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Editorial Open Access

Metal Exposure and Alzheimer's Pathophysiology

Xudong Huang[1*], Jack T. Rogers[1], Charles R. Vanderburg[2], Barry Lai[3] and Alpaslan Dedeoglu[4]

[1]*Department of Psychiatry, Neurochemistry Laboratory, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA*

[2]*Department of Neurology, Advanced Tissue Resource Center, Harvard NeuroDiscovery Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA*

[3]*X-ray Science Division, Argonne National Laboratory, Argonne, IL 60439, USA*

[4]*Translational Neurotherapeutics Laboratory, VA Boston Healthcare System and Department of Neurology, Boston University Alzheimer's Disease Center, Boston University School of Medicine, Boston, MA 02130, USA*

Alzheimer's disease (AD) is the most common form of senile dementia that affects 5.4 million Americans, and at least $183 billion was spent in 2011 on management of AD and related dementia patients. The situation is worsening as our aging population is burgeoning. By 2050, the projected number of AD patients could range from 11 to 16 million people in the United States alone if neither effective cure nor preventive measure for AD is identified. As such, AD has quickly become a pandemic and exacted a huge socioeconomic toll [1]. The National Alzheimer's Project Act (NAPA) that has been passed by the Congress and signed by the President Obama is merely an urgent call for fighting these debilitating medical conditions.

AD is manifested by a gradual onset of a progressive and irreversible cognitive decline. Memory impairment appears in the earliest stage of the disease followed by motor and sensory impairment in the later stages [2]. AD is a genetically complex disease. The majority of AD cases are sporadic while 5-10% of cases are early-onset familial AD (FAD) with an autosomal dominant inheritance pattern. The neuropathology of AD is characterized by the accumulation of insoluble Aβ amyloid peptides, neurofibrillary tangles (NFTs, the misfolded microtubule-associated tau protein), neuropil threads, and neuronal losses in postmortem AD brains [3,4].

As shown in the Figure 1 from one of our recent review paper [5], Aβ amyloid peptides (39-43 amino acid residues, ≈ 4 kDa), the main constituents of both senile plaques and cerebrovascular amyloid deposits [3,4], are generated from a much larger metalloprotein-amyloid precursor protein (APP) [6-8]. APP cleavage by α-secretase generates neurotrophic APP(s), while its synergistic cleavage by β- and γ-secretases leads to production of a pool of Aβ peptides with carboxyl-terminal heterogeneity [9]: Aβ1-40 (40 amino acid residues) is the major soluble Aβ species, which is found in the CSF at low nanomolar concentrations [10]; Aβ1-42 (42 residues) is a minor Aβ species, but more neurotoxic than Aβ1-40, and is heavily enriched in interstitial plaque amyloid. However, the amyloid cascade hypothesis remains to be fully validated as AD is a polygenic and multifactorial complex disease [11]. Although exact AD etipathology remains to be fully elucidated, brain Aβ amyloidosis is still considered to be one of AD neuropathological hallmarks. A recent genetic study has identified a coding mutation (A673T) in APP gene. This mutation is close to β-secretase action site, and it can engender 40% reduction in Aβ amylodosis and protect against AD and cognitive decline in non-AD seniors. This provides further support for the essential role of Aβ amyloidosis in AD pathology [12]. However, environmental risk factors that directly interact with AD pathogenic pathways and contribute to AD pathophysiology are not well studied [11].

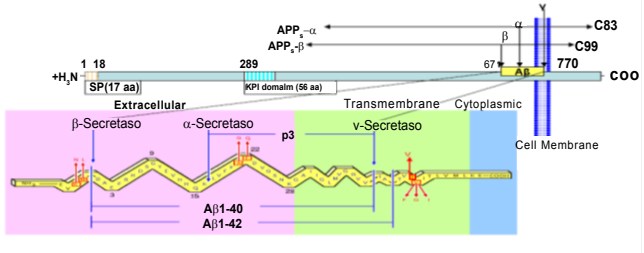

Figure 1: Schematic illustration of APP protein and its Aβ product after cleavage by α-, β- and γ-secretases. β- and γ-secretase cleaves on the N- and C-terminal ends of the Aβ region respectively. γ-Secretase cleavage yields a 39-43 amino acid product. Long and more fiblillogenic and neurotoxic 42-43 amino acid Aβ species are implicated in AD pathogenesis and may seed the formation of Aβ40 fibrils. Mutations in the APP gene and in genes encoding proteins known as presenilins increase the production of long Aβ.

Numerous experimental data indicate that abnormal brain metal metabolism is intimately involved in AD pathology [11,13-17]. The gene expression profile of AD brain implicates the dysregulation of cerebral metal metabolism [18]. Compared to age-matched controls, gene expression levels for metal regulatory proteins such as metallothionein III (MT-III) and metal regulatory factor-1 (MTF-1) decreased more than 4-fold in AD brain [19]. Moreover, MT-III protein concentration was reduced in AD brain [20,21]. In addition, biometals such as Fe, Cu, and Zn interact with Aβ amyloid peptides and APP in vitro, implying that they may promote Aβ amyloid pathogenesis *in vivo* [11]. Moreover, it has been recently demonstrated that low levels of Cu exposure disrupt cerebral Aβ homeostasis by influencing its production and clearance [22]. These data indicate that exposure of metals such as Cu could be an environmental risk factor that contributes to AD pathophysiology. As such, Alzheimer's metallobiology has emerged as an active field in AD research. Based on brain metal hypothesis [23], a modified 8-hydroxyquinoline analogue and a Cu/Zn ionophore- PBT2 has shown positive effects in a Phase IIa double-blind, randomized, placebo-controlled clinical trial [24].

Our group has first shown that the 5'-untranslated region (5'UTR) of APP mRNA has a functional metal-response element [25], and Fe, Cu, and Zn ions are able to interact with APP directly and promote its translation via its 5'UTR of mRNA in a dose-dependent manner [26]. Thus, 5'UTR of APP mRNA seems likely to be a key target intimately

***Corresponding author:** Xudong Huang, Department of Psychiatry, Neurochemistry Laboratory, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA, Tel: 617-582-4711; E-mail: Huang.Xudong@mgh.harvard.edu

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associated with metal-mediated APP processing and Aβ homeostasis. Indeed, our recent in vitro study further indicates that blocking of 5'UTR of APP mRNA attenuates neural APP and Aβ production [27]. It further suggests that the 5'UTR of APP mRNA, which is a metal-responsive regulator for APP translation, may potentially influence Alzheimer's Aβ amyloid pathology *in vivo*. However, further studies are needed on *in vivo* effects and associated redox stress, neuroinflammatory responses, and cognitive function deficits of metals such as Cu upon the 5'UTR of APP mRNA to fully appreciate potential therapeutic value of this novel and potentially druggable target.

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