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Regulation of Copper and Iron Homeostasis by Metal Chelators: A Possible Chemotherapy for Alzheimer's Disease

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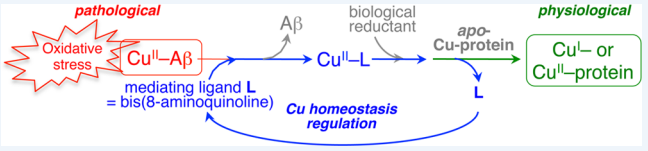
CONSPECTUS: With the increase of life expectancy of humans in more than two-thirds of the countries in the World, aging diseases are becoming the frontline health problems. Alzheimer's disease (AD) is now one of the major challenges in drug discovery, since, with the exception of memantine in 2003, all clinical trials with drug candidates failed over the past decade. If we consider that the loss of neurons is due to a high level of oxidative stress produced by nonregulated redox active metal ions like copper linked to amyloids of different sizes, regulation of metal homeostasis is a key target. The difficulty for large copper-carrier proteins to directly extract copper ions from metalated amyloids might be considered as being at the origin of the rupture of the copper homeostasis regulation in AD brains. So, there is an urgent need for new specific metal chelators that should be able to regulate the homeostasis of metal ions, specially copper and iron, in AD brains.



As a consequence of that concept, chelators promoting metal excretion from brain are not desired. One should favor ligands able to extract copper ions from sinks (amyloids being the major one) and to transfer these redox-active metal ions to copper-carrier proteins or copper-containing enzymes. Obviously, the affinity of these chelators for the metal ion should not be a sufficient criterion, but the metal specificity and the ability of the chelators to release the metal under specific biological conditions should be considered.

Such an approach is still largely unexplored. The requirements for the chelators are very high (ability to cross the brain−blood barrier, lack of toxicity, etc.), few chemical series were proposed, and, among them, biochemical or biological data are scarce. As a matter of fact, the bioinorganic pharmacology of AD represents less than 1% of all articles dedicated to AD drug research. The major part of these articles deals with an old and rather toxic drug, clioquinol and related analogs, that do not efficiently extract copper from soluble amyloids.

We have designed and developed new tetradendate ligands such as **21** and PA1637 based on bis(8-aminoquinolines) that are specific for copper chelation and are able to extract copper(II) from amyloids and then can release copper ion upon reduction with a biological reducing agent. These studies contribute to the understanding of the physicochemical properties of the tetradentate copper ligands compared with bidentate ligands like clioquinol. One of these copper ligands, PA1637, after selection with a nontransgenic mouse model that is able to efficiently monitor the loss of episodic memory, is currently under preclinical development.

INTRODUCTION

Currently, 44 million patients are suffering from Alzheimer's disease (AD), a neurodegenerative disease related to aging, and this number is expected to reach 100 million in 2050.[1] The duration of the pathology (5−8 years) places a considerable burden on patients, families, caregivers, and public health costs. Therefore, the search for efficient anti-AD therapies is currently one of the major challenges in drug discovery.

Current AD therapies are based on four acetylcholine esterase (AChE) inhibitors and memantine, a weak antagonist of the *N*-methyl-D-aspartate (NMDA) receptor.[2] These drugs are not curative, offering short-term symptomatic relief. Moreover, they have side effects and their efficiency/cost ratios are questionable. Since the approval of memantine in 2003, no new AD drug has been approved. Although the clinical trials undertaken from 2002 to 2012 for AD involved 244 new compounds, all of them, except memantine, failed at different stages, corresponding to an attrition of 99.6%.[3] By comparison, the success rate is 20% for drugs for cardiovascular diseases and varies from 19% to 5% (a rate considered as unacceptably low) in oncology.[3] Therefore, there is an urgent need for new disease-modifying therapies to slow or stop the neurodegenerative process.

AD is characterized by abnormal deposition of the amyloid proteins (Aβ) and hyperphosphorylated tau protein, two proteins that have been considered as the main drug targets up to now. It should be important to enlarge the panel of drug targets for a disease induced by many different parameters. Moreover, drug screening using transgenic mouse models that do not accurately reflect human pathogenesis and, consequently, do not reliably predict drug efficacy is probably one of the reasons of the research failures.[4]

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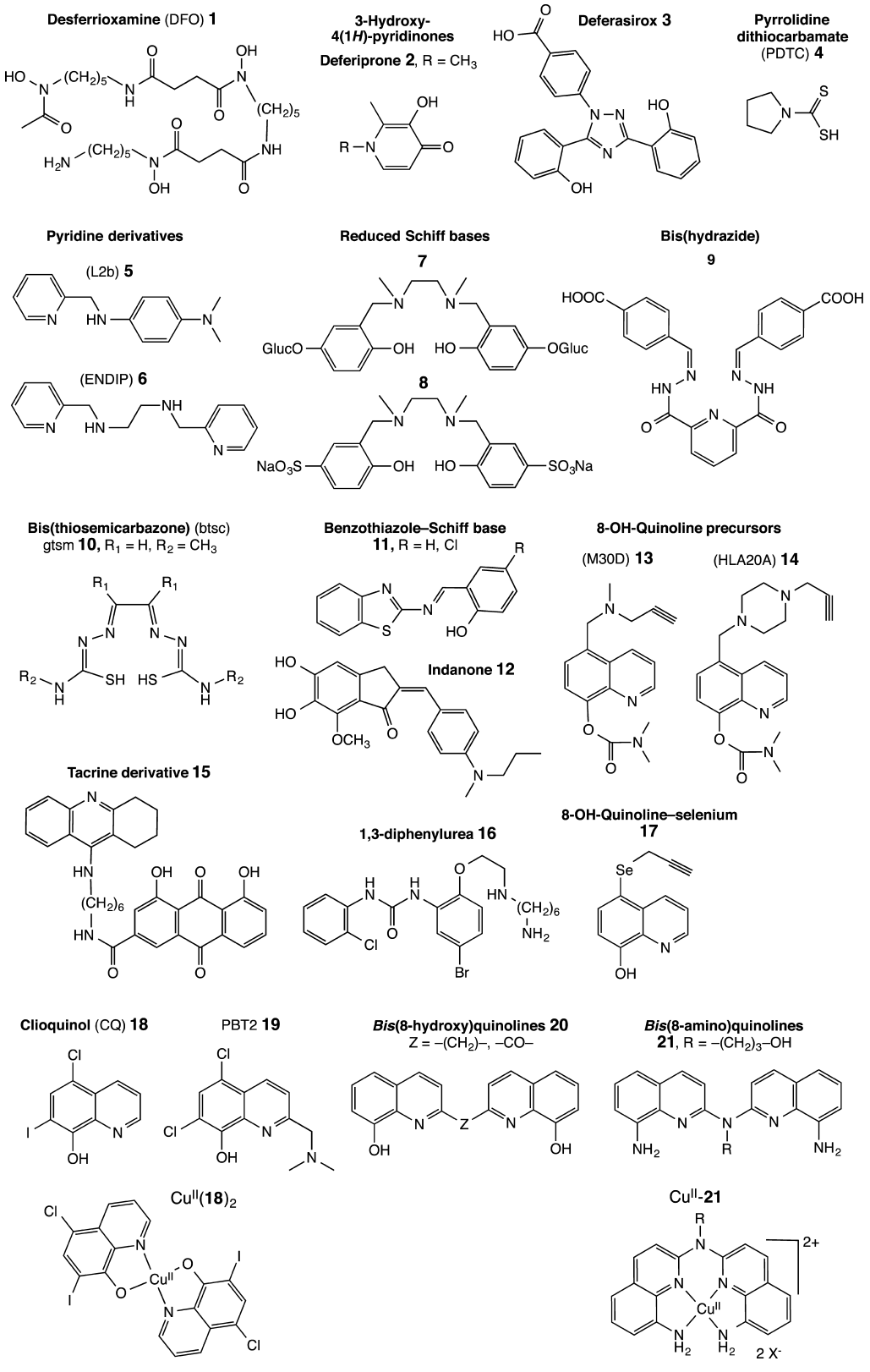

Figure 1. Structures of representative metal chelators. Structure of the complexes Cu^{II}–**21** and $Cu^{II}(\mathbf{18})_2$, according to monocrystal X-ray diffraction reported in refs 75 and 66, respectively.

Main Current Therapeutic Approaches

AD is a multiparameter disease outside of the simple concept "one disease, one target protein, one drug".[5] There is extensive evidence linking AD to (i) tau pathology, (ii) Aβ-aggregation, and (iii) metal dysregulation. These targets are probably interconnected. For instance, excessive Aβ production from β-amyloid precursor protein (APP) has been considered important, but amyloid aggregates alone are not a sufficient

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cause of disease.[6] Soluble Aβ oligomers appear to be more closely correlated with synaptotoxicity and impairment of long-term potentiation than senile plaques. These Aβ oligomers also contribute to abnormal tau phosphorylation, making a direct link between amyloid and tau.[7] Several caspases are involved in neuron degeneration, suggesting that an apoptotic process coexists with necrotic cell death evidenced by inflammation.[8]

Loss of Metal Homeostasis in AD

The post-mortem analysis of amyloid plaques indicates an excessive accumulation of copper, iron, and zinc by 5.7, 2.9, and 2.8 times the levels observed in normal brains, respectively.[9] Copper(II) and iron(III) peptide complexes can be readily reduced by endogenous reductants (Cu^{II}–Aβ exhibit reduction potential of +0.33−0.34 V/NHE).[10] Cu−amyloids induce oxidative damage via reduction of dioxygen by Cu(I)−amyloid, producing reactive oxygen species (ROS) involved in neuron death. Moreover, such a catalytic process causes overconsumption of endogenous antioxidants, causing their depletion in neurons. Aβ−Cu(II) is also involved in mitochondrial dysfunction.[11] The uncontrolled metal ions also influence NMDA receptor activation,[12] APP processing, and tau phosphorylation.[6] Copper sequestered in amyloid plaques may generate a deficit in other compartments of the brain or reduced SOD-1 activity, explaining why dietary copper supplementation has been proposed.[13]

To restore metal homeostasis in the AD brain, chelators promoting metal excretion from brain should be avoided. One should favor mild chelators able to extract copper ions from sinks (amyloids being the major one) and transfer them to copper-carrier proteins. Blood−brain barrier (BBB)-permeable ligands should be developed as therapeutic agents for a better homeostasis of copper in AD brains.

Iron homeostasis is also disturbed in several neurodegenerative diseases, including AD.[14] It was shown *in vitro* that iron(II) binds amyloids and can be responsible for oxidative stress.[15] The compartmentalization of Zn is also disturbed in AD brains,[6] and Zn(II) competes with Cu(II) for coordination to β-amyloids.[16] Zinc, but not copper, induces a dose-dependent increase in Aβ resistance to the Aβ-degrading protease matrix metalloprotease-2, MMP2.[17]

The distribution of these three metal ions is connected to amyloid metabolism. Like the copper carrier ceruloplasmin, APP interacts with ferroportin, oxidizes Fe(II), and loads Fe(III) into transferrin, thus taking part in iron regulation.[18] This APP ferroxidase activity is inhibited by Zn(II) supplied by extracellular Zn−Aβ deposits.[18] So, a failure of APP ferroxidaxe activity due to deregulation of Zn(II) might cause the cortical Fe(II) accumulation that characterizes AD pathology. This may explain why nonspecific copper chelating agents having some affinity for Zn(II), such as clioquinol, have some efficacy in APP transgenic murine models of AD.[18] In addition, modulation of tau phosphorylation and APP processing are linked to the zinc-induced activation of synaptic NMDA receptors.[6,19]

METAL CHELATORS AS POTENTIAL DRUGS AGAINST AD

The restoration of metal ion homeostasis is considered as a valuable challenge for AD chemotherapy.[6,20−23] For the period of January 2002 to January 2015, the Web of Science database contained 42 661 entries for research topics on "Alzheimer's disease AND (drug OR therapy)". However, only 390 entries, less than 1%, were obtained with "Alzheimer's disease AND metal (chelator OR regulator OR homeostasis)" as keywords. Among these 390 articles, most of them deal with the role of metal ions in the disease, and only a small proportion are devoted to potential curative drugs. These facts strongly indicate that metal regulation is only at its beginning in AD strategies. Such limited development of chelators might be because "classical chelators" and, by abusive extension, all chelators are considered to be toxic by some medical doctors. Toxic chelators, led by EDTA, are in fact non-specific ligands binding a large range of metal ions including calcium, magnesium, zinc, copper, iron, etc. However, little attention has been paid to the necessity of having specific chelators in order to limit toxic side effects. Representative chelators evaluated as anti-AD drugs during the last decade are listed in Figure 1. Biological data are cited, where they exist. For most of these ligands, very limited data are available concerning *in vivo* efficiency or safety. The drugs are presented as ligands for one particular metal, but metal selectivity is rarely experimentally documented.

Targeting Iron

Disruption of iron homeostasis due to aging or pathological conditions can induce neurodegeneration.[24] In fact, intracerebral microhemorrhages that release heme[25a] and up-regulation of the enzymatic degradation of heme may take part in neurotoxicity.[25b] The investigation of iron chelators as potential anti-Alzheimer's disease therapy is still preliminary. It mainly consists of experiment ligands that have already been approved to treat chronic iron overload from repeated blood transfusion in thalassemia patients (deferoxamine, also known as deferrioxamine B, deferiprone, and deferasirox) or conjugates of these drugs.

Deferoxamine (DFO). Intranasal DFO **1** (Figure 1) treatment reversed Fe-induced memory defects and inhibited amyloidogenic APP processing in APP/PS1 AD mice. DFO may block the production of ROS by inhibiting the iron redox cycle and subsequently modulates the gene expressions of hypoxia-induced factor, iron-regulatory protein-1, and APP.[26]

Deferiprone. Based on deferiprone structure **2**, various substituted 3-hydroxy-4-pyridinones were studied for iron chelation,[27] including bis- and tris(3-hydroxy-4-pyridinone) derivatives.[28] To facilitate the crossing of BBB, which has a high density of GLUT-1 transporters, glycoside derivatives able to release the 3-hydroxy-4-pyridinone upon enzymatic cleavage of the glycosyl residue have been proposed.[29] However, the 3-hydroxy-4-pyridinone moiety is not specific for iron chelation with respect to Zn(II)[29a] and Cu(II).[30] To enhance copper binding affinity, dendritic chelators containing 6−18 3-hydroxy-2-methyl-4-pyridinone residues have been synthesized.[31] To enhance brain drug delivery, conjugation of deferiprone with nanoparticles[32] or linkage of deferasirox **3** with lactoferrin[33] have been investigated.

Targeting Copper

Pyrrolidine Dithiocarbamate (PDTC). PDTC **4** is capable of transferring external Cu(II) into a cell to rescue *in vitro* hippocampal neurons from the toxicity of Aβ oligomers and to reduce tau phosphorylation in the hippocampus of transgenic APP/PS1 mice. Compound **4** was reported to prevent the cognitive decline of transgenic APP/PS1 mice, without altering the β-amyloid burden, probably by interfering with the Cu activation of the Akt pathway both in neurons and in astrocytes.[34]

Pyridine Derivatives. The 2-methylaminopyridine derivative **5** was shown to chelate Cu(II) and Zn(II) giving rise in both cases to a mixture of 1/1 and 1/2 metal/ligand complexes. The

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affinity of **5** was much higher for copper than for zinc, with K_d values comparable to those reported for Cu−Aβ and Zn−Aβ. *In vitro*, **5** was able to control Cu- or Zn-induced Aβ aggregation and to modify the structure of metal-induced Aβ aggregates, possibly via a ternary **5**−Zn−Aβ complex. This ligand restored the survival of human neuroblastoma cells treated with Aβ/Cu(II) or Aβ/Zn(II) and was able to disassemble human Aβ aggregates.[35] After intraperitoneal administration to 5XFAD AD mice, **5** was considered to specifically interact with metal−Aβ complexes and reduce Aβ aggregation and ROS production.[35] The dipyridine derivative ENDIP **6** forms a highly stable tetradentate 1/1 complex at physiological pH with Cu(II) and Zn(II), with log K_{app} values of 16.6 and 11.4, respectively. Compound **6** is able to displace Cu(II) from Aβ and thus to prevent the metal-induced amyloid aggregation and resolubilize amyloid precipitates.[36]

Reduced Schiff Base Derivatives. Compounds **7** and **8**, containing a reduced salen structure, were proposed to retrieve Cu(II) from Cu−Aβ, to prevent Aβ aggregation, and to act as antioxidants.[37,38] These water-soluble ligands form tetradentate complexes with copper(II) in a typical N_2O_2 square planar environment. For ligand **7**, zinc and nickel complexes with a similar structure were also obtained. The log K_{app} values of Cu^{II} and Zn^{II} were determined to be around 9 and 6, respectively, at physiological pH. The log K_{app} values of **8** for Cu(II) and Zn(II) at neutral pH are 14.6[38] and 6.1,[39] respectively, indicating a marked copper selectivity for this ligand. Putative biological activities of these ligands have not been published.

Bis(hydrazide) 9. In an Aβ overexpressing *Drosophila* transgenic model of AD, treatment with **9** reduces the Cu-induced retinal neurotoxicity.[40] This ligand forms a Cu/L complex with log K_{aff} = 6 in a mixture DMSO/water, 1/9.

Bis(thiosemicarbazones) (btsc). Cu^{II}(btsc) complexes are stable (log K_{aff} = 18) with a square planar N_2S_2 geometry and are capable of crossing cell membranes. A leader of this series, Cu^{II}−**10**, is reduced by intracellular reductants to Cu(I), which then dissociates from ligand. Treatment of APP overexpressing neuron-like cells with Cu^{II}−**10** resulted in an intracellular release of copper, a reduction of secreted monomeric Aβ levels, and an induction of the phosphorylation of phosphoinositol 3-kinase, Akt, and glycogen synthase kinase 3, involved in apoptosis.[41] Treatment with less stable Zn^{II}(btsc) complexes increased intracellular zinc levels with a subsequent dose-dependent depletion of monomeric Aβ levels.

Peptides (Not Drawn). A dodecapeptide prochelator was designed to be enzymatically activated by β-secretase to yield a chelator able to extract copper from Aβ and to protect against copper-induced ROS formation.[42] This approach is to generate the metal-binding functionality at the site of Aβ production and to specifically target the Cu−Aβ complex. Another peptide, SEN304, completely reversed $A\beta_{1-42}$ toxicity in human neuroblastoma SH-SY5Y cells and significantly increased the synaptic function in Aβ-treated cortical neurons. When incubated with slices of rat hippocampus, SEN304 completely abolished the inhibition of long-term potentiation induced by $A\beta_{1-42}$.[43]

Multifunctional Ligands. In order to improve efficiency and selectivity, ligands able to chelate metal ions and to interact with other Alzheimer's disease targets have been proposed. For example, several ligands able to interact with Aβ (**11**)[44] or to inhibit monoamine oxidase (**12**)[45] or AChE or BuChE (**13**, **14**, **15**) were proposed.[46−48] Diphenylurea **16** combines in a single molecule an Aβ-secretase inhibitor and a potential metal binding site.[49] Compound **17** combines the chelating properties of an 8-hydroxyquinoline (see below) and selenium as "redox buffer".[50] It is noteworthy that glutathione peroxidase, involved in the reduction of H_2O_2 to water by glutathione, contains a selenocysteine as redox active residue.[51]

Clioquinol, PBT2, and Other 8-Hydroxyquinolines. Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline, CQ, **18**, Figure 1) is a nonspecific copper−zinc chelator, able to decrease Aβ deposits and to improve learning and memory capacities of APP transgenic mice.[52] *In vitro*, CQ also partly restored sensitivity to MMP2 degradation of Zn-containing Aβ amyloids.[17] Unfortunately, clioquinol, formerly used as antifungal and antiprotozoal, induced subacute myelo-optic neuropathy[53] and was withdrawn from the market in 1983.[54] The neurotoxicity has been attributed to zinc chelation.[55,56] In fact, 8-hydroxyquinolines are nonspecific metal chelators,[57] and the affinity constant of CQ for Cu(II) is only 1 order of magnitude higher than that for Zn(II) (log K = 10 and 9, respectively).[20,58] Clioquinol was a prototype for other 8-hydroxyquinolines able to limit metal−Aβ interactions and has been followed by PBT2 (**19**), whose structure has been recently revealed.[20] This drug candidate was well tolerated and exhibited noticeable efficacy in a phase IIa, double-blind, placebo controlled clinical trial.[59] However, PBT2 did not meet its primary end point of a statistically significant reduction of the levels of β-amyloid plaques in the brains of prodromal/mild Alzheimer's disease patients. No improvement was observed on the secondary end points of brain metabolic activity, cognition, and function, and as a result, the trial was stopped in March 2014.[60] PBT2 is currently being evaluated in patients with early to midstage Huntington's disease.[61]

To favor a targeted delivery, clioquinol was also encapsulated in mesoporous nanoparticles linked to glucose coated cerium oxide nanoparticles ($GCeO_2NPs$). Oxidative cleavage of these bonds allowed H_2O_2-triggered CQ release and protected rat pheochromocytoma cells from Aβ-induced oxidative stress.[62] However, the safety of CeO_2NPs remains a controversial issue.[63] A similar delivery system based on gold nanocages has been reported. In this case, the drug release can also be promoted by near-IR irradiation.[64] In an attempt to obtain chelators with lower toxicity and enhanced aqueous solubility compared with CQ, 8-hydroxyquinoline-appended cyclodextrins were recently reported.[65]

Mechanism of Action. Clioquinol is a bidentate ligand that forms 2/1 (ligand/metal ratio) square planar complexes with Cu(II) and Zn(II) ions (Figure 1).[66] Whereas clioquinol is effective for alleviating Aβ toxicity in yeast, analogs lacking either the hydroxyl group or the nitrogen atom are ineffective, indicating that CQ efficacy requires bidentate metal binding. These data also confirm that Aβ toxicity is correlated with its ability to store metal ions.[67] Besides competing with amyloid for the chelation of Zn and Cu, CQ increased the intracellular copper concentration in yeast.[68] Therefore, CQ and PBT2 were proposed to promote the translocation of Cu(II) and Zn(II) from the extracellular environment to the inside of the cell, thus rectifying the misbalance of metal ions.[20,69] However, *in vitro*, in the presence of Cu^{II}−Aβ, a stoichiometric amount of CQ forms a stable ternary CQ−Cu^{II}−Aβ complex that we recently characterized.[70] The same result was also observed with an analogue of PBT2.[71] As a consequence, 8-hydroxyquinolines are unable to extract copper(II) from soluble amyloids, indicating that these bidentate ligands are not really adapted as mediators between soluble Cu−amyloids and Cu carrier proteins for regulation of copper ions in AD brains.

Bis(8-hydroxyquinolines). Contrary to mono(8-hydroxyquinolines), bis(8-hydroxyquinolines), **20**, offer four binding sites

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N_2O_2 within a single molecule, giving rise to complexes with a ligand/metal ratio = 1/1 at low concentration.[72,73] Such tetradentate ligands have an affinity for copper(II) that is 4−6 orders of magnitude higher than that of mono(8-hydroxyquinolines), with log K_{app} of 15.5−16.6 at physiological pH. The ligand selectivity for copper with respect to zinc is 100 to 1000 (log K_{app} for Zn(II) = 12.5−14.2). These ligands are also highly efficient at solubilizing Aβ peptides and as inhibitors of H_2O_2 production by the system Cu−Aβ/ascorbic acid.

*Bis(8-aminoquinolines), **21**.* Following our search for specific copper chelators, we prepared a series of bis(8-aminoquinoline) ligands (**21**, Figure 1) linked by the C2 position of two quinolines, forming stable mononuclear N_4 square planar complexes with Cu(II) with log K_{app} values ranging from 16 to 17 at physiological pH.[74] Ligand **21** is a close analogue of PA1637 that is currently in preclinical development. The X-ray structure of the complex Cu^{II}−**21** was reported.[75] More importantly, the affinity of these ligands for Zn^{II} and Fe^{III} is negligible. In addition, these tetradentate ligands can also inhibit the catalytic production of H_2O_2 induced by Cu−Aβ, suggesting that they should be able to play a protective role against oxidative damage induced by copper loaded amyloids.[75] Most noticeably, and contrary to clioquinol under the same conditions, bis(8-aminoquinoline) ligands are able to fully abstract Cu(II) from Cu−Aβ and subsequently generate the Cu(II)−bis(8-aminoquinoline) complex.[70] Upon reduction of the Cu(II) complexes, copper is easily released from the bis(8-aminoquinoline) ligands whose geometry is unable to accommodate the tetrahedral geometry required for Cu(I). The electrochemical reduction potential of Cu^{II}−**21** was measured at −0.23 V/NHE, suggesting that it should be reduced by GSH and NADPH ($E^{\circ\prime}$ = −0.24 and 0.32 V/NHE, respectively).[75] Upon physiological reduction, Cu(I) ions should be released from these bis(8-aminoquinoline) "mediating" ligands and transferred to large copper-carrier proteins that are unable to directly extract copper from Cu−amyloids (Figure 2). These tetradentate ligands demonstrate two

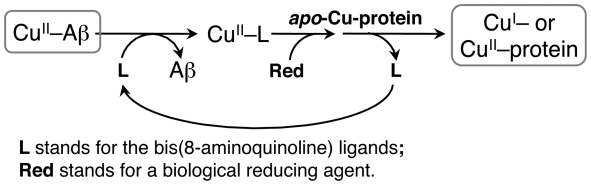

Figure 2. Regulation of copper homeostasis using bis(8-aminoquinolines).

key properties copper mediators should have: (i) ability to extract Cu(II) ions from copper−amyloids and (ii) capacity to release copper when the copper mediator is reduced. Then the released copper(I) ions can be easily trapped by endogenous copper carriers (unpublished data). The measured pK_a value of the bis(8-aminoquinoline) cycle was 3.3, and calculated log P was in the range of 3.3−3.8, sufficiently hydrophobic to be able to cross the BBB.

One of these ligands, PA1637 (an analogue of **21**, structure not drawn), has been selected as drug candidate and is able to fully reverse the memory deficit after oral treatment in a non-transgenic mouse model of AD.[76] Such effect was initially observed with a rather short treatment of 25 mg/kg, three times a week, 8 doses in total, and was later confirmed at only 12.5 mg/kg (unpublished data). This fast and efficient animal model was obtained by a single intracerebroventricular injection of short oligomers of Aβ_{1-42} in the hippocampal area of the mouse brain. The absence of memory loss by injection of Aβ_{42-1} and efficacy of memantine to inhibit the memory loss of mice treated with Aβ_{1-42} are strong validations of this mouse model. To reverse the memory loss induced by Aβ_{1-42} injection, PA1637 was slightly more active and much less toxic than CQ used as comparator. All mice survived after oral administration of PA1637 at 450 mg/kg, while the LD_{50} value of CQ in the same conditions was 100 mg/kg (ip data, LD_{50} = 400 and 50 mg/kg for PA1637 and CQ, respectively).[76] No ocular toxicity was observed with PA1637, which is currently in preclinical development.

CONCLUSION

The development of metal regulators as drugs to restore metal homeostasis in AD brains is still at its very early stage compared with other pharmacological approaches. We have shown that the selectivity for copper chelation is distinctly improved by using tetradentate 2,2′-bis(8-aminoquinolines) compared with bidentate 8-OH-quinolines like PBT2. In addition, the copper mediators that we are developing easily release copper ions when they are reduced by endogenous reductants, since these square-planar ligands are unable to accommodate Cu(I). The bis(8-aminoquinolines) like **21** and PA1637 are small hydrophobic tetradentate copper(II)-specific ligands. The capacity to fully reverse the deficit of episodic memory in a reliable nontransgenic mouse model of Alzheimer's disease suggested that these compounds should be considered as drug candidates for copper regulators in AD brains. In addition, studies of metal chelator properties should help to understand the role of metal ions in AD pathology.

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Notes

The authors declare no competing financial interest.

Biographies

Anne Robert was born in 1959 and received degrees from the Chemical Engineering School of Toulouse and from the University of Toulouse. She joined the research group of Bernard Meunier at the Laboratoire de Chimie de Coordination in 1985. She is currently Director of Research of the CNRS. Her major research interests are the chemical models of heme enzymes, the role of redox metals in biology (she especially studied the mechanism of action of peroxide based antimalarial drugs and how to target iron(II)-heme to develop drugs against blood parasites), and selective complexation of copper for chemotherapy of Alzheimer's disease.

Yan Liu received her Ph.D. degree from Sun Yat-sen University in 2007. From 2007 to 2009, she worked at Hong Kong Baptist University as a postdoctoral fellow in the group of Prof. Zhi-Hong Jiang in Hong Kong. She then moved to Japan and worked with Prof. Keiji Maruoka as a postdoctoral fellow at Kyoto University from 2010 to 2013. She joined the faculty of Guangdong University of Technology in 2013 and worked

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in the research group of Prof. Bernard Meunier. She has a wide range of research interests in synthetic organic chemistry and medicinal chemistry. Her current research is focused on developing specific copper chelators for potential anti-Alzheimer's disease agents.

Michel Nguyen received Ph.D. degrees from the University of Toulouse in 2001. He has worked for 6 years in medicinal chemistry at the Palumed company, where he developed new molecules against bacterial infections and malaria. He is currently researcher at the CNRS, working in the field of the selective complexation of metal ions for chemotherapy of Alzheimer's disease.

Bernard Meunier was born in 1947 and received degrees from the universities of Montpellier and Paris-Orsay. After a postdoctoral stage at Oxford, he joined the "Laboratoire de Chimie de Coordination du CNRS" in 1979. His recent research interests include the mechanism of action of antimalarial and antischistosomal drugs. He is also developing specific copper chelators for potential anti-Alzheimer's disease agents. He is actually President of the French Academy of Sciences (Member since 1999) and Foreign Member of the Polish Academy of Science since 2005. He is also the founder of Palumed, a small company devoted to medicinal chemistry (2002). He is currently Emeritus Director of Research at the CNRS, Distinguished Professor at the Guangdong University of Technology (Guangzhou, China), and Invited Professor at the Collège de France (Chaire d'Innovation Technologique Liliane Bettencourt, 2014−2015).

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■ DEDICATION

In memory of Dr. Guy Lavigne (deceased on April 23rd, 2015).

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