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The Immunopathogenic Role of Reactive Oxygen Species in Alzheimer Disease

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ABSTRACT

Reactive oxygen species (ROS) are produced in many normal and abnormal processes in humans, including atheroma, asthma, joint diseases, cancer, and aging. Basal levels of ROS production in cells could be related to several physiological functions including cell proliferation, apoptosis and homeostasis.

However, excessive ROS production above basal levels would impair and oxidize DNA, lipids, sugars and proteins and consequently result in dysfunction of these molecules within cells and finally cell death. A leading theory of the cause of aging indicates that free radical damage and oxidative stress play a major role in the pathogenesis of Alzheimer disease (AD). Because the brain utilizes 20% more oxygen than other tissues that also undergo mitochondrial respiration, the potential for ROS exposure increases.

In fact, AD has been demonstrated to be highly associated with cellular oxidative stress, including augmentation of protein oxidation, protein nitration, glycoloxidation and lipid peroxidation as well as accumulation of Amyloid β (Aβ). The treatment with anti-oxidant compounds can provide protection against oxidative stress and Aβ toxicity.

In this review, our aim was to clarify the role of ROS in pathogenesis of AD and will discuss therapeutic efficacy of some antioxidants studies in recent years in this disease.

Keywords: Alzheimer disease; Reactive oxygen species

INTRODUCTION

A number of studies have been performed for seeking a correlation between Alzheimer disease (AD), inflammation, and oxidative stress and or nitrosative stress.[1] During physiological aging, the emergence of some neurodegenerative related aging diseases like AD with damaged mitochondria of brain cells are unable to maintain the energy required for the cells.[2]

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Thus, the reduced energy for metabolism in AD may be due to dysfunction of some key metabolic enzymes of mitochondria.[3] Moreover, neurons are particularly sensitive to oxidative stress as compared to other organs or tissues; therefore the brain is more vulnerable to reactive oxygen species (ROS)-induced damage due to its high rate of oxygen consumption, high polyunsaturated lipid content, and relative weariness of classic antioxidant enzymes.

In fact, oxidative stress and Aβ production are positively correlated to each other. When the brain attempts to repair itself from oxidative damage, which is characterized by over expression of Amyloid β (Aβ)

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precursor protein (AβPP), it initiates the formation and accumulation of Aβ that appears to be its end product.[4,5] This process can lead to an increased production of free radicals mainly superoxide anion by mitochondria which induces the interruption of oxidative phosphorylation and results in decreased levels of ATP molecules. ROS are potentially toxic for neurons and oligodendrocytes and may induce toxicity by damaging lipids, proteins and nucleic acids of cells and mitochondria.[6]

Therefore, mitochondrial dysfunction results from molecular defects in oxidative phosphorylation (OXPHOS), which most likely plays a key role as a component for the development and maturation of AD.[7] Moreover, the increased ROS level triggers the opening of mitochondrial permeability transition pore and inner membrane anion channel and a transient increase in ROS generation by the electron transport chain. The involvement of mitochondrial permeability transition pore (mPTP) is implicated in Aβ-induced mitochondrial dysfunction, such as perturbation of intracellular calcium regulation, ROS generation, release of pro-apoptotic factors and impairing mitochondrial morphology.

The ROS burst in the cytosol can activate ROS-induced ROS release in neighboring mitochondria, leading to potentially significant mitochondrial and cellular injuries.[8] Furthermore, studies indicate that Aβ oligomers can impair mitochondrial function via ROS production and further increase ROS levels. Oxidative stress in brain could also stimulate additional damage via the overexpression of inducible nitric oxide synthase (iNOS) and the action of constitutive neuronal NOS (nNOS) which increases the production of nitric oxide (NO) and its derivative (reactive nitrogen species).[9,10]

The oxidative stress for a long time has been speculated to play a major role as a cause and consequence of AD. Thus, attenuation and/or suppression of oxidative stress have been evaluated as an alternative therapeutical choice for AD treatment.

ROS

ROS are formed continuously in cells as a consequence of oxidative biochemical reactions along with internal and external factors. In general, there are more than six primary sources of free radicals formed endogenously within living organisms: 1. the respiratory generation of ATP using oxygen;[11] 2. peroxisomal oxidation of fatty acids, which generates H_2O_2 [12] 3. cytochrome P450 enzymes;[11] 4. chronic inflammatory cells, which use a mixture of oxidants to overcome infection by phagocytosis;[12,13] 5.other enzymes which are capable to generate oxidants under normal or pathological conditions.[14]

Oxygen-derived free radicals are highly reactive chemical species involved in a variety of diseases, including neurodegenerative disorders. Superoxide anion (O2), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2), known as reactive oxygen species are produced by the reduction of molecular oxygen to water in mitochondria by some amino oxidase-catalyzed reactions and during the activation of phagocytic NADPH oxidase.[15,16] ROS including superoxide, hydrogen peroxide, and hydroxyl radicals, and their reactive products which are classically described as harmful products of aerobic metabolism are capable of DNA mutations, lipid peroxidation, and protein oxidation, microglial proteosome malfunction, astrocyte activation, inflammation and cell death.[17]

The main role of ROS function in immune system is to form an integral part of the organism's defense against invading microbial agents. The formed ROS by NADPH oxidase in phagocytic cells are mainly used to kill invading pathogens and therefore, the lack of functional NADPH oxidase complex results in low resistance to bacterial and fungal infections in humans and chronic granulomatous disease.[15,18] In addition to its role in killing process and host defense, a large amount of evidence has shown the important roles of ROS in cell proliferation, apoptosis, homeostasis, intracellular signaling, angiogenesis, endocrine-related functions, and oxidative modification of the extracellular matrix.[15] For example, autophagy which is a lysosome-dependent catabolic process mediating turnover of cellular components plays an important role in regulating cellular homeostasis in the nervous system. Because the accumulation of misfolded proteins is a common feature in multiple human neurodegenerative diseases, thus the activation of autophagy can be proposed as a strategy for combating neurodegeneration.[19,20] The increase in the levels of ROS is a frequent consequence of the accumulation of misfolded proteins and expired organelles such as old mitochondria. Moreover, ROS may serve as an important intracellular signal for the homeostatic activation of autophagy under basal physiological conditions, as well as in neurodegenerative diseases

including AD. The studies indicate that autophagy is specifically up-regulated in AD, due to ROS-dependent activation of the type III PI3 kinase. Indeed it is presented as an acute and long-term attempt by the affected neuronal cells to rid themselves of the harmful effects of Aβ exposure, such as accumulation of defective mitochondrial and protein aggregates.[21] However, if ROS are produced in excess in certain abnormal conditions, such as inflammation and ischemia or in the presence of catalytic iron ions, they could be harmful to cells. Since neurons have an age-related decrease in the capacity to compensate for redox imbalance, even minor cellular stress has also the ability to lead to irreversible injury and, it can contribute to the pathogenesis of neurodegenerative diseases.[22]

ROS have been also identified as important second messenger molecules that carry out a part of signaling steps transduced by pro-inflammatory cytokines. The vascular endothelium, which regulates the passage of macromolecules and circulating cells from blood to tissue, is a major target of oxidant stress in increased vascular endothelial permeability as well as promoted leukocyte adhesions that are involved in alterations in endothelial signal transduction and redox-regulated transcription factors. Therefore, oxidative stress plays a critical role in the pathophysiology of vascular diseases.[5,23] ROS signals could be the important factors during lymphocyte transendothelial migration. Interestingly, ROS from NADPH oxidase have been shown to mediate Aβ- induced cerebrovascular dysfunction.[24] The evidence supports this fact that NADPH oxidase may be a common pathway moreover for microglia-mediated neuronal damage. It was shown that ROS production is stimulated by lymphocyte binding to the adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1). The VCAM-1 stimulates endothelial cell NADPH oxidase for the production of low levels of ROS (1 μM H_2O_2) and this is required for VCAM-1-dependent lymphocyte migration.[25,26]

Moreover, there is profound evidence that the pathogenesis of several neurodegenerative diseases, including Parkinson's disease, Friedreich's ataxia, multiple sclerosis, amyotrophic lateral sclerosis and AD may due to the generation of reactive nitrogen species (RNS) associated with mitochondrial dysfunction.[27] In MS, macrophages produce a variety of inflammatory mediators like nitric oxide (NO), and proinflammatory cytokines, which all contribute to neuroinflammation and disease progression.[28] Furthermore, Peroxynitrites ($ONOO^-$) ,another component of oxidative stress, formed from NO and O_2^- is a highly reactive oxidizing and nitrating agent, leading to oxidize cellular components, including proteins, lipids, carbohydrates, and DNA and increased aggregated Aβ , and stimulate inflammatory response, so that $ONOO^-$ scavenging and ROS inhibitory effects could be considered as potential anti-AD candidates.[1,29]

ROS in AD

In the central nervous system (CNS), the high metabolic demand for oxygen can lead to a higher level of oxidative stress via the production of free radicals. Since the extent of ROS formation is associated with oxygen consumption, so that the higher level of ROS is produced by neurons with higher metabolic activity or neuronal segments enriched in mitochondria, such as synapses.[30] Loss of mitochondrial membrane can increase the release of cytochrome c, a pathway leading to neuronal apoptosis that is mediated by the Bcl-2 family of proteins.[31] Under pathological conditions such as AD, oxidative stress can enhance the progression of the disease. Partial deficiency of the mitochondrial manganese superoxide dismutase (MnSOD) increased amyloid plaques in Tg19959 mice and tau phosphorylation in Tg2576 mice.[32,33] In addition, the over expression of MnSOD reduced amyloid plaques, improved memory function and protected synapses. A major link between oxidative stress and mitochondrial dysfunction is the α-ketoglutarate dehydrogenase complex (α-KGDHC). In human AD brains, the mitochondrial α-ketoglutarate dehydrogenase activity is markedly reduced in either damaged or relatively undamaged areas[34,35] α-KGDHC is a crucial mitochondrial enzyme complex that mediates oxidative metabolism. Its activity is reduced in AD patient brain.[32]

Furthermore, depending on whether AβPP is cleaved via the amyloidogenic or the nonamyloidogenic process, AβPP fragments themselves are known to induce oxidative stress or act as neuroprotective.[36] In fact, alterations in the lipid composition of cellular membranes and/or in membrane fluidity induced by a permanently increased oxidative microenvironment pave the way to change many different metabolic processes taking place in distinct membrane compartments. Moreover, the higher

plasma membrane fluidity due to methyl-β-cyclodextrin-induced cholesterol depletion has been shown to promote α-secretase cleavage of AβPP and, following, the nonamyloidogenic form.[37] The increased lanosterol levels (cholesterol precursor) correlate to enhanced α-secretase activity in oxidative-stress-resistant cells. In contrast, cholesterol accumulation in the plasma membrane has been reported to increase the rigidity of the plasma membrane and to decrease α-secretase processing of APP.[38]

The Role of ROS in Signaling Pathway in AD

Epidemiological studies have supported the role of inflammation in AD, where results have shown a decreased incidence and severity of AD in patient populations treated with nonsteroidal anti-inflammatory drugs (NSAIDs). The studies are shown that patients taking anti-inflammatory medicine for rheumatoid arthritis are six times less likely to develop AD.[39] Moreover, NADPH oxidase initiates an intracellular ROS signaling pathway that can activate microglia and amplify the production of multiple pro-inflammatory cytokines, such as TNFα or PGE2.[40,41] In fact, several triggers of NADPH oxidase activation in microglia amplify proinflammatory signaling. The microglial activation occurs early in AD development, before neuropil damage, supporting a contributing role of microglia in disease pathology.[42] It is thought that interaction of microglia with Aβ peptide gives rise to ROS and several other chemokines and cytokines, which work as inflammatory mediators and finally may cause neuronal damage, so that, TNF-α, nitric oxide, and superoxide are produced by microglia in response to Aβ.[39] Furthermore, activation of complement cascade forms membrane attack complexes, which not only cause substantial damage to the neurons but also can lead to phosphorylation of Tau protein leading to formation of neurofibrillary tangles.[43] Aβ has also been shown to recruit and activate microglia, suggesting a critical role in AD progression.[44] It was also found that the level of nuclear factor kappa B (NFkB) in the brain is significantly increased in the presence of APOE e4 when compared with its activiation in the presence of APOE e3. Several molecules are capable of activating NFkB including TNFα, Aβ, and secreted AβPP. It should be noted that the activation of NFkB increases transcription of AβPP and BACE-1, which finally leads to increase in Aβ production.[42,45,46]

Moreover, Aβ-induced toxicity appears to involve one or more of the three major mitogen-activated protein kinase (MAPK) pathways, c-jun N-terminal kinase (JNK), p38, and extracellular signal regulated kinase (ERK), which are known to mediate oxidative stress-induced neuronal death.[47] Moreover, many oxidative stress factors have been shown to trigger apoptosis by stimulating stress-activated protein kinases (SAPKs) such as JNK and p38MAPK.[10] In AD model cells, it was shown that the amyloid precursor protein swedish (double mutation at amino acids 670 and 671found in a swedish family is located before the Aβ region of AβPP and result in increased Aβ) enhanced oxidative stress, finally leading to apoptotic cell death through the activation of the c-Jun N-terminal kinase, caspases 3 and 9 and a shift in the BclxL/Bax ratio toward Bax.[48,49] Protein phosphatase 5 (PP5) is a ubiquitously expressed serine/threonine phosphatase related to PP1, PP2A, and PP2B.[47] The PP5 is suggested to inhibit MAPK pathways through dephosphorylation of Raf-1, a MAPK kinase initiating the ERK MAPK pathway, and apoptosis signal regulating kinase 1 (ASK1), which activates the JNK and p38 MAPK pathways.[50,51] The results suggest that understanding the function and regulation of PP5 in brain can provide insight into neuronal responses to Aβ, as well as potential therapeutic strategies for the prevention of Aβ-induced neurodegeneration.

Aβ is the product of amyloid precursor protein cleaved by β and γ secretase. Aβ generates oxidizing products during its aggregation.[52] The oxidizing products as well as Aβ affect the functions of sodium-potassium ATPase and calcium ATPase,[53] which in turn cause dysregulation of L type voltage sensitive calcium channel (LVSCC) [54], α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPAR),[55] and N-methyl D-aspartate receptor (NMDAR) [56] and inositol 1,4,5-trisphosphate receptors[52,57] that then mediate significantly increased calcium flux into the cytosol. Aβ-mediated abnormalities in mitochondrial function are rescued by adding the mitochondrial permeability transition pore (mPTP) inhibitor. Indeed, cyclosporine D (CypD) plays a key role in stabilizing mitochondrial permeability transition (mPT) and serves to open the mPTP, thereby allowing the diffusion of calcium and cytochrome c out of mitochondria matrix into the cytoplasm where they may induce cell death via necrosis and/or apoptosis. There is strong protective effect of CypD deficiency on Aβ-mediated mitochondrial and neuronal toxicity. Thus, CypD

inhibition could be a feasible and possibly significant therapeutic approach. The inhibitor of CypD, Cyclosporine A, broadly was used in a clinical application, which might be a potential therapeutic option for the treatment of AD.[52]

On the other hand, both Aβ- and glutamate-induced toxicities in neurons are largely dependent on cyclin-dependent kinase (Cdk5).[8] However, the role of CdK5 in promoting oxidative stress in AD has not completly been elucidated. Cdk5, a serine-threonine kinase, belongs to the Cdk family. It was shown that Cdk5 directly causes excessive oxidative stress and mitochondrial dysfunction in neurons leading to cell death, the downstream of Aβ and glutamate, both of which play key roles in AD pathology. Two antioxidant enzymes, Prx-I and Prx-II which belong to the Prx family of peroxidases can efficiently scavenge cellular ROS.[58,59] Identification of Prx-I and Prx-II as Cdk5 substrates suggested that Cdk5 deregulation may maintain sustained oxidative stress in AD by compromising the cellular anti-oxidant defense system. Furthermore, Cdk5 deregulation increases oxidative stress via inactivation of two antioxidant enzymes, Prx1 and Prx2, which lead to ROS-mediated JNK and c-Jun activation. In neuronal cells, JNK is preferentially activated by oxidative stress and is a key mediator of Aβ, glutamate induced neurotoxicity and Neurofibrillary Tangles (NFT) formation which are critical in AD.[60,61] Recent studies have further identified a vital role for JNK in neurotoxic Aβ formation by activating γ-secretase upon oxidative stress. Uncontrolled Cdk5 activates c-Jun via ROS-mediated activation of JNK. Thus, Cdk5 inhibition endows superior protection against neurotoxicity, suggesting that Cdk5 could be a preferable therapeutic target for AD.[61,62]

In addition, recent studies showed that oxidative stress induced by H_2O_2 and 4-hydroxy-nonenal (HNE) treatments activate the feedback between the γ- and β-secretase cleavages of the β-amyloid precursor protein, leading to an increase in Aβ40 and Aβ42 production as well as Aβ42/40 ratios. This kind of feedback requires the activation of the JNK/c-jun pathway.[63] On the other side, the MAPK pathway which play a role in AD pathology, was found that after treatment of N2a/APP695 and N2a/APPswe cells with H_2O_2, exhibited an enhanced protein expression level of ERK and JNK activation compared to control cells that were not treated with H2O2.[10,64]

The Role of Metal Ions Associated with ROS in AD

The *in vitro* and *in vivo* studies indicate the important role of metal ions in AD.[65] Metal-mediated ROS generation is one of the leading causes of oxidative stress and formation of ROS at the metal site as well as the reactivity of the "metallo-ROS" center in CuAβ which may contribute to the oxidative stress in AD [66]. Interestingly, iron, zinc and aluminum tend to co-localize with Aβ42 peptides in the senile plaque cores that characterize AD brain.[67] Excessive Cu and Fe ions binding to Aβ were suggested to have a deleterious effect on promoting both the aggregation of Aβ and the generation of ROS. A large body of evidence shows that Cu ion is bound to Aβ in AD and Cu (I/II)–Aβ complex is involved in ROS (H_2O_2, OH) production. Although *in vitro* studies demonstrated a particular role for Cu (I/II)–Aβ complex in ROS production, the pro-oxidant role of the Cu(I/II)–Aβ systems is controversial.[65,68,69] The oxidation of Aβ peptide has two different properties, a protective role, Aβ acting as a sacrificial scavenger of the ROS produced and/ or a toxic role, Aβ being as an initiator of ROS propagation. In the former case, residues involved in the Cu coordination are most affected whereas in the latter case, Tyr10 and/or Met35 in Aβ peptide are affected.[70,71] It has been shown that Aβ directly generates ROS in the presence of iron or copper ions via methionine-35.[32] Two electrons of Met oxidations leading to Met sulfoxide can also be a way of trapping free radicals and thus be neuroprotective, with reduced Aβ peptide aggregation property.[72,73] It has been suggested that Met35 in Aβ1–40 serve, as a reducing agent responsible for the initiation of the redox cycling of the CuII center in CuAβ1–40 which can lead to H_2O_2 production.[66] The oxidation of the thioether moiety of Met to its sulfoxide form in Aβ1–40 is involved in aggregation, lipid peroxidation and a redox reaction in association with the metal center. Despite the lack of Met and/or any redox-active amino acid, the fragments CuAβ1–16 and CuAβ1–20 exhibit a significant metal-centered oxidative activity which indicates the redox role of Met35 might have been overstretched.[74,75]

Moreover, cultured human neural cells (HN) of the central nervous system are highly sensitive to nanomolar amounts of aluminum, a known, environmentally abundant neurotoxin that is ubiquitous in biosphere.[67] The genotoxic and neurotoxic effects of aluminum are due to the excessive aluminum mediated

cellular generation of ROS and activation of pathogenic gene expression that redirects brain cells toward genetic dysfunction, neural cell atrophy, apoptosis and cell death. Treatment of HN cells with 100 nM of aluminum-sulfate can emulate many of the gene expression changes observed in the brains of moderate-to-late stage AD.[76-78]

Oxidative Stress and Apolipoprotein E

Apolipoproteins act as antioxidants, however, apolipoprotein E4 allele is less effective.[12] It is reported that polymorphisms of the ApoE gene correlate with onset and risk of developing AD, thus 50% of AD patients have at least one ApoE4 allele that is a major genetic risk factor of the more common late onset form of AD.[79,80] APOE gene has three common alleles, epsilon 2 (ε2), epsilon 3 (ε3), and epsilon 4 (ε4). The ε2 allele is considered as a protective factor but presence of the ε4 could be a risk factor for developing late onset AD, and this allele increases the risk for AD from 20% to 90% and decreases the age of onset from 84 to 68 years depending on gene dose of ε4 alleles.[42] ApoE is a 34-kDa glycoprotein that is synthesized and secreted mainly by astrocytes and microglia in the CNS. Moreover, increased oxidative damage is found in specific brain regions of AD patients with the ApoE4 genotype.[81] The detrimental processes of ApoE4 have been shown to influence on AD pathological processes, including lipid homeostasis and NFT formation, suggesting the brain vascular alternations play a key role in the progression of AD. If the delivery of lipophilic antioxidants is impaired due to ApoE4, this could lead to oxidative stress.[5,82,83]

Furthermore, the relationship between hypercholesterolemia and AD arose in great extent from ApoE4, a major carrier of cholesterol in the CNS. The studies demonstrate that dietary cholesterol increases Aβ accumulation and accelerates AD-related pathology in animals.[84] The diet-induced hypercholesterolemia in AD mice leads to a significantly elevated levels of formic acid-extractable Aβ peptides in CNS. The total level of Aβ is strongly correlated with the level of cholesterol in both the plasma and CNS.[5]

Antioxidants

The oxidative stress induced by Aβ could be triggered through a number of reactions including increased ROS production, decreased endogenous antioxidant defenses due to glutathione peroxidase (GPx) and superoxide dismutase activities and decrease in the levels of non-enzymatic antioxidants such as reduced glutathione (GSH), vitamin E and ascorbic acid.[85]

Moreover, One of other endogenous antioxidants is heat-shock proteins (HSPs) which could be up-regulated in several neurodegenerative diseasess. HSPs can also protect brain cells against free radical injury and oxidative stress. [86] In the CNS, HSP synthesis is induced after hyperthermia, by alterations in intracellular redox environment and by exposure to heavy metals, amino acid analogs and/or cytotoxic drugs. In AD, HSP expression is associated with Aβ deposition and neurofibrillary tangles. Recent findings suggest that HSPs prevent the accumulation of Aβ.[87,88] HSP 27, among all HSPs, is strongly induced after stresses such as oxidative stress, anticancer drugs, or irradiation.[86] High level of HSP 27 might be the cause of the occurrence of hyperphosphorylated tau protein (tau proteins are microtubule-associated proteins that are abundant in neurons in the central nervous system) and consequent formation of NFTs. Many investigations showed that HSP 27 directly binds to hyperphosphorylated tau, thereby protecting against cell death.[89] Thus, the alterations in chaperone protein systems might be a mechanism in pathogenesis and progression of AD, so that a therapeutic approach to induce HSP levels could be a potential strategy to treat or delay the onset of AD.

In general, substances that can reduce oxidative stress are proposed as potential drug candidates for treatment or preventative therapy of neurodegenerative diseases such as AD. In addition, the studies have shown that high antioxidant in diets may decrease the risk of developing AD.[39]

In this review, we will discuss the therapeutic efficacy of substances or drugs which have antioxidant property and might be effective in treatment of AD.

Alkaloids

As mentioned above, protection and inhibition against oxidative stress such as $ONOO^-$ plays an important role in the production of anti-AD agents. $ONOO^-$, formed from NO and O_2^-, is a highly reactive oxidizing and nitrating agent, leading to oxidize cellular components, increased aggregated Aβ, and stimulated inflammatory response.[1,90] Studies on both cholinesterases (ChEs) and BACE1 (β secretase) inhibitory effects, as well as antioxidant effects, including $ONOO^-$ scavenging and ROS inhibitory

effects of coptidis rhizoma alkaloids, could be considered as promising anti-AD agents. Protoberberine alkaloids such as groenlandicine and jateorrhizine exhibited potent $ONOO^-$ scavenging effects compared to a well known $ONOO^-$ scavenger, penicillamine (in a dose-dependent manner).[1]

Moreover, mitochondrial antioxidant therapy is a promising treatment for AD patients. Brain, an organ with high energy metabolism and abundance of oxidizable materials is exceedingly susceptible to oxidative damage.[91,92] Epidemiological evidence demonstrated that nicotine has beneficial and protective property in some neurodegenerative diseases including AD. The complex I respiratory chain which generates superoxide anion and nicotine is able to inhibit ROS generation on rat brain mitochondria. Nicotine binds to complex I of the respiratory chain and inhibits the NADH-ubiquinone reductase activity.[93] Furthermore, nicotine prevents activation of NF-κB and c-Myc by inhibiting the activation of MAP kinases. In fact, nicotine decreases Aβ by the activation of a7nAChRs through MAPK, NF-κB, and c-myc pathways. Nicotinic cholinergic receptor stimulation also induces neuroprotection against glutamate cytotoxicity by its inhibitory action on NO-formation and consequently, the activity of iNOS and the production of NO are down-regulated.[94]

On the other hand, galantamine is a tertiary alkaloid originating from botanical sources, in addition to its neuroprotective property, galantamine prevents ROS production and lipoperoxidation induced by Aβ1–40, suggesting its antioxidant action. Recently, it was also reported that galantamine prevented ROS production and mitochondrial dysfunction induced by H_2O_2 in a neuroblastoma cell line.[95]

Therefore, alkaloids may be accounted as exogenous drug agents for AD antioxidant therapy. However, the precise and detailed mechanism of function of these alkaloids remains unknown.

NSAIDs

The epidemiological studies has shown that taking NSAIDs for at least one month is associated with lower probability of AD.[39] The aggregated synthetic Aβ 1-40 peptides can induce COX-2 expression in SH-SY5Y neuroblastoma cells, since Aβ1-40 has been shown to stimulate COX-2 oxygenase and peroxidase activity in a cell free system. Furthermore, the two step oxygenase and peroxidase action of COX leads to the formation of ROS and prostaglandin H_2.[96,97] Targets of ROS include activation of COX-1 and-2, which could be blocked by NSAIDs. Daily doses of NSAIDs can increase circulating levels of antioxidants. Furthermore, COX-2 does play an important role in the oxidative stress in AD that may be controlled using selective COX-2 inhibitors like rofecoxib. It has been shown rofecoxib may reduce the free radical load in the rat brain with chronic administration. Flurbiprofen, another NSAID that possesses analgesic and antipyretic properties may also interact with the anti-oxidant system in the AD model rat brain to disrupt the normal oxy-radical (anti-oxidant balance in the brain).[96,98]

Moreover, dextromethorphan (DXM) which has anti-inflammatory effects and is a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist exerts its neuroprotective effects through inhibition of microglial activation and NADPH oxidase activation.[99] In addition, DXM, has been reported in studies of *in vitro* and *in vivo* models of Parkinson's disease to protect patients against neuron damage through the inhibition of microglial activation in methamphetamine-induced neurotoxicity.[100,101]

Thus, NSAIDs have protective role in AD and COX-2 inhibitor of NSAIDs is also an important target for reducing AD-related oxidative stress.

Polyphenols

To date, one of the most important aspects of current polyphenol research is the focus on the neuroprotective capacity of this broad family of compounds.[102] Polyphenols are a class of phytoalexins found in the tissues of a widespread range of plants. Resveratrol (3–4′-5-trihydroxy stilbene), curcumin, quercetin, and (−)-epigallocatechin-3- gallate (EGCG) of polyphenolic compounds have antioxidant property. The polyphenols have the capacity to chelate metal ions and to directly quench free radical species that contribute to oxidative damage.[103]

Resveratrol was reported to reduce Aβ production in cell line HEK293 expressing Swedish mutant APP695.[104] Additionally, studies indicate the involvement of resveratrol in proteosome clearance of Aβ and reducing toxicity in AD brains. No reduction in the activity of γ-secretase mediated-cleavages of AβPP in the presence of resveratrol was found.[105] Thus, it excludes the possibility that resveratrol lowers Aβ by promoting the proteosomal degradation of C99 (C terminal fragment of AβPP upon cleavage by BACE).

Several studies have investigated curcumin's anti-oxidant and anti-inflammatory properties. Curcumin enhances the activity of detoxifying enzymes like glutathione-S-transferase.[42] Low concentrations of curcumin upregulate endothelial heme oxygenase 1 gene and protein expression Heme oxygenase 1 can indirectly protect endothelial cells from peroxide mediated toxicity by degradation heme to iron and biliverdin which later converts to bilirubin and bilirubin then protects endothelial cells from oxidative damage.[106] Curcumin and one of its stable metabolites tetrahydrocurcumin (THC) can significantly decrease production of both iNOS protein and mRNA in transgenic mice brain. In addition, metal chelation activity of curcumin with binding to copper and iron ions reduces Aβ plaque and subsequent ROS generation.[107]

Recent investigations have shown that oral administration of green tea polyphenols to mice induces prostate cancer and decrease the production of NF-κB among other regulatory molecules.[102] Green tea polyphenols such as EGCG were capable of reducing the inflammatory markers, cyclooxygenase-2 and prostaglandin-E2, which were associated with development of tumor skin.[108] Moreover, EGCG may be involved in the downregulation of NO production in 4T1 murine mammary carcinoma cells under *in vitro* conditions.[109]

In addition to antioxidant capacity of resveratrol and EGCG, these compounds also can regulate the cytotoxic effects of Aβ oligomers and fibrils via phosphorylation of phosphokinase C (PKC) and activation of α-secretase protein. α-secretase catalyzes the formation of a soluble, non-amyloidogenic (non transmembrane plaque-forming) protein from the AβPP which is specifically located in the membrane of neuronal cells. Via this pathway, soluble AβPP is formed and thus does not allow for the formation of neuritic plaques, a hallmark feature of AD.[102,110]

Quercetin, another component of polyphenol family, is believed to show pharmacological properties to address diseases and risk-factors associated with aging.[111] The beneficial effect of quercetin against the development of atherosclerosis is inhibition of cell adhesion molecules such as ICAM-1 and VCAM-1 induced TNF-α, however, the prevalent quercetin conjugates were not able to downregulate the pro-inflammatory ICAMs and VCAMs produced by human umbilical artery smooth muscle cells exposed to either TNF-α or LPS. This finding indicates the need to encourage the focus of research efforts to the metabolic alterations of polyphenolic compounds against various risk factors of aging.[102]

Statins

Statins can increase cerebrovascular perfusion by upregulating eNOS that might decrease the inflammation related to Aβ deposition.[42] The main mechanism of action of statins is based on the inhibition of 3- hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and limitating of the enzyme in the biosynthesis of cholesterol. In addition to, cholesterol-dependent mechanisms of action, statins also directly up-regulate endothelial nitric oxide synthase (eNOS, also termed NOS3 or NOS III) expression, independent of cholesterol levels.[15] Statins could also alter isoprenoid levels. Inhibition of isoprenylation (the process by which isoprenoids are transferred in to target proteins) resulting in the inhibition of small GTPases Ras and Rho activation, both of which are critical for iNOS transcription.[112] Furthermore, statins could inhibit endotoxin induced activation of the IκB/NF-κB pathway in a small GTPase-dependent/ independent manner. In the primary astrocytes and macrophages, lovastatin was also found to reduce IFNγ-induced STAT1 phosphorylation and iNOS expression.[113] Thus, the anti-inflammatory effects of statins may have clinical impact in a number of non-vascular conditions including multiple sclerosis, rheumatoid arthritis and decreased inflammations in Aβ depositions.

It has been shown that simvastatin and lovastatin reduce intracellular and extracellular levels of Aβ 42 and Aβ 40 in primary cultures of hippocampal and mixed cortical neurons.[114] In addition, guinea pigs treated with high-dose simvastatin showed a reduction in cerebral Aβ levels, including the Aβ 42 isoform.[115] Moreover, lovastatin can reduce the production of components of the senile plaques in AD. Lovastatin is able to reduce cellular formation of Aβ in living hippocampal neurons by 70%, and this effect was reversed by the re-addition of cholesterol to previously depleted cells.[116]

Thus, statins possess beneficial effects in neurological diseases due to their antioxidant and anti-inflammatory properties and may be used as a therapeutic drug in neurodegenerative diseases including AD.

Catalpol

Catalpol, an iridoid glucoside derived from the root of rehmannia glutinosa, possesses a broad range of biological and pharmacological activity. The protective effects of catalpol on H_2O_2, LPS, MPP^+ and rotenone induced neurotoxicity *in vitro* and *in vivo* has been reported.[117,118] Moreover, exposure of cortical neurons to catalpol attenuated (β-Amyloid), Aβ1-42-induced apoptosis mainly via mitochondrial-dependent caspase, as well as decreasing intracellular ROS accumulation, Bax level, cytochrome c release and increasing integrity of mitochondrial membrane potential. These results suggested that catalpol, might be potentially an anti-apoptotic agent against neurodegenerative diseases including AD.[119]

CONCLUSION

The oxidative damage of cellular molecules plays an important role in neurodegenerative disorders. The brain is a sensitive tissue to oxidative damage, because it contains high concentrations of oxidizable polyunsaturated fatty acids, a high rate of oxygen consumption per unit mass, along with a relatively modest antioxidant defense system. The inhibition of ROS accumulation by different antioxidants is connected to the location of ROS generation. In addition, the mitochondrial dysfunction results in molecular defects in oxidative phosphorylation, which most likely plays a key role in the development and maturation of AD. Thus, targeting mitochondria with antioxidants might be a therapeutic aim, capable of eliminating oxidative damage in the brain, restoring cell integrity and improving cognitive function and spatial memory.

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