

NEW INSIGHTS ON THE INVOLVING OF AMYLOID BETA PEPTIDE IN ALZHEIMER'S DISEASE PATHOLOGY

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder that affects millions of people worldwide causing massive economic burden and the number of cases is expected to rise dramatically. Currently, there is no treatment that can stop or reverse the effects of AD. This review attempts to present the current status of research, bio-pathological approach mechanisms, biomarkers and therapeutic interventions of AD.

INTRODUCTION

Alzheimer's disease (AD) is characterized by successive degradation and destructive neuro human brain structure and affect over 37 million people worldwide (Mount and Downton, 2006), with a loss of over \$ 600 billion in 2010 (Wimo and Prince, 2010). Overall, 5 million new cases of AD are reported annually (Alzheimer's Association, 2015). The risk of developing AD is strongly age, ending in a deterioration in mood, behavior, in performance, knowledge and memory, therefore (Alzheimer et al., 1995), AD is becoming a crisis increasing social with growing life expectancy. Despite this, there is no current treatment that can stop or reverse the effects of AD (Citron, 2010). The disease is closely related to brain pathology involving (a) extracellular amyloid aggregates (known as senile plaques) (SP) formed by A β amyloid and (b) neurofibrillary tangles (NFTs) of tau protein (p-tau) (Belluti et al., 2013; Saido, 2013). Accordingly to amyloid cascade hypothesis, A β is primarily responsible for many of the pathological features of the disease, its oligomers representing the most toxic species (Sakono and Zako, 2010). Accumulation of A β (1-42) plaques inflammatory reactions starts by microglial activation due to pro-inflammatory cytokines in the brain areas that are the most representative: the right neocortex and hippocampus. Moreover, disturbances of the kinase and phosphatase which results in hyperphosphorylation of tau protein, which leads to deterioration and loss of neurons (Thota et al., 2007). Despite existing strong genetic links, including APP and PS-1 mutations, the PS-2 mutation (Bothwell and Giniger, 2000) is the dominant form of sporadic AD. In this regard, AD research deals with mechanisms for early onset of disease with a wider range of factors that lead to sporadic forms, which could be one reason for the failure of the majority of therapeutic trials and lack of preventive measures by more 20 years from proposal amyloid hypothesis (Hicks et al., 2012).

MEANS OF FORMING A β

The A β peptide, derived from the larger amyloid precursor protein (APP), was first isolated as the principal component of amyloid deposits in the brain and cerebrovasculature of AD (Glenner and Wong, 1984; Masters et al., 1985; Selkoe, 2001). Although the function of APP itself has not been resolved, extensive research has advanced our knowledge of how the A β peptide is produced, and how it is subsequently degraded within the brain, or transported out into the periphery. The final amount of A β that accumulates as amyloid deposits within the brain is determined by the interplay of these factors. Changes with disease progression could contribute to the age of disease onset and disease duration.

The enzymatic processes responsible for the metabolism of APP to A β are now reasonably well understood. APP is sequentially cleaved by two membrane-bound endoprotease activities, β - and γ -secretase. β -secretase first cleaves APP to release a large secreted derivative, sAPP β . A fragment of 99 amino acids (CTF β , which begins with the N-terminal aspartyl residue of A β) remains membrane bound, and is in turn rapidly cleaved by γ -secretase to generate A β . Cleavage by γ -secretase is somewhat imprecise, resulting in a C-terminal heterogeneity of the resulting peptide

population. Hence, numerous different A β species exist, but those ending at position 40 (A β 40) are the most abundant (~80-90%), followed by 42 (A β 42, ~5-10%). The slightly longer forms of A β , particularly A β 42, are more hydrophobic and fibrillogenic, and are the principal species deposited in the brain (Giacobini, 2004; Rochette and Murphy, 2002; Selkoe, 2001).

β -Secretase activity is believed to be the rate-limiting step in the amyloidogenic pathway and processes ~10% of the total cellular APP. The remaining APP, close to 90%, is constitutively cleaved by α -secretase (a collection of metalloprotease enzymes), generating sAPP α and the 83 amino acid CTF α . The subsequent γ -secretase cleavage of CTF α produces the more benign p3 fragment instead of A β . γ -Secretase cleavage of either membrane bound CTF also generates a cytosolic element, AICD (APP intracellular domain, sometimes referred to as CTF γ), which may play a role in signal transduction. Because of their essential role in the generation of A β , both β - and γ -secretase are considered to be prime targets for the development of anti-AD pharmaceuticals (Murphy et al., 1999; Shah et al., 2005).

γ -Secretase is now known to be a multisubunit enzyme composed of the proteins APh1, PEN2, nicastrin, and presenilin (PS1 or PS2). The enzyme complex likely contains one copy of each subunit, and is responsible for the cleavage of multiple membrane proteins in addition to APP. Although the exact functional roles of each component have yet to be fully elucidated, presenilin is believed to form the active site of the aspartyl protease (Kessels et al., 2010; Querfurth and LaFerla, 2010), and nicastrin likely serves as a substrate docking subunit (Scheuner et al., 1996). All four components are necessary for γ -secretase to mature and function correctly (Kosicek and Hecimovic, 2013). γ -Secretase has a relatively novel mechanism in that it cleaves within the lipid bilayer and can only process substrates that are first cleaved by another protease to remove a large ectodomain region. The enzyme does not have identified specific sequence requirements for substrate recognition, and cleavage within the membrane is instead controlled by a variety of other factors, such as the length of the transmembrane domain (Bennett et al., 2000; Giacobini, 2004). Although the amount of γ -secretase activity does not appear to increase in AD, alterations in γ -secretase activity leading to the production of longer forms of A β are the major genetic cause of early-onset, familial AD (Hussain et al., 2000; Yan et al., 2001), an effect that can be mimicked with a variety of allosteric γ -secretase modulating agents (Basi et al., 2003).

β -Secretase is a membrane-bound aspartyl protease, but one that cleaves APP and its other substrates outside of the bilayer (Holsinger et al., 2002). There are two major forms of the enzyme, BACE1, and BACE2, which are >65% homologous. The major form of the enzyme responsible for A β production, BACE1, is highly expressed in brain, but is also found at lower levels in other organs (Fais et al., 2013; Shah et al., 2005). In contrast, the second form of the enzyme, BACE2, is low in the brain but is present in most peripheral tissues at higher levels (Rochette and Murphy, 2002). The knockout of BACE1 in mice leads to a massive reduction in the levels of the downstream products of the enzyme (A β and CTF β) in brain. Although these studies indicate that BACE1 is the major β -secretase activity in brain, some residual activity might be attributable to BACE2 (Marcinkiewicz and Seidah, 2000), and both forms of BACE can compete for substrate (Hussain et al., 2000). β -Secretase activity and protein are both significantly increased in sporadic AD. This effect shows a brain regional selectivity that roughly parallels disease affected regions, and is related to both plaque burden and disease duration. β -Secretase activity has also been seen to increase with age in rodents and nonhuman primates, although these species do not develop AD. Recently, evidence has emerged that cathepsin B or cathepsin D may also be able to serve as β -secretase-like enzymes under some circumstances, although this view is controversial.

FACTORS INFLUENCING THE INITIATION AND PROGRESSION OF AD

The factors influencing the initiation and progression of the disease that have a role in the pathophysiology of AD are A β (1-42)/A β (1-40) oligomers, oxidative stress, proinflammatory cytokines produced by activated glial cells, changes in cholesterol homeostasis and changes in the cholinergic nervous system (Allam et al., 2008).

LIPID RAFT REDOX SIGNALING

Lipid raft microdomains are able to form membrane microdomains or platforms on different simulations, including redox signaling platforms, serving as a signaling mechanism critical for mediating or regulating cellular activities and functions. In particular, installation of NADPH oxidase subunit and binding to other receptors of related effector and control components, which serve to turn in the activation of NADPH oxidase and the redox regulation of downstream cellular functions (Jin et al., 2011).

OXIDATIVE STRESS AND NEURONAL DEATH

Increasing evidence highlights the role played by oxidative stress in AD (Cioanca et al., 2013; Hritcu et al., 2014). Central administration of A β induced learning and memory deficits in rats (Hritcu et al., 2015), cholinergic dysfunction (Olariu et al., 2001) and neuronal apoptosis in rats (Hritcu et al., 2014; Ruan et al., 2010), as well as increased the oxidative stress (Bagheri et al., 2011) and promoted neuroinflammation (Wang et al., 2012).

Elevated levels of reactive oxygen species (ROS) is one of the most important age-related harmful agents produced by normal mitochondrial activity, increased levels of glutamate, inducing acceleration characteristic neurodegenerative AD (Huber et al., 2006). A β stimulates the accumulation of hydrogen peroxide in cultured hippocampal neurons which causes oxidative damage to cellular phospholipid membranes thus suggesting the role of lipid peroxidation in the development of AD. The loss of membrane integrity due to A β and free radicals leading to cellular dysfunction, such as inhibition of the ionic motor of the ATPase, loss of calcium homeostasis, inhibition of glial glutamate-dependent Na⁺ absorption system, loss of function of the carrier protein, disrupting signaling pathway and activation of nuclear transcription factors and apoptotic pathways (Allam et al., 2008).

INFLAMMATION AND NEURONAL DEATH

The significant increase in dose-dependent production of prointerleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), monocyte chemoattractant protein-1, macrophage inflammatory peptide-1, IL-8, mitogen activation of the pathway of protein kinase and macrophage colony stimulating factor as were observed after exposure to pre-aggregated A β (1-42) as foreign material, because during brain development in young nervous system (Allam et al., 2008). The involvement of the inflammatory process in the pathogenesis of AD is further supported by the observation that inhibiting or neutralizing TNF actions could be benefits for these patients with AD disease (Allam et al., 2008; Rosenberg, 2006).

CHOLINERGIC SYSTEM AND AD

A primary clinical symptom of Alzheimer's dementia is progressive deterioration of memory and learning capacity. There is a profound loss in the cholinergic system of the brain, including dramatic loss level acetylcholine, choline uptake and acetylcholine (ACh) from the neocortex and hippocampus and there is a small number of cholinergic neurons in the brain and core basal Meynert, which are closely linked to cognitive deficits in AD. Pharmacological actions that improve or block ACh levels fall through cholinergic neurotransmission therefore to improve the known improvements in learning and memory in AD (Allam et al., 2008; Giacobini, 2004). A β could increase the generation of free radicals and induce inflammation that may lead to profound loss of a cholinergic system of the brain (Allam et al., 2008). ACh also has anti-inflammatory action and, therefore, decreasing its level may further aggravate the inflammatory process and progression of AD. This cholinergic anti-inflammatory pathway" works by inhibiting the production of pro-inflammatory cytokines early TNF, IL-1, and suppresses the expression of NF - KB activation. Furthermore, systemic injection of IL-1 decreases extracellular ACh in the hippocampus. In addition, the IL-1 is APP mRNA positive cells and the ability to promote APP gene expression suggests that IL-1 plays an important role in AD (Pavlov and Tracey, 2004). Lipid raft location was recently linked to acetylcholinesterase (AChE), although its functional implications are still unclear (Hicks et al., 2011). AChE inhibition by compounds such as rivastigmine or galantamine is a major treatment option for the cure of cognitive impairment seen in early stages of AD. Also, inhalation of the juniper volatile oil presents both antiacetylcholinesterase and antioxidant activities in A β (1-42) rat model of AD and may contribute to increase the levels of acetylcholine in cholinergic neurons, while simultaneously helping to prevent further degradations caused by radical oxygen species (Cioanca et al., 2015). AChE exists in a number of different molecular forms (monomeric - G1, dimeric - G2, tetrameric - G4). The tetrameric G4 form is predominant in the brain. In AD, G4 AChE levels in the brain decrease as the disease progresses, while the G1 SG2 levels increase somewhat compared to normal brain. In some regions of the AD brain pathology, practically all the pain is located in the complex, which lead to the suggestion that AChE may promote Ap aggregation (García-Ayllón et al., 2010). It was proposed a direct interaction between A β and AChE, binding occurs at the peripheral anionic (PAS) enzyme. Those inhibitors of AChE holding PAS (e.g., propidium) showed the most significant reduction in fibril formation because the active site is not required for interaction with the A β . In addition, monoclonal antibodies directed against aspartyl proteinase (SAP) inhibit the formation of fibrils, which has led to the development of blocking PAS as well as compounds DUO, occupying also the active site. They show inhibitory activity on AChE and fibril formation and inhibition of A β 40 have been suggested as potential therapeutic agents targeting novel AD two facets of the disease (Alptüzün et al., 2010). AChE is a transmembrane protein, rather it is anchored to the plasma membrane rich in proline membrane anchor, which is a type I transmembrane protein, and may be acylated. The first contains the cholesterol recognition amino acid consensus motif that first seizes the lipid rafts and, therefore, also part of AChE is associated with plugs (Alptüzün et al., 2010).

EXOSOMES AND microRNAs

Plasma membrane-derived exosomes vesicles with a diameter 30-90 nm are secreted into the extracellular milieu (Vârna, Artenie, 2007; Fais et al., 2013). Besides containing different proteins

and the molecular components of cells reflective of origin, these vesicles contain microRNAs as their most abundant nucleic acids (Alexandrov et al., 2012). The body may be capable of paracrine transfer of genetic information between cells or in the local environment of the brain or spinal or systemically throughout the circulation, at least in part dependent on the plasma membrane mediated biological mechanisms (Alexandrov et al., 2012; Fais et al., 2013).

DIETARY AND ENVIRONMENTAL FACTORS

Environmental factors influencing food and plasma membrane effects such as flexibility and lipid raft may not be relevant to amyloidogenesis but also paracrine microRNA trafficking and the spread of these mobile genetic signals and soluble intercellular only. For example, biophysics of the plasma membrane, dynamic, and lipid raft field disturbance cholesterol statins would not be able to take only effect on cholesterol incorporation into the membranes and the formation of lipid raft, also on the exocytosis of exosomes (Fais et al., 2013; Kosicek and Hecimovic, 2013; Murphy and LeVine, 2010). More cholesterol can disrupt the structure of membrane biophysics and reorganize lipid raft domains, the protein, and protein-protein interactions lipids, contribute to membrane homeostatic dysfunction mediated APP neurobiology (Lukiw, 2013; Murphy and LeVine, 2010). The involvement of potential AD neurotrophic viral infection that involves processes that are plasma membrane-mediated proinflammatory and innate immune response elusive brain (Alexandrov et al., 2012; Kosicek and Hecimovic, 2013).

DIAGNOSTIC

Certain DNA diagnosis can only be done a postmortem. However, today, specialized clinics, using a combination of tools that include taking a history of the disease on patients and their families, as well as evaluating cognitive function by neuropsychological tests in combination with neuroimaging (CT, MRI and PET) to rule out other causes of dementia (Blennow et al., 2010) can diagnose AD with accuracy greater than 95%. Neurological tests, which are still the gold standard for diagnosis of AD are largely accurate in identifying people with dementia already developed. It provides structural MRI brain atrophy measures, reflecting the loss of dendrites, synapses, and neurons (Kosicek and Hecimovic, 2013).

CONCLUSIONS

AD is a devastating age-related neurodegenerative disease, which has a serious impact on an economic development system and healthcare worldwide. Although AD has been studied for over 100 years since the 1906, its exact pathogenity and mechanism remain to be clarified. Also, up to now there are no discovered treatments or diagnostic methods ideal for AD. The combination of a poor diet, unhealthy lifestyle, vascular problems, and genetic factors may increase the likelihood precursor of amyloid and the advanced rapid onset AD. Although the role of lipid rafts in the pathogenesis of AD is still controversial (lipid rafts that are controversial in itself), it is clear that specific membrane platforms are involved in APP, β - and γ - secretase co-location, in APP processing and formation of pathogen A β . Phospholipids provide an optimal environment for protein interactions.

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