Published in final edited form as:

J Toxicol Environ Health A. 2016 ; 79(8): 339–341. doi:10.1080/15287394.2016.1151392.

Arsenite Accumulation in the Mouse Eye

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Abstract

Elevated arsenic (As) concentrations in drinking water are a major worldwide public health concern. Exposure to As is associated with carcinogenesis, skin lesions, cardiovascular disease, cognitive deficits and other disorders. However little is known regarding chronic As-mediated effects on the eye. Oxidative stress is believed to be an important factor in As-related pathology and is also implicated in certain eye diseases such as cataract. Thus, elevated exposure to arsenic could potentially be a contributing factor for ocular pathology. A pilot study was therefore initiated to determine if As could be detected in eye tissue of mice exposed to sodium arsenite in drinking water. Total As concentrations were determined by ICP/Mass Spectroscopy in whole eyes, lens, liver, heart, lung, kidneys, spleen, brain and hair from mice given 0, 10, 50 or 250 ppm sodium arsenite in their drinking water for 4 weeks or 0, 10 or 50 ppm for 6 months. Dose dependent increases in As concentration were observed in all organs and tissues. Surprisingly, As concentrations in the eye and lens were significantly higher than those in liver, lung, heart, spleen and brain and similar to that found in kidneys. The relatively high concentration in the eye and the lens in particular suggests As exposure may be a contributing factor in cataract formation in parts of the world where As in drinking water is endemic.

Keywords

Arsenic; Sodium Arsenite; Eye; Lens; Mice

Introduction

Arsenic (As) is abundant in the earth's crust and can be released into groundwater through natural geochemical processes (Smedley and Kinniburgh, 2002). Exposure to elevated concentrations of As in drinking water is a major human public health concern worldwide

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(Naujokas et al, 2013; Nacano, et al., 2014). Long-term As exposure increases risk of several cancers (Bernstam and Nriagu, 2000; Kapaj, et al., 2006), diabetes, respiratory disease, cardiovascular disease, adverse pregnancy outcomes, and decreased cognitive function in children (Lin, et al, 1998; Bustaffa, et al., 2014; Souza, et al., 2016). *In-vitro* and *in-vivo* human and animal lab investigations indicate that oxidative stress mediates As-induced toxicity and carcinogenicity (Bernstam and Nriagu, 2000; Jomova et al., 2011).

Oxidative stress is also believed to be an initiating or early event in many eye diseases (Oduntan and Mashige, 2011), particularly in cataract development (Spector, 1995). There are no data available on As concentrations in the mammalian eye. High levels have been reported in eyes of fish living in As contaminated lakes (Lunde, 1977; Takatsu and Uchiumi, 1998; Takatsu, et al., 1999; Suhendrayatna et al., 2001). In humans, ocular symptoms of acute As poisoning include optic nerve atrophy and blindness (Duke Elder, 1941; Tassman, 1951).

Materials and Methods

Four week old male C57BL/6J were purchased from the Jackson Laboratory (Bar Harbor, ME) and maintained on a 12 hr light/dark cycle with food and water *ad libitum*. Food and water consumption and animal weights were measured weekly. Between 3 and 5 animals were used for each experimental condition. At 8 weeks, when mice weighed an average of 26 g, sodium arsenite (0.5% w/v, Ricca Chemical Co., Arlington, TX) was added to their drinking water for one month at 0 (control), 10, 50 or 250 ppm or 6 months (0, 10 or 50 ppm only). After either 1 or 6 month of continuous As administration, mice were sacrificed for tissue collection and analysis by cervical dislocation after ketamine/xylazine anesthesia. Selected organs and tissues were removed, weighed and completely digested in 100% HNO₃ (Fisher Optima) for elemental As determination by ICP/Mass Spectroscopy using a Perkin Elmer Elan DRC11 as previously described (Wasserman et al., 2014).

Mice were cared for in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals. Experimental protocols, animal handling and care were approved by the Columbia University Institutional Animal Care and Use Committee (IACUC).

Statistics

Data were analyzed by unpaired t-test using GraphPad software. The level of significance was set at p-value < 0.05

Results and Discussion

No marked differences in weight or water consumption were noted between exposed and control animals during this 6 month study. No apparent clinical symptoms or differences in animal behavior were observed. No deaths occurred in either exposed or unexposed mice.

Table 1 presents As concentrations in various organs and tissues harvested 4 weeks after exposure to 0, 10, 50 or 250 ppm sodium arsenite. Organs and tissues from control mice

contained only trace As levels. In contrast, dose dependent increases in elemental As concentrations were noted for each selected organ or tissue. Surprisingly, As levels in the eye were relatively high, nearly equal in magnitude to that of kidneys and significantly higher than liver, lung, heart, spleen and brain. As expected, concentrations of As in hair were quite elevated, consistent with the high sulfhydryl content of its major structural protein, keratin (Lin et al, 1998; Yáñez et al., 2005).

Figure 1 illustrates the concentrations of As in various organs and tissues harvested from male mice 6 months after exposure to 10 ppm sodium arsenite. The relative levels of As are similar to those noted in Table 1, with hair having the highest concentration, followed by kidney, lens (eye), skin, lung, liver, heart and brain. Higher concentrations but similar relative proportions were found for mice exposed to 50 ppm sodium arsenite for 6 months (not shown). In contrast to Table 1, which reports As concentration in whole eyes, Figure 1 depicts As levels in isolated lenses only. As both whole eye and lens exhibit similar high As concentrations (Table 1 and Figure 1, respectively), the lens may be the primary target tissue for As sequestration in the eye. This observation supports the hypothesis that elevated As concentrations in the lens may contribute to cataract formation and provide a mechanistic explanation for the recent finding of a dose-response related association between chronic As exposure and prevalence of human posterior subcapsular cataract in arseniasis endemic regions of Taiwan (See et al., 2007).

In summary, evidence indicates that chronic exposure of mice to arsenite in drinking water results in significant As accumulation in the eye and particularly, the lens. These findings further suggests a need for additional investigation into the mechanism(s) whereby As accumulates in eye tissue, whether other species of As concentrate in the eye, and which, ocular pathologies, if any, may be associated with As exposure.

Acknowledgments

This work was supported by National Institute of Environmental Health Sciences grants P42 ES 10349 and P30 ES 09089.

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Figure 1.

Relative concentrations of inorganic As in tissues from male mice 6 months after continuous exposure to 10 ppm sodium arsenite in drinking water.

Elemental analysis was performed as described. The eye lens was dissected from the globe before analysis.

* Significant from lens $p < 0.05$.

Arsenic elemental analysis in tissues from male mice four weeks after continuous exposure to 0, 10, 50 or 250 ppm sodium arsenite in drinking water.

Table 1

	Lung	Heart	Kidney	Brain	Eye	Liver	Hair	Spleen
(<i>ug As/g wet mass</i>)								
Control	0.008 ± 0.001	0.010 ± 0.001	0.014 ± 0.001	0.002 ± 0.000	0.018 ± 0.008	0.017 ± 0.004	0.111 ± 0.014	0.018 ± 0.012
10 ppm Arsenite	0.06 ± 0.13	* 0.08 ± 0.00	* 0.64 ± 0.04	* 0.012 ± 0.001	* 0.26 ± 0.09	* 0.18 ± 0.01	* 3.18 ± 0.04	nd
50 ppm Arsenite	* 0.21 ± 0.05	* 0.19 ± 0.04	* 2.49 ± 0.15	* 0.039 ± 0.018	* 1.15 ± 0.36	nd	* 25.64 ± 3.54	nd
250 ppm Arsenite	nd	* 1.35 ± 0.24	* 8.33 ± 1.10	nd	* 7.49 ± 0.17	* 4.66 ± 0.31	* 114.43 ± 17.77	* 0.80 ± 0.13

Tissues and organs were dissected immediately after animal sacrifice, digested in nitric acid and subjected to arsenic elemental analysis by ICP/Mass Spectroscopy.

Values are expressed as mean +/- SEM of 3–5 animals. nd = not determined.

* Significant from control p<0.05.