Review Article

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The Neurobiology of Bipolar Disorder: An Integrated Approach

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Bipolar disorder is a heterogeneous condition with myriad clinical manifestations and many comorbidities leading to severe disabilities in the biopsychosocial realm. The objective of this review article was to underline recent advances in knowledge regarding the neurobiology of bipolar disorder. A further aim was to draw attention to new therapeutic targets in the treatment of bipolar disorder. To accomplish these goals, an electronic search was undertaken of the PubMed database in August 2015 of literature published during the last 10 years on the pathophysiology of bipolar disorder. A wide-ranging evaluation of the existing work was done with search terms such as "mood disorders and biology," "bipolar disorder and HPA axis," "bipolar disorder and cytokines," "mood disorders and circadian rhythm," "bipolar disorder and oxidative stress," etc. This endeavor showed that bipolar disorder is a diverse condition sharing neurobiological mechanisms with major depressive disorder and psychotic spectrum disorders. There is convincing evidence of crosstalk between different biological systems that act in a deleterious manner causing expression of the disease in genetically predisposed individuals. Inflammatory mediators act in concert with oxidative stress to dysregulate hormonal, metabolic, and circadian homeostasis in precipitating and perpetuating the illness. Stress, whether biologically or psychologically mediated, is responsible for the initiation and progression of the diathesis. Bipolar spectrum disorders have a strong genetic component; severe life stresses acting through various paths cause the illness phenotype.

Key Words: *Bipolar disorder; Circadian rhythm; Oxidative stress*

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INTRODUCTION

Bipolar disorder (BD) is unique among psychiatric conditions in that its symptoms swing between two opposite mood states: mania and depression.[1] Almost 70 years ago John Cade found out that lithium had beneficial effects in his patients suffering from "mania, dementia praecox and melancholia."[2] The favorable outcome with lithium treatment in patients with major mental illnesses was a breakthrough in that era. Since that discovery, however, no pharmacological agent for the specific treatment of BD has been ascertained, and for all intents and purposes the management of this condition is with psychotherapeutic drugs developed for other indications.[3] In the past few decades, more and more refined investigational techniques have been employed to uncover the pathophysiology of BD. As a result, several important discoveries have been made; the translational nature of the research gives rise to the expectation that new insights will lead to more effective treatments for patients with BD and that the fruits of scientific knowhow will be passed on from the bench to the bedside.

BD is a complex medical condition whose etiology involves genetic and epigenetic factors acting alongside environmental stresses in causing expression of the disease.[4] This diathesis is currently viewed as a multisystem ailment that not only affects brain functioning but also results in physical comorbidities like cardiovascular disease, diabetes mellitus, disorders of immunity, and endocrine dysfunction. Genome-wide studies have failed to detect any single gene to account for the incidence of BD, fostering the prevailing assumption that it is a polygenic condition.[5] The involved genes interact with life stresses to cause disruption in biological and homeostatic mechanisms. Research efforts in recent years have disclosed that dysregula-

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tion of vital biochemical pathways acts in an orchestrated manner in the pathogenesis of BD. There is disruption of glucocorticoid signaling, immune-inflammatory imbalance, increased oxidative stress, abnormalities of tryptophan metabolism, and derangement of phospholipid turnover with shifts in the 1-carbon cycle of methionine and homocysteine.[6] These identified mechanistic pathways offer opportunities for the development of novel and state-of-the-art therapeutic agents, which hold the promise of opening fresh avenues in the treatment of BD.

Life stresses acting on predisposed individuals have an enduring effect on the neural substrate, causing rewiring of the nervous system with increased sensitization and proneness to recurrent affective episodes.[7] There is mounting evidence that manic and major depressive exacerbations have a neurotoxic effect, damaging the neurons as well as the glial elements in the brain.[8] The results of preclinical and human studies consistently show accumulating organ damage both in the center and in the periphery with illness progression. The neuroprogressive nature of BD is clinically manifested as increased frequency and severity of episodes, greater suicidal risk, and cognitive and functional impairment.[9] In the final stages of the disorder there is no illness remission, persistence of inter-episode subthreshold affective symptoms, and eventual loss of autonomy.[10] The course of BD is malignant in many cases; currently available medications fail to control the disease manifestations, with very high rates of polypharmacy, soaring frequency of treatment-emergent adverse effects, and meager compliance from the patients.[11] Considering that BD is a prevalent condition, the application of less than optimal treatment strategies and consequent illness progression place a huge burden on the individual patient, his or her family, and society as a whole. In view of these concerns, it is vitally important to cultivate better understanding of the disease mechanisms so that adequate cures are made available to the numerous people afflicted by this intractable illness. The purpose of this was review to clarify the key interacting pathophysiological mechanisms that drive the disease process in bipolar spectrum disorders and to uncover potential new treatment targets for these and related mood disorders.

SEARCH STRATEGY

In August 2015, the PubMed electronic database was searched for literature on the neurobiology of mood disorders, with particular reference to BD. The investigative approach was broadly based to include articles on animal models with extrapolative value for human disease. During the appraisal of the literature, special emphasis was placed on the translational significance of the research work. This policy was employed with the specific intent to uncover the pathophysiology of bipolar spectrum disorders while at same time identifying novel therapeutic targets for the treatment of these conditions. The aim of conducting a wide-ranging evaluation of the extant body of work was driven by the understanding that the management of BD is particularly challenging considering the heterogeneity, developmental trajectory, and neuroprogressive nature of the disease. An attempt was made to highlight original concepts in the neurobiology of BD that were both innovative and had heuristic value. During the preparation of the article, only studies conducted in the last 10 years were included. Several combinations of search terms were used; some examples are "mood disorders and biology," "bipolar disorder and HPA axis," "bipolar disorder and cytokines," "bipolar disorder and circadian," "mood disorders and circadian rhythm," "mood disorders and inflammation," "bipolar disorder and oxidative stress," and "bipolar disorder and neurobiology." Investigative work on animals and humans as well as review articles were assessed; articles that were considered to be especially pertinent were read in full and their reference lists were also consulted. Finally, the data were integrated in a narrative review in a concise and coherent style.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS DYSFUNCTION

Early in the trajectory of BD, episodes occur secondary to stress but there is blighted psychobiological resilience and defective coping that increase vulnerability to recurrent affective exacerbations with illness advancement.[12] This impairment is principally provoked by the hypothalamic-pituitary-adrenal (HPA) axis, which does not function properly in patients with BD.[13] Patients with BD have a hyperactive HPA axis, high levels of systemic cortisol, and nonsuppression of its circulating levels in the dexamethasone suppression test or the dexamethasone/corticotrophin-releasing hormone (DEX/CRF) test.[14] Furthermore, subjects with increased susceptibility, such as first-degree relatives, have also been shown to have increased baseline cortisol levels and aberrant responses to the DEX/CRF test.[15] From this perspective, HPA axis irregularities seem to be a genetic attribute endowing vulnerability to mood disorders. The glucocorticoid receptor (GR) is the most important factor in the formulation of the cortisol response; it binds to the hormone in the cytosol and shuttles it to the nucleus where it functions as a transcription factor. The action of the GR is dependent on a hefty molecular complex consisting of several chaperone proteins and cofactors, including FK506 binding protein 51 (FKBP51).[16] In vitro experiments in humans reveal that overexpression of FKBP51 reduces hormone binding affinity and nuclear translocation of GR, whereas high levels of this chaperone cause GR insensitivity and raised peripheral levels of cortisol in nonhuman primates.[17] Intriguingly, this hormone acting via an intracellular ultra-short negative feedback loop for GR activity can stimulate the expression of FKBP51.[18]

There is a known familial contribution to the neurobiology of BD, and it is probable that most of the cortisol-GR-related mechanisms alluded to above are a sign of the putative genetic underpinning. In this regard, research

has shown that the hereditary component in BD largely acts through gene-environment associations. In essence, biological and psychosocial stressors reprogram gene activity by altering epigenetic modifications, thus escalating the risk for the disease in predisposed people, as well as meddling with the illness trajectory in those with the expressed phenotype. Among the purported epigenetic modifications, alterations in DNA methylation have been repeatedly shown in bipolar patients.[19] Significantly, in murine models, prolonged exposure to glucocorticoids is known to bring about changes in DNA methylation at the *FKBP5* gene. In human studies, such alterations have been noted in the *Fkbp5* gene in patients with a stressor-related comorbid condition of BD, namely, post-traumatic stress disorder. As such, *FKBP5* methylation may be one of paths through which the HPA system acting in response to stress malfunctions in BD pathophysiology.[20] Given that the mechanisms of HPA axis dysregulation are incompletely known at present, as is its role in dictating the risk of the disease in vulnerable subjects, current work is beginning to unravel the molecular targets of illness development and progression in BD.[21] The crucial function of GR in the actions of cortisol is depicted schematically in Fig. 1.

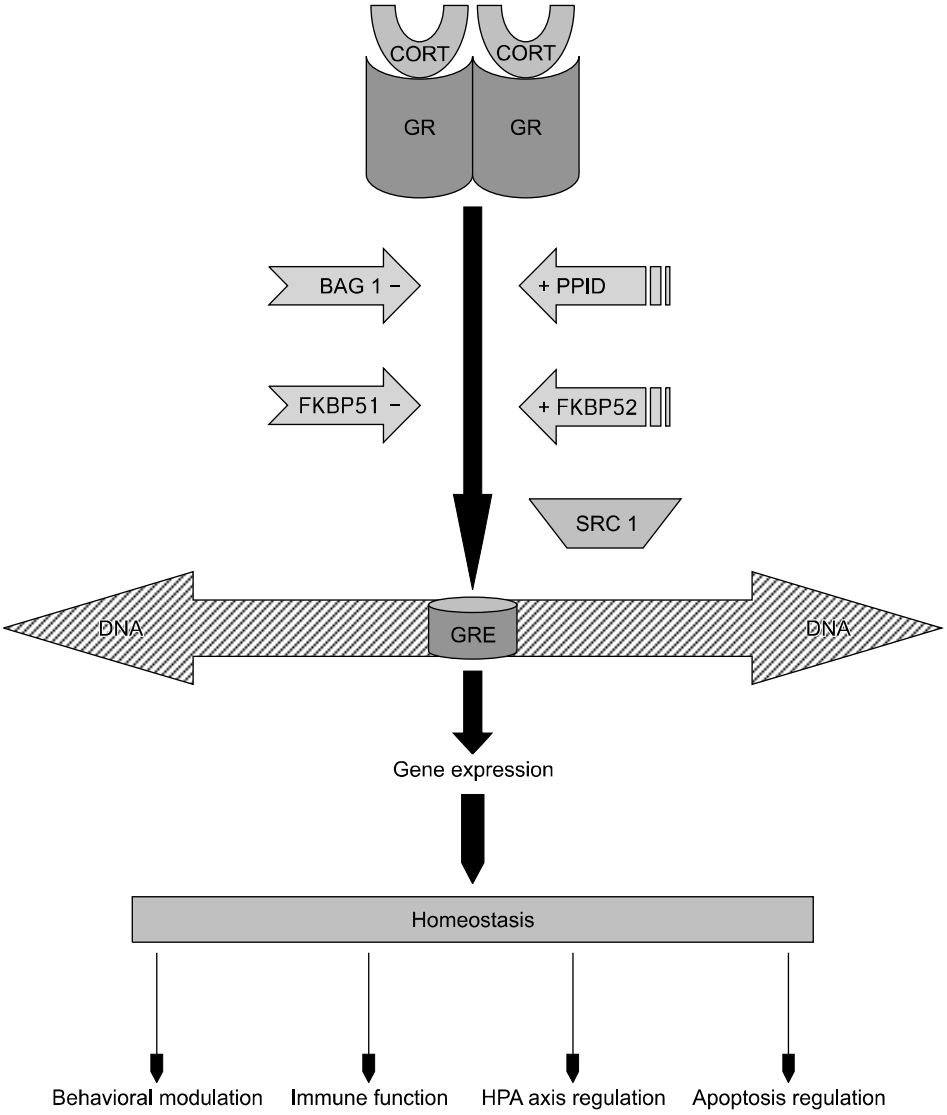

FIG. 1. The central role of glucocorticoid receptor in the biological functions of cortisol. Cortisol (CORT) enters the cytosol by passive diffusion and binds to the glucocorticoid receptor (GR) which is a dynamic multiprotein complex composed of an array of chaperones. These have inhibitory as well as facilitatory actions and induce conformational change, homodimerization and translocation of the glucocorticoid receptor. The GR homodimer shuttles to the nucleus where it binds to glucocorticoid response element (GRE) on the promoter region of the DNA resulting in gene expression. This attachment to the GRE is facilitated by steroid receptor coactivator-1 (SRC-1); the subsequent gene transcription plays diverse roles in physiological functioning. FKBP: FK506 binding protein, BAG 1: Bcl-2-associated gene product-1, PPID: petidylprolyl isomerase D.

IMMUNOLOGICAL FACTORS

1. Immune-inflammatory imbalance

In bipolar patients, major mood episodes of either polarity result in an inflammatory response that has been convincingly shown in several studies. This is evident as an increase in the levels of proinflammatory cytokines (PIC) and C-reactive protein in the peripheral blood.[22] The PIC include most importantly interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α). Treatment with mood stabilizers and resolution of acute affective exacerbations has been shown to normalize the levels of some PIC like IL-6 but not TNF-α, whereas a chronic, low-level inflammatory state persists even in euthymic patients.[23] This points to the fact that immune-inflammatory dysregulation is fundamental to the pathophysiological processes in BD.[24]

It is suggested that unrelieved strain in BD activates the HPA axis with increased secretion of cortisol; in addition, there is stimulation of the sympatho-adrenal medullary axis with increased circulating levels of epinephrine and norepinephrine. These stress hormones acting by virtue of their membrane and cytosolic receptors affect the transcription of genes encoding cytokines via decreased inhibition of the canonical nuclear factor-kappa B (NF-κB) and the noncanonical inflammatory signal transduction pathways like activator-protein 1 (AP-1), Janus kinase-signal transducer and activator of transcription (JAK-STAT) factors, and mitogen-activated protein kinases (MAPK).[25] The cells of the innate immune system (for example, monocytes, macrophages, and T-lymphocytes) secrete PIC, chemokines, and cell adhesion molecules that diffuse to the brain and trigger microglia, causing neuroinflammation and further activating the HPA axis.[26] The unrelenting secretion of stress hormones leads to a constant low-grade inflammatory milieu in the body that is considered to be liable for the neuroprogression of the bipolar diathesis and also predisposes to cardiovascular and metabolic abnormalities often encountered in these patients.[27] Additionally, with repeated mood episodes and advancement of BD, there is a shift of the immune response from T-helper 2 (TH2) cells, which mainly secrete anti-inflammatory mediators like IL-10, to TH1 cells, which produce PIC (for example, TNF-α).[28] Several case-control studies, mainly having cross-sectional designs, have revealed dysregulation of the immune-inflammatory response in BD. Table 1 summarizes recently published work in this area.

2. IL-6 trans-signaling in mood disorders

IL-6 is a ubiquitous inflammatory cytokine performing diverse biological actions that vary from regeneration and repair of cellular elements to augmenting the response to injury in various types of tissue damage.[35] Several studies have documented an increase in peripheral circulating levels of IL-6 during acute mood episodes of either polarity.[36] Because the brain is no longer considered privileged from the effects of peripheral inflammatory mediators, IL-6 gains access to this organ from the circulation. Upon stimulation, microglia and astrocytes also secrete IL-6 locally.[37] However, the receptor IL-6R, which binds to this cytokine in nanomolar concentrations, is expressed by a few cell types only (including some leukocytes and hepatocytes). The complex of IL-6 and IL-6R binds with a second glycoprotein, gp 130, that subsequently dimerizes and kicks off intracellular signaling via the JAK/STAT pathways.[38] Unlike IL-6R, gp 130 is expressed on all cells; however, the latter alone has no affinity for the cytokine and cells lacking IL-6R cannot respond to this mediator. Of note, a soluble form of IL-6R (sIL-6R) consisting of the extracellular portion of the receptor was detected in humans in plasma and other body fluids. sIL-6R is generated by partial proteolysis of the membrane-bound receptor by "a disintegrin and metalloprotease" (ADAM17).[39] The sIL-6R interacts with IL-6 with similar binding properties as the membrane-bound IL-6R. IL-6 trans-signaling is the path by which gp 130–expressing cells, even in the absence of membrane-bound IL-6R, can be stimulated by the complex of IL-6 and sIL-6R.[40] Because of this phenomenon, the inflammatory process can affect every organ system in the body, but under the steady state condition, uncontrolled inflammation is kept in check and physiological homeostasis is maintained.[41]

In the course of inflammation, proteolysis of the IL-6R from neutrophils by virtue of ADAM17 leads to the activation of endothelial cells which do not express IL-6R on their membranes and are therefore insensitive to the cytokine. Priming of the endothelial cells by the IL-6/sIL-6R complex leads to the secretion of the mononuclear cell attracting cytokine MCP-1. Thereby, the shedding of the IL-6R acts as a measure of preliminary injury as shown by the number of neutrophils involved, since these cells are the first to arrive at the site of damage.[42] Furthermore, experimental models in mice have determined that classic IL-6 signaling has a regenerative and anti-apoptotic role during inflammation, for example, in the cecal puncture and ligation sepsis paradigm during which the animals are subjected to extreme stress. In contrast, IL-6 trans-signaling reflects the proinflammatory arm of the cytokine's biological activities.[43] Since the proteolysis of IL-6R is mainly governed by ADAM17, it is highly likely that ADAM17 has a key function in inflammation-related phenomena (Fig. 2).[44]

There are therapeutic implications in this pattern, as specific agents can be developed that block the proinflammatory properties of IL-6 without stalling its anti-inflammatory actions.[45] Many if not all neural cells are the target of IL-6 trans-signaling, and inhibition of this activity can be expected to have important salutary affects in neuropsychiatric disorders.[46] A soluble fusion glycoprotein sgp 130Fc has been engineered from the extracellular portion of gp 130 that exclusively restrains IL-6 trans-signaling. Administration of this engineered protein is a viable treatment approach in major psychiatric conditions, including BD.[47] Thus, current evidence provides a rationale for un-

TABLE 1. Circulating cytokine abnormalities in bipolar disorder

Study	Sample	Measurements	Main findings	Interpretation
Fiedorowicz et al, 2015. (29)	37 BD (mania=15, depression=9, euthymia=13), 29 NC	Primary measure TNF-α	BD subjects and NC did not differ significantly in TNF-α concentration. However, among BD subjects compared to patients with euthymia, cases with abnormal mood states had significantly elevated TNF-α, sTNFR1/sTNFR2, IL-1β, IL-6, IL-10, IL-18 in addition to some other immune-inflammatory factors	Increased levels of inflammatory markers found in manic and depressive mood states in BD subjects. Prospective studies are required to determine the evolution of such abnormalities
Li et al, 2015. (30)	41 cases with BD type I in acute manic episodes, 36 NC. BD patients received combination treatment with LI and quetiapine	Blood samples of cases taken at the start of the study and at conclusion (week 8). Plasma samples of controls taken at baseline. Primary measures included TGF-β1 and IL-23	TGF-β1 and IL-23 significantly higher in cases than controls on initial measurements. In patients achieving remission (YMRS reduction $\geq 50\%$) TGF-β1 higher and IL-23 lower at initial assessment compared to non-remitters. Circulating levels of TNF-α, TGF-β1, IL-23 and IL-17 significantly decreased in manic patients achieving response	High initial TGF-β1 and low IL-23 levels in BD type I patients experiencing manic episodes of prognostic significance. Reduction in overall cytokine levels shows that the pro-inflammatory state resolves with successful treatment. Limitation-small sample size
Munkholm et al, 2015. (36)	37 BD subjects with rapid cycling, 40 matched NC on demographic variables. Study was longitudinally designed with repeated measurements of circulating cytokines in both groups	Over a 6 to 12 month period repeated measures of peripheral cytokines including IL-6, IL-10, IL-18, IL-1β and TNF-α taken from BD patients and NC	In BD patients with rapid cycling, IL-6 and IL-18 significantly increased during manic/hypomanic states, compared with a depressed and a euthymic state. In comparison with NC, IL-6 and IL-18 significantly elevated in manic/hypomanic BD cases	There is increased inflammatory response in rapid cycling BD. IL-6 and IL-18 are putative biomarkers of manic episodes
Wieck et al, 2014. (31)	13 BD type I cases in euthymic state, 15 matched NC. Both groups underwent the Trier Social Stress Test (TSST) procedure	Plasma measurements done on both groups before and after TSST on IL-2, IL-6, IL-33, TNF-α, sTNFR1, sTNFR2 and sST2 (soluble receptor of IL-33)	Regardless of stress exposure, BD cases showed increased IL-33 and reduced sST2 as compared to NC. After TSST paradigm both groups showed higher IL-2 and decreased sTNFR1, however the magnitude of change was higher in NC as compared to BD subjects	These results indicate that BD patients have discrepant reactivity to stress as compared to healthy subjects which is allegedly due to disparity in immunologic response and dysfunction of the homeostatic apparatus
Bai et al, 2014. (32)	130 BD, 149 UD, 130 NC	Soluble interleukin-6 receptor (sIL-6R), soluble interleukin-2 receptor (sIL-2R), C-reactive protein (CRP), soluble tumor necrosis factor type 1 receptor (sTNF-R1), soluble p-selectin receptor (sP-selectin), monocyte chemotactic protein-1 (MCP-1)	Higher levels of sIL-6R, sIL-2R, CRP, sTNF-R1, MCP-1 in BD subjects as compared to UD subjects and NC	More severe inflammatory dysregulation in BD as compared to UD

TABLE 1. Continued

Study	Sample	Measurements	Main findings	Interpretation
Bai et al, 2014. (23)	130 BD, 130 NC. Among BD subjects 77 had BD type I, 53 had BD type II; 75 in euthymia, 14 manic/hypomanic, and 41 in depressive state	sIL-6R, sIL-2R, CRP, sTNF-R1, sP-selectin, MCP-1	BD subjects had significantly higher levels of all cytokine as compared to NC. BD type II patients had significantly lower levels of sTNF-R1 than BD type I patients. Patients in a depressive state had significantly lower levels of sTNF-R1 than patients in manic/hypomanic and euthymic states	Immune dysregulation in BD sTNF-R1 may be a potential biomarker for different phases and types of BD
Brambilla et al, 2014. (28)	20 chronic SCZ, 20 chronic BD, 20 NC	Chemokines, chemokine receptors, cytokines, regulatory T-cell markers	Classical monocyte activation (M1) markers IL-6, ccl3 significantly increased in BD as compared to SCZ and NC. Markers of alternative (M2) monocyte activation ccl1, ccl22, IL-10 coherently decreased in BD. T-cell markers-ccr5 down regulated and IL-4 up regulated in BD compared to NC. Down regulated ccl2 and TGF-beta in BD compared to SCZ and NC. All explored immune markers preserved in SCZ	Coherent increased M1/decreased M2 signature in peripheral blood of BD patients with potential Th1/Th2 shift Proinflammatory response in chronic BD as compared to chronic SCZ
Barbosa et al, 2014. (33)	46 BD patients (23 in mania and 23 in euthymia), 23 NC	IL-33 and its soluble receptor sST2	IL-33 higher in BD patients; no difference in sST2 between BD and NC	IL-33 is a cytokine with multiple functions and may act as a nuclear factor regulating transcription BD is a multisystem condition with a proinflammatory profile
Doganavsargil-Baysal et al, 2013. (34)	54 BD type I patients in euthymia, 18 NC	TNF-alpha, sTNF-R1, sTNF-R2	sTNF-R1 and sTNF-R2 levels higher in euthymic BD subjects than NC. No difference TNF-alpha	Proinflammatory process continues in euthymic period in BD subjects

BD: bipolar disorder, IL: interleukin, MCP: monocytes chemotactic protein, NC: normal controls, SCZ: schizophrenia, TGF: transforming growth factor, TNF: tumor necrosis factor, UD: unipolar depression, YMRS: Young Mania Rating Scale.

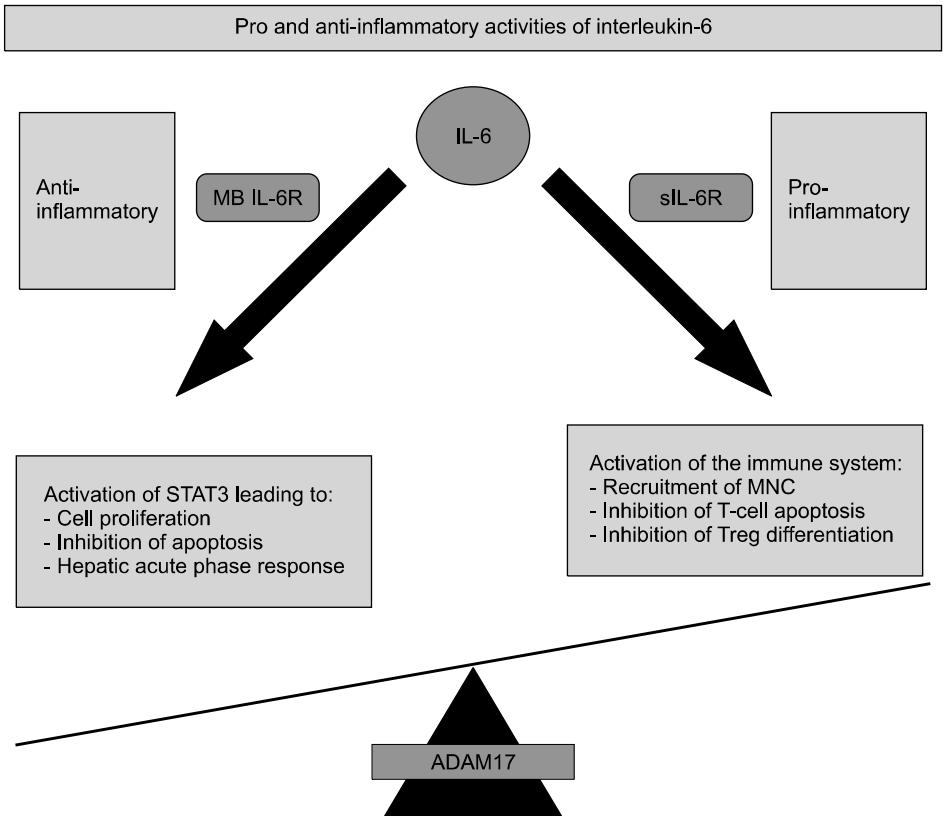

FIG. 2. Pro and anti-inflammatory activities of IL-6. Anti-inflammatory activities of IL-6 include STAT3 dependent regeneration of cells and the induction of the hepatic acute phase response, mediated by membrane bound IL-6R (MB IL-6R). Pro-inflammatory activities of IL-6 via soluble IL-6R (sIL-6R) include recruitment of inflammatory cells and inhibition of regulatory T-cell differentiation. ADAM17 plays the key balancing role in determining the direction of IL-6 biological actions. ADAM17: a disintegrin and metalloproteinase 17, MNC: mononuclear cells, STAT3: signal transducer and activator of transcription 3.

dertaking preclinical studies in mood disorders to determine the therapeutic prospects of IL-6 blocking strategies.

OXIDATIVE STRESS

1. Physiological role of free radicals

In biological terms, oxidative stress can be considered as a continuing discrepant interaction between antioxidants and prooxidants with a tilt toward the latter.[48] The result of this fact is the disproportionate formation of free radicals, the reactive oxygen species (ROS). At low physiological concentrations, ROS perform important functions in the central nervous system (CNS).[49] These include regulation of the destiny of neurons either through growth or programmed cell death via stimulation of the AP-1 transcription factor and the nerve growth factor pathways.[50] ROS take part in critical signaling cascades such as the regulation of the membrane potential and cellular H^+ fluxes, the execution of cardiovascular homeostasis and management of blood pressure through the angiotensin II receptor, and the control of the glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor.[51] In addition, ROS are engaged in the neuroinflammatory response by means of priming of the microglia.[52] Free radical actions may have a key function in fine-tuning the responses of neuronal cells to adverse events, either by promoting resiliency through stress-induced molecular cascades such as MAPK or by getting rid of the severely impaired cells by apoptosis.[53]

2. Pathophysiological mechanisms

On the flip side, the buildup of ROS is found to enhance the vulnerability of brain tissue to damage and has an important part in the pathophysiology of a number of neuropsychiatric conditions. Unequivocal proof of increased brain oxidative damage has been revealed for neurodegenerative conditions like Alzheimer's and Parkinson's diseases, cerebrovascular disorders, demyelinating diseases, and severe psychiatric ailments such as schizophrenia, major depressive disorder, and BD.[54] ROS cause glutamate excitotoxicity and alter mitochondrial activity. Mitochondrial dysfunction in turn causes NMDA receptor up-regulation and further increases oxidative stress, resulting in a detrimental self-sustaining and aggravating cellular process.[55] Oxidative stress products such as superoxide and hydroxyl radicals have been shown to induce cortisol resistance by impairing the GR movement from the cytosol to the nucleus. HPA axis dysregulation by ROS in turn causes a proinflammatory response with increased circulating levels of PIC.[56] Unrestricted ROS activity is also responsible for increased blood-brain barrier permeability through launching of matrix metalloproteinases and subsequent degradation of tight junctions, unrepressed neuroinflammation, and enhanced apoptosis of neurons.[57]

3. Redox balance in the brain

The assumed pathophysiological association between

oxidative stress and mood disorders may be due to the fact that the nervous system is increasingly susceptible to oxidative damage for a number of reasons. First, of all the organs, the brain has the highest consumption rate of oxygen; it is roughly 2% of body weight but uses 20% of total inspired oxygen. This fact predisposes it to greater formation of ROS during the process of mitochondrial energy metabolism. Second, the brain's lipid content is very high, and lipids act as a substrate for the ROS. Third, there is the redox potential of several neurotransmitters, for instance, dopamine. Fourth, the defense systems against free radicals are relatively inefficient. Last, the brain has a high content of metal ions, for example, iron and copper, involved in redox reactions.[58] The protective arrangement against prooxidants is composed of an enzymatic and a nonenzymatic component. Glutathione peroxidase and glutathione reductase are recognized intracellular antioxidant enzymes. The former changes peroxides and hydroxyl radicals into benign moieties, with the oxidation of reduced glutathione (GSH) into the oxidized form glutathione disulfide (GSSG), and glutathione reductase regenerates GSH from GSSG. Additionally, other enzymes such as catalase (CAT) and superoxide dismutase (SOD) also take part in the cellular resistance against oxidative stress and act along with glutathione peroxidase, thus forming the principal enzymatic defense against accumulated free radicals. Further, glutathione-S-transferase and glucose-6-phosphate dehydrogenase are important in sustaining a stable provision of metabolic products like GSH and nicotinamide adenine dinucleotide-phosphate (NADPH), which are required for proper operation of the main antioxidant enzymes.[59]

4. Measurement of oxidative stress

The main ROS include the superoxide radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH^{\cdot}$). Interaction between ROS and nitric oxide results in the formation of highly reactive nitrogen species, such as the peroxynitrite ions ($ONOO^{-}$), which are very damaging to the basic structural molecules of the cells.[60] Because ROS and reactive nitrogen species possess very short half-lives, these are hard to quantify. Therefore, it is necessary to search for and determine indirect pointers of oxidative stress; these include lipid, protein, and DNA peroxidation indicators. Whereas measurements of key enzymes involved in the neutralization of free radicals also serve as putative markers.[61] Biosignatures of oxidative stress in body fluids include oxidized proteins like protein carbonyls and oxidized lipids such as 4-hydroxynonenol, thiobarbituric acid–reactive substances, malondialdehyde, and isoprostanes, which are isomers resulting from the oxidation of arachidonic acid. In addition, neuroprostanes are emerging as definitive markers of oxidative stress emanating from the CNS.[62] The oxidation of DNA at the guanine residue site produces 8-hydroxydeoxyguanosine, which is associated with telomere shortening detectable in peripheral blood cells or fibroblasts.[63] Telomere shortening is an indicator of accelerated aging and premature mortality owing to the increased incidence of cardiovascular and other comorbidities in major psychiatric conditions.[64] There are reliable data from work on circulating markers that the brain's main antioxidants, namely, GSH, CAT, SOD, and GSH peroxidase, have changed values in bipolar subjects. In this vein, recent meta-analyses have shown increased biomarkers of oxidative stress.[65] Foremost discoveries are enhanced lipid peroxidation, DNA injury, and increased amino acid nitration in bipolar patients in contrast with healthy subjects, with lipid peroxidation being the predominant finding.[66]

5. NADPH oxidase enzymes as a potential therapeutic target

The sole purpose of NADPH oxidase (NOX) enzymes is the generation of ROS, and their induction is purportedly a significant cause of oxidative stress in major psychiatric disorders.[67] These enzymes utilize cytoplasmic NADPH and catalyze the transfer of electrons to molecular O_2 to produce ROS. Acting along the transmembrane electron transport chain, NOX enzymes generate ROS in the extracellular space or the lumen of intracellular organelles. Seven NOX genes have thus far been discovered, and the best described isoform is NOX2.[68] These enzymes are found in several tissues of the body, and the presence of NOX transcripts has been confirmed in total brain samples as well as in neurons, microglia, and astrocytes. In the presence of severe life stress, these are induced, causing increased production of ROS in the brain and thereby playing a role in the expression of the main psychiatric disorders.[69] Animal experiments in rodents and primates with paradigms such as social isolation and establishment of communal hierarchy models have been very helpful in revealing the contribution of these enzymes to prooxidant injury and the resulting expression of different types of abnormal behavior. In the case of persistent severe life stress, the neurophysiologic impact of excessive ROS generation gives rise to continued excitatory, glutamatergic transmission leading to changes suggestive of alterations seen in psychotic spectrum disorders. These include down-regulation of the NMDA receptors, failure of the inhibitory trait of GABAergic interneurons, and reduction of hippocampal volume.[70] In view of these animal experiments, the cause of oxidative stress has been shown to be the increased expression of NOX enzymes. If these findings are confirmed in humans, these enzymes might emerge as potential therapeutic targets.[71] Fig. 3 illustrates this supposed model of disease development in major psychiatric disorders.

INFLAMMATION, KYNURENINES, AND MOOD DISORDERS

There is limited knowledge regarding the etiopathogenesis of affective disorders, which serves as a major obstacle in the discovery of effective preventive and curative therapies. Several converging sources of evidence point to a contribution of inflammation in the neurobiology of major

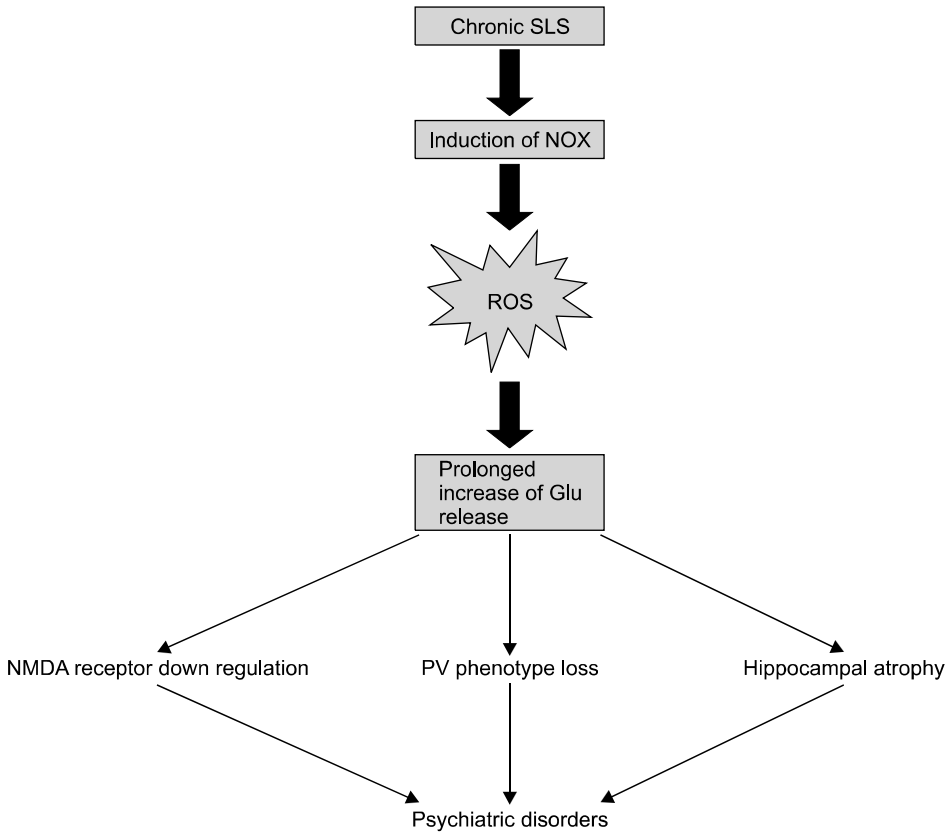

FIG. 3. Development of psychiatric disorders as a consequence of prolonged SLS. When subjected to long lasting severe life stress (SLS) pathophysiological changes take place in the brain. NADPH oxidase (NOX) enzymes are induced, particularly NOX2 with ensuing increased generation of reactive oxygen species (ROS). The later enhance the release of glutamate (GLU) from neurons; prolonged glutamatergic discharge has such resultant effects as N-methyl D-aspartate (NMDA) receptor down regulation, loss of phenotype of inhibitory parvalbumin (PV) interneurons and apoptotic changes in the hippocampus. These alterations are similar to those seen in psychosis; the putative model of major psychiatric disorders described here is extrapolated from animal experiments carried out in rodents and primates.

depressive disorder and BD with the participation of several biological systems in the initiation and progression of these conditions.[72] There is crosstalk among disturbed immune, hormonal, and metabolic systems causing aberration in the functioning of neurotransmitters and leading to the manifestations of affective disorders.[73] With regard to BD, circulating levels of PIC have been shown to be increased during the course of acute episodes, returning to baseline with successful mood-stabilizing treatment.[74] The strongest evidence for the contributory role of inflammation in the causation of major depressive disorder comes from the observation that cytokine immunotherapy based on chronic administration of interferon-alpha and/or IL-2 to patients with kidney cancer or melanoma with metastasis induces depressive episodes in a considerable number of patients.[75] Furthermore, anti-TNFα treatment with etanercept and infliximab is emerging as a possible option in the management of resistant mood disorders, either as monotherapy or adjunctive therapy.[76]

PIC stimulate indoleamine 2,3-dioxygenase (IDO), which is a ubiquitous enzyme that metabolizes tryptophan along the kynurenine (KYN) pathway. The latter is an essential amino acid acquired from food; 5HT is produced from about 1% of the accessible tryptophan in the body, whereas the remaining 99% is metabolized in the hepatocytes by tryptophan 2,3-dioxygenase (TDO). TDO activity is chiefly governed by the amino acid's level itself, and therefore its biological action is usually steady and not influenced by inflammatory mediators.[77] During conditions of inflammation and increased oxidative stress, IDO activation in the extrahepatic tissues shifts the metabolism of tryptophan away from the liver. KYN formed by the action of IDO is further metabolized to compounds that have neuroactive properties.[78] Fig. 4 shows the main enzymes and products in the KYN pathway downstream of IDO.

In circumstances of stress, extra KYN is formed in the brain *in situ*, whereas its central availability is further enhanced because it can pass through the blood-brain barrier. In fact, tryptophan and KYN can cross the blood-brain barrier via a sodium-independent large neutral amino acid transporter known as System L. By contrast, the remaining KYN metabolites are exclusively formed in the brain itself because these cannot cross from the periphery into the CNS.[79] In summary, under the influence of biological stimuli triggered by stress, the KYN pathway is greatly stimulated in the brain. On the basis of the facts presented

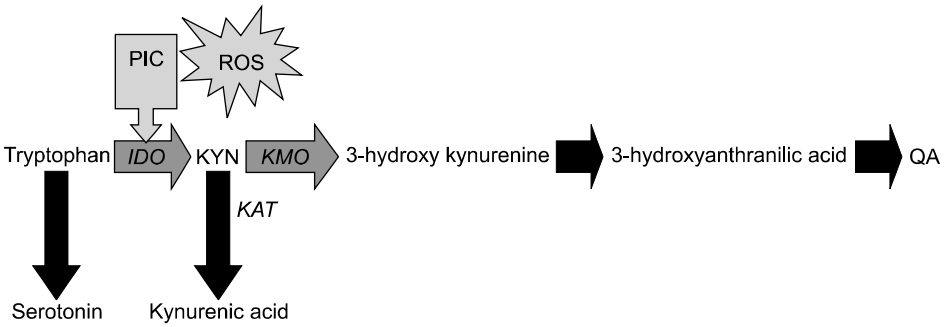

FIG. 4. The kynurenine pathway of tryptophan metabolism. Tryptophan is the biochemical precursor for the production of serotonin. Activation of the enzyme indoleamine 2, 3 dioxygenase (IDO) by pro-inflammatory cytokines (PIC) and reactive oxidative species (ROS) metabolizes tryptophan into kynurenine (KYN) which can then be metabolized by kynurenine aminotransferase (KAT) into the neuroprotective kynurenic acid or by kynurenine mono-oxygenase (KMO) into the potentially neurotoxic 3-hydroxykynurenine and subsequently to quinolinic acid (QA).

above, inflammation-induced mood disorders should be amenable to treatment by the following:

a) Targeting the development of inflammation, for example, with cytokine inhibitors or cytokine signaling pathway antagonists.
b) Preventing the formation of peripheral KYN with IDO competitive blocker, 1-methyl tryptophan. In the normal brain, up to 78% of KYN derives from the blood, while during systemic inflammation nearly all of the brain KYN originates from the periphery.
c) Stopping the transport of KYN into the brain by increasing the availability of large, branched-chain amino acids.

This approach would certainly work best when deployed in a preemptive manner before mood disorders occur.[80] Once an affective episode has come about, the neuroactive KYN pathway metabolites are formed *in situ* in the brain and an alternate strategy aimed at repairing the inflamed brain must be put in place.

Among the products of the KYN pathway, kynurenic acid has a putative neuroprotective role by acting as an antagonist of NMDA receptor, while it also decreases glutamate levels via inhibition of α7-nicotinic receptors. 3-Hydroxykynurenine is a free radical generator, and quinolinic acid is an NMDA receptor agonist that also exerts neurotoxic effects via oxidative damage to lipids and interruption of the blood-brain barrier. The neurotoxic activity of quinolinic acid has been known for more than 30 years. This metabolite should a priori be a therapeutic target by blocking its formation or antagonizing its excitotoxic effect on NMDA glutamatergic receptors.[81] However, in the context of an inflamed brain, the microglia are activated, which results in the release of large quantities of glutamate, a process facilitated by the uptake of extracellular glutamine that is converted to glutamate by the enzyme glutaminase. Moreover, oxidative stress generated by 3-hydroxykynurenine and 3-hydroxyanthranilic acid further contributes to microglia priming. In the normal brain, the clearance of glutamate is efficient because astrocytes take up this substance and convert it to glutamine via glutamine synthetase, which is recycled back to neurons for the continued formation of glutamate. However, in conditions of excitotoxicity, the extracellular concentration of glutamate can increase up to 100-fold, overwhelming this mechanism of glutamate reprocessing.[82] Such pathologically increased levels of glutamate result in atrophic changes in key mood-regulating areas like the hippocampus and amygdala.[83]

An important mechanism for the clearance of brain extracellular glutamate is represented by the extrusion of glutamate from the brain interstitial fluid into the circulation. The brain-to-blood movement of glutamate is limited owing to the relatively high levels of plasma glutamate, so that an efficient way to substantially enhance this process is to accelerate the degradation of glutamate in the blood by administering oxaloacetate, which activates glutamic oxaloacetate transaminase. This enzyme catalyzes the transformation of glutamate into 2-ketoglutarate. Blood glutamate scavenging can be enhanced further by adding recombinant glutamic oxaloacetate transaminase to oxaloacetate. The neuroprotective effect of blood glutamate scavenging has been confirmed in a number of experimental conditions associated with high brain concentrations of glutamate, such as traumatic brain injury, epilepsy, and ischemic stroke.[84]

Finally, to achieve personalized treatment it is necessary to develop suitable biomarkers for identifying those subjects who would most likely gain by targeting the sequence of actions leading from inflammation to major mood disorders. The events to be marked in this chain are the transport of KYN into the brain; the production and action of KYN metabolites, particularly quinolinic acid; and possibly the increased concentrations of glutamate in the brain interstitial fluids.[85]

CIRCADIAN RHYTHM ABNORMALITIES IN MOOD DISORDERS

1. Circadian markers

Chronotropic representations have added to our knowledge of the neurobiology of mood disorders, and dysfunc-

tions in the circadian system are linked with the bipolar phenotype. The evident abnormalities include hormonal dysregulations (melatonin and cortisol fluctuations), actigraphic patterns (sleep/wake cycles), and chronotypic activity preferences (dimensional variations), which serve as circadian markers.[86] These aberrations are seen not only during acute affective exacerbations but also in the euthymic periods. Most of these indicators are also found in the healthy relatives of bipolar patients, thus signifying a robust familial predisposition. Therefore, these may be considered as genetic attributes of the disorder.[87] A number of circadian genes are known to be correlated with BD: several studies have shown affirmative links for *CLOCK, NPAS2, ARNTL1, NR1D1, PER3, RORB*, and *CSNK1-epsilon*. Thus, disruption of the molecular circadian clock is supposedly involved in the genetic vulnerability to BD.[88] The circadian hypothesis has directed the use of treatment methods such as interpersonal and social rhythms therapy and chronotherapeutics (bright light therapy, total sleep deprivation). Furthermore, this hypothesis may elucidate how mood stabilizers, particularly lithium, which inhibits the enzyme GSK3β, resynchronize the molecular clock and bring about their therapeutic effects.[89]

2. Social zeitgeber theory

Over the years many theories have been expounded to clarify the etiology of mood disorders. The propositions include disturbance in monoamine neurotransmission, HPA axis malfunction, immune dysregulation, decreased neurogenesis, mitochondrial dysfunction, and altered neuropeptide signaling. Almost all patients with mood disorders have major interruptions in circadian rhythms and the sleep/wake cycle. No wonder that disruption in normal sleep pattern is one of the main diagnostic criteria for these conditions. Furthermore, environmental disturbances to circadian rhythms such as shift work, trans-meridian travel, and lopsided social timetables often induce or aggravate affective exacerbations.[90] It has been shown in current research work that molecular clocks exist everywhere in the brain and body, where they partake in the working of nearly all physiological functions.[91] The social zeitgeber premise of mood disorders assumes that stressful life events cause alterations in the sleep/wake pattern, which then affect molecular and cellular rhythms in susceptible people, inducing affective episodes. This postulate is supported by a number of clinical studies showing an unambiguous connection between the extent of rhythm disruptions and the severity of mood episodes; also, rhythms are re-established with successful treatment.[92] In essence, all present therapies for mood disorders modify or even out circadian rhythms.

3. The molecular clock

The principal circadian synchronizer is placed in the suprachiasmatic nucleus of the hypothalamus where it gets light input by a direct connection, the retinohypothalamic tract. The suprachiasmatic nucleus subsequently conveys signals via direct and indirect projections all over the brain. It also manages the timing of the discharge of several peptides and hormones, including melatonin, the sleep-promoting agent. Of note, the suprachiasmatic nucleus appears to synchronize the timing of rhythms in the periphery through changes in body temperature, which serve as a common signal to harmonize multiple organ systems to the light/dark cycle.[93] The molecular clock hub consists of a sequence of transcriptional and translational periodic loops that lead to the recurrent expression of clock genes on a time scale of just over 24 hours. In the primary feedback loop, circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like protein 1 (BMAL1) heterodimerize and bind to E-box-containing sequences in a number of genes including the three period genes (*Per1, Per2*, and *Per3*) and two cryptochrome genes (*Cry1* and *Cry2*). Next in the sequence, PER and CRY proteins dimerize and translocate to the nucleus, where CRY proteins can directly stall the action of CLOCK and BMAL1. Further to this mechanism, the CLOCK and BMAL1 proteins control the expression of Rev-erbα and Rora (retinoic acid–related orphan nuclear receptors), which subsequently inhibit or trigger *Bmal1* transcription, respectively, by acting via the Rev-Erb/ROR response element in the promoter.

There are a number of important catalysts that adjust the timing of the molecular clock through the biochemical processes of phosphorylation, sumoylation, etc. Casein kinases phosphorylate the PER, CRY, and BMAL1 proteins, affecting their functioning and nuclear translocation. Another enzyme, glycogen synthase kinase 3 beta (GSK3β), also phosphorylates the PER2 protein, promoting its movement into the nucleus.[94]

4. Circadian mechanisms in mood disorders

The action of the antidepressant agomelatine, a melatonin receptor agonist and a weak 5-HT_{2C} receptor antagonist, causes enhancement in monoaminergic neuronal activity, pointing to a regulatory function of melatonin in monoaminergic transmission and connecting the circadian and monoamine neurotransmitter systems.[95] Circadian rhythm dysregulation results in an increase in PIC, and subsequently TNF-α, INF-γ, and IL-6 alter the sleep/wake cycle and circadian gene expression via NF-κB transduction.[96] Glucocorticoids show a robust diurnal variation in rhythm and crest in level just before wakening, when melatonin falls to undetectable levels in the peripheral blood. CRY proteins acting together with the GR in a ligand-dependent manner induce rhythmic suppression of its activity. Moreover, CLOCK directly acetylates GR, leading to indifference to cortisol in the morning and increased affinity at night when acetylation is annulled.[97] The immediate control of GR function by circadian genes is allegedly of great importance in modulating the reaction to persistent stress.[98]

There is a very high incidence of metabolic diseases in mood disorders, whereas circadian oscillations in the liver, stomach, adipose tissue, and gut are very strong.[99] The pep-

tides that play a role in metabolism and feeding comprise ghrelin, orexin, leptin, and cholecystokinin, and these demonstrate a noteworthy circadian rhythm in activity. The association between corpulence, stress, and poor sleep signifies a vicious cycle, and mood disorders can be included in this sequence for a subgroup of patients.[100]

The nicotinamide cofactors NADPH/NADP+ and NADH/NAD+ have lately been recognized as indispensable associates of CLOCK, NPAS2, and SIRT1, establishing an immediate connection between the redox status of the cell and circadian rhythms.[101] Besides, CLOCK/BMAL1 directly controls the expression of nicotinamide phosphoribosyltransferase in a circadian manner, determining the production of NAD+ in the cell over the daily cycle.[102] Brain-derived neurotrophic factor (BDNF) and its receptor tyrosine kinase B (TrkB) are known to be crucial in the effects of antidepressants and mood stabilizers, and both of these have a strong circadian rhythm in expression in the hippocampus.[103] BDNF is no longer effective as a neurotrophic agent in the nonexistence of a normal diurnal rhythm of glucocorticoids, demonstrating that the daily oscillations of cortisol control the salutary activity of psychotropic drugs on neuronal growth via BDNF/TrkB signaling in the hippocampus.[104] Fig. 5 gives an overview of the links between mood disorders and the circadian system.

CONTRIBUTORY NEUROBIOLOGICAL MECHANISMS IN MAJOR MENTAL DISORDERS

There are many commonalities in the psychopathology of major depressive disorder, BD, and schizophrenia. Schizoaffective disorder is an intermediary phenotype and the retention of the "not otherwise specified" category in current classificatory systems reflects that many patients with major mental disorders do not easily fall into clear-cut diagnoses. This is demonstrated in neurobiological groundwork, and recent studies bear out this actuality. Table 2 provides an outline of this area of research.

NEUROPROGRESSION IN BIPOLAR DISORDER

BD has its usual onset in adolescence or early adulthood following a stressful event. Its course is malignant in many cases, marked by repeated affective episodes of increasing severity, development of substance use disorders, and myriad physical diseases with increased morbidity and mortality. The allostatic load model has been proposed to explain the progressive nature of BD. Table 3 recapitulates representative studies delineating the pathophysiological foundations of this framework.

IDENTIFICATION OF NEW THERAPEUTIC TARGETS

Throughout this article, an effort has been made to al-

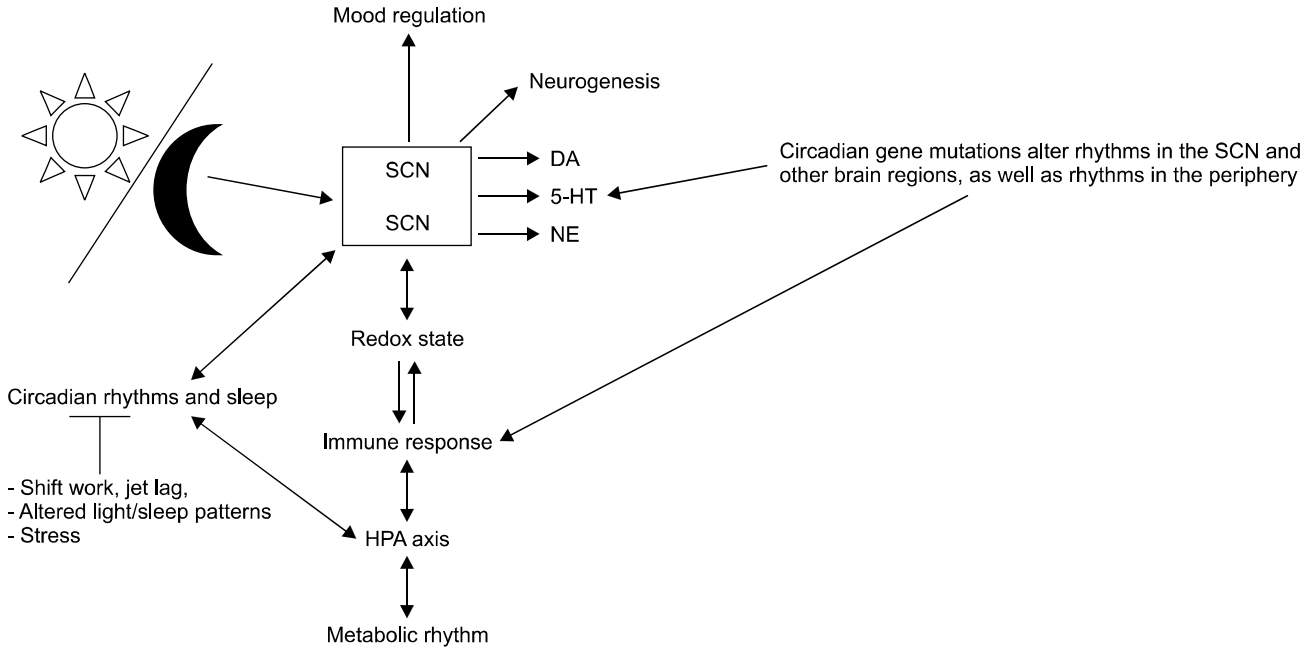

FIG. 5. The relationship between mood regulation and the circadian system. The circadian clock affects several systems and pathways which are supposedly the cause of mood disorders. In the majority of patients there are shared aberrant connections which lead to dysregulated daily oscillations. Circadian gene mutations possibly make a person more susceptible to affective disturbances and these are worsened by environmental variations in the daily timetable. 5-HT: 5-hydroxytryptamine, DA: dopamine, HPA-axis: hypothalamic pituitary axis, NA: norepinephrine, SCN: supraschiasmatic nucleus.

TABLE 2. Shared mechanisms in the pathophysiology of major psychiatric disorders

Study	Type	Main findings
Hope et al, 2009. (105)	Case-control study, cross-sectional design	BD and SCZ are severe mental disorders with dysregulation in several immune-mediated pathways. Aim of the study was to determine whether these patients differed from NC in key circulating inflammatory mediators and to establish any divergence between the two diagnostic groups. Results showed that sTNFR1 and vWF were significantly elevated in BD and SCZ cases compared to NC, while there were no major differences between the two types of patients. In conclusion, in BD and SCZ there was imbalance in endothelium-related inflammatory processes
Hope et al, 2013. (106)	Cross-sectional study design	The psychopathology of BD and SCZ shares many similarities. This study investigated whether these conditions also had common pathophysiological underpinnings related to cytokine factors. A number of cytokines, their receptors and related immune-inflammatory factors were measured in the peripheral blood of psychotic spectrum and bipolar subjects. Results showed that after controlling for confounders IL-1Ra and sTNFR1 were statistically associated with current level of symptoms and past history illness severity in both groups. This demonstrated that inflammatory activation had a key role in the neurobiology of severe mental disorders
Sinclair et al, 2013. (107)	Postmortem study of brain in BD, SCZ and NC	GR is the principal mediator of cortisol stress response in humans. A number of co-factors and chaperones are integrally involved in its mechanism of action. This study measured mRNA of these proteins in the prefrontal cortex tissue of cases and controls. FKBP51 mRNA expression was significantly increased and BAG 1 mRNA decreased in SCZ and BD subjects compared to NC. This indicated directed cortical imbalance in GR related genes in the domain of cortisol signaling in psychotic conditions
Wang et al, 2009. (108)	Postmortem study of brain in patients with BD, SCZ, MDD and NC	Sections of anterior cingulate gyrus were made in the study subjects and measures of 4-HNE, a major lipid peroxidation product obtained as protein adducts. After controlling for confounders, levels of 4-HNE were significantly raised in BD and SCZ subjects but not in MDD and NC. This finding raises the possibility that oxidative damage to the brain occurs in BD and SCZ. Further, treatment efforts should be directed towards reducing oxidative stress in these conditions
Myint et al, 2012. (77)	Review of the relevant literature	Major psychiatric disorders are known to be correlated with a persistent, low-grade inflammatory state. PIC and ROS can activate the neurotoxic division of the kynurenine pathway. Induction of the pathway enzyme KMO as opposed to KAT results in increased conversion of tryptophan to QA in contrast to the putatively neuroprotective kynurenic acid. This imbalance has been demonstrated in MDD, BD and SCZ. QA is an NMDA receptor agonist and causes exicitotoxicity. This is allegedly a principal contributing pathophysiological means in these conditions. Better understanding of this mechanism can lead to the development of potential biomarkers as well as new therapeutic opportunities
Etain et al, 2011. (109)	Narrative review	Mood disorders occur on a spectrum represented by MDD, BD and SAD. These are associated with circadian rhythm disturbances not only during acute episodes but also during periods of remission, predominantly in the case of BD. Circadian markers may represent endophenotypes influenced by clock genes. Association studies have shown that variation in clock machinery genes such as CLOCK, ARNTL1, NPAS2, PER3 and NR1D1 increase vulnerability to mood spectrum disorders. This relationship is especially strong for BD pointing to fresh avenues in the knowledge regarding the neurobiology, diagnosis and treatment of these disorders

TABLE 2. Continued

Study	Type	Main findings
De Berardis et al, 2015 (110)	Narrative review	In recent years pharmacotherapy of mood disorders has targeted the circadian system and agomelatine represents the first agent in this respect. It is an MT1/MT2 agonist and 5HT2c antagonist, acts rapidly and restores the dysregulated circadian clock. It not only acts on the sleep promoting pineal hormone melatonin but enhances serotonin, norepinephrine and dopamine neurotransmission in fronto-limbic areas. Agomelatine's pleiotropic action has extended its therapeutic usefulness beyond MDD to conditions such as bipolar depression, anxiety spectrum disorders and substance use disorders

ARNTL1: aryl hydrocarbon receptor nuclear translocator-like protein 1, BAG 1: Bcl-2 associated gene product-1, BD: bipolar disorder, CLOCK: circadian locomotor output cycles kaput, FKBP51: FK506-binding protein51, 4-HNE: 4-hydrooxynonenol, GR: glucocorticoid receptor, IL-1Ra: interleukin 1 receptor antagonist, KAT: kynurenine aminotransferase, KMO: kynurenine mono-oxygenase, MDD: major depressive disorder, MT: melatonin receptor, NC: normal control, NMDA: N-methyl D-aspartate receptor, NPAS2: neuronal PAS domain-containing protein 2, NR1D1: nuclear receptor subfamily 1, group D, member 1, PER3: period circadian protein homolog 3, PIC: pro-inflammatory cytokines, QA: quinolinic acid, ROS: reactive oxygen species, SAD: seasonal affective disorder, SCZ: schizophrenia, sTNFR1: soluble tumor necrosis factor receptor1, vWF: von Willibrand factor.

lude to novel therapeutic measures for BD, which is in essence a recalcitrant condition. Refractoriness to conventional mood stabilizers is the rule rather than the exception and targeting the monoamine neurotransmitter systems results in less than satisfactory results for many patients. In this regard, Table 4 presents new therapeutic targets that may open fresh avenues in the treatment of BD.

UNIFYING HYPOTHESIS OF THE NEUROBIOLOGY OF BIPOLAR DISORDER

Conceptualized as a polygenic condition, the expression of BD is secondary to a stressful event. There is evidence for HPA axis dysregulation, failure of mechanisms that mediate resiliency, and breakdown of homeostasis. Fig. 6 illustrates key biological abnormalities that act in concert and explains why so many body systems are adversely affected by the bipolar diathesis.

LIMITATIONS

The following caveats should be kept in mind while deducing any inferences with respect to the neurobiology of BD:

1) Not all predisposed individuals are afflicted by BD, which underscore the issues of genetic epistasis and hitherto little known mechanisms that mediate resiliency.
2) There are large gaps in knowledge due to the absence of good animal models replicating BD.
3) Technological advances are needed to reproduce findings from animal research in human samples.

FUTURE DIRECTIONS

Ongoing research on the neurobiology of BD is leading to a better understanding of the condition. Dysfunction of the molecular clockwork genes has repeatedly been shown and circadian disturbances are present not only during acute episodes but also in remission. Future research should clarify how a dysregulated internal clock precipitates affective episodes and suggest measures that could lead to the prevention and early treatment of mood disturbances, which come in innumerable flavors. A vicious cycle of immune-inflammatory imbalance, increased oxidative stress, and derangement of metabolic parameters accompanied by neurophysiological disturbances is at the foundation of this disorder. Further research should elaborate this mechanism, providing a composite view of the initiation and progression of BD. Finally, more effective and targeted therapies are likely to be discovered that are not palliative but curative in nature.

CONCLUSION

A broad assessment of the current literature was done to bring to light the underpinnings of mood disorders in general and BD in particular. These are stress-related con-

TABLE 3. Neurobiological correlates of illness progression in bipolar disorder

Study	Type	Main findings
Kauer-Sant'Anna, et al, 2009. (111)	Cross-sectional, case-control study	BD is currently conceptualized as a neuroprogressive condition with cognitive and functional decline in the latter stages of the illness. In this study circulating markers, BDNF and cytokines were compared in BD type I cases in early and late stages of the illness with matched controls. In BD subjects with illness duration $\geq$ 10 years, BDNF levels were significantly decreased and TNF-α increased suggesting that decreased neurotrophic support and persistent inflammatory state were mediators of illness advancement
Andreazza et al, 2009. (112)	Cross-sectional study design	Oxidative stress markers are increased in BD. This study investigated the premise that patients with long duration of illness $\geq$ 10 years had greater severity of oxidative damage as compared to those with $\leq$ 3 years of disease. 3-NT levels were increased in both groups, whereas there was enhanced activity of the enzymes glutathione reductase and glutathione S-transferase in the latter stages of the illness. This indicated nitrosative damage evident from early course of BD, whereas increased substantiation of glutathione metabolism in latter stages was of a compensatory nature
Elvsashagen et al, 2011. (113)	Cross-sectional design, case-control study	BD is associated with numerous physical comorbidities and accelerated aging. Oxidative damage to the DNA is manifested as telomere shortening. This study investigated the load of shortened telomeres in BD type II patients with matched controls. Augmented telomere attrition was seen in cases as compared to controls which was of the magnitude of 13 years of increased aging. This was correlated to more number of depressive episodes rather than to longer duration of illness
Strakowski et al, 2002. (114)	Cross-sectional, case-control study	BD patients with repeated mood episodes have neuroprogression manifested as cognitive and functional deterioration. This morphometric study utilized brain MRI to measure ventricular volume in early versus late patients compared with matched controls. The volume of lateral ventricles was significantly increased in cases with multiple episodes of manic polarity versus patients with fewer episodes and controls. Conclusion: loss of brain volume occurred in BD subjects after taking into account potential confounders
Kapczinski et al, 2008. (115)	Narrative review	Illness progression in BD is compounded by a persistent symptomatic state, treatment resistance, substance abuse and increased physical comorbidities. Allostatic load (AL) model is a conceptual framework proposed to explain these phenomena. Mediators of AL include PIC, oxidative stress, HPA axis dysfunction and decreased BDNF. Increased programmed cell death in key mood regulating areas like the hippocampus and altered functioning of limbic and paralimbic regions is responsible for neuroprogression and functional decline. Increased incidence of DM, obesity and CVS morbidity and mortality can also be elucidated by the AL discourse

AL: allostatic load, BD: bipolar disorder, BDNF: brain derived neurotrophic factor, CVS: cardiovascular system, DM: diabetes mellitus, HPA axis: hypothalamic-pituitary-adrenal axis, MRI: magnetic resonance imaging, 3-NT: 3-nitrotyrosine, PIC: pro-inflammatory cytokines.

TABLE 4. Potential new therapeutic targets with relevance to bipolar disorder

Target	Mode of action of novel therapeutic agents	Study
Glucocorticoid receptor chaperone proteins, principally FKBP51	FKBP51 inhibitors	Gaali et al, 2015. (116)
IL-6 trans-signaling, representing pro-inflammatory actions of the cytokine	Selective inhibitors of IL-6 trans-signaling	Fonseka et al, 2015. (47)
NOX enzymes, particularly NOX 2 responsible for ROS mediated deleterious effects on the brain	Inhibitors of NOX enzymes	Sorce et al, 2009. (50)
Neurotoxic kynurenine metabolites	1) Development of IDO inhibitors 2) Preventing peripheral kynurenine from crossing into brain 3) Facilitation of efflux of quinolinic acid from the brain	Dounay et al, 2015. (117)
Melatonergic system involved in synchronizing circadian system which is invariably disrupted in BD	New MT1/MT2 receptor agonists with potential benefits in mood spectrum disorders	Abreu et al, 2015. (89)

BD: bipolar disorder, FKBP51: FK506-binding protein51, IDO: indoleamine 2, 3 dioxygenase, IL-6: interleukin-6, NOX: NADPH oxidase, MT: melatonin receptor, ROS: reactive oxygen species.

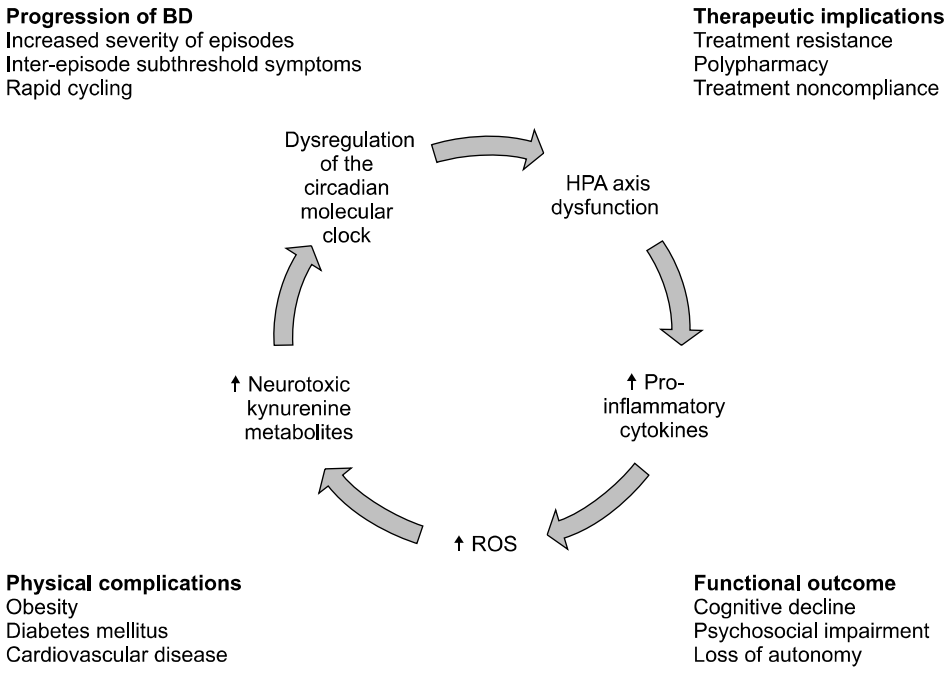

FIG. 6. The integrative model of bipolar disorder pathophysiology. Dysfunctions in crucial bodily homeostatic systems acting in an orchestrated manner feed into one another leading to a progressively worsening course of bipolar disorder. The result is a persistent symptomatic state, treatment resistance, psychosocial functional deterioration and numerous physical complications. BD: bipolar disorder, HPA axis: hypothalamic-pituitary-adrenal axis, ROS: reactive oxygen species.

ditions with overt expression in individuals with an underlying genetic vulnerability. Modern neuroscience is utilizing animal models and conducting human research with increasingly sophisticated methods to unravel their pathophysiology. Significant strides have been made in understanding the neurobiology of affective illnesses, and in this regard new targets and biomarkers have been identified. Diverse biological systems act in concert in perpetuating the disorders. While obstacles in research remain in the basic scientific and clinical domains, there is no doubt that a representation is emerging that is providing a consolidated view regarding the development of these intractable conditions. It is hoped that new knowledge will translate into novel therapeutic measures that have both preventive and curative value for patients with bipolar spectrum disorders.

CONFLICT OF INTEREST STATEMENT

None declared.

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