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Review

Is Glycogen Synthase Kinase-3 a Central Modulator in Mood Regulation?

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Little is known regarding the mechanisms underlying the complex etiology of mood disorders, represented mainly by major depressive disorder and bipolar disorder. The 1996 discovery that lithium inhibits glycogen synthase kinase-3 (GSK3) raised the possibility that impaired inhibition of GSK3 is associated with mood disorders. This is now supported by evidence from animal biochemical, pharmacological, molecular, and behavioral studies and from human post-mortem brain, peripheral tissue, and genetic studies that are reviewed here. Mood disorders may result in part from impairments in mechanisms controlling the activity of GSK3 or GSK3-regulated functions, and disruptions of these regulating systems at different signaling sites may contribute to the heterogeneity of mood disorders. This substantial evidence supports the conclusion that bolstering the inhibitory control of GSK3 is an important component of the therapeutic actions of drugs used to treat mood disorders and that GSK3 is a valid target for developing new therapeutic interventions. *Neuropsychopharmacology* (2010) **35,** 2143–2154; doi:10.1038/npp.2010.105; published online 28 July 2010

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WHAT IS GLYCOGEN SYNTHASE KINASE-3 (GSK3)?

GSK3 is a protein kinase originally identified and named for its ability to phosphorylate and inactivate the metabolic enzyme glycogen synthase (Embi *et al*, 1980). Subsequently, GSK3 was found to be a broadly influential enzyme in neural systems that modulates many aspects of neuronal function, such as gene expression, neurogenesis, synaptic plasticity, neuronal structure, and neuronal death and survival (Doble and Woodgett, 2003; Frame and Cohen, 2001; Jope and Johnson, 2004). Although commonly referred to as isoforms, the two GSK3 proteins, GSK3α and GSK3β, are paralogous proteins that are encoded by independent genes, but share 85% sequence homology, including 97% homology in the kinase domain (Woodgett, 1990). Both GSK3α and GSK3β are expressed throughout the brain (Yao *et al*, 2002), with GSK3α especially abundant in the hippocampus, cerebral cortex, striatum, and the Purkinje cells of the cerebellum, and GSK3β more universally expressed in all brain regions (Allen Brain Atlas).

Over 50 substrates of GSK3 have been identified (Doble and Woodgett, 2003; Jope and Johnson, 2004). A majority of these substrates are primed by another kinase before being phosphorylated by GSK3 at the fourth residue N-terminal to the primed site (pS/TXXXpS/T), but there are also unprimed substrates phosphorylated by GSK3 on a Ser/Thr-Pro motif (Doble and Woodgett, 2003). Several instances of substrates being phosphorylated by one GSK3 isoform but not the other have been identified, showing that the actions of the two isoforms are not always redundant (Chen *et al*, 2009; Force and Woodgett, 2009; Hoeflich *et al*, 2000; Liang and Chuang, 2006, 2007; Phiel *et al*, 2003; Wang *et al*, 1994).

Unlike many other protein kinases, both GSK3 isoforms are partially active in unstimulated cells, and they are regulated predominantly in an inhibitory manner by similar signaling mechanisms (Doble and Woodgett, 2003). Several protein kinases, such as Akt (Cross *et al*, 1995), protein kinase C (Goode *et al*, 1992), and protein kinase A (Fang *et al*, 2000; Li *et al*, 2000), phosphorylate GSK3 at an N-terminal serine residue, the serine-21 of GSK3α and the serine-9 of GSK3β (Stambolic and Woodgett, 1994; Sutherland and Cohen, 1994; Sutherland *et al*, 1993). This modification inhibits the ability of GSK3 to phosphorylate its primed substrates (Cross *et al*, 1995; Kockeritz *et al*, 2006), and is targeted by many neuromodulators and psychotropic drugs (Figure 1), as discussed in the next two sections. In addition to inhibition by the N-terminal serine phosphorylation, phosphorylation by p38 mitogen-activated protein kinase on the C-terminal serine-389 of GSK3β may also contribute to the inhibitory control of GSK3 (Thornton *et al*, 2008), but there is no information regarding pharmacological regulation of the C-terminal modification. Opposite to serine-phosphorylation, GSK3 activity is promoted by tyrosine phosphorylation at tyrosine-279 of GSK3α and tyrosine-216 of GSK3β, which facilitates access for substrate binding to GSK3 (Hughes *et al*, 1993). The function of this modification remains unresolved, as some evidence indicates that tyrosine-phosphorylation is an auto-phosphorylation event occurring when GSK3 is

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synthesized (Cole *et al*, 2004), while other evidence indicates that the tyrosine phosphorylation is a dynamic process regulated by intracellular signaling (Hartigan *et al*, 2001; Lesort *et al*, 1999b; Takahashi-Yanaga *et al*, 2004).

Besides being regulated by phosphorylation, GSK3 often associates with protein partners and phosphorylates substrates within these protein complexes. The best characterized example of this is the Wnt signaling pathway in which GSK3 is associated with the scaffold Axin, which also binds other proteins, notably β-catenin (Behrens *et al*, 1998; Rubinfeld *et al*, 1996). The proximity of GSK3 to β-catenin in the Axin protein complex allows β-catenin phosphorylation by GSK3, which facilitates β-catenin degradation by the proteasome (Davies *et al*, 2001; Henderson, 2000) (Figure 1). Wnt activation results in inactivation of GSK3 in the Axin complex by a mechanism that is still not well understood (Doble *et al*, 2007), which allows β-catenin stabilization and import into the nucleus in which it regulates gene expression (Papkoff and Aikawa, 1998). Therefore, protein complex formation is an important mechanism that allows regulation of GSK3 in a substrate-specific manner.

REGULATION OF GSK3 BY LITHIUM AND OTHER PSYCHOTROPIC DRUGS

The first evidence that GSK3 may be involved in mood disorders emerged from two reports showing that the classical mood stabilizer lithium is a direct inhibitor of GSK3 (Klein and Melton, 1996; Stambolic *et al*, 1996) by a magnesium-competitive mechanism (Ryves and Harwood, 2001). However, the direct effect of lithium measured *in vitro* is rather weak, as a therapeutically relevant concentration of lithium (1 mM) only inhibits GSK3 activity by approximately 25–50% depending on the magnesium concentration used in the kinase assay, in which 50% inhibition may be reached at physiological magnesium concentrations (Gurvich and Klein, 2002). Besides direct inhibition, lithium also inhibits GSK3 by increasing the inhibitory N-terminal serine phosphorylation in cultured cells (Chalecka-Franaszek and Chuang, 1999), mouse brain (De Sarno *et al*, 2002), and human peripheral blood mononuclear cells (PBMCs) (Li *et al*, 2007a). Importantly, increased serine phosphorylation of GSK3 in mouse brain (De Sarno *et al*, 2002) and human PBMCs (Li *et al*,

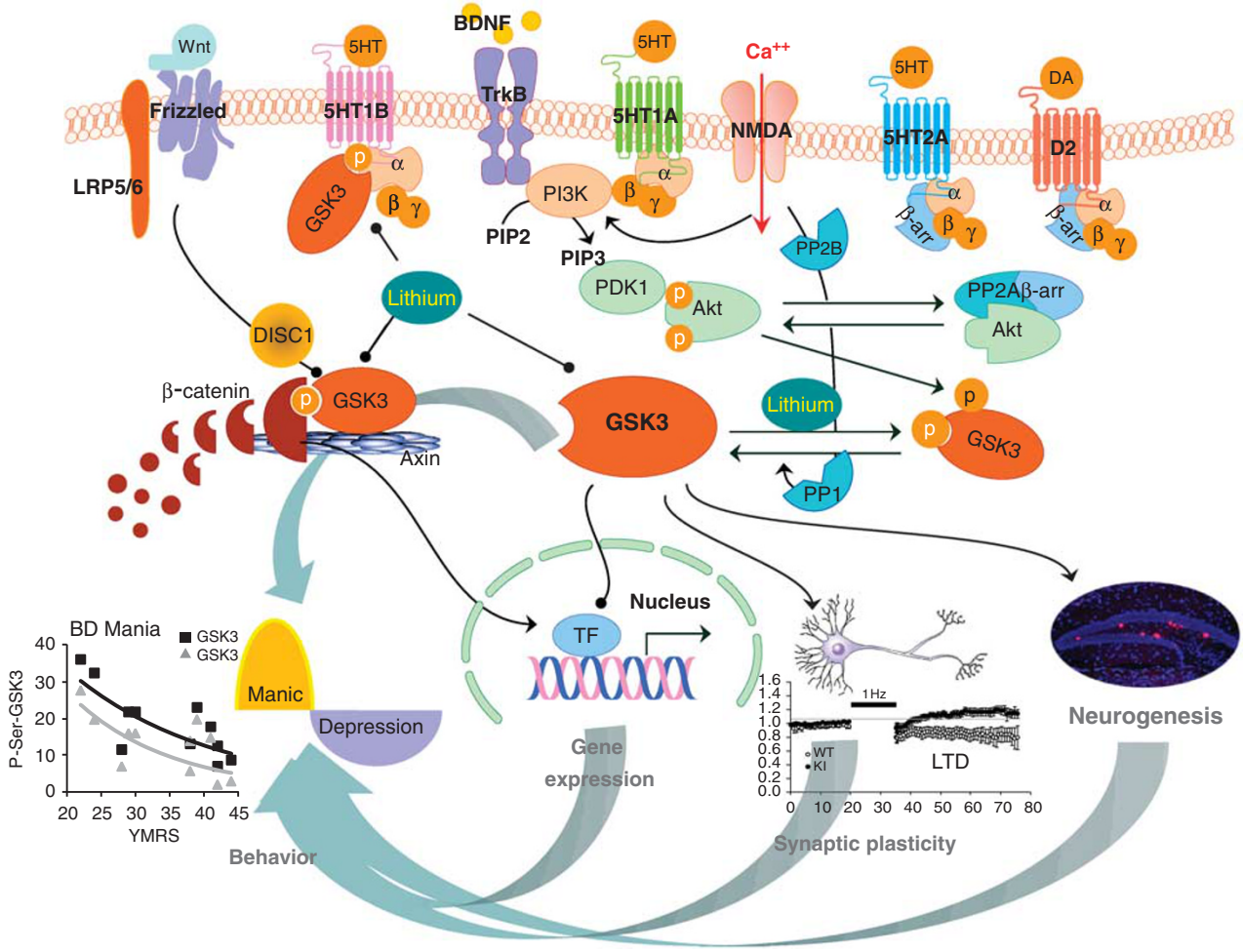

Figure 1 Schematic illustration of signaling pathways regulating GSK3 and functions of GSK3 related to mood regulation. GSK3 is regulated by BDNF, serotonin, and dopamine through the Akt signaling pathway, by the NMDA receptor through protein phosphatases, and by Wnt signaling in the Axin-β-catenin protein complex. Active GSK3 phosphorylates substrate proteins and affects gene expression, synaptic plasticity, and neurogenesis, which in turn regulate mood-related behaviors. Abbreviations: α,β,γ, G-protein subunits; β-arr, β-arrestin; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; DA, dopamine; D2, type 2 dopamine receptor; DISC1, disrupted in schizophrenia 1; GSK3, glycogen synthase kinase-3; 5HT, serotonin; 5HT1A, 1B, 2A, serotonin receptor subtypes; LTD, long term depression; NMDA, *N*-methyl-D-aspartic acid; P, phosphorylated; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol-3-kinase; PP1, PP2A, PP2B, protein phosphatase 1, 2A, and 2B; TF, transcription factors; TrkB, type B tropomyosin-receptor-kinase; YMRS, Young Mania Rating Scale.

2007a) occurs with therapeutically relevant lithium administration (0.8–1 mEq/l serum lithium concentration after 4 weeks of administration). Although the mechanism of this action by lithium has not been clearly established, it may involve the disruption of a β-arrestin/Akt/PP2A complex that results in Akt activation or an indirect inhibition of protein phosphatase 1 (PP1) (Beaulieu *et al*, 2008a; Chalecka-Franaszek and Chuang, 1999; Zhang *et al*, 2003). Lithium-induced increase in GSK3 serine-phosphorylation seems to amplify the direct inhibitory effect of lithium to produce a substantial inhibition of GSK3 *in vivo* with a therapeutic concentration of lithium (Figure 1). Besides these inhibitory effects on GSK3, other actions of lithium also have been suggested to contribute to its mood stabilizing effects, as detailed in other reviews (O'Brien and Klein, 2009; Quiroz *et al*, 2004; Rao *et al*, 2008).

The discovery that lithium is an inhibitor of GSK3 raised interest in determining if other mood stabilizers directly modulate GSK3 activity. Several studies reported that the anticonvulsant mood stabilizer valproate directly inhibited GSK3 activity (Chen *et al*, 1999b; Kim *et al*, 2005; Werstuck *et al*, 2004), but other studies did not find a direct inhibitory effect of valproate on GSK3 (Eickholt *et al*, 2005; Hall *et al*, 2002; Jin *et al*, 2005; Phiel *et al*, 2001). The reasons for these conflicting results remain unknown, but increasing evidence suggests that the mood stabilizing actions of valproate results, at least in part, from inhibition of histone deacetylases (HDACs) (Phiel *et al*, 2001). Interestingly, inhibition of HDACs by valproate or other HDAC inhibitors caused increased inhibitory serine-phosphorylation of GSK3 (Aubry *et al*, 2009; De Sarno *et al*, 2002; Kozlovsky *et al*, 2006; Lamarre and Desrosiers, 2008), raising the possibility that a combined action on HDAC and GSK3 has a significant role in mood regulation by valproate. However, the therapeutic targets of valproate in mood disorders remain to be established. Few studies have tested if GSK3 is inhibited by other mood stabilizers, such as carbamazepine and lamotrigine. No evidence has been reported for inhibition of GSK3 by carbamazepine (Aubry *et al*, 2009; Mai *et al*, 2002; Ryves *et al*, 2005); one study in cultured cells found no effect of lamotrigine on GSK3 serine phosphorylation (Aubry *et al*, 2009); whereas chronic treatment (28 days) of mice with lamotrigine increased serine phosphorylation of GSK3 in the hippocampus and the cerebral cortex (unpublished data). Thus, it remains unclear if mood stabilizers other than lithium directly affect GSK3, but their actions on targets in signaling pathways up- or down-stream of GSK3 may effectively counteract mood disturbance caused by dysregulated GSK3.

Clinically, a group of atypical antipsychotics have indications in mood disorders, either as anti-bipolar or adjunct antidepressant treatments (Derry and Moore, 2007; Philip *et al*, 2008). A majority of these agents, including risperidone, olanzapine, clozapine, quetiapine, and ziprasidone, increased serine phosphorylation of GSK3 in mouse brain (Alimohamad *et al*, 2005; Li *et al*, 2007b; Roh *et al*, 2007), and the effect was observed when administrated at low doses (Li *et al*, 2007b). Also interesting, a combination treatment with risperidone and fluoxetine enhanced the effect of either alone (Li *et al*, 2007b). Clinically, atypical antipsychotics have implications not only in mood disorders, but are also used therapeutically in the treatment of psychotic disorders. One of the major pharmacological difference between atypical antipsychotics and conventional antipsychotics is the dual antagonistic action on 5-HT2 receptors and dopamine D2 receptors of atypical antipsychotics, in contrast to the primary D2 receptor blockade of conventional antipsychotics (Schotte *et al*, 1995). Haloperidol is the only conventional antipsychotic that has been reported to have an effect on brain GSK3, including altering the serine phosphorylation and increasing the protein level of GSK3 (Alimohamad *et al*, 2005; Kozlovsky *et al*, 2006; Roh *et al*, 2007). As discussed below, both 5-HT2 and D2 receptors regulate GSK3, it is thus possible that the therapeutic significance of this regulatory mechanism in mood or psychotic disorders depends on the brain regions, neurotransmitter systems, and the GSK3 regulatory mechanisms these agents target in different disease-specific brain abnormalities.

Not only mood stabilizers and antipsychotics inhibit GSK3, but substantial evidence has shown that monoamine-regulating antidepressants also promote inhibitory control of GSK3. Administration of the monoamine reuptake inhibitor antidepressants fluoxetine and imipramine greatly increased the inhibitory serine phosphorylation of GSK3 in mouse brain (Beaulieu *et al*, 2008b; Li *et al*, 2004). The inhibitory effect of these antidepressants on GSK3 occurs within hours after an acute *in vivo* treatment, suggesting that this may be a response to the rapid increase in brain monoamines induced by these antidepressants, but whether the rapid inhibition of GSK3 is involved in the therapeutic actions of antidepressants that usually require chronic administration is a critical question remaining to be addressed.

These pharmacological studies show that inhibition of GSK3 is a common mechanism of action shared by several classes of drugs used in treating mood disorders (Table 1). A critical question remaining is to determine whether the effects of these pharmacological agents on GSK3 is related to their therapeutic actions in mood regulation, and how GSK3 serves as a target for both anti-manic and anti-depressive treatments.

EFFECTS OF NEUROMODULATORS ON GSK3

In addition to being modulated by mood stabilizers and other psychotropics used in mood disorders, evidence for a role of GSK3 in mood disorders is further supported by findings that GSK3 is regulated by neuromodulators thought to be involved in mood disorders. For example, brain-derived neurotrophic factor (BDNF) is a well-recognized neurotrophin with mood-regulating effects and is upregulated by antidepressants (Duman and Monteggia, 2006; Schmidt and Duman, 2007). Similar to other growth factors (Cross *et al*, 1995), BDNF binds to tyrosine kinase receptor B to activate phosphatidylinositol-3-kinase (PI3K) and Akt, and the latter phosphorylates the N-terminal serine of GSK3, thus inhibiting GSK3 activity (Johnson-Farley *et al*, 2006; Mai *et al*, 2002) (Figure 1). However, the behavioral effects of BDNF are brain region-dependent (Berton *et al*, 2006; Duman, 2004), thus it is important to determine if BDNF-induced inhibition of GSK3 mediates any BDNF-regulated behaviors.

Dysregulation of serotonin neurotransmission has long been thought to contribute to mood disorders (Jans *et al*, 2007), but the molecular basis of this consequence remains

unclear. Recent evidence suggests that impaired inhibitory serine-phosphorylation of GSK3 may be a factor contributing to depression associated with dysregulated serotonergic activity. In mouse brain, enhancing serotonergic activity by D-fenfluramine administration or activation of serotonin type 1A (5-HT1A) receptors increased inhibitory serine-phosphorylation of GSK3 in several brain regions (Li *et al*, 2004). This effect of serotonin is likely mediated by Akt because serotonin and 5-HT1A receptor agonists activate Akt through the PI3K-dependent pathway (Cowen *et al*, 2005; Polter *et al*, 2009). Conversely, in serotonin-deficient mice that carry a mutation in the tryptophan hydroxylase-2 gene equivalent to a rare human variant (R441H) identified in a few individuals with major depressive disorder (Zhang *et al*, 2005), serine phosphorylation of GSK3 is low and GSK3 activity is elevated (Beaulieu *et al*, 2008b). Regulation of GSK3 by serotonin may partly explain the mechanism of acute antidepressant treatment-induced GSK3 serine phosphorylation in brain (Beaulieu *et al*, 2008b; Li *et al*, 2004).

However, the effect of serotonergic activity on GSK3 is rather complicated because more than one serotonin receptor subtype is involved in regulating GSK3. Although serotonin type 2A (5-HT2A) receptor stimulation had minimal effects on GSK3, blocking 5-HT2 receptors increased serine phosphorylation of GSK3 in several brain regions (Li *et al*, 2004). In addition, 5-HT2 receptor antagonist administration potentiated the 5-HT1A receptor agonist-induced increase in GSK3 serine phosphorylation (Li *et al*, 2004). Although an integrative mechanism remains

Table 1 Effects of Mood Disorder Therapeutic Drugs on GSK3

Drug	Effect on GSK3 (α and/or β)	Experimental treatment	References
Lithium	↓ Activity	*In vitro*	(Klein and Melton, 1996; Stambolic *et al*, 1996)
	↑ Ser-phosphorylation	In cells	(Aubry *et al*, 2009; Chalecka-Franaszek and Chuang, 1999; Jin *et al*, 2005)
		Acutely in animal brain	(Beaulieu *et al*, 2004)
		Chronically in animal brain	(De Sarno *et al*, 2002; Kozlovsky *et al*, 2006; Roh *et al*, 2005)
		In human PBMCs	(Li *et al*, 2007a)
Valproate	↓ Activity	In cells	(Chen *et al*, 1999b)
	↑ Ser-phosphorylation	In cells	(De Sarno *et al*, 2002)
		Acutely in animal brain	(Roh *et al*, 2005)
		Chronically in animal brain	(Li, unpublished data)
	↑ Total level	Subchronically in animal brains	(Kozlovsky *et al*, 2006)
	No effect	*In vitro*	(Hall *et al*, 2002)
		In cells	(Eickholt *et al*, 2005; Jin *et al*, 2005; Phiel *et al*, 2001)
Carbamazepine	No effect	In cells	(Aubry *et al*, 2009; Mai *et al*, 2002; Ryves *et al*, 2005)
Lamotrigine	↑ Ser-phosphorylation	Chronically in animal brain	(Li, unpublished data)
	No effect	In cells	(Aubry *et al*, 2009)
Fluoxetine	↑ Ser-phosphorylation	Acutely in animal brains	(Beaulieu *et al*, 2008b; Li *et al*, 2007b; Li *et al*, 2004)
Imipramine	↑ Ser-phosphorylation	Acutely in animal brains	(Li *et al*, 2007b; Li *et al*, 2004; Roh *et al*, 2005)
Clozapine	↑ Ser-phosphorylation	In cells	(Aubry *et al*, 2009; Kang *et al*, 2004)
		Acutely in animal brains	(Li *et al*, 2007b; Roh *et al*, 2007)
		Subacutely in animal brains	(Park *et al*, 2010)
		Chronically in animal brains	(Alimohamad *et al*, 2005)
	↑ Total level	Chronically in animal brains	(Alimohamad *et al*, 2005; Kozlovsky *et al*, 2006)
Olanzapine	↓ Activity	*In vitro*	(Mohammad *et al*, 2008)
	↑ Ser-phosphorylation	In cells	(Aubry *et al*, 2009; Kim *et al*, 2008)
		Acutely in animal brains	(Li *et al*, 2007b)
Risperidone	↑ Ser-phosphorylation	Acutely in animal brains	(Li *et al*, 2007b)
		Chronically in animal brains	(Alimohamad *et al*, 2005)
	↑ Total level	Chronically in animal brains	(Alimohamad *et al*, 2005)
Quetiapine	↑ Ser-phosphorylation	Acutely in animal brains	(Li *et al*, 2007b)
Ziprasidone	↑ Ser-phosphorylation	Acutely in animal brains	(Li *et al*, 2007b)
Aripiprazole	↑ Ser-phosphorylation	In cells	(Park *et al*, 2009)
Haloperidol	↑ Ser-phosphorylation	Acutely in animal brains	(Roh *et al*, 2007)
		Chronically in animal brains	(Alimohamad *et al*, 2005)
	↓ Ser-phosphorylation	Chronically in animal brains	(Kozlovsky *et al*, 2006)
	↑ Total level	Chronically in animal brains	(Alimohamad *et al*, 2005)
	No effect	In cells	(Park *et al*, 2009)

to be elucidated, it is possible that regulation of brain GSK3 by serotonin differs among brain regions and cell types depending on the serotonin receptor subtypes expressed, with the overall regulatory effect of serotonin on brain GSK3 involving a balanced response among several serotonin receptor subtypes (Figure 1).

GSK3 is also regulated by dopaminergic activity (Figure 1). Elevation of extracellular dopamine in dopamine transporter knockout mice was shown to reduce serine phosphorylation of GSK3 in the striatum, an effect that was reversed by administration of a dopamine D2 receptor antagonist (Beaulieu *et al*, 2004). Regulation of GSK3 by D2 receptor involves inactivation of Akt in a protein complex including the scaffolding protein β-arrestin2 and PP2A (Beaulieu *et al*, 2005). It is noteworthy that the effect of D2 receptor antagonists on GSK3 is similar to the effect of blocking 5-HT2 receptors, raising the possibility that the reported interaction of 5-HT2 receptors with β-arrestin2 (Schmid *et al*, 2008) may also be involved in the regulation of GSK3 by 5-HT2 receptors.

Taken together, mood-regulating neuromodulators, exemplified by BDNF, serotonin, and dopamine, regulate GSK3 through different mechanisms of action, supporting the notion that disrupted GSK3 regulation occurs in mood disorders. The associations between behavioral effects and regulation of GSK3 by neuromodulators need to be clarified to fully understand the significance of GSK3 in mood disorders. In addition, the inhibitory serine phosphorylation of GSK3 seems to be a common mode of regulation by these neuromodulators, but the significance of this major GSK3 regulatory mechanism in mood-related behaviors remains to be determined.

BEHAVIORAL STUDIES IN MICE WITH ALTERED GSK3 EXPRESSION OR ACTIVITY

Behavioral studies in rodents using a variety of experimental strategies support the postulate that GSK3 is an important regulator of mood-related behaviors. GSK3β haploinsufficient (lacking one copy of the gene encoding GSK3β) mice showed reduced immobility in the forced swim test, increased exploratory activity (O'Brien *et al*. 2004), and reduced amphetamine-induced hyperactivity (Beaulieu *et al*, 2004), similar to the behavioral effects of lithium in these tests. Reducing GSK3β in this animal model was also effective in normalizing the impaired tail suspension behavior in serotonin-deficient mice that otherwise have increased GSK3 activity (Beaulieu *et al*, 2008b). However, another group failed to replicate these behaviors reported in GSK3β haploinsufficient mice (Bersudsky *et al*, 2008). Conversely, transgenic mice postnatally overexpressing constitutively active S9A-GSK3β in neurons show hyperactivity in the open field test and increased acoustic startle response (Prickaerts *et al*, 2006), suggesting that excessive GSK3β could be a precipitating factor in heightened locomotor activity and sensory responses. However, instead of showing behaviors opposite to those of GSK3β haploinsufficient mice, GSK3β overexpressing mice also show decreased immobility in the forced swim test. An important factor complicating studies of these GSK3β overexpressing mice is that their brain size is reduced by approximately 20% (Spittaels *et al*, 2000, 2002), which may have confounding influences on their behaviors. A recent study focusing specifically on GSK3α found that GSK3α knockout mice show decreased exploratory activity, decreased immobility time in the forced swim test, and reduced aggressive behavior, among other phenotypes (Kaidanovich-Beilin *et al*, 2009), showing that both GSK3 isoforms have similar effects on behavior. However, a direct comparison of GSK3α- and GSK3β-selective regulation of behaviors is still lacking, a topic needing further investigation because each GSK3 isoform has independent functions (Chen *et al*, 2009; Liang and Chuang, 2006, 2007; Phiel *et al*, 2003; Wang *et al*, 1994).

As discussed above, the activity of GSK3 is predominantly regulated by posttranslational phosphorylation and regulation in protein complexes, whereas GSK3 protein expression is relatively stable (Doble and Woodgett, 2003). Although behavior findings in mice with altered expression of GSK3 have provided useful information linking GSK3 to regulating these behaviors, altering GSK3 expression may not accurately model a pathological condition in which GSK3 activity, but not expression, is dysregulated, such as by altered neuromodulators in mood disorders (Cousins *et al*, 2009; Duman, 2004; Jans *et al*, 2007). In addition, GSK3α and GSK3β share similar regulatory mechanisms, and selectively manipulating one isoform could cause compensational changes in the other (Liang and Chuang, 2006, 2007; Lucas *et al*, 2001). Thus, behavioral changes of altered GSK3α and GSK3β in combination should also be evaluated. Behavioral studies incorporating both these approaches have been conducted (Polter *et al*, 2010) in mice with serine-to-alanine mutations to block inhibitory serine-phosphorylation of both GSK3α and GSK3β (GSK3α/$\beta^{21A/21A/9A/9A}$ knockin mice) (McManus *et al*, 2005). A striking feature of these mice is that they show increased susceptibility to both amphetamine-induced hyperactivity and stress-induced depressive-like behaviors, whereas their baseline behaviors are similar to strain-matched wild-type mice. This suggests that insufficient inhibitory serine phosphorylation of GSK3 is a risk factor for developing mood-related behavioral disturbances, which complements the findings that lithium and many other psychotropics increase serine phosphorylation of GSK3 (Alimohamad *et al*, 2005; Beaulieu *et al*, 2008b; Chalecka-Franaszek and Chuang, 1999; De Sarno *et al*, 2002; Li *et al*, 2007a, b, 2004; Roh *et al*, 2007).

The robust behavioral effects of altered GSK3 suggest the importance of maintaining normal GSK3 activity in brain, and this is supported by several studies of behavior using GSK3 inhibitors that are either small molecule ATP competitors or a substrate-mimicking peptide that blocks substrate phosphorylation by GSK3 (Cohen and Goedert, 2004; Martinez *et al*, 2006; Meijer *et al*, 2004). Intracerebroventricular injection in rats of a small peptide GSK3 inhibitor, L803-mts, decreased immobility in the forced swim test (Kaidanovich-Beilin *et al*, 2004), suggesting that this GSK3 inhibitor has antidepressant-like actions. Subacute systemic administration of a small molecule GSK3 inhibitor AR-A014418 not only reduced immobility in the forced swim test, but also reduced amphetamine-induced hyperactivity (Gould *et al*, 2004). Similar behavioral effects were also found with other GSK3 inhibitors (Beaulieu *et al*, 2004; Rosa *et al*, 2008), suggesting that these small molecule GSK3 inhibitors have

similar mood-regulating effects as lithium, and may be developed for mood disorder treatment.

GSK3 IN HUMAN BRAIN AND PERIPHERAL TISSUES

Investigations of GSK3 in humans are necessary to confirm a relationship between abnormal regulation of GSK3 and mood disorders because animal behavioral measurements do not fully model mood disturbances in humans. A post-mortem study with 40 brain samples from suicide and non-suicide subjects revealed an increase in GSK3β activity and a decrease in Akt activity in depressed but not in non-depressed suicide subjects (Karege *et al*, 2007). Although two other studies reported no difference in GSK3 levels in post-mortem brains between bipolar disorder and healthy subjects (Kozlovsky *et al*, 2000; Lesort *et al*, 1999a), these studies did not investigate if the activity of GSK3 was altered. Assessing GSK3 activity or its serine phosphorylation may be difficult in post-mortem brains since in mice serine phosphorylation of GSK3 rapidly declines within minutes of death (Li *et al*, 2005). There are other limitations to using post-mortem brain tissues to evaluate GSK3 activity in mood disorders, as this cannot test mood state-dependent changes in GSK3 activity during manic or depressive episodes, and pre-mortem medications may alter GSK3 phosphorylation and complicate the interpretation of post-mortem findings.

An alternative is to use peripheral tissues from live patients to assess GSK3, such as in PBMCs (Li *et al*, 2007a). In PBMCs from a small group of human subjects, serine phosphorylation of both GSK3α and GSK3β in symptomatic bipolar disorder patients was lower than in healthy controls (Polter *et al*, 2010). Remarkably, reduction in serine phosphorylation of GSK3 also significantly correlated with severity of manic and depressive symptoms, suggesting that GSK3 activity is affected by mood states. Studies in several other cohorts measuring the expression of GSK3 mRNA and proteins generated varied results. The level of total GSK3 tends to be higher in type I bipolar manic patients than healthy controls in a Chinese population (unpublished data), whereas lower GSK3 mRNA was found in PBMCs of teenage suicide victims and lower GSK3 protein levels in platelets of bipolar patients (Pandey *et al*, 2010). Apparently, large cohorts in different mood states are needed to validate findings from human patients.

PBMCs have also been used to evaluate responses of GSK3 to mood disorder treatment. The level of phospho-Ser9-GSK3β of bipolar patients stabilized on lithium treatment was eightfold higher than healthy controls who were not exposed to lithium (Li *et al*, 2007a), suggesting that GSK3 in PBMCs in bipolar disorder patients responds to lithium. In bipolar type I manic patients, a combination treatment with lithium and olanzapine also significantly increased serine phosphorylation of GSK3 (unpublished data), further supporting the pre-clinical findings showing that GSK3 activity is inhibited by mood stabilizing and antipsychotic treatments (Beaulieu *et al*, 2004; Li *et al*, 2007b, 2004; Polter *et al*, 2010).

Genetic variations in GSK3 also have been examined in mood disorders. A series of studies in an Italian population reported that a single-nucleotide polymorphism (SNP) in the promoter region of GSK3β (−50T/C) is associated with bipolar disorder (Benedetti *et al*, 2004a, b, 2005). The C-variant was found to be linked to a later onset and better response to acute sleep deprivation in bipolar depressed patients, and a favorable response to lithium treatment for mood stabilization. In an independent study, the C-carriers of the −50T/C SNP had better response to lithium augmenting treatment in acutely depressed antidepressant-resistant bipolar and major depressive disorder patients (Adli *et al*, 2007), whereas another study did not find an association of this SNP with the degree of prophylactic lithium response in bipolar disorder (Szczepankiewicz *et al*, 2006). Another pharmacogenomic study genotyped four SNPs (rs334558, rs13321783, rs2319398, and rs6808874) in the non-coding region of the GSK3β gene in 230 depressed patients and 415 controls in a Chinese population (Tsai *et al*, 2008), and identified significant association of three polymorphisms with 4-week antidepressant (fluoxetine or citalopram) therapeutic effects. In the four-locus haplotype analysis, the GSK3β TAGT carriers showed a poorer response to antidepressants, suggesting that they are likely non-responders to antidepressant treatment. A recent study evaluated the association of 15 GSK3β SNPs with brain structural changes in major depressive disorder (Inkster *et al*, 2009). The study found that the gray matter volume in the right hippocampus and bilateral superior temporal gyri is associated with a common SNP (rs6438552), an intronic polymorphism that regulates the selection of splice acceptor sites of GSK3β and thus affects GSK3β transcription. The lowered gray matter volume was specific to the AA genotypes of patients with major depressive disorder when compared to healthy controls. Therefore, GSK3 genetic variations may be involved in disease vulnerability and treatment response, and an important goal for future genetic research is to identify the functional correlates of these genetic variants on GSK3 function.

HOW MIGHT INHIBITION OF GSK3 PROMOTE MOOD STABILIZATION?

If, as much evidence suggests, GSK3 is dysregulated in mood disorders, a critical goal is to identify the substrates phosphorylated by GSK3 that mediate its regulation of mood. Some candidate proteins that are phosphorylated by GSK3 and seem to have mood-regulating functions have been identified. Prominent among these is the transcription factor cyclic AMP response element-binding protein (CREB), the most extensively studied transcription factor involved in mood disorders (Carlezon *et al*, 2005; Duman *et al*, 1997). The expression and activity of CREB are upregulated by lithium and antidepressants (Chen *et al*, 1999a; Mai *et al*, 2002; Nibuya *et al*, 1996; Ozaki and Chuang, 1997; Thome *et al*, 2000), and CREB overexpression in the dentate gyrus, has an antidepressant-like effect (Chen *et al*, 2001). Conversely, CREB is inactivated by GSK3-mediated phosphorylation on the serine-129 residue, and this inactivation is blocked by lithium treatment (Bullock and Habener, 1998; Fiol *et al*, 1994; Grimes and Jope, 2001).

β-Catenin is a major transcriptional modulator inhibited by GSK3 (Behrens *et al*, 1998; Rubinfeld *et al*, 1996), and is activated by GSK3 inhibitors that have mood-regulating effects, such as lithium (Hedgepeth *et al*, 1997; Stambolic

et al, 1996). Transgenic mice overexpressing a constitutively active form of β-catenin in the adult CNS show behavioral changes similar to those observed after the administration of lithium, including decreased immobility time in the forced swim test and reduced D-amphetamine-induced hyperlocomotion, whereas forebrain-specific knockout of β-catenin caused a mild depressive-like behavior in mice (Gould *et al*, 2007, 2008). Recently, β-catenin was found to be regulated by disrupted in schizophrenia 1 (DISC1), which binds GSK3 to inhibit phosphorylation of β-catenin, allowing accumulation and activation of β-catenin (Mao *et al*, 2009). Genetic linkage studies have implicated mutations in DISC1 as a risk factor for mood disorders and other psychiatric diseases (Chubb *et al*, 2008; Millar *et al*, 2000; St Clair *et al*, 1990), and mutated DISC1 is unable to inhibit GSK3 to upregulate β-catenin. Modeling this by knocking-down DISC1 levels in mouse hippocampal dentate gyrus resulted in impaired neurogenesis, hyperactivity in the open field, and increased immobility in the forced swim test, which were reversed by a selective GSK3 inhibitor (Mao *et al*, 2009). Thus, regulation by DISC1 connects impaired inhibition of GSK3 with susceptibility to mood disorders.

As GSK3 regulates a large group of transcription factors and transcriptional modulators (Jope and Johnson, 2004), it could regulate the expression of genes involved in mood regulation and mood disorders, such as neurotrophins (Shaltiel *et al*, 2007). One example of this is that lithium increases BDNF expression in brain (Fukumoto *et al*, 2001). In cultured rat cortical neurons, therapeutic concentrations of lithium selectively increased the levels of exon IV-containing BDNF mRNA, and the lithium-induced activation of promoter IV was mimicked by pharmacological inhibition of GSK3 or short interfering RNA-mediated gene silencing of GSK3α or GSK3β (Yasuda *et al*, 2009). As substantial evidence shows that BDNF is involved in regulating mood and mediating effects of antidepressant and lithium (Duman, 2004; Post, 2007), inhibition of GSK3 may promote mood stabilization by increasing BDNF expression.

Not only is GSK3 regulated by serotonin, but GSK3 also selectively modulates the activity of serotonin receptors. GSK3β directly interacts with serotonin type 1B (5-HT1B) receptors, but not 5-HT1A receptors, at a GSK3 consensus phosphorylation site (S154-XXX-T158) in the second intracellular loop of the receptor (Chen *et al*, 2009). GSK3β-dependent phosphorylation of 5-HT1B receptors seems to be required for agonist-induced decrease in cAMP production. This finding extends several previous reports that lithium regulates 5-HT1B receptor activity (Januel *et al*, 2002; Massot *et al*, 1999; Redrobe and Bourin, 1999), and provides a mechanistic explanation for this action of lithium. As the primary action of 5-HT1B receptors located on axon terminals is to negatively regulate neurotransmitter release (Riad *et al*, 2000; Sari, 2004), altering neurotransmitter release by impaired control of GSK3 activity may be associated with mood disturbances. Identification of a direct interaction between GSK3 and 5-HT1B receptors also raises the likelihood that some other members of the large family of G-protein coupled receptors (GPCRs) may be regulated by GSK3. As GPCRs are the most common target for pharmacological interventions in the treatment of psychiatric disorders, future studies should examine the relationships between the proper control of GSK3 activity and the effect on pharmacological treatments targeting GPCRs.

An important component of neuroplasticity is neurogenesis, neural precursor cell proliferation and differentiation into neurons (Lie *et al*, 2004). Evidence that impaired neurogenesis in the hippocampus may be involved in mood disorders stems primarily from findings that neurogenesis is increased in mice by antidepressants (David *et al*, 2009; Malberg and Duman, 2003; Malberg *et al*, 2000; Manev *et al*, 2001; Santarelli *et al*, 2003; Warner-Schmidt and Duman, 2007), and is decreased by chronic stress that increases depressive-like behavior (Dranovsky and Hen, 2006; Malberg and Duman, 2003; McEwen, 2008). Lithium also increases neurogenesis (Chen *et al*, 2000; Hashimoto *et al*, 2003; Silva *et al*, 2008; Wexler *et al*, 2008), which may result from its inhibition of GSK3. This was shown in recent studies showing that neurogenesis was impaired in GSK3 knockin mice with blocked inhibitory serine-phosphorylation of GSK3 (Eom and Jope, 2009), and GSK3 deletion increased proliferation of neural progenitors (Kim *et al*, 2009). Therefore, disrupted neurogenesis in mood disorders can partially be a result of impaired control of GSK3.

GSK3 also regulates other processes associated with neuroplasticity, such as synaptic and structural plasticity (Citri and Malenka, 2008; Schloesser *et al*, 2008). In GSK3 knockin mice that lack the inhibitory serine phosphorylation of GSK3, NMDA receptor-dependent long-term depression (LTD) in area CA1 was converted to a slow onset long-term potentiation-like response (Polter *et al*, 2010). Interestingly, this conversion was previously noted in wild-type rats that were pre-exposed to acute swim stress (Maggio and Segal, 2009). Conversely, GSK3 inhibitors block the NMDA receptor-dependent induction of LTD (Peineau *et al*, 2007). In addition, GSK3 also modulates structural plasticity, such as growth cone formation and synaptogenesis. For example, inhibition of GSK3 by Wnt led to a decrease in the phosphorylation of microtubule-associated protein-1B and a concomitant decrease in microtubule stability (Salinas, 1999), whereas lithium treatment increased microtubule stability in neuronal growth cones (Goold *et al*, 1999). Although these neuroplasticity processes regulate neuronal maturation and adaptation, their relevance to mood disorders remains to be more firmly established, and further research is needed to determine if the influence of GSK3 on neuroplasticity is related to the pathophysiology or treatment of mood disorders.

One of the most well-established properties of GSK3 inhibitors is their neuroprotective actions, as previously reviewed (Beurel and Jope, 2006; Chuang, 2005). On a cellular level, the neuroprotective actions of GSK3 inhibitors are often experimentally identified by measuring cell survival in response to insults. For example, GSK3 inhibitors reduce many types of apoptosis-inducing insults, such as misfolded protein accumulation (Song *et al*, 2002) and DNA damage (Watcharasit *et al*, 2002). Although apoptosis is unlikely to contribute directly to mood disorder etiology, neuroprotection strengthens adaptive responses of cells to better withstand many types of stress, and enhances neuronal functions that counteract stress-induced mood disturbances. GSK3 inhibitors block a number of actions of GSK3 that impair neuronal function after stress. For example, by inhibiting the transcription factor HSF-1 (Chu *et al*, 1996), GSK3 reduces the expression of chaperone proteins,

a major cellular protective mechanism against neuronal insults, and GSK3 inhibitors strengthen cellular responses to stress by upregulating the expression of chaperone proteins (Bijur and Jope, 2000; Ren *et al*, 2003). Similarly, GSK3 promotes, and GSK3 inhibitors counteract, impairments associated with DNA damage, exemplified by the non-homologous end-joining DNA repair pathway that is promoted by lithium (Yang *et al*, 2009). Thus, along with promoting production and actions of neuroprotective neurotrophins (Machado-Vieira *et al*, 2009) and β-catenin (Toledo *et al*, 2008), inhibition of GSK3 bolsters intracellular mechanisms that provide neuroprotection. Although these neuroprotective actions of GSK3 inhibitors are clearly important in counteracting neurodegenerative conditions such as ischemia, further research is needed to determine if they contribute to regulation of mood disturbances.

GSK3 has a strong regulatory effect on inflammation that is now recognized as having an important influence on the pathology and treatment of mood disorders, especially depression (Miller *et al*, 2009; Raison *et al*, 2006). Inflammatory molecules are often increased in depressed patients (Hayley *et al*, 2005; Lotrich *et al*, 2009; O'Brien *et al* 2007, 2006; Reichenberg *et al*, 2001), and in rodents, inflammation-induced depressive-like behaviors can be attenuated by antidepressants (Dantzer and Kelley, 2007; Dantzer *et al*, 2008; Rivest, 2009; Roumestan *et al*, 2007). A crucial role for GSK3 in promoting inflammation was first established by the finding that GSK3 promotes the production of several pro-inflammatory cytokines after stimulation of multiple types of Toll-like receptors in human monocytes, which are reduced by GSK3 inhibitors or by inducing GSK3 deficiency (Martin *et al*, 2005). Remarkably, GSK3 regulates oppositely the anti-inflammatory cytokine IL-10, because GSK3 inhibition increased IL-10 levels (Hu *et al*, 2006; Martin *et al*, 2005). *In vivo*, the GSK3 inhibitors lithium and SB216763 rescued approximately 70% of mice from an otherwise 100% lethal inflammatory response to lipopolysaccharide (Martin *et al*, 2005). Subsequently, GSK3 inhibitors were found to reduce by $>90\%$ inflammatory cytokine production in mouse primary astrocytes and microglia (Beurel and Jope, 2009; Yuskaitis and Jope, 2009). Thus, GSK3 strongly promotes inflammatory reactions, which may contribute to its role in mood disorders, and reducing GSK3-promoted production of inflammatory molecules may contribute to the therapeutic actions of mood stabilizers and antidepressants that inhibit GSK3.

SUMMARY

Cumulative evidence from *in vitro* measurements, pharmacological studies, animal behavioral tests, and investigations with human tissues strongly support the postulate that GSK3 has a pathological role in mood disorders and is likely a therapeutic target in mood disorder treatment. However, remaining questions must be addressed before GSK3 can be concluded to be a pathogenic molecule and therapeutic target in mood disorders. Although mood stabilizers, antidepressants, and antipsychotics can inhibit GSK3, it is important to determine if this inhibition of GSK3 is critical for their therapeutic actions. Perhaps most important is identifying the GSK3-regulated protein substrates that mediate the physiological and behavioral effects of GSK3 on mood regulation. Further investigation is required to understand how altered activity of GSK3 affects behavior, and to determine the mechanisms of how each mood state—manic or depressive—is affected by altered GSK3 activity. This emphasizes the need for human studies to determine if clinical findings support the ample preclinical evidence suggesting a link between dysregulated GSK3 and mood disorders, and if GSK3 could be a biomarker for differential diagnosis of mood disorders or a treatment predictor. Preclinical and clinical studies are also needed to test if selective GSK3 inhibitors are therapeutic for mood disorders. Only with such additional evidence will the role of dysregulated GSK3 in the etiology of mood disorders be firmly established, and clinical applications targeting GSK3, its regulatory signaling pathways, and its mood-regulating substrates be implemented.

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DISCLOSURE

The authors declare no conflict of interest.

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