Effects of glutathione on the in vivo metabolism and oxidative stress of arsenic in mice

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ABSTRACT — In this study, we investigated the in vivo effects of exogenous glutathione and buthionine sulfoximine on arsenic methylation and antioxidant capacity in mice exposed to arsenic via drinking water. Thirty-six female albino mice were randomly divided into six groups. All groups were given free access to drinking water that contained arsenic continuously except the control group. After ten days, mice were treated with different levels of glutathione or buthionine sulfoximine. The levels of the metabolites of arsenic were determined in the liver and urine. The levels of glutathione and total antioxidant capacity were determined in the whole blood and liver. Our results showed that the increase of arsenic species in the liver as well as the decrease of blood and hepatic glutathione and total antioxidant capacity, were all relieved by exogenous glutathione consistently. We also observed the involvement of glutathione in promoting arsenic methylation and urinary elimination in vivo. Increase of total arsenic in the urine was mainly due to the increase of dimethylated arsenic. Furthermore, administration of glutathione increased the first methylation ratio and secondary methylation ratio in the liver and urine, which resulted in the consequent increase of dimethylated arsenic percent and decrease of inorganic arsenic percent in the urine. Opposite effects appeared with the administration of buthionine sulfoximine, a scavenger of glutathione. Our study indicated that exogenous glutathione not only accelerated the methylation and the excretion of arsenic, but also relieve the arsenic-induced oxidative stress. This provides a potential useful chemopreventive dietary component for human populations being at risk of arsenic exposure.

Key words: Arsenic, Glutathione, Buthionine sulfoximine, Methylation, Oxidative stress

INTRODUCTION

Arsenic (As) is a naturally occurring element which is commonly present in air, water, and soil (Mandal and Suzuki, 2002). It has been classified as group one carcinogen for humans by the International Agency for Research on Cancer (IARC, 2012). Long-term exposure to high levels (> 50 ppb) of As in drinking water is associated with various adverse health effects including skin lesions (Wen et al., 2012), liver diseases (Kunrath et al., 2013) and cancers of several organs. Arsenic contamination in drinking water is thus an international concern due to its potential health hazards and widespread distributions. However, the mechanisms of adverse effects associated with arsenic are still not well understood.

Generally, the main form of arsenic in drinking water is inorganic arsenic (iAs). As is absorbed in the intestine, biotransformed in the liver, and excreted in the urine. Until now, two important theories concerning As biotransformation attracted much attention of researchers in this field. One is the classic metabolic pathway of As in mammals consists mainly of two reduction steps and two methylation steps as follows: pentavalent iAs (iAsV) → trivalent iAs (iAsIII) → pentavalent monomethylated arsenic (MMAV) → trivalent monomethylated arsenic (MMAIII) → pentavalent demethylated arsenic (DMAV) → trivalent demethylated arsenic (DMAIII) (Aposhian et al., 2004). The other is the newly discovered pathway which is based on the formation of As-
GSH complexes (Hayakawa et al., 2005). Both theories suggest that the two methylation and reduction steps are necessarily involved in the metabolism of iAs, and that reduced glutathione (GSH) is an essential factor for the reduction of As from the pentavalent form to the trivalent form or the formation of As–GSH complexes. Therefore, methylation of As is the key to understanding the biotransformation of As. In addition, cytotoxicity assays revealed the following order of toxicity of the arsenicals: MMAIII>iAsIII>iAsV>MMAV=DMAV (Petrick et al., 2000). Our previous study in an arsenicosis epidemic area in Inner Mongolia observed that clinical manifestations of arsenic related lesions, such as skin lesion, vary considerably among persons, which were mainly attributed to the variation of individual arsenic methylation capability (Sun et al., 2007). Interindividual variability in arsenic methylation capability is considered to be the key factor responsible for the difference of the susceptibility to arsenic toxicity and the manifestations of the arsenic-related disease (Li et al., 2013). It is widely accepted that the proportion of As methylation is a good indicator of arsenic methylation capability (Hopenhayn-Rich et al., 1996).

GSH, a tripeptide of γ-L-glutamyl-L-cysteinyl-glycine, has been found in all mammalian tissues and is especially highly concentrated in the liver. GSH is an essential factor in the reduction of As. It has been proposed that methylation of iAs is a process relying on reduced GSH, in which GSH serves as the reductant or forms the thiolarsenal complexes which are obligatory substrates for methylation reactions (Thomas et al., 2010). Accumulating evidence has revealed that oxidative stress occurs in response to inorganic arsenite exposure, and that reactive oxygen species (ROS) can be formed during the process of arsenic methylation (Wang et al., 2012). Exogenous GSH is capable of chelating metal ions reducing their catalytic activity to form ROS responsible for arsenic-induced oxidative stress (Jomova and Valko, 2011).

Since GSH is not only an essential factor involved in arsenic methylation, but also an important inhibition of arsenic-induced oxidative stress. Until now, few studies have been undertaken to further clarify the effects of exogenous GSH on the methylation of ingested iAs and arsenic-induced oxidative stress. The level and proportion of arsenic metabolites in liver and urine, and the total antioxidant capacity (TAC) and GSH in liver and blood were determined with the aim to find the role of GSH on the in vivo metabolism of arsenic and arsenic-induced oxidative stress in vivo.

**MATERIALS AND METHODS**

**Animals and experimental procedures**

Thirty-six female albino mice (18-22 g, 6-7 weeks old) were obtained from the Center for Experimental Animals at China Medical University (Shenyang, China) with a National Animal Use License number of SCXK-LN2011-0009. The animal room was kept at a temperature of 20-24°C with a 12-hr light/dark cycle and a relative humidity of 50-60%. Free access to food and water was allowed of all times. Mice were housed six per cage in sterilized plastic cages with wood shaving bedding. All experiments and surgical procedures were approved by the Animal Care and Use Committee at China Medical University, which complies with Chinese National Guidelines for the protection of laboratory animal in animal experiments. All efforts were made to minimize the number of animals used and their suffering.

After one-week adaptation, the mice were divided randomly into six groups with six mice in each group. Among the six groups, one was randomly selected as the control, in which the mice were supplied with deionized water as drinking water. Mice in the other five groups were supplied with As-containing drinking water (50 mg/L As). After ten days, mice in the As treatment groups were injected intraperitoneally with 200 mg/kg body weight (b.w.) of GSH (iAs + GSH200 group), 400 mg/kg b.w. of GSH (iAs + GSH400 group), 600 mg/kg b.w. of GSH (iAs + GSH600 group), 800 mg/kg b.w. of GSH (iAs + GSH800 group), 600 mg/kg b.w. of BSO (iAs + BSO group) or the same volume of saline solution (iAs group), respectively. Each treatment was given every 12 hr for 2 days. GSH and BSO were dissolved in sterile saline solution. Mice in the control group were injected with the same volume of saline solution intraperitoneally. The amount of water intake was recorded every day. The dose of arsenite used in this study was well tolerated and did not alter the body weight. The day before the end of the experiment, the mice were housed in metabolism cages (one mouse per cage) to collect 24-hr cumulative urine for the analysis of the urinary arsenic species. During these 24 hr, the mice were also maintained on the same diet with water ad libitum as the whole experiment. On the end day of the treatment, all mice were weighed and killed by ether anesthesia. Blood was collected through eyeball extirpating and put into non-heparinized vials for serum separation and the subsequent biochemical assays. The serum samples obtained by centrifugation (3,000 × g, 4°C, 10 min) were kept frozen at -80°C until assayed as described below. During the autopsy, the entire liver was promptly removed and weighed. A portion of the liver was fixed for analysis of arsenic species, and the remaining
GSH accelerate metabolism of arsenic

tissues were stored at -80°C for future use.

**Analysis of GSH in whole blood and liver**

GSH levels were determined by modified 5,5′-dithio bis-2-nitrobenzoic acid (DTNB) method (Sedlak and Lindsay, 1968), using commercially available kits according to the manufacturer’s recommended protocol. Whole blood and liver samples were put on ice and the level of GSH determined without any delay. Hemoglobin (Hb) was used for calibration. The levels of GSH in the whole blood and liver were expressed as mg/g Hb and μg/g tissue.

**Total antioxidant capacity assays**

The TAC activities were measured by spectrophotometric analysis using commercial diagnostic kits (Jiancheng, Nanjing, China) according to the manufacturer’s instructions. Briefly, the protein content in liver supernatant was determined based on method of coomassie brilliant blue dyeing using bovine serum albumin (BSA) as the standard and expressed as milligram per milliliter (mg/mL). Enzymatic activities of TAC level were determined according to the methods of ferric reducing/antioxidant power reaction system. TAC was expressed as unit per milligram of protein (U/mg protein) in liver or unit per milliliter in serum (U/mL). The computational formula is: 

\[
\text{TAC} = \frac{(\text{ODu} - \text{ODc})/0.01/30 \times N/\text{Cprot}}{\text{ODc}},
\]

where ODu is absorbance of sample tube, ODc is absorbance of control tube, N is dilution ratio and Cprot is protein level of sample.

**Analysis of arsenic species**

We determined As species (iAs, MMA and DMA) in the urine and liver using atomic absorption spectrophotometer (AA-6800) with an As speciation pretreatment system (ASA-2SP; Shimadzu Co., Kyoto, Japan) as we reported previously (Sun et al., 2007). Total As species (tAs) were calculated as sum of iAs, MMA and DMA. Briefly, 1 mL of urine that had been stored at -80°C was thawed at room temperature and digested with 2 M NaOH solutions at 100°C for 3 hr in a 15-mL polymethylpentene test tube (Sarstedt) followed by dilution with deionized water. The assay samples were stirred once every 60 min. The concentrations of arsenicals in urine were corrected by individual urinary concentration of creatinine (Cr). The calculation formula of As species in the urine is tAs*N/Cr (μg As/g Cr), where N is the dilution ratio. A 50-mg liver sample was homogenized by adding 2.0 mL of deionized water, and then mixed with 1.0 mL of 3 M H₂SO₄. The samples were digested in a focused microwave field during a period of 10 min in a 10-mL polymethylpentene test tube. The calculation formula of As species in the liver is tAs*3/50 (μg As/g wet wt). Two indices, the first methylation ratio (FMR) and secondary methylation ratio (SMR) were introduced to evaluate methylation capacity, which were calculated as (MMA+ DMA)/tAs and DMA/(MMA+DMA), respectively.

**Statistical analysis**

A statistician was consulted before the start of the experiment for the minimum number of mice required to give viable statistical and reproducible data and for statistical analysis. Data were presented as mean ± standard deviation (SD). Statistical significance was determined by one-way analysis of variation (ANOVA) followed by post hoc analysis using Student-Newman-Keuls test (SNK) (SPSS 13.0, SPSS Inc., Chicago, IL, USA). All p values of less than 0.05 were considered statistically significant.

**RESULTS**

**General status, amount of arsenic intake and organ coefficient**

No changes in the general appearance, including posture, appearance of coat, nose, eyes and limbs of the mice, were observed throughout the entire experiment. There was also no obvious abnormality found during the autopsy. We calculated total ingestion of As from drinking water and found it varied from 5.79 to 8.01 mg As/kg b.w./day. There were no differences in percent gain from initial weight among groups. At the end of the study, the entire liver, lungs and kidneys were promptly removed, weighed and the organ coefficient was calculated correspondingly. The organ coefficient of liver of the mice in iAs + BSO group and iAs group were obviously higher than those of the other groups (p < 0.05). There were no significant difference in organ coefficient of kidneys and lungs among all groups (data not shown).

**Analysis of As metabolites**

Arsenic species of iAs, MMA, DMA and arsenic percentage of iAs%, MMA% and DMA% were measured in the liver and urine so as to confirm the potential effects of GSH and BSO on arsenic methylation and urinary excretion. We found that the level of all the arsenic species including tAs in mice exposed to 50 mg As/L for 10 days were higher than those of the control group (p < 0.05). The levels of arsenic species in the liver of the GSH-treated groups were significantly decreased compared with those of the iAs group in a concentration-dependent manner (Table 1). In the iAs + GSH₂₀₀ group, only the hepatic level of iAs was significantly decreased compared with that of the iAs group, and the concentrations of MMA,
DMA and tAs were nearly at the same level as those of the iAs group. The hepatic levels of all the arsenic species in both the iAs + GSH400 and iAs + GSH800 groups were markedly lower than those of the iAs group as shown in Table 1 (*p* < 0.05). The same situation was found about arsenic percentage of iAs%, MMA% and DMA% in the iAs + GSH200 group. That is to say, only the hepatic level of iAs% was significantly decreased compared with that of the iAs group, and the MMA% and DMA% were almost at the same level as those of the iAs group (Table 2).

Arsenic percentages of iAs% and MMA% in the liver of both the iAs + GSH400 and iAs + GSH800 groups were significantly decreased compared with those of the iAs group, while DMA% in both the iAs + GSH400 and iAs + GSH800 groups were markedly higher than those of the iAs group (Table 2). The results for arsenic methylation capability characterized by FMR and SMR showed that hepatic FMR of the iAs + GSH200 group was significantly higher than that of the iAs group, and hepatic FMR and SMR of both the iAs + GSH400 and iAs + GSH800 groups were markedly increased compared with those of the iAs group (Table 2).

The levels of urinary arsenic species and percentage are shown in Tables 3 and 4, respectively. The urinary levels of DMA and tAs in the GSH-treated groups were markedly higher than those of the iAs group (Table 3). Compared with the iAs group, there were no significant decreases in the concentration of urinary arsenic iAs and MMA after GSH treatment (Table 3), but urinary iAs% and MMA% were significantly lower, and urinary DMA% was significantly higher (Table 4). Urinary FMR and SMR significantly increased in all the GSH-treated groups (Table 4).

The hepatic levels of iAs, MMA, tAs (Table 1), iAs% and MMA% (Table 2) of the BSO-treated group were significantly increased compared with those of the iAs group, while hepatic levels of DMA (Table 1) and DMA% (Table 2) were markedly decreased. The urinary levels of MMA, DMA, tAs (Table 3), and DMA% (Table 4) of the BSO-treated group were significantly decreased compared with those of the iAs group, while the urinary levels of iAs% and MMA% (Table 4) were markedly increased. FMR and SMR in both the liver and urine of the BSO-treated group were significantly lower than those of the iAs group (Table 2, Table 4).

**Effects of arsenic on GSH concentration and TAC**

TAC has been developed to assess the general antioxidant activity in biological samples without distinguishing the contribution from each individual component. In this study, arsenic-induced oxidative stress was obviously demonstrated by the decrease of TAC in both blood and liver (Table 5). The findings of the significant decreased level of GSH in both the blood and liver of the iAs group (compared with those of the control group), and the further decreased level of TAC in the iAs + BSO group (compared with that of the iAs group) provided further evidence of arsenic-induced oxidative stress. Treatment

| Table 1. Arsenic species levels in the liver among different groups (mean ± S.D. μg As/g wet wt). |
|---|---|---|---|---|
| **Group** | **Case** | **iAs** | **MMA** | **DMA** | **tAs** |
| Control | 6 | 0.075 ± 0.012 | ND | ND | 0.075 ± 0.012 |
| iAs | 6 | 0.273 ± 0.028 | 0.161 ± 0.018 | 0.215 ± 0.022 | 0.648 ± 0.049 |
| iAs + GSH400 | 6 | 0.225 ± 0.016 | 0.163 ± 0.017 | 0.208 ± 0.030 | 0.596 ± 0.036 |
| iAs + GSH800 | 6 | 0.127 ± 0.014 | 0.060 ± 0.014 | 0.164 ± 0.006 | 0.351 ± 0.025 |
| iAs + GSH800 | 6 | 0.109 ± 0.011 | 0.052 ± 0.010 | 0.172 ± 0.024 | 0.333 ± 0.032 |
| iAs + BSO | 6 | 0.533 ± 0.036 | 0.266 ± 0.030 | 0.122 ± 0.018 | 0.921 ± 0.079 |

ND: not detected.

Table 2. Percent of arsenic species, FMR and SMR in the liver among different groups (mean ± S.D. %).

<table>
<thead>
<tr>
<th><strong>Group</strong></th>
<th><strong>Case</strong></th>
<th><strong>iAs</strong></th>
<th><strong>MMA</strong></th>
<th><strong>DMA</strong></th>
<th><strong>FMR</strong></th>
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<td>iAs</td>
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<td>33.15 ± 2.86</td>
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<td>iAs + GSH400</td>
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<td>37.84 ± 2.68</td>
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<td>29.06 ± 1.15</td>
<td>12.51 ± 1.28</td>
<td>0.42 ± 0.01</td>
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</tr>
</tbody>
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Table 3. Percent of arsenic species, FMR and SMR in the liver among different groups (mean ± S.D. %).

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Table 4. Percent of arsenic species, FMR and SMR in the liver among different groups (mean ± S.D. %).

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with exogenous GSH significantly increased the level of TAC, which recovered to the normal level at the dose of 800 mg/kg b.w. (Table 5).

**DISCUSSION**

Endemic arsenic poisoning is considered a severe public health problem throughout the world. In China, it has been estimated that 19.6 million people are at risk of being affected by the consumption of arsenic-contaminated groundwater (Rodríguez-Lado et al., 2013). It has been reported that the liver is the main organ of arsenic methylation in mammals, including multiple steps catalyzed by methyltransferase (Ford, 2006; Naujokas et al., 2013). In this study, the findings that the organ coefficient of liver of the mice in iAs + BSO group and iAs group were obviously higher than those of the other groups indicated that compensatory adjustment occurred in the liver so as to increase the capability of arsenic methylation. However, arsenic methylation also occurs in the extrahepatic tissues (Naranmandura et al., 2013). In this study, we found that FMR and SMR in the urine were significantly higher than those in the liver, which indicated that apart from the liver, arsenic methylation occurred in the extrahepatic tissues. FMR and SMR represent the capability of methylation from iAs to MMA, and from MMA to DMA, respectively. Since arsenic metabolites were finally excreted into the urine, urinary FMR and SMR could reflect the total methylation capability of the body.

Urinary arsenic level is the best indicator of exposure because it is the main route of excretion for most arsenicals. In addition, the profile of arsenic species reflects the methylation capability of ingested iAs, and in turn the related toxicity in the body (Chen et al., 2013). iAs%,
MMA%, DMA%, FMR and SMR were widely used as the index of methylation efficiency (Concha et al., 2002). It has been reported that the higher proportion of MMA or iAs in the urine was associated with the development of many arsenic-induced disease. Our previous study indicated that lower SMR was related to the higher susceptibility of individuals to oxidative DNA damage (Xu et al., 2009), lower SMR and higher MMA% were associated with the severity of arsenic-related skin lesions (Li et al., 2011), and that higher concentration of urinary MMA and lower DMA% might be related to the increased susceptibility to hypertension (Li et al., 2013). Since individual methylation capability was associated with arsenic-related lesions and GSH is the essential factor involved in the methylation process, it is important to observe the role of exogenous GSH in the biotransformation of arsenic in the body.

The findings that administration of GSH increased FMR and SMR in both liver and urine in this study indicated that GSH might potentiate the methylation efficiency in the body, which resulted in the decrease of iAs% in the liver and urine. We could also infer that SMR was much more efficient than FMR because there was a decreased trend of MMA% but an increased trend of DMA% in both the liver and urine. Moreover, the finding that administration of BSO, a scavenger of GSH, induced the opposite effect of decreased DMA%, FMR and SMR but increased iAs% and MMA% in the liver and urine further confirmed the role of GSH in the acceleration of arsenic methylation.

Apart from as an essential factor involved in the arsenic methylation process, GSH is important as an intracellular reductant for arsenic-induced oxidative stress and critical as a cellular antioxidant. It is accepted that arsenic-induced oxidative stress plays an important role in the mechanism of arsenic poisoning (Jomova and Valko, 2011; Nesnow et al., 2003). In this study, the findings that GSH level and TAC in both the liver and urine of A. exposed group were significantly lower than those of the control group confirmed the arsenic-induced oxidative stress. Along with the increase of the administration of exogenous GSH, the levels of GSH and TAC were found to show a trend of increase. At the dose of 800 mg/kg b.w., the levels of GSH and TAC in both the liver and blood returned to the normal level. Therefore, 800 mg/kg b.w. seemed to be the appropriate administration dose of GSH in this mouse model with both the capability of antioxidation and acceleration of arsenic methylation.

In conclusion, all together, we provided evidence with a mouse model confirming that appropriate administration of exogenous GSH could promote arsenic methylation, accelerate arsenic excretion in vivo and enhance the body's antioxidant capacity. Our study may therefore suggest a potential useful chemopreventive dietary component to counteract the harmful injuries of arsenic poisoning.

ACKNOWLEDGEMENTS

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Conflict of interest— The authors declare that there is no conflict of interest.

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tion with skin lesions induced by contaminated drinking water consumption in residents of chronic arsenicosis area. Environ. Toxicol., 26, 118-123.


