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Review article

# Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease

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ABSTRACT

Neurodegenerative diseases are among the most challenging diseases with poorly known mechanism of cause and paucity of complete cure. Out of all the neurodegenerative diseases, Alzheimer's disease is the most devastating and loosening of thinking and judging ability disease that occurs in the old age people. Many hypotheses came forth in order to explain its causes. In this review, we have enlightened Glycogen Synthase Kinase-3 which has been considered as a concrete cause for Alzheimer's disease. Plaques and Tangles (abnormal structures) are the basic suspects in damaging and killing of nerve cells wherein Glycogen Synthase Kinase-3 has a key role in the formation of these fatal accumulations. Various Glycogen Synthase Kinase-3 inhibitors have been reported to reduce the amount of amyloid-beta as well as the tau hyperphosphorylation in both neuronal and nonneuronal cells. Additionally, Glycogen Synthase Kinase-3 inhibitors have been reported to enhance the adult hippocampal neurogenesis *in vivo* as well as *in vitro*. Keeping the chemotype of the reported Glycogen Synthase Kinase-3 inhibitors in consideration, they may be grouped into natural inhibitors, inorganic metal ions, organo-synthetic, and peptide like inhibitors. On the basis of their mode of binding to the constituent enzyme, they may also be grouped as ATP, nonATP, and allosteric binding sites competitive inhibitors. ATP competitive inhibitors were known earlier inhibitors but they lack efficient selectivity. This led to find the new ways for the enzyme inhibition.



**Contents**



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## 1. Neurodegeneration

Gradual deterioration of structure and function of neurons which includes neuronal death in the central nervous system (CNS), collectively refers the term "neurodegeneration". The occurrence of age related diseases like AD, Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), Progressive supranuclear palsy, Corticobasal degeneration, Creutzfeldt-Jakob disease (CJD), and Pick's disease are likely to increase significantly with the linear inclination of life expectancy and changing population demographics. Worldwide millions of people are reported to fall prey of different types of NDs [1]. Patients fail to remember simple things in its early stages and later become unable to speak, learn new things, and even think rationally [2]. Amyloid-β (Aβ) formation and aggregation of hyperphosphorylated tau are the two concrete causes of ND. Beside this, excess of free radicals and oxidants are also believed to play roles in ND [3,4]. The actual mechanism of the occurrence of such diseases is not fully understood and lacks a successful treatment. In addition, blood–brain barrier (BBB) and blood-cerebrospinal fluid barrier (BSSFB) are the other factors which are associated to the resistant to its treatment. Some of the antineurodegenerative drugs are enlisted below (Figs. 1 and 2).

Among the above mentioned neurodegenerative diseases, AD is the most common pathological subtype of ND which currently affects more than 30 million people worldwide [5], causing a heavy personal loss on the patient and their family.

## 2. Alzheimer's disease

AD is a chronic, multifactorial, personality changing, neurodegenerative disorder which underlies the common cause of dementing cerebral cortex pathology [6,7]. It results in the decline of thinking and judging ability along with the difficulty in remembering new things leading to the loss of independence. About 60–80% cases of dementia patients are having AD. AD is mostly found in the people over 65 years of age. This figure rises rapidly to 40% of those over 85 years of age. The average period of survival is about 9 years after the onset of clinical symptoms. Its risk increases with the age but it is not the part of normal aging. The AD brain may weigh one third less than the normal brain of a person with the same age. The most essential events which are believed to cause AD are senile plaques and neurofibrillary tangles.

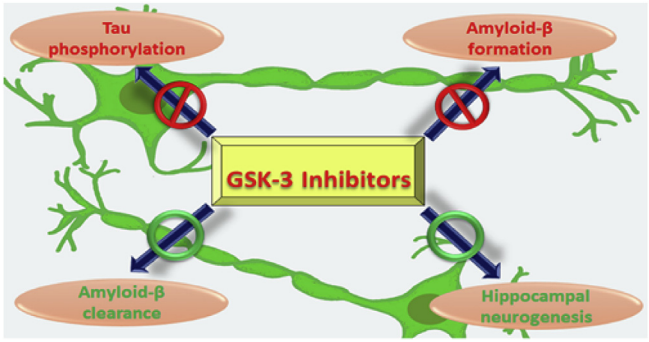


**Fig. 1.** Graphical abstract to represent the major roles of GSK-3 inhibitors.

A transmembrane protein called amyloid precursor protein (APP) on its endoproteolytic cleavage by a series of enzymes like β- and γ-secretase or by metalloprotease enzymes [8] gives birth to oligomers, protofibrils, or other intermediates leading to fibril formation. These misfolded proteins get aggregated extracellularly called Aβ or senile plaques. The Aβ is 93–42 residues long peptide fragment of APP [9]. The membrane-bound fragments of APP are usually Aβ (1–40 residues) and Aβ (1–42 residues), the later being considerably more toxic to neurons and prone to aggregation. Aβ peptide consists of a large hydrophilic N-terminal domain (1–28 residues) and a hydrophobic C-terminal domain (29–40 residues or 29–42 residues). There are six negatively charged residues (Asp1, Glu3, Asp7, Glu11, Glu22, and Asp23) and three positively charged residues (Arg5, Lys16, and Lys28), which results in a net negative charge. The three histidine residues (His6, His13, and His14) have pKa values (of the conjugate acids) close to physiological pH with isoelectric point about 5.5. Tau is a microtubule-associated phosphoprotein mostly found in neuronal axons in the central nervous system (CNS). The abnormal hyperphosphorylation of the tau protein results in its detachment from the microtubule which leads to accumulation and formation of insoluble neurofibrillary tangles (NFTs) [10]. The intracellular aggregation of hyper phosphorylated forms of Tau has 84 putative phosphorylation sites, of which 45 are ser, 35 thr, and 4 tyr [11].

### 2.1. Hypotheses for AD

A series of hypotheses came forth from time to time to explain the causes of AD, among which amyloid cascade hypothesis, metal ion hypothesis, oxidative stress hypothesis, cholinergic hypothesis, familial hypothesis, and GSK-3 hypothesis are of the central importance [12].

Amyloid cascade hypothesis states that when there is increase in accumulation of Aβ with respect to its clearance. Aβ is obtained from the proteolytic cleavage of APP, a transmembrane protein which is found in the outer cell membrane and also in the membrane of cell organelles like mitochondria. A group of secretase enzymes are responsible for the cleavage of APP. In order to maintain a balance between the two in the brain, Aβ is simultaneously cleared by a spectrum of protease enzymes *viz.*, neprilysin, angiotensin-converting enzyme, and matrix metalloprotease-2 and -9 [13]. Any imbalance between these two sets of antagonistic enzymes results in the accumulation of insoluble filamentous aggregates in the extracellular matrix called senile plaques which in turn disturb the normal functioning of the cell and finally lead to cell death.

Metal ion hypothesis asserts that the irregular metal homeostasis especially Zn, Cu, and Fe with Aβ imbalance, is one of the