



Alzheimers Disease: A Brief Overview

R K SUNDARAM, A K NAMBIAR, P SUNDARAM*

Recombinant Technologies, LLC. 1090 Meriden Waterbury Rd, Cheshire, CT 06410, USA

Article Info: Received: March 3rd, 2014; Accepted: March 18th, 2014

Introduction

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is an irreversible, progressive neurodegenerative disorder clinically characterized by memory loss and cognitive decline. The principal risk factor for AD is increasing age. Absence of biologic markers makes direct pathologic examination of brain tissue derived from either biopsy or autopsy as the only definitive method for establishing a diagnosis of AD [1]. Macroscopically, there is gross cortical atrophy and microscopically, widespread cellular degeneration and neuronal loss. These changes are accompanied by intracellular neurofibrillary tangles (NFT) and extracellular amyloid plaques [2]. The main structural part of NFT is a normal constituent of cellular microtubules, but in AD is an abnormally phosphorylated form, known as tau protein [3] is present.

A number of *in vitro* and *in vivo* studies have shown A β peptides to be directly toxic to neurons, leading to the aggregation and secondary phosphorylation of the tau protein [4]. Accumulation of A β peptides leads to amyloid plaques [extracellular aggregates of beta-amyloid of about 50–100 μ m in diameter] intimately surrounded by dystrophic axons and dendrites, reactive astrocytes, and activated microglia. The A β hypothesis postulates that the progressive rise, either by increased production or decreased clearance, in A β cerebral levels is the central event in the pathogenesis of AD [5]. Genetic evidence not only indicates that the metabolism of A β is clearly linked to the disease, but also points to specific metabolic

pathways with the potential for developing diagnostic and therapeutic agents, and though there is a poor correlation between the density of deposits and disease severity, there is a correlation between the levels of soluble A β and cognitive impairment [6].

The Amyloid Hypothesis

Through the years, several hypotheses have been postulated to explain the molecular mechanisms leading to AD, but the A β theory is the dominant etiologic paradigm at this time [7] because it is the only one that can best or most comprehensively articulate the current available knowledge regarding the cellular, molecular, and functional alterations observed in AD. There is a wealth of histopathological, biochemical, genetic, animal model, and functional neuroimaging data that support the key role of A β in the pathogenesis of AD, but no alternative hypothesis has emerged in the past two decades of intensive AD research. The main criticisms of the amyloid hypothesis has come from some of the interpretations of the work of Braak and Braak [8,9], who stated that neurofibrillary degeneration of cell bodies and their neurites not only predate morphologically detectable amyloid plaques but they also increase gradually with age. However, as Hardy and Selkoe point out [10], the postmortem cases used to establish the Braak Stage I neuropathology criteria were non-demented older individuals, in whom it is impossible to determine whether their neurofibrillary changes represents early stages of AD or a different process altogether, because it has been well established in patients with Down syndrome that A β deposition predates the formation of neurofibrillary tangles [11].

Genes and A-beta: To date only four different genes, associated with either A β production or removal, are implicated in the pathophysiology of AD. They are

*Corresponding Author

P Sundaram, PhD

Recombinant Technologies, LLC., 1090 Meriden Waterbury Rd, Cheshire, CT 06410, USA.

Email: pazhani_sundaram@yahoo.com



Presenelin1, Presenelin2, Apolipoprotein E and Amyloid precursor protein [PS1, PS2, ApoE and APP]. Abnormalities in these genes manifest as a similar clinical entity, all leading to increased levels of A β and to A β buildup in the brain [12]. APOE ϵ 4 is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an APOE ϵ 4 allele does not mean that a person will definitely develop Alzheimer's. Dozens of studies have confirmed that the APOE ϵ 4 allele escalates the risk of developing Alzheimer's, but how that happens is not yet understood. These studies also help explain some of the variation in the age at which Alzheimer's disease develops, as people who inherit one or two APOE ϵ 4 alleles tend to develop the disease at an earlier age than those who do not have any APOE ϵ 4 alleles. Using a relatively new approach called **genome-wide association study (GWAS)**, researchers have identified a number of genes in addition to APOE ϵ 4 that may increase a person's risk for late-onset Alzheimer's, including BIN1, CLU, PICALM, and CR1. Finding genetic risk factors like these helps scientists better understand how Alzheimer's disease develops and identify possible treatments to study.

A β is Toxic

A common factor in the postulated mechanisms of A β toxicity is the oligomerization of A β , whether as dimers, trimers, protofibril, or as fully formed fibrils [13]. Despite several attempts, the main obstacle to the full validation of the A β hypothesis lies in the identification in vivo of the specific neurotoxic A β soluble oligomer. There is an inverse relationship between amyloid burden and oxidative damage in vivo as assessed by 8-OH guanosine levels in AD-affected tissue [14]. Several lines of evidence demonstrate that diffusible soluble A β oligomers, but not monomers or insoluble amyloid fibrils, are toxic to cultured neurons and responsible for the neurotoxicity and synaptic dysfunction present in AD [15]. Microinjection into rats of culture medium containing soluble oligomers of human A β (in the absence of monomers and amyloid fibrils) inhibits long-term potentiation in the hippocampus [16]. A β fibrils injected into the brain of aged primates induces local gliosis and neuronal loss [17]. Similar changes are observed in young APP transgenic mice before plaque formation, though the diversity and unstable nature of A β intermediates, from monomers to mature fibrils, makes it difficult to identify the specific species responsible for the neurotoxic effects.

Mechanisms of A β Toxicity

As a result of its high lipid content and high oxygen consumption, the brain is particularly susceptible to oxidative stress. Several mechanisms have been proposed to explain A β neurotoxicity: production of reactive oxygen species (ROS) such as hydrogen peroxide, nitric oxide, superoxide, highly reactive hydroxyl radicals and nitric oxide (NO), excitotoxicity with intracellular calcium accumulation, decreased membrane fluidity, energy depletion, alteration of the cytoskeleton, and

inflammatory processes. All of these events converge into similar pathways of necrosis or apoptosis, leading to progressive dysfunction and loss of specific neuronal cell populations [18,19].

Extra- and intracellular production of ROS initiates and promotes neurodegeneration in AD [20]. Evidence of oxidative stress in AD is manifested through higher levels of oxidized proteins, advanced glycation, lipid peroxidation products, formation of toxic species, such as peroxides, alcohols, aldehydes, ketones, cholesterol oxide (toxic to microglial cells), cholestenone, altered gene expression, damaged DNA, and induced apoptosis. A β ¹⁻⁴² induces lipoperoxidation of membranes and lipid peroxidation products [21,22]. Lipids are modified by ROS and there is a high correlation between lipid peroxides, antioxidant enzymes, amyloid plaques, and NFT in AD brain. Markers of oxidative DNA damage have been localized in plaques and NFT. Catalase, superoxide dismutase (SOD), glutathione peroxidase, and glutathione reductase, indicators of cellular defense mechanisms against oxidative stress, are increased in the hippocampus and amygdala of AD patients. DNA bases are vulnerable to oxidative stress damage involving hydroxylation, protein carbonylation, and nitration. ROS-induced calcium influx, via activation of glutamate receptors, triggering an excitotoxic response leading to cell death have also been observed in AD brains.

Animal models for AD

Animal disease models are considered important in the development of drugs for Alzheimer's disease. Various transgenic models have been developed. None of the current models of Alzheimer's disease have either construct or predictive validity, and no model probably ever will. Clearly, specific animal experiments contribute to our understanding of the disease and generate hypotheses. Ultimately, however, the hypothesis can only be tested in human patients and only with the proper tools. These tools are a pharmacologically active intervention (in humans) and a clinical trial suited to evaluate the mechanism of action. Integration of knowledge in quantitative (sub) models is considered important if not essential in this process [23].

Drug development for AD

Currently, more than 90 drugs are in clinical trials for Alzheimer's disease, and more are in the pipeline awaiting Food and Drug Administration (FDA) approval to enter human testing. Monoclonal antibodies like Solanezumab, Bapineuzumab, Gantenerumab, Ponezumab, MABT5102A, GSK933776A and BAN-2401 are in the clinical trials. Additionally, intravenous immunoglobulins- Gammagard (IGIV 10%) is also undergoing clinical trial. We have investigated the affinity of small peptides derived from the Abeta-42 sequence, in particular KLVFF, and have shown to be effective binders of Abeta peptides and thus could be useful in delaying progression of the disease. We have taken advantage of this property by generating the retro-inverso

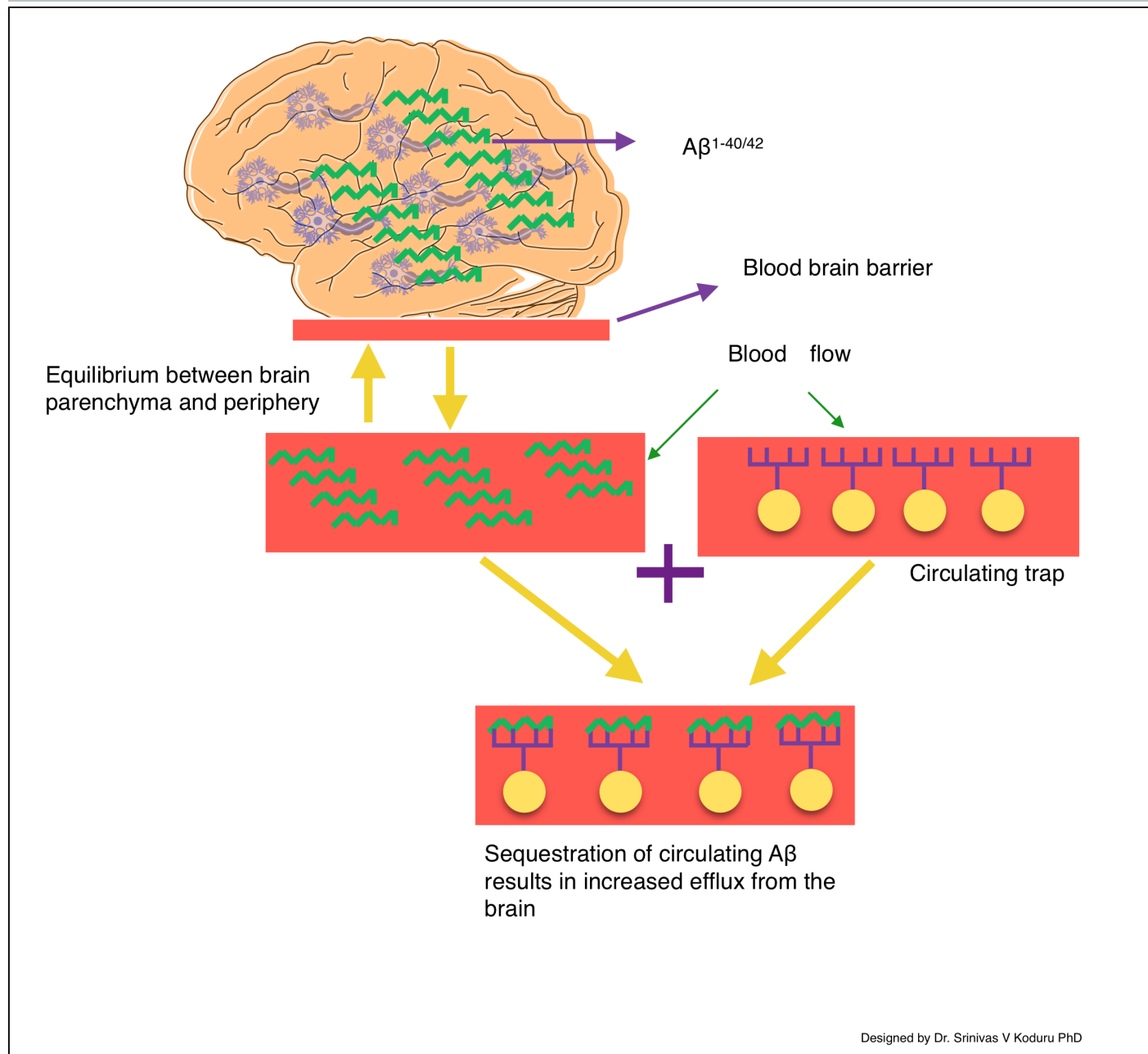


Figure 1: Peripheral sink for amyloid using non immunogenic methods: Schematic diagram gives a pictorial description on the method in which the peripheral sink works. $A\beta^{1-40/42}$ is in equilibrium between the brain and circulation. Circulating traps bind $A\beta^{1-40/42}$ and clear it from the brain. This leads to lesser amyloid availability for deposition in plaques.

(RI) version of this peptide, fflvk, in different formats. We hypothesize that detox gel incorporating RI peptides will act like a 'sink' to capture the Abeta peptides from the surrounding environment. We tested these detox gels for their ability to capture biotinylated Abeta-42 peptides in vitro. The results showed that the detox gels bound Abeta-42 peptides effectively and irreversibly. Gels incorporating the tetramer RI peptide exhibited maximum binding capacity. The detox gel could be a potential candidate for treatment strategies to deplete the brain of toxic amyloid peptides [24].

Conclusions

Alzheimer's disease is a neurodegenerative disorder branded by a

slow but unrelenting progressive cognitive decline and memory loss. It has a overwhelming consequence not only on the sufferer but also on their caregivers, with a incredible socioeconomic impact not only on families but also on the health care system which will increase in the upcoming years. The neuropathologic hallmarks of the disease are extracellular deposits of $A\beta$ in senile plaques, NFT, with selective neuronal and synaptic loss in cortical areas of the brain associated with cognitive and memory functions. $A\beta$ is the main constituent of the amyloid plaques. All the available evidence points at the breakdown of the economy of $A\beta$ as playing the key role in AD pathogenesis. Genetic

studies have shed light on the pathogenesis and progression of AD. To date, four genes have been linked to autosomal dominant, early-onset familial AD: APP, PS1, PS2, and ApoE. All mutations linked to APP and PS proteins lead to an increase in A β production. A β not only aggregates into amyloid plaques but is toxic while having an effect on intracellular tangle formation and other factors (e.g., cytokines, neurotoxins, etc.) that also play an important role in the neurotoxic progression of AD. A β is neurotoxic through a number of possible mechanisms including oxidative stress, excitotoxicity, energy depletion, inflammatory response, and apoptosis, and while the precise mechanism by which A β might produce synaptic loss and neuronal death is controversial, it is believed that a toxic oxidative interaction between various metal species and A β triggers an oxidative response with free-radical production leading to progressive disruption of neuronal function and eventually to cell death. At this point, there is no cure for AD. Recently, Mapstone et al described a lipidomic approach to detect preclinical Alzheimer's disease in a group of cognitively normal older adults. They validated a set of ten lipids from peripheral blood that predicted phenocconversion to either amnesic mild cognitive impairment or Alzheimer's disease within a 2–3 year timeframe with over 90% accuracy. The test could be a “potentially” huge development but could take many years to develop [25]. A deeper understanding of the molecular mechanism of A β formation, degradation, and neurotoxicity is being deciphered into new neuroimaging and therapeutic approaches. Most of the approved palliative treatment regimens involve the use of acetylcholinesterase inhibitors, glutamatergic agents, nonsteroidal anti-inflammatory drugs, as well as antioxidants. The most promising approaches focus on either reducing A β formation through secretase inhibitors or increasing its removal either by immunotherapy or administration of retro-inverse peptides aiming at blocking the formation of A β oligomers and fibrils therefore inhibiting neurotoxicity.

References

- Urbanelli L, Magini A, Ciccarone V, Trivelli F, Polidoro M, Tancini B, Emiliani C: **New perspectives for the diagnosis of Alzheimer's disease.** *Recent patents on CNS drug discovery* 2009, **4**:160-181.
- Blurton-Jones M, LaFerla FM: **Pathways by which A facilitates tau pathology.** *Current Alzheimer Research* 2006, **3**:437-448.
- Iqbal K, Grundke-Iqbal I: **Ubiquitination and abnormal phosphorylation of paired helical filaments in Alzheimer's disease.** *Molecular neurobiology* 1991, **5**:399-410.
- Imahori K, Hoshi M, Ishiguro K, Sato K, Takahashi M, Shiurba R, Yamaguchi H, Takashima A, Uchida T: **Possible role of tau protein kinases in pathogenesis of Alzheimer's disease.** *Neurobiology of aging* 1998, **19**:S93-S98.
- Selkoe DJ: **Aging, amyloid, and Alzheimer's disease: a perspective in honor of Carl Cotman.** *Neurochemical research* 2003, **28**:1705-1713.
- Selkoe DJ: **Alzheimer's disease beyond 1994: The path to therapeutics.** *Neurobiology of aging* 1994, **15**:131-133.
- Hayden EY, Teplow DB: **Amyloid β -protein oligomers and Alzheimer's.** 2013.
- Braak H, Braak E: **Diagnostic criteria for neuropathologic assessment of Alzheimer's disease.** *Neurobiology of aging* 1997, **18**:S85-S88.
- Braak H, Braak E: **Argyrophilic grain disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria.** *Journal of neural transmission* 1998, **105**:801-819.
- Hardy J, Selkoe DJ: **The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics.** *Science* 2002, **297**:353-356.
- Guiroy DC, Miyazaki M, Multhaup G, Fischer P, Garruto RM, Beyreuther K, Masters CL, Simms G, Gibbs CJ, Gajdusek DC: **Amyloid of neurofibrillary tangles of Guamanian parkinsonism-dementia and Alzheimer disease share identical amino acid sequence.** *Proceedings of the National Academy of Sciences* 1987, **84**:2073-2077.
- Hutton M, Pérez-Tur J, Hardy J: **Genetics of Alzheimer's disease.** *Essays Biochem* 1998, **33**:117-131.
- Soto C: **Unfolding the role of protein misfolding in neurodegenerative diseases.** *Nature Reviews Neuroscience* 2003, **4**:49-60.
- Cuajungco MP, Goldstein LE, Nunomura A, Smith MA, Lim JT, Atwood CS, Huang X, Farrag YW, Perry G, Bush AI: **Evidence that the β -amyloid plaques of Alzheimer's disease represent the redox-silencing and entombment of A β by zinc.** *Journal of Biological Chemistry* 2000, **275**:19439-19442.
- Rijal Upadhaya A, Capetillo-Zarate E, Kosterin I, Abramowski D, Kumar S, Yamaguchi H, Walter J, Fändrich M, Staufenbiel M, Thal DR: **Dispersible amyloid β -protein oligomers, protofibrils, and fibrils represent diffusible but not soluble aggregates: their role in neurodegeneration in amyloid precursor protein (APP) transgenic mice.** *Neurobiology of aging* 2012, **33**:2641-2660.
- Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ: **Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo.** *Nature* 2002, **416**:535-539.
- Leung E, Guo L, Bu J, Maloof M, Khoury JE, Geula C: **Microglia activation mediates fibrillar amyloid- β toxicity in the aged primate cortex.** *Neurobiology of aging* 2011, **32**:387-397.
- Tabner BJ, Turnbull S, El-Agnaf O, Allsop D:

- Production of reactive oxygen species from aggregating proteins implicated in Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases. *Current topics in medicinal chemistry* 2001, 1:507-517.
19. Lahiri DK, Maloney B: **Beyond the signaling effect role of amyloid- β 42 on the processing of APP, and its clinical implications.** *Experimental neurology* 2010, 225:51-54.
20. Prasad KN, Hovland AR, Cole WC, Prasad KC, Nahreini P, Edwards-Prasad J, Andreatta CP: **Multiple antioxidants in the prevention and treatment of Alzheimer disease: analysis of biologic rationale.** *Clinical neuropharmacology* 2000, 23:2-13.
21. Hegde ML, Hegde PM, Rao K, Mitra S: **Oxidative genome damage and its repair in neurodegenerative diseases: function of transition metals as a double-edged sword.** *Journal of Alzheimer's Disease* 2011, 24:183-198.
22. Sultana R, Perluigi M, Allan Butterfield D: **Lipid peroxidation triggers neurodegeneration: A redox proteomics view into the Alzheimer disease brain.** *Free Radical Biology and Medicine* 2013, 62:157-169.
23. Laurijssens B, Aujard F, Rahman A: **Animal models of Alzheimer's disease and drug development.** *Drug Discovery Today: Technologies* 2013, 10:e319-e327.
24. Sundaram P, Sundaram RK, Kasinathan C, Stein S: **Detoxification Depot for Amyloid Peptides.** *Current Alzheimer Research* 2008, 5:26-32.
25. Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH, Hall WJ, Fisher SG, Peterson DR, Haley JM: **Plasma phospholipids identify antecedent memory impairment in older adults.** *Nature medicine* 2014.

Note: VRI Press, Vedic Research Inc. is not responsible for any data in the present article including, but not limited to, writeup, figures, tables. If you have any questions, directly contact authors.

Visit us @ www.vedicjournals.com : DOI: <http://dx.doi.org/10.14259/mn.v1i1.106>

Copyright © 2013-2014 VRI Press, USA. All rights reserved.


Authors Column