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Bioaccessibility and degradation of naturally occurring arsenic species from food in the human gastrointestinal tract

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ABSTRACT

Humans are exposed to organic arsenic species through their diet and therefore, are susceptible to arsenic toxicity. Investigating the transformations occurring in the gastrointestinal tract will influence which arsenic species to focus on when studying metabolism in cells. Using a physiologically based extraction test, the bioaccessibility of arsenic species was determined after the simulated gastrointestinal digestion of rice, seaweed and fish. Pure standards of the major arsenic species present in these foodstuffs (arsenic glutathione complexes, arsenosugars and short chain fatty acids) were also evaluated to assess the effect of the food matrix on bioaccessibility and transformation. Approximately 80% of arsenic is released from these foodstuffs, potentially becoming available. Hydrolysis and demethylation of arsenic glutathione complexes and arsenosugars standards was observed, but no transformations occurred to arsenosugars present in seaweed. Demethylation of MA and DMA from rice occurs increasing the amount of inorganic arsenic species available for metabolism.

1. Introduction

Arsenic is widely distributed in the environment and naturally present at high concentrations in seafood and some terrestrial crops (International Agency for Research on Cancer, 2012). Even though it has been shown that humans are able to adapt to arsenic-rich habitats (Schlebusch et al., 2015), chronic exposure to inorganic arsenic is still associated with the development of diseases that, if not directly derived from arsenic uptake, can be enhanced in its presence (International Agency for Research on Cancer, 2012). Currently, the highest intake of arsenic by humans arises from the consumption of contaminated edibles and beverages, especially drinking water, seafood and rice (International Agency for Research on Cancer, 2012). In drinking water, arsenic exists mainly as the inorganic species arsenate (As(V)) and arsenous acid (As(III)) (Fig. 1) (International Agency for Research on Cancer, 2012). In rice it can also be found as methylarsonic acid (MA), dimethylarsinic acid (DMA) and the arsenic glutathione complexes arsenotriglutathione (ATG), monomethylarsonic diglutathione (MADG) and dimethylarsoglutathione (DMAG) (Fig. 1) (Duan et al., 2011). Seaweeds are rich in arsenosugars, such as arsenosugar-glycerol (O-Gly), arsenosugar-sulfate (O-SO_4), arsenosugar-sulfonate (O-SO_3) and arsenosugar-phosphate (O-PO_4) (Tukai, Maher, McNaught, Ellwood, & Coleman, 2002). In fish, arsenobetaine (AB) is the major arsenic species found (Maher, Foster, & Krikowa, 2009) and arsenolipids comprise about 10–30% of the total arsenic content (Fig. 1) (Sele et al., 2013). Arsenic toxicity depends on the chemical species absorbed and metabolised once inside an organism (Michalski, Szopa, Jabłonska, & Łyko, 2012); hence the way each arsenic species affects human health is different. For example, arsenite and arsenate are categorised as Group 1 carcinogens, while MA and DMA are possibly carcinogenic or Group 2B carcinogens (International Agency for Research on Cancer, 2012). Arsenolipids have been shown to be toxic to human hepatocytes (Meyer et al., 2014) and arsenosugars toxicity has been suggested in terms of the arsenic species produced after metabolism in cells (Leffers, Ebert, Taleshi, Francesconi, & Schwerdtle, 2013). In contrast, arsenocholine and arsenobetaine are non-toxic to mammals (International Agency for Research on Cancer, 2012).

To evaluate the effects of arsenic in human health, it is important to understand what happens when specific arsenic species enter the body. To date, most studies have focused on the metabolism of inorganic arsenic in mammalian cells (Hayakawa, Kobayashi, Cui, & Hirano, 2004; Rehman & Naranmandura, 2012), as well as the identification of arsenic metabolites in human urine

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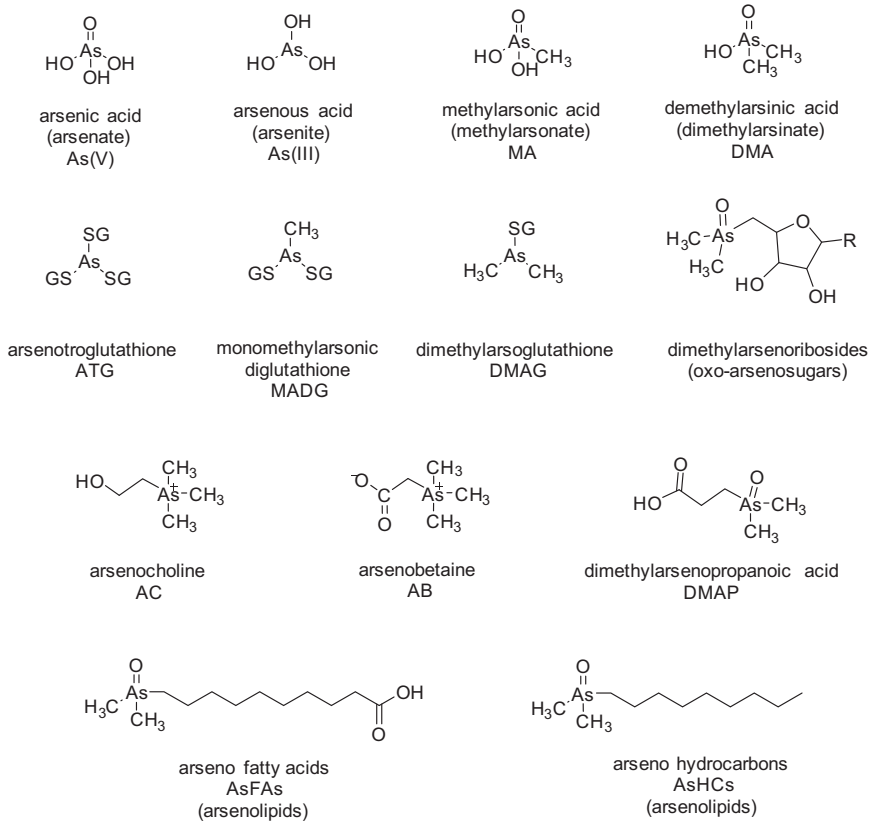

Fig. 1. Structures of arsenic species commonly encountered in food and water. The moiety –SG in ATG, MADG and DMAG corresponds to a molecule of glutathione, in which a sulfur atom is bound to arsenic.

(Crecelius, 1977; Le et al., 2000; Raml, Goessler, Traar, Ochi, & Francesconi, 2005; Schmeisser, Goessler, & Francesconi, 2006). Little attention, however, has been paid to the initial processes after ingestion, which are the transformations occurring in the stomach and small intestine. These are key in understanding the bioaccessible fraction of arsenic, that is the species potentially reaching the bloodstream after enteric absorption (Ruby et al., 1999); it is this fraction that needs to be accounted for when investigating metabolic processes in cells. To study the human digestion process of trace elements, both *in vivo* and *in vitro* approaches have been developed (Ruby et al., 1999). The limitations of *in vivo* experiments are economics, ethics and their complexity, and, furthermore, it has been shown that *in vitro* studies can be correlated to the results obtained after *in vivo* experiments (Ruby et al., 1999). Nowadays, the most reliable *in vitro* model is known as physiologically based extraction test (PBET), which involves two extractions that mimic the gastric and small intestinal stages of digestion (Karadaş & Kara, 2011).

Few studies have been published on arsenic bioaccessibility (Almela et al., 2005; Calatayud, Bralatei, Feldmann, Devesa, & Vélez, 2013; Gamble et al., 2002; Laparra, Velez, Montoro, Barbera, & Farre, 2003; Ruby, Davis, Schoof, Eberle, & Sellstone, 1996; Zhao et al., 2014). Ruby et al. (1996) and Laparra et al. (2003) focused on inorganic arsenic, which is already known to enter metabolic pathways in cells; whereas Gamble et al. (2002) conducted experiments on the *in vitro* gastrointestinal digestion of four arsenosugar standards (O-Gly, O-SO_4, O-SO_3 and O-PO_4) in simulated gastric juices and reported their degradation to dimethylarsinoylribose (O-Ribose). These experiments only followed the chemical effects of the stomach pH (~2) and pepsin on the arsenic species tested. Almela et al. (2005) considered the effect of both the stomach and small intestine conditions on arsenosugar-containing seaweeds. Their findings contradicted Gamble et al. (2002) results, as arsenosugars in seaweed were intact after digestion. Calatayud et al. (2013) reported the *in vitro* gastrointestinal digestion of As (V), MA and DMA added to vegetables. They observed that, after exposure to the stomach and intestine conditions, the water soluble arsenic fraction contained trivalent MA and DMA, as well as thiomethylarsonic acid (thio-MA) and thio-dimethylarsinic acid (thio-DMA). The digestion of As(V), MA and DMA standards in the absence of vegetables did not produce these species, suggesting that sulfur-containing components in the vegetables, together with the cooking procedure, had important effects on arsenic metabolism. Zhao et al. (2014) reported the transformations of As(III), As (V), MA and DMA in various seaweeds after *in vitro* gastrointestinal digestion. It was shown that, for some seaweeds, digestion of DMA and MA produced As(III); however, they did not conduct a comprehensive analysis of arsenic species due to the lack of arsenosugar standards. The ingestion of arsenosugars and arsenolipids has also been investigated regarding their excretion products in human urine (Francesconi, Tanggaard, McKenzie, & Goessler, 2002; Raml et al., 2005; Schmeisser et al., 2006). Arsenobetaine, in contrast, has been shown to be stable and excreted unchanged after human ingestion (Schmeisser et al., 2006).

In this study we use PBETs to evaluate the bioaccessibility and degradation of arsenic glutathione complexes, arsenosugars and dimethylarsenopropanoic acid (DMAP) as a model compound of arsenic fatty acids. The foodstuffs known to contain these arsenic species were also examined. Given the wide variety of gut flora among different human populations and individuals (Clemente, Ursell, Parfrey, & Knight, 2012), we have only considered the enzymatic and chemical conditions of the human gastrointestinal tract, excluding the microbiota existing in the stomach and small intestine.