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The Role of Glutathione in the Metabolism and Detoxification of Trivalent Arsenicals.

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Abstract:
Inorganic arsenicals (iAs) are metabolized and excreted mainly in urine as dimethylarsinic acid (DMA^V). Glutathione (GSH) plays an important role in the metabolism of iAs. In rat bile, the major metabolites of iAs have been reported to be arsenic-glutathione (As-GSH) complexes, such as arsenic triglutathione (ATG) and methylarsenic diglutathione (MADG). Recently, we proposed a new metabolic pathway of iAs in which As-GSH complexes are substrates for S-adonosyl-L-methionine (SAM)-dependent arsenic methyltransferase, Cyt19. Arsenite (iAs^{III}) forms a complex with GSH producing ATG, and ATG is methylated to MADG by Cyt19, and finally As-GSH complexes excreted into hepato-enteric and/or hepato-blood circulation. We showed that both ATG and MADG were unstable in both bile and phosphate buffer (PBS) and were hydrolyzed to iAs^{III} and monomethylarsonous acid (MMA^{III}). Furthermore, MMA^{III} appeared to be oxidized to MMA^V in bile faster than in PBS. Cytotoxicity of MMA^{III} and dimethylarsinous acid (DMA^{III}) were higher than that of iAs. The concentration of biliary GSH increased in As-treated rats, and synthetic As-GSH complexes were stabilized by GSH. Very recently, we reported that dimethylarsenic glutathione (DMAG) generated volatile arsenicals when GSH exists in culture medium at low concentration, and GSH inhibited cellular uptake of DMAG and generation of volatile arsenicals at high concentration. The volatile arsenicals dissolved into solution and formed an unstable arsenical and finally converted DMA^V. These results suggested that GSH plays an important role in preventing hydrolysis of As-GSH complexes and the generation of toxic trivalent arsenicals, and that the oxidation of trivalent arsenicals plays an important role in the detoxification of arsenicals.

Key words: arsenic, metabolism, arsenic-glutathione complex, Cyt19, glutathione, HPLC-ICP MS

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