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REVIEW

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Akt signaling pathway: a potential therapy for Alzheimer's disease through glycogen synthase kinase 3 beta inhibition

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Abstract

Alzheimer's disease (AD) is a form of dementia marked by the accumulation of neuritic plaques and neurofibrillary tangles through the action of GSK-3β with both significant epidemiological and clinical impact. Current pharmacological treatment approaches are focused on symptomatic relief and aims to suppress AD's progression rather than disease modification. This issue has triggered further investigations about tau pathology as an important component in AD's pathophysiology, one of them being the Akt signaling pathway. Based on the problem served by AD, combined with the non-existence of conclusive therapy for this disease; hence, this study strives to further investigate the potential therapeutical benefit of Akt signaling towards AD. A total of 82 studies are included, consisting of both national and international articles creating a narrative review based on the PRISMA checklist. Variables searched on this study, include Alzheimer's disease (AD), Akt signaling, serine-9 phosphorylation, and GSK-3β. Tau protein accumulation has been a mainstay in the physiopathology of AD, which are largely influenced by the GSK-3β expression. Akt signaling has been shown to inactivate GSK-3β through serine-9 phosphorylation. Thus, modulating and optimizing the Akt signaling pathway present encouraging prospects for the development of innovative and efficacious therapeutic strategies in addressing AD. Several studies have tried to estimate the harm and benefit as well as dose–effect relationship between Akt signaling and AD, concluding a promising beneficial effect for AD therapy. Here, we show the beneficial therapeutic effects of Akt signaling towards AD through both theoretical and empirical standpoints.

Keywords Alzheimer disease (AD), Glycogen synthase kinase-3 beta (GSK-3β) protein, Phosphorylation, Physiopathology, Protein kinase B

Introduction

Alzheimer's disease (AD) is the most prominent form of dementia, presenting itself with significant morbidity, as well as causing major quality of life deterioration [1]. It is a slowly progressive neurodegenerative disease, marked by the presence of neuritic plaques and neurofibrillary tangles. These neurofibrillary tangles cause loss of synapses, impaired axonal transport, abnormalities of the mitochondria and cytoskeleton, and oxidative stress [2]. AD has rapidly become an increasingly heavy burden on countries all over the world [3]. It was predicted that in 2030, the number of Americans diagnosed with AD will experience an increase of 35% [4]. From 1990 to 2019, the global incidence has increased by 147.95%, resulting in 7.24 million cases recorded in 2019. In 2050, the incidence of AD is projected to reach 152.8 million cases worldwide [5].

AD is characterized by widespread pathological changes, with the hippocampus and prefrontal cortex being two pivotal brain regions heavily affected by neurodegeneration [6]. Structural and functional

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abnormalities in these areas contribute to cognitive impairment, a hallmark of AD [7]. The hippocampus, crucial for memory formation and consolidation, undergoes significant atrophy in AD [8]. Neuroimaging studies have consistently shown reduced hippocampal volume, particularly in the CA1 subfield and dentate gyrus, correlating with cognitive decline. Additionally, neuronal loss, synaptic deficits, and alterations in dendritic spine morphology have been identified as pathological hallmarks [9, 10]. The prefrontal cortex, responsible for executive functions, attention, and decision-making, is also profoundly affected in AD [11]. Structural alterations, including cortical thinning and reduced gray matter density, have been observed, contributing to impaired cognitive flexibility and planning abilities [12, 13]. Functional abnormalities within the prefrontal cortex manifest as reduced activity during cognitive tasks, leading to deficits in attention, working memory, and problem-solving. Aberrant functional connectivity between the prefrontal cortex and other brain regions further contributes to cognitive impairment in AD patients [14]. The combined use of neuropharmacological adjuvants and brain neurostimulation techniques exhibits compelling potential as a curative intervention for AD [15, 16].

Although the cause behind the onset of AD is still not well understood, there are several hypotheses proposed to explain the onset of the disease, the established hypothesis is due to the accumulation of amyloid-beta peptides (Aβ) [17]. Recently, the role of tau pathology in AD has been further studied, and it is believed that Aβ accumulation increases hyperphosphorylation of tau in the brain [2]. Tau hyperphosphorylation is mediated by glycogen synthase kinase-3 beta (GSK-3β) [18]. The orchestration of higher-order neural circuits entails an intricate array of molecular players, including neurotransmitters, neurotrophic factors, and intracellular signaling pathways [19]. The aberrant molecular cascades witnessed in AD could be caused by the activation of the tryptophan (Trp)–kynurenine (KYN) metabolic system and exert deleterious effects on higher-order neural circuits [20]. Dysregulation of neurotransmitter systems disrupts synaptic transmission and compromises cognitive functions such as memory, learning, and executive processing [21]. Additionally, impaired neurotrophic support hampers neural resilience and repair, contributing to progressive neuronal loss. The intricate interplay between molecular dysregulation and neuropathological alterations in AD contributes to a vicious cycle of neurodegeneration [16, 22]. Neuroinflammatory processes, modulated by molecular signaling, potentiate amyloid-beta deposition and tau pathology, thereby exacerbating the disease pathology and cognitive decline.

Therefore, inhibition of GSK-3β is an especially intriguing alternative strategy for therapy of AD. AD is considered to be a complex disease involving multiple factors with various risk factors contributing to its onset [1]. People who are of older age, female, diagnosed with Down syndrome, and genetically predisposed, have a higher risk of developing AD [23]. Environmental risk factors also play a role, it has been discovered that exposure to certain metals, such as zinc and copper, although exposure to aluminum is still a controversy, may increase risk of AD. In a study, a diet rich in β-carotene, flavonoids, vitamin C, and vitamin E, may potentially lower the risk of AD onset [24].

Currently, there is no definitive cure for AD. Most therapies target in delaying the development of AD and only provide temporary symptomatic relief [25]. Due to several unsuccessful attempts on targeting Aβ, researches have turned to targeting tau pathology [26, 27]. The tau pathology hypothesis presents an opportunity for further investigation of tau targeted therapies. Therapies may target to inhibit phosphorylation, aggregation, glycosylation, nitration, acetylation, or increase clearance of tau [2]. Several of these compounds have entered later stages of development, showing promising advancements [28].

The intricate molecular landscape of AD involves the PI3K/Akt/mTOR signaling cascade, a pathway known to be implicated in various neurodegenerative and neuropsychiatric disorders. Specifically, hyperactivation of mTORC1 and increased downstream activity, stemming from TSC1/TSC2 mutations, can induce neuronal dysfunction, perturb axon regulation, and disrupt dendritic morphogenesis and synapse formation [29]. To counteract the deleterious effects of Aβ peptides in AD, vitamin K2 supplementation has emerged as a potential protective mechanism [30, 31]. By reducing ROS formation and inhibiting caspase-3 mediated apoptosis, vitamin K2 exerts a likely safeguarding influence against Aβ-induced cell death [32]. Moreover, the intricate signaling network involved in neuronal development and function is orchestrated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1), a crucial mediator of extracellular signals within the PI3K pathway, which, in turn, plays a central role in regulating neuronal processes [32, 33]. The involvement of the PI3K/Akt signaling pathway in diverse neurological and somatic manifestations is further underscored by intricate factor interactions, indicative of a complex interplay shaping the elicitation of various neurovascular symptoms and somatic growth alterations in AD and related neurodegenerative conditions [34, 35]. The PI3K/Akt/mTOR signaling cascade presents multifaceted interactions that hold promise as potential therapeutic targets to address the complex nature of AD and enhance patients' quality of life [34, 36].

The Akt signaling pathway plays a crucial role in the development and progression of AD. Activation of Akt leads to the phosphorylation of downstream substrates, which in turn modulate various cellular processes such as cell proliferation, survival, metabolism, and gene expression. Akt also regulates the phosphorylation of tau [37]. Evidence has shown that dysregulation of Akt signaling has been implicated in the development of AD [36]. One of the protein kinases which is vital for its activation is phosphoinositide 3-kinase/protein kinase B (PI3K). Therefore, optimization of the Akt signaling pathway through PI3K should be studied further. The PI3K/AKT signaling pathway is an important target, as modulation of PI3K/AKT signaling may be able to alter the production and clearance of amyloid beta and tau, potentially slowing the progression of the disease [38]. Thus, a comprehensive review is necessary to reevaluate the optimization of PI3K/Akt/ GSK-3β signaling pathway through PI3K as a potential therapy for AD.

Several scientific sources are used in the processing of creating this review paper following several criteria. Articles are collected in accordance to its relevance towards this study, with several inclusion criteria, including national and international articles as well as using keywords such as alzheimer, akt signaling, ser-9, and GSK-3β. The information found in these articles are then analyzed and systematically arranged based on the PRISMA guideline in correspondence to the topic. Based on their correspondence, quality, and timeframe, these studies have shown the most relevant and enough materials for the foundation of this paper. The number of articles that are included in this review paper are 82 studies. All relevant narrative reviews, clinical trials, and randomized controlled trials were identified from PubMed, Medline, and Cochrane without language restriction. The author uses the terms Headings for Medical Subjects (MeSH terms) "Alzheimer's Disease", "Akt Signaling", "Serine-9", "Glycogen Synthase Kinase-3 Beta (GSK-3β)", "Phosphorylation", "Pathophysiology", and "Protein Kinase B" as well as Boolean logic in search engines. All articles on Akt utilization and Alzheimer's disease were included in this literature review.

Two authors conducted a literature search and data extraction. Any ambiguity regarding the feasibility of the study was resolved by consensus after review by a third author. The following inclusion criteria were applied: studies under investigation could not be older than 20 years and no recent studies contradicted previous findings. Exclusion criteria included inaccessible exhaustive papers, studies with patients with multiple other complicating diseases, and studies involving patients on polytherapy. Additionally, identified study references were manually reviewed to find additional relevant studies.

Alzheimer's overview

Alzheimer's disease is a well-known neurodegenerative illness linked to the buildup of beta-amyloid plaques and is characterized by gradual cognitive decline and disruption of fundamental activities such as walking, speech, attention, and memory [39]. There is a significant presence of neuritic amyloid plaques, neurofibrillary tangles of tau protein, and enormous loss of neurons on individuals who experienced from memory impairment and emotional changes before dying, and the illness was defined as a severe cerebral cortex disease [1]. It is projected that 40 million individuals worldwide suffer from dementia, with the figure expected to double every two decades until 2050 [40]. Despite all of the efforts, there are still no promising therapeutic strategies for the condition [41].

The present studies reveal that the main neuropathology defects of AD are external amyloid plaques and intracellular Tau neurofibrillary tangles causing a destructive cascade of tau pathology and neurodegeneration [42, 43]. Among the several post-translational changes that tau may go through, phosphorylation is of utmost significance due to its role in neurodegenerative illnesses defined as tauopathies [44]. Phosphorylation is essential for tau activity in normal settings, but the protein's affinity for tubulin microfilament declines in pathological processes, and the protein begins to deposit in the cytoplasm of somatodendritic regions in which insoluble aggregates are formed [45]. Calmodulin-dependent protein kinase II (CaMKII), microtubule affinity-regulating kinases, cyclic AMP-dependent protein kinase A and tyrosine kinases including Src family members are all involved in the phosphorylation of tau [46–54]. It is possible to cause tau hyperphosphorylation by the stimulation of tau phosphorylation-associated kinases, such as CDK-5 and GSK-3β, which enables tau protein to separate from microtubules [55]. Similarly, a study found that GSK3β-dysregulation affects Aβ synthesis and deposition, encourages tau phosphorylation and harmful tau species production, induces pro-inflammatory responses, and reduces neurogenesis and memory [56]. The route of GSK3 inhibition is through phosphorylation at Ser9, which is regulated through Akt kinases [57, 58]. Thus, optimizing the Akt kinases such as protein kinase B can potentially inhibit the accumulation of tau protein in AD (Figs. 1, 2).

Protein kinase B overview

Protein kinase B (PKB), also known as Akt, is a 57-kDa serine/threonine protein kinase which contains protein

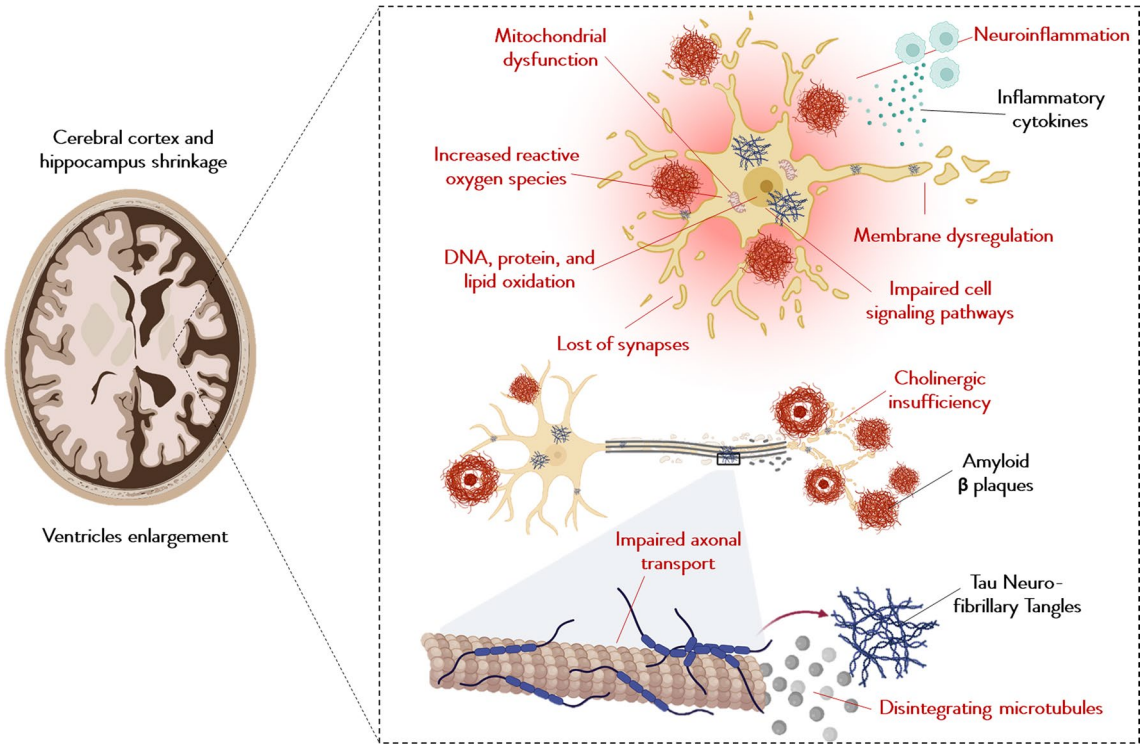

Fig. 1 Pathophysiology of Alzheimer's disease

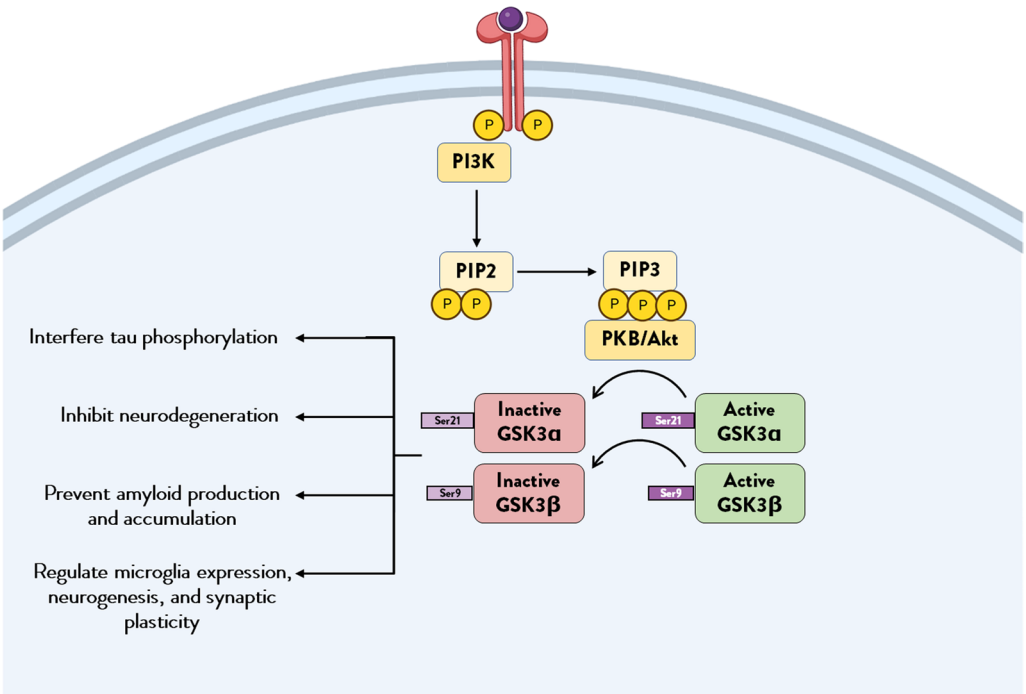

Fig. 2 AKT signaling in Alzheimer's disease

kinases of the AGC family [59]. There are currently three known isoforms of protein kinase B found in the genome of mammals—PKBα/Akt1, PKBβ/Akt2, and PKBγ/Akt3 [60]. These isoforms are mostly similar, all possessing a central kinase domain, an amino-terminal pleckstrin homology (PH) domain, and a carboxyl-terminal hydrophobic domain [61]. Each of the isoforms are expressed distinctively in different regions of the brain. PKBα and PKBγ can be found dispersed across the somatic layers of the hippocampus, and PKBβ can be found mostly in astrocytes [62]. Activation of all three isoforms depends on two phosphorylation sites, the first one found at the kinase domain, and the second can be found at the hydrophobic domain. Phosphorylation of serine 473, 474, 472 belonging to Akt1, Akt2, and Akt3, respectively, is also required for full activation of PKB/Akt signaling [59, 63]. Akt activation is induced by the phosphorylation of mTORC2 and PDK1, which in turn may positively affect synaptic plasticity and formation of memory [64].

The role of PKB/Akt signaling pathway has been rigorously studied among various fields such as in cancer, autoimmune, cardiovascular, and neurological disorders [65]. Intracellular processes such as cell multiplication, metabolism, motility, and survival are also all regulated by PKB/Akt signaling [66]. A study has shown that inactivation of FoxO3A via PI3K/Akt signaling, reduces the progression of AD in mice by exerting neuroprotective effects, such as protecting dopaminergic, cortical, and hippocampal neurons, and microglia inactivation [67, 68]. Proliferation, myelination, differentiation, and survival of oligodendrocytes are also influenced by Akt signaling in AD mice [69]. Individuals with AD experience changes predominantly in the insulin–PI3K–Akt signaling cascade due to lower PI3K subunits and reduced phosphorylation of Akt [63]. However, the correlation between the previous changes and the progression of AD is still poorly comprehended.

AKT signaling in Alzheimer's disease

In its relation to the AD's pathophysiology, protein kinase B plays a role in suppressing neurofibrillary tangle accumulation through the AKT signaling pathway. The corresponding process of suppression are as follows: (1). protein kinase B act as an important effector kinase of PI3K/AKT signaling pathway; (2). AKT pathway promotes phosphorylation of Ser9; (3) phosphorylation of Ser9 act as an inhibitory component of GSK3β; (4) inhibition of GSK3β interferes with the process of tau phosphorylation; (5) the minimal amount of phosphorylated tau accumulation results in neurofibrillary tangles reduction, hence acting as a therapeutic modality for Alzheimer's dementia.

The Ser/Thr kinase Akt, or widely known as the protein kinase B (PKB) is found to play a role in cell metabolism, proliferation, growth and survival through a multistep control approach which involves the PI3K (phosphoinositide-3-kinase) [70]. Akt is a small kinase group that can be classified into Akt 1, 2, and 3 with its properties as a negative regulator of GSK3 [71]. It is known that Akt plays a role in the phosphorylation of Ser9 and Ser21 which results in the inactivation of GSK3β [72, 73]. Both GSK3α and GSK3β can be positively regulated by the tyrosine residues and negatively regulated by the serine group phosphorylation. Specifically, Ser21 phosphorylation causes the inhibition of the GSK3α, while the phosphorylation of Ser9 inhibits GSK3β [74].

GSK3 is a group of kinase that is a key component that contributes to the abnormal phosphorylation of the protein-tau microtubule-binding process which then leads to the accumulation of neurofibrillary tangles (a key process in Alzheimer's pathophysiology) [75, 76]. These contributions of GSK3 in disease pathophysiology cause its new role in becoming a targeted substance for therapeutic advancements, specifically through the regulation of its expression. The serine group phosphorylation can be correlated with the expression of GSK3 inside the human cell. Phosphorylation process of ser21 and ser9 in GSK3α and GSK3β, respectively, results in the abnormal change of the GSK3 N-terminal tail into a pseudo-substrate or known as a pre-phosphorylated substrate. This change occurs because of the association between the phosphorylated tail of ser9 and ser21 with the primed-substrate binding pocket of GSK3 [74]. It is known that phosphorylated ser9 and ser21 can act as a competitive inhibitor of the primer–substrate binding pocket by mimicking primed substrate of the GSK3 N-terminal [77]. The abnormal association that occurs in the primed-substrate binding pocket blocks the substrate docking inside the GSK3 N-terminal, hence hindering its activation [78]. In normal condition, when serine phosphorylation does not occur, this GSK3 enzyme can be considered "active" through the docking of other "primed-substrates" in its binding pocket (one of them being tyrosine 216) [77]. In simpler term, the inactivation of GSK3 N-terminal caused by AKT signaling through serine phosphorylation results in a competitive inhibition of primed substance which renders the GSK3 inactive.

The inactivation of GSK3 by the AKT signaling pathway ought to be a breakthrough in understanding the concept surrounding protein kinase B's potential as a therapy for Alzheimer's disease. Although both the GSK3α and GSK3β isoforms are found in the normal physiology of human nervous system, GSK3β are known to be more abundant in the CNS (central nervous system) [79, 80]. It is also known that the amount of GSK3β found in the

CNS will increase in correspondence with aging process [81]. Although GSK3β can be correlated with the normal aging process, it is also found to be abnormal within the process of Alzheimer's pathophysiology. This over-activity of GSK3β inside the human brain can contribute to the progression of Alzheimer's through various mechanism of actions, mainly in memory inhibition, Aβ, and tau metabolism [56]. Pragmatically, this abnormal activity inside the brain can result in memory consolidation.

Specifically, there are 5 GSK3β pathways that are linked to the progression of memory inhibition in Alzheimer's disease: (1) GSK3β stimulates neurodegeneration through the promotion of tau hyperphosphorylation [82–87]; (2) GSK3β stimulates amyloid production and accumulation hence causing apoptosis and neuronal damages [88–92]; (3) GSK3β regulates the expression of microglia resulting in a pro-inflammatory reaction [93–100]; (4) GSK3β also regulates hippocampal neurogenesis [101–104]; and (5) GSK3β has a contribution in synaptic plasticity and memory [105–111]. Hence, the overactivation of GSK3β can result in the inhibition of hippocampal long-term potentiation (LTP). In a nutshell, the hippocampal LTP is a mechanism needed for memory formation. Therefore, the inhibition of hippocampal LTP by GSK3β can be a lead cause of memory degradation in the progression of Alzheimer's disease [56].

Secondly, GSK3β also plays a role in the formation and accumulation of Aβ through modulating the APP (Aβ precursor protein) cleavage. The cleavage of APP in the brain occurs through 2 different mechanisms, non-amyloidogenic and amyloidogenic pathways in accordance to its proteases [112]. The non-amyloidogenic pathway occurs through an α-secretase complex that includes ADAM-10, ADAM-17, and γ-secretase. APP cleavage done by the non-amyloidogenic pathway produces peptides that are more degradable [113]. On the other hand, the amyloidogenic pathway occurs through the help of BACE-1 (β-secretase) enzyme. This enzyme is followed by γ-secretase complex processing which leads to the generation of Aβ peptides which then will fibrilize and oligomerize into Aβ deposits in the brain [56].

It is observed that γ-secretase plays an important role in APP cleavage through both non-amyloidogenic and amyloidogenic pathways, hence securing its place as one of the most important substances in Alzheimer's pathophysiology. Studies have shown that a component known as PS1 is a catalytic component of γ-secretase [112]. Not only that, PS1 is also known as a GSK3β substrate, demonstrating GSK3β's influence in the formation of γ-secretase. Specifically, GSK3β's ability in modulating γ-secretase through the regulation of cellular localization and PS1 activity [114]. Subsequent to GSK3-β phosphorylation, there will be a reduction of cell-surface expression and a decrease in PS1's binding affinity to N-cadherin. This process will then alter the PS1/γ-secretase substrate specificity resulting in γ-secretase modulation by GSK3β. In addition to γ-secretase modulation, GSK3β also has the capability to interfere with the regulation of BACE-1 in the progression of Alzheimer's disease. In general, there are 2 functional NF-kB-binding sites in the human BACE1 promoter region. In vitro and in vivo evidence have shown that NFK-β/p65 nuclear translocation and binding to the BACE1 promoter sites are both influenced by GSK3-β activation [114]. This process ultimately increased the BACE1 protein levels and BACE1-mediated APP processing resulting in a higher Aβ production [56]. Hence through this complex pathophysiological network, it can be concluded that the elevation of GSK3β activity will result in a higher amount of Aβ accumulation and subsequent deposition causing a progression in Alzheimer's disease [114, 115].

Lastly, GSK3-β overactivation also contributes to Alzheimer's pathophysiology through tau hyperphosphorylation inside the human brain [116]. Pragmatically, the hyperphosphorylation of tau protein by GSK3-β will result in hippocampal neurodegeneration and axonal transport alterations, both in which are often observed in Alzheimer's patients [117, 118]. Numerically, GSK3-β is able to influence tau phosphorylation in 42 out of 85 phosphorylation sites [119, 120]. An in vitro study proves the connection between overexpression of GSK3-β and tau hyperphosphorylation. In that study, overexpression of GSK3-β in the forebrain shows hyperphosphorylation of tau and somatodendritic accumulation of tau in hippocampal neurons [121]. Another in vitro study which shows GSK3-β insufficiency reported the reduction of tau phosphorylation, reduced synaptic accumulation, aggregation, and trans-cellular spread in the brain [122]. The existence of tau hyperphosphorylation induces by GSK3-β overexpression will cause several complications in the brain function, mainly showing Alzheimer's symptoms [123]. Firstly, tau hyperphosphorylation plays a role in the impairment of c-Jun N-terminal kinase-interacting protein 1 (JIP1). JIP1 is a protein that contributes in the regulation of cargo binding to kinesin motors. Hence, the impairment of JIP1 by tau hyperphosphorylation will then result in MT disassembly, which hinders motor protein and cargo binding [124, 125]. Secondly, the hyperphosphorylation of tau causes a disturbance in the axonal transport leading to vesicular aggregation [126]. Research shows that this axonal transport abnormality is a common occurrence found in patients with Alzheimer's disease [124]. However, the vesicular aggregation caused by axonal transport impairment can be reversed through the inhibition of GSK3-β [127]. Based on these mechanisms, it can be concluded that GSK3-β plays a role in

Alzheimer's pathophysiology through the induction of tau hyperphosphorylation. On the other hand, the inhibition of GSK3-β also proves to have a reversible effect on the pathological mechanism that occurs in the human brain.

In conclusion, AKT signaling pathways, also known as protein kinase B (PKB) pathway can be a potential biomolecular target for Alzheimer's therapy. Through the activity of AKT signaling pathway in the serine group phosphorylation, GSK3-β's activity as a prominent factor in Alzheimer's pathophysiology can be reduced. The enormous implication of GSK3-β in deteriorating the human brain can therefore be negated or to say the least, inhibited through the AKT signaling pathway. Moreover, this inhibition can also be used to reverse the pathological impact that has been done to the human brain, showing not only a preventive measure against Alzheimer, but also a curative one.

Dose relationship

Fosgonimeton is an akt signaling prodrug that is designed for subcutaneous delivery and is a selective small-molecule that quickly transforms into the active metabolite in circulation. Designed to induce cascade action through the PI3k/Akt and MAPK pathways, as well as enhancing NMDA receptor-mediated activation through protein kinase C, fosgonimeton penetrates the blood–brain barrier and improves the binding of HGF with its receptor tyrosine kinase MET [128]. In a randomized controlled trial, neither a negative effect on memory was shown in healthy senior adults after numerous doses (20 mg to 80 mg) nor in healthy subjects after a single dosage (2 mg to 90 mg). Following SC administration, fosgonimeton was quickly absorbed (Tmax 0.25 h) and transformed to the active metabolite (Tmax 0.5 h). The active metabolite and the prodrug both had a short plasma elimination time (t1/2) of around 0.3 and 1.5 h, respectively. As plasma concentrations declined below 1% of Cmax at dosages over 40 mg, an elimination stage with a t1/2 of 5 h was observed [129]. Another study found that Formula 9002A exhibited its neuroprotective effects through activating the akt signaling system. This was shown by the outcomes of pharmacodynamics, involving cell studies and animal behavioral assays. It was established that GSK3 and APP are the primary targets in the Alzheimer's disease cascade. The findings of the research shown that Aβ oligomers could drastically lower the viability of SH-SY5Y cells, and that the intervention group could increase SH-SY5Y cell survival rates in comparison to the Aβ model group. This shows that Formula 9002A protects SH-SY5Y cells from damage brought on by the Aβ oligomer [130].

Furthermore, BACE1 inhibition may have facilitated PI3K/Akt signaling pathway activation and therefore limiting the Aβ produced by APP. After a single dose in vitro, the new BACE1 inhibitor elenbecestat (E2609) showed sustained decreases in plasma beta-amyloid concentrations [131]. The findings of a phase I trial revealed that E2609 was generally tolerated, had no treatment-emergent side effects, had no clinically significant effects on vital signs and electrocardiogram, as well as did not necessitate constraints or dosages modifications when co-administered with CYP3A inhibitors [132]. Moreover, umibecestat was reported to be safe and well tolerated in a multi-center phase II dose-ranging safety and tolerability trial in 2015 in participants over 60 years old, resulting in a substantial dose-dependent CSF Aβ decrease [133].

Potential benefits and risks

It is evident that accumulated tau hyperphosphorylation is a potential target for therapy of AD. Various tau phosphorylation inhibitors to ameliorate the progression of AD has been studied. Several of these compounds include kinase inhibitors, phosphatase activators, and p-tau immunotherapy. However, some studies regarding several of these drugs have shown ambivalent effects and have severe side effects [134]. Optimization of PI3K/Akt signaling pathway is therefore an appealing alternative, as Akt plays a vital role in various cell functions and life cycle. The use of Akt activators is the most common approach in activation of the Akt signaling pathway. A pre-clinical study in rodents has shown that overactivation of Akt signaling pathway leads to reduction in infarct size [135]. A study done in silico identified 13 molecules acting as Akt activators, which can potentially alleviate damage caused by tau hyperphosphorylation [136]. Other than that, SC79, a novel Akt activator, is a both highly efficient and selective drug, and has proven to have neuroprotective effects against oxidative stress [137]. Another study mentions that Akt activation leads to various neuroprotective and restorative effects on AD model mice [64].

While numerous studies have provided the basis of the potential of PI3K/Akt signaling as therapy for AD, there are still concerns regarding the plausible negative effects the compound may exert. The side effects to activation of PI3K/Akt signaling pathway is still largely debatable, as overactivation of the pathway may result in imbalance between cell proliferation and apoptosis, increasing the risk of tumor growth [138]. However, there are no recorded cases of the aforementioned potential side effect, which may be caused by lack of epidemiological research following administration of Akt activators. In another study, it was mentioned that Akt overactivation may cause enlargement of the liver [139]. Furthermore,

overexpression of Akt has been associated with increased resistance to chemotherapy in various cancers [140]. Another concern is that there have been uncertain results regarding the activity of Akt in the brain, as several experiments have shown opposite results. Therapy with Akt activators also is potentially time-sensitive, in the sense that the therapy may exert its effects in patients diagnosed early with AD, but not in patients that have moderate-to-severe AD [64].

Overall, considering limited successful potential therapies for AD and the previously mentioned benefits of PI3K/Akt signaling activation, the subject is definitely worth to be explored further. Studies have reported minimal to no side effects on the use of Akt activators as therapy, although research on long-term side effects should be conducted. By combining the therapy with other efforts to diagnose AD in its early stage, the activation of PI3K/Akt signaling may have a positive significant impact on the progression of AD.

Clinical effects and comparisons

The role of protein kinase B (PKB) and AKT signaling pathway in the phosphorylation of serine groups have also been studies in several studies. One of them done by Fan et al. (2015) that attempted to observe the effect of AKT pathway towards ser9 phosphorylation of GSK3β. Fan et al. conclude that ser9 phosphorylation is a process that plays a role in the RANKL-induced osteoclast differentiation. Through the comparison process, this study found that the induction of ser9 phosphorylation was more prominent in the sample group with an activated AKT signaling pathway. Moreover, Fan et al. also then reported that ser-9 phosphorylation by AKT pathway is a requirement of this particular physiologic process [141]. This study serves as a prove of AKT signaling and PKB activation as a probable therapeutic management in AD through GSK3β inhibition.

A study that examined donepezil's therapeutic has also found the relation between AKT pathway and beta-amyloid plaques in the Alzheimer's pathophysiology. This study shows the significant effect of donepezil in showing a neuroprotective effect against beta-amyloid induced neuronal toxicity [142]. Combined literatures state that these neuroprotective effect of donepezil anti-cholinergic activity are mediated by AKT activation in various types of cells related to cognitive functions through GSK3 inhibition [143–145]. In another study by Park et al. (2014) that attempted to find a potential therapeutic agent against beta-amyloid plaque also reported a similar finding. This study utilizes GV1001, a potential anti-cancer agent with its novel clinical effect in fighting the accumulation of beta-amyloid plaques. Park et al. reported several beneficial therapeutic effects of this GV1001 agent, both presenting an important measure for beta-amyloid plaques. Firstly, GV1001 enables the recovery of mitochondria that has been damaged by the beta-amyloid plaque through the evaluation of ATP levels and membrane potential. Secondly, GV1001 also cause the restoration of abnormal protein level caused by beta-amyloid plaques into its normal value. Lastly, death-related proteins that have increased because of beta-amyloid plaques are also being re-increased through GV1001 usage. Based on this empirical evidence, Park et al. continues to summarize their findings and this leads to the interaction of GV1001 and AKT signaling pathway. It is speculated that this potential clinical benefit that GV1001 brings are correlated with the activation of AKT and serine group phosphorylation, namely ser473 and ser9 with its relationship with GSK3β [146]. In correspondence with this study by Park et al., it can be concluded that the participation of AKT signaling pathway is to some extent crucial for fighting against damages caused by beta-amyloid plaques.

Through the numerous theoretical landscapes, it can already be deduced that protein kinase B with its butterfly effect can be a potential therapeutic target for future Alzheimer's treatment. Currently the pharmacological treatments used for Alzheimer's disease are mainly symptomatic. Cholinesterase inhibitors, such as donepezil and galantamine as well as NMDA antagonist including memantine are drugs that can be used to suppress Alzheimer's symptoms and its progression. Regardless of their effectiveness as an Alzheimer's therapy, both of these drug families have their own adverse effect that may negatively impact the patient. In addition, there also exist various contraindications that follow the usage of these drugs. Donepezil for example can cause sleep disturbance as well as being contraindicated for patients with end-stage renal disease and severe liver dysfunction. Memantine on the other hand can also slightly increase the risk of stroke [147]. Based on this, it is evident that Alzheimer's medications that are currently available still have their own negative impact towards the patient. Hence, because of these weaknesses, it is reasonable to compare these medications to protein kinase B as a potential therapy for Alzheimer's disease. Aside from being theoretically probable, a clinical trial using NP031112 have also been done to try and estimate the effectiveness of AKT/GSK3β pathway for patients with Alzheimer's disease. However, in its second phase of clinical trial, NP031112 has not been able to prove the AKT/GSK3β pathway's efficacy, hence still making this a "potential" drug. Although that was the case, NP031112 have already been proven as a safe medication and can probably go through another step of research, which is the third phase of clinical trial [148]. Based on both the

potential effectiveness and its safety, although not much was confirmed, the usage of AKT signaling pathway as a novel therapy can certainly be worth to push through, especially knowing that there is no cure for Alzheimer in the current medical world.

The inverse relationship between Akt and protein tau in AD patients are further proven by a study done by Mohamed et al. (2019) using the effects of lactoferrin. Prior to the administration of lactoferrin, Mohamed et al. found a lower level of PI3K (58.9%) and p-AKT (69.9%) levels, as well as a higher level of tau protein (3.5-fold difference) in AD patients compared to the control group. After lactoferrin administration, however, this statistical data changed to the opposite direction. PI3K and p-Akt levels are shown to increase 1.85- and 2.6-fold, respectively, while tau protein levels decline 2.5-fold compared to AD patients that does not receive lactoferrin. These results prove to be statistically significant ($p < 0.05$) in the Mohamed et al. study. In the midst of lactoferrin administration, this data demonstrated the possible negative correlation between Akt and tau protein in patients with AD [149].

Another pathway in AD pathophysiology that has been numerically proven to be a potential target by Akt signaling is the serine-9 phosphorylation and its correlation to GSK3β. A study by Sancheti et al.. (2013) on transgenic (Tg) and non-transgenic (nonTg) mice, as well as lipoic acid administration has also shown result that possibly indicates the correlation between Akt and serine-9 phosphorylation. In accordance to their study, the administration of lipoic acid has shown to increase Akt activation by 10% and 40% in Tg-mice and nonTg-mice, respectively. This administration in turn, also have shown its effect on GSK3β phosphorylation, or in other words their inactivation. Lipoic acid has resulted in a slight increase of GSK3β phosphorylation in Tg-mice population, as well as a substantial increase in GSK3β phosphorylation for the nonTg-mice population (35%) [150].

The non-existence of complete cure for AD in the current status quo proves to be a hindrance in the patient's recovery. The discovery of the link between Akt signaling and AD pathophysiology can be a potential therapeutic advancement in the process of AD management. Future development of these findings, especially in regard to its specific dose–effect relationship, side effects, pharmacokinetics specificity, as well as financial burden may prove to be important in determining Akt signaling pathway's exact effect towards AD pathophysiology.

Conclusion

Akt signaling has the capacity to interfere with AD's pathophysiology progression, specifically within the tau protein accumulation process. Several existent drugs have been trialed and show a prominent potential clinical effect towards AD. Although these trialed drugs can be used to estimate its dose–effect relationship, the utilization of Akt signaling as AD therapy still needs further investigation in regard to dose calculation. Nevertheless, it can be concluded that Akt signaling can theoretically be used to treat AD with a less significant adverse effect, hence becoming a promising novel therapy for AD. Through the findings in this paper, a new theoretical breakthrough for a complete recover for AD patients can potentially be attained. Hence, stressing a more important significance for the findings in this study to be further investigated. Moreover, Akt signaling pathway's interaction with many molecular components of the human body may also open up opportunities to several other disease processes to be intervened. This is true especially in neurological disorders in which its correlation has been described in this study.

Limitations of the study

In similarities to other narrative reviews, this paper has several limitations that need to be addressed. Firstly, this paper has yet to explain the proper theoretical, as well as empirical adverse reactions in patients with AD. Secondly, there need to be a better visualization of a direct therapeutic effect between Akt signaling towards AD pathophysiology. Lastly, this study has not found the necessary vehicle and specific exogenous material in order to heighten Akt signaling pathway expression inside AD patients.

Implications and directions for future research

This narrative review sheds light on the Akt signaling pathway as a promising therapeutic avenue for AD, primarily through the inhibition of GSK-3β. By providing a deeper understanding of GSK-3β's role in Alzheimer's pathology and its interaction within the Akt pathway, this review offers a compelling rationale for researchers and pharmaceutical companies to focus on drug development targeting this pathway. Furthermore, it encourages investigations into the screening of compounds capable of modulating Akt and GSK-3β, potentially identifying novel drug candidates. Practical implications include the design of clinical trials centered around Akt pathway modulators, with a focus on safety and efficacy, the potential for personalized medicine approaches, and the exploration of broader neuroprotection strategies. This research also carries public health implications, prompting discussions on research funding, healthcare planning, and public awareness campaigns related to Alzheimer's disease and its potential treatments. Additionally, it may foster interdisciplinary collaboration among researchers from various disciplines, while raising ethical

considerations about the use of Akt pathway modulators in the treatment of AD, including patient consent, long-term effects, and equitable access to emerging therapies.

The primary aim of this narrative review is to offer future researchers valuable insights into the potential of GSK-3β inhibition in AD management, in hopes of finding a definitive cure for AD. Nonetheless, various challenges, such as limited knowledge and inadequate technological advancements, continue to impede research progress in its application. These challenges include the difficulty in achieving specificity by targeting GSK-3β within the Akt pathway. Ensuring that GSK-3β inhibitors are able to pass through the BBB is another challenge that may present as a significant challenge in terms of their bioavailability. Moreover, significant challenges stemming from current technological limitations also affect the research progress in this field. Current imaging modalities may lack the sensitivity required to detect structural alterations or changes in neural activity affected by GSK-3β inhibition through Akt signaling modulation. These complex challenges impede the effective utilization of the Akt signaling pathway in AD therapy, underlining the urgency of advancing research, particularly in the definitive management of AD.

Discussion

In the exploration of AD, we have uncovered the potential of the Akt signaling pathway to modify the course of this devastating condition. This discussion section summarizes our findings and their significance, outlines avenues for future research, and highlights the ultimate goal, challenges, and requirements for success in this endeavor.

Our study builds upon earlier research that recognized Akt's role in curbing neurofibrillary tangle formation in AD. The Ser/Thr kinase Akt operates as a negative regulator of GSK3, primarily through phosphorylation at serine-9 and serine-21 [1, 2]. GSK3 itself plays a pivotal role in the abnormal phosphorylation of tau protein, leading to neurofibrillary tangle formation, a key pathological process in AD [3, 4]. As such, GSK3 has emerged as a promising target for therapeutic interventions in AD, particularly through the regulation of its expression. This heightened GSK3β activity can contribute to various pathological processes in AD, including memory inhibition, amyloid-beta production and accumulation, pro-inflammatory reactions, regulation of hippocampal neurogenesis, and interference with synaptic plasticity and memory, particularly by inhibiting hippocampal LTP [5]. The inhibition of hippocampal LTP is detrimental to memory formation, making it a significant factor in AD-related memory degradation [6]. GSK3β influences the formation and accumulation of Aβ through its modulation of γ-secretase and BACE-1 activity [7]. GSK3β's phosphorylation of PS1, a catalytic component of γ-secretase, alters its cell-surface expression and binding affinity to N-cadherin, subsequently impacting γ-secretase substrate specificity [8]. This process further exacerbates Aβ production [9].

The implications of our findings are nothing short of transformative within the context of AD research and therapy. By focusing on the phosphorylation of serine-9 and its downstream effects on GSK3β, we uncover a promising avenue for disease modification rather than mere symptomatic relief. The pivotal role of GSK3β in tau hyperphosphorylation and neurofibrillary tangle formation has long been recognized, and our findings align with the emerging consensus that targeting this pathway may mitigate AD's devastating effects. Our study serves as a harbinger of future inquiries into the therapeutic potential of the Akt signaling pathway. The intricacies of this pathway, its interplay with GSK3β, and the downstream consequences on tau phosphorylation beckon for further investigation. To traverse this terrain effectively, researchers will need to embark on mechanistic studies, engage in thorough animal model experimentation, and ultimately undertake clinical trials to validate the translational viability of Akt signaling modulation in AD. Collaboration across diverse scientific disciplines, ranging from neuroscience to pharmacology and molecular biology, will be essential to harness the full potential of this research avenue. Our ultimate aim is to transform AD management. We focus on modulating Akt signaling to reduce GSK3β activity and tau phosphorylation, ultimately slowing AD progression.

The path from promising preclinical findings to clinically approved therapeutics is a labyrinthine journey, replete with scientific, ethical, and logistical challenges. The intricate nature of AD, marked by multifactorial etiology and intricate neural networks, poses a formidable hurdle. The development and validation of targeted pharmacological interventions entail arduous testing and scrutiny, demanding substantial time and resources. To navigate this terrain effectively, a robust infrastructure of knowledge and technology is imperative. This encompasses a profound understanding of the molecular intricacies underpinning Akt signaling, GSK3β regulation, and tau phosphorylation. Advanced methodologies spanning molecular biology, neuroimaging, and biomarker analysis will be pivotal in monitoring treatment outcomes and patient responses. Furthermore, the development of specific and safe pharmacological agents tailored to target key components within the Akt signaling pathway constitutes a technological imperative.

The importance of this research trajectory cannot be overstated. AD poses a global health crisis, exacting a profound toll on society and the economy. The absence

of disease-modifying treatments places an immense burden on individuals, caregivers, and healthcare systems. Research that delves into innovative therapeutic strategies, such as Akt signaling modulation, not only offers hope to those grappling with AD but also carries the potential to mitigate the broader societal and economic repercussions of this affliction. Success in this endeavor could enhance the quality of life for millions while simultaneously alleviating the healthcare exigency associated with AD.

While our review provides a comprehensive synthesis of extant literature and presents a cogent hypothesis, its nature remains primarily observational and hypothesis-generating. To ascertain the clinical applicability of Akt signaling modulation in AD, rigorous preclinical investigations and large-scale clinical trials are essential. The merits of our study lie in its potential to reshape the trajectory of AD research and therapy. By emphasizing the Akt signaling pathway as a promising therapeutic target, it stimulates further exploration and innovation within the field. Our thorough examination of existing evidence provides a robust foundation for future research endeavors. The translation of our findings into clinical practice represents a formidable and lengthy endeavor, fraught with uncertainties. However, the potential benefits for AD patients, their families, and society as a whole underscore the nobility and necessity of this pursuit.

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid beta
GSK-3β	Glycogen synthase kinase-3 beta
PI3K	Phosphoinositide 3-kinase
CaMKII	Calmodulin-dependent protein kinase II
PKB	Protein kinase B
APP	Aβ precursor protein
BACE-1	β-Secretase enzyme
JIP1	C-Jun N-terminal kinase-interacting protein 1

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Author contributions
The initial concept for this literature review was hatched by JL. The text was written by JL, BGL, and JCS. JL, BGL, and JCS completed, copyedited and revised the manuscript. All authors assisted in reviewing, composing the manuscript, creating the figures and reviewing the final manuscript.

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