Biological Action of Various Arsenic Metabolites

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The metabolism of arsenic is generally accepted to proceed by repetitive reduction and oxidative methylation; the latter is mediated by arsenic methyltransferase (Cyt19). In human and rat urine, the major metabolites of inorganic arsenicals are monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), while the major metabolites in rat bile are trivalent arsenic-glutathione (As^{III}-GSH) complexes, such as arsenic triglutathione (ATG^{III}) and monomethylarsonic diglutathione ($MADG^{III}$). We have generated recombinant human and rat Cyt19 and investigated how arsenic is methylated by this enzyme using high performance liquid chromatography-inductively coupled plasma mass spectrometry (HPLC-ICP MS). It appears that inorganic arsenicals are first converted to ATG^{III} chemically rather than enzymatically and then Cyt19 catalyzes transfer of a methyl group from S-adenosyl-L-methionine to ATG^{III}.

Although MMA^V and DMA^V are much less toxic than inorganic arsenicals, hydrolysis products of $MADG^{III}$, monomethyarsonous acid (MMA^{III}), has been reported to be highly cytotoxic and genotoxic. The toxicity of chemically synthesized dimethylarsinous acid (DMA^{III}) is comparable to that of MMA^{III}. However, both DMA^{III} and dimethylarsinic glutathione ($DMAG^{III}$) seem to be too unstable to be detected in either in vivo or in vitro. The stability of As^{III}-GSH complexes depends on the concentration of GSH and the overall toxicity of those complexes appears to be changed by hydrolysis (generation of toxic trivalent arsenicals) and oxidation of the complexes (conversion to less toxic pentavalent arsenicals).