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REVIEW ARTICLE

A Review – Can metal ions be incorporated into drugs?

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ABSTRACT
Metallopharmaceuticals used as anticancer agents, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics, andradiosensitizing agents appear in therapeutic medicinal inorganic chemistry.

KEY WORDS Metallopharmaceuticals; metallodrugs

INTRODUCTION:
Metals have played an important role in medicine for years, ever since humans have walked the planet. Many are essential in our diets in varying quantities, although people have recently realized their significance. This could probably be attributed to our increased awareness of personel and families' health and increased media involvement in our life.

However, at the other extreme, certain metals remain toxic in trace amounts, which can enter the body via a variety of routes and often cannot be excreted leading to metal toxicity. Until recently many people were unaware of the extent of the risk of metal toxicity, for example, in the use of lead piping in houses; the legacy of which continues to this very day.

Many metallic elements play a crucial role in living systems. A characteristic of metals is that they easily lose electrons from the familiar elemental or metallic state to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metals play their role in biology whereas metal ions are electron deficient, most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules. This same principle applies to the affinity of metal ions for many small molecules and ions crucial to life, such as oxygen. Given this wide scope for the interaction of metals in biology, it is not surprising that natural evolution has incorporated many metals into essential biological functions. Metals perform a wide variety of tasks such as carrying oxygen throughout the body and shuttling electrons. Haemoglobin, an iron-containing protein that binds to oxygen through its iron atom, carries this vital molecule to body tissues. Metal ions such as zinc provide the structural framework for the zinc fingers that regulate the function of genes in the nuclei of cells.

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Similarly, calcium-containing minerals are the basis of bones, the structural framework of the human body. Zinc is a natural component of insulin, a substance crucial to the regulation of sugar metabolism. Metals such as copper, zinc, iron and manganese are incorporated into catalytic proteins-the metalloenzymes-which facilitate a multitude of chemical reactions needed for life[1].

Since nature has made such extensive use of metal ions in biological systems, the following questions arise:

Can metal ions be incorporated into drugs? Are coordination compounds potential medicinal agents? Can coordination chemistry be used for medicinal purpose?

Medicinal inorganic chemistry as a discipline has only existed for about the last 30 years,since the discovery of antitumor activity of cisplatin. By the field existing as a discipline, we specify where a known chemical compound has been discovered to have a specific activity and where studies have been done to elucidate the mechanism of action as well as to optimize and improve the activity of (e.g platinum) compounds in general. Pt-based combination chemotherapy is still the mainstay for the treatment of solid malignancies (especially testicular, ovarian and small cell lung cancers).Newer Pt analogues are emerging that expand the spectrum of activity of the original drugs. The unique lesion made by Pt has not, to date, been mimicked by any organic drugs-clearly the metal-biomolecule interaction is critical to the antitumor activity of any metallodrug.

Medicinal inorganic chemistry has been practiced, however, for almost 5000 years. As far back as 3000BC the Egyptians used copper to sterilize water. Gold was used in a variety of medicine in Arabia and China 3500years ago, more as a result of the precious nature of gold than of its known medicinal activities. Various iron remedies were used in Egypt about 1500BC, around the sametime that zinc was discovered to promote the healing of wounds. In Renaissance era Europe, mercurous chloride was used as a

diuretic and nutritional essentiality of iron was discovered. It is in the last 100years, however, that the medicinal activity of inorganic compounds has slowly been developed in a rational manner, starting in the early 1900s with K [Au (CN) $_2$] for tuberculosis, various antimony compounds for leishmaniasis, and the antibacterial activity of various gold salts in a number of different conditions. When one thinks of drugs, one often thinks of organic compounds such as the antibacterial penicillins, the nutrient vitamin C and the psychoactive drugs, such as LSD, THC, etc. The Biochemical literature of the last 30years chronicles the burgeoning understanding that many of the biological activities of proteins and enzymes can be ascribed to the metal centers, with the organic backbone acting as a scaffold to hold the metal ion in place for the requisite transformation. Because of this rapid growth of biological inorganic chemistry, it seems logical to explore in parallel the medicinal properties of the various metal ions that are found naturally and even of those that are not found naturally and even of those that are not known to have essential benefit. In the last 50 years, knowledge of the central importance of inorganic elements in organisms has opened up the possibility for inorganic chemists to contribute to health and well-being of man and all other organisms.

It is ironic to note that the first structure-activity relationship, which was developed by Paul Ehrlich in the first decade of the 20th century, involved the development of the inorganic compound *arsphenamine* (otherwise known as Salvarsan or Ehrlich 606) as a successful treatment for syphilis. Ehrlich was the founder of chemotherapy, which he defined as the use of drugs to injure an invading organism without injury to the host. He also discovered the preferential accumulation of lead in the central nervous system, first formulated the chemotherapeutic index as well as the "magic bullet" concept,and was awarded the Noble Prize in 1908 for his discovery of immunochemistry. Many of these ideas are considered to be the fundamental concepts of medicinal chemistry,which is mostly based on the development of organic molecules, yet this first structure-activity relationship evolved from medicinal inorganic chemistry.

The intentional introduction of a metal ion into a biological system will be for either therapeutic or diagnostic purpose. As was noted by Peter Sadler some years ago, most of the elements of periodic table upto and including bismuth, with an atomic number of 83,have potential uses in the design of new drugs and diagnostic agents. Sadler also pointed out that medicinal inorganic chemistry provides active metal complexes, active metal ions, or even active ligands, as potential agents. In diagnostic medicinal inorganic chemistry, the γ-emitting radiopharmaceuticals(e.g ^{99m}Tc-involved in millions of nuclear medicine scans per year),the magnetic resonance imaging contrast agents(there are now four complexes of Gd^{3+} on the market).and X-ray contrast agents($BaSO_4$) are all in heavy clinical use.

Following on these uses in diagnosis, we believe that there will be a huge growth in therapeutic application of metal complexes in the next 10-20years.In British Columbia, Canada, companies such as AnorMED and Kinetek Pharmaceutical, both of which currently have metal complexes in clinical trials, are part of a vibrant and growing biotechnology industry with a significant emphasis on medicinal inorganic chemistry.

Chemotherapeutics, such as anticancer agents, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics and radiosensitizing agents, also appear in therapeutic medicinal inorganic chemistry, as do the radiopharmaceuticals (β-emitters are being intensively studied for selective radiation therapy). Cisplatin (an active complex) is the archetypal inorganic drug it contains not one atom of carbon.

Any metal ion or complex, or indeed any chemical compound, is subjected to the potential limitations in the Bertrand diagram, which is usually used in discussing the essentiality of elements. The area of optimum physiological response will vary greatly according to the element, its speciation and oxidation state and the biochemistry of the specific compound in which it is found. Therefore, the areas of deficiency, toxicity and optimum physiological response can be dramatically varied by considering a combination of these variables, as well as design features of the potential ligand which may be altered to tune the delivery of that metal ion into the biological system. This refinement of the biological properties of metal complexes by ligand modification along with the design of ligands to alter the homeostasis of endogenous metal ions, will provide many therapeutic and diagnostic agents over the coming years and will direct medicinal inorganic chemistry into discipline of central importance in medicine and science.

James Cowan's new molecules, called metal co-ordination complexes, mimic the activity of natural enzymes that break apart DNA, RNA and proteins in the body. They have tailor-made different complexes to break apart portions of RNA that enable HIV and Hepatitis C viruses to function, as well as the ACE enzyme that constricts blood vessels in the body.

The complexes work in one of the two ways: some use a process called redox chemistry to steal electrons from the bonds holding the target molecules together. Others use hydrolysis, meaning that they breakdown the target's chemical waterproofing, so that the water that is naturally present in a cell dissolves the target.

With proper tailoring to certain metabolic enzymes, these strategies could work against cancer. He also sees applications in homeland security, such as complexes that destroy the Anthrax bacterium.

Even though these new complexes are partly made of metal, drugs based on them could potentially be less toxic to the body than conventional treatments.

Metals can be toxic, but so can some organic molecules that are used as drugs.

One of these complexes could destroy a target, and then move on to another, eventually destroying many targets. So a smaller dose of a metal complex could do the work of a larger dose of a traditional drug.

Completely destroying the target molecule also lowers the chance that a virus will develop a drug-resistant strain.
These metal complexes represent a good first step towards the development of multi-functional drugs called dual activity agents.

Metal ions play a key role in the actions of synthetic and natural metalloantibiotics, and are involved in specific interactions of these antibodies with proteins, membranes, nucleic acids and other biomolecules. For e.g, the binding of Fe/Co-Bleomycin,Fe/Cu-Streptonigrin,Mg-quinolone,Mg-quinobenzoxazine, Mg-Aureolic,and cisplatin with DNA impairs DNA function or results in DNA cleavage; the involvement of Mg/Fe in the binding of tetracyclines; the binding of metallobacitracin to undecaisoprenyl pyrophosphate prohibits the recycling of the pyrophosphate to phosphate which inturn inhibits cell wall synthesis; and the binding of metal ions to siderophores or ionophores allows their transport through cell membrane which can cause disruption of the potential across the membrane, enables the microorganisms.

In addition to the metalloantibiotics, a number of drugs and potential pharmaceutical agents also contain metal-binding or metal-recognition sites, which can bind or interact with metal ions and potentially influence their bioactivities and might also cause damages on their target biomolecules. Numerous examples these “metallodrugs” and “metallopharmaceuticals” and their actions can be found in literature, for instance:a)several anti-inflamatory drugs, such as *aspirin* and its metabolite salicylglycine, ibuprofen, the indole derivative *indomethacin*, bioflavonoid *rutin*, *diclofenac, suprofen* and others are known to bind metal ions and affect their antioxidant and anti-inflammatory activities; b)the potent histamine H-2-receptor antagonist *cimetidine* can form complexes with Cu2+ and Fe3+,and the histidine H2 blocker antiulcer drug *famotidine* can also form stable complex with Cu2+ c) the anthelmintic and fungistatic agent *thiabendazole*, which is used for the treatment of several parasitic diseases, forms a Co2+ complex with metal: drug ratio of 1:2 d)the Ru2+ complex of the antimalarial agent *chloroquine* exhibits an activity two to five times higher than the parent drug against drug-resistant strains of Plasmodium falciparum e)a number of Ru2+/3+ and Rh3+/2+ complexes are found to bind DNA and exhibit antitumor activities f)the antiviral *trifluoperazine* forms complexes with with VO2+,Ni2+,Cu2+,Pd2+ and Sn4+ which exhibit higher inhibition activities than the metal-free drug when tested on Moloney murine leukemia virus reverse transcriptase g)the clinically useful β-lactamase inhibitor *sulbactam* can form complexes with Ni2+,Cu2+ and Fe3+ h)a few hormone-anchored metallodrugs have been prepared which show enhanced receptor binding and higher activities against cancer cells i)the *thiosemicarbazone-conjugated isatin* can bind late first-row transition metal ions and exhibit activity toward human leukemia cell lines, however, without inducing cell apoptosis j)metal complexes(including Be2+,Mg2+,Mn2+,Cu2+,Cd2+,Zn2+,Pb2+,Fe3+,Al3+ and La3+) of several *carbonic anhydrase inhibiting sulfonamides* have been investigated for their topical intraocular pressure lowering properties and as potential agents against gastric acid imbalance.

There are also a number of metallodrugs and metallopharmaceuticals which have been utilized for the treatment of diseases and disorders or as diagnostic agents, such as gold antiarthritic drug, bismuth antiulcer drugs, gadolinium MRI contrast agents, technetium radiopharmaceuticals, metal based X-ray contrast agents and photo-and radio-sensitizers, vanadium as insulin mimics, and lithium psychiatric drugs. The metal ion Li+ can be considered the the smallest effective metallodrug whose carbonate and citrate salts exhibit significant therapeutic benefit in the treatment of manic depression. The metal ion Sb3+ may be regarding as the simplest “metalloantibiotics” whose salts(including N-methylglucamine antimonite and Na-stibogluconate) have been utilized for the treatment of leishmaniasis against the protozoan parasite Leishmania. The antiprotozoal mechanism of Sb3+ is thought to be attributed to its binding to trypanothione that is essential for the growth of the parasite.

The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance.

The field of inorganic chemistry in medicine may usefully be divided into two main categories: firstly, ligands as drugs which target metal ions in some form, whether free or protein-bound;and secondly metal-based drugs and imaging agents where central metal ion is usually the key feature of the mechanism. This latter class may also be conveniently expanded to include those radionuclides used in radioimmunoimaging and radioimmunetherapy.

The application of inorganic compounds to medicine requires detailed examination of the fundamental aqueous chemistry of the proposed drug, including its pharmaceutics, the metabolic fate in blood and intracellularly and the effects of the drug on the target of choice. Coordination and organometallic complexes present a wide variety of coordination spheres, ligand designs, oxidation states and redox potentials, giving the ability to systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors.

The usefulness of any drug is a balance between its toxicity and activity.

The crystal structure, combined with physical and biophysical studies, allows visualization of likely binding sites of many potential inorganic drugs. Abundant cysteine-rich small peptides, especially glutathione and proteins such as metallothionein represent detoxifying but also deactivating pathways for inorganic drugs.

The nature of the target to be attacked by any drug obviously depends on the specific application, Many cytotoxic metal complexes target DNA because of its importance in replication and cell viability. Coordination compounds offer many binding modes to polynucleotides, including outer-sphere non covalent binding, metal coordination to nucleobase and phosphate backbone sites, as well as strand cleavage included by oxidation using redox-active metal centers. The later transition metals such as platinum and ruthenium favor binding to electron-rich nitrogens on the bases, especially guanineN7.Titanium and early metals may display a mixture of nucleobase and phosphate backbone binding. The accessibility of different oxidation states of metals such as Fe,Cu,Co,Ru,Mn,etc. may allow for redox chemistry resulting in strand breakage. Anticancer antibiotic *bleomycin*, whose mode of action on target DNA is strand scission mediated by Fe binding to the drug.

A challenge for the medicinal inorganic chemist is the placement of coordination chemistry within this new paradigm.

Medicinal applications of metals can be traced back almost 5000years.The many activities of metal ions in biology have stimulated the development of metal based therapeutics. Metal centers, being positively charged biomolecules; the constituents of proteins and nucleic acids offer excellent ligands for binding to metal ion. The pharmaceutical use of metal complexes therefore has excellent potential. Designing ligands that will interact with free or protein-bound metal ions is also a recent focus of medicinal inorganic research. Developing metal complexes as drugs, however,is not an easy task. Accumulation of metal ions in the body can lead to deleterious effects. Thus biodistribution and clearance of the metal complex as well as its pharmacological specificity are to be considered. Favourable physiological responses of the candidate drugs need to be demonstrated by in vitro study with targeted biomolecules and tissues as well as in vivo investigation with xenografts and animal models before they enter clinical trials. A mechanistic understanding of how metal complexes achieve their activities is crucial to their clinical success, as well as to the rational design of new compounds with improved potency.

A significant rising interest in the design of metal compounds as drugs and diagnostic agent is currently observed in the area of scientific inquiry appropriately termed medicinal inorganic chemistry. Investigations in this area focus mostly on the speciation of metal species in biological media based on possible interactions of these metal ions with diverse biomolecules, in an effort to contribute to future development of new therapeutics or diagnostic agents. A wide range of metal complexes are already in clinical use,and encourage further studies for new metallodrugs, such as metal-mediated antibiotics, antibacterial, antiviral, antiparasitic, radiosensitizing agents and anticancer compounds. However, their mechanisms of action are often still unknown. Recently more than a thousand potential anticancer metal compounds, from the National Cancer Institute (NCI) tumor-screening database, were analyzed based on putative mechanisms of action and classified into four broad classes, according to their preference for binding to sulhydryl groups, chelation, generation of reactive oxygen species and production of lipophilic ions.

Additionally, increasing knowledge of the biological activities of simple metal complexes guided many researchers to the development of promising chemotherapeutic compounds which target specific physiological or pathological processes. Many potential antitumoral agents have been investigated based on their anti-angiogenesis or pro-apoptotic behaviour. These studies involve both designed and natural products, in association with essential metal ions such as copper, or iron.

Disturbed redox equilibrium, described as oxidative stress, is usually pathological and changes the oxidation state of cells over long time periods usually cause damage to biomolecules (lipid peroxidation, protein oxidation, DNA strand breaks).Intracellular redox state unbalance in cell is responsible for induction of apoptosis, an ordered sequence of events that lead to cell programmed death. Apoptosis can be triggered by physical or chemical stimuli, such as UV and γ-radiations, hypoxic conditions and prooxidant agents. The cell-sucide program is then activated through induction of gene transcription, following DNA damage and inducing protein repair or the cell cycle arrest. If damaged DNA is not repaired, the induction of caspase-dependent apoptosis occurs, followed by removal of apoptotic cell through macrophages or neighboring cell phagocytic-activity without inflammation.

Redox active complexes can provide an alternative tool for redox regulation as a therapeutic basis, interfering in oxidative trigger mechanisms in cells. Specific ligands can be useful in the modulation of metal ion reactivity, by modifying their redox potential, hydrophilic or lipophilic characteristics or saturating its coordination sphere and therefore, avoiding undesirable interactions with cell components.

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