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The Role of Glycogen Synthase Kinase(Gsk-3) In Pathophysiology of Diabetes Mellitus And Alzheimer's Disease

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ABSTRACT

Glycogen synthase kinase-3 (GSK-3) is an intermediary enzyme in various cellular pathways, and has been implicated in the Pathophysiology and treatment of numerous diseases, including Alzheimer, diabetes, and bipolar disorder. Alzheimer's disease (AD) is a disorder without a molecular marker in peripheral tissues or a disease modifying treatment. Evidence suggest that the co-relation of diabetes and Alzheimer is clear with the GSK-3. Now day's researchers taking efforts basically to develop the new GSK-3 inhibitors like lithium. For the development of new GSK-3 inhibitors, we have to understand its molecular mechanism and their involvement in pathological condition. So here we summarize brief introduction and mechanism of GSK-3.

Keywords: Glycogen synthase kinase-3 (GSK-3), Alzheimer's disease, diabetes, bipolar disorder

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INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disease in human beings with characteristic symptoms of hyperglycaemia and impaired insulin secretion or insulin resistant[1]. T2DM is one of the fastest growing epidemics of modern times. 6 million new cases reported each year, affecting 250 million people worldwide. According to mortality rate in the world it ranks fourth. People with T2DM are more likely to develop heart disease and kidney failure, and present data suggests that T2DM also increases the risk of developing dementias, such as Alzheimer's disease[2]. Chronic hyperglycaemia induces biological toxicity via glycation of proteins, altered redox potential, altered signal transduction and generation of reactive oxygen species[3]. AD is a prevalent dementia characterized by the presence of senile plaques and neurofibrillary tangles (NFT) of b-amyloid (Ab)[4] and hyperphosphorylated tau protein[5]. T2DM increases the risk of dementias; therefore it is vital to understand the molecular connexions between T2DM and AD. It has been reported that about 60–70% of DM patients also present the diabetic neuropathy manifestations in either peripheral or central nervous systems[1]. Association of DM with higher risks of cognitive impairment and neurodegenerative diseases, such as Alzheimer's disease (AD) are indicated by many clinical studies. Main key in AD pathogenesis is the hyperphosphorylation of brain microtube-associated protein tau[6].

Insulin, a very useful signalling molecule, is capable of regulating the activity of some kinases that are responsible for tau phosphorylation. Hence, both abnormal insulin signaling and pathological glucose fluctuations may cause the tau hyperphosphorylation, particularly in those patients with diabetes. In vivo, insulin controls the intracellular and plasma glucose level through a multi-enzyme signalling cascade including Akt and GSK-3.Akt is a positive regulator in this pathway, which is activated by phosphorylation of Thr308 and Ser473 by insulin signaling. GSK-3 activity is inhibited when Ser21 of its α-isoform or Ser9 of its β-isoform (GSK-3β) is phosphorylated by Akt. Thus down-regulation of insulin signaling leads to the dephosphorylation and consequent activation of GSK-3. GSK-3β phosphorylates tau at most sites in relation to tauopathies of AD which therefore could be the hinge of DM and AD. Based on these facts, insulin resistance or deficit could be a key factor that over-activates GSK-3 for tau hyperphosphorylation in DM patients.

Diabetes mellitus

Diabetes mellitus is caused either by lack of hormone insulin (Type 1 diabetes) or body's inability to use insulin (Type 2 diabetes). Type II diabetes often triggered by obesity, stress and

sedentary lifestyle. Type I, diabetes is also called juvenile diabetes or insulin dependent diabetes mellitus (IDDM), accounts for about 10% of total cases of diabetes. This generally afflicts the sufferers quite early in the life. Type II or, also called non–insulin dependent diabetes mellitus (NIDDM), accounts for almost 90% of diabetes cases. It is associated with defect in insulin secretion as well as insulin resistance. Treatment is implicated by several factors inherent to the disease process. Typically insulin resistance is an elderly feature of the condition, which is initially compensated in part by increased production of insulin by pancreatic ß-cells. Subsequently these cells become exhausted and combined effects of insulin resistance and impaired insulin secretion reduce insulin mediated glucose uptake and utilization by skeletal muscle, and prevent insulin-mediated suppression of hepatic glucose output. Continuing deterioration of endocrine control exacerbates the metabolic disturbances and increases hyperglycaemia[7].

The main consequences of Diabetes result from Insulin Deficiency State which is manifested by hyperglycaemia. Hyperglycaemia occurs due to any of the following causes:

(1) Decreased entry of Glucose into the cells

(2) Decreased glucose utilization by insulin dependent tissues

(3) Increased production of glucose by liver[8].

Insuline signalling-

Insulin regulates glucose homeostasis by increasing glucose uptake and storage. The major form of glucose storage is glycogen and glycogen levels in cells are tightly regulated by glycogen synthase (GS) (synthesis) and glycogen phosphorylase (lysis)[9]. While insulin appears to regulate both GS and glycogen phosphorylase activity, its regulation of GS is better understood. At secondary condition, GSK3 inhibits glycogen synthesis by suppressing GS through inhibitory phosphorylation. Upon insulin stimulation, however, activation of the linear signalling cascade IR/ IRSs/PI3K/Akt leads to the phosphorylation of GSK3 at the regulatory Ser21 or 9 residue (a and b, respectively), and GSK3 kinase activity is inhibited. This activates GS and thereby glycogen synthesis[10,11]. In addition, GSK3 regulates protein synthesis by controlling the activity of initiation factor 2B (eIF2B) in the same manner as GS [12,13]. During basal conditions, GSK3 phosphorylates and inactivates eIF2B, but on stimulation of insulin, the inhibition of GSK3 induces the dephosphorylation and activation of eIF2B (since there are reports suggesting that p70 S6 kinase rather than Akt may be responsible for the phosphorylation and inhibition of GSK3 in this pathway)[14,15]. Insulin receptor signaling leads to the activation of two major signalling pathways, the mitogen-activated protein kinase (MAPK) pathway and the Akt

signalling pathway. MAPK signaling is an important component for cell differentiation, cell proliferation and cell death, whereas Akt signalling is involved in the regulation of cell growth, cell proliferation, protein synthesis (via the mammalian target of rapamycin signalling pathway) and cell survival (through the inhibition of several pro-apoptotic agents). Both the MAPK and Akt pathways are implicated in AD pathogenesis[16].

Alzheimer's disease

Alzheimer's disease (AD) is a progressively debilitating neurodegenerative disease involving several characteristic pathological features. Prominent among these are amyloid plaques, neurofibrillary tangles, and neuronal dysfunction and loss[17].

The two classical neuropathological features of Alzheimer's disease are neurofibrillary tangles – intraneuronal filamentous aggregates composed primarily of hyperphosphorylated tau – and amyloid plaques, which are extracellular deposits, composed primarily of Aβ. GSK3 might contribute to both of these neuropathologies[18].

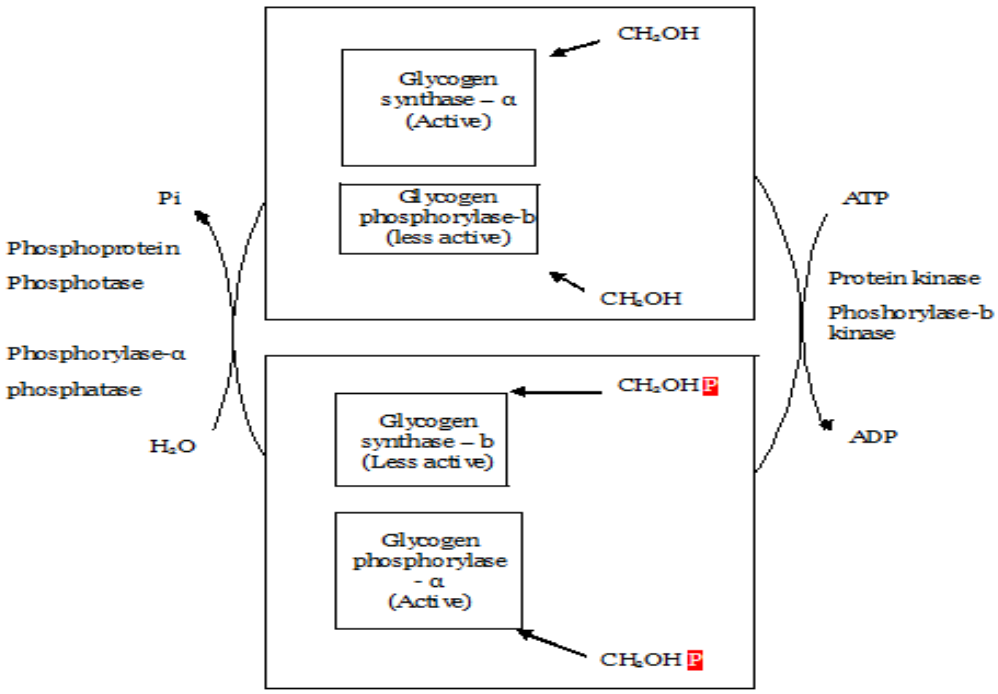

Figure 1: Conversion of Glycogen synthase inactive to active

GSK-3

GSK3 is a serine/threonine kinase that is present in mammals in two isoforms: α & β[10]. Glycogen synthase kinase 3 (GSK3), originally recognized for its role in glycogen synthesis, is a multifunctional kinase involved in important biological processes such as insulin sensitivity, hematopoietic stem cell repopulation, survival of tumour cells, cytoprotection in normal and

pathological neurons and in cardiomyocytes[19]. Activation of the insulin receptor leads to the activation of protein kinase B (PKB, also called Akt), which in turn phosphorylates GSK-3, thereby inactivating it. The inhibition of GSK-3 presumably leads to the activation of glycogen synthesis. The intricate insulin-signalling pathway is further complicated by negative-feedback regulation of insulin signalling by GSK-3 itself, which phosphorylates insulin receptor substrate-1 on serine residues[20]. GSK 3 enzyme has several intriguing regulatory characteristics, it is centrally involved in regulating cellular structure, function and survival, and it is linked to several prevalent diseases, such as diabetes and Alzheimer's disease.

The role played by GSK3 in insulin resistance

Since GSK3 is a key regulator enzyme in glycogen synthesis, it has generally been thought that GSK3 mainly participates in the development of insulin resistance by inhibiting GS activity, thereby suppressing insulin-stimulated glycogen synthesis. Therefore, studies on the role of GSK3 in insulin resistance have been historically focused on the regulation of glycogen synthase activity or glycogen synthesis[21]. It has been shown that Type 2 Diabetes (T2D) is strongly associated with a decrease in insulin-stimulated GS activity and glycogen synthesis along with increased GSK3 protein levels in the muscle.

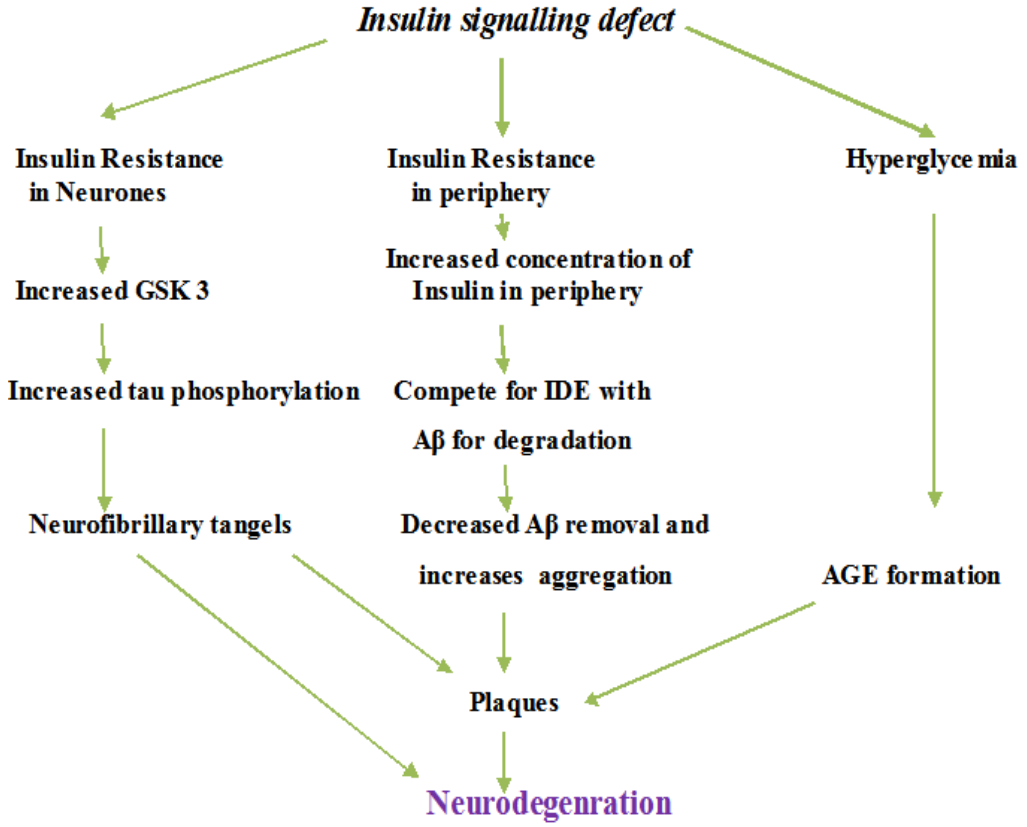

Figure 2: Mechanism of GSK-3 In Alzheimer's disease

The role of GSK3 in AD

The evidence that GSK3 plays a central role in AD and that its deregulation accounts for many of the pathological hallmarks of the disease in both sporadic and familial AD cases, has led us to formulate the 'GSK3 hypothesis of AD.' GSK3 is intimately involved in the hyper-phosphorylation of tau, memory impairment, and the increased production of Aβ and in inflammatory responses[22]. GSK3 also reduces acetylcholine synthesis, which is in accordance with the cholinergic deficit present in AD. Moreover, GSK3 is a key mediator of apoptosis and thereby might directly contribute to neuronal loss in AD[17].

Glycogen synthase kinase 3: new therapeutic target

Protein kinases, the enzymes that phosphorylate protein substrates, are key players in the signalling of extracellular events to the cytoplasm and the nucleus, and take part in practically any event relating to the life and death of cells, including mitosis, differentiation and apoptosis[23]. Glycogen synthase kinase-3 (GSK-3) member of the family of protein kinases. GSK-3 is a serine/threonine protein kinase that has recently emerged as a key target in drug discovery. It has been implicated in multiple cellular processes and linked to the pathogenesis of several diseases. Glycogen synthase kinase-3 also can be regulated pharmacologically, since Klein and Melton[24] discovered that lithium is a direct inhibitor of GSK3. This finding raised the possibility that inhibition of GSK3 may contribute to the therapeutic effects of lithium in mood disorders[25]. Lithium competes with magnesium (Mg) of the Mg2-adenosine triphosphate (ATP) complex for binding to GSK3 [26]. Activation of the insulin receptor leads to the activation of protein kinase B (PKB, also called Akt), which in turn phosphorylates GSK-3, thereby inactivating it. The inhibition of GSK-3 presumably leads to the activation of glycogen synthesis. The intricate insulin-signalling pathway is further complicated by negative-feedback regulation of insulin signalling by GSK-3 itself, which phosphorylates insulin receptor substrate-1 on serine residues[20]. GSK-3 inhibitors might prove useful as therapeutic compounds in the treatment of conditions associated with elevated levels of enzyme activity, such as type 2 diabetes and Alzheimer's disease. Several synthetic GSK-3 inhibitors have been reported. Two structurally distinct compounds, SB-216763 and SB-415286, developed by Glaxo Smith Kline. Treatment with these inhibitors activated glycogen synthesis and protested against neuron death[27].

In vitro exposure of GSK-3 inhibitors to isolated skeletal muscles of Zucker diabetic rats enhanced insulin-induced stimulated glucose transport[28]. As inhibition of GSK-3 leads to accumulation of β-catenin, which has been linked with the occurrence of colon cancer and melanoma, there is a concern that these inhibitors carry a risk of promoting cancer. On the other

hand, chronic treatment with lithium has not been reported to cause cancer. Controlled administration of appropriate doses of GSK-3 inhibitors, possibly in combination with tissue targeting design, might be a safer approach in the use of these inhibitors. In the future, it might be desirable to develop inhibitors that will be capable of affecting distinct cellular targets, for example glycogen synthase (a primed substrate) without affecting β- catenin (a nonprimed substrate).

The activities of protein kinase B (AKT) and GSK-3b kinase decrease and increase, respectively, in cells from familial AD patients[29]. Down-regulation of insulin signalling leads to the dephosphorylation and consequent activation of GSK-3. GSK-3β phosphorylates tau at most sites in relation to tauopathies of AD[30]. GSK-3 is involved in neuronal cell death and there are numerous examples of the neuroprotection provided by GSK-3 inhibitors following different insults[31]. The tau protein in neurofibrillary tangles (also termed PHF-tau) is hyperphosphorylated on serine and threonine residues, and this is believed to be the primary cause of the generation of AD tangles. GSK-3 was shown to phosphorylate tau both *in vitro* and in intact cells on multiple sites, some of which are aberrant in the abnormally hyperphosphorylated tau[32,33].

In summary, the emerging field of GSK-3 inhibitors continues to grow, and it is becoming evident that GSK-3 is a promising therapeutic target. Its unique biochemical properties distinguishing it from most protein kinases should enable the development of specific and selective drugs. One function is to phosphorylate glycogen synthase (GS), implicating GSK-3 in type-2 diabetes[34]. In addition, GSK-3 inhibition is a therapeutic target for the treatment of neurodegenerative diseases such as Alzheimer,[35] and neurological diseases such as bipolar disorder.[36,37] Lithium is indicated as a preferential treatment for bipolar disorders, and the ability of this action to inhibit GSK-3 has been proposed as a potential mechanism of action[38]. Due to this therapeutic potential, identification of GSK-3 inhibitors is a focus of research for both pharmaceutical companies and academic centers[39]. The availability of GSK-3b crystal structures[40,41]. enables structure based lead discovery and optimization.

CONCLUSION

Since there are substantial data strongly implicating GSK3 in the pathogenesis of AD and diabetes. GSK3 activity and/or protein levels are increased in afflicted individuals with AD and cell biological, epidemiological and genetic evidence points to an association between diabetes, AD and pathways that regulate GSK3. We postulate these pathways augment the GSK3 activity through secondary changes in both regulatory Ser and Tyr phosphorylation, mediated either

directly or through alterations in the insulin and/or Wnt signalling cascades. AD increasing GSK3 activity leads to the hyperphosphorylation of tau, increased Ab generation and deficits in learning and memory accompanied with neurodegeneration. Most importantly inhibiting GSK3 activity reverses some of the pathological effects of over-expression of mutated APP and tau in the best available models of AD. This hypothesis strongly implicates GSK3 inhibitors as a novel treatment strategy for AD and diabetes.

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