BRAIN RESEARCH REVIEWS 58 (2008) 96–105

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BRAIN RESEARCH REVIEWS

Review

Inflammation, genes and zinc in Alzheimer's disease

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ARTICLE INFO

Article history:
Accepted 1 December 2007
Available online 8 December 2007

Keywords:
Alzheimer's disease
Immunogenetic
Inflammation
Zinc

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 metal biological pathway. 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 β-amyloid precursor protein (APP) and neurofibrillary tangles. Amyloid deposition, due to the accumulation of Aβ peptide, 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. At the biochemical level metals such as zinc are known to accelerate the aggregation of the amyloid peptide and play a role in the control of inflammatory responses. In particular, zinc availability may regulate mRNA cytokine expression, so influencing inflammatory network phenotypic expression.

Contents

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doi:10.1016/j.brainresrev.2007.12.001

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the Western world. It was identified for the first time by Alois Alzheimer, a Bavarian psychiatrist, who defined the pathological syndrome in a woman named Auguste D., showing several cardinal features of the disorder that are currently observed in most patients (Maurer et al., 2007). Symptoms like progressive memory impairment, disordered cognitive function, and altered behaviour including paranoia, delusions, loss of social appropriateness, and a progressive decline in language function are common in many patients affected by AD. The first phases of this gradual, relentless process, is characterized by well conserved patient's awareness, and intact mechanical and sensory functions (McKhann et al., 1984). However, as individuals keep on losing ground cognitively, occupations, such as walking and movement synchronization often resemble extrapyramidal motor disorders similar to Parkinsonism (Allan et al., 2005). In the absence of proven biological markers, the diagnosis of AD remains based on the clinical judgment that the patient's cognitive function has declined from the past level of ability. An internationally agreed upon standard for clinical diagnosis of AD includes a detailed history, functional measurement of decline such as instrumental activity of daily living scales, neuropsychological evaluation, neurological and psychiatric examination, blood tests and brain imaging. The accuracy of diagnosis of probable AD is now more than 90% based on autopsy confirmation. The risk factors for AD include age, gender, genetics, Down's syndrome, diet and head trauma (McKhann et al., 1984; Aronson et al., 1991).

The most important risk factor for AD is age. AD prevalence is approximately 1% between 65 and 69 years and is higher than 50% in individuals above 95 years. Although the mean age of AD onset is around 80 years, early-onset disease, defined arbitrarily as the illness occurring before the age of 60 years, can happen, though it is rare. Thus, early-onset cases make up about 6–7% of all AD evaluation (Aronson et al., 1991; Campion et al., 1999).

AD is a heterogeneous and progressive neurodegenerative disease that in Western societies accounts for the majority of clinical senile dementia. Neuro-pathological hallmarks are senile plaques and neurofibrillary tangles (Nussbaum and Ellis, 2003; Findeis, 2007). Extracellular senile plaques result from the accumulation of several proteins and an inflammatory reaction around deposits of amyloid. It is a fibrillar protein (Aβ), produced by the cleavage of a much larger protein, the β-amyloid precursor protein (APP), by a series of proteases (Akiyama et al., 2000; Findeis, 2007). The senile plaques are believed to evolve over a long period of time and the fibrillary nature is due to 42 amino acid long Aβ peptide accumulation. Besides, Aβ plaques contain dystrophic neurites, activated microglia and reactive astrocytes (Rogers et al., 1988; Dickson et al., 1988; Akiyama et al., 2000). Aggregated amyloid fibrils and inflammatory mediators secreted by microglial and astrocytic cells equally contribute to neuronal dystrophy (Nussbaum and Ellis, 2003; Findeis, 2007). Neurofibrillary tangles are intracellular deposition of hyperphosphorylated degenerate filaments, which result from aggregations of the microtubular protein tau (Selkoe, 2001). Neurofibrillary tangles occur in several neurological disorders in the absence of Aβ deposition. This suggests that they can arise secondarily during the course of a variety of etiologically distinct neuronal insults (Selkoe, 2001). On the other hand, reducing endogenous tau ameliorates Aβ-induced deficits in an AD mouse model (Roberson et al., 2007). However, mutations in the tau gene have not been identified in AD patients (Kwon et al., 2000), although they are seen in another, rarer neurodegenerative disorder, frontotemporal degeneration with Parkinsonism (Hutton et al., 1998).

As all these cellular changes progress, neurons are lost in a specific brain area like hippocampus, entorhinal cortex, and association areas of the neocortex (Nussbaum and Ellis, 2003).

2. Pathophysiology of AD

AD is a complex, multifactoral disease. Autosomal dominant mutations on APP, Presenilin-1 (PS1) and Presenilin-2 (PS2) genes may be accountable for early-onset familial AD by increasing Aβ42 peptide production (Bird, 2005; Nussbaum and Ellis, 2003). APP is the Aβ peptide precursor and is a *trans*-membrane glycoprotein widely expressed (it is also present on platelets), produced by the endoplasmatic reticulum and mainly involved in the neuronal and dendritic growth, and synapses formation (Priller et al., 2006). The catabolitic feature of APP is influenced by different enzymes as α-β-γ secretases (PS1 and PS2 are co-factors in the processing of APP by secretases); with respect to the different enzymes different amounts of Aβ can be produced. APP is processed by two competing pathways: the amyloidogenic and the not amyloidogenic (Selkoe, 2001; Findeis, 2007). The amyloidogenic pathway is due to the consecutive action of two proteases, β- and γ-secretases, catalysing the release of the N- and C-terminal of the protein, respectively producing Aβ40 and Aβ42 isoforms. In the non amyloidogenic pathway, α-secretase protects the protein from amyloidogenic changes by cleaving within the Aβ sequence (Selkoe, 2001; Bird, 2005; Findeis, 2007). The peptide Aβ40 which constitutes most of the 90% secreted Aβ protein, is more soluble and less amyloidogenic compared to the Aβ42 isoform. The great part of amyloid tissue is constituted by Aβ42 isoform which is highly amyloidogenic (Selkoe, 2001; Findeis, 2007). This peptide is highly neurotoxic especially, due to the self aggregation and its capacity to form insoluble plaques either in vitro or in vivo (Nussbaum and Ellis, 2003; Findeis, 2007; Newman et al., 2007).

Most AD is late-onset (>65 years of age) and does not show a clear Mendelian pattern of segregation. In spite of this, genetic factors play an important role in determining late-onset AD risk (Bird, 2005). Besides inflammatory genes (see below), the apolipoprotein E (ApoE) gene ε4 allele is the only known genetic variant that has been clearly associated with increased late-onset AD risk (see below) (Nussbaum and Ellis, 2003; Bird, 2005). Moreover, a great amount of experimental evidence indicates that several neuronal-type nicotinic acetylcholine receptors (nAChRs) are related to AD pathophysiology (Auld et al., 2003). Biochemical analyses of the brains of AD patients have revealed deficits in the neuronal nAChRs and a consistent reduction in activity of acetylcholine, acetylcholinesterase and choline acetyltransferase (Wevers et al., 1999; Auld et al., 2003).

Such observations formed the basis of the 'cholinergic hypothesis' explaining cognitive decline in dementia (Guan et al.,

2004). Neuronal nAChRs are ligand-gated ion channels composed of different subunits assembled in pentameric structure; they are divided into two principal subtypes based on their subunit composition. Heteromeric nAChRs consist of combinations of α (α2–α6) and β (β2–β4) subunits, whereas homomeric nAChRs consist of α7, α8, or α9 subunits. Neuronal nAChRs are also involved in a range of cerebral functions including attention, learning, and memory (Tohgi et al., 1998). A loss of nAChRs subunits is associated with diseases such as AD, dementia with Lewy bodies, Parkinson's disease, and schizophrenia. The majority of the nAChRs are most commonly found in complexes consisting of α4 and β2 subunits especially located in the central nervous system. It has been proposed that the high-affinity α4β2 nAChR may be particularly vulnerable in AD (Martin-Ruiz et al., 1999; Kihara et al., 1997, 1998; Zoli et al., 1999). Reduced α4 nAChR protein levels have been confirmed in AD brains both immunohistochemically and by western blot analysis (Wevers et al., 1999). Further evidence of the involvement of the α4β2 nAChR in AD has come from studies wherein α4β2 antagonists and selective agonists were found to block the protective effects of nicotine against Aβ induced neuronal death in cultured cells; such observations are consistent with a loss of high-affinity nAChRs in AD, which may potentiate the neurotoxicity of Aβ (Kihara et al., 1997, 1998; Tohgi et al., 1998; Wevers et al., 1999; Martin-Ruiz et al., 1999; Zoli et al., 1999; Guan et al., 2004). The consistent disruption of the cholinergic neurotransmitter system observed in the demented individuals prompted to begin the screening of nAChR α4 (CHRNA4) and β2 (CHRNB2) subunit genes as candidate risk factors for AD (Vasto et al., 2006a, 2007c). In addition, there is strong evidence that acetylcholine influences the inflammatory response (Borovikova et al., 2000), that is present in AD brain.

The basic idea is that the vagus nerve stimulation inhibits Tumor Necrosis Factor (TNF) release from macrophages, with the subsequent reduction in the inflammatory response. This physiological mechanism is termed "cholinergic anti-inflammatory pathway" because it is mediated by the neurotransmitter acetylcholine (Borovikova et al., 2000). In any case, several studies coupled nAChR α4 subunit mutations with AD, as well as other neurologic diseases characterized by behavioural and cognitive impairment (Vasto et al., 2006a). Recently we have performed a population-based population association study, testing the hypothesis that variants of the nAChR gene confer genetic susceptibility to AD. We analyzed two cohorts constituted by controls and AD patients in which significant increase of 594T polymorphism in patients affected by AD versus controls was found (Vasto et al., 2006a).

3. Inflammation

Inflammation is a teleonomic response to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult. If tissue health is not restored in response to stable low grade irritation, inflammation becomes a chronic condition that continuously erodes the surrounding tissues. In fact, in chronic inflammation immune responses, tissue injury and healing proceed simultaneously. The lateral damage caused by this type of inflammation usually accumulates slowly, sometimes asymptomatically for years and can lead to severe tissue deterioration (Mitchell and Cotran, 2003). Brain inflammation is a pathological hallmark of AD. However, the characteristic inflammatory features such as rubor (redness), tumor (swelling), calor (heat), and dolor (pain) are not present in the brain and therefore we refer to chronic inflammation, instead of acute inflammation (Akiyama et al., 2000). A characteristic feature of chronic inflamed tissues is the presence of an increased number of monocytes, as well as monocyte derived tissue macrophages, i.e. microglia cells in the central nervous system (Akiyama et al., 2000; Mitchell and Cotran, 2003) .

Inflammation clearly occurs in pathologically vulnerable regions of the AD brain, with increased expression of acute phase proteins and pro-inflammatory cytokines which are hardly evident in normal brain (Griffin and Mrak, 2002; Cacquevel et al., 2004; Mrak and Griffin, 2005; Finch and Morgan, 2007). Microglia, astrocyte and neurons are responsible for the inflammatory reaction. Activated cells strongly produce inflammatory mediators as pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, and TNF-α as well as the chemokines IL-8, macrophage inflammatory protein-1α, and monocyte chemo-attractant protein-1, prostaglandins, leukotrienes, thromboxanes, coagulation factors, reactive oxygen species and other radicals, nitric oxide, complement factors, proteases, and protease inhibitors and pentraxins, as C-reactive protein and amyloid P (Mrak et al., 1995; Griffin et al., 1998; Akiyama et al., 2000; Town et al., 2005; Tuppo and Arias, 2005). Since Aβ represents a chronic stimulus, the innate immune system is clearly making an initial attempt to clear these potentially toxic products. The hypothesis is that the intractable nature of the plaques and tangles stimulates a chronic inflammatory reaction to clear this debris (Town et al., 2005).

Chronically activated glia can kill adjacent neurons by the release of highly toxic products such as reactive oxygen intermediates, nitric oxide, proteolytic enzymes, complement factors or excitatory amino acids (Halliday et al., 2000). In turn, inflammatory mediators and a number of stress conditions enhance APP production and amyloidogenic processing of APP to generate Aβ42 peptide production and inhibiting the soluble fraction of APP with neuronal protective effect, the so called "kindergarten effect" (Del Bo et al., 1995; Ringheim et al., 1998; Fassbender et al., 2000, Misonou et al., 2000; Friedlander, 2003; Atwood et al., 2003). On the other hand, Aβ induces expression of pro-inflammatory cytokines in glia cells in a vicious cycle (Griffin et al., 1998; Lindberg et al., 2005).

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 (Wilson, 2003) 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 (Schmidt et al., 2002). Besides, in experimental animals, chronic systemic inflammatory response induced by lipopolysaccharide administration also induces glial activation (Sheng et al., 2003). After activation, the microglia cells modify their morphology and become tissue macrophages producing inflammatory mediators.

The importance of inflammation in AD is further suggested by data showing that anti inflammatory non steroid drugs

(NSAIDs) diminish the risk to develop AD. Patients who received NSAIDS for a period of 2 years had less AD incidence with relative risk of 0.2 (Veld in t et al., 2001). The incidence of AD appears to be reduced in some post hoc studies, by about 13% for aspirin and 28% NSAIDs (McGeer et al., 1996; Breitner, 2003; Etminan et al., 2003). On the other hand, recent randomized, placebo-controlled 1-year clinical trials failed to detect any effect on cognition impairment by naproxen or rofecoxib administration in mild to moderate AD patients (Aisen et al., 2003; Reines et al., 2004). This failure could be due to a number of factors, including the pharmacological characteristics of the drugs, their brain penetration properties, and the dosing schedule. However, patients already had established AD and that could be the most important factor responsible for the failure.

Studies on possible therapeutic effect of statins on AD also suggest a role of inflammation in the disease. At the beginning, statins were clinically used to lower blood cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) (Sviridov et al., 2007; Zipp et al., 2007), and statin users appeared to have a lower risk of AD development in post hoc studies (Rockwood et al., 2002; Blain and Poirier, 2004; Finch, 2005). However, in animal models and human beings, statins have anti-inflammatory activities that are not directly dependent on lowering blood cholesterol, which include lowering blood CRP, inflammatory cell infiltration and cell death (Albert et al., 2001; Stuve et al., 2003; Wierzbicki et al., 2003; Finch, 2005). In particular, it has been seen that statins reduce Aβ-mediated microglia neurotoxicity in vitro independently from cholesterol lowering (Cordle and Landreth; 2005), providing a rationale for their use in AD (Zipp et al., 2007). However, contrastant therapeutic results have been obtained, so additional studies are necessary to definitively assess the effects of statins on AD (Finch, 2005; Kuller, 2007). (see also below, paragraph on ApoE and cholesterol).

Furthermore, some functional polymorphisms, mostly single nucleotide polymorphisms (SNPs), in the promoter region or other untranslated regions of genes encoding inflammatory mediators or their enzymes, have been found more frequently in AD cases. Actually, the genes involved in the inflammation process are numerous and the role of an individual genetic background might show a predisposition to inflammation and its healthy or chronic resolution. Primary responses are mediated by pathogen recognition receptors such as Toll-like receptor (TLR), pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, anti-inflammatory cytokines such as IL-10 and eicosanoids (Imahara and O'Keefe 2004; Vasto et al., 2007c). As such, we reviewed several data clearly showing that inflammatory genetic variation may contribute to AD susceptibility, strengthening the role of inflammation in AD. In fact, pro-inflammatory genotypes were significantly overrepresented in AD patients, whereas anti-inflammatory genotypes were significantly under-represented (Candore et al., 2006; Candore et al., 2007; Vasto et al., 2007c; Table 1).

Table 1 – List of studies concerning AD and inflammatory gene polymorphisms

Gene	Polymorphisms	Type of study	AD association	Reference
TLR4	Asp299Gly	Case-control	Pos	Minoretti et al., 2006
COX-2	Rs20417	Case-control	Pos	Abdullah et al., 2006
COX-2	Rs689466	Case-control	Neg	Reiman et al., 2007
COX-2	Rs689466	Case-control	Pos	Ma et al., 2007
5-LOX	Tandem repeats GGGcGGG	Case-control	Pos	Qu et al., 2001
5-LOX	Various SNPs	Case-control	Neg	Morgan et al., 2007
IL-1α	−889	Meta-analysis	Pos	Rainero et al., 2004
IL-1β	−511	Meta-analysis	Pos	Di Bona et al. Ms to be submitted
IL–1β	+3953	Meta-analysis	Pos	Di Bona et al. Ms to be submitted
IL-6	−174	Meta-analysis	Neg	Di Bona et al. Ms to be submitted
IL-10	−1082	Meta-analysis	Pos	Di Bona et al. Ms to be submitted

In the positive studies the pro-inflammatory alleles of LPS co-receptor TLR4, the enzymes involved in prostaglandins (COX-2) and leukotrienes (5-LOX) synthesis, the pro-inflammatory cytokines IL-1α, IL-1β and the anti-inflammatory cytokine IL-10 were significantly increased in AD patients.

4. ApoE and cholesterol

As previously stated, a well-known genetic risk factor in late-onset AD is represented by ApoE which is the gene encoding apolipoprotein E, a constituent of the low density lipoprotein (LDL) particle. In the human population three variants of the genes have been found which result from a change in a single amino acid. There are three alleles of ApoE ε2, ε3 and ε4 which influence the concentration of the lipoprotein in the blood stream, ε4 being associated to higher levels (Strittmatter and Roses, 1996). ApoE is capable of solubilising hydrophobic compounds by incorporating them into core lipid-binding domain and delivering them to target cells via ApoE receptors. The ApoE binds several receptors among these the LDL receptor and the protein LDL receptor co-related. The different alleles influence the strength of the binding between receptor and lipoprotein. The ApoE proteins are associated with 10% of the difference in cholesterol concentration in the blood stream while the allele ε4 is tightly associated with the highest concentration (Mahley and Rall, 2000; Smith, 2002). Actually, ε4 allele accelerates amyloid deposition and promotes Aβ aggregation in cholesterol rich lipid rafts enhancing aggregation into senile plaques (Cordy et al., 2006). It has been demonstrated that subjects carrying ApoE ε4 nearly doubles the chance to develop AD whereas individuals not carrying ApoE ε4 allele decreases the risk of AD by 40%. Yet fewer than half of all AD patients possess the ε4 allele but not all ε4 carriers develop the disease. It has also been suggested that the main effect of the allele is to anticipate the onset of the disease (Seshadri et al., 1995; Meyer et al., 1998; Nussbaum and Ellis, 2003; Bird, 2005).

Besides its role in Aβ aggregation, it is well-argued that ApoE ε4 allele promotes inflammatory responses (Finch and Morgan, 2007). Human monocytes from ε4 carriers produced more NO than from ε3 carriers, while in transgenic ApoE knock-in mice, ε4 had greater microglial brain inflammatory responses (Colton et al., 2004). These data are supported by recent cell culture studies that indicate, that the ApoE ε4 genotype is associated with increased inflammation (Jofre-Monseny et al., 2007a). Thus mouse macrophages transfected with ApoE ε4 genotype secrete significantly more pro-inflammatory cytokines, compared to those transfected with ApoE ε3 genotype (Tsoi et al., 2007; Jofre-Monseny et al., 2007a). Furthermore, the secretion of the anti-inflammatory cytokine IL-10 is reduced in humans carrying ApoE ε4 genotype, compared to those with the ApoE ε3 genotype (Bagnoli et al., 2007). The increased inflammation reaction with ApoE ε4 is possibly due to an increased transactivation of the inducible transcription factor NF-κB (Jofre-Monseny et al., 2007a), that is controlled by the signal activation cascades and that controls a number of genes involved in immuno-inflammatory responses, cell cycle progression, inhibition of apoptosis, and cell adhesion, thus promoting chronic inflammatory responses (Camandola and Mattson, 2007). Moreover, it has been seen that the mouse macrophages carrying ApoE ε4 exhibit higher plasma-F2-isoprostan levels, as a biomarker of an increased lipid peroxidation and an in vitro increased production of superoxide radicals were documented (Yao et al., 2004; Jofre-Monseny et al., 2007b). It was furthermore documented that the increased inflammation reaction of ApoE ε4 mouse macrophages, possibly compensatory, is associated with an increased expression of the heme oxygenase-1 (Jofre-Monseny et al., 2007a).

The evolutionary history of ApoE allele shows that ApoE ε4 is the ancestral allele and that ApoE ε3 spread in ancient human populations about 235,000 years ago. It has been suggested that ApoE ε3 is evolutionary advantageous versus long-living humans since it enhances cholesterol distribution in humans getting used to animal protein diet (Finch and Stanford, 2002). So, ApoE ε4 allele is maintained by balancing selection due its pro-inflammatory properties (Finch and Morgan, 2007). Thus, the adverse effects of ApoE ε4 (and the other inflammatory genes) may have been compensated in an earlier era of higher rate of infectious diseases by increasing host resistance. On the other hand the adverse effects have been amplified during the modern time with increasing ageing, where pro-inflammatory traits acquired during evolution results into detrimental effects in terms of chronic inflammation (Caruso et al., 2005).

On the other hand, high cholesterol levels at midlife are a considerable risk factor for dementia/AD in most of long-term follow-up studies (Kivipelto and Solomon, 2006). Moreover, the influence of dietary fats on AD development was observed in ApoE ε4 subjects only. In fact, humans show different cholesterol synaptic distribution according to different APOE alleles. Even if there is moderate evidence that high total cholesterol at midlife is a risk factor for dementia/AD, data on triglycerides and lipoproteins are currently still insufficient to allow conclusions regarding their pattern of change with age or their impact on brain function. In any case, the brain, is very rich in cholesterol; i.e., about 25% of the total amount of unesterified cholesterol is contained in the brain, although it accounts for only 2% of the entire body mass. Cholesterol in the brain is actively turned over among neurons and glial cells via apolipoproteins and their receptors and plays an essential role in synaptic plasticity (Sambamurti et al., 1999; Yanagisawa, 2002; Kivipelto and Solomon, 2006; Ghribi et al., 2006). Several studies indicate that lipid rafts may play an important role in these processing pathways and therefore in AD pathogenesis (Cordy et al., 2006). Studies showed that glycosylphosphatidylinositol-anchored proteins that reside in lipid rafts facilitate Aβ production. Furthermore, a form of ganglioside-bound Aβ that aggregates more readily and also seeds aggregation more readily is generated in the presence of high cholesterol that also stimulates β-secretase processing (Sambamurti et al., 1999; Yanagisawa, 2002).

Epidemiological studies have suggested a possible protective effect for cholesterol lowering drugs statins in patients with AD (Rockwood et al., 2002; Blain and Poirier, 2004). However, a recent *meta*-analysis shows that the statin users did not demonstrate a significant beneficial effect on the risk of dementia or AD development (Zhou et al., 2007). In spite of that, the possibility remains that statin therapy may reduce risk of dementia and AD. Hence, further studies are warranted (Finch, 2005; Kuller, 2007). As previously stated, statins lower cholesterol by inhibiting the first step in the *de novo* cholesterol biosynthesis pathway catalyzed by HMGCR and by increasing the ability of the liver to remove LDL-cholesterol from the blood (Sviridov et al., 2007); the HMGCR is the rate-limiting enzyme for cholesterol synthesis and is regulated via a negative feedback mechanism mediated by sterols and non-sterol metabolites derived from mevalonate, the product of the reaction catalyzed by reductase (Chong et al., 2002; Zipp et al., 2007). A SNP in the promoter of this gene was investigated in case-control studies. Genotype distribution and allele frequency in two groups of AD patients and non demented controls were investigated. A cohort of AD patients was also followed up for 2 years, cognitive performances recorded and a possible influence of this SNP on the disease progression was tested. The results show that the HMGCR SNP was associated with a reduced risk of AD. These findings reinforce the notion that cholesterol plays a role in the pathogenesis of the disease (Porcellini et al., 2007).

5. Zinc

Zinc (~3 g) is the second most abundant trace element in the body after Fe (4 g) and considerably more abundant than copper. The body does not store Zn and a constant dietary intake is essential. Zn is normally obtained from red meat and other animal proteins, which have a high Zn content and it is also of easy absorption. Zinc deficiency is diffused in aged individuals who tend to have an inappropriate diet due to several factors like difficulty in chewing because of lack of teeth, lack of taste, fatigue and frailty. Changes in appetite, taste, and swallowing can impact the eating habits of the elderly individual, hence micronutrients are not consumed in adequate amounts (Martin 2006).

The bulk of body Zn is tightly bound within cellular metalloenzymes and Zn finger proteins. This fixed pool of Zn turns over very slowly and is mainly responsible for housekeeping

functions in cellular metabolism and gene expression. The remaining 10–15% of Zn (labile Zn) comprises more dynamic pools that are readily depleted in Zn deficiency. While fixed Zn is distributed uniformly throughout the body, labile Zn is concentrated in certain tissues and in specific regions within tissues (Vasto et al., 2006b, 2007a).

The brain has the highest zinc content compared other organs. The average of total brain zinc concentration was estimated to be approximately 150 μmol/L (about ten-fold serum zinc levels). However, free zinc ion concentration estimated in the cytosol from cultured neurons is subnanomolar and it is approximately 500 nM in brain extracellular fluids. On the contrary, the zinc content in the synaptic vesicles of some neurons in the forebrain was found to be approximately >1 mmol/L (Frederickson and Moncrieff, 1994). Studies in the hippocampus, amygdala and neo-cortex revealed that these neurons in the forebrain represent a subgroup of excitatory glutamatergic neurons, called nowadays gluzinergic neurons (Frederickson et al., 2000). Neurons that contain free zinc ions in the vesicles of their pre synaptic buttons are present also in other brain areas and are generally termed zinc-enriched neurons, which are not uniformly distributed, therefore distribution of zinc itself in the brain is not uniform. Zinc released by vesicles behaves as extracellular signal factor in synaptic neurotransmission in a calcium- and impulse-dependent manner (Slomianka, 1992; Takeda, 2000; Weiss et al., 2000). Interestingly, this zinc released in extra cellular space can enhance formation and fibril assembly of Aβ peptides in vivo (Huang et al., 1997). Zinc concentration is influenced by pro-inflammatory cytokines and by metallothioneins (MT) homeostasis, which are in turn affected by pro-inflammatory cytokines (Vasto et al., 2007a). MTs are a class of low-molecular weight metal-binding proteins that exert a critical role in buffering cytosolic Zn^{2+}. MTs are essential to intracellular zinc homeostasis by sequestration and release of the metal at the occurrence and thereby controlling available free zinc ions (Stankovic et al., 2007). In the central nervous system, MTs are present with three isoforms and show distinct patterns of expression: MT-1 and MT-2 are largely found in astrocytes and spinal glia but are largely absent in neurons, while MT-3 is abundant in neurons but poorly expressed in glial cells (Hidalgo et al., 2001). MT-3 seems to be particularly relevant to neuronal Zn^{2+} homeostasis in critical brain regions such as the hippocampus where it is abundantly present in the same hippocampal glutamatergic terminals that are also strongly enriched in vesicular Zn^{2+} (Hidalgo et al., 2001). The MTs are constituted of 61–68 amino acids with a highly conserved sequence of 20 cysteine residues that are grouped into two domains for Zn^{2+} binding the cysteine sulfur ligands in the cluster structure of MT can be reduced (zinc sequestration) or oxidized (zinc release) with thus concomitant changes in the relative amount of bound and free zinc (Kagi and Schaffer 1988, Hidalgo et al., 2001). Following an injurious stimulus, such as a transient inflammation, the subsequent oxidative stress induces the release of zinc from MT via NO, in order to promote the activity and expression of antioxidant enzymes, including MT itself, thus reducing the oxidative damage and the consequences of the injurious stimulus (Frazzini et al., 2006). In chronic inflammation, as it occurs in ageing and age-related diseases as AD, high MTs are unable to release zinc with subsequent low ion bioavailability to fight stress and to support immune/

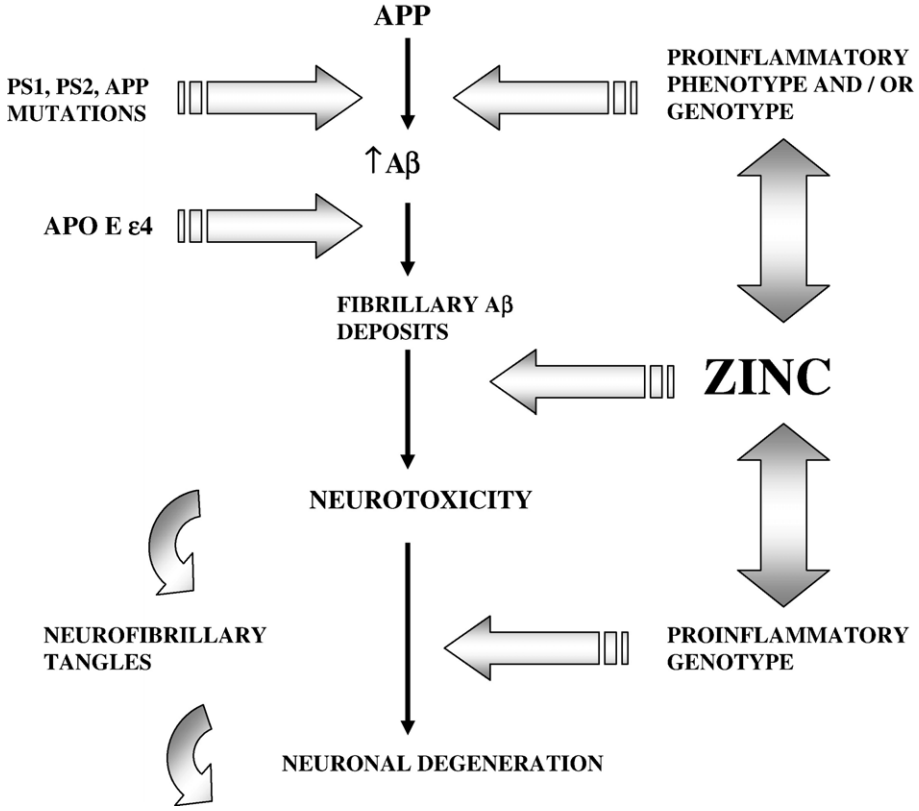

Fig. 1 – Role of environmental and genetic factors in the pathophysiology of AD. For the explanation see text.

inflammatory responses (Moroni et al., 2005; Vasto et al., 2007a, b). As a consequence, also a large number of genes that act as zinc sensors and transcriptional activators and/or repressors are altered (Mocchegiani et al., 2006). This may have a deep impact on the regulation of zinc-dependent transcription factors, because they, not only regulate "zinc-sensitive" genes, but also control their own transcription through positive autoregulatory mechanisms (Bao et al., 2003; Vasto et al., 2007a,b). The discovery that zinc may down-regulate the genes of pro-inflammatory cytokines may be in line with this assumption. This phenomenon may lead to an altered immune/inflammatory response in the elderly (Mocchegiani et al., 2000; Maret, 2000; Roy et al., 2002).

The biochemical mechanisms by which zinc may affect the inflammatory immune response are related to some transcriptional factors, such as NF-κB which is involved in TNF-α and other protein production. Zinc acts to inhibit NF-κB and subsequently limit TNF-α effects. Taking into account that both NF-κB and some proteins are zinc-dependent, it is evident that a lack of intracellular zinc ion bioavailability in ageing may provoke no inhibition of NF-κB, with subsequent maintenance of chronic inflammation with obviously a deleterious effect (Opipari et al., 1990; Rink and Kirchner, 2000; Heyninck and Beyaert, 2005). Moreover, the continuous lack of intracellular zinc ion availability leads to increased reactive oxygen species activity, due to a zinc quenching activity (Frederickson et al., 2005). On the other hand, Zn itself may be a strong inducer of oxidative stress by promoting mitochondrial and extra-mitochondrial production of reactive oxygen species (Frazzini et al., 2006). Therefore, zinc has a narrow range of concentration for its beneficial effect in inflammatory/immune response. Thus, zinc has to be used with caution in an eventual zinc supplementation in old individuals, in order to avoid unexpected side effects.

6. Conclusions

In AD, amyloid deposition is the main pathogenetic mechanism due to the accumulation of Aβ peptide. There are two different forms of AD, early and late-onset. About 7 percent of early-onset cases are familial and are caused by gene mutations, as PS1, PS2 and APP mutations (Campion et al., 1999). In the late-onset, several genetic and environmental factors play a role (Nussbaum and Ellis, 2003; Bird, 2005), in particular, as discussed, environmental (Schmidt et al., 2002; Wilson 2003) and genetic (Candore et al., 2006, 2007; Vasto et al., 2007c) inflammatory factors in influencing AD development, i.e. the. pro-inflammatory status can depend either on phenotype or on genotype. The well-known pro-inflammatory status of elderly can explain (Vasto et al., 2007b), at least in part, why the most important risk factor for AD is age. In any case, polymorphisms involved in age-related inflammatory diseases as AD are fairly common in the general population, so there is a strong likelihood that any given individual will inherit one or more of the high-risk alleles: the occurrence of the disease is likely to depend on interaction between different high-risk alleles, exposure to pathogens, environmental factors and lifestyle choices (Imahara and O'Keefe 2004; Vasto et al., 2007c). In this regard, combinations of alleles in eight inflammatory genes and ApoE ε4 that discriminate AD risk groups were recently found (Licastro et al., 2007).

As an example of a possible interaction with environment and lifestyle choices, we have among others, dietary factors which despite their "extrinsic" nature, are able to interact with the genome. This interaction may result in changes of gene expression that, in turn, affects many aspects of health including the immune system (Mocchegiani et al., 2006). A special emphasis has been given to zinc, because its bioavailability, as previously discussed, can play a key role in regulating inflammatory responses. In fact, the amount of intracellular zinc is fundamental because zinc can have a double role from anti-inflammatory to pro-inflammatory roles depending on intracellular free zinc ion concentration (von Bulow et al., 2005). In particular, zinc availability may regulate mRNA cytokine expression, so influencing inflammatory network phenotypic expression (Bao et al., 2003; Vasto et al., 2007a,b).

Furthermore, it has been demonstrated that elevated zinc levels in cortex of patients with AD are biochemically linked to Aβ burden and to the severity of the disease, although it has not yet been determined if altered zinc levels precede or follow deposition of Aβ (Religa et al., 2006). However, the 8HQ (8-hydroxyquinoline) derivative CQ (clioquinol), a zinc chelant, has shown promising results in animal models and small clinical trials; interestingly in AD patients treated with the drug there was a significant elevation in plasma zinc levels compatible with the movement of excess zinc out of the brain (Ritchie et al., 2004; Religa et al., 2006).

Fig. 1 goes over the topics that are until now pointed out on the role of genetics in early-onset AD, and inflammation on late-onset disease by taking into account the role of zinc.

Acknowledgments

This work is supported by the European Commission ZINCAGE project (contract n. FOODCT-506850; Coordinator: Dr. Eugenio Mocchegiani). The "Immunosenesence Research Group" coordinated by Prof. C. Caruso in association with INRCA was enlarged through a joint contract (Longevity and elderly disability biological markers).

REFERENCES

Abdullah, L., Ait-Ghezala, G., Crawford, F., et al., 2006. The cyclooxygenase 2-765 C promoter allele is a protective factor for Alzheimer's disease. Neurosci. Lett. 395 (3), 240–243.

Aisen, P.S., Schafer, K.A., Grundman, M., et al., 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer's disease progression: a randomized controlled trial. JAMA 289, 2819–2826.

Akiyama, H., Barger, S., Barnum, S., et al., 2000. Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383–421.

Albert, M.A., Danielson, E., Rifai, N., Ridker, P.M., 2001. PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 286 (1), 64–70.

Allan, L.M., Ballard, C.G., Burn, D.J., Kenny, R.A., 2005. Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. J. Am. Geriatr. Soc. 53 (10), 1681–1687.

Aronson, M.K., Ooi, W.L., Geva, D.L., Masur, D., Blau, A., Frishman, W., 1991. Dementia. Age-dependent incidence, prevalence, and mortality in the old. Arch. Intern. Med. 151, 989–992.

Atwood, C.S., Obrenovich, M.E., Liu, T., Chan, H., Perry, G., Smith, M.A., Martins, R.N., 2003. Amyloid-beta: a chameleon walking in two worlds: a review of the trophic and toxic properties of amyloid-beta. Brain Res. Brain Res. Rev. 43 (1), 1–16.

Auld, D.S., Kornecook, T.J., Bastianetto, S., Quirion, R., 2003. Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies. Prog. Neurobiol. 3, 209–245.

Bagnoli, S., Cellini, E., Tedde, A., et al., 2007. Association of IL10 promoter polymorphism in Italian Alzheimer's disease. Neurosci. Lett. 418 (3), 262–265.

Bao, B., Prasad, A.S., Beck, F.W., Godmere, M., 2003. Zinc modulates mRNA levels of cytokines. Am. J. Physiol: Endocrinol. Metab. 285, E1095-1020.

Bird, T.D., 2005. Genetic factors in Alzheimer's disease. N. Engl. J. Med. 352, 862–864.

Blain, J.F., Poirier, J., 2004. Cholesterol homeostasis and the pathophysiology of Alzheimer's disease. Expert Rev. Neurother. 4 (5), 823–829.

Borovikova, L.V., Ivanova, S., Zhang, M., et al., 2000. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405, 458–462.

Breitner, J.C., 2003. NSAIDs and Alzheimer's disease: how far to generalise from trials? Lancet Neurol. 2, 527.

Cacquevel, M., Lebeurrier, N., Chéenne, S., Vivien, D., 2004. Cytokines in neuroinflammation and Alzheimer's disease. Curr Drug Targets 5 (6), 529–534.

Camandola, S., Mattsonm, M.P., 2007. NF-kappa B as a therapeutic target in neurodegenerative diseases. Expert Opin Ther Targets 11 (2), 123–132.

Campion, D., Dumanchin, C., Hannequin, D., et al., 1999. Early-onset autosomal dominant Alzheimer's disease: prevalence, genetic heterogeneity, and mutation spectrum. Am. J. Hum. Genet. 65 (3), 664–670.

Candore, G., Balistreri, C.R., Grimaldi, M.P., et al., 2007. Polymorphisms of pro-inflammatory genes and Alzheimer's disease risk: a pharmacogenomic approach. Mech. Ageing Dev. 128, 67–75.

Candore, G., Balistreri, C.R., Grimaldi, M.P., et al., 2006. Age-related inflammatory diseases: role of genetics and gender in the pathophysiology of Alzheimer's disease. Ann. N. Y. Acad. Sci. 1089, 472–486.

Caruso, C., Candore, G., Colonna Romano, G., Lio, D., Franceschi, C., 2005. Inflammation and life-span. Science 307, 208–209.

Chong, P.H., Kezele, R., Franklin, C., 2002. High-density lipoprotein cholesterol and the role of statins. Circ. J. 66, 1037–1044.

Colton, C.A., Needham, L.K., Brown, et al., 2004. APOE genotype-specific differences in human and mouse macrophage nitric oxide production. J. Neuroimmunol. 147, 62–67.

Cordle, A., Landreth, G., 2005. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors attenuate beta-amyloid-induced microglial inflammatory responses. J. Neurosci. 25 (2), 299–307.

Cordy, J.M., Hooper, N.M., Turner, A.J., 2006. The involvement of lipid rafts in Alzheimer's disease. Mol. Membr. Biol. 23, 111–122.

Del Bo, R., Angeretti, N., Lucca, E., De Simoni, M.G., Forloni, G., 1995. Reciprocal control of inflammatory cytokines, IL-1 and IL-6, and beta-amyloid production in cultures. Neurosci. Lett. 188 (1), 70–74.

Dickson, D.W., Farlo, J., Davies, P., Crystal, H., Fuld, P., Yen, S.H., 1988. Alzheimer's disease. A double-labeling immunohistochemical study of senile plaques. Am. J. Pathol. 132 (1), 86–101.

Etminan, M., Gill, S., Samii, A., 2003. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ 327, 128–133.

Fassbender, K., Masters, C., Beyreuther, K., 2000. Alzheimer's disease: an inflammatory disease? Neurobiol. Aging 21, 433–436.

Finch, C.E., 2005. Developmental origins of aging in brain and blood vessels: an overview. Neurobiol. Aging 26 (3), 281–291.

Finch, C.E., Morgan, T.E., 2007. Systemic inflammation, infection, ApoE alleles, and Alzheimer's disease: a position paper. Curr. Alzheimer Res. 4, 185–189.

Finch, C.E., Stantford, C.B., 2002. Lipoprotein genes and diet in the evolution of human intelligence and longevity. In "Brain and Longevity. Research and Perspectives in Longevity. Foundation IPSEN, Sprinter.

Findeis, M.A., 2007. The role of amyloid beta peptide 42 in Alzheimer's disease. Pharmacol. Ther. 116 (2), 266–286.

Frazzini, V., Rockabrand, E., Mocchegiani, E., Sensi, S.L., 2006. Oxidative stress and brain aging: is zinc the link? Biogerontology 7, 307–314.

Frederickson, C.J., Moncrieff, D.W., 1994. Zinc-containing neurons. Biol. Signals 3, 127–139.

Frederickson, C.J., Koh, J.Y., Bush, A.I., 2005. The neurobiology of zinc in health and disease. Nat. Rev., Neurosci. 6 (6), 449–462.

Frederickson, C.J., Suh, S.W., Silva, D., Frederickson, C.J., Thompson, R.B., 2000. Importance of zinc in the central nervous system: the zinc-containing neuron. J. Nutr. 130, 1471–1483.

Friedlander, R.M., 2003. Mechanisms of disease: apoptosis and caspases in neurodegenerative diseases. N. Engl. J. Med. 348, 1365–1375.

Ghribi, O., Golovko, M.Y., Larsen, B., Schrag, M., Murphy, E.J., 2006. Deposition of iron and betaamyloid plaques is associated with cortical cellular damage in rabbits fed with long-term cholesterol-enriched diets. J. Neurochem. 99, 438–449.

Griffin, W.S., Mrak, R.E., 2002. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. J. Leukoc. Biol. 72 (2), 233–238.

Griffin, W.S., Sheng, J.G., Royston, M.C., et al., 1998. Glial-neuronal interactions in Alzheimer's disease, the potential role of a 'cytokine cycle' in disease progression. Brain Pathol. 8, 65–72.

Guan, Z.Z., Zhang, X., Ravid, R., Nordberg, A., 2004. Decreased protein levels of nicotinic receptor subunits in the hippocampus and temporal cortex of patients with Alzheimer's disease. J. Neurochem. 74, 237–243.

Halliday, G., Robinson, S.R., Shepherd, C., Kril, J., 2000. Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. Clin. Exp. Pharmacol. Physiol. 27, 1–8.

Heyninck, K., Beyaert, R., 2005. A20 inhibits NF-kappaB activation by dual ubiquitin-editing functions. Trends Biochem. Sci. 30, 1–4.

Hidalgo, J., Aschner, M., Zatta, P., Vasak, M., 2001. Roles of the metallothionein family of proteins in the central nervous system. Brain Res. Bull. 55 (2), 133–145.

Huang, X., Atwood, C.S., Moir, R.D., et al., 1997. Zinc-induced Alzheimer's Abeta1-40 aggregation is mediated by conformational factors. J. Biol. Chem. 272, 26464–26470.

Hutton, M., Lendon, C.L., Rizzu, P., et al., 1998. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 393, 702–705.

Imahara, S.D., O'Keefe, G.E., 2004. Genetic determinants of the inflammatory response. Curr. Opin. Crit. Care 10, 318–324.

Jofre-Monseny, L., Loboda, A., Wagner, A.E., et al., 2007a. Effects of apoE genotype on macrophage inflammation and heme oxygenase-1 expression. Biochem. Biophys. Res. Commun. 357, 319–324.

Jofre-Monseny, L., de Pascual-Teresa, S., Plonka, E., Huebbe, P., Boesch-Saadatmandi, C., Miniane, A.M., Rimbach, G., 2007b. Differential effects of apolipoprotein E3 and E4 on markers of oxidative status in macrophages. Br. J. Nutr. 97 (5), 864–871.

Kagi, J.H., Schaffer, A., 1988. Biochemistry of metallothionein. Biochemistry 27, 8509–8515.
Kihara, T., Shimohama, S., Urushitani, M., et al., 1998. Stimulation of alpha4beta2 nicotinic acetylcholine receptors inhibits beta-amyloid toxicity. Brain Res. 792, 331–334.
Kihara, T., Shimohama, S., Sawada, H., et al., 1997. Nicotinic receptor stimulation protects neurons against beta-amyloid toxicity. Ann. Neurol. 42, 159–163.
Kivipelto, M., Solomon, A., 2006. Cholesterol as a risk factor for Alzheimer's disease — epidemiological evidence. Acta Neurol. Scand. 114, 50–57.
Kuller, L.H., 2007. Statins and dementia. Curr. Atheroscler. Rep. 9 (2), 154–161.
Kwon, J.M., Nowotny, P., Shah, P.K., 2000. Tau polymorphisms are not associated with Alzheimer's disease. Neurosci. Lett. 284 (1–2), 77–80.
Licastro, F., Porcellini, E., Caruso, C., Lio, D., Corder, E.H., 2007. Genetic risk profiles for Alzheimer's disease: integration of APOE genotype and variants that up-regulate inflammation. Neurobiol. Aging 28, 1637–1643.
Lindberg, C., Hjorth, E., Post, C., Winblad, B., Schultzberg, M., 2005. Cytokine production by a human microglial cell line: effects of beta-amyloid and alpha-melanocyte-stimulating hormone. Neurotox. Res. 8, 267–276.
Ma, S.L., Tang, N.L., Zhang, Y.P., et al., 2007. Association of prostaglandin-endoperoxide synthase 2 (PTGS2) polymorphisms and Alzheimer's disease in Chinese. Neurobiol. Aging. doi:10.1016/j.neurobiolaging.2006.12.011.
Mahley, R.W., Rall Jr., S.C., 2000. Apolipoprotein E: far more than a lipid transport protein. Annu. Rev. Genomics Hum. Genet. 1, 507–537.
Maret, W., 2000. The function of zinc metallothionein: a link between cellular zinc and redox state. J. Nutr. 130, 1455S–1458S.
Martin, C.M., 2006. Vitamins for the elderly: from A to zinc. Consult. Pharm. 21, 450–464.
Martin-Ruiz, C.M., Court, J.A., Molnan, E., et al., 1999. Alpha4 but not alpha3 and alpha7 nicotinic acetylcholine receptor subunits are lost from the temporal cortex in Alzheimer's disease. J. Neurochem. 4, 1635–1640.
Maurer, K., Volk, S., Gerbaldo, H., 1997. Auguste D and Alzheimer's disease. Lancet 349 (9064), 1546–1549.
McGeer, P.L., Schulzer, M., McGeer, E.G., 1996. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 47 (2), 425–432.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939–944.
Meyer, M.R., Tschanz, J.T., Norton, M.C., et al., 1998. APOE genotype predicts when—not whether—one is predisposed to develop Alzheimer's disease. Nat. Genet. 119, 321–322.
Minoretti, P., Gazzaruso, C., Vito, C.D., et al., 2006. Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer's disease. Neurosci. Lett. 391 , 147–149.
Misonou, H., Morishima-Kawashima, M., Ihara, Y., 2000. Oxidative stress induces intracellular accumulation of amyloid beta-protein(Abeta) in human neuroblastoma cells. Biochemistry 13, 6951–6959.
Mitchell, R.N., Cotran, R.S., 2003. Acute and chronic inflammation. Robbins Basic Pathology. Saunderrs, Philadelphia, USA.
Mocchegiani, E., Costarelli, L., Giacconi, R., et al., 2006. Nutrient-gene interaction in ageing and successful ageing. A single nutrient (zinc) and some target genes related to inflammatory/immune response. Mech. Ageing Dev. 127, 517–525.
Mocchegiani, E., Muzzioli, M., Giacconi, R., 2000. Zinc and immunoresistance to infection in aging: new biological tools. Trends Pharmacol. Sci. 21, 205–208.
Morgan, A.R., Turic, D., Jehu, L., et al., 2007. Association studies of 23 positional/functional candidate genes on chromosome 10 in late-onset Alzheimer's disease. Am. J. Med. Genet. B Neuropsychiatr. Genet. 144, 762–770.
Moroni, F., Di Paolo, M.L., Rigo, A., et al., 2005. Interrelationship among neutrophil efficency, inflammation, antioxidant activity and Zinc pool in very old age. Biogerontology 6, 271–281.
Mrak, R.E., Griffin, W.S., 2005. Glia and their cytokines in progression of neurodegeneration. Neurobiol. Aging 26, 349–354.
Mrak, R.E., Sheng, J.G., Griffin, W.S., 1995. Glial cytokines in Alzheimer's disease: review and pathogenic implications. Hum. Pathos. 26, 816–823.
Newman, M., Musgrave, F.I., Lardelli, M., 2007. Alzheimer disease: amyloidogenesis, the presenilins and animal models. Biochim. Biophys. Acta. 1772, 285–297.
Nussbaum, R.L., Ellis, C.E., 2003. Genomic medicine: Alzheimer's disease and Parkinson's disease. N. Engl. J. Med. 348, 1356–1364.
Opipari Jr., A.W., Boguski, M.S., Dixit, V.M., 1990. The A20 cDNA induced by tumor necrosis factor alpha encodes a novel type of zinc finger protein. J. Biol. Chem. 265, 14705–14708.
Porcellini, E., Calabrese, E., Guerini, F., et al., 2007. The hydroxy-methyl-glutaryl CoA reductase promoter polymorphism is associated with Alzheimer's risk and cognitive deterioration. Neurosci. Lett. 416, 66–70.
Priller, C., Bauer, T., Mitteregger, G., Krebs, B., Kretzschmar, H.A., Herms, J., 2006. Synapse formation and function is modulated by the amyloid precursor protein. J. Neurosci. 26, 7212–7221.
Qu, T., Manev, R., Manev, H., 2001. 5-Lipoxygenase (5-LOX) promoter polymorphism in patients with early-onset and late-onset Alzheimer's disease. J. Neuropsychiatry Clin. Neurosci. 13, 304–305.
Rainero, I., Bo, M., Ferrero, M., Valfre, W., Vaula, G., Pinessi, L., 2004. Association between the interleukin-1alpha gene and Alzheimer's disease, a meta-analysis. Neurobiol. Aging 25, 1293–1298.
Reiman, E.M., Webster, J.A., Myers, A.J., et al., 2007. GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. Neuron 54, 713–720.
Reines, S.A., Block, G.A., Morris, J.C., et al., 2004. Rofecoxib protocol 091 study group. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 62, 66–71.
Religa, D., Strozyk, D., Cherny, R.A., et al., 2006. Elevated cortical zinc in Alzheimer's disease. Neurology 67, 69–75.
Ringheim, G.E., Szczepanik, A.M., Petko, W., et al., 1998. Enhancement of beta-amyloid precursor protein transcription and expression by the soluble interleukin-6 receptor/interleukin-6 complex. Brain Res. Mol. Brain Res. 55, 35–44.
Rink, L., Kirchner, H., 2000. Zinc-altered immune function and cytokine production. J. Nutr. 130, 1407S–1411S.
Ritchie, C.W., Bush, A.I., Masters, C.L., 2004. Metal-protein attenuating compounds and Alzheimer's disease. Expert Opin. Investig. Drugs 13, 1585–1592.
Roberson, E.D., Scearce-Levie, K., Palop, J.J., Yan, F., Cheng, I.H., Wu, T., Gerstein, H., Yu, G.Q., Mucke, L., 2007. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 316, 750–754.
Rockwood, R., Kirkland, S., Hogan, D.B., et al., 2002. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch. Neurol. 59, 223–227.
Rogers, J., Luber-Narod, J., Styren, S.D., Civin, W.H., 1988. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. Neurobiol. Aging 9, 339–349.
Roy, A.K., Oh, T., Rivera, O., Mubiru, J., Song, C.S., Chatterjee, B., 2002. Impacts of transcriptional regulation on aging and senescence. Ageing Res. Rev. 1, 367–380.

Sambamurti, K., Sevlever, D., Koothan, T., et al., 1999. Glycosylphosphatidylinositol-anchored proteins play an important role in the biogenesis of the Alzheimer's amyloid beta-protein. Biol. Chem. 274, 26810–26814.

Schmidt, R., Schmidt, H., Curb, J.D., Masaki, K., White, L.R., Launer, L.J., 2002. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann. Neurol. 52, 168–174.

Selkoe, D.J., 2001. Alzheimer's disease: genes, proteins, and therapy. Physiol. Rev. 81, 741–766.

Seshadri, S., Drachman, D.A., Lippa, C.F., 1995. Apolipoprotein E epsilon 4 allele and the lifetime risk of Alzheimer's disease. What physicians know, and what they should know. Arch. Neurol. 52, 1074–1079.

Sheng, J.G., Bora, S.H., Xu, G., Borchelt, D.R., Price, D.L., Koliatsos, V.E., 2003. Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APPswe transgenic mice. Neurobiol. Dis. 14, 133–145.

Slomianka, L., 1992. Neurons of origin of zinc-containing pathways and the distribution of zinc-containing boutons in the hippocampal region of the rat. Neuroscience 48, 325–352.

Smith, J.D., 2002. Apolipoproteins and aging: emerging mechanisms. Ageing Res. Rev. 1, 345–365.

Stankovic, R.K., Chung, R.S., Penkowa, M., 2007. Metallothioneins I and II: neuroprotective significance during CNS pathology. Int. J. Biochem. Cell Biol. 39, 484–489.

Strittmatter, W.J., Roses, A.D., 1996. Apolipoprotein E and Alzheimer's disease. Annu. Rev. Neurosci. 19, 53–77.

Stüve, O., Youssef, S., Steinman, L., Zamvil, S.S., 2003. Statins as potential therapeutic agents in neuroinflammatory disorders. Curr. Opin. Neurol. 16, 393–401.

Sviridov, D., Nestel, P., Watts, G., 2007. Statins and metabolism of high density lipoprotein. Cardiovasc. Hematol. Agents Med. Chem. 5, 215–221.

Takeda, A., 2000. Movement of zinc and its functional significance in the brain. Brain Res. Brain Res. Rev. 34, 137–148.

Tohgi, H., Utsugisawa, K., Yoshimura, M., Nagana, Y., Mihara, M., 1998. Age related changes in nicotinic acetylcholine receptor subunits α4 and β2 messenger RNA expression in post-mortem human frontal cortex and hippocampus. Neurosci. Lett. 245, 139–142.

Town, T., Nikolic, V., Tan, J., 2005. The microglial "activation" continuum, from innate to adaptive responses. J. Neuroinflammation 2, 24.

Tsoi, L.M., Wong, K.Y., Liu, Y.M., Ho, Y.Y., 2007. Apoprotein E isoform-dependent expression and secretion of pro-inflammatory cytokines TNF-alpha and IL-6 in macrophages. Arch. Biochem. Biophys. 460, 33–40.

Tuppo, E.E., Arias, H.R., 2005. The role of inflammation in Alzheimer's disease. Int. J. Biochem. Cell Biol. 37, 289–305.

Vasto, S., Candore, G., Aquino, A., et al., 2006a. The nACHR4 594C/T polymorphism in Alzheimer's disease. Rejuvenation Res. 9, 107–110.

Vasto, S., Mocchegiani, E., Candore, G., et al., 2006b. Inflammation, genes and zinc in ageing and age-related diseases. Biogerontology 7, 315–327.

Vasto, S., Mocchegiani, E., Malavolta, M., et al., 2007a. Zinc and inflammatory/immune response in aging. Ann. N. Y. Acad. Sci. 1100, 111–122.

Vasto, S., Candore, G., Balistreri, C.R., et al., 2007b. Inflammatory networks in ageing, age related diseases and longevity. Mech. Ageing Dev. 128, 83–91.

Vasto, S., Candore, G., Duro, G., Grimaldi, M.P., Lio, D., Caruso, C., 2007c. Alzheimer's disease and genetics of inflammation: a pharmacogenomic vision. Pharmacogenomics 8, 1735–1745.

Veld in t, B.A., Ruitenberg, A., Hofman, A., Launer, L.J., van Duijn, C.M., Stijnen, T., et al., 2001. Non steroidal anti-inflammatory drugs and the risk of Alzheimer's disease. N. Engl. J. Med. 345, 1515–1521.

von Bulow, V., Rink, L., Haase, H., 2005. Zinc-mediated inhibition of cyclic nucleotide phosphodiesterase activity and expression suppresses TNF-alpha and IL-1 beta production in monocytes by elevation of guanosine 3′,5′-cyclic monophosphate. J. Immunol. 175, 4697–4705.

Weiss, J.H., Sensi, S.L., Koh, J.Y., 2000. Zn(2+): a novel ionic mediator of neural injury in brain disease. Trends Pharmacol. Sci. 21, 395–401.

Wevers, A., Monteggia, L., Nowacki, S., et al., 1999. Expression of nicotinic acetylcholine receptor subunits in the cerebral cortex in Alzheimer's disease: histotopographical correlation with amyloid plaques and hyperphosphorylated-tau protein. Eur. J. Neurosci 11, 2551–2565.

Wierzbicki, A.S., Poston, R., Ferro, A., 2003. The lipid and non-lipid effects of statins. Pharmacol. Ther. 99 (1), 95–112.

Wilson, J.T., 2003. Head injury and Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 74, 841.

Yanagisawa, K., 2002. Cholesterol and pathological processes in Alzheimer's disease. J. Neurosci. Res. 70 (3), 361–366.

Yao, J., Petanceska, S.S., Montine, T.J., et al., 2004. Aging, gender and APOE isotype modulate metabolism of Alzheimer's Abeta peptides and F-isoprostanes in the absence of detectable amyloid deposits. J. Neurochem. 90, 1011–1018.

Zhou, B., Teramukai, S., Fukushima, M., 2007. Prevention and treatment of dementia or Alzheimer's disease by statins: a *meta*-analysis. Dement. Geriatr. Cogn. Disord. 23 (3), 194–201.

Zipp, F., Waiczies, S., Aktas, O., et al., 2007. Impact of HMG-CoA reductase inhibition on brain pathology. Trends Pharmacol. Sci. 28, 342–349.

Zoli, M., Picciotto, M.R., Ferrari, R., Cocchi, D., Changeux, J.P., 1999. Increased neurodegeneration during ageing in mice lacking high affinity nicotine receptors. EMBO J. 18, 1235–1244.