Molecular Biophysics and Biochemistry

Research Article ISSN: 2398-970X

Biochemical pathways of arsenic uptake from the environment to human cells

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Abstract

Arsenic is one of the most toxic elements on Earth and causal factor of serious poisonings and diseases. Agency for Toxic Substance and Disease Registry placed this metaloid on the 1st place of Substance Priority List. The explanation of mechanisms of As migration from environment to organisms is crucial step on a way to limit poisonings caused by this element. This review presents the most actual knowledge about As transporters involved in migration and distribution of As from the environment via food chain into human body, focusing on molecular cell transporters of arsenic. The mechanism of translocation depends on the As form. Three allotropes and nine states of oxidation either organic As (As_{org}) and inorganic As (As_{in}) were identified. In biochemical aspect the most significant are As(III) and As(V) forms. Pit and Pst are transporters responsible for As(V) intake in every organism regarding As(V) form similarity to phosphate compounds. In plants, e.g. domesticated Oryza sativa different specialized transmembrane PHT proteins like OsPht1;1 and OsPht1;8 and their homologues uptake and distribute As(V) compounds within plant. As_{in}(III) migration pathway leads via aquaglyceroporins such like GlpF in E. coli, NIPs members (e.g. AtNip, OsNip, OsPIP) in plants or AQPs in mammalian cells. In dependence on type of organism aquaglyceroporins are transporters involved in uptake as well as efflux of As(III) from the cell. Therefore, organisms can contribute to increase of more toxic As form in environment. Another pathways for As(III) uptake are hexose permeases identified in yeast and mammalian cells. Organic arsenic compounds intake was studied mainly on As methylated derivatives and it was shown that is processed via aquaglyceroporins like As_{in}(III) forms, although molecular mechanism of As_{org}(III) and As_{org}(V) seems to be different.

Abbreviations and symbols: APL: Acute Promyelocytic Leukemia; AQP: Aquaporin; $As_{in:}$ Inorganic Arsenic Compounds; $As_{org:}$ Organic Arsenic Compounds; ATSDR: Agency For Toxic Substance And Disease Registry; DMA^{III}: Dimethylated Derivatives of As(III); DMA^{V}: Dimethylarsinic Acid; EPA: Environmental Protection Agency; ER: Endoplasmic Reticulum; GLUT1: Glucose Transporter 1; Mas(III): Methylated As(III); MIP: Major Intrinsic Proteins; MMA^{III}: Monomethylated Derivatives of As(III); MMA^{V}: Monomethylarsonic Acid; NIP: Nodulin 26-Like Intrinsic Proteins; PHS: Phosphate H+ Symporter; PHT: Phosphate Transporter; P_i: Inorganic Phosphate; PIP: Plasma Membrane Intrinsic Proteins; Pit: Low-Affinity Inorganic Phosphate Transporter; Pst: Inorganic Phosphate-Specific Transporter; TIP: Tonoplast Intrinsic Proteins; TMA^{III}: Trimethylated Derivatives of As(III); $TMAO^{V}$: Trimethylarsine Oxide; WHO: World Health Organisation

Introduction

Arsenic – a representative of metaloids group – is one of the most toxic elements on Earth (Ghosh, *et al.,* 2008). It is causal factor of different types of cancer, nervous and peripheral vascular system diseases, neurological disorders and diabetes [1-3]. What is more, As demonstrates teratogenic activity, causing low birth weight and fetal loss, as well as delays of infant mental and physiological development [4]. As limits the uptake of important microelements, such as iron or zinc [5,6]. Considering As toxicity, Agency for Toxic Substance and Disease Registry (ATSDR) placed this metaloid on the very top of Substance Priority List (http://www.atsdr.cdc.gov/spl/) [7]. Despite of the toxic properties, As is still applied as a chemotherapeutic agent in several diseases therapy, but in 18th and 19th centuries it was basis of pharmacology of that time. Nowadays, drugs with As are used in therapy of acute promyelocytic leukemia (APL) (e.g. Trisenox) or diseases caused by protozoan parasites [8,9]. In nature As forms three allotropes [10] and nine states of oxidation, from -III to V depending on type of chemical bonds. In terms of biochemical aspects, the most significant are As(III) and As(V) compounds [11-13]. Under reducing conditions, such as flooded rice paddy fields, As(III) dominates As(V). On the other hand, As(V), the oxidized form, dominates As(III) under oxidative conditions. As is involved in forming about 200 minerals, out of which the most commonly spread are arsenopyrite, loellingite or realgar.

Arsenic content in upper layers of Earth crust is small and according to recent analyses reaches 2 ppm on average. As a consequence of weathering processes As infiltrates to soils, waters and the air, but the major amount of this element is a result of anthropogenic activity, mainly mining and metallurgy industry, usage of pesticides and wood

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Key words: *arsenic uptake, aquaporins, permeases, phosphate transporters, rice*

Received: August 27, 2016; **Accepted:** September 22, 2016; **Published:** September 26, 2016

preservatives or semiconductors [7,14] Apart from mineral compounds As forms also organic arsenic (As_{org}) compounds [7], several of them are produced as ingredients of pesticides. The most widely spread in the environment As_{org}(V) compounds are monomethylarsonic acid (MMA^V), dimethylarsinic acid (DMA^V) and trimethylarsine oxide ($TMAO^V$). Comparing to inorganic As (As_{in}) compounds, the concentration of organic forms is low [15], moreover the concentration of mono-, di-, and trimethylated derivatives of As(III) (MMA^{III}, DMA^{III}, TMA^{III}) is even lower because of high volatility they present [16]. Organic As compounds can be also created by organisms as an effect of biotransformation of As_{in} [17]. Transformation of As_{in} into methyl derivatives is common metabolic reaction of mammals. Methylated forms of As(III) are considered to be more toxic than As_{in}(III), on the other hand As_{in}(III) forms are about 60 times more toxic than As_{in}(V) compounds. On the other hand, the toxicity of As_{in}(V) is about 70 times higher in comparison with two common As_{org} forms, *i.e.,* MMA^V and DMA^V, which are characterized by moderate toxicity level [18, 19]. MMA^V and DMA^V in mammalian organisms are excreted with urine and feaces as products of TMA^{III} oxidative biotransformation [7]. According to Environmental Protection Agency (EPA) the most common reason of poisoning with As is consumption of water and foods contaminated with this element [7]. It was estimated that about as many as 40 million people in the world are exposed to consumption of water contaminated with As (Nordstrom, 2002). It was the reason why World Health Organization (WHO) lowered allowable content of As in waters from 50 μgAs/l to 10 μgAs/l, but in several countries, such like Bangladesh, India, Vietnam, Thailand or Taiwan the contamination of waters by As is significantly higher. Analyzed drinking water samples from West Bengal contained As of concentration reaching level up to 1000 μg/l, whereas the highest concentration was detected in Ramnagar village and reached 3700 μg/l [20,21].

Among food products the most contaminated with As is rice, which intakes from soil higher amounts of As in comparison with other domesticated plants [22,23]. Results of some research show, that people consuming rice of amounts higher than average, have even 40% higher As content in organism than another. Significant concentrations of As were also detected in Brussel's sprout [24]. High concentrations of As_{in} was confirmed in research on hijiki brown algae (*Hizikia fusiformis*), called brown sea vegetable in Japan, Korea and China. According to Japanese folklore, regular consumption of small amounts of hijiki aids health and beauty, including lustrous, thick, black hair. It was also adopted to culinary applying in United Kingdom and North America. Recently it has been shown that it contains potentially toxic quantities of As_{in}, and consumption of hijiki have been discouraged by the food safety agencies of several countries, such as Canada, the United Kingdom and the United States but not in Japan [25] 2014: *Survey of Total and Inorganic Arsenic in Seaweed - Food Safety Research Information Office". United States Department of Agriculture. 2004. Retrieved 30 September 2014*; Anon., 2015: *Inorganic Arsenic and Hijiki Seaweed Consumption. Canadian Food Inspection Agency. 20 March 2012. Retrieved 12 March 2015*).

The source of As are also sea fish as well, such as tuna, mackerel, salmon or sardines, but fortunately the As in their tissues is incorporated in less toxic As_{org} compounds such as arsenobetaine and arsenocholine which are easily removed from human organism. Despite of this, it was proved that in the case of people consuming mentioned fish species once a week, the concentration of As in the body was 7% higher than in the case of those who consume once a month or less frequently [24]. In general sea organism's bodies contain more As than fresh water ones, which is explained by the effect of water salinity on ability of As accumulation [26,27]. The ingestion of As consumed with water or food from gastrointestinal tract depends mainly on the solubility and can reach up to 95% [28]. Organisms are exposed mainly to As in the form of arsenates(V) ($HAsO_4^{2-}$, $H_2AsO_4^-$) and arsenates(III) (arsenines) ($As(OH)_3$, $H_2AsO_3^-$). Both forms are transported in random way, as the same mechanism is used for transport of another compounds which are indispensable for metabolism [29]. Thus, arsenates(V) are taken up via phosphate transporters [30,31]. Whereas arsenates(III) via aquaglyceroporins transporting e.g. water and glycerin [32-34]. Arsenates(III), which under physiological pH conditions are not ionized, migrate inside to cells faster than negatively charged arsenates(V) [35,36]. As(III) transporters characterizes two-way transport, what is used particularly by microorganisms taking up As(V) and reducing to As(III) to remove this form out of the cell. The process of reduction As(V) to As(III) is typically frequent in habitats under oxygen deficiency conditions [7]. The explanation of As intake mechanisms from environment and distribution of its compounds through the food chain and within human body would be important information for protection and therapy of poisoning with this element. This review deals with that topic focusing on the most actual knowledge about arsenic transporters involved in migration and distribution of As from the environment via food chain into human body.

Biochemical pathways of arsenic(V) influx

Pit and Pts transport arsenic(V) in bacteria

Regarding structural similarities, the mechanism of arsenates(V) intake in every living organism is the same and is conducted via phosphate transporters (Figure 1). Some of them present high affinity to inorganic phosphate (P_i), whereas another one is low. In 70' research on *Escherichia coli* resulted with discovering of two phosphate channels, which don't distinguish P_i from arsenate(V). One of them is Pit, a low-affinity, high capacity constitutive system playing crucial role in process of As(V) intake. Cells dependent upon the Pit system have a K_M of 38.2 ± 0.4 μM and a V_{max} of 55 ± 1.9 nmol of P_i (mg [dry weight]$^{-1}$min^{-1}), and cannot grow in the presence of an As(V) to P_i ratio of 10 in the medium [30,37,38]. The second transporter is high-affinity but low-capacity system induced by phosphate starvation, named Pst [39]. It transports As(V) into cells less efficiently than Pit. K_M of cells dependent upon Pst system have nearly 90 times higher P_i affinity (K_i

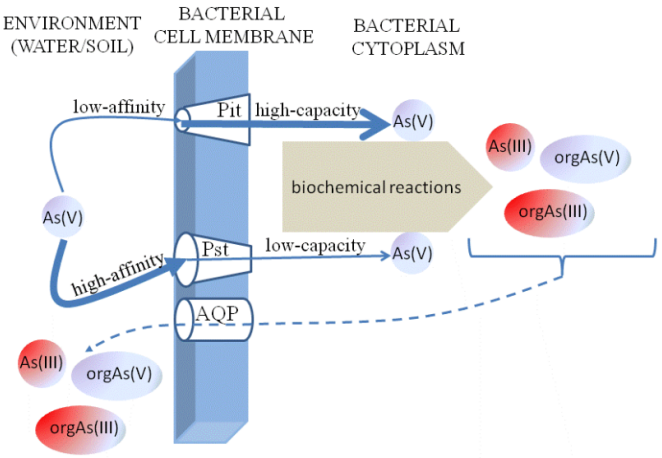

Figure 1. The share of the best-known bacterial As_{in}(V) transporters in As uptake. Pit – low affinity, high capacity phosphate transporter; Pst - high affinity, low capacity phosphate transporter; AQP – aquaporins

of Pst is 0.43 ± 0.2 μM P_i) than cells with Pit system. However, they uptake P_i with V_{max} more than 3 times lower (15.9 ± 0.3 nmol of P_i (mg [dry weight]$^{-1}$min^{-1}) than cells dependent upon the Pit system. Additionally, the cells dependent upon Pst system can easily grown in the presence of arsenate in the environment and probably it is the only one P_i transporter synthesized by bacteria constantly exposed to As(V) in environment [38]. It is claimed, that the lack of Pit expression is the protective mechanism limiting non-specific As(V) ingestion into the cells [40].

Members of Pht1 family are guilty of introducing arsenic(V) into the trophic chain

In the case of plants there is a specified group of incorporated in plasma membrane phosphate transporters which presents high affinity to phosphate(V), called P_i transporter 1 (Pht1; TC 2.A.1.9, the PHS family) (Figure 2). The characteristic property of this protein family is presence of 12 membrane spanning domains [41]. Results of the research have shown, that in the case of *Arabidopsis thaliana* possessing nine proteins Pht1 (PHT1 proteins), six of them are involved in processes of uptake and transport of As_{in}(V) (AtPht1;1, 4, 5, 7, 8, 9) (Figure 2). Eight out of those nine proteins are synthesized in roots under condition of P_i deficiency [41,42,43]. First identified AtPht1;1 and AtPht1;4 are involved in uptake of P_i and arsenates(V) from soil in presence of high, as well as low phosphorus content [44]. AtPht1;5 supports translocation of As_{in}(V) and P_i from older leaves to sink (young leaves, growing roots and developing seeds) organs (Figure 2) [41,23]. It was also observed that deficiency of P_i induces expression of *AtPht1;5,* especially in the flowers, cotyledons and phloem cells of older leaves [43]. Also AtPht1;7 specifically expressed in reproductive tissues of *Arabidopsis* participates in As_{in}(V) influx. AtPht1;8 and 9, which dominate in *Arabidopsis* roots, under conditions of phosphorus deficiency contribute to As_{in}(V) uptake from soil [45]. Recently several transcription factors of *A. thaliana* were identified and they are involved in control of As_{in}(V) intake by regulation of *AtPht1* genes expression *AtPht1* [46,47]. What is more, in the endoplasmic reticulum (ER) of *A. thaliana* there was AtPhf1 (P_i Transporter Traffic Facilitator 1) identified. This protein inhibits AtPht1;1 transport from ER to the plasma membrane, by this way limiting the number of AtPht1;1 and as a consequence the uptake of As_{in}(V) [48].

AtPht1 show from 60% to 95% similarity of sequence in comparison to its homologues identified in such plants like rice (*Oryza sativa*), wheat (*Triticum aestivum*), potato (*Solanum tuberosum*), tomato (*Solanum lycopersicum*), tobacco (*Nicotiana tabacum*) or *Pteris vittata* known from its arsenic hyper-accumulation abilities [49-51]. What is more, in case of many monocots and dicots species, and both As-hyper accumulators and non- hyper accumulators it was proved, that As_{in}(V) competes P_i while ingestion process into cell via phosphate transporters of high as well as low affninity to P_i [15,52-58]. This fact indicates on common contribution of plant Pht1 proteins not only in P_i transport, but also in uptake of As_{in}(V) and its distribution in plant [23]. The promoting effect of As on plants growth in the presence of its small concentrations is a result of P_i intake stimulation by As [56].

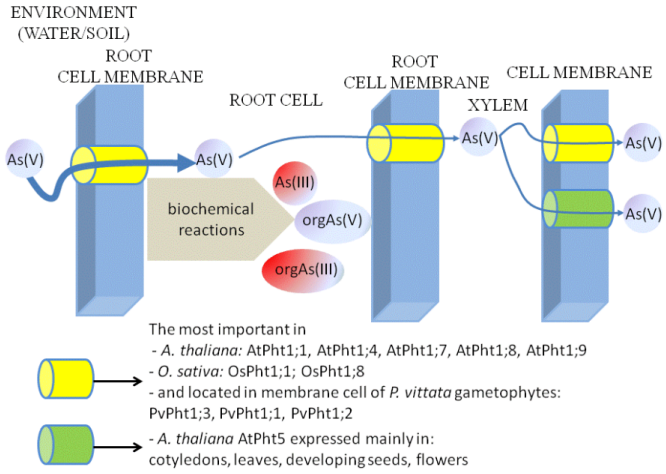

Figure 2. The most accurately researched plant As_{in}(V) transporters.

In plant biochemistry and genetics studies *A. thaliana* is a model organism, but it cannot be applied directly for practical, significant for human organism pathways analysis of As translocation from the environment to the human cells. In contrast to *A. thaliana*, rice (*O. sativa*) is a domesticated plant significant for nutrition. *O. sativa* is able to accumulate As and additionally is often grown on areas contaminated with this element. Two of twelve identified in rice P_i transporters, i.e. OsPht1;1 and OsPht1;8 are involved in processes of uptake and translocation of As_{in}(V) in plant (Figure 2). Both *OsPht1;1* and *OsPht1;8* are expressed independently on concentration of phosphorus. Transport OsPht1;1 from ER to the plasma membrane depends on OsPhf1 responsible for synthesis of protein with function similar to AtPhf1 in *A. thaliana*. Transcription factor regulating expression of *OsPht1;8* called OsPhr2 (P_i starvation response 2) was also identified [23,59-62]. Recent research resulted with identification of three Pht1 transporters of *Pteris vittata* (PvPht1) (Figure 2). By using transgenic yeast cells and radiolabeling with 32P it was observed that PvPht1;3 demonstrates the same affinity to P_i as AtPht1;5, but its affinity to As_{in}(V) is significantly higher. Moreover, yeast cells with PvPht1;3 were able to accumulate more As_{in}(V) than with AtPht1;5.

Pht1 transporters does not participate only in uptake As_{in}(V) from environment, but are also involved in its direction to xylem vessels and then can be distributed between cells or even from one cell compartment to another as well [60,63-65]. As an example can be given As_{in}(V) which is co-substrate for three mitochondrial proteins localized to the inner-mitochondrial membrane and responsible for dicarboxylate exchange with co-substrates such as P_i, between the mitochondrial matrix and the cytosol [66]. However, it should be regarded, that in case of non-hyperaccumulators only about 3% of As ingested by roots is translocated into stem [67]. It was demonstrated, that in *A. thaliana* leaves even 97%–100% of As exists in form of As on III state of oxidation [68] similarly like in the roots and shoots of *Brassica juncea* (96–100%) [69] or roots of tomato and rice (92–99%) [70]. Those examples prove very efficient and fast reduction of ingested As_{in}(V) compounds. An interesting phenomenon is the process of widely spread, efficient and quick reduction of As_{in}(V) within all groups of organisms, starting from bacteria to the final biotransformations of As in human body [71]. Additionally, arsenates(V) compete with P_i during translocation into cell because of the structural analogy [56,57], what is the reason why increase of P_i concetration limits the As_{in}(V) intake and inversely – deficiencies of P_i enhance the uptake of As_{in}(V).

Biochemical pathways of As_{in}(III) influx

The mechanism of uptake As_{in}(V) via phosphate transporters was well studied, however the pathway of As_{in}(III) transport into cell was explained only in 2004. [72] discovered that *E. coli* protein GlpF responsible for antimony(III) uptake [32] is involved in transport of As_{in}(III) into cell as well (Figure 3). GlpF protein is the first identified

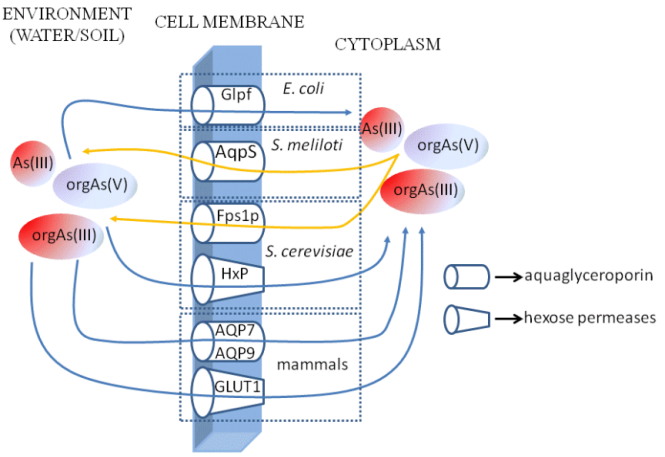

Figure 3. The most accurately researched As_{in}(III) and As_{org} transporters of bacteria, yeast and mammals.

representative of aquaporin's known also as major intrinsic membrane proteins (MIP) [74]. Aquaporin's family is divided into two groups: true aquaporin's which are water channels, and aquaglyceroporins which GlpF belongs to, with larger pore channels but low to no water permeability. Aquaglyceroporins facilitate transport of non-charged particles, such like glycerol, urea, ammonia or boric and silicic acid [75-78]. Several studies demonstrated also that aquaglyceroporins of *E. coli* (GlpF), yeast (Fps1p) and mammals (mouse AQP7, rat and human AQP9) are able to transport As_{in}(III) (Figure 3) [71]. Whereas *E. coli* GlpF transports As_{in}(III) form environment into cell, the GlpF orthologue, AqpS of the legume symbiont *Sinorhizobium meliloti* is responsible for As_{in}(III) efflux [79]. Similarly, to many other bacterial or yeast species, *S. meliloti* uptakes As_{in}(V) compounds, reduces in enzymatic pathway to As(III) form and finally remove this product from the cell to environment [71,80] (Figure 3). Yeast cells also influx As_{in}(V) via phosphate ion channels and subsequently reduce it to As(III) and then removed with aquaglyceroporin Fps1p which is an orthologue of *E. coli*. Although AqpS as well as Fps1p are both the GlpF orthologues they transport As_{in}(III) *in* reverse to GlpF direction (Figure 3). The examples given above allow to conclude, that depending on type of organism, aquaglyceroporins are transporters involved either in As_{in}(III) uptake or As_{in}(III) efflux by the cells (Figure 3). Plants also have aquaglyceroporins, which make them significant link of food chain intermediating efficiently in migration of As from the environment to animal and human organism.

Aquaglyceroporins are broad gates for As_{in}(III) uptake from environment to the cells

Plant aquaporins are the most researched As_{in}(III) transporters facilitating efficient transport of these compounds from environment into cell. They are classified as representatives of nodulin 26-like intrinsic protein (NIP; TC 1.A.8, the MIP family) family [76-78,81]. NIPs are one of the four plant aquaporins subfamilies. The another three groups are: plasma membrane intrinsic proteins (PIPs), tonoplast intrinsic proteins (TIPs) and small basic intrinsic proteins (SIPs) [82,83]. It is believed that plants obtained NIPs genes as a result of horizontal gene transfer from bacteria [75].

Six of nine identified *A. thaliana* NIPs (AtNip) participate in As_{in}(III) transport, similarly to the *O. sativa*, where six of ten identified OsNip proteins have this function towards As_{in}(III). It was proved, that two Nip proteins of *Lotus japonica* and one of *Hordeum vulgare* are able to translocate As_{in}(III). The most important for As_{in}(III) uptake from environment to the root AtNips are AtNip1;1, AtNip3;1, AtNip5;1 and AtNip6;1. Additionally, AtNip5;1 and AtNip6;1 are involved in transmembrane As_{in}(III) transport and AtNip3;1 facilitates As_{in}(III) translocation from the root to the stem (Figure 4). AtNip7;1 is selectively expressed in anthers and pollen tissues and gene encoding AtNip1;2 is strongly expressed in seeds [23,76,77,84,85]. In *O. sativa* OsNip2;1 is responsible for As_{in}(III) uptake from the environment into root, whereas OsNip3;2 is expressed primarily in anthers and suspension cells (Figure 4). OsNip2;1 participates in As_{in}(III) uptake, but together with OsNip3;2 facilitates migration of this form through cellular membranes, having contribution to distribution of As throughout plant organs. Both studied Nips representatives of *L. japonicus*, i.e. LjNip5;1 and LjNip6;1 and HvNIP1;2 of *H. vulgare* are also involved in transport of As_{in}(III) through cellular membranes (Figure 4) [23].

If consider the plant transfer of As from the environment to animal and human cells, the most significant role plays rice (*O. sativa)* consumption [86]. It is cultivated in soil of low aeration level, where As_{in}(III) dominates another forms. The rice contaminated with As, besides water, is factor causing serious poisonings. By aquaglyceroporins rice easily and efficiently absorb As_{in}(III) from the soil and water and accumulate in seeds [22]. The concentrations of As in grain reach the level which can endanger health of people for whom rice is the base of diet [86]. OsNip2;1 is the example of aquaglyceroporin which is major rice As_{in}(III) transporter, but it is also called silicon (Si) influx transporter (OsLsi1) as its function is uptake of Si from environment. The diameter of silicic acid molecule (4.38 Å) is close similar to diameter of tetrahedron of $[As(OH)_3]$ (4.11Å) which dominates form of arsenite at pH below value of its pK_a of 9.2. Under physiological conditions arsenite forms non-charged arsenous acid particles and OsNip2;1 (OsLsi1) channel also remains electrically neutral, what facilitates transport of this As compound [78].

The another silicic transporter, OsLsi6 (OsNip2;2), belongs to OsNip – subfamily, similarly to OsNip1;1 and OsNip3;1 is characterized by low level of expression and it is suggested, that does not possess significant function in process of uptake As_{in}(III) from the environment [23,78]. Studies on recently identified transporter OsNip3;3 demonstrated that it uptakes As_{in}(III) from the environment

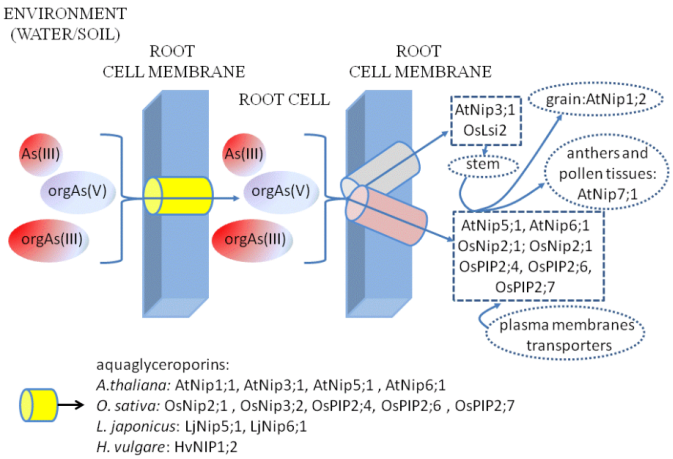

Figure 4. Simplified scheme of occurrence and functions of identified plant As_{in}(III) and As_{org} transporters.

and does not require the presence of As_{in}(III) to be synthetized, but more precise research is required [23,87,88]. Whereas OsNip2;1 (OsLsi1) located in the distal side of epidermal and endodermal membrane cells of rice root, transport As_{in}(III) from the environment, the another silicic transporter OsLsi2 located in the membranes on the proximal side of the same cells is responsible for transport of As_{in}(III) from root cells to xylem (Figure 4). By this OsLsi2 contributes to distribution of As in rice and as a consequence to accumulation of As_{in}(III) in rice grain. Thus, OsLsi2 transporter is the main factor enhancing accumulation of As_{in}(III) in rice grain, and by this toxic effect of contaminated with As rice on health of millions people on the world [78,89,90]. The expression of this protein in rice is not high, but independent on the presence of arsenic in the environment. The increase of Si concentration in soil inhibits accumulation of As_{in}(III) [78] and application of sulfur fertilizers counteracts contamination of grain by decreasing As_{in}(III) and As_{in}(V) concentration in rice seeds as well [91,92].

Another mechanism of As uptake limitation is forming the Fe plaques in rice and other plants growing on flooded areas (e.g. water species) rhizosphere [93,94]. Fe plaque consists of ferrihydrite, a widespread on the Earth's surface hydrous ferric oxyhydroxide mineral, and is formed on the root surface as a result of Fe^{2+} to Fe^{3+}oxidation by the oxygen released through aerenchyma of the roots of the plants growing in anaerobic soils.

Oxidized iron strongly adsorbs to arsenate. It was shown, that the concentrations of As_{in}(V) within iron plaques of rice roots were 5 times higher than in root tissues of rice. Iron plaques on the roots of tested plants contain 70-80% As_{in}(V) and 20-30% As_{in}(III). Thus, the iron plaque formed on roots surface is natural barrier protecting from migration of As to the plant. Results of short-term experiments on As uptake by excised rice roots demonstrated, that whereas iron plaques limit As_{in}(V) uptake, on the other hand increase this process in case of As_{in}(III) [93,95-99] It was supposed, that this relation is associated with As_{in}(III) transporters efficiently operating within rice cell membranes. These transporters shift the balance of As_{in}(III) binding reaction to the form not associated with iron plaques but quickly ingested by the roots of rice.

Apart from members of the NIPs family there were identified three other aquaporins belonging to the rice plasma membrane intrinisic proteins in rice (PIP TC 1.A.8, MIP family) marked: OsPIP2;4, OsPIP2;6 and OsPIP2;7. These proteins are involved in transport of As_{in}(III) in the root and stem of rice and in contrast to the family of aquaporins Nip their synthesis is strongly down-regulated in response to As_{in} (III) [100].

The process of uptake and transport of As_{in}(III) was well studied for mammals, which use aquaglyceroporins similarly to other groups of organisms. At least for 13 aquaporines indentified in mammals As_{in}(III) uptake was documented for AQP7 translocating As_{in}(III) the most efficiently, and for AQP9 (Figure 3), which transports As_{in}(III) better than hAQP7. Among other researched aquaporins only two, *i.e.,* hAQP3 i hAQP10 demonstrated ability of As_{in}(III) uptake, but of not significant amounts and the study results have been not equivocal [98].

As_{in}(III) inlux by gatesother than aquaglyceroporins

Apart from aquaglyceroporins there were identified another types of proteins responsible for As_{in}(III) uptake. In yeast cells the major As_{in}(III) influx transporters are transmembrane hexose permeases [101] (Figure 3). In plants, proteins with strong homology to the yeast hexose permeases are present, however it is still unexplored if they are involved in As_{in}(III) migration to the plant cells. In contrast to plants, in mammalian cells additional to aquaglyceroporins As_{in}(III), transporter of glucose 1 (GLUT1) was identified (Figure 3). GLUT1 is the homologue of yeast hexose permease and is the most explored and ubiquitous isoform of GLUT family. Under physiological conditions high expression of GLUT1 is observed in erythrocytes (3–5% of total transmembrane proteins), endothelium and epithelium, blood-brain barrier, eye, placenta and mammary gland [102]. GLUT1 is responsible for transport of glucose and 2-deoxyglucose, but also galactose, mannose, glucosamine and ascorbic acid [102,103]. Results of comparable analyses of As_{in}(III) transport ability by GLUT1 and yeast permeases Hxt1p, Hxt3p, Hxt4p, Hxt5p, Hxt7p, Hxt9p and Hxt10p demonstrated, that GLUT1 is the least efficient As_{in}(III) transporter. However, when the efficiency of methylarsenous(III) acid (MAs(III)) transport was tested, GLUT1 activity occurred to be the most efficient [104].

Biochemical mechanisms of organoarsenic compounds influx

Intake of As_{org} compounds was studied by experimental analyses of its methylated derivatives. It is believed that these forms migrate into cell *via* aquaglyceroporins (Figure 3), the same pathways like As_{in}(III) and independently on their oxidation states, although it was demonstrated that Fps1p identified in yeasts was unable to transport MAs(III) [105]. Yeast cells influx MAs(III) by their hexose permeases, however rate of the MAs(III) uptake by this way is slower than for As_{in}(III) forms [104]. In case of the *E. coli*, the same transport rate by GlpF was shown for MAs(III) and As_{in}(III) [7,105].

Despite that in plants the high concentrations of methylated As have been detected, present knowledge about plant mechanisms of As_{org} compounds uptake still requires research. Previous studies have shown, that in rice the concentration of DMA is two times higher than As_{in} forms, although MMA^{III} is influxed faster than DMA^{III} [106,107]. It is believed that rice roots are able to uptake organoarsenic compounds by the same transporters which are active for As_{in}(III), e.g. OsLsi1 (OsNip2;1) [108] (Figure 3). Similarly, to As_{in}(III), also uptake of methylated As by rice is inhibited with Si [109-111]. Another studies demonstrated, that uptake of MMA^{III} and DMA^{III} was decreased significantly in association with increase of glycerol concentration, what indicates on influx of mentioned As_{org} forms by the pathways of glycerol [106]. The mechanism of organoarsenic compounds uptake in mammalian cells is similar to plants and *E. coli* and is processed by aquaglyceroporins. Additionally, it was observed that rat AQP9 is more efficient transporter of MAs(III) than of As_{in}(III) [7]. Apart from aquaglyceroporins also GLUT1 in mammal's cells is involved in transport of MAs(III). Analyzes of substrate specificity of GLUT1 expressed in *Xenopus laevis* oocytes demonstrated, that GLUT1 transports MAs(III) more effectively than yeast permeases, and the affinity of this common mammalian transporter to MAs(III) (K_M ~1.2mM) is more than two times higher than to glucose (Km~3 mM) [112] and over four times higher than to 2-deoxyglucose (Km~5 mM) [113]. It was also concluded that inhibition of glucose uptake by GLUT1 caused by MAs(III) is not a competitive inhibition. MAs(III) binds to GLUT1 in another site than glucose. Additionally, both forskolin and cytochalsin B which are commonly known inhibitors of glucose transport, do not inhibit uptake MAs(III) by GLUT1 [104].

The pathways of uptake organic and inorganic As(III) forms seem to be the same (Figure 3), however if consider the mechanisms

of As_{org}(V) and As_{in}(III) migration into cell, they are different [7,114] demonstrated that *X. laevis* oocytes with human AQP9 cRNA showed enhanced uptake of both MMA^V and DMA^V, however Hg(II) which is aquaporin inhibitor prevented influx of arsenicals through AQP9. On the other hand, while application of phloretin, an inhibitor of glycerol and water permeation via AQP9, it was observed that only MMA^V and DMA^V forms uptake was inhibited, in contrast to As_{in}(III) and MAs(III) [114]. The mechanism of this phenomenon remains unexplained as far.

Despite the progressing knowledge about the molecular mechanisms of various As compounds intake by different organisms cells, there are still many unexplained aspects related to migration of As from the environment to the food chain, and as a consequence – human organism. Comprehensive research of those mechanisms will allow to limit the endangers and health complications caused by arsenic poisonings.

Conflicts of interest

The authors declare no conflict of interest.

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