Environmental Toxicology and Pharmacology 48 (2016) 214–224

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

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

Review or Mini-review

Metabolism and toxicity of arsenicals in mammals

Adeel Sattar[a], Shuyu Xie[a,*,1], Mian Abdul Hafeez[d], Xu Wang[a,b,c], Hafiz Iftikhar Hussain[c], Zahid Iqbal[c], Yuanhu Pan[a], Mujahid Iqbal[a], Muhammad Abubakr Shabbir[c], Zonghui Yuan[a,b,c,*,1]

[a] National Reference Laboratory of Veterinary Drug Residues (HZAU), Huazhong Agricultural University, Wuhan, Hubei 430070, China
[b] MAO Key Laboratory for Detection of Veterinary Drug Residues, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[c] MOA Laboratory for Risk Assessment of Quality and Safety of Livestock and Poultry Products, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[d] University of Veterinary and Animal Sciences, Lahore, Pakistan

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 26 October 2016
Accepted 27 October 2016
Available online 3 November 2016

Keywords:
Arsenic
Metabolism
Toxicity
Trivalent arsenic
Pentavalent arsenic
Organic
Inorganic

ABSTRACT

Arsenic (As) is a metalloid usually found in organic and inorganic forms with different oxidation states, while inorganic form (arsenite As-III and arsenate As-v) is considered to be more hazardous as compared to organic form (methylarsonate and dimethylarsinate), with mild or no toxicity in mammals. Due to an increasing trend to using arsenicals as growth promoters or for treatment purposes, the understanding of metabolism and toxicity of As gets vital importance. Its toxicity is mainly depends on oxi-reduction states (As-III or As-v) and the level of methylation during the metabolism process. Currently, the exact metabolic pathways of As have yet to be confirmed in humans and food producing animals. Oxidative methylation and glutathione conjugation is believed to be major pathways of As metabolism. Oxidative methylation is based on conversion of Arsenite in to mono-methylarsonic acid and di-methylarsenic acid in mammals. It has been confirmed that As is only methylated in the presence of glutathione or thiol compounds, suggesting that As is being methylated in trivalent states. Subsequently, non-conjugated trivalent arsenicals are highly reactive with thiol which converts the trivalent arsenicals in to less toxic pentavalent forms. The glutathione conjugate stability of As is the most important factor for determining the toxicity. It can lead to DNA damage by alerting enzyme profile and production of reactive oxygen and nitrogen species which causes the oxidative stress. Moreover, As causes immune-dysfunction by hindering cellular and humeral immune response. The present review discussed different metabolic pathways and toxic outcomes of arsenicals in mammals which will be helpful in health risk assessment and its impact on biological world.

Contents

1. Introduction 215
   1.1. Species of arsenic 216
2. Absorption and distribution of arsenicals in mammals 216
3. Metabolism of arsenic 216
   3.1. Oxidation and reduction 216
   3.2. Methylation of arsenic 216
4. Excretion of arsenic 218
5. Arsenic toxicity 218

* Corresponding authors at: National Reference Laboratory of Veterinary Drug Residues (HZAU), Huazhong Agricultural University, Wuhan, Hubei 430070, China.
E-mail addresses: snxsy1@126.com (S. Xie), yuan5802@mail.hzau.edu.cn (Z. Yuan).
[1] These authors correspond equally.

http://dx.doi.org/10.1016/j.etap.2016.10.020
1382-6689/

5.1. Toxicity of pentavalent arsenicals 218
5.2. Toxicity of trivalent arsenicals 218
5.3. Oxidative stress 218
5.4. DNA damage 219
5.5. Neurodegenerative mechanism 220
5.6. Immune dysfunction 220
6. Concluding remarks and future perspective 221
Conflict of interest 221
References 222

1. Introduction

Heavy metal toxicity is of concern now a days because of its abiotic stress which leads to precarious effects on biota (Govind and Madhuri, 2014). Arsenic (As) is the most abundant element in the environment due to natural or human activities, including volcanic eruptions, contamination due to mining and smelting ores, and most importantly at present, its use in pesticides and medicines to treat animals as well as humans (Lazo et al., 2003; Murphy and Aucott, 1998; Smedley and Kinniburgh, 2002). More than 100 million people are exposed to As worldwide, mainly due to consumption of contaminated food and water in countries such as Bangladesh, China, India, Pakistan, Chile, Taiwan and the United States where an alarming situation has been observed due to high level of As in ground water (Chakraborti, 2016; Mukherjee et al., 2006). Since the 1960s, chronic As prevalent zones have been identified in China where more than 19 provinces were found to have As in drinking water exceeding the standard level of 0.05 mg L^{-1} (Ministry of Health PRC, 2012). Central Mongolia, Shanxi and Xinjiang provinces are well-known historic hotspots of As contamination in which the concentration in water has been reported to exceed 500 μg L^{-1} (He and Charlet, 2013). Exposure also occurs through food and inhalation due to agriculture and industrial settings (Li et al., 2016; Liu et al., 2002; Man et al., 2010; Roychowdhury et al., 2003). As is present in the environment in both organic and inorganic forms, which ultimately taken up by many food and beverage items (Raber et al., 2012; Yosim et al., 2015), if they are grown on soil with high level of As irrespective of fact that whether they are grown under organic or conventional farm practices (Malmauret et al., 2002). Several As-based products have been used in medicine and agriculture industry for decades for treatment of various diseases and as pesticides or feed additives (Chen et al., 1997; Murphy and Aucott, 1998; Silbergeld and Nachman, 2008). Organo-arsenic products enter the environment through disposal of poultry litter, decomposition of poisoned insects, and the dust from burning of straw (Fisher et al., 2015; Mandal and Suzuki, 2002; Pal et al., 2007; Silbergeld and Nachman, 2008).

This metalloid is usually found in different forms (organic and inorganic) with different oxidation states, while inorganic form arsenite (As-III) and arsenate (As-v) considered to be more hazardous as compared to organic forms (methylarsonate and dimethylarsinate) which show mild or no toxicity in mammals (Jomova et al., 2011; Khan et al., 1997). Trimethylarsine oxide (TMAO) and tetramethylarsonium (TETRA) are considered moderately toxic, while arsenobetaine (AsB) and arsenocholine (AsC) show no toxicity in mammals. The toxicity and mobility of As in the body goes from inorganic to organic form in the manner As(iii) > As(v) > organo-arsenic (Cullen and Reimer, 1989; Gebel, 2001; Vahter and Marafante, 1988).

The organo-arsenic drugs such as roxarsone (4-hydroxy-3-nitrophenylarsonic acid, ROX) (Chapman and Johnson, 2002) and *p*-arsenilic acid (4-aminophenylarsonic acid, PASA) (Chabot et al., 2009) have been extensively used as feed additives and for treatment purpose in animal husbandry for decades. Rocxarsone (ROX) was officially approved by U.S food and drug administration authority in 1944 to be used in animal industry as growth promoter as well as to treat various diseases such as coccidiosis in poultry (Silbergeld and Nachman, 2008). In 2010, industry legislatures assessed that 88% of 9 billion chickens that were raised for human consumption received ROX in united states (Nachman et al., 2013). So the use of ROX in poultry industry is of great concern because of its exposure to humans (Schmidt, 2012).

High levels of As have been found in the tissues of birds fed As (Lasky et al., 2004), though, the level of As decreases rapidly below the FDA limit of 0.5 μg kg^{-1} when the usage is restricted to five days before slaughtering (FDA). Nevertheless, the major part of PASA and ROX is excreted unchanged into poultry litter, which becomes a major source of release into the environment when litter is used as organic fertilizer (Jackson and Bertsch, 2001; Morrison, 1969; Rutherford et al., 2003). In past, many scientists used As-based medicines to treat various diseases including ulcer and abscesses (Riethmiller, 2005; Waxman and Anderson, 2001). In 1786, Flower's solution was developed as a tonic and eventually used against a range of diseases including eczema, malaria, asthma, syphilis and chorea. In 1910, a new As-based drug called Salvarsan (magic bullet) was introduced which was used effectively against syphilis until penicillin was introduced in 1940s (Gibaud and Jaouen, 2010; Lloyd et al., 2005; Potter, 1916). However, the use of Flower's solution was declined due to its toxic effects. As-III was found to be an effective drug to treat the acute promyelocytic leukemia (Murgo, 2001; Rust and Soignet, 2001; Sekeres, 2007; Zhang et al., 2001). Due to these reasons, the use of As-III to treat the other cancers should be taken in to consideration.

The precise mechanism of As metabolism is still unclear. However, reduction and oxidation methylation of trivalent and pentavalent arsenicals are supposed to be major metabolic pathways of As metabolism. Pentavalent arsenicals replace the phosphate group in several biochemical reactions, but, in the trivalent state, either inorganic or organic (methylated) As may react with thiol groups in proteins and hinder its activity (Hughes, 2002). The toxicity of As is dependent on species, whereas, inorganic forms (arsenite, arsenate) are considered to be more toxic. Liver, kidneys, heart and lungs are considered to be major storage reservoirs of As, with little accumulation in brain and muscle tissues (Ismail and Roberts, 1992; Kreppel et al., 1990). This accumulation is associated with various disorders including diabetes, hepatotoxicity, cancer and nephrotoxicty. Characterizing the metabolism of As is of much importance, its toxicity derived from effects on more than 200 enzymes involved in DNA repair and cellular energy pathways (Ratnaike, 2003). According to International Agency for Research on Cancer (IARC, 1980), inorganic As exposure causes skin, lungs and bladder cancer and also associated with many non-cancerous outcomes like cardiovascular dysfunction 1980 (Chen et al., 2011; Medrano et al., 2010; Sohel et al., 2009), adverse pregnancy outcomes (Ahmed et al., 2011), cognitive deficits (Wasserman et al., 2007) and type-2 diabetes (Navas-Acien et al., 2008). At present, the FDA is investigating further regarding these and other long last-