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Evaluation of the ability of arsenic species to traverse cell membranes by simple diffusion using octanol–water and liposome–water partition coefficients

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ABSTRACT

Arsenic metabolism in living organisms is dependent on the ability of different arsenic species to traverse biological membranes. Simple diffusion provides an alternative influx and efflux route to mediated transport mechanisms that can increase the amount of arsenic available for metabolism in cells. Using octanol–water and liposome–water partition coefficients, the ability of arsenous acid, arsenate, methylarsonate, dimethylarsinate, thio-methylarsonate, thio-dimethylarsinic acid, arsenotriglutathione and monomethylarsonic diglutathione to diffuse through the lipid bilayer of cell membranes was investigated. Molecular modelling of arsenic species was used to explain the results. All arsenic species with the exception of arsenate, methylarsonate and thio-methylarsonate were able to diffuse through the lipid bilayer of liposomes, with liposome–water partition coefficients between 0.04 and 0.13. Trivalent arsenic species and thio-pentavalent arsenic species showed higher partition coefficients, suggesting that they can easily traverse cell membranes by passive simple diffusion. Given the higher toxicity of these species compared to oxo-pentavalent arsenic species, this study provides evidence supporting the risk associated with human exposure to trivalent and thio-arsenic species.

Introduction

Arsenic is a well-known environmental contaminant, readily available to living organisms from both natural and anthropogenic sources (Mandal and Suzuki, 2002). In humans, exposure to arsenic can result in major health problems such as skin lesions, cancer and cardiovascular diseases (International Agency for Research on Cancer, 2012). Arsenic toxicity not only depends on the concentration of exposure, but also on the chemical form of arsenic (Cullen and Reimer, 1989; Le et al., 2004) and their specific metabolic pathways in living organisms; some of which require transport across biological membranes, *i.e.*, absorption, distribution and excretion (Charoensuk et al., 2009; Styblo et al., 2000; Vega et al., 2001). Biological membranes consist of a lipid bilayer with embedded proteins and cholesterol, according to the so-called "fluid mosaic model" (Elliot and Elliot, 2005). The bilayer is formed by glycerophospholipids and glycosphingolipids (glycolipids) arranged with their polar heads and non-polar tails pointing outwards and inwards, respectively. Proteins can be both integral and peripheral to the bilayer, and

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their role is to favour selective transport; whereas cholesterol controls the fluidity of the membrane and restricts the permeability of small molecules (Elliot and Elliot, 2005). Since one of the main functions of cell membranes is to limit the movement of undesirable substances, transportation across the lipid bilayer needs to be controlled. When movement occurs in the same direction as the concentration gradient, passive transport can take place with or without assistance. Non-mediated passive transport (simple diffusion) is governed by Fick's first law of diffusion, in which molecules randomly collide against the bilayer and traverse it proportionally to the concentration on each side of the membrane. Simple diffusion depends on the lipophilicity of the molecule, *i.e.*, size, shape and charge; along with the viscosity of the lipid bilayer (Mathews et al., 2013). When faster speeds are required, passive transport can be mediated by channels or pores, carrier molecules and permeases (facilitated diffusion) (Mathews et al., 2013). Active transport occurs when molecules are pumped against their concentration gradient, with the consumption of energy in the form of adenosine triphosphate (Mathews et al., 2013). Despite the prevailing selectivity of most transport mechanisms, there are a number of undesired substances that can still be mistaken for the target species in terms of their size, structure and charge; and make use of the existing intrusion and extrusion systems in biological membranes. This is the case for metalloids, such as arsenic, which was initially thought to enter cells by simple diffusion, but then shown to use integral membrane proteins (Zangi and Filella, 2012). For this reason, the study of arsenic transport mechanisms in cells has predominantly been restricted to facilitated diffusion and active transport, with little attention given to the potential for passive simple diffusion.

The different arsenic uptake systems in both prokaryotic and eukaryotic cells are summarised in Table 1. Under physiological conditions, arsenous acid (As(III)) is a neutral hydroxide (Fig. 1) that is able to traverse lipid membranes using aquaporins and aquaglyceroporins (Liu et al., 2002; Rosen, 2002). These bidirectional channels belong to the Major Intrinsic Protein family (MIP) and are responsible for assisting the transport of small uncharged molecules across a concentration gradient. Aquaporins are specific for water; whereas aquaglyceroporins transport a range of small molecules, such as glycerol, carbon dioxide, ammonia, carbamides, polyols, purines and urea (Liu et al., 2002). Since As(III) is physically similar to glycerol, it can easily use certain MIPs to traverse membranes (Zangi and Filella, 2012). In humans, the aquaglyceroporins that facilitate As(III) uptake are *AQP7* and *AQP9* (Liu et al., 2002). The first exists in kidney, testis and adipose tissue (Liu et al., 2006b) and the second in lung, liver and leukocyte tissues (Liu et al., 2002); but their level of expression depends on the age, gender and nutritional status of the individual (Liu et al., 2002). Human *AQP9* expressed in *Xenopus laevis* oocytes also facilitates the uptake of the pentavalent organic arsenic species methylarsonate (MA) and dimethylarsinate (DMA) (McDermott et al., 2010). In mammalian epithelial and blood cells, the influx of As(III) and methylarsonous acid (MA(III)) is assisted by the glucose transporter *GLUT1* (Liu et al., 2006b). Arsenate (As(V)) is an anion (Fig. 1) at physiological pH (~7.4) and thus, the way it enters the cell is different to As(III). Given its comparable volume and electronic configuration to orthophosphate, As(V) uptake had been suggested to be achieved by phosphate carriers (Rosen, 2002; Zhang et al., 2000); but this was not demonstrated until 2010 (Villa-Bellosta and Sorribas, 2010),

Table 1 – Arsenic uptake systems in cells.
Adapted from Zangi and Filella, 2012.

Arsenic species	Transporter name		Organism
	Facilitated diffusion	Active transport	
As(III)	MIP: *GlpF* (glycerol channel)		*E. coli* (prokaryote)
As(III)	MIP: *AqpS*		*S. meliloti* (prokaryote)
As(III)	MIP: *Fps1*, *Rgc1*, *Rgc2* (glycerol channels)		*S. cerevisiae* (eukaryotic)
As(III)	Hexose permeases		Yeasts
As(III)	MIP: *TbAQP2*		*T. brucei* (eukaryotic)
As(III)	MIP: *LmAQP1*		*Leishmania* (eukaryotic)
As(III)	MIP: *NIP7;1*		*Arabidopsis* (plants)
As(III)	MIP: *NIP2;1*, *NIP5;1*, *NIP6;1*, *NIP3;2*		*A. thaliana*, *L. japonicus* and *O. sativa* (plants)
As(III), MA and DMA	MIP: *Lsi1*		*O. sativa* (rice) roots
As(III)	MIP: *HvLsi1*, *ZmNIP2-1*, *ZmNIP2-2*, *ZmNIP2-3*		Plants
As(III) and MA(III)	MIP: *Aqp9a*, *Aqp9b*, *Aqp3*, *Aqp3I* and *Aqp10*		Zebrafish
MA and DMA	MIP: human AQP9		*X. laevis*
As(III) and MA(III)	MIP: *AQP7* and *AQP9* Glucose transporter: *GLUT1*		Mammals (including humans)
As(III)	MIP: *AQP3* and *AQP9*		Human cancer cells
As(V)		Phosphate transporters: *PiT-1*, *PiT-2* (sodium-coupled)	*E. coli* (prokaryote)
As(V)		Phosphate transporters: *Pho84*, *Pho87* (proton-coupled)	*S. cerevisiae* (eukaryotic)
As(V)		Phosphate transporters: *NaPillb* (sodium-coupled)	Mammals

MIP: Major Intrinsic Protein family.

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