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Review

Organ damage by toxic metals is critically determined by the bloodstream

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ABSTRACT

Past poisoning epidemics have revealed that the chronic exposure to exceedingly small daily doses of toxic metal and metalloid species can – over time – severely affect human health. Today, several potentially toxic metals and metalloids have been accurately quantified in the bloodstream of the average population, but the interpretation of these from a public health point of view remains problematic. Conversely, the biomolecular origin for a multitude of grievous human diseases remains unknown. Supported by recent epidemiological evidence, these seemingly unrelated facts suggest that human exposure to the aforementioned pollutants may be linked to the etiology of more adverse health effects than we currently know. Based on the interaction of toxic metal and metalloid species with essential trace elements, plasma and erythrocytes in the bloodstream, we have previously argued that a better understanding of these bioinorganic chemistry processes are destined to provide important new insight into their mechanisms of chronic toxicity. This perspective provides an update on recent advances to better understand these bioinorganic processes and attempts to integrate these findings with the whole organism in order to establish connections with the etiology of human diseases. Based on the recent observation of the arsenite-induced perturbation of the whole-body distribution of selenite in mammals and the mercuration of hemoglobin in erythrocyte cytosol it is argued that bioinorganic processes in the bloodstream critically determine which metal and/or non-metal containing species will impinge on the toxicological target organ(s). Accordingly, the bioinorganic chemistry that unfolds in the bloodstream represents a critical bottleneck in terms of linking the exposure of humans to toxic metal species with the etiology of diseases. Furthermore, a better understanding of the blood-based detoxification of environmentally abundant toxic metal species is of direct practical use to develop palliative treatments to ameliorate the adverse effect that toxic metal species exert on certain human populations.

Contents

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1. Introduction and scope

An estimated 9 million premature deaths globally were attributed to diseases caused by pollution in 2015 [1]. Since the effects of chemical pollution on human health are in general poorly defined, its contribution to the global burden of disease is almost certainly underestimated and the costs of premature death and disease caused by pollution continue to rise rapidly [1]. Related to these facts, a multitude of grievous illnesses that afflict people in developed countries, including Alzheimer's disease, asthma, autism, diabetes, inflammatory bowel disease, Lou Gehring's disease, multiple sclerosis, Parkinson's disease and rheumatoid arthritis do not appear to have a genetic origin [2,3]. Considering that every organism – since its conception – is exposed to 'environmental factors' that may be present in the inhaled air and/or the ingested food/drinking water throughout life, their potentially adverse effects on human health are being increasingly recognized [4–7]. While environmental factors, such as persistent organic pollutants are implicated in the in the etiology of type 2 diabetes [8], and intestinal microbiota are linked to lung inflammation [9], it is the unsustainable emission of inorganic pollutants by our high-tech society into the global environment [10,11] which prompted our previous perspective entitled "Probing bioinorganic chemistry processes in the bloodstream to gain new insights into the origin of human diseases" [12]. Given that this perspective was published in 2010, we thought it to be useful to provide an update on recent advances that have been made to better understand the aforementioned bioinorganic processes and to critically discuss their toxicological significance. The overall focus of this review will be on studies with mammalian model organisms and studies that were conducted with blood plasma and erythrocyte lysates. For the sake of clarity, the term 'toxic metal species' will be used instead of 'toxic metals and metalloid species' throughout this manuscript and chronic toxicity is defined as the long-term exposure of humans to low levels of an individual inorganic pollutant or a mixture of inorganic pollutants.

We will start by briefly re-iterating how toxic metal species that have invaded the bloodstream can engage in bioinorganic chemistry processes that are toxicologically relevant. Then we will provide an update of recent epidemiological studies which have strengthened the importance of environmental exposure-disease relationships. Thereafter, we will recapture the major problems that need to be overcome to gain insight into relevant bioinorganic chemistry-based processes that unfold in the bloodstream. The core of this manuscript is intended to provide a succinct summary of the recent progress that has been made in terms of better understanding the interaction of toxic metal species with the components of the bloodstream, namely essential trace and ultratrace elements, plasma proteins/small molecular weight compounds/metabolites, erythrocytes as well as the mobilization of toxic metal species from organs to the bloodstream. Some promising avenues for future research will also be identified. The interaction of potentially toxic metal species with erythrocyte cell membranes will not be discussed in depth as this topic was the focus of an excellent recent review [13]. Likewise, readers that are interested in the mechanisms by which Cd^{2+} and As^{III} can result in oxidative stress in target organ cells that may eventually result in diseases are referred to another comprehensive review [14].

1.1. Relevance of blood-based bioinorganic chemistry of toxic metal species in toxicology

In every human being the dynamic exchange of essential elements between the environment, the bloodstream and internal organs – which is orchestrated by tightly regulated biochemical mechanisms throughout life – is inextricably linked to the maintenance of its health and wellbeing [15]. Since the earth's crust also contains toxic metals (e.g. Hg, Cd, Pb) and metalloids (e.g. As, Se), all organisms have been chronically exposed to background concentrations of species of these potentially toxic elements throughout evolution. The onset of the industrial revolution was associated with an increased production of – amongst other chemicals – As, Pb, Cd and Hg for various practical end uses [11]. The large scale production of these particular elements initially resulted in the occupational exposure of humans in factories and eventually in the environmental exposure of humans by contaminated food and drinking water [16] in ways that are still being detailed [17]. The seriousness that is associated with the chronic exposure of human populations to toxic metal species came to the fore during a few pollution disasters that involved the aforementioned elements [11]. A couplet by the Indian poet Pandit Chakbast (1881–1925) probably captures the situation best when he stated: "What is life but the emergence of order in the co-mingling of elements? What is death, but the disintegration of life's active components."

Based on the flow of dietary matter through mammalian organisms, the contained toxic metal species enter the stomach, the gastrointestinal (GI) tract and – if they are bioavailable – the bloodstream form where they are then distributed to toxicological target organs (e.g. Cd^{2+} damages the kidneys [18]). From a purely bioinorganic chemistry perspective, the bloodstream provides an extremely rich environment of biomolecules for toxic metal species to interact with. This is because blood plasma contains thousands of proteins [19] some of which have binding sites for toxic metal species that can compete with essential ones [15] and because erythrocytes, which constitute ~45% of whole blood, can absorb a variety of toxic metal species [12] which can subsequently undergo toxicologically highly relevant redox-reactions in their reducing cytosolic environment that are of eminent toxicological relevance [20]. Accordingly, the interactions of toxic metal species with plasma and erythrocytes will significantly impact essentially all internal organs 'downstream' (Fig. 1) [20,21]. If we want to explain how exceedingly small daily doses of one toxic metal species can result in dramatic adverse health effects [22], however, it behooves us to strive to uncover those particular biomolecular mechanisms which provide the required 'leverage'. Given the biochemical complexity of the bloodstream itself, the elucidation of these bioinorganic mechanisms can be a rather daunting task.

The concerted application of advanced spectroscopic tools has eventually revealed that arsenite (As^{III}) and mercuric mercury (Hg^{2+}) target the metabolism of the essential ultratrace element selenium [23]. In particular it was demonstrated that the intravenous co-administration of rabbits with each of these toxic metal species and selenite (Se^{IV}) resulted in the formation of metabolites with As-Se [24] and Hg-Se [21,25] bonds that are either rapidly excreted via the bile (Fig. 2A) [26] or are essentially non-toxic (Fig. 2B) [24]. The formation of the metabolite which contained an As-Se bond – the seleno-bis(S-glutathionyl) arsinium ion or $[(GS)_2AsSe^-]$ – is a redox reaction that involves endogenous glutathione (GSH) (Eq. (1) and likely involves a mechanism that is depicted in Eqs. (2)–(4) [27]:

$$As(OH)_3 + HSeO_3^- + 8GSH \rightarrow \left[(GS)_2AsSe\right]^- + 3GSSG + 6H_2O \quad (1)$$

$$As(OH)_3 + 2GSH \rightarrow (GS)_2As - OH + 2H_2O \quad (2)$$

$$HSeO_3^- + 6GSH \rightarrow HSe^- + 3GSSG + 3H_2O \quad (3)$$

$$(GS)_2As - OH + HSe^- \rightarrow \left[(GS)_2AsSe\right]^- + H_2O \quad (4)$$