Environment International 69 (2014) 148–158

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review

Arsenic and selenium toxicity and their interactive effects in humans

Hong-Jie Sun [a], Bala Rathinasabapathi [b], Bing Wu [a], Jun Luo [a], Li-Ping Pu [c], Lena Q. Ma [a,d,*]

[a] State Key Laboratory of Pollution Control and Resource Reuse, School of the Environment, Nanjing University, Nanjing, Jiangsu 210046, China
[b] Horticultural Sciences Department, University of Florida, Gainesville, FL 32611, United States
[c] Suzhou Health College, Suzhou, Jiangsu 215000, China
[d] Soil and Water Science Department, University of Florida, Gainesville, FL 32611, USA

ARTICLE INFO

Article history:
Received 5 February 2014
Accepted 29 April 2014
Available online 20 May 2014

Keywords:
Arsenic
Selenium
Glutathione
Arsenite methyltransferase
Synergistic
Antagonistic

ABSTRACT

Arsenic (As) and selenium (Se) are unusual metalloids as they both induce and cure cancer. They both cause carcinogenesis, pathology, cytotoxicity, and genotoxicity in humans, with reactive oxygen species playing an important role. While As induces adverse effects by decreasing DNA methylation and affecting protein 53 expression, Se induces adverse effects by modifying thioredoxin reductase. However, they can react with glutathione and *S*-adenosylmethionine by forming an As–Se complex, which can be secreted extracellularly. We hypothesize that there are two types of interactions between As and Se. At low concentration, Se can decrease As toxicity via excretion of As–Se compound $[(GS_3)_2AsSe]^-$, but at high concentration, excessive Se can enhance As toxicity by reacting with *S*-adenosylmethionine and glutathione, and modifying the structure and activity of arsenite methyltransferase. This review is to summarize their toxicity mechanisms and the interaction between As and Se toxicity, and to provide suggestions for future investigations.

Published by Elsevier Ltd.

Contents

1. Introduction

Arsenic (As) is ubiquitous in the environment and it exists in four oxidation states: arsenate (+5), arsenite (+3), elemental arsenic (0) and arsine (−3). It is released to the environment through both natural processes and anthropogenic activities. Arsenic is widely distributed in the earth, ranking 20th in abundance in the earth's crust. It has been widely used in agriculture as pesticides and wood preservatives (Sharma and Sohn, 2009). On the one hand, As has been used to cure acute promyelocytic leukemia in humans (Miller et al., 2002). On the other hand, As causes adverse health effects including cancers in human. At present, millions of people worldwide suffer from chronic arsenic poisoning (Hughes et al., 2011; Rodríguez-Lado et al., 2013) mainly due to consumption of As-contaminated water and food.

* Corresponding author at: Soil and Water Science Department, University of Florida, Gainesville, FL 32611, USA. Tel./fax: +86 25 8969 0631.
E-mail address: lqma@ufl.edu (L.Q. Ma).

http://dx.doi.org/10.1016/j.envint.2014.04.019
0160-4120/Published by Elsevier Ltd.

Arsenic contamination in the environment is becoming a serious public health problem in several regions. It is known that arsenite (As^{III}) is more toxic than arsenate (As^{V}), with inorganic As being more toxic than organic As (Petrick et al., 2000). However, different organic As species have different toxicity. For example, as final As metabolites, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) are less toxic than inorganic arsenic, whereas the toxicity of intermediate metabolites such as monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) are much more toxic than inorganic arsenic (Petrick et al., 2000). The toxicity of various arsenic species increases in the order of $As^{V} < MMA^{V} < DMA^{V} < As^{III} < MMA^{III} \approx DMA^{III}$.

Selenium (Se) is a metalloid in group VIA and an analog of sulfur, with four oxidation states in nature: selenate (+6), selenite (+4), elemental selenium (0), and selenide (−2) (Tinggi, 2003). Unlike As, Se is an essential nutrient for humans, animals, and bacteria. It is important for many cellular processes because it is a component of several selenoproteins and selenoenzymes with essential biological functions (Table 2) (Letavayová et al., 2008). Furthermore, many studies demonstrated that proper doses of Se can prevent cancers in animals and humans (Clark et al., 1996; Ganther, 1999). However, it is toxic at levels slightly above homeostatic requirement (Zhang et al., 2014). Similar to As where As^{V} is less toxic than As^{III}, Se^{VI} is less toxic than Se^{IV} in eukaryote and prokaryote (Rosen and Liu, 2009). Abbreviations are listed in Table 1.

It is of considerable interest to examine their dual role as a toxicant and nutrient. Se and As are both metalloids with similar chemical properties, playing dual roles regarding cancer. Arsenic is known for its carcinogenicity, yet it is also used in treating certain cancers. Similarly, Se is a known anticarcinogen, but it also triggers cancer. Much research was done to understand their carcinogenic mechanisms (Bansal et al., 1990; Rossman, 2003), and the relation between cancer and their dual roles as carcinogen and anticarcinogen (Bode and Dong, 2002; Chakraborti et al., 2003). However, there still exist contradictory results as both synergistic and antagonistic toxicity between As and Se has been reported (Biswas et al., 1999).

Hence the relation between As and Se has attracted increasing attention. This review summarizes and compares their toxicity mechanisms to better understand the relation between As and Se toxicity.

2. As and Se uptake and metabolism

2.1. Arsenic

In terrestrial environment, As is mainly present as inorganic As, which exists as pentavalent (As^{V}) under aerobic condition and trivalent (As^{III}) under anaerobic environment (Matschullat, 2000). However, As^{III} and As^{V} exert toxicity differently.

As^{III} is typically present as a neutral species ($As(OH)_3°$, $pK_a = 9.2$) in aqueous solution at physiological pH (Gailer, 2007). Due to its structural similarity to glycerol, As^{III} can be transported into cells through aquaglycerolporins, a pore protein for transporting small organic compounds such as glycerol and urea (Liu et al., 2002). However, As^{V} uses a different pathway into animals and human cells. As a phosphate analog, they have similar dissociation constants (pKa of arsenic acid: 2.26, 6.76, and 11.3 and pKa of phosphoric acid: 2.16, 7.21, and 12.3) (Villa-Bellosta and Sorribas, 2008). Similar to phosphate, As^{V} is present as an oxyanions in solution, i.e., $H_2AsO_4^-$ and $HAsO_4^{2-}$ at pH 5–7. As chemical analogs, they compete for entry through phosphate transporters (Huang and Lee, 1996).

After entering the cells in animals and humans, As^{V} is rapidly reduced to As^{III}. Then As^{III} undergoes multistep in cells through arsenite methyltransferase (AS3MT) using *S*-adenosylmethionine (SAM) as the methyl donor, producing methylated As compounds including MMA^{III}, DMA^{III}, MMA^{V}, and DMA^{V} (Kojima et al., 2009). A classical pathway of arsenic methylation was first proposed by Challenger (1945) who suggested that arsenic methylation involves a series of reduction and oxidation steps (Fig. 1A). Thereafter, Zakharyan and Aposhian (1999) reported that As^{III} can be methylated non-enzymatically in the presence of both methylcobalamin and glutathione (GSH) (Fig. 1B).

In subsequent studies, investigators further explored the mechanism of arsenic methylation and found enzymes play an important role in arsenic methylation. A new enzymatic metabolic pathway for arsenic methylation is proposed (Fig. 1C). The –OH groups of $As(OH)_3$ are substituted by glutathionyl moieties, forming GSH conjugates $As(GS)_2$ –OH and $As(GS)_3$ (Hayakawa et al., 2005). Subsequently, as the major substrates for AS3MT, As^{III}–glutathione complexes are further methylated to monomethylarsonic diglutathione $MMA(GS)_2$ and dimethylarsinic glutathione DMA(GS). Since DMA(GS) is unstable, it is immediately oxidized to pentavalent DMA^{V}, which is the major metabolite and is excreted from cells (Rehman and Naranmandura, 2012). In addition, during arsenic methylation and in the absence of GSH, endogenous reductants (e.g., thioredoxin/thioredoxin reductase/NADPH) play an important role (Waters et al., 2004).

Recently, Naranmandura et al. (2006) demonstrated a different pathway of arsenic metabolism via investigating the hepatic and renal metabolites of arsenic after an intravenous injection of As^{III} in rats (Fig. 1D). They confirmed that As^{III} bound to proteins (AsS_3 protein) is metabolized in the body during the successive reductive methylation by AS3MT in the presence of GSH and SAM and the reduced products are excreted externally. Consistent with the mechanisms, both trivalent and pentavalent inorganic and organic arsenicals have been detected in the urine of individuals after chronic exposure to arsenic and in cell medium following *in vitro* exposure to arsenic (Devesa et al., 2004).

Table 1
Abbreviations used.

Chemical	Abbreviations	Chemical	Abbreviations
Arsenic	As	Selenide	Se^{2-}
Arsenite	As^{III}	Selenopersulfide	GSSeH
Arsenate	As^{V}	Hydrogen selenide	H_2Se
Monomethylarsonic	MMA^{V}	Methylselenol	CH_3SeH
Dimethylarsinic	DMA^{V}	Dimethyselenide	$(CH_3)_2$–Se
Monomethylarsonous	MMA^{III}	Trimethylselenonium	$[(CH_3)_3Se]^+$
Dimethylarsinous	DMA^{III}	Reactive oxygen species	ROS
Selenium	Se	Selenomethionine	Se–Met
Selenite	Se^{IV}	Poly ADP-ribose polymerase	PARP-1
Selenate	Se^{VI}	Xerodermapigmentosum protein A	XPA
Arsenite methyltransferase	AS3MT	Cardiovascular disease	CVD
S-adenosylmethionine	SAM	Mitogen-activated protein kinases	MAPK
Arsenite-glutathione complex	$As(GS)_2$–OH, $As(GS)_3$	Damage-regulated autophagy modulator	DRAM
Monomethylarsonic diglutathione	$MMA(GS)_2$	Excision repair cross-complement	ERCC1
Dimethylarsinic glutathione	DMA(GS)	Seleno-bis (*S*-glutathionyl) arsinium ion	$[(GS)2AsSe]^-$
Selenocysteine	Se–Cys	Tumor necrosis factor	TNF
Dimethylselenide	DMSe	Thioredoxin reductase	TR
Glutathione	GSH	Thioredoxin	Trx