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Cholinergic System Aggravates Sik-1/Sik-3 Mediated Suppression Of Ca2+ Pathway Associated Oxidative Stress-Inflammatory Axis In Neurotoxic Alzheimer's Type Dementia

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Abstract:

The AD is an age-related neurodegenerative disorder characterized by progressive anterograde amnesia, cerebral atrophy, functional decline, and eventual death. among people of ages ranging from 60 to 84, 24.3 million are suffering from AD. with the number of cases estimated to rise to nearly 106 million by 2050. The pathophysiology of AD includes both structural and functional abnormalities including multiple anatomical lesions occur in the brain, including the appearance of senile plaques consisting of Aβ and neurofibrillary tangles containing phosphorylated tau, and major synaptic changes leads to substantial loss of synaptic profiles. In AD, there are also significant oxidative stress- inflammation leads to mitochondrial abnormalities and severe synaptic damage and neuronal death due to overactivation of Ca2+ pathway mediated by various factors including glutamate hyperactivity. Furthermore, the cholinergic system activation achieving the equilibrium of overactivated Ca2+ path and further activate downstream salt-inducible kinases (SIK1/SIK3) belong to AMP-activated protein kinase (AMPK) family, and functions mainly involve in regulating energy response-related physiological processes, such as gluconeogenesis and lipid metabolism. However, compared with another well-established energy-response kinase AMPK, SIKs roles in human diseases, especially in AD are rarely investigated. Thus, in this review our primary aim to investigate the Ca2+ pathway associated increase in oxidative stress- neuroinflammatory axis in AD progression and the effectiveness of cholinergic system via aggravation of SIK-1/SIK-3 mediated suppression of progression of AD is more efficient therapeutic strategy.

Keywords: Alzheimer's disease, Neurodegeneration, Oxidative stress- Inflammatory axis, Aβ peptides, Tau protein, Glutamate, Ca2+ pathway, Donepezil, SIKs, ROS, TNF-α, Interleukins, NF-κB signaling

Introduction:

Today, aging human populations around the globe are facing an epidemic of Alzheimer's disease (AD). Furthermore, among people of ages ranging from 60 to 84, 24.3 million are suffering from AD(1), with the number of cases estimated to rise to nearly 106 million by 2050 (2). The AD is an age-related neurodegenerative disorder characterized by progressive anterograde amnesia, cerebral atrophy, functional decline, and eventual death.In addition to, AD is the most common dementia type followed by vascular dementia(3). Dementia is a cognitive disability characterised by a decline in mental ability and globally occurs every 3 s. As dementia progressively leads to complete loss of autonomy requiring a permanent support, this disease represents a tremendous social and economic cost for our societies(4). Apart from genetic and socio-demographic factors such as gender and educational level, some modifiable factors such as vascular risk factors(5) or drugs consumption(6) are suspected to be associated with the risk of dementia. Clinical symptoms of AD include progressive memory decline, impaired executive function and difficulties executing routine daily activity; early symptoms of AD onset include changes in thinking or unconscious behavior, memory impairment with respect to new information, and dysfunctional changes in language and speech(7). In addition, 20 to 30% of early AD patients show significant depressive symptoms and mood changes (8). Patients in advanced stages of AD suffer from severe memory loss, hallucinations, disorientation, and lack self-sufficiency, where individuals eventually die due to respiratory syndrome(9). Although possible pharmacological interventions such as donepezil hydrochloride, a cholinergic system activator have been suggested, there are no popular therapies that decelerate or terminate its progression(10, 11). Moreover, recent study also explores blocking of cholinergic system with anti-cholinergic type of drugs increase the risk of incident mild cognitive impairment and cognitive decline, and effects were significantly enhanced among individuals with genetic risk factors and CSF-based AD pathophysiological markers(12). Thus, conforming the involvement of cholinergic system in AD. However, the treatment has limited efficacy, are symptomatic, and are unable to decelerate disease progression (13, 14) possibly because they are administered at advanced AD stages when synapse loss is too pronounced. This lack of disease modifying treatment is due to poor identification of effective biomarkers for early diagnosis. Accordingly, intense efforts are ongoing to understand neurological changes associated with AD progression. Thus, in this review our primary aim to investigate the Ca2+ pathway associated increase in oxidative stress- neuroinflammatory axis in AD progression and the effectiveness of cholinergic system via aggravation of salt inducible kinas-3 (SIK-3) mediated suppression of progression of AD is more efficient therapeutic strategy.

Selection of literature for review:

The potentially relevant studies were retrieved from the ScienceDirect/Medline/PubMed/Public library of science/Mendeley/Springer link and Google Scholar. Multiple keywords were used for the literature search both alone as well as in combination. Some of the important keywords used for literature search were 'Definition of AD', 'Epidemiology of AD', 'AD associated inflammation', 'Mechanism of apoptosis in AD', 'Involvement of Aβ in neurodegeneration, 'AD associated glutamate receptor activation', 'Risk factor for AD', 'Pathogenesis of AD', 'Reactive oxygen species mediated mitochondrial defect, 'Role of donepezil for improving inflammation', 'Mechanism of action of donepezil', 'salt-inducible kinases association in inflammatory signalling', 'Cellular metabolism in AD', 'Inflammasome pathway in cell death', 'Cholinergic system and calcium pathway', 'Innate and Adaptive

immunity in AD'. Only articles with English language were considered in the present study. The reference lists of retrieved articles were also screened to find relevant articles that were not identified by the initial search strategy.

Pathophysiology of Alzheimer's disease:

The pathophysiology of AD includes both structural and functional abnormalities. As AD progresses, multiple anatomical lesions occur in the brain, including the appearance of senile plaques consisting of Aβ and neurofibrillary tangles containing phosphorylated tau, and major synaptic changesleads to substantial loss of synaptic profiles(15). In AD, there are also significant oxidative stress-inflammationleads to mitochondrial abnormalities and severe synaptic damage and neuronal death(15). Glutamate is the most abundant excitatory neurotransmitter in the mammalian Central Nervous System (CNS), acting at ionotropic and metabotropic glutamate receptors. Ionotropic glutamate receptors (iGluRs), responsible for fast neuronal communication at excitatory synapses, comprise three subfamilies: α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and NMDARs(16). NMDARs are glutamate-triggered ion-gated cationic channels which play a pivotal role in excitatory synaptic transmission, plasticity and excitotoxicity in the nervous system(17). Seven NMDAR subunits have been characterized in total for GluN1, GluN2 and GluN3 subtypes: GluN1, GluN2A through D, and GluN3A and B. Structurally, functional NMDAR comprises two GluN1 and GluN2 or GluN3 subunits which can form a Ca^{2+}-permeable ion channel(18)It is extensively distributed in the CNS whereas it is almost exclusively located intracellularly. Activation of NMDARs through the accumulation of Aβ likely occurs during early stages of disease progression(19). Similar to NMDA stimulation, Aβ evoke immediate cellular Ca^{2+} influx through the activation of GluN2B-containing NMDARs in primary neurons.Glutamate is prevalent in neocortical and hippocampal pyramidal neurons and plays a role in synaptic plasticity, learning, and memory consolidation. Synaptic glutamate signaling is tightly regulated by clearance through high-affinity excitatory amino acid transporters(20). However, postmortem analysis shows that vesicular glutamate transporter 1 boutons were elevated in pre-clinical AD cases(21) while glutamate transporters were decreased in AD patients(22). Indicating mechanisms responsible for glutamatergic regulation are altered during different stages of disease progression. A contributing factor to this dysregulation is the accumulation of soluble Aβ isoforms that initiates synaptic dysfunction causing the eventual neurodegeneration(23, 24). Moreover, the underlying cause of selective hippocampal CA1 neuronal degeneration is a result of glutamate-mediated excitotoxic mechanisms involving excessive calcium influx through NMDAR activation, mitochondrial dysfunction, and reactive oxygen species. These events culminate in necrotic cell loss that releases more glutamate into the extracellular space thus propagating damage to surrounding neurons(25). In addition to that, tau phosphorylation is regulated by multiple protein kinases and phosphatases. Tau kinases can be classified to two categories: 1) Ser/Thr kinases such as CDK5, glycogen synthase kinase 3β (GSK3β), mitogen-activated protein kinase, Ca^{2+}/calmodulin-dependent protein kinase II, microtubule-affinity regulating kinase, protein kinase A (PKA), protein kinase C, Akt, TTBK1/2, CK1, DYRK1A, and 2) tyrosine kinases including Fyn, Src, Syk and c-Abl(26). Tau is dephosphorylated by protein phosphatase 1 (PP1), PP2A, PP2B and PP5(27-29). Tau hyperphosphorylation may result from imbalanced activity or expression of tau kinases and protein phosphatases. In support of this, increased GSK3β expression and CDK5 activity, decreased expression of PP1 and PP2A, and decreased PP2A activity has been observed in

specific brain regions in AD patients(30-34). Since hyperphosphorylated tau species are enriched in NFTs, strategies to suppress tau phosphorylation may be a viable therapeutic strategy in AD and other related tauopathies. Unfortunately, attempts to target hyperphosphorylated tau or inhibit tau kinases have not seen success so far.Therefore, understanding changes to glutamatergic signaling at different stages of AD progression could lead to the development of disease-stage specific therapeutics (Figure 1).

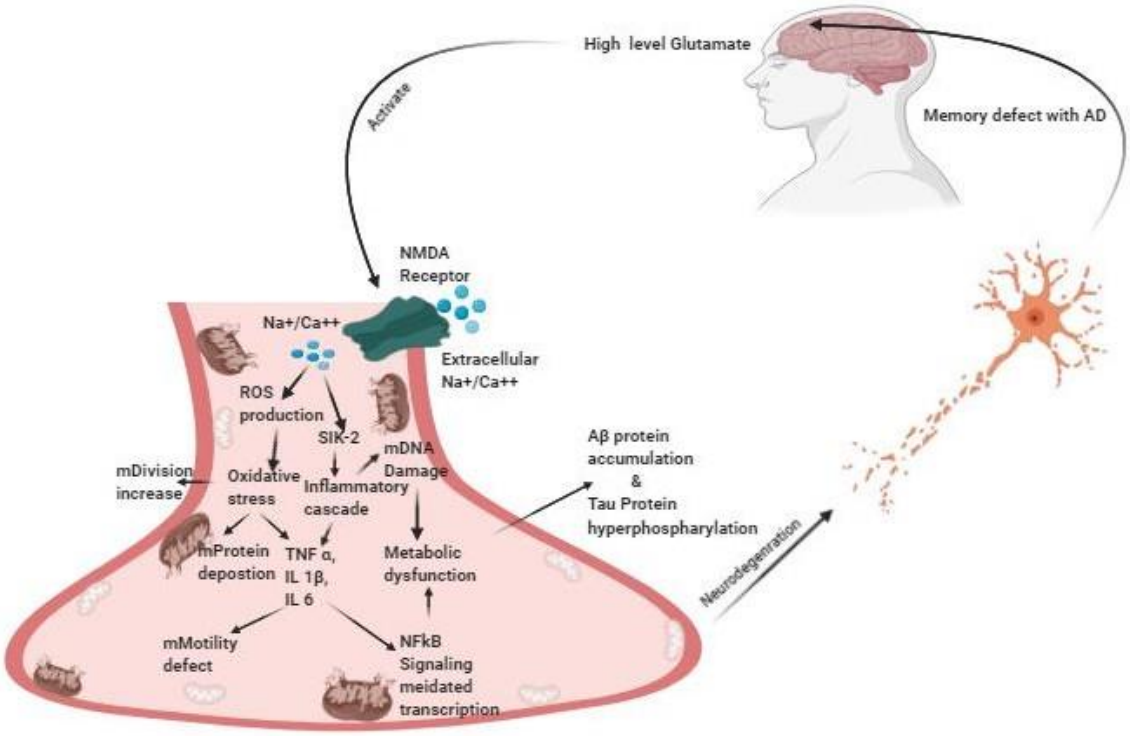

Figure 1: The mechanistic bio-molecular involvement of calcium pathway mediated aggravation of oxidative stress inflammatory axis defect and Alzhiemer's disease progression

Involvement of ca2+ pathway associated oxidative stress- inflammatory axis in disease progression:

In the biomolecular pathology of AD accompanied by neuroinflammatory reactions, oxidative stress, and free radical formation probably associated with mitochondrial dysfunction, excitotoxic reactions, alterations in cholesterol metabolism and lipid rafts, deficiencies in neurotransmitters (especially acetylcholine) and neurotrophic factor function, defective activity of the ubiquitin-proteasome, and chaperone systems and cerebrovascular dysregulation(35). Accumulating evidence demonstrates that the toxicity is principally mediated by excessive Ca^{2+} entry, primarily through NMDARs(36-39). since NMDARs have a much higher permeability for calcium ions compared to other iGluRs(40). In this regard,

the modest depolarization of the postsynaptic membrane and other factors that relieve the Mg^{2+} blockade can activate NMDARs in a mild and chronic way, which causes the prolonged Ca^{2+} influx into the postsynaptic neuron. The pathological level of Ca^{2+} signaling leads to gradual loss of synaptic function and ultimate neuronal cell death, which correlates clinically with the progressive decline in cognition/memory and the development of pathological neural anatomy seen in AD patients, and this, in turn, rationalizes the clinical trial of memantine, an NMDAR antagonist, as a symptomatological and neuroprotective treatment for AD(41-43).Furthermore, a pathological increase in the amount of Aβ explore the functional and morphological changes in glial cells, including calcium dysregulation. In fact, microglia and astrocytes are activated close to senile plaques to internalize and break down Aβ (44). This cellular activation may result in an inflammatory response and OS, playing a dual role in the pathophysiology of AD with both detrimental and neuroprotective results. Inflammatory mediators (i.e., bradykinin) may increase intracellular calcium concentration via nicotinic receptors and PI3K–Akt pathway in cultured astrocytes(45). In the CNS, nAChRs are expressed in neurons and glial cells, including microglia, oligodendrocytes and astrocytes, with highest expression in astrocytes among the glial cells that release Ca2+ dependent release of glutamate neurotransmitters(46, 47). Oxidative stress manifests early in AD, which supports the notion that oxidative stress may drive Aβ-induced AD pathogenesis (48). Aβ peptides can induce ROS production from mitochondria, leading to release of cytochrome c and apoptosis-inducing factor, thereby driving mitochondrial dysfunction, cell apoptosis and neuronal loss (49).However, Aβ interacts with several types of surface receptors in astrocytes which leads to calcium entry through the activation of calcium channels, including purinergic receptor P2Y1(50)and glutamate metabotropic receptor mGluR5(51, 52). Furthermore, Aβ can induce abnormal elevations in extrasynaptic glutamate levels and subsequent extrasynaptic N-methyl-D-aspartic acid receptor (NMDAR)-mediated excitotoxicity. In addition to excreted glutamate can activate extrasynaptic NMDAR in neurons residing within neuron/astrocyte conjugates, resulting in Ca^{2+} efflux. This triggers multiple events, including mitochondrial dysfunction, caspase 3 activation, tau hyperphosphorylation, and excessive production of NO, ROS and VEG-F. These events result in damage to dendritic spines and neuronal synapses, disrupting neuronal/astrocytic communication(53, 54). Additionally, oligomeric Aβ can disrupt intracellular calcium balance, impair mitochondria dysfunction, and induce the production of reactive oxygen species (ROS). Mitochondria are the primary source of intracellular ROS and excessive ROS accumulation can further aggravate oxidative stress and mitochondrial DNA damage and dysfunction. All of these events eventually lead to neuronal apoptosis and cell death(55). As several study reports that psychological and chronic stress long-term activation of the HPA axis eventually leading to the secretion of glucocorticoid into the bloodstream, where blood glucocorticoid enters the brain through the BBB to activate the glucocorticoid receptor (GR in human) and mineral corticosteroid receptor (MR in mice) accompanied by permanent depletion of receptors and loss of hippocampal neurons suggesting the contributing factor in the pathogenesis of AD and other neurodegenerative diseases(56-59). Oxidative stress is further exacerbated by glutamate excitotoxicity through upregulation of glutamate receptors. In response to this, neurons and glial cells (i.e., microglia, astrocytes, and oligodendrocytes) mediate neuroimmune reactions through interactions with neuroimmune factors such as Toll-like receptors (TLRs), high-mobility group protein box 1 (HMGB1), and pro-inflammatory cytokines. In addition, Aβ-induced inflammation may also contribute to tau pathology. Aβ plays a primary role in activating several innate immune pathways, causing inflammatory response

and releasing inflammatory cytokines, such as interleukin-1β (IL-1β)(60, 61). Microglia may express other putative Aβ receptors, including Toll-like receptor 2/4 (TLR2/4) (62), complement receptor 3 (CR3)(63), Fc γ receptors IIb (FcγRIIb)(64), CD36(65, 66), advanced glycation end product receptor (RAGE)(67). These receptors cooperatively bind, internalize and clear Aβ, in addition to modulating microglial activation mediated neurotoxicity and memory impairment triggered by Aβ.The TLR can participate in AD pathogenesis and induce microglial inflammation phagocytosis through interactions with Aβ (68). Specifically, TLR4 activation induced NF-κB nuclear translocation, leading to the production of proinflammatory mediators(69). Moreover, activated microglia can also release proinflammatory cytokines including IL-1β, IL-6, as well as tumor necrosis factor-α (TNFα) in AD, and enhance oxidative stress through induced ROS generation(70, 71). It has been shown that IL-1β, lipopolysaccharide (LPS), prostaglandin E2 and tert-butyl hydroperoxide can reduce the microglial phagocytosis, thereby enhancing Aβ aggregation(72).The activated astrocytes in AD can aggravate inflammation by producing proinflammatory cytokines and active nitrogen and oxygen species (RNS, ROS) which interfere with synaptic germination and axonal growth(73, 74). Additionally, Aβ can indirectly induce glutamatergic toxicity by reducing distribution of the astrocytic glutamate transporter, GLT1 (EAAT2, SLC1A2) to the cell surface(75). Moreover, pathogenic tau species can also activate microglia and astrocytes independently of Aβ. Tau-dependent microglial activation can further enhance secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α(76-78), along with recent transcriptomic studies exhibiting the role of NF-κB activation and NLRP3-ASC for the inflammatory process in AD. Notably, Aβ also can activate NF-κB signaling and the NLRP3-ASC inflammasome (79, 80), suggesting that Aβ and tau share common mechanisms in microglia activation along with inflammatory events in AD. Furthermore, tau can be ubiquitinated by several E3 ligases including TNF receptor-associated factor 6 (TRAF6), induces Lys63-linked tau polyubiquitination and 26S proteasome-mediated tau degradation. Thus, consequence of ubiquitination on tau degradation and pathogenesis exert important relationship with TRAF6 activity. Henceforth, the achieving equilibrium in overall Ca^{2+} level in CNS, mediated by NMDAR leading to damage-associated learning and long-term memory deficits may be disease-stage specific therapeutics and help in prevention of overall progression of disease (Figure 2).

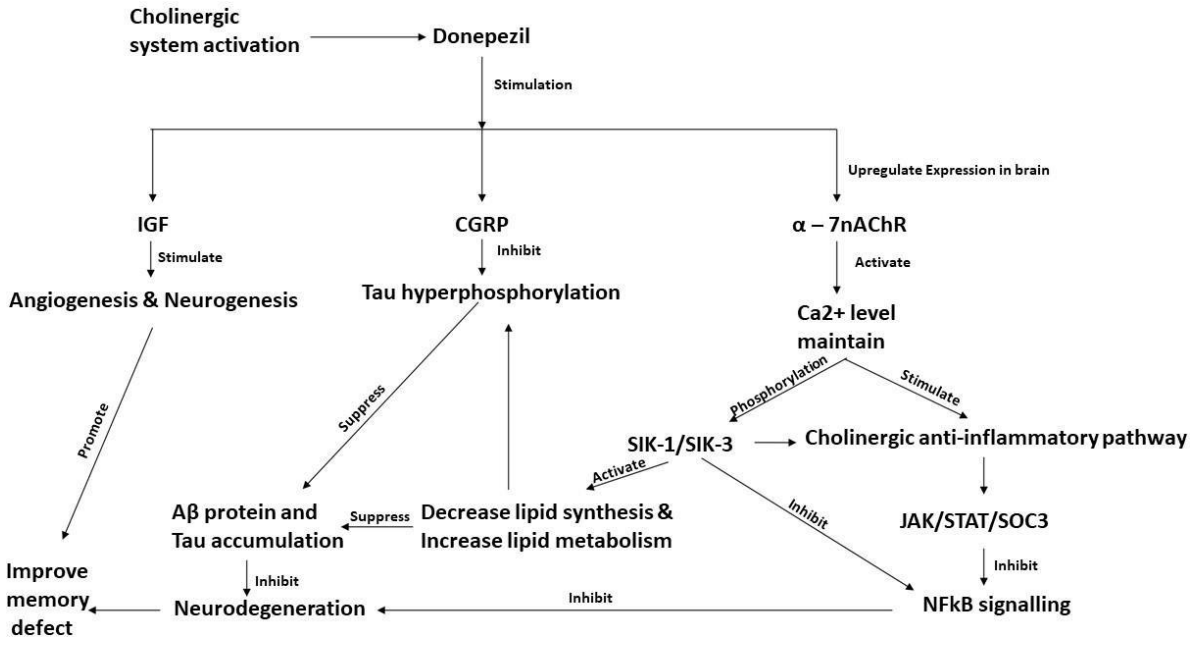

Figure 2: Explore cholinergic system aggravates SIK-1/SIK-3 mediated suppression of oxidative stress-inflammatory axis in neurotoxic Alzheimer's type dementia

Relationship of salt-inducible kinases (SKIs) with factors contributing alzheimer's disease:

Salt-inducible kinases (SIKs) belong to AMP-activated protein kinase (AMPK) family, and functions mainly involve in regulating energy response-related physiological processes, such as gluconeogenesis and lipid metabolism. However, compared with another well-established energy-response kinase AMPK, SIK roles in human diseases, especially in AD are rarely investigated.

Salt-inducible kinase (SIK) was first identified in the adrenal glands of high salt diet-fed rats in 1999(81). Further, the SIK family members, including SIK1–SIK3, are characterized as serine/threonine kinases that belong to AMP-activated protein kinase (AMPK) family(82, 83). Later, SIKs have shown self-phosphorylation, and play an important role in regulating adrenocortical function under the stimulation of high salt or adreno-cortico-tropic-hormone (ACTH)(81).SIK1 gene is located in human chromosome 21, while SIK2 and SIK3 genes are both located on chromosome 11(82). Beyond that, SIKs are also composed of a central sucrose non fermenting (SNF-1) homology (SNH) domain, and a long C-terminal domain (84, 85). The N-terminal KD contains a LKB1 phosphorylation site and is relatively conserved across SIK family. However, the SNH domain is distinct in SIKs, specifically, the similarity percentage of SIK2 and SIK3 compared that of SIK1 is 70% and 37% respectively. The C-terminal domain contains multiple protein kinase A (PKA) phosphorylation sites and is highly conserved between SIK1 and SIK2 (85). Of note, the SIK1 is abundantly expressed in the adrenal cortex, as well as in the adipose and neural tissues(83, 86, 87), while both SIK2 and SIK3 are ubiquitous in humans and mainly expressed in adipose and neural tissues, respectively(83).

In recent years, although the roles of SIKs in AD have drawn much attention due to their association

with neuroinflammation and undergo apoptosis through NF-κB signaling pathway.

It has been seen that alcohol consumption not only causes neuroinflammation and increase a variety of immune-related signaling processes but also responsible for Alzheimer's type dementia. Furthermore, A study establishes not only that SIK1 depletion promoted alcohol-induced neuroinflammation and microglial apoptosis, but also that the NF-κB signaling pathway is required for its activity(88).There are indications that overexpression of SIK-3 and SIK-1 but not SIK-2 inhibits NF-κB activation in response to TLR4 stimulation and decreases production of proinflammatory cytokines(89). Furthermore, SIK-3, but not SIK-1 and SIK-2, deficiency is responsible for the profound inflammatory response on lipopolysaccharide(90). In addition to, SIK1and SIK3 has been reported to interacts with TGF-β-activated kinase 1-binding protein 2 (TAB2) and interrupt the complex of TAB2-TNF receptor-associated factor 6 (TRAF6)(91). Thereby inhibits TLR4-mediated NF-κB signaling which is crucial for ubiquitination on tau in AD(91). Although SIK-1 and SIK-3 activation seems to be anti-inflammatory, the activation of SIK-2, on the contrary, is harmful and suppress neuronal survival both in cell culture and in whole animals after ischemic stroke(92). Meanwhile, CRTC and class IIa HDACs, two important downstream substrates of SIKs, negatively regulate NF-κb signaling pathway. However, a study exploring the effectiveness of bosutinib in the model of chronic inflammation in AD via SIK-2 inhibition mediated dephosphorization of CRTC-3, inducing the translocation of CRTC-3 to the nucleus. The translocation activates CREB, promoting CREB-dependent gene transcription and inhibiting NF-κB(93).

It is well established that insulin-like growth factor I (IGF-I) enhances SIK1 activity in a PI 3-kinase-dependent manner via PDK1. further evidence suggested WNK1 mediated activation of SIK1 by IGF-I(94) where the later one is essential for progression of angiogenesis and neurogenesis during neurodegeneration(95). SIK1 can be activated by an increase of cytosolic Ca^{2+} activity, an effect presumably mediated by calmodulin-dependent protein kinase kinase (CaMKK)(96). SIKs are considered rapid turnover proteins due to the phosphorylation by PKA, PKC, and tyrosine kinase in their C-terminal region(97). SIKs could be specifically activated by the sodium homeostasis(82). As a result, sodium intake-induced calcium influx affected by Na^{+}/Ca^{2+} exchange system (NCE1), could cause CaMK-mediated SIK1 phosphorylation and activation(96, 98, 99). Phospholipase C (PLC) can boost Ca^{2+} influx from endoplasmic reticulum (ER) to the cytoplasm via inositol triphosphate (IP3) receptor, thus activating the CaMK, which leads to the phosphorylation and activation of SIK2 at Ser358(100). Interestingly, a study found that CaMK I/IV phosphorylated SIK2 at Thr484, leading to SIK2 degradation and promoting CREB-mediated transcription(101). SIK-1 directly phosphorylate some specific substrates, including CRTC/CREB and PPase methylesterase-1 (PME-1) to involve in metabolic homeostasis(99). SIK1 was first found to inhibit gluconeogenesis in the hepatocytes, and its mRNA and protein levels under fasting conditions increased fourfold relative to feeding conditions(102). In-addition to, SIK3 plays a key role in regulating gluconeogenesis and expression of GLUT1 (provide glucose to damage neurons) rather than SIK2 the process could be helpful during neurodegenerative process of AD(103, 104). Moreover, overexpression of SIK1 result repression of lipogenic genes (FAS, ACC2 and SCD1) &SIK3 has been reported as a new energy regulator by promoting lipid storage in Drosophila through compromising the activity of HDAC4 and CRTC(97, 105).In addition, SIK3 also regulated cholesterol and bile acid metabolism by combining with retinoic acid metabolism and might alter energy storage in mice(106). Meantime, SIK2 also promotes cholesterol synthesis by upregulating SREBP2 expression, to transcriptionally elevate cholesterol synthetase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase

(HMGCR)(107). Henceforth, the process of lipid metabolism, mediated by SIK1/SIK3 may helpful in utilization/suppression of formation of Aβ and taueffective in prevention of progression of AD.

Potential of cholinergic drugs and SIK--1/SIK-3 mediated suppression of Alzheimer's disease

Previous studies have shown that cognitive deficits associated with AD may be partly caused by dysfunction of cholinergic receptor subtype α7nAChR (α7nAChRs) in hippocampal neurons. α7nAChRs activation results in Ca^{2+} influx and participate in the release of neurotransmitters; α7nAChRs also regulate neuronal excitability and LTP response, implicating a role for these receptors in neuronal function (108-110). Donepezil up-regulates nicotinic receptors in cortical neurons, this probably contributing to enhance neuroprotection(111). Furthermore, it has been suggested that AChEIs can activate reflex cholinergic anti-inflammatory pathway via α7nACh R one ofthe main mechanistic pathways by which this receptor exerts its anti-inflammatory efficacy isthrough the janus kinase2/ signal transducer and activator of transcription 3, as well as theirfeedback regulator suppressor of cytokine signaling 3 (JAK2/ STAT3/ SOCS3) signalingpathway; Such pathway plays a role in regulating IL-6 and the transcriptional factor nuclearfactor- kappa B (NF-κB)(112). One more study also explore that AChEIs also influence pro-inflammatory cytokines released from peripheral blood mononuclear cells, increasing oncostatin M, IL-1β, and IL-6 levels in AD patients after treatment(113). Other studies indicate that donepezil has a neuroprotective effect against oxygene-glucose deprivation injury and glutamate toxicity in cultured cortical neurons, and that this neuroprotection may be partially mediated by inhibition of the increase of intracellular calcium concentration(114). Previous study by singh et al.(95) demonstrating the relationship of donepezil and cholinergic system mediated increase calcium level reduce inflammatory mediators along with increase IGF and CREB involvement in reduced tau hyperphosphorylation leading neurogenesis in AD type dementia.

In summary, donepezil activates cholinergic subtype α7nAChR, further activate Gq type protein of G-protein mediate enhance calcium level which could be at downstream activate PLC and CaMK mediated activation of SIK1/SIK3 responsible for suppression of AD. Additionally, PKA expression is also stimulated via CGRP that is directly associated with the administration of donepezil.

Conclusion:

In conclusion, other factors such as aging, metal ion, virus, and microbiota may also contribute to AD pathogenesis via various mechanisms. Despite much knowledge that we have gained, no effective treatment strategies for AD have been successfully developed. Intervention for early-onset AD may require treatment at a young age, as calcium dependent Aβ aggregation and accumulation manifests early onset forms of the disease which further contribute in neuroinflammation and neurodegeneration in AD. Importantly, there are no drugs targeting SIKs that have been proven safe for clinical treatment for youths.Furthermore, future study warranted to provide new insights to therapeutic targets for treatment.

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