Lithium: Potential Therapeutics Against Acute Brain Injuries and Chronic Neurodegenerative Diseases

Akihiko Wada1,*, Hiroki Yokoo1, Toshihiko Yanagita1, and Hideyuki Kobayashi1

1Department of Pharmacology, Miyazaki Medical College, University of Miyazaki, Miyazaki 889-1692, Japan

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Abstract. In addition to the well-documented mood-stabilizing effects of lithium in manic-depressive illness patients, recent in vitro and in vivo studies in rodents and humans have increasingly implicated that lithium can be used in the treatment of acute brain injuries (e.g., ischemia) and chronic neurodegenerative diseases (Alzheimer’s disease, Parkinson’s disease, tauopathies, and Huntington’s disease). Consistent with this novel view, substantial evidences suggest that depressive illness is not a mere neurochemical disease, but is linked to gray matter atrophy due to the reduced number/size of neurons and glia in brain. Importantly, neurogenesis, that is, birth/maturation of functional new neurons, continues to occur throughout the lifetime in human adult brains (e.g., hippocampus); the neurogenesis is impaired by multiple not-fully defined factors (e.g., aging, chronic stress-induced increase of glucocorticoids, and excitotoxicity), accounting for brain atrophy in patients with depressive illness and neurodegenerative diseases. Chronic treatment of lithium, in agreement with the delayed-onset of mood-stabilizing effects of lithium, up-regulates cell survival molecules (e.g., Bcl-2, cyclic AMP-responsive element binding protein, brain-derived neurotrophic factor, Grp78, Hsp70, and β-catenin), while down-regulating pro-apoptotic activities (e.g., excitotoxicity, p53, Bax, caspase, cytochrome c release, β-amyloid peptide production, and tau hyperphosphorylation), thus preventing or even reversing neuronal cell death and neurogenesis retardation.

Keywords: lithium neuroprotection/neurogenesis, glycogen synthase kinase-3, brain-derived neurotrophic factor, Bcl-2, cyclic AMP-responsive element binding protein

Introduction

Manic-depressive illness is one of the most common (worldwide prevalence approximately 3%–5%), chronic, recurrent (90%), and life-threatening psychiatric diseases, which is predicted to become the second most prevalent disease by the year 2020 (1, 2). Suicide is estimated to be the cause of death in approximately 15% of patients with major depressive disorders (2). Far from being diseases with purely psychological manifestations, mood disorders are now considered to be systemic diseases with multiple deleterious syndromes such as cognitive, motoric, autonomic, endocrine, and sleep/wake abnormalities (1, 2). However, neither the pathogenesis of manic-depressive illness, nor the therapeutic mechanisms of lithium are well understood, partly because of an array of potential targets of lithium action (3).

Trace amount of lithium occurs normally in animal tissues, including brain, but it has unknown physiological role. In the nineteenth century, lithium was used as a sedative and a putative anticonvulsant; thereafter, lithium was erroneously employed as a salt substitute for cardiac and other chronically ill patients, leading to the severe lithium intoxication and hence, its withdrawal as a therapeutics until the late 1940s (1). In 1948, Australian physician John Cade (4) rediscovered that administration of lithium exerted a lethargic effect in guinea pigs and then in 10 human patients suffering from mania. However, lithium was not used for the treatment of mania in the North America until 1970, in part due to the physicians’ concerns of lithium-induced toxicity.

*Corresponding author. FAX: +81-985-84-2776
E-mail: akihiko@fc.miyazaki-u.ac.jp

Invited article
intoxication (1).

Lithium is now a mainstay for the treatment of manic-depressive illness and displays a variety of benefits, including acute anti-manic and antidepressant effects, antidepressant-enhancing effect, long-term prophylactic effects, and even anti-suicidal effects (1). Since the pioneering studies of D’Mello et al. (5) and Volonte et al. (6) in 1994, it has become increasingly evident that lithium displays neuroprotective effects against cell injuries caused by a variety of noxious insults in cultured cells (Table 1), as well as animal models of various neurodegenerative diseases and human patients with

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 manic-depressive illness (Table 2). These insults include ischemia (7, 8), glutamate excitotoxicity (9 – 16), \( \beta \)-amyloid (17 – 23), \( C_2 \)-ceramide (24), colchicine (25), growth factor withdrawal (26), switching of high \( K^+ \) to normal \( K^+ \) medium (5, 27), irradiation (28), exposure to heat shock (29), high dose of anticonvulsants (30), *Bungarus multicinctus* \( \beta \)-bungarotoxin (31), animal model of Alzheimer’s disease (21), in vitro (32) and in vivo (33) models of Parkinson’s disease, animal models of Huntington’s disease (34 – 36), tauopathies caused by tau protein (37 – 39), and thapsigargin-induced, cytoplasmic \( Ca^{2+} \) overload-mediated, endoplasmic reticulum (ER) stress (40).

In 1996, Klein and Melton (41) provided the first evidence that lithium inhibited glycogen synthase kinase-3\( \beta \) (GSK-3\( \beta \)), a serine/threonine protein kinase, at concentrations similar to those in human plasma after therapeutic administration of lithium. Mood-stabilizing effects of lithium in manic-depressive illness require long-term rather than short-term effects of lithium, and are not immediately reversed upon the discontinuation of lithium administration, suggesting the involvement of transcriptional and translational events in mood-stabilizing effects of lithium (Fig. 1). In 1999, two laboratories documented that long-term in vivo and in vitro treatment with lithium up-regulated neuroprotective protein Bcl-2 (B-cell lymphoma/leukemia-2) in the frontal cortex of rat brains (42) and cultured rat cerebellar granule cells (43); in addition, chronic in vitro lithium treatment down-regulated pro-apoptotic proteins p53 and Bax in cerebellar granule cells (43).

Although mood disorders have traditionally been considered to be attributed to neurochemical abnormalities in brain, there are now substantial evidences that depressive disorder is associated with morphometric abnormalities (e.g., reductions in volume of gray matter, and in numbers/sizes of neurons and glia in discrete brain regions) via as yet fully-defined mechanisms (2). Multiple lines of studies also documented that lithium can interact with a multitude of cell survival and cell

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**Fig. 1.** Neuroprotective mechanisms of lithium: signaling pathways. Lithium directly inhibits ATP/Mg\( ^{2+} \)-dependent catalytic activity of GSK-3 and also inactivates GSK-3 via Ser-phosphorylation of GSK-3, which is regulated by multiple, as yet, not fully-defined protein kinases and protein phosphatases, including lithium-induced activation of the PI3K/Akt pathway. Inhibition by lithium of GSK-3 is thought to be the major neuroprotective mechanism of lithium. In addition, lithium attenuates phosphorylation of NMAD receptor, protecting glutamate-induced excitotoxicity. These lithium-induced events ultimately lead to activation of transcriptional factors (e.g., CREB), up-regulating the expression of neuroprotective genes (e.g., Bcl-2 and BDNF), and down-regulating pro-apoptotic genes (e.g., p53 and Bax). BDNF acts via RTK, activating ERK and PI3K/Akt signaling pathways, activating CREB, and inhibiting pro-apoptotic Forkhead transcription factor and Bad (not shown here). Bcl-2 inhibits mitochondrial cytochrome c release and caspase activation caused by p53 and Bax (see reviews 51, 54, 56). RTK, receptor tyrosine kinase family; NMDA, \( N \)-methyl-\( D \)-aspartate; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; GSK-3, glycogen synthase kinase-3; JNK, c-Jun N-terminal kinase; p38, mitogen-activated p38 protein kinase.
death signaling pathways, up-regulating cell survival molecules and promoting neurogenesis, that is, birth of progenitor cells, as well as their maturation and survival as functional new neurons in an already established neuronal network (1, 2, 44, 45). In 2000, Moore et al. (46, 47) documented that administration of therapeutically relevant doses of lithium into manic-depressive illness patients exerted regenerative neurostructural (increased gray matter volume in brains) and neurochemical effects (increased level of N-acetyl-aspartate, a marker of neuronal viability and function). These exciting results unveil that in human patient brains, brain atrophy is reversible, and neurogenesis may be promoted by pharmacological strategies. In addition to its current use in manic-depressive illness, it has been proposed that lithium could be used to treat acute brain injuries (e.g., ischemia) and chronic progressive inexorable neurodegenerative diseases (e.g., Alzheimer’s disease, Parkinson’s disease, tauopathies, and Huntington’s disease). In the present review, we summarized historical and recent findings about the neuroprotective and neuroregenerative effects of lithium.

Neuroprotective and neuroregenerative effects of lithium: in vitro treatment in cultured cells and in vivo administration in whole animals

**Historical view**

With respect to the neuroprotective effect of lithium, the pioneering study may date back to 1994, when D’Mello et al. (5) initially observed that treatment of rat immature cerebellar granule neurons with lithium (10 mM for 48 h) caused cell apoptosis, accompanied by DNA fragmentation. D’Mello et al. (5) also documented that following in vitro maturation of the immature cerebellar granule neurons, the mature (but not immature) neurons became dependent on increased concentration of extracellular K+ ([K+]o) for their survival, and they underwent apoptosis when 25 mM [K+]o was decreased to 5 mM [K+]o; lithium prevented apoptosis of mature neurons caused by reduction of [K+]o at the concentration range at which lithium induced apoptosis in immature neurons. Insulin-like growth factor-I (IGF-I) also prevented cell death caused by reduction of [K+]o. In the same year, Volonte et al. (6) reported that addition of 5 mM lithium in the culture medium prolonged by 2 weeks the survival span of γ-aminobutyric acid (GABA)-containing neurons prepared from adult rat cerebellum and newborn rat cerebral cortex.

**Prevention of glutamate excitotoxicity: inhibition of N-methyl-D-aspartate (NMDA) receptor activity**

In 1998, Nonaka et al. (9) reported that pretreatment with lithium remarkably protected cultured rat cerebellar granule, cerebral cortical, and hippocampal neurons against glutamate-induced, NMDA receptor-mediated, excitotoxicity by inhibiting Ca2+ influx via the NMDA receptor. Cells were treated with 0.1 – 5 mM lithium for various periods (0 – 7 days) before exposure to glutamate at the 7th day; the neuroprotective effect of lithium remained long-lasting even after the first 3 days' lithium pretreatment, occurred at therapeutically relevant concentrations of lithium (EC50 = 1.3 mM), and required 6 days' pretreatment for complete protection to occur. A subsequent study from the same laboratory (11) analyzed the underlying mechanism of lithium to inhibit Ca2+ influx via NMDA receptors. Treatment of cultured rat cerebral cortical neurons with 1 mM lithium for up to 6 days attenuated constitutive phosphorylation at Tyr416 of the NR2B subunit of the NMDA receptor, which was catalyzed by Fyn, a member of the Src tyrosine kinase family; the effect of lithium was time-dependent, causing a maximum 40% decrease between 4 and 6 days. Because Tyr416-phosphorylation of NR2B is positively correlated with NMDA-receptor-mediated synaptic activity and excitotoxicity, lithium-induced attenuation of NR2B phosphorylation reduces NMDA receptor-mediated Ca2+ influx and contributes to neuroprotective effect of lithium.

Brain ischemia increases Tyr416-phosphorylation of the NR2A subunit catalyzed by Src, Fyn, and prolinerich tyrosine kinase-2 (Pyk2), enhancing NMDA receptor activity. Zhang’s laboratory showed that in rats subjected to 6-h reperfusion after 15-min cerebral ischemia due to bilateral carotid artery occlusion, abdominal injection of lithium for 7 days prior to ischemia significantly prevented Tyr416-phosphorylation of NR2A in hippocampus (13). In addition, lithium prevented PSD-95 (95-kDa postsynaptic density protein)-mediated hetero-protein complex formation between NR2A and Src/Fyn/Pyk2, leading to the attenuated phosphorylations of both Src at Tyr416 and Pyk2 at Tyr402 (14). Shao et al. (15) treated cultured rat cerebral cortical cells with 1 mM lithium for 7 days and then exposed them up to 100 μM glutamate for up to 18 h; lithium inhibited glutamate-induced increase of cytoplasmic free Ca2+ concentration, lipid peroxidation, protein oxidation, DNA fragmentation, and cell death.

In cultured rat cerebellar granule neurons, Chen et al. (16) observed that glutamate-induced, NMDA receptor-mediated, excitotoxicity required activation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase to causeSer63-phosphorylation of c-Jun and Ser^{12}-phosphorylation of p53, leading to the enhancement of DNA binding activity of activator protein-1 (AP-1); these glutamate-induced signaling events and apoptosis
were prevented by treatment with lithium (0.5 – 2 mM for 7 days).

**Up-regulation of anti-apoptotic Bcl-2 and down-regulation of apoptotic p53 and Bax**

Intracellular mechanisms of lithium’s neuroprotective effect have been further examined. By using differential display of mRNA, Chen et al. (42) demonstrated that intraperitoneal injection of lithium for 9 days or 4 weeks in rats increased DNA binding activity of transcription factor PEBP2α/β, elevating cellular level of anti-apoptotic Bcl-2 protein (known to be transcriptionally regulated by PEBP2) by approximately 2-fold in the frontal cortex; immunohistochemical study revealed a marked increase in the number of Bcl-2-immunoreactive cells in layers 2 and 3 of frontal cortex. In cultured rat cerebellar granule cells, Chen and Chuang (43) also documented that treatment with 0.5 – 5 mM lithium for up to 7 days increased Bcl-2 mRNA and protein levels, while decreasing mRNA and protein levels of pro-apoptotic p53 and Bax; both changes occurred by lithium in a concentration-dependent manner between 0.5 and 5 mM. They also found that glutamate exposure for 4 or 8 h rapidly increased p53 and Bax (but not Bcl-2) mRNA and protein levels, as well as stimulated cytochrome c release from mitochondria; all of these deleterious effects of glutamate were protected by 7 days’ pretreatment with 3 mM lithium.

**Up-regulation of c-Fos and 78-kDa glucose-regulated protein (Grp78) in ER stress**

In 2005, Hiroi et al. (40) examined whether lithium pretreatment could prevent ER stress-associated cytotoxicity evoked by cytoplasmic Ca$^{2+}$ overload. In PC12 cells treated with thapsigargin, an inhibitor of sarco(endo)plasmic reticulum Ca$^{2+}$-ATPase, pretreatment with lithium (0.5 – 2.5 mM for up to 7 days) displayed cytoprotective effects against ER stress. Lithium attenuated thapsigargin-induced cytoplasmic Ca$^{2+}$ increase and induced up-regulation of transcription factor AP-1 family c-Fos and molecular chaperone Grp78 levels. Reduction of Bcl-2 level by thapsigargin was protected by lithium. Conversely, an inhibitor of the AP-1 family blocked neuroprotective effects of lithium. Neuroprotective effects of Bcl-2 and lithium are concisely summarized in Tables 1 and 2 in the previous review article (1).

**Up-regulation of brain-derived neurotrophic factor (BDNF)**

In 1995, Nibuya et al. (48) showed that in rats, intraperitoneal injection of various antidepressants (i.e., tranylcypromine, sertraline, desipramine, and mianserin) for 21 days (but not 1 day) increased BDNF mRNA level by up to 81% in hippocampus, while only tranylcypromine raising BDFN mRNA level by 103% in frontal cortex; in addition, the same successive 21 day antidepressant administration completely prevented the down-regulation of hippocampal BDNF mRNA level caused by restraint stress, when examined at the 21st day. In 2001, Fukumoto et al. (49) provided the evidence that chronic (up to 28 days) treatment of rats with lithium-containing diet increased BDNF protein level by up to 90% in hippocampus, temporal, and frontal cortex; in contrast, the same lithium treatment did not alter levels of TrkB, a receptor of BDNF, as well as glia-derived neurotrophic factor and its receptor. By using cultured cerebral cortical neurons prepared from wild-type mice (+/+) or heterozygous (−/+) and homozygous (−/−) mice lacking BDNF, Hashimoto et al. (50, 51) showed that lithium failed to protect against in vitro glutamate excitotoxicity in cultures from BDNF knock-out mice, in contrast to the complete protection in cultures from wild-type mice. They also observed that long-term treatment of cultured rat cerebral cortical neurons with 1 mM lithium increased BDNF protein level by 40% at day 3 and Tyr$^{490}$-phosphorylation of TrkB by 50% at day 5, suggesting that lithium enhanced BDNF expression and its extracellular secretion, thereby causing BDNF-induced activation of TrkB receptor in an autocrine/paracrine manner. K252a, an inhibitor of the Trk tyrosine kinase family, or a neutralizing antibody against BDNF suppressed the neuroprotective effect of lithium. In rats, Jakobsen and Mørk (52) observed that lithium diet for 3 weeks, causing plasma lithium concentrations at therapeutic range (0.8 – 1.1 mM), increased BDNF protein level by 41% in frontal cortex and by 22% in hippocampus, without altering BDNF mRNA level in these brain regions.

In 2002, Shirayama et al. (53) demonstrated that single 15-min bilateral infusion of BDNF into rat hippocampal dentate gyrus produced an antidepressant effect in behavioral models of depression, the learned helplessness model and forced swim test, while having no effect on locomotor activity and passive avoidance. These effects were observed as early as 3 days after a single infusion of BDNF and lasted for at least 10 days. Similar antidepressant effects were observed with single bilateral hippocampal infusion of neurotrophin-3, but not with nerve growth factor. In addition, infusion of either K252a, or U0126, an inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase (i.e., MAPK/ERK kinase is abbreviated to MEK) blocked the effect of BDNF on learned helplessness, suggesting that antidepressant effect of BDNF involves TrkB-induced activation of...
the MEK-ERK pathway. Critical roles of BDNF in mood disorder pathogenesis and antidepressant therapeutic mechanism are reviewed in a recent article (51).

**Activation of cell survival signaling pathways**

The phosphoinositide 3-kinase (PI3K)/phosphoinoside-dependent kinase 1/Akt (also called protein kinase B)/GSK-3 pathway and Ras/Raf-1/MEK/ERK pathway are conserved from Caenorhabditis elegans to mammals; and they are pivotal to formation/maintenance/repair of the neuronal network, cell survival, and longevity (54 – 57). Conversely, dysregulation of these signaling pathways is the major mechanism underlying the pathology of neurodegenerative diseases (e.g., Alzheimer’s disease) (54 – 57). GSK-3 is constitutively active in nonstimulated cells and catalyzes phosphorylation of signaling proteins (e.g., glycogen synthase), transcription factors (e.g., ß-catenin), translation initiation factor eIF2B, and structural proteins (e.g., tau), thereby keeping these protein substrates in an inactive state or promoting their degradation (54, 56, 57). Stimulation of tyrosine kinase family (e.g., BDNF, insulin, and IGF-I), G protein-coupled receptors, or Wnt receptor causes Ser/Thr-phosphorylation of GSK-3α/β and inhibits GSK-3 activity, turning on the signaling pathways constitutively repressed by GSK-3 in nonstimulated cells; thus, the inhibition of GSK-3 activity is a critical convergence event in the promotion of cell survival caused by receptor tyrosine kinase family, G protein-coupled receptors and Wnt receptor (56). The discovery of GSK-3β inhibition by lithium in 1996 (41) has greatly aided the cytoprotective molecular mechanisms of lithium. Lithium is a competitive inhibitor of Mg2+ (3), suppressing ATP-Mg2+-dependent catalytic activity of GSK-3. In addition, lithium increases Ser/Thr-phosphorylation of GSK-3α/β via as yet fully-defined mechanisms, inhibiting catalytic activity of GSK-3α/β (58).

In cultured rat cerebellar granule cells, Chalecka-Franaszek and Chuang (10) showed that treatment for 4 days with Ly294002 or wortmannin, an inhibitor of PI3K, abolished constitutive activity of Akt and induced neuronal death, which were attenuated by pretreatment with 3 mM lithium. In addition, glutamate-induced reduction of Akt-1 activity, as well as the associated excitotoxicity and caspase-3 activation were prevented by lithium. They found that lithium activated PI3K itself, which in turn, resulted in PI3K-dependent phosphorylation/activation of Akt-1 and Akt-catalyzed phosphorylation/inactivation of GSK-3, protecting against glutamate excitotoxicity.

In cultured rat cerebellar granule cells, Mora et al. (27) observed that switching from 25 mM [K+]o, to 5 mM [K+]o, would induce activation of as yet unidentified serine/threonine phosphatase, which dephosphorylates/inactivates Akt and then dephosphorylates/activates GSK-3, resulting in caspase-3 activation for apoptosis; in the presence of lithium, this phosphatase was inhibited, and hence, Akt and GSK-3 remained phosphorylated, suppressing caspase-3 activation and apoptosis caused by 5 mM [K+]o, medium.

In PC12 cells, Bhat et al. (26) observed that nerve growth factor withdrawal increased Tyr216-phosphorylation of GSK-3β, thus activating GSK-3β, and induced cell death, with no effect on Ser9-phosphorylation of GSK-3β. They also found that 10 mM lithium prevented the cell death and induced Ser9-phosphorylation/inactivation of GSK-3β, without appreciably changing Tyr216-phosphorylation of GSK-3β. Although the functional relationship between Ser-phosphorylation and Tyr-phosphorylation of GSK-3α/β for regulating catalytic activity of GSK-3α/β is not satisfactorily elucidated (56), their study may implicate that Ser9-phosphorylation of GSK-3β is sufficient to override GSK-3β activation by Tyr216-phosphorylation.

Colchicine-induced apoptosis in cerebellar granule cells is a model of programmed cell death mediated by cytoskeletal derangement, associated with release of various pro-apoptotic molecules from mitochondria (25). In cultured rat cerebellar granule cells, Jordà et al. (25) showed that colchicine treatment (1 ìM for 24 h) caused Ser9-dephosphorylation and Tyr216-phosphorylation of GSK-3β, thus activating GSK-3β. Colchicine-induced activation of GSK-3β and apoptosis were prevented by 1 – 5 mM lithium; in contrast, SB216763 or SB415286, an inhibitor of GSK-3, failed to prevent colchicine-induced apoptosis, suggesting that the anti-apoptotic effect of lithium was not mediated by GSK-3β inhibition in this condition. They also observed that colchicine increased cyclin-dependent kinase 5 (Cdk5) level and stimulated breakdown of the regulatory p35 subunit of Cdk5, generating the p25 subunit, a condition known to cause hyperphosphorylation of tau catalyzed by dysregulated constitutive active Cdk5/p25; these effects of colchicine were prevented by pretreatment with lithium (5 mM for 24 h). These results suggest a previously unrecognized neuroprotective mechanism of lithium, that is, promotion of normal hetero-protein complex formation between Cdk5 and p35.

Pardo et al. (59) found that lithium exhibited opposite effects between glial cells and neurons, independent of GSK-3β inhibition by lithium. In cultured rat astrocytes, lithium (1 – 10 mM for up to 7 days) significantly reduced phosphorylation of MEK and ERK in a time- and concentration-dependent manner, leading to DNA synthesis inhibition and cell cycle arrest at the G1/M

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*Note: The text contains abbreviations and terms specific to the field of neuroscience and molecular biology. The full context of these terms would require additional background knowledge.*
phase. In contrast, treatment of cultured rat cerebellar granule neurons with lithium (5 and 10 mM for 24 h) enhanced phosphorylation of MEK and ERK. The authors conclude that these opposite effects of lithium on astrocytes and neurons make lithium treatment a promising strategy to favor neuronal repair and reduce reactive gliosis after neuronal injuries.

Activation of cyclic AMP-responsive element binding protein (CREB)

One of the downstream substrates of cell survival signaling pathways is CREB, which promotes transcription of neuroprotective molecules, including BDNF and Bcl-2 (51, 60). BDNF and serotonin (5-hydroxytryptamine, 5-HT) function in a cooperative manner to regulate neuronal plasticity and survival; stimulation of 5-HT receptors followed by CREB activation increases transcription of BDNF gene, whereas BDNF promotes growth and sprouting of 5-HT neuronal axons innervating the cerebral cortex (60).

In rats, Nibuya et al. (61) showed that intraperitoneal injection of various antidepressants (i.e., tranylcypromine, sertraline, desipramine, imipramine, and fluoxetine) for 21 days increased CREB mRNA and protein levels, as well as BDNF and trkB mRNA levels in hippocampus. In human neuroblastoma SH-SY5Y cells, Grimes and Jope (62) found that DNA binding activity of CREB was increased by approximately 130% with lithium treatment (1 mM for 1 h) in the absence of extracellular serum. It is known that transcriptional activity of CREB requires Ser<sup>133</sup>-phosphorylation of CREB, which is regulated by adenylate cyclase, Ca<sup>2+</sup>, and growth factors (62). In addition, Ser<sup>129</sup>-phosphorylation of CREB is the priming event for permitting Ser<sup>129</sup>-phosphorylation of GSK-3β (56), leading the authors to conclude that lithium increased DNA binding activity of CREB by inhibiting GSK-3β-catalyzed Ser<sup>129</sup>-phosphorylation/inactivation of CREB (62). Furthermore, addition of serum caused both phosphorylation/activation of Akt and Ser<sup>9</sup>-phosphorylation/inactivation of GSK-3β, increasing DNA binding activity of CREB (62). Conversely, overexpression of active GSK-3β completely blocked enhancement of CREB DNA binding activity caused by epidermal growth factor, IGF-I, forskolin, and cyclic AMP; these blocking effects of overexpressed GSK-3β were reversed by lithium (62).

In cultured rat cerebellar granule neurons, Kopnisky et al. (12) showed that glutamate-induced, NMDA receptor-mediated, excitotoxicity was associated with reduction of Ser<sup>129</sup>-phosphorylation of CREB; the latter was prevented by chronic (but not acute) treatment with lithium (3 mM for 7 days) via multiple mechanisms, including reduction of protein phosphatase 1 activity and increase of MEK activity. In rats subjected to intraperitoneal injection of lithium for up to 28 days, Son et al. (63) showed that long-term potentiation in hippocampal slices was enhanced, largely due to the up-regulation and activation of various proteins (e.g., CREB, BDNF, TrkB, and Bcl-2).

In 2001, the herpes simplex virus-mediated gene transfer study by Chen et al. (64) demonstrated that bilateral overexpression of CREB in rat hippocampal dentate gyrus produced antidepressant effects, as evaluated by the learned helplessness model and the forced swim test; in contrast, overexpression of CREB in rat CA1 pyramidal cell layer of hippocampus or prefrontal cortex had no effect.

Promotion of neurogenesis by antidepressant drugs

In the adult human brain, loss of neurons has long been thought to be irreversible, because of the apparent no birth of new neurons. In contrast to this traditional view, Eriksson et al. (65) documented that neurogenesis continues to occur in hippocampus obtained from autopsy of 5 cancer patients, as previously shown to occur in adult brains of various animal species (e.g., birds, rodents, and nonhuman primates) (2, 44, 45). In normal adult brain, newborn cells from the subgranular zone of hippocampus, located at the border between the granule cell layer and the hilus, give rise to granule cells in the granule cell layer; in addition, newborn cells from the subventricular zone (also called subependymal zone) migrate toward the olfactory bulb via the rostral migratory stream (44, 45). In adult human brain, however, replenishment of newborn cells from the subventricular zone to olfactory bulb was recently debated, due to the apparent lack of rostral migratory stream in human subventricular zone specimens from 65 neurosurgical resections and 45 autopsied brains (66).

Adult brain neurogenesis is a dynamic process that is positively and negatively regulated by various intrinsic and extrinsic factors. Among others, neurogenesis-promoting factors include learning task, enriched environment (67); physical exercise (68); various growth factors [e.g., BDNF (see review 51) and IGF-1 (57, 68, 69)]; neurotransmitters/hormones [e.g., serotonin (see review 60), dopamine (70, 71), noradrenaline (see review 72), estrogen, and dehydroepiandrosterone]; CREB; and antidepressants (e.g., lithium) (44, 45). In contrast, aging, stress, opioids, as well as activation of NMDA receptors and hypothalamic-pituitary-adrenal axis retard neurogenesis (44, 45). In particular, chronic stress-induced increase in plasma glucocorticoid level may account for the development of brain atrophy associated with depressive illness. In granule neuron progenitor cells in the hippocampal dentate gyrus of...
adult rats, corticosterone-induced reduction of cell proliferation was prevented by MK-801, an inhibitor of NMDA receptor; glucocorticoids and NMDA receptor activation may retard neurogenesis via a common as yet unidentified mechanisms (73). Antidepressant treatment may prevent or even reverse neurogenesis retardation, which involves activation of CREB and increased expression of BDNF (1, 2, 44, 45). Importantly, impairment of neurogenesis is proposed to be the common unifying pathogenesis for various neurodegenerative diseases (e.g., tauopathies, Alzheimer’s disease, Parkinson’s disease, Lewy body dementia, and α-synucleinopathies), which exhibit distinct, yet continuous spectrum of overlapping, clinical symptoms and neuropathological abnormalities (e.g., original identification of α-synuclein pathology in Alzheimer’s disease, prior to its well-known involvement in Parkinson’s disease) (72, 74, 75).

**Lithium-induced proliferation and neuronal differentiation of newborn cells**

In 2000, Chen et al. (76) documented that treatment of adult mice with lithium diet for up to 4 weeks (mouse plasma lithium, 0.97 ± 0.20 mM; human therapeutic plasma lithium, 0.6 – 1.2 mM) caused 25% increase in the number of dividing hippocampal dentate gyrus cells, as evidenced by the increased incorporation of [3H]bromo-deoxy-uridine into DNA during S-phase of mitotic cell cycle, as well as by the double-labeling of bromo-deoxy-uridine and neuron-specific protein marker NeuN; it was associated with 38% increase of Bcl-2 level in hippocampus. In the same year, Malberg et al. (77) found that chronic (but not acute) intraperitoneal injection of antidepressants (e.g., fluoxetine, a selective serotonin reuptake inhibitor) or electroconvulsive shock in rats increased the number of dividing cells in dentate gyrus and hilus of hippocampus; these newborn cells underwent proliferation and neuronal differentiation. In cultured rat cerebellar granule cells and cerebral cortical cells, Hashimoto et al. (78) showed that 5-day treatment with lithium increased progenitor cell proliferation, with cerebral cortical cells being approximately 10-fold more sensitive to lithium than cerebellar granule cells. In addition, lithium prevented loss of neuronal progenitor cell proliferation caused by glutamate, glucocorticoids, and haloperidol in cerebellar granule cells. Kim et al. (79) showed that treatment of cultured rat embryonic hippocampal neuronal progenitor cells with lithium (1 and 3 mM for 4 days) increased both cell proliferation and differentiation toward a neuronal phenotype, while decreasing an astrocytic phenotype, when cultured in high-cell density condition; in low-cell density culture condition, the same lithium treatment increased neuronal differentiation, but did not increase number of proliferating cells. Lithium-induced cell proliferation and neuronal differentiation observed in high-cell density culture condition were dependent on phosphorylation/activation of both ERK and CREB. The same lithium treatment, however, did not increase Bcl-2 and BDNF levels, implicating that lithium-induced neurogenesis took place via signaling pathways distinct from those of lithium-induced, Bcl-2/BDNF-mediated, cell survival. In addition, intraperitoneal injection of lithium for 28 days in adult rats facilitated hippocampal neurogenesis via signaling pathways that involve phosphorylation/activation of both ERK and CREB.

**Lithium-induced neuronal regeneration**

Adult mammalian optic nerve regenerates poorly after injury. Injured retinal ganglion cells undergo apoptotic cell death because they express extremely low level of Bcl-2; the expression of Bcl-2 in retinal ganglion cells coincides with the regenerative capacity of the cells after injury. By using the regeneration assay model, in which axons projecting from mouse retinal ganglion cells were transected before culture, Huang et al. (80) showed that lithium (0.5 – 5 mM for 5 days) promoted the survival of cultured retinal ganglion cells, and it increased the neurite number and length of regenerating retinal ganglion cells, concomitant with up-regulation of Bcl-2 level. In retinal ganglion cells prepared from wild-type mice, or mice overexpressing or lacking Bcl-2, it was found that lithium-induced up-regulation of Bcl-2 was essential to lithium-induced axonal regeneration; the overexpression of Bcl-2 promoted per se axonal regeneration and eliminated additional increasing effect of lithium on axonal regeneration.

**Fate of newborn cells: intracellular signalings for survival and maturation**

Although many of the newborn cells survive and develop into mature granule cells in hippocampal dentate gyrus, 50% – 60% of the newborn cells undergo degeneration by several weeks after birth (81). The number and survival of newborn cells are increased by hippocampus-dependent learning and enriched environment, whereas the underlying mechanisms remain unknown. By using adult mice, Nakagawa et al. (81) examined the intracellular signaling pathways that promote survival of newborn cells. In virtually all immature hippocampal neurons, CREB was constitutively phosphorylated; 3-week intraperitoneal injection of rolipram, an inhibitor of cyclic AMP-specific phosphodiesterase type 4, or fluoxetine, a selective serotonin reuptake inhibitor that increases expression and phos-
phorylation of CREB in hippocampal granule cell layer (61), increased the survival of dividing neuronal cells. In addition, the cyclic AMP-CREB pathway promoted gene transcription of polysialic acid synthase that catalyzes the rate-limiting reaction for the synthesis of polysialic acid-neural cell adhesion molecule, a marker of immature neurons undergoing remodeling and plasticity.

Fujoka et al. (82) reported that the cyclic AMP-CREB pathway stimulated morphological maturation of newborn cells. In mice, 2 week-intraperitoneal injection of rolipram, an inhibitor of phosphodiesterase type 4, increased branch number and length of dendrites in the subgranular zone of the hippocampus, concomitant with increased level of phosphorylated CREB; these morphological changes were not observed in hippocampus prepared from transgenic mice expressing a dominant-negative mutant form of CREB.

**Functional and morphological integrity of newborn neurons**

Conventional methods have been employed to study adult brain neurogenesis by using the fixed tissue preparation. In 2002, however, van Praag (83) showed that in the living hippocampus of adult mouse brains, newly generated cells were integrated into the hippocampal circuitry; they displayed action potential and functional synaptic inputs, as well as neuronal morphology, similar to those found in mature dentate granule cells.

**Phenotypic characterization of newborn neurons**

Laeng et al. (84) characterized the neurotransmitter phenotype of proliferating progenitor cells that were responsive to antidepressants. In cultured embryonic rat cortical primordial stem cells, treatment with lithium (1 mM for 6 days) or valproate, an anticonvulsant drug used as a mood-stabilizer in the treatment of manic-depressive illness, increased neurogenesis and Bcl-2 gene transcription of polysialic acid synthase that catalyzes the rate-limiting reaction for the synthesis of polysialic acid-neural cell adhesion molecule, a marker of immature neurons undergoing remodeling and plasticity.

Focal X-ray irradiation to mouse brain directed toward the hippocampus prevented both neurogenesis and behavioral improvements caused by fluoxetine and imipramine.

**Potential molecular mechanisms of lithium-induced neurogenesis**

A mature neuron typically has a single axon and multiple dendrites. Dendrites usually receive signals, whereas axon usually sends signals; thus, the specification of axon and dendrite, referred to as neuronal polarity, is a critical step in neuronal maturation. One of the hallmarks distinguishing growing axon from dendrite is their different growing rates. Embryonic neurons extend several equipotential neurites; the fast growing neurite is destined to become an axon, whereas the others eventually become dendrites.

The molecular mechanisms of neuronal polarity are largely unknown (86, see reviews 87 – 89). In brain, GSK-3β is developmentally regulated, with peak level of expression during axogenesis; GSK-3β is present in growing axon, but completely excluded from the axon at the end of axogenesis, being restricted to the cell body and dendrites of mature neurons (87). In 2005, Jiang et al. (86) documented that expression of a constitutively active mutant form of GSK-3β in cultured embryonic rat hippocampal neurons inhibited axon formation; in contrast, reduction of GSK-3β activity by various methods (e.g., 1 mM lithium, 5 μM SB216763, and 10 μM SB415286) led to the formation of multiple axons from a single neuron. In particular, GSK-3β inhibitors led to the conversion of existing dendrites into axons, leading Jiang et al. to propose that application of GSK-3β inhibitors can be a novel approach to promote generation of new axons after neuronal injuries.

Cell polarity is a fundamental property of virtually all cells. Although the effect of GSK-3β inhibitor has not been examined, Etienne-Manneville and Hall (90) documented that cell polarity of astrocyte is also directed by the monomeric GTPase Cdc-42/ atypical protein kinase C-ζ/GSK-3β pathway and the resultant interaction between adenomatous polyposis coli protein and plus ends of microtubules.

**Neurogenesis and voltage-dependent sodium channels**

It is known that voltage-dependent sodium channels are indispensable for the generation and conduction of action potentials of motor, sensory, and autonomic neurons in an established neuronal circuit. Different patterns of action potentials are decoded via not-fully identified mechanisms and translated into other ionic and metabolic signals in a spatiotemporal-specific manner, regulating specific short- and long-term cellular
events (91–94). More importantly, evidences have emerged that sodium channels play previously unrecognized pivotal roles in neurogenesis. Extending axon with higher electrical activity developed its growth cone into the functionally competent nerve terminal, whereas extending neighboring axon with lower electrical activity failed to do it, an event termed axonal competition (91). Sodium channels were essential for the extending axon to find its way to form correct neuroeffector synapse, referred to as pathfinding (92). Sodium channels are scaffold proteins to assist the formation of spatial-specific hetero-protein complex at the initial segment of axon (sodium channels/ankyrinβ/neuron-glia cell adhesion molecule-related cell adhesion molecule/neurofascin) and the node of Ranvier, maintaining structural integrity and function of neurons (93).

According to the general view, the profile of neurotransmitters that the particular neuron expresses for communicating with other neurons via elaborating synaptic connections may be encoded by the genetic program and invariable. Surprisingly, however, the differing degrees of neuronal activity can specify the phenotypic expression of the particular neurotransmitters (94). In developing spinal cord of Xenopus laevis embryos, Borodinsky et al. (94) documented that enhancement of electrical activity caused by overexpression of sodium channels culminated in the increased expression of inhibitory neurotransmitters (GABA and acetylcholine); the reverse occurred when the electrical activity was decreased by overexpression of inward rectifier Kir2.1 potassium channels (94).

Much remains elusive about the molecular and cellular mechanisms of lithium- or antidepressant-induced neurogenesis. In particular, no study to date examined whether sodium channels could be involved in the neurogenesis. In cultured bovine adrenal medullary chromaffin cells (embryologically derived from the neural crest), we observed that chronic (=24 h) treatment with therapeutic concentrations of valproate or lithium increased sodium channel α- or β1-subunit mRNA level, and up-regulated the number of cell surface sodium channels by up to 40%, as evidenced by [3H]saxitoxin binding assay (57, 95). Lithium accelerated sodium channel α-subunit gene transcription by up to 50% without changing α-subunit mRNA stability. In valproate-treated cells, 22Na influx via voltage-dependent sodium channels was increased, enhancing 45Ca influx via voltage-dependent calcium channels and exocytic secretion of catecholamines. Up-regulation of cell surface sodium channels by lithium and valproate, and the subsequent enhanced exocytosis of neurotransmitters may be instructive in understanding the neurogenesis mechanisms of lithium and antidepressant drugs.

Alzheimer’s disease

Defining neuropathological hallmarks of Alzheimer’s disease include the intracellular neurofibrillary tangles attributed to abnormal hyperphosphorylation of microtubule-binding protein tau and the extracellular neuritic plaques consisting of insoluble aggregation of β-amyloid peptide (55, 96, 97). It has become increasingly evident that aggregates of β-amyloid peptide may be the trigger causing hyperphosphorylation of tau, proposing the amyloid cascade hypothesis (18, 96, 97). In 1997, Hong et al. (98) documented that lithium (0.5–25 mM) inhibited GSK-3β-catalyzed phosphorylation of tau, then enhanced binding of tau to microtubules, and promoted microtubule assembly in cultured human NT2N neurons. In PC12 cells and cultured rat cerebellar granule cells, Wei et al. (17) found that 24-h treatment with β-amyloid increased cell death; it was significantly prevented by pretreatment with 3 mM lithium, associated with lithium-induced 2-fold up-regulation of Bcl-2 level. In differentiated Neuro 2A cells and cultured rat hippocampal neurons, De Ferrari et al. (21) showed that β-amyloid-induced cytotoxicity and destabilization of β-catenin were prevented by lithium.

In 2002, Sun et al. (19) found that lithium (5–20 mM) decreased extracellular secretion of β-amyloid from COS7 cells transfected with amyloid precursor protein. In Chinese hamster ovary cells expressing amyloid precursor protein, Phiel et al. (20) reported that lithium inhibited β-amyloid production with an IC50 of 1–2 mM via inhibiting GSK-3α (but not GSK-3β), as evidenced by short interference RNAs directed against GSK-3α and GSK-3β; in addition, 3 week-feeding of lithium gavage in mice, with serum lithium level of 0.8–1.2 mM, decreased β-amyloid level in the brain. In human embryonic kidney 293 cells and transgenic mouse brains of Alzheimer’s disease model, Su et al. (23) observed that therapeutically relevant concentration of lithium (e.g., plasma lithium concentration 0.6 mM) decreased β-amyloid production via inhibiting GSK-3β, as evidenced by using a dominant negative GSK-3β kinase-deficient construct or GSK-3β antisense oligonucleotide.

In cultured cholinergic neurons in rat septal and basal forebrain, Hoshi et al. (22) reported that β-amyloid increased GSK-3β activity by 2.8-fold and induced neuronal cell death, both of which were prevented by lithium (IC50 = 2 mM). Preventive effect of lithium against β-amyloid toxicity was observed, even when lithium was added even 1 h after β-amyloid insult. Beneficial effects of lithium treatment on tau phosphory-
loration and β-amyloid-induced neurodegeneration have been summarized in a review article (18).

Parkinson’s disease

In cultured human SH-SY5Y cells and rat cerebellar granule neurons, treatment with 6-hydroxydopamine (6-OHDA), a compound widely used to create sporadic Parkinson’s disease model, caused ER stress, which is characterized by phosphorylation/inactivation of eukaryotic translation initiation factor-2α, up-regulation of anti-apoptotic Grp78, as well as apoptotic CHOP and cleavage of caspase-12 (32). In addition, 6-OHDA decreased Ser\(^\beta\)-phosphorylation/inactivation of GSK-3β, whereas 6-OHDA increased Tyr\(^\beta\)-phosphorylation/activation of GSK-3β. Lithium prevented 6-OHDA-induced caspase-3 cleavage, DNA fragmentation, and cell death. Stimulation of BDNF receptor TrkB prevented 6-OHDA-induced Ser\(^\beta\)-dephosphorylation/activation of GSK-3β and ameliorated the neurotoxicity.

In vivo neuroprotective and neuroregenerative effects of lithium: animal models of various neurodegenerative diseases and human patients with manic-depressive illness

Brain ischemia

In rats subjected to permanent ischemia due to occlusion of the left middle cerebral artery, pretreatment with subcutaneous injections of therapeutically relevant doses of lithium for 16 days reduced ischemic infarct size by 56% and improved neurological deficits, including abnormal posture and hemiplegia (7). In the rat model of 1-h occlusion of the left middle cerebral artery followed by reperfusion, infarct volume was decreased by up to 50% in a dose-dependent manner by subcutaneous injection of lithium, even when administered up to 3 h after the onset of ischemia (8). Ischemia/reperfusion-induced neurological deficits, as evaluated by ten different tests for motor, sensory, and reflex abnormalities, were significantly ameliorated by post-insult daily administration of lithium for up to 6 days (8). Also, ischemia/reperfusion-induced increase of neurons with DNA damage was reduced by post-insult daily administration of lithium. Immunohistochemistry and Western blot analysis revealed that these neuroprotective effects of lithium were associated with up-regulation of 70-kDa heat-shock protein (Hsp70) in neuronal cells, which was preceded by an increase in DNA binding activity of heat shock factor 1, a transcriptional factor that regulates transcription of the Hsp70 gene (8).

Alzheimer’s disease model

In rats injected with β-amyloid fibrils into the dorsal hippocampus, De Ferrari et al. (21) observed that intraperitoneal injection of lithium prevented the β-amyloid-induced hippocampal neurodegeneration, destabilization of β-catenin, and improved the β-amyloid-induced spatial learning deficit, as evaluated by Morris water maze test.

Model of tauopathies

Abnormal hyperphosphorylation of tau and the subsequent formation of neurofibrillary tangles in the absence of β-amyloid deposition are the defining neuropathologies of tauopathies, including frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), and Alzheimer’s disease (74). In addition, it has become increasingly evident that clinical symptoms and pathological findings of tauopathies (e.g., Alzheimer’s disease) could be overlapped with those of α-synucleinopathies (e.g., Parkinson’s disease and Lewy body dementia), accounting for most late-onset age-related human progressive neurodegenerative diseases; in fact, α-synuclein pathology was originally identified in Alzheimer’s disease (72, 75). Furthermore, in Alzheimer’s disease, formation of neurofibrillary tangles is stimulated by β-amyloid; in mice that overexpressed a mutant form of tau, as occurring in FTDP-17, injection of β-amyloid into the hippocampus increased tau phosphorylation and filament formation in the amygdala, one of the brain regions affected in Alzheimer's disease (18, 96, 97).

FTDP-17 may be caused by dominant missense mutations in the tau gene. In transgenic mice expressing three missense mutations of tau, 6 week-feeding of lithium diet (plasma lithium concentration 1.24 ± 0.1 mM) attenuated GSK-3-catalyzed phosphorylation of tau, reducing neurofibrillary tangle formation by 60% (37). In transgenic mice overexpressing mutant human tau, Noble et al. (39) showed that intraperitoneal injection of lithium for 30 days (plasma concentrations of lithium was maintained at physiologically relevant levels) increased Ser\(^\beta\)-phosphorylation of GSK-3β with the reduction of GSK-3β activity in brain; it was associated with the reduction of tau phosphorylation at sites to be hyperphosphorylated in Alzheimer’s disease and with reduced levels of aggregated insoluble tau. The levels of aggregated tau correlated strongly with axonal degeneration, and the axonal degeneration was attenuated in lithium-treated mice.

In the fruit fly Drosophila, Mudher et al. (38) showed that overexpression of wild-type human tau disrupted axonal transport of motor neurons and caused paralysis of dorsal musculature, without inducing neuron death;
coexpression of constitutively active GSK-3β enhanced, whereas lithium or AR-A014418, an inhibitor of GSK-3β, reversed both the axonal transport deficit and muscle paralysis, suggesting that neuronal function-imparing effects of tau are tau phosphorylation-dependent, which may occur before the formation of classical neuro-pathological hallmarks of aggregated tau.

Parkinson’s disease model
In the mouse model of Parkinson’s disease rendered by intraperitoneal injection of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 4-week feeding of various doses of lithium (plasma lithium concentrations between 0.2 and 1.7 mM) prior to MPTP insult prevented MPTP-induced decreases of dopamine level, as well as of tyrosine hydroxylase activity and protein level in striatum (33). MPTP significantly decreased Bcl-2 level, while increasing Bax level in striatum; lithium increased striatal Bcl-2 level in MPTP-nontreated mice and prevented MPTP-induced changes of Bcl-2 and Bax levels.

Huntington’s disease model
In a rat model of Huntington’s disease in which quinolinic acid was unilaterally infused into the striatum, subcutaneous injection of lithium 24 h before and 1 h after quinolinic acid injection significantly protected against neuronal cell loss, when evaluated 7 days later (34). Lithium prevented apoptosis by attenuating quinolinic acid-induced DNA damage and activation of caspase 3, concurrent with up-regulation of Bcl-2 level; in addition, lithium promoted neuronal and astroglial progenitor cell proliferation, protecting against apoptosis (36).

Huntington’s disease is caused by an abnormal polyglutamine expansion in the coding region of the affected gene. In COS-7 cells transfected with the 74 glutamines, pretreatment with lithium reduced polyglutamine toxicity via inhibiting GSK-3β activity; SB216763, an inhibitor of GSK-3, or overexpression of dominant-negative mutant GSK-3β also prevented the cytotoxicity (35). GSK-3β inhibition by lithium or SB216763 increased β-catenin level, promoting β-catenin-dependent gene transcription that is otherwise inhibited by polyglutamine toxicity.

Human patients with manic-depressive illness
In 1997, Drevet et al. (99) documented that cerebral blood flow and glucose metabolism rate were abnormally decreased in the prefrontal cortex of patients with familial bipolar manic-depressive illness and familial unipolar depressive disorder; in addition, mean gray matter volumes in the same brain area were reduced by 39 and 48% in bipolar and unipolar patients (see review 2). Moore et al. (46, 47) reported that 4-week masked lithium treatment, at doses producing therapeutic plasma concentrations of lithium, increased total gray (but not white) matter volume by up to 8% in 8 out of 10 manic-depressive illness patients examined (7 men, 3 women; average age 33.0 years). In 21 manic-depressive illness patients without medication and 9 healthy volunteers, the same 4-week lithium treatment caused up to 8% increase in the level of N-acetyl-aspartate, a putative functional marker of mature neurons (but not glia), in occipital, temporal, frontal, and parietal lobes. Sassi et al. (100) showed that total gray matter volume was significantly increased in lithium-treated manic-depressive illness patients (747.9 ± 69.8 cm³, n = 17), compared with nontreated patients (639.2 ± 91.2 cm³, n = 12) and healthy individuals (675.8 ± 61.8 cm³, n = 46).

Conclusions
The last decade has witnessed three surprising, previously unexpected, findings that 1) mood disorders are attributed to the impairments of cell survival and cell death signaling pathways, finally culminating into abnormalities in functional and morphological plasticity in neurons; 2) antidepressants (e.g., lithium) protect or even could reverse these functional and morphometric derangements; and 3) neurogenesis occurs throughout the lifetime in hippocampus of adult human brain, suggesting that increased neuronal cell death and/or decreased neurogenesis are associated with mood disorders, which are prevented or restored by antidepressants. In this context, mood disorders are considered to be a novel class of neurodegenerative diseases; in addition, antidepressants are expected to be beneficial in the treatment of acute neuronal injuries and chronic progressive inexorable neurodegenerative diseases.

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