ALZHEIMER'S DISEASE
AND TREATMENT

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Design of Metal Complexes as Anti-AD Agents

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Abstract

Alzheimer's Disease (**AD**) is a neurodegenerative (gradual loss of biological functions of nerves) disease characterized by precipitation of β-amyloid protein, so called amyloid plaque formation via metal-peptide interactions in the brain causing dementia (a syndrome due to brain disease, characterized by progressive deterioration in intellectual abilities). Two types of biochemical features of Alzheimer's Disease (**AD**) that contribute to neurodegeneration are intracellular oxidative stress and elevated level of trace metal ions, especially Fe^{III}, Cu^{II} and Zn^{II}. A growing body of evidence indicates that dysregulation of cerebral biometals (Fe^{III}, Cu^{II} and Zn^{II}) and their interactions with Amyloid Precursor Protein (**APP**) and Aβ amyloid may contribute to the Alzheimer's amyloid pathology. In fact, amyloid plaques have been described as "metallic sinks" because remarkably high concentrations of Fe^{III}, Cu^{II} and Zn^{II} have been found within these deposits in AD brains, and thus metal chelation could be a rational therapeutic approach for interdicting AD pathogenesis. However, poor target specificity and consequential clinical safety of current metal-complexing agents have limited their widespread clinical use. Enhancing the targeting and efficacy of metal-ion chelating agents through sugar appended ligand is a recent strategy in the development of the next generation of metal chelators.

Superoxide radical anion ($O2.^-$) and its derivatives (generally addressed as Reactive Oxygen Species, **ROS**) are formed during enzyme-catalyzed metabolic processes in living systems, which are essential for the biological defense system against the invasion of bacteria and viruses. However, their uncontrolled production is the price that respiring organisms have to pay during their life cycle. Hence, all aerobic organisms have developed a host of defense mechanisms aimed at minimizing, either directly or indirectly, the formation or propagation of ROS. Normally, the native Superoxide Dismutase (**SOD**) antioxidant enzymes catalytically accelerate the dismutation (scavenging) of superoxide radical, an important agent of oxygen toxicity. This provides sufficient defense against $O2.^-$ for the normal life cycle of living organisms.

Under certain conditions, the imbalance between oxygen toxicity and antioxidant levels, the SODs leave the living systems without adequate protection against $O2.^-$ and ROS. As a result, tissues suffer injuries from the excessive presence of ROS due to oxidative stress of biological systems. In fact, overproduced ROS have been shown to oxidize various biomolecules, including DNA, proteins, and lipids, which can cause various forms of damage to cells and tissues that may lead to several pathophysiological conditions, such as, Alzheimer's and Parkinson's disease, cardiac ischemic/reperfusion injury, atherosclerosis, cancer, diabetes mellitus and variety of other age-related diseases. Nowadays, it is well established that superoxide anion produces tissue injury and associated inflammation in all tissues in similar ways. These call forth the need for exogenously administered compounds, either naturally occurring or completely synthetic molecules, which could augment endogenous cellular defense levels. In this context, the failure of clinical attempts to use natural SOD, due to several reasons (high cost, short plasma halflife, bio-inaccessibility, high molecular weight, etc.) has lead to the development of a number of synthetic low molecular weight SOD mimics which could ideally overcome these limitations. Therefore, attempts are being made to develop such catalytic mimetics of antioxidant enzymes include Fe(III), Cu(II), Zn(II), Mn(II), Mn(III), etc. with ligands of different chemical nature, capable of detoxifying superoxide radical. These compounds all bear a redox active metal centre, similar to the active site metals of the native SODs, i.e. Cu, Fe, Zn or Mn [1,2].

In view of the two issues addressed above, the following two objectives are generally considered:

(i) Development of some new suitably anchored carbohydrate based metal chelators relevant to medical treatment

of disorders on human health caused by metal (Fe, Cu and Zn) overload, such as, dementia in Alzheimer disease. The strategy behind the development of such chelating molecules is aimed at reducing neurodegeneration from oxidative stress by passivating the pro-oxidant metal ions, Fe^{III} and Cu^{II} and removing the main three metal ions (Fe^{III}, Cu^{II} and Zn^{II}) by complexation responsible for amyloid plague formation.

(ii) Synthesis, characterization and evaluation of Superoxide Dismutase (**SOD**) activities of some new Fe(III), Cu(II) and Zn(II) complexes of suitably anchored carbohydrate based ligating molecules. The strategy behind the development of such low molecular weight complexes is aimed to reduce oxidative stress catalytically in mammals responsible for several pathophysiological conditions.

Introductory: Medicinal Inorganic Chemistry

Medicinal inorganic chemistry is a discipline of growing significance in both therapeutic and diagnostic medicine. Inorganic and bioinorganic medicinal agents have made a growing contribution to medical science and human health in the past half century. The clinical success of cisplatin, and related platinum based drugs, as anti-cancer agents worldwide constitutes the most impressive contribution to the use of metals in medicine, and thus establishing the field of medicinal inorganic chemistry. The field now encompasses active metal complexes, metal ions, and even metal binding compounds as potential agents. Metal ions can be introduced into a biological system either for therapeutic effect or as diagnostic aids. Alternatively, metal ion can be removed from a biological system by judicious use of metal binding molecules, termed ligands.

Ligands are most often, but not limited to, organic compounds that bind metal ions, thus modifying the physical and chemical properties of the ion(s). Ligands can be introduced into a system to limit the adverse effects of metal ion overload, inhibit selected metalloenzymes, or facilitate metal ion re-distribution. Some of the aforementioned effects include modifying reactivity and lipophilicity, stabilizing specific oxidation states, and contributing to substitution inertness. However, purposeful design today can go well beyond these effects. Tailored, multifunctional ligands for metal-based medicinal agents offer many exciting possibilities, and can play an integral role in muting the potential toxicity of a metallodrug to have a positive impact in areas of diagnosis and therapy.

(i) Carbohydrates as Ligating Molecules and their Complexes

Carbohydrates are of primary importance as energy sources for living organism [3]. They are an inexpensive, naturally occurring, non-toxic, oxygen-rich, chiral source. Due to the properties inherent to this class of molecules, carbohydrates have been utilized to prepare bioactive materials [4], better targeted drugs [5] as well as functionalization of hydrophobic materials [6].

The ability of sugar to sequester/ligating metals is of current interest in the possible development of metal chelators [7] for clinical use, that is, for the medical treatment of disorder on human health caused by metal rich environment. Metal-carbohydrate interactions are also of significance interest in bioinorganic chemistry [8]. However, direct metal ion-carbohydrate interactions are difficult to study due to multifunctionality, complicated stereochemistry, and weak coordination ability typical of carbohydrates.

Carbohydrate ligands with well-tailored binding/anchoring groups [9] for metal ions to generate a well defined binding environment as well as to increase the stability of the resultant metal complexes. In fact, on introduction of an anchoring group into a sugar molecule, which as a primary coordination sites, may promote the deprotonation and coordination of alcoholic hydroxyl groups of the carbohydrate moiety. The complex forming ability may thus be enhanced several times of magnitude, even in acidic or neutral solution. These anchoring/donor groups [10] might be the carboxyl, amino, thiol, phosphate or other groups. A potential benefit of utilizing this approach is that the carbohydrate can remain pendent and thereby being freely available to interact with carbohydrate transport and metabolic pathways in the body. Examples of this approach in medicinal inorganic chemistry include carbohydrate appended cisplatin as potential antitumour agents [11], antifungal Ni(II) complexes [12] as well as carbohydrate appended metal complexes of the radioisotopes ^{99m}Tc and ^{186}Re for potential use in nuclear imaging and therapy (radiopharmaceuticals) [13].

(ii) Alzheimer Disease: Statistical Data, Cause, Consequences and Potentiality of Sugar Based Metal Chelators for its Combating

The prevalence of the disease, which increases with age, ranges from 1-2% at age 65 years to 35% or higher by age 85. With improvements in health care, longer life expectancy, and continued rise of the average age of the population, the prevalence of AD is projected to increase over the coming years With 27 million cases worldwide documented in 2006, Alzheimer's Disease (**AD**) constitutes an overwhelming health, social, economic, and political problem to the nation. Unless a new medicine capable to delay disease progression is found, the number of cases will reach 107 million in 2050. According to The World Alzheimer's report released in September'09 by King's College London, there would be 35 million people worldwide with dementia (a syndrome due to brain disease, characterized by progressive deterioration in intellectual abilities) by 2010. What's worse, almost 60% of people with dementia in 2010 will be from India, rising to 70% by 2050. (**Times of India, New Delhi, September 24, 2009**).

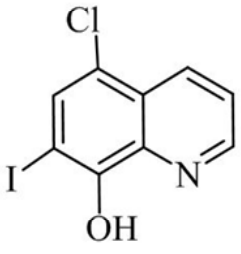
A growing body of evidence [14] indicates that dysregulation of cerebral biometals (Fe^{III}, Cu^{II} and Zn^{II}) and their interactions with Amyloid Precursor Protein (**APP**) and Abeta (**Aβ**) amyloid may contribute to the Alzheimer's amyloid pathology, and thus metal chelation could be a rational therapeutic approach for interdicting AD pathogenesis. However, poor target specificity and consequential clinical safety of current metal-complexing agents have limited their widespread clinical use. At present, enhancing the targeting and efficacy of metal-ion multitarget directed tailored chelating agents [15] is a main strategy in the development of the next generation of metal chelators for the treatment of Alzheimer's disease.

Metal chelators are used in medicine to protect patients from the consequences of metal overload and metal toxicity due to exogenous metal ion intoxication by ingestion or by metabolic defects of endogenous metals. One of the most serious health problems in the world is **β**-thalassemia major, where iron overload plays a very important load. The only iron chelating drugs in clinical uses are desferrioxamine (Desferal) and Defriprone. In spite of their success they have some drawbacks, such as high cost and non-oral effectiveness. Thus, a research on orally effective iron chelating drugs [16] is of the greatest importance. Another most studied important metal chelator is EDTA. EDTA improves calcium and cholesterol metabolism by eliminating

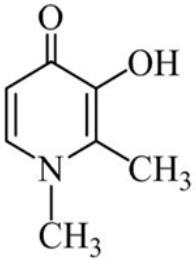
metallic catalysts which cause damage to cell membranes by producing oxygen free radicals. Free radical pathology is now believed by many scientists to be an important contributing cause of atherosclerosis, cancer, diabetes and other diseases of aging. EDTA helps to prevent the production of harmful free radicals. Other chelation agents include Vitamin C (Ascorbic Acid), methionine, cysteine, malic acid, DMSA (dimercapto succinic acid) and Garlic.

Data accumulated during the last one decade show that two of the biochemical features of Alzheimer Disease that contribute to neurodegeneration are intracellular oxidative stress and elevated levels of trace metal ions [17], especially Fe^{III}, Cu^{II} and Zn^{II}. Oxidative stress, protein aggregation and redox active metal ions can all be considered promising pharmacological targets for the treatment of neurodegeneration. The critical role of iron and copper, in both oxidative stress and protein aggregation processes, renders chelation therapy a sensible therapeutic strategy. A chelating agent suitable for neurodegenerative disorders could have two possible actions: (a) scavenging the free redox active metal present in excess in the brain to form a non toxic metal complex, which is then excreted; and (b) capping the metal at its protein binding site (β-amyloid, α-synuclein), preventing any redox activity [18]. Capping the metal at the protein binding site would be expected to involve additional interactions between the chelating agent and the target protein. A chelating agent suitable for the treatment of neurodegenerative disorders must fulfill critical requirements, among which Blood-Brain Barrier (**BBB**) permeability is of uttermost importance. Lipophilicity should represent a compromise between a high BBB penetration and a low liver extraction. Furthermore, with the necessity of ready permeation of the BBB, the size of the chelator should small [19], thereby excluding most of the hexadentate ligands

Therapeutic studies under current investigation include clioquinol (I) [20] and desferrioxamine (II) [21], which are metal chelators that target elevated metal ions in the brain, although neither are intended to affect oxidative stress directly and nor are they targeted to the brain. Antioxidant supplements [22] have been studied separately as palliative- only measures for alleviation of the symptoms of AD.

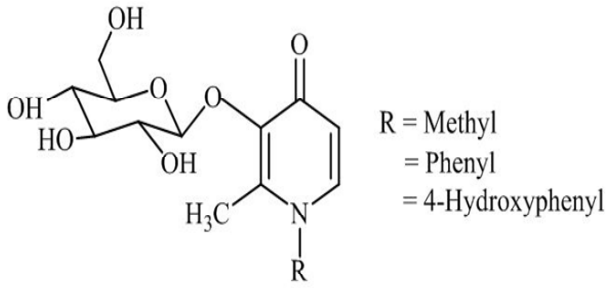


(I)



(II)

So far, the therapeutic paradigm one-compound-one-target has little success. This could be due to the multiple pathogenic mechanisms involved in AD. In view of this complex pathogenic mechanisms, and the successful treatment of chronic diseases such as HIV or cancer, with multiple drugs having complementary mechanisms of action, the concern is growing that AD could better be treated with a single compound targeting two or more of the pathogenic mechanisms leading to neuronal death. A trifunctional approach to AD therapy exploiting modified and functionalized bidentate hydroxypyridinone pro-ligands is reported in 2007 by Schugar et al. [23] to address both the metal ion and the oxidative imbalance in AD while incorporating a glucose-receptor targeting feature (III). These pro-ligands are designed to cross the blood brain barrier, lose the pendent carbohydrate by the enzymatic cleavage passivate the excess metal ions in the brain and also protect neuronal cells against Reactive Oxygen Species (**ROS**).



(III) Glycosylated pro-ligands

Recent researches carried [24,25] in search of metal chelators for Alzheimer therapy have shown that carbohydrate appended metal chelators are promising candidates in combating Alzheimer disease as multifunctional approach. In sugar appended ligands, sugars are there to stop the ligands binding to any metals before reaching their target (brain, because sugar is brain fuel), and to improve the ligands solubility and uptake by the brain. Once absorbed by the brain, the carbohydrates are removed by enzymes. This activates the ligands'-metal binding properties. The multitarget-directed ligands approach for the treatment of Alzheimer's disease has recently been reviewed by Leon et al. [26] of the University of Cambridge.

(iii) Superoxide Dismutase (SOD) and Metal Complexes Displaying (SOD) Activity:

Many disease states affecting humans and many other mammals are the result of a failure to control and limit the overproduction of undesired metabolic by-products. One example of these potentially harmful products is the Reactive Oxygen Species (**ROS**). All mammals consume oxygen as the ultimate oxidant supporting cellular respiration. Although the routine reduction of oxygen by the mitochondrial electron-transport chain to produce water is a relatively safe process, a considerable portion of the oxygen is metabolized through successive one-electron reduction reactions generating ROS [27]. One of these ROS is the superoxide radical ($O2.^-$), formed following a one-electron reduction of molecular oxygen (1-5% of the total oxygen consumed by humans is converted to $O2.^-$) [28,29]. This radical ion has both reducing and oxidizing properties, reacting mainly with metal ions and iron–sulfur clusters, and it can be readily converted to even more toxic species such as peroxynitrite ($ONOO^-$) (formed at diffusion controlled rates from the reaction of superoxide and nitric oxide radicals, NO^-) [30,31] which is a strong oxidizing, nitrating and nitrosylating agent. Consequently, superoxide radicals are potentially dangerous for all cellular systems.

Superoxide Dismutases (**SODs**) are metalloenzymes that catalyze the conversion of superoxide radical ($O2.^-$) to oxygen (O_2) and hydrogen peroxide (H_2O_2) at rates approaching the diffusion controlled limit (Eq. (1)). Therefore, they play a crucial role in protecting biological systems against the damage mediated by this deleterious radical [28,29,32,33]. Since the identification of Erythrocupreinas a SOD, the first metalloenzyme to be classified as such [34], different metalloenzymes have been discovered that catalyze the same overall reaction. They use different metal ion cofactors and based on this, SODs can be

classified into four major groups: copper-Zinc SOD (CuZn-SOD), manganese SOD (Mn-SOD), iron SOD (Fe-SOD) and nickel SOD (Ni-SOD) [32,35,36].

$$2O_2^{\cdot-} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2 \qquad (1)$$

Various investigations have shown that mammals possess two different classes of SODs to keep the level of superoxide radicals under control: the CuZn-SOD which is present in the cytoplasm, nuclear compartments and in the inter membrane space of the mitochondria (SOD_1) [32,33] or in extracellular space (SOD_3) [34], and the Mn-SOD, that is located in mitochondrial matrix (SOD_2) [35]. However, there are circumstances where the production of superoxide radicals is excessive and the endogenous SODs cannot eliminate them leading to a variety of disease states. In recent years, oxidative stress, defined as an impairment in the balance between generation and clearance of ROS by these and other antioxidant enzymes (such as catalase and glutathione peroxidase) has been implicated in a variety of degenerative processes, diseases, and syndromes [37-40]. Some of these include cardiovascular diseases; chronic and acute inflammatory conditions; central nervous system disorders, cancer and a variety of other age-related diseases. Evidence shows that the formation of superoxide radicals ($O2.^-$) is a common denominator associated with all these conditions [37]. Superoxide dismutase enzymes (SODs) have demonstrated therapeutic efficacy in animal models of some of these disease states including myocardial [41,42], cerebral ischemia-reperfusion injury [43-47], neurodegeneration [48], inflammation [49], and cancer [50,51]. Indeed, bovine CuZn-SOD preparations (Palosein and Orgotein, manufactured by M/s Oxin International, Inc., USA) are available for the treatment of inflammatory diseases in horses and dogs, and have had limited use in humans (Orgotein). The potential therapeutic application of the SOD enzymes for the treatment of human diseases faces several limitations; chiefly among them being the lack of oral activity, the immunogenicity when the SOD derives from non-human sources, short half-lives (they are quickly eliminated from the blood stream), the inability to gain access to the intracellular space of cells where the superoxide radical is produced, and high manufacturing costs.

Considering the above limitations of nature's SOD enzymes, it is not surprising to see the interest of the coordination and bio-chemists in developing non-toxic and cost effective low molecular weight synthetic catalysts [52] that mimic the natural SOD enzyme's ability of eliminating superoxide radicals under physiological conditions having biological stability, membrane permeability. These compounds all bear a redox active metal centre, similar to the active site metals of the native SODs, i.e. Cu, Fe, Zn or Mn complexes with ligands of different chemical nature, capable of detoxifying superoxide radical. Studies on the reactivity of low molecular weight complexes which exhibit SOD like activity have attracted major attention for the development of SOD mimics and for expanding the biomimetic chemistry of transition metals complexes. The pharmaceutical use of metal complexes has therefore excellent potential and a broad array of medicinal applications have been investigated as summarized by several recent reviews [53] in this field.

Conclusions

So far rigorous literature survey has been made through Scopus on the subject matter. Multifunctional carbohydrate appended ligands are designed in this context. The objectives to develop some novel carbohydrate based compounds not reported hitherto to overcome two types of health related problems in human beings: (1) Dementia in AD brains in old aged persons due to oxidative stress and elevated levels of trace metal ions, especially Fe^{III}, Cu^{II} and Zn^{II}, and (2) Oxidative stress, defined as an impairment in the balance between generation and clearance of Reactive Oxygen Species (**ROS**) in any aged persons responsible for a variety of degenerative processes, diseases, and syndromes. Obviously, the proposed investigations on these two medicinal aspects will have substantial scientific as well a technological impact in biomedical field for the welfare of mankind. Indeed it is probably the approach to develop sugar based metal chelators for cerebral metals such as iron, cooper and zinc in AD brain and the metal complexes of these sugar based chelating molecules with Fe(III), Cu(II) and Zn(II) as potential superoxide dismutase mimics.

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