Advances in the pathophysiology of bipolar disorder

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Purpose of review
Due to bipolar disorder clinical heterogeneity, a plethora of studies have provided new genetic, epigenetic, molecular, and cellular findings associated with its pathophysiology.

Recent findings
Genome-wide association studies and epigenetic evidence points to genotype–phenotype interactions associated with inflammation, oxidative stress, abnormalities in signaling pathways, hypothalamic–pituitary–adrenal axis, and circadian rhythm linked to mitochondrial dysfunction in bipolar disorder. Although the literature is constantly increasing, most of the genetic variants proposed as biomarkers remain to be validated by independent groups and use bigger samples and longitudinal approaches to enhance their power and predictive ability.

Summary
Regardless of which of the mechanisms described here plays a primary or secondary role in the pathophysiology of bipolar disorder, all of these interact to worsen clinical outcomes for patients. Identifying new biomarkers for early detection, prognosis, and response to treatment might provide novel targets to prevent progression and promote general well being.

Keywords
bipolar disorder, circadian rhythm, epigenetics, inflammation, mitochondrial dysfunction

INTRODUCTION

Bipolar disorder (BD) is a chronic and often severe psychiatric disorder affecting approximately 1–4% of the world population. There are three types of BD, including bipolar I disorder (BD-I), bipolar II disorder (BD-II), and cyclothymic disorder. All three types involve clear changes in mood, energy, and activity levels [1]. Systemically, BD is not only associated with strong individual suffering and increased probability of suicide but also with physical complications such as hypertension, diabetes, autoimmune diseases, immunological impairments, cancer, and accelerated aging [2]. In the past few years, long-term BD has frequently led to enduring functional and cognitive impairment and is associated with a higher risk of dementia, which has been linked with low-grade stress, inflammation, and brain structural alterations [3].

Even though the pathophysiological pathways underlying BD remain elusive, there was a significant advance in BD's pathophysiology in the last decades, suggesting that it is likely due to a multifactorial etiology involving interaction between multiple genetic, neurochemical, and environmental factors. Moreover, mechanisms underlying the impaired neuroplasticity and cellular resilience in BD could also explain the increased vulnerability to stressful events and episode recurrence among the patients. Recent and ongoing studies have proposed that the pathophysiology of BD is orchestrated by the interaction of several mechanisms, including genetic load, epigenetic mechanisms, mitochondrial dysfunction, oxidative stress, inflammation, neurotrophic factors, circadian rhythm abnormalities, and biological aging acceleration [4].

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KEY POINTS

- Genetic variants and epigenetic mechanisms are associated with bipolar disorder (BD's) pathophysiology and might be promising biomarkers for patient stratification, environmental risk, and treatment response.
- In a bidirectional relationship, mitochondrial dysfunction and inflammation could lead to cellular damage that might be associated with disease severity, cognitive impairment, psychotic features, and treatment responsivity.
- The hypothalamic–pituitary–adrenal axis is the primary biological response to stress as a trigger to the development of BD, associated with the clinical course and an increased risk of clinical relapse.
- Circadian rhythm abnormalities are associated with BD during acute and inter-episode periods.
- Pathophysiology of BD is a combination of factors that interact and induce a cascade of damage pathways that could play a role in the disease course and poor outcomes.

Understanding the biological basis of BD is crucial for finding new targeted treatments and improving risk assessment, diagnosis, and progression. Although of growing concern, the field still lacks an understanding of how the mechanisms cited above moderate clinical phenotypes and treatment responses. In this review, we aim to provide an overview of the progress made and future directions, highlighting upcoming challenges that may generate new insights to improve treatment outcomes.

GENETICS AND EPIGENETICS OF BIPOLAR DISORDER

BD is known to be a highly heritable and polygenic disorder, but its genetics and inherited risk still do not account for its clinical variability. Evidence from genome-wide association studies (GWAS) reports at least three genes with considerable genetic risk factors for the development of BD: *ANK3*, encoding ankyrin 3, a protein involved in axonal myelination; *CACNA1C*, encoding an L-type voltage-gated ion channel with recognized functions in neural development and synaptic communication; and *TRANK1*, encoding a protein expressed in multiple tissues, especially in the brain, and it is reported that valproic acid mood stabilizer therapy increases its expression [5]. In a recent GWAS of 41 917 BD cases, 64 associated genomic loci were identified, 33 being novel discoveries [6▪▪]. The results show consistent replication of known BD loci, including loci from the second Psychiatric Genomics Consortium (PGC2) GWAS [7]. However, the biological consequences of most BD risk loci identified through several larger GWASs and their contribution to the pathophysiology of BD remain undefined. Chen *et al.* [8] identified 16 SNPs that disrupted the binding of seven transcription factors by using a functional genomic approach, suggesting that these functional SNPs may exert their effects on BD by regulating gene expression [8]. By combining functional genomic approaches with expression quantitative trait loci analysis, this study also suggested that rs3862386 and rs10896081 might confer risk for BD by modulating *PACS1* and *YIF1A* expression.

The genetic correlation of BD with other psychiatric disorders has been consistent in several reports [6▪▪], showing overlap of genome-wide significant loci between mood disorders, schizophrenia [9], and major depression [10]. Interestingly, regarding the BD subtypes, studies showed that patients with BD-I are more genetically correlated with schizophrenia [6▪▪], whereas patients with BD II have a stronger genetic correlation with patients with major depressive disorder [11]. Another difference among BD subtypes is that genetic liability to insomnia as indexed by polygenic risk score (PRS) was associated with an increased risk of BD-II compared with control and participants with BD-I [12]. Although the two subtypes are highly genetically correlated, they are not identical in composition and, for this reason, may contribute to the genetic heterogeneity of BD and the inability to find molecular diagnostic markers.

Epigenetic mechanisms, especially DNA methylation, are associated with BD's pathophysiology. Alterations in DNA methylation have also been associated with accelerated aging in the blood and postmortem brains of BD patients [13,14]. The same research group assessed multiple epigenetic clocks in a large sample of BD patients and controls and their relevance in association with multiple clinical and cognitive variables. They observed accelerated epigenetic aging, as measured by GrimAge acceleration, which was increased in BD and significantly associated with smoking, blood cell proportions, and cognitive dysfunction [15▪▪]. Although there are no large-scale epigenome-wide studies in BD, the methylation of several candidate genes has been explored by targeted approaches, including genes from the hydroxytryptamine receptor (*5HTR*) family and brain-derived neurotrophic factor (*BDNF*); however, the data are still inconsistent. Another important epigenetic marker is noncoding RNA, particularly microRNAs (miRNAs). They regulate posttranscriptional gene expression by impacting

the translation or stability of the target mRNA. In general, the miRNAs targets dysregulated in BD neurons are transcripts involved in glutamatergic/GABAergic neurotransmission, neuronal development, and function [16]. Usually, miRNAs are located in BB susceptibility loci, and transcription is regulated by DNA methylation. They can be released into the bloodstream by CNS cells, so peripheral circulatory miRNAs might be promising biomarkers for patient stratification, environmental risk, and treatment response in BD [17▪▪].

There has been a growth in the number of studies exploring associations between BD and genetic polymorphisms, epigenetic alterations, and gene-gene or gene-environment interactions. However, in most cases, the sample size used in these studies was small or with limited power. Thus, future studies guided by candidate genes for functional follow-up experiments with greater sample sizes and cohorts from diverse populations should be considered.

MITOCHONDRIA AND INFLAMMATION IN BIPOLAR DISORDER

One leading hypothesis is that BD pathology is partly due to the failure of mitochondrial function to support adequate neurotransmission and synaptic plasticity, thus affecting mood regulation, memory, and executive function. This hypothesis is supported by studies showing a higher frequency of mitochondrial DNA (mtDNA) mutations, decreased mitochondrial respiration and electron transport chain complexes, lower levels of high-energy phosphates and pH, changes in mitochondrial morphology and mitochondrial quality-control network, downregulation of the nuclear mRNA molecules and proteins involved in mitochondrial respiration, and increased maternal inheritance in generational transmission of BD [18▪▪]. Moreover, a recent review proposes that mitochondrial-nuclear incompatibility, in addition to environmental factors, leads to a desynchronization of machinery required for efficient electron transport and cellular energy production and an increased risk of BD [19].

Recently, it has become clear that mitochondrial quality control mechanisms have a key role in BD since it is crucial to maintaining mitochondrial function across the health span. Marques *et al.* [20▪] found that mitochondrial morphology in fibroblasts of early-stage BD patients was altered compared to controls, as demonstrated by increased roundness and decreased length. These results are in accordance with previous studies using postmortem prefrontal cortical neurons, peripheral cells, fibroblasts, and young hippocampal dentate-gyrus-like neurons from human induced pluripotent stem cells (iPSCs). They all have shown that patients with BD presented abnormalities in mitochondrial morphology, including more mitochondria of smaller size, abnormal patterns of clumping and marginalization, and atypically shaped mitochondria (ring- or cup-shaped mitochondrial profiles) [21]. It is known that dynamic processes regulate mitochondrial morphology, and studies suggested that an impairment in the mitochondrial dynamic process may be the mechanism responsible for an increase in mitochondrial fragmentation. In this line, our group found downregulation of mitochondrial fusion-related proteins, Mfn-2 and Opa-1, and upregulation of fission protein Fis-1 in peripheral blood mononuclear cells (PBMCs) from patients with BD, showing imbalanced mitochondrial fission and fusion towards mitochondrial fragmentation by an increase in the fission process followed by an increase in apoptosis activation [22].

During cellular stress, there is concomitant activation of mitophagy and apoptosis, in which enhanced mitophagy is an early response to promote cell survival by removing damaged mitochondria, and apoptosis is activated after overwhelming mitochondrial damage or when mitophagy is impaired [23]. Based on previous studies and our studies, we have suggested that mitophagy is impaired in PBMCs from BD patients characterized by downregulation of Parkin, p62/SQSTM1, and LC3A in response to an upregulation of TSPO and VDAC [24▪]. On the contrary, Marques *et al.* [20▪] showed that mitophagy and mitochondrial biogenesis increased in the early stage of BD. Taking together, these findings suggest that in the early stage of BD, an adaptive mechanism to alleviate mitochondrial dysfunction and maintain cell homeostasis and survival is activated. At the same time, in the long term, the number of damaged mitochondria exceeds the capacity of mitophagy, causing apoptosis to become the dominant pathway to minimize tissue damage. The lack of mitophagy leads to loss of tissue homeostasis, resulting in a release of damage-associated molecular patterns (DAMPs), such as fragments of mtDNA. In the circulation, DAMPs can induce inflammation by activating NF-κB and NLRP3 inflammasome and interacting with toll-like receptor 9 (TLR9). In fact, inflammation has been associated with BD by many studies and research groups, as shown in a recent review [25▪].

Hyperactivation of the immune system, propagated by increased levels of interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α), and peripheral sTNF-R1, correlates with disease severity, cognitive

impairment, psychotic features, and treatment responsivity in bipolar patients [26,27]. Furthermore, neuroimaging and postmortem studies have described that BD patients present increased neuroinflammation through excessive microglial activation [28]. Corroborating these data, Vadodaria *et al.* [29▪▪] showed that BD hiPSC-derived astrocytes mounted a unique response to inflammatory stimuli, showing a unique inflammatory gene expression signature, increased secretion of IL-6, and less support for neuronal activity [29▪▪]. In the meantime, Benevenuto *et al.* [30] showed that unaffected youth offspring of bipolar parents and patients with BD present similar alterations in terms of peripheral kynurenine pathway metabolites levels and that kynurenine metabolites were significant predictors of the severity of depressive symptoms in BD patients and unaffected high-risk offspring, suggesting that alterations in the kynurenine pathway might underlie the familial risk of BD.

Overall, these new shreds of evidence affirm the role of mitochondrial dysfunction, inflammation, and oxidative stress in BD, which may affect the development of more advanced treatment. Although the importance of these abnormalities in activating cell damage may differ among patients with BD based on the unique biological, environmental, and genetic factors of each individual, any of these abnormalities could induce the other two to complete the vicious circle to mediate and amplify cellular dysfunction and death, highlighting the reduced cellular resilience in BD cells and contributing to the increased vulnerability of BD patients upon exposure to stressful environmental situations.

STRESS AND CIRCADIAN RHYTHM IN BIPOLAR DISORDER

Another theory of BD is that chronobiological disrhythmicity could contribute to BD by dysregulating systems involved in mood and emotion regulation, contributing to the insurgence and the disease progression. Sleep disturbance in BD is one of the main symptoms related to circadian rhythm [31▪], and the risk for relapse in BD patients is higher when related to circadian rhythm sleep disorder [32]. Typically, there is a reduced sleep period during manic episodes and insomnia or hypersomnia during depressive episodes [33]. A recent meta-analysis should that BD invidious in the remission phase demonstrates sleep-circadian dysfunction, characterized by greater sleep latency and fragmentation and an increase in sleep duration [34]. Palagini *et al.* [35▪▪] showed that BD individuals with circadian rhythm disturbances showed higher severity of depressive symptoms, suicidal risk, lower resilience, and more disturbances in emotion regulation, including impulsivity and regulatory strategies.

The circadian alterations in BD may correlate to a biological abnormality, such as melatonin rhythm and light sensitivity. Studies have suggested abnormal melatonin release patterns in mania versus depression, which may be due to the activity of the noradrenergic system [36]. More recently, Ritter *et al.* [37▪▪] described that melatonin suppression by monochromatic blue light or monochromatic red light and differences in melatonin concentrations during dark conditions did not differ between euthymic patients with BD-I and healthy controls, suggesting that the circadian mediating mechanism is unlikely to be related to increased melatonin suppression by melanopsin-weighted light. Moreover, the evening BD chronotype is a higher risk factor for depressive disorders and substance use disorders, while the morning chronotype is a protective factor [38▪]. Furthermore, studies have also suggested that increased inflammatory cytokines may follow a circadian pattern, while inflammatory cytokines can disrupt spontaneous electrical activity rhythms in the suprachiasmatic nucleus [39].

In accordance with circadian rhythm hypotheses, several studies have revealed a close link between circadian genes and BD. A recent study by Yegin *et al.* [40] found an association between *PER3* VNTR and hypomania in BD patients. Compared to the patients with *PER3* 4/4 repeat genotype, those with *PER3* 5/5 repeat genotype displayed a higher ratio of hypomania. The authors also described that *PER2* rs2304672G allele frequency increased the risk for BD. Though the *CLOCK* gene variants analyses did not detect any differences neither in genotypes or in alleles, significant associations were found in patients in terms of clinical and behavioral patterns, including higher mean age of disease onset in the patients with GG genotypes and higher BRIAN total scores in the patients with AA [40]. In summary, these recent studies add to the emerging evidence that circadian rhythm alterations might play a key role in BD outcomes. However, further investigation with larger sample sizes and different populations should be conducted to verify the effects of period and clock genes on the clinical and behavioral variables.

Like circadian dysfunction, cortisol secretion is significantly higher in BD patients compared to controls, independent of the clinical BD phase [41,42▪▪], suggesting that hypercortisolism and neurotoxic effects of cortisol may be central to the pathogenesis of depressive mood and cognitive impairment. Meanwhile, manic episodes are preceded by increased cortisol and adrenocorticotropic

hormone concentrations. Early life stress affects the developing brain related to psychiatric illness, especially BD [43▪]. Several studies demonstrated that stress directly stimulates the hypothalamic–pituitary–adrenal (HPA) axis and increases cortisol secretion [43▪]. It is already known that BD patients have a vulnerability to stress, with aberrant HPA axis activation [44]. However, the HPA axis activity mechanism underlying BD is more complex, and it depends on the state of the disease [45]. Altogether, these lines of evidence allow us to consider the role of hypercortisolism and long-term HPA axis dysfunction in the pathogenesis of BD.

CONCLUSION

Although many studies have provided clues to possible pathways associated with BD, the current literature is insufficient to draw conclusions to a critical question: how do particular molecular and cellular abnormalities lead to one specific clinical presentation rather than another? As the field moves forward and based on the currently available data, we believe that because BD is phenotypically heterogeneous, several mechanisms act synergistically. In line with this, only a subset of patients with BD presents a neuroprogression life course associated with clinical, cognitive, functional, and biological impairments, reinforcing the hypothesis that BD is a heterogeneous symptomatology disorder with various comorbidities, cognitive impairment, and a wide range of genetic and environmental factors.

Current knowledge about the BD's pathophysiology discussed above indicates that [1] genetic and environmental factors, [2] mitochondria dysfunction and inflammation, and [3] HPA axis and circadian rhythm alterations are related to the development and progression of this disease. However, regardless of which of the mechanisms described above plays a primary or secondary role in the pathophysiology of BD, we suggest that all of these interact to form a deadly downward spiral. In other words, each of these abnormalities can induce a cascade of events that mediate and amplify cellular dysfunction and death in response to 'allostatic load' – the cost of chronic exposure to heightened immune-endocrine and neural activities resulting from the organism's attempts to deal with repeated or chronic environmental stressors – in BD (Fig. 1). Moreover, the evidence mentioned above suggests that several alterations are clearer and more significant in a specific disease state or by clinical dimensions, suggesting that clinical dimensions other than diagnosis (BD-I and BD-II) should be considered as approaches for better understanding BD's pathophysiology.

New treatments for BD are being studied, and most target disparate effector systems, mainly related to molecular targets in neuroplasticity, neurotrophic factors, inflammation, stress, mitochondrial function, and related metabolic pathways [46–48]. Clinical trials have demonstrated the efficacy of adjunctive inflammatory modulation with celecoxib in treatment-resistant bipolar depression, showing that add-on celecoxib reduces treatment resistance and enhances antidepressant response in patients with treatment-resistant bipolar depression [49,50]. Seminally, a recent meta-analysis showed that a moderate antidepressant effect was observed for mitochondrial modulators (*N*-acetyl-cysteine and coenzyme) compared with placebo in the treatment of bipolar depression [51▪▪]. Moreover, results from open-label studies and randomized controlled trials showed promising results of repeated ketamine administration because of its rapid-acting and sustained antidepressant effects [52]. Peng *et al.* [53▪▪] summarized in this review the potential molecular and cellular mechanisms of ketamine based on the preclinical and clinical evidence, showing that ketamine has effects on glutamatergic transmission, mammalian target of rapamycin complex 1 (mTORC1) signaling, BDNF–TrkB cascade, the morphology of astrocytes, neuroinflammation and mitochondrial function, which altogether are responsible for regulating neural circuits, synaptic plasticity, microenvironment, synaptic homeostasis, synaptogenesis, and neuroplasticity. Kryst *et al.* [54] showed in a meta-analysis that a single administration of ketamine reduces depressive symptoms and that repeated ketamine administration effectively sustains initial antidepressant effects observed after single dosing. Another meta-analysis also found higher antidepressant response rates in patients with BD and improvement in suicidal ideation after ketamine administration [55]. On the other hand, several clinical trials of BD have found some negative effects and contradictory findings, which can be explained by the inclusion of a broader patient population instead of subgroups of the illness [51▪▪,56].

Despite the progress made, we have not yet identified biomarkers that could improve early clinical diagnosis, disease progression, and treatment response. Furthermore, most of the findings described below must be interpreted in light of some limitations since most studies are cross-sectional, which can identify associations but not causal relationships or longitudinal patterns of BD development. Therefore, more extensive longitudinal studies are needed to reproduce the present findings, allowing us to build a clear picture of BD phenotypes that can help clinicians assess the risk, determine diagnosis, and provide better treatments for these patients.

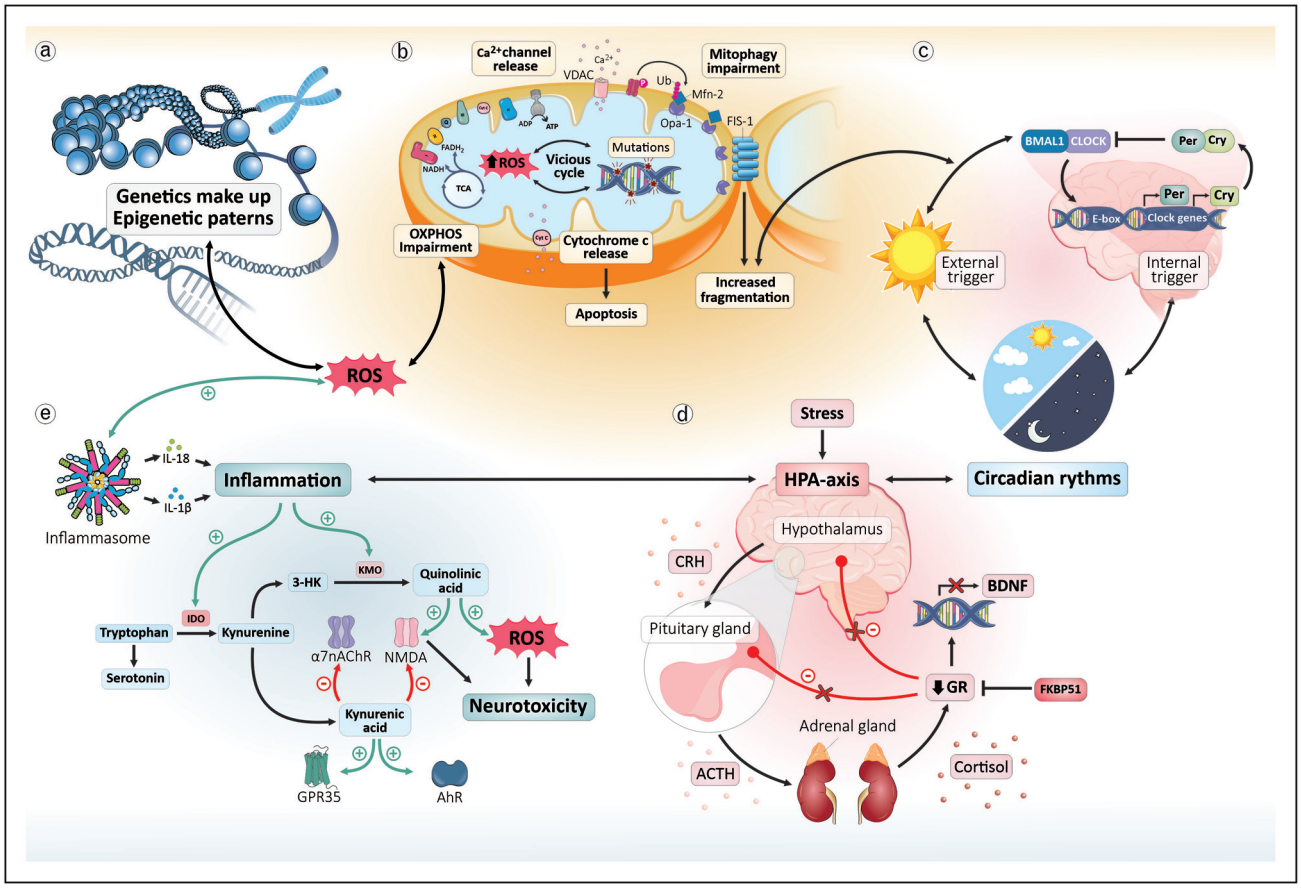

FIGURE 1. Summary of recent research on neurobiological mechanisms underlying BD. Biochemical pathways interact simultaneously to cause cellular and molecular impairment. (a) BD presents a robust genetic and epigenetics component. GWAS identified more than 60 loci associated with BD. However, these variants still do not account for high heritability of BD, suggesting the involvement of other mechanisms, such as gene–gene and gene-environment interactions, through DNA methylation and miRNA alterations. (b) in BD pathophysiology, mitochondrial dysfunction is based on alterations that affect energy production, oxidative phosphorylation, formation of ROS, mitochondrial DNA damage, Ca^{2+} imbalance, membrane permeability, and impairment in mitochondrial dynamics and mitophagy. (c) Corticosteroids are secreted rhythmically with circadian patterns, and CLOCK-related genes regulate glucocorticoid receptor expression directly. Circadian rhythms are related to mitochondrial function by regulating biogenesis, fission/fusion, and mitophagy. These alterations can initiate a vicious cycle where multiple systems and mechanisms aggravate and accelerate cellular and molecular impairment, synaptic dysfunction, and impaired neurogenesis, resulting in progressive structural brain changes and cognitive decline to contribute to the neuroprogression of BD. (d) Inflammatory mediators and stress activate the HPA axis resulting in an increased secretion of corticosteroids from the adrenal cortex. In BD, it is thought that the negative feedback of cortisol to the hypothalamus and pituitary components is impaired, resulting in continuous activation of the HPA axis and excessive release of cortisol. Cortisol receptors become desensitized, with increased activity of pro-inflammatory immune mediators and downregulation of neurotrophic factors such as the brain-derived neurotrophic factor (BDNF). (e) ROS can lead to mitochondrial dysfunction, inflammation, and epigenetic changes in a two-way relationship. Inflammation might be responsible for activating enzymes such as indoleamine 2,3-dioxygenase and kynurenine 3-monooxygenase (KMO), offsetting the kynurenine metabolic balance toward increased neurotoxicity. ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; BD, bipolar disorder; CRH, corticotropin-releasing hormone; Ca, calcium; FKBP51, FK506-binding protein 51; Fis-1, mitochondrial fission 1 protein; HPA, hypothalamic–pituitary–adrenal; GR, glucocorticoid receptor; GWAS, genome-wide association studies; IL, interleukin; IDO, indoleamine 2,3-dioxygenase; KMO, kynurenine 3-monooxygenase; NMDA, *N*-methyl-D-aspartate; OXPHOS, mitochondrial oxidative phosphorylation; P, phosphorus; ROS, reactive oxygen species; 3-HK, 3-hydroxykynurenine.

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Conflicts of interest

There are no conflicts of interest.

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