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Bipolar Disorder: A Neurobiological Synthesis

Husseini K. Manji,

Johnson and Johnson Pharmaceutical Research and Development, 1125 Trenton-Harbourton Road, E32000, Titusville, NJ, USA

Ioline D. Henter, and

Mood and Anxiety Disorders Program, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, 10 Center Drive, MSC-1026, Bldg. 10, Rm. B1D43, Bethesda, MD, USA

Carlos A. Zarate Jr.

Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Mark O. Hatfield Clinical Research Center, 10 Center Dr., Unit 7 SE, Rm 7-3465, Bethesda, MD 20892, USA

Husseini K. Manji: hmanji@its.jnj.com; Ioline D. Henter: ioline.henter@nih.gov; Carlos A. Zarate: zaratec@mail.nih.gov

Bipolar disorder (BPD) is a common, chronic, recurrent mental illness affecting 1–2% of the general population (Goodwin and Jamison 2007). Clinically, it is one of the most debilitating medical illnesses, and a growing number of recent studies indicate that outcome is quite poor for many individuals with BPD. Afflicted patients generally experience high rates of relapse, a chronic recurrent course, lingering residual symptoms, cognitive and functional impairment, psychosocial disability, and diminished well-being. Furthermore, the disorder is frequently unrecognized, misdiagnosed, and mismanaged, and much still remains unknown about its pathophysiology.

With this book, we sought to bring together clinicians and researchers to provide a unique and broad perspective on BPD and to compile the most recent research drawn from a variety of disciplines investigating this complex disorder. Toward that end, the diverse chapters in this volume touch upon a broad swath of interrelated disciplines, from clinical phenomenology to basic molecular and cellular neurobiology, genetics, neuroimaging, and circadian physiology. The chapters in this volume clearly show that there have been tremendous advances in our understanding of the functioning (both normal and abnormal) of the brain. Indeed, we firmly believe that the impact of molecular and cellular biology—which has been felt in every corner of clinical medicine—will ultimately, and perhaps shortly, also have major repercussions for our understanding of the fundamental, core pathophysiology of BPD.

As the chapters in this volume highlight, recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic transmission,

the molecular mechanisms of receptor and postreceptor signaling, and a finer understanding of the process by which genes code for specific functional proteins that in toto reduce the complexity of gene to behavior pathways (Gould and Manji 2004). In turn, a better understanding of the neurobiological underpinnings of this condition, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly, and are better tolerated than currently available treatments. Notably, advances in our understanding of the neurobiology of BPD continue to be made and do hold promise for future clinical applications.

As the information reviewed in these chapters has demonstrated, BPD is a multifactorial disorder, likely resulting from genetic vulnerability and environmental stressors interconnected and characterized by dysfunction in diverse biological systems. Indeed, the biological basis of its pathophysiology involves the dysfunction of an intricate network of interconnected limbic, striatal, and frontocortical neurotransmitter neuronal circuits that mediate mood state, cognition, self-awareness, insight, and functions, such as drive, and autonomic and circadian systems. Thus, BPD appears to arise from abnormalities within discrete brain networks (e.g., the anterior limbic network). Taken together, the information presented throughout these chapters makes it clear that abnormalities in multiple systems and at multiple levels characterize BPD. Here, we synthesize some of this available information.

1 Genetics

As Drs. McMahon and Wendland succinctly review in this volume, genetic factors clearly play a major role in the etiology of BPD. Indeed, the strong familiarity and heritability of BPD have long been some of the best clues to its etiology. The most consistent data suggesting a role for genetic factors in BPD come from twin studies, which show a higher concordance in monozygotic compared to dizygotic twins (reviewed in Goodwin and Jamison 2007).

Furthermore, it is clear that we are on the verge of truly identifying susceptibility (and likely protective) genes for BPD. It is also clear that there is no one-to-one relationship between genes and behaviors, so that different combinations of genes –and the resultant changes in neurobiology – contribute to complex behaviors (normal or abnormal) (Hasler et al. 2006). It is also critically important to remember that gene polymorphisms will likely simply be *associated* with BPD; that is, such genes are more likely to lend a higher probability for the subsequent development of BPD than invariably determine outcome. Obviously, genes will never code for abnormal behaviors per se, but rather code for proteins that make up cells, thereby forming circuits that in combination determine facets of both abnormal and normal behaviors. These expanding and interconnected levels of interaction have, in part, made the study of psychiatric diseases so difficult. The next task of psychiatric genetic research is to study how and why variations in these genes impart a greater probability of developing BPD and then to direct therapeutics at that pathophysiology (Gould and Manji 2004).

In recent years, epigenetics – the study of changes to the genome that, unlike mutations, do not alter DNA sequence – has emphasized the link between nature and nurture. Epigenetics

purports to define the molecular mechanisms by which different cells from different tissues of the same organism, despite having identical DNA sequences, exhibit different cellular phenotypes and perform different functions. Presumably, phenotypic and functional differences are the cumulative result of a large number of developmental, environmental, and stochastic events, some of which are mediated through epigenetic modifications of DNA and chromatin histones. Epigenetic regulation is thus one of the molecular substrates for “cellular memory” that may extend our understanding of how environmental impacts result in temporally dissociated altered behavioral responses.

Epigenetic factors appear to influence the development of BPD, acting via stable but reversible modifications of DNA and chromatin structure. Indeed, the chapter by Dr. Petronis and colleagues in this volume argues that molecular studies of BPD will benefit significantly from adding an epigenetic perspective. Epigenetic mechanisms are consistent with various non-Mendelian features of BPD, such as the relatively high degree of discordance in monozygotic twins, the critical age group for susceptibility to the disease, clinical differences in males and females, and fluctuation of disease course, notably cycling between manic and depressive phases (Petronis 2003, 2004). Furthermore, recent studies have shown that the epigenomic state of a gene can be established through behavioral programming, and is potentially reversible (Weaver et al. 2004). This line of research is particularly notable because early life stressors (which have been associated with suicide attempts in later life) in BPD (Leverich et al. 2003) might be amenable to treatment with agents to “undo” the epigenetic changes (e.g., histone deacetylase inhibitors (HDACs)) (Zarate et al. 2006). This work has great potential to enhance our understanding of the molecular basis of BPD.

The term “endophenotype” is also used with increasing frequency in relation to BPD, particularly because genes predisposing to BPD may be transmitted without expression of the clinical phenotype. Loosely defined as an internal, intermediate phenotype that fills the gap in the causal chain between genes and distal diseases (Gottesman and Shields 1973), the concept of endophenotypes in BPD may help to resolve key questions regarding the molecular genetic basis of this disorder. It is important to note that studies of endophenotypes in humans and in animal models of BPD are looking at specific aspects of behavior rather than trying to capture the broader spectrum of “mania” or “depression.” Interestingly, individuals with BPD have subtle neuropsychological abnormalities, even during periods of symptom remission. As Drs. Glahn and Burdick review in this volume, some of these neurocognitive deficits are present in unaffected family members of probands with BPD, suggesting that these measures may be quantitative endophenotypes for the disorder. Similarly, both individuals with BPD and their unaffected family members display specific personality traits (e.g., reduced inhibition, increased risk-taking). While much work remains to be done in further evaluating candidate endophenotypes with respect to specificity, heritability, temporal stability, and prevalence in unaffected family members, this research avenue has enormous potential for unraveling the etiology and pathophysiology of BPD.

2 The Neurobiological Evidence

Although genetic factors play a major, unquestionable role in the etiology of BPD, the biochemical abnormalities underlying the predisposition to, and the pathophysiology of, BPD remain to be fully elucidated. To date, the monoaminergic neurotransmitter systems have received the greatest attention in neurobiologic studies of these illnesses. Clinical studies over the past 40 years have attempted to uncover the biological factors mediating the pathophysiology of BPD using a variety of biochemical and neuroendocrine strategies. Indeed, assessments of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have, in fact, demonstrated a number of abnormalities of the serotonergic, noradrenergic, and other neurotransmitter and neuropeptide systems in mood disorders (summarized by Dr. Walderhaug and colleagues in this volume). While such investigations have been heuristic over the years, they have been of limited value in elucidating the unique biology of BPD, which must include an understanding of the underlying basis of the course of the illness characterized by episodic and often profound mood disturbance that can become progressive over time. Thus, BPD likely arises from the complex interaction of multiple susceptibility (and protective) genes and environmental factors, and the phenotypic expression of the disease must include a constellation of cognitive, motoric, autonomic, endocrine, and sleep/wake abnormalities.

Furthermore, while most antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or norepinephrine, their clinical antidepressant effects are only observed after chronic (days to weeks) administration, suggesting that a cascade of downstream effects is ultimately responsible for their therapeutic effects. These observations have led to the sense that while dysfunction within the monoaminergic neurotransmitter systems is likely key to mediating some facets of the pathophysiology of BPD, such dysfunction likely represents the downstream effects of other, more primary abnormalities (Manji and Lenox 2000).

We should also keep in mind that a true understanding of the pathophysiology of BPD must address its neurobiology at different physiological levels (i.e., molecular, cellular, systemic, and behavioral). Abnormalities in gene expression undoubtedly underlie the neurobiology of the disorder at the molecular level and, as noted previously, this will become evident as we identify the susceptibility and protective genes for BPD in the coming years. Once this has been accomplished, however, the even more difficult task of examining the impact of the faulty expression of these gene products (proteins) on integrated cell function must begin. The task becomes even more daunting when one considers the possibility that a major component of the pathophysiology of BPD may stem from discordant biological rhythms that ultimately drive the periodic recurrent nature of the disorder (see the chapter by Drs. Levenson and Frank in this volume for a thorough review of this topic).

Despite these formidable obstacles, there has been considerable progress in our understanding of the underlying molecular and cellular basis of BPD in recent years. In particular, recent evidence demonstrating that impaired signaling pathways may play a role in the pathophysiology of BPD, and that mood stabilizers exert major effects on signaling

pathways that regulate neuroplasticity and cell survival have generated considerable excitement among the clinical neuroscience community, and are reshaping views about the neurobiological underpinnings of this disorder (Duman 2002; Manji et al. 2001; Nestler et al. 2002).

Overall, it should be clear from the information reviewed in this book that there are abnormalities in multiple systems and at multiple levels in BPD. It is our strong contention that BPD arises from abnormalities in cellular plasticity cascades, leading to aberrant information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative function. Cellular signaling cascades form complex networks that allow the cell to receive, process, and respond to information (Bhalla and Iyengar 1999; Bourne and Nicoll 1993). These networks facilitate the integration of signals across multiple time scales, the generation of distinct outputs depending on input strength and duration, and regulate intricate feed-forward and feedback loops (Weng et al. 1999). These signaling cascades play a critical role as molecular switches subserving acute and long-term alterations in neuronal information processing.

As the chapters by Drs. Young and Gawryluk, and by Dr. Du and colleagues in this volume ably review, a considerable body of evidence supports abnormalities in the regulation of signaling as integral to the underlying neurobiology of BPD. As noted previously, the pathophysiology of this illness must account for not only profound changes in mood seen in BPD, but also a constellation of neurovegetative features derived from dysfunction in limbic-related regions, such as the hippocampus, hypothalamus, and brainstem. Notably, the highly integrated monoamine and prominent neuropeptide pathways are known to originate and project heavily within these regions of the brain, and it is thus not surprising that abnormalities have been noted in their function across clinical studies. In fact, the contribution of these pathways to the pathophysiology of BPD must be reasonably robust, given the variability that might be expected in assessing such dynamic systems under the constraints in experimental design imposed upon such research (Manji and Lenox 2000).

Signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in BPD. While dysfunction within these neurotransmitter and neuropeptide systems is likely to play an important role in mediating some facets of illness pathophysiology, they likely represent the downstream effects of other, more primary abnormalities in cellular signaling cascades. Indeed, even minor variations in ubiquitous regulators of signaling pathways can affect complex functions, yielding detrimental effects on behavior; this is clearly seen in many mouse models, where some genetic mutations in expressed proteins have little effect on non-CNS functions, but major effects on behavior (Manji et al. 2003). This observation also underscores the urgent need to develop more useful animal models for BPD (see the chapters by Dr. Einat and by Dr. Chen and colleagues in this volume for a comprehensive discussion of this topic). One issue of particular relevance to this area is the distinction between “animal models” and “model animals” (Chen et al. 2010). Loosely, the animal model approach begins by identifying behavioral stressors or chemical treatments that induce specific behavior(s) thought to cross-species phenocopy particular mood symptoms to study the biological basis of these induced behaviors. Conversely, the initial step of the model animal approach is to introduce specific

gene or pathway alterations implicated in BPD into animals, which are then evaluated using batteries of behavioral tests. Both animal models and model animals can be used to evaluate novel therapeutics, but the increased use of model animals is expected due to the unique ability of such animals to evaluate pathophysiology-driven target treatments.

Abnormalities in cellular signaling cascades that regulate diverse physiologic functions also likely explain the tremendous comorbidity with a variety of medical conditions (notably cardiovascular disease, diabetes mellitus, obesity, and migraine) and substance abuse seen in BPD. As a corollary, it is worth noting that genetic abnormalities in signaling components are often fully compatible with life, and in many instances – despite the often-ubiquitous expression of the signaling protein – one sees relatively circumscribed clinical manifestations. These overt, yet relatively circumscribed, clinical manifestations are believed to ultimately arise from vastly different transcriptomes (all of the transcripts present at a particular time) in different tissues because of tissue-specific expression, haploinsufficiency, genetic imprinting, alternate splicing, varying stoichiometries of the relevant signaling partners in different tissues, and differences in the ability of diverse cell types to compensate for the abnormality (Manji et al. 2003).

Furthermore, signaling pathways are clearly major targets for hormones that have been implicated in the pathophysiology of BPD, including gonadal steroids, thyroid hormones, and glucocorticoids. In addition, alterations in signaling pathways likely represent the neurobiological substrates subserving the evolution of the illness over time (e.g., cycle acceleration). Signaling networks play critical roles in cellular memory; thus, cells with different histories, and that therefore express different repertoires of signaling molecules interacting at different levels, may respond quite differently to the same signal over time.

As noted previously, alterations in signaling pathways affect circadian rhythms known to be abnormal in BPD. It is important to note that although this tendency to recur is one of the most distinguishing features of BPD in both its bipolar and its unipolar forms, it is poorly described and not well understood. As Drs. Levenson and Frank review in their excellent chapter in this volume, studies have begun to uncover the molecular underpinning of circadian cycles. The core clock mechanism appears to involve a transcriptional/translational feedback loop in which gene products are involved in negative feedback of themselves and other genes in the pathway. It is also important to note that cellular signal transduction cascades are clearly the targets for our most effective treatments for BPD. Indeed, it is likely that the identification of signaling cascades as targets for the actions of lithium and other mood stabilizers, such as valproate, has already had a profound impact upon our understanding of the cellular neurobiology of BPD (Bezchlibnyk and Young 2002; Manji and Lenox 2000). While most of our drug development efforts in the past have been aimed at treating the affective states of mania or depression, the unique clinical action of lithium is its ability to prophylactically stabilize the underlying disease process by effectively reducing the frequency and severity of profound mood cycling. Reasonable evidence exists to suggest that once the disease process has been triggered and clinically manifest, long-term adaptive changes in the central nervous signaling systems set the stage for predisposing an individual to more frequent and severe affective episodes over time. A correction of dysregulated trans-synaptic signaling by mood stabilizers represents a physiological process able to curtail the

oscillations in behavioral states associated with BPD. Indeed, regulation of signal transduction within the critical regions of the brain by mood stabilizers affects the intracellular signal generated by multiple neurotransmitter systems; these effects undoubtedly represent targets for their therapeutic efficacy, since the behavioral and physiological manifestations of the illness are complex and are likely mediated by a network of interconnected neurotransmitter pathways.

Finally, abnormalities in cellular plasticity cascades likely also represent the underpinnings of the impaired structural plasticity seen in morphometric studies of BPD. Many of these pathways play critical roles not only in “here and now” synaptic plasticity, but also in long-term cell growth/atrophy and cell survival/cell death. For instance, the atrophic changes observed in multiple cell types (neurons and glia), as well as the reversibility of the changes with treatment, support a role for intracellular plasticity cascades. It is likely that the major defect is in the ability to regulate neuroplastic adaptations to perturbations (both physiological and pathophysiological) – an inability to handle “normal loads” (neurochemical, hormonal, stress-induced, pharmacologically induced, etc.) without failing or invoking compensatory adaptations that overshoot and predispose to oscillations. This allostatic load contributes to long-term disease progression (and potentially to cycle acceleration). Many of the very same “plasticity regulators” also play a critical role in cell survival, cell death, and cellular resilience. These observations serve to explain the atrophic, and perhaps degenerative, aspect of the illness in some patients, as well as the presence of signs normally associated with ischemic/hypoxic insults, such as white matter hyperintensities. This information is reviewed more fully in the chapters by Drs. Savitz and Drevets, and by Drs. Blond and Blumberg in this volume, which explore the most recent neuroimaging findings in BPD.

3 Conclusions

The last decade has been marked by tremendous advances in our understanding of the circuits, and especially of the molecular and cellular underpinnings of BPD. As discussed above, evidence consistently suggests that BPD involves structural impairments potentially related to dysfunctions in cellular plasticity and resilience, which may be prevented or even reversed with the use of mood stabilizers. Further insights into the pathophysiology of BPD have resulted from the use of technologies such as PET and fMRI, gene interaction analyses, and comprehensive gene expression analysis using DNA microarray. Future genetic linkage and association studies may be relevant, but it is important to emphasize that BPD is clearly a complex and multifactorial disorder and that the identification of the genes involved in the illness may remain elusive for some time. The related study of epigenetics and endophenotypes may soon yield profound insights into this condition.

Through functional brain imaging studies (see the chapters by Drs. Savitz and Drevets, and by Drs. Blond and Blumberg in this volume), affective circuits have been identified that mediate the behavioral, cognitive, and somatic manifestations of BPD. Key areas include the amygdala and related limbic structures, orbital and medial prefrontal cortex, anterior cingulate, medial thalamus, and related regions of the basal ganglia. Imbalance within these circuits, rather than an increase or decrease in any single region of the circuit, seems to

predispose to and mediate the expression of BPD. Moreover, studies of cellular plasticity cascades in BPD are leading to a large-scale reconceptualization of the pathophysiology, course, and optimal long-term treatment of the illness. These data suggest that while BPD is clearly not a classic neurodegenerative disease, it is in fact associated with impaired cellular plasticity and resilience. As a consequence, there is a growing appreciation that optimal long-term treatment will likely be achieved by attempting to prevent underlying disease progression and its attendant cellular dysfunction, rather than exclusively focusing on treating signs and symptoms. The study of lithium (and other mood stabilizers)-responsive gene networks related to neuroprotection is promising and may provide a better understanding of critical nuclear downstream targets expressing key proteins and peptides. In addition, the search for neurobiological predictors of response, state, and trait markers is critically relevant and may provide new insights into potential biomarkers associated not only with the biological effects of lithium and other mood stabilizers but also with those relevant to clinical and translational paradigms.

As the last few chapters of this book have highlighted, little progress has been made in developing truly novel drugs specifically for the treatment of BPD; most recent additions to the pharmacopeia are brain-penetrant drugs developed to treat other disorders such as epilepsy or schizophrenia (although see the chapter by Dr. Bowden in this volume for an excellent review of pharmacological strategies for treating BPD with currently available therapeutics). More recently, the glutamate system has received much attention in the hope of developing improved therapeutics for BPD (see the chapter by Dr. Machado-Vieira and colleagues in this volume for a review). In addition, a number of novel pharmacologic “plasticity-enhancing” strategies that may be useful in treating BPD are being developed. Indeed, these next-generation drugs, in addition to treating the core symptoms of BPD, might be able to target other important aspects of the illness. For example, they may be able to enhance cognition independent of whether mood symptoms improve, to prevent or reverse epigenetic factors that may negatively affect the long-term course of the illness, or to reduce certain medical comorbidities such as diabetes.

We are optimistic that the advances outlined throughout these chapters will result in an expanded understanding of this devastating disorder, and concomitantly, the discovery of new approaches to treat and ultimately prevent BPD.

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