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Role of *GSK-3 β* in neurodegenerative disorders

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Abstract

Glycogen synthase kinase (GSK-3) is a ubiquitously expressed, highly conserved serine/threonine protein kinase found in all eukaryotes. The GSK-3 was first characterized for its role in glycogen metabolism by phosphorylating and inactivating the enzyme glycogen synthase. There are two mammalian GSK-3 isoforms encoded by distinct genes: GSK-3α and GSK-3β.

GSK-3β is involved in the regulation of a wide range of cellular functions including differentiation, growth, proliferation motility, cell cycle progression, embryonic development, apoptosis, and insulin response. Dysregulation of GSK-3β expression leads to many pathological conditions, including diabetes or insulin resistance and neurodegeneration. Here we review on role and association of GSK-3β polymorphisms in different neurodegenerative disorders. Several lines of evidences including association and gene expression studies have suggested GSK-3β as a susceptible gene for neurodegenerative disorders, and its expression alteration caused by the risk SNP in the promoter region may contribute to the etiology of neurodegenerative disorders. This suggests that pertaining to the molecular clock as possible endophenotypes of neurodisorders, and for GSK-3β as a target of a new class of antidepressant drugs.

INTRODUCTION

Glycogen synthase kinase (*GSK-3*) is a ubiquitously expressed in all eukaryotes. It is highly conserved serine/threonine protein kinase first characterized in glycogen metabolism by phosphorylating and inactivating the enzyme glycogen synthase [1, 2]. *GSK-3* is present in a multiprotein complex in two iso forms (*GSK-3α* and *GSK-3β)* that targets β-catenin for ubiquitin- mediated degradation and has an important role in several signaling cascades *viz*. cell fate regulation, embryonic development, protein synthesis, glycogen metabolism, mitosis, apoptosis, transcriptional activity, *etc* [3-7]. It is highly expressed in brain and causes a variety of neurological, CNS disorders and other metabolic disorders.

GSK-3β (46 kDa) is comprised of 12 exons in humans (433 aa) and 11 exons (420 aa) in mice.

It is involved in the regulation of various cellular functions via neuronal, endothelial, hepatocyte, fibroblast and astrocyte cell death in response to various stimuli including differentiation, growth, proliferation motility, cell cycle progression, embryonic development, apoptosis and insulin response [816]. Its dysregulation *leads to many pathological conditions, including diabetes, neuronal dysregulation, alzheimer's disease* [17-19], schizophrenia [20], Dopamine-associated behaviors [21], bipolar disorders [22], Parkinson's disease [23] and cancer [24-27]. Thus the kinase has dual functions in cancer, both in regulation of cell survival and activate/inhibit apoptosis [28, 29].

Biochemical Regulation of *GSK3*

As *GSK-3* is involved in diverse processes, regulation of its activity is critical to ensure that the pathways can be appropriately coordinated by multiple levels of regulation mediated by phosphorylation, cellular localization and proteinprotein interactions. *GSK-3β* phosphorylate both prime substrates (glycogen synthase, eukaryotic initiation factor 2B (eIF2B), β catenin) and unprimed substrates (cyclin D3, axin) but efficiency for unprimed substrates is less than prime substrate [14]. The phosphorylated priming site of the substrate interacts with three positive residues (Arg 96, Arg 180 and Lys 205) in *GSK-3β forming substrate binding pocket* [30, 31].

Phe 67, Gln 89 and Asn 95 are required for specific substrate binding with precise positioning of the substrate binding pocket in *GSK-3β* substrate recognition [32]. The impact of *GSK-3* protein activity depends on amino acid modification by self multiple phosphorylation events [33, 34]. N terminal Phosphorylation of Ser 21 for *GSK-3α* and Ser 9 for *GSK-3β* (pseudo substrate) inhibits the regulation of *GSK-3* function in insulin signaling [35, 36]. By this Serine phosphorylation in Akt/ PKB (protein kinase B) during insulin signaling leads enzyme inactivation and activation of glycogen substrate. Several other kinases like AGC kinase, p70 ribosomal S6 kinase and p90 ribosomal S6 kinase are also involved during the phosphorylation of Ser residues (21/9) [37]. Phosphorylation of Tyr 279 for *GSK-3α* and Tyr 216 for *GSK-3β* in C terminus activates the enzyme while activity decreases by mutation in it [33, 34]. However, its activity is also decreased by p38 mitogen- activated protein kinase (MAPK) phosphorylation [38]. *GSK-3* has been known for more than 20 years as part of the insulin signaling pathway, and is still receiving a great deal of attention, due to its role in this and other disease-related signaling pathways. Glycogen synthase is the terminal enzyme in the insulin signalling pathway that regulates glycogen synthesis. In response to insulin, *GSK-3* becomes inhibited, facilitating the dephosphorylation and activation of glycogen synthase [39].

The *GSK-3* inhibition by preventing the aggregation of β-amyloid and hyperphosphorylation of tau protein will give a lead to ameliorate neurodegenerative developments. Moreover, the series of pathological changes have been induced by the over expression/over activation of *GSK-3 especially in* Type 2 Diabetes mellitus and Alzheimer disease.

Association of GSK-3β polymorphism in multiple disorders

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a combination of motor symptoms. The T allele

is associated with altered splicing in lymphocytes and increased levels of *GSK-3β* transcripts that lack exons 9 and 11 (*GSK* Delta exon 9+11). Increased levels of *GSK* Delta exon 9 +11 correlated with enhanced phosphorylation of its substrate, Tau (τ). In a comparison of PD and control brains, there was increased in frequency of T allele (rs6438552) and corresponding increase in *GSK* Delta exon 9+11 and Tau phosphorylation in PD brains. Conditional logistic regression indicated gene-gene interaction between T/T genotype of rs334558 and H1/H1 haplotype of microtubule-associated protein Tau (MAPT) gene (p=0.009).

There was association between a haplotype (T alleles of both *GSK-3β* polymorphisms) and disease risk after stratification by Tau haplotypes ((H1/H2+H2/H2 individuals: odds ratio, 1.64; p = 0.007; (H1/H1 individuals: odds ratio, 0.68; p < 0.001). These results suggest *GSK-3β* polymorphisms alter transcription and splicing and interact with Tau haplotypes to modify disease risk in PD [40].

The *GSK-3β* gene encodes a protein kinase which is abundant in the brain, and its product is involved in signal transduction cascades of neuronal cell development, energy metabolism and body pattern formation. Previous studies have suggested that *GSK-3β* might act as a potential candidate locus for schizophrenia susceptibility. Genotyping of six SNPs within the gene in the Chinese population has shown that allele and genotype frequencies and haplotype distributions in the schizophrenic patients. These results failed to replicate the association of the *GSK-3β* gene with susceptibility to schizophrenia in the Chinese population [41].

Alzheimer disease

The variant ion in *GSK3β* showed positive associations with Alzheimer disease (AD), familial front temporal dementia (FTD), primary progressive aphasia, *etc* [42]. Recent reviews on *GSK-3* have been published both on general issues [4345]. and on its involvement in neurodegenerative disease, cell fate and tumorigenesis [4648]. The importance of *GSK-3* is highlighted by its possible use as a drug target for the treatment of neurodegenerative diseases and diabetes [49, 50]. The neuroprotective effects of novel drugs developed to treat T2DM, glucagon- like peptide 1(GLP-1) and its long-lasting analogs have a possible link to *GSK-3* modification.

Aberrant phosphorylated tau is the major component of the neurofibrillary tangles in Alzheimer's disease (AD) brains. *GSK-3β* phosphorylates tau protein, and increased *GSK-3β* expression has been associated with neurofibrillary tangles. Saitohin (*STH*) is a recently identified protein that shares tissue expression pattern with tau, and previous evidence in the Spanish population indicated that a polymorphism at codon 7 (Q7R) of the *STH* gene was associated with late-onset AD. Since both *GSK-3β* and *STH* are related to tau, the association between a polymorphism in the promoter region (-50) of the *GSK-3β* gene and AD, through an independent effect or through interaction with the *STH* (Q7R) polymorphism in a Spain [51].

Bipolar Disorder

GSK3-β codes for an enzyme which is a target for the action of lithium and valproic acid and the inhibition of which causes antidepressant like behaviors. Genetic variation of *GSK-3β* have been involved in Lithium prophylaxis in bipolar patients [52]. However, negative correlation was observed with schizophrenia [51]. While, homozygous mutant allele of *GSK3-β* promoter (-50T/C) showed a later onset of bipolar illness and better acute effects of total Sleep Deprivation treatment on perceived mood. Overall, previous reports suggested that it plays a protective role in bipolar illness. As a help of the mechanism elucidation of alcoholism, the relationship between *GSK-3β -50T/C* and *-1727A/T* polymorphisms, which are reported to relate to bipolar disorder. The two polymorphisms in gene have been genotyped and no significant difference between alcoholics and controls was found.

GSK-3β -50T/C polymorphism, which is reported to have the relationship for bipolar disorder and Japanese alcoholics and the relationship between *GSK-3β*, *-50T/C* polymorphism which is one of the risk factor for alcoholism was investigated. It was suggested that bipolar disorder may not be one of the pathogenesis of alcoholism [51].

Major Depressive Disorders

As a known fact of increased activity of *GSK-3β* in brain of patients with major depressive disorders (MDD) it can be a key feature for the development of antidepressants. *GSK-3β* genetic variants play a role in the antidepressant therapeutic response and support the hypothesis that drugs regulating *GSK-3β* activity may represent a novel treatment strategy for MDD [52].

These studies show that there is an association between the *GSK-3β* gene and temporal lobe brain structure specific to patients with major depressive disorder (MDD), suggesting that *GSK-3β* genotypes might interact with MDD status. In psychiatric genetics, alternative phenotypic markers for genetic association studies that are more closely related to the underlying neurobiology of the disease are increasingly being used. This derives partly from a need to address problems of clinical heterogeneity in psychiatric disorders such as MDD, and partly from the need to delineate the functional consequences of identified risk variants at the level of brain structure and function. Imaging genetics is particularly useful in both regards by enabling an elucidation of the impact of genes at the level of the brain, which can then be related to the pathophysiology of the disease. The concept that differences in brain structure are associated with MDD is supported by several studies, and some found specific changes in patients with MDD, e.g. related to the serotonin transporter polymorphism. In the study by Inkster *et al*, [53] a large sample of 134 patients with MDD and 143 healthy volunteers were investigated using structural MRI with an analysis of grey matter density and 15 *GSK-3β* single- nucleotide polymorphisms (SNPs). The *GSK-3β* gene has previously been implicated in MDD. In vitro data have demonstrated that this intronic polymorphism regulates the selection of splice acceptor sites and, thus, alters *GSK-3β* transcription, so that it likely is functionally relevant. Results of the study suggest that variation in grey matter volume in temporal lobe regions, including the hippocampus, were associated with *GSK-3β* polymorphisms in a manner distinguishable between patients and healthy controls (particularly for the right hippocampus). While the exact mechanism of how *GSK-3* influences the brain structures remains unsolved, the finding is interesting because inhibition of *GSK-3* activity might play a role in the therapeutic effects of antidepressants and lithium in patients with refractory MDD. The activity of *GSK-3β* has been shown to be regulated by selective serotonin reuptake inhibitors in mice. As hippocampal integrity has previously been associated with depression, the effect seen here of *GSK-3β* polymorphisms on hippocampal structure may represent a pathway by which this effect occurs. The *GSK-3β*

gene may have a role in determining regional grey matter volume differences of the right hippocampus and bilateral superior temporal gyri. The association between genotype and brain structure was specific to the patients with MDD, suggesting that *GSK-3β* genotypes might interact with MDD status. This is a consequence of regional neocortical, glial, or neuronal growth or survival. In considering core cognitive features of MDD, the association of *GSK-3β* polymorphism with structural variation in the temporal lobe and hippocampus is of particular interest in the context of other evidence for structural and functional abnormalities in the hippocampi of patients with MDD [53].

Diabetes

Activation of glycogen synthesis in skeletal muscle is a response to insulin, results from the combined inactivation of glycogen synthase kinase-3 (*GSK-3*) and activation of the protein phosphatase-1, changing the ratio between the inactive phosphorylated glycogen synthase to the active dephosphorylated state. In a search for genetic defects responsible for the decreased insulin stimulated glycogen synthesis seen in patients with non- insulin-dependent diabetes mellitus (NIDDM) and their glucose-tolerant first-degree relatives, mutational analysis of the coding region of the 2 isoforms of *GSK-3*α and *GSK-3β* in 72 NIDDM patients and 12 control subjects has been performed. No structural changes were detected apart from a few silent mutations. Mapping of the *GSK-3*α to chromosome 19q13.1-13.2 and the *GSK-3β* to chromosome 3q13.3-q21 outside known genetic loci linked to NIDDM further makes it unlikely that these genes are involved in the pathogenesis of common forms of NIDDM [54].

Moreover, diabetes has recently been strongly linked to CNS diseases such as schizophrenia and bipolar illness. *GSK-3* is both directly and indirectly inhibited by lithium, a key compound for treatment of bipolar disorder. Several antipsychotic drugs also affect the *GSK-3* mediated pathways and postmortem study of brain in schizophrenia led to reports of alterations of *GSK-3* activity or mRNA message. However, other reports are contradictory. Development of *GSK-3* inhibitors for CNS diseases is complicated by the importance of *GSK-3* in glucose metabolism and pancreas function and the possible effect of *GSK-3* inhibition to be oncogenic [54]. The function of two key targets of insulin action, glycogen synthase and insulin receptor substrate-1, are suppressed by *GSK-3*, as well as the fact that *GSK-3* activity is higher in diabetic tissues, makes it a promising drug discovery target for insulin resistance and Type 2 diabetes. Thus, the development of *GSK-3* inhibitors has received attention as an attempt to control both the spread of disease and its severity [55].

The possible association between the Xbal polymorphism of the glycogen synthase gene and non- insulin-dependent diabetes mellitus (NIDDM) could not be used as a genetic marker for NIDDM in Chinese population [56]. However, Nine alleles (-4G, -3G, -2G, -1G, 0G, 1G, 2G, 3G, and 4G) were identified in the study group of 164 patients with NIDDM and 115 non-diabetic subjects. The overall frequency distribution of the glycogen synthase gene alleles was significantly different between the two groups ($p = 0.0316$). The 2G allele was found more frequently in patients with NIDDM than in non-diabetic subjects (17.7% vs 8.7%, $p = 0.0016$). These results suggested that the 2G allele could be a genetic marker of NIDDM in Japanese subjects [57].

CONCLUSION

GSK3, has increased the focus on this Ser/Thr kinase that was already characterized as having a tentacular capacity to influence numerous aspects of cell function, often acting as a centralized integrator of many intracellular signals. Abnormal function of GSK3 was already implicated in a large number of prevalent diseases, such as mood disorders, Alzheimer Disease, Parkinson's disease, bipolar disorder, diabetes, and cancer. These conditions are associated with a high rate of mortality and inadequate therapeutic options.

In overall, *GSK-3β* is a key gene in neurodevelopment, and also an important target of antipsychotics. Several lines of evidences including association and gene expression studies have suggested *GSK-3β* as a susceptibility gene for neurodegenerative disorders, and its expression alteration caused by the risk SNP in the promoter region may contribute to the etiology of neurodegenerative disorders. Results of these data suggest that pertaining to the molecular clock as possible endophenotypes of neurodisorders, and for *GSK-3β* as a target of a new class of antidepressant and antidiabetic drugs.

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