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Enhancing synaptic plasticity and cellular resilience to develop novel, improved treatments for mood disorders

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Despite the devastating impact that mood disorders have on the lives of millions worldwide, there is still a dearth of knowledge concerning their underlying etiology and pathophysiology. The brain systems that have

heretofore received the greatest attention in neurobiological studies of major depressive disorder (MDD) are the monoaminergic neurotransmitter systems, which are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders.^{1,2} The treatment of depression was revolutionized about a half-century ago with the introduction of two classes of agents that were discovered—entirely by serendipity—to be effective antidepressants: the tricyclic antidepressants (monoamine reuptake inhibitors) and the monoamine oxidase inhibitors. The discovery of the acute protein target of the antidepressant medication led to the development of numerous

There is mounting evidence that recurrent mood disorders—once considered “good prognosis diseases”—are, in fact, often very severe and life-threatening illnesses. Furthermore, although mood disorders have traditionally been conceptualized as neurochemical disorders, there is now evidence from a variety of sources demonstrating regional reductions in central nervous system (CNS) volume, as well as reductions in the numbers and/or sizes of glia and neurons in discrete brain areas. Although the precise cellular mechanisms underlying these morphometric changes remain to be fully elucidated, the data suggest that mood disorders are associated with impairments of synaptic plasticity and cellular resilience. In this context, it is noteworthy that there is increasing preclinical evidence that antidepressants regulate the function of the glutamatergic system. Moreover, although clearly preliminary, the available clinical data suggest that attenuation of N-methyl-D-aspartate (NMDA) function has antidepressant effects. Recent preclinical and clinical studies have shown that signaling pathways involved in regulating cell survival and cell death are long-term targets for the actions of antidepressant agents. Antidepressants and mood stabilizers indirectly regulate a number of factors involved in cell survival pathways, including cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), brain-derived neurotrophic factor (BDNF), the antiapoptotic protein bcl-2, and mitogen-activated protein (MAP) kinases, and may thus bring about some of their delayed long-term beneficial effects via underappreciated neurotrophic effects. There is much promise for the future development of treatments that more directly target molecules in critical CNS signaling pathways regulating synaptic plasticity and cellular resilience. These will represent improved long-term treatments for mood disorders.

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Selected abbreviations and acronyms

AMPA	<i>α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid</i>
BDNF	<i>brain-derived neurotrophic factor</i>
cAMP	<i>cyclic adenosine monophosphate</i>
CREB	<i>cAMP response element binding protein</i>
FC	<i>frontal cortex</i>
HPA	<i>hypothalamic-pituitary-adrenal</i>
LTP	<i>long-term potentiation</i>
MAP	<i>mitogen-activated protein</i>
MDD	<i>major depressive disorder</i>
NAA	<i>N-acetylaspartate</i>
NGF	<i>nerve growth factor</i>
NMDA	<i>N-methyl-D-aspartate</i>
PDE4	<i>phosphodiesterase</i>
PFC	<i>prefrontal cortex</i>
SSRI	<i>serotonin-selective reuptake inhibitor</i>
VPA	<i>valproic acid</i>

second-generation medications (eg, serotonin-selective reuptake inhibitors [SSRIs] and norepinephrine-selective reuptake inhibitors), which are widely used today. Thus, clinical studies over the past 40 years have attempted to uncover the specific defects in these neurotransmitter systems in mood disorders by utilizing a variety of biochemical and neuroendocrine strategies. Indeed, assessments of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have, in fact, demonstrated a number of abnormalities of the serotonergic, noradrenergic, and other neurotransmitter and neuropeptide systems in MDD.

While such investigations have been heuristic over the years, they have been of limited value in elucidating the unique neurobiology of mood disorders. Furthermore, while most antidepressants exert their *initial* biochemical effects by increasing the intrasynaptic concentrations of serotonin and/or norepinephrine, their clinical antidepressant effects are only observed after chronic administration (days to weeks), suggesting that a cascade of downstream effects are ultimately responsible for their therapeutic effects. These observations have led to the appreciation that, while dysfunction within the monoaminergic neurotransmitter systems is likely to play important roles in mediating some facets of the pathophysiology of mood disorders, these disorders likely rep-

resent the downstream effects of other *more primary abnormalities*.

In addition to the growing appreciation that investigations into the pathophysiology of mood disorders have been excessively focused on monoaminergic systems, it is increasingly being recognized that progress in developing truly novel and improved antidepressant medications has consequently also been limited. The SSRIs, for example, have a better side-effect profile for many patients, and are easier for physicians to prescribe. However, these newer medications have essentially the same mechanism of action as the tricyclic antidepressants and, as a result, the efficacy of the newer agents and the range of depressed patients they treat are no better than the older medications. Moreover, today's treatments remain suboptimal for many patients afflicted with depressive syndromes.

A recognition of the lack of significant advances in our ability to develop novel, improved therapeutic agents for these devastating illnesses has led to the investigation of the putative roles of intracellular signaling cascades in the pathophysiology and treatment of mood disorders. Multicomponent, cellular signaling pathways interact at various levels, thereby forming complex signaling networks, which allow neurons to receive, process, and respond to information, and to modulate the signal generated by multiple different neurotransmitter and neuropeptide systems.^{3,4} This is noteworthy since mood disorders undoubtedly arise from a complex interaction of multiple susceptibility (and likely protective) genes and environmental factors, and the phenotypic expression of these diseases includes not only episodic and often profound mood disturbance, but also a constellation of cognitive, motoric, autonomic, endocrine, and sleep/wake abnormalities. Thus, intracellular signaling cascades are critically involved in regulating complex psychological and cognitive processes, as well as diverse neurovegetative functions, such as appetite and wakefulness. Consequently, recent evidence that impairments of neuroplasticity and cellular resilience underlie the pathophysiology of MDD, and that antidepressants and mood stabilizers exert major effects on the signaling pathways that regulate neuroplasticity and cell survival, has generated considerable excitement among the clinical neuroscience community, and is reshaping views about the neurobiological underpinnings of these disorders.

“Neuroplasticity” subsumes diverse processes of vital importance by which the brain perceives, adapts to, and

responds to a variety of internal and external stimuli. The manifestations of neuroplasticity in the adult central nervous system (CNS) have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and even neurogenesis (see Mesulam, 1999, for an excellent overview⁵). Although the potential relevance of neuroplastic events to the pathophysiology of psychiatric disorders has been articulated for some time,⁶ recent morphometric studies of the brain (both in vivo and postmortem) are beginning to lead to a fuller appreciation of the magnitude and nature of the neuroplastic events involved in the pathophysiology of mood disorders.⁷⁻⁹ In this perspectives paper, we review these data and discuss their implications not only for changing existing conceptualizations regarding the pathophysiology of MDD, but also for the strategic development of improved therapeutic agents.

Evidence for impairments of structural plasticity and cellular resilience in mood disorders

Positron emission tomography (PET) imaging studies have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic and prefrontal cortex (PFC) structures in mood disorders. These abnormalities implicate limbic-thalamic-cortical and limbic-cortical-striatal-pallidal-thalamic circuits, involving the amygdala, orbital, and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of mood disorders. Interestingly, recent morphometric magnetic resonance imaging (MRI) and postmortem investigations have also demonstrated abnormalities of brain structure that persist independently of mood state and may contribute to the corresponding abnormalities of metabolic activity (discussed in references 2 and 10). Thus, structural imaging studies have demonstrated reduced gray matter volumes in areas of the orbital and medial PFC, ventral striatum, and hippocampus, and enlargement of the third ventricle in mood-disordered samples relative to healthy control samples (*Table I*).¹¹⁻⁷⁷ Complementary postmortem neuropathological studies have shown abnormal reductions in cortex volume, glial cell counts, and/or neuron size in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, and amygdala (*Table II*).^{8,78-84} It is not currently known whether these deficits constitute developmental

abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes per se. Understanding these issues will partly depend upon experiments that delineate the onset of such abnormalities within the illness course and determine whether they antedate depressive episodes in individuals at high familial risk for mood disorders. Nevertheless, the marked reduction in glial cells in these regions has been particularly intriguing in view of the growing appreciation that glia play critical roles in regulating synaptic glutamate concentrations and CNS energy homeostasis, and in releasing trophic factors that participate in the development and maintenance of synaptic networks formed by neuronal and glial processes.^{80,81,85-88} Abnormalities in glial function could thus prove integral to the impairments of structural plasticity and overall pathophysiology of mood disorders.

Stress and glucocorticoids modulate neural plasticity: implications for mood disorders

In developing hypotheses regarding the pathogenesis of these histopathological changes in MDD, the alterations in cellular morphology resulting from various stressors have been the focus of considerable recent research. Thus, although MDD undoubtedly has a strong genetic basis, considerable evidence has shown that severe stressors are associated with a substantial increase in risk for the onset of mood disorders in susceptible individuals. In rodents, certain stressors are capable of producing dendritic atrophy, death, or endangerment (priming the substrate so that it is more vulnerable to other pathophysiological insults) of hippocampal CA3 pyramidal neurons.⁸⁹⁻⁹¹ The extent to which such stress-induced neuronal changes also occur in other brain regions remains unclear. Activation of the hypothalamic-pituitary-adrenal (HPA) axis appears to play a critical role in mediating these effects, since stress-induced neuronal atrophy is prevented by adrenalectomy, and duplicated by exposure to high concentrations of glucocorticoids (reviewed in references 89 to 91). These observations are noteworthy with respect to the pathophysiology of mood disorders, since a significant percentage of patients with MDD display some form of HPA axis activation, and the subtypes of depression most frequently associated with HPA axis activation are those most likely to be associated with hippocampal volume reductions.⁹⁰ A significant percent-

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Table 1. Brain-imaging studies demonstrating volumetric changes suggestive of cell loss/atrophy in mood disorders (including studies that have demonstrated volumetric changes; negative studies are not included).

Study	Subjects	Measurement	Technique	Major finding
Althuler et al, 1991 ¹¹	10 BP patients and 10 controls	Temporal lobe volume	MRI	Smaller temporal lobe volume in BP patients, bilaterally
Andreassen et al, 1990 ¹²	24 BP patients, 27 UP patients with depression, 108 SZ patients, and 75 controls	VBR	CT	Male BP patients had increased VBR. Depressed patients showed no significant difference
Ali et al, 2001 ¹³	26 BP patients	Temporal lobes, HC, V3, areas of lateral ventricles	MRI	Larger V3 associated with a greater number of episodes
Ashtari et al, 1999 ¹⁴	40 UP depressed geriatric patients and 46 controls	HC volume, anterior HC/amygdala complex	MRI	No differences between BP patients and controls. In patients, reduced HC volumes correlated with age and depression ratings
Bakshi et al, 2000 ¹⁵	19 depressed multiple sclerosis patients and 29 nondepressed multiple sclerosis patients	Cortical atrophy, ventricle size, hyperintensities	MRI	Severity of depression was predicted by superior frontal, superior parietal and temporal T1 lesions, lateral and V3 enlargement, and frontal atrophy
Baumann et al, 1997 ¹⁶	23 patients with exogenous depression, 28 patients with neurotic depression, and 56 controls	VBR, V3, frontal sulci, parieto-occipital sulci, interhemispheric fissure, sylvian fissure	CT	Female patients with exogenous depression exhibited widened bilateral upper cortical sulci and V3 enlargement
Beats et al, 1991 ¹⁷	25 elderly MDD (4 BP) patients and controls	Ventricle size, hyperintensities	CT	Larger V3 associated with greater number of episodes, age, and duration of illness
Brambilla et al, 2001 ¹⁸	22 BP patients and 22 controls	Posterior fossa: cerebellum, vermis, brain stem. Brain ventricles	MRI	No differences between BP patients and controls. Age correlated with V3 volume in patients. Number of prior episodes correlated with right lateral ventricle volumes. Familial patients had smaller cerebellar hemispheres and total vermis volumes, and larger left ventricles than nonfamilial patients
Brambilla et al, 2001 ¹⁹	22 BP patients and 22 controls	Caudate and putamen gray matter volumes, globus pallidus total volume	MRI	No differences between BP patients and controls. Age inversely correlated with left putamen volume in patients. Length of illness predicted smaller left putamen volumes
Bremner et al, 2000 ²⁰	16 MDD patients in remission and 16 matched controls	HC, amygdala, caudate, frontal lobe, temporal lobe, and whole brain volumes	MRI	MDD patients had a 19% smaller left HC volume
Coffey et al, 1993 ²¹	48 patients with affective disorder (44 UP, 4 BP) and 76 controls	Cerebral volume, cortical atrophy, ventricle size, hyperintensities	MRI	Affective disorder patients showed decreased frontal lobe volume
Coffman et al, 1990 ²²	30 BP patients and controls	Midsagittal areas, frontal area, and cognitive tasks	MRI	Patients had smaller mean corpus callosum area and tended to have smaller mean frontal area
Dahabra et al, 1998 ²³	23 elderly patients recovered from MDD (12 late-onset and 22 early-onset) and 15 controls	Ventricle size, subcortical white matter lesions	MRI	Patients with late-onset depression had larger V3 and lateral ventricle, and increased VBR than early-onset patients
Dasari et al, 1999 ²⁴	Adolescents: 15 BP patients, 20 SZ patients, and 16 normal controls	Thalamic area	MRI	Reduced thalamic area in patients vs controls. No difference between patient groups
DelBello et al, 1999 ²⁵	16 first-episode BP patients, 14 multiple-episode BP patients, and 15 controls	Cerebellum	MRI	V3 area was significantly smaller in multiple-episode patients compared with first-episode patients or controls
Dewan et al, 1988 ²⁶	26 BP patients and 22 controls	Ventricle size, cortical atrophy, brain density	CT	BP patients had increased V3 width
Dolan et al, 1986 ²⁷	101 patients with UP depression and 52 controls	VBR, cortical atrophy	CT	Depressed patients showed increased sulcal widening and lateral ventricle size
Drevets et al, 1997 ²⁸	21 BP patients, 21 patients with MDD, and 21 healthy controls	Cortex volume of subcallosal anterior cingulate gyrus (subgenual PFC)	MRI	Reduced volume on the left in both BP patients and MDD patients relative to controls
Friedman et al, 1999 ²⁹	Adolescents: 20 SZ patients, 16 BP patients, and 16 controls	Intracranial volume and ventricular and sulcal enlargement	MRI	In the combined SZ/BP group, reduced intracranial volume and increased frontal and temporal sulcal size

Hauser et al, 1989 ³⁰	17 patients with primary affective disorder and 21 controls	Ratio of temporal lobe to cerebral area	MRI	Temporal lobe/cerebral area ratio was smaller in patients than in controls on both left and right
Hauser et al, 2000 ³¹	25 BPI, 22 BP/II patients, and 19 controls	Temporal lobe, HC, and ventricular areas	MRI	Lateral ventricule area and lateral ventricule/cerebrum area ratio were larger in BPI vs BP/II patients or controls in left hemisphere
Hirayasu et al, 1999 ³²	24 first-episode affective disorder patients, 17 first-episode SZ patients, and 20 controls	Subgenual cingulate volume	MRI	Smaller left subgenual cingulate volumes in familial affective disorder patients compared with nonfamilial patients or controls. SZ patients did not differ from controls
Husain et al, 1991 ³³	41 patients with depression and 44 controls	Putamen volume	MRI	Smaller putamen volume in depressed patients; age negatively correlated with putamen size in both patients and controls
Johnstone et al, 1986 ³⁴	19 neurotic patients, 22 manic-depressive outpatients, and 10 manic-depressive inpatients	VBR, lateral ventricular size	CT	19% of manic-depressive patients had VBR more than two SDs above the neurotic mean
Kato et al, 1994 ³⁵	40 BP patients (31 BPI and 9 BP/II) and 60 controls	Ventricular enlargement	MRI	Patients had larger ventricular size than controls
Krishnan et al, 1992 ³⁶	50 patients with depression and 50 controls	Caudate volume, cerebral volume, bicaudate distance, bifrontal distance	MRI	Depressed patients had decreased bilateral caudate volumes
Kumar et al, 1997 ³⁷	28 subjects with late-life MDD, 29 controls, and 34 subjects with probable DAT	CSF volumes, high-intensity signals	MRI	Depressed subjects showed increases in CSF volumes comparable to the DAT group
Kumar et al, 1998 ³⁸	18 patients with late-onset minor depression, 35 patients with late-onset MDD, and 30 controls	Prefrontal brain, temporal brain, whole brain	MRI	Normalized prefrontal lobe volumes showed a significant linear (negative) trend with severity of depression
Kumar et al, 2000 ³⁹	51 patients with late-life MDD and 30 nondepressed controls	Absolute and normalized measures of brain and lesion volumes	MRI	Patients with MDD had significantly smaller frontal lobe volumes
Lai et al, 2000 ⁴⁰	20 elderly MDD patients and 20 controls	Orbital FC	MRI	Reduced right and left orbital FC in patients
Lim et al 1999 ⁴¹	9 BP patients, 9 SZ patients, and 16 controls	Global cortical gray matter, white matter and sulcal CSF, and lateral ventricle and V3 volume	MRI	BP patients had widespread volume deficits for cortical gray matter, but not for cortical white matter, compared with controls, but less than SZ patients
Mervaala et al, 2000 ⁴²	34 drug-resistant MDD patients and 17 controls	Amygdala and HC	MRI	Smaller left HC in patients vs controls. Patients had significant asymmetry in amygdala volume (right smaller than left)
Nasrallah et al, 1982 ⁴³	55 patients with SZ, 24 patients with mania, and 27 controls	VBR	CT	Both SZ and manic patients had greater VBRs than controls; no differences between patient groups
Noga et al, 2001 ⁴⁴	6 pairs of MZ twins discordant for BP disorder and 11 pairs of normal MZ twins	Basal ganglia, amygdala-HC, and cerebral hemisphere volumes	MRI	Right HC was smaller in the sick vs the well BP twins. Less HC asymmetry in the affected vs unaffected BP twin and the normal MZ twins
Pantel et al, 1997 ⁴⁵	19 patients with late-onset MDD, 27 AD patients, and 13 controls	Whole brain, CSF, frontal and temporal lobes, amygdala-HC complex	MRI	Lower whole-brain volume and increased CSF volume and VBR in depressed patients
Parashos et al, 1998 ⁴⁶	72 patients with MDD, 38 controls	Whole brain, whole-brain ratio, frontal, orbitofrontal, frontal ratio, caudate, putamen, thalamus, cerebellum, corpus callosum, lateral ventricles	MRI	Lower volumes of the basal ganglia (caudate and putamen) in depressed patients
Pearlson and Veroff, 1981 ⁴⁷	16 affective disorder patients, 22 SZ patients, and 35 controls	VBR, cortical atrophy	CT	Both SZ and affective disorder patients showed increased VBR
Pearlson et al, 1984 ⁴⁸	27 BP patients and 27 controls	VBR	CT	BP patients had larger VBR than controls, associated with frequent hospitalizations
Pearlson et al, 1989 ⁴⁹	26 elderly patients with depression (including 15 cognitively impaired), 13 AD patients, and 31 controls	VBR, brain density	CT	Depressed patients with cognitive impairment (not depression alone) showed increased VBR and decreased brain density

Table 1. Continued.

Study	Subjects	Measurement	Technique	Major finding
Pillay et al, 1998 ⁵⁰	38 UP depressed patients and 20 controls	Caudate and lenticular nucleus gray matter	MRI	Overall, no difference between depressed patients and controls, but caudate nucleus-gray matter volume and severity of depression were inversely correlated
Rabins et al, 1991 ⁵¹	21 elderly patients with depression, 16 AD patients, and 14 controls	Ventricle size, cortical atrophy, hyperintensities	MRI	Depressed patients had increased cortical atrophy, larger ventricles, and more subcortical hyperintensities
Rabins et al, 2000 ⁵²	14 late-life BP patients; 14 late-life UP MDD, 14 late-onset SZ, and 21 controls	Sylvian fissures, temporal sulci, temporal horns, V3, lateral ventricles, cerebral sulci, periventricular, and deep white matter changes	MRI	Patients with BP and UP disorder had greater left sylvian fissure and left and right temporal sulcal enlargements, and more bilateral cortical atrophy than controls
Roy et al, 1998 ⁵³	22 patients with chronic SZ, 14 BP patients, and 15 controls	Temporal lobes, STG, hemispheres, lateral ventricles, temporal horns, V3	MRI	Both patient groups had significantly larger temporal horn volumes than controls
Sassi et al, 2001 ⁵⁴	23 BP patients, 13 UP patients, and 34 controls	Pituitary volume	MRI	BP patients had smaller pituitary volumes than controls and UP patients
Sax et al, 1999 ⁵⁵	17 patients with mania and 12 controls	Frontosubcortical volume	MRI	Manic patients had smaller prefrontal cortical volumes than controls
Schlegel and Kretschmar, 1987 ⁵⁶	60 affective disorder patients (33 UP, 22 BP [17 depressed, 5 manic], 5 unspecified) and 60 controls	Ventricle size, cortical atrophy	CT	Frontal horns, bicaudate distance, and V3 were enlarged in affective disorder patients
Shah et al, 1992 ⁵⁷	27 MDD patients and 36 controls	Morphology of posterior fossa: medulla, pons, midbrain, anterior and posterior cerebellar vermis, fourth ventricle	MRI	Patients had smaller brain stem, and anterior and posterior cerebellar vermis
Shah et al, 1998 ⁵⁸	20 MDD patients, 20 patients recovered from depression, and 20 controls	Gray matter	MRI	Chronic depression patients showed reduced gray matter density in the left temporal cortex including the HC
Sheline et al, 1996 ⁵⁹	10 depressed patients and 10 controls	HC volume	MRI	Depressed patients had significantly smaller left and right HC volumes
Sheline et al, 1998 ⁶⁰	20 patients with depression and 20 controls	Volume of total amygdala and core amygdala nuclei	MRI	Depressed patients had bilaterally reduced amygdala core nuclei volumes, but no significant difference in total amygdala volumes
Sheline et al, 1999 ⁶¹	24 female patients with depression and 24 controls	HC volume	MRI	Depressed patients had smaller HC volumes bilaterally than controls. HC volume related to duration of depression
Shima et al, 1984 ⁶²	46 depressed (2 BP) patients and 46 controls	VBR	CT	Patients had increased VBR
Shiraishi et al, 1992 ⁶³	45 nondelusional and 29 delusional MDD patients and 77 controls	CAR and VBR	CT	Nondelusional depressed patients had higher CAR than controls. Delusional depressed patients had greater VBR and CAR than nondelusional patients and controls
Simpson et al, 1999 ⁶⁴	44 elderly MDD patients (34 nonpsychotic, 10 psychotic)	Whole brain, lateral ventricle and V3, frontal lobe, parietal lobe, temporal lobe, brain stem, subcortical hyperintensities	MRI	Psychotic patients had more brain stem, frontotemporal atrophy and marked enlargement of the V3 compared with nonpsychotic patients
Simpson et al, 2001 ⁶⁵	44 elderly MDD patients. Response to antidepressants was assessed prospectively	Frontal, temporal, parietal lobes, lateral ventricles	MRI	Trend for smaller frontotemporal volumes in treatment-resistant patients. Ventricular enlargement associated with prior use of ECT and later age at onset of depression. Reduced frontal and parietal lobe volume associated with impaired immediate working memory
Steffens et al, 2000 ⁶⁶	66 geriatric depressed patients and 18 elderly controls	HC volume	MRI	Elderly depressed patients had smaller right HC volume

Strakowski et al, 1993 ⁶⁷	17 patients with first-episode mania and 16 controls	Cerebral hemispheres, lateral ventricle and V3, caudate, thalamus, and cingulate gyrus	MRI	Patients with first-episode mania had significantly larger V3 volumes, possibly increased lateral ventricular volumes and differences in gray/white matter distribution compared with controls
Strakowski et al, 1999 ⁶⁸	24 BP patients and 22 controls	Prefrontal, thalamic, HC, amygdala, pallidum and striatal volumetric measurements	MRI	BP patients demonstrated a significant overall difference in structural volumes in these regions compared with controls
Swayze et al, 1990 ⁶⁹	48 BP patients, 54 SZ patients, and 47 controls	Lateral ventricular volumes, hyperintensities	CT	BP patients had trends towards enlarged lateral ventricles; BP patients with focal hyperintensities showed trends toward larger lateral ventricle size compared with those without focal hyperintensities
Swayze et al, 1992 ⁷⁰	58 SZ and 48 BP patients, and 47 controls	Putamen, caudate, temporal lobe, HC, amygdala	MRI	Smaller right HC in BP patients vs controls
Tanaka et al, 1982 ⁷¹	40 manic-depressive patients and 40 controls	Ventricle size, cortical atrophy, asymmetry	CT	Compared with controls, patients ≥50 years old showed cortical atrophy and patients had reversed cerebral asymmetry
Vakili et al, 2000 ⁷²	38 MDD patients and 20 controls	HC volume	MRI	No differences between patients and controls. Negative correlation between left HC volume and baseline score of depression in men. Responder women had higher right HC volume than nonresponders
Velakoulis et al, 1999 ⁷³	46 patients with chronic SZ, 32 patients with first-episode psychosis, and 140 controls	HC and whole brain volumes	MRI	Patients with first-episode SZ/schizophreniform or affective psychosis had significantly smaller left HC volumes compared with controls
Weinberger et al, 1982 ⁷⁴	23 affective disorder patients, 35 patients with a first schizophreniform episode, 17 chronic SZ patients, 27 patients with other psychiatric diagnoses, and 26 controls	Ventricular size and vermis	CT	Affective patients had vermian atrophy vs other diagnostic groups and controls
Wurthmann et al, 1995 ⁷⁵	34 patients with MDD, 29 patients with degenerative dementia, and 43 controls	Frontal and parieto-occipital sulci, sylvian fissures, lateral ventricle and V3	CT	Predominant left temporal CSF enlargement in patients with depression. Enlargement of the left sylvian fissure was more pronounced in the depressed group than in the demented group. Demented patients showed more generalized brain atrophy
Young et al, 1999 ⁷⁶	30 geriatric patients with manic disorder and 18 controls	Cortical sulcal widening, VBR	CT	Patients had greater cortical sulcal widening scores compared with controls
Zipursky et al, 1997 ⁷⁷	23 patients with SZ, 14 BP patients, and 17 controls	Quantitative measures of CSF gray matter and white matter volumes	MRI	BP patients had larger ventricles than controls

AD, Alzheimer's disease; BP, bipolar; BPI, bipolar type I disorder; CAR, cerebral atrophy ratio; CSF, cerebrospinal fluid; CT, computed tomography; DAT, dementia of the Alzheimer type; ECT, electroconvulsive therapy; FC, frontal cortex; HC, hippocampus; MDD, major depressive disorder; MRI, magnetic resonance imaging; MZ, monozygote; PFC, prefrontal cortex; STG, superior temporal gyrus; SZ, schizophrenia; UP, unipolar; V3, third ventricle; VBR, ventricle/brain ratio.
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↓ Volume/cortical thickness
<ul style="list-style-type: none">• Cortical thickness rostral orbital FC, MDD• Volume of subgenual PFC in familial MDD and BD• Laminar cortical thickness in layers III, V, and VI in subgenual anterior cingulate cortex in BD• Volumes of NAcc (left), basal ganglia (bilateral) in MDD and BD• Parahippocampal cortex size in suicide
↓ Neurons
<ul style="list-style-type: none">• Pyramidal neuronal density, layers III and V in dorsolateral PFC in BD• Nonpyramidal neuronal density in layer II (-27%) in anterior cingulate cortex in BD• Neuronal density and size in layer II/III in rostral orbital FC in MDD• Neuronal size in layer VI (-23%) in anterior cingulate cortex in MDD• Neuronal density in layer III, V, and VI in subgenual anterior cingulate cortex in BD• Layer-specific interneurons in anterior cingulate cortex in BD and MDD• Nonpyramidal neuron density in the CA2 region in BD
↓ Glia
<ul style="list-style-type: none">• Density/size of glia in dorsolateral PFC and caudal orbital FC, in MDD and BD; layer-specific• Glial (but not neuron) number in subgenual PFC in familial MDD (-24%) and BD (-41%)• Glial cell density in layer VI (-22%) in anterior cingulate cortex in MDD• Glial cell counts, glial density, and glia-to-neuron ratios in amygdala

Table II. Postmortem morphometric brain studies in mood disorders demonstrating cellular atrophy and/or loss.^{8,78-84} NAcc, nucleus accumbens; FC, frontal cortex; BD, bipolar disorder; MDD, major depressive disorder; PFC, prefrontal cortex. Modified and reproduced from reference 10: Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorder: implications for the development of novel therapeutics. *Psychopharmacol Bull.* 2001;35:5-49. Copyright © MedWorks Media LLC.

age of patients with Cushing's disease, in which pituitary gland adenomas result in cortisol hypersecretion, are also known to manifest prominent depressive symptoms, as well as hippocampal atrophy. Furthermore, some patients with Cushing's disease show a reduction in hippocampal volume that correlates inversely with plasma cortisol concentrations; following corrective surgical treatment, enlargement of hippocampal volume is observed in proportion to the treatment-associated decrement in urinary free cortisol concentrations.^{92,93}

In addition to directly causing neuronal atrophy, stress and glucocorticoids also appear to reduce cellular resilience, thereby making certain neurons more vulnerable to other insults, such as ischemia, hypoglycemia, and excitatory amino acid toxicity.⁹⁰ Thus, recurrent stress (and presumably recurrent MDD episodes, which are often associated with hypercortisolemia) may lower the threshold for cellular death/atrophy in response to a variety of physiological (eg, aging) and pathological events. Such processes may conceivably also play a role in the relationship between mood disorders and cerebrovascular events, considering that individuals who develop their first depressive episode in late

life have an increased likelihood of showing MRI evidence of cerebrovascular disease.^{39,94-98}

The precise mechanisms by which glucocorticoids exert these deleterious effects on the hippocampus remain to be fully elucidated, but likely involve the inhibition of glucose transport (thereby diminishing capability of energy production, leading to a cellular failure to handle increasing "loads"), and the facilitation of glutamatergic signaling.⁹⁰ The latter observation is noteworthy since, as we discuss below, there is increasing evidence for an association between alterations of brain glutamatergic neurotransmission and the pathophysiology of mood disorders.

The role of the glutamatergic system in the pathophysiology and treatment of mood disorders

Although somewhat overlooked due to a monoaminergic preoccupation, there has been evidence for a possible role of the glutamatergic system in mood disorders since the 1950s, when D-cycloserine, a partial agonist at the N-methyl-D-aspartate (NMDA) receptor glycine site

(used as a part of multidrug antituberculosis treatment) was reported to have mood-elevating effects.⁹⁹ The beneficial effects of D-cycloserine at doses of 500 mg/day occurred in a high proportion of the patient studies with respect to depressed mood, insomnia, and reduced appetite (as discussed in reference 100). Although D-cycloserine clearly exerts multiple pharmacologic effects at the doses employed to treat tuberculosis, it has mild acute, dose-related euphoric and amnesic effects in humans that resemble the effects of subperceptual doses of noncompetitive NMDA antagonists.¹⁰⁰ Thus, it has been suggested that the antidepressant effects of D-cycloserine may reflect consequences of its capacity to reduce NMDA receptor function.¹⁰⁰

Since these early serendipitous clinical observations, a growing body of preclinical and clinical research suggests that the NMDA class of glutamate receptors may be involved in the pathophysiology of MDD and the mechanism of action of antidepressants (*Table III*).¹⁰¹⁻¹²² NMDA receptor antagonists such as dizocilpine and AP-7 (2-amino-7-phosphonoheptanoic acid), and an α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor potentiator, the biarylpropylsulfonamide LY392098, have demonstrated antidepressant effects in animal models of depression (including the application of inescapable stressors, forced-swim, and tail suspension-induced immobility tests), in learned-helplessness models of depression, and in animals exposed to a chronic mild stress procedure (reviewed in references 100 and 121). In some of these studies, NMDA receptor antagonists had dose-related effects that were comparable in magnitude, but more rapid, than imipramine. Moreover, chronic administration of “conventional” antidepressants has been shown to affect NMDA receptor function^{100,121,123} and NMDA receptor-binding profiles, and to regionally alter expression of mRNA that encode multiple NMDA receptor subunits.^{100,121,123-125}

Recently, Berman et al¹⁰⁹ reported the first placebo-controlled, double-blind trial assessing the treatment effects of a single dose of an NMDA receptor antagonist, ketamine, in 7 patients with depression. The ketamine infusion produced mild psychosis and euphoria that dissipated within 120 min. In contrast, the antidepressant effects of ketamine infusion emerged over the first 180 min and persisted over 72 h. Within this intriguing study, some patients reported antidepressant effects lasting as long as a week.^{100,109} Similarly, several case reports and open studies have reported the efficacy of lamotrigine

(which among other effects, robustly reduces glutamate release) in bipolar depression. A randomized, placebo-controlled, 7-week study comparing two doses of lamotrigine with placebo in 195 patients with moderate-to-severe bipolar depression has now been completed. Lamotrigine was superior to placebo after 3 weeks as assessed by changes on the Montgomery-Åsberg Depression Rating Scale (MADRS).¹⁰⁸

Overall, the data suggest that regionally selective abnormally enhanced glutamatergic functioning—either primary or secondary to enhanced glucocorticoid release—may contribute to the impairment of neuroplasticity and cellular resilience observed in mood disorders. More importantly for the present discussion, although quite preliminary, the existing data suggest that medications that attenuate glutamatergic functioning (and perhaps more specifically, NMDA throughput) may possess antidepressant effects.^{100,121} Ongoing studies investigating the putative antidepressant effects of riluzole (which reduces glutamate release) and memantine (an NMDA antagonist) may ultimately lead to the development of novel antidepressant strategies targeting the glutamatergic system.

The role of the neurotrophic signaling cascades in the pathophysiology and treatment of mood disorders

The reduction in neuroplasticity and cellular resilience may also reflect the propensity for various stressors (and potentially mood disorders) to decrease the expression of neurotrophic factors.^{7-9,126,127} Neurotrophins are a family of regulatory factors that mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity. Neurotrophins can be secreted constitutively or transiently, and often in an activity-dependent manner.¹²⁷ Recent observations support a model wherein neurotrophins are secreted from the dendrite and act in a retrograde manner at presynaptic terminals, where they act to induce long-lasting modifications. Within the neurotrophin family, brain-derived neurotrophic factor (BDNF) is a potent physiological survival factor, which has also been implicated in a variety of pathophysiological conditions, such as Parkinson's disease, Alzheimer's disease, and diabetic peripheral neuropathy.¹²⁷ BDNF and other neurotrophic factors are necessary for the survival and function of neurons,¹²⁸ implying that a sustained reduction of these factors could affect neuronal viability. Although endoge-

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Reference	Measurement	Finding
Clinical studies		
Mathis et al, 1988 ¹⁰¹	Plasma levels of gln and other aa	Higher gln level in 59 depressed patients (49 MDD, 20 BP) than controls
Holemans et al, 1993 ¹⁰²	Binding of [³ H]dizocilpine sites	No changes in binding in 22 depressed, medication-free suicide victims, in cortex, hippocampus, thalamus, or basal ganglia. Negative correlation between age and NMDA receptor binding in FC of suicide victims
Altamura et al, 1993 ¹⁰³	Plasma and platelet levels of glu	Increased plasma and decreased platelet level in medication-free depressed patients (4 MDD, 11 BP) versus controls
Altamura et al, 1995 ¹⁰⁴	Plasma levels of gly, glu	Lower in 25 medication-free MDD patients than controls
Nowak et al, 1995 ¹⁰⁵	High-affinity glycine displaceable [³ H]CGP39653 binding to glu receptors	Reduced binding in suicide victims (50% of them depressed) vs controls, in FC. No difference in [³ H]dizocilpine binding
Mauri et al, 1998 ¹⁰⁶	Plasma and platelet levels of glu, asp, and other aa	Higher glu plasma level and asp platelet level in 29 MDD patients than controls, not altered by fluvoxamine
Maes et al, 1998 ¹⁰⁷	Plasma levels of asp and other aa	No differences between patients and control. Lower asp level in MDD patients who were nonresponders to antidepressant treatment for 5 weeks. Treatment reduced levels of asp and glu, and increased gln
Calabrese et al, 1999 ¹⁰⁸	Antidepressant response to lamotrigine (double-blind, placebo-controlled study)	Significant antidepressant efficacy in 195 depressed BPI patients
Berman et al, 2000 ¹⁰⁹	Antidepressant response to ketamine (double-blind, placebo-controlled study)	Improvement of symptoms in depressed patients (8 MDD, 1 BP) lasted longer (3 days) than euphoric effects (hours)
Castillo et al, 1999 ¹¹⁰	glu/gln ratio measured by MRS	Elevated in frontal lobe and basal ganglia in BP medication-free children vs controls in FC, temporal cortex, and basal ganglia
Auer et al, 2000 ¹¹¹	Levels of glu measured by MRS	Decreased in anterior cingulate cortex of depressed patients (1 BP, 18 MDD) vs controls (7 patients were medication-free and 12 on antidepressants)
Levine et al, 2000 ¹¹²	CSF gln levels	Elevated in medication-free depressed patients vs control (2 BP, 16 MDD) and correlated with CSF Mg level
Berk et al, 2001 ¹¹³	Platelet intracellular calcium response to glu stimulation	Greater in 15 MDD medication-free patients than controls
Meador-Woodruff et al, 2001 ¹¹⁴	NMDA mRNA subunit levels in striatum	Postmortem brain analysis. Only NR2D (a subunit of the NMDA receptor) mRNA is higher in BP (15) vs MDD (15). Only gluR1 (a subunit of the AMPA receptor) mRNA is lower in BP vs controls (15). [³ H]AMPA binding was higher in BP than MDD
Relevant preclinical studies		
Trullas and Skolnick, 1990 ¹¹⁵		Competitive NMDA antagonist AP-7, noncompetitive antagonist dizocilpine, and a partial agonist at strychnine-insensitive glycine receptors ACPC mimicked the effects of clinically effective antidepressants in inescapable stress model in rats
Skolnick et al, 1996 ¹¹⁶		Chronic (14 days) antidepressant administration (17 different antidepressants, especially imipramine, citalopram, and ECT) cause adaptive changes in radioligand binding to NMDA (CGP39653, DCKA, and [³ H]dizocilpine) in mice
Nowak et al, 1996 ¹¹⁷		Chronic citalopram in mouse lowered 6.2-fold high-affinity gly-displaceable [³ H]CGP39653 binding to glu receptors, reduced 1.5-fold the potency of gly to inhibit [³ H]DCKA binding in cortex. Also increases asp concentration 110% in cortex and 33% in hippocampus
Boyer et al, 1998 ¹¹⁸		Chronic administration (16 days) of citalopram in mouse lowered NMDA ϵ 1-subunit mRNA level in FC, CA2 of hippocampus, and amygdala, whereas imipramine only does so in amygdala. Imipramine lowered NMDA ϵ 2-subunit mRNA level in cortex, CA1-4 of hippocampus, and amygdala, whereas citalopram only does so in amygdala. Both drugs reduce transcript levels of ζ -subunit in cortex, thalamus, striatum, and cerebellum
Bouron and Chatton, 1999 ¹¹⁹		Desipramine enhanced spontaneous vesicular release of glu in hippocampal neurons dissociated from neonatal rats
Michael-Titus et al, 2000 ¹²⁰		Imipramine and phenelzine decreased stimulated (K-induced) glu outflow in rat PFC and not in striatum
Chen et al, 2001 ¹²¹		Ketamine pretreatment attenuated ECS-induced mossy fiber sprouting in dentate gyrus and BDNF expression in medial PFC and the dentate gyrus in rats
Li et al, 2001 ¹²²		AMPA receptor potentiator LY392098 (a biarylpropylsulfonamide) produced antidepressant-like effect in rats and mice

Table III. Evidence for abnormalities in glutamatergic function in mood disorders. aa, amino acid; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; asp, aspartate; BDNF, brain-derived neurotrophic factor. BP, bipolar patients; BPI, bipolar type I disorder; CSF, cerebrospinal fluid; DCKA, dichlorokynurenic acid; ECS, electroconvulsive shock; ECT, electroconvulsive therapy; FC, frontal cortex; gln, glutamine; glu, glutamate; gly, glycine; MDD, major depressive disorder; MRS, magnetic resonance spectroscopy; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex.

nous neurotrophic factors have traditionally been viewed as increasing cell survival by providing necessary trophic support, it is now clear that their survival-promoting effects are mediated in large part by an inhibition of cell death cascades.¹²⁹ Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the mitogen-activated protein (MAP) kinase signaling pathway and the phosphatidylinositol-3 kinase (PI-3K)/Akt pathway (Figure 1).¹³⁰ One important mechanism by which the MAP kinase signaling cascades inhibits cell death is by increasing the expression of the antiapoptotic protein bcl-2.^{131,132} The neurotrophic factor/MAP kinase/bcl-2 signaling cascade may thus play a critical role in cell survival in the CNS, since there is a very fine balance maintained between the levels and activities of pro- and antiapoptotic factors; modest changes in this signaling cascade or in the levels of the bcl-2 family of proteins (potentially due to genetic, or illness- or insult-related factors) may therefore profoundly affect cellular viability.^{133,134}

In addition to regulating synaptic efficacy, BDNF appears to function as a modulator that is required for the induction, expression, and/or maintenance of LTP. Thus, genetic deletion of BDNF in mice disrupts normal induction of LTP, which can be rescued by reintroducing BDNF either by transfecting hippocampal slices with BDNF-expressing adenovirus or the exogenous administration of BDNF.¹²⁷ The information reviewed here clearly shows that neurotrophin signaling cascades play a major role in regulating various forms of neuronal and synaptic plasticity, as well as neuronal survival—all of which may be impaired in severe recurrent mood disorders. We now turn to a discussion of the evidence that neurotrophic signaling cascades are long-term targets for antidepressants and mood stabilizers.

Influence of antidepressant treatment on cell survival pathways

In an extensive series of studies, Duman and associates have demonstrated that the cyclic adenosine monophosphate (cAMP)–cAMP response element binding protein (CREB) cascade—an important pathway involved in cell survival and plasticity—is upregulated by chronic antidepressant treatment, in a timeframe that parallels clinical response.^{7,135-138} The results include increased coupling of the stimulatory G-protein, G_s, to adenylyl cyclase, increased protein kinase A (PKA) activity in the partic-

ulate fraction of limbic structures, increased PKA levels in the nuclear fractions of cerebral cortex, and increased mRNA expression of the type 1 adenylyl cyclase in the rat hippocampus.^{7,135}

The same workers have found that chronic administration of different classes of antidepressants—SSRIs (fluoxetine and sertraline), a selective norepinephrine reuptake inhibitor (desipramine), a dual aminergic reuptake inhibitor (imipramine)—and chronic electroconvulsive seizures upregulate the expression of CREB.^{7,135} By contrast, the nonantidepressant psychotropic drugs cocaine and haloperidol, did not influence CREB mRNA expression indicating the specificity of CREB induction to antidepressants. Chronic administration of these antidepressants has also been demonstrated to increase mRNA and protein levels of the cAMP-specific phosphodiesterase PDE4 isozymes, PDE4A and PDE4B, in rat frontal cortex (FC) and hippocampus.^{7-10,135} The upregulation of PDE4 gene expression in response to sustained activation of the cAMP–CREB cascade likely represents a compensatory adaptation that would reduce cAMP levels back to baseline. As we discuss below, inhibition of specific phosphodiesterases may thus represent a new strategy for developing novel agents for the treatment of depression.

One way in which CREB can mediate antidepressant-induced neural plasticity is by regulating target genes that are essential for maintaining synaptic function and cell survival, most notably BDNF.^{7-10,135} Several studies have shown that chronic administration of different types of antidepressant increases the expression of BDNF in limbic brain areas, particularly the hippocampus, and blocks the stress-induced downregulation of BDNF in the hippocampus.^{7-10,135} The possibility that increased expression of BDNF may contribute to the therapeutic effects of antidepressants is supported by the rodent behavioral studies in which direct infusion of BDNF into the rat midbrain showed efficacy in the learned-helplessness and forced-swim “depression behavioral models.”^{77-10,135} Although the human post-mortem studies are quite limited and subject to numerous methodological confounds, they have revealed increased BDNF levels in hippocampal regions in subjects treated with antidepressant medications at the time of death, compared with unmedicated subjects.¹³⁹

As discussed above, BDNF is known to play a major role in regulating structural plasticity. Do antidepressants, via effects on this major growth factor, actually

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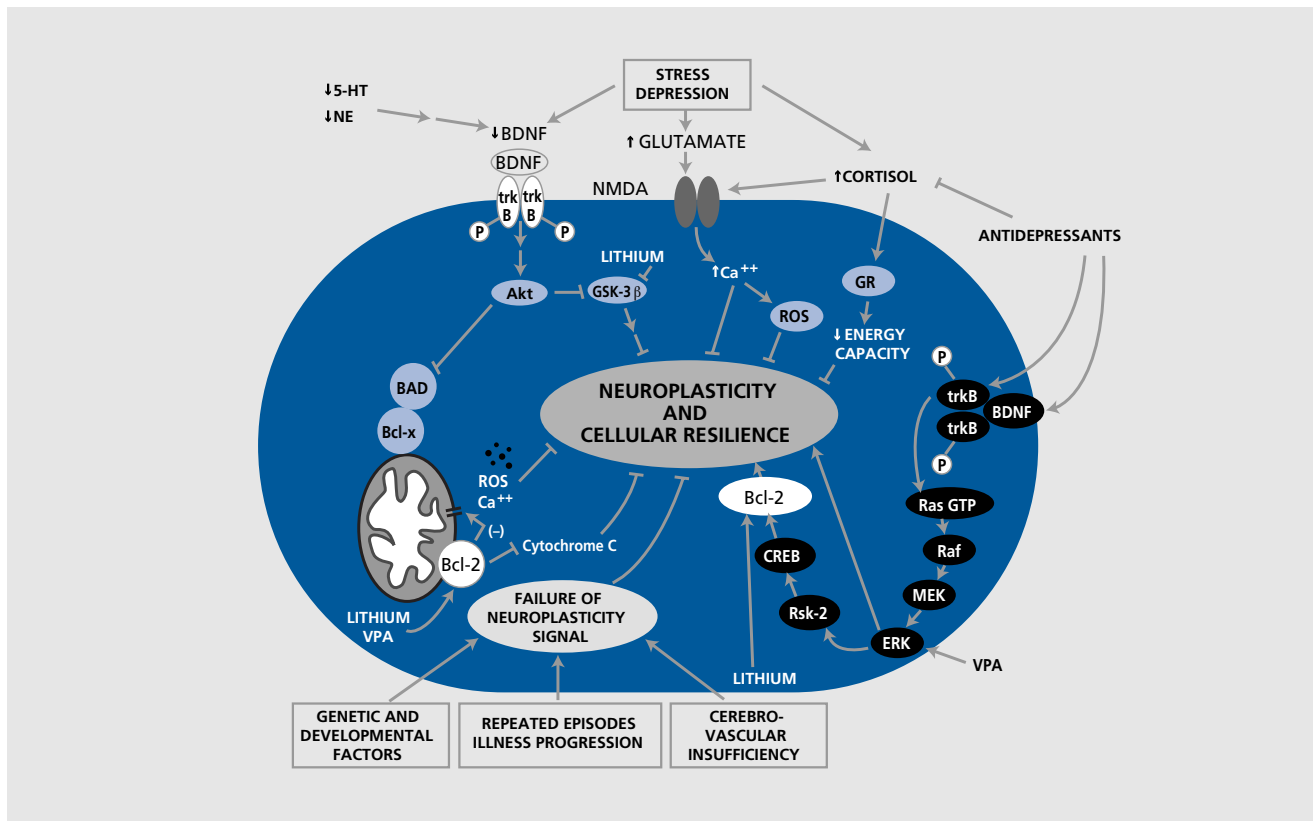


Figure 1. Neuroplasticity and cellular resilience in mood disorders. There are multiple influences on neuroplasticity and cellular resilience in mood disorders. Genetic/neurodevelopmental factors, repeated affective episodes, and illness progression may all contribute to the impairments of cellular resilience, volumetric reductions, and cell death/atrophy observed in mood disorders. Stress and depression likely contribute to impairments of cellular resilience by a variety of mechanisms, including reductions in the levels of brain-derived neurotrophic factor (BDNF), facilitating glutamatergic transmission via *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors, and reducing the cell's energy capacity. Neurotrophic factors such as BDNF enhance cell survival by activating two distinct signaling pathways: the phosphatidylinositol-3 (PI-3) kinase pathway, and the extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase pathway. One of the major mechanisms by which BDNF promotes cell survival is by increasing the expression of the major cytoprotective protein, bcl-2. Bcl-2 attenuates cell death via a variety of mechanisms, including impairing the release of calcium and cytochrome C, and by sequestering proforms of death-driving cysteine proteases (called caspases), and by enhancing mitochondrial calcium uptake. The chronic administration of a variety of antidepressants increases the expression of BDNF, and its receptor trkB. Lithium and valproic acid (VPA) robustly upregulate the cytoprotective protein bcl-2. Lithium and VPA also inhibit glucocorticoid synthase kinase (GSK-3 β), biochemical effects shown to have neuroprotective effects. VPA also activates the ERK MAP kinase pathway, effects which may play a major role in neurotrophic effects and neurite outgrowth. trkB, tyrosine kinase receptor for BDNF; NGF, nerve growth factor; Bcl-2 and Bcl-x, antiapoptotic members of the bcl-2 family; BAD and Bax, proapoptotic members of the bcl-2 family; Ras, Raf, MEK, ERK, components of the ERK MAP kinase pathway; CREB, cyclic adenosine monophosphate (cAMP) response element binding protein; Rsk-2, ribosomal S-6 kinase; ROS, reactive oxygen species; GR, glucocorticoid receptor; 5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; GTP, guanine triphosphate; Akt, a serine-threonine kinase member of the phosphatidylinositol-3 kinase pathway.

Modified and reproduced from reference 130: Moore GJ, Bechuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet*. 2000;356:1241-1242. Copyright © 2000, Elsevier Science.

bring about structural changes in the brain? Because the dendrite is the dynamic compartment of neuronal cell body processes that forms synapses with other neurons, these changes in its spine density could dramatically alter neurotransmission, synaptic function, and ultimately, neural plasticity.^{7-10,135} In this context, an important study demonstrated that chronic administration of

tianeptine (an antidepressant that *facilitates* serotonin reuptake) blocked stress-induced dendritic remodeling of hippocampal CA3 pyramidal neurons.¹³⁹ However, precluding the generalizability to all antidepressants is the observation that chronic fluoxetine and fluvoxamine treatment (more traditional antidepressants that inhibit serotonin reuptake) had no influence on dendritic

remodeling.¹⁴⁰ More recently, the influence of chronic antidepressant treatment on neurogenesis of hippocampal neurons has been examined.^{7,135} Chronic, but not acute, antidepressant treatment was found to increase the number of new cells in the dentate gyrus granule cell layer. Furthermore, these effects were observed with different classes of antidepressants, but not with several other psychotropic medications investigated.^{7,135} A very recent detailed study investigated the effects of tianeptine in the chronic psychosocial stress model of depression in adult male tree shrews.¹⁴¹ Animals were subjected to a 7-day period of psychosocial stress to elicit stress-induced endocrine and CNS alterations before the onset of daily oral administration of tianeptine (50 mg/kg). The psychosocial stress continued throughout the treatment period of 28 days. The proliferation rate of the granule precursor cells in the dentate gyrus was reduced (-33%) by stress, effects that were prevented by the simultaneous administration of tianeptine yielding normal values. In stressed animals treated with tianeptine, hippocampal volume increased above the small decrease produced by stress alone. While these effects of tianeptine are intriguing indeed, a detailed study using several different classes of antidepressants is clearly needed to determine the precise influence of antidepressants on dendritic remodeling and synaptic function.

In toto, although some of the evidence is correlational rather than clearly causal, the evidence indicates that BDNF is associated with an antidepressant response and its induction may represent a key strategy for developing novel antidepressant medication. In this context, a subtle mechanism to facilitate antidepressant-induced increase in CREB/BDNF expression/function may be by the use of cAMP-specific PDE4 inhibitors. Indeed, the possibility that inhibitors of this enzyme have antidepressant efficacy is supported by older studies with rolipram, a relatively selective inhibitor of PDE4. Rolipram is reported to have efficacy in clinical trials and in preclinical models of depression, but it also produces intolerable nausea.⁷ Molecular cloning studies demonstrate that there are four separate PDE4 genes, three of which are expressed in brain (PDE4A, PDE4B, and PDE4D). Current evidence suggests that PDE4A and PDE4B may be relevant targets for development of selective inhibitors.⁷⁻¹⁰ Studies are currently underway in PDE4A, PDE4B, and PDE4D null mutant mice, as well as with more selective inhibitors, to further validate these PDE4 isozymes as targets of antidepressant treatments.⁷⁻¹⁰

Mood stabilizers regulate the MAP kinase signaling cascade

As discussed above, several endogenous growth factors—including nerve growth factor (NGF) and BDNF—exert many of their neurotrophic effects via the MAP kinase signaling cascade. In view of the important role of MAP kinases in mediating long-term neuroplastic events, it is noteworthy that lithium and valproic acid (VPA), at therapeutically relevant concentrations, have recently been demonstrated to robustly activate the extracellular signal-regulated kinase (ERK) MAP kinase cascade in rat FC and hippocampus, as well as in human neuroblastoma SH-SY5Y cells (*Figure 1*).^{39,52,127,142} Since the ERK MAP kinases are known to mediate many of the effects of various neurotrophic factors and to promote neurite outgrowth,^{132,143} VPA's effects on the morphology of human neuroblastoma cells have been examined in detail. Human neuroblastoma SH-SY5Y cells exposed to VPA (1.0 mM) in serum-free media for 5 days exhibited prominent growth cones and dramatic neurite outgrowth. Growth cone-associated protein-43 (GAP-43) is a protein expressed at elevated levels during neurite growth during development or regeneration, and a >3-fold increase in GAP-43 levels was observed after 5 days' VPA exposure.^{127,142} Follow-up studies have recently shown that, similar to the effects observed in neuroblastoma cells in vitro, chronic lithium or VPA also robustly increases the levels of activated ERK in areas of brain that have been implicated in the pathophysiology and treatment of BD: the FC and hippocampus.¹⁴² Interestingly, neurotrophic factors are now known to promote cell survival by activating MAP kinases to suppress intrinsic, cellular apoptotic machinery, *not* by inducing cell survival pathways (see above).^{129,131-134,144-146} Thus, a downstream target of the MAP kinase cascade, ribosomal S-6 kinase (Rsk) phosphorylates CREB and this leads to induction of bcl-2 gene expression (*Figure 1*). Recent studies have therefore undertaken to determine if lithium or VPA regulates the expression of bcl-2. Chronic treatment of rats with "therapeutic" doses of lithium and VPA produced a doubling of bcl-2 levels in FC, effects that were primarily due to a marked increase in the number of bcl-2 immunoreactive cells in layers II and III of FC.¹⁴⁷⁻¹⁴⁹ Interestingly, the importance of neurons in layers II to IV of the FC in mood disorders has recently been

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emphasized, since primate studies indicate that these areas are important for providing connections with other cortical regions, and that they are targets for subcortical input.¹⁵⁰ Chronic lithium also markedly increased the number of bcl-2 immunoreactive cells in the dentate gyrus and striatum¹⁴⁴; and detailed immunohistochemical studies following chronic VPA treatment are currently underway. Subsequent to these findings, it has been demonstrated that lithium also increases bcl-2 levels in C57BL/6 mice,¹⁴⁶ in neuroblastoma SH-SY5Y cells (human neuronal origin) in vitro,¹⁵¹ and in rat cerebellar granule cells in vitro.¹⁵² The latter study was undertaken as part of investigations into the molecular and cellular mechanisms underlying the neuroprotective actions of lithium against glutamate excitotoxicity (see below). These investigators found that lithium produced a remarkable increase in bcl-2 protein and mRNA levels. Moreover, lithium has recently been demonstrated to reduce the levels of the proapoptotic protein p53 both in cerebellar granule cells¹⁵² and in neuroblastoma SH-SY5Y cells.¹⁵³ Thus, overall, the data clearly show that chronic lithium robustly increases the levels of the neuroprotective protein bcl-2 in areas of rodent FC, hippocampus, and striatum in vivo, and in cultured cells of both rodent and *human neuronal origin* in vitro. Furthermore, at least in cultured cell systems, lithium has also been demonstrated to reduce the levels of the proapoptotic protein p53.

Consistent with bcl-2's known cytoprotective effects, lithium, at therapeutically relevant concentrations, has been shown to exert neuroprotective effects in a variety of preclinical paradigms. Thus, lithium has been demonstrated to protect against the deleterious effects of glutamate, NMDA receptor activation, aging, serum/NGF deprivation, ouabain, thapsigargin (which mobilizes intracellular methlphenylpyridinium (MPP⁺), Ca²⁺), and β -amyloid in vitro.¹⁴⁹ More importantly, lithium's neurotrophic and cytoprotective effects have also been demonstrated in rodent brain in vivo. Thus, lithium treatment has been shown to attenuate the biochemical deficits produced by kainic acid infusion, ibotenic acid infusion, and forebrain cholinergic system lesions,^{149,154,155} to exert dramatic protective effects against middle cerebral artery occlusion,¹⁵⁶ and to enhance hippocampal neurogenesis in the adult rodent hippocampus.¹⁵⁷ The potential therapeutic relevance of these preclinical findings is discussed below.

Human evidence for the neurotrophic effects of mood stabilizers

While the body of preclinical data demonstrating neurotrophic and neuroprotective effects of lithium is striking, considerable caution must clearly be exercised in extrapolating to the clinical situation with humans. In view of lithium and VPA's robust effects on the levels of the cytoprotective protein bcl-2 in the FC, Drevets and associates²⁸ reanalyzed older data demonstrating approximately 40% reductions in subgenual PFC volumes in familial mood disorder subjects. Consistent with neurotrophic/neuroprotective effects of lithium and VPA, they found that the patients treated with chronic lithium or VPA exhibited subgenual PFC volumes, which were significantly higher than the volumes in non-lithium-treated or VPA-treated patients, and not significantly different from controls.¹⁵⁸

Although the results of the study by Drevets¹⁵⁸ suggest that mood stabilizers may have provided neuroprotective effects during naturalistic use, considerable caution is warranted in view of the small sample size and cross-sectional nature of the study. To investigate the potential neurotrophic effects of lithium in humans more definitively, a longitudinal clinical study was recently undertaken using proton magnetic resonance spectroscopy (MRS) to quantify *N*-acetylaspartate (NAA, a putative marker of neuronal viability) levels. It was found that chronic lithium administration at therapeutic doses increases NAA concentration in the human brain in vivo.¹⁵⁹ These findings provide intriguing indirect support for the contention that, similar to the findings observed in the rodent brain and in human neuronal cells in culture, chronic lithium increases neuronal viability/function in the human brain. Furthermore, a striking approximately 0.97 correlation between lithium-induced NAA increases and regional voxel gray matter content was observed,¹⁵⁹ thereby providing evidence for colocalization with the region-specific bcl-2 increases observed in the rodent brain cortices (eg, gray versus white matter). These results suggest that chronic lithium may exert not only robust neuroprotective effects (as has been demonstrated in a variety of preclinical paradigms), but also neurotrophic effects in humans.

In follow-up studies to the NAA findings, it was hypothesized that, in addition to increasing functional neurochemical markers of neuronal viability, lithium-induced increases in bcl-2 would also lead to neuropil increases,

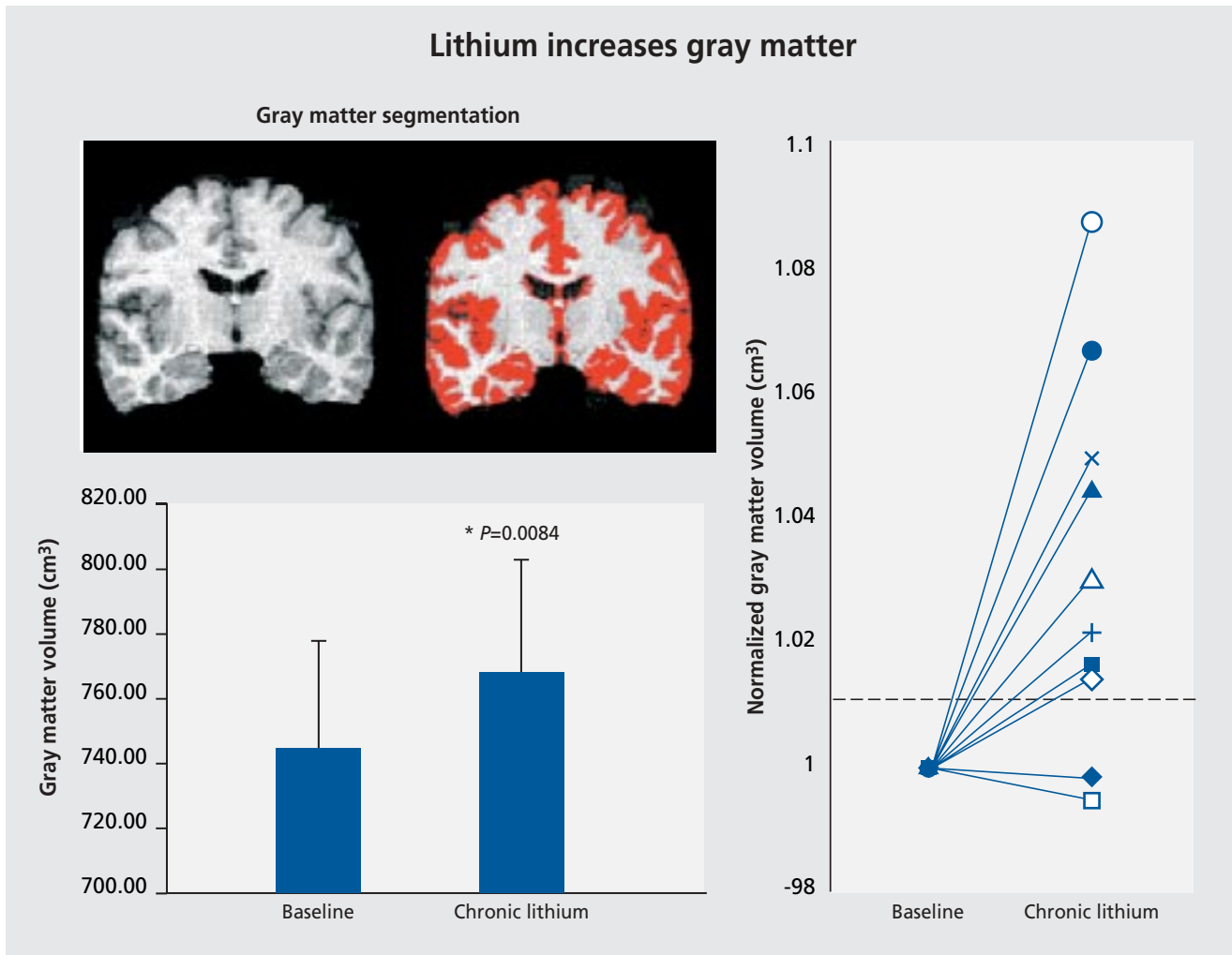


Figure 2. Brain matter is increased following 4 weeks of lithium administration at therapeutic levels in bipolar disorder patients. A slice of brain tissue volumes using high-resolution three-dimensional magnetic resonance imaging (MRI) (124 images, 1.5-mm thick coronal T₁ weighted spoiled gradient (SPGR) images), and validated quantitative brain tissue segmentation methodology to identify and quantify the various components by volume, including total brain white and gray matter content. Measurements were made at baseline (medication-free, after a minimum 14-day washout) and then repeated after 4 weeks of lithium at therapeutic doses. Chronic lithium significantly increases total gray matter content in the human brain of patients with bipolar disorder. No significant changes were observed in white matter volume, or in quantitative measures of regional cerebral water.

Modified and reproduced from reference 2: Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. *Nat Med.* 2001;7:541-547. Copyright © 2001, Nature Publishing Company.

and thus to increased brain gray matter volume in patients with bipolar disorder. In this clinical research investigation,¹³⁰ brain tissue volumes were examined using high-resolution three-dimensional MRI and validated quantitative brain tissue segmentation methodology to identify and quantify the various components by volume, including total brain white and gray matter content. Measurements were made at baseline (medication-

free, after a minimum 14-day washout) and then repeated after 4 weeks of lithium at therapeutic doses. This study revealed that chronic lithium significantly increases *total gray matter content* in the human brain of patients with bipolar disorder (*Figure 2*).¹³⁰ No significant changes were observed in brain white matter volume or in quantitative measures of regional cerebral water content, thereby providing strong evidence that the observed

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increases in gray matter content are likely due to neurotrophic effects as opposed to any possible cell swelling and/or osmotic effects associated with lithium treatment. A finer-grained subregional analysis of this brain imaging data is ongoing, and suggests that lithium produces a regionally selective increase in gray matter, with prominent effects being observed in hippocampus and caudate (unpublished observations).

Concluding remarks: implications for development of new medications

As discussed, there is a considerable body of evidence both conceptually and experimentally in support of the regulation of signaling cascades regulating synaptic plasticity and cellular resilience in the treatment (and potentially pathophysiology) of mood disorders. Regulation of signal transduction within critical regions of the brain affects the intracellular signal generated by multiple neurotransmitter systems; these effects thus represent attractive putative mediators of the pathophysiology of mood disorders and the therapeutic actions of antidepressants and mood stabilizers.

It is also becoming increasingly clear that, for many refractory mood disorder patients, new drugs that simply mimic many “traditional” drugs, which directly or indirectly alter neurotransmitter levels, and those which bind to cell surface receptors may be of limited benefit. This is because such strategies implicitly assume that the target receptor(s)—and downstream signal mediators—are functionally intact, and that altered synaptic activity will thus be transduced to modify the postsyn-

naptic “throughput” of the system. However, the possible existence of abnormalities in signal transduction pathways suggests that, for patients refractory to conventional medications, improved therapeutics may only be obtained by the direct targeting of postreceptor sites. Recent discoveries concerning a variety of mechanisms involved in the formation and inactivation of second messengers offers the promise for the development of novel pharmacological agents designed to target signal transduction pathways.

Although clearly more complex than the development of receptor-specific drugs, it may be possible to design novel agents to selectively affect second messenger systems, because they are quite heterogeneous at the molecular and cellular level, are linked to receptors in a variety of ways, and are expressed in different stoichiometries in different cell types. Additionally, since signal transduction pathways display certain unique characteristics depending on their activity state, they offer built-in targets for relative specificity of action, depending on the “set-point” of the substrate. It is also noteworthy that a variety of strategies to enhance neurotrophic factor signaling are currently under investigation. An increasing number of strategies are being investigated to develop small molecular switches for protein–protein interactions, which have the potential to regulate the activity of growth factors, MAP kinase cascades, and interactions between homo- and heterodimers of the bcl-2 family of proteins⁶⁰; this progress holds much promise for the development of novel therapeutics agents for the long-term treatment of severe mood disorders, and for improving the lives of millions. □

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El aumento de la plasticidad sináptica y de la resiliencia celular como medio para desarrollar originales y mejores terapias para los trastornos del ánimo

Existe una evidencia creciente de que los trastornos del ánimo recurrentes – antiguamente considerados “enfermedades de buen pronóstico” – constituyen, de hecho, patologías a menudo muy severas y con riesgo vital. Aun cuando los trastornos del ánimo han sido tradicionalmente conceptualizados como trastornos neuroquímicos, actualmente existen evidencias de una variedad de fuentes que demuestran reducciones de volumen de ciertas regiones del sistema nervioso central (SNC), como también disminuciones en el número y/o tamaño de la glía y de neuronas en pequeñas áreas cerebrales. Aunque los mecanismos celulares precisos a la base de estos cambios morfológicos están por aclararse totalmente, los datos sugieren que los trastornos del ánimo están asociados con deterioros de la plasticidad sináptica y la resiliencia celular. En este contexto cabe destacar que existen evidencias crecientes preclínicas que los antidepressivos regulan la función del sistema glutamatérgico. Por otra parte, aunque claramente preliminares, los datos clínicos disponibles sugieren que la reducción de la función del N-metil-D-aspartato (NMDA) tiene efectos antidepressivos. Recientes estudios preclínicos y clínicos han demostrado que las vías de señales que participan en la regulación de la supervivencia y de la muerte celular son blancos a largo plazo para las acciones de los agentes antidepressivos. Los antidepressivos y los estabilizadores del ánimo regulan indirectamente un número de factores que participan en las vías de supervivencia celular, los que incluyen: el elemento de respuesta de adenosina monofosfato cíclico (cAMP) unido a proteína (CREB), el factor neurotrófico, tradicionalmente derivado del cerebro (BDNF), la proteína antiapoptótica bcl-2 y las protein-quinasas activadas por mitógenos (MAP); de este modo pueden ejercer algunos de sus efectos benéficos retardados a largo plazo a través de los efectos neurotróficos tradicionalmente subestimados. Existen muchas promesas para el futuro desarrollo de tratamientos con moléculas que apunten directamente a vías de señales del SNC que sean críticas en la regulación de la plasticidad sináptica y en la resiliencia celular. Esto representará mejores tratamientos a largo plazo para los trastornos del ánimo.

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Amélioration de la plasticité synaptique et de la résilience cellulaire en vue de développer de nouveaux et meilleurs traitements pour les troubles de l'humeur

Il a été montré à maintes reprises que les troubles de l'humeur récidivants, considérés naguère comme « maladies de bon pronostic », sont en fait souvent très sévères et présentent un risque vital. En outre, bien que les troubles de l'humeur soient envisagés traditionnellement comme étant d'origine neurochimique, nous disposons actuellement de tout un faisceau de preuves démontrant l'existence de réductions régionales du volume du système nerveux central (SNC) comme du nombre et/ou de la taille des neurones et de la névroglie dans certaines zones distinctes du cerveau. En dépit de lacunes dans la compréhension des mécanismes cellulaires précis mis en jeu dans ces modifications morphométriques, les données suggèrent une association entre les troubles de l'humeur et des déficits de la plasticité synaptique et de la résilience cellulaire. Dans ce contexte, il convient de souligner que les études précliniques montrent de plus en plus clairement que les antidépresseurs agissent au travers d'une régulation du fonctionnement du système glutamatergique. De plus, bien qu'il s'agisse à l'évidence de résultats préliminaires, les données cliniques disponibles suggèrent l'existence d'un effet antidépresseur lié à une diminution de la fonction du N-méthyl-D-aspartate (NMDA). Des études cliniques et précliniques récentes ont montré que les voies de signalisation impliquées dans la régulation de la vie et de la mort cellulaires représentent des cibles à long terme pour l'action des antidépresseurs. Les antidépresseurs et les régulateurs de l'humeur modulent indirectement certains facteurs agissant sur les voies de la survie cellulaire, comme le facteur de transcription CREB (cyclic [adenosine monophosphate] response element binding protein), le facteur neurotrophique dérivé du cerveau (FNDC), la protéine antiapoptotique bcl-2 et les protéines kinases mitogènes activées (PMA). De ce fait, certains des effets retardés bénéfiques à long terme attribuables à ces médicaments peuvent être occasionnés par ces effets neurotrophiques par ailleurs sous-estimés. Davantage prometteur pour l'amélioration du traitement à long terme des troubles de l'humeur est le développement de futurs traitements plus directement axés sur les molécules des voies critiques de signalisation du SNC régulant la plasticité synaptique et la résilience cellulaire.

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