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Emerging Novel Treatments for Severe Mood Disorders Involving Cellular Plasticity Cascades

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Abstract

Mood disorders are the most prevalent psychiatric disorders. Despite recent advances in the understanding of therapeutically relevant biochemical pathways associated with mood regulation, patients with bipolar disorder and major depression present high rates of recurrences, residual symptoms, and pharmacologic refractoriness. Increasing evidence supports the observations that mood disorders are accompanied by regional brain volumetric reductions accompanied by cellular atrophy/loss. In this paper, we review and critique the data suggesting that neurotrophic signaling cascades may play a role in the pathophysiology and treatment of mood disorders. This suggests that effective treatments will need to provide both trophic and neurochemical support, which serves to enhance and maintain normal synaptic connectivity, thereby allowing the chemical signal to reinstate optimal functioning of critical circuits necessary for normal affective functioning. For many refractory patients, drugs mimicking "traditional" strategies, which directly or indirectly alter monoaminergic levels, may be of limited benefit. Newer "plasticity enhancing" strategies that may have utility in the treatment of mood disorders include inhibitors of glutamate release, NMDA antagonists, AMPA potentiators, cAMP phosphodiesterase inhibitors, and glucocorticoid receptor antagonists.

Introduction

Major depression and bipolar disorder (BPD) are severe and recurrent medical illnesses, which often present with high rates of comorbidities, relapse, recurrence, residual mood symptoms, and poor functioning and quality of life in spite of adequate treatment with current pharmacologic therapies. A complex and integrative connection between genetics and environmental factors may explain the pathophysiologic basis of mood disorders. Adherence to long-term treatment with pharmacologic treatments in mood disorders represents a crucial factor in achieving full syndromic, symptomatic, and functional recovery [1]. Ideally, an effective drug for the treatment of mood disorders should present therapeutic response in a wide range of symptoms and clinical presentations, display few adverse effects, have a rapid onset of action, and stabilize the course of illness. In reality, current pharmacologic options for mood disorders are far from ideal. A majority of patients with mood disorders receive polypharmacy often with little support for this strategy and have high rates of treatment nonadherence, pharmacologic refractoriness, and chronicity.

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Thus, the development of new effective pharmacologic treatments for mood disorders is of great relevance. As we discuss in greater detail below, there have recently been new insights into the potential role of impairments of cellular plasticity and resilience in the pathophysiology of mood disorders; in this perspectives paper, we discuss these findings, particularly with regard to the potential develop of completely novel therapeutics for severe mood disorders (Table 1).

Clinical Evidence for Impairments of Cellular Plasticity and Resilience in Mood Disorders

Methodologies to investigate structural and functional deficits within the human brain have exponentially increased in recent years allowing for a more complete and intensive analysis of potential deficiencies in the brains of patients suffering from neuropsychiatric disorders. Recent years have also seen the size and availability of postmortem brains repositories for patients with mood disorders increase as well. The functional and morpho-metric findings in bipolar disorder have been extensively reviewed elsewhere [2]; we here provide a brief overview of these findings.

Structural imaging studies demonstrate reduced gray matter volumes in areas of the orbital and medial pre-frontal cortex (PFC), temporal lobe, and enlargement of third ventricle in subjects with mood disorders compared with healthy controls [2]. Also consistent is the increased presence of white matter hyperintensities (WMH) in the brains of elderly depressed patients and both young and elderly patients with BPD [3]. Although the cause of WMH in mood disorders is unknown, their presence—particularly in the brains of young patients with bipolar—suggests importance in the pathophysiology of the disorder. Relatively recent postmortem neuropatho-logic studies are complementary, showing reductions in cortex volume and region- and layer-specific reductions in number, density, and/or size of neurons and glial cells in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, amygdala, and in basal ganglia and dorsal raphe nuclei in individual with BPD and other severe mood disorders compared with controls [4]. Important to note, however, is that it is not currently known if these alterations—whether they be functional and structural imaging or postmortem—constitute developmental abnormalities conferring vulnerability to severe mood episodes, compensatory changes to other pathogenic processes, the sequelae of recurrent affective episodes, or solely epiphenomenon which lack real significance in the pathophysiology of pathogenesis of these disorders. Understanding these issues will partly depend upon experiments that delineate the onset of such abnormalities within the illness course and determine whether they antedate mood episodes in high-risk individuals. How-ever, a recent report showed that individuals at high risk of developing mood disorders exhibited reduced subgenual prefrontal cortical volumes, raising the possibility that this endophenotype may constitute a heritable vulnerability factor in these patients [5]. Overall, the data reviewed clearly show that severe mood disorders, undoubtedly neurochemical illnesses, are also disorders associated with impairments of cellular plasticity.

Cellular Mechanisms Underlying the Impairments of Cellular Plasticity and Resilience in Mood Disorders: Clues from Preclinical Models

In developing hypotheses regarding the cellular mechanisms underlying the histopathologic changes in mood disorders, the alterations in cellular morphology resulting from various stressors have been the focus of considerable recent research. It is beyond the scope of this paper to discuss these findings in detail; the interested reader is referred to several outstanding recent reviews [6•,7•,8•]. One of the most consistent effects of stress on cellular morphology is dendritic remodeling of hippocampal neurons [6•,7•,8•]. The remodeling of dendrites is observed profoundly in the CA3 pyramidal neurons as atrophy-decreased number and length of the apical dendritic branches. Additionally, profound changes in the morphology of the mossy fiber terminals and significant loss of synapses have also been observed.

Microdialysis studies have shown that stress increases extracellular levels of glutamate in hippocampus, and N-methyl-d-aspartate (NMDA) glutamate receptor antagonists attenuate stress-induced atrophy of CA3 pyramidal neurons [6•,7•,8•). Although a variety of methodologic issues remain to be fully resolved, the preponderance of the evidence to date suggests that the atrophy, and possibly death, of neurons in hippocampus and frontal cortex is caused, at least in part, from increased glutamate neuro-transmission [6•,7•8•]. Overactivation of the NMDA receptors is known to contribute to the neurotoxic effects of a variety of insults, including repeated seizures and ischemia; most relevant for the present discussion, enhancing mitochondrial function exerts major protective effects against various forms of excitotoxicity [6•,7•,8•].

In addition to directly causing neuronal atrophy, stress also appears to reduce cellular resilience, thereby making certain neurons more vulnerable to other insults, such as ischemia, hypoglycemia, and excitatory amino acid toxicity [8•,9) The precise mechanisms by which glucocorticoids reduce cellular resilience remain to be fully elucidated but appear to involve the inhibition of glucose transport (thereby diminishing capability of energy production and augmenting susceptibility to hypoglycemic conditions) and the aberrant, excessive facilitation of glutamatergic signaling [10].

In addition to the cellular mechanisms described above, it is now clear that stressors may exert major effects on cellular plasticity and resilience by regulating the expression and function of growth factor cascades [11,12]. Neurotrophic factors (eg, nerve growth factor and brain-derived neurotrophic factor [BDNF]) are known to increase cell survival via binding of these factors to membrane receptors and regulation of intracellular signal transduction pathways that can control apoptosis, including regulation of Bd-2 family members. The signal transduction cascades that are currently believed to mediate many of effects of neurotrophic factors are the mitogen activated protein (MAP) kinase cascade, the phosphotidylinositol-3 kinase (PI-3K)/Akt pathway, and the PI-3-kinase cascade [13,14] .

Recent studies have demonstrated that the activation of the MAP kinase pathway can inhibit apoptosis by inducing the phosphorylation of Bad (a major pro-apoptotic protein) and increasing the expression of Bcl-2 (a major anti-apoptotic protein); the latter effect likely involves the cyclic adenosine 5’-triphosphate (cAMP) response element binding protein

(CREB) [15,16). CREB phosphorylation leads to induction of Bcl-2 gene expression. Accumulating data suggest that not only is Bcl-2 neuroprotective but that it also exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth, and axonal regeneration [17-21]. A recent study revealed that severe stress exacerbates stroke outcome by suppressing Bcl-2 expression [22]. In this study, stressed mice expressed approximately 70% less Bcl-2 mRNA than unstressed mice following stroke. In addition, stress greatly exacerbated stroke in control mice but not in transgenic mice that express increased neuronal Bcl-2. High corticosterone concentrations were significantly correlated with a greater stroke size in wild-type mice but not in Bcl-2 overexpressing transgenic mice. Thus, enhanced Bcl-2 expression appears to be capable of offsetting the potentially deleterious consequences of stress-induced neuronal endangerment and suggests that pharmacologically induced upregulation of Bcl-2 may have considerable utility in the treatment of a variety of disorders associated with endogenous or acquired impairments of cellular resilience. Overall, it is clear that the neurotrophic factor-extracellular signal-regulated kinase (ERK) 1/2-MAPK-Bcl-2 signaling cascade plays a critical role in cell survival in the central nervous system (CNS) and that there is a fine balance' maintained between the levels and activities of cell survival and cell death factors. Dysregulation of the BDNF-ERKl/2-CREB-Bcl-2 cascade may be a key mechanism by which prolonged stress induces atrophy of selective subpopulations of vulnerable neurons, distal dendrites, or both. It is likely that dysregulation of this cascade reduces the probability of neuronal survival; however, the differential survival is likely modulated not only by the region-specific expression of protective factors but also by the network properties of vulnerable structures. The dynamics of the impairments of cellular plasticity and resilience is thus also likely to be determined by intrinsic properties of the affected areas. Most importantly, it is now clear that many of the long-term effects of neurotrophic factors on cellular plasticity and resilience are mediated by regulating mitochondrial function (Fig. 1A-B).

In toto, the data suggest that the impairments in plasticity and cellular resilience in severe mood disorders likely arise via pathologic perturbations of glutamatergic (notably alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] to NMDA balance) glucocorticoid-neurotrophin signaling. It is thus noteworthy that many of the most promising novel therapeutics for severe mood disorders target components of these very same cascades.

Glucocorticoid Receptor Antagonists

As discussed, glucocorticoids have been shown to decrease the expression of the neurotrophin BDNF in the hippocampus; furthermore, an ample range of biological stresses can precipitate both depressive and manic symptoms in susceptible subjects presumably by producing dysfunctions in glucocorticoid receptors (GR). A depressive syndrome occurs in more than one half of patients with Cushing's syndrome or under treatment with exogenous corticosteroids [23]. Neurobiological findings have demonstrated that a hyperactive hypothalamic-pituitary-adrenocortical (HPA) axis, mostly due to elevation in cerebrospinal fluid corticotrophin-releasing factor (CRF) levels, precipitates the arousal of depressive symptoms [24].

GR antagonists have been demonstrated to limit the deleterious effects of hypercortisolemia, mostly due their ability to block GR receptors. Administration of GR antagonists has been shown to induce an acute antiglucocorticoid effect, which may lead to a negative feedback in the HPA axis. For example, mifepristone (RU-486), a non-selective antagonist of the GR receptor, has been reported to possess antidepressant and antipsychotic properties in patients presenting psychotic depression [25,26]. In bipolar depression, treatment with mifepristone (600 mg/d) improved not only depressive symptoms compared with placebo but also cognitive functioning, especially spatial memory [27]. These and other GR antagonists in development are shown in Table 1.

Glucocorticoid Synthesis Inhibitors

Inhibition of glucocorticoids synthesis and release has been considered a potential therapeutic target for the treatment of major depression. Treatment with glucocorticoid synthesis inhibitors (GSis), such as ketoconazole and metyrapone have been shown to improve depressive symptoms in preclinical and clinical studies (26], but these preliminary clinical results are inconclusive and in need of further study. Examples of GSis are provided in Table 1.

CRFI Receptor Antagonists

The CRF family of neuropeptides and receptors is considered an important regulatory system for mood modulation, which has been demonstrated to control neural substrates of emotionality, locomotor activity, sleep-wake cycle, and aversive processes [28,29). A number of observations have suggested changes of CRF functions in patients with depression. CRF1 receptor antagonists have been proposed to induce therapeutic antidepressant-like effects in animal models of depression. Antalarmin (a pyrropyridimine compound) significantly decreased stress-induced CRF-stimulated corticotrophin release. This latter compound also was shown to reverse stress-induced inhibition of exploratory and sexual behaviors.

Dehydroepiandrosterone

The adrenal steroid dehydroepiandrosterone (DHEA) has antiglucocorticoid properties and also interacts with many neurotransmitters [26]. It acts as a precursor of the sexual hormones testosterone and estrogen. The anti-depressant efficacy of DHEA was reported in the treatment of major depressive episodes [30]. In parallel, an elevated cortisol/DHEA ratio has been found to be associated with higher scores for anxiety, anger, depression, and hostility in psychotic patients (31]. Overall, the current data support the hypothesis that a dysfunctional HPA axis represents a state marker of major depression. The exact mechanism by which glucocorticoids may induce these harmful effects on the hippocampus is not clear but seems to involve the facilitation of glutamatergic signaling and inhibition of glucose transport.

Glutamatergic Strategies for the Treatment of Mood Disorders: Focus on Cellular Plasticity and Energy Metabolism Pathways

Glutamate is a dicarboxylic excitatory neurotransmitter directly involved in the modulation of synaptic plasticity, learning, and memory. Increased excitatory glutamate neurotransmission (hyperglutamatergic states) may induce cellular energy metabolism dysfunction due to activation of complex signaling cascades. Subsequently, there is an increase in calcium influx and generation of oxygen-free radicals, which is believed to result in a dysfunction of the synaptic plasticity pathways. In addition, hyperglutamatergic states may lead to impairment of mitochondrial function [32]. Elevated calcium levels and gene mitochondrial dys-function have been associated with the pathophysiology of BPD (33,34]. These integrated findings may support the role for glutamatergic system dysfunction (notably AMPA to NDMA balance) in the pathophysiology of severe mood disorders [35,36). Several glutamatergic modulators are currently being tested in patients with mood disorders; these agents may also presumably activate cascades for neuroprotection and cellular plasticity [26].

Inhibition of glutamate release

Lamotrigine and riluzole: Lamotrigine is an anticonvulsant that has neurotrophic and neuroprotective properties. This anticonvulsant has demonstrated clinical improvement in the treatment of bipolar depression [37]. Lamotrigine reduces excessive pre-synaptic glutamate release and inhibits hyperglutamatergic consequences due to NMDA receptor dysfunctions [38]. Its mechanism of action is mostly secondary to the neuronal membrane blockade on the voltage-sensitive sodium channels, which seems to activate neurotrophic cascades. Additional clinical evidence that inhibitor of glutamate may be important to the mechanism of antidepressant action can be attributed to riluzole. Riluzole is a neuroprotective and neurotrophic agent, which exerts its antiglutamatergic effects through the inhibition of voltage-dependent sodium channels in neurons and by reducing glutamate [39]. The glutamatergic modulator riluzole was found to present significant antidepressant effects in patients with treatment-resistant major depression and bipolar depression [39,40]. Also, preclinical studies have demonstrated that riluzole stimulates synthesis of growth factors, such as BDNF, in cultured mouse astrocytes [41]. Recently, studies have shown that the anticonvulsants with a predominantly antidepressant profile, lamotrigine and riluzole, as well as imipramine increase cell surface expression of GluR1 and GluR2 in rat hippocampus; by contrast, the predominantly antimanic drugs, lithium and valproate, reduce cell surface expression of these AMPA subtype receptors [35]. AMPA trafficking is indicated by the cell surface expression of GluR subtype receptors and represents an important aspect of synaptic plasticity. The potential utility of agents to more directly potentiate AMPA receptor function is an exciting area of medication development.

Ionotropic glutamate receptors

AMPA receptor: AMPA receptors (AMPAr) are a subfamily of iono-tropic glutamate receptors, which mediate the majority of fast excitatory glutamatergic signal in the brain. The fast component of glutamatergic neurotransmission has been directly involved in the modulation of plasticity, learning, and memory [42] . Recently, positive allosteric

modulators of AMPA receptors (AMPAkines) have been developed. The therapeutic role for AMPAkines in mood disorders is currently being evaluated. AMPAkines have shown antidepressant effects in animal models of learned helplessness, chronic mild stress, and behavioral despair. Besides its putative role as antidepressant agents, studies have also demonstrated a strong association between its clinical and preclinical effects and the activation of neuro-plasticity cascades. Supporting the latter, studies have shown significant positive effect on cellular plasticity induced by AMPAkines [42]. AMPAkines seem to enhance cognitive function in rodents by increasing hippo-campal neuroplasticity secondary to increased BDNF expression [42]. Similarly, enhanced BDNF mRNA in neuronal cultures was also associated with positive modulation by AMPAr [43]. These preliminary findings suggest that the use of AMPAkines may have a role in the treatment of mood disorders by its ability to increase neurotrophic support (Table 1). An AMPA potentiator is currently being tested in major depression at the National Institute of Mental Health.

NMDA receptor: NMDA receptors (NMDAr) are the most complex ionotropic receptors and represent the primary glutamatergic target for therapeutics in mood disorders. Preclinical and clinical data have suggested the involvement of NMDAr in the mechanism of action of antidepressant and mood stabilizers [44]. The original observations date back to the 1960s, based on reports of mood-elevating effects induced by D-cycloserine (an NMDAr partial agonist) [26] . In humans, a single intravenous dose of ketamine, a noncompetitive NMDA glutamate receptor antagonist, resulted in rapid (within 2 hours), robust and relatively sustained (1 week) antidepressant effects in patients with treatment-resistant major depression [45]. Ketamine has also been demonstrated to have antidepressant effects in animal models [46]. Other studies have examined the possible therapeutic role of several NMDA antagonists in mood disorders such as felbamate and zinc. Felbamate is an anticonvulsant and neuroprotective agent, which presents stimulant-like effects in patients with epilepsy [47]. Studies have described positive effects induced by felbamate on mood modulation (mostly antidepressant effects) . The putative anticonvulsant and neuroprotective effects induced by felbamate may occur throughout the inhibition of NMDA receptor function [26] . Zinc is also considered a potent inhibitor of the NMDA receptors, and recent evidences suggest a possible role of zinc metabolism in the pathophysiology of depression [48] . Chronic imipramine treatment has been shown to increase the ability of zinc to inhibit the NMDA receptor complex. Similarly, data have shown that treatment with zinc increases cortical BDNF mRNA levels. These data suggest a critical role for zinc antidepressant effects in the NMDA receptor modulation, but further controlled studies are necessary.

Metabotropic glutamate receptors—The metabotropic glutamate receptors (mGluRs) are a family of eight G-protein-coupled receptors, which regulate slower glutamatergic neurotransrnission preand post-synaptically. The mGluRs are divided into three groups based upon second messenger coupling and ligand sensitivity. Activation of mGluRs commonly induces inhibition of calcium currents by interaction with ionotropic glutamate receptors. These effects have been hypothetically associated with the activation of neuroprotective cascades [49]. Specifically, studies have shown that group II/III agonists inhibit glutamate release. Also, the selective activation of mGluRs II-III can lead to antidepressant-like effects, mostly due its ability to depress glutamate release in excitatory

synapses [40,50]. Considering that each mGluR can simultaneously couple and interact with different G-protein subunits, ionotropic receptors, and/or ion channels, this complex glutamatergic modulation may present a significant role in the search for novel therapeutics for mood disorders. Also, future studies evaluating the possible regulatory role of the anticonvulsant and neuro-protective properties of group II mGluRs agonists and group I mGluRs antagonists in mood stabilization may be relevant for the study of new treatments for BPD.

Molecules in Neurotrophic Signaling Cascades that Represent Attractive Targets for the Treatment of Mood Disorders

cAMP phosphodiesterase IV inhibitors—Recent studies demonstrate that the expression and function of the transcription factor CREB is increased by different types of antidepressants [51]. The time course for the induction of CREB is consistent with that for the therapeutic actions of antidepressant treatments (ie, 10-21 days of treatment) [52]. CREB regulates gene transcription by binding to cAMP response element (CRE), a cis-acting enhancer element in the regulatory region of various genes Upregulation of CREB also indicates that there are specific target genes that are regulated by antidepressant treatment. One target gene of particular interest is BDNF. Chronic antidepressant treatment increases the expression of BDNF in the hippocampus of rodents [51,53]. Induction of BDNF is observed with the different classes of antidepressants, as observed for upregulation of CREB, consistent with the hypothesis that BDNF is a common gene target of this class of psychotropic drugs.

The possibility that BDNF could mediate the action of antidepressant treatment is also supported by behavioral studies. Administration ofBDNF into the midbrain increases performance in behavioral models of depression, including the forced swim and learned helplessness paradigms [54]. BDNF has been shown to promote the differentiation and survival of neurons during development and in adult brain [55]. Malberg et al. [55]. demonstrated that chronic antidepressant treatment increased neurogenesis (cell proliferation) in adult rat hippocampus. This effect was observed with several different classes of antidepressants including noradrenaline and serotonin selective reuptake inhibitors (specifically tranylcypromine, reboxetine, and fluoxetine). This new information indicating a possible role for the cAMP pathway and CREB in the actions of antidepressant treatments suggest new approaches to develop more effective agents. This model suggests that agents, which activate the cAMP intracellular cascade, would potentially be effective antidepressant agents. One approach is to use an inhibitor of phosphodiesterase (PDE), the enzymes responsible for the breakdown of cAMP. Preclinical studies demonstrate that PDE inhibitors have antidepressant-like effects in behavioral models [56–58]. Takahashi et al. [59] demonstrated that chronic antidepressant administration increases the expression of cAMP-specific PDE 4A and 4B isoforms. Long-term administration of inhibitors of PDE increases the expression of CREB and BDNF in the hippocampus of rats [51]. These findings provide support for the hypothesis that the cAMP system regulates the expression of BDNF and suggest that the inhibition of cAMP metabolism may provide a mechanism for treatment of depression.

Glycogen-synthase kinase-3 mediated pathways—Glycogen-synthase kinase (GSK)-3 plays a critical role in a diversity of neuronal processes such as progenitor cell fate determination, neuronal survival, apoptosis, and synaptic plasticity. Notably, GSK-3 is a downstream target for insulin and BDNF [60]. In 1996, lithium was shown to inhibit GSK-3 activity within its therapeutically-relevant concentrations in both direct and indirect mechanisms [61]. Subsequent studies later demonstrated that chronic lithium treatment induces phosphorylation of GSK-3β in mouse brain. Valproate has also been found to inhibit GSK-3 activity in vitro within its therapeutic concentrations, but these results were inconsistent [60]. Interestingly, several studies suggest that lithium is likely to exert at least some of its neuroprotective effects through inhibition of GSK-3. In most systems, overactivity of GSK-3 induces apoptosis, whereas inhibition of the enzyme prevents it [60]. Evaluation of mood-stabilizer-induced GSK-3 inhibition on rodent behavior revealed that GSK-3β knockout or GSK-3-inhibitor treated mice exhibit reduced depression-like and manic-like behaviors, suggesting that GSK-3 inhibition mediates the behavioral effect of mood-stabilizers [60]. It is an intriguing possibility that regulation of GSK-3 in different circuits may underlie these behavioral effects is an exciting area for future research.

Bcl-2—Bcl-2 is a major neuroprotective protein in the Bcl-2 family, which consists of anti-apoptotic (Bcl-2 and Bcl-x) and proapoptotic (Bad/Bik, Bax, Bak, tBid, Bim) proteins, localized on the mitochondria membrane, endoplasmic reticulum, and golgi. Bcl-2 knockout mice studies and viral-mediated delivery of the gene demonstrated the importance of the protein as a major neuroprotective factor that not only protects against apoptotic and necrotic cell death but also promotes regeneration of axons in the CNS [62]. Thus, it has been postulated that increasing CNS Bcl-2 levels may serve as an effective therapeutic approach for treating neurodegenerative diseases.

To date, a substantial interest in the possible involvement of Bcl-2 in the pathophysiology and treatment of BPD has arisen from mRNA differential display (DD) studies which suggested that Bcl-2 might represent a common target for the actions of both chronic lithium and valproate. These mRNA DD were further validated by protein studies, which demonstrated that chronic lithium or valproate robustly increased Bcl-2 levels in rat frontal cortex (twofold increases) [63]. Subsequent studies demonstrated an increase in Bcl-2 in a variety of areas in the rodent brain and in human neuroblastoma cells following mood-stabilizers treatment [26]. These studies were followed-up by a series of human studies which showed that chronic lithium increased gray matter in BPD (presumably reflecting a reversal of illness-related atrophy) [64]. Not surprisingly, given the effects of mood stabilizers on BDNF/ERK, GSK-3, and Bcl-2; their cyto-protective effects have been investigated in a variety of paradigms with very robust effects [65-68].

It is noteworthy that—in addition to the well-known function of energy production via oxidative phosphorylation—neuronal mitochondria also have important roles in apoptosis and the regulation of intra-cellular calcium; increasing evidence suggests that the latter action may be critically important in regulating the release of, and response to, neurotransmitters. Furthermore, mounting evidence suggests that activation of mitochondrial-apoptotic cascades may lead to a process of “synaptic apoptosis,” in which apoptotic processes are activated in a highly localized manner. Furthermore, abnormalities

of mitochondrial function may play important roles in the abnormalities of calcium signaling that have been observed in BPD [69]. The interested reader is referred to an outstanding review article positing that the many facets of the complex neurobiology of BPD can be fit into a more cohesive bioenergetic and neuro-chemical model [70]. Specifically, they propose that the existence of mitochondrial dysfunction in BPD that involves impaired oxidative phosphorylation, a resultant shift toward glycolytic energy production, a decrease in total energy production and/or substrate availability, and altered phospholipids metabolism.

How then, is one to conceptualize mitochondrial-associated impairments of cellular plasticity and resilience in the pathophysiology and treatment of severe mood disorders (BPD and major depression)? Recent observations suggest that regulation of mitochondrial function is likely to play important roles in regulating synaptic strength neuronal circuitry mediating complex behaviors. In support of such a contention, Hovatta et al. [71] have recently used a combination of behavioral analysis of six inbred mouse strains with quantitative gene expression profiling of several brain regions. Intriguingly, they found that genes involved in oxidative stress metabolism were related to complex affective behaviors. Together, these results suggest that the mitochondria-mediated impairments of plasticity observed in BPD may have ramifications not only for long-term disease progression/course of illness/functional impairments but also “here and now” symptomatology. These observations raise the intriguing possibility that enhancing mitochondrial vigor may represent an important adjunctive strategy for the optimal long-term treatment of BPD. Novel molecular targets to improve mitochondrial function include pharmacologic attempts to bypass defects in the respiratory chain, scavenging excessive oxygen radicals [26] and enhancers of mitochondrial membrane stabilization. It is also noteworthy that pramipexole also upregulates bcl-2 in several brain areas and has been shown to exert antidepressant effects in preliminary studies. Although the dopamine agonistic effects of pramipexole may clearly also contribute to its purported antidepressant effects, its robust neurotrophic effects suggest that it may have broader utility as an antidepressant potentiator. In this context, recent studies have found pramipexole to be more effective than placebo in treating bipolar depression [72].

Conclusions

Increasing evidence supports the contention that—although BPD is clearly not a classical neurodegenerative disorder—it is accompanied by regional brain volumetric reductions, and cellular atrophy/loss. Furthermore, as we have described here, a considerable amount of evidence that has been accumulated supporting neurotrophic signaling regulation aberrations may play a role in the pathophysiology of BPD and certainly appear to be relevant targets for the actions of mood stabilizers. These findings have a number of practical ramifications: 1) they raise the possibility that early intervention to prevent some of the atrophic changes may have a major beneficial effect on the course/trajectory of BPD; 2) the data suggest that lithium or valproate may have utility in the treatment of degenerative disorders (although these drugs certainly would not “cure” these illnesses, any impact that they have on slowing down disease progression might be very worthwhile); and 3) most importantly, they suggest

a number of novel targets for improved therapeutics, many of which are currently under investigation [40].

Drugs that act as "plasticity enhancing" agents in diverse intracellular biochemical cascades may represent promising targets for therapeutics. Modulation of the HPA axis through inhibition of CRF receptors, GRs, or other means such as glucorticoid synthesis may designate a novel class of medications that directly target pathophysiologic processes involved in mood disorders. As we discussed, there is a growing body of data suggesting that agents which modulate the glutamatergic system, may have utility in the long-term treatment of severe mood disorders. In general glutamatergic "plasticity enhancing" strategies include NMDA antagonists, inhibitors of glutamate release agents, metabotropic receptor agonists/antagonists and AMPA potentiators. PDE inhibitors may additionally be advantageous as a mechanism to increase the levels of neurotrophic molecules such as BDNF and Bcl-2, which are responsive to increases in CREB. This progress holds much promise to the development of novel therapeutics for the long-term treatment of mood disorders.

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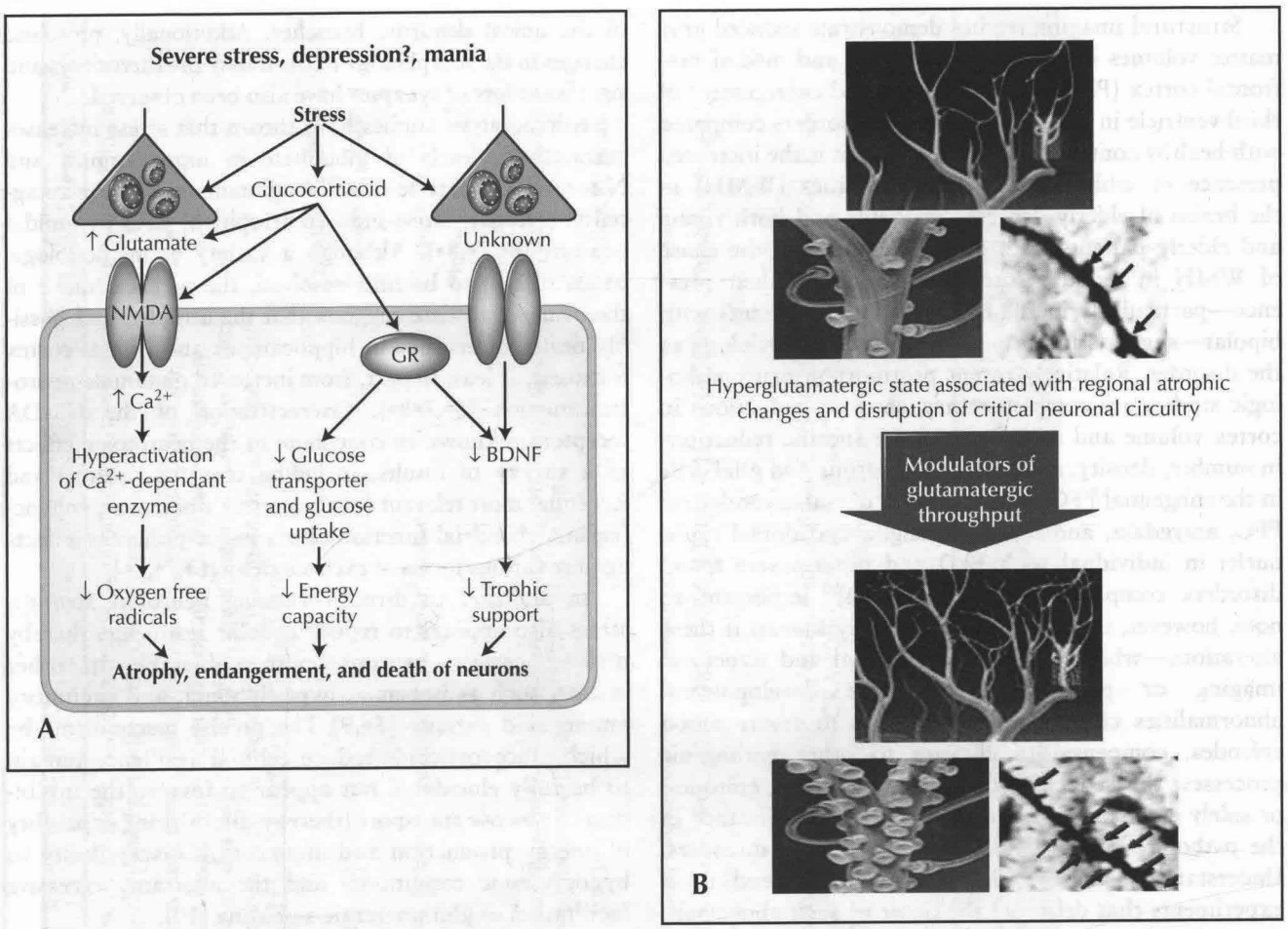

Figure 1.

Pathophysiologic changes associated with stress or severe mood disorders. Stress or severe mood disorders can induce a chronic increase on glucocorticoids levels (**A**), which in turn, may bring about an excessive glutamatergic activity (hyperglutamatergic state [**B**]) and hyperactivation of calcium-dependent enzymes. These changes may lead to cell atrophy and decreased cellular resilience secondary to both dysfunctions on energy metabolism, neuroplasticity and oxidative stress-related pathways. BDNF—brain-derived neurotrophic factor; GR—glucocorticoid receptor; NMDA—N-methyl-0-aspartate.

Table 1

Targets and related therapies

Target	Potential therapy	Examples	Stage of development*
GSK-3	GSK inhibitors	Zinc, indirubines, maleimides, hymenialdesine, paullones, thiaziazolidones, synthetic phosphorylated peptide, azole derivatives	Preclinical-clinical
HDAC	HDAC inhibitors	Small-molecular weight carboxylates (butyrate, valproic acid, sodium phenylbutyrate), hydroxamic acids (trichostatin A), suberoylanilide and LAQ-824, benzamides (MS-275, CI-994), epoxyketones (2-Amino-8-oxo-9,10-epoxydecanoic acid and trapoxin B), cyclic peptides (depsipeptide, apicidin), hybrid molecules (CHAP31, CHAP50)	Phase I, II, III
PKC	PKC inhibitors	Tamoxifen	Preclinical, phase I, II
Glutamate release and AMPA receptor	Inhibitor of glutamate release and AMPA potentiator	Lamotrigine, riluzole	Preclinical, phase II
NMDA	NMDA antagonists	Zinc, memantine, ketamine, acamprosate, neramexane	Phase II, III, IV
	Partial agonist	D-cycloserine	Phase II
AMPA	AMPA receptor potentiators	Org24448	Phase II
	AMPA antagonist	Talampanel, benzoylpiperidone (aniracetam), benzoylpyrrolidines (ampakines), arylpropylsulfonames (LY392098, LY451616), S18986	Preclinical, phase II
mGluR	mGluRs: group I antagonists, group II antagonists, group III agonists	LY2140023, MGS0039	Preclinical, phase II
Glucocorticoid synthesis	Glucocorticoid synthesis inhibitors	Aminogluthethimide, ketoconazole, metyrapone	Phase II
GR type II	GR II antagonist	Mifepristone (RU-486), ORG 34517, ORG 34850, ORG 34116, AL082D06, cyproterone acetate	Phase II, Phase III
Dihydroepiandrosterone			Phase II
Corticotrophin releasing hormone receptor	Corticotrophin-releasing factor (CRF) 1R antagonist	Peptides (astressin, -helCRF), small molecule nonpeptides (CP-154526, antalarmin, DMP-695, DMP-696, CRA-1000, R-121919, SSR-125543, NBI 35965, NBI 27914, R278995/CRA0450), N-phenylphenylglycines	Preclinical, Phase I
Bcl-2	Bcl-2 enhancer	Pramipexole	Phase II, IV
Phosphodiesterase	Phosphodiesterase inhibitors	Dipyridamole, rolipram	Phase II, IV

AMPA—alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CHAP—cyclic hydroxamic-acid-containing peptide; GR—glucocorticoid receptor: GSK—glycogen synthase kinase; HDAC—histone deacetylase; mGluR—metabolic glutamate receptor; NMPA—N-methyl-d-aspartate; PKC—protein kinase C.

*Drugs/compounds are at different stages of development; some may have been tested for “proof-of-concept” rather than for clinical use and others at this time may not be able to be used on a long-term basis because of treatment-limiting side effects. Although valproate has plasticity enhancing characteristics it remains unclear whether it is due to its ability to inhibit GSK-3 and HDAC.