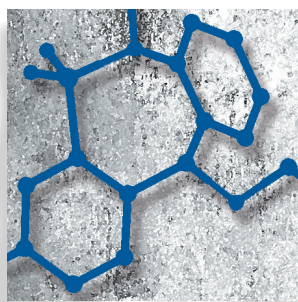


The neurotrophic and neuroprotective effects of psychotropic agents

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Accumulating evidence suggests that psychotropic agents such as mood stabilizers, antidepressants, and antipsychotics realize their neurotrophic/neuroprotective effects by activating the mitogen activated protein kinase/extracellular signal-related kinase, PI3-kinase, and wingless/glycogen synthase kinase (GSK) 3 signaling pathways. These agents also upregulate the expression of trophic/protective molecules such as brain-derived neurotrophic factor, nerve growth factor, B-cell lymphoma 2, serine-threonine kinase, and Bcl-2 associated athanogene 1, and inactivate proapoptotic molecules such as GSK-3. They also promote neurogenesis and are protective in models of neurodegenerative diseases and ischemia. Most, if not all, of this evidence was collected from animal studies that used clinically relevant treatment regimens. Furthermore, human imaging studies have found that these agents increase the volume and density of brain tissue, as well as levels of N-acetyl aspartate and glutamate in selected brain regions. Taken together, these data suggest that the neurotrophic/neuroprotective effects of these agents have broad therapeutic potential in the treatment, not only of mood disorders and schizophrenia, but also neurodegenerative diseases and ischemia.

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Historically, psychiatric disorders such as mood disorders and schizophrenia have been conceptualized as neurochemical illnesses. However, accumulating data from both postmortem and brain imaging studies reveal morphological changes in the brains of individuals with these illnesses. These changes include ventricle enlargement, volumetric reduction, attenuation of neuronal viability marker N-acetyl aspartate (NAA), and atrophy or loss of neurons and glial cells in selective cortical and limbic brain regions. Several *psychotropic agents*—defined as chemical substances that act primarily on the central nervous system (CNS) to alter brain function—are used to treat psychiatric disorders. These psychotropic agents include mood stabilizers, antidepressants, and antipsychotic medications. Many of these drugs exert significant effects on signaling pathways enhancing neurotrophic and neuroprotective cellular mechanisms. Loosely defined, *neurotrophic effects* can be considered a therapeutic strategy intended to augment proliferation, differentiation, growth, and regeneration, whereas *neuroprotective effects* slow or halt the progression of neuronal atrophy or cell death following the onset of disease or clinical decline.

In this article, we review evidence from animal and human studies reporting that psychotropic agents affect molecular targets and signaling cascades associated with enhanced

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Selected abbreviations and acronyms

| | |
|----------------|--|
| BDNF | <i>brain-derived neurotrophic factor</i> |
| CREB | <i>cAMP response element binding</i> |
| ERK | <i>extracellular signal-related kinase</i> |
| MAPK | <i>mitogen activated protein kinase</i> |
| NAA | <i>N-acetyl aspartate</i> |
| PI3K | <i>PI3-kinase</i> |
| Wnt/GSK | <i>wingless/glycogen synthase kinase</i> |

neurotrophic and neuroprotective mechanisms, as well as reverse or reduce behavioral deficits associated with pre-clinical animal models of mania and depression and other psychiatric illnesses. While much of this work has focused on the mood stabilizers lithium and valproate, we will also review the available evidence that antidepressants and antipsychotics exert similar neurotrophic effects.

Mood stabilizers

Mood stabilizers are used to treat bipolar disorder (BPD), which is characterized by mood shifts between mania (characterized by elevated mood, increased energy, impaired judgment, and racing thoughts) and depression (characterized by low mood, anhedonia, etc). These therapeutic agents do not simply target a particular neurotransmitter system or cellular signaling cascade, but diverse targets implicated in many signaling pathways. This may be because mood stabilizers were often designed to treat different disorders, and their use in the treatment of BPD frequently arose through serendipity; for instance, the mood stabilizers carbamazepine and valproate—both used to treat the manic symptoms of BPD—have anticonvulsant properties and were developed for the treatment of epilepsy. In addition, our incomplete understanding of the pathophysiology of BPD, in which both genetic and environmental predispositions may impair cellular resilience and lead to dysfunctional circuits and synapses, further supports the notion that these agents affect diverse targets. Indeed, mood stabilizers may achieve their therapeutic effects by working through these diverse targets to restore cellular resilience; notably, however, chronic treatment is necessary for their neurotrophic and neuroprotective actions to improve functional plasticity in cortical and limbic circuits and synapses.

Below we focus on several intracellular signaling pathways targeted by mood stabilizers that may underlie these therapeutic mechanisms: i) the mitogen activated protein kinase/extracellular signal-related kinase

(MAPK/ERK) pathway, ii) the phosphatidylinositol 3 kinase (PI3K) pathway, and ii) the wingless/glycogen synthase kinase 3 (Wnt/GSK3) pathway.

Mood stabilizers activate neurotrophic signaling pathways

Mood stabilizers have been reported to activate the intracellular MAPK/ERK signaling pathway (*Figure 1*).¹⁻³ This pathway is used by neurotrophins, neurotransmitters, and neuropeptides to exert their neurotrophic and neuroprotective effects by specifically enhancing progenitor cell proliferation and differentiation, neuronal process growth and regeneration, neuronal survival, and long-term synaptic remodeling and plasticity.^{4,7} The key components of the pathway are three serine/threonine-selective kinases: RAF, MEK, and MAPK/ERK. GTP bound RAS, a small G protein, induces RAF activity. RAF then phosphorylates and activates MEK, which in turn phosphorylates and activates MAPK/ERK. The targets of ERK include protein kinases such as RSK and MNK, ion channel, neurotransmitter receptors, and transcription factors. RSK and MNK are thought to phosphorylate and activate transcription factor cAMP response element binding (CREB). CREB regulates the expression of many different genes, including B-cell lymphoma 2 (Bcl-2)^{1,8} and brain-derived neurotrophic factor (BDNF)⁹ to enhance neuroprotection and neuronal survival mechanisms.

In SH-SY5Y human neuroblastoma cells, the mood stabilizers lithium and valproate activated AP-1 transcription factors, and that activation was blocked by a MEK inhibitor.¹⁰ That study also demonstrated that valproate increased levels of activated phospho-ERK and reporter gene expression driven by ELK, an ERK-regulated transcription factor; that activation was further blocked by RAS and RAF functional null mutant.¹⁰ Valproate also promoted neurite outgrowth and expression of GAP-43 in these cells, which could be blocked by an ERK pathway inhibitor.¹⁰ Taken together, these data indicate that valproate activates the ERK pathway and produces neurotrophic-like cellular effects through this activation. Follow-up studies showed that in cultured cerebral cortical cells, valproate induced ERK pathway activation in a manner that was more sustainable than activation by growth factors.³

Valproate-induced activation of the ERK pathway has also been identified in primary cortical neurons,¹¹ cerebral progenitor cells,¹² hippocampal progenitor cells,¹³ and endothe-

lial cells.¹⁴ Lithium similarly increased activation-phosphorylation of ERK in SY5Y cells,¹⁵ cerebellar granular cells,^{16,17} hippocampal progenitor cells,^{18,19} and primary cortical neurons.¹¹ Lithium inhibited the ERK pathway in cultures of serum-deprived, quiescent astrocytes.¹⁷ Furthermore, lamotrigine, an anticonvulsant prescribed to prevent recurrences of depression or mania in BPD, did not affect the ERK pathway in SH-SY5Y cells¹⁵ or primary cortical neurons¹¹; however, lamotrigine still showed neuroprotective effects in models of ischemia and kainate (KA)-induced neurotoxicity, perhaps through glutamate release inhibition.^{20,21} Taken together, these in vitro data suggest that activation

of the ERK pathway is common to only a subgroup of mood stabilizers and is cell-type specific. In a series of in vivo studies, Chen and colleagues found that chronic treatment with lithium or valproate increased levels of activated phospho-ERK, phospho-RSK1, and activated phospho-CREB in prefrontal cortex and hippocampus.^{2,3} Lithium-induced increases in activated phospho-ERKs were also observed in the caudate/putamen of infant mouse brains.²² Another study found that valproate increased levels of activated phospho-ERK and activated phospho-CREB in mice with intracerebral hemorrhage.²³ Another study found that

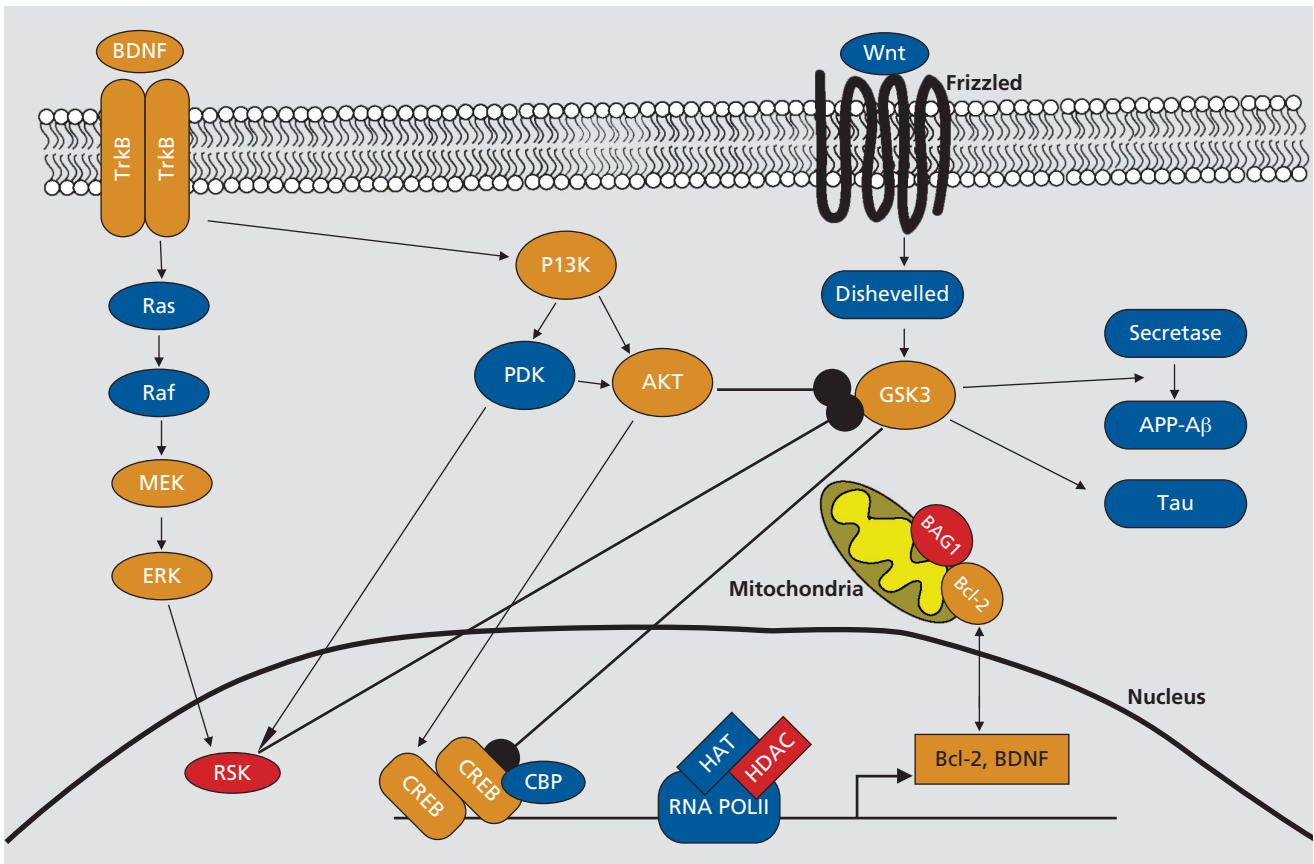


Figure 1. Intracellular signaling pathways targeted by psychotropic agents. The MAPK/ERK, PI3K, and Wnt/GSK3 signaling cascades. Psychotropic agents such as mood stabilizers, antidepressants, and antipsychotics target these signaling cascades. Targets reported to be regulated by antidepressants, antipsychotics, mood stabilizers (red), or multiple types of treatments (orange) are highlighted. Molecules in blue are critical constituents of the selected pathways that have not been found to be affected by any of the treatments discussed in this review. Arrowheads indicate activation; circles indicate inhibition. Akt, serine/threonine protein kinase; BAG-1, Bcl-2 associated athanogene; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding; ERK, extracellular regulated kinase; GSK-3, glycogen synthase kinase 3; HDAC, histone deacetylase; PI3K, phosphatidylinositol 3 kinase; TrkB, neurotrophic tyrosine kinase receptor, type 2; Ras, resistance to audiogenic seizures; Raf, RAF proto-oncogene serine/threonine-protein kinase; RSK, ribosomal protein S6 kinase, 90kDa; MEK or Map2k1, mitogen-activated protein kinase kinase 1; CBP, CREB binding protein; RNA POLII, RNA polymerase II; HAT, histone acetyltransferase; PDK, pyruvate dehydrogenase kinase; APP-AB, amyloid beta (A4) precursor protein; Wnt, wingless

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valproate did not induce changes in phospho-ERK levels in the nucleus accumbens, and reduced phospho-ERK levels in the amygdala,²⁴ suggesting that mood stabilizer-induced ERK pathway activation/inactivation may be brain region-specific.

The phosphatidylinositol 3 kinase (PI3K) pathway—a regulator of neuronal survival and plasticity—is also regulated by growth factors (*Figure 1*).^{6,25-27} Upon trophic factor stimulation (*Figure 1*), the regulatory subunit of PI3K is stimulated by the adapter proteins Grb-2 and Grb-2-associated binding protein 1/2 (Gab1/2), resulting in PI3K activation. The catalytic subunit of PI3K is also stimulated by direct interaction with activated RAS. Activated PI3K converts plasma membrane lipid phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 provides docking sites for phosphoinositide-dependent kinase (PDK) and the serine-threonine kinase Akt (also known as protein kinase B, PKB). Simultaneous binding of PDK and Akt at the PI3K activation site facilitates phosphorylation of Akt by PDK1 and enhances Akt activity. Akt then phosphorylates glycogen synthase kinase-3 (GSK-3), which in contrast to most phosphorylations, leads to the inactivation of this enzyme.²⁸ PI3K, PDK, Akt, and GSK-3 are thought to be the major components of the PI3K pathway.

Mood stabilizers target several of these major components of the PI3K pathway. Acute (minutes to hours) or subacute (several days) lithium treatment of cerebellar granule cells, for instance, increased levels of activated phospho-Akt as well as phospho-GSK-3, a product of Akt-catalyzed phosphorylation.²⁹ Interestingly, similar effects were noted in human SH-SY5Y cells treated with lithium and valproate.^{1,30} The increases were blocked by PI3K inhibitors, indicating that they required PI3K activation.²⁹ Chronic lithium and valproate treatment also increased levels of phospho-GSK-3 β in mouse cerebral cortex and hippocampus.³⁰⁻³² Lithium injections (200 mg/kg of body weight, IP) significantly increased levels of phospho-Akt, phospho-GSK-3 α and phospho-GSK-3 β in the striatum of dopamine transporter knockout (DAT KO) mice within 30 minutes of administration.³³ Valproate increased activated brain phospho-Akt in skeletal muscle in a mouse model of Duchenne's muscular dystrophy,³⁴ as well as in a mouse model of intracerebral hemorrhage.²³ These data demonstrate that lithium and valproate stimulate the PI3K pathway in vivo and subsequently inactivate GSK-3.

Mood stabilizers upregulate levels of neurotrophic and neuroprotective molecules

Studies show that lithium and valproate increased mRNA and protein levels of neurotrophins such as BDNF, glial cell-line derived neurotrophic factor (GDNF), neurotrophin 3 (NT-3), and vascular endothelial growth factor (VEGF) in cultured cells and brain regions.^{2,35-46} Furthermore, lithium increased serum BDNF levels in patients with Alzheimer's disease.⁴⁷ The effects of mood stabilizers on BDNF levels are thought to be mediated via several different mechanisms. These mechanisms may include enhancing BDNF promoter activation^{40,43,45} by stimulating the ERK and PI3K pathways using lithium or valproate, leading to CREB activation and CRE-mediated gene transcription of BDNF. Valproate's inhibition of histone deacetylase (HDAC) via an epigenetic mechanism—a molecular process that leads to gene activation and deactivation—may also play a role.^{40,43,45}

In addition to targeting neurotrophic mechanisms, mood stabilizers also target neuroprotective molecules such as Bcl-2. Bcl-2 and its family proteins are the major modulators of apoptosis. Notably, numerous studies have shown that chronic treatment with lithium or valproate upregulates Bcl-2 and Bcl-2 associated athanogene (BAG-1) levels in the brain or nerve tissues.^{23,32,48-54} This upregulation appears to be partially due to activation of the ERK and PI3K pathways, as well as increased transcriptional activity of CREB.¹

Mood stabilizers promote neurogenesis and neuronal process growth

The discovery that mood stabilizers can regulate growth factors and produce neurotrophin-like molecular effects led investigators to explore whether these agents could augment hippocampal neurogenesis. Lithium and valproate were indeed found to promote hippocampal neurogenesis in neuronal cell culture and rodent studies.^{3,18,19,32,55} In vitro evidence showed that lithium induced neuronal differentiation of hippocampal neural progenitor cells via a phospho-ERK and phospho-CREB dependent pathway.¹⁹ An in vivo study showed that lithium increased survival of newborn cells in hippocampus, and that an ERK pathway inhibitor blocked lithium's survival effects.⁵⁶ Valproate activated the ERK pathway and promoted differentiation of hippocampal

neural progenitor cells in culture; however, valproate's differentiation effects were thought to be mediated through HDAC inhibition, not ERK pathway activation.^{13,57} Whether valproate uses multiple mechanisms to induce hippocampal neurogenesis in intact animals remains to be elucidated.

Valproate also promoted neurite growth in cultured cells (for reviews see refs 6,7), which was blocked by ERK pathway inhibition.^{3,10} Animal studies have found that valproate facilitated axonal regeneration and motor function recovery after sciatic nerve axotomy.^{51,58} Lithium similarly enhanced survival and axonal regeneration of cultured retinal ganglion cells,⁴ protected retinal ganglion cells following partial optic nerve crush in rats,⁵⁹ and promoted axonal regeneration of rubrospinal tract (RST) neurons following injury to the spinal cord.⁵³ These neuroprotective findings are, in part, thought to be mediated by Bcl-2. Another recent study showed that lithium facilitated motor function recovery and axonal regeneration after spinal cord injury, and these effects were associated with increased inactivated-phospho-GSK-3. Further support for GSK-3's role in lithium's neuroprotective effects came from a study where lithium's effects were mimicked by the GSK-3 inhibitor SB415286.⁶⁰

Another area where lithium exerts neuroprotective effects is in stress-induced morphological alterations. Chronic behavioral stress shortens apical dendrites in the CA3 region of the hippocampus in rodents. Lithium treatment initiated 2 weeks before the stress and continued throughout a 3-week period of stress attenuated these stress-induced reductions in apical dendritic lengths.⁶¹ Although the molecular mechanisms of this lithium-induced morphological action are still not fully understood, they are particularly important because social-psychological and behavioral stress cause a variety of brain changes and are key contributing factors to mood disorders.⁶²⁻⁶⁵

Evidence from human imaging studies for neurotrophic/neuroprotective actions of mood stabilizers

As noted previously, brain imaging studies show brain ventricular enlargements,^{66,67} cortical regional morphometric reductions,⁶⁸⁻⁷² and cerebral and hippocampal level reductions of NAA⁷²⁻⁷⁸ in individuals with mood disorders, especially in unmedicated patients with a family history of mood disorders.

Intrigued by the discovery that Bcl-2 is upregulated by mood stabilizers, investigators used imaging tools to assess the effects of mood stabilizers on brain morphometric and neurochemical measures. In a magnetic resonance imaging (MRI) study, Moore and colleagues found that lithium treatment increased cerebral grey matter volume.⁷⁹ Similar findings were also obtained in other longitudinal and cross-sectional studies of cerebral grey matter volume,⁸⁰ left anterior cingulate volume,⁷⁰ right anterior cingulate volume,⁸¹ hippocampal volume,⁸²⁻⁸⁶ and amygdala volume.⁸⁶ A cross-sectional study found that valproate similarly increased left anterior cingulate volume in individuals with BPD.⁸⁷

One initial longitudinal MRS study found brain regional increases in NAA levels in individuals with BPD and healthy subjects treated for 4 weeks with lithium,⁷⁹ a finding replicated by other investigators.⁸⁸⁻⁹⁰ NAA levels were also found to be correlated with brain lithium levels in a study of elderly patients with BPD.⁹¹ Valproate was similarly found to increase hippocampal NAA levels.⁷²

Mood stabilizers produce neuroprotective effects in animal models of disease

Mood stabilizers are known to protect cultured cells from a variety of insults (for reviews see refs 6,7,92,93). In this section, we review the neuroprotective effects of lithium and valproate in a series of models of brain ischemia, neurodegeneration, and neuroinflammation (eg, cerebral ischemia, Alzheimer's disease (AD), Huntington's disease, amyotrophic lateral sclerosis (ALS), HIV-associated cognitive impairments, and spinocerebellar ataxia).

In a seminal study using an animal model of ischemia, Chuang and colleagues found that ischemic infarct size induced by occlusion of the left middle cerebral artery was markedly reduced by lithium treatment administered before⁹⁴ or after⁹⁵ the induction of ischemia; these findings have since been replicated by other investigators.⁹⁶⁻¹⁰⁴ Follow-up studies showed that valproate had similar protective effects on ischemia-induced brain infarction.^{105,106}

ALS is a progressive, lethal neurodegenerative disease with no known cure. Riluzole, which prolongs the survival of patients by several months, is the only FDA-approved treatment for this disease. Interestingly, riluzole itself has been associated with neuroprotective

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properties.¹⁰⁷ SOD1-G93A mice, a model for ALS, carry a high copy number of this transgene with the G93A human SOD1 mutation. Studies show that valproate¹⁰⁸ and lithium^{109,110} both delay disease onset and prolong lifespan in SOD1-G93A mice. Furthermore, lithium and valproate together produce an additive protective effect in SOD1-G93A mice compared with either treatment alone.¹¹⁰ Notably, a clinical trial found that lithium, compared with riluzole, further delays disease progression and death in individuals with ALS.¹⁰⁹

With regards to AD, diverse studies have suggested that lithium's neuroprotective effects may have a potential role in the therapeutics of this disease. AD is a leading cause of dementia in the aging population and the most common neurodegenerative disease without an effective treatment. Briefly, the histological hallmarks of AD include amyloid plaques, neurofibrillary tangles, and neuronal loss. The plaques consist of insoluble deposits of amyloid-beta (A β) protein and cellular material outside and around neurons. A β protein is derived from amyloid precursor protein (APP) through an endoproteolytic cleavage catalyzed by β - and γ -secretase. Mutations in the genes of presenilins—the core component of γ -secretase, APP, and tau are associated with AD. One series of experiments in cultured cells found that GSK-3 α increased A β production,¹¹¹ and that chronic lithium treatment reduced A β produced in a genetic mouse model of AD. These mice expressed APP-Swedish (Tg2576) and also carried a knock-in mutation of presenilin-1 (PS1P264L). In a transgenic mouse strain overexpressing mutated (London V717I and Swedish K670M/N671L) human APP (hAPP751), lithium treatment reduced A β production, improved performance in the water maze, and preserved dendritic structure in the frontal cortex and hippocampus, all of which are associated with decreased APP phosphorylation and increased levels of phospho-GSK-3 β .¹¹² In another animal model of AD where APP23 transgenic mice carried human APP751 cDNA with the Swedish double mutation at positions 670/671, Qing and colleagues observed that valproate treatment decreased A β production, reduced neuritic plaque formation, and improved memory deficits; these effects were also associated with increased phospho-GSK-3 β .^{113,114}

Neurofibrillary tangles are formed by hyperphosphorylated tau, a microtubule-associated protein. GSK-3 is a major tau kinase and GSK-3 β hyperactivity is known to contribute to tau hyperphosphorylation in cell and ani-

mal models. Interestingly, lithium treatment reduced tau phosphorylation in the brains of mice overexpressing mutated (London V717I and Swedish K670M/N671L) human APP (hAPP751).¹¹² In another AD model (3xTG-AD), lithium treatment reduced brain tau phosphorylation and increased brain GSK-3 α and β phosphorylation at the inhibitory sites; however, it did not improve memory or reduce A β production.¹¹⁵

Given these promising preclinical data, studies began to examine the potential long-term neurotrophic/neuroprotective effects of lithium and valproate in humans. While some studies suggest that naturalistic lithium treatment may indeed be associated with neuroprotective effects in individuals with AD (see, for instance refs 47,116-118), considerably more data are required. Nevertheless, this remains a promising and exciting area for further investigation.

Spinocerebellar ataxia type 1 (SCA1) is a dominantly inherited neurodegenerative disorder characterized by progressive motor and cognitive dysfunction. In a SCA1 mouse model, chronic administration of lithium initiated before or after the deficit onset had a positive effect on multiple behavioral measures and hippocampal neuropathology.¹¹⁹ Indeed, clinical trials of lithium in patients with SCA1 are currently ongoing (see <http://clinicaltrials.gov/> for more information).

Finally, the neuroprotective effects of lithium and valproate have also been reported in additional disease and insult models, including animal models of Huntington's disease,^{120,121} Parkinson's disease,¹²² HIV-induced encephalitis and dementia,^{123,124} and aluminum-induced neurodegeneration.⁵⁰ At least some of these effects are associated with increased Bcl-2 levels.^{50,120,121,122}

Antidepressants

Chemical antidepressants used to treat depressive disorders, or depressive symptoms in other psychiatric disorders, include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or selective norepinephrine reuptake inhibitors (SNRIs). These chemical antidepressants act by increasing monoamines (serotonin and/or norepinephrine) in the synaptic cleft, which occurs immediately; however, for most patients, therapeutic effects are observed only after a few days, and often not until 2 weeks or more. This suggests that adaptive changes in cellular signaling cascades may underlie

their therapeutic effects.¹²⁵ Two such pathways that will be considered below include the MAPK/ERK and the Wnt/GSK signaling cascade (*Figure 1*), which may enhance neurotrophic and neuroprotective mechanisms in addition to neurogenesis. Interestingly, nonchemical antidepressants such as electroconvulsive therapy (ECT) and exercise also target these pathways and may employ similar therapeutic mechanisms.

Antidepressants affect prominent signaling cascades involved in neuronal protection and survival

As noted above, activation of the MAPK/ERK and Wnt/GSK signaling cascades (*Figure 1*) ultimately targeted by antidepressants may result in enhanced neuroprotective and survival mechanisms. For instance, both chemical antidepressants and ECT increase BDNF levels. In rats, ECT increased BDNF and its receptor (trkB) in the hippocampus.¹²⁶ A similar effect was also found following chronic (21 days) but not acute treatment with different classes of antidepressants (the MAOI tranylcypromine, the SSRI sertraline, and the TCA desipramine). Furthermore, chronic antidepressant treatment also increased the expression of CREB mRNA in the rat hippocampus,¹²⁷ suggesting a potential regulatory mechanism for BDNF through CRE-mediated gene transcription.

Exercise has also been reported to upregulate many factors in the MAPK signaling pathway including BDNF, trkB, MEK2, and ERK2.¹²⁸⁻¹³³ A recent study found that exercise-induced upregulation of BDNF at the mRNA and protein level and phosphorylation of survival factor Akt both occurred via a CREB-dependent mechanism.¹³⁴ Interestingly, the SNRI reboxetine also depends on CREB activation (phosphorylation) in order to show similar changes in BDNF and Akt.

In humans, serum levels of BDNF levels are decreased in unmedicated depressed patients compared with depressed patients currently taking antidepressants or healthy controls.¹³⁵ BDNF serum levels were also found to be negatively correlated with depression scores as assessed by the Hamilton Depression Rating Scale (HDRS). Interestingly, BDNF itself also possesses antidepressant-like effects in rodent models used to screen antidepressants following direct infusion into either the midbrain¹³⁶ or hippocampus.¹³⁷ This enhancement in BDNF by antidepressants may help promote mechanisms of neuronal protection and survival key to reducing stress-induced damage.

Antidepressants have also been found to have neuroprotective effects. For instance, the SSRI fluoxetine prevented the neurotoxic effects of ecstasy (3,4-methylenedioxymethamphetamine, MDMA).^{138,139} Mechanistically, fluoxetine's neuroprotective effects, in addition to restoring serotonin levels, may result from activation of p38 MAPK, BDNF, and GDNF.¹⁴⁰

MAOIs (eg, pargyline, nialamide, tranylcypromine) inhibiting both MAO-A and MAO-B protected against 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced dopaminergic neural toxicity.¹⁴¹ Interestingly, Ladoestigil, a MAOI used to treat both depression and neurodegeneration that has promising neuroprotective effects, reportedly activated Bcl-2 family members and BDNF¹⁴² in addition to ERK1/2 (p44/42 MAPK).¹⁴³

Notably, exercise also possesses neuroprotective effects. Carro and colleagues showed that rodents subjected to treadmill running were protected against various insults ranging from treatment with the neurotoxin domoic acid to inherited neurodegeneration affecting Purkinje cells of the cerebellum.¹⁴⁴ These protective effects depended in part on the neurotrophic factor insulin-like growth factor I (IGF-1); infusing a blocking anti-IGF-1 antibody reduced the protective effects of exercise.

Effects of antidepressants on neurogenesis in animals

Antidepressants increase hippocampal adult neurogenesis following chronic but not acute treatment. Chronic treatment with the SSRI fluoxetine, the MAOI tranylcypromine, or the SNRI reboxetine produced an approximately 20% to 40% increase in bromodeoxyuridine BrdU-labeled hippocampal cells¹⁴⁵; at least 2 weeks of fluoxetine treatment was required to enhance neurogenesis. Furthermore, while stress decreases hippocampal neurogenesis, chronic antidepressant treatment prevented these stress-induced changes.^{146,147} ECT also increased neurogenesis in rodents,¹⁴⁸ as well as hippocampal synapse number.¹⁴⁹ ECT was similarly found to increase neurogenesis in nonhuman primates,¹⁵⁰ and exercise increased hippocampal neurogenesis¹⁵¹ in addition to enhancing hippocampal-dependent learning and long-term potentiation (LTP).¹⁵¹

The molecular mechanisms underlying these antidepressant-induced enhancements in neurogenesis may involve the MAPK/ERK and/or Wnt/GSK-3 pathways. A very recent study found that suppression of the gene disrupted in schizophrenia 1 (*DISC1*), which has been

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implicated in BPD, major depressive disorder (MDD), and schizophrenia, decreased neurogenesis by acting through GSK3 β .¹⁵²

Antidepressants and the reversal of stress-induced changes in neuronal plasticity

In terms of clinical implications, a recent meta-analysis found enhanced antidepressant response in the Met variant of the BDNF 66Val/Met polymorphism in individuals with MDD.¹⁵³ Curiously, 66Met allele carriers have a lower neuronal distribution of BDNF in addition to decreased activity-dependent BDNF secretion. Given the hypothesis that antidepressant effects are partially mediated through enhanced BDNF secretion, it would seem contradictory that 66Met allele carriers, with their attenuated BDNF secretion, have a more robust response to antidepressants. In addition to enhanced antidepressant treatment response, this BDNF polymorphism was also associated with decreased episodic memory performance, lower hippocampal activation (as measured by fMRI), and lower hippocampal NAA levels in humans.¹⁵⁴ In a mouse model of the BDNF-Met variant in which BDNF-Met was expressed at normal levels, but regulated secretion from neurons was reduced, fluoxetine was unable to ameliorate a stress-induced anxiety phenotype.¹⁵⁵ Taken together, these data suggest a more complicated picture that requires a better understanding of proper BDNF function (and not just its expression); however, normal BDNF function does appear to be important for proper hippocampal function and mood regulation.

Notably, severely depressed patients show elevated levels of the stress hormone cortisol, which is thought to result from a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis negative feedback circuit,^{156,157} and which may ultimately contribute to the hippocampal damage and volumetric changes reported in the literature. Subjects with MDD were found to have significantly smaller hippocampal volumes, and these reductions correlated with total duration of depression but not with age,^{158,159} suggesting that the stress associated with depression may have contributed to these volumetric changes. Further support for this notion comes from studies reporting that individuals with post-traumatic stress disorder (PTSD) had impaired hippocampal function (deficits in short term memory, total recall, long-term storage, and retrieval) but no overall IQ differences

when compared with controls¹⁶⁰; MRI studies found that these PTSD patients had an 8% smaller right hippocampus than controls.¹⁶¹ In addition, the polymorphism in the BDNF gene (val(66)met) has also been associated with reduced hippocampal volume.¹⁶²

Interestingly, antidepressants can reverse some of these changes. In tree shrews, the selective serotonin reuptake enhancer (SSRE) tianeptine prevented the decreased brain metabolites (NAA, creatine, phosphocreatine), suppressed neurogenesis, and reduced hippocampal volume associated with chronic psychosocial stress.¹⁴⁷ In another study, chronic treatment with antidepressants induced hippocampal neurogenesis, blocked inescapable foot shock stress-induced decreases in hippocampal neurogenesis, and normalized corticosterone levels and behavioral deficits.^{145,163} Finally, repetitive transcranial magnetic stimulation (rTMS) has also shown putative neurotrophic properties in patients with MDD. In one study, rTMS improved refractory depression by augmenting catecholamines and BDNF,¹⁶⁴ while another study found that rTMS augmented BDNF in drug-resistant patients.¹⁶⁵

Antipsychotics

Antipsychotic medications are traditionally categorized as typical (also known as traditional, conventional, or classic neuroleptics) or atypical (second generation). Several typical antipsychotics have a higher dopamine D₂ receptor affinity than atypical antipsychotics, which bind to a broader group of receptors, including dopamine, serotonin, glutamate, histamine, α -adrenergic, and muscarinic receptors.¹⁶⁶ While antipsychotics can have an immediate impact on symptoms such as agitation, it often takes weeks before improvement is seen in other symptoms, such as delusions; however, recent findings suggest these improvements may emerge more rapidly than previously believed.^{167,168} As with mood stabilizers and antidepressants, it is likely that these drugs improve many facets of psychosis through mechanisms beyond their fundamental interaction with dopaminergic, serotonergic, muscarinic, and other receptor families.

Chronic treatment with conventional antipsychotics can lead to adverse extrapyramidal side effects (EPS), which mimic the neurodegenerative disorder Parkinson's disease, as well as the potentially irreversible condition known as tardive dyskinesia.¹⁶⁹ These effects are less common with atypical antipsychotics, which also have

improved efficacy in treating the negative symptoms associated with schizophrenia, though their overall benefit is still unclear¹⁷⁰; atypical antipsychotics also have their own adverse metabolic side effects like weight gain and diabetes.¹⁷¹ As highlighted below, these two classes of antipsychotics show markedly different profiles for activating neuroplasticity cascades, and for enhancing neuroprotection and neurogenesis in both animal studies and patient-based studies.

Antipsychotics alter the expression of prominent intracellular cascades and influence neuroplasticity and neuroprotection in animal models

Studies conducted in rodents and cell lines have demonstrated that some antipsychotics can induce significant changes in intracellular cascades that are involved in neuroplasticity and neuroprotection against excitotoxic insults, including ERK/MAPK, Akt, Bcl-2, and BDNF pathways. Acute treatment with the atypical antipsychotic clozapine led to increased levels of active (phosphorylated) MEK1/2 in rat prefrontal cortex,¹⁷² while chronic treatment with the atypical antipsychotic olanzapine increased pERK1/2 levels in rat prefrontal cortex (PFC).¹⁷³ Interestingly, Browning and colleagues observed decreases in pERK1/2 following either a single injection of olanzapine or haloperidol (a typical antipsychotic), but chronic haloperidol did not alter pERK1/2 levels. Multiple studies in phenochromocytoma (PC12) cells have also noted upregulation of pERK1/2, pAkt, and PI3K following olanzapine treatment.^{174,175} Antipsychotics have also been shown to influence other prominent cascades discussed above, including Bcl-2,¹⁷⁶ GSK-3,¹⁷⁷ and CREB.¹⁷⁸

Many studies have assessed the effects of antipsychotics on neurotrophic factors such as BDNF and nerve growth factor (NGF), and have noted significant differences between typical and atypical antipsychotics. Typical antipsychotics such as haloperidol tend to reduce BDNF expression in regions of the hippocampus¹⁷⁹⁻¹⁸¹ and striatum.¹⁸² Atypical antipsychotics do not consistently downregulate BDNF, and their more diverse set of responses make critical evaluations more challenging (see ref 183). One recent study noted that, after chronic (90-day) treatment with haloperidol, transitioning to the atypical antipsychotics olanzapine or risperidone appeared to rescue BDNF expression back to near baseline levels.^{182,184}

Studies have demonstrated that chronic or high doses of typical antipsychotics, like haloperidol and reserpine, can be neurotoxic, inducing apoptosis and reducing cell viability. Though the mechanism remains unclear, high doses of haloperidol induced apoptosis in the striatum and substantia nigra of rats treated via acute intraperitoneal injection.¹⁸⁵ In vivo investigations have further noted that brain regions like the striatum, hypothalamus, and limbic structures were some of the most drastically altered cytoarchitecturally by conventional antipsychotics.¹⁸⁶ Macaque monkeys treated for 17 to 27 months with therapeutic levels of either haloperidol or olanzapine had reduced brain volumes by ~10%, most prominently in the parietal and frontal brain lobes.¹⁸⁷ Other studies found the opposite effect, that chronic treatment of rats with haloperidol increased striatal volume.¹⁸⁸

In contrast, atypical antipsychotics appear to have some neuroprotective functions. For example, pretreatment with the atypical antipsychotics clozapine, quetiapine, or risperidone prevented PC12 cell death following serum withdrawal,¹⁸⁹ while olanzapine reduced cell death in PC12, SH-SY5Y, and 3T3 cells following a number of death-inducing treatments.¹⁷⁴ Neuroprotective properties have also been demonstrated for the atypical antipsychotic olanzapine against various insults, such as oxidative stressors¹⁹⁰ and ischemia.¹⁹¹ Olanzapine also upregulated the expression of Bcl-2 in rat frontal cortex and the hippocampus, as well as the expression of BDNF in the hippocampus.^{176,181} Studies have suggested that other atypical antipsychotics, such as risperidone and quetiapine, have neuroprotective properties that might be relevant to their clinical efficacy.^{192,193} For instance, one study found that the effects of stress-induced decreases of BDNF could be prevented by pretreatment with quetiapine.¹⁹⁴

Overall, the findings suggest that antipsychotics can alter prominent intracellular cascades and ultimately induce neurotrophic or neurotoxic responses in vivo and in vitro, depending upon the drug conditions, time course, and brain region under consideration.

Effects of antipsychotics on neurogenesis in animals

Initial studies detected increased neurogenesis in the gerbil hippocampus following haloperidol treatment,¹⁹⁵ but not in the rat hippocampus.¹⁴⁵ Two more recent studies found that haloperidol did not affect neurogenesis,^{196,197} although a study that used osmotic pumps

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(instead of daily intraperitoneal injections or delivery in drinking water) found that haloperidol increased neural stem cell (NSC) proliferation in the adult rat forebrain.¹⁹⁸ Furthermore, the researchers demonstrated that this proliferation was mediated through D₂ receptor stimulation *in vitro*, suggesting that under certain conditions, haloperidol could promote neurogenesis through its suppression of D₂-mediated pathways that normally prevent NSC proliferation.

Atypical antipsychotics have shown a more consistent profile of enhancing neurogenesis, but do not necessarily increase neuronal survival or differentiation into adult neurons. Chronic treatment of rats with clozapine or olanzapine, for example, augmented the number of BrdU-labeled cells in the dentate gyrus¹⁹⁶ or prefrontal cortex and dorsal striatum.¹⁹⁷ Although both studies detected increased proliferation of precursor cells, neither found a significant difference in the number of BrdU-positive, mature neurons in the weeks following treatment with antipsychotics. Quetiapine has also been shown to reverse the inhibition of hippocampal neurogenesis caused by chronic restraint stress, and significantly increase the number of BrdU-labeled immature neurons detected compared with vehicle-treated, stressed rats.¹⁹⁹

Effect of antipsychotics on NAA levels, brain volume, and density in patients

Studies conducted with schizophrenic patients have examined NAA measures and volumetric brain changes using 1H-MRS and MRI, respectively, to elucidate the effects of chronic antipsychotic treatment. Patients treated with atypical antipsychotics had higher NAA measures in the frontal lobes²⁰⁰ and anterior cingulate gyrus²⁰¹ than those treated with typical antipsychotics. Another study measured NAA changes during antipsychotic treatment and after cessation for at least 2 weeks in individual patients using a within-subject design and found significant decreases (~9%) in NAA levels in the dorsolateral prefrontal cortex after ending antipsychotic treatment; no differences were found in other brain regions.²⁰²

Schizophrenia, the disorder most often treated with antipsychotics, is well-known to be associated with reduced regional volumes, increased ventricle size,²⁰³ and deteriorating course,²⁰⁴ making it difficult to distinguish volumetric changes induced by antipsychotic treatment.

Overall, studies suggest that there are differences in the brain volumes of patients treated with antipsychotics compared with controls, or within groups of patients treated chronically with typical versus atypical antipsychotics; for a thorough analysis, see ref 186. One study of patients with first-episode psychosis found that treatment with haloperidol reduced grey matter volume; in contrast, olanzapine-treated patients showed no significant reductions compared with controls.²⁰⁵ Another recent study found that olanzapine increased NAA in the prefrontal cortex of remitted adolescent patients with mania compared with nonremitted patients.²⁰⁶ Although this suggests a possible *in vivo* neurotrophic effect, this finding needs further replication because the primary aim of the study—a NAA increase following olanzapine treatment, independent from clinical change—was negative. In fact, it is possible that the NAA increase seen in responders was more closely related to improved mood than to olanzapine's neurotrophic properties.

Closing remarks

The growing data from molecular, cellular, animal, and human studies described in this review support the notion that psychotropic agents used to treat the major psychiatric disorders—especially mood stabilizers—are associated with significant neurotrophic/neuroprotective effects. These effects may enhance cellular resilience and plasticity in dysfunctional synapses and neural circuitry implicated in psychiatric disorders. The crux of such research is that, in addition to their proven ability to treat psychiatric disorders, these agents may be useful in the treatment of neurodegenerative illnesses and ischemia. Similarly, psychotropic agents developed for the treatment of neurodegenerative illnesses may be beneficial as therapeutics for major psychiatric illnesses. Currently, several clinical trials are being conducted to evaluate the feasibility of using lithium and valproate to treat a variety of neurodegenerative diseases. Indeed, neuroprotection is the most consistent biological outcome associated with lithium treatment. There is hope that these clinically safe and widely used agents will slow disease progression, and perhaps produce functional improvements. Furthermore, because lithium and valproate stimulate the ERK and PI3K pathways, increase BDNF, Bcl-2, and BAG-1 expression, block HDAC activity (valproate only), and inhibit GSK-3 alpha and

beta activities, continued study of these agents may elucidate other clinically relevant targets, ultimately leading to improved treatments for these devastating disorders. Additional data are also needed to understand whether the neurotrophic and neuroprotective effects of mood stabilizers, antidepressants, and antipsychotics are cell-type or circuitry specific, and to what extent their neurotrophic/neuroprotective effects contribute to their therapeutic action. Finally, gaining insight into rapid-act-

ing versus long-term compensatory changes facilitated by these psychotropic agents will pave the way for the next generation of therapeutics, whose dual nature will provide both a rapid treatment response to restore function, as well as support long-term changes to maintain successful treatment and prevent relapse. □

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Los efectos neurotróficos y neuroprotectores de los agentes psicotrónicos

La evidencia acumulada sugiere que los agentes psicotrónicos como los estabilizadores del ánimo, los antidepresivos y los antipsicóticos producen sus efectos neurotróficos/neuroprotectores mediante la activación de la quinasa relacionada con la señal de la proteínquinasa extracelular activada por mitógeno, la quinasa PI3 y las vías de señales de la wiggless/glicógeno sintetasa quinasa 3 (GSK). Estos agentes también regulan hacia arriba la expresión de moléculas tróficas/protectoras como el factor neurotrófico cerebral, el factor de crecimiento neural, la proteína 2 del linfoma de células B, la quinasa serina-treonina y el atonogen 1 asociado a Bcl-2, e inactivan moléculas proapoptóticas como la GSK-3. Ellos también promueven la neurogénesis y son protectores en modelos de enfermedades neurodegenerativas e isquemia. La mayor parte, sino toda esta evidencia se recolectó a partir de estudios animales que utilizaron esquemas terapéuticos clínicamente relevantes. Además, en humanos los estudios de imágenes han encontrado que estos fármacos aumentan el volumen y la densidad del tejido cerebral, como también los niveles de N-acetil aspartato y glutamato en determinadas regiones cerebrales. Tomados en conjunto, estos datos sugieren que los efectos neurotróficos/neuroprotectores de estos fármacos tienen un gran potencial terapéutico en el tratamiento no sólo de los trastornos del ánimo y de la esquizofrenia, sino que también en enfermedades neurodegenerativas y en la isquemia.

Effets neuroprotecteurs et neurotrophiques des psychotropes

D'après un nombre croissant d'arguments, les psychotropes, comme les régulateurs de l'humeur, les antidépresseurs et les antipsychotiques, exercent leurs effets neurotrophiques et neuroprotecteurs en activant 3 voies de signalisation : la MAP (mitogen activated protein)/ERK (extracellular signal-related) kinase, la kinase PI3 et la Wnt/GSK (wiggless/kinase glycogène synthase). Ces voies régulent également positivement l'expression des molécules trophiques/protectrices comme le BDNF (brain-derived neurotrophic factor), le NGF (nerve growth factor), la protéine BCL2 (B-cell lymphoma 2), la kinase sérine-thréonine et le BAG-1 (athanogène 1 associé à BCL-2), et des molécules proapoptotiques inactivées comme la GSK-3. Elles favorisent aussi la neurogenèse et exercent un effet protecteur dans les maladies neurodégénératives et l'ischémie. La plupart de ces preuves, si ce n'est toutes, sont issues d'études animales utilisant des schémas thérapeutiques cliniquement pertinents. De plus, des études d'imagerie sur l'homme ont montré que ces agents augmentaient le volume et la densité du tissu cérébral ainsi que les taux de N-acétyl aspartate et de glutamate dans les régions cérébrales sélectionnées. Au total, ces données suggèrent que leurs effets neurotrophiques/neuroprotecteurs ont un potentiel thérapeutique large non seulement dans les troubles de l'humeur et la schizophrénie mais aussi dans les maladies neurodégénératives et l'ischémie.

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