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Alzheimer's Disease and role of GSK inhibitors

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Abstract

The global prevalence of dementia can be characterized by a progressive deterioration in cognition, function, behavior, considered as a neurodegenerative age-related disorder that can have genetic as well as non-geneticorigin. It can be considered multifactorial as only a limited number of cases supporting genetic theory have been identified. Alzheimer's is a particularly captivating subject because of its number of causes and factors and increasing targets.

Furthermore, the article discusses a few famous hypotheses that are believed for the progress of Alzheimer'sdisease, factors affecting and responsible for the development of this disease. Adding to it pharmacological, non-pharmacological as well as the ayurvedic perspective has been deliberated.

It briefly presents glycogen synthase inhibitors as new targets for AD and explains how it is related to this disease and how it can bring a huge alteration in the treatment of AD by providing appropriate proof and theories supporting the same.

Key words: Alzheimer's, dementia, treatment, risk factors, amyloid, tau, hypothesis, mitochondria, Ayurveda

1. Introduction to Alzheimer and GSK inhibitors

Alzheimer's disease is considered to be the most common cause and most prevailing dementia which escalated up to 44 million population in 2015 and was predicted to be quadruple by 2050. The estimated cost for the treatment of this disease was $172 billion per year also Alzheimer's is particularly fascinating because itattempts to harness the true complexity of pathology and how molecular variation can affect how neurons interact with one another on a grander scale. (1)

Even though there is no certain treatment to cure AD there are treatments that can reduce the progression of disease and worsening of dementia symptoms and the drugs and treatments were decided based on the hypothesis mentioned below in the article also GSK3β inhibitors have been identified as novel targets

since they have shown major effects on pathway leading to AD. Adding to the section non-pharmacological, prophylactic, and Ayurvedic treatments are also discussed with the factors responsible for the development ofthis disease.(2)

The serine/threonine kinase GSK-3, A conserved signaling molecule that is involved in neuroinflammatory cascades interacts with several proteins associated with AD. The data collected categorizes GSK-3 inhibitors asone of the most promising approaches for the upcoming treatment of AD and a reduction of the deviant overactivity of this enzyme might decrease several aspects of the neuronal pathology in AD. In this review, weprovide an overview of the rationale for the growth of GSK-3 inhibitors for the treatment of AD, discussing therisks and benefits of this approach. (3)

2. Understanding Alzheimer's Disease

It is neurodegenerative cognition impairment characterized by loss of memory, language impairment, and problem-solving skills and on the biological level it is understood as loss and damage of neurons and lesseningof cognitive skills Even though the epidemiology of this disease is widely understood there are two main points AD focuses on first, abnormal metabolism of amyloid β and second tau phosphorylation and therefore,

AD may be explained within the following steps Aβ aggregation: Aβ macromolecule initiates the event, triggering downstream toxin mechanisms furthermore because the dysregulation of tau and it's thought-about the key event within the initiation of AD.It may be caused by intrinsic/genetic factors (1% or less) as an example traumatic brain injury, neural reserve,vascular/heart unwellness, lifestyle, or foreign factors like AβPP, PS1/2, degradation/rescue machinery.

1) Tau phosphorylation: Aβ aggregation activates abnormal tau phosphorylation and aggregation and Accumulation of tau primes to loss of perform, that sources nerve fiber transport disruption by tubule disassembly

2) The physiological performance of tau is to reassure the assembly of microtubules and to stabilize them, entailing a neighborhood in cyst transport and Hyperphosphorylated letter of the alphabet is that the main element of Neurofibrillary Tangles in pyramidic neurons and neuropil threads in distal dendrites in AD. (3)

3. Risk factors for Alzheimer’s

3.1 Unmodifiable risk factors

3.1.1 Age:

Age is one amongst the chief risk factors. most of the people with this malady are age sixty-five or older. folks younger than sixty-five can have Alzheimer’s but as age will increase so does the probability of AD. Keeping up with 2020 information, the age of 75-84 has additional chance of obtaining this malady (2.7 million people) outof 5.8 million cases known. Though older age may be a risk issue, Alzheimer’s cannot be thought-about a standard a part of aging, and older age alone isn't spare to cause the malady. (4)

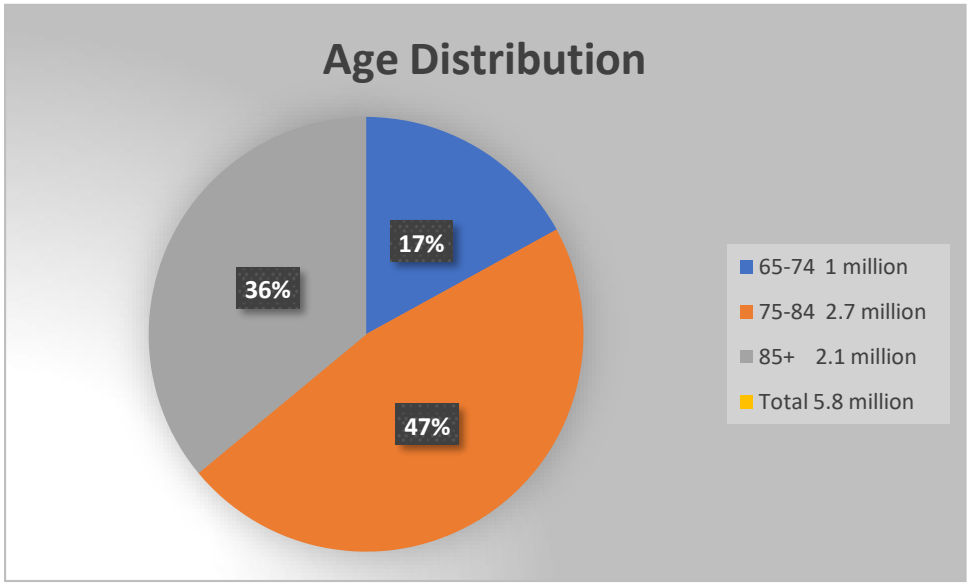

Figure1: Age distribution in Alzheimer's disease

3.1.2 Family history of Alzheimer's

An individual having a brother, sister, or parent with Alzheimer's is more likely to develop these diseases compared to those not having first-degree relatives, and those having more than one first-degree relative areat higher risk. (5)

When diseases run in families or is inherited (genetics), common environmental and lifestyle aspects, or both,may play a role. The amplified risk associated with having a family history of Alzheimer's is not completely explicated through whether the individual has inherited the APOE 34 risk gene.

APOE gene is the gene that provides information for coding APOLIPOPROTIEN E, the protein responsible for packing cholesterol and other fats and transporting them to the bloodstream. Everyone is inherited with eitherof the three genes: ε2, ε3, or ε4 from each of the parent ε3 being the most and ε2 being the least common.

Ones having ε4 are at higher risk of developing AD compared to those who were not inherited. The ones having one copy of ε4 form have a three-fold higher risk of developing AD and individuals having two copy have an 8-12-fold risk of developing the disease but inheriting this gene does not guarantee the development of Alzheimer's. (5)

3.2. Modifiable risk factors

Though there are factors that are not under one's control, there are several factors that can be controlled or
modified to slower the progression of disease or reduce the probability of it occurring.

This includes the factors like cardiovascular disease risk factors like diabetes, mid-life obesity and hypertensionand hyperlipidemia

life style risk factors including alcohol, smoking, diet, physical activity, cognitive training and social

engagement Other factors include years of formal education, traumatic injury, depression and sleep.

3.2.1 Cardiovascular disease risk factors

3.2.1.1 Diabetes

Recent studies and meta-analysis showed that the individuals with Diabetes have a higher risk of development of AD compared to those not having Diabetes. Furthermore, a study suggested that individuals with mild cognitive impairment and Diabetes were more likely to progress dementia compared to individuals with no diabetes and MCI

Some evidence advocates diabetes rises dementia risk not lone through vascular pathways but also throughinteractions of additional biological mechanisms related to diabetes itself. (6)

3.2.1.2. Mid-life obesity

Based on several meta- analyses midlife obesity is associated with increased risk of dementia and recent cohort studies also concluded that being underweight according to age can also be associated with development of dementia (6)

3.2.1.3. Mid- life hypertension

Population with either a history of mid-life hypertension or a existing measurement of hypertension have nearly twofold the danger of emerging vascular dementia compared to people without hypertension. The conclusions of certain theories emphasis the likely benefits of rigorously treating hypertension to prevent vascular dementia. (6)

3.2.1.3. Hyperlipidemia

Five of the eight studies reporting on cognitive decline, cognitive impairment, and MCI found a noteworthy association between the conclusion and Total cholesterol. High Total Cholesterol in late-life was stated to beassociated with a decreased risk of both cognitive decline and cognitive impairment while according to somestudies high amount of cholesterol increased risk of dementia in mid and late life. (5)

3.3. Life style Risk factors

3.3.1 Current Smoking

Certain prospective and longitudinal studies have found strong evidence that people with smoking habits have more risk of developing dementia and cognitive dementia. Quitting smoking may lessen the associated risk to levels compared to those who have not smoked. One study of a large multi-ethnic cohort found heavy smokingin middle-age as much as doubled the risk of later-life dementia. (7)

3.3.2. Physical Activity

According to certain studies individuals who perform physical activity are less prone to have dementia but stillthere is no absolute evidence that the people who perform physical activity does not suffer from dementia.

While a meta-analysis and experimentation show that there is relative evidence between physical activity and dementia. Several randomized controlled experimentations and a Cochrane review of such trials have found that sedentary, but otherwise healthy, seniors who instigate an exercise program experience significantly improved cognitive function. (7)

3.3.3. Diet

Effects of various nutrients as the factor for dementia or development of AD has been a thought-provoking topic because Evidence on the effects of numerous aspects of diet (including various nutrients and vitamins, foods, or food collections) on reducing risk is inadequate and conflicting. Given that many fundamentals of dietare interconnected and interactive, the knowledge of a whole dietary pattern approach has expanded up to some ground. Nevertheless, interpretation is stimulating as dietary pattern often diverges with additional lifestyle factors and with demographic variables that may also have an influence on risk.

For the reference adherence to a Mediterranean diet has been linked with lesser risk of several age-related diseases as well as dementia. Although, narrative reviews have been issued, no systematic review has synthesized studies on the association amongst Mediterranean diet adherence and cognitive function or

dementia. Advanced adherence to Mediterranean diet was associated with improved cognitive function, inferior rates of cognitive decline, and reduced risk of Alzheimer disease in 9 from 12 studies carried out, whereas outcomes for mild cognitive impairment were unpredictable. (8,9)

3.3.4. Alcohol

The studies overpoweringly found that moderate drinking either reduced or had no effect on the risk of dementia or cognitive impairment. Both light and moderate drinking provided a parallel benefit, but heavy drinking was connected with non-significantly higher cognitive risk for dementia as well as cognitive impairment. Although, the analysis carried out with a on group of individuals also indicated that wine was healthier than beer or spirits, this was based on a relatively a smaller number of studies since most studies did not discriminate among these different categories of alcohol. Furthermore, a sum of the studies that did make the distinction reported no difference among the effects of these different types of alcohol.

Some analysis also exhibited that the occurrence of the apolipoprotein E epsilon 4 allele eradicated the benefit of moderate drinking. This was constructed on a relatively smaller number of studies and several other studies have found an advantageous effect of the epsilon e4 allele. Overall, mild to moderate drinking did not appear to impair cognition in younger subjects but actually seemed to diminish the risk of dementia and cognitive deterioration in older focusses. (8,9)

3.3.5 Cognitive training

Individuals with dementia are frequently recommended that 'mental exercise' may be supportive in decelerating memory loss. One of the evaluations that were carried out for a form of mental exercise, whichwas described as cognitive stimulation. There is dependable evidence from abundant trials that cognitive stimulation programs assist cognition in individuals with mild to moderate dementia over and above any medication effects. However, the trials were of inconstant quality with small sample sizes and onlylimited facts of the randomization method were apparent in numerous trials. (10,11)

3.3.6 Social engagement

Social engagement index that is marital status, contacts, new informative performing activities, emotional support, and instrumental support are considered to alleviate cognition decline and there was a review that provides enough evidence to support the hypothesis that an active and socially integrated lifestyle in late life seems to protect against AD and dementia. To date, there is no information to help unscramble whether thesocial, mental, and physical stimulation in late life can decline the lifetime risk of disease or merely delay theonset of dementia. (10,11)

Table 1: Summary of factors

Increases risk	Decreases risk
Traumatic Brain Injury	Years of Formal Education
Mid-life Obesity	Physical Activity
Mid-life Hypertension	Mediterranean Diet
Current Smoking	Cognitive Training
Diabetes	Moderate Alcohol Consumption
History of Depression	Social Engagement
Sleep Distribution	
Hyperlipidemia	

3.4 Other theories and factors

3.4.1. Formal education and cognitive reserve hypothesis

It was determined that people with more years of formal education have lesser tendency to develop dementia and to support the same fact The Cognitive Reserve hypothesis was carried out. The concept of brain reserve or cognitive reserve (CR) refers to the ability to tolerate and maintain the age-related

fluctuations and disease associated pathology in the brain without developing clinical symptoms or signs of disease. It also enlightens the relationship between education, occupational complexity, reading ability, formal education, IQ,dementia and cognitive decline. The reserve is seen to be a consequence of changes in the brain itself, resulting from changes in brain structure and processing. Furthermore, Cognitive Reserve acts through both protective and compensatory mechanisms. Individuals with higher levels of CR will have a lower prevalence and incidence of dementia particularly AD. (12,13)

3.4.2. Traumatic brain injury

There was certain evidence that moderate to severe head injuries may cause late life dementia as it affects thestructure of brain and neuronal network and individuals experiencing repetitive head injuries may be at higherrisk. While it is not known yet which specific aspect of traumatic brain injury (example force, repetitiveness, site of injury) Is responsible for development of dementia. (12,13)

3.4.3. Depression

The association between depression and risk of dementia can be confounded by several factors, such as sociodemographic factors (including age, gender, education) and cognitive, functional performance, and biological status (e.g., health status, vascular risk factors, ApoE genotype, hippocampal volume, white matter lesions). Also, recent cohort study came to a conclusion that depressive indications are independently associated with cognitive decline. (14,15,16)

3.4.4. Sleep

Although there is no strong evidence on what duration of sleep or nature of sleep are contributing to the development of AD A recent study recommended that treatment for breathing disorders that occur during sleep—precisely with continuous positive airway pressure (CPAP) may reduce the risk of cognitive decline. Consistent with this hypothesis, the presence of Sleep Disordered Breathing was connected with an earlier age at cognitive decline. Other conclusions in CPAP+ participants propose that CPAP treatment of SDB may delay progression of cognitive impairment. (14,15,16)

4. Hypothesis used for development of treatments

Several hypotheses have been considered as the basis of developing treatments for AD and some of them are listed below

i) Amyloid cascade hypothesis
ii) Cholinergic hypothesis
iii) Dendritic hypothesis
iv) Mitochondrial cascade hypothesis
v) Metabolic hypothesis
vi) Other hypotheses (oxidative stress, neuroinflammation).

4.1 Amyloid Cascade hypothesis

The amyloid cascade hypothesis is suggesting that the formation, aggregation and deposition of Aβ peptides specifically Aβ (1-40) is primary event in AD pathogenesis. This Aβ is obtained when APP is cleaved in to smaller fragments by β-secretase 1 (BACE) and catabolized by the α-secretase to produce a soluble APPα fragment(sAPP), which remains in the extracellular space and is considered as a fundamental transmembrane protein (found in glial cells and neurons). BACE fragments APP into soluble APPβ and 99 amino acid membrane bound fraction(C99) and additional fragmentation of this C99 by γ-secretase consequences in the generation of either Aβ (1-40) or Aβ (1-42) peptides.

The APPα fragment so formed is involved in the regulation of neuronal excitability, improves synaptic plasticity, learning, and memory, and increases neuronal resistance to oxidative and metabolic stresses. While another fragment Aβ peptides may lead to synaptic loss, decrease neuronal plasticity, alter energy metabolism, induce oxidative stress and mitochondrial dysfunction, and may provoke disruptions in cellular calcium homeostasis and also triggers neurotoxicity and neurodegeneration as excessive extracellular Aβ may also presumably lead to increased Tau phosphorylation and the formation of neurofibrillary tangles. Molecular genetics studies into the mechanisms of FAD gave credibility to studied

hypothesis that suggested potential novel therapeutics for example inhibitors of β- and γ- secretase or enhancers of α-secretase activityand the principal targets and clinical trials of the compounds aimed at reducing Aβ formation and plaques aresummarized in Table 2. (17,18,19,20)

Table 2: treatments focused on amyloid hypothesis

Activity	Compound	Clinical trail	Mechanism
Inhibitors of β-secretase	(i) E2609 (ii) MK-8931 (iii) LY2886721	(i) NCT01600859 (ii) NCT01739348 (iii) NCT01807026 and NCT01561430	Beta enzyme one (BACE1) work by Inhibiting BACE1 which can limit the assembly of and end in decrease of production of toxinfibrils and plaques.
Inhibitors and modulators of γ-secretase	(i) Semagacestat (LY450139) (ii) Avagacestat	(i) NCT00762411, NCT01035138, and NCT00762411 (ii) NCT00810147, NCT00890890, NCT00810147, NCT01079819	γ-Secretase was originally known because the proteolytic enzyme accountable for the generation of Aβ and cleavage and thus its inhibition and modulation may be thought-about as a target
Selective γ-secretase modulators (SGSM)	(i) Ibuprofen, sulindac, indomethacin, and R- flurbiprofen (Tarenflurbil) (ii) NIC5-15	NCT00322036, NCT00105547	compounds noted as γ-secretase modulators (GSMs) does not only inhibit γ-secretase, but modulate γ-secretase progressively and thereby shift the profile of the following secreted amyloid β peptides (Aβ) that are produced.
Inhibitors of Aβ aggregation	(i) Glycosaminoglycans 3- amino acid, 1- propanesulfonic synthetic (3APS, Alzhemed, tramiprosate) (ii) Colostrinin (iii) Scyllo-inositol compound (ELND005) (iv) PBT1 (clioquinol) andPBT2	i) Phase III in 2007 ii) Granted iii) Granted in 2015 (US FDA status inactive) iv) Planned phase III trial of PBT1	The assembly of present amyloid peptides into cytotoxic oligomeric and fibrillar aggregates is believed to be a big pathologic and thus these inhibitors block or interferes with the aggregation of amyloid peptides like amyloid-β (Aβ) exploitation very little organic molecules, peptides, peptidomimetics, and nanoparticles

		was been abandoned and PBT2 requires larger group studies.	
Modulation of β-amyloid transport from the brain to the peripheral circulation	(i) PF-0449470052 (ii) (ii) TTP4000 (NCT01548430)	(i) Phase II (ii) Phase I (February 2013)	The continuous removal of Aß species from the brain bytransport across the BBB and/or metabolism is crucial to forestall their probably toxin accumulations in brain.

4.2 The cholinergic hypothesis

Cholinergic neurons that are found on the septum and the vertical limb of the diagonal band project mainly to the hippocampus that is the main brain region involved in memory processing, is influenced by cholinergic modulation. Degeneration of cholinergic neurons in the nucleus basalis of Meynert and the loss of cholinergic inputs to the neocortex and hippocampus. Several studies reported decreases in choline acetyltransferase (ChAT), acetylcholine (ACh) release, as well as reductions in nicotinic and muscarinic receptors in the cerebral cortex and hippocampus of post-mortem AD brains. Acetylcholinesterase inhibitors (AChEI), one amongstthe sole 2 classes of medicine presently approved for treatment. They act by increasing neurotransmitter bioavailability at the colligation or by reducing the break down of Ach by inhibitingneurotransmitter breakdown and resulting in accumulation of constant to extend the amount of Ach.

But none of the studies carried out are able to prove that they are capable of reversing the course of AD or even decelerate the rate of disease progression. The entire therapy including this class is palliative but works as disease modifying compound.

The compounds so far discovered are Ladostigil (TV3326) which is individually a reversible inhibitor of AChE and is a selective and irreversible inhibitor of brain monoamine oxidases A and B, the usage is known to improve extrapyramidal symptoms additionally providing antidepressant effect. It also gives the impression to be a potent antiapoptotic, antioxidant, anti-inflammatory, and neuroprotective agent. NCT01429623 and also NCT01354691 phase 2 trials with ladostigil are on way to get to market. (17,18,19,20)

4.3 The Dendritic hypothesis

Dendritic abnormalities appear in the relatively early stages of AD and dystrophic neurites, alleviated dendriticcomplexity, and dendritic spine damage are all documented. Some studies propose that soluble Aβ oligomers are the principal neurotoxic species accountable for dendritic pathology. (21,22)

Aβ oligomers may source deviant N-methyl-D-aspartate receptor (NMDAR) activation post-synaptically by forming complexes with the cell-surface prion protein (PrPC). PrPC is augmented at the neuronal postsynapticdensity, where it interrelates with Fyn tyrosine kinase-metabotropic glutamate receptor 5 complex (FynmGluR5). Fyn activation arises when Aβ is bound to PrPCFyn-mGluR5 complex. Triggered in this way, Fyn can result into tyrosine phosphorylation of the NR2B subunit of this NMDAR which results in

preliminary increase and then a loss of cell-surface NMDARs. According to a data Fyn overexpression accelerated synapseloss and the onset of cognitive impairment. In addition, Fyn can also contribute to Tau hyperphosphorylation.Moreover, Fyn was shown to phosphorylate Tau at Tyr18 residue.

Saracatinib (AZD0530) and masitinib (AB1010) are Fyn kinase inhibitors were in phase II and phase III clinical trials for mild-to-moderate AD (NCT01864655, NCT02167256, NCT00976118, NCT01872598) in 2016. These compounds were capable of blocking Fyn in a nanomolar range. In an NCT00976118 clinical trial, oral masitinibwas administered for a period of 24 weeks, concomitantly with one of the AChEIs (donepezil, rivastigmine, or galantamine) and/or memantine. In that study, a significant improvement in the ADAS-Cog test response was reported. (21,22)

4.4 Mitochondrial cascade hypothesis

It was studied that mitochondrial dysfunction could potentially yield Alzheimer-related molecular phenomenafor example increased oxidative stress markers. Additionally, other studies already proved mitochondrial dysfunction affects tau phosphorylation and can induce inflammation.

The mitochondrial hypothesis was proposed back then in 2004 and was divided into 3 parts and assumptions

i) The mitochondrial cascade hypothesis preserves gene inheritance describes an individual's baseline mitochondrial function. In this respect, together mothers and fathers contribute to their offspring's Alzheimer's risk, but because mitochondrial DNA (mtDNA) is maternally inherited mothers contribute more.

ii) Inherited and ecological factors regulate the proportion at which age-associated mitochondrial changes progress and manifest. According to some studies declining mitochondrial function or effectiveness drives aging phenotypes, then greater mitochondrial durability should associate with slower brain aging and lesser mitochondrial durability should assist with faster brain aging.

iii) An individual's baseline mitochondrial function and functional change rate impact their Alzheimer's chronology. Those having low baseline function and high rates of mitochondrialdecline would develop symptoms and Alzheimer's histology variations at younger ages thanthose with high baseline function and slow rates of mitochondrial decline. Those with less extreme combinations, for instance, those with lower baseline function and slower rates of
mitochondrial decline, or with high baseline function and fast rates of mitochondrial decline, will progress symptoms and Alzheimer's histology changes at intermediate ages.

Also, Oxidative mitochondrial DNA, RNA, lipid, and protein damage intensifies ROS production and activatesthree events:

i) A reorganized response in which cells respond to raised ROS by generating the beta-sheet protein,beta-amyloid, which further bothers mitochondrial function,

ii) An elimination response in which compromised cells are eliminated via PCD mechanisms, and

iii) A replace response in which neuronal forerunners unsuccessfully attempt to re-enter the cell cycle, with succeeding aneuploidy, tau phosphorylation, and neurofibrillary tangle formation.

Besides defining a role for aging in AD pathogenesis, the mitochondrial cascade hypothesis also permits andaccounts for histopathologic overlap amid the sporadic, late-onset, and autosomal dominant, early-onset forms of AD. (21,221

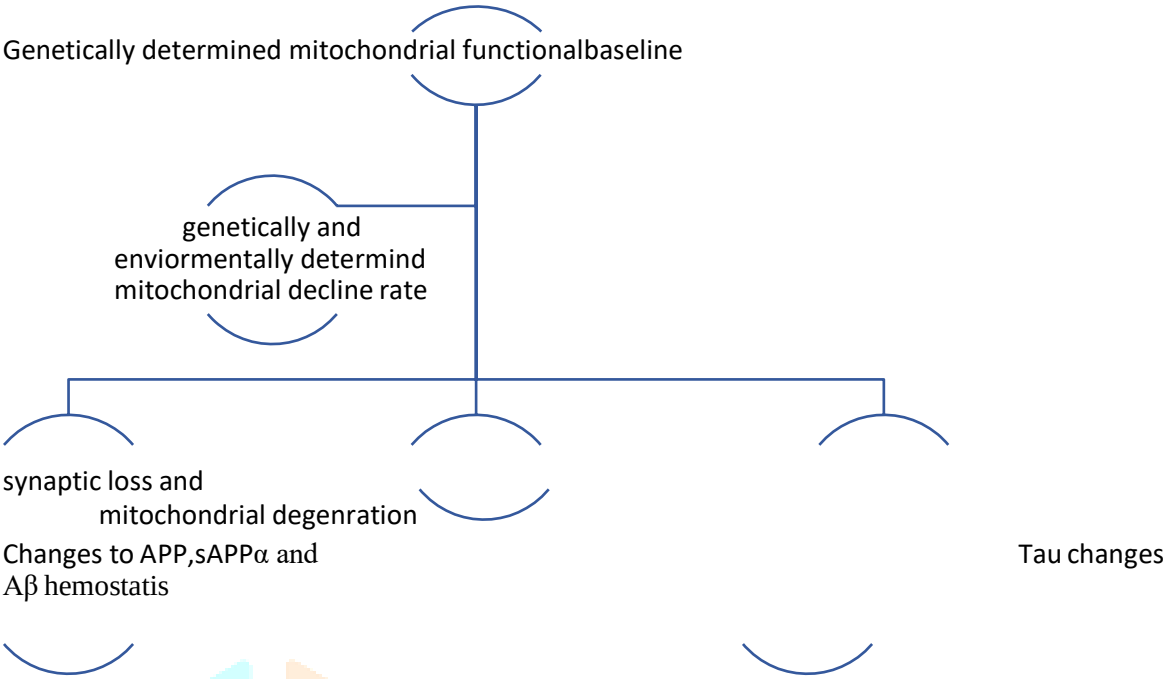

Figure 3: Mitochondrial hypothesis (21,22)

The Metabolism Hypothesis

The perception of central insulin resistance and dysfunctional insulin signaling in Alzheimer's disease (AD) hasbeen established by Siegfried Hoyer in 1985-2000. It is extensively recognized that a Cerebro-metabolic deficiency is one of the most pertinent characteristics of sporadic AD, with functional deficits in oxidative glucose breakdown, oxidative stress, and intensifying the action of glucocorticoids in the brain. Insulin receptors and insulin are widely distributed in the brain and are diminished in the post-mortem Alzheimer's brain.Functionally, transformed insulin signaling may promote synaptic dysfunction and impaired connectivity, especially in highly connected and metabolically active regions of the brain, which in turn inclines towards AD pathology. Thus, the hypothesis has been proposed that defects in the brain insulin signal transduction system and associated consequences, e.g., oxidative stress, are centrally involved in the etiopathogenesis of sporadic AD. (21,22)

5. Treatments

The existing AD treatment standard is one of multifaceted management of symptoms aimed at retaining the quality of life, modifying the burden of illness, and reducing long-term clinical decline. Successful long-term pharmacotherapy with FDA-approved AD medications, primarily including monotherapy with a cholinesterase inhibitor (ChEI) and ultimately involving add-on dual-combination treatment with a ChEI and memantine,requires emerging, executing, and satisfying a solid foundation of psychoeducation, nonpharmacological and behavioral care strategies, and clarity in care goals and expectations. (23,24)

Treatment of AD is not curative and successful management to mitigate the burden of illness relies on three basic pillars:

(1) timely and accurate syndromic and etiological diagnoses combined with proactive educationaland care planning that is customized to the patient-caregiver dyad (the dyad)– without accurate diagnosis and tailored psychoeducation, appropriate dyad-cantered treatment, and care can’t be provided;

(2) nonpharmacological interventions and behavioral approaches and pharmacological interventions

(3) holistic care planning that is proactive, pragmatic and dynamic, and includes monitoring and adjustment of the care plan according to the dyad’s goals, capacity, condition, and resources. (23,24)

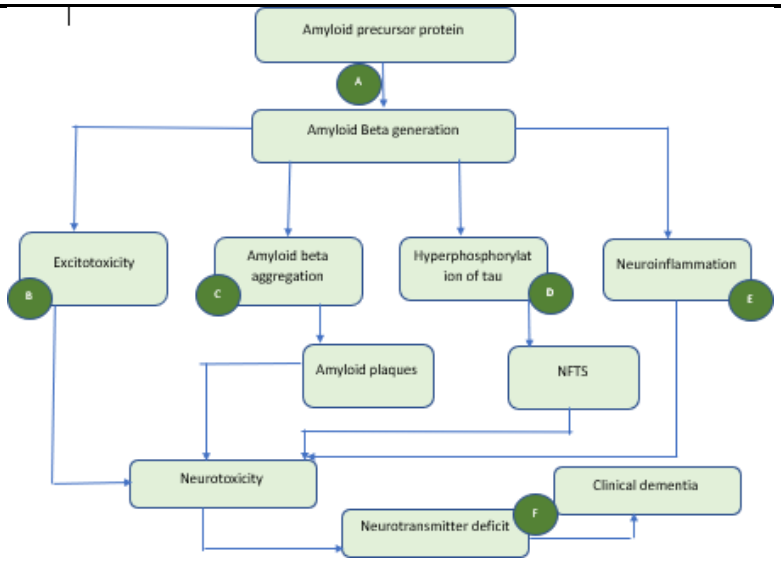

Figure 2: 1. Etiology of Alzheimer's disease with therapeutic targets. A is secretase enzyme inhibitors;B is NMDA receptor modulators, eg memantine; C is immunotherapy, including immunization and direct anti-amyloid therapy, including monoclonal antibodies; D is anti-tau therapy; E is anti-inflammatory treatments, including NSAIDs; F is anticholinesterase inhibitors, eg donepezil. (23,24)

5.1 Pharmacological Management

The current AD medication treatment paradigm is to reduce the progression of symptoms and disability; expectations are for pharmacological treatments to unassumingly retard expected clinical deterioration in ways that are nonetheless meaningful. Despite ongoing efforts, a magic bullet or “cure” for AD in the dementiastages is impractical shortly; by the time Alzheimer’s is in the dementia stages, degeneration has wrought multilevel brain destruction for one or more decades. Combined, nonpharmacologic and pharmacologic management in AD seeks to minimize the incapacitating effects of cognitive and functional decline and emergence and severity of BPSD. The FDA-approved AD medications, the ChEI’s donepezil, galantamine, and rivastigmine, and the N-methyl-d-aspartate (NMDA) antagonist memantine, can reduce the progression of clinical symptoms and disability. From a public health and economics perspective, therapies that minimize caregiver burden.

Approved symptomatic treatment

- Donepezil (AChEI)
- Galantamine (AChEI)
- Rivastigmine (AChEI)
- Memantine (NMDA receptor antagonist)
- Donepezil+memantine combination

Combination with disease-modifying therapy

Combination with symptomatic therapy

Target Agents Agents

Amyloid cascade

hibitors 5-HT receptor Antagonist

oclonal antibody MOA B inhibitors

3) Aβ vaccine Anti-convulsant

Melatonin and serotonin receptor

Tau aggregates

1) Tau active immunization agonist

ssive immunization glutamate modulator

Other sine kinase inhibitor
inhibitor
3) Anti-inflammatory
4) Angiotensin II receptor antagonist
5) Src/abl kinase family inhibitor 6)GM-CSF
7) Vitamin B3
8) 11 β hydroxysteroid dehydrogenase inhibitor
9) Sigma 1 chaperone agonist10) Deep brain stimulation
11) rTMS
12) Sigma 2 receptor ligand
13) PPARδ/γ agonist
14) Microtubule stabilizer

Figure 4: Approved pharmacological treatment

5.2 Non-pharmacological treatment

Nonpharmacological treatments are significant for the anticipation of AD or as adjuvants in other treatments.AD prevention approaches can be divided into two groups, the first associated with lifestyle and the second with diet and chemical compounds.

Lifestyle approaches include physical activity, mental challenges, energy restriction, and socialization as preventive factors in AD. Physical activity such as aerobic exercise was linked with the reduction of AD deficits in a cohort study. The exercise was testified to improve hippocampal neurogenesis andlearning in aging rodents.

The three mechanisms projected to clarify the exercise neuroprotective effect of exercise are:

(1) the release ofneurotrophic factors like BDNF and insulin-like growth factor (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) from neurons in synaptic activity, that arouses neurogenesis and synaptic neural plasticity through the stimulation of CREB transcription factor;

(2) the decrease of free radicals in the hippocampus and also the increase in superoxide dismutase and endothelial nitric oxide synthase

(3) peripheral signals that support the necessity of active neuronal networks such as BDNF release with to energy restriction on the brain. Socialization is important to mental and physical human development and a lack thereof induces loneliness, which has been associated with various diseases such as depression, alcohol abuse, obesity, diabetes, hypertension, AD, and cancer. (25,26)

5.2.1 Prophylactic treatment

5.2.1.1 Diet and Chemical Substances.

The following are the dietary supplements: vitamins B6, B12, folates, and E, C, and D vitamins. Vitamin B studies produced mixed results. It has been projected that folic acid has neuroprotective activity through an epigenetic mechanism that prevents amyloid-β peptide accumulation. Studies and experiments on Vitamin Eand C did not show any significant results. Furthermore, vitamin D supplementation did show improvement in cognitive performance. Regarding the intake of chemical substances, the outcomes in alcohol studies did show an association between the prevention of AD with small levels of red wine consumption due to its polyphenol's composition while the increased level of alcohol showed the risk of developing AD. Different molecules had their effect on neuroprotective function including glucosamine, omegas 3 and 6 which persuades interleukins or prostaglandins for inflammatory responses, and antioxidants such as β-carotene and lycopene 6.

Consumption of plant-related products such as flavonoids, alkaloids, or terpenoids. Flavonoids are considered safe and their neuroprotection was established in 90 people treated with flavanol.

Flavonoids inhibit acetylcholinesterase and enhance memory with constraining glutamate release. Resveratrol, A polyphenol found in various plants, especially berries, peanuts, and red grapes, as well as in redwine. Shows numerous biological activities such as antioxidant, anti-inflammatory, phytoestrogen, vasodilator, cardioprotective, and anticarcinogenic activities, establishing it as a molecule having therapeutic potential in neurodegenerative diseases such as AD. It has also been established that initiation of SIRT1 stimulated by resveratrol reduced NF-κB signaling pathway activation in glial cells exposed to Aβ.

Another flavonoid is luteolin which has been defined to exhibit significant action in Alzheimer's inhibition

linked with its antioxidant, anti-inflammatory, and microglia-inhibiting effects along with improved spatial memory. (27,28,29,30,31,32)

5.2.1.2 Diet

The Mediterranean diet may advance neuroprotection as it is based on condensed intake of saturated fatty acids, but has amplified consumption of unsaturated fatty acids with vegetables, fruits, legumes, olive oil, fish along with polyphenols such as oleuropein aglycone (OLE), which inhibit with amyloid aggregation, and lessenthe LDL cholesterol levels. The monosaturated fatty acids are defined to have antioxidant and anti- inflammatory effects, as well as endothelial function improvement and condensed cognitive decline, while polysaturated fatty acids are important in neuronal membrane integrity and function.

Omega 3 might affect the inflammatory procedure, nerve membranes neuroplasticity, andsynaptic transmission. Asiatic diet includes alleviated levels of green tea consumption with or without antioxidant curcumin with dietary addition Gingko Biloba, well-thought as a protector in contradiction of memory deterioration due to its antioxidant effect and the decline of Aβ aggregation.

Moreover, the western diet has more consumption of sugar and animal products, with a progressive content of saturated fats, which negatively affect cognitive function, Aβ-deposition, and oxidative stress. OLE is animportant compound with neuroprotective effects as it interferes with amylin, tau, and Aβ peptide aggregation and toxicity and has activities such as cardioprotective, antioxidant, anticancer, antimicrobial, andantiviral effects; also avoids low-density lipoprotein oxidation and platelet aggregation. (33,34,35,36,37,38,39,40)

5.2.1.3 Probiotics

The intake of probiotics causes alleviation of the proinflammatory cytokines associated with gut microbiota which changes during aging. Probiotics administration in the elderly may improve gut health and improvement anti-inflammatory activity. Furthermore, the valuable effects of probiotics in AD have been connected with their production of metabolites by fermentation, for example, short-chain fatty acids (SCFAs) such as propionic and butyric acids.

A recent study described a neuroprotective effect of Clostridium butyricum which re- established brain levels of butyrate in a mouse model of vascular dementia. Probiotics upsurge intestinalbarrier integrity by activation of epithelial cells shielding against pathogen. Additionally, preceding work showed downregulation of TNF-α levels and growth in IL-10 production resulting from the administration of Lactobacillus rhamnoses. It is a significant note that the intake of probiotics, such as Lactobacillus Plantarum, may also bring behavioral changes, through monoamine neurotransmitter augmentation. (33,34,35,36,37,38,39,40)

Table 4: Summary of factors responsible for developing AD

Increases risk	Decreases risk
Traumatic Brain Injury	Years of Formal Education
Mid-life Obesity	Physical Activity
Mid-life Hypertension	Mediterranean Diet
Current Smoking	Cognitive Training
Diabetes	Moderate Alcohol Consumption
History of Depression	Social Engagement
Sleep Distribution	
Hyperlipidaemia	

5.3. Ayurvedic treatment of Alzheimer's

Ayurvedic Holistic approach for Management of Brain Disorders In Ayurveda, the general line of treatment of mental disorders is

(i) Nonpharmacological: Daivavyapashraya Chikitsa (spiritual healing or mantra therapy) and Satvavajaya Chikitsa (psychotherapy/counseling/yoga/meditation),

(ii) Pharmacological: Yuktivyapashraya Chikitsa (rationale therapy/ medicinal treatment). (40,41)

5.3.1.Botanicals for treatment of AD

Many of the plants have antioxidant and anti-inflammatory properties as well as exhibit Antiamyloid aggregation effect. Furthermore, they have tendency to improve ACh levels or limit AChE within the brain, which can help in the treatment of AD and other neurological disorders. Traditional plants and their phytoconstituents effective in AD are listed below. (40,41)

Ayurvedic herb	Scientific name	Commonname	Part used	Active constituents	Possible mechanism of action	Reference
Shankhapushpi	ConvuvulusPluricaulis (Convolvulaceae)	Morning glory, Bindweed	Wholeplant	Tri terpenoids, Glycosides, anthocyanins	Anti-dementia, AChE inhibition, Nootropic	72,73
Guggulu	Commiphorawhighitti (Burseraceae)	Guggul	Resin	Guggulsterones, Manusumbionic Acid	Anti-dementia AChE inhibiton, Nootropic	74
Ardraka	Zingiber officinale (Zingiberaccae)	Zinger	Rhizome	Zingerone(4-(4-hydroxy-3-methoxypheyl)-2-butanone)	Improves recall, RetentionAnd Acquisition	75
Amalaki	Emblica Officinalis (Phyllanthaceae)	Amla, Indian gooseberry	Fruit	Tannins, Phyllembelin, Pectins, Vitamin C Antioxidant	Antioxidant improves amnesia and memory deficits	76
Ashwagandha	Withania somnifera (Solanaceae)	Indian ginseng, poison gooseberry, or winter cherry	Roots	Sitoindoside IX, Sitoindoside X, Withanolides, withanol	Antiinflammatory y, antioxidant, Aβinhibition, AChE inhibition, regenerate s damaged axons, dendrites, and synapses	77
Brahmi	Bacopa monniera (Scorphularaceae)	Brahmi, water hyssop, Indian pennywort	Leaves and roots	Bacoside A	Antioxidant, nootropic, cognitive enhancer	78
Guduchi	Tinospora cordifolia (Menisperma ceae)	Giloy	Stem	Tinosporine, Tinosporide, Giloin, Magnoflorine	Antioxidant, antipsychoti c, neuroprote ctive, Nootropic, ACh synthesis	79
Haridra	Curcuma longa (liliacea)	Common Turmeric	Rhizome or root	Curcumin	Antiamyloidoge nic, antiinflammator y, anti-ChE, anti-βsecretase	80
Shigru	Moringa oleifera (Moringaceae)	Drum stick plant	Leaf	9- octadecenoicacid	Antioxidant, modify levels of monoamine s such as norepinephrine, dopamine serotonin	81
Jatamansi	Nardostachys jatamansi (Valirenaceae)	Spikenard	Dried rhizomeand root	Jatamansic acid, Jatamansone, valeranone	Improves stress-induced memory deficit and amnesia	82
Kumkum	Crocus sativus(Liliaceae)	Saffron	Dried stigma	Safranal	Inhibits impairment of hippocampal	83

					synaptic plasticity and fibrillogenesis	
Shatavari	Asparagus racemosus(Liliaceae)	Water roof,wild carrot, shatavari	Freshtuber	Asparagine,shatavarin	Antioxidant, Inhibiting MAO -A and MAO-B	84
Yasthimadhu	Glycyrrhiza glabra (Fabaceae)	Licorice, Liquorice	Root	Glycyrrhizin, 2,2',4'-Trihydroxychalcone	Neuroprote ctive, antiinflammator y,	85

6.Introduction to GSK inhibitors

Glycogen synthase kinase-3 (GSK-3) is an extremely conserved protein-serine/threonine kinase that was initially isolated from skeletal muscle in 1980 as one of five enzymes capable of phosphorylating glycogen synthase. It was then demonstrated that insulin triggers the inactivation of this kinase. In mammals, GSK-3 is encoded by two highly related genes encoding GSK-3α and GSK-3β. In the brain, GSK-3β controls many crucial cellular processes, acting as a key switch that controls numerous signaling pathways.

In vitro studies propose that GSK-3β affects PS1 function, which is required for the generation of the toxic Aβ. The expression level and activity of BACE1 be elevated in AD patients. Accordingly, GSK3β inhibition decreases the rate of BACE1-mediated cleavage of APP through a NF-κB signaling-mediated mechanism. The observation above suggests that by inhibiting GSK-3β activity leads to reduction in Aβ pathology. A feed-forward loop was established after GSK-3β pathological activation by Aβ, which afterwards contributes to abnormal APP processing and to synaptic failure. Consistent with this, GSK-3βinhibition has been shown to decrease Aβ production in AD murine models and to lessen Aβ-induced neurotoxicity in cultured neurons.

The three tau kinases, GSK-3β, CDK-5, and PKA, associated with both tau and microtubules. It has been studied that there is direct relation of tau and GSK inhibitors functionally. GSK-3β phosphorylates at least 36 residues in tau and the main phosphorylation sites identified for this kinase are Ser199, Thr231, Ser396, and Ser413. A reasonable phosphorylation of Ser46, Thr50, and Ser202/Thr205 has been reported. In the pre-tangle stage of AD, scattered deposits of phosphoThr231-tau are professed in the brains of patients. Unlike all other residues of tau protein Thr123 needs a combined action of CDK5 and GSK-3β. This phosphorylation reduces tau binding to microtubules. Ser404 and other residues work with the same mechanism. Thus, the combined action of CDK-5 and GSK-3β seems to be required for the development of the epitope characteristics of PHFtau.
Increasing evidence stipulates that hyperphosphorylated tau triggers GSK-3β through a surge in oxidative stress, neuroinflammation, and apoptosis. Additionally, GSK-3β impairs lysosomal acidification that is a progression that entails an inadequate clearance of non-functional proteins. Moreover, establishing normal levels of GSK-3β activity reverses spatial memory deficits, reduces tauhyperphosphorylation, and decreases reactive gliosis and neuronal death.

6.1. NEURAL CONSEQUENCES OF THE DYSREGULATION OF GSK-3β ACTIVITY

6.1.1 CHOLINERGIC SYSTEM ALTERATION

Loss of cholinergic neurons in certain cortical areas like basal forebrain and hippocampus is a well-known feature of AD brain. It has been projected that GSK-3β plays a key role in choline metabolism, which involves the regulation of choline acetyltransferase (ChAT) and acetylcholinesterase. Correlating it witha transient decrease in Ser9 phosphorylation of GSK-3β and an associated increase in tau phosphorylation. Also, cholinergic stimulation in the hippocampus, striatum, and cortex causes a swift increase in Ser9 phosphorylation of GSK-3β. (48,49,50,51,52)

6.1.2 AXONAL TRANSPORT AND MICROTUBULE DYNAMICS IMPAIRMENT

GSK-3β having the dimensions to phosphorylate several Maps and regulate axonal stability through direct interaction with microtubules and its phosphorylated forms of tau and MAP-2 exhibit condensed affinity toward microtubules and are less stable and this microtubule destabilization is unfavourable for the maintenance of axonal structure and appropriate synapse function. Importantly, Aβ plaques can lead to axonal dystrophy, causing profound impairment of axonal transport, great detriment to cognitive function, extensive synapse loss, and cell death. (48,49,50,51,52)

Additionally, GSK-3β is involved in axon formation and elongation. With the same context they impair mitochondrial anterograde and retrograde axonal transport in vitro, a procedure involving tau and MAP-1B, respectively, and the alterations seem to have severe consequences on function of synapse function resulting in energy depletion and in Accordance with that tau overexpression seems to disrupts axonal transport which causes vesicular aggregation known as a phenomenon that is overturned by GSK-3β inhibitors. Additionally, PS1 regulates kinesin-related axonal transport by a mechanism involving GSK-3β activity and the modulation of its role in controlling kinesin binding to microtubules at sites of vesicle release. (48,49,50,51,52)

6.1.3 APOPTOSIS

GSK-3β promotes both pro-and anti-apoptotic effects and hence it seems to regulate the two major apoptotic pathways: intrinsic and extrinsic. GSK-3β triggers cell death through the activation of the mitochondrial intrinsic pro-apoptotic pathway while it inhibits the death receptor-mediated extrinsic apoptotic pathway. As a part of pro-apoptotic cascade, GSK-3β phosphorylates and inhibits eIF2B . A murine model of neuronal showed that GSK-3β overexpression lead to apoptosis in certain sensitive areas of the brain such as the hippocampal formation, which is vital for memory and learning and strongly affected in AD. The elaborative mechanism by which GSK-3β over expression is inducing apoptosis is not known yet but by given regulation on how it functions extrinsically we should consider that the kinase mentioned plays a crucial role and modulates 2 major pathways of apoptosis in opposite direction to eachother. Later explaining how inhibition of GSK-3β delivers protection from intrinsically acting apoptotic signalling but also potentiates extrinsic apoptosis. (53,54,55,56,57,58)

6.1.4 SYNAPTIC EFFECTS

The use of GSK-3β inhibitors guards' synapses from the deleterious effects of Aβ, suggesting that GSK-3β activation is compulsory for the pathological effect of Aβ on synaptic plasticity. GSK-3β is a significant positive regulator of the inflammatory process. Within the brain, microglial cells are measured to be equivalent to macrophages in the periphery and key guardian immune cells. Numerous stressors trigger microglia, leading to a chronic inflammatory response and migration of responsive cells from the periphery. All through long-term inflammatory responses, chronically activated (primed) glia seem to be detrimental to neuronal function and survival recognizing GSK as prominent regulator of inflammation. GSK-3β also promotes the production of some proinflammatory cytokines including interleukin-6 (IL-6)/ IL-1β, and also tumor necrosis factor.
Data from a group showed that GSK-3β overexpression in neurons lead to the appearance of a unique pattern of cytokines in the brain in vivo. (53,54,55,56,57,58)

6.1.5 CELL CYCLE DYSREGULATION

Recent evidence specifies that molecular mechanisms regulating synaptic plasticity and cell cycle are shared inthe same cells, and, therefore, attempts to increase plasticity during initial stages of AD are sometimes devastating for hippocampal function. At the molecular level, the Sonic hedgehog (Shh) and Wnt signaling pathways collaborate to orchestrate cellular proliferation, differentiation, and pattern formation during both development and adult neurogenesis. ADULT HIPPOCAMPAL NEUROGENESIS says new neurons are uninterruptedly added to the hippocampal dentate gyrus (DG) throughout lifetime rough differentiation stages, new-born neurons sequentially surge their dendritic tree complexity and send axons toward the CA3 region. Rising evidence indicates that new born neurons are crucial for hippocampal function and hippocampal-dependent memory and one of the most important regulators of adult hippocampal neurogenesis (AHN) is GSK-3B and it has been demonstrated that overexpression of this kinase impairs adult neurogenesis and cause a depletion in the number of proliferative clusters within the hippocampal DG. It has been observed that GSK-3B overexpression leads to modifications in the rate of death and survival of new born neurons, as well as in the expression pattern of the immature neuron marker doublecortin. (59)

6.2. Some GSK3β inhibitors

6.2.1 Lithium

Lithium was the first "natural" GSK-3 inhibitor discovered. Lithium (meaning lithium salts) is a mood stabilizer long used in treatment of bipolar disorders and is known to inhibits GSK-3 directly by competition with magnesium ions and circuitously via enhanced serine phosphorylation and autoregulation.Treatment with lithium increases cellular β catenin levels, reduces tau phosphorylation at GSK-3 epitopesin neurons which activates glycogen synthase, and promotes embryonic axis duplication. (60,61,62)
Some GSK 3β inhibitors are listed below in table

Table 6: Introduction to some GSK 3β inhibitors with mechanism and status

Type	Source	Inhibitor	Biological activity in AD	Inhibitionpotency	Drug developmentphase
Cations	Inorganicatom	Lithium	Mood stabilizer Neuroprotection Tau phospholyration Aß aggregation inhibition	2 mM	Conducting results
ATP Competitive	Marine organism	1.Indirubins	Neuroprotection Axon formation Maintain pluripotency Reduced tau phosphrylation	5-50 mM	Pre- clinical
		2.hymenialdisine	tau phosphorylation Neuroprotection	10 nM	Pre-clinical
		3. meridianines	tau phosphorylation		----------
ATP competitive	Organic synthesis	1.Paullones	Neuroprotection Reduced Aß aggregation Reduced tau phosphrylation	4-80 nM	Pre-clinical
Non-ATP competitives	Organic synthesis	Thiadiazolidindiones TDZD 8 NP00111	Neuroprotection Reduced Aß aggregation Reduces tau phosphrylation Beta amyloid and gliosis invivoAffects locomotor activity Promotes tissue recovery from spinal cord injury	2ùM	PhaseII

6.3 GSK-3 INHIBITORS AS DRUGS FOR AD: Risk versus Benefit

GSK 3β have proved efficacy in several animals' models effecting increased learning ability, decreased neuronal loss, amyloid plaque loading and tau hyperphosphorylation, the biological responses obtained in different animal models after GSK-3 inhibitors treatment are truly relevant for AD pathology. Indeed, if these benefits might be translated to human patients, an important disease modifying effect would be produced after treatment with GSK-3 inhibitors. However, typically, there are two major concerns for the clinical use of GSK-3 inhibitors for chronic treatments such as that required for AD.

(i) since GSK-3 plays important roles in so many tissues, the risk of severe side effects is present. (ii)Chronic inhibition of GSK-3 might also lead to activation of targets that are proliferative such as certain transcription factors and β-catenin which is a human oncogene.(63)

Fortunately, preclinical studies using moderate to long treatments in animals, including rodents, with GSK-3 inhibitors have not shown any of these two concerns. Nevertheless, to discourse the first point, it is known, for example, that GSK-3 is necessary for the regulation of glycogen synthase and its purposefor the glycogen synthesis in the muscle after insulin signaling. Though, the fact that the levels of glycogen in the muscles were alike in control and GSK-3 knock-in animals. Arguments toward other pathways for glycogen synthase regulation in muscle and liver when GSK-3 is inhibited, such an allosteric modulation and exercise. The recent results show the prospect of partial inhibition of GSK-3 without affecting key physiological functions such as the muscle glycogen synthesis and storage, especially in those pathologies where an over-expression of the enzyme is produced like AD. (64)

If future treatment of AD with GSK-3 inhibitors prospers, the partial inhibition of GSK-3 produced in the whole body with this therapy will signify a delay or halt of brain dysfunction by declining the pathological neuro-overactivity of GSK-3 without upsetting other physiological functions of the enzyme where substitute compensatory mechanism will act. Regarding the β-catenin question, it is known that several small-molecules inhibitors of GSK-3 and lithium have indeed been shown to uplift the level of β-catenin in altered cell lines after numerous hours of treatment. However, in contrast, treatment of non-transformed epithelial cells with the same GSK-3 inhibitors does not cause any increase in β-catenin. Moreover, two cell lines, MEFs and non-transformed rat intestinal epithelial cells, did not show elevated levels of β-catenin asa result of decreased GSK-3 activity compared with control cells. These observations suggest that inhibition of GSK-3 by itself might not be sufficient to elevate the level of β-catenin in primary cells unless other transforming events have already taken place.

It has lately become clear that GSK-3 is not the only kinase capable of phosphorylating the residues important for β-catenin stability ,other kinases, such as CK1, CK2, PKA, IKK-α and I-KKβ, are also reported to be involved. Therefore, in the absence of GSK-3 the cell may harbor other independent mechanism to regulate β-catenin degradation. (65)

Conclusion

Alzheimer's disease (AD) is the most common form of dementia affecting more than 15 millions individuals worldwide. While the cause is unknown, there are two major neuropathological abnormalities present in the brains of patients with AD, the extracellular senile plaques and the intracellular neurofibrillary tangles. The above discussed factors contribute to development of AD and also the present treatment listed above have been able to alleviate the rate of progression of the disease but there is strong evidence that glycogen synthase kinase-3 (GSK-3) plays an important role in AD being involved in the regulation of these neuropathological hallmarks.

Increased activity and/or over expression of this enzyme in AD is associated with increased tau hyperphosphorylation and alterations in amyloid-β processing that are thought to precede the formation of neurofibrillary tangles and senile plaques, respectively. Some caution is advised in the use of GSK-3 inhibitors to avoid non desirable secondary effects and what it is more important, a mild inhibition (25–40%) of the enzyme to prevent potential severe adverse effects related to the overexpression of β-catenin. Apart from thisGSK 3β can be considered as an important target for development of new treatment.

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