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BIOCHEMICAL CHANGES IN ALZHEIMER'S DISEASE: AN OVERVIEW

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ABSTRACT

Most important to know the early risk factors for Alzheimer's disease as the neurodegenerative progressions of the disease may begin in midlife. Early detection of these risk factors may hut some light on the pathophysiology of Alzheimer's disease and a plausible paths for its prevention and treatment. It is speculated from the preliminary findings that it is an association between vascular risk factors and Alzheimer's disease need to be invented in self-regulating populations. No population based study has yet been documented the correlation of both mid-life high blood pressure level and cholesterol concentrations with Alzheimer's disease in older age in both sexes.

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INTRODUCTION

Dementia in the elderly population is most commonly caused by Alzheimer's disease (AD). The characteristic features of AD are the appearance of extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT) in the intracellular environment, neuronal death and the loss of synapses results inprogressive brain disorder. AD is a terminal and incurable disease (Popova *et al*., 2012). The most important risk factor of AD is age, with the prevalence rising exponentially after 65 years of age (Blennow *et al*., 2006; Sheng *et al*., 2012).The overall prevalence of AD is expected to double within 20 years as the average lifespan increases in developing countries.Genetic analysis has showed four genes responsible for the development ofAD as an autosomal dominant trait (Tianz, *2012*). Mutations in three genes lead to virtually all early-onset, familial AD: amyloid protein precursor on chromosome 21, presenilin 1 (PS1) on chromosome 14, and presenilin 2 (PS2) on chromosome 1. One allele of apolipoproteinE (ApoE) on chromosome 9 is linked with late-onset AD in patients with and without a strong family history.

Bio chemical changes

Amyloid Precursor Protein

The central feature of the pathology of AD is the deposition of amyloid β-protein (Aβ) in plaques and in the walls of cerebral blood vessels (Selkoe, 1994). Aβ, is a 39 to 43 amino acid peptide which arises from the cleavage of a larger amyloid precursor protein (APP). APP is a type I transmembrane glycoprotein whichis encoded by a gene on chromosome 21 and is expressed in a variety of cells. Different genetic and environmental factors can trigger Aβ deposition.Alterations in the metabolism of APP and increased production of Aβ occur due to missense mutations within the APP gene (Zou *et al*.,

2014). Patients with Down's syndrome (trisomy 21) almost invariably develop the pathology of AD by the age of 40 due to overexpression of theAPP gene and subsequent processing of the protein via the amyloidogenic (fibril-forming) pathway (Head *et al*., 2012). Several researchers found no correlation between the amount of Aβ deposits and the severity of the disease, whereas others described a positive correlation (Cummings & Cotman, 1995; Nagy *et al*., 1995; Murayama & Saito, 2004). AD-related 'transcript mutations' affect APP (but also other proteins withless apparent connections to AD), which is considered as another indication for the involvement of APP/Aβ in the pathogenesis of AD (Van Leeuwen *et al*., 1998). Transgenic mice that overexpresshuman mutant APP genes produce amyloid deposits in the hippocampus and cortex as well as cognitive lesions with advancing age (Games *et al*., 1995). Although paired helical filaments and signs of inflammationhavebeen observed in these animals,yetthe process of fibril formation is not restricted to Aβ in AD. Seventeen different proteins are known to produce amyloid deposits, such as transthyretin in familial amyloid neuropathy, prions in bovine spongiform encephalopathy and Creutzfeldt-Jakob disease, and amylin in type II diabetes mellitus (Kelly, 1998). These phenomena indicate that amyloidogenesis is a critical event in the onset of several diseases, despite the chicken-or-egg status ofAβ deposits and etiology of AD. Biological effects of Aβ are correlated with its physical state as shown by several *in vitro* studies. Solubilised Aβ or freshly prepared solutions of either Aβ (1-40) or Aβ (1-42) possess a random coil or α-helical conformation and produce neurotrophic actions (Cotman *et al*., 1992). Prolonged incubation leads to structural change to β-sheet conformation resulting in the formation of fibrils that are neurotoxic (Pike *et al*., 1993; Yankner& Lorenzo, 1996). The equilibrium between random-coil and β-pleated sheet conformation depends onthe pH, which is shifted to the fibril structure upon nucleation. Stimulating effect on Aβ fibril formation also have been shown by other proteins such as apoE, α-1-antichymotrypsin and acetylcholinesterase (Wisniewski *et al*., 1994; Eriksson *et al*., 1995).

Non-Amyloidβ Component Protein

The non-Aβ component of AD amyloid (NAC), the second major biochemical component, was detected in the amyloid purified from brain tissue of patients with AD (Iwai A, 2000). It is a hydrophobic peptide fragment derived from a 140-amino acid precursor protein (NACP = α-synuclein), which is not a significant component of plaques, and is a presynaptic protein found in membrane and vesicular fractions (Irizarry *et al*., 1996; Iwai A, 2000).The physiological function of NACP isunknown, but it may be involved in neuronal function due to its localization at presynaptic nerve terminals (Iwai A, 2000). Significant parts ofNACPare unfolded as reported in studies based on circular dichroism and Fouriertransform infrared spectroscopy (Kim, 1997a). The unfolded structure of NACP makes it extremelysensitiveto proteolysis and may result in the hydrophobic peptide fragment found in the centre of amyloid cores. The hydrophobic peptide is probably able to bindAβ, seeding amyloidogenesis. It has been found that a shorter splice variant of NACP containing the NAC sequence known as NACP-112 was able to bind Aβ, but a deletion mutant lacking this sequence destroyed the binding capacity (Yoshimoto *et al*., 1995). TheNAC isa self-aggregating peptide in a time-, concentration-and temperature-dependent manner posing green birefringence after Congo redstaining and fibre-like structures when analysedultra-structurally (Iwai A, 2000). This signifies that NAC, by itself, is amyloidogenic, and may be another centralfactor in amyloidosis in the AD brain, either by itself or by binding Aβ.

Tau

The degree of neurofibrillary pathology,rather than the degree of detectable amyloid deposition, is associated with the extentof dementia aswell as the progression of neurodegeneration through the brain (Thal&Braak, 2005). This pathology consists of the (mainly intracellular) presence of neurofibrillary tangles, dystrophic neurites and neuropil threads. Tau, the microtubule-associated protein, is the main component of tangles and threads. This protein is realigned into paired helical filaments in the somatodendritic compartment in the form of dystrophic neurites and tangles in AD-affected areas of the brain. Thus,AD is primarily a disorder of the cytoskeleton of a few vulnerable neuronal cell types (Braak *et al*., 2006). Tau promotes polymerisationand stabilisation of tubulin in the axons. The pattern of isoforms and the degree of phosphorylation, differentially regulated during development, defines the functional properties of Tau (Avila *et al*., 2004). Tau phosphorylation at the distal end of the axon regulates interactions between cytoskeleton and plasma membrane (Sánchez *et al*., 2001). Highly phosphorylated forms of tau tanglesare probably less effective in microtubule binding and stabilisation. A tangle-characteristic pattern of tau isoforms containing various degrees of phosphorylation has not yet been established (Sergeant *et al*., 1997). The putative effect of Aβ on tau modification and the sequential relationship between tangle and plaque formation are not clear. However, one mutation in tau, which is associated with inherited frontotemporal dementia, as well as with the presence of Alzheimer-like paired helical filaments, lies near residues that are phosphorylated in Alzheimer tangles (Hutton *et al*., 1998). This reflects the phosphorylation of abnormal tau may be upstream in the neurodegeneration process. It is still in the experimental stage that not only the degree of phosphorylation, but also heparin sulfate-induced dimer formation, followed by glycation and/or transglutaminase-induced crosslinking contribute to the formation of insoluble paired helical filaments. Modifications of tau may be responsible for early events in AD-related neurodegeneration. Additional evaluation of the role of such modifications in the regulation of tau interactions is essential to understand the exact role it fulfills in this complex neurodegenerative pathology. The neurodegeneration-associated mutations in tau lead to an increase in tau isoforms with abnormal microtubule binding (Sergeant *et al*., 1997),highlighting thatfuture research should focuson microtubule-mediated aspects of cell homeostasis (Avila *et al*., 2004; Sánchez *et al*., 2001).

Presenilins

The presenilins were discovered by genetic analyses of families of patients with early-onset autosomal AD showing mutations in presenilin genes, PS1 on chromosome 14 and PS2 on chromosome 1 and detected in the majority of the pedigrees (Czech *et al*., 2000). PS1 and PS2 are highly homologous integral membrane proteins of 52 kDa in neurons, and are located mainly in the nucleus, in the endoplasmic reticulum, and in the Golgi apparatus, with very little, if any, in the plasma membrane. Theoretical models predict the existence of

7 to 10 hydrophobic domains, with topological studies indicating 6 or 7 membrane-spanning regions (Lehmann *et al*., 1997; Dewji *et al*., 1997a). Two different molecular weight proteins, (25 to 28 and 16 to 19 kDa) have been detected after natural endo-proteolytic processing which may be a preparation-related artifact (Dewji *et al*., 1997b). Neitherthe processing nor the intracellular localisations of the proteins affect AD-associated mutations (Hendriks *et al*., 1997; Kovacs *et al*., 1996). Presenilins seem to be involved in signal transduction (possibly in a complex together with APP), protein trafficking, and/or in proper chromosome segregation during mitosis (Xia *et al*., 1997; Li *et al*., 1997). APP processing has been found to beaffected by the expression of presenilin variants with the same mutations as found in AD, culminatingin increased Aβ (1-42) secretion in transfected cell lines, and in increased Aβ concentrations in transgenic (mutant PS1) mice (Li *et al*., 1997; Czech *et al*., 2000; Citron *et al*., 1997).In the plasma and brains of AD patients harboring mutations in PS1 or PS2, the concentrations of Aβ secretion has been detected to increase (Lamb, 1997). This phenomenon strongly supports the 'amyloid hypotheses. This does not exclude the initial effect of presenilinmutations, whichmay be a fatal disturbance of cell homeostasis and is not primarily related to APP. Indeed, it has been speculated that presenilins are involved in the apoptosis process based on the function of their nonhuman homologues (Czech *et al*., 2000). Furthermore, increased expression of PS2 in neuronal cells increases their susceptibility to induced cell death whereas lack of expression is related to tangle formation (Wolozin *et al*., 1996). The presenilins are cleaved at sites during apoptosis *in vitro*that are different from normal processing (Kim *et al*., 1997b). Cumulatively, an altered processing of APP to amyloidogenic Aβ may be secondary to the disturbance of a process in which presenilins are primarily involved.

Apolipoprotein E

Epidemiological investigations have reported the overexpression of apoEε4 allele in late-onset patients with AD, both in familial and in sporadic cases (Chia-Chen *et al*., 2013). It has been notedthat the presence of the ε4 allele is not a risk factor by itself, but that the other alleles, especially the ε2 allele, protect against the development of AD (Chia-Chen *et al*., 2013).The apoEgenotype, which represents the susceptibility factor for AD,is mostly associated with the onset of AD before the age of 70 (Jacquier *et al*., 2001; Betard *et al*., 1994). The association between the ε4 allele and risk of late-onset AD may be not as high as initially reported in population-based studies. This indicates that the ε4 allele doesnot lead to AD and its incidence would be reduced by only 14% (Chia-Chen *et al*., 2013). These suggest that the hunt for the additional genes , which are linked with the development of AD at later age - such as mutations in mitochondrial DNA, polymorphisms of intron 8 of the presenilin genes, and variants in the α1- antichymotrypsin and very low density lipoprotein receptor genes - should continue in all earnest (Tanzi*, 2012*). ApoE, one of the major plasma apolipoproteins, is responsible for the transport and metabolism of cholesterol and triglycerides (Weisgraber *et al*., 1994). ApoEissynthesized by astrocytes and is taken up by neurons in the brain (Einstein *et al*., 2001). It may affect metabolism and possibly interact with the microtubule-associated proteins tau and protein 2 in the neuronal cytoplasm (Einstein *et al*., 2001). ApoE influences the transition from soluble Aβ (1-40) peptides into aggregates as evidenced by *in vitro* studies and plays the role of pathological chaperon (Soto *et al*., 1995; Barger *et al*., 1997).In contrast, the complex formation between apoE and Aβ (1-40) may cease aggregate formation by inhibiting fibril extension (Naiki *et al*., 1997). The isoform-specific binding of apoE to Aβ (1-40) (apoE2 binds better than apoE3, and apoE3 much better than apoE4) in conjugation with the epidemiological data suggest that the apparently beneficial effect of the presence of apoE2 may be based on its inhibitory effect on the transition from soluble peptides into pathological amyloid(Carter, 2005).

Animal Models

The mechanisms of AD have been elucidated by experiments usinganimal models. Several transgenic models have been developed inthe last decade (Duff, 2001).Overexpression of transforming growth factor (TGF)β-1 promotes Aβ deposition in cerebral blood vessels and meninges in aged transgenic mice (Ongali *et al*., 2010).TGFβ-1may be a risk for factor for developing AD by promoting amyloidogenesis, as it has been observed thatco-expression of TGFβ-1 in transgenic mice overexpressing APP accelerated the deposition of Aβ. Age-relatedAβ deposits associated with prominentgliosis have been found in transgenic mice expressing mutated APPs, but there have no evidence of neuronal loss (Johnson-Wood *et al*., 1997; Irizarry *et al*., 1997). This indicates that Aβ is not acutely neurotoxic, but can disrupt neuronal processes and induce an inflammatory response. Aβ (1-42/43) have been noticed to increase in mutant PS1 transgenicmice without any abnormal pathology (Borchelt *et al*., 1996; Duff, 2001; Citron *et al*., 1997). Various amyloid deposits far earlier than age-matched singlemutant APP transgenic mice have been developed in mice with co-expression of mutant PS1 and mutant APP (Borchelt *et al*., 1997; Holcomb *et al*., 1998). Both double and single transgenic mice showed changes in behavior before substantial Aβ deposition was apparent (Holcomb *et al*., 1998). This indicates the involvement of Aβwithout any deposits (plaques) in AD pathogenesis, whichindicates towardsthe possible lack of correlation between plaque burden and degree of dementia in humans. Behavioral deficits in the absence of deposits have been detected in transgenic mice overexpressing mutant APP (Saura *et al*., 2005). Phosphorylation/dephosphorylation regulates the mechanisms leading to Aβ deposits and paired helical filaments. Tangle-like phosphorylation of tau and deposition of Aβ maybe induced due to inhibition of phosphatase 1 and 2A by chronic infusion of okadaic acid in rat brain ventricles. Kinases associated with tau phosphorylation or with altered production of Aβ have been indirectly activated by okadaic acid (Arendt *et al*., 1995). Hence a chronic disturbance of the balance between protein phosphorylation and dephosphorylation can lead to the 2 major changes observed in AD. This indicates that Aβ, although it seems to dominate all AD phenomena, is at the end of the pathophysiological cascade.

Conclusion

In the population Alzheimer's disease will become a massive public health problem in future. The risk of Alzheimer's disease in later life mainly due to high systolic blood pressure and high serum cholesterol concentration.Alzheimer's disease (AD) may be instigated by deposition of amyloid β-peptide (Aβ) in plaques in brain tissue. As per amyloid hypothesis, accumulation of Aβ in the brain is the primary influence pouring AD pathogenesis. The disease process, including

formation of neurofibrillary tangles containing tau protein, is anticipated to result from an imbalance between Aβ production and Aβ clearance.

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