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Review

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Regulation of GSK-3 Activity as A Shared Mechanism in Psychiatric Disorders

Ceren Sahin[1], Gokhan Unal[1], Feyza Aricioglu[2]

ÖZET:

Psikiyatrik hastalıklarda ortak bir mekanizma olarak GSK-3 aktivitesinin düzenlenmesi

Serin/Treonin kinaz ailesinin üyelerinden bir kinaz olarak ilk kez glikojen sentaz'ı inhibe ettiği keşfedilen glikojen sentaz kinaz-3 (GSK-3), günümüzde bilinen 50'den fazla substratı ile birçok hücre içi düzenleyici mekanizmada görev alan geniş etki spektrumlu bir enzim olarak kabul edilmektedir. GSK-3'ün memelilerde GSK-3α ve GSK-3β olmak üzere yapısal olarak yüksek homoloji gösteren iki izoformu bulunmaktadır. Her iki izoform birçok dokuda yaygın dağılım göstermekle beraber, en yüksek oranda beyinde bulunmakta ve genellikle benzer fonksiyonlar göstermektedirler. Diğer protein kinazların aksine GSK-3 uyarılmamış hücrede yapısal olarak aktif yani defosforile halde bulur. Protein kinaz A (PKA), protein kinaz B (PKB;AKT) ve protein kinaz C (PKC) gibi diğer protein kinazlarla fosforilasyona uğrayarak olarak inaktive edilir. Günümüzde artmış GSK-3 aktivitesinin major depresyon, bipolar bozukluk, hiperaktivite bozuklukları gibi hastalıklar ve şizofreni oluşumunda rol oynayabileceğine ilişkin önemli bulgular mevcuttur. Bu nedenle söz konusu psikiyatrik hastalıklarda arttığı gösterilen GSK-3 aktivitesinin azaltılmasının tedavide umut verici bir yaklaşım olabileceği kabul edilebilir. Bu gözden geçirme çalışmasında yukarıda sözü edilen psikiyatrik hastalıkların oluşmasında görev alan GSK-3 aracılı mekanizmalara kısaca değinilerek GSK-3'ün aktivitesinin düzenlenmesinde rol oynadığı gösterilen klinikte kullanılan ilaçlara yer verilmiştir.

Anahtar sözcükler: GSK-3, depresyon, bipolar bozukluk, şizofreni

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ABSTRACT:

Regulation of GSK-3 activity as a shared mechanism in psychiatric disorders

Glycogen synthase kinase-3 (GSK-3), a member of the serine/threonine kinase family was first identified as an inhibitor of the metabolic enzyme glycogen synthase and is now accepted as a widely influential enzyme responsible for many intracellular regulatory mechanisms with over 50 known substrates characterized. There are two mammalian GSK-3 isoforms encoded by separate genes: GSK-3α and GSK-3β with high structural homology. Both GSK-3α and GSK-3β are widely expressed in many tissues with the highest levels in the brain and their functions are generally considered to be indistinguishable. Unlike many other protein kinases, GSK-3 is constitutively dephosphorylated and active in resting cells. Phosphorylation of GSK-3 by other protein kinases such as PKA (Protein kinase A), AKT (Protein kinase B) and PKC (Protein kinase C) inhibits its activity. Today a growing body of evidence strongly suggests that increased GSK-3 activity is involved in the development of schizophrenia and mood disorders such as bipolar disorder, major depression and hyperactivity associated disorders. Thus, inhibition of overactive GSK-3 has become a promising target in the treatment of these psychiatric disorders. Herein we will briefly discuss the underlying mechanisms related to how GSK-3 is thought to participate in such diseases and will give examples of clinically important treatments that have a role in GSK-3 regulation.

Keywords: GSK-3, depression, bipolar disorder, schizophrenia

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INTRODUCTION

Glycogen synthase kinase-3 (GSK-3), a member of the serine/threonine kinase family, was first identified as an inhibitor of the metabolic enzyme glycogen synthase by inactivation through phosphorylation mechanism[1]. In the following years over 50 known substrates of GSK-3 have been characterized and it is not surprising that GSK-3 is accepted as a widely influential enzyme, which is responsible for a myriad of intracellular regulatory mechanisms. These mechanisms include cell

polarity[2], cell fate[3], development[4], apoptosis[5], microtubule function[6], neuronal structure, growth, differentiation and synaptic plasticity[7].

Unlike many other protein kinases, GSK-3 is constitutively active in resting cells being dephosphorylated. Otherwise when stimulated, the regulatory mechanisms of GSK-3 are mainly based on its inactivation through phosphorylation at the N-terminal serine residue by other protein kinases such as PKA (Protein kinase A), AKT (Protein kinase B) and PKC (Protein kinase C). In addition, GSK-3 has the ability to phosphorylate itself with its kinase activity resulting in auto-inhibition[8-11]. Apart from N-terminal serine phosphorylation, GSK-3 is also regulated by protein-protein interactions such as canonical Wnt signaling mediated with Frizzled receptors, which results in inhibition of GSK-3 activity therefore preventing β-catenin phosphorylation by GSK-3 and consequently its degradation. Unphosphorylated β-catenin later migrates to the cell nucleus where it trans-activates genes regulated by specific transcription factors such as T-cell factor/lymphoid enhancer factor[12-15].

There are two mammalian GSK-3 isoforms encoded by separate genes, GSK-3α and GSK-3β, with approximately 85% structural homology[16]. They are phosphorylated by other protein kinases at the N-terminal serine-21 (GSK-3α) and serine-9 (GSK-3β) residues, and GSK-3α differs from GSK-3β with its glycine-rich-N-terminal domain. Both GSK-3α and GSK-3β are widely expressed in many tissues with the highest levels in the brain and their functions are generally considered as indistinguishable[15,17].

Today an abundance of evidence strongly suggest that dysregulation of GSK-3 particularly resulting in increased kinase activity is involved in the development of schizophrenia and mood disorders such as bipolar disorder, major depression and hyperactivity associated disorders. Thus, inhibition of overactive GSK-3 has become a promising target in the treatment of these psychiatric disorders. Herein we will briefly discuss the underlying mechanisms related to how GSK-3 is thought to participate in such diseases and give examples of clinically important treatments having a role in GSK-3 regulation.

GSK-3β in Mood Disorders

Today, a growing body of evidence strongly points to the possibility that hyperactivated GSK-3β might be involved in the development of mood disorders such as major depression, bipolar disorder and hyperactivity associated disorders. Inhibition of induced GSK-3β activity may serve as a common target for the treatment of each disorder[15,18]. Therefore, in the following sections we will briefly highlight the underlying mechanisms that are considered to contribute to the GSK-3β involvement in mood disorders with examples of the current therapies that have been shown to have effects on GSK-3 regulation.

GSK-3β and major depression: The role of 5-HT receptors on the PI3K/AKT pathway

AKT-mediated phosphorylation of GSK-3β (ser-9) is one of the major mechanisms, which is responsible for suppressing GSK-3β activation. This controlling mechanism of AKT on GSK-3 requires phosphoinositide 3-kinase (PI3K) activation in order for AKT to be phosphorylated and consequently activated so that it has the ability to phosphorylate GSK-3 resulting in inhibition of its activity. As Gi-coupled receptors are known to activate the PI3K/AKT signaling pathway, it was important to show that the stimulation of Gi-coupled 5-HT1A receptors activated PI3K/AKT signaling, possibly resulting in inhibition of GSK-3 activity (Figure 1)[18,19].

On the other hand, 5-HT2 receptor activation is considered to stabilize the dephosphorylated form of GSK-3β, therefore causing increased kinase activity (Figure 1). Since in depression, 5-HT1A receptor mediated serotonergic neurotransmission is known to be decreased in contrast to enhanced serotonergic 5-HT2 receptor mediated neurotransmission, it is intriguing to argue that high GSK-3 activity may be due to this imbalance between 5-HT1A and 5-HT2 receptors. Agents that

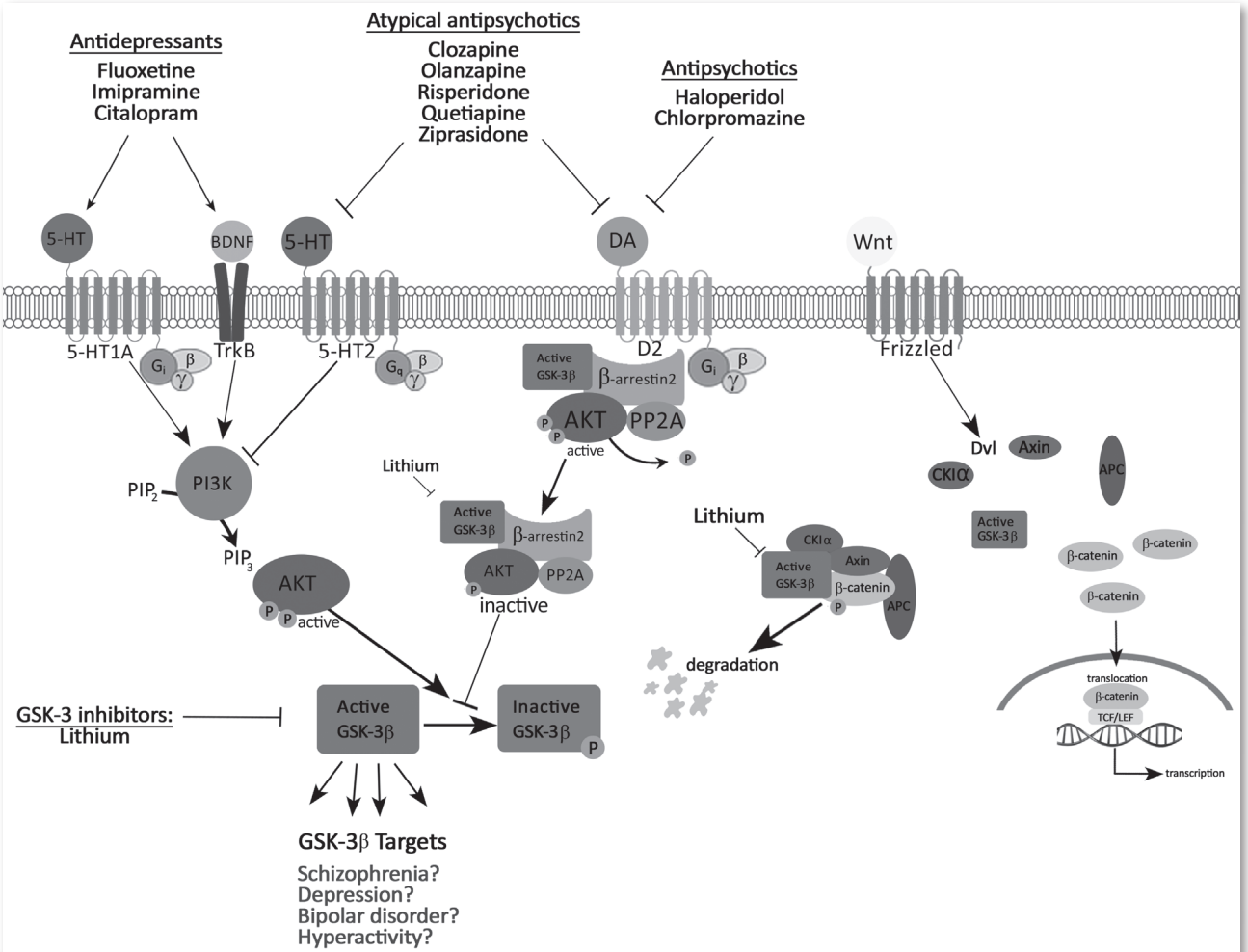


Figure 1: Physiological and pharmacological regulation of GSK-3β.
Stimulation of 5-HT1A and TrkB receptors by antidepressants activates PI3K/AKT signaling that results in phosphorylation and inactivation of GSK-3β. Whereas, 5-HT2 receptor activation reversely inhibits PI3K/AKT signaling and increases active form of GSK-3β. D2 receptors stimulation leads to β-arrestin2 recruitment and stabilization of AKT-β-arrestin2-PP2A signaling complex resulting in AKT inhibition by PP2A. This process is also strengthen by the active GSK-3 that joins the complex through binding with β-arrestin2 and responsible for further stabilizing AKT-PP2A binding. Therefore inhibitory control of AKT on GSK-3β is prevented and active GSK-3β levels are induced. Antipsychotics reverse this process by blocking D2 receptors resulting in decreased GSK-3β activity. Since atypical antipsychotics also block 5-HT2 in addition to D2 receptors, they decrease GSK-3β activity via two distinct mechanisms. GSK-3 is responsible for phosphorylation and degradation of β-catenin, a transcriptor factor, through 'destruction complex' known as CKIα-Axin-β-catenin-APC-GSK-3β. Stimulation of Frizzled receptors by Wnt, leads to the disruption of this complex, therefore β-catenin is released from GSK-3β and translocates to the cell nucleus where it serve as a transcriptor factor for TCF/LEF. Lithium inhibits GSK-3β activity directly or indirectly by causing a disruption in AKT-β-arrestin2-PP2A signaling complex. Active GSK-3β effects its target substrates and somehow contributes to behavioral responses in psychiatric disorders. (5-HT, 5-hydroxytriptamine; BDNF, brain-derived neurotrophic factor, GSK-3β, glycogen synthase kinase-3β; TrkB, tyrosine kinase B; DA, dopamine; PIP2, phosphoinositol diphosphate;PI3K, phosphoinositide-3 kinase; PIP3, phosphoinositol triphosphate; PP2A, protein phosphatase 2A; P, phosphor; APC, adenomatous polyposis coli; CKIα, casein kinase 1α; TCF/LEF, T-cell factor/Lymphoid enhancer factor.)

enhance serotonergic activity via blocking 5-HT re-uptake transporter, inhibiting 5-HT metabolism or inducing 5-HT release from the presynaptic neuron have been shown to increase the inhibitory serine-9 phosphorylation of GSK-3β. According to these findings it has been speculated that serotonergic neurotransmission has an important role in regulating GSK-3β activity in brain by serine-9 phosphorylation-mediated inhibition. In support of this hypothesis, the deficiency of serotonergic neurotransmission seen in depression would contribute to abnormal GSK-3β activity[18,20].

Administration of GSK-3 inhibitors to subjects has been shown to produce antidepressant-like effects in different experimental studies[21-23]. Although it is not yet clear how inactivated or activated GSK-3 contributes to anti-depressive or depressive-like states, respectively, all together,

Table 1: The effects of certain antidepressants on GSK-3

Antidepressant	Effect on GSK-3(β or α)	Method	References
Fluoxetine	Ser-phosphorylation	in vitro cell culture mouse hippocampus rat PFC* and striatum mouse PFC* mouse cerebral cortex and HC**	(20), (24), (25), (26), (27)
Sertraline	No effect	Human platelets	(28)
Citalopram	Ser-phosphorylation	rat hippocampus rat mPFC *	(29), (30)
Mirtazapine	Ser-phosphorylation	rat PFC*	(31)
Imipramine	Ser-phosphorylation reduced protein levels	rat PFC*and striatum mouse PFC* mouse brain Rat amygdala, PFC*, HC**	(20), (26), (32), (33)
Tianeptine	Ser-phosphorylation	rat PFC*	(31)

*PFC; prefrontal cortex, **HC; hippocampus

Table 2: The effects of certain mood stabilizers on GSK-3

Mood stabilizer	Effect on GSK-3(β or α)	Method	References
Lithium	Ser-phosphorylation Reduced activity	rat PFC* and striatum mouse cerebral cortex and HC** mouse brain human cell culture	(26), (27), (32), (44), (45), (34)
Valproic acid	Ser-phosphorylation No effect	rat striatum human cell culture rat cell culture	(26), (41), (44), (45), (46), (47)
Carbamazepine	No effect	rat cell culture	(47)
Lamotrigine	reduced protein levels	Rat amygdala, PFC*, HC**	(33)

*PFC; prefrontal cortex, **HC; hippocampus

these findings strongly suggest that GSK-3 hyperactivation is coupled with a depression-like state by the deficiency of 5-HT-mediated negative control on GSK-3. Since certain commonly used antidepressant drugs are identified in terms of being at least partially effective on GSK-3 regulation (Table 1), targeting GSK-3 inhibition is assumed to possibly bring new aspects or contributions to the treatment of depression.

GSK-3β and bipolar disorder

The first evidence that GSK-3 might be involved in bipolar disorder originated from two reports showing that the classical mood stabilizer lithium was a direct inhibitor of GSK-3 by a magnesium-competitive mechanism[34,35]. Later it was shown by a number of studies that direct inhibition of GSK-3 is not the only mechanism of action of lithium. Disruption of the AKT-β-arrestin2- protein phosphotase 2A (PP2A) signaling complex by lithium results in AKT being rescued from PP2A inhibition and being activated, which later phosphorylates and inhibits GSK-3. What is more interesting is that this mechanism of action of lithium is dependent on β-arrestin2 in terms of exerting behavioral responses (Figure 1)[36].

Although lithium treatment is widely used as a GSK-3 inhibitor, one should note that lithium's actions are not only restricted to GSK-3 inhibition and therefore, highly selective GSK-3 inhibitors need to be developed[37].

Moreover, genetically altered GSK-3 activity in mice has been shown to produce behaviors resembling mood disorders. Reduced GSK-3 activity resulted in behaviors that reşect chronic lithium treatment, whereas overexpression of GSK-3β caused hyperactivity, consistent with mania in humans[38,39]. In addition, overexpression of GSK-3β reverses lithium sensitive behaviors[40].

Valproic acid, a well-known anticonvulsant, is widely used at present as a mood stabilizer in bipolar disorder. Although there is contradictory evidence of the effect of valproic acid on GSK-3, a number of studies have indicated that valproic acid inhibits GSK-3[41-43]. In vitro valproic acid administration with the relevant dose used in the treatment has been reported to cause AKT activation followed by increased GSK-3 phosphorylation[44]. The effects of certain mood stabilizers on GSK-3 have also been demonstrated by a number of studies (Table 2).

Other metal ions such as zinc, mercury, beryllium and copper are reported to be more potent GSK-3 inhibitors considering their IC50 values[48-50] compared to lithium. Zinc in particular is more interesting because it exists naturally in tissues unlike the other ions[50]. It is worth mentioning that zinc is linked with major depression by findings provided not only by experimental studies suggesting that zinc deficiency induces depressive and anxiety-like behaviors, but also from clinical observations of major depression patients with zinc deficiency, who experienced attenuated depressive symptoms with zinc supplementation[51-54].

GSK- 3β and tyrosine kinase B (TrkB) receptors

The involvement of GSK-3 in depression is supported by the fact that GSK-3 is also regulated by neuromodulators such as brain-derived neurotrophic factor (BDNF), a well-known neurotrophin that regulates differentiation, survival and development of neurons and synaptic plasticity[15]. When binding to TrkB, BDNF is responsible for activating the PI3K/AKT pathway and consecutively phosphorylating GSK-3 finally resulting in its inhibition[55].

It has been well documented that BDNF levels were decreased in plasma and hippocampus of depressed patients and that antidepressant therapies were able to elevate the reduced BDNF levels seen in depression[56-58]. Additionally, recombinant BDNF treatment causes antidepressant-like activity in different experimental models[59]. What is more interesting is that treatment with lithium, a GSK-3β inhibitor, is coupled with elevated transcription of BDNF[60]. This is thought to be mediated by CREB, a transcription factor of BDNF[61] which is directly inhibited by GSK-3β via phosphorylation[62].

Consequently, elevated GSK-3 activity is a result and also a cause of decreased BDNF signaling via the PI3K/AKT pathway and CREB phosphorylation, respectively, which is a major risk factor for the development of mood disorders and schizophrenia[15,18].

GSK-3β and neuroinflammation

At present, a growing body of evidence strongly suggests the link between inflammatory processes and depression. High plasma levels of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α have been reported by several clinical studies in patients with depression[63-65]. In addition, plasma levels of these pro-inflammatory cytokines are shown to be decreased with antidepressant therapies[66]. Thus, great effort has been made to discover novel therapeutic implications targeting immune mechanisms that would replace currently available antidepressants. In fact, targeting Toll like receptors as initiator molecular mechanisms of cytokine-mediated inflammatory responses, namely NLRP3 inflammasome, is now holding huge promise[67].

In this context, GSK-3β has been shown to play a regulatory role in immune responses through nuclear factor kappa B (NF-κB) mediated cytokine production namely as TNF-α and IL-6[68,69]. Lithium has been shown to attenuate the production of pro-inşammatory cytokines in human monocytes

at high concentrations in response to stimulation of Toll like receptors, key components of the innate immune system[69,70]. In a very recent study, it was found that pharmaceutical inhibition of GSK-3 by lithium or SB216763 in vitro resulted in reduction of pro-inşammatory cytokine levels elevated by lipopolysaccaridepre-treatment in rat glial cultures[71]. In the same study it was also shown that inhibition of GSK-3 increased the anti-inflammatory cytokine IL-10 levels compared to lipopolysaccaride treatment alone.

The Wnt pathway that is crucial for synaptic plasticity, circadian rhythms and cell survival, is also considered to be a key component for immune cell signaling[72,73]. Lithum and valproic acid treatments that are known to target GSK-3β in the Wnt pathway, have been shown to result in accumulation of β-catenin, a transcription substance of neurotrophic factors such as BDNF, and to be responsible for the inhibition of microglia activation[74]. It is important to note that the function of GSK-3β in neuroinflammation processes is highly integrated with other mechanisms such as overactivation of the hypothalamo-pituitary-axis and the kynurenine pathway which is an alternative way for tryptophan metabolism to reduce serotonin neurotransmission and cause excessive glutamatergic activity[73-75].

GSK-3β and hyperactivity

Recent evidence has directed much attention to the dysregulation of GSK-3 in hyperactivity associated disorders such as attention deficit hyperactivity disorder (ADHD) and bipolar disorder[37]. It has been well reported that changes in dopaminergic activity are highly related to ADHD and treatment with psychostimulants such as amphetamine or methylphenidate results in GSK-3 activation coupled with increased locomotion in experimental studies[76,77]. In addition, administration of GSK-3 inhibitors such as lithium reduces amphetamine-induced hyperactivity in mice[78].

The link between increased GSK-3 activity and locomotion has recently been established. D2 receptor stimulation with amphetamine or methylphenidate results in the stabilization of the AKT-β-arrestin2-PP2A complex with active GSK-3, causing AKT to be dephosphorylated and deactivated by PP2A. Therefore inhibitory control of AKT phosphorylation on GSK-3 is prevented[76,79,80].

Impairments in DISC1 (disrupted in schizophrenia 1) functions are also found to correlate with the increase of amphetamine-induced hyperactivity that can be postulated as a disruption in inhibitory control of GSK-3 by DISC1[81]. These findings all together suggest that elevated GSK-3 activity might be involved with hyperactivity associated disorders thus more advanced research is required for determining new targets in this area.

GSK-3β and Schizophrenia

Schizophrenia is a common psychiatric disease that leads to certain corrupted brain abilities. Although there are several hypotheses that are thought to be responsible for the development of schizophrenia, the underlying mechanism is not certain yet. Dysregulation of dopamine neurotransmission has long been accepted as a key mechanism in schizophrenia and all the current available treatments targeting schizophrenia exert their effects at least partially on the dopaminergic system. It has been well reported that in schizophrenia there is an imbalance between D1 and D2 receptor mediated dopaminergic neurotransmission[18] characterized by enhanced D2 receptor function particularly in the striatum and reduced D1 receptor functions in the prefrontal cortex[82-84].

The link between dopaminergic neurotransmission and GSK-3β has been examined by several studies. In the first study, it was found that administration of psychostimulants which enhance dopaminergic neurotransmission, such as amphetamine, metamphetamine and apomorphine resulted in reduced AKT activity accompanied with enhanced GSK-3β activity in

Table 3: Effect of certain antipsychotics on GSK-3

Antipsychotic	Effect on GSK-3	Method	References
Amisulpride	Phosphorylation	Cell culture (SH SY5Y)	(88)
Aripiprazole	Phosphorylation	Rat HC* Cell Culture (SH SY5Y)	(89), (90)
Clozapine	Phosphorylation	Mouse Cortex, HC* Striatum,Cerebellum	(91)
Olanzapine	Phosphorylation	Mouse Cortex, HC*, Striatum,Cerebellum Cell culture (SH SY5Y)	(45), (91), (92)
Quetiapine	Phosphorylation	Mouse brain	(91)
Risperidone	Phosphorylation	Mouse Cortex, HC*, Striatum,Cerebellum	(91)
Ziprasidone	Phosphorylation	Mouse Cortex, HC*, Striatum,Cerebellum	(91)
Chlorpromazine	Phosphorylation	Mouse brain	(93)
Haloperidol	Phosphorylation No effect	Mouse brain In vitro	(88), (89), (90)

*HC; hippocampus

mice[76,79,85]. In another study, Beaulieu et al. showed that elevated dopamine levels increased GSK-3β activity as a consequence of decreased AKT phosphorylation in dopamine transporter knockout mice[76,86].

Dopaminergic D1 and D2 receptors use G protein signaling for controlling the cAMP level in neuronal cells. When D1 class receptors are activated, they stimulate the Gαs subunit of G protein and enhance cAMP production; whereas D2 class receptors coupled with Gαi protein reduce cAMP production. Recent studies have indicated that the effect of D2 receptors on GSK-3β enzyme activity is not regulated by cAMP levels in dopaminergic neurons. Instead, it is modulated by a multifunctional scaffolding protein β-arrestin, which is known to be responsible for G protein coupled receptor desensitization[87]. Stimulation of D2 receptors leads to recruitment of β-arrestin and stabilizes the β-arrestin-PP2A-AKT complex. By stabilizing the complex, AKT is dephosphorylated/deactivated by PP2A and GSK-3β activity is increased because of the prevention of the inhibitory control of AKT on GSK-3β[87]. In summary, D2 receptor activation resulted in an increased activity of GSK-3β and this was a β-arrestin dependent mechanism (Figure 1)[79].

The effect of certain widely used antipsychotic drugs on regulation of GSK-3β activity has been reported in a variety of in vivo and in vitro studies (Table 3). It has been found that administration of atypical antipsychotics such as clozapine, olanzapine, quetiapine, risperidone and ziprasidone increased GSK-3β phosphorylation in mouse brain[91]. In another study, it was reported that SH SY5Y cells treated with olanzapine showed increased GSK-3β phosphorylation[92]. Not only atypical antipsychotics regulate phospho-GSK-3β level in brain but also classical antipsychotics can change the phosphorylation rate of GSK-3β. Supportively, administration of typical antipsychotics such as chlorpromazine and haloperidol resulted in an enhanced phosho-GSK-3β level in mouse brain[89,93].

Since atypical antipsychotics exert their effect partially on 5-HT2 receptors, it was speculated that serotonergic neurotransmission might have a regulatory effect on GSK-3β activity. Recent studies have revealed that 5-HT2 receptors play an important role in regulation of GSK-3β phosphorylation[20,91]. It was found that administration of the 5-HT2 receptor antagonist LY53857 resulted in induced GSK-3β phosphorylation in wild type mouse brain[20]. In another study, it was shown that mice that

lacked the tryptophan hydroxylase-2 gene that is responsible for 5-hidroksitriptamine synthase expression, a rate limiting enzyme, have an increase in GSK-3β activity in the frontal cortex[94]. In summary, these findings indicated that several antipsychotics that are used in the treatment of schizophrenia were able to inhibit GSK-3β activity through blocking D2 and also 5-HT2 receptor (atypical antipsychotics) mediated neurotransmission (Figure 1).

DISC1, an upstream regulator of GSK-3β, is one of the most important genes related to schizophrenia and mood disorders because of its role in several neurodevelopmental processes[15]. It has been shown that DISC1, a scaffolding protein, is responsible for cAMP degradation in the brain by activating phosphodiesterase 4b (PDE4b), an inactivating enzyme of cAMP[95]. In addition to this, it directly binds and inhibits GSK-3, consequently preventing its substrates, namely β-catenin, from being phosphorylated by GSK-3. This increase in β-catenin activation later promotes transcription and translation in the nucleus. In the case of DISC1 mutation, this process is reversed resulting in impaired β-catenin stabilization as a result of increased GSK-3β activity. Consequently, disruption of the DISC1 gene gives rise to the belief that impaired neurogenesis in the brain, particularly in the developing brain, contributes to schizophrenia and mood disorders[15].

Another pathway associated with schizophrenia is the canonical Wnt pathway. Stimulation of frizzled receptors by Wnt facilitates the dissociation of an intracellular destruction complex consisting of GSK-3β, axin, adenomatous polyposis coli and casein kinase 1α, and prevents β-catenin from being phosphorylated and degraded by GSK-3β (Figure 1)[96].

At present, hypo-glutamatergic neurotransmission is considered to be highly involved in the development of schizophrenia[97]. It has been reported that GSK-3β activity is increased in response to phencyclidine, a NMDA receptor antagonist, in rat hippocampus, striatum and frontal cortex[97]. It was also shown that administration of NMDA resulted in increased serine phosphorylation of GSK-3β in rats[98]. A limited number of studies have indicated that NMDA receptor stimulation enhanced GSK-3β phosphorylation whereas its blockade increased GSK-3β activity.

CONCLUSION

In conclusion, dysregulation of GSK-3 appears to be highly associated with mood disorders and schizophrenia. A growing body of evidence points out that GSK-3 activity tends to be increased in such psychiatric disorders whereas it has been repeatedly shown to be reduced by different therapeutic approaches used in treatment. Despite the fact that the underlying mechanisms of how GSK-3 is involved in each psychiatric disease have unique features, there are certain notable mechanisms including dysregulation of β-arrestin2 dependent dopaminergic neurotransmission, interruption of PI3K/AKT signaling by deficiencies in serotonergic and neurothropic factor transmission, and over degradation of β-catenin resulting from disrupted inhibitory control of DISC1 over GSK-3. Ever since the discovery of lithium's inhibitory effect on GSK-3, the story of the role of GSK-3 in psychiatric disorders has continued; however, there is still much effort required to identify how GSK-3 regulation contributes to both the pathological and improved behavioral states.

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