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Challenges Associated with Metal Chelation Therapy in Alzheimer's Disease

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Abstract

A close association between brain metal dishomeostasis and the onset and/or progression of Alzheimer's disease (AD) has been clearly established in a number of studies, although the underlying biochemical mechanisms remain obscure. This observation renders chelation therapy an attractive pharmacological option for the treatment of this disease. However, a number of requirements must be fulfilled in order to adapt chelation therapy to AD so that the term “metal targeted strategies” seems now more appropriate. Indeed, brain metal redistribution rather than brain metal scavenging and removal is the major goal of this type of intervention. The most recent developments in metal targeted strategies for AD will be discussed using, as useful examples, clioquinol, curcumin, and epigallocatechin, and the future perspectives will also be outlined.

Keywords

Alzheimer's disease; clioquinol; cuprizone; metal dishomeostasis; metal ions; nanomedicine; Parkinson's disease; polyphenols

Introduction

Despite an enormous increase in the understanding of the neuropathological and neurochemical events taking place in Alzheimer's disease (AD) as well as in other neurodegenerative diseases,

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the etiopathogenesis of progressive and mental cognitive dysfunction concomitant with aging remains largely obscure [1]. So far, there are no effective drugs that can be prescribed to reverse or reduce, safely, the mental decline of affected patients.

Metal ions have been shown to abnormally accumulate in the brain with aging as well as in the course of several neurodegenerative disorders including AD [2–7]. Particularly, the interplay of metal-protein interactions with oxidative stress was recently highlighted by several laboratories [4,8–11]. Accordingly, metal chelation therapy may now be considered as a promising clinical approach to AD [1,12–16].

There is compelling evidence that the etiology of AD involves, among other features, characteristic amyloid-β (Aβ) deposition, severe oxidative stress, and metal-Aβ interactions [14,17,18]. Recent studies have implicated physiological transition metals such as copper (Cu), iron (Fe), and zinc (Zn) and prooxidant non-physiological elements, such as aluminum (Al), as key factors in the pathophysiology of AD [3,7,19]. Al was very much in the public eye for a long time before the turn of this century with scares over its standard utilization as a flocculant in the purification of drinking water. So far, however, there has been no direct attributable connection between AD and Al [20]. Nonetheless, several studies have documented build up of Al in patients with AD [3,21,22], but the results remain rather controversial due to the complexity of Al chemistry in biological systems. It was also shown that there is a high focal increase of Al in the core and around amyloid plaques and neurofibrillary tangles in AD [23]. However, the discovery that clioquinol (CQ), which is a specific Cu-Zn chelator, can inhibit Aβ accumulation has led to the shift in the focus, in our opinion rather imprudently, from Al to Cu and Zn as key players in AD [24]. Recent controversial clinical and experimental results concerning the therapeutic use of CQ reversed the first mechanistic hypothesis stating that the efficacy of CQ essentially arises from its ability to remove metal ions from the brain [25,26]. This underlines the necessity to improve the basic studies in order to better understand the biochemical properties of metal chelators and optimize their use in neurodegenerative therapies.

As the demand for new and more effective drugs for AD treatment continues to grow, pharmacological strategies aimed at lowering brain metal ions and targeting Aβ/metal ions interactions might offer a large potential to chelation therapy. In spite of the conspicuous theoretical basis for chelation therapy in AD, there is still a substantial lack of relevant and reliable data as well as definitive conclusions regarding the clinical advantages of chelation in neurodegenerative conditions. Indeed, the studies concerning the application of chelating agents in neurodegeneration that have appeared so far mainly considered the bioinorganic aspects of the metal complexation reactions; in contrast very scarce interest has been directed to both preclinical and clinical experimentation. However, as there is yet no effective treatment for many neurological diseases, the therapeutic use of effective chelators remains a well grounded option that requires strong interdisciplinary investigation. In this connection, we propose that differential biodistribution and intracellular sub-accumulation of metals concomitantly with the progression of disease severity has to be elucidated and understood precisely before administering any metal chelation therapy [27].

Limited studies exist on metal levels in different phases of AD pathology. We reported data on different elemental levels with respect to the severity of the disorder [3]. In the present paper we advocate that the approach of metal chelation should be furtherly developed and optimized through an understanding of the gradual metal accumulation during disease progression. In addition it must be paid attention to the use of specific chelators and to the time and dosage of administration.

Metal Dishomoestasis in Alzheimer's Disease

Metal ions have been shown to be involved in cell-cell communication and signal transduction, as well as in influencing transcription and translation *via* metal responsive regulators. Neurodegeneration in AD is characterized, among other features, by a marked accumulation of metals, mainly Cu, Zn, Fe, and Al, in various regions of the brain [2,3,28–30] and by disruption in the metabolism of these metals leading to their altered transport and accumulation in senile plaques and other topological sites [31]. Indeed, very high levels of Cu (400 μM) and Zn (1 mM) were found in amyloid plaques and AD neuropil regions in comparison to healthy brain (70 μM Cu and 350 μM Zn) [2,32]. A progressive accumulation of metals in AD brain during disease progression from moderate to severe AD was also observed [3]. Remarkably, this latter study revealed that divalent cations increase in the early phase of AD, while trivalent metal ions start increasing significantly in the later phase of AD, mainly in frontal cortex and hippocampus (Fig. 1) [3]. This displacement of divalent metals by Al in the severe AD is a likely result of differences in the metal-ligand affinity exchange rates [3]. In general, it seems that a common trait to many processes underlying neurodegeneration in AD is a (direct or indirect) perturbation in the homeostasis of Cu, Zn, Fe, Al, calcium (Ca) etc. (metal dishomeostasis). Nonetheless, the overall brain metal burden is never dramatically increased in AD as it occurs, instead, in specific alterations of brain metal metabolism on a genetic base (e.g., Wilson's disease, neuroferritinopathy, etc.) [33,34].

Chelation Therapy Definition and Specificity

Chelation therapy has been proposed as the appropriate treatment for reducing the abnormal accumulation of essential heavy metals, such as Fe, Cu, and Zn, or nonessential and poisonous metals, such as lead (Pb), mercury (Hg), cadmium (Cd), and Al [35–37]. Typically, chelators bind to metal ions enhancing their urinary and fecal excretion and causing a progressive decrease of their body concentrations. Chelation therapy became a popular alternative treatment, in spite of its still controversial clinical results [38,39], when ethylenediaminetetraacetic acid (EDTA) turned out to be effective in chelating and removing toxic metals from blood. Following the introduction of EDTA in clinical practice, other suggestions were made that a treatment based on a metal chelator might benefit patients with atherosclerosis as the hardened arteries could be “softened” due to removal of Ca from artery walls [40]. This was the earliest recorded report on the use of chelation therapy and since then metal ion chelators have been suggested as potential therapies for diseases involving metal ion imbalance as well as metal poisoning. However, regarding the effectiveness of chelation therapy, it is important to note that positive results obtained from some laboratories are by no means unanimous and contradictory evidence counterbalance these claims [41–44]. Thus, EDTA therapy in cardiology has been considered by the Food and Drug Administration (FDA) as a highly controversial and questionable issue. In contrast, the use of chelating agents to treat acute metal poisoning is now well established.

Effective chelation treatments of metal poisoning require a precise understanding of the pharmacodynamic and pharmacokinetic of the administered chelator which, in turn, depends on the physical and chemical characteristics of metals and chelators such as ionic radius, solvation sphere size and deformability, hardness/softness of electron donors and acceptors, chemical stability, administration route, bioavailability, metabolism, organ and intra/extra cellular specific compartmentalization, and, of course, natural excretion [36].

Hydrophilic chelators enhance renal excretion, but their mainly extracellular localization limits activity only to extracellular metal pools. Conversely, lipophilic chelators might decrease intracellular stores, but may also redistribute toxic metals to more vulnerable organs, e.g., the brain. The metal selectivity of chelators is very important, due to the risk of essential metal

depletion. Moreover, in chronic metal induced disease, necessitating long-life chelation, toxicity and side effects of the chelator may drastically limit the time of treatment. Hence, development of new and safer chelators suited to long-term oral administration to remove metal deposits still remains an important research challenge. In addition, a significant teratogenic potential has been demonstrated for most chelators due to induced trace element deficiencies [45], and hence mineral supplementation during treatment is recommended. Improved chelator design should aim at enhancing selectivity, affinity, stability, renal clearance and oral activity, while maintaining a low toxicity and also a low cost. Finally, it must be remembered that adaptation of chelation therapy to neurodegenerative conditions is a very complex task. Upon critical consideration of the studies on CQ, metal redistribution rather than metal removal seems to be the most important therapeutic goal for the treatment of these pathologies. From this perspective, it may be preferred to denote these kinds of therapeutic approaches as metal targeted strategies for neurodegenerative diseases.

Chelators for Alzheimer's Disease: CQ and Related Compounds

Researchers have postulated that metal chelation might promote beneficial results in AD patients by inhibiting Al [46] and/or Cu, Zn deposition in the brain and/or preventing Fe from catalyzing the formation of toxic hydroxyl radicals [47–49]. Few case studies and animal experimentation have been reported in this area [50–52]; however, no clinical evidence has been provided so far to support the use of chelating agents as an adjunctive treatment for AD or other neurodegenerative disorders with similar etiology. Accordingly, neurodegeneration represents an excellent target for exploiting the metal chelator approach to therapeutics. However, in the light of recent experience deriving from the several studies on CQ, a United States Pharmacopoeia (USP) antibiotic, (5-chloro-7-iodo-8-hydroxyquinoline, MW 305.5) [13,24,53–56], a very different point of view has emerged as detailed below. In contrast to the direct chelation approach developed for metal overload disorders and aimed at removing excess metals, the main goal in AD seems to be a better and more suitable modulation of metal ion homeostasis and of metal-Aβ interactions, aimed at restoring broken ionic balance. Known chelators that have been clinically tested include desferrioxamine (DFO) [46]; rasagiline, an Fe chelator approved by the FDA in 2005; and CQ [50–52], an antibiotic banned for internal use in the USA since 1971 that appeared to block the genetic action of Huntington's disease in mice and in cell culture [57]. DFO is a chelator of tripositive metals still used against Al overloading in chronic dialysis treatment and in the treatment of Fe overload conditions, but no longer being pursued clinically for AD. Conversely, CQ has completed a first Phase II clinical trial, however, with rather controversial results [25,52,58] and has been recently withdrawn from human experimentation. In any case the story of CQ remains emblematic and very instructive. After Cherny and colleagues [24] first reported that CQ treatment is beneficial in a mouse model of AD, many researchers have focused on its potential promise in AD. CQ selectively binds Cu and Zn with a far higher affinity than Ca and magnesium (Mg) [k_1(Zn) = 7.0, k_1(Cu) = 8.9, k_1(Ca) = 4.9, and k_1(Mg) = 5.0] [24,26]. CQ is hydrophobic and freely crosses the blood-brain barrier (BBB) [59]; hence it possesses the prototypic properties for a potential therapeutic agent that might solubilize Zn/Cu-assembled Aβ deposits *in vivo* and inhibit Aβ aggregation [60] and redox toxicity. The findings that CQ reverses Cu and Zn induced Aβ aggregates and solubilizes, postmortem, Aβ deposits in AD-affected brain tissue [24], supported by the observation that CQ complexes with Zn in the brain [61], argue in favor of this drug. After showing that CQ can reduce plaque load in transgenic mouse models of AD, Ritchie et al. further reported that CQ lowered plasma Aβ_{42} levels [52]. However, it is unclear whether this was a result of attenuated Aβ/metal ion interactions or of some other mechanism. Patients with mild disease had a lowering of plasma Aβ_{42} but no significant cognitive benefit, while those with severe disease appeared to have a cognitive benefit but no change in plasma Aβ_{42} [52]. They also noted that the study is subject to the usual caveats associated with small-scale trials. Recently, Treiber and coworkers [25] reported that oral treatment with CQ

significantly elevated brain Cu and Zn uptake by 19% and 13% respectively. These results led to the conclusion that CQ does not induce a loss in over-accumulated metal ions (as it was originally believed) but acts in the opposite way with respect to the action of metal chelators. However, CQ is apparently able to reduce Aβ deposition in the brain [25] acting, at least potentially, as an anti-amyloidogenic molecule but not as a metal chelator. Notably, two recent studies have reported some apparently favorable effects for another hydroxyquinolne ligand (PBT2), structurally related to CQ, in a mouse model of AD and in a Phase IIa, double bind trial [62,63]. In the 12-weeks randomized trial PBT2 shows to possess a safe profile and the ability to significantly reduce cerebrospinal fluid (CSF) Aβ_{42} concentrations compared with patients on placebo [62]. Moreover, the unchanged plasma concentrations of Aβ_{42} and Aβ_{40} highlight the ability of PBT2 to selectively affect brain but not peripheral Aβ. Adlard and colleagues hypothesized that PBT2 can capture metal ions from oligomerized Aβ thus favoring peptide clearance [63]. In addition, PBT2 was found to decrease insoluble and soluble phosphorylated tau in APP/PS1 mice and insoluble total tau in Tg2576 mice [63].

Nevertheless, other investigations as well as larger clinical trials are necessary to draw firm conclusions about the clinical efficacy of PBT2 [64].

Challenges to be Overcome with Metal Chelation Therapy

Beyond being a metal ligand, CQ may also act as an anti-aggregating agent, but this aspect needs to be better explored. Recent reports describe successful treatment using Cu chelation therapy in neurodegenerative animal models. However, the success claimed for chelation therapy in neurodegenerative diseases is still rather controversial. Recently Zatta and collaborators utilized cuprizone, a very sensitive and selective Cu-chelating agent with well-known neurotoxic properties, as a relevant chemical model in mice [11]. Upon cuprizone treatment, mice developed a pronounced astrocytosis, with brain edema and spongiosis characterized by vacuolizations of the neuropil predominantly in the white matter. In addition, cuprizone treatment severely altered Cu and Zn homeostasis in the central nervous system (CNS) as well as in all other examined tissues, leading to a generalized increasing of metal ion concentrations, particularly in the CNS. Concomitant with this increase in the Cu and Zn brain concentration, metallothionein-I and -II were also highly immunoreactive in astrocyte, consistent with the astrocytosis and demyelination that were observed.

As stated above, there is a differential and sequential build up of metals during disease progression in AD [3]. In early or moderate AD patients, the divalent metals mainly comprising of Fe, Cu, and Zn are elevated (see Fig. 1). Closer examination of this study indicates that a potential divalent metal chelator may be useful only in patients within the early phase of AD and in patients with severe AD, thus a chelator specific to a trivalent metal ion like Al may be a more relevant option. Moreover, the use of divalent chelators like CQ in the severe AD case may further deplete the essential divalent metals that are already in lower amounts than required and thus worsen the AD pathology. Hence, we suggest that the progressive deposition of various metals in relation with the severity of AD needs to be more systematically established which would dictate the suitability of a particular chelator for the given case.

It is well known that Aβ has the ability to bind transition metal ions, which play an enhancing role in Aβ toxicity. Metals have also been shown to potentiate Aβ aggregation *in vitro* [16, 65,66]. In the Aβ aggregation pathway, from monomers to plaques, several definite intermediates have been identified such as partially/misfolded peptides, soluble oligomers, and protofibrils (see Fig. 2). Presently, the biological significance of the monomeric, misfolded isoforms, soluble Aβ-oligomers and the fibrillar aggregates is not clear. For a variety of technical reasons, biophysical studies on the conformational diversity of different forms of Aβ and the conformational conversion between the normal cellular form and the pathological

conformations have failed to provide us with a clear picture of these events in AD. However, recent studies advocate that the soluble oligomers and protofibrils of Aβ and not the fibrils are the active species that lead to neurodegeneration and dementia [67]. We have shown that the Aβ oligomers are more toxic than the aggregates in terms of their ability to damage DNA [68,69]. Studies carried out by Cherny and colleagues have shown that the metal chelator CQ can reduce Aβ plaques by solubilizing them [24]. But it is not known whether CQ can reverse the plaques to monomers or to any of the intermediate forms. If the aggregates are to be dissolved to soluble oligomers by chelators, then as for the current concept of toxicity of soluble forms of Aβ, the benefits of this need to be reviewed. The above questions create a renewed need to clarify how metals deposit with the progression of AD and which form of Aβ is generated by solubilizing the plaques with metal chelators.

Recent Challenges in Nanomaterials

Nanomedicines are systems that exhibit similarity in size and structure to natural carriers like viruses and serum lipoproteins, and offer multi-faceted specific properties, useful in applications for delivery of imaging and therapeutic agents to CNS. Recently, Liu et al. reviewed the potential role of nanoparticles as chelation agents in relation to AD [70]. Nanomaterials synthesized from natural or artificial polymers, ranging in sizes of about or less than 300 nm have been shown to possess the ability to cross the BBB. Nanoparticles conjugated to metal chelators have shown a unique ability to cross the BBB, chelate metals, and exit through the BBB bound to the metal ion [70,71]. This method would be safe and effective in reducing metal burden in the brain. However, the long term toxicity of nanoparticles needs to be ascertained. It is assumed that specific biocompatible nanoparticles have low drug toxicity, efficient biodistribution, and therapeutic potential [72]. Nanoparticles mimic low density lipoproteins (LDL) and interact with the LDL receptor, thereby resulting in their uptake by brain endothelial cells [73]. The transferrin transcytosis mechanism may play a key role in nanoparticles drug delivery system. Scientists can bind metal chelators (Fe, Al, and Pb) covalently on nanoparticles as drug delivery vehicles to deliver the chelator to the brain. For example, hydrophilic hexadentate Fe chelators, with a large molecular weight, have been attached to nanoparticles and delivered to the brain [74]. Recent studies have reported the synthesis of a series of Fe chelators with functional side chains, which can be conjugated to nanoparticles and increase their efficiency in entering the brain [75–77]. Early studies from Liu's group showed that these nanochelators can effectively remove Fe from tissue sections of AD brain and also from ferritin (important Fe storage protein). Further, they also showed that these particles are more effective than DFO. Thus, nanotechnology is very helpful to deliver even hydrophilic compounds to the brain. Scientists can develop biopolymers as nanotools for conjugating metal chelators, because these nanoparticles are biodegradable. Liposomes, nanospheres, nanotubes, nanogels, polymeric micelles, and dendrimers pose some interesting and important challenges in their potential for clinical application [78]. Further work is needed for clinical validation and for assessing the safe and efficient use of these unique particles. In addition, to design useful means of chelation therapy based on specific metal levels in the moderate or severe phase of the disease, future studies should focus on the safer chelators targeting such as nanoparticle-linked chelators, which could also be useful for a wide range of other metal-toxicity disorders. Furthermore, it is important to study the surface chemistry of the chelator and nanoparticle complex, enhancing the desired characteristics by modulating linkages, coating materials, etc. These modifications will help to synthesize optimized nanometal chelators which can enter the brain and remove metals without being toxic. After all these basic data have been developed, then it is necessary to understand the clinical validation of these unique particles. In addition, to design useful means of chelation therapy based on specific metal levels in the moderate or severe phase of the disease, future studies should focus on the safer chelators such as nanoparticle-linked chelators, which could also be used for a wide range of other metal-related disorders.

Natural Compounds as Iron Chelators: Curcumin and Epigallocatechins

Beyond the case of CQ and of the few metal ligands described above, some other molecules were recently reported to show promising effects in AD, probably mediated by direct interactions with brain metals. We describe here the case of two natural compounds, curcumin and epigallocatechin, that were found to significantly affect brain Fe level and contrast AD progression.

Curcumin, the wonder molecule

Curcumin is abundantly used in cuisine of several Asian countries. India, for example, is a major producer of a variety of spices and herbs which constitutes an excellent source for natural molecules, which not only can impart odor, color, and flavor to food, but also possesses several interesting preservative as well as medicinal properties. Curcumin (Fig. 3-I) is the major curcuminoid of the three found in tumeric, which also contains minor amounts of demethoxycurcumin (Fig. 3-II) and bisdemethoxycurcumin (Fig. 3-III).

Studies on neuronal degeneration in the brains of patients with AD show that hippocampus is one of the primary regions affected during the early stages of the disease [79]. Neurotoxic heavy metals like Pb [80] and Cd [81] are known to disrupt structural features of the cells also in this region of the brain. Recent studies suggest that curcumin significantly reduces Pb- and Cd-induced neurotoxicity in rat hippocampal neurons [82,83] and increased hippocampal neurogenesis in chronically stressed rats [84]. The ability of curcumin to bind toxic metals and to form tight and inactive complexes could be a plausible pathway by which curcumin offers protection to the brain. The anti-inflammatory property of curcumin could also contribute to the reduced amount of swelling observed within neuronal cells [85]. The use of phytochemical products as an alternative strategy for the reduction or amelioration in neurotoxic mechanisms has been gaining a lot of attention recently. Curcumin has the phenolic hydoxyls, the enolic proton, the keto moieties and the methylene group alpha to the two carbonyl groups as the potential reactive centers. Of these, the phenolic and the enolic hydroxyls have the ability to form metal complexes [86]. The ability of curcumin to bind effectively with redox-active metals like Cu and Fe and the enhanced radical scavenging efficacy of the curcumin-metal complexes, indicate a possible potent neuroprotective role for curcumin [87]. The interaction of curcumin with Cu and Fe reaches half-maximum at approximately 3–12 and 2.5–5 μM levels respectively [87]. In fact, the ability of curcumin to bind to several metals [82,86,88] and thereby potentially reduce their toxicity is well documented. Curcumin, in addition to providing protection to the brain by direct binding and complex formation with toxic metals, could also afford protection against oxidative damage and inflammation [89,90].

Polyphenols

Polyphenols are natural compounds that are largely present in plant products. Polyphenols, that are abundant in natural compounds such as green tea, curcumin flavanoids, and blueberry extracts, have been shown to reveal pronounced antioxidant, metal chelating, and anti-inflammatory properties [91]. These compounds have also been demonstrated to exert neuroprotective activities. Flavanoids are the largest group of polyphenols, which include anthocyanins and anthoxanthins, the latter further subdivided into flavones, isoflavones, flavanols, and flavans. Dried leaves of the plant *Camellia sinesis* are used to prepare the well-known beverage green tea. The ingredients of the green tea have been proposed for the treatment of various cardiovascular, inflammatory, and certain neurodegenerative diseases [92,93]. The major green tea component is the polyphenolic compound (-)-epigallocatechin-3-gallate (EGCG) [94–100]. The green tea polyphenols act as relatively potent metal chelators, binding to metal ions such as Fe and Cu. It has been proposed that AD pathogenesis is associated with the accumulation of Fe and hence tea polyphenols and curcumin may gain significance

in the metal chelation treatment of AD. However, the efficacy of natural product chemistry for metal chelation properties may still be further explored.

Curcumin and polyphenols for AD: potential iron scavengers

Mandel and colleagues [96] in a recent review proposed that either curcumin or green tea EGCG might be conveniently employed for AD treatment. Indeed, both these substances have been reported to have easy access to the brain and to possess multifunctional activities such as metal chelation, radical scavenging, anti-inflammation, and neuroprotection. Interest in the use of these molecules is further motivated by the fact that they are relatively safe and are usually very abundant in the diet. It was specifically hypothesized that these two substances might act primarily as Fe chelators, again implying an important role for Fe in the etiopathogenesis and progression of AD. Remarkably clinical studies are currently underway to define more precisely whether the use of natural, non-toxic, neuroprotective compounds with brain access could offer potential therapeutic benefits in order to reduce Fe burden in those brain areas where it preferentially accumulates and causes severe neuronal damage.

Conclusions and Perspectives

We have critically reviewed here a number of chelation therapy approaches applied to AD during the last two decades. AD is most likely a multifactorial disease with a complex and still largely unknown origin. However, as it is increasingly evident that there are close links between brain metal dishomeostasis and AD onset and/or progression, a therapeutic strategy aimed at targeting brain metals is theoretically well grounded and justified. As it is also evident that brain metal alterations in AD patients predominantly consist of both a perturbed distribution and an anomalous metal protein interactions rather than of a large metal overload, metal targeting approaches for AD should not be aimed at removing metals but rather at favoring their redistribution and disrupting pathologically relevant metal-protein interaction. Thus, metal targeted therapies based on intermediate strength ligands are to be preferred to aggressive chelation strategies. From this perspective, the case of CQ has contributed significantly to our basic knowledge. Despite several controversies, it seems that CQ and some related hydroxyquinoline ligands are of some significant benefit to AD patients as they may slow down cognitive decline. Further work is thus needed in this direction and other molecules behave as good drug candidates. We refer in particular to the case of two natural compounds, curcumin and EGCG, that are known to be appreciable Fe ligands and were reported to favorably affect the AD neurodegenerative processes. Given that they are safe, they can be straightforwardly proposed for combination therapies. Other strategies have been described based on the use of functionalized nanoparticles. Based on the above arguments, it is evident that metal targeted strategies, either alone or in combination with other drugs, may play a significant role in the medical treatment of AD as they have the potential to attenuate metal mediated effects. A synergism with antioxidant substances capable of counteracting metal induced oxidative stress could be expected.

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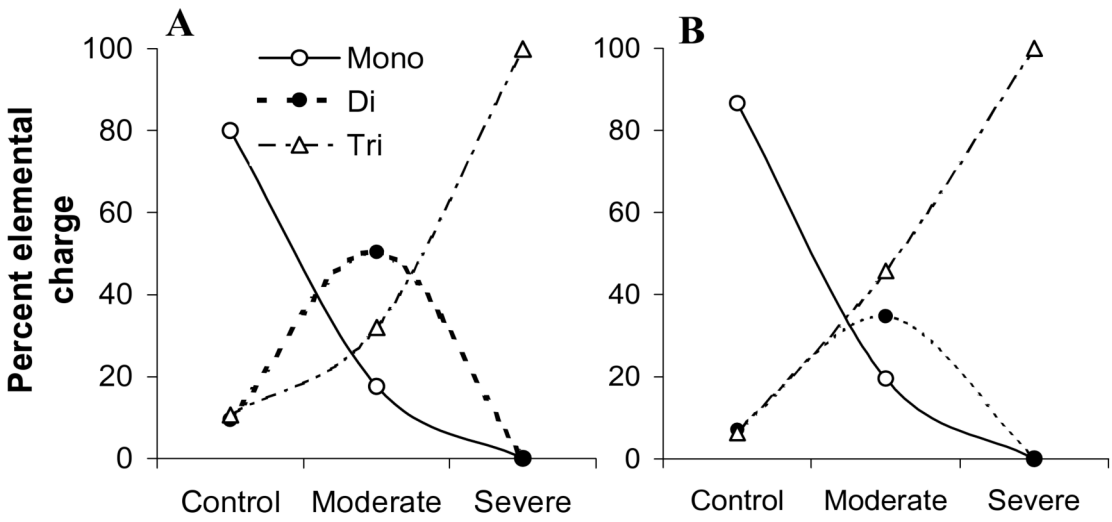

Fig. 1.
Percentage of elemental charge distribution in control and AD brains. A, frontal cortex; B, hippocampus [3].

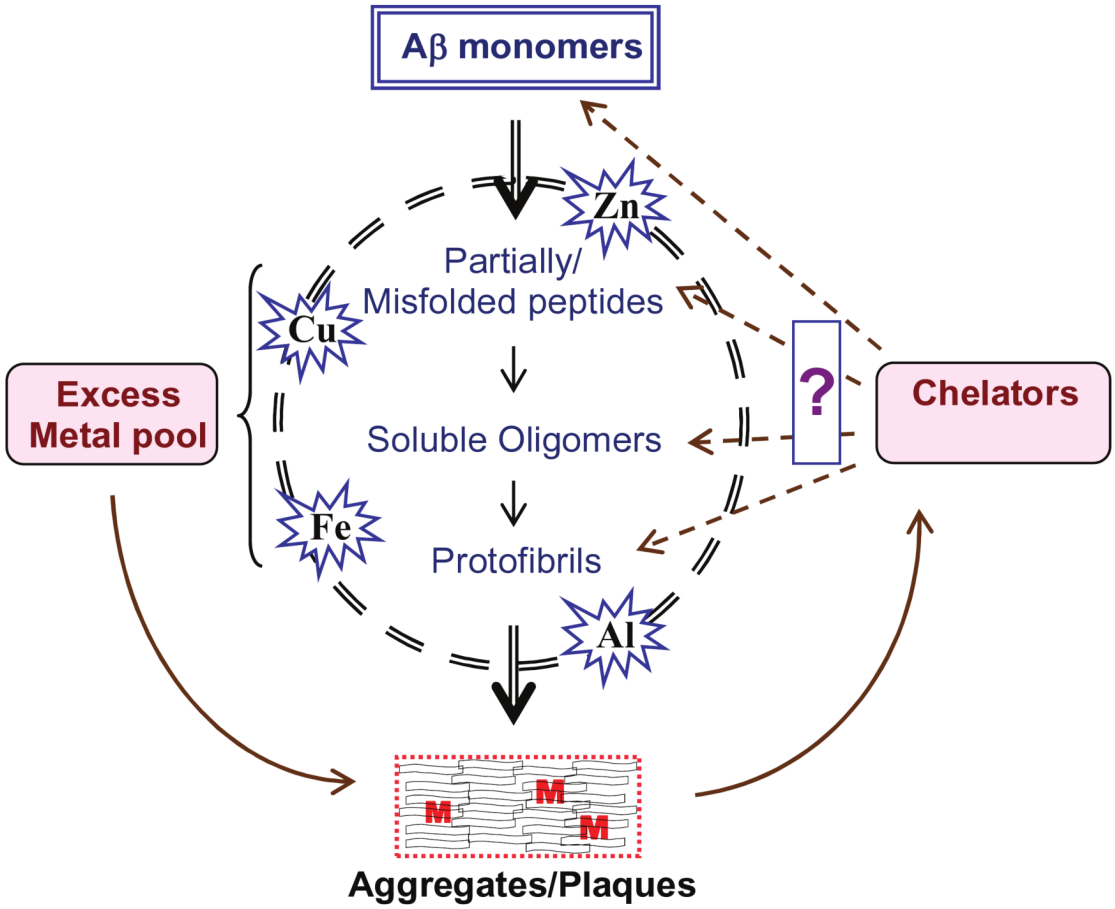

Fig. 2.

Schematic representation of A*β* aggregation pathway. The A*β* monomers and the intermediate forms bind the excess metal ions (M) giving rise to higher-order structures. There is a need to understand which form of the peptide is generated by the solubilization of plaques by metal chelators. (Colours are visible in the electronic version of the article at www.iospress.nl.)

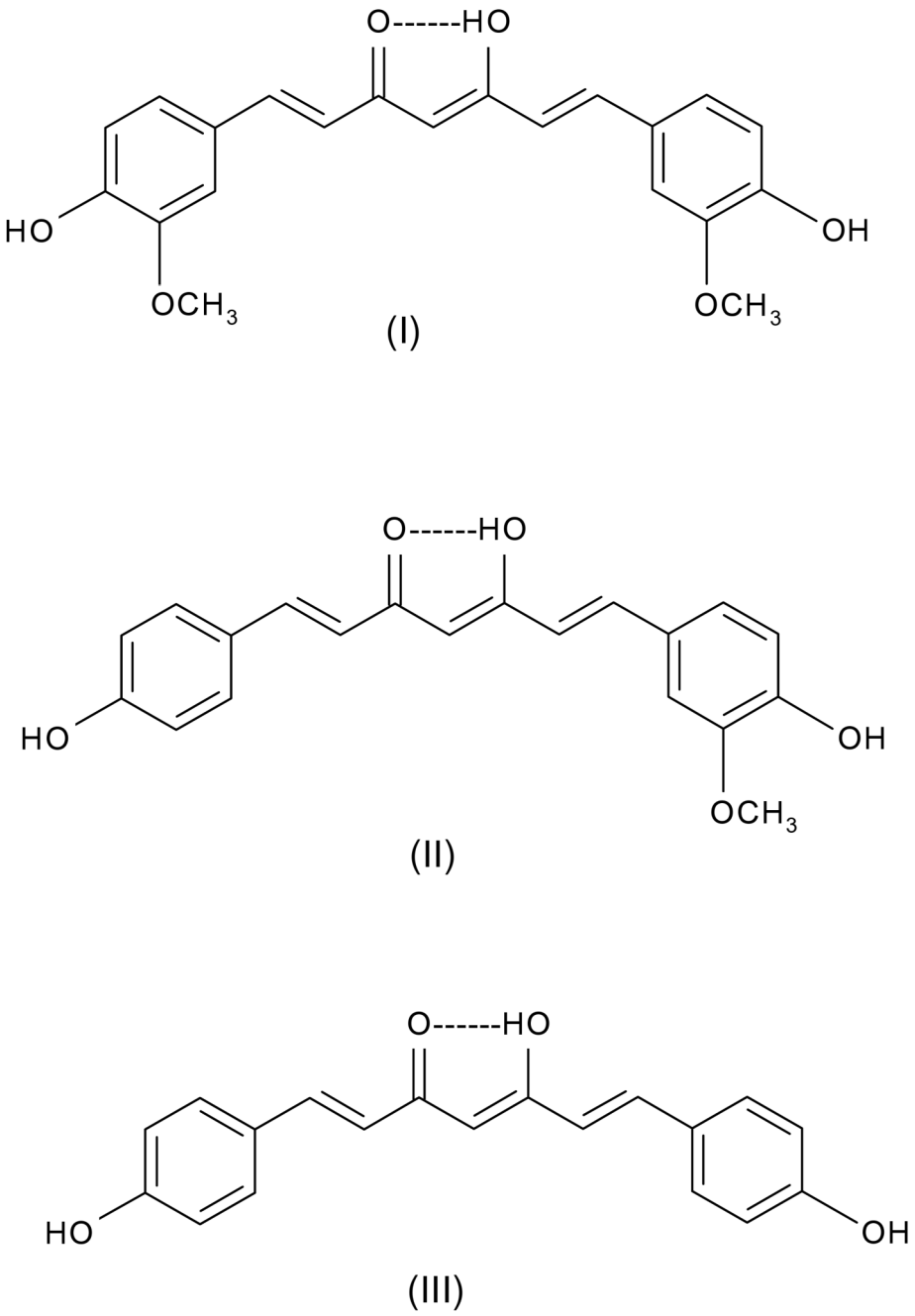

Fig. 3.
Molecular structures of curcumin (I), demethoxycurcumin (II), and bisdemethoxycurcumin (III).