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Review

Mass spectrometry as a powerful tool to study therapeutic metallodrugs speciation mechanisms: Current frontiers and perspectives

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ABSTRACT

Metal-based compounds form a promising class of therapeutic agents, whose mechanisms of action still need to be elucidated, and that are in general prone to undergo extensive *speciation* in physiological environment. Thus, determination of the fate of the metal compounds in complex biological systems, contributing to their overall pharmacological and toxicological profiles, is important to develop more rationalised and targeted metal-based drugs. To these aims, a number of spectroscopic and biophysical methods, as well as analytical techniques, are nowadays extensively applied to study the reactivity of metal complexes with different biomolecules (e.g. nucleic acids, proteins, buffer components). Among the various techniques, molecular mass spectrometry (MS) has emerged in the last decade as a major tool to characterise the interactions of metallodrugs at a molecular level.

In this review, we present an overview of the information available on the reactivity of various families of therapeutic metallodrugs (mainly anticancer compounds based on Pt, Ru, Au and As) with biomolecules studied by different MS techniques, including high-resolution ESI-, MALDI- and ion mobility-MS among others. Representative examples on the potential of the MS approach to study non-covalent interactions are also discussed. The review is organized to present results obtained on samples with different degrees of complexity, from the interactions of metal compounds with small model nucleophiles (amino acids and nucleobases), model peptides/oligonucleotides, target proteins/nucleic acids, to the analysis of serum, cell extracts and tissue samples. The latter requiring combination of proteomic methods with advanced MS techniques. Correlations between molecular reactivity of metallodrugs and biological activity are hard to establish, but differences in the reactivity of metallodrugs to biomolecules and their different adducts, as revealed by MS methods, may indicate differences in their modes of action. Overall, the knowledge offered by MS methods on metallodrugs speciation is invaluable to establish new rules and define new trends in the periodic table aimed at rationalizing the behavior of metal compounds in complex living systems.

Abbreviations: A, adenine; AcO, acetate; Atox1, antioxidant protein 1; BEOV, bis(ethyl-maltolato)oxovanadium(IV); bipy, bipyridine; bipy^{dmb}, 6-(1,1-dimethylbenzyl)-2,20-bipyridine); BMOV, bis(maltolato)oxovanadium(IV); cbdca, 1,1-cyclobutanedicarboxylate; CE, capillary electrophoresis; CID, collision induced dissociation; cisplatin, *cis*-[$PtCl_2(NH_3)_2$]; Cyt *c*, cythochrome *c*; CZE, capillary zone electrophoresis; DACH, diaminocyclohexane; dAMP, 2′-deoxyadenosine 5′-monophosphate; dG, 2′-deoxyguanosine; dGMP, 2′-deoxyguanosine 5′-monophosphate; dien, diethylenediamine; DMSO, *S*-dimethylsulphoxide; DTT, dithiothreitol; ECD, electron capture dissociation; EFTEM, energy filtered transmission electron microscopy; en, ethylenediamine; ESI-MS, electrospray ionization mass spectrometry; ETD, electron transfer dissociation; 9-EtG, 9-ethylguanine; FASP, fast aided sample preparation; FID, fluorescent intercalator displacement; FRET, fluorescence resonance energy transfer; FT, fourier transform; FT-ICR, fourier transform ion cyclotron resonance; G, guanine; G4, G-quadruplex; GF, gold finger; GSH, glutathione; Gpx, glutathione peroxidase; Hb, haemoglobin; hCtr1, human copper transporter 1; HSA, human serum albumin; HSAB, hard and soft acids and bases; HPLC, high performance liquid chromatography; hTf, human serum transferrin; ICP-AES, inductively coupled plasma absorption emission spectroscopy; ICP-MS, Inductively Coupled Plasma Mass Spectrometry; ICP-OES, inductively coupled plasma optical emission spectroscopy; IEF, isoelectric focusing; Im, imidazole; IM-MS, ion mobility mass spectrometry; In, indazole; IRMPD, infra-red multi photon dissociation; IUPAC, international union of pure and applied chemistry; KCE, kinetic capillary electrophoresis; KP1019, InH[*trans*-In_2RuCl_4]; KP1339, Na[*trans*-In_2RuCl_4]; LA-ICP-MS, laser ablation inductively coupled plasma mass spectrometry; LC, liquid chromatography; LTQ, linear trap quadrupole; MALDI-MS, matrix assisted laser desorption ionization mass spectrometry; MP-11, microperoxidase-11; MS, mass spectrometry; MS/MS or MS^n, tandem mass spectrometry; MudPIT, multidimensional protein identification technology; NAMI-A, ImH[*trans*-Im(DMSO)$RuCl_4$]; NHC, *N*-heterocyclic carbene; nESI, nanospray; nLC, nano-liquid chromatography; OmpA, outer membrane protein A; PAGE, 1D polyacrylamide gel electrophoresis gel electrophoresis; phen, 1,10-phenanthroline; PPCs, polynuclear platinum complexes; pta, 1,3,5-triaza-phosphatricyclo-[3.3.1.1]decane; py^{dmb}, 2-(1,1-dimethylbenzyl)-pyridine); QqQ, triple quadrupole; QToF, quadrupole-time of flight; RAPTA, [(η^6-arene)$RuCl_2$(pta)]; RAPTA-C, [(η^6-p-cymene)$RuCl_2$(pta)]; RAPTA-T, [Ru(η^6-toluene)Cl_2(pta)]; RP, reversed phase; SCX, strong cation-exchange; SEC, size exclusion chromatography; Sec, seleno-cysteine; SOD, superoxide dismutase; SORI, sustained off-resonance irradiation; T, thymine; TCEP, 2-carboxyethylphosphane; terpy, 2,2′:6′,2″-terpyridine; ToF, time of flight; TrxR, thioredoxin reductase; Ub, ubiquitin; XRD, X-ray diffraction; ZF, zinc finger.

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Contents

1. Introduction

Ancient civilizations discovered centuries ago the potential of metals as pharmaceuticals and, in the last decades, the field of Bioinorganic Chemistry has importantly contributed to the research of new drugs for various diseases. Notably, the first commercially available inorganic compound with therapeutic properties was the arsenic(III)-based drug arsphenamine (Salvarsan®) discovered in 1910 by Paul Ehrlich as anti-syphilis agent. Ehrlich was awarded the Nobel Prize in Physiology and Medicine also for having developed the concept of the "Magic Bullet" according to which it could be possible to kill specific microbes (such as bacteria) that cause diseases without undesired side-effects. Interestingly, the structure of arsphenamine has been recently characterized by mass spectrometry methods, showing that it is actually a mixture of trimeric and pentameric scaffolds [1]. Nowadays, a few arsenic drugs are still in use, including arsenic trioxide (As_2O_3, Trisenox®) (Fig. 1) the greatest clinical success in the treatment of hematological cancers, most notably in acute promyelocytic leukemia [2]. Arsenic trioxide almost certainly forms inorganic $As(OH)_3$ in aqueous environment and as such it is transported intracellularly *via* the aquaglyceroporin channels and forms various metabolites able to inactivate key enzymes, including thioredoxin reductases. Among the successful organoarsenical drugs, melarsoprol (2-[4-[(4,6-diamino-1,3,5-triazin-2-yl) amino] phenyl]-1,3,2-dithiarsolane-4-methanol) (Fig. 1) is a *prodrug* currently used as treatment for late-stage east *African trypanosomiasis*, commonly known as sleeping sickness [3]. Melarsoprol is metabolized into the highly reactive melarsen oxide, which irreversibly binds to vicinal sulfhydryl groups causing the inactivation of various enzymes.

Interestingly, in recent years, antimony-based drugs also find applications in the treatment of protozoal diseases. Specifically, pentavalent antimony-containing drugs of Sb(V) with *N*-methyl-D-glucamine such as Pentostam® (sodium stibogluconate) (Fig. 1) and Glucantime® (meglumine antimoniate) are the treatments of choice for *Leishmania* infections (leishmaniasis) [4], a disease caused by the protozoan parasite *Leishmania*, from the same family as *Trypanosoma*.

Vanadium complexes have been developed to alleviate insufficient insulin response in diabetes mellitus [5]. Although they may not be able to completely make up for the lack of insulin (as in type 1 diabetes), they can certainly reduce reliance on exogenous insulin, or replace other oral hypoglycaemic agents, in type 2 diabetes [6]. Both bis(maltolato)oxovanadium(IV) (BMOV) (Fig. 1) and the ethylmaltol analogue, bis(ethyl-maltolato)oxovanadium(IV) (BEOV), have undergone extensive pre-clinical testing for safety and efficacy [6], and BEOV has even advanced to phase II clinical trials. Mechanistic studies justify the observed antidiabetic properties in terms of the ability of vanadium complexes to inhibit protein phosphatases [7]. These significant developments in vanadyl insulin mimetics have prompted further research into the biological applicability of vanadium complexes particularly as anticancer agents and to treat diseases triggered by viruses, bacteria, amoebae and flagellate protozoan parasites. Generally, the active form of vanadium remains elusive, although several studies have reported a number of promising compounds with different geometries and oxidation states [8].

Specifically concerning cancer treatment, in the late 60 s, cisplatin (*cis*-$[PtCl_2(NH_3)_2]$, Fig. 1), a platinum(II) coordination complex, revolutionised research in chemotherapeutic agents and is still nowadays considered as the main pioneering discovery in the field of metallodrugs [9]. Since its FDA approval for clinical use in 1978, cisplatin and two second generation platinum(II) complexes (carboplatin and oxaliplatin) are often used in different chemotherapeutic regimes, generally in combination with organic drugs. The initial studies on the mechanism of action of these anticancer agents identified DNA as the primary target due to the

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