Archives of Toxicology (2018) 92:3251–3253
https://doi.org/10.1007/s00204-018-2311-z

EDITORIAL

Contemporary trends in toxicological research on arsenic

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Received: 4 September 2018 / Accepted: 13 September 2018 / Published online: 22 September 2018

Introduction

Historically, arsenic has played an eminent role in human poisoning (Bolt 2012; Nepovimova and Kuca 2018). Nowadays, a major environmental focus is on nutritional arsenic exposure by drinking water and food, world-wide (Gundert-Remy et al. 2015; Hettick et al. 2015; Medina-Pizzali et al. 2018). Against this background, the number of research articles on arsenic toxicity has increased steadily, which has led to several editorials in *Archives of Toxicology* (Golka et al. 2010; Bolt and Stewart 2010; Bolt 2012, 2013, 2015). The continuous peer review process of manuscripts published within the last 2–3 years in our journal has provided insights into current research trends, which are highlighted below.

Effects of pre- and post-natal exposure to arsenic

A field of high research interest are effects of human pre- and postnatal exposure to arsenic. For instance, Gliga et al. (2018) studied 9-year-old children from a longitudinal mother–child cohort in rural Bangladesh ($n = 551$). Prenatal and concurrent exposures to As were assessed via concentrations in maternal urine at gestational week 8 and in the urine of children at 9 years. In multivariable-adjusted linear regression models, prenatal As (natural log-transformed), but not children's concurrent urinary As, was positively associated with IGFBP3 concentrations ($\beta = 76$, 95% CI 19, 133). DNA methylation analysis revealed CpGs associated with both prenatal As and IGFBP3. Prenatal exposure to As was positively associated with IGFBP3 concentrations in children at 9 years, independent of IGF1. It was suggested that this association may be, at least in part, epigenetically mediated.

Experimentally, attention has been given to alterations in learning and behavioural alterations. For instance, gestational exposure of mice to inorganic As^{3+} may alter glutamate disposition in the mouse hippocampus and ionotropic glutamate receptor expression, which has been linked to memory impairment in the offspring (Nelson-Mora et al. 2018).

Another focal point is an association between prenatal arsenic exposure and development of diabetes mellitus (v.i.). Recent experimental evidence in mice shows that prenatal arsenic exposure may impair glucose metabolism in the offspring in a sex-specific manner, which may be counteracted by folate/B12 supplementation (Huang et al. 2018).

Rahman et al. (2017) published a systematic review on early-life arsenic exposure in children. Studies on arsenic exposure and morbidity showed an increased risk of respiratory tract infections and diarrhoea. Findings of different studies on arsenic exposure and foetal, infant, and child growth were heterogeneous. Arsenic exposure was not associated with foetal growth, but there was limited evidence of negative associations between arsenic exposures and birth weight and growth during early childhood.

Diabetes mellitus

Environmental exposure to inorganic arsenic has a negative effect on glucose homeostasis, leading to diabetes mellitus. Experimental studies have pointed to some mechanisms underlying the diabetogenic effects, including (1) inhibition of insulin signalling (leading to insulin resistance) in glucose metabolising peripheral tissues; (2) inhibition of insulin secretion by pancreatic β cells; (3) dysregulation of the methylation or expression of genes involved in maintenance of glucose or insulin metabolism and function and (4) impaired glucose homeostasis by hepatic metabolism of glycogen (Zhang et al. 2017; Dover et al. 2018).

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Inorganic As^{3+} is methylated in the brain by arsenic(III)-methyltransferase (As3mt) in a process that requires glutathione. Susceptibility to toxic effects of inorganic arsenic depends, in part, on this methylation. *As3mt*-knockout (KO) mice cannot efficiently methylate As^{3+}, and this is associated with an adverse metabolic phenotype that is characterised by obesity and insulin resistance. The extent of this impairment depends on sex and As exposure (Douillet et al. 2017).

Other targets of arsenic toxicity

Knockout of Asw3mt in mice also leads to consequences in phospholipid metabolism with a likely impact on the central nervous system (Huang et al. 2016).

A classical matter of research is the role of oxidative stress in As-induced toxicity (e.g. renal toxicity; Gong et al. 2016) and carcinogenicity (Bach et al. 2016). This is further investigated with regard to associated gene expression changes.

A field study was conducted by Fujihara et al. (2016) in a Vietnamese population exposed to elevated As levels in the drinking water. Associations of four single-nucleotide polymorphisms (p.Arg194Trp, p.Arg280His, p.Pro206Pro, and p.Arg399Gln) in X-ray repair with urinary arsenic metabolites and 8-hydroxy-2′-deoxyguanosine (8-OHdG) were studied. Individuals with genotype AA in p.Pro206Pro showed significantly higher urinary monomethylarsonic acid (MMAV) and lower dimethylarsinic acid (DMAV)/MMAV ratio than genotype AG. As for p.Arg399Gln, both Arg/Arg homozygous subjects and Arg/Gln heterozygous individuals showed a significantly higher urinary inorganic As concentration and lower 8-OHdG concentrations than Gln/Gln homozygous individuals. The results suggested Arg399Gln to be a functional SNP that may be related to DNA repair activity.

The skin is a primary target of As carcinogenesis and toxicity, which calls for development of refined experimental models (Weinmueller et al. 2018). Skin hyperpigmentation is the most sensitive objective symptom in patients with arsenicosis. However, there is only limited information on the mechanism of arsenic-mediated skin hyperpigmentation. Now, results of Yajima et al. (2017) suggest that interaction between keratinocytes and melanocytes in the skin through ET-1 and its receptor contributes to the characteristic arsenic-mediated skin pigmentation.

With regard to immunotoxicity, chronic arsenic exposure of women from drinking water has been related to changes in the transcriptome and methylome of CD4-positive T cells, both genome-wide and in specific genes, supporting the hypothesis that arsenic causes immunotoxicity by interfering with gene expression and regulation (Engström et al. 2017).

Organoarsenic compounds/arsenolipids

A rapidly developing field is research on organic arsenicals. Exposure of humans may occur, as compounds of this group can be applied in polymers and biomaterials (Tanaka et al. 2018). Aromatic organoarsenic compounds are even used in some countries as feed additives for livestock and in the poultry industry (Fei et al. 2018), and arsenic-containing hydrocarbons may be present in fish and edible algae (Müller et al. 2018a, b). As organic arsenic compounds tend to accumulate in the brain, current interest is focussed on potential neurotoxicity and its mechanisms (Masuda et al. 2017; Witt et al. 2017). Arsenobetaine, which is the major water-soluble organoarsenic compound in fish, exerts no toxicity to humans (Borak and Hosgood 2007).

Arsenolipids can be classified into four groups (Witt et al. 2017): arsenic-containing fatty acids (AsFAs), arsenic-containing hydrocarbons (AsHCs), arsenosugar-phospholipids (AsPLs) and trimethylarsenic fatty alcohols (TMAsFOHs). AsFAs may occur esterified in triglycerides.

A substantial neurotoxic potential is ascribed to AsHCs. Members of this group easily cross the blood–brain barrier, and even at sub-toxic concentrations these may lead to barrier disruption. Thus, the hypothesis has been advanced that these could facilitate the transfer of accompanying foodborne toxicants into the brain (Müller et al. 2018a). AsHCs are biotransformed to a considerable extent. Identified metabolites formed in vitro include respective thioxo-analogues and As-containing fatty acids and fatty alcohols (Müller et al. 2018b).

Final remark

Progress reached within the last few years demonstrates that arsenic research is a vital contemporary focus in both epidemiological and experimental toxicology, encompassing a wide methodological horizon. Relevant submissions to *Archives of Toxicology* covering this field are therefore further invited.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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