Critical Review

Lithium and Neuropsychiatric Therapeutics: Neuroplasticity via Glycogen Synthase Kinase-3β, β-Catenin, and Neurotrophin Cascades

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Abstract. Mood disorders are not merely attributed to the functional defect of neurotransmission, but also are due to the structural impairment of neuroplasticity. Chronic stress decreases neurotrophin levels, precipitating or exacerbating depression; conversely, antidepressants increase expression of various neurotrophins (e.g., brain-derived neurotrophic factor and vascular endothelial growth factor), thereby blocking or reversing structural and functional pathologies via promoting neurogenesis. Since the worldwide approval of lithium therapy in 1970, lithium has been used for its anti-manic, antidepressant, and anti-suicidal effects, yet the therapeutic mechanisms at the cellular level remain not-fully defined. During the last five years, multiple lines of evidence have shown that the mood stabilization and neurogenesis by lithium are due to the lithium-induced inhibition of glycogen synthase kinase-3β (GSK-3β), allowing accumulation of β-catenin and β-catenin–dependent gene transcriptional events. Altered levels of GSK-3β and β-catenin are associated with various neuropsychiatric and neurodegenerative diseases, while various classical neuropsychiatric drugs inhibit GSK-3β and up-regulate β-catenin expression. In addition, evidence has emerged that insulin-like growth factor-I enhances antidepression, anti-anxiety, memory, neurogenesis, and angiogenesis; antidepressants up-regulate expression of insulin-like growth factor-I, while insulin-like growth factor-I up-regulates brain-derived neurotrophic factor expression and its receptor TrkB level, as well as brain-derived neurotrophic factor-induced synaptic protein levels. More importantly, physical exercise and healthy diet raise transport of peripheral circulating insulin-like growth factor I into the brain, reinforcing the expression of neurotrophins (e.g., brain-derived neurotrophic factor) and the strength of cell survival signalings (e.g., phosphoinositide 3-kinase / Akt / GSK-3β pathway). This review will focus on the rapidly advancing new trends in the last five years about lithium, GSK-3β/β-catenin, and neurotrophin cascades.

Keywords: lithium, glycogen synthase kinase-3β (GSK-3β)/β-catenin pathway, mood disorder, neuroplasticity, neurotrophin cascade

1. Introduction

Since the worldwide approval of lithium therapy in 1970, lithium has been the mainstay for the treatment of manic-depressive illness, exhibiting various benefits, including anti-manic and antidepressant effects, a long-term prophylactic effect, and an anti-suicidal effect (see reviews 1 – 3). The last decade has witnessed the

following discoveries about neuropsychiatric disorders: 1) mood disorders are not solely attributable to functional impairments of neurotransmission, but also caused by aberrant decreased expression of neurotrophins (e.g., brain-derived neurotrophic factor and vascular endothelial growth factor) with the subsequent defect of neuroplasticity, thus sharing the common morphological deficits with neurodegenerative diseases; 2) antidepressants block or reverse these pathologies; and 3) neurogenesis (i.e., a birth of new neurons) continuously occurs in the hippocampus even in adult human brain (see reviews 2, 4, 5). Therefore, increasing evidence suggests that lithium can be used in the treatment of acute brain

injuries (e.g., ischemia) and chronic neurodegenerative diseases (e.g., Alzheimer's disease); the downstream mediator molecules of lithium's effects have been increasingly elucidated, ranging from up-regulation of cell survival molecules (e.g., brain-derived neurotrophic factor and vascular endothelial growth factor) to down-regulation of pro-apoptotic activities (e.g., excitotoxicity) (see reviews 1 – 3). Since 2004, it has been documented that among the multiple direct target molecules of lithium identified so far (e.g., inositol monophosphatase), the beneficial effects of lithium, such as mood stabilization, behavioral amelioration, and neurogenesis, are due to the inhibition of glycogen synthase kinase-3β (GSK-3β) by lithium, which promotes β-catenin–dependent transcriptional events (see reviews 1 – 3, 6, 7).

Although mood disorders are frequently associated (i.e., co-morbidity) with other pathological components (e.g., insulin resistance and proinflammatory cytokines) (see review 8), new trends in the last five years have revealed that insulin-like growth factor-I (IGF-I), IGF-II, and insulin enhance mood (9 – 12), memory (13, 14), neurogenesis (13, 14), and angiogenesis (15); anti-depressants up-regulate expression of IGF-I (16 – 18) and IGF-II (19), while IGF-I up-regulates brain-derived neurotrophic factor and its receptor TrkB (17, 20, 21) (see reviews 6, 22 – 28).

GSK-3, a serine/threonine protein kinase, controls multiple aspects of physiological events (e.g., cell membrane signal-to-gene transcription/protein translation, cytoskeletal organization, neuronal polarity, and cell survival/apoptosis) (see reviews 2, 6, 29 – 31). Consistent with these pleiotropic roles, GSK-3 activity is exquisitely regulated via GSK-3's phosphorylation, subcellular (i.e., cytoplasmic, nuclear, and mitochondrial) translocation, and interaction with other proteins. GSK-3α (51 kDa) and GSK-3β (47 kDa) are encoded by different genes, GSK-3β being more enriched in the nervous system. GSK-3 is constitutively active in nonstimulated cells under the basal quiescent state; thus, GSK-3 continuously phosphorylates signaling molecules (e.g., glycogen synthase), transcription factors (e.g., β-catenin), translational initiation factor eIF2B, and structural proteins (e.g., tau), thereby keeping these GSK-3 substrates in an inactive state or promoting their degradation. Stimulation of receptor tyrosine kinases (e.g., insulin receptor and IGF-I receptor), G-protein–coupled receptors, Ras, and exposure to hyperglycemia activate Akt, protein kinase C, cyclic AMP–dependent protein kinase and p90 ribosomal S6 kinase, which catalyze Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β; this phosphorylation event inhibits the catalytic activity of GSK-3α/3β, thereby turning on signaling pathways otherwise constitutively suppressed by GSK-3α/3β in nonstimulated quiescent cells. In addition, Wnt signaling inhibits GSK-3 activity via an unknown mechanism, independent of Ser-phosphorylation of GSK-3 (see reviews 7, 29). Dysregulated hyperactivity of GSK-3β is associated with insulin resistance, diabetes mellitus, tumorigenesis, inflammation, and neuropsychiatric and neurodegenerative diseases (see reviews 2, 6, 29 – 31). With respect to GSK-3α and GSK-3β, their differences and similarities in tissue distribution and biological roles are summarized (see review 31).

β-Catenin, when sequentially phosphorylated at Ser^{45} by casein kinase I, and at Ser^{33}, Ser^{37}, and Thr^{41} by GSK-3β, undergoes proteasomal degradation; conversely, lithium prevents GSK-3β–catalyzed phosphorylation of β-catenin, enabling β-catenin to accumulate and translocate to the nucleus, where β-catenin facilitates gene transcription (see reviews 7, 29).

Figure 1 summarizes the signaling pathway of receptor tyrosine kinases (RTK), phosphoinositide 3-kinase (PI3K), Akt, and GSK-3β and the β-catenin pathway; the inhibition of GSK-3β by various therapeutics (e.g., lithium) allows β-catenin–induced *de novo* synthesis of IGF-I, IGF-II, brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF). Table 1 lists the multiple mechanisms, whereby mood amelioration, cognition, and neuroplasticity are elaborated by lithium, GSK-3α/3β, IGF-I, IGF-II, BDNF, and VEGF.

2. Lithium: mood stabilization via GSK-3β inhibition and β-catenin activation

2.1. Historical view

Multiple lines of in vitro studies have demonstrated that direct target molecules of lithium include GSK-3 (32, 33; see reviews 29 – 31, 34), phosphoinositide 3-kinase (35), protein phosphatase 2A (36), and other enzymes (e.g., inositol monophosphatase and its structurally related phosphomonoesterases) (see reviews 1 – 3). Among them, GSK-3 has attracted widespread attention as a therapeutic target molecule of lithium.

Lithium is a competitive inhibitor of Mg^{2+}, directly inhibiting Mg^{2+}-ATP–dependent catalytic activity of GSK-3 (33); in addition, lithium increases Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β via as yet not fully-defined mechanisms (e.g., GSK-3–dependent protein phosphatase/inhibitor complex) (37), thereby inhibiting GSK-3 activity (see review 34). By using purified preparation of GSK-3β, a previous in vitro assay showed that lithium inhibits GSK-3β activity with an IC_{50} value of 2 mM (32) or between 1 and 2 mM (38). However, these assays were performed in the presence of 10 mM Mg^{2+}; intracellular concentration of Mg^{2+} in the brain is estimated to be between 0.2 and 1.2 mM (39), thus the
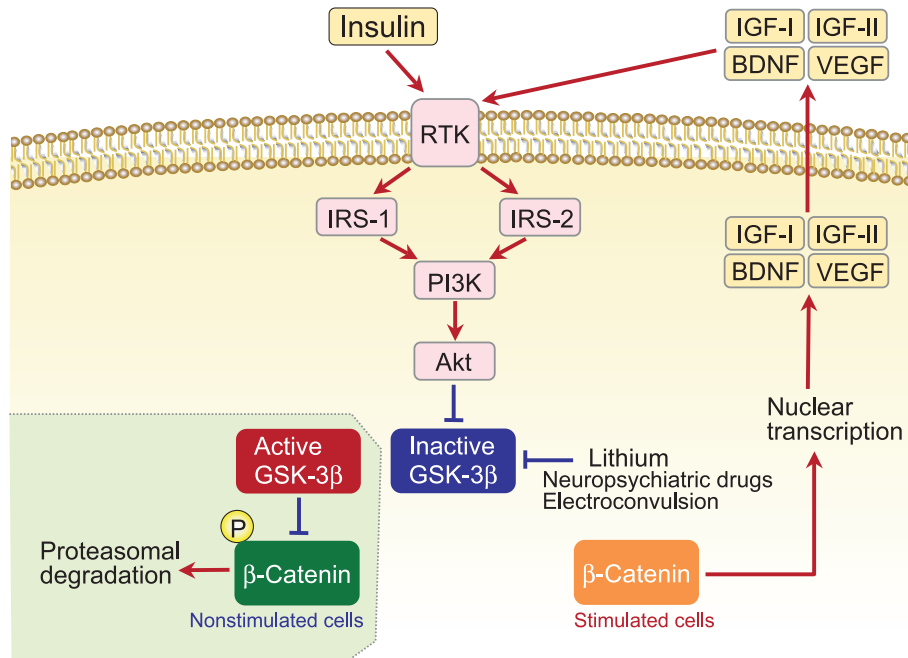
Fig. 1. Signaling cascade of lithium, neuropsychiatric drugs, IGF-I, IGF-II, insulin, and BDNF for antidepression, anti-anxiety, cognition, neurogenesis, and angiogenesis. In neurotrophin-nonstimulated or therapeutics-nontreated cells, constitutive activity of GSK-3β phosphorylates β-catenin, causing proteasomal degradation of β-catenin (shown in left bottom corner). The right half of the figure shows that therapeutics (e.g., lithium) or neurotrophins (e.g., IGF-I) induce inhibitory Ser[9]-phosphorylation of GSK-3β, allowing nuclear translocation of β-catenin and β-catenin–induced gene transcription of IGF-I, IGF-II, BDNF, and VEGF (16 – 21, 50). These neurotrophins may be secreted into the extracellular space and act as autocrine/paracrine factors via RTK, activating the cell survival PI3K/Akt pathway (19). Lithium up-regulates IGF-II expression (19). Antidepressants up-regulate expression of IGF-I (16, 18) and BDNF (17). IGF-I up-regulates BDNF expression (17, 20) and its receptor TrkB level (21). Physical exercise (13 – 15, 20; see reviews 26, 27) and a non-western (i.e., non-cafeteria) style diet (96) increase IGF-I level in the brain via IGF-I synthesis in the brain and transport of peripheral circulating IGF-I into the brain via the blood-brain barrier. Intranasal administration of insulin raises mood in both healthy individuals and Alzheimer's patients (12; for a review, see ref. 6). IRS-1 may be essential for the transcriptional event of β-catenin (105, 106). Constitutive activity of GSK-3β maintains steady-state levels of insulin receptor (108), IRS-1 (104), IRS-2 (104), and Akt-1 (105). In *Caenorhabditis elegans*, lithium increases longevity by inhibiting GSK-3β–dependent methylation of histone in chromatin nucleosomes (52). In a mouse model of depression, imipramine-induced acetylation of histone in chromatin nucleosomes is involved in its antidepressant effect (51). Abbreviations: IGF-I and IGF-II, insulin-like growth factor-I and -II, respectively; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; RTK, receptor tyrosine kinases; IRS-1 and IRS-2, insulin receptor substrate-1 and -2, respectively; PI3K, phosphoinositide 3-kinase; GSK-3β, glycogen synthase kinase-3β. Red arrow, stimulation; Blue T bar, inhibition. Reference numbers are given in parentheses.

concentration of lithium to inhibit GSK-3β activity being considerably lower than 1 – 2 mM. Besides, the in vitro assay of a purified preparation of GSK-3β may not allow lithium-induced inhibitory Ser[9]-phosphorylation of GSK-3β to occur. Therefore, therapeutic serum range (0.5 to 1.2 mM) of lithium inhibits GSK-3β in vivo (39).

2.2. Antidepressant effect: GSK-3β inhibition and β-catenin activation

It has been thought that inhibition of GSK-3 may be a key event in the therapeutic mechanism of several mood stabilizers. Lithium controls mania and stabilizes mood in bipolar disorder patients, but is not generally thought to be an antidepressant; thus, the role of GSK-3 in depressive behavior has not been convincingly demonstrated. In mice, Kaidanovich-Beilin et al. (40) provided the first evidence that intracerebroventricular injection of GSK-3 inhibitor (i.e., L803-mts) exerted a rapid antidepressive-like behavioral effect, when evaluated 1 h later in the forced swimming test. In addition, L803-mts injection increased β-catenin level in the hippocampus, suggesting that in vivo inhibition of GSK-3 in hippocampus produced antidepressive-like behavior.

In normal mice, O'Brien et al. (41) showed that feeding with chow containing 0.2% or 0.4% LiCl for up

Table 1. Lithium, GSK-3α/3β, β-catenin, IGF-I, IGF-II, insulin, brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF): amelioration of mood, cognition, and neuroplasticity

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to 15 days produced a dose-dependent antidepressant effect, as evaluated by the increased mobility in multiple behavioral tests (e.g., forced swimming test). In these mice, LiCl treatment increased β-catenin level in the hypothalamus and accelerated Wnt/β-catenin–dependent in vivo gene transcription in the hippocampus, amygdala, and hypothalamus. Notably, these behavioral and biochemical alterations in LiCl-treated mice were seen in mice lacking one copy of the GSK-3β (+/−) gene.

Dysregulation of brain serotonin neurotransmission has been implicated in depression, anxiety, bipolar disorder, autism, and schizophrenia. Beaulieu et al. (42)

generated knock-in mice expressing a mutant loss-of-function form of brain serotonin synthesis enzyme, a model for human unipolar major depression. The homozygous and heterozygous mutant mice exhibited marked reduction (up to 80%) of brain serotonin production and behavioral abnormalities, with increased activity of GSK-3β and decreased Ser^9-phosphorylation of GSK-3β in the frontal cortex; inhibition of GSK-3β by intraperitoneal injection of a GSK-3 inhibitor (i.e., TDZD-8) or GSK-3β(+/−)-knockdown alleviated aberrant behaviors produced by serotonin deficiency.

In the hippocampus of normal adult brain, continuous birth of new neurons occurs in the subgranular zone, giving rise to granule cells in the granule cell layer of the dentate gyrus; in addition, newborn neurons from the subventricular zone migrate toward the olfactory bulb via the rostal migration stream (see review 2). Chronic stress, a method used to create an animal model of depression, inhibits neuronal proliferation and promotes apoptosis in the hippocampus. In rats, Silva et al. (43) observed that 14-day mild stress task increased plasma corticosterone level and induced depressive behaviors in the forced swimming test, which were associated with decreased cell proliferation/differentiation, increased apoptosis, and increased GSK-3β level in the hippocampus (but not in the subventriculat zone, a brain region unrelated to mood dysregulation); intraperitoneal injection of LiCl or the GSK-3β–selective inhibitor AR-A014418 abrogated stress-induced hormonal, behavioral, and cell turnover defects, as well as the increased GSK-3β level.

Gould et al. (39) provided the first evidence that in vivo oral administration of lithium inhibited GSK-3; in adult rats, chows containing lithium and the subsequent therapeutic plasma concentration range (0.5 – 1.2 mM) of lithium increased cytoplasmic (but not membrane-associated) β-catenin level. Because it is known that cytoplasmic (but not membrane-associated) β-catenin level is decreased by GSK-3–catalyzed phosphorylation of β-catenin and its subsequent proteasomal degradation (Fig. 1), their study suggests that therapeutic concentration of lithium inhibited GSK-3β in vivo, causing accumulation of β-catenin. They also observed that lithium decreased β-catenin mRNA level, presumably representing the compensation for an increase of β-catenin stability by lithium. To examine whether lithium-induced β-catenin accumulation could be relevant to the therapeutic antidepressive effects of lithium on bipolar disorder, Gould et al. (44) utilized transgenic mice overexpressing β-catenin; the mice exhibited behavioral ameliorations similar to those of lithium, suggesting that the therapeutic antidepressive effects of lithium were mediated via lithium-induced β-catenin accumulation.

Conversely, Gould et al. (45) showed that forebrain (frontal cortex, hippocampus, striatum)-specific 60% – 70% conditional knockdown of β-catenin in mice resulted in a depression-like phenotype in the tail suspension test, but not in other behavioral tests (e.g., forced swimming test).

2.3. Anti-manic effect: GSK-3β inhibition

Dopamine is a neurotransmitter involved in the control of locomotion, emotion, cognition, and reward; conversely, dopamine abnormality has been implicated in a variety of brain diseases (e.g., Parkinson's disease, schizophrenia, attention deficit hyperactivity syndrome, addiction). Beaulieu et al. (46) showed that the dysregulated increased neurotransmission of dopamine due to intraperitoneal injection of amphetamine in wild-type mice or due to dopamine transporter knockout in mice caused locomotor hyperactivity and stereotypic movements, which were associated with the increased activities of GSK-3α/3β in brain striatum. In dopamine transporter knockout mice, intraperitoneal injection of GSK-3α/3β inhibitor (e.g., LiCl, SB216763) antagonized dopamine-induced abnormal locomotor behaviors in a dose-dependent manner; in addition, heterozygote GSK-3β (+/−) knockdown mice were not different from wild-type mice in locomotor activity tests, but responded to a lesser extent to amphetamine, compared to wild-type mice.

Prickaerts et al. (47) documented that transgenic mice overexpressing GSK-3β mimicked hyperactivity as observed in the manic phase of bipolar disorder (e.g., increased locomotor activity), with reduction in brain weight; interestingly, it was associated with up-regulation of both Akt-1 and brain-derived neurotrophic factor protein levels; these up-regulations may be compensatory mechanisms against GSK-3β over-expression and brain weight reduction, respectively.

3. Lithium: neurogenesis and chromatin remodeling via GSK-3β inhibition

3.1. Neurogenesis via GSK-3β inhibition and β-catenin activation

Neural stem cells give rise to new hippocampal neurons throughout adulthood; conversely, defective neurogenesis may predispose an individual to mood disorders (e.g., major depression) (see reviews 2, 4, 5). In cultured hippocampal progenitors prepared from adult female rats, Wexler et al. (48) showed that chronic (2 – 7 days) treatment with 1 – 6 mM lithium promoted these progenitors to neurons. Besides, expression of either inactive GSK-3β or constitutively active β-catenin mimicked the proliferative effect of lithium; conversely,

overexpression of wild-type GSK-3β or knockout of β-catenin decreased basal mitosis or abolished the proliferative effect of lithium. In cultured hippocampal neural precursor cells derived from dentate gyrus of adult rats, Boku et al. (49) showed that the glucocorticoid dexamethasone decreased proliferation of neural precursor cells, which was prevented by the lithium / GSK-3β / β-catenin pathway. In rats, Silva et al. (50) found that chronic mild stress decreased the expression level of vascular endothelial growth factor in the hippocampus, which was associated with up-regulation of GSK-3β and down-regulation of β-catenin. Intraperitoneal injection of LiCl restored GSK-3β, β-catenin, and vascular endothelial growth factor levels to the control levels of non-stressed rats.

3.2. Epigenetic chromatin remodeling via GSK-3β inhibition

In nucleosomes, epigenetic post-translational covalent modifications (e.g., acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation) of histone proteins or DNA can alter the chromatin architecture; in contrast to the genetic permanent and irreversible modifications, the epigenetic modifications are stable (i.e., long-lasting), but reversible (i.e., plasticity), thus controlling the transcriptional activation or repression of target genes in response to physiological (e.g., neuronal differentiation and environmental adaptation) and pathological (e.g., cancer) events (4). Recently, these epigenetic regulations have been increasingly unveiled to be involved in stress-induced depression and the antidepressant mechanisms (4). In 2006, by using a mouse model of defeat stress–induced depression, Tsankova et al. (51) documented first that 28-day treatment with imipramine increased histone acetylation via down-regulating expression of histone deacetylase-5, being causally involved in the antidepressant action of imipramine. In addition, a histone deacetylase inhibitor (i.e., sodium butyrate) displayed an antidepressant effect (51). In *Caenorhabditis elegans*, McColl et al. (52) documented that lithium elongated the life-span of the nematode; lithium down-regulated expression of histone demethylase via mechanisms including GSK-3β inhibition by lithium.

4. GSK-3β abnormalities in human patients and rodents

4.1. Depressive patients

Karege et al. (53) examined Akt and GSK-3β activities and protein levels in postmortem human brain samples (i.e., ventral prefrontal cortex). Akt activity was decreased by 31%, while GSK-3β activity was increased by 53% in patients with major depressive disorder (10 suicide and 10 non-suicide), compared with control subjects (10 suicide and 10 non-suicide); however, Akt and GSK-3α/3β protein levels were not changed between depressive patients and control subjects (54). In human peripheral blood mononuclear cells isolated from 23 healthy subjects, 9 bipolar disorder patients treated with lithium and 13 lithium-free bipolar disorder patients, Li et al. (55) measured Ser[9]-phosphorylation levels of GSK-3β; the levels were 8-fold higher in lithium-treated patients than healthy subjects. However, the levels of lithium-free bipolar disorder patients were intermediate between healthy subjects and lithium-treated patients (54); other therapeutic drugs used in these lithium-free patients have been shown to increase Ser[9]-phosphorylation of GSK-3β in animal models and cultured cells (56 – 60).

4.2. Alzheimer's patients

As a potential diagnostic assay of neuropsychiatric diseases, Hye et al. (61) measured GSK-3α/3β protein levels and GSK-3β activity in human peripheral white cells; GSK-3α/3β protein levels were increased, while Ser[9]-phosphorylated GSK-3β level was decreased in 60 Alzheimer's patients and 33 mild cognition defective individuals, compared with 20 healthy age-matched elderly people. In human postmortem brains, Leroy et al. (62) showed that the level of stimulatory Tyr[216]-phosphorylation of GSK-3β (but not inhibitory Ser[9]-phosphorylation of GSK-3β) was increased by twofold in the frontal cortex of Alzheimer's patients, compared with nondemented control subjects; in addition, the activation of GSK-3β was an early event preceding formation of neurofibrillary tangles.

4.3. Lithium treatment in Alzheimer's patients: prevention of dementia

In a study of 1423 outpatients at a university psychiatric clinic, Terao et al. (63) reported that lithium therapy prevented the dementia in Alzheimer's disease, when their cognition and memory capacity were evaluated by Mini-Mental State Examination. Further studies may be required to establish lithium's favorable effect (64).

4.4. Amyotrophic lateral sclerosis patients

In amyotrophic lateral sclerosis with cognitive impairment, deposition of aberrant hyperphosphorylated tau has been observed in the brain. In postmortem human brains, Yang et al. (65) showed that GSK-3β, Tyr[216]-phosphorylated GSK-3β, and phosphorylated β-catenin levels were increased in amyotrophic lateral sclerosis patients even without or with cognitive impairment,

compared with control subjects.

4.5. Schizophrenia patients

In schizophrenic human patients and a schizophrenia-related neonatal rat model, Kozlovsky et al. (66) showed that GSK-3β protein and mRNA levels were decreased by over 40% in the frontal cortex (but not in the occipital cortex and lymphocytes); in the rat model, chronic stress or chronic treatment of various therapeutics (e.g., lithium or haloperidol) did not change GSK-3β protein level, leading the authors to suppose that low GSK-3β level in schizophrenia was not secondary to stress or drug treatment.

4.6. Traumatic brain injury in mice

Traumatic brain injury triggers neurological and psychological dysfunctions (e.g., depressive behavior), activating both apoptotic and survival signals. Shapira et al. (67) showed that mice that underwent a focal injury to their left hemisphere caused by a 75-g weight-drop device exhibited increased Ser^{473}-phosphorylation of Akt, increased Ser^9-phosphorylation of GSK-3β, and β-catenin accumulation in the hippocampus, which were associated with depressive behavior. Intracerebro-ventricular injection of lithium or GSK-3 inhibitor (i.e., L803-mts) prior to brain injury prevented traumatic brain injury–induced depression. The authors concluded that 1) GSK-3 inhibitors have therapeutic benefits in brain injury and 2) in response to the brain injury, a pro-survival cascade of Akt / GSK-3β / β-catenin was activated as a compensatory preventive program (Fig. 1).

5. GSK-3α/3β inhibition by classical therapeutics

5.1. Neuropsychiatric drugs

There is accumulated evidence showing that GSK-3 is a common therapeutic target for different classes of neuropsychiatric drugs (e.g., selective serotonin-reuptake inhibitors, antidepressants, monoamine oxidase inhibitors, antipsychotics) (60). In mice, Li et al. (56) showed that intraperitoneal injection of d-fenfluramine (to stimulate serotonin secretion and block its reuptake) rapidly increased Ser^9-phosphorylation of GSK-3β by up to 500% at 1 h in the prefrontal cortex, hippocampus, and striatum. The same treatment with fluoxetine (selective serotonin-reuptake inhibitor) or imipramine (tricyclic antidepressant inhibiting reuptake of both serotonin and norepinephrine) increased Ser^9-phosphory-lation of GSK-3β. By using selective agonists and antagonists, it was found that 5-HT$_1$ receptors increase, while 5-HT$_2$ receptors decrease Ser^9-phosphorylation of GSK-3β; the serotonin system finely regulates GSK-3β activity. Therefore, dysregulated serotonergic activity

(e.g., depression, anxiety, bipolar disorder, autism, or schizophrenia) may impair regulation of GSK-3β activity.

Atypical antipsychotics are used in the treatment of mood disorders and schizophrenia. In mice, Li et al. (58) showed that intraperitoneal injection of risperidone rapidly increased Ser^{21}/Ser^9-phosphorylation of cytoplasmic (but not nuclear) GSK-3α/3β at 1 h in the cortex, hippocampus, striatum, and cerebellum. Similar effects were observed by olanzapine, clozapine, quetiapine, and ziprasidone. Besides, risperidone plus imipramine or risperidone plus fluoxetine produced a larger increase of Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β in these brain regions, compared to each drug alone.

5.2. Therapeutic drugs for Alzheimer's disease

For the treatment of Alzheimer's disease, acetyl-cholinesterase inhibitor and N-methyl-D-aspartate receptor inhibition are currently approved. In mice, De Sarno et al. (59) showed that intraperitoneal injection of acetyl-cholinesterase inhibitor (i.e., physostigmine) increased Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β at 15 min in a dose-dependent manner in the cerebral cortex, hippocampus, and striatum. Memantine, an N-methyl-D-aspartate–receptor antagonist, caused a similar effect. Co-administration of both drugs, however, increased Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β equally to the level achieved by either drug alone.

5.3. General anesthetics

In mice, Li et al. (57) showed that intraperitoneal injection of pentobarbital or chloral hydrate or exposure to halothane vapor rapidly (approximately 2 min) increased Ser^{21}/Ser^9-phosphorylation of GSK-3α/3β in the cerebral cortex, hippocampus, striatum, and cerebellum.

6. GSK-3β inhibition: up-regulation of Na$_v$1.7 sodium channel

6.1. Multiple roles of sodium channels in elaboration, maintenance, and repair of the neuronal circuit

Voltage-dependent sodium channels trigger hetero-geneous patterns of action potentials in a spatiotemporal-specific manner; they are decoded into distinct ionic and metabolic signalings, governing the directions of neurotrophin-induced phenotypic expression (68); e.g., infusion of brain-derived neurotrophic factor into the hippocampus promotes antidepression, whereas the same infusion into the ventral tegmental area/nucleus accumbens or amygdala causes depression (4, 5).

Besides initiating and propagating action potential in the established neuronal circuit, spontaneous and experi-

ence-driven electrical activities of voltage-dependent sodium channels sculpt the neuronal network from early development through adulthood, being crucial to elaborating/maintaining/repairing both structure and function (e.g., neurogenesis, synapse formation, neuroplasticity, and pain) of the neuronal circuit (see reviews 68, 69). The pioneering studies may be dated back to 1959 – 1982, when Hubel and Wiesel (70) observed that normal visual experience in the early stage of life was essential to the proper development of the visual system.

6.2. $Na_v1.7$ and axon growth cone

Axon growth cone is a neuronal compartment sensing its environment for correct synapse formation during normal development and during regeneration following neuronal injury (71 – 73; see reviews 68, 74). Among the nine isoforms ($Na_v1.1 – Na_v1.9$) of sodium channels, $Na_v1.7$ is localized at the axon growth cone (75, 76); in addition, cell surface number of $Na_v1.7$ was up-regulated by neuronal differentiation (76, 77). In the axon growth cone, gating of sodium channels increased both plasmalemmal expansion (71) and plasmalemmal insertion of sodium channels from the cytoplasm (72). Growth cone outgrowth was promoted by IGF-I (but not by brain-derived neurotrophic factor) via the phosphoinositide 3-kinase / GSK-3β pathway; in contrast, brain-derived neurotrophic factor caused the translocation of IGF-I receptor to the growth cone (73, 78 – 81; see reviews 2, 6).

6.3. $Na_v1.7$ / Ca^{2+} influx / GSK-3β cascade: growth cone outgrowth and tau phosphorylation attenuation in adrenal chromaffin cells

Adrenal chromaffin cells (embryologically derived from the neural crest) express $Na_v1.7$ (75; see reviews 68, 69). In cultured frog (*Rana pipiens*) or bovine adrenal chromaffin cells, gating of $Na_v1.7$ by veratridine (82), brief electrical stimulation, or high-K$^+$ depolarization (83) immediately increased formation of the growth cone, where its constantly exploratory sprouting filopodia and lamellipodia culminated in the synapse-like contacts with neighboring cells.

In cultured bovine adrenal chromaffin cells, our laboratory showed that veratridine-induced Na$^+$ influx via $Na_v1.7$ and the subsequent Ca^{2+} influx via voltage-dependent calcium channel resulted in the activation of both phospholipase C/protein kinase C-α and phosphoinositide 3-kinase/Akt pathways, which converged on Ser^9-phosphorylation of GSK-3β, thereby causing attenuation of constitutive Ser^{396}-phosphorylation of tau (84). Previous studies documented that decreased Ser^{396}-phosphorylation of tau promoted the binding of tau's C-terminal to tubulin in the cytoskeletal location; more importantly, in lipid rafts of the plasma membrane,

decreased Ser^{396}-phosphorylation of tau was required to form heteroprotein complexes between tau's N-terminal and the Src homology 3 domains of various proteins (e.g., phosphoinositide 3-kinase, phospholipase C and Src family tyrosine kinases) (85, 86), thus the decreased phosphorylation level of tau promoting growth cone elaboration and its outgrowth (78 – 81). In an expression study in Chinese hamster ovary (CHO) cells, Leory et al. (78) showed that tau-induced increased outgrowth of neuronal processes was inhibited by GSK-3β–catalyzed phosphorylation of tau; in contrast, concentration-dependent graded inhibition of GSK-3β by LiCl (0.1 – 25 mM) produced the concentration-dependent graded restoration of tau-induced outgrowth of neuronal processes.

6.4. Up-regulation of $Na_v1.7$ by chronic GSK-3β inhibition in adrenal chromaffin cells

In cultured bovine adrenal chromaffin cells, our laboratory showed that chronic treatment with insulin (87), IGF-I (see review 6), GSK-3 inhibitors (i.e., lithium, SB216763, or valproic acid) (88; see reviews 6, 89) up-regulated cell surface expression of $Na_v1.7$ via multiple mechanisms, including $Na_v1.7$ gene transcription, up-regulation of $Na_v1.7$ augmented ^{22}Na$^+$ influx via $Na_v1.7$, ^{45}Ca^{2+} influx via voltage-dependent calcium channels, and exocytic secretion of catecholamines.

7. Regulation of GSK-3α/3β and β-catenin by electroconvulsion and neuropsychiatric drugs: neurogenesis and memory

7.1. Electroconvulsive seizure: β-catenin up-regulation and neurogenesis

In rats, Madsen et al. (90) showed that repeated 10-day electroconvulsive seizure, a treatment for severe depressive diseases, up-regulated β-catenin protein and mRNA levels in the dentate gyrus of the hippocampus, with increased level of Wnt-2 mRNA. In rats, Warner-Schmidt et al. (91) showed that electroconvulsive seizure restored hippocampal neurogenesis and hippocampus-dependent fear memory, which were previously disrupted by irradiation.

7.2. Neuropsychiatric drugs: up-regulation of GSK-3α/3β, β-catenin, and neurogenesis

In rats, Alimohamad et al. (92, 93) showed that chronic (up to 28 days) injection of haloperidol, clozapine, or risperidone increased GSK-3α/3β and β-catenin levels in the ventral midbrain and hippocampus. Raclopride produced similar effects, suggesting that D$_2$ dopamine–receptor inhibition mediated up-regulation of GSK-3α/3β and β-catenin caused by antipsychotics. In

contrast, amphetamine, a drug capable of inducing psychotic episodes, decreased GSK-3α/3β and β-catenin levels in ventral midbrain. In rats, Sutton et al. (94) showed that injection of haloperidol or clozapine or feeding of rat chow supplemented with 0.2% LiCl for 14 days increased levels of GSK-3α/3β, β-catenin, and Wnt signaling molecules (i.e., dishevelled-3 and axin) in the prefrontal cortex. In PC12 cells and neuroblastoma SH-SY5Y cells, they also observed that lithium or GSK-3 inhibitor (i.e., SB216763) accelerated transcriptional activity of β-catenin.

Increasing lines of evidence suggest that anti-depressants could enhance hippocampal neurogenesis, but the underlying mechanisms are still obscure (48). In rats implanted with a subcutaneous osmotic minipump, Mostany et al. (95) demonstrated that infusion of venlafaxine (reuptake inhibitor for both serotonin and norepinephrine) for 14 days increased neurogenesis and β-catenin level in the subgranular zone of the hippocampus. Nuclear existence of β-catenin was observed in venlafaxine-treated (but not nontreated) cells, implicating that β-catenin–dependent gene transcription contributed to the neurogenesis.

8. Neurotrophin cascades in mood, neurogenesis, and memory: emerging pivotal roles of IGF-I

8.1. IGF-I: neurogenesis, angiogenesis, learning, and mood in normal and neuropsychiatric/neurodegenerative brain

In the developing and adult brain, IGF-I acts on neuronal and glial cells, promoting neurogenesis, angiogenesis, and neuroplasticity; conversely, a dysregulated IGF-I system is involved in various neuropsychiatric and neurodegenerative diseases by virtue of its multiple cellular mechanisms, including axon remyelination after neuronal injury (96); thus, IGF-I is therapeutic against these disease states (see reviews 22 – 25, 28). Physical exercise promotes brain health via the IGF-I system, while a sedentary life-style or western-style cafeteria diet impairs it due to IGF-I system dysfunction (15, 97; see reviews 26, 27). Since 2005, it has become increasingly evident that IGF-I exerts pivotal roles in anti-depression, as shown below. For comprehensive information about IGF-I and the IGF-II system, readers are advised to refer to previous excellent review articles (see reviews 98 – 100). In addition, the rapidly advancing new trends in research on the neurotrophin cascade and antidepression may be readily understood by referring to Table 1 (D) in this review article.

8.2. IGF-II: autocrine/paracrine survival factor induced by lithium / GSK-3β inhibition / β-catenin activation

Previous studies have not convincingly identified the downstream mediator molecules (e.g., neurotrophins) of the lithium-induced GSK-3β / β-catenin pathway, which promote mood stabilization and neurogenesis. Sinha et al. (19) provided the first evidence for up-regulation of IGF-II by the lithium / GSK-3β / β-catenin pathway (Fig. 1). In mouse renal proximal tubular epithelial cells, treatment with lithium (10 mM for up to 48 h) or GSK-3β inhibitor (i.e., BIO) prevented the epithelial cells from undergoing serum starvation-induced apoptosis; the cell survival was associated with Ser^9-phosphorylation of GSK-3β, decreased phosphorylation of β-catenin, nuclear translocation of β-catenin, β-catenin–dependent gene transcription, and increased expression of IGF-II and cyclin D1. Importantly, lithium-, or BIO-free conditioned medium harvested from lithium- or BIO-exposed cells mimicked the protective effects of lithium or BIO in serum-starved cells, implicating that IGF-II synthesized in lithium- or BIO-treated cells was secreted into the extracellular milieu and acted as a soluble survival factor via an autocrine/paracrine manner (Fig. 1). Indeed, lithium or BIO increased Akt phosphorylation and inhibited apoptosis during serum deprivation. Inhibition of phosphoinositide 3-kinase by LY294002 or wortmannin prevented lithium- or BIO-induced Akt phosphorylation and attenuated cell survival without changing Ser^9-phosphorylation of GSK-3β; thus, extracellular IGF-II activated the anti-apoptotic phosphoinositide 3-kinase / Akt pathway via an autocrine/paracrine manner during serum deprivation.

8.3. Up-regulation of IGF-I by antidepressant drugs: neurogenesis

In 2004, Khawaja et al. (16) showed that intraperitoneal injection of venlafaxine or fluoxetine for 14 days in adult rats increased the number of proliferating cells and long-term survivability of progenitor stem cells in the subgranular zone of the hippocampus. They performed proteomic analysis of the hippocampal cytoplasmic extracts by two-dimensional gel electrophoresis; among over 700 protein spots, venlafaxine or fluoxetine up-regulated 31 protein spots, including a 2.5- to 3-fold increase of the IGF-I level.

In adult rats, Grunbaum-Novak et al. (18) showed that chronic (3 times/week × 3 weeks) oral administration of fluoxetine increased IGF-I mRNA and IGF-I receptor protein levels in the frontal cortex, while decreasing those levels in the hippocampus.

8.4. Antidepressant effect of IGF-I

In 2005, Hoshaw et al. (9) provided the first evidence that a single intracerebroventricular injection of IGF-I in rats produced long-lasting (up to 6 days) antidepressant-like effects (i.e., reducing immobility and increasing swimming), as evidenced by the forced swimming test. They also found that the antidepressant potency of IGF-I was comparable to that of brain-derived neurotrophic factor, a well-documented antidepressant neurotrophin (see reviews 4, 5). The same laboratory further showed that the antidepressant effect of IGF-I was mediated via the IGF-I receptor, resulting in the IGF-I–induced increased level of serotonin in the ventral hippocampus (10).

8.5. Physical exercise-induced memory enhancement: IGF-I–dependent activation of brain-derived neurotrophic factor signalings

Physical exercise promotes learning/memory, protection against neurodegeneration, and alleviation of depression; IGF-I and brain-derived neurotrophic factor mediate exercise-induced beneficial effects on learning/memory and depression, while IGF-I and vascular endothelial growth factor mediate exercise-induced neurogenesis and angiogenesis (13 – 15; see reviews 26, 27).

In rats, Ding et al. (20) documented that 5-day voluntary physical exercise enhanced spatial memory acquisition and retention via IGF-I/IGF-I receptors; the memory enhancement was abolished by delivery of IGF-I receptor antibody into the hippocampus. The exercise increased IGF-I (but not IGF-II) mRNA level in the hippocampus; it was mediated via its autocrine/paracrine activation of IGF-I receptors by IGF-I because IGF-I–receptor antibody inhibited exercise-induced up-regulation of IGF-I–mRNA level. Furthermore, in the hippocampus, exercise increased the levels of brain-derived neurotrophic factor mRNA, brain-derived neurotrophic factor precursor protein, and brain-derived neurotrophic factor-induced synaptic proteins (i.e., synapsin I, phosphorylation level of calcium/calmodulin-dependent protein kinase II, and phosphorylation level of mitogen-activated protein kinase II); surprisingly, these exercise-induced enhancements of brain-derived neurotrophic factor events were abolished by IGF-I–receptor antibody. Therefore, the IGF-I/IGF-I receptor system led to the enhancement of brain-derived neurotrophic factor signalings, thus the IGF-I system initiating exercise-induced synaptic and cognitive plasticity.

In cultured mouse cerebrocortical neurons, McCuster et al. (21) showed that 24-h treatment with IGF-I increased the level of TrkB, a receptor for brain-derived neurotrophic factor, augmenting the ability of brain-derived neurotrophic factor to phosphorylate extracellular signal-regulated kinase-1 and -2.

8.6. Antidepressant-induced up-regulation of brain-derived neurotrophic factor: dependency on transport of peripheral circulating IGF-I into brain

In addition to the exercise-induced synthesis of IGF-I in the brain (20), exercise increased the transport of peripheral circulating IGF-I into the brain via the blood-brain barrier, elevating brain-derived neurotrophic factor mRNA and protein levels, as well as pro-survival signaling molecules in the brain (see reviews 26, 27). Chen and Russo-Neustadt (17) examined whether the effects of an antidepressant on brain-derived neurotrophic factor also depend on the transport of circulating IGF-I into the brain. In rats, intraperitoneal injection of a monoamine oxidase inhibitor (i.e., tranylcypromine) for 7 days increased brain-derived neurotrophic factor mRNA and protein levels in various brain regions; antiserum raised against IGF-I reversed the increases in brain-derived neurotrophic factor mRNA and protein levels caused by exercise or tranylcyoromine, thus transport of circulating IGF-I into brain being essential to exercise- and antidepressant-induced increased expression of brain-derived neurotrophic factor in the brain.

8.7. Circulating IGF-I: neurogenesis, memory, and anti-anxiety

By decreasing or increasing plasma IGF-I level, Trejo et al. (14) showed that adult mutant mice with low plasma IGF-I level exhibited reduced hippocampal neurogenesis and impaired spatial learning; these deficits were ameliorated by subcutaneous administration of exogenous IGF-I. Exercise reduced anxiety in normal mice; in the adult mutant mice with low serum IGF-I level, however, the exercise-induced anxiolytic effect was observed only in some (but not all) behavioral tests.

Epidemiological studies in humans suggest that circulating IGF-I promotes cognition. Trejo et al. (13) showed that mice with low plasma IGF-I level due to liver-specific targeted disruption of the IGF-I gene exhibited cognitive deficits, as evaluated by a hippocampus-dependent spatial recognition task. Mice with plasma IGF-I deficiency displayed disrupted long-term potentiation and reduced density of glutamatergic boutons in the hippocampus; conversely, systemic administration of IGF-I ameliorated these behavioral and synaptic deficits and normalized the density of glutamatergic boutons. Declining plasma IGF-I level during aging may therefore contribute to age-related

cognitive loss.

8.8. Circulating IGF-I–binding proteins in plasma: roles of antidepression and anti-anxiety

Insulin-like growth factor–binding proteins (IGFBP-1 through IGFBP-6) are carrier proteins that bind to IGF-I in plasma; they are known to coordinate biological activities of IGF-I in several ways (e.g., transport of IGF-I in plasma, prevention of IGF-I metabolism, and regulation of free IGF-I level available to bind IGF-I receptors) (see review 97). Free IGF-I level in the brain can be increased by administering IGF-I or by blocking interaction between IGF-I and IGFBP. In mice, Malberg et al. (11) showed that intracerebroventricular administration of IGF-I or IGFBP inhibitor (i.e., NBI-31772) produced anxiolytic and antidepressant effects, which were blocked by coadministration of an IGF-I–receptor antagonist.

8.9. Altered levels of IGF-I–binding proteins in cultured cells and depressive human brain

IGFBP-2 is the major isoform of IGFBP in the brain. In cultured cortical neurons of fetal rats, Bezchlibnyk et al. (101) showed that 7-day treatment of lithium (0.5 – 2 mM) lowered IGFBP-2 mRNA and protein levels by up to 60% in a concentration- and time-dependent manner. In the prefrontal cortex of postmortem brains obtained from human patients with bipolar disorder and major depressive disorder, Bezchlibnyk et al. (102) showed that IGFBP-2–mRNA levels were decreased, compared to age-matched subjects; among bipolar disorder patients, the lithium-treated group had higher IGFBP-2–mRNA level, compared to the lithium-nontreated group. In rat hepatoma cell H4-II-E, Lewitt et al. (103) showed that lithium (1 – 5 mM) inhibited IGFBP-1 secretion and lowered IGFBP-1–mRNA level in a concentration-dependent manner.

8.10. Intranasal insulin in human subjects: increased mood

In healthy individuals and Alzheimer's patients, intranasal administration of insulin has been shown to improve memory and increase mood (see review 6). In a double-blind test of 38 healthy subjects, Benedict et al. (12) found that acute intranasal administration of insulin raised the feeling of well-being and self-confidence, while decreasing anger.

8.11. Insulin receptor substrate-1 in nucleus: partner for β-catenin transcription

Insulin receptor substrate-1 (IRS-1) and IRS-2 are scaffold proteins for receptor tyrosine kinases (e.g., insulin receptor and IGF-I receptor), G-protein–coupled receptors, and cytokine receptors, as well as integrins, cell adhesion molecules (104, 105) (Fig. 1). In addition, IRS-1 and IRS-2 were translocated into the nucleus, functioning as transcription factors (104). In mouse embryo fibroblasts, Chen et al. (106) showed that β-catenin bound to and co-localized with IRS-1 in the cytoplasm and nucleus. In breast cancer BT20 cells lacking IRS-1, β-catenin failed to translocate into the nucleus even after stimulation with IGF-I. In BT20 cells transfected with IRS-1, IGF-I stimulation caused nuclear translocation of β-catenin. In human colorectal cancer C10 cells, Playford et al. (107) found that IGF-I elongated the half-life of β-catenin from 3 to 6 h. In a reporter gene assay in HEK293 cells, however, 3-h treatment with IGF-I or insulin failed to enhance gene transcriptional activity of β-catenin; however, the concurrent treatment of IGF-I and LiCl enhanced the transcriptional activity via an unknown mechanism.

8.12. Homologous regulation by GSK-3β: insulin receptor, IRS-1, IRS-2, and Akt-1 levels

In cultured bovine adrenal chromaffin cells, our laboratory showed that LiCl, SB216763, or insulin increased Ser^9-phosphorylation of GSK-3β and β-catenin level (104, 105, 108; see review 89), which were followed by decreased levels of cell surface insulin receptor (108), IRS-1, IRS-2 (104, see review 89), and Akt-1 (105) (Fig. 1). LiCl, SB216763, or insulin decreased mRNA levels of insulin receptor (108), IRS-2 (104), and Akt-1 (105), while increasing proteasomal degradation of IRS-1 and IRS-2 (104). The increased Ser^9-phosphorylation of GSK-3β and the decreased levels of these signaling molecules were gradually (approximately by 24 h) restored to the control levels of nontreated cells after the test compound–treated cells were washed (104, 105, 108). Thus, constitutive activity of GSK-3β maintains steady-state levels of insulin receptor, IRS-1, IRS-2, and Akt-1 in nonstimulated chromaffin cells. In contrast, LiCl did not change the levels of phosphoinositide 3-kinase and extracellular signal-regulated kinase-1 and -2 (105).

9. Conclusions

There is to date compelling evidence indicating that the GSK-3β/β-catenin pathway is the convergent therapeutic target of lithium and various classical neuropsychiatric drugs, ameliorating behavior, mood, anxiety, cognition, and neurogenesis. Much remains, however, elusive about the downstream signaling molecules of the GSK-3β/β-catenin pathway, which culminate in neuropsychiatric homeostasis. In addition to the well-

documented classical neurotrophins (i.e., brain-derived neurotrophic factor and vascular endothelial growth factor), IGF-I has proved to be a crucial factor in mood disorders. Antidepressants up-regulate IGF-I and IGF-II levels in the brain, and physical exercise and a healthy diet increases IGF-I synthesis in the brain and transport of peripheral circulating IGF-I to the brain via the blood-brain barrier. Importantly, IGF-I up-regulates the levels of brain-derived neurotrophic factor and its receptor TrkB, increasing synthesis of its downstream synaptic proteins. The demonstration of this neurotrophin cascade from IGF-I to brain-derived neurotrophic factor suggests that the cooperative network/sequential cascade of various neurotrophins may become an important issue in future research. Another rapidly growing frontier is the stable (i.e., long-lasting) but reversible (i.e., plasticity) epigenetic remodeling of chromatin, which may be involved in the pathogenesis of mood disorders and the therapeutic mechanisms of antidepressants.

Acknowledgments

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