Review Article

Involvement of neuroinflammatory mediators in the pathogenesis of neurodegeneration

Rishabh Singh*, Anant Srivastava

Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research, Faizullaganj, Lucknow 226020, Uttar Pradesh, India

Received: 13 September 2019 Revised: 26 November 2019 Accepted: 27 November 2019

Abstract

The primary objective of this review is to understand the role of different inflammatory mediators, mechanisms involved in the disease pathogenesis and to identify new therapeutic approaches involved in the treatment of neurodegerative diseases. Neuronflammation is like a two-edged sword because in acute conditions, or at low levels, it deals with the anomaly and is healing in nature. However, in chronic conditions, or at continued high levels it causes massive damage to the viable host tissue. Neuroinflammation accelerates the progression of neurodegeneration in Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). This review aims to study different inflammatory mediators like prostaglandins, cytokines, microglial activation, astrocytic activation, etc and understand the underlying mechanisms (deposition of misfolded proteins, oxidative stress, lipidperoxidation, mitochondrial dysfunctioning) involved in the disease pathogenesis. This range of inflammatory mediators and underlying pathogenic mechanisms provides a variety of potential targets for new anti-inflammatory agents.

Keywords: Neuronflammation, autotoxicity, alzheimer's disease, microglias, astrocytes

Introduction

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, is characterized by the progressive deterioration of behavior, cognition and functionality, which significantly impairs daily living activities. According to most recent publications by the Alzheimer's Association around 5 million people are suffering from AD in the United States and with this progress the number of AD patients will quadruple by the middle of the century (Maalouf et al., 2011). Alzheimer's disease (AD) is the most common cause of dementia in the elderly (Korczyn et al., 2002). Later, progressive disorientation, memory loss, and aphasia become manifested, indicating sever cortical dysfunction (Tarawneh et al., 2012). Eventually in 5-10 years, the affected individual becomes profoundly disable, mute, and immobile (Karishma et al., 2017). Most cases are sporadic, and although 5%-10% are familial cases, the study of such familial cases has provided important insight into the pathogenesis of the more common sporadic form (Qiu et al., 2009). The combination of clinical assessment and modern radiological methods provides 80%-90% accuracy in the diagnosis of AD (Sabbagh et al., 2017). The neuropathological characterstics of AD comprise "positive" lesions like amyloid plaques, neurofibrillary tangles and glial responses, and "negative" lesions like neuronal and synaptic loss. Clinicopathological evidences are necessary to create new hypotheses associated with disease pathogenesis, and establishing relationship between "normal" aging and AD dementia. There are evidences that the accumulation of amyloid plaque occurs primarily before the commencement of cognitive deficits, whereas the formation and deposition of neurofibrillary tangles, neuron loss, and principally synaptic loss occurs parallel with the progression of cognitive decline (Serrano-Pozo et al., 2011).

There are numerous connections between risk factors and development of neuroinflammation which involve many complex reactions and contribute to vascular compromise, oxidative stress and finally brain damage. Once this cascade of events is initiated, the process of neuroinflammation becomes activated, resulting in further cellular damage and loss of neuronal functions (Aschner et al., 2011). The immune response is triggered with several other stressors and

Address for Corresponding Author:
Rishabh Singh,
Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research, Faizullaganj, Lucknow 226020, Uttar Pradesh, India
Email: rishabh.s007@gmail.com

DOI: https://doi.org/10.31024/ajpp.2020.6.1.2

injury, with a few features likely to be neurotrophic and others neurotoxic in nature (Milatovic et al., 2004). The CNS is an immune privileged organ with the innate and acquired immune response being closely controlled in relation with the periphery (Carson et al., 2006). Evidence suggests that a strong inflammatory response in the periphery from systemic LPS (Li et al., 2018) or viral infections (Zhou et al.,2013) results in the subsequent infiltration of leukocytes from the periphery to the CNS with consequent neuroinflammation and neurodegeneration (Chen et al., 2016). It is reported that certain viruses are able to directly injure neurons by direct killing or inducing apoptosis, leading to neurodegeneration. Neuroinflammation includes several cellular responses and the underlying mechanisms which help us to understand the link between neuronal homeostasis and neurodegeneration. As a result, therapies are being designed to target the immune response in diseases such as multiple sclerosis, and other neurodegenerative diseases (Elmore et al., 2007).

The neurodegeneration is characterized by the progressive loss of the structure and functions of neuronal materials, which lead to impaired motor and cognitive functions (Gao et al., 2008). While the causes associated with neuronal degeneration remain poorly understood, the incidence of neurodegeneration increases with age, in mid to late adult life (Carson et al 2006). This phenomenon, which primarily affects elderly individuals, occurs in neurodegenerative diseases like Alzheimer's disease [AD], Parkinson's disease [PD], multiple sclerosis [MS] and amyotrophic lateral sclerosis (ALS) following viral infections.

Pathogenesis in neurodegenerative diseases

Neuroinflammation involves a series of biochemical processes which are mediated by the nervous system in response to specific injury, infection or neurodegenerative diseases. It is a complex response to brain injury which involves the microglia activation, release of inflammatory mediators, such as cytokines and chemokines, and generation of reactive oxygen and nitrogen species. An offense is followed by the initial activation of microglia, which induce the release of pro-inflammatory mediators that alter the permeability of the BBB. The subsequent infiltration of peripheral leukocytes occurs inside of the CNS, including T cells and macrophages, which share several functional features with microglia including, the expression of toll-like receptors (TLRs), and consequently the ability to be activated by aggregated proteins or pathogen-associated molecular patterns. Inflammatory mediators and activated microglia act as a driving force in the pathogenesis of Alzheimer's disease (AD) (DiSabato et al., 2016).

In Alzheimer's disease, the activated microglia generates a non-resolving immune response that fails to clear accumulating Aß peptides but accelerates neuronal and synaptic injury in the process. Neuroinflammation may also occur as a result of abnormal protein aggregation and formation of inclusions arising from mutations (i.e., α-synuclein) or disruption of the ubiquitin–proteasome system (UPS), immunologic challenges (bacterial or viral infections), neuronal injury (brain trauma or stroke), or other epigenetic factors (Takalo et al., 2013). Chronic inflammatory syndromes (rheumatoid arthritis, Crohn's disease, and multiple sclerosis) and environmental toxins (pesticides and particulate matter) are the most notable epigenetic factors which trigger neuroinflammation (Casella et al., 2015). Neuroinflammation is a complex host defence mechanism that isolates the damaged brain tissue from uninjured area, destroys injured cells, and repairs the extracellular matrix (Farooqui et al., 2007). Neuroinflammation is orchestrated by microglia and astrocytes to re-establish homeostasis in the brain after injury-mediated disequilibrium of normal physiology (Harry et al., 2008).

Mediators in neuroinflammation

Microglial activation

Microglias are derived from embryonic hematopoietic cells in the yolk sac, which are seeded in brain during the fetal development. Microglia cells proliferate rapidly after birth and self-renew during adult life (Ginhoux et al., 2013). Microglia cells are phagocytic in nature and are predominantly present in the CNS. Microglia cells share a number of features with peripheral tissue macrophages and monocytes. Phagocytosis is the most important property of the CNS and is frequently used by the microglial cells in the modulation of neurotransmission by regulating the existing synaptic connections and thus maintaining the normal neurophysiology (Streit et al., 2004). Few of the major roles of microglia involve the regulation of synaptic plasticity and remodeling of neuronal circuits. Additionally, microglia cells guard the cerebral parenchyma against invading pathogens and thus contribute to homeostasis (Kim et al., 2013). This ability is facilitated by their numerous cytoplasmic extensions known as filopodia. Filopodia maintains close contact with neurons, perivascular cells, and astrocytes. They also contribute in neurogenesis, synaptogenesis and removal of cell debris resulting from apoptotic cell death (Miyamoto et al., 2016). Microglia actively surveys their environment through, and changes their cell morphology significantly in response to neural injury (Harry, 2013).

Whenever a brain injury occurs, microglial activation takes place with the aim of removing injurious stimuli. To this aim, activated cells undergo a series of morphological and functional changes and acquire a reactive phenotype (Donat

et al., 2013). Microglial activation may led to a series of neurological alternations like glial hypertrophy, astrocyte end feet retraction, and gain of amoeboid microglial structure. These changes may disturb neuronal homeostasis and cause synaptic dysfunction, neurovascular endothelial dysfunction, loss of three-dimensional network and blood-brain barrier (BBB) hyperpermeability (DiSabato et al., 2016). In addition, reactive microglia release a wide range of proinflammatory mediators aimed at removing the primary injury. However, uncontrolled and prolonged activation goes beyond physiological control and results in neurodegeneration (Rosskothen-Kuhl et al., 2018).

Astrocytic activation

A little is known about the role of astrocytes ion the pathogenesis of AD. Astrocytes are one of the most common cells present in the brain and were considered to play a nutritive role and provide structural support for neurons. However, according to recent studies, astrocytes are known to play a multiple role in neurophysiology. Astrocytes are significantly involved in the neurotransmission (especially glutamatergic transmission). On sensing the neurotransmitter release, the astrocytes release their own signalling molecules (gliotransmitters) to communicate with the neighbouring neurons (Stehberg et al., 2012). Astrocytes are closely associated with the synapse and this quality has given rise to the term "tripartite" synapse to reveal the significance of glia in neurotransmission (Ota et al., 2013). Additionally, astrocytes also associate with the cerebrovasculature through specific processes called endfeet. The astrocyte end feet is sheathed with intraparenchymal blood vessels and is responsible in the maintenance of ionic and osmotic homeostasis and gliovascular signaling. Also, astrocytes are in close contact with microglia cells with bidirectional signaling among them (Rajkowska et al., 2013). A number of stimuli are responsible for astrocytic activation and like microglial activation it also serves as an element of neurodegeneration. Astrocytes are known to underwent age related changes thus they may play a leading role is the pathogenesis of late-life neurodegenerative disorders such as AD (Sofroniew et al., 2010). Astrocytic activation increases the cytokine production and the release of signalling molecules that may affect the basic neurophysiology through (either directly or indirectly) microglial activation (Wang et al., 2015). NFkB-activated astrocyte release of complement protein C3 is one of the major pathways in which C3aR is activated and induces neuronal damage. Thus, inhibition of NFkB signaling or neuronal C3aR may be beneficial in the treatment of AD (Lian et al., 2015). CD40 ligand is another astrocytic signaling molecule of interest. The binding of CD40 ligands to their respective receptors on microglial cells increases the production of tumor necrosis factor (TNF)-alpha. TNF-alpha is an important pro-inflammatory mediator which plays a major role in the pathogenesis of AD (Kawabe et al., 2011).

Cytokines

The postmortem analysis of the AD brains has shown the accumulation of cytokines (IL-1β, IL-6 and TGF-β) around the amyloid plaques in the brain of AD patients. These findings directed the researchers to study and investigate the levels of inflammatory and anti-inflammatory cytokines in the cerebral spinal fluid (CSF) or serum of patients with mild cognitive impairment (MCI) or AD (Zheng et al., 2016). The levels of both proinflammatory (IL-1β, IL-6, TNF-α) and anti-inflammatory cytokines (IL-1 receptor antagonist (IL-1ra), IL-10) were found elevated in the CSF and plasma of AD patients. Cytokines are a broad category of small proteins that regulates inflammation, cell signaling, and various other cellular processes like growth and survival (Shaftel et al., 2008). Chemokines are subset of cytokines. Chemokines regulate cell migration, such as attracting immune cells to a site of infection or injury (Turner et al., 2014). Physiologically, chemokines are neuromodulators which control inflammation and neuronal development. In brain, cells secrete cytokines to create a local inflammatory environment to engage microglia and clear the infection or injury. But, in neuroinflammation, cells may have continued release of cytokines and chemokines that may compromise the blood–brain barrier. Peripheral immune cells are called to the site of injury via these cytokines and may now migrate across the compromised blood brain barrier into the brain (Ramesh et al., 2013). Common cytokines produced in response to brain injury include: interleukin-6 (IL-6), which is produced during astrogliosis, and interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α), which can induce neuronal cytotoxicity. Although the pro-inflammatory cytokines may cause cell death and secondary tissue damage, they are necessary to repair the damaged tissue. For example, TNF-α causes neurotoxicity at early stages of neuroinflammation, but contributes to tissue growth at later stages of inflammation (Khandelwal et al., 2011).

Prostaglandins

Increased levels of prostaglandins are found in the cerebral spinal fluid (CSF) and brain parenchyma of the AD patients (Cudaback et al., 2014). Prostaglandins are associated with the cognitive impairments in AD, thus may connect the link between neuroinflammation and cognitive decline in age-related neurodegeneration (Simen et al., 2011). Prostaglandins are synthesized and released in response to inflammatory stimuli and then freely diffuse from cellular into the extracellular compartments. A family (SLCO2A1) of organic anion-transporting polypeptide (OATP2A1) transporter is involved in the clearance and recycling of extracellular prostaglandins (Hagenbuch et al., 2013). Prostaglandins act on their respective G protein-coupled

receptors (GPCRs) to induce an inflammatory response (Lei et al., 2012). PGE2 is one of the five prostaglandins that play a major role in the pathogenesis of AD (Johansson et al., 2015). PGE2 is synthesized by microsomal prostaglandin E synthase (mPGES), in the membrane and by cytosolic PGES (cPGES), in the cytosol (Nakano et al., 2015). Neuroinflammation is directly related with elevated brain levels of prostaglandins (PGs), principally PGE2, which plays a key role in the pathogenesis of numerous neurodegenerative disorders (Ricciotti et al., 2011). PGE2 signalling is mediated by interactions with four distinct G protein-coupled receptors, EP1–4, which are differentially expressed on neuronal and glial cells throughout the CNS (Cimino et al., 2008). In order to recognize the significance of various EP receptors in AD, several groups developed genetic mouse models of AD that lacked specific PGE2 receptor subtypes were studied and then the measured outcomes like cognitive decline, amyloid plaque deposition, proinflammatory cytokine expression, and oxidative stress were analyzed. A significant reduction in amyloid plaque deposition was observed in EP1 knockout mice expressing both the Swedish amyloid precursor protein (APP) and PS1 mutations that were identified in human familial AD. A significant reduction in the oxidative damage was observed in EP2 receptor knockout AD mice. Furthermore, EP2 receptor knockout AD mice were found to develop cognitive defects, suggesting an important role for EP2 receptor signalling in normal cognitive functioning. EP2 activation has been shown to mediate microglial-induced paracrine neurotoxicity, but its role also is dependent on the specific cell type in which EP2 signalling is activated. In neuroinflammation, elevated PGE2 and inflammatory mediators are also intrinsic characteristics of an aging brain. The role of the inflammatory cyclooxygenase-PGE_2 pathway in the pathogenesis is highly critical. The cyclooxygenase-PGE_2 pathway regulates the inflammatory response to accumulating Aß peptides through E-prostanoid G-protein coupled receptors (Johansson et al., 2015).

Neurodegenerative mechanisms

Misfolded proteins deposition

These involve the extracellular protein deposit in the cortex of AD patients (Murphy et al., 2010). The major protein in neuritic plaques is amyloid β- peptide (Aβ), which is a 40-42 amino acid peptide derived from a membrane protein, the β-amyloid precursor protein (APP) after sequential cleavage by enzymes. APP encoded by gene on chromosome 21. APP act together with extracellular matrix and promote the growth of neuritis in neuronal culture, its physiological role is likely related to the modulation of synaptic activity although still controversial. Genetic data implicates Aβ in the pathogenesis of Alzheimer's disease. Most of the patients with trisomy 21 (Down syndrome) develop pathologic changes indistinguishable from those seen in Alzheimer's disease, suggesting that having an increased copy of the APP gene increases the metabolism of APP to Aβ (Castro et al., 2017). Microtubules are proteins that are associated with the primary cytoskeletal components of the neurons. Tau protein is a microtubule associated protein normally located in the neuronal axon, where it physiologically facilitates the axonal transport by binding and stabilizing the microtubules (Patterson et al., 1988). However, in certain pathological conditions like Alzheimer's disease, tau is translocated to the somatodenderitic compartment, where it undergoes hyperphosphoration, misfolding and aggregation giving rise to neurofibrillary tangles and neuropil threads. The accumulation of hyperphosphorylated Tau protein to such a toxic level cause the inhibition and breakdown of microtubule structures in neuron and further causes impairment in axonal transport. Tautopaties are the diseases associated with the abnormal accumulation of the Tau proteins (Simic et al., 2016).

Oxidative Stress and Lipid peroxidation

Oxygen is required for the normal functioning of eukaryotes. The role of oxygen is linked to its high redox potential that makes it an excellent oxidizing agent capable of accepting electrons easily from reduced substrates. On the basis of their metabolic needs, different tissues have different oxygen demand. Neurons and astrocytes, the two major types of brain cells, are largely responsible for the brain's massive consumption of O_2 and glucose; indeed, the brain represents only ~2% of the total body weight and yet accounts for more than 20% of the total consumption of oxygen (Gandhi et al., 2012). Despite the essentiality of oxygen for living organisms, the state of hyperoxia produces toxicity, including neurotoxicity (Ahdab-Barmada et al., 1986). An imbalanced redox states may either generate excessive reactive oxygen species (ROS) or may cause dysfunction of the antioxidant system, thus creating oxidative stress (Devydov et al., 1988). Previous studies have demonstrated that oxidative stress plays a central role in a common pathophysiology of Alzheimer's disease (Kim et al., 2015). Brain is the most metabolically active organ in the human body and is highly vulnerable to the oxidative stress particularly because of the following mentioned reasons. First, the brain has a high oxygen demand, which constitutes 20% of the body oxygen consumption. Second, the redox-active metals such as iron or copper exist abundantly in the brain and they are actively involved to catalyze ROS formation. Third, the high levels of polyunsaturated fatty acids are found in the brain cell membranes and react as substrates for lipid peroxidation

(Wang et al., 2010). Fourth, there are relatively low levels of GSH in the brain, which plays a role of endogenous antioxidant in the elimination of ROS (Ferreira et al., 2015).

The pathophysiology of AD is mainly associated with the extracellular deposition of amyloid beta (Aβ) plaques and the accumulation of intracellular tau neurofibrillary tangles (NFT) (Zuo et al., 2015). Aβ plaques may drain calcium ions (Ca^{2+}) storage in endoplasmic reticulum (ER) and may result in cytosolic Ca^{2+} overload (Querfurth et al., 2010). In response to increase levels of cytosolic Ca^{2+}, endogenous GSH levels are reduced and ROS can accumulate inside the cells (Ferreiro et al., 2008). ROS induced oxidative stress is an important factor in pathogenesis of AD as ROS overproduction is thought to play a critical role in the accumulation and deposition of Aβ in AD (Bonda et al., 2015). Mitochondrial dysfunction can lead to ROS overproduction, reduced production of adenosine triphosphate (ATP), altered Ca^{2+} homeostasis, and excitotoxicity. All these alterations may be implicated in the progression of AD (Huang et al., 2016). Previous studies have implicated that Aβ-induced oxidative imbalance may increase the levels of the byproducts related to lipid peroxidation (e.g. 4-hydroxynonal, malonidialdehyde), protein oxidation (e.g. carbonyl) and DNA/RNA oxidation (e.g. 8-hydroxyldeoxyguanosine and 8-hydroxylguanosine). In contrast, decreased levels of antioxidants (e.g. uric acid, vitamin C and E) or antioxidant enzymes (e.g. superoxide dismutase, catalase etc.) have been found in patients with AD (Wang et al., 2014). Based on the hypothesis that oxidative stress is pathogenic in neurodegenerative disease, the rationale for the use of antioxidants as therapies is clear. Coenzyme Q10 is involved in the transfers electrons from complexes I and II to complex III in respiratory chain (Gandhi et al., 2012). As major antioxidant enzymes, superoxide dismutases (SODs) play a crucial role in scavenging O^{-2} (Zhao et al., 2013). The superoxide dismutase family is particularly involved in the elimination of superoxide anion radicals resulting from extracellular stimulants, ionizing radiation and oxidative insults, together with those primarily produced within the mitochondrial matrix as by-products of oxygen metabolism through the electron transport chain (Miao et al., 2009). Catalase is a ferriheme-containing enzyme that is responsible for the conversion of hydrogen peroxide (but not other peroxides) to water. Glutathione (GSH) is the most abundant small molecule, non-protein thiol (present in millimolar concentration in the brain). Glutathione peroxidase is the comman name for a family of many isozymes that catalyze the reduction of H_2O_2 or organic hydroperoxides to water or corresponding alcohols using reduced glutathione (GSH) as an electron donor ($H_2O_2 + 2\ GSH \rightarrow GS\text{-}SG + 2H_2O$) (Dringen et al.,2003). Reduced GSH react nonenzymatically with free radicals, notably superoxide radicals, hydroxyl radicals, nitric oxide, and carbon radicals for their removal. GSH peroxidase and GSH reductase can act enzymatically to remove H_2O_2 and maintain GSH in a reduced state (Kim et al., 2015).

Lipid peroxidation occurs as a result of free radical-mediated injury that directly or indirectly damages plasma membranes by generating various secondary products, which possess neurotoxic activity. The brains of AD patients have demonstrated increased lipid peroxidation in comparison to age-matched controls. Immunohistochemical and biochemical studies were performed to quantify and localise various lipidperoxidation products like 4-hydroxy-2-nonenal, acrolein, isoprostanes and neuroprostanes in AD brain samples. Cerebrospinal fluid (CSF) levels of isoprostanes were found to increase in the early dementia of AD and may act diagnostic biomarker of AD. Brain lipidperoxidation plays an important role in the pathogenesis of AD and may also act as a potential drug target in the treatment of AD (Montine et al., 2002).

Mitochondrial dysfunctioning

Aβ has been found to accumulate in the mitochondria of the post-mortem brains of the AD patients, brains of the living AD patients and the brains of transgenic AD mice. The presence of Aβ in the mitochondria even before the formation of amyloid plaques indicates that mitochondria are early targets for Aβ accumulation and may be the initiation of AD pathogenesis (Reddy et al., 2008). However the exact mechanism of Aβ neurotoxicity is still unknown. Recent studies have identified a proapoptotic protein that interact with APP and plays a major role in the pathogenesis of AD. This proapoptotic protein was named as appoptosin and was considered as a connecting link between APP interaction and neuronal apoptosis (O'brien et al., 2011). Appoptosis is required in the transportation of glycine and 5-amino-levulinic acid (δ-ALA) across the mitochondria for heme synthesis. In order to maintain homeostasis and cellular integrity, it is essential to maintain a balance between free heme and protein-bound heme. The homeostatic disturbances occur when free heme levels increase. Increased free heme levels facilitate ROS production, destabilize mitochondrial cytoskeleton and finally results in faulty heme metabolism (Dufay et al., 2017). The intrinsic caspase-dependent apoptosis is controlled by appoptosin through heme biosynthesis, thus making it one of the potential drug targets in the AD related therapeutics (Atamna et al., 2004).

Current therapeutical approaches in the treatment of neurodegenerative disease

A number of pharmaceutical compounds are in the market which has been used for their neuroprotective property. Neuroprotective drugs work by altering the neurotransmitters balance in the brain, improving cerebral blood flow, cerebral oxygen usage, metabolic rate and cerebral glucose metabolic rate in chronic impaired human brain function i.e., multi-

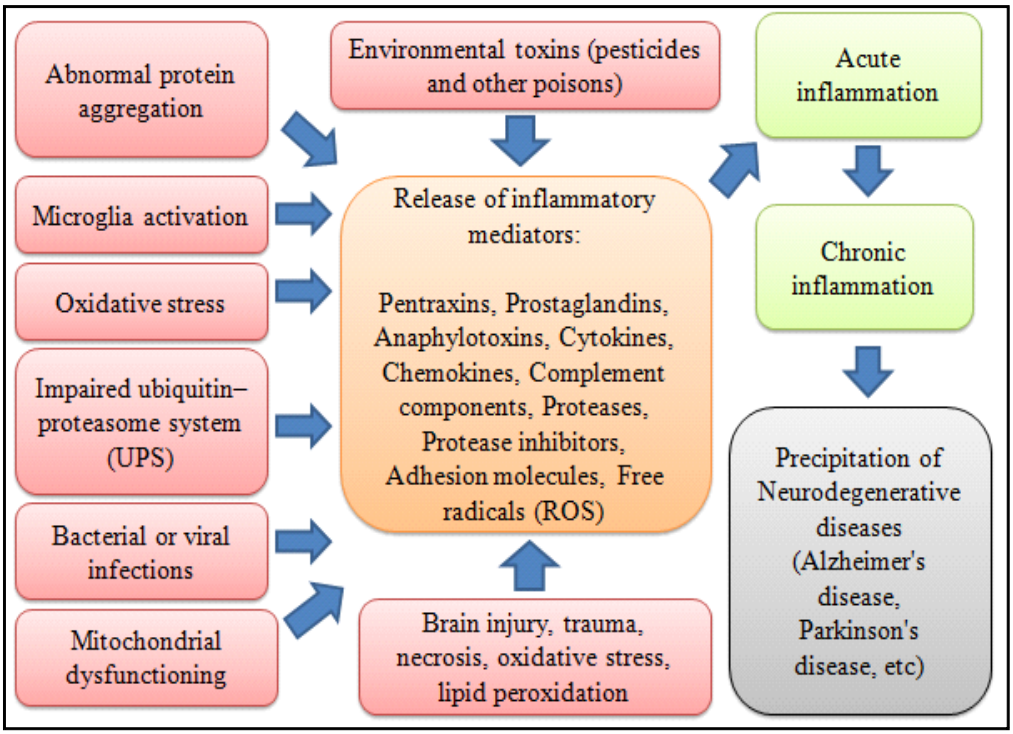

Figure 1. Different inflammatory mediators (pentraxins, prostaglandins, anaphylotoxins, cytokines, chemokines, complement components, proteases, protease inhibitors, adhesion molecules, and free radicals) and neurodegenerative factors (Abnormal protein aggregation, microglial activation, oxidative stress, lipid peroxidation, impaired ubiquitin protease system (UPS), mitochondrial dysfunctioning, exposure to neurotoxins, brain trauma.) that may precipitate neurodegenerative diseases.

infarct (stroke) dementia, senile dementia in AD and pseudo dementia, ischaemic cerebral (poor brain blood flow) infarcts. Few of the most commonly used compounds used in the treatment of neurodegenerative diseases are as follows:

Aminoacids

Dietary aminoacids provide large quantity of carbon and nitrogen to the body and play a significant role in neuronal signaling, energy production, and nitrogenous waste production and elimination. It is possible that aminoacid supplements may improve neural functioning in AD patients. The plasma levels of amino acids were found to be significantly low in AD patients. The bioavailability of individual amino acids and dipeptides is more superior to polypeptides since monomers are absorbed more quickly without the need for further enzymatic hydrolysis in the gut. The blood levels of both acidic (aspartate and glutamate) and basic (arginine, lysine, and histidine) amino acids were found to be significantly low in AD patients (Griffin et al., 2017). Glutamine supplementation is reported to decreases tau phosphorylation and has shown other neuroprotective effects in a mouse model of AD (Wang et al., 2015). L-theanine is commonly found in green tea and it effectively crosses BBB. L-theanine is reported to possess neuroprotective properties and is known to increase neurotrophic factor (BDNF) in brain (Kim et al., 2004).

Vitamins

Vitamins are efficient antioxidants and thus be used as an adjuvant in AD treatment (Bhatti et al., 2016). Vitamin A and beta carotenes play a significant role in neuronal development (Grune et al., 2010). The blood plasma and CSF levels of vitamin A were found to be significantly low in AD (Wildea et al., 2017). Vitamin E is one of the most frequently studied antioxidant therapy since it is the major scavenger of lipid peroxidation in brain; whereas, vitamin C acts as an intracellular reducing molecule. Furthermore, vitamin A and beta carotene hampers the formation and promote the destabilization of Aβ fibrils in AD (Ono et al., 2004). The plasma levels of vitamin B12 were found to be significantly low in AD patients. It is a well established fact that deficiency of vitamin B12 may exacerbate cognitive decline and dementia in AD patients. Dementia and cognitive decline were more predominant in AD patients with low plasma levels of vitamin B12 levels (Morris et al., 2006). The plasma levels of vitamin C were found to be significantly low in AD patients. Vitamin C has potential to prevent the oligomerization of Aβ peptides and can impede the structural progression of AD. Vitamin C Supplementation improves the brain levels of SOD and thus may helps in lowering the oxidative stress and resultant brain injury (Monacelli et al., 2017). Vitamin E comprises a group of 8 antioxidants (4 tocotrienols and 4 tocopherols). The decreased plasma levels of vitamin E are reported in AD patients. Low plasma levels of vitamin E are associated with Mild Cognitive Impairment (MCI) in AD (Sen

et al., 2006). The plasma levels of 5-nitro-γ-tocopherol (one of the vitamin E degradation products) were found to be significantly high in patients with Mild Cognitive Impairment (MCI) in AD (Mangialasche et al., 2012). Long term vitamin E deficiency may lead to neurodegeneration in late life. Vitamin E is a potent antioxidant and hampers the AD progression at many levels. Free radicals facilitate the formation of Aβ plaque and thus play a major role in the AD pathogenesis (Boccardi et al., 2016). Vitamin E is a free radical scavenger and thus provides neuroprotection against oxidative stree induced neuronal injury (Duval et al., 1995). Vitamin E consumption is reported to increase the SOD levels in brain (Gugliandolo et al., 2017). Among the different forms of vitamin E, α-tocopherols and γ-tocopherols provide greater degree of neuroprotection against and cognitive decline in AD (Morris et al., 2015). Vitamin E appears to neutralize the effect of peroxide and prevent lipid per oxidation in membranes (Traber et al., 2007).

Flavanoids

Flavanoids is a group of natural substances with a phenolic structure. Flavanoids are present in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. Flavanoids are well known for their beneficial effects on health. Flavanoids are known for their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties. Flavanoids are free radicals scavengers and may prevent ROS induced neuronal injury (Panche et al., 2016). Flavanoids are easily oxidized by free radicals are form more stable and less reactive product (Pietta, 2000). Flavanoids are known to inhibit several enzymes like aldose reductase, xanthine oxidase (Lin et al., 2015), phosphodiesterase (Ko et al., 2004), Ca^{2+} ATPase (Ogunbayo et al., 2008), lipoxygenase (Sadik et al., 2003) and COX (Ribeiro et al., 2015) in preventing neurodegenerative diseases. Flavanoids like quercetin, rutin, kaempferol 3-O-β-D-galactoside and macluraxanthone are reported to possess anti-cholinesterase activity (Panche et al., 2016). Fisetin is a commonly present flavanoid in strawberries and is used as a memory boosting supplement for AD patients (Khan et al., 2013).

Nootropics

Nootropics are smart drugs are may also be described as medical drugs and nutritional supplements that have a positive effect on brain function. Natural nootropics are known to reduce neuroinflammation. Nootropic supplementation protects the brain against toxins and minimise neurodegeneration. Nootropics are known to play an important role in neurogenesis. Nootropic improves the thinking and memory abilities by enhancing neuroplasticity (Suliman et al., 2016). Donepezil is generally marketed under the trade name Aricept, is a medication used in the palliative treatment of Alzheimer's disease. Donepezil is used to improve cognition and behavior of people with Alzheimer's (Gauthier et al., 2002). Donepezil reversibly binds with the cholinesterases and cause their inactivation, thus inhibiting hydrolysis of acetylcholine. This increases acetylcholine concentrations at cholinergic synapses (Colovic et al., 2013). Alzheimer's disease is associated with a significant loss of the elements of the cholinergic system and it is generally accepted that the symptoms of Alzheimer's disease are related to this cholinergic deficit, mainly in the cerebral cortex and other parts of the brain. It is noted that the hippocampal formation plays an important role in the processes of control of attention, memory and learning. Just the severity of the loss of cholinergic neurons of the central nervous system (CNS) has been found to correlate with the severity of cognitive impairment. Donepezil is also reported to suppress high fat diet (HFD) induced neuroinflammation by attenuating microgial activation (Dasuri et al., 2016).

Melatonin

Melatonin, which plays an important role in maintaining circadian rhythm, is also a highly potent endogenous free radical scavenger. Based on the ability of melatonin (N-acetyl-5-methoxytryptamine) and its metabolites to scavenge a wide variety of free radicals (FR), it is not surprising to consider it as one of its important functions in living organisms leading to protect them from oxidative stress (Hardeland et al., 2005). This neurohormone act as a direct scavenger and remove free radicals, like singlet oxygen, superoxide anion radical, hydroxyl radical and the lipid peroxide radical. Moreover, a single melatonin molecule may generate products in a scavenger cascade, which may collectively eliminate up to ten FR (Tyagi et al., 2010). Melatonin can develop indirect antioxidant actions through the improvement of the mitochondrial efficiency, the stimulation of the gene expression and the activation of some of the most important antioxidant enzymes, including superoxide dismutase (SOD), catalase, glucose-6-phosphate dehydrogenase, glutathione reductase and glutathione peroxidase and also with the strengthening of the antioxidant effect of substances, like glutathione, vitamin E and vitamin C (Esposito et al., 2010).

Statins

Statins are 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, which reduce low-density lipoprotein (LDL) cholesterol levels by blocking the mevalonate pathway and increase LDL cholesterol receptor expression in the liver. Inhibition of HMG-CoA reductase activity in monocyte and rat mesangial cells treated with lipopolysaccharide (LPS) and granulocyte macrophage-colony stimulating factor reduced the production of cytokines like IL-8, IL-6, and MCP-1 (Monocyte Chemotactic Protein-1), which are responsible for leukocyte recruitment at the site of infection. Statins are effective endothelium-protective agents that reduce leukocyte-endothelial cell interactions and improve the endothelial function via increasing endothelial nitric oxide synthase (eNOS) (Greenwood et al., 2007). Also, cerivastatin

administered intraperitoneally (i.p.) significantly improved the survival of mice with LPS-induced sepsis and reduced TNF-α, IL-1β and IL-6 over production (Ando et al., 2000).

Conclusion

A number of neurodenerative disease of aging like Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis, all of the tauopathies, and age-related macular degeneration is associated with chronic inflammation. Microglial cells act as a major type of active immune defence in the brain and are a part of the monocyte phagocytic system. Intensity of microglial activation is associated with the levels of different inflammatory mediators like prostaglandins, chemokines, proteases, protease inhibitors, adhesion molecules, and free radicals, produced by a variety of local cells. ROS induced oxidative stress play a major role in the pathogenesis of AD. Overproduction of ROS promotes the accumulation and deposition of Aβ in AD. Mitochondrial dysfunction can lead to ROS generation, reduced adenosine triphosphate (ATP), altered Ca^{2+} homeostasis, and excitotoxicity. All these alterations may be concerned with the disease progression.A number of animal experiments and clinical studies have recognised the role of neuroinflammatory mediators in the progression of neurodegenerative diseases. Though, the exact underlying mechanism involved in the disease progression is still unknown. Furthermore, the existing relationship between different in inflammatory pathways is still unclear. These drawbacks impede the improvement of disease modifying therapeutics. In addition, different types of microglia activation further increase the difficulty and complexity of manoeuvring of microglial responses in the disease pathogenesis. Future research must focus on identifying more precise drug targets through understanding the basic processes involved in inflammation at different levels of disease progression.

Future direction

Since ages, a number of plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD) and other memory related disorders. Since last few years, an intense interest in herbal medicines in which phytochemical constituents can have long-term health promoting or medicinal qualities. However, many medicinal plants are known to possess specific medicinal actions with no nutritional role in the human diet and may be used in response to specific health problems over short or long-term intervals. Vegetables and fruits contain a number of phytochemicals, which are believed to reduce the risk of several major diseases including cardiovascular diseases, cancers as well as neurodegenerative disorders. Hence people consuming higher vegetables and fruits are less vulnerable to diseases caused by neuronal dysfunction. Most of the drugs currently used in the treatment of AD are derived from the alkaloid class of plant phytochemicals (Wightman et al., 2017). Such drugs like galantamine and rivastigmine attenuates the decline in the cholinergic system but are considered to occupy the dangerous end of the phytochemical spectrum and possess a number of side effects. A number of phytochemicals like benign terpene (*Ginkgo biloba, Panax ginseng, Melissa officinalis and Salvia lavandulaefolia*) and phenolic (such as resveratrol) are known to possess neuroprotective activity and research is going on to use them more efficiently as a therapeutic aid in cholinesterase inhibition, improving cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid-β neurotoxicity in the treatment of AD.

Conflicts of interest

The authors claim no conflict of interest to declare.

References

Ahdab-Barmada M, Moossy J, Nemoto EM, Lin MR. 1986. Hyperoxia produces neuronal necrosis in the rat. Journal of Neuropathology and Experimental Neurology, 45: 233–246.

Ando H, Takamura T, Ota T, Nagai Y, Kobayashi K. 2000. Cerivastatin improves survival of mice with lipopolysaccharide-induced sepsis. Journal of Pharmacology and Experimental Therapeutics, 294(3): 1043-6.

Aschner M, Milatovic D, Montine TJ,Breyer RM. 2011. Neuroinflammation and oxidative injury in developmental neurotoxicity. Reproductive and Developmental Toxicology, 56: 847-854.

Atamna H, Frey WH. 2004. A role for heme in Alzheimer's disease: Heme binds amyloid β and has altered metabolism. Proceedings of the National Academy of Sciences of the United States of America, 101(30): 11153–11158.

Bhatti AB, Usman M, Ali F, Satti SA. 2016. Vitamin Supplementation as an Adjuvant Treatment for Alzheimer's disease. JOURNAL of CLINICAL And DIAGNOSTIC Research, 10(8): 7-11.

Boccardi V, Baroni M, Mangialasche F, Mecocci P. 2016. Vitamin E family: Role in the pathogenesis and treatment of Alzheimer's disease. Alzheimer's & Dementia, 2(3): 182–191.

Bonda DJ, Wang X, Perry G et al. 2015. Oxidative stress in Alzheimer disease: a possibility for prevention. Neuropharmacology, 59: 290–294.

Carson MJ, Thrash JC, Walter B. 2006. The cellular response in neuroinflammation: The role of leukocytes, microglia and astrocytes in neuronal death and survival. Clinical Neuroscience Research, 6 (5): 237-246.

Casella G, Tontini GE, Bassotti G, Pastorelli L, Villanacci

V, Spina L, Baldini V, Vecchi M. 2015. Neurological disorders and inflammatory bowel diseases. World Journal of Gastroenterology, 20(27): 8764-8782.

Castro P, Zaman S, Holland A. 2017. Alzheimer's disease in people with Down's syndrome: the prospects for and the challenges of developing preventative treatments. Journal of Neurology, 264(4): 804–813.

Chen WW, Zhang X, Huang WJ. 2016. Role of neuroinflammation in neurodegenerative diseases. Molecular Medicine Reports, 13(4): 3391–3396.

Cimino PJ, Keene CD, Breyer RM, Montine KS, Montine TJ. 2008. Therapeutic targets in prostaglandin E2 signaling for neurologic disease. Current Medicinal Chemistry, 15(19):1863-9.

Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. 2013. Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. Current Neuropharmacology, 11(3): 315–335.

Cudaback E, Jorstad NL, Yang Y, Montine TJ, Keene CD. 2014. Therapeutic Implications of the Prostaglandin Pathway in Alzheimer's disease. Biochemical Pharmacology, 88(4): 565–572.

Dasuri K, Zhang L, Kim SOF, Bruce-Keller AJ, Keller JN. 2016. Dietary and donepezil modulation of mTOR signaling and neuroinflammation in the brain. Biochimica et Biophysica Acta, 1862(2): 274–283.

Davydov BI, Drobyshev VI, Ushakov IB, Fyodorov VP. 1988. Morphological analysis of animal brain reactions to short-term hyperoxia. Kosmicheskaya Biologiya I Aviakosmicheskaya Meditsina, 22: 56–62.

DiSabato D, Quan N, Godbout JP. 2016. Neuroinflammation: The Devil is in the Details. Journal of Neurochemistry, 139: 136-153.

Donat CK, Scott G, Gentleman SM, Sastre M. 2017. Microglial Activation in Traumatic Brain Injury. Frontiers in Aging Neuroscience, 9: 1-20.

Dringen R and Hirrlinger J. 2003. Glutathione pathways in the brain. Biological Chemistry, 384: 505–516.

Dufay JN, Fernández-Murray JP, McMaster CR. 2017. SLC25 Family Member Genetic Interactions Identify a Role for HEM25 in Yeast Electron Transport Chain Stability. G3: Genes, Genomes, Genetics, 7(6): 1861–1873.

Duval C, Poelman MC. 1995. Scavenger effect of vitamin E and derivatives on free radicals generated by photoirradiated pheomelanin. Journal of Pharmaceutical Sciences, 84(1): 107-10.

Elmore S. 2007. Apoptosis: A Review of Programmed Cell Death. Toxicologic Pathology, 35(4): 495-516.

Esposito E, Cuzzocrea S. 2010. Antiinflammatory Activity of Melatonin in Central Nervous System. Current Neuropharmacology, 8(3):228–242.

Farooqui AA, Horrocks LA, Farooqui T. 2007. Modulation of inflammation in brain: a matter of fat. Journal of Neurochemistry, 101: 577–599.

Ferreira ME, Vasconcelos AS, Costa VT, Silva TL, Silva BA, Gomes AR, Dolabela MF, Percário S. 2015. Oxidative Stress in Alzheimer's Disease: Should We Keep Trying Antioxidant Therapies? Cellular and Molecular Neurobiology, 35: 595-614.

Ferreiro E, Oliveira CR, Pereir CM. 2008. The release of calcium from the endoplasmic reticulum induced by amyloid-beta and prion peptides activates the mitochondrial apoptotic pathway. Neurobiology of Disease, 30: 331–342.

Gandhi S, Abramov AY. 2012. Mechanism of Oxidative Stress in Neurodegeneration. Oxidative Medicine and Cellular Longevity, 1: 1-11.

Gao HM, Hong JS. 2008. Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. Trends in Immunology, 29 (8): 357-365.

Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P. 2002. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. Current Medical Research and Opinion, 18(6): 347-54.

Ginhoux F, Lim S, Hoeffel G, Low D, Huber T. 2013. Origin and differentiation of microglia. Frontiers in Cellular Neuroscience, 7(45): 1-14.

Greenwood J, Mason JC. 2007. Statins and the vascular endothelial inflammatory response. Trends in Immunology, 28(2): 1-19.

Griffin JWD, Bradshaw PC. 2017. Amino Acid Catabolism in Alzheimer's Disease Brain:Friend or Foe?. Oxidative Medicine and Cellular Longevity, 1: 1-16.

Grune T, Lietz G, Palou A, Ross AC, Stahl W, Tang G, Thurnham D, Yin S, Biesalski HK. 2010. β-Carotene Is an Important Vitamin A Source for Humans. Journal of Nutrition, 140(12): 2268S–2285S.

Gugliandolo A, Bramanti P, Mazzon E. 2017. Role of Vitamin E in the Treatment of Alzheimer's Disease: Evidence from Animal Models. International Journal of Molecular Sciences 18(12): 1-21.

Hagenbuch B, Stieger B. 2013. The Slco (Former Slc21) Superfamily of Transporters. Molecular Aspects of Medicine, 34(2-3): 396–412.

Hardeland R, Pandi-Perumal SR. 2005. Melatonin, a potent agent in antioxidative defense: Actions as a natural food constituent, gastrointestinal factor, drug and prodrug. Journal of Nutrition and Metabolism, 2 (22): 1-15.

Harry GJ, Kraft AD. 2008. Neuroinflammation and

Microglia: Considerations and approaches for neurotoxicity assessment. Expert Opinion on Drug Metabolism & Toxicology, 4(10): 1265–1277.

Harry GJ. 2013. Microglia During Development and Aging. Pharmacology & Therapeutics, 139(3): 313–326.

Huang WJ, Zhang X, Chen WW. 2016. Role of oxidative stress in Alzheimer's disease. Biomedical Reports, 4: 519–522.

Johansson JU, Woodling NS, Shi J, Andreasson KI. 2015. Inflammatory Cyclooxygenase Activity and PGE2 Signalling in Models of Alzheimer's disease. Current Immunology Reviews, 11(2): 125–131.

Karishma SK et al.2017. A Short Review on Alzheimer's Diseases. International Journal of Pharmacy and Pharmaceutical Research, 10 (3): 264-273.

Kawabe T, Matsushima M, Hashimoto N, Imaizumi K, Hasegawa A. 2011. Cd40/Cd40 Ligand Interactions in Immune Responses and Pulmonary Immunity. Nagoya Journal of Medical Science, 73(3-4): 69–78.

Khan N, Syed DN, Ahmad N, Mukhtar H. 2013. Fisetin: A Dietary Antioxidant for Health Promotion. Antioxidants & Redox Signaling, 19(2): 151–162.

Khandelwal PJ, Herman AM, Moussa CEH. 2011. Inflammation in the early stages of neurodegenerative pathology. Journal of Neuroimmunology, 238(1-2): 1–11.

Kim GH, Kim JE. 2015. The Role of Oxidative Stress in Neurodegenerative Diseases. Experimental Neurobiology, 24 (4): 325-340.

Kim KH, Son SM, Mook-Jung I. 2013. Contributions of Microglia to Structural Synaptic Plasticity. Journal of Experimental Neuroscience, 7: 85–91.

Kim TI, Lee YK, Park SG, Choi IS, Ban JO, Park HK, Nam SY, Yun YW, Han SB, Oh KW, Hong JT. 2004. l-Theanine, an amino acid in green tea, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways. Free Radical Biology and Medicine, 68(10): 2087-94.

Ko WC, Shih CM, Lai YH, Chen JH, Huang HL. 2004. Inhibitory effects of flavonoids on phosphodiesterase isozymes from guinea pig and their structure-activity relationships. Biochemical Pharmacology, 68(10): 2087-94.

Korczyn AD, G.C. Roman GC, N.M. Bornstein NM. 2002. Vascular dementia may be the most common form of dementia in the elderly. JOURNAL of the Neurological Sciences, 203-204: 7-10.

Lei S, Richard DY. 2012. Role of G protein-coupled receptors in inflammation. ACTA Pharmacologica SINICA, 33(3): 342–350.

Li JJ, Wang B, Kodali MC, Chen C, Kim E, Patters BJ, Lan L, Kumar S, Wang X, Yue J, Liao FF. 2018. In vivo evidence for the contribution of peripheral circulating inflammatory exosomes to neuroinflammation. Journal of Neuroinflammation, 15(8): 1-16.

Lian H, Yang L, Cole A, Sun L, Chiang ACA, Fowler SW, Shim DJ ,Rodriguez-Rivera J, Taglialatela G, Jankowsky JL , Lu HC , Zheng H. 2015. NFκB-activated Astroglial Release of Complement C3 Compromises Neuronal Morphology and Function Associated with Alzheimer's Disease. Neuron.vol. 85(1): 101–115.

Lin S, Zhang G, Liao Y, Pan J, Gong D. 2015. Dietary Flavonoids as Xanthine Oxidase Inhibitors: Structure-Affinity and Structure-Activity Relationships. Journal of Agricultural and Food Chemistry, 63(35): 7784-94.

Maalouf M, Ringman JM, Shi J. 2011. An update on the diagnosis and management of dementing conditions. Revue Neurologique, 8(3-4): e68–e87.

Mangialasche F, Xu W, Kivipelto M, Costanzi E, Ercolani S, Pigliautile M, Cecchetti R, Baglioni M, Simmons A, Soininen H , Tsolaki M, Kloszewska I, Vellas B, Lovestone S, Mecocci P. 2012. Tocopherols and tocotrienols plasma levels are associated with cognitive impairment. Neurobiology of Aging, 33(10): 2282-2290.

Miao L and Clair DKS. 2009. Regulation of superoxide dismutase genes: implications in disease. Free Radical Biology and Medicine, 47: 344–356.

Milatovic D, S. Zaja-Milatovic S, Montine KS, Shie FS, Montine TJ. 2004. Neuronal oxidative damage and dendritic degeneration following activation of CD14-dependent innate immune response in vivo. Journal of Neuroinflammation, 1(20): 1-7.

Miyamoto A, Wake H, Ishikawa A, Eto K. 2016. Microglia contact induces synapse formation in developing somatosensory cortex. Nature Communications, 7: 1-12, 2016.

Monacelli F,Acquarone E, Giannotti C, Borghi R, Nencioni A. 2017. Vitamin C, Aging and Alzheimer's Disease. Nutrients, 9(7): 1-26.

Montine TJ, Neely MD, Quinn JF, Beal MF, Markesbery WR, Roberts LJ, Morrow JD. 2002. Lipid peroxidation in aging brain and Alzheimer's disease. Free Radical Biology and Medicine, 33(5): 620-6.

Morris MC, Schneider JA, Li H, Tangney CC, Nag S, Bennett DA, Honer WG, Barnes L. 2015. Brain Tocopherols Related to Alzheimer Disease Neuropathology in Humans. Alzheimer's & Dementia, 11(1): 32–39.

Morris MC, Schneider JA, Tangney CC. 2006. Thoughts on B-vitamins and dementia. Journal of Alzheimer's

Disease, 9(4): 429–433.

Murphy MP, LeVine H. 2010. Alzheimer's disease and the β-Amyloid Peptide. Journal of Alzheimer's disease, 19(1):311.

Nakano Y, Kuroda E, Kito T, Uematsu S , Akira S, Yokota A, Nishizawa S, Yamashita U. 2008. Induction of prostaglandin E2 synthesis and microsomal prostaglandin E synthase-1 expression in murine microglia by glioma-derived soluble factors. Laboratory investigation, 108(2):311-9.

'Obrien RJ, Wong PC. 2011. Amyloid Precursor Protein Processing and Alzheimer's disease. Annual Review of Neuroscience, 34: 185–204.

Ogunbayo OA, Harris RM, Waring RH, Kirk CJ, Michelangeli F. 2008. Inhibition of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase by flavonoids: a quantitative structure-activity relationship study. International Union of Biochemistry and Molecular Biology, 60(12):853-8.

Ono K, Yoshiike Y, Takashima A, Hasegawa K, Naiki H, Yamada M. 2004. Vitamin A exhibits potent antiamyloidogenic and fibril-destabilizing effects in vitro. Experimental Neurology, 189(2): 380-92.

Ota Y, Zanetti AT, Hallock RM. 2013. The Role of Astrocytes in the Regulation of Synaptic Plasticity and Memory Formation. Neural Plasticity, 1: 1-11.

Panche AN, Diwan AD, Chandra SR. 2016. Flavonoids: an overview. Journal of Nutritional Science; 5: 1-15.

Patterson D, Gardiner K, Kao FT, Tanzi R, Watkins P, Gusella JF. 1988. Mapping of the gene encoding the beta-amyloid precursor protein and its relationship to the Down syndrome region of chromosome 21. Proceedings of the National Academy of Sciences of the United States of America, 85(21): 8266–8270.

Pietta PG. 2000. Flavonoids as antioxidants. Journal of Natural Products, 63 (7): 1035-42.

Qiu C, Kivipelto M and von Strauss E. 2009. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies towards intervention. Dialogues in Clinical Neuroscience, 11(2): 111-128.

Querfurth HW and LaFerla FM. 2010. Alzheimer's disease. The New England Journal of Medicine, 362: 329– 344.

Rajkowska G, Hughes J, Stockmeier CA, Miguel-Hidalgo JJ, Maciag D. 2013. Coverage Of Blood Vessels By Astrocytic Endfeet Is Reduced In Major Depressive Disorder. Biological Psychiatry, 73(7): 613-621.

Ramesh G, MacLean AG, Philipp MT. 2013. Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediators of Inflammation, 1: 1-21.

Reddy PH, Manczak M, Mao P, Calkins MJ, Reddy AP, Shirendeb U. 2008. Amyloid-β and Mitochondria in Aging and Alzheimer's Disease: Implications for Synaptic Damage and Cognitive Decline. Journal of Alzheimer's Disease, 15(19): 1863–1869.

Ribeiro D, Freitas M, Tomé SM, Silva AM, Laufer S, Lima JL, Fernandes E. 2015. Flavonoids inhibit COX-1 and COX-2 enzymes and cytokine/chemokine production in human whole blood. Journal of Inflammation Research, 38(2): 858-70.

Ricciotti E, FitzGerald GA. 2011. Prostaglandins and Inflammation. Arteriosclerosis, Thrombosis, and Vascular Biology, 31 (5): 986–1000.

Rosskothen-Kuhl N, Hildebrandt H, Birkenhäger R, Illing RB. 2018. Astrocyte Hypertrophy and Microglia Activation in the Rat Auditory Midbrain Is Induced by Electrical Intracochlear Stimulation. Frontiers in Cellular Neuroscience, 12 (43): 1-20.

Sabbagh MN, Lue LF, Fayard D, Shi J. 2017. Increasing Precision of Clinical Diagnosis of Alzheimer's Disease Using a Combined Algorithm Incorporating Clinical and Novel Biomarker Data. Neurology and Therapy, 6: 83-95.

Sadik CD, Sies H, Schewe T. Inhibition of 15-lipoxygenases by flavonoids: structure-activity relations and mode of action. 2003. Biochemical Pharmacology, 65(5): 773-81.

Sen CK, Khanna S, Roy S. 2006. Tocotrienols: Vitamin E Beyond Tocopherols. Life Sciences, 78(18): 2088–2098.

Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. 2011. Neuropathological Alterations in Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine, 1(1): 1-23.

Shaftel SS, Griffin WST, O'Banion MK. 2008. The role of interleukin-1 in neuroinflammation and Alzheimer disease: an evolving perspective. Journal of Neuroinflammation, 5(7):1-12.

Simen AA, Bordner KA, Martin MP, Moy LA, Barry LC. 2011. Cognitive Dysfunction with Aging and the Role of Inflammation. Therapeutic Advances in Chronic Disease, 2(3): 175–195.

Simic G, Leko MB, Wray S, Harrington C, Delalle I, Jovanov-Milosevic N, Bažadona D, Buee L, de Silva R, Di Giovanni G, Wischik C, Hof PR. 2016. Tau Protein Hyperphosphorylation and Aggregation in Alzheimer's disease and Other Tauopathies, and Possible Neuroprotective Strategies. Biomolecules, 6(1): 6.

Sofroniew MV, Vinters HV. 2010. Astrocytes: biology and pathology. Acta Neuropathologica, 119(1): 7–35.

Stehberg J, Moraga-Amaro R, Salazar C, Becerra A, Echeverría C, Orellana JA.2012. Release of gliotransmitters through

astroglial connexin 43 hemichannels is necessary for fear memory consolidation in the basolateral amygdala. Federation of American Societies for Experimental Biology, 26(9): 3649-57.

Streit WJ, Mrak RE, Griffin WS. 2004. Microglia and neuroinflammation: a pathological perspective. Journal of Neuroinflammation, 1 (1): 1-4.

Suliman NA, Taib CNM, Aris M, Moklas M, Ilham Adenan M, Taufik Hidayat Baharuldin M, Basir R. 2016. Establishing Natural Nootropics: Recent Molecular Enhancement Influenced by Natural Nootropic. Evidence-Based Complementary and Alternative Medicine, 01: 1-12.

Takalo M, Salminen A, Soininen H, Hiltunen M, Haapasalo A. 2013. Protein aggregation and degradation mechanisms in neurodegenerative diseases. American Journal of Neorodegenerative Disease, 2 (1):1-14.

Tarawneh R, Holtzman DM. 2012. The Clinical Problem of Symptomatic Alzheimer Disease and Mild Cognitive Impairment. Cold Spring Harbor Perspectives in Medicine, 2 (5): 1-16.

Traber MG, Atkinson J. 2007. Vitamin E, Antioxidant and Nothing More. Free Radical Biology and Medicine, 43(1): 4–15.

Turner MD, Nedjai B, Hurst T, Pennington DJ. 2014. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochimica et Biophysica Acta, 1843 (11): 2563-2582.

Tyagi E, Agrawal R. 2010. Effect of melatonin on neuroinflammation and acetylcholinesterase activity inducedby LPS in rat brain. European Journal of Pharmacology, 640: 206–210.

Wang WY, Tan MS, Yu JT, Tan L. 2015. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Annals of Translational Medicine, 3(10): 136.

Wang X, Michaelis EK. 2010. Selective neuronal vulnerability to oxidative stress in the brain. Frontiers in Aging Neuroscience, 2: 1-13.

Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. 2014. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochimica Et Biophysica Acta, 1842: 1240-1247.

Wightman EL. 2017. Potential benefits of phytochemicals against Alzheimer's disease. Proceedings of the Nutrition Society, 76(2): 106-112.

Wildea MC, Vellasb B, Giraulta E, Yavuza AC, Sijbena JW. 2017. Lower brain and blood nutrient status in Alzheimer's disease: Results from meta-analyses. Alzheimer's & dementia, 3(3): 416–431.

Zhao Y, Zhao B. 2013. Oxidative stress and the pathogenesis of Alzheimer's disease. Oxidative Medicine and Cellular Longevity, 1: 1-11.

Zheng C, Zhou XW, Wang JZ. 2016. The dual roles of cytokines in Alzheimer's disease: update on interleukins, TNF-α, TGF-β and IFN-γ. Translational Neurodegeneration, 5 (7): 1-15.

Zhou L, Miranda-Saksena M, Saksena NK. 2013. Viruses and Neurodegeneration. Journal of Virology, 10 (172): 1-17.

Zuo L, Hemmelgarn BT, Chuang CC and Best TM. 2015. The role of oxidative stress-induced epigenetic alterations in amyloid-beta production in Alzheimer's disease. Oxidative Medicine and Cellular Longevity, 1:1-13.