# Role of Glycogen Synthase Kinase 3 in Molecular Pathology of Alzheimer's Disease

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## ABSTRACT

**Background:** *Glycogen synthase kinase 3 (GSK-3) is the evolutionary well-preserved multifunctional ubiquitously expressed kinase. In brain, GSK-3 mediates its effects via cascade of intra-cellular signalling pathways that regulate several functions including memory, behaviour, synapse plasticity, bioenergetics, and neuronal fate determination.*
*Several evidences on transgenic mice models and reports from the post-mortem of AD brains posit that altered levels of GSK-3 are closely linked with several pathological features including impaired splitting of amyloid precursor protein, hyperphosphorylation of Tau, mitochondrial dysfunctions, impaired energetics, maladaptive plasticity of neuronal circuitries in dementia, culminating into pathology of Alzheimer's disease along with other neurodegenerative diseases.*
**Aim & Objective:** *Present paper has an aim to analyse the role of GSK3b in molecular pathology of Alzheimer's disease. The involvement of dysregulated GSK3b in the pathophysiology of Alzheimer's disease is discussed in the critical review paper covering several factors that either contribute to GSK3b dysregulation or interact with dysregulated GSK3b in the pathogenesis of AD.*
**Research Methodology:** *Critical analytic, qualitative cum retrospective research study design is adopted utilizing secondary data from books, monographs, journals, conference proceedings for the critical evaluation leading to conclusions beneficial either in future research study or in understanding intricate molecular events for pharmaceutical intervention either to ameliorate the clinical manifestations of Alzheimer's disease or to delays the progression of disease for the benefit of patients with AD.*
**Findings/Result:** *Several stressors induce overexpression/aberrant activity of GSK3b leading to increased Amyloid beta formation, tau phosphorylation, mitochondrial dysfunction, impaired synaptic activity, release of pro-inflammatory cytokines and other manifestations implicated in the molecular pathology of Alzheimer's disease.*
**Originality of Paper:** *Comprehensive approach was adopted to include papers related to the topic within frame-work of inclusion and exclusion criteria to deduce conclusion.*
**Paper Type:** *Critical analytic review paper.*
**Keywords:** Amyloid beta, Alzheimer's disease, GSK3b, Mitochondrial dysfunction, Tau protein.

## 1. INTRODUCTION :

### 1.1. Overview of Alzheimer's disease

Alzheimer's disease (AD) is the chronic and progressive neurodegenerative disease. It was mentioned by the Alois Alzheimer, German psychiatrist[1] in 1906. This disease is the commonest pattern of age-dependent dementia [1].
As per "2020 Alzheimer's Disease Facts and Figures", about 5.8 million [2] Americans aged sixty five years and more in age are affected with Alzheimer's dementia [2] in 2020. The prevalence of Alzheimer's dementia could involve 13.8 million [2]. Americans aged 65 years and older population by 2050 year [2]. Alzheimer disease characterizes into familial form or early-onset Alzheimer's disease (FAD), and Sporadic form or late-onset- Alzheimer's disease (LOAD) [3].

The FAD form constitutes around 5% of the total AD, while the LOAD for represents 95% of the Alzheimer's disease [3]. Genetic factors contribute to FAD which manifests in younger age before age of 65 years. The environmental factors and non-genetic factors contribute to the sporadic form of disease [3]. The Alzheimer's disease is clinically expressed as gradual loss of episodic memory, cognitive functions, and changes in normal behaviour. Presence of extraneuronal senile plaque while intraneuronal neurofibrillary tangles formation are the cardinal markers of the Alzheimer's disease.

### 1.2. Overview of Glycogen synthase kinase 3

Glycogen synthase kinase-3 (GSK-3) is the serine/threonine protein kinase catalysing addition of phosphate moiety to the serine and threonine amino acid residues. It was discovered in 1980 and named as a regulatory kinase for enzyme glycogen synthase [4].

GSK3 exists into two isoforms namely GSK-3$\alpha$ and GSK-3$\beta$, which are encoded by two homologous genes but possess the similar function [5]. Structurally, GSK-3$\alpha$ has molecular weight of 51 kDa while GSK-3$\beta$ possesses 47 kDa molecular weight. The former isoform of GSK3 contains glycine-rich fragment at the N-terminal [5].

Both isoforms of GSK3 are expressed in brain with higher expression in the Purkinje cells of the cerebellum, hippocampus, and cerebral cortex [5]. But the GSK-3$\beta$ expression dominates in the brain regions over the GSK3a. The GSK-3 activity is phosphorylation dependent at different sites. Phosphorylation of Serine residue at $9^{th}$ position in GSK-3$\beta$, or Serine residue at $21^{st}$ position in GSK-3$\alpha$ leads to inhibition of GSK3 activity [6]. While phosphorylation of Tyrosine residue at $216^{th}$ position in GSK-3$\beta$ and Tyrosine residue at $279^{th}$ position in GSK-3$\alpha$ results into enhancement of activity of GSK3 [7].

It is involved in a number of cellular processes, including the division, proliferation, differentiation, and adhesion of cells [8]. Dysfunction of GSK-3 is implicated in diverse human diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), type 2 diabetes, bipolar disorder (BPD), and cancer [9].

### 1.3 Aim of Study:

In the present paper, it was aimed to study "Role of GSK3b in the Molecular Pathology of Alzheimer's disease".

### 1.4 Objectives:

i. To find out role of GSK3, and caspase activation in Alzheimer's disease
ii. To find out role of GSK3 in apoptosis
iii. To find out activity of GSk3 in amyloid beta production in Alzheimer's disease
iv. To find out role of GSK3 in hyperphosphorylation of Tau Protein in Alzheimer's disease
v. To find out role of GSK3 in mitochondrial dysfunction in Alzheimer's disease
vi. To find out role of GSK3, amyloid beta peptides and voltage-dependent anion channel 1 (VDAC1) in Alzheimer's disease
vii. To find out effect of interaction between GSK3 and P53 in Alzheimer's disease
viii. To find out role of GSK3 in alteration in Hippocampal Neurogenesis
ix. To find out role of GSK3 in Neuroinflammation in Alzheimer's disease

### 1.5 Scope of Study:

Present study has scope in the field of neurology. Study delineates molecular signaling cascades involved in pathogenesis of Alzheimer's disease mediated with activity of GSK3. Study helps to understand the precise role of GSK3 in Alzheimer's disease. Present study has scope in the field of pharmaceuticals. GSK3 could be target of novel drug molecules for the amelioration of the manifestations and to delay the progression of Alzheimer's disease.

### 1.6 Significance of Study:

Present study is significantly provides clinical and practical knowledge to physicians, neurologist and neurosurgeons, while it provides basic knowledge to the students and research scholars in the field of life science and medicine.

### 1.7 Limitations of Study:

- ✓ Paper is focused to study role of GSK3 enzyme in Alzheimer's disease, while there could be additional factors that need study to grasp complete knowledge
- ✓ Paper is focused to include only Alzheimer's disease excluding other neurodegenerative diseases
- ✓ The sources of secondary data are limited. Additional sources could be included.

## 2. LITERATURE REVIEW :

A literature review represents the overview of the study works on a specific topic published previously. Literature review can be narrative where discussion of the previous works is done, while it can be critical review of the previously published works in which critical analysis is carried out about the work based on the previous studies that in turn result into productive conclusions which serve either as source for future study or source of knowledge for the implication in the particular field to overcome the present day issue affecting the mankind.

In the present study, critical literature review was conducted pertaining to glycogen synthase kinase 3, its actions, regulation, and role in the molecular pathology of Alzheimer's disease. Critical literature review is presented in the section, study of papers.

## 3. RESEARCH METHODOLOGY :

### 3.1 Research Design:

Critical analytic, Qualitative cum Retrospective research design.

### 3.2 Sampling Design:

#### 3.2.1 Sampling Method

Purposive sampling, also termed as Judgement sampling method was adopted for the study. This is the non-probability sampling method. Study papers were selected based upon the sample selection criteria.

#### 3.2.2 Study Population

Study population is finite. All the review papers, research papers, meta- analysis papers, books, monographs available through internet sources pertaining to the glycogen synthase kinase 3b, Alzheimer's disease and the activity of GSK3b on the pathophysiology of Alzheimer's disease constitute study population.

#### 3.2.3 Sample selection criteria

**Sample Inclusion criteria**

- ✓ Study papers describing glycogen synthase kinase 3b (GSK3b)
- ✓ Study papers describing Alzheimer's disease
- ✓ Study papers describing role of GSK3b on Alzheimer's disease

**Sample Exclusion criteria**

- ✓ Study papers describing role of GSK3b on neurodegenerative diseases other than Alzheimer's disease
- ✓ Study papers describing role of GSK3b on ischaemic injury of brain
- ✓ Study papers describing role of GSK3b on psychiatric disorders
- ✓ Study papers describing role of GSK3b on accidental brain injury

#### 3.2.4 Sample size

Study papers (n=230) were selected based on keywords as mentioned in the data collection design. Based on sample selection criteria, study papers (n=140) were excluded. Sample size (n=90) study papers were selected by judgement sampling method.

### 3.3 Data Collection Design:

#### 3.3.1 Type of Data

Secondary data was utilized for the study.

#### 3.3.2 Sources of Data

Data was collected from the review papers, research papers, meta- analysis papers, books, monographs available online.

#### 3.3.3 Data Collection sites

Secondary data were collected from PubMed, National Library of Medicine (NCBI), ScienceDirect, Frontiers, ACS Publications, Wiley online, Nature, Biomed Central, Hindawi, Researchgate, Mdpi, The Lancet, JAMA Neurology, The Journal of Clinical Investigation, IJPS online, BMJ, BMJ Molecular Degeneration, Uniport, and others.

**3.3.4 Data Collection Technique**

Keywords namely Alzheimer's disease, GSK3b, Neurodegenerative diseases, Mitochondrial dysfunction, Amyloid beta, Tau phosphorylation, VDAC1, neurofibrillary tangles, oxidative stress, neuroinflammation, neuronal apoptosis, synaptic plasticity and others were used to search study papers. Keys words were entered into Google Search Engine to select the papers. Total 230 papers constituted the study population, while 90 papers were selected as sample based on sample selection criteria.
Study papers were selected from the period 1995 to 2022.

## 4. STUDY OF PAPERS :

### 4.1. Role of GSK3 and Caspase activation in Neurodegenerative diseases:

Caspases belong to family of endopeptidases. These are cysteine-aspartate proteases or also termed as cysteine proteases owing to presence of cysteine thiol residue at active site of enzyme that shares a common mechanism of catalysis of proteins. Caspases cleaves by nucleophilic attack on the protein after the aspartate residue. Caspases are mainly involved in cell inflammation and apoptosis [10].
Caspases exist in tissues in inactive form (zymogen) and termed as Procaspases. The activation of Procaspases is tightly regulated by cascade of enzymatic events leading to their assembly into dimers or oligomers gaining catalytic potential. The caspases are mainly subdivided into apoptosis caspases and inflammation caspases based on the functions these enzymes execute in body [11]. The caspases inducing apoptosis are caspase-3, -6, -7,-8, and caspase-9 in humans while caspases mediating inflammation in humans are caspase-1, -4, -5, and caspase -12 and in mice are caspase-1, -11, and caspase-12 [10].
Furthermore, caspases with apoptotic potential can be subdivided into executioner caspases namely caspase-3, -6, and caspase -7 and initiator caspases namely caspase-8 and caspase -9 depending upon the mechanism of action of caspases [11].
Caspases in the form of zymogens structurally contain N-terminal prodomain that is followed by large subunit, designated as p20 having molecular weight of nearly 20 kDa, and small subunit labelled as p10 with molecular weight of nearly 10 kDa. Presence of small linker domain connects the p20 and p10 subunits in Procaspases [10].
Additionally, caspases can also be classified based on length of prodomain. The caspases with larger prodomain are included into group 1 caspases and group 2 caspases possessing inflammatory potential, and initiator of apoptosis potential, respectively. The caspases with smaller prodomain are kept in group 3 (20 amino acids length) with effector of apoptosis potential [10, 12].
Caspases are secrete and released as zymogens named Procaspases in tissues. These are in monomeric form. Activation of Procaspases require dimerization and cleavage. Several adaptor proteins (contain proteins binding domains [12], favour protein-protein interaction) can bond to protein binding site located in the prodomain of procaspase. The protein-protein interaction sites in the caspases are different that enable them to bind with separate adaptor proteins. The caspase recruitment domain (CARD) is present in caspase 1, -2, -4, -5, and caspase-9 while the caspase -8 and caspase-10 contain the death effector domain (DED) [12].

**4.1.1 Activation of GSK3b and Caspase 3 in Brain**

The transgenic mice model of 6-Hydroxydopamine (6-OHDA) is ideal model for study of intricate molecular events of the neurodegenerative disease in humans for establishing approved drug molecules for the therapeutic purpose.
Study [13] involving activation of caspase 3 and glycogen synthase kinase 3β (GSK-3β) in substantia nigra compacta in transgenic mice model (6-OHDA). Study [13] reported decline in number of tyrosine hydroxylase secreting dopaminergic neurons in substantia nigra compacta in mice model (6-OHDA). Furthermore, rise in immunoreactivity against cleaved caspase-3, Apoptin, and GSK-3β in substantia nigra compacta was observed by authors indicating the activation of caspase 3 and glycogen synthase kinase 3β.
Authors [13] identified elevated caspase-3 immunoreactivity in the tyrosine hydroxylase + cells from the 1$^{st}$ day after the lesion and continued up to next 15 days along with localization of activated caspase 3 in the astrocytes and microglia.

Study [13] concluded the role of activation of caspase-3 and GSK-3β implicated in the apoptosis of dopamine secreting neurons in the substantia nigra compacta inducing neuroinflammation and pathophysiology of neurodegenerative diseases.

Another previous study [14, 15] augments the potential of caspase 3 in dopaminergic neurons death after the injection of 6-OHDA in mice model. Previous study by Ebert et al [14] contradicts the role of caspase 3 activation and mediated apoptosis of dopaminergic neurons after 6-OHDA injection in mice model. The controversy in the potential apoptotic role of caspase 3 and GSK3b in death of dopaminergic neurons might be reporting by authors during separate stages of neuroinflammation in neurons [14].

The glycogen synthase kinase 3b is phosphorylated at tyrosine 216 residue (Y216) present in the kinase domain of enzyme. The enzyme is thus activated while its phosphorylation at serine 9 residue (S9) led to its inactivation. The activated and phosphorylated [16, 17] enzyme is involved in the neuronal apoptosis in mice model after injection of 6-OHDA.

Study [18] was conducted in human-DA cell line (SH-SY5Y cells) and reported the role of activated and phosphorylated GSK-3β in mediating apoptotic signalling pathway in the neuroinflammation involved in pathology neurodegenerative diseases.

Study [19] found role of endoplasmic reticulum stress induced by several stressors including Amyloid beta peptides, senile plaque, neurofibrillary tangles, ROS and others on the caspase activation and apoptosis of affected cells including neurons.

Study [19] identified that stressor named thapsigargin, that inhibits ER Ca(2+)-ATPase leading to endoplasmic reticulum stress, was involved in mediating effector caspases 3 activation and neuronal apoptosis together with prolonged overactivity of glycogen synthase kinase-3beta (GSK3b) in the affected cells.

Study [19] posited that thapsigargin-mediated activation of caspase-3 always mandates activation of glycogen synthase kinase-3beta because it was observed that suppression of GSK3beta overexpression either with the help of dominant-negative GSK3beta or through the use of lithium chloride (GSK3beta inhibitor) led to inhibition of the activation of effector caspase 3 in the affected cells.

**Conclusively, stressors mediated endoplasmic reticulum stress could induce apoptosis of neurons via effector caspase 3 activation that always necessitates the overexpression of GSK3b otherwise activation of caspase 3 and associated neuronal apoptosis is suppressed in the cells. Thus, GSK3b is the novel target of therapeutics in the treatment of Alzheimer's disease.**

### 4.1.2 Pro-apoptotic as well as Apoptotic Potential of GSK3

The GSK3 serves dual role in mediating apoptosis under specific conditions while acting as antiapoptotic in other conditions. The duality of the action of GSK3 is manifested into either neurodegenerative diseases when it induces apoptotic signalling pathway or malignancy when it serves as antiapoptotic molecule in body. Regarding apoptotic signalling by GSK3, it can be intrinsic apoptosis or extrinsic apoptosis.

### 4.1.3 Intrinsic Apoptosis pathway

**Apoptotic Role of GSk3**

GSK-3 is implicated into inducing apoptotic signalling pathways based on the nature of ligand. Diverse array of stimuli including oxidative stress, DNA damage ER stress might be implicated in the intrinsic apoptotic signalling pathway. Furthermore, study [20] posited that suppression of the supply of trophic factors as well as blocking the PI3 kinase signalling pathway when studied in rat cortical neurons in laboratory culture resulted into GSK3 mediated intrinsic apoptotic pathway in rat cortical neurons in culture.

Thapsigargin belongs to family of non-competitive inhibitor of the sarco/endoplasmic reticulum $Ca^{++}$ ATPase enzyme, hence inducing ER stress that might be involved in apoptosis of neurons in regions of brain insinuated in the pathology of Alzheimer's disease along with other neurodegenerative diseases [20].

Study [21] reported that application of thapsigargin enhanced enzymatic activity of GSK2 for prolonged period leading to activation of apoptosis effector caspase-3. Application of lithium (inhibitor of GSK3) or promoting expression of dominant-negative GSK3β led to suppression of activation of apoptotic effector caspase-3.

The apoptotic stimuli including oxidative stress, hypoxia, amyloid beta protein, hyperphosphorylated Tau activate GSK3 in the cytoplasm to mediate the intrinsic apoptotic signalling inside the cells or neurons [22]. The role of GSK3 is disruption of mitochondrial function that might involve molecular events starting with active conformational change of pro-apoptotic proteins as Bax and further its

translocation into the mitochondria from cytosol. The voltage-dependent anion channel 1 (VDAC1) represents the mitochondrial protein located on outer membrane that controls the transport of ions and molecules across the membrane of mitochondria [22].
The VDAC1 dysregulation [23] is key component in the mitochondrial dysfunction mediated by GSK3. The activated Bax protein leads to sequestration of anti-apoptotic protein in mitochondria. The Bax protein can also undergo oligomerization with the outer membrane. Overall, events lead to interruption of mitochondrial membrane potential and liberation of mitochondrial intermembrane space located apoptotic proteins into the cytoplasm [24].
The cytochrome c is the most important apoptotic protein released into cytoplasm, binds with ATP and apoptotic protease activating factor-1 (APAF-1)leading to formation of apoptosome that activates the procaspase 9 into caspase 9 in the cytoplasm of cell or neuron. Caspase 9 is the initiator caspase leading to start of procaspase 3 activation into caspase 3 that plays essential role in the neuronal apoptosis and neurodegeneration [25].
**Multiple stimuli are involved in neuronal apoptosis and neurodegeneration in brain regions initiated and propagated by GSk3 through activation of apoptotic proteins and sequestration of antiapoptotic proteins leading to dysfunction of mitochondrial gatekeeper, VDAC1 resulting into mitochondrial dysfunction, activation of procaspase-9 and finally effecting of apoptosis by activated caspase 3 in the cells and neurons implicated in the pathophysiology of neurodegenerative diseases including Alzheimer's disease**.

#### 4.1.4. Extrinsic Apoptosis pathway:
#### Antiapoptotic Role of GSK3
The tumor necrosis factor receptors (TNF-Rs) belong to family of cytokine proteins located in the cell membrane where each receptor binds with specific ligands [26]. The ligands are termed as tumor necrosis factors (TNFs) that belong to class II Transmembrane proteins possessing TNF homology domain. TNF receptors need adaptor proteins for the activation of downstream molecules for activation of inflammation and apoptosis [27].
Extrinsic apoptotic pathway starts with the activation of death domain (subclass of protein containing death effector domain and caspase recruitment domain). Ligands including damaged DNA, amyloid beta, Tau phosphorylated, unfolded proteins response, hypoxia, ischaemia can bind with specific [28] TNF-R and undergoes trimerization with subsequent activation of death domain and recruitment of procaspase 8 and forming death inducing signalling complex (DISC)25. The procaspase 8 is activated into caspase 8 that in turn activate effector caspase 9 resulting into neuroinflammation and neuronal apoptosis [28].
Study [29] described that the GSK3 remain localized with death domain and suppresses the formation of death inducing signalling complex. After ligand induced activation of death domain, the GSK3 activity is suppressed leading to apoptosis.
**So, GSK3 exhibit anti-apoptotic activity in the extrinsic pathway of apoptosis. The key concepts of the role of GSK2 either apoptotic or anti-apoptotic in diverse conditions would help understand the potential of GSK3 inhibitors as drug molecules in reducing the harmful effects of drugs and improving their therapeutic effects on the diseases involving role of GSK3 in their manifestations including neurodegenerative diseases.**

### 4.2 Activity of GSK3 in formation of Amyloid beta in Alzheimer's disease:
There is evidence [30] about the enzymatic over-activity of GSK3 that is insinuated in the pathophysiology of Alzheimer's disease in familial AD as well as Sporadic AD. The overactivity of GSK3 is manifested in terms of increased production of amyloid beta peptides in brain areas along with decline in parasympathetic discharge from the nerve endings responsible for cholinergic deficiency in the Alzheimer's disease [31].
Indirect evidence namely co-localization of GSK3 with neurofibrillary tangles [32] and dystrophic neuritis [32] in autopsy report from AD brain regions support the overactivity of GSK3 in Alzheimer's disease. Additional evidence came from the elevated immunoreactivity [33] for GSK3 phosphorylated at tyrosine residue at 216 resulting into over-activity of GSK3 in the frontal region of cortex in patients with AD.
The GSK3 is actively involved in the regulation of amyloid precursor protein cleavage [34] resulting into raised formation of amyloid beta peptide in brain regions. Study [35] reported that the GSK3

overactivity and its role in cleavage of amyloid precursor proteins to produce Ab peptides. The cleavage is sequential starting with catalysis by aspartyl protease, beta secretases 1(BACE) and further led by gamma secretases induced splitting.

Abeta peptides are derived from the amyloid precursor protein (APP) by sequential proteolysis, catalysed by the, followed by presenilin-dependent gamma-secretase cleavage [35].

The presenilins [35] (Transmembrane proteins representing the catalytic subunits of gamma secretases enzyme) interact with glycogen synthase kinase-3 that signifies the functional role of the enzyme in the catalytic property of gamma secretases.

**The above cited molecular event is further authenticated by the study in which lithium was used to inhibit activity of GSK-3 leading to inhibition of proteolysis of amyloid precursor protein and production of amyloid beta peptide, hence authenticating the role of overactivity of GSK3 enzyme in the over production of amyloid beta peptide that in turn reciprocate negatively to enhance the activity of GSK3 culminating into pathophysiology of Alzheimer's disease**.

### 4.3 Activity of GSK3 in Hyperphosphorylation of Tau Protein in Alzheimer's disease:

The overactivity of GSK3 is involved in the Hyperphosphorylation of tau protein inside the neurons in brain region. The GSK3 is a tau protein involved in the formation of neurofibrillary tangles in brain that are hallmark lesion in brain regions in Alzheimer's disease.

Study [36] posited that transgenic mice expressing GSK3b presented with Hyperphosphorylation of tau protein and formation of neurofibrillary tangles leading to neuroinflammation and neurodegeneration.

Furthermore, study [36] identified the role of GSK3b inhibitor, Lithium as a drug for prolonged period on the GSK3b transgenic mice. Authors [36] reported the suppression of formation of neurofibrillary tangles by inhibiting Hyperphosphorylation of Tau protein in the neurons in brain of transgenic mice expressing tau and overactive GSK3b.

Study [37] reported the behaviour of GSK3 in phosphorylation of Tau protein in neurons in forebrain to detect identify molecular changes involved in pathogenesis of Alzheimer's disease. The study was conducted on conditional system, Tet-OFF [38] in transgenic mice CamKIIα-tTA/GSK-3β [38] inducing overexpression of GSK-3β exclusively in the adulthood period.

CaMK2a-tTA transgenic mice [38] (under regulatory control of the forebrain-specific calcium-calmodulin-dependent kinase II (Camk2a) promoter, mice express the tetracycline-controlled transactivator protein (tTA) [38]. Study [37] reported Hyperphosphorylation of Tau protein in forebrain neurons manifesting in terms of reactive astrocytosis, neuronal apoptosis, spatial learning deficiency in mice model.

**Conclusively, GSK3 overexpression is closely linked with Hyperphosphorylation of tau protein inside the neurons leading to multiple molecular events culminating as neurodegeneration that could be focus for the pharmaceutical industry to design a specific drug molecule with minimum side effects and maximum therapeutic efficacy in Alzheimer's disease.**

### 4.4. Role of GSK3 in Mitochondrial dysfunction in Alzheimer's disease:

The GSK-3 exhibits two isoforms as GSK3α and GSK3β having similar functions. Regarding their localization in cell, the GSK-3β localizes in cytosol and small fraction is present in mitochondrial matrix while mitochondrial localization of GSK-3α is not reported [39].

#### 4.4.1 GSK-3β and Impaired Mitochondrial Biogenesis

Overactivity of GSK3b reduces the biogenesis of mitochondria and bioenergetics [40]. The lithium chloride is the inhibitor of GSK-3β. The study[40] involving lithium chloride inhibition resulted in the enhanced expression of Peroxisome proliferator-activated receptor-gamma co-activator (PGC-1alpha)[40] that belongs to family of transcription co-activators and up-regulated expression of Mitochondrial transcription factor A (mtTFA). These two molecular events led to enhanced biogenesis of mitochondria represented by rise in DNA content in the cells [40].

**Thus overactivity of GSK3b manifests as impaired mitochondrial biogenesis and its functions which might be implicated in the pathophysiology of neurodegenerative diseases including Alzheimer's disease.**

**Furthermore, overactivity of GSK3β is associated with pathophysiology of Alzheimer's disease via Hyperphosphorylation of tau protein, amyloid beta peptides deposition leading to mitochondrial impaired biogenesis, impaired functions as has been evidenced by study [42] on**

**post-mortem report that indicated increased activity of GSK3b in tissues in brain regions of patients suffering from AD. The GSK3b is crucially implicated in detachment of VDAC1 protein hexokinase leading to impaired glucose metabolism, impaired bioenergetics and neuronal apoptosis[42].**

#### 4.4.2 GSK-3β and Impaired Mitochondrial Trafficking

The impaired cytosolic trafficking of mitochondria is closely involved in pathophysiology of neuronal apoptosis and neurodegeneration as reported in Alzheimer's disease.

GSK-3β is essential for functions of kinesin and dynein (motor proteins). The GSK-3β attaches to Trafficking Kinesin **Protein** 1 (TRAK1) [41], Disrupted in schizophrenia 1 protein (DISC1) and Nuclear distribution **protein 1(**NDE1) [41] that together constitute trafficking complex, thus enhancing mitochondrial trafficking in hippocampal neurons in the culture [41].

**Overactivity of GSK-3β raises mitochondrial trafficking similar to activity by Tau protein without changing velocity of mitochondria[42] that could be involved in neurodegeneration.**

#### 4.4.3 GSK-3β and Impaired Mitochondrial Bioenergetics

GSK-3β has a role in regulating activity of electron transport chain and mitochondrial bioenergetics. Study [43] reported that up-regulation of expression of GSK-3β is linked to inhibition of complex I and hence decline in the synthesis of ATP and enhanced production of reactive oxygen species. The oxidative stress could mediate procaspase-3 action and caspase-3 mediated neuronal apoptosis that constitutes the main feature in Alzheimer's disease.

**Study [43] was confirmed by inhibition of the activity of GSK3b by lithium chloride and thus confirm the role of overactivity of GSK3b in the production of ROS and decline in ATP inflicting oxidative stress and initiating vicious cycle of neurodegeneration as has been the features of pathophysiology of Alzheimer's disease.**

#### 4.4.4 GSK-3β and Impaired Mitochondrial Permeability in Alzheimer's disease

The mitochondrial permeability transition pore (mPTP) is positioned in inner mitochondrial membrane and it is the non-specific ion channel. Under normal cellular condition, it remains closed. Under cellular stress conditions, the mitochondrial permeability transition pore [44] (mPTP) is opened and permits passage of ions and molecules of size less than 1.5 kDa into the matrix of mitochondria. It leads to edema of matrix [44], depolarization of mitochondrial membrane [44], outer membrane disruption and depletion of ATP materializing into neuronal apoptosis and cell death [44]. Several factors including oxidative stress, calcium overload, ATP depletion and DNA damage can contribute to opening of mPTP. The above cited molecular features have been studied in the cardiac muscle fivers undergoing hypo-perfusion and ischaemic necrosis [44].

The GSK3b is involved in the opening of mPTP under cellular stress condition. Study [44] reported that GSK-3β responds to amino-terminal domain of VDAC2 leading to opening of mPTP. The transgenic mice model with targeted deletion of VDAc2 gene led to failure of overactivity of GSK3b and failure of opening of mPTP and prevention of neuronal apoptosis.

#### 4.4.5 Role VDAC1, GSK3b, and amyloid beta peptides in Alzheimer's disease

Voltage-dependent anion channels, or also termed as mitochondrial porins (VDAC) is the ion channel located on the outer mitochondrial membrane. It regulates the influx and efflux of several metabolites in mitochondria [45]. The VDAC exists in three isoforms namely VDAC1, VDAC2, and VDAC3 in mitochondria. The VDAC1 is the ubiquitously expressed ion channel in mitochondria than other two isoforms of VDAC. Additionally, VDAC1 is closely linked with neurodegeneration and neurodegenerative diseases [46].

Study [47] found post mortem brain tissues of patients who suffered from Alzheimer's disease in different phases of disease as well as the cortical tissues taken from the brains of transgenic mice expressing amyloid beta precursor protein at different stages of age.

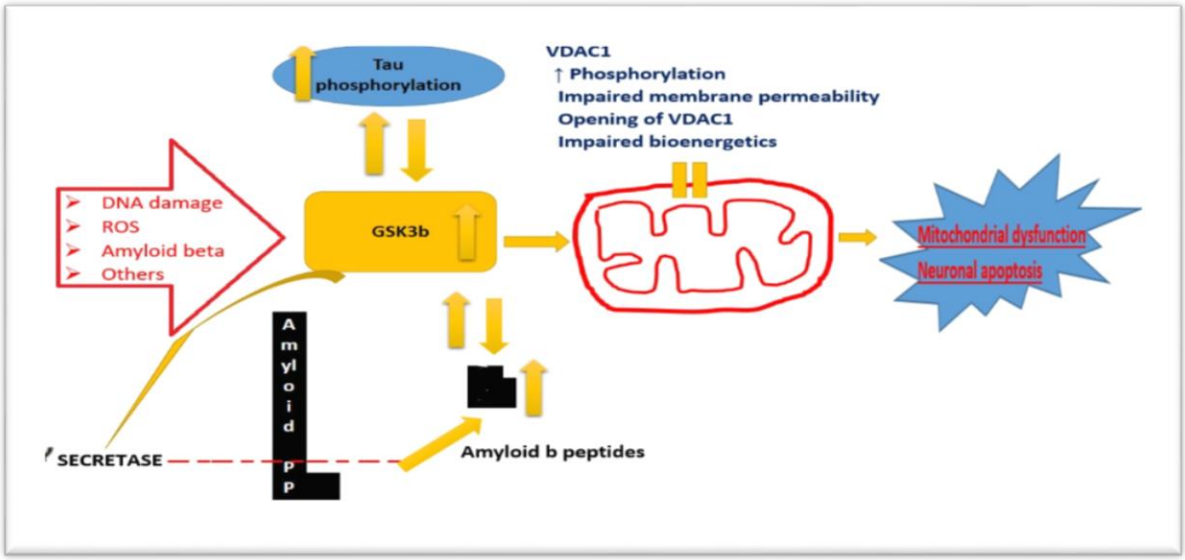


**Fig. 1:** Hyppothetical Diagram Showing Role of Vdac1, Gsk3b and Amyloid Beta in Mitochondrial Dysfunction

Study [47] identified that progressive rise in the amount of VDAC1 protein in different phases of AD from early stage to severe stage together with rise in VDAC1 protein consistent with increase in age from 6 months to 24 months in the cortical tissues of transgenic mice as shown in figure1.

Study [48] reported that GSK3β has a close association in the pathology of AD by mediating hyperphosphorylation of tau protein [49], enhancing cleavage of APP [50] and formation of increased amount of amyloid beta peptides and oligomers in brain [51]. Additionally, study reported that increased Ab in turn induces overactivity of GSK3b in brain and the vicious cycle perpetuates repeatedly [48]. The overactivity of GSK3b phosphorylates VDAC1 [52] at the threonine residue at position 51$^{st}$ leading to its dissociation from hexokinase II and antiapoptotic protein, Bcl2 protein [53]. These molecular events disturbs mitochondrial membrane permeability and depletion of ATP takes place resulting into lesser access of ATP to hexokinase II that finally culminate into reduced glycolysis and impaired bioenergetics and favour neuronal apoptosis [54,55]. The overactivity of GSK3b in turn inhibits the Akt kinases favouring neuronal apoptosis [56].

The N-terminal domain of VDAC1 harbours GxxxG motif [57]. Similar GxxxG motif is reported on the C-terminal domain in the Aβ1-42 and Aβ1-40 amyloid peptides. Study [58] posited that amyloid beta could interact with VDAC1 through its GxxxG motif leading to opening of VDAC1 in outer membrane of mitochondria, and membrane perturbation in hypometabolic neurons promoting mitochondrial dysfunction and neuronal apoptosis.

**Conclusively, the GSK3b, and amyloid beta peptides interact in a vicious cycle of molecular events leading to added neurotoxicity in regions of brain coupled with outer mitochondrial membrane perturbation by negatively affecting function of VDAC1 by the amyloid beta peptides resulting into mitochondrial dysfunction in the pathophysiology of Alzheimer's disease.**

### 4.5. Interaction between GSK3 and P53 in Alzheimer's disease:

The potential of glycogen synthase kinase-3β (GSK3β) is well established in the pathophysiology of both familial form and sporadic form of Alzheimer's disease [60]. The GSK3b under normal cellular condition, localizes in the cytoplasm and its nuclear fraction is negligible. But in cellular stress condition, GSK3b is transported to nucleus where it interacts [60] with p53.

Tumour suppressor protein [61] (p53) is essentially related to the pathophysiology of apoptosis, cell cycle arrest, and repair of DNA. The p53 protein has a role in ageing physiology [61]. Possibly, p53 protein has a causative role in the pathology of neurodegenerative diseases that is evinced by the study that reported rise in the p53 immunoreactivity in the cortical neurons in persons suffering from sporadic form of Alzheimer's disease [62].

Under unstressed and normal cellular conditions [63], p53 is maintained at low levels by sustained degradation of p53. In this process, the Mdm2 protein also called as ubiquitin ligase binds with the p53

and transports it from nucleus to cytoplasm[45]. The p53 binds with ubiquitin with help of Mdm2 and is tagged for proteasomal degradation thus keeping its levels in the nucleus low and preventing its transcriptional role [63].

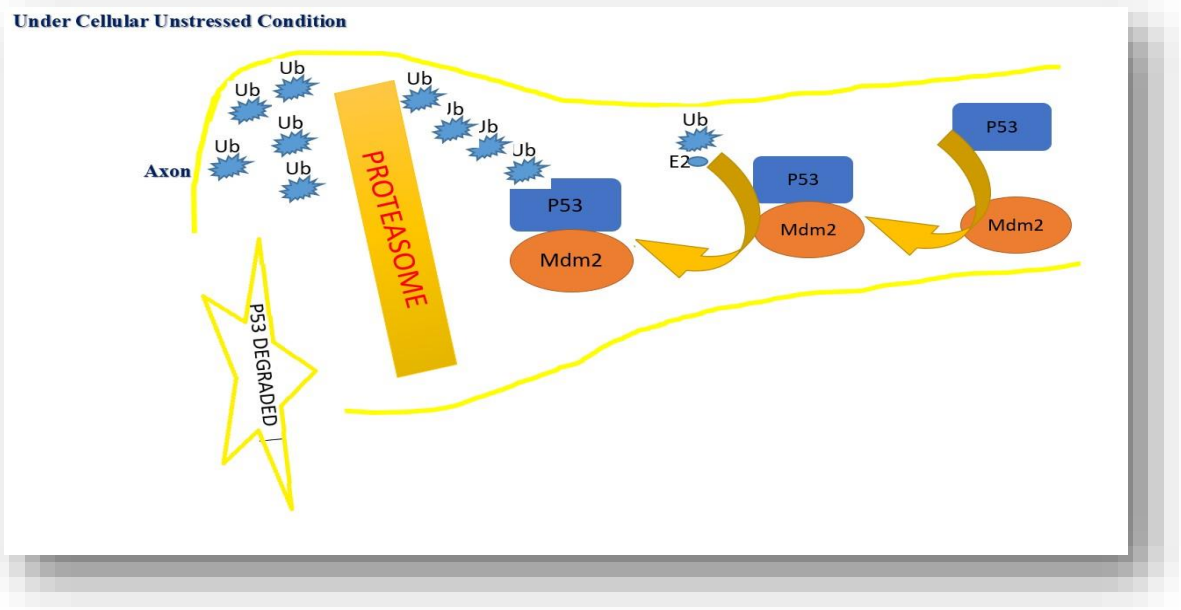


**Fig. 2**: Hypothetical Diagram Shwoing Low Level of P53 Protein Under Cellular Unstressed Condition

Under cellular stress conditions [64], association between p53 and Mdm2 is broken and p53 is localized in the nucleus. Its N-terminal contains several phosphorylation sites for action by protein kinases. P53 undergoes phosphorylation [65], activation and p53 levels in nucleus are raised as in fig2. The cellular stress conditions transport GSK3b from cytoplasm to nucleus. The activated p53 protein binds with GSK3b and raises its activity that further stabilizes the p53 in nucleus. The overactivity of GSK3b in turn catalyzes Hyperphosphorylation of Tau protein and favours formation of neurofibrillary tangles. The overactivity of GSK3b additionally increases cleavage of amyloid precursor protein and enhances amyloid beta peptide formation [64, 65].

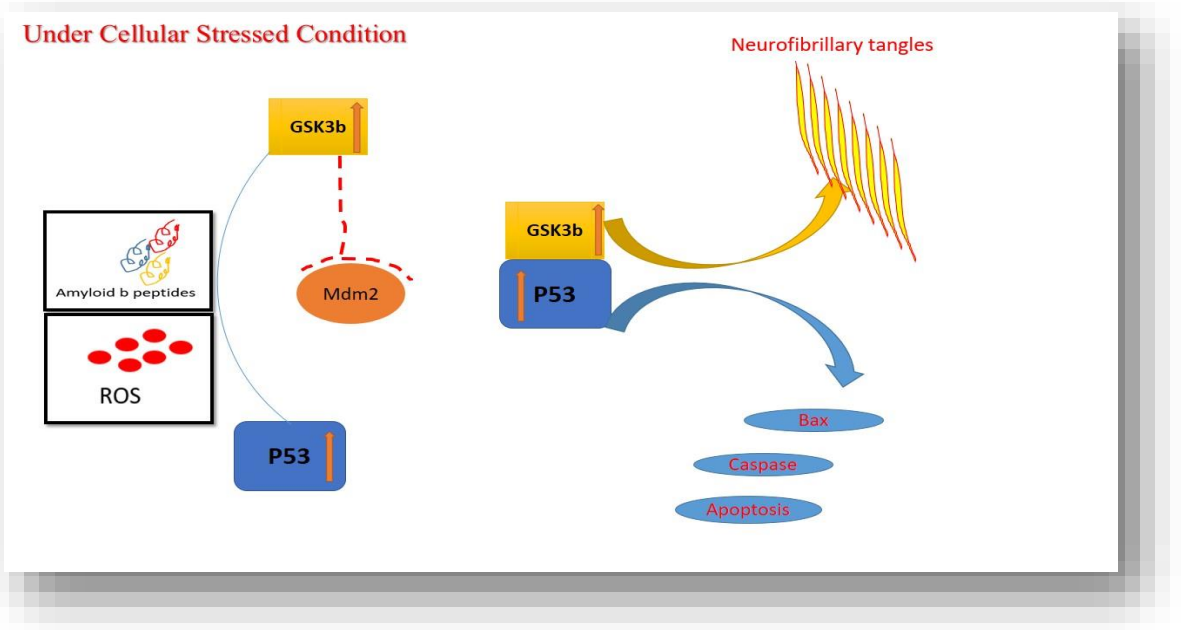


**Fig. 3:** Hypothetical Diagram Shwoing High Level of P53 Protein and Gsk3b Under Cellular Stressed Condition

**Conclusively, cellular stress conditions mediate activation and nuclear stabilization of p53 as in fig 3, followed by simultaneous nuclear transportation of GSK3b and interaction between two leading to overactivity of GSK3b manifested in the increase in tau protein Hyperphosphorylation, neurofibrillary tangles formation, rise in cleavage of amyloid precursor protein and formation of amyloid beta peptides, the cardinal lesion of Alzheimer's disease.**

### 4.6. GSK3b and Alteration in Hippocampal Neurogenesis:

Neurogenesis contribute to the lifetime addition of newborn neurons in the dentate gyrus of hippocampus [66]. Study [66] shows essentiality of newborn neurons in the memory and hippocampal-dependent functions [67]. The GSK3b is most significant in maintaining healthy hippocampal neurogenesis. The overexpression of GSK-3β is implicated in the impairment of adult neurogenesis [68].

Study [69] identified the role of GSK3b in the post-natal maturation of newborn neurons in transgenic mice model with overexpression of GSk3b.

Study [70] proved that overexpression GSK3b induces morphological changes in dendritic tree in neurons along with post-synaptic density alterations[71] in the transgenic mice model and these changes were reported to be similar as identified in the granule neurons in brain region of patients with Alzheimer's disease.

**Conclusively, newborn neurons are essential for the hippocampal-dependent functions and memory, thus alterations in adult hippocampal neurogenesis might be implicated in the cognitive dysfunction and memory deficit as reported in the Alzheimer's disease and GSK-3β is necessary for hippocampal function, supporting the idea that GSK3b could be the target of novel drugs for management of Alzheimer's disease.**

### 4.7. GSK3 in Neuroinflammation and Alzheimer's disease:

Neuroinflammation is recognized as the causative factor in several brain diseases including Alzheimer's disease, dementia, schizophrenia and multiple sclerosis [72]. In the pathology, unusual levels or overactivity of glycogen synthase kinase 3b imparts a significant role [73].

Studies revealed that activity of GSK3b mediates expression of proinflammatory as well as anti-inflammatory cytokines in the neurons and cells [74].

Several factors including Amyloid b peptides [75], Tau phosphorylation [76], reactive oxygen species [77], damaged DNA [78] can induce de-phosphorylation and activation of GSK3b [79]. After activation, it further activates the nuclear factor kappa b (NF-κB) [80, 81, 82] which undergoes translocation from cytoplasm to nucleus. Inside nucleus, activated NF-κB binds along with CREB-binding protein [83, 84] on the transcriptional sites of genes responsible for transcription of pro-inflammatory cytokines namely TNF-α, IL-1β, and IL-6 [85, 86, 87].

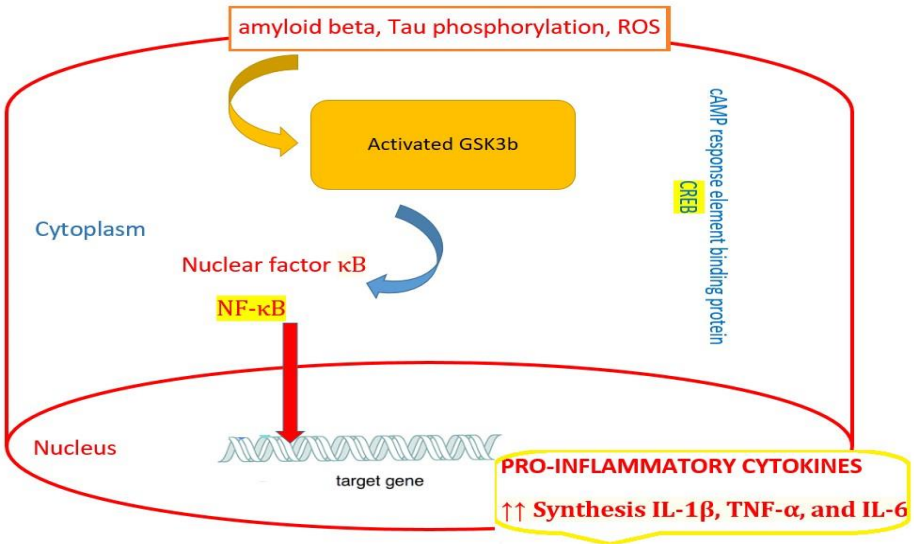


**Fig. 4:** Hypothetical Diagram Showing Activated Gsk3b, and Release of Proinflammatory Cytokines

**Thus, activation of GSK3b mediated by stressors as in fig 4, is implicated in the transcription of genes synthesizing proinflammatory cytokines and has a role in inducing neuroinflammation implicated in Alzheimer's disease.**

Contrarily, phosphorylation and inactivation of GSK3b as in fig 5, could lead to translocation of cytosolic CREB to nucleus where CREB-binding protein binds with CREB protein and act as transcriptional activator of genes responsible for synthesis of anti-inflammatory cytokines like IL-10 [88, 89, 90]

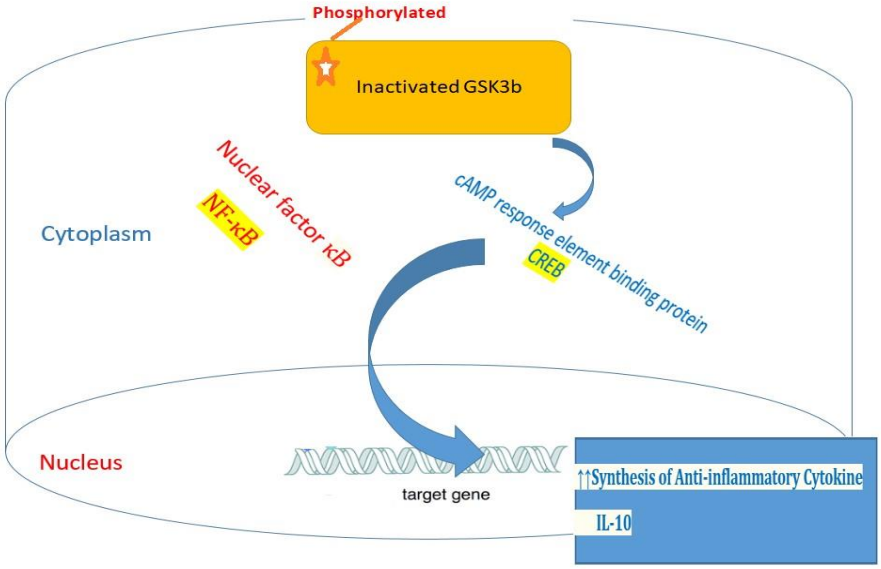


**Fig. 5:** Hypothetical Diagram Showing Inactivated Gsk3b and Its Anti-Inflammatory Role

## 5. SUMMARY :

- ✓ Stressors mediated endoplasmic reticulum stress could induce neuronal apoptosis through activation of effector caspase 3 that always necessitates the overexpression of GSK3b otherwise activation of caspase 3 and associated neuronal apoptosis is suppressed in the cells. Thus, GSK3b is the novel target of pharmacological intervention in the treatment of Alzheimer's disease.
- ✓ Multiple stimuli are involved in neuronal apoptosis and neurodegeneration in brain regions initiated and propagated by GSk3 through activation of apoptotic proteins and sequestration of antiapoptotic proteins leading to dysfunction of mitochondrial gatekeeper, VDAC1 resulting into mitochondrial dysfunction, activation of procaspase-9 and finally execution of apoptosis by activated caspase 3 in the cells and neurons implicated in the pathophysiology of neurodegenerative diseases including Alzheimer's disease.
- ✓ The GSK3 exhibit anti-apoptotic role in the extrinsic pathway of apoptosis. The key concepts of the role of GSK2 either apoptotic or anti-apoptotic in diverse conditions would help understand the potential of GSK3 inhibitors as drug molecules in reducing the harmful effects of drugs and improving their therapeutic effects on the diseases involving role of GSK3 in their manifestations including neurodegenerative diseases.
- ✓ The molecular events of study are further authenticated by the study in which lithium was used to inhibit activity of GSK-3 leading to inhibition of proteolysis of amyloid precursor protein and production of amyloid beta peptide, hence authenticating the role of overactivity of GSK3 enzyme in the over production of amyloid beta peptide that in turn reciprocate negatively to enhance the activity of GSK3 culminating into pathophysiology of Alzheimer's disease.
- ✓ GSK3 overexpression is closely linked with Hyperphosphorylation of tau protein inside the neurons leading to multiple molecular events culminating as neurodegeneration that could be focus for the pharmaceutical industry to design a specific drug molecule with minimum side effects and maximum therapeutic efficacy in Alzheimer's disease.

- ✓ Thus over-activity of GSK3b manifests as impaired mitochondrial biogenesis and its functions which might be insinuated in the pathophysiology of neurodegenerative diseases including Alzheimer's disease.
- ✓ Over-activity of GSK3β is associated with pathophysiology of Alzheimer's disease via Hyperphosphorylation of tau protein, amyloid beta peptides deposition leading to mitochondrial impaired biogenesis, impaired functions as has been evidenced by study[42] on post-mortem report that indicated increased activity of GSK3b in tissues in brain regions of patients suffering from AD. The GSK3b is crucially implicated in detachment of VDAC1 protein hexokinase leading to impaired glucose metabolism, impaired bioenergetics and neuronal apoptosis[42].
- ✓ Overactivity of GSK-3β raises mitochondrial trafficking similar to activity by Tau protein without changing velocity of mitochondria[39] that could be involved in neurodegeneration.
- ✓ Study was confirmed by inhibition of the activity of GSK3b by lithium chloride and thus confirm the role of overactivity of GSK3b in the production of ROS and decline in ATP inflicting oxidative stress and initiating vicious cycle of neurodegeneration as has been the features of pathophysiology of Alzheimer's disease.
- ✓ The GSK3b, and amyloid beta peptides interact in a vicious cycle of molecular events leading to added neurotoxicity in regions of brain coupled with outer mitochondrial membrane perturbation by negatively affecting function of VDAC1 by the amyloid beta peptides resulting into mitochondrial dysfunction in the pathophysiology of Alzheimer's disease.
- ✓ Cellular stress conditions mediate activation and nuclear stabilization of p53 as in fig 3, followed by simultaneous nuclear transportation of GSK3b and interaction between two leading to overactivity of GSK3b manifested in the increase in tau protein Hyperphosphorylation, neurofibrillary tangles formation, rise in cleavage of amyloid precursor protein and formation of amyloid beta peptides, the hallmark lesion of Alzheimer's disease.
- ✓ Newborn neurons are essential for the hippocampal-dependent functions and memory, thus alterations in adult hippocampal neurogenesis might be implicated in the cognitive dysfunction and memory deficit as reported in the Alzheimer's disease and GSK-3β is necessary for hippocampal function, supporting the idea that GSK3b could be the target of novel drugs for management of Alzheimer's disease.
- ✓ Activation of GSK3b mediated by stressors as in fig 4, is implicated in the transcription of genes synthesizing proinflammatory cytokines and has a role in inducing neuroinflammation involved in Alzheimer's disease.

## 6. CONCLUSION :

Irrespective summary points, precise causative activity of GSK3b in the pathogenesis of Alzheimer's disease is yet to be decoded, however, present review has provided extensive and updated knowledge concerning role of GSK3b in the pathology of Alzheimer's disease.

The overexpression of GSK3b is closely linked to tau hyperphosphorylation and increased production of amyloid beta peptides that are hallmark lesions in Alzheimer's disease. Hence, GSK3b is the target of novel drug molecule in the treatment of disease.

Further study could provide more precise and alternative factors that interact with GSK3b would definitely sharpen the understanding about the intricate molecular events in pathogenesis of disease.

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