Commentary

Metal Ions & Alzheimer's Disease: The Inorganic Chemistry Perspective

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Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder and the most common cause of dementia in aging population. The disease was named after the German psychiatrist and neuropathologist Aloysius Alzheimer as he described in 1906 for the first time the presence of protein assemblies which were later named as amyloid plaques and neurofibrillary tangles. AD has become a significant focus of research in last few decades for the scientists across subject boundaries. There are ~47 million patients affected worldwide, which is expected to quadruple by 2050. More than 60% of people with dementia are from low and middle income countries like India. This number is expected to rise to more than 70% by 2050. Dementia is an acquired syndrome which is characterized by a group of symptoms mainly loss or decline in memory, difficulties with language, problem-solving and other cognitive abilities to perform everyday activities. Unfortunately, due to the lack of early warning symptoms, the disease remains undetected until the advanced stage. Early detection of AD is still difficult even after a great deal of research leading to many revelations about the disease pathology. The emotional and physical cost for the disease is really high as people in the final stages of the disease are nearly bed-bound and need constant attention [1].

Science Associated with AD

The prime pathological changes associated with AD are the presence and accumulation of extraneuronal senile plaques commonly known as beta-amyloid plaques and hyperphosphorylated neurofibrillary tangles of tau protein inside neurons. Other brain changes include altered levels of prime neurotransmitters, inflammation, atrophy or shrinkage of brain, oxidative stress, metal ion dyshomeostatis, impaired energy metabolism and reduced glucose uptake, diabetes-like pathologies, elevated homocysteine and abnormal expression of homeostatic metalloproteins such as metallothioneins [2]. According to the classical Amyloid Cascade Hypothesis, amyloid plaques are de-

posits of Aβ peptide which are formed from sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases as depicted in Figure 1 [3]. Aβ peptides spontaneously aggregate into soluble oligomers and amyloid fibrils which ultimately get deposited as senile plaques. Accumulation of beta-amyloid plaques eventually lead to neuronal cell death by interfering with neuron-to-neuron communication at synapses, while the transport of nutrients and other essential molecules is blocked inside neurons due to tangles of tau protein. The lack of clinical success of anti-amyloid drugs has led to the expansion of the amyloid cascade hypothesis. Various anomalies, such as the observations that neuron loss in AD is not correlated to amyloid load. The metal ion hypothesis was inspired by early suggestions and later observations that AD is correlated with dyshomeostasis of metal ions, notably first Fe, and later Zn and Cu [4,5]. Presented herein is to introduce learners about the role of metal ions especially Cu and Zn which are found in a high concentration in these amyloid plaques. In addition, brief discussions on common treatment strategies for AD and development of multifunctional metal chelators (MFCs) which is emerging as a new treatment strategy are made [6].

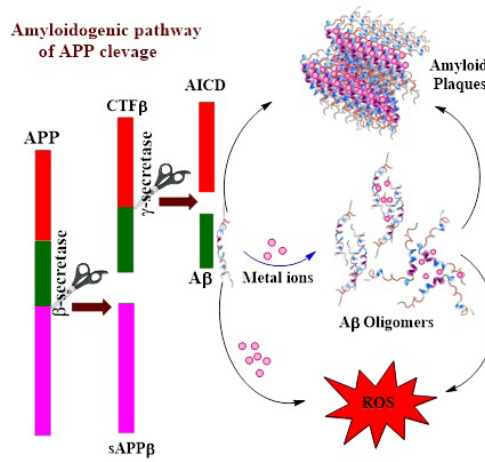

Figure 1: Schematic depiction of APP cleavage and formation of Aβ peptides followed by their aggregation into Aβ oligomers and plaques in presence or absence of metal ions.

Proposed Role of Metal Ions in AD

Smallest alterations in the concentration of metal ions in brain have been linked with pathogenesis of various neurological disorders including AD [4,7,8]. Dyshomeostasis of "natural" calcium, zinc, iron, and copper levels is a well-understood feature of AD [9]. Fe, Cu and Zn have been found to be in specifically high concentrations (~950, ~ 400 and ~1100 μM respectively) within the core and periphery of senile plaques. Living organisms requires metal ions as essential trace elements for various critical cellular functions in form of metalloproteins or cofactors. Brain being a much specialised organ, require optimal levels of metal ions for several complex processes such as neurotransmission, dioxygen transport, neuron signalling, apoptosis, inflammation, oxidative stress control, and cell proliferation, to count a few [10]. Owing to their different characteristics including variable coordination modes, redox activity and reactivity, they are

tightly controlled under normal conditions. Redox active metals are known to cause neuronal cell damage by promoting the production of reactive oxygen species (ROS) [11,12]. The chemical basis of the production of ROS is the activation of molecular oxygen with the redox-active metals copper and iron through Fenton and Haber-Weiss reactions by utilising the ability of these metal ions to occupy multiple valence states and undertake facile redox cycling (Scheme 1). Though utilisation of dioxygen is vital for aerobic life forms, unregulated production becomes destructive and lead to oxidative stress [13]. These metal ions can interact with various amyloid forming proteins and form different coordination complexes and consequently intervene peptide aggregation pathways which eventually leads to the formation of toxic amyloid plaques and soluble neurotoxic oligomers [14-16].

Scheme 1

Common Treatment Strategies

It's been more than a century since the discovery of AD and despite its rapidly growing prevalence, progress in the development of AD therapeutics has been unacceptably slow. In fact, currently there is as such no treatment available for its cure. There are only five drugs available which are US Food and Drug Administration (FDA) approved but just to treat the symptoms and do not prevent the progression of disease. Four out of five these drugs are acetylcholinesterase inhibitors (tacrine, rivastigmine, galanthamine, and donepezil), fifth is N-methyl D-aspartate receptor antagonist (memantine) prescribed to improve memory, attention, reason, language and the ability to perform simple tasks. It is a long journey which requires tremendous energy, time and efforts for a molecule to achieve the heights of being called as a probable drug and enter into clinical trials [17]. A great deal of efforts is put in this direction as evident from the fact that between 1998 and 2011, there were 101 unsuccessful AD drugs in development which led to only three approvals. No new agent has been approved in last 15 years neither for symptomatic relief nor for cura-

tive purpose. Among the several likely reasons for the string of disappointments in the drug development process for AD, the most crucial one is lack of understanding as the disease is extremely complicated. Few reasons for these recent AD trial failures can be identified as (i) targeting the wrong pathophysiological mechanisms; (ii) the drugs do not engage the intended targets in patients; and (iii) the drugs are hitting the right targets but are doing so at the wrong stage of the disease; and many others listed elsewhere [17-19].

Multiple Targets at One Shot Should be the Better Strategy

It is essential to explore other aspects of AD pathophysiology, which could provide additional therapeutic targets. It is rightly said that failure is a step towards success, so there is a lot to learn for scientific community from a very little clinical success to date. In order to tackle the multifactorial nature of AD pathogenesis, an effective drug must target multiple factors contributing to the disease pathology.

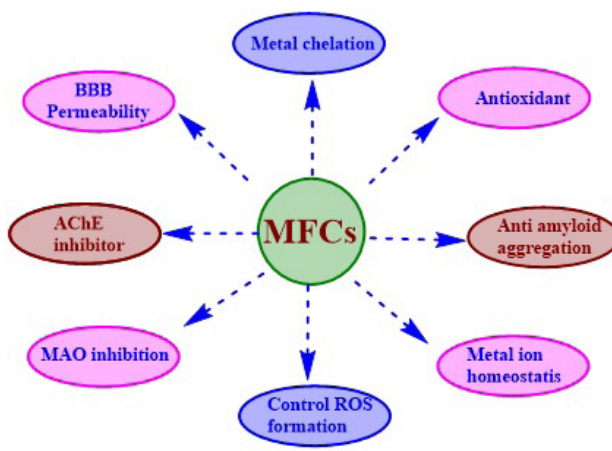

Figure 2: Depiction of selected drug targets of multifunctional drug molecules for AD.

Multifunctional Chelators (MFCs) to Control Metal Mediated Abnormalities

It has been proposed that the major source of oxidative stress and free-radical production in the brain are the redox active transition metal ions like Cu and Fe with or without Aβ. Coordination chemistry of these ions (Fe, Cu and Zn) with Aβ peptide and its consequences on Aβ aggregation has been well documented recently [14,20]. Employing the various spectroscopic techniques, it has been concluded that high affinity metal binding lies on the N-terminus and $A\beta_{1-16}$ is exclusively the coordinating entity possibly the reason for amyloid plaques being the metal ion sink. It is essential to maintain the balance between functionality against toxicity and restore metal ion homeostasis in biological systems. Traditional metal chelators like EDTA (ethylenediaminetetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), EGTA (ethyleneglycolbis(2-aminoethylether)-N,N,N,N-tetraaceticacid), bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) etc. were evaluated for solubilisation of amyloid plaques from the post-mortem of AD affected brain tissues. Most of these have been stopped due to their inability to cross through the blood brain barriers (BBB) and the lack of specificity for individual metal ions [21]. It has been proposed that instead of using a common metal chelator, using it in conjugation with other pharmacophores for each disease target, thereby facilitating a multi-targeting approach which is expected to be better for such diseases. The basic idea behind the rational design is to include multiple functions of two or more molecular scaffolds with known properties and to combine them into a single molecular entity. It can be done using various design principles like functionalization, attachment or linking, incorporation or by a combination of these. Modulating binding affinities of compounds towards Aβ at different conditions can be valuable, specifically toward the development of therapeutics with metal chelating capabilities without disrupting essential enzymatic activities of met-

alloproteins. It was followed by the discovery of the first generation of metal chelators by the introduction of a small lipophilic molecule clioquinol (5-chloro-7-iodo-8-hydroxyquinoline, CQ) that is capable of crossing the BBB and is able to bind a range of metal ions with moderate affinity. It was inspired by the concept of metal–protein attenuating compound (MPAC) that involves the interruption of abnormal metal-protein interactions by competing with the target protein for the metal ions. Unfortunately, CQ resulted into adverse side effects and was stopped eventually [22]. PBT-2 was a successor molecule of clioquinol which also bind copper and zinc and prevent their interaction with Aβ, decrease oligomerization of Aβ and promote their dissolution of larger aggregates [21]. A large number of these so called multifunctional compounds (which binds to Aβ as well metal ions, reduce ROS and Aβ aggregation etc.) were developed based on various molecular scaffolds (Figure 2, 3). The common molecular scaffolds that have been utilized to design and develop various MFCs are Thioflavin-T (ThT) [23,24], Congo-Red (CR) [25], IMPY[26], resveratrol, quericitin, EGCG and other natural products for amyloid binding and antioxidant properties [27]; tacrine and related molecules for AChE activity; CQ, 8-HQ, other amino-pyridyl units for metal binding; etc. [28]. The majority of multifunctional compounds are being developed around these molecular frameworks and are shown in Figure 3. However, the details of each of these MFC can be obtained in readily available literature [21,28].

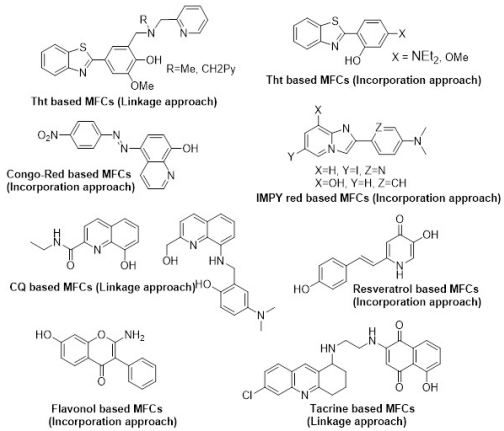

Figure 3: Chemical structures of selected MFCs.

Conclusion

AD is the most common dementia in ageing population occurring across the globe and is a challenge for scientific community across subject boundaries to find a suitable cure. Presence of metal ions in brain and their role in AD pathophysiology is now becoming increasingly clear. Metal ions, especially copper, zinc and iron has become the major drug target recently due to their roles in peptide aggregation and ROS formation leading to neuronal cell death. A large number of multifunctional compounds are being developed to tackle metal mediated abnormalities. However, only a few of them can reach the stage of clinical trial. The most widely studied therapeutic chelator for AD is PBT2 which was designed for easier chemical synthesis, higher solubility, and increased blood barrier permeability. It has been realized to change the strategies used for the drug design and to target them with mechanism based therapies to have a reasonable chance to make a real impact on this devastating disease.

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