New Ideas in Chelation Therapy

Introduction

The cornerstone of the treatment of Wilson's disease is a reduction of copper levels *in vivo* using the orally-administered chelating agents **D-penicillamine** and **trientine dihydrochloride**. Patients with side-effects from receiving multiple blood transfusions for the amelioration of inherited anaemias are also successfully treated with chelating agents. Blood transfusion elevates these patients' iron concentrations, which, if not reduced by chelation, will damage vital organs. In recent years the deleterious role of metal ions in neurological diseases has come under the spotlight. In particular, some investigators believe that iron, copper and zinc have a role in the progression of Alzheimer's disease (AD) and that chelating agents could mitigate the disease.

The treatment of the blood disorder β-thalassemia and the world-wide research into Alzheimer's disease has produced some new ideas on the design of metal ligands for treating metal-related diseases. It is the aim of this article to briefly review a few of these developments in the hope that some impetus can be given to finding new ways of treating Wilson's disease, and in particular the neurological form of the disease. Of necessity, only a brief outline can be given here, and much of the information is codified in the structural formulae used by organic chemists. But the author would be pleased to provide more information, if requested, on the molecules which might be considered as candidates for testing in animals models of Wilson's disease.

Chelating agents introduced between 1940-1970 for treating metal intoxication

Some of the chelating agents which have been successfully used to treat metal intoxication are shown in **Figure 1**. **BAL** was originally developed to treat arsenic toxicity, but its potential for treating Wilson's disease was recognised by J. N. Cumings in 1948. The need to find an oral alternative to **BAL** for treating Wilson's disease led to the introduction of **D-penicillamine** and **trientine** by Dr John Walshe in 1956 and 1969, respectively. **DMSA** and **DMPS** are less toxic and more hydrophilic analogues of **BAL**, and are used to treat mercury intoxication. **EDTA** and its congener **DTPA** can be used to treat lead poisoning and are effective in removing radionuclides.

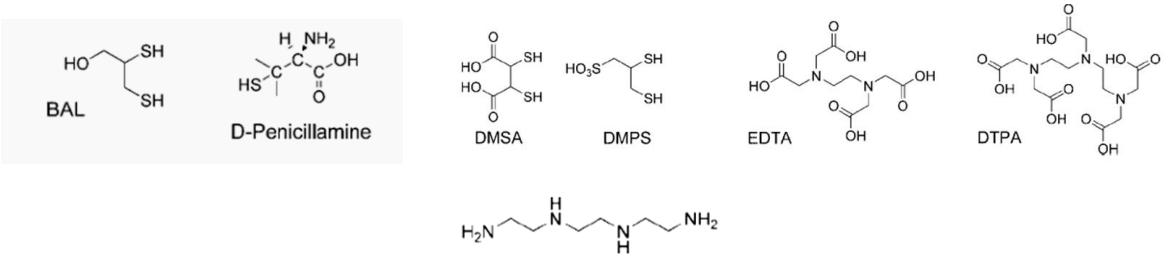

Figure 1: *Ligands developed from 1940-1970 to treat chronic and acute metal intoxication*

Chelating agents for treating transfusion-related iron overload disorders

Desferrioxamine (**DFO**) (**Figure 2**) is a hydroxamate-based hexadentate ligand, which has been used to treat iron overload since the 1970s. Disadvantages of using **DFO** (long subcutaneous infusion times; multiple reported side-effects) led to a search for new iron-chelating agents. Two of these are shown in **Figure 2**. **Deferiprone**, also known as **L1**, is a 3-hydroxy-4-pyridone derivative and has been used, with reservations, as an oral alternative to **DFO**. It effectively coordinates with Fe(III) *via* a deprotonated canonical di-oxo form derived from the parent molecule. A more accepted oral drug for iron overload disorders is **deferasirox** (**ICL670**) (**Figure 2**), first reported in 1999. This compound is a tridentate chelator, which selectively coordinates Fe(III) over Fe{II) and has little affinity for Zn(II) or Cu(II) ions.

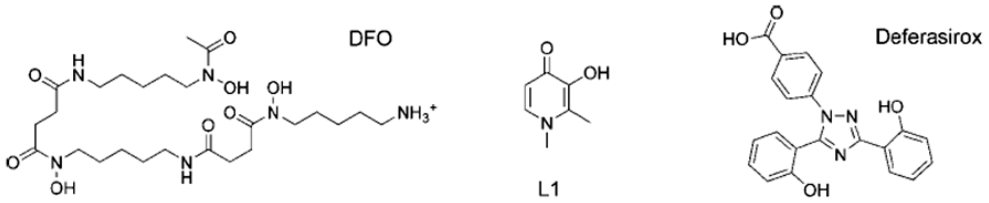

Figure 2: *Multidentate ligands used for the treatment of transfusion-related iron-overload conditions: DFO; deferiprone (L1); deferasirox*

The design of chelating agents for treating Alzheimer's disease

A characteristic pathology of Alzheimer's disease (AD) is the presence of extracellular fibrillized plaques, which are formed from β-amyloid (Aβ) peptides. Metal ions, especially zinc, copper and iron ions, are implicated in Aβ amyloidogenesis. Age-related increases in brain metal ion concentrations are associated with Aβ plaque deposition. In addition, the Aβ peptide can reduce Cu(II) and Fe(III) ions leading to Fenton and Haber-Weiss chemistry, the formation of hydroxyl radicals, and oxidative damage in brain tissue. Metal ions are therefore a therapeutic target for treating AD, and the disease might be amenable to chelating agents, which can either remove or redistribute localised concentrations of metal ions. Early promising results were shown both *in vitro* and in clinical trials with AD patients with the iron-chelator **DFO** (**Figure 2**). Chelating agents for treating AD need to cross the blood brain barrier (BBB), and should target specific sites rather than disrupt net metal homeostasis. These goals have resulted in several new strategies for designing ligands. One example, from the laboratory of Professor Chris Orvig at the University of British Columbia, Vancouver, Canada, is shown in **Figure 3**.

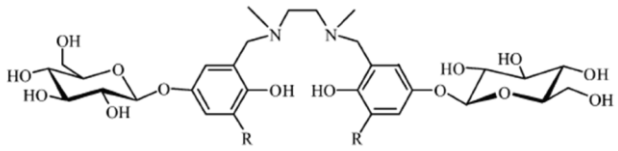

Figure 3: *Two multifunctional carbohydrate-containing ligands designed for brain-directed metal chelation and redistribution*

The two compounds shown in **Figure 3** contain a modified ethylenediamine metal chelating group, which is substituted on each nitrogen atom with a glucose-substituted phenolic moiety. The phenolic part of these compounds has antioxidant capability (for counteracting cellular oxidative stress), and the glucose residues are designed to aid water solubility and improve targeting, possibly by facilitating passage across the BBB. Both $\mathbf{H_2GL^1}$ and $\mathbf{H_2GL^2}$ were found to reduce Zn^{2+}- and Cu^{2+}-induced Aβ aggregation *in vitro*, and have potential as multifunctional agents in AD therapeutics.

Some other rationally-designed ligands, which have been tested in models of AD, are illustrated in **Figure 4**. **Feralex** is a glucose-bearing variant of **deferiprone**. In AD brain issue experiments, **Feralex** was comparable with **DFO** in removing Fe(III) ions from neurofibrillary tangles. This ligand is also likely to be effective for chelating Cu(II) ions. **DP-109**, which may be regarded as a highly substituted analogue of **EDTA,** is a hexadentate ligand with long-chain ester substituents to enhance lipophilicity. **DP-109** was designed for oral administration, greater brain penetration, increase residence time in the brain, and selective chelation of Zn(II), Cu(II), and Fe(III) ions within membrane compartments. In a mouse animal model of AD, **DP-109** reduced the amount of aggregated insoluble Aβ peptide while increasing the level of soluble Aβ forms. The ligand **XH1** contains two modified benzothiazole substituents, which are designed to covalently link with Aβ peptides, and a

DTPA-metal chelating core. *In silico* **XH1** binds to the $A\beta_{1-40}$ peptide and reduces zinc-induced $A\beta_{1-40}$ aggregation in solution. *In vivo*, in a mouse model, **XH1** attenuated amyloid pathology in the brain.

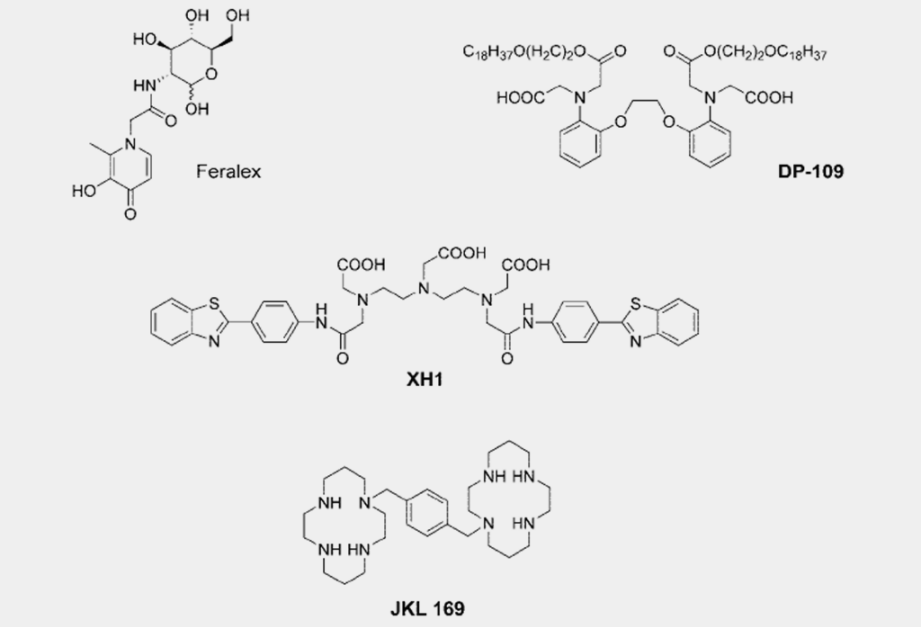

Figure 4: *Compounds developed for therapeutic metal ion manipulation: Feralex, a glucose-bearing deferiprone derivative; prodrug compound DP-109; a putative Aβ-associating chelator XH1; bicyclam JKL 169*

The copper chelator **JKL 169** contains two tetradentate cyclam rings (cyclic variants of **trientine**) linked through a *para*-phenylene group. In rats, **JKL 169** decreased copper concentrations of cerebrospinal fluid, slightly reduced serum copper, and significantly increased copper levels in the brain cortex. **JKL 169** therefore alters the distribution of copper *in vivo*, and is considered to be a viable AD therapeutic.

Conclusion

Research into a treatment for AD has stimulated new ways of targeting metals in the brain. Some of the ideas reported in this article should be applicable for treating Wilson's disease. The molecules shown here, although seemingly complex, are accessible using the armoury of modern synthetic chemistry. A first step would be to test some of these compounds in an animal model of WD, for example in the Long-Evans Cinnamon rat.

Reference

Professor Orvig's research group has contributed much to the literature of medicinal inorganic chemistry in recent years. This article is based mainly on one of Professor Orvigs's reviews: Scott, L. E.; Orvig, C., 'Medicinal Inorganic Chemistry Approaches to Passivation and Removal of Aberrant Metal Ions in Disease', *Chemical Reviews*, 2009, **109**(10), 4885-4910; doi: 10.1021/cr9000176

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