ScienceDirect

Coordination Chemistry Reviews

Volume 417, 15 August 2020, 213343

Review

Sulfhydryl groups as targets of mercury toxicity

Olga P. Ajsuvakova [a b c 1], Alexey A. Tinkov [a b c 1], Michael Aschner [c d], João B.T. Rocha [e], Bernhard Michalke [f], Margarita G. Skalnaya [a], Anatoly V. Skalny [a b c], Monica Butnariu [g h], Maryam Dadar [i], Ioan Sarac [g h], Jan Aaseth [c j], Geir Bjørklund [k]

Show more

https://doi.org/10.1016/j.ccr.2020.213343 ↗

Get rights and content ↗

Highlights

- Interaction of Hg with biomolecules is mediated through its affinity to Cys thiol.
- Cys and GSH Hg-conjugates play a significant role in Hg transport *in vivo*.
- Hg-SH affinity interferes with Akt/CREB, Keap1/Nrf2, NF-κB-mediated apoptotic pathways.
- Hg binding to Mn-SOD (Cys_{196}) and TrxR (Cys_{497}) may underlie its prooxidant effects.
- Hg binding limits GSH and Trx ($Cys_{32, 35, 62, 65, 73}$) availability for redox reactions.

Abstract

The present study addresses existing data on the affinity and conjugation of sulfhydryl (thiol; -SH) groups of low- and high-molecular-weight biological ligands with mercury (Hg). The consequences of these interactions with special emphasis on pathways of Hg toxicity are highlighted. Cysteine (Cys) is considered the primary target of Hg, and link its sensitivity with thiol groups and cellular damage. *In vivo*, Hg complexes play a key role in Hg metabolism. Due to the increased affinity of Hg to SH groups in Cys residues, glutathione (GSH) is reactive. The geometry of Hg(II) glutathionates is less understood than that with Cys. Both Cys and GSH Hg-conjugates are important in Hg transport. The binding of Hg to Cys mediates multiple toxic effects of Hg, especially inhibitory effects on enzymes and other proteins that contain free Cys residues. In blood plasma, albumin is the main Hg-binding (Hg^{2+}, CH_3Hg^+, $C_2H_5Hg^+$, $C_6H_5Hg^+$) protein. At the Cys_{34} residue, Hg^{2+} binds to albumin, whereas other metals likely are bound at the N-terminal site and multi-metal binding sites. In addition to albumin, Hg binds to multiple Cys-containing enzymes (including manganese-superoxide dismutase (Mn-SOD), arginase I, sorbitol dehydrogenase, and δ-aminolevulinate dehydratase, etc.) involved in multiple processes. The affinity of Hg for thiol groups may also underlie the pathways of Hg toxicity. In particular, Hg-SH may contribute to apoptosis modulation by interfering with Akt/CREB, Keap1/Nrf2, NF-κB, and mitochondrial pathways. Mercury-induced oxidative stress may ensue from Cys-Hg binding and inhibition of Mn-SOD (Cys_{196}), thioredoxin reductase (TrxR) (Cys_{497}) activity, as well as limiting GSH ($GS\text{-}HgCH_3$) and Trx ($Cys_{32,\ 35,\ 62,\ 65,\ 73}$) availability. Moreover, Hg-thiol interaction also is crucial in the neurotoxicity of Hg by modulating the cytoskeleton and neuronal receptors, to name a few. However, existing data on the role of Hg-SH binding in the Hg toxicity remains poorly defined. Therefore, more research is needed to understand better the role of Hg-thiol binding in the molecular pathways of Hg toxicology and the critical role of thiols to counteract negative effects of Hg overload.

Introduction

World Health Organization (WHO) has listed mercury (Hg) as one of the ten pollutants of particular concern for public health [1]. Despite the Minamata Convention agreement on Hg emission reduction, human exposure, and its adverse health effects persist [2], with global Hg emissions increasing by 1.8%/year in 2010–2015 [3]. Southeastern Asia is considered the main contributor to Hg emissions [4]. Small-scale gold mining and artisanal work represent

a key source of anthropogenic Hg emissions accounting for 37% of all Hg emitted into the environment. Other significant (>10%) sources of Hg emission include coal and fossil fuel combustion (25%) and non-ferrous metal production (10%) [5]. Wildfires also have a critical effect on the global Hg emissions [6]. Although the projections for 2050 demonstrate a sustained trend for increased Hg emissions, it is hopeful that legislative and technological efforts will reverse and abate this trend [7].

Adverse health effects at current Hg levels of exposure vary related to the geographic area [8], with arctic and tropical communities being at particularly high risk of Hg overexposure [9]. Mercury toxicity may aggravate neurological and neurodegenerative [10], metabolic [11], renal [12], and cardiovascular diseases [13]. For elemental Hg, the brain and kidneys are considered as the main targets [14]. The overall costs of current adverse Hg effects have been estimated to be in the range of 23 thousand to 52 thousand EUR/kg predominantly due to cardiovascular morbidity and mortality [15].

Multiple mechanisms of Hg toxicity underlie the wide spectrum of detrimental health effects due to Hg exposure. Particularly, Hg was shown to cause enzyme inactivation [16], oxidative stress [17], inflammation, and autoimmunity [18]. However, the particular molecular mechanisms have yet not been fully disclosed.

The high affinity of Hg-compounds to sulfhydryl (–SH) groups has been reported in numerous studies [19]. For example, a detailed proteomic analysis of murine liver revealed 7682 Hg-reactive cysteine (Cys) residues from 5664 proteins [20]. However, data on a particular involvement of Hg-thiol interaction in mechanisms of Hg toxicity are still insufficient.

Therefore, we discuss in this review the present data on affinity and conjugation of SH groups of low- and high-molecular-weight biological ligands with Hg, as well as the outcome of such interactions with a special emphasis on pathways of Hg toxicity.

Section snippets

Forms of mercury

Exposure to Hg occurs in different forms, in principle, either as elemental (Hg^0), inorganic, or organic Hg^{n+}. Metallic or elemental Hg (Hg^0) as a liquid metal has low absorption by dermal and gastrointestinal routes [21], [22]. Although it has a high vapor pressure, and at saturation, a cubic meter of air holds 20 mg Hg at room temperature. Upon inhalation, this colorless, odorless vapor is highly toxic [23]. Mercury vapor, which also is released from dental amalgams, is absorbed by the lungs …

Sulfhydryl groups and mercury

It has been reported that sulfhydryl (SH) is ubiquitous in peptides and proteins throughout the body. Molecules with SH groups are referred to as thiols or mercaptans (from Lat. mercurium captans, meaning ‘capturing mercury’) [35]. Proteins containing Cys residues are abundant throughout the body, both in enzymes, organelles, and in intracellular and extracellular membranes. Since most SH groups are important for the function or structure of numerous proteins [36], the particular goals for Hg, …

Mercury transport

The Hg S-conjugates contribute to Hg transport, which is in agreement with the molecular mimicry (especially at Lα region of amino acid) of transport of Hg conjugates with Cys or GSH [150]. MeHg-S-Cys complex structurally closely resembles L-methionine, being a substrate for L-type large neutral amino acid carrier transport (LAT1) system that is at least partially responsible for MeHg transport through BBB [151]. GS-CH_3Hg has also been reported to be moved by LAT1 [152]. The human organic anion …

Neurotoxicity

The brain is considered as one of the key targets for Hg toxicity by different mechanisms [33]. In turn, thiol homeostasis is critical for brain development and functioning at all steps of ontogenesis [222]. Particularly, prenatal MeHg exposure induces a remarkable elevation in cerebellar Hg levels, along with depleting thiol content, which is related to impaired motor functions [223]. In turn, impaired thiol redox balance in adults is associated with neurodegeneration [224]. Although the …

Concluding remarks

Data published to date demonstrate that different species of Hg (Hg^{2+}, $HgCH_3$) readily interact with thiol groups of endogenous molecules, which includes tubulin, GSH, ion channels, transporters, and enzymes therefore potentially change normal biological function. The latter may underlie a significant portion of toxic effects of Hg species through modulation of oxidative stress, apoptosis, leading to the ensuing neurotoxicity. In this regard, the use of thiol-group donors (NAC, ALA) may provide …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgments

The study was performed with the support of the Russian Ministry of Science and Higher Education, Project № 0856-2020-0008. MA was supported by NIH grants NIEHS R01 10563, R01ES07331, and NIEHS R01ES020852. …

Recommended articles

References (247)

D.C. Evers *et al.*
Sci. Total Environ. (2016)

D.G. Streets *et al.*
Atmos. Environ. (2019)

E.G. Pacyna *et al.*
Atmos. Environ. (2010)

A. Kumar *et al.*
Atmos. Environ. (2018)

P. Rafaj *et al.*
Atmos. Environ. (2013)

L.T. Budnik *et al.*
Sci. Total Environ. (2019)

S.E. Orr *et al.*
Toxicol. Lett. (2019)

J.-D. Park *et al.*
J. Preventive Med. Public Health (2012)

G. Bjørklund *et al.*
Environ. Res. (2017)

N.S. Gould *et al.*
Chem. Biol. (2015)

View more references

Cited by (226)

Hesperidin and hesperetin against heavy metal toxicity: Insight on the molecular mechanism of mitigation

2022, Biomedicine and Pharmacotherapy

Show abstract

Self-assembling fluorescent hydrogel for highly efficient water purification and photothermal conversion

2022, Chemical Engineering Journal

Show abstract

Ferroptosis as a mechanism of non-ferrous metal toxicity

2022, Archives of Toxicology

Molecular mechanisms of environmental metal neurotoxicity: A focus on the interactions of metals with synapse structure and function

2021, Toxics

Mercury interactions with selenium and sulfur and the relevance of the Se:Hg molar ratio to fish consumption advice

2021, Environmental Science and Pollution Research

Review heavy metals and human health: Possible exposure pathways and the competition for protein binding sites ↗

2021, Molecules

View all citing articles on Scopus ↗

1 OPA and AAT contributed equally to the paper.

View full text