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Review

Common Signaling Pathways Involved in Alzheimer's Disease and Stroke: Two Faces of the Same Coin

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Abstract. Alzheimer's disease (AD) and stroke are two interrelated neurodegenerative disorders which are the leading cause of death and affect the neurons in the brain and central nervous system. Although amyloid-β aggregation, tau hyperphosphorylation, and inflammation are the hallmarks of AD, the exact cause and origin of AD are still undefined. Recent enormous fundamental discoveries suggest that the amyloid hypothesis of AD has not been proven and anti-amyloid therapies that remove amyloid deposition have not yet slowed cognitive decline. However, stroke, mainly ischemic stroke (IS), is caused by an interruption in the cerebral blood flow. Significant features of both disorders are the disruption of neuronal circuitry at different levels of cellular signaling, leading to the death of neurons and glial cells in the brain. Therefore, it is necessary to find out the common molecular mechanisms of these two diseases to understand their etiological connections. Here, we summarized the most common signaling cascades including autotoxicity, ApoE4, insulin signaling, inflammation, mTOR-autophagy, notch signaling, and microbiota-gut-brain axis, present in both AD and IS. These targeted signaling pathways reveal a better understanding of AD and IS and could provide a distinguished platform to develop improved therapeutics for these diseases.

Keywords: Alzheimer's disease, Apolipoprotein E, excitotoxicity, glucose, insulin, ischemic stroke, microbiota-gut-brain axis, mTOR-autophagy, Notch signaling, PI3K/Akt

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia causing higher death rates worldwide. Extracellular amyloid-β (Aβ) aggregation, intracellular tau hyperphosphorylation, and inflammation are the main pathophysiological hallmarks of AD [1, 2]. Accumulating evidence suggests that the amyloid hypothesis of AD has not been proven and anti-amyloid therapies that remove amyloid deposition have not yet slowed cognitive decline [3–5]. Around 7.1 million people will be diagnosed with

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AD in 2025 and it will increase to 13.8 million by 2060 [6]. In addition, cerebral amyloid angiopathy (CAA) a major contributor to AD pathogenesis is defined by the deposition of Aβ in the walls of small leptomeningeal, cortical arteries, and cortical capillaries. The chief clinical appearances of CAA are lobar intracerebral hemorrhage (ICH) and cognitive impairment. CAA is the predominant vascular lesion in AD and more prevalent in strokes especially in ischemic stroke (IS) which is caused by cerebral blood flow interruption that induces severe neural injuries leading to death. Every year globally around 15 million elderly people are affected by stroke [7, 8]. The impaired Aβ clearance could accelerate IS and this might make the brain more susceptible to AD pathology. The association between AD and IS seems to be strong in the presence of common vascular risk factors. In addition, common risk factors such as diabetes, hypertension, and hyperlipidemia may contribute to both AD and IS.

Epidemiological studies indicate that AD patients have a higher incidence of stroke than normal people [9]. Also the occurrence of dementia is fifty times higher after a major stroke but the widespread dementia risk is substantially reduced after a transient ischemic attack or minor stroke [10]. Cross-sectional epidemiological studies have reported that within three months after an IS incidence, one-fourth of elderly patients meet the criteria for dementia [11]. Another population-based study indicated that the increased risk of dementia might be started five years before the onset of stroke and would reach the maximum in one year after the stroke, also the risk continued for more than eleven years [12]. Therefore, it is intricate to disclose the occurrence of dementia as pre- and post-stroke or vice-versa.

In AD and IS, loss of neuronal cell bodies and axons cause pathological changes in the neuronal circuitry. Microglia and astrocytes are also drastically changed after IS and AD. Ramified microglia can be converted to archaeocytes or amoebocytes [13–15] and accelerate the production of reactive oxygen species (ROS) and pro-inflammatory cytokines [16]. These substances disrupt the blood-brain barrier (BBB) permeability and also release a variety of neurotoxic elements all over the brain [17]. AD and IS cause cerebral neuropathological changes such as cellular excitotoxicity, mitochondrial dysfunctions, neuroinflammation, BBB impairment, neuronal cell death, and eventually severe neurological deficits. Several signaling pathways become stimulated or deactivated during these pathophysiological shifts [18]. Therefore, it is essential to better understand the pathophysiological association between AD and IS. Hence the present review provides the common targeted signaling pathways between AD and IS, also proposing the therapeutic strategies for these diseases (Fig. 1).

EXCITOTOXICITY IN AD AND STROKE

Excitotoxicity is known as neuronal cell death by the deleterious effects of excitatory amino acids, deficiency of glucose and oxygen, disruption of oxidative phosphorylation, and deprivation of energy in the brain [21]. It creates an ionic imbalance, calcium (Ca^{2+}) overload, and finally cell membrane depolarization which triggers the excessive secretion of glutamate (Fig. 2). Excitotoxicity creates harmful events on neuronal cells such as dysregulation of calcium homeostasis, free radical formation, increasing oxidative stress, mitochondrial dysfunction, and stimulation of several transcription factors and gene expression [17]. Therefore, excitotoxicity is recommended as a common main contributing aspect to the initial stage of AD and IS.

Association between excitotoxicity and AD

Glutamate is the key excitatory neurotransmitter involved in perception and cognition. The excess glutamate and glutamatergic receptor activation can cause neuronal dysfunction and cell death. Glutamate-mediated neurotoxicity is associated with AD pathology. Continuous activation of N-methyl-D-aspartate (NMDA) receptors causes an enormous influx of Ca^{+2} and boost in synaptic "noise," which diminishes the long-term potentiation process, neuronal plasticity, and neuronal damage [19, 26]. Disturbance of glutamate homeostasis can be provoked by energy deficits, free radical formation, and dysregulation of other signaling pathways [26]. Literature also proposed that there is a relationship between Aβ production and NMDA receptors activation, Aβ activates NMDARs, whereas activation of NMDARs enhances Aβ and tau protein production in AD [24, 25] (Fig. 2). Glutamatergic dysfunction was observed in postmortem AD brains [27] and in epidemiological studies [28]. Therefore, the most favorable action should be essential to restore the concentration of glutamate for the maintenance of synaptic plasticity and ongoing neurodegeneration.

In recent years, AD pathology has spread in multiple dimensions including the pathogenic role of the

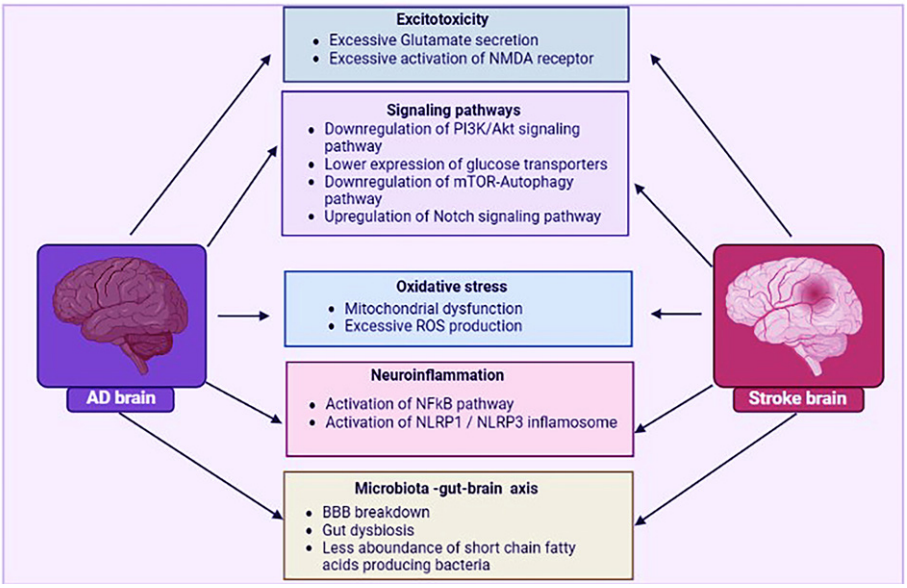

Fig. 1. A brief summary of the contributing factors present in both Alzheimer's disease (AD) and ischemic stroke (IS). Excessive glutamate secretion from astrocytes cause extrasynaptic NMDA activation leading to AD [19, 20] and IS [21–23] pathologies. Cell signaling systems mainly PI3K/Akt, mTOR-autophagy, and Notch signaling pathway are involved in AD and IS; oxidative stress due to mitochondrial dysfunction and excessive ROS production; NFkB and NLRP1/3 inflammasome are involved in neuroinflammation; and microbiota-gut-brain-axis is dysregulated by blood-brain-barrier (BBB) break down and gut dysbiosis due to the reduction of small chain fatty acids (SCFAs) producing bacteria. NMDA receptor, N-methyl-D-aspartate receptors; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; ROS, reactive oxygenated species; NFkB, Nuclear factor-κB; NLRP, nucleotide-binding oligomerization domain like receptor pyrin domain-containing protein.

nonneuronal cells such as astrocytes, and microglia. In normal physiological conditions, astrocyte plays important role in several cerebral functions such as the development and maintenance of the BBB [23], promotion of neurovascular coupling [29], the attraction of cells through the release of chemokines [23], K^+ buffering [30], uptake of glutamate [31], and GABA by specific transporters [32], control of pH in the brain [33]; and their dysfunction promote neurodegeneration in AD [34]. By the deposition of Aβ in the AD brain, astrocytes become activated and cause detrimental consequences including the reduction of the glutamate uptake due to low expression of re uptake transporters, altered ions homeostasis (K^+ and Ca^+), increased the release of cytokines and inflammatory mediators and reduced levels of aquaporins [35].

Over-accumulation of extracellular glutamate during Aβ aggregation causes neurotoxicity in AD pathogenesis [25]. In AD, morphological alteration of astrocytes causes modifications in K^+ neurovascular regulation by downregulation of rectifying K^+ channels (Kir) 4.1 which causes irregular cerebral blood flow. Disruption of gliotransmission by enhancing calcium signaling in astrocytes is altered by Aβ accumulation [23]. This calcium/gliotransmission alteration could underlie an important role of astrocytes in AD pathology. These alterations cause the over-expression and overstimulation of α7 subunit-containing nicotinic acetylcholine receptors (7αnAChR), purinergic receptor P2Y1, metabotropic glutamate receptor 5 (mGluR5), and changes in Ca^{2+} homeostasis which increases the levels of glutaminase and glutamine in the astrocyte of the hippocampal regions. It increases internal Ca^{2+} levels and finally stimulates hemichannels to release more glutamate and led to the downregulation of glutamate transporter (GLT1) in astrocytes causing glutamate excitotoxicity in AD [36]. In addition, long-term exposure to $A\beta_{1–42}$ can cause GLT-1 loss in astrocytes that are mediated by numerous inflammation-related transcriptional processes [37].

Furthermore, aquaporins 4 (AQP4) controls various functions of astrocytes. AQP4 plays an important role in the clearance of Aβ [38]. About 55–65% of Aβ clearance was decreased in AQP4 knockout mice [39]. Increasing Aβ accumulation and memory deficits were found in the AQP4 deleted 12-month-old APP/PS1 mice [40]. From the postmortem AD brain, it was found that loss of perivascular AQP4

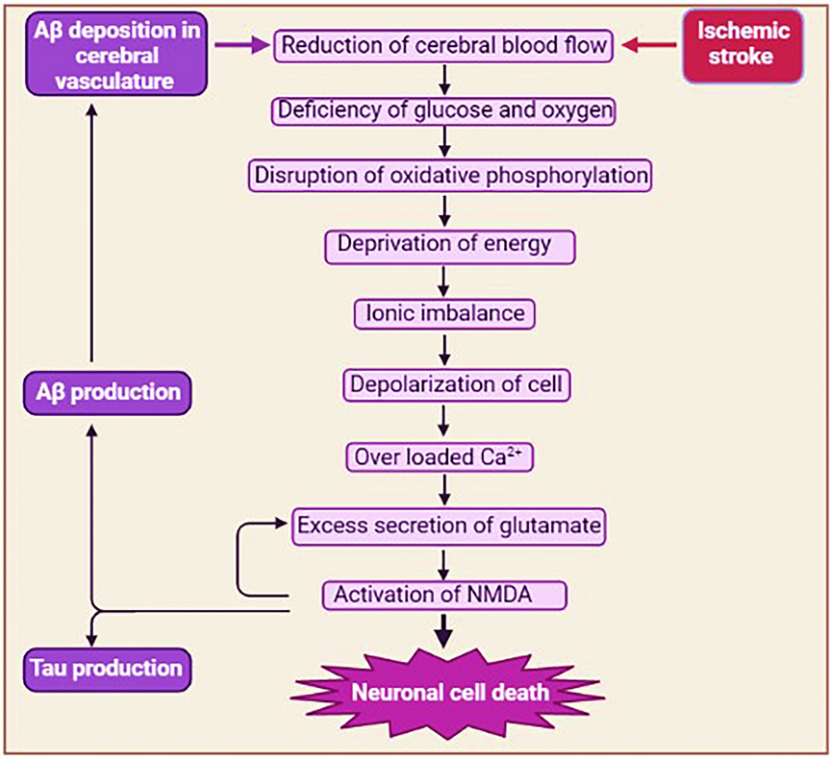

Fig. 2. Schematic representation of excitotoxicity pathway in Alzheimer's disease (AD) and ischemic stroke. In AD, Aβ deposition reduces the blood flow in the brain and causes excitotoxicity by the excess secretion of glutamate. In addition, activation of extrasynaptic N-methyl-D-aspartate receptors (NMDA) accelerates the production of Aβ and tau protein in AD [24, 25]. Similarly, in ischemic stroke reduced blood flow in the brain causes neuronal cell death.

localization and its low expression level might be reduced Aβ disaggregation and Aβ clearance in AD [41]. Literature indicated that deficiency of AQP4 leads to the downregulation of GLT1 which affects synaptic plasticity and memory [42]. Using GLT1 expression regulators such as ceftriaxone rescues hippocampal memory deficit in AQP4 knockout mice via GLT-1 activation [43]. Therefore, AQP4 can be a molecular target for AD treatment.

Another important innate immune cell of the central nervous system (CNS), microglia contribute to the Aβ clearance through phagocytosis and degradation of Aβ. M2 microglia secretes anti-inflammatory cytokines and growth factors which have a neuroprotective effect. In AD progression, Aβ triggers microglial activation (M1 microglia) which secretes pro-inflammatory cytokines and reduces the efficacy of Aβ clearance, causing inflammation in AD [44].

Association between excitotoxicity and stroke

Cerebral blood flow is substantially diminished immediately after IS. As a result, the availability of glucose and oxygen in the neuronal tissues are reduced too. Deprivation of energy creates mitochondrial dysfunction, induces oxidative stress, and eventually triggers ROS production. Insufficiency of energy simultaneously contributes to the ionic imbalance of Na^+, K^+, and Ca^{2+} concentration, causing cellular depolarization and glutamate secretion. Excessive glutamate activates NMDA receptors initiating cell toxicity and serious damage to the CNS [45] (Fig. 2). Enhanced Ca^{2+} influx disturbs ionic homeostasis, resulting Ca^{2+} overload in mitochondria and cytosol [46]. These events trigger the production of free radicals, lipases, kinases, phosphatases, endonucleases [47] and stimulate calpain [48], mitochondrial dysfunction and oxidative stress, and finally neuronal cell death [49].

Glutamate has an important role in ischemia-induced excitotoxicity. Astrocytes dynamically control synaptic transmission and trigger excitotoxicity by the secretion of glutamate in stroke [22]. The mechanism of astrocytic glutamate secretion has been mysterious. Some researchers believe that glutamate transporters such as EAAT1 (also known

as GLAST) and GLT-1 (known as EAAT2) are downregulated which increases glutamate concentration, and leads to cell death via excitotoxicity in ischemia or reperfusion injury conditions [50]. During post-cerebral injury, more excitotoxicity was found in mutated GLT-1 gene knockout mice than in their wild-type counterparts [51]. Other researchers suggested that astrocytic Swell1 subunit containing volume-regulated anion channel release glutamate, regulate synaptic transmission, and contribute to the excitotoxicity in stroke [52]. Furthermore, another glutamate transporter, EAAT4, is highly expressed following brain injury [53]. Under conditions of ischemia, the excessive influx of Na^+ into astrocytes triggers cell death by the overload of Ca^{2+} through a reversed activity of the cell membrane Na^+ -Ca^{2+} exchanger [54].

Like AD, AQP4 also plays a significant in IS. In the early stage of a stroke, APQP4 prevents the swelling of astrocytes, leads to decrease water inflation in the brain, and decreases BBB destruction, inflammation, and neuronal death [55]. After 1-hour post-stroke, the expression of AQP4 is rapidly increased in perivascular endfeet of astrocytes. Upregulated AQP4 promotes water uptake, emerges cellular damage, disrupts BBB, and finally, shifts vasogenic edema to hemorrhagic conversion [56]. Brain edema was reduced after IS in AQP4-deficient mice [57]. Therefore, inhibition of AQP4 may contribute to a novel therapeutic option for stroke treatment.

Additionally, microglia have a ramified morphology in homeostatic conditions. During all stages of IS, microglia are activated and can produce both detrimental and neuroprotective mediators. After instant IS, microglia (M1) immediately shift towards the lesion site and aggravate tissue injury by producing pro-inflammatory cytokines and cytotoxic substances. On the other hand, microglia (M2) also engulf debris and produce anti-inflammatory cytokines and growth factors, maintaining a suitable microenvironment for new neural circuity [58].

In addition, there is a dynamic interaction between microglia and other cells like astrocytes, neurons, oligodendrocytes, and endothelial cells in the neurovascular unit. This dynamic interaction plays a significant role in continuing acute injury and post-stroke recovery. After IS, microglia are activated earlier and promote the activation of astrocytes. Astrocyte activation accelerates pro-inflammatory cytokines and damages oligodendrocytes in ischemic white matter injury. It also disrupts BBB integrity and damage blood vessels. M2 microglia normalize endothelial cell proliferation and help angiogenesis in a biphasic manner in the brain [59, 60]. Therefore, M1/M2 microglial activation has significant translational value to boost the defensive role and /or diminish the adverse effect of stroke.

APOLIPOPROTEIN E IN AD AND STROKE

Apolipoprotein E (ApoE) is a main lipid transporter that has a fundamental role in the development, maintenance, and repair of CNS. It also controls various crucial signaling pathways in the brain. ApoE is mostly expressed by astrocytes and microglia, and it plays dynamic roles in AD and stroke pathogenesis [61] (Fig. 3). Three major isoforms namely ApoE2, ApoE3, and Apo4 are encoded by three different alleles namely *APOE* ε2, *APOE* ε3, and *APOE* ε4, located on chromosome 19. Three isoforms are structurally and functionally different due to the substitution of a single amino acid residue. ApoE4 is involved in the neurodegeneration in AD and IS while ApoE2 and ApoE3 are protective in nature [62].

Association between ApoE4 and AD

APOE ε4 is a major threat for late-onset AD and increases the risk of AD by 3-fold [63]. Although the exact mechanism of *APOE* ε4 in the onset of AD progression is not fully revealed, numerous evidence suggests that ApoE4 influences Aβ aggregation and deposition in AD. The isoform ApoE4 impairs synaptic function, causes neurotoxicity, tau hyperphosphorylation, and neuroinflammation which are the contributing factors in the onset of AD [64] (Fig. 3). The molecular mechanism of ApoE4 remains unclear. Recently, it was found that ApoE4 quickens the BBB disruption by the activation of cyclophilin A-matrix metalloproteinase-9 (CypA-MMP-9) in aged *APOE* knock-in mice crossed with 5xFAD. The reduced level of cerebral blood flow deficits the behavioral activity and causes neuronal loss in this mouse model [65], suggesting more research work will be needed to understand the role of ApoE4 in AD.

Association between APOE ε4 and stroke

Several studies revealed the connection between *APOE* gene polymorphisms and the possibility of developing a stroke. *APOE* ε4 allele increases cholesterol levels, amyloid deposition in blood vessels, development of hypertension, hypometabolism of

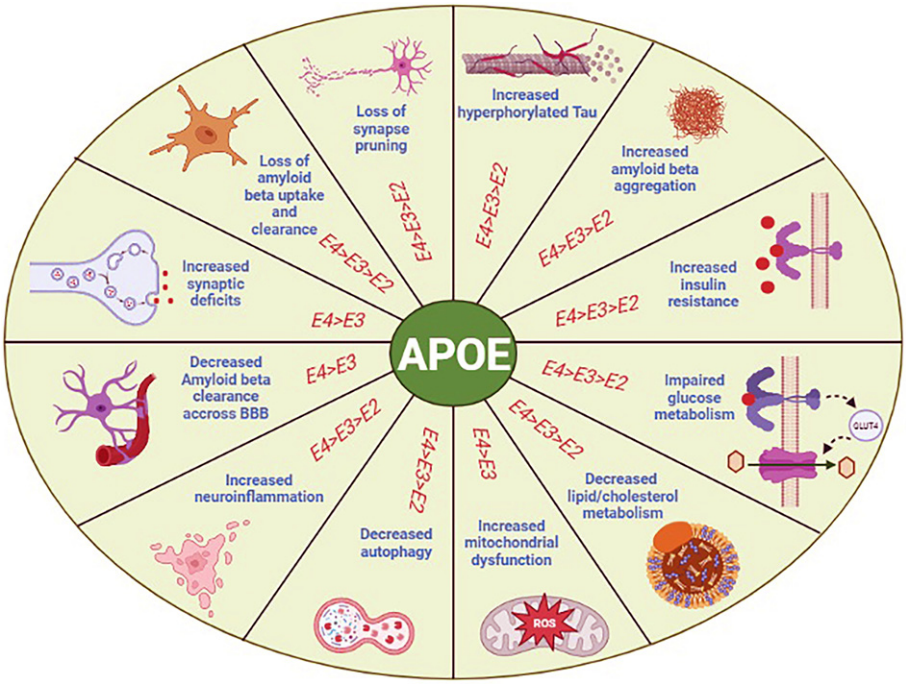

Fig. 3. Schematic representation of *APOE* isoform-dependent effects on the common features of Alzheimer's disease (AD) and stroke. Specifically, *APOE4* carriers are more susceptible to produce more plaques and tangles, and to have advanced insulin resistance, mitochondrial dysfunction, neuroinflammation, and synaptic deficits. The *APOE4* isoform is also responsible for decrease metabolism of glucose, lipid, cholesterol, autophagy, Aβ clearance across the blood-brain barrier (BBB), and a gradual loss of Aβ uptake and clearance by microglia causing neurodegenerative diseases such as AD and ischemic stroke.

glucose, and insulin resistance which are underlying triggers for ischemic cerebrovascular disorders [66] (Fig. 3). It is well documented that carriers of the ε4 allele show an increased risk of ICH but ε2 allele carriers are not at risk of having ICH in the future. Recent research indicated that the occurrence of the *APOE* ε4 allele significantly increases the risk of IS in the populations from rural Eastern India [67], China [68], and Korea [69], and deteriorates cognitive function [70]. However, the influence of ApoE4 in pre-and post-stroke is not clear. Some researchers believe that ApoE4 quickens dementia progression after stroke [65]. Though the interaction between ApoE4, Aβ, and tau pathways after transient IS in the cerebrovascular system, and their contribution to cognitive impairment in the development of dementia remains uncertain [65].

PHOSPHATIDYLINOSITOL 3-KINASE/AKT (PI3K/AKT) SIGNALING IN AD AND STROKE

Hypometabolism of glucose is one of the remotest factors responsible for the onset of AD and IS and is linked with PI3K/Akt signaling pathway. Dysregulated PI3K/Akt signaling may have a vital role in impaired cognition such as in AD [71] and IS [17]. In aged people with no dementia, PI3K/Akt signaling maintains both the volume and function of the brain and protects the brain from atrophy and slow the progression of associated complications [72]. Therefore, an impaired PI3K/Akt signaling pathway may cause neurodegenerative diseases such as stroke and AD (Fig. 4).

Association between PI3K/Akt signaling and AD

Abundant evidence suggests that impaired brain insulin signaling and dysregulation of brain glucose metabolism may lead to cognitive deficits in AD [71]. Recently, we found the insulin signaling proteins IRβ, IGF-1, IRS-1, IRS-2, p-Akt (Ser473), and Akt were noticeably decreased in AD rats. The downregulation of PI3K/Akt signaling was conveyed by the activation of glycogen synthetase kinases 3 (GSK3), phospho-GSK3β (Tyr216), total GSK3β and cyclin-dependent kinase 5 (Cdk5) has been identified as important candidates for irregular tau hyperphospho-

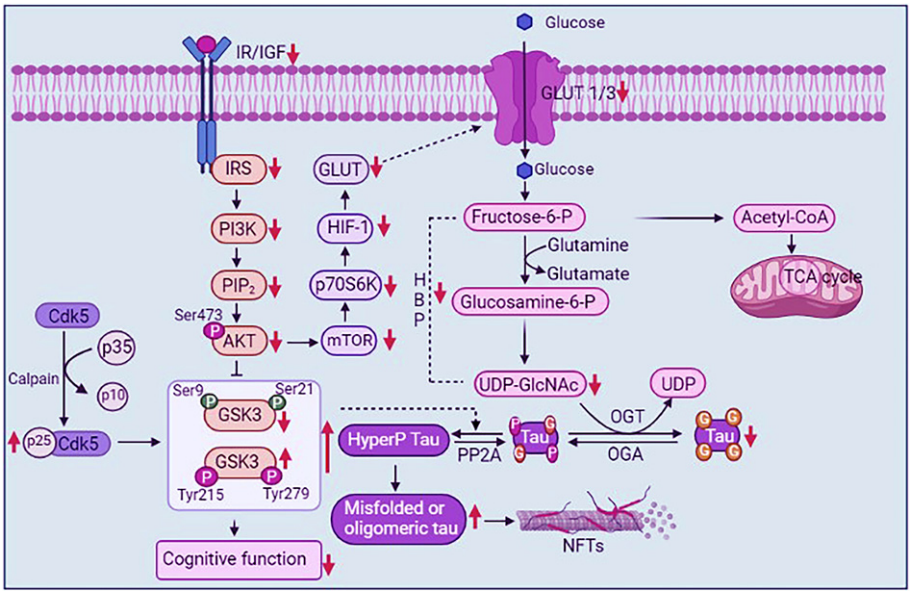

Fig. 4. Regulation of PI3K/Akt signaling in Alzheimer's disease (AD) and ischemic stroke (IS). In both of the diseases, PI3K/Akt signaling is dysregulated by the reduced protein expression levels of insulin signaling related proteins such as IR, IRS, PI3K, PIP2, and Akt. The downstream signaling proteins such as GSK3 is over activated and Cdk5/p25 pathway leads to tau hyperphosphorylation in AD. In AD and IS, insulin resistance in the brain diminishes the glucose receptor GLUT4, and due to impaired PI3k/Akt signaling pathway, the glucose receptors such as GLUT 1, 2, and 3 may reduce in the brain, causing the decrease of glucose metabolism. In addition, lower levels of glucose reduce UDP-GlcNAc concentration via the hexosamine biosynthetic pathway (HBP) and subsequently diminished tau O-GlcNAcylation. Reduced O-GlcNAcylation helps in tau hyperphosphorylation, tau oligomerization and ultimately neurofibrillary tangles are produced in AD [73]. Akt, protein kinase B; CdK 5, cyclin-dependent kinase 5; Fructose-6-p, fructose-6-phosphate; GlcNAc, β-N-acetylglucosamine; Glucosamine-6-P, glucosamine-6-Phosphate; GLUT, glucose transporter; GSK3, glycogen synthetase kinases 3; HBP, hexosamine biosynthetic pathway; HIF-1, hypoxia inducible factor-1; IGF, insulin growth factor; IR, insulin receptor; IRS, insulin receptor substrate; m-TOR, mammalian target of rapamycin; NFTs, neurofibrillary tangles; OGA, O-GlcNAcase; OGT, O-GlcNAc transferase; P, phosphate group; p70S6K, ribosomal protein S6 kinase with a molecular weight of 70 kD; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol (3,4)-bisphosphate; TCA, tricarboxylic acid cycle; UDP, uridine diphosphate.

rylation. The levels of phospho-GSK3 at Ser9 and phospho-GSK3 at Ser21 were significantly decreased in AD. The PI3K-Akt signaling molecules are negatively connected with the tau hyperphosphorylation at Ser396, Ser202/Thr205, and Cdk5 and to its cofactors p35 and p25 in the brain. The downregulation of Akt decreases the expression of main glucose transporters such as GLUT3 and GLUT4. The overactivation of GSK3β increases the tau hyperphosphorylation and decreases the microtubule-binding activity of tau of a sporadic AD rat model [71, 73, 74] (Fig. 4). It has also been recommended that impaired brain insulin signaling may lead to the reduction of IRS-1 and PI3K phosphorylation, downregulation of O-GlcNAcylation, overactivation of GSK3β, and acceleration of tau hyperphosphorylation in 3xTg-AD mice before the onset of peripheral insulin resistance, whereas Tg2576 mice show dysregulation of these signaling proteins after the onset of peripheral insulin resistance. These inconsistencies may be specific to the tau pathology that develops in 3xTg-AD mice [75]. Reducing CNS insulin signaling dysfunction in patients with mild cognitive impairment or early-stage AD may support a decrease in peripheral insulin resistance [76]. Analysis of post-mortem human AD brain revealed that the protein expression of IRS, IGFs, and glucose receptors are significantly diminished [77]. Therefore, it is suggested that impairment of glucose metabolism is due to both pre-and post-peripheral insulin resistance, causing Aβ and tau pathologies.

Association between PI3K/Akt signaling and stroke

PI3K/Akt signaling pathway is directly involved in the neuroprotection against ischemic brain damage and displays a critical role in promoting neuronal survival after IS [17]. Decreased level of phosphorylation of GSK3β on Ser9 was found in the penumbra cortex in IS rat brain [78]. The expression levels of p70S6K on Thr389 reduced at 1, 4, and 24 h of reper-

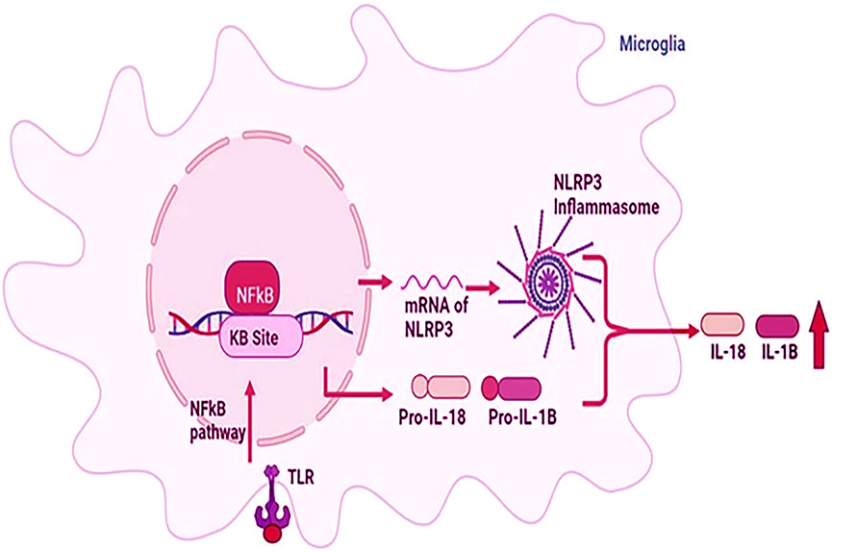

Fig. 5. Schematic representation of inflammasome in Alzheimer's disease (AD) and ischemic stroke (IS). Inflammation is triggered by the activation of the NFkB pathway and NLRP1/3 inflammasome pathway in AD and IS. Finally, IL-18 and IL-1β are produced as proinflammatory cytokines. IL, interleukin; IL-1B, interleukin 1-beta; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding oligomerization domain like receptor pyrin domain-containing protein 3; TLR, toll-like receptor.

fusion, while the levels of total p70S6K remained the same at 1 and 4 h of reperfusion and then declined at 24 h of reperfusion [79]. The consequences suggest that cell survival pathways by Akt1 and p70S6K signaling are suppressed after ischemia, which may donate to the progression of neuronal cell death after ischemic stroke (Fig. 4). Protein expression of p-Akt and total Akt were also reduced after 24 hours of cerebral ischemia in male rat brains [80]. Therefore, PI3K/Akt signaling pathways is broadly considered to play a critical role in the neuroprotective effect against ischemic brain injury.

Hyperglycemia is an indicator of IS, contributing to a significant increase in brain ischemia [81, 82]. Considerable evidence demonstrates that glucose transporters mainly GLUT1 and GLUT3 are important to maintain energy homeostasis, especially in IS patients [83]. In the post-ischemic condition after day-1, the expression of GLUT1 mRNA increases at 175% and returns to the normal level by day 3 [84]. During ischemia, the cerebral glucose level is lower than normal [85]. Three days after ischemic stroke, the expression of mRNA of GLUT3 protein starts improving but is still below the normal level, causing neuronal death [85]. Therefore, increasing the expression of GLUT3 and regulating the brain glucose metabolism during pre and post-ischemic cerebral injury is urgently needed.

INFLAMMATORY SIGNALING PATHWAY IN AD AND STROKE

Inflammation is one of the most important pathophysiological conditions in AD and stroke (Fig. 5). It is mainly mediated by microglia [86, 87], oligodendrocytes [88, 89], and astrocytes [90, 91] in the brain.

Association between inflammation and AD

Extracellular Aβ deposition activates microglia and triggers pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) in the AD brain [92]. Microglia and astrocytes have an important role in Aβ clearance and degradation [93], but in case of overproduction of Aβ and pro-inflammatory cytokines, microglia fail to activate the effective phagocytic response to clear the Aβ from the brain, causing the deposition of more pro-inflammatory cytokines in the AD brain [93].

Recent findings showed significant elevated TLR2 activation in Tg2576 AD mice [94, 95] which may also contribute to Aβ accumulation in the brain [96]. However, TLR9 can decrease in both Aβ and tau pathologies in various AD transgenic mouse models and rescue their cognitive deficits [97]. In AD patho-

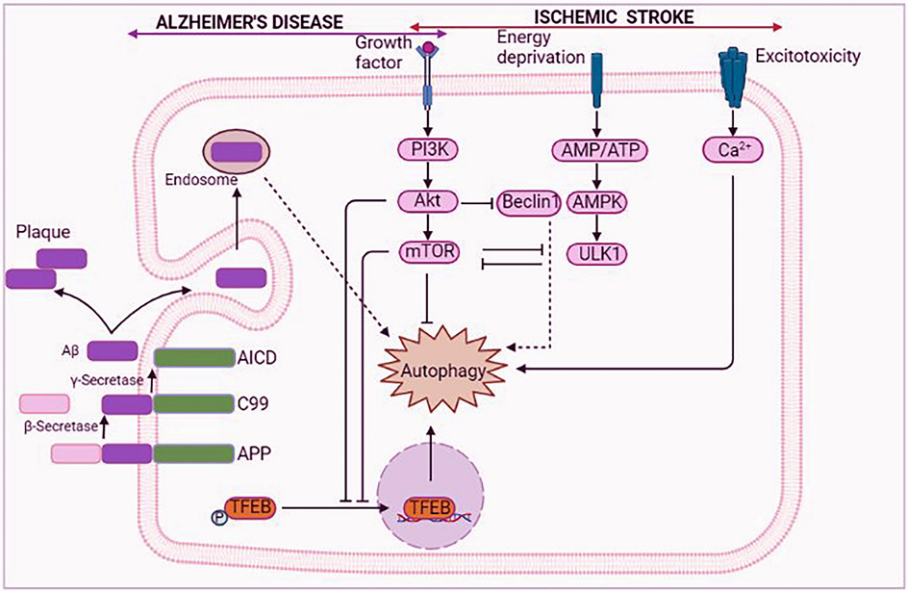

Fig. 6. Schematic representation of mTOR-autophagy pathway in Alzheimer's disease (AD) and ischemic stroke (IS). In AD, Aβ participate in autophagy via the endosome. The downregulation of mTOR-autophagy pathway is found in AD and IS. AICD, amyloid precursor protein intracellular domain; Akt, protein kinase B; AMP, adenosine 5'-monophosphate; AMPK, adenosine monophosphate-activated protein kinase; APP, amyloid precursor protein; ATP, adenosine tri-phosphate; Aβ, amyloid-β; C99, 99-residue C-terminal fragment; mTOR, mammalian target of rapamycin; PI3k, phosphatidylinositol 3-kinase; TFEB, transcription factor EB; ULK1, Unc-51 like autophagy activating kinase 1.

genesis, NF-kB stimulates NLRP3 inflammasome, and proinflammatory cytokines such as IL-1β and IL-18 are produced, finally getting mature IL-1β and IL-18 and released from microglia to the extracellular environment [98] (Fig. 5).

Association between inflammation and stroke

Oxidative stress and inflammation are mainly involved in the pathological development of late post-ischemic conditions [99]. NF-kB signaling cascade is activated within 2 hours after brain injury in a middle cerebral artery occlusion (MCAO) rat model [100]. Stimulated NF-kB controls the gene expression of proinflammatory cytokines such as TNF-α and IL-1β. In addition, toll-like receptors (TLR) mediated signaling pathway via NF-kB is also stimulated and upregulated in ischemic brain injury by MCAO in C57BL/6 mice [101]. TLRs play a vital role in cerebral brain injury. The protein expression of TLRs is augmented which is linked with the inflammatory cascade in IS [102]. In addition, TLR4 also rises brain ischemic lesions. The protein expression of TLR4, TNF-α, caspase-1, NLRP3, and IL-8 significantly increased in the cerebral ischemia-reperfusion mice model [103]. Oxidative stress markers such as nitric oxide and malondialdehyde are increased whereas superoxide dismutase is reduced in these mice brains. The levels of NLRP1, NLRP3, IL-1β, and IL-18 were elevated in the animal model and human brain with IS [104] (Fig. 5). Therefore, a thorough understanding of the widespread mechanisms of post-ischemic neuroinflammatory signaling pathways is needed for the new treatment strategies for IS.

AUTOPHAGY PATHWAY IN AD AND STROKE

Autophagy is a cellular degradation process and is essential for the maintenance of cellular homeostasis through the synthesis, deprivation, and turnover of different cellular components. The mechanism of autophagy is carried out through the formation of vesicle nucleation, vesicle elongation, and autophagosome. Then autophagosome is fused with the lysosome, forming an autolysosome in which engulfed material and inner membrane is degraded [105]. Dysfunction of autophagy accelerates AD and stroke progression and pathogenesis [106, 107] (Fig. 6).

Association between autophagy and AD

Dysregulation of autophagy is associated with AD pathogenesis. The precise role of autophagy in AD through the endosomal-lysosomal system is still debatable. Some researchers suggested that abnormal autophagy induction helps to create the necessary compartment for the accumulation of autophagic vacuoles holding Aβ and finally forming Aβ plaques [108, 109]. Other evidence indicated that either impaired autophagic clearance or deteriorating autophagic activity may play in AD pathogenesis and progression [110]. Therefore, autophagy is a key regulator of Aβ generation and clearance. Aβ is released in an autophagy-dependent manner from neurons in AD pathology [111]. In the early stage of AD, amyloid-β protein precursor (AβPP) processing and Aβ accumulation-mediated autophagy facilitate the removal of toxic protein aggregates via mechanistic target of the rapamycin (mTOR)-dependent and -independent pathways [112, 113]. In addition, autophagy-related genes and AβPP are believed to influence AD development and offer a bidirectional link between autophagy and AD progression. Fewer extracellular Aβ plaques were found in the autophagy-deficient AβPP transgenic mice by the inability of cells with disrupted autophagy to secrete Aβ in the brain [114]. In AD the mechanism of autophagy modulation in AβPP processing and Aβ metabolism and its pathogenesis are not well known. The mTOR signaling pathway controls autophagy in AD (Fig. 6).

Numerous studies suggest that the levels of phospho-mTOR and its downstream signaling molecules such as ribosomal protein S6 kinase beta-1 (p70S6K) and the eukaryotic translation factor 4E (eIF4E) are elevated in postmortem human AD brains, suggesting increased mTOR activity in the AD brains [115]. The increased mTOR activity was connected with enhanced tau hyperphosphorylation [112]. In short, the downregulation of mTOR signaling proteins may reduce autophagy which accelerates the Aβ aggregation and tau hyperphosphorylation in AD pathogenesis.

Association between autophagy and stroke

Numerous evidence indicates that autophagy is triggered in neurons, glial cells, and brain microvascular cells upon IS [116]. But the exact molecular mechanism of autophagy in IS is not well known. However, recent accumulating evidence in IS showed that autophagy inhibits inflammasome activation by triggering mTOR and AMPK pathways in cellular homeostasis. The autophagy-forming markers such as LC3-II and Beclin-1 are upregulated in IS. Autophagy can retrieve the neuronal tissue after IS by the phenotypic alteration of microglia through the NF-κB pathway [107]. Additionally, the autophagy-mediated death-promoting mechanism promotes numerous relevant stimuli in post-ischemic neuronal damage through the downregulation of autophagy signaling molecules such as autophagy-related protein 7, Beclin-1, and LC3-II [117]. In addition, mTOR signaling molecules are reduced in autophagy via phosphorylation of its downstream signaling factors (p70S6K) and 4E binding protein 1 (4EBP1) [117, 118] (Fig. 6). Hence, activation of the mTOR signaling pathway could be an effective strategy for the reduction of infarct size after post-cerebral ischemia.

NOTCH SIGNALING PATHWAY IN AD AND STROKE

Notch signaling is intermediated by the communication of one the ligand of Delta/Serrate/LAG2 (i.e., JAG1, JAG2, DLL3, and DLL4) in one cell with one of the Notch receptors (i.e., Notch1, Notch2, Notch3, and Notch4) in the neighboring cell during development and aging processes. The notch intercellular domain (NICD) is the most contributing factor in Notch signaling. It is produced by the proteolytic cleavage of the receptor-ligand interaction cascade and then NICD is translocated into the nucleus and induces the gene expression which is involved in proliferation, differential, and development (Fig. 7). Notch signaling is activated in AD [119] and IS [120].

Association between Notch signaling and AD

Presenilin (PS), the catalytic member of the γ-secretase proteolytic complex, plays an important role in the cleavage of AβPP and Aβ production through Notch signaling in the early-onset familial AD pathogenesis. Alterations in proteolysis of the Notch by γ-secretase may participate in the pathogenesis of AD [121]. Notch proteins also interact with PSs and with AβPP in postmitotic neurons in AD. Mutations in the genes encoding the AβPP and PS1, and PS2 are occasionally responsible for early-onset AD. Loss of specific memory and learning and behavioral and cognitive impairment is associated with the Notch signaling pathway in AD [119, 121] (Fig. 7). High expression of Notch1 was observed in

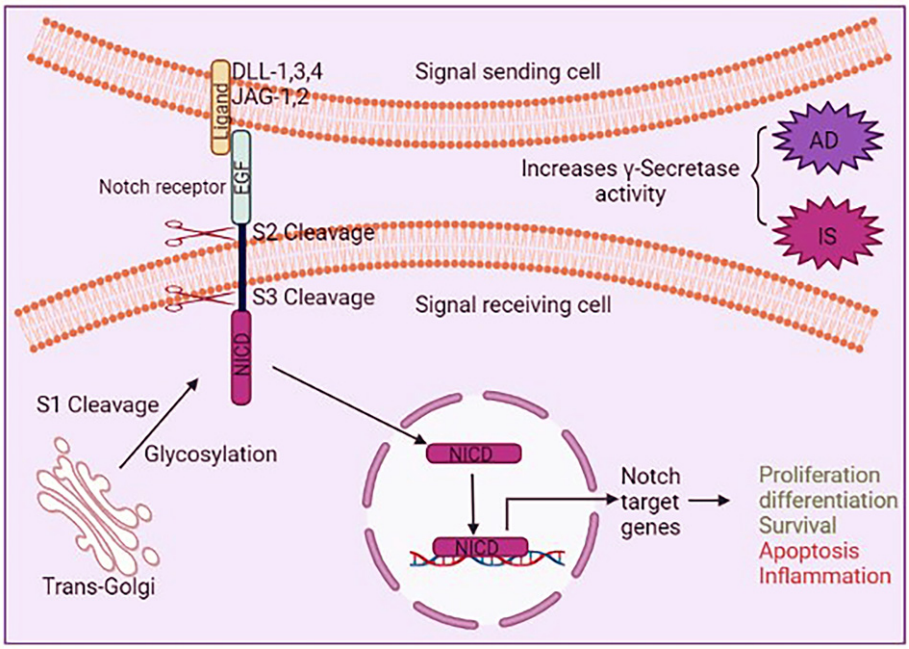

Fig. 7. Schematic representation of the Notch signaling. Notch signaling is started by three sequential proteolytic cleavages. First, Notch is cut by Furin at the trans-Golgi and it is known as S1 cleavage. Glycosylation occurs in this step. Then the extracellular domain of Notch, EGF repeats, interacts with several ligands such as Jagged-1, -3, and -4 and Delta 1 and 2 on signal sending cells is cleaved (S2 cleavage) by metalloproteases of the ADAM family. Then Notch intercellular domain (NICD) is cut by a γ-secretase activity of presenilin (PS) (S3 cleavage). γ-secretase activity is improved in AD and ischemic stroke conditions. Activated Notch increases apoptotic and inflammation in the brain. DLL, Delta-like; JAG, jagged protein; NICD, Notch intracellular domain.

the AD cortex, indicating the enhancement of Aβ production and alteration of Notch signaling in the AD brain [122]. Two-fold Notch expression was higher in the AD brain than in the age-matched control human brain [123]. It suggested that higher Notch signaling and expression could be a detrimental effect on AD. Therefore, altered Notch signaling in AD is needed to be further investigated.

Association between Notch signaling and stroke

In vivo and *in vitro* studies indicated that Notch signaling contributes to IS. The levels of γ-secretase and NICD were augmented in post-ischemia-transgenic mice [124]. Increased levels of NICD were also found in primary neuron culture upon ischemia-like conditions. Furthermore, it has been conveyed that Notch is upregulated instantly after initiation of ischemia in animal models [124, 125]. The contribution of the Notch pathway has been recognized in the growth and proliferation of blood vessels in IS pathogenesis. The levels of NICD and Jag1 positive endothelial cells amplified by activation of downstream signals including Bim, P65, and NFκB donated to the development and deterioration of IS in stroke brains of human and mouse models [120, 125]. The γ-secretase inhibitor might recover the stroke signs through the downregulation of NICD and downstream targets (Fig. 7). Therefore, Notch signaling has a vital role in brain damage in IS.

GUT-BRAIN AXIS IN AD AND STROKE

Gut microbiota has a proven role in regulating multiple neurochemical pathways through the highly interconnected "gut-brain axis (GBA)". "Gut-brain axis" states a bidirectional communication network between the CNS and the gastrointestinal tract involving multiple overlapping pathways such as the autonomic, neuroendocrine, and immune systems and; directly affecting the vagus nerve to the brain. The gut microbiome controls BBB integrity, neural development, aging, and CNS immune activation. Alteration of gut-microbiota diversity breaks the gut barrier integrity and activates systemic neuroinflammation, promotes neuronal injury, and finally neurodegenerative diseases such as AD and stroke. Dysbiosis accelerates or causes impaired GBA sig-

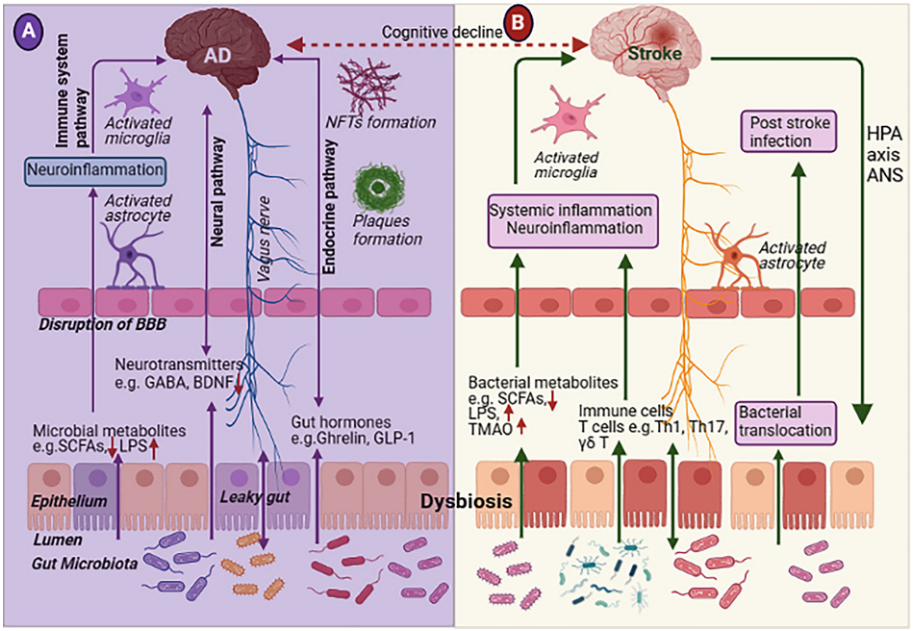

Fig. 8. Schematic representation of microbiome-gut-brain axis in (A) Alzheimer's disease (AD) and (B) stroke. The bidirectional gut-brain interaction communicates by mainly four pathways such as metabolic, immune, neural and endocrine signaling pathways. Gut dysbiosis changes gut-microbiota diversity and gut microbiota enter to blood circulation by leaky gut in both AD and stroke. In addition, the ischemic brain triggers the gut-microbiota diversity by the hypothalamic-pituitary-adrenal (HPA) pathway which plays an important role in stroke outcomes. BBB, blood-brain barrier; BDNF, brain derived neurotrophic factor; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide 1; HPA, hypothalamus-pituitary-adrenal; LPS, lipopolysaccharide; NFTs, neurofibrillary tangles; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide.

naling in AD [126] and in stroke [127]. Therefore, the GBA is an important pathway of communication between the gut and the brain, and dynamically contributes to AD and IS pathogenesis (Fig. 8).

Association between gut-brain axis and AD

Gut dysbiosis may worsen BBB permeability and cause AD pathogenesis. Numerous evidence suggests that gut microbiota can control brain and behavioral function and produce bacterial amyloid (also known as curli). Curli may trigger the immune cells in the gut and/or brain and activates neuroinflammation [128]. Bacteria containing lipopolysaccharides may upregulate pro-inflammatory cytokines through GBA [129]. Also, reduced beneficial bacteria may impact the levels of short-chain fatty acid (SCFAs) bioavailability which may subsequently change the metabolic pathways and further contribute Aβ deposition in AD brain [130, 131]. Elevated levels of *Helicobacteraceae Desulfovibrionaceae* and *Odoribacter* were found in APP/PSI mice [132]. Reduced levels of *Acetobacter* and *Lactobacilli* were found in an AD Drosophila model, and it was associated with reduced SCFAs levels [133]. Higher quantities of *Bacteroids, Ruminococci*, *Actinobacteriae, Lachnospiraceae,* and *Selenomonadales* levels were observed in the fecal samples of AD patients [134]. Low loads of *Firmicutes* and *Bifidobacterium* and high loads of Bacteroidetes were found in the fecal samples of AD patients, suggesting the presence of gut dysbiosis in AD patients [135]. Gut microbiota may impact AD pathogenesis via numerous pathways such as neuroinflammation, oxidative stress, pathogenic translocation, and neurotransmitter dysregulation. The gut microbiome needs more attention and understanding the interaction in terms of amyloid pathology may help with beneficially modifying the bacterial consortium to improve the quality of life in pre-symptomatic AD patients.

Association between gut-brain axis and stroke

Emerging clues propose the important role of gut microbiota in the pathology of stroke. Dysbiosis increases the risk factors of strokes such as systemic inflammation, atherosclerosis, and cardiometabolic disorders. Dysbiosis induces systemic inflammation,

neuroinflammation, and infection in acute cerebral ischemia which has a detrimental effect on stroke outcomes. Several pathways such as bacterial components, gut metabolites, immune cells, and bacterial translocation are involved in stroke. The ischemia brain also stimulates the gut microbial diversity through the neural or hypothalamic-pituitary-adrenal pathways, which have a harmful effect on stroke outcomes [136]. In addition, many gut microbiota such as *Bacteroides, Prevotella*, and *Faecali bacterium* are significantly reduced in IS patients compared with their healthy counterparts [137]. Increased levels of *Lactobacillus ruminis* and decreased *Lactobacillus sakei* were identified in IS patients, which induce the proinflammatory cytokine IL-8 secretion [137, 138]. Though the research on the gut inflammatory and immune response after stroke is still in its initial stages, recent investigations between clinical trials [138–142] and animal experiments [143–145] have provided some interesting clues regarding the role of gut microbiota in IS outcomes. Hence, the gut microbiome plays a pivotal role in gut inflammation and the immune response to pre/post-ischemic brain injury and stroke.

CONCLUSION

In a nutshell, we concluded that both diseases share several common abnormalities including excitotoxicity, ApoE4, impaired PI3K/Akt pathway, increased neuroinflammation, decreased mTOR-autophagy signaling, decreased Notch signaling, and gut dysbiosis. It has been recommended that AD and stroke disrupt common cellular and molecular pathways and each disease reinforces the progression of the other. This review mainly focused on the biochemical pathways shared by AD and IS. Understanding the key mechanisms underlying the toxic interaction between these diseases may provide opportunities for designing effective therapeutic strategies. Whether stroke is directly involved in AD or acts indirectly as a contributing factor to AD pathogenesis needs to be established. Hence, the prevention of stroke and its treatment may have important implications for the alleviation of AD and warrant further investigations.

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