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Medicinal bio-inorganic chemistry: papers from the Third International Summer School of Bioinorganic Medicinal Chemistry, Cagliari, Italy



The Third International Summer School of Bioinorganic Medicinal Chemistry for Ph.D. students, sponsored by University of Cagliari, was held in Cagliari at the end of August 2017. I am particularly grateful to all the colleagues, who answered unreservedly to our invitation to deliver their lectures. They have been present for the whole extent of the School and fully available to support the students sharing with them their knowledge and their experience. More than 25 students from all over Europe attended the School with extreme interest and profit.

I am also grateful to Prof. Dawson, who allowed to publish a number of selected papers on a special issue of Journal of Inorganic Biochemistry devoted to our School, and to all the authors, who, in addition to their lectures, gave their contribution to this issue.

Fifteen papers on topics of great novelty and interest, subdivided into reviews and full papers, constitute this issue. They deal with different topics that span from the use of ^{13}C – ^{13}C NOESY in Bioinorganic Chemistry to the chelating principles in Menkes and Wilson diseases. All these papers will be briefly summarized in the following.

Horn et al. [1] present a stimulating review on the chelating principles in Menkes and Wilson diseases, two genetic diseases of copper transport, which show opposite clinical pictures, copper deficiency or overload, respectively. Therapy of Menkes disease with copper-histidine, thiocarbamate, nitrilotriacetate or lipoic acid is discussed. In Wilson disease combination of a hydrophilic chelator e.g. trientine or dimercaptosuccinate with a brain shuttle e.g. thiomolybdate or lipoate, is discussed. New chelating principles for copper removal or delivery are outlined.

In the review of Gerosa et al. [2] Wilson disease (WD) is faced by the different viewpoint of pathologists. The role of epigenetic changes in the clinical presentation and evolution of liver disease in WD patients is discussed. The importance of transmission electron microscopy in the diagnosis of WD-related liver disease is underlined; mitochondrial changes, increased peroxisomes fat droplets, lipolysosomes and intranuclear glycogen inclusions are reported as the most frequent ultrastructural changes in the liver of WD carriers. Histochemical stains for copper are analyzed, and the Timm's method is suggested as the most sensitive one for revealing hepatic copper overload in all stage of WD.

Tinkov et al. [3] discuss the role of organotins in obesity and in the associated metabolic disturbances. Particularly, organotin exposure results in increased adipogenesis both in cell and animal models. Moreover, transgenerational inheritance of organotin-induced obese phenotype is demonstrated *in vivo*. Other mechanisms involved in organotin-induced obesity may include estrogen receptor and corticosteroid signaling, altered DNA methylation, and gut dysfunction. In addition to cellular effects, organotin exposure may also affect neural circuits of appetite regulation. The existing data demonstrate that

organotins are potent adipogenic agents, despite no epidemiologic studies have been performed and the existing indirect human data are contradictory.

Bjørklund et al. [4] treat the potential role of α -lipoic acid and its reduced form dihydrolipoic acid in their supposed Hg detoxifying potential. These ligands have been long time considered excellent antioxidants and oxidative stress scavengers. They can react not only with several reactive oxygen species, but also with trace metals, being able to strengthen the primary antioxidant defense system during cell injury or damage. In this perspective, their use is suggested for scavenging one of the major environmental toxicant, mercury.

Gibson presents [5] an intriguing review on Pt(IV) complexes; they act as prodrugs that are activated inside cancer cells releasing cytotoxic Pt(II) drugs such as cisplatin as well as two axial ligands. These ligands can be used to confer favorable pharmacological properties to the prodrug. When the ligands are bioactive moieties such as enzyme inhibitors or antiproliferative agents, the prodrug attacks several cellular targets at the same time acting as a multi-action prodrug. This class of multi-action Pt(IV) prodrugs seems to have great potential in the attempts to overcome resistance.

Zoroddu et al. [6] introduce a brief overview to highlight the importance of essential elements and the current knowledge about their essentiality. The human body needs about 20 essential elements in order to function properly and among them, for certain, 10 are metal elements. Until about 1950 poor attention was given to the so-called “inorganic elements” and while researches on “organic elements” (C, N, O and H) and organic compounds were given high priority, studies on essential inorganic elements were left aside. Based on current knowledge it is ascertained that metals such as Na, K, Mg, Ca, Fe, Mn, Co, Cu, Zn and Mo are essential elements for life and our body must have appropriate amounts of them.

Turano et al. [7] display examples of the application of the ^{13}C – ^{13}C Nuclear Overhauser Effect Spectroscopy (NOESY) experiment to the study of metalloproteins and critically discuss the advantages and drawbacks of the method as a function of the molecular size of the investigated systems. The contribution is focused on a few case studies among the systems analyzed in the group of the corresponding author.

Alghrably et al. [8] discuss in their review the interaction of amylin species with transition metals and membranes. Amylin is complementary to insulin in regulating and maintaining blood glucose levels in the human body. The misfolding and aggregation of amylin is primarily associated with type 2 diabetes mellitus, which is classified as an amyloid disease. The focus of this work is on how the chemistry and structural properties of amylin are affected by the interaction with metal ions. In particular, recent studies on the interactions of amylin

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with copper, zinc, iron, nickel, gold, ruthenium, and vanadium are presented.

Hecel et al. [9] discuss on how copper ions and membrane environment influence the structure of the human and chicken tandem repeats domain. Prion proteins (PrPs) from different species have the enormous ability to anchor copper ions. Due to the fact that PrP is a membrane-anchored glycoprotein and its unstructured and flexible N-terminal domain may interact with the lipid bilayer, these studies were carried out in presence of the surfactant sodium dodecyl sulfate (SDS) mimicking the membrane environment *in vitro*. The obtained results provide a fundamental first step in describing the thermodynamic and structural properties of Cu(II) binding to both human Octa4 and chicken Hexa4 repeats in both a DMSO/water and SDS micelle environment.

Valensin et al. [10] present a work of biological relevance: the interaction between copper and Amyloid β displays the interplay between the two copper oxidation states, Cu(II) and Cu(I), and their involvement in redox reactions. Both copper ions share the ability to bind Amyloid β . The data were obtained by means of NMR spectroscopy which provided relevant structural details of the metal complexes. The findings are consistent with the involvement of two or three His in the Cu(I) coordination sphere and indicate that His6 effectively participates to the metal binding.

Nurchi et al. [11] report a comprehensive study of the protonation equilibria of a series of polyamine ligands along with their complex formation equilibria with Cu^{2+} and Zn^{2+} . The primary aim was the achievement of homogeneous thermodynamic data on these ligands, in order to evaluate their influence on the homeostatic equilibria of essential metal ions in biological fluids. These polyamines are also largely used as linkers in the building of chelating agents for iron overload. The characterization of the formed complexes is discussed together with selected solid-state crystal structures, remarking the influence of the length of the chain on the stability of the complexes.

Pecoraro et al. [12] report an interesting work on the functionalization of luminescent lanthanide-gallium metallacrowns. The synthesis and characterization of $\{\text{Ln}[\text{12-MCGaIIIN}(\text{eshi})\text{-4}]\}_2(\text{iph})_4$ and $\{\text{Ln}[\text{12-MCGaIIIN}(\text{shi})\text{-4}]\}_2(\text{miph})_4$ metallacrowns (MCs). The ethynyl functionality allows for coupling of MCs to azides using copper(I) catalyzed alkyne-azide cycloaddition (CuAAC), while the maleimido functionality allows for coupling of the MCs to thiol-bearing compounds. The authors demonstrate these coupling reactions using benzyl azide for the former and cysteamine for the latter, with complete conversion shown by ESI-MS. With the Sm analogues, the MCs exhibit characteristic luminescent emission of Sm(III), which is preserved after introducing the ethynyl and maleimido groups onto the MC scaffold.

Crisponi et al. [13] present the simple and low cost synthesis of a new tripodal ligand in which three units of kojic acid are coupled to a tris(2-aminoethyl)amine (tren) backbone molecule. The protonation equilibria, together with the complex formation equilibria of this ligand with Fe^{3+} , Al^{3+} , Cu^{2+} and Zn^{2+} ions were studied. The stability of the formed complexes with Fe^{3+} and Al^{3+} are high enough to consider the new ligand for further studies for its clinical applications as a chelating agent. Biodistribution studies carried out to assess the capacity the ligand for mobilization of gallium in ^{67}Ga -citrate injected mice suggest that the new ligand can be a promising candidate as sequestering agent of iron and other hard trivalent metal ions.

Aaseth et al. [14] present a review on the effects of metals in the pathogenesis of Parkinson's disease (PD). In fact, environmental factors

appear to play a pathogenic role in most of the PD, and, in particular, epidemiological studies highlighted a connection between PD and metal exposure, including exposure to iron, mercury, manganese, and lead. The paper is also focused on strategies for the therapy of PD, mainly by using chelation therapy to reduce the level of iron.

The last paper by Al-Harathi et al. [15] consists in an overview of the current knowledge of Human Serum Albumin (HSA) structural characteristics, and of its coordination chemistry with transition metal ions. Considering the fact that HSA is a current clinical tool for drug delivery systems and a potential contender as molecular cargo and nano-vehicle used in biophysical, clinical and industrial fields, the authors underline the need for novel approaches to target the dynamic functional coordination chemistry of HSA in blood solution, at the atomic level.

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