

The Neurobiology of Bipolar Disorder

GREGORY S. BERNIS* AND CHARLES B. NEMEROFF

The neurobiology of bipolar disorder is reviewed. Bipolar disorder is associated with alterations in central nervous system (CNS) function from the level of large-scale brain circuits to intracellular signal transduction mechanisms. Because of the broad spectrum over which these abnormalities appear, the causative effects are most likely present in the lowest common denominator of all of these systems. Current evidence points to subtle alterations in signal transduction that reverberate downstream both intra- and extracellularly to produce the symptoms of bipolar disorder. © 2003 Wiley-Liss, Inc.

KEY WORDS: bipolar disorder; schizophrenia; magnetic resonance imaging

INTRODUCTION

Bipolar disorder has been known to mankind since at least the time of the ancient Greeks, but it was not until the 20th century that it was truly recognized as an illness distinct from other psychiatric disorders. The German psychiatrist Emil Kraepelin was likely the first to draw attention to the distinction between manic depression and schizophrenia. While the acute presentations of both illnesses can appear identical with delusions and hallucinations, manic depression is characterized by an abrupt onset and a fluctuating course in which the individual returns to a relatively normal state between episodes, particularly early in the course of the disorder.

In contrast, untreated schizophrenia is generally characterized by a long progressive decline without any significant return to the premorbid state.

Estimates of bipolar I disorder, or classic manic-depressive illness, have ranged from 0.8–1.6% of the population [Kessler et al., 1994]. These patients experience both full-blown manic episodes and syndromal major depressions. Various subtypes have been described that include rapid cycling bipolar disorder and mixed states, the latter characterized by patients who exhibit concurrent symptoms of both mania and depression. Bipolar II disorder is characterized by syndromal major depressions and manic episodes that do not fulfill criteria for mania but are of

lesser severity and termed hypomania. Bipolar II disorder has a lifetime prevalence rate of 0.5% [Angst, 1998]. Thus, bipolar I and II disorders have a combined prevalence rate of about 2%, which is equal to or greater than that of schizophrenia. It is important to note that one-third of patients with bipolar disorder have their first episode during their adolescent years, and 50% exhibit comorbid drug or alcohol abuse.

In trying to understand the biology of bipolar disorder, we struggle to link the obviously complex manifestations of the illness and its cyclic nature with its biological substrate. How can one ferret out the roots of a mental illness when we are only beginning to understand the complex machinery of the brain? Even so, extraordinary discoveries, using techniques of molecular biology, genetics, and neuroimaging, consistently point to the fact that individuals with bipolar disorder have fundamental alterations in brain function. We present here some of the recent advances in neurobiology that firmly root the pathophysiology of bipolar disorder in the brain.

ALTERATIONS IN BRAIN STRUCTURE

The idea that bipolar disorder may be related to an alteration in brain structure was derived from the astute clinical observation that certain brain lesions produced by brain tumors, stroke, or head injury resulted in manic-like behavior

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Grant sponsor: NIH; Grant numbers: MH-61010, DA-00367, MH-42088, MH-39415, MH-58922.

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DOI 10.1002/ajmg.c.20016

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[Cummings and Mendez, 1984; Cummings, 1993]. In general, any brain lesion is far more likely to cause depression than mania, but lesions that induce mania occur more commonly in the frontal and temporal lobes and subcortically in the head of the caudate and the thalamus [Cummings and Mendez, 1984; Starkstein et al., 1991], so-called secondary manias. It has been repeatedly suggested that lesions of the left frontal lobe result in depression, whereas right fronto-temporal lesions produce mania. However, these generalizations about laterality are far too simplistic, and many exceptions to this rule have been observed.

Before the advent of noninvasive brain imaging techniques, the only methods available to examine patients' brains were autopsy, brain biopsy, and pneumoencephalography. There have been few postmortem anatomic studies of patients with confirmed bipolar disorder; however, neuroimaging using both computed tomography (CT) and magnetic resonance imaging (MRI) has revealed multiple structural alterations. CT scans were the first noninvasive modality to systematically scrutinize brain structure, but the relatively poor demarcation between different brain regions allowed for only the grossest of observations. Several investigators have suggested that patients with bipolar disorder have larger ventricles than normal controls, a finding much more clearly established in patients with schizophrenia [Schlegel and Krtezschar, 1987; Dewan et al., 1988; Swayze et al., 1990; Strakowski et al., 1993]. Ventricular

enlargement is typically characteristic of cell loss, such as the neurodegenerations observed in Alzheimers disease or perhaps alterations in neural circuit development, but issues of controlling for other potentially important confounding factors, such as alcohol and drug abuse and head injury, preclude an easy interpretation of the results. Given these limitations, volumetric imaging studies have provided intriguing findings in bipolar disorder. As recently reviewed by Strakowski et al. [2002a], both bipolar and unipolar depression are reportedly associated with smaller prefrontal lobe volumes, but in contrast both the basal ganglia and thalamus are larger in bipolar patients [Aylward et al., 1994; Strakowski et al., 2002a]. Moreover, both hippocampal and amygdala enlargement in bipolar disorder has also been occasionally reported [Swayze et al., 1992; Strakowski et al., 2002a], but not consistently.

Volumetric measurements of various brain regions are of interest, especially to identify structures that deserve further scrutiny, but the interpretation of volumetric assessments remains problematic. Specific changes in regional volume may occur in response to a variety of factors and may not be permanent. MRI has the capability of looking beyond simple structure by yielding information about both neurochemical alterations and the neural activity of specific regions. When brain MR images were obtained in bipolar patients, it was quickly noted that such patients had an inordinate number of hyperintense regions. These unidentified bright objects (UBOs) are typically associated with vascular diseases, including systemic hypertension, Binswangers disease, and carotid arteriosclerosis. Why are they present in patients with a mental disorder? Further studies revealed that they tend to localize in deep white matter structures. The percentage of bipolar patients exhibiting these findings has ranged from 5–50%, compared with about 3% for controls [Aylward et al., 1994; Altshuler et al., 1995; Dupont et al., 1995; Norris et al., 1997; McDonald et al., 1999]. Elderly bipolar patients have larger and a higher number

of white matter hyperintensities. Their location suggests a potential role in disrupting communicating fibers between fronto-temporal regions, which lends support to earlier observations that lesions in these regions cause mania. Follow-up postmortem studies of patients with UBOs have demonstrated a number of histologic changes in these regions, including small vascular malformations, dilated perivascular spaces, brain cysts, infarcts, and necrosis. These are surprisingly nonspecific lesions that can occur from multiple causes. It is possible that these lesions represent damage from a comorbid disease process unrelated to bipolar disorder; however, recent studies in children and adolescents with mania continue to reveal an abundance of these UBOs [Lyoo et al., 2002; Pillai et al., 2002]. More recently, the MRI changes in bipolar disorder have been noted to bear a striking similarity to an autosomal dominant disorder called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and there is some evidence for a higher incidence of bipolar disorder in CADASIL patients [Ahearn et al., 1998, 2002].

ALTERATIONS IN BRAIN FUNCTION

Both CT and MRI yield static information about brain structure—a kind of snapshot—but the brain is a dynamic organ, and to understand function we must choose different techniques. Functional neuroimaging can measure subtle changes in receptor density, blood flow, and glucose metabolism. Although we cannot yet image neuronal activity directly, recent technological advances in MRI have led to the development of functional MRI (fMRI), which can detect changes in blood flow on the scale of seconds with millimeter resolution, and such changes are clearly coupled to neuronal activity [Ogawa et al., 1990; Kwong et al., 1992].

Most functional neuroimaging studies take advantage of a critical observation about neuronal activity and brain blood flow. When synaptic activity

increases in a particular brain region, the blood flow to that region transiently increases [Logothetis et al., 2001]. The blood flow apparently increases beyond the metabolic requirements of the tissue, so a surfeit of oxygenated blood temporarily bathes the region. Both positron emission tomography (PET) and fMRI can be used to measure this blood flow increase, thereby indirectly measuring neuronal activity. PET can also be used to measure directly local glucose metabolism. By using a glucose analog, 2-deoxy-glucose (2-DG), this compound can be labeled with a positron emitter, fluorine-18. Like glucose, 2-DG is transported into cells and metabolized. Unlike glucose, 2-DG is metabolized through only one step of glycolysis and subsequently becomes trapped in the cell. Thus it serves as a marker of both glucose uptake and metabolism. Because the process of uptake and metabolism takes some time, fluoro-deoxyglucose (FDG) studies are more appropriate for the measurement of stable state changes in the brain.

The earliest functional imaging studies focused on large-scale changes in both cerebral blood flow and metabolism [Strakowski et al., 2002b]. These studies showed that bipolar-depressed patients had significantly lower cortical metabolism than either controls or patients with unipolar depression [Baxter

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et al., 1985; Buchsbaum et al., 1986]. Furthermore, these changes were state dependent, meaning that when the

patients recovered from their depression, these abnormalities disappeared. These findings have not been completely replicated. Some studies have reported relatively normal cortical metabolism, but more localized abnormalities in subcortical regions such as the caudate or subgenual prefrontal cortex [Drevets et al., 1995].

Frontal regions, especially the dorsolateral prefrontal cortex (DLPFC), have been identified as having both decreased metabolism and blood flow in depression. Decreases in left DLPFC metabolism have been correlated with severity of depression, but this is not likely to be specific to bipolar disorder [Strakowski et al., 2002b]. Frontal hypometabolism has been reported repeatedly in schizophrenia. Presumably, any alteration in these regions is associated with profound effects on cognition and emotion. These brain regions are well known to be integral to many functions that are altered in psychiatric disorders such as attention and working memory. Other frontal regions, especially those on the innermost folds of the brain, are poorly understood but seem to be involved in conflict monitoring [Carter et al., 1998], reward valuation [Montague and Berns, 2002], and response inhibition. This suggests that both state- and trait-dependent interactions with performance on cognitive tasks may serve as a finer probe of dysfunction with brain imaging [Berns et al., 2002].

Functional neuroimaging in bipolar disorder dispelled a common myth about the organization of the brain, namely, that specific cognitive processes can be completely localized to isolated brain regions. Virtually every imaging study has identified networks of activity. In this context, it becomes clear why the search for regional abnormalities has not yielded consistent results. If a cognitive process requires the coordinated function of several brain regions, then a small alteration in one region may cause dramatic effects on the whole circuit.

Both mania and depression are characterized by profound global changes in brain function. These state changes are manifest at multiple levels in the nervous

system. Is there some aspect of neuronal function that renders patients with manic-depressive illness more prone to these shifts? The new science of chaos theory characterizes these states as attractors. Consider the simplistic case of three mood states: euthymia (normal mood), depression, and mania. For most individuals, euthymia is the usual state. Unpleasant events cause transient dysphoria, but most people quickly return to their usual mood state. Similarly, winning a lottery makes most people very happy, but does not shift them to a permanent state of elation. Euthymia is therefore a stable state for most people—perturbations are small and the return to euthymia is invariant. Patients with bipolar disorder often switch into extreme mania or depression without returning to a euthymic state for a considerable period of time.

ALTERATIONS IN BRAIN CHEMISTRY

MR spectroscopy (MRS) has been used extensively to measure changes in relative concentrations of several important neuroregulators in the brains of bipolar patients. The most common method, proton-MRS, is used both routinely and now clinically. Proton-MRS measures the relative concentrations of N-acetyl aspartate (NAA), creatine (Cr), phosphocreatine (PCr), and various choline (Cho)-containing compounds. Because lithium increases Cho concentrations in human red blood cells [Jope et al., 1978], it was reasonable to look for similar changes in Cho concentration in the brain. The MRS data on Cho concentrations are not entirely consistent, but there does seem to be a consensus that there is at least an elevated Cho/Cr ratio in the basal ganglia of bipolar patients [Stoll et al., 2000; Strakowski et al., 2002b]. It is likely that this finding is state dependent because similar elevations have been observed in depression.

Because the Cho peak in proton-MRS represents several compounds, phosphorous-MRS has been used to further delineate the nature of these alterations. Phosphorous-MRS can distinguish ATP, PCr, and phosphomonoesters (PMEs)

like phosphocholine, phosphoinositol, and phosphoethanolamine; it can also measure indirectly intracellular pH and free magnesium. However, because of the relatively low concentrations of these compounds, phosphorous-MRS is technically demanding and suffers from limited sensitivity. Like the proton-MRS data, there are discordant findings. Most studies have found changes in PME's in the frontal lobes of symptomatic patients, but whether it is increased or decreased, or whether there are left/right asymmetries, is not agreed upon [Stoll et al., 2000; Strakowski et al., 2002b]. At a minimum, these studies suggest that alterations in phospholipid metabolism occur in bipolar disorder [Yildiz et al., 2001].

NEUROCHEMICAL CHANGES

Changes are evident at virtually all levels of the central nervous system (CNS) in bipolar patients. If the illness is manifest by changes in brain attractor states, as opposed to lesions of a specific region, then we have merely shifted the search for the cause to more fundamental levels. Numerous biochemical abnormalities have been detected by measuring one or another neurotransmitter metabolites or hormones in plasma, cerebrospinal fluid (CSF), and postmortem tissue studies. Although depression has often been conceptualized as due to a relative deficiency in the activity of certain monoamine-containing systems, e.g., serotonin, dopamine, and norepinephrine (NE), these have not yet been clearly implicated in the pathophysiology of bipolar disorder. Many antidepressants, which increase the activity of one or more of these neurotransmitter circuits, can precipitate the development of mania.

Concentrations of NE, or its major metabolite, are consistently altered in the CSF of patients with bipolar disorder. NE was originally proposed by Schildkraut [1965] as the major culprit in both depression and mania. The catecholamine hypothesis stated that depression resulted from low levels of NE and mania resulted from high levels [Schildkraut, 1965]. This has been remarkably diffi-

cult to precisely document. NE, like many neurotransmitters, appears extracellularly in small amounts. Furthermore, it is metabolized to several other compounds that appear in CSF, plasma, and urine. Thus, alterations in NE circuits may appear as a change in either the neurotransmitter or any of its metabolites. Most evidence points to a deficiency in depression and an excess in mania, but this may simply reflect the global neural activity of these states, as well as contributions from the sympathetic nervous system, which utilizes NE as the neurotransmitter of postganglionic neurons. Interestingly, NE elevations purportedly precede the

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switch into mania. Although NE may not itself be the causative mediating factor, it is further evidence for the idea of unstable cortical states. In one comprehensive postmortem study, there were no differences in the concentration of NE, serotonin, or dopamine in any brain region of bipolar patients [Young et al., 1994], but NE turnover, as measured by the ratio of

its metabolite, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), to NE, ranged from 64–107% greater in several cortical regions. Significant decreases in both serotonin and dopamine metabolism were found in the same brain regions.

In addition to the monoamine neurotransmitters, others have also been implicated in the pathophysiology of bipolar disorder. Because of its preponderance in the brain, glutamate has received growing attention. Glutamate exerts its effects through four major receptor families. Three are ionotropic: N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and kainate. The ionotropic receptors are coupled to different ion channels, and when glutamate binds to them, the ionic conductances are altered. The fourth family is metabotropic, and these receptors are coupled to intracellular G-proteins. A recent postmortem of the striatum found increased expression of mRNA transcripts for both the NR2D subtype of the NMDA receptor and the AMPA receptor in bipolar patients [Meador-Woodruff et al., 2001].

NEUROENDOCRINE CHANGES

For many years it has been recognized that certain endocrine disorders are associated with a greater than expected occurrence in bipolar disorder. The hypothalamic-pituitary-adrenal (HPA) axis has received the most attention in mood disorders. Corticotropin-releasing factor (CRF) is released from neurons in the paraventricular nucleus of the hypothalamus, and CRF is transported to the anterior pituitary, causing ACTH to be released systemically. ACTH acts upon the adrenal cortex, where it releases cortisol [Wang and Nemeroff, 2003]. Mixed mania has been associated with both an elevated CSF and urinary free cortisol concentration [Swann et al., 1992], but this has also been observed in unipolar major depression. The assessment of HPA function has typically been done with either of two tests: the dexamethasone suppression test (DST)

and the CRF-stimulation test. The practical limitations of the DST have been covered elsewhere [Shapiro et al., 1983], but the CRF-stimulation test retains utility. In the latter, CRF is administered intravenously (usually 1 $\mu\text{g}/\text{kg}$ or 100- μg dose), and blood samples are obtained for ACTH and cortisol at 30-min intervals for 2–3 hr. When compared to normal control subjects, the ACTH response to exogenous CRF is blunted in depression but not in mania. When dexamethasone was combined with CRF-stimulation, depressed bipolar patients were reported to have a significantly greater elevation of cortisol than either normal controls or unipolar depressed patients [Schmider et al., 1995; Rybakowski and Twardowska, 1999]. The mechanisms for these alterations in the HPA axis of patients with affective disorders are unknown, but glucocorticoid resistance, which is analogous to the insulin resistance of diabetes mellitus, has been one mechanism proposed [Pariante and Miller, 2001; Watson and Young, 2002].

SIGNAL TRANSDUCTION

The heterogeneity of both imaging findings and neurotransmitter alterations has not yielded a single underlying hypothesis for the pathophysiology of bipolar disorder. There does, however, appear to be consistent evidence pointing to signal transduction as one major locus of pathophysiology. For historical reasons alluded to above, the signal transduction pathway for catecholamine receptors has been the most extensively characterized in mood disorder. What follows is largely related to the NE system [Duman and Nestler, 1995].

The neurotransmitter itself, in this case NE, is referred to as the first messenger, and it binds to one or more adrenergic receptor subtypes (see above). Depending on the receptor subtype, a number of different intracellular events may occur. G-proteins on the intracellular side of the receptor can bind to ion channels, thereby influencing the membrane potential of the cell. The G-proteins are generally composed of three subunits, labeled α , β , and γ , and it is the

α -subunit that typically binds to the ion channel. In addition to regulation of ion channels, G-proteins interact with several intracellular second messengers, including cyclic AMP (cAMP), cyclic

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GMP (cGMP), calcium, metabolites of the phosphatidyl-inositol (PI) pathway, arachidonic acid, and nitric oxide. Upon neurotransmitter binding, the $\beta\gamma$ -subunit separates from the receptor and modulates the activity of adenylate cyclase, in effect changing intracellular levels of cAMP. cAMP then phosphorylates a number of cAMP-dependent protein kinases, activating their respective functions. Protein kinase A (PKA) is the most prominent of these kinases and is referred to as a third messenger.

Particular attention has been focused on the cAMP/PKA transduction pathway for several reasons. First, lithium exerts complex effects on adenylate cyclase [Risby et al., 1991], and this is believed to be manifest as downstream changes on the cAMP/PKA pathway [Manji and Lenox, 2000]. Consistent with this notion, an increased concentration of G α -subunits was reported in the CNS in a postmortem study of bipolar patients [Young et al., 1991, 1993]. Looking farther downstream, Rap1, a PKA substrate, has been reported to exhibit increased levels of phosphorylation in the platelets of bipolar patients [Perez et al., 2000]. Rap1 may be involved in several intracellular

events, including calcium mobilization, cytoskeletal organization, and phosphoinositol metabolism. Rap1 has also been found to be involved in the regulation of signal cascades coupled to neurotrophic factors [Bos et al., 2001]. This is very intriguing because recent data also suggest a role for both antidepressants and mood stabilizers as neuroprotective agents [Duman et al., 2001; Manji and Duman, 2001]. Interestingly, another downstream substrate, cAMP response element-binding protein (CREB) has not been found to be increased in bipolar patients and may be decreased in the temporal lobes [Stewart et al., 2001].

Protein kinase C (PKC) is yet another second messenger-dependent kinase, dependent on calcium, not cAMP. At rest, PKC isozymes exist as both cytosolic and membrane-bound forms, but mostly cytosolic. Activation of receptors coupled to phospholipase C facilitates the translocation of cytosolic PKC to the membrane [Manji et al., 1995]. Like PKA, PKC is elevated in the platelets of bipolar patients [Friedman et al., 1993]. Acute lithium exposures apparently facilitate many PKC-mediated effects, but longer exposure results in downregulation of some PKC isozymes. The effects of lithium-induced changes of the PKC signaling pathway can be measured on downstream products, just as in the PKA system. Chronic lithium exposure has been demonstrated to reduce the expression of myristoylated alanine-rich C kinase substrate (MARKS), especially in the hippocampus. MARKS has been implicated in the regulation of neuroplastic events [Manji and Lenox, 2000].

LITHIUM

Because lithium revolutionized the treatment of bipolar disorder, it also provided a potential window into understanding the disease-related alterations that occur at the cellular level. Lithium was identified as an element more than 150 years ago, and it wasn't long after its discovery that it was used as a therapeutic agent for a variety of

ailments. Lithium's mood-stabilizing effects were demonstrated in the 1950s. Unlike other medications used to treat psychiatric patients, lithium is a salt, and consequently, it does not have a receptor to which it binds in the brain. Rather, it is actively transported into the cell through the sodium channel. When a neuron depolarizes, the sodium channel opens and both sodium and lithium rush into the cell. The sodium is then actively pumped out, using the sodium-potassium-ATP pump, but lithium remains in the intracellular compartment.

As described above, lithium appears to modulate several second messenger systems, including cAMP and phosphoinositol pathways. Lithium may blunt receptor activation of adenylate cyclase activity, although separating the effects of lithium from the alterations that occur naturally in bipolar disorder is not always easy. Rather than causing large changes in baseline cellular activity, lithium seems to attenuate responsivity to other neurotransmitters. One might say that it "turns down the gain." This may explain its efficacy in bipolar disorder—decreasing sensitivity to both internal and external stimuli. Lithium also affects other neurotransmitter systems, including serotonin, dopamine, and γ -aminobutyric acid (GABA) circuits, and its efficacy may possibly be related to its wide-ranging neurobiological effects rather than to a single mechanism.

One of the intriguing properties of lithium treatment in mania is that a time lag of several days is required before lithium exerts its clinical effect. Moreover, lithium's beneficial effects on mood stabilization do not disappear immediately upon its discontinuation [Goodwin and Jamison, 1990]. One possibility is that lithium exerts its effects by resetting the ionic homeostasis in neurons either directly or through its interaction with second messenger systems. Lithium also protects cells from other chemical insults [Nonaka et al., 1998]. The neuroprotective properties of lithium may explain lithium-induced inhibition of NMDA receptor-mediated calcium influx. Beyond neuroprotection, lithium, like antidepressants,

has been reported to increase neurogenesis in the hippocampus [Chen et al., 2000].

CLINICAL CORRELATES

The term bipolar disorder is somewhat misleading because it implies that individuals exist in either a depressed or manic state, and that these states are at opposite ends of a spectrum. The reality is more complex, and this has important implications for treatment. While it is true that the depressed and manic states are far beyond the realm of normal emotions, they are not at opposite ends of a continuum. In fact, these states may represent two dimensions of emotion that, to a certain degree, are independent of each other. As many as 40% of bipolar patients enter a mixed state, a condition with either the coexistence or rapid alternation of symptoms of both depression and mania, sometimes called dysphoric mania. Similarly, the depression of bipolar disorder is generally not the same symptomatically as the depression of unipolar major depression. Bipolar depression tends to be atypical with prominent fatigue, hypersomnia, and reverse diurnal mood variability, as opposed to insomnia in unipolar depression.

For these and other reasons, bipolar disorder is generally more difficult to treat than simple major depression. Antidepressants do not typically work as well for bipolar disorder, and they can destabilize patients by switching them into manic or mixed states. Of the available antidepressants, the best choices based on the current limited database would support the use of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, sertraline, etc.) and bupropion. There is a growing consensus that to obtain an optimal response in most bipolar disorder patients, multiple-drug therapy is required. Lithium is one of the few Food and Drug Administration (FDA)-approved drugs for acute treatment of mania, and it is the only FDA-approved maintenance treatment for bipolar disorder. Lithium, however, has a disturbingly narrow therapeutic index, with

lethal doses as little as two times the therapeutic dose. Lithium treatment is often associated with a number of untoward effects, ranging from tremor and gastrointestinal side effects (nausea, diarrhea, and cognitive slowing) to hypothyroidism and diabetes insipidus. Fortunately, results from studies utilizing biological models of bipolar disorder served as an impetus for research on other pharmacologic treatments, and one line of research led to the anticonvulsants carbamazepine and valproic acid; they are now accepted as effective treatments. Valproic acid is FDA-approved for the treatment of mania. Olanzapine, a recently FDA-approved atypical antipsychotic, is also effective in the treatment of mania and perhaps in the depression of bipolar disorder as well.

Manic-depressive cycles are neither random nor predictable. Many, if not most, patients show a pattern of increasing frequency over time. This phenomenon occurs in other areas of neuroscience and has suggested a model based on kindling and sensitization. Kindling refers to increased responsivity to repeated low-level electrical stimulation. This is analogous to a seizure disorder, in which a seizure focus becomes increasingly sensitive to other electrical events (i.e., the more seizures one has, the more likely the occurrence of additional seizures). The kindling hypothesis also explains the observation that early manic episodes tend to be triggered by external events, like crossing time zones or drug abuse, whereas after several episodes they tend to occur without any precipitants. Certain anticonvulsants, especially carbamazepine and valproic acid, are effective treatments for certain patients with bipolar disorder, lending further support to the kindling hypothesis. It should be noted, however, that not all anticonvulsants are effective in the treatment of bipolar disorder (e.g., phenytoin, phenobarbital). Moreover, the clinical trial data supporting the efficacy of the anticonvulsants ranges from valproic acid, which is FDA approved, to gabapentin and topiramate, which have no published efficacy data. Moreover, in spite of the attractive

nature of the kindling hypothesis, no convincing neurobiological data have provided any support that this phenomenon actually occurs in patients with bipolar disorder.

Manic-depressives suffer profound alterations in sleep-wake cycles during both the manic and depressive phases of their illness, but subtle disturbances in circadian rhythms often precede the full-scale shift in mood state. Mania is characterized by a markedly decreased need for sleep. It is well known that sleep deprivation [Wehr, 1989] or even traveling across time zones may trigger a manic episode in vulnerable individuals [Jauhar and Weller, 1982; Young, 1995]. Here again is evidence for some basic circuit instability that is subject to transient changes in sleep patterns. The normal sleep-wake cycle is determined by a combination of internal circadian rhythms and external cues—day and night. The basic internal rhythm can be observed across many biologic measures: body temperature, heart and respiration rate, and secretion of various hormones (e.g., growth hormone, cortisol). The discovery of a “master clock” in the suprachiasmatic nucleus (SCN) has revolutionized our understanding of the coordination of circadian rhythms [Reppert and Weaver, 2002]. It is now known that the SCN entrains a multitude of pacemakers both in the brain and out (e.g., liver). The basic oscillatory function depends on two transcriptional factors, termed CLOCK and BMAL1. Emerging data in both depression and bipolar disorder are suggestive of mutations in these genes [Bunney and Bunney, 2000; Mitterauer, 2000], but further research is necessary to investigate this exciting link. Interestingly, lithium has been reported to lengthen the circadian period of individual SCN neurons [Abe et al., 2000].

Phase instability, that is, sensitivity to perturbations in the circadian rhythm, appears to be one characteristic of bipolar disorder. This is concordant with the idea of a chaotic system that is more sensitive to slight changes—changes that throw the entire system from one state to another. Although transitions to mania

or depression are usually discrete, rapid eye movement (REM) sleep and body temperature cycles change more slowly and have been documented to precede the switch in mood [Goodwin and Jamison, 1990]. Although these cycles change slowly, it appears that once some threshold is reached, the bipolar patient is catapulted into either mania or depression. The outward manifestations of mood may therefore appear to change quite suddenly, even though the underlying dynamics are more subtle.

PUTTING IT ALL TOGETHER

In reviewing the data ranging from behavior to brain state to intracellular events, one is struck both by the diversity and discordance of the extant findings in bipolar disorder. Although there is no smoking gun, there is a biological crime scene. Our job is to sift through the evidence and determine what happened. Continuing the analogy, we deal with a contaminated crime scene. The diagnosis of bipolar disorder is never straightforward, sometimes being confused with schizophrenia, and frequently it is overlaid against a background of substance use. The panoply of medications used to treat the illness wreak further havoc on the CNS changes, making it increasingly difficult to sort out nascent brain changes from pharmacologically induced ones. Nevertheless, it is worthwhile to attempt at least some generalizations about the neurobiology.

The fact that there are not grossly consistent alterations in regional brain function is the clearest evidence that bipolar disorder is not localized to a specific part of the brain. Although strokes can induce manic behavior, these are more likely syndromic expressions of a final behavioral phenotype that coincidentally resembles the manic state of bipolar disorder. What functional alterations do exist in the brains of bipolar patients seemingly represent an extension of the phenotype, the so-called endophenotype.

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Although largely qualitative at this point, much is known about what happens when collections of oscillators, like the SCN and its slaves, interact with each other. It will now be possible to model how even subtle alterations in clock synchronization might lead to chaotic behavior, both biologically and behaviorally. At this point, we do not know which is cause and effect, but one lesson from dynamical systems theory is that any alteration in the function of a complex system will be manifest throughout the system. This occurs precisely because all the parts are interconnected.

If we continue looking into smaller scales in the brain, then we run into the most incontrovertible evidence of systemic dysfunction at the level of signal transduction. Although the catecholamine hypothesis may be correct roughly in the extreme, it too should be considered as part of the endophenotype and not causative. Alterations in signal transduction appear to offer the most explanatory power for the range of symptomatology in bipolar disorder. The symptoms manifest themselves as amplifications of the range of both human emotion and behavior. Unlike schizophrenia, the fact that most bipolar patients return to a state of relative normality, even in the absence of treatment, is strongly suggestive for alterations in a modulatory mechanism.

ACKNOWLEDGMENTS

The authors are supported by grants from the NIH: MH-61010 and DA-00367 (G.S.B.); MH-42088, MH-39415, and MH-58922 (C.B.N.).

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