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Biomedical uses and applications of inorganic chemistry. An overview

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Contents

Abstract

This article serves as an overview of the topics covered in this special issue dealing with aspects of biomedical inorganic chemistry. Topics include metal ions in disease (the use of chelating agents), metalloproteins as drug targets, organelles as targets (the mitochondrion), metal–drug interactions, metal-based chemotherapuetic drugs, and radioisotopes in medicine. The current activity and topical importance of these various areas are briefly discussed.

Keywords: Biomedical; Inorganic chemistry; Coordination chemistry

1. Introduction

The interest in uses and application of inorganic chemistry in medicine continues to expand. Major international conferences such as the International Conference on Bioinorganic Chemistry (ICBIC) and the European Conference on Bioinorganic Chemistry (EUROBIC) now contain a significant fraction of presentations dedicated to 'metals in medicine'. The first Gordon Research Conference dedicated solely to aspects of metals in medicine, an offshoot of the popular Metals in Biology meeting (http://www.grc.org) took place in July 2002. Recent dedicated volumes or sections in Metal Ions in Biological Systems, Chemical Reviews and Coordination Chemistry Reviews further testify to the growing importance of the discipline. As such, it is important to categorize and quantify major areas of research to identify new targets and opportunities for intervention of coordination chemistry. The articles in this issue contribute to this endeavor.

Continuing our previous categorization [1], the field of inorganic chemistry in medicine may be usefully divided into two main categories—drugs (ligands) which target metal ions in some form, whether free or protein-bound, and secondly, metal-based drugs and imaging agents where the central metal ion is usually the key feature of the mechanism of action. This latter class may also be conveniently expanded to include those radionuclides used in radio-immunoimaging and radio-immunotherapy. In such a broad array of uses and applications, it is difficult to be comprehensive—nevertheless the need remains to approach this field from a didactic and systematic manner, to enhance advances in understanding and development. The 'case studies' presented here represent a number of examples on the

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forefront of new and exciting examples of uses and applications of novel coordination chemistry in medicine.

2. Metal ions in disease. The use of chelating agents

Chelating agents are used to treat excess of metal ion whether due to exogenous metal ion intoxication by ingestion or by metabolic defects of endogenous metals leading to buildup, such as in Wilson's disease (Cu) and Thalassemia (Fe). The use of chelating agents may even be traced to a collaboration between Werner (the father of coordination chemistry) and Ehrlich (the father of chemotherapy, to find less toxic arsenic compounds for the treatment of syphilis [2]. An early, clinically useful chelator for lead toxicity and elimination of radionuclides was ethylenediaminetetraacetic acid (EDTA). The efficacy of chelation treatment is influenced by a number of factors including metal ion specificity, pharmacokinetics and metabolism of the chelating ligand. The treatments for copper and iron overload are well documented and a list of clinically used chelating agents is found in most textbooks [3]. New chelating agents continue to be sought and the contribution of Hider and Liu summarize recent developments for iron chelators with therapeutic applications.

3. Metalloproteins as drug targets

The role of metalloproteins in human health and disease is of increasing interest and importance as the genetic consequences of metalloprotein regulation become ever more recognized. Advances in our understanding of how cells process metals and the genetic basis of disease is naturally expanding the traditional directions of bioinorganic chemistry toward an appreciation of its medical importance—especially with respect to the role of metalloproteins in human health and disease. The major endogenous metals iron, copper and zinc all have well defined mechanisms of action. Zinc is the second most prominent trace metal in the human body after iron. Zinc deficiency may cause growth effects, although unlike copper and iron, few noxious effects of excess zinc have been observed. Zinc is involved in a large number of enzymatic functions, fulfilling both structural and catalytic roles [4]. These functions include DNA transcription and regulation as well as oxidation and hydrolysis, cleavage of peptide bonds as well as formation of phosphodiester bonds. Two important classes of zinc proteins have been extensively studied as attractive targets for chemotherapy-matrix metalloproteinases [5] and zinc fingers for AIDS and cancer [6]. In general terms, the medicinal approach to drug development is to develop as inhibitor substrate analogs, which will competitively bind to the zinc active site.

A relatively more recent aspect of zinc enzymes as targets—aminopeptidases—is covered here. These ubiquitous enzymes have a wide variety of biological functions that include protein maturation, protein degradation, hormone level regulation, and cell-cycle control. A type-2 methionine aminopeptidase from eukaryotes has been identified as the molecular target for the clinically relevant anti-angiogenesis drugs ovalicin and fumagillin (AGM-470) [7]. Angiogenesis is the process whereby new blood vessels are formed from pre-existing blood vessels. Improper regulation of angiogensis has detrimental effects in arthritis, inflammation and tumor growth, where tumors stimulate angiogenesis for oxygen supply and nourishment. Thus targeting these enzymes for potential inhibition through understanding of their metal-binding properties is a valid approach and is reviewed by Holz.

4. Organelles as targets. The mitochondrion

Mitochondria contribute to the regulation of energy production, metabolism, redox status and programmed cell death [8]. Mitochondria are thus an attractive drug target. Mitochondrial DNA is also an attractive target, because it is significantly more sensitive to covalent damage than nuclear DNA, because of lack of protective histones, and a limited capacity for repair. The pioneering work of Chen showed that enhanced mitochondrial membrane potential is a prevalent cancer cell phenotype [9]. Lipophilic cations accumulate inside mitochondria as a consequence of the higher membrane potentials [10]. Treatment strategies directed at novel cellular targets but which are differentiated between normal and tumor cells is an attractive approach to selective tumor cell killing. The interesting gold–phosphine complexes are examples of lipophilic cations which may also have a role in mitochondrial toxicity. This aspect is explored by Berners-Price and McKeage.

5. Metal–drug interaction

Many useful drugs contain metal-binding sites, which may alter the physiological profile of the free species. The cardiac toxicity of adriamycin is mediated through iron chelation. Cellular uptake of copper-chelated thiosemicarbazones is advanced over that of free ligand because of the enhanced lipophilicity of the metal–drug combination. Two contributions discuss drug–metal ion interactions. The quinolones are a group of synthetic antibacterial agents related to nalidixic acid. The potential effects on uptake and stability upon metal chelation are summarized.

Oxidative damage to plants and animals is a natural and unavoidable consequence of the use of oxygen for fuel. Superoxide has been implicated as a mediator of disease states such as inflammation, myocardial ischemia-reperfusion injury, cancer and AIDS [11]. Superoxide dismutase (SOD) enzymes are critical in removing such oxidative damage. Non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin inhibit cycloxygenase and eventually prostaglandin synthesis [12]. Copper and zinc complexes of NSAIDS may exhibit 'SOD-like' activity and may be useful in modulating the properties of the parent drugs.

6. Metal-based chemotherapeutic drugs

Cisplatin is probably the best known example of a small metal-containing drug. Its use and effectiveness in cancer chemotherapy is by now well documented [13,14]. The natural course of events has led to many 'second-generation' compounds based on the cisplatin structure in attempts to improve toxicity and/or expand the range of useful anticancer activity. Only carboplatin and, to a lesser extent, oxaliplatin have achieved clinical use [15]. It is highly unlikely that new direct structural analogues of cisplatin will find clinical use-exceptional properties would need to be found. This latter consideration led us to formulate the hypothesis that development of platinum compounds structurally dissimilar to cisplatin may, by virtue of formation of different types of Pt–DNA adducts, lead to compounds with a spectrum of clinical activity genuinely complementary to the parent drug. Newer, novel structures, which break the cisplatin paradigm by binding to DNA in other ways, have now advanced to clinical tests. The leading example is the charged trinuclear compound BBR3464, currently in Phase II clinical trials [16,17]. An interesting area is that of *trans*-platinum(II) compounds. Although, no exceptionally active compounds have been prepared as of yet [18,19] this area is worthy of further exploration.

Another avenue in platinum chemistry is to manipulate chemical and biological properties through oxidation. Indeed, the early Rosenberg studies recognized Pt(IV) as an active anticancer agent [20]. A number of Pt(IV) compounds have since undergone clinical trials-including Tetraplatin, CHIP (or Iproplatin) and most recently the potentially orally active JM-216. Interestingly, *trans*-Pt(IV) compounds were also tested because their kinetic inertness give more reasonable in vivo activity than its analogous Pt(II) compound [21]. A review of these factors is, therefore, pertinent for many reasons, not least the fact that the cytotoxicity is dependent on the reduction potential of the Pt(IV) compound-allowing suitable modification of pharmacokinetic parameters.

In early analog development of platinum compounds, complexes with 'windows of reactivity' similar to platinum may find similar uses. It is well documented that Ni and Pd analogs are too kinetically reactive to be of use as drugs, whereas Ir and Os compounds are too inert. Ruthenium and rhodium have produced compounds with the greatest promise. Indeed, the interesting ruthenium–sulfoxide complex, NAMI-A, has entered clinical trials as a possible anti-metastatic agent. Since the recognition of the messenger role of the small inorganic molecule NO in the early 1990s, a significant body of data has been accumulated. The rich chemistry of Ru–NO species may find use in design of new M–NO molecules with appropriate release rates of the cellular messenger NO as well as molecules which may scavenge endogenous NO or its potentially damaging oxidation products such as peroxynitrite. These and many other possible uses of ruthenium are summarized by Clarke.

Chemotherapy is the use of drugs to injure an invading organism without injury to the host. Coupled to the approaches of new compounds is the need to understand the metabolism of metal-based drugs. Especially since target interactions may not be as important in differentiating drug activity as aspects of metabolism and deactivation. The principal receptor for any drug system is plasma proteins, especially human serum albumin. Despite the intense study of Pt–DNA interactions only recently have detailed studies on the albumin–platinum interaction been presented [22]. The interaction of antitumor platinum-group metallodrugs with albumin is covered in this volume.

7. Radioisotopes in medicine

Finally, the in vivo use of metal radioisotopes in cancer detection and imaging is an important and well documented use of metal chelates [23]. The growing interest in coordination compounds to deliver boron for use in boron neutron capture therapy is summarized in the chapter by Valliant.

8. Summary and acknowledgements

This necessarily brief overview introduces the contributions covering a wide area of coordination chemistry with the goal of understanding and enhancing the use and applications of inorganic chemistry in medicine.

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