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Glycogen Synthase Kinase-3: A New Therapeutic Target in Mood Disorders

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ÖZET:

Glikojen sentaz kinaz-3: duygudurum bozukluklarının tedavisinde yeni bir hedef

Majör depresyon ve bipolar bozukluğu kapsayan duygudurum bozuklukları sık rastlanılan, fakat gerektiği gibi tedavi edilemeyen rahatsızlıklardır. Ayrıca, bu hastalıkların etiyolojileri ile ilgili bilinenler yeterli değildir. Bir serin/treonin protein kinaz olan glikojen sentaz kinaz-3 (GSK-3) birçok hücre içi sinyal yolağını modüle eder. 1996 yılında lityumun GSK-3 inhibitörü olduğunun keşfedilmesi, azalan GSK-3 inhibisyonunun duygudurum bozukluklarıyla olası bağlantısını düşündürmüştür. Yapılan deneysel çalışmalar bu veriyi desteklemektedir. Bulgular, depresyonun azalan GSK-3 inhibisyonu, maninin ise aşırı GSK-3 aktivasyonu ile bağlantılı olabileceğini göstermiştir. Ayrıca bahsi geçen rahatsızlıklar, GSK-3 aktivitesini kontrol eden çeşitli sinyal yolaklarıyla da bağlantılı olabilir. Sonuç olarak, GSK-3 aktivitesinin kontrol altında tutulması duygudurum bozuklukları tedavisinde yeni bir hedef haline gelmiştir. Yapılacak çalışmalar duygudurum bozukluklarında GSK-3 aktivitesinin rolüne ve GSK-3 aktivitesinde meydana gelen değişikliğin sebeplerini ortaya çıkarmaya odaklanmalıdır.

Anahtar sözcükler: Glikojen sentaz kinaz (GSK-3), duygudurum bozuklukları, lityum, beyin-kaynaklı nörotrofik faktör (BDNF), nöroinflamasyon, nöroplastisite, depresyon

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ABSTRACT:

Glycogen synthase kinase-3: a new therapeutic target in mood disorders

Mood disorders, including major depressive disorder and bipolar disorder, are common and largely inadequately treated. Additionally, little is known about their etiologies. Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase, interacting with many signaling pathways. In 1996, lithium was found to inhibit GSK-3 and this discovery led us to the possibility that impaired GSK-3 inhibition is related with mood disorders. In time, animal and human studies encouraged this finding. Evidence is reviewed that depression may be associated with impaired inhibitory control of GSK-3, and mania with hyperstimulation of GSK-3. Mood disorders may result in part from impairments in mechanisms controlling the activity of GSK-3 or GSK-3-regulated functions and substantial evidence supports the conclusion that bolstering the modulatory control of GSK-3 is an important component of the therapeutic actions of drugs used to treat mood disorders and that GSK-3 is a valid target for developing new therapeutic interventions. Future research should identify the causes of dysregulation of GSK-3 in mood disorders and the actions of GSK-3 that contribute to these diseases.

Key words: Glycogen synthase kinase (GSK-3), mood disorders, lithium, brain-derived neurotrophic factor (BDNF), neuroinflammation, neuroplasticity, depression

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INTRODUCTION

Glycogen synthase kinase-3 (GSK-3) is a widely expressed and highly conserved serine/threonine protein kinase. During the last three decades, GSK-3 has been shown to regulate a great variety of cellular functions including cell polarity (1), cell fate (2), development (3), apoptosis (4), microtubule function (5), and neuronal growth and differentiation (6). In addition, crucial cellular checkpoints and regulation of protein levels are responsible for the precise control of GSK-3 activity. GSK-3 is active in cells under resting conditions and is primarily regulated through inhibition or diversion of its activity (7). It is encoded in mammals by two genes that generate two isoenzymes: GSK-3α and GSK-3β

(8). Both GSK-3α and GSK-3β are expressed throughout the brain. However, GSK-3α is especially found in the hippocampus, cerebral cortex, striatum, and Purkinje cells of the cerebellum, while GSK-3β is universally expressed in all brain regions. While GSK-3 is one of the few protein kinases that can be inactivated by phosphorylation, the mechanisms of GSK-3 regulation are more varied and not fully understood.

Several kinases, such as PKA (Protein kinase A), AKT (Protein kinase B) and PKC (Protein kinase C), phosphorylate GSK-3 to inhibit its activity. GSK-3 itself has also the ability to inhibit its own activity, which may be called "autophosphorylation". GSK-3 is associated with different protein complexes, such as Wnt (wingless-int) and β-catenin. All of these associations are involved in regulation of GSK-3 activity (9).

Dysregulation of signaling pathways involving GSK-3 is associated with the pathogenesis of numerous neurological and psychiatric disorders and there are data suggesting isoform-selective roles of GSK-3 in several of these. Many studies point to fundamental roles for these protein kinases in learning, memory, behavior, and neuronal fate determination and provide insights into possible therapeutic interventions, especially in Alzheimer's disease, schizophrenia and mood disorders.

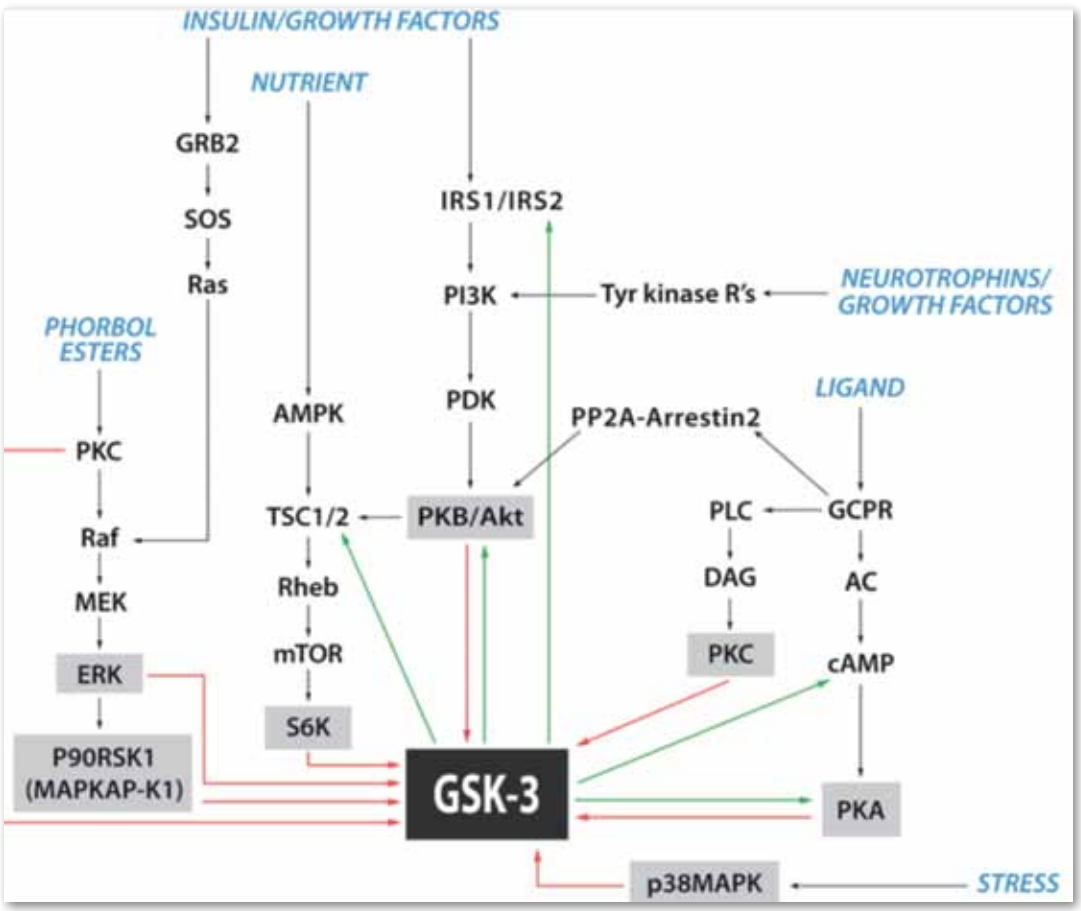

Figure 1: Related signaling pathways and regulation of GSK-3. red arrows: inhibition, green arrows: stimulation (AC: adenylyl cyclase, AMPK: AMP-activated protein kinase, cAMP: cyclic adenosine monophosphate DAG: diacylglycerol, ERK: extracellular-signal-regulated kinase, GCPR: G coupled protein receptor, GRB2: Growth factor receptor bound protein 2, GSK-3: glycogen synthase kinase-3, IRS1/IRS2: insulin receptor substrate 1/2, MEK: mitogen-activated protein kinase kinase, mTOR: mammalian target of rapamycin, p38MAPK: p38 mitogen-activated protein kinase, P90RSK1 (MAPKAP-K1): p90 ribosomal S6 kinase 1, PDK: phosphoinositide dependent kinase, PI3K: phosphatidylinositol-3-kinase, PKA: protein kinase A, PKB/Akt: Protein kinase B, PKC: protein kinase C, PLC: phospholipase C, PP2A-Arrestin 2: protein phosphatase 2A-Arrestin 2Raf: proto-oncogene serine/threonine specific protein kinase, Ras: GTPase activating protein, Rheb: Ras homolog enriched in brain, S6K: S6 kinase, SOS: son of sevenless, TSC1/2: tuberculosis sclerosis protein 1/2, Tyr kinase R's: tyrosine kinase receptors.).

Signaling Pathways and Regulation Mechanisms Associated with GSK-3

GSK-3 has been found to modulate many different pathways. Additionally, it is one of a few protein kinases that is inhibited by extracellular signals inducing a rapid and reversible increase in serine phosphorylation of GSK-3 causing a decrease in enzymatic activity. For example, growth factor (7,10), insulin (11), or serum treatment decreases GSK-3 activity by 30–70% within 10 min. Regulation mechanisms are varied and not yet fully understood; precise control appears to be achieved by a combination of phosphorylation, localization, and sequestration by a number of GSK-3-binding proteins. The kinase is positively regulated by "T-loop" tyrosine phosphorylation (12) and negatively regulated by N-terminal phosphorylation of serine residue (7). p38 mitogen-activated protein kinase (p38 MAPK), involved in apoptosis and autophagy and stimulated by stress, is also able to inactivate GSK-3β via phosphorylation (13). There are conşicting data about whether tyrosine phosphorylation of GSK-3 is catalyzed by GSK-3 itself (autophosphorylation) or by a distinct tyrosine kinase (12). Insulin leads to inhibition of GSK-3 via insulin receptor substrate-1-dependent induction of phosphatidylinositol 3 kinase (PI3K), which then stimulates PKB/Akt (11). Growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) can also inhibit GSK-3 activity, not only through the PI3K pathway (14), but also through induction of the mitogen-activated protein kinase (MAPK) cascade (15). Serine residue phosphorylation of GSK-3 can be modiŞed either by amino acid deprivation through mammalian target of rapamycin (mTOR) (16), or by elevated intracellular levels of cAMP through PKA (17). PKC agonists can also regulate GSK-3, while certain PKCs specifically regulate GSK-3β, but not GSK-3α (18,19) (Fig. 1)

GSK-3 and Its Role in Mood Disorders

Mental disorders, including bipolar disorder, attention-deficit/hyperactivity disorder, depression and schizophrenia are a major public health problem worldwide and little is known about the mechanisms underlying their complex etiology. Additionally, several pharmacological agents affecting monoamine neurotransmission are used for the management of these illnesses, but with concerns about the exact molecular mechanisms responsible for their therapeutic effects.

The first evidence that GSK-3 may be involved in mood disorders originated from two reports showing that the classical mood stabilizer lithium is a direct inhibitor of GSK-3 (20,21) by a magnesium-competitive mechanism (22). Although the mechanism of this action by lithium is not clear, it may involve the disruption of a β-arrestin/AKT/PP2A (protein phosphatase 2A) (23). The effect of lithium through GSK-3 is a promoting effect to its mood stabilizing effect via different pathways (24). Studies pointing to the effect of lithium on GSK-3 caused an interest in evaluating other antipsychotics for the same mechanism of action. However, only a few studies claimed that some mood-stabilizing agents, such as valproic acid and haloperidol have a similar action (25,26).

GSK-3 in neuromodulation

While it can be modulated by mood stabilizers and psychotropics used in mood disorders, encouraging evidence for a role of GSK-3 in mood disorders is supported by its regulation by neuromodulators thought to be involved in mood disorders. One of these neuromodulators is brain-derived neurotrophic factor (BDNF), a well-known neurotrophin, activating phosphatidylinositol-3-kinase (PI3K) and Akt and phosphorylating GSK-3. This results in inhibition of GSK-3 activity (27).

Serotonergic dysfunction is explained within the scope of the early hypothesis of mood disorders. Recently, impaired inhibition of GSK-3 serine-residue phosphorylation has been thought to be a factor causing depression with dysregulated serotonergic activity. Activation of serotonergic 5HT-1 receptors results in an increase in inhibition of GSK-3 serine-residue phosphorylation (28). This effect may be explained by activation of Akt through PI3K by 5HT-1A receptor functioning (29).

The dopaminergic system also takes part in

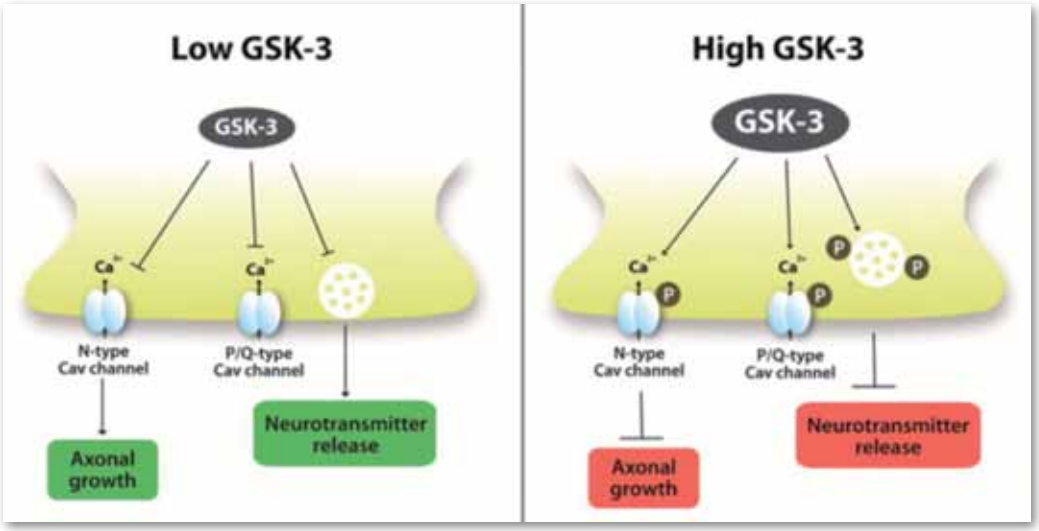

Figure 2: Effects of low and high levels of GSK-3. Under low GSK-3 conditions, interaction between P/Q Cav channels and neurotransmitter vesicles enhance neurotransmitter release and N-type Cav channel provides axonal growth. Opposite effects are seen upon high levels of GSK-3.

regulation of GSK-3 activity. Elevation of extracellular dopamine reduced serine phosphorylation of GSK-3 in striatum of dopamine transporter knockout mice (30). This effect may be explained by the activation of dopaminergic D2 receptors. D2 receptors inactivate the β-arrestin/AKT/PP2A pathway (23).

GSK-3 in neurogenesis and neuroplasticity

Neurogenesis is the major component of neuroplasticity. In mood disorders, neurogenesis in the hippocampus is impaired. Lithium increases neurogenesis as a result of its inhibition of GSK-3 (31), as well as antidepressants.

GSK-3 also regulates synaptic and structural plasticity (32). In the CA1 area of GSK-3 knock-in mice that lack inhibitory serine phosphorylation of GSK-3, N-methyl-D-aspartate receptor-dependent long-term depression (LTD) has been converted to long-term potentiation (33). GSK-3 inhibitors reverse the induction of LTD.

GSK-3 acts as an enzymatic sensor for the fate of the neuronal cell. Low levels of GSK-3 in cells are a result of growth factor/Wnt signaling, which promotes proliferation and inhibits apoptosis. It also promotes survival in the case of intoxication, such as hypoxia (34). However, high levels of GSK-3 and a dysregulation in the GSK-3 regime results in destabilization of mood, characterized by decreased axonal growth and neurotransmitter release, induced by environmental and genetic factors (35). Low levels of GSK-3 promote long-term potentiation and high levels result in long-term depression (Fig. 2). A therapeutic approach using GSK-3 as the target should consider this delicate balance between two opposite effects caused by the same molecule.

GSK-3 in neuroinflammation

GSK-3 has a strong effect on inflammation, which is recognized to be a component of depression. GSK-3 promotes the production of several pro-inflammatory cytokines, via stimulation of Toll-like receptors on human monocytes. GSK-3 inhibition allows IL-10 levels to be increased (36). GSK-3 inhibition has been found to reduce pro-inflammatory cytokine levels in astrocytes and microglia in mice (37). As a result, GSK-3 triggers inflammatory reactions, which may provide a novel basis for its role in mood disorders.

CONCLUSION

In conclusion, stress response mechanisms, neurogenesis, circadian rhythm alterations,

mitochondrial function, neurotransmitter release and receptor-induced signaling and immune system abnormalities are examples of processes regulated by GSK-3 that may be disrupted in mood disorders. Cumulative evidence suggests that GSK-3 has a pathological role in mood disorders and is likely a therapeutic target in mood disorder treatment. Although mood stabilizers, antidepressants, and antipsychotics can inhibit GSK-3, it is important to determine if this inhibition of GSK-3 is critical for their therapeutic actions. Further investigation is required to understand how the altered activity of GSK-3 affects behavior, and to determine the mechanisms of how each mood state, manic or depressive, is affected by altered GSK-3 activity.

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