Immune-Inflammatory Responses and Oxidative Stress in Alzheimer's Disease: Therapeutic Implications

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Abstract: Alzheimer's disease (AD) is a heterogeneous and progressive neurodegenerative disease which in Western society mainly accounts for clinical dementia. AD has been linked to inflammation and oxidative stress. Neuro-pathological hallmarks are senile plaques, resulting from the accumulation of several proteins and an inflammatory reaction around deposits of amyloid, a fibrillar protein, Aβ, product of cleavage of a much larger protein, the beta-amyloid precursor protein (APP) and neurofibrillary tangles. Inflammation clearly occurs in pathologically vulnerable regions of AD and several inflammatory factors influencing AD development, i.e. environmental factors (pro-inflammatory phenotype) and/or genetic factors (pro-inflammatory genotype) have been described. Irrespective of the source and mechanisms that lead to the generation of reactive oxygen species, mammalian cells have developed highly regulated inducible defence systems, whose cytoprotective functions are essential in terms of cell survival. When appropriately activated, each one of these systems has the possibility to restore cellular homeostasis and rebalance redox equilibrium. Increasing evidence support the notion that reduction of cellular expression and activity of antioxidant proteins and consequent augment of oxidative stress are fundamental causes for ageing processes and neurodegenerative diseases, including AD. The better understanding of different molecular and cellular inflammatory mechanisms is crucial for complete knowledge of AD pathophysiology, hence for its prevention and drug therapy. Accordingly, two lines of preventive therapeutics can be outlined, the first based on anti-inflammatory drugs, the second one on anti-oxidative properties.

Keywords: Alzheimer's disease, curcumin, IL-6, inflammation, oxidative stress.

INTRODUCTION

Alzheimer's disease (AD) is a heterogeneous and progressive neurodegenerative disease which in Western society mainly accounts for clinical dementia. AD has been linked to inflammation and oxidative stress. Neuro-pathological hallmarks are senile plaques, resulting from the accumulation of several proteins and an inflammatory reaction around deposits of amyloid, a fibrillar protein, beta-amyloid (Aβ), product of cleavage of a much larger protein, the Aβ precursor protein (APP) and neurofibrillary tangles. Amyloid deposition, due to the accumulation of Aβ, is the main pathogenetic mechanism. Inflammation clearly occurs in pathologically vulnerable regions of AD and several inflammatory factors influencing AD development, i.e. environmental factors (pro-inflammatory phenotype) and/or genetic factors (pro-inflammatory genotype) have been described [1-3]. A growing number of studies in AD have also reported alterations in systemic immune responses including changes in lymphocyte distribution and activation. Studies in animal models for AD support the notion that immune cells infiltrate the brain and may modulate the disease [4].

On the other hand, irrespective of the source and mechanisms that lead to the generation of reactive oxygen species, mammalian cells have developed highly regulated inducible defensive systems, whose cytoprotective functions are essential in terms of cell survival. When appropriately activated, each one of these systems has the possibility to restore cellular homeostasis and rebalance redox equilibrium. Activation of antioxidant pathways is particularly important for tissue with relatively weak endogenous antioxidant defences, such as the brain. Increasing evidence, in fact, support the notion that reduction of cellular expression and activity of anti-oxidant proteins and consequent augment of oxidative stress play a central role in ageing processes and neurodegenerative diseases, including AD [3,5].

The better understanding of different molecular and cellular immune-inflammatory mechanisms as well as oxidative stress is crucial for complete knowledge of AD pathophysiology, and for its prevention and drug therapy.

PATHOPHYSIOLOGY OF AD

Amongst the existing entities of dementia spectrums, AD and dementia with vascular component are the most prevalent forms of dementia. These disorders have common and unique molecular pathological characteristics that result in serious reductions in nervous-system functionality [6]. AD, the most common cause of dementia, accounts for 50 to 70 percent of dementia cases. It is a severe neurodegenerative disorder characterized by progressive memory and cognitive impairment [7,8].

Under physiological conditions, APP is processed by the non-amyloidogenic pathway, where cleavage by α-secretase releases a soluble fragment. In AD, this process is significantly altered, where increased amount of APP is cleaved by other endo-proteases such as β- and γ-secretase, generating highly amyloidogenic protein molecules of 40-42 amino acid residues. Soluble Aβ rapidly aggregates into fibrils triggering the misfolding of other Aβ species. *In vitro* studies have shown that extracellular fibrillar Aβ peptides induce apoptosis in cultured neurons [9]. The amyloid cascade hypothesis is the central hypothesis for the cause of AD, which states that the initiating event in AD is an imbalance between the production and clearance of Aβ in the brain [10]. Another neuro-pathological hallmark of AD is the appearance of neurofibrillary tangles that consist of a hyperphosphorylated form of the microtubule-stabilizing protein tau, often conjugated with ubiquitin. The abnormal hyperphosphorylation of tau makes it resistant to proteolysis and this might lead to several-fold increase in the levels of tau in AD. The hyperphosphorylated tau causes sequestration of normal tau and other microtubule-associated proteins, leading to

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inhibition and disruption of microtubules and impaired axonal transport [11]. Tau also becomes prone to aggregation leading to formation of intracellular neurofibrillary tangles, compromising neuronal and synaptic function.

Although the complete etiopathogenesis of AD still remains unclear, genetic studies over the past two decades have provided valuable insights into this complex and heterogeneous disorder. Twin and family studies have shown that certain genes contribute to the development of AD, especially with respect to the age at which the disease manifests, and more recently, the development of non-cognitive symptomatology [12]. Early onset familial AD is a very rare autosomal dominant disorder caused by highly penetrant mutations in APP and presenilin genes, both linked to Aβ metabolism. Around twelve different mutations have been identified in APP gene at the level of α-, β-, or γ-secretase cleavage sites, which can lead to alteration in the normal proteolysis of amyloid precursor protein. Similarly, more than fifty missense mutations of the presenilin-1 gene (PS1) are associated with familial AD; several mutations of presinilin-2 gene (PS2) are associated with rare cases of early onset familial AD [13]. These mutations of APP, PS1 and PS2 may share a common pathogenetic mechanism leading to accumulation of β-amyloid protein as a result of abnormal amyloid precursor protein metabolism. In contrast, sporadic AD is a very common disorder.

Many studies have reported association of the APOE-4 allele with late-onset AD, and APOE-2 has shown a protective effect. Moreover, APOE-4 may influence AD pathology by interacting with APP metabolism and Aβ protein accumulation, enhancing hyperphosphorylation of tau protein and neurofibrillary tangle formation, reducing choline acetyltransferase activity, increasing oxidative processes, modifying inflammation-related neuroimmunotrophic activity and glial activation, altering lipid metabolism, lipid transport and membrane biosynthesis in sprouting and synaptic remodelling, and inducing neuronal apoptosis [2].

Several studies have reported susceptibility loci on chromosome 1, 2, 5, 9, 10, 12, 14, 18, 19 (close to APOE), and 21 (close to the APP gene) [14]. Other polymorphisms that may also be associated with AD are linked to the angiotensin-converting enzyme, Cystatin C, tau genes, estrogen receptor [15-18]. Genes involved in the neurodevelopmental process have also been considered good candidates to confer susceptibility to AD. All these genetic factors may interact in unknown genetic networks leading to a cascade of pathogenic events characterized by abnormal protein folding, with subsequent accumulation of abnormal proteins, ubiquitin-proteosome system dysfunction, exicitotoxic reactions, oxidative stress, mitochondrial injury, synaptic failure, altered metal homeostasis, axonal and dendritic transport dysfunction and chaperone misoperation [19,20].

IMMUNOLOGY OF AD

Aβ deposition plays a key role in AD pathogenesis, indeed it causes a chronic inflammatory response which contributes to neurodegeneration. The immune response that occurs secondary to amyloid deposition in the brain, results in the activation of complement cascade and microglial cells, and the recruitment of astrocytes [21]. Complement activation contributes to the local inflammatory response by the production of inflammatory mediators that leads to the migration of activated glial cells towards amyloid plaques causing neuronal cell dysfunction and finally degeneration [22].

Aggregated amyloid fibrils and inflammatory mediators secreted by microglial and astrocytic cells equally contribute to neuronal dystrophy. The microglia activation can be due to local or systemic inflammation. In fact a strong local inflammatory stimulus such as a previous head trauma is a risk factor for AD and several epidemiological studies clearly show that blood elevations of acute phase proteins, markers of systemic inflammatory stimuli, may be risk factors for cognitive decline and dementia. Furthermore, in experimental animals, chronic systemic inflammatory response induced by lipopolysaccharide administration also induces glial activation [23].

Microglial cells represent 10% of the cells of the adult central nervous system (CNS), but following activation they undergo morphological and phenotypic changes and differentiate into macrophage-like cells. In response to amyloid beta deposition in AD, microglial cells express different cells surface receptor and they can gain phagocytic or neurotoxic properties with an increased production of reactive oxygen species (ROS) [22,24]. The basic function of astrocytes is to protect neurons. In the early phase of AD there is an astrogliosis that represent a response to the accumulation of the amyloid beta in the brain parenchyma and in the cerebral microvasculature [25]. Migration of astrocytes to amyloid beta plaques is promoted by the chemochines CCL2 and CCL3 released by activated microglial cells that surround the plaques [26]. There is evidence that indicate an involvement of the immune system, other than neuroinflammatory processes in CNS, accompanied by changes or defects in immune responses in the blood of AD subjects [27]. It is possible that injury signals or peptide derived from the AD brain stimulate peripheral immune responses. This phenomenon seems to be due to the communication between central and systemic immune responses in neurodegeneration. There are changes of efflux of CNS proteins, like Aβ, or inflammatory mediators, like cytokines and chemokines, across the blood-brain-barrier (BBB) that may induce systemic immune reaction and the recruitment of lymphocytic or myeloid cells into the CNS [4].

Concerning T cells, many studies find an increased number of these cells in the brain of subjects affected by AD when compared with other neurological disease and age-matched controls [28]. The BBB consists of endothelial cells with tight junctions, but T cells could migrate from blood to brain in AD because peripheral T cells of AD patients overexpress MIP-1α, which is the ligand of CCR5 on brain endothelial cells. This interaction promotes T cells migration to the endothelial tight junctions [29]. Studies on peripheral blood mononuclear cells of AD patients have shown that there is an increased expression of the chemokines receptor CCR2 and CCR5, the chemokine RANTES (CCL5) and the Th1 cytokine interferon (IFN)-γ while MCP-1 chemokine and the Th2 cytokine interleukin(IL)-4 are decreased. So chemokines, chemokine receptors and cytokines production are altered not only in the CNS but also in the blood cells [27].

The molecular and cellular components that mediate the communication between peripheral inflammation and the brain have been studied in experimental models, and major routes of communication are known, all of which lead to the synthesis of cytokines and inflammatory mediators in the brain parenchyma, which are typically associated with tissue injury [30].

Other changes in immune function that occur in AD include an altered lymphocyte subpopulation distribution. Richartz-Salzburger and collaborators have shown a significant decrease of CD3+ T cells and CD19+ B cells, indicating a general decline of immune activity in AD. A slight increase of CD4+ Th cells and a decrease of the CD8+ CTL without significant change of the CD4+/CD8+ ratio. On the contrary CD16+CD56+ NK cells are not altered [31]. Recent studies on circulating CD4+ and CD8+ cells demonstrate dramatic alteration in naïve and memory subsets of CD4+ lymphocytes in AD patients, with an enhanced decrease on percentage of naïve CD4+ cells, elevated memory cells and increased proportions of CD4+ but not CD8+ cells lacking the costimolatory molecule CD28. These data evidence that the immune system of AD undergoing persistent antigenic challenge and it could lead to a premature immunosenescence [32].

Recently, we reported data on immune-inflammatory parameters evaluated in PBMC obtained from AD patients. We showed no changes in lymphocytes subsets with the exclusion of B cells that are reduced in AD subjects. The study of B cell naïve/memory compartment shows a reduction of IgD-CD27- B cells in AD patients compared with age-matched healthy controls. Inflammatory cytokines IL-1β, IL-6, IFN-γ, tumor necrosis factor(TNF)-α, chemokines MIP-1β and RANTES as well as chemokines receptors CCR2 and CCR5, are up-regulated in AD patients after *in vitro* stimulation with recombinant Aβ peptide. Also CD36, a scavenger receptor, is over-expressed in monocytes of AD patients.

All together these data confirm the involvement of systemic immunity in AD and suggest to continue these kind of study to obtain biomarkers useful in the monitoring the effectiveness of therapeutics [33].

IMMUNE-INFLAMMATORY GENES

Variations in immune-inflammatory genes such as cytokine, cyclo-oxygenase, lipo-oxygenease, toll-like receptor have also been considered to be important in the risk for AD [1,2]. In particular, cytokine gene polymorphisms have been claimed to play a key role in pathophysiology of AD, as demonstrated by two recent meta-analysis performed by our group on IL-1β and TNF-α [34,35]. Therefore, in the present paper, we present data on a meta-analysis focused on IL-6.

IL-6 is a pleiotropic cytokine involved in the regulation of the acute inflammatory response. The expression of IL-6 mRNA resulted to be increased in brain areas where amyloid deposition and astroglia activation are prominent in AD patients and increased IL-6 levels in the brain have been implicated in early stages of plaque formation [36].

Polymorphisms in the genes regulating the expression of IL-6 have been hypothesized to enhance the risk of developing AD. In particular, the most studied polymorphism of IL-6, the G/C polymorphism at the position -174 in the 5' flanking region of IL-6 gene, was shown the be associated with a decreased expression and also with a reduced plasma level of IL-6 [37]. However, genetic association studies, investigating the association with this polymorphism and the risk of AD gave very contrasting results. The main causes explaining the lack of replicability of the results between different studies seems to be the heterogeneity of the enrolled study populations, and the small sample size of most studies, leading to a loss of statistical power. To overcome some of the limitation mentioned above and to increase the relevance of statistical analysis a meta-analysis of all available case-control studies on the association between IL-6 -174 single nucleotide polymorphism (SNP) and the risk of AD have been performed. The studies were selected and analysed according to criteria and methods discussed in the previous meta-analysis [34,35]. In particular, the putative risk genotype in homozygosity (GG) was compared to the other two aggregated genotypes data (CG+CC), condensing the results into one statistic. This allowed us to highlight the effect of the putative risk genotype, as well as to maintain the statistical power compared to analyze separately all possible transmission models which would have lead to a loss of observation and, thus, of statistical power.

Sixteen case-control studies on the association between IL-6 -174 SNP and AD were identified [38-53]. The studies selected included a total of 3811 patients and 10716 healthy controls (6303 of which in the only study of van Oijen *et al.* [51]). The percentage of AD females patients ranged from 58% to 73%, but it was missing in the study from van Oien *et al.* [51,52]. The mean age of AD patients ranged from 63,9±10.4 to 80.6±7.8. The sample size of the studies varied greatly ranging from 51 to 753, as well as the number of controls, ranging from 36 to 6303. Neuropathological examination was assessed only in one study [39], the imaging examination of the brain to support the clinical diagnosis only in 3 out of 16 [33,44,50]. Only in three studies [39,44,53] controls were selected by mini-mental state examination (MMSE). All studies were performed on Caucasian population, except 3, which were conducted on Asian population [41]. The effect of the IL-6 -174 GG genotype on the risk of AD is shown in the Fig. (**1**).

The effect of the TT genotype was to increase the AD risk in 9 [38-40,42,47-50,52] out of 16 studies, but a statistical significant difference was observed in only three [40,48,50]. The pooled summary OR was 1.04 (GG vs CG+CC: OR=1.00; 95% C.I.: 0.84-1.22) and did not achieve statistical significance suggesting that subjects with the high producer IL-6 genotype (GG) do not have a higher risk of developing AD. There was evidence of heterogeneity between the results of individual studies ($\chi 2$=59.20, d.f.=15, p=0.00001, I2=73.4%). To reduce heterogeneity and to evaluate whether there was a different genotype effect in predefined subgroups of studies we performed subgroup analysis in relation to patient (age, gender) and study characteristics (type of AD diagnosis, MMSE in controls, sample size and statistical power of individual studies), but we did not find any difference in the overall effect (data not shown).

The current meta-analysis summarizes the evidence regarding the association between IL-6 -174 SNP and AD, representing a pooled total of 3811 cases and 10716 controls. The analysis of pooled data ruled out the role of IL-6 -174 SNP in modifying AD risk that was hypothesized by some investigators. However, a remarkable heterogeneity was observed between the results of individual studies, suggesting differences among the enrolled populations, and a possible population specific genetic effect of the -174 IL-6 SNP. Alternatively, also genetic or environmental factors may play a contributing role and may explain differences between the result of individual studies. We tried to explain heterogeneity by subgroup analysis, taking into account study and patients characteristics, but we fail in identifying variables explaining the observed heterogeneity. However, we must consider that we analyzed summary results which describe only variation between-study, not between patients because they reflect group averages rather than individual patient data. Only an individual patient data meta-analysis could address this issue, but no study reported such detailed information, which call for development of publicly available databases aimed at the collection and analysis of biologic information on a single-patient basis.

So, these data do not seemingly support a role for this IL-6 SNP in pathophysiology of AD. However, it is to take into account that inflammatory mediators do not act alone but they act in a complex network reciprocally interacting [54]. Accordingly, we found combinations of alleles in eight inflammatory genes (including this SNP) and APOE that distinguish AD risk groups [55].

OXIDATIVE STRESS

Oxidative stress has been implicated in a variety of pathophysiological conditions, including neurodegenerative disorders, and oxidative stress–mediated neuroinflammation has been demonstrated to actively concur to AD ethiopathology (extensively reviewed [56]). In particular, cortical and hippocampal oxidative stress is a very early event in the pathogenesis of sporadic AD and correlates with the development of specific cognitive deficits in this condition. Inflammation is strictly related to ROS production, which act as signals to activate inflammatory genes. Within the cell, ROS are physiologically present at minimal concentration as by-products of aerobic metabolism as well as second messengers in many signal transduction pathways and, in normal conditions, there is a steady-state balance between pro-oxidants and antioxidants. However, when the rate of free radical generation exceeds the capacity of antioxidant defences, oxidative stress ensues with consequential severe damage to DNA, protein and lipid. One of the major sources of ROS production and oxidative stress in AD brain is believed to be the impaired mitochondrial electron transport

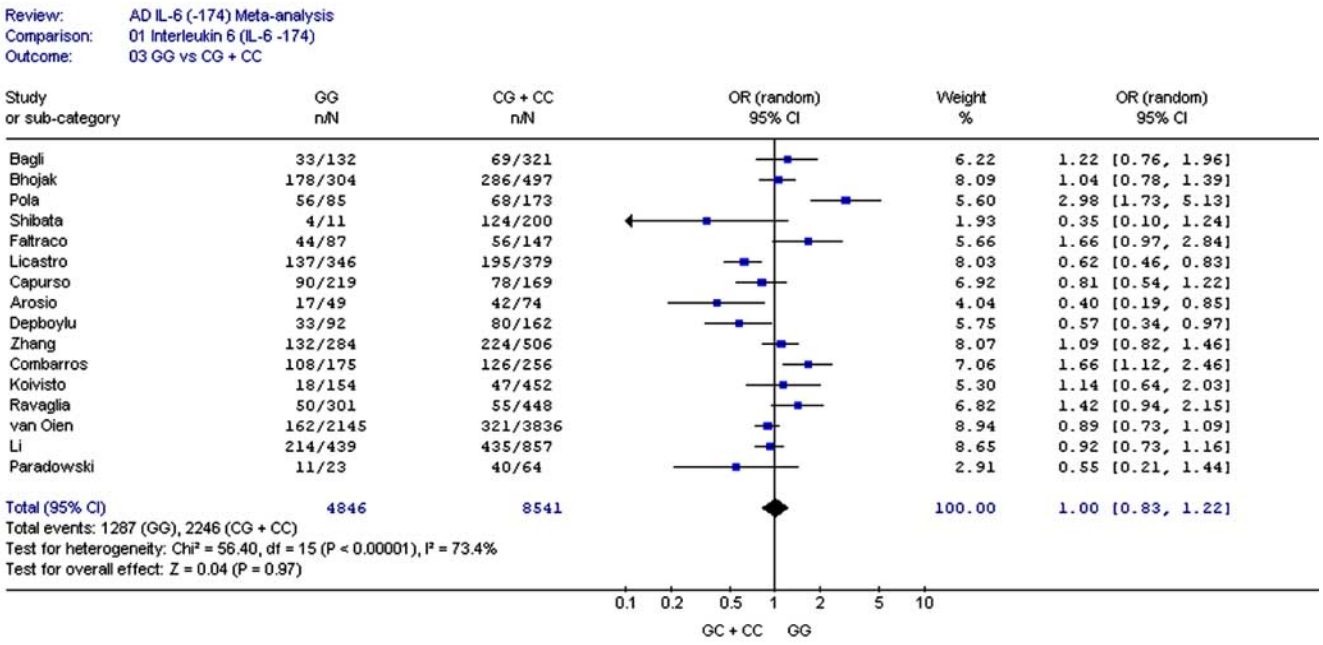

Fig. (1). Meta-analysis of 16 case-control studies of the IL-6 -174 polymorphism and the risk for AD using the random-effects model. Odds Ratio (OD) for each study and the pooled estimate of the OD for the risk of AD with its Confidence Interval (CI) are plotted on the graph. Studies are arranged chronologically based on the year of publication.

chain. Aβ soluble oligomers, which have been shown to be cytotoxic via the formation of ROS, represent another source of oxidative stress, as well as the activation of microglial oxidase [57] and the inflammatory response [2]. These conditions well explain why the biomarkers of lipid peroxidation, such as free 4-hydroxynonenal (HNE), are abundantly present in several areas of the AD brain [58]. Furthermore the presence of carbonylated-, HNE- and nitrated-proteins demonstrates the occurrence of protein modification by oxidation [59]. Signs of oxidative damage in AD patients have also been found in the cerebrospinal fluid, in urine, and in serum, and, although the results of some studies are contradictory, it seems that the levels of oxidative damage parallels the progression of the disease [3].

Oxidative stress is counteracted in biological systems by a large set of endogenous antioxidants, including enzymes such as superoxide dismutases, catalase, and glutathione peroxidase, as well as low molecular weight compounds, such as glutathione, generally found at levels sufficient enough to defend cells from oxidative insult. The brain is particularly low in the antioxidant enzymes, particularly those scavenging H2O2, namely glutathione peroxidase or catalase. On the other hand mammalian cells have developed highly regulated inducible defensive systems that have the possibility to restore cellular homeostasis and rebalance redox equilibrium [3]. One of the more important system devoted to the antioxidant defense in brain is represented by the so called "heat shock response" sustained by the "heat shock proteins" (Hsps). Among the Hsps family, an emerging role has been attributed to heme oxygenase-1 (HO-1 or Hsp-32) which is responsible of the transformation of the heme moieties into carbon monoxide and biliverdin. All the byproducts of HO-1 activity play a significant role in physiological cell functions [60]. In the CNS, the HO system has been reported to be very active [61,62] and its modulation seems to play a crucial role in the pathogenesis of neuro-degenerative disorders. Deregulation of the HO system has been associated with the pathogenesis of AD, multiple sclerosis and brain ageing [63,64]. Many studies clearly demonstrate that activation of HO-1 in neurons is strongly protective against oxidative damage and cell death [65]. In a very elegant study, Panahian *et al*. using transgenic mice over-expressing HO-1 in neurons, demonstrated the neuroprotective effect of this enzyme in an experimental model of ischemic brain damage [66]. The neuroprotective effects of over-expressed HO-1 can be attributed to: (*i*) increase in cGMP and bcl-2 levels in neurons; (*ii*) inactivation of p53, a protein involved in promoting cell death; (*iii*) increase in antioxidant sources and (*iv*) increase in the iron sequestering protein, ferritin [66]. Particularly interesting is the role played by HO-1 in AD. Significant increases in the levels of HO-1 have been observed in AD brains in association with neurofibrillary tangles and also HO-1 mRNA was found increased in AD neocortex and cerebral vessels [63,67]. HO-1 increase was not only in association with neurofibrillary tangles, but also co-localized with senile plaques and glial fibrillary acidic protein-positive astrocytes in AD brains [68]. In addition Takeda *et al*. explored the relationship between HO-1 and tau protein, this latter being the major component of neurofibrillary tangles, the intraneuronal AD lesion. In transfected neuroblastoma cells overexpressing HO-1, the activity of this enzyme was increased, and conversely, the level of tau protein was significantly decreased when compared with antisense HO-1 or vector transfected cells [63]. The suppression of tau protein expression was almost completely counteracted by zinc-deuteroporphyrin, a specific inhibitor of HO activity [63]. Thus HO-1 is thought to down regulate the production of tau and recently HO-1 polymorphisms have been considered as a possible responsible for susceptibility to AD [69]. Thus, modulation of HO-1 should represent a potential pharmaceutical strategy for the treatment of neurodegenerative disorders [70].

The role of smoking in AD has been debated [71]. In the last years, several case-control studies suggested that smoking was associated with decreased risk of dementia [72,73]. On the other hand, it has been hypothesized that findings obtained in case-control studies were a consequence of survival bias rather than a true protective effect of smoking [74]. However, the mechanisms by which smoking would prevent the risk of AD should be related to the positive nicotinic effects of smoking on cognitive functioning

[72,75]. On the other hand, the increased frequency of cardio-vascular and cerebrovascular illnesses among smokers [71] is likely to increase the risk of AD in later life [76,77]. However, the results of a recent meta-analysis of prospective studies clearly showed that, when compared with people who have never smoked, current smokers have an increased risk of dementia and cognitive decline ranging from 40 percent to 80 percent, depending on the outcome examined [73]. Oxidative stress is a possible mechanism consistent with dangerous effects of smoking since cigarette smoke contains free radicals that activate inflammatory cells with inflammatory mediator production and further oxidative damage by triggering a vicious cycle [2,71].

CONCLUSIONS

A major goal of ongoing research in AD is to improve early detection by developing tools to move diagnosis backward in disease temporal course, i.e. before the clinical manifestation of the disease, where a treatment might play a decisive role in preventing or significantly retarding the manifestation of the disease [1,2]. So, the knowledge of the pathophysiology of the diseases is crucial for its therapeutic prevention. Accordingly to the data discussed in the present review, two lines of preventive therapeutics can be discussed, the first based on anti-inflammatory drugs, the second one on anti-oxidative properties.

Concerning anti-inflammatory drugs, patients who received non-steroidal anti-inflammatory drugs (NSAIDs) for a period of 2 years had less AD incidence with relative risk of 0.2 [78]. The incidence of AD appears to be reduced in some post hoc studies, by about 13%for aspirin and 28% for other NSAIDs [79-81]. However, a recent report based on a longitudinal study of men and women aged 70 years and older with a family history of AD (ADAPT study) showed that use of naproxen or celecoxib did not improve cognitive function [82]. However, several critical issues have been raised concerning the study results, i.e. it has been claimed that the ADAPT study does not indicate that NSAIDs, if taken during adulthood and for an extended period, cannot prevent or delay the onset of dementia [83]. In addition, examining the effects on AD risk of NSAID use for >5 years in a large health care database including 49,349 cases and 196,850 controls, Vlad *et al.* clearly demonstrated that long-term NSAID use was protective against AD [84].

Regarding molecules with anti-oxidant properties, a number of experimental and epidemiological studies have recently supported the beneficial effects of some commonly used natural products in preventing various pathologic conditions ranging from cardio-vascular diseases to cancer. Spices and herbs often contain phenolic substances with potent antioxidative and chemopreventive properties [85]. However, since curcumin studies are a growing area in AD research as well as in other pathological conditions [86,87], we will insight into its possible effect on AD.

Curcumin (1,7-bis[4-Hydroxy-3-methoxyphenyl]-1,6-hepta-diene-3,5-dione), a colouring agent and food additive commonly used in Indian culinary preparations extracted from the rhizome of *Curcuma Longa*, polyphenolic substance has the potential to inhibit lipid peroxidation and to effectively intercept and neutralize ROS [70]. Curcumin has been shown to significantly increase HO-1 expression and activity in vascular endothelial cells [88], in rat astrocytes [89] and in cultured hippocampal neurons [90]. This latter effect on HO-1 can explain, at least in part, the strong anti-oxidant and anti-inflammatory properties of curcumin, that depends more by its action as cellular signals than by its radical scavenger effect [70]. Curcumin has been demonstrated to stimulate the mitogen-activated protein kinase pathway and to activate *heterodimers of NF-E2-related factors 2*, leading to induction of the antioxidant responsive element activated reporter genes [91]. By this pathways curcumin strongly induce the expression of phase II detoxification enzymes and of HO-1, resulting in cell protection and enhancing cell survival [90]. The involvement of curcumin in restoring cellular homeostasis and rebalancing redox equilibrium, suggests that it might be a useful adjunct also in AD treatment. Epidemiological studies suggested that curcumin, as one of the most prevalent nutritional and medicinal compounds used by the Indian population, is responsible for the significantly reduced (4.4-fold) prevalence of AD in India compared to United States [92]. Furthermore, Elderly Singaporeans who ate curry with turmeric had higher MMSE scores than those who did not [93]. However, the relatively short duration of follow-up, cultural factors and other potential confounders suggest caution in interpreting these findings. Consistent with these data, Lim and colleagues have provided convincing evidence that dietary curcumin, given to an Alzheimer transgenic mouse model (Tg2576) for 6 months, resulted in a suppression of indices of inflammation and oxidative damage in the brain of these mice and to reverse Aβ-induced cognitive deficits [94,95]. The same group demonstrated in a successive research that curcumin was a better Aβ40 aggregation inhibitor than ibuprofen and naproxen, and prevented Aβ42 oligomer formation and toxicity at very low concentration (between 0.1 and 1.0 microM) [96]. They also shown that curcumin readily entered the brain to label plaques *in vivo* inhibiting the formation of Aβ oligomers and their toxicity [96]. Among the several mechanisms by which curcumin is able to clear amyloid is the induction of HSPs, that function as molecular chaperones to block protein aggregate formation [97]. Recently curcumin has been evaluate in a pilot clinical trial in AD patients, with preliminary encouraging results [98]. Curcumin is highly lipophilic and might cross the BBB and reach the brain, and although its bioavailability is very low, since the drug is rapidly metabolized by conjugation, curcumin may reach brain concen-trations sufficient to activate signal transduction events and to decrease Aβ aggregation [99]. Other plant-derived phenolic agents with analogous chemical structures to curcumin have been demonstrated to strongly activate HO-1 expression and to defend cells against oxidative stress. In particular, ethyl ferulate, resveratrol (a phitoalexin derived from grape) and caffeic acid phenethyl ester, are able to protect neurons via HO-1 induction [100]. These and other studies identify a novel class of natural substances that could be used for therapeutic purposes as potent inducers of HO-1 in the protection of tissues against inflammatory and neurodegenerative conditions. It needs to be emphasized that curcumin, and other plant constituents eventually become part of the human diet and can be consumed daily as herbal supplements. Further *in vitro* and *in vivo* studies using curcumin-like molecules will give important information on the feasibility of developing new pharmacological strategies for maximizing heme oxygenase activity in targeted tissues as an alternative to or in combination with HO-1 gene therapy.

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ABBREVIATIONS

Aβ	=	beta-amyloid
AD	=	Alzheimer's Disease
APP	=	Aβ Precursor Protein
HNE	=	4-Hydroxynonenal
HO-1	=	Heme Oxygenase-1
Hsps	=	Heat Shock Proteins
IFN	=	Interferon
IL	=	Interleukin
MMSE	=	Mini-Mental State Examination

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

PS1 = Presenilin-1 gene

PS2 = Presenilin-2 gene

ROS = Reactive Oxygen Species

TNF = Tumor Necrosis Factor

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