

Preface

The introduction, several years ago, of biological inorganic chemistry provided the amalgamation of concepts at the foundation of Inorganic Chemistry and Biochemistry. The interdisciplinary nature of *Biological Inorganic Chemistry* has the potential of coordinating the efforts of scientists in fields like biochemistry, inorganic and coordination chemistry, molecular and structural biology, enzymology, environmental chemistry, physiology, toxicology, biophysics, pharmacy and medicine. The inorganic biochemist is, therefore, potentially able to combine knowledge about the chemistry of metal ions with consideration of biomolecules with the aim of understanding how complex living systems function.

The progress in experimental investigation of the CNS at molecular level is now opening an unprecedented opportunity for the inorganic biochemist to contribute to the understanding of the roles that metal ions play in synaptic transmission, memory formation, and in the causes and treatments of neurological diseases. These concepts have been recently summarized in introducing the term *metalloneurochemistry* to describe the study of metal ions in the brain and nervous system at the molecular level.[†] Most work in this area is in its early stage, but the progress in the field is continuous and very significant, especially in delineating the role of metal ions in neurodegenerative diseases.

As the world's population lives longer and gets older, brain disorders, generally called neurodegenerative diseases, become one of the most difficult challenges for health care systems and human life protection of elderly. Most neurodegenerative disorders are fatal diseases and some of them like Alzheimer's disease (AD) are major cause of death in the developed societies. AD is the most common cause of dementia affecting several percent of humans of 65 and up to 40 to 50% of those above 90 years old. The annual cost of Alzheimer's in USA is estimated to be around 100 billion dollars. Parkinson's disease (PD) is the second most common brain disease affecting around 1% of those being 65–69 years old and around 3% of those above 80 years old. The increase of longevity of the human race, especially in the industrialized west, is great news, but the value to individuals and society is limited by the brain disorders, which can have great personal toll on the individual, friends and family and are very costly to the health system of any country. Thus, to make life longer and acceptable one needs to resolve several real problems including finding the causes of these age-related diseases and understanding the

[†]S.C. Burdette and S.J. Lippard, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 3605.

mechanisms of particular pathologies. From such findings, it should then be possible to create the effective set of therapeutic agents able to cure or at least slowdown the onset of neurodegenerative disease.

Although AD is certainly the most common cause of death among neurodegenerative disorders the most exciting of these must be prion diseases. Prion diseases are very rare, but captured world attention because of the recent epidemic of bovine spongiform encephalopathy or “mad cow disease.” Although prion diseases are rare indeed (around 10,000 times rarer than Alzheimer’s) and besides their headline grabbing high profile, they play a fundamental role in learning the neurodegenerative disorders due to very efficient animal models that are not available for other disorder such as Alzheimer’s.

Neurodegenerative disorders have different clinical symptoms but they have also mechanistic similarities, *e.g.*, protein misfolding, oxidative stress or a potential role of metal ions. More than 20 diseases could be related to deposition of protein aggregates, often amyloid fibrils, in which in some cases the major components are either short peptide fragments (as in AD) or whole fragments (*e.g.*, prion diseases). Many of these diseases relate to misfolding of a protein expressed normally in the brain. While the role of the protein in disease is known, the cellular activity of the normal isoform often remains poorly understood. We knew of “bad prions” long before we learned that the normal prion protein could be also very useful in a cellular context. The same concerns amyloid precursor protein involved in production of the beta-amyloid peptide in AD or alpha-synuclein implicated in PD pathology. There is a strong research drive going on to establish these protein’s biological functions as well as their structure destabilization resulting in protein misfolding, aggregation and fibril formation.

Only recently it was recognized that most, if not all, neurodegenerative disorders are closely related to oxidative stress, essential for development of disease and can cause death of neurons. Oxidative stress results from unbalanced pro-oxidant-antioxidant homeostasis leading to the over-production of the reactive oxygen and nitrogen species. Both in the oxidative stress as well in protein, regular and pathological functioning metal ions are strongly involved, and therefore understanding neurodegeneration is very closely related to chemistry of essential as well as toxic metal ions involved in brain functioning.

The role of metals in neurodegenerative diseases stems from all these aspects. The main proteins in three neurodegenerative diseases (Alzheimer’s, Parkinson’s and prion diseases) have all been shown to bind copper. Metals have been implicated in the misfolding and aggregation of beta-amyloid peptide, alpha-synuclein, and prion protein. Lastly, the metals associated with the pathology of these diseases are linked to the formation of oxidative stress. Therefore understanding the role that metals play in these disorders is becoming more and more central to unraveling their mystery. The genetic, biochemical and chemical aspects of protein behavior, and the impact of oxidative stress and metal ions on protein functioning and misfolding are the major objectives of this book.