- and postsynaptic aspects of neurotransmission, including neuronal excitability, neurotransmitter release, and long-term alterations in gene expression and plasticity. Considerable biochemical data support the potential involvement of PKC in BD, including changes in PKC and its substrates in bipolar patients (Friedman et al 1993; Lenox et al 1992; Wang et al 1999; Young et al 1999) and changes in PKC signaling pathways after treatment with mood stabilizers (Chen et al 2000; Manji and Lenox 1994; Young et al 1999). Additionally, psychostimulants, which can trigger manic episodes in susceptible individuals (Fibiger 1995; Goodwin and Jamison 1990) and induce manic-like behaviors in rodents (Nestler et al 2002b; Post and Contel 1981), are known to activate PKC (Giambalvo 1992; Iwata et al 1997a, 1997b).

To date, however, the possible relationship between the PKC signaling cascade and mania has largely been investigated biochemically, without full elaboration at the behavioral level. In one of the few such published studies to date, Birnbaum et al (2004) have demonstrated that excessive activation of PKC dramatically impaired the cognitive functions of the prefrontal cortex, exposure to stress activated PKC, and resulted in prefron-