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MINIREVIEW ARTICLE

Polyamines and membrane transporters

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Abstract In recent years, our understanding of the importance of membrane transporters (MTs) in the disposition of and response to drugs has increased significantly. MTs are proteins that regulate the transport of endogenous molecules and xenobiotics across the cell membrane. In mammals, two super-families have been identified: ATP-binding cassette (ABC) and solute carrier (SLC) transporters. There is evidence that MTs might mediate polyamines (PA) transport. PA are ubiquitous polycations which are found in all living cells. In mammalian cells, three major PA are synthesised: putrescine, spermidine and spermine; whilst the decarboxylated arginine (agmatine) is not produced by mammals but is synthesised by plants and bacteria. In addition, research in the PA field suggests that PA are transported into cells via a specific transporter, the polyamine transport system(s) (PTS). Although the PTS has not been fully defined, there is evidence that some of the known MTs might be involved in PA transport. In this mini review, eight SLC transporters will be reviewed and their potential to mediate PA transport in human cells discussed. These transporters are SLC22A1, SLC22A2, SLC22A3, SLC47A1, SLC7A1, SLC3A2, SLC12A8A, and SLC22A16. Preliminary data from our laboratory have revealed that SLC22A1 might be involved in the PA uptake; in addition to one member of ABC superfamily (MDR1 protein) might also mediate the efflux of polyamine like molecules.

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Introduction

Polyamines (PA) are aliphatic compounds that are found in all biological materials. They are involved in the growth and function of both normal and cancer cells (Tabor et al. 1961; Wallace and Niiranen 2007). Three PA are synthesised in mammalian cells: these are putrescine (Put), spermidine (Spd) and spermine (Spm) (Wallace et al. 2003). In addition, decarboxylated arginine [Agmatine (Agm)] is synthesised by plants and bacteria including the normal flora in intestine (Pegg 2009). Great efforts in the PA field have focused on producing therapeutic agents to treat both cancer and parasitic infections. The polyamine metabolic pathway and polyamine transport system (PTS) have been targeted as potential sites of intervention where agents might be developed to treat cancer in man (Palmer and Wallace 2010). Studies on many cancer cell lines have revealed that PTS is highly active and it is promiscuous accepting a diverse range of PA like molecules (Phanstiel et al. 2007; Palmer and Wallace 2010). Recently, Poulin, Casero and Soulet have reviewed the molecular biology of the PTS elegantly in metazoan and they have summarised the general characteristics of this system according to seven main parameters, for more details see (Poulin et al. 2011). In addition, three putative models of PA transport have been proposed including glypican-mediated endocytosis, plasma transport and vesicular sequestration, and caveolin-mediated endocytosis (Belting et al. 2003; Soulet et al. 2004; Uemura et al. 2010; Palmer and Wallace 2010; Poulin et al. 2011). Despite this progress, the full picture of the PTS is not clear. There is

evidence that some of the known membrane transporters (MTs) might be involved in the PA transport; therefore, we have attempted to address this suggestion in our laboratory.

Recently, MTs have attracted significant attention during the drug development process as they are an important determinant of drug failure or success. This is in addition to the role of the metabolising enzymes. MTs are proteins that govern the transport of molecules into or out of the cell. These proteins can transfer various substrates such as sugars, vitamins, amino acids, bile acids, hormones and drugs (Ho and Kim 2005). In the human genome, more than 400 MTs have been discovered belonging to two major superfamilies which are solute carrier (SLC) and ATP-binding cassette (ABC); many members of these super-families have been cloned, localised and characterised in human body (Giacomini et al. 2010). However, in this mini review, we will focus on the MTs that might be involved in the PA transport.

SLC superfamily is the second largest group of membrane proteins in human genome by 384 members after the G protein-coupled receptors group which has 800 members (Fredriksson et al. 2008). The SLC proteins can translocate diverse endogenous substrates, environmental toxicants and drugs. As a result, they have key roles in the development of disease and in therapy (He et al. 2009). These MTs can translocate their substrates through several mechanisms including facilitated diffusion, ion coupling and ion exchange which in some cases required the activity of ABC members (Degorter et al. 2012). So far, research in this particular area has implicated eight SLC members that are/might be involved in the PA transport (Table 1).

SLC22A1/OCT1, SLC22A2/OCT2 and SLC22A3/OCT3/EMT

SLC22A1 is a gene encoding the polyspecific organic cation transporter, OCT1, which is widely distributed in human organs and tumour cells. It is most strongly expressed in liver (Koepsell et al. 2007). The SLC22A2 gene encodes for OCT2 protein and it is more tissue specific than OCT1 as it is mainly localised at the luminal membrane of distal tubules in the human kidney. However, there is evidence that OCT2 is also transcribed in human brain neurons (Koepsell 1998). The SLC22A3 variant encoding for OCT3 protein is distributed in many tissues but it has strong expression in liver, skeletal muscle, heart and placenta (Koepsell et al. 2007). OCT3 can take up noradrenaline with a similar sensitivity to noradrenaline uptake2 system; therefore, it has also been referred to as extraneuronal monoamine transporter (EMT) (Koepsell 2004).

It has been reported in the rat that OCT1 can translocate cations across the plasma membrane and this translocation is Na^+ independent and insensitive to changes in pH (Busch et al. 1996). Busch et al. (1996) have also found that Spd and Spm can be transported by this transporter (Table 1).

In addition, it has been found that Put and Spd influx depends on plasma membrane potential which has been described as one of the features of the PTS (Poulin et al. 1998, 2011). Furthermore, it has been discovered that cation transport by OCT1 and OCT3 is mediated via plasma membrane potential (Koepsell et al. 2007). Moreover, it has been proposed that PA uptake might be an electrogenic diffusion process enhanced by one of the SLC22A transporters (Soulet et al. 2004). Consequently, there is a possibility that PA transport might be mediated by one of the OCT transporters and preliminary data from our laboratory support this suggestion.

Whilst investigating drug–drug interactions (DDIs) at the PTS level by utilising a Spd conjugate, we have discovered that OCT1 might be involved in the uptake of the conjugate in cancer cells since the cytotoxicity of the conjugate has been decreased in the presence of a specific OCT1 inhibitor in comparison to control (Abdulhussein and Wallace, unpublished work). As a result, we suggest that OCT1 might accept Spd as a substrate.

Whilst the diamine Put has not been reported to be taken up by OCT1, it has been discovered that Agm can be transported by this membrane protein in human embryonic kidney HEK293 cells stably transfected with SLC22A1–A3 (OCT1–3) (Gründemann et al. 2003; Winter et al. 2010). However, Agm uptake by OCT1 was less efficient than OCT2 or OCT3 transporters and the affinity of the OCT1 for Agm was tenfold lower than the affinities of the other transporters (Gründemann et al. 2003). Winter et al. (2010) have supported Grundemann et al. results concerning the Agm transport by OCT1 and they suggested that OCT1 might have an important role in the hepatic secretion of Agm in vivo. In addition, Winter et al. have also concluded that OCT1, OCT2 and SLC47A1 might also contribute to central nervous system drug disposition. However, a separate study has shown that OCT1, OCT2, OCT3, OCTN1 and OCTN2 transporters did not mediate Agm transport in human glioma SK-MG-1 cells (Molderings et al. 2001). Further work has demonstrated that transfection of HEK293 with SLC22A1–3 did not enhance Agm accumulation in comparison to non-transfected cells (Molderings et al. 2003). Thus, the findings of Molderings et al. are contradictory to those of Grundemann et al. and Winter et al. (Molderings and Haenisch 2012).

SLC47A1/MATE1

SLC47A1 is a gene encoded for the multidrug and toxin extrusion transporter-1 (MATE1) which has a key role in

Table 1 Summary of polyamines substrates and membrane transporters

Gene	Transporter	Substrate	Reference
SLC22A1	OCT1	Spd and Spm	Busch et al. (1996)
		Spd conjugate	Abdulhussein and Wallace, unpublished work
		Agm	Gründemann et al. (2003), Winter et al. (2010)
SLC22A2	OCT2	Agm, Put	Winter et al. (2010)
SLC22A3	OCT3	Agm	Gründemann et al. (2003)
SLC47A1	MATE1	Agm	Winter et al. (2010)
SLC3A2	DAX	Put	Uemura et al. (2008, 2010)
SLC12A8A	CCC9a	PA and amino acids	Daigle et al. (2009)
SLC22A16	OCT6/CT2/Flipt2	PA and BLM-A5	Aouida et al. (2010)
ABCB1	MDR1	Spd conjugate	Abdulhussein and Wallace, unpublished work

PA polyamines: not specified by author(s), *Put* putrescine, *Spd* spermidine, *Spm* spermine, *Agm* agmatine, *BLM-A5* bleomycin-A5

the renal and hepatic secretion of organic cations (Otsuka et al. 2005; Winter et al. 2010). Although MATE1 has been detected in several tissues and organs including skeletal muscle, heart and liver; the highest expression has been found at the apical membrane of the proximal and distal convoluted tubules in kidney (Meyer zu Schwabedissen et al. 2010). The transport process by MATE1 has been identified as an electroneutral H^+-coupled organic cations export (Otsuka et al. 2005). A recent study has suggested that the MATE1 transporter does not influence Put and the higher PAs transport. However, these PA can partially inhibit Agm accumulation in OCT1, OCT2 and MATE1 transfected HEK293 (Winter et al. 2010). In this study, a bidirectional novel Agm transport system has been suggested including OCT1 and OCT2 as influx transporters, whereas MATE1 as exporter under physiological conditions. However, at an extracellular pH of 8.0, Agm accumulation was significantly enhanced in MATE1 cells in comparison to mock transfected cells indicating that MATE1 can also influx Agm under alkaline condition. Agm transport by OCT1 and OCT2 was concentration dependent but OCT2 was also pH dependent. Furthermore, OCT2 affinity for Agm was higher than OCT1 by tenfold (Winter et al. 2010). Moreover, Put transport has been reported to be mediated by OCT2; however, it was described as concentration and pH dependent, because Winter et al. have observed that under alkaline conditions, both Agm and Put transport by OCT2 were enhanced.

SLC7A1/CAT-1

CAT-1/SLC7A1 belongs to cationic amino acid transporter (CAT) family which is widely expressed in mammalian tissues (Palacin et al. 1998; Yang et al. 2007). CAT-1 is expressed in all tissues except in liver (Rotmann et al. 2004; Deves and Boyd 1998). Members of this family including CAT-1, CAT-2A, CAT-2B and CAT-3 form "system y^+" which represents the activity of these transporters (Deves and Boyd 1998; Palacin et al. 1998). This system can transport basic amino acids including lysine, arginine and ornithine. However, researchers suggest that system y^+ might also accept PA as substrates because of the structural similarity of basic amino acids and PA as well as the fact that both substrates are transported with high affinity and are Na^+ independent (Sharpe and Seidel 2005). As a result, Sharpe and Seidel suggested that there might be a common transport site for the basic amino acids and PA. It was proposed that this site might be CAT-1. However, it was discovered that this transporter protein did not transport PA since the transfection of Chinese hamster ovary—PA transport deficient derivative (CHO-MG) cells with CAT-1 did not affect PA transport. Furthermore, lysine transport was unaffected by antizyme overexpression which indicates that lysine was not travelling through a PA site. As a result, it was suggested that PA and lysine transport might be mediated by a common unidentified y^+ transport site (Sharpe and Seidel 2005).

SLC3A2

SLC3A2 is a gene encoding for the heavy chain of the cell antigen 4F2 which is the component of the heteromeric amino acid transporters (Palacin and Kanai 2004). This gene has also been described as an amino acid transporter which has been found to be involved in the PA transport in mammalian cell (Uemura and Gerner 2011). Recently, this transporter has obtained therapeutic importance as a target for cancer chemoprevention (Wood et al. 2011; Babbar and Gerner 2011) and as a novel biomarker for type II renal cell cancer (Prager et al. 2009).

In CHO cells, SLC3A2 was identified as a component of diamine exporter (DAX) which has the ability to export Put (Xie et al. 1997; Uemura et al. 2008). In human colorectal carcinoma cells, HCT116, which have an activated K-ras, SLC3A2 was also identified as a part of an arginine transporter which can export Put and its expression is

negatively regulated by K-ras oncogene (Uemura et al. 2008). In the latter study, it was found that SLC3A2 and spermidine/spermine N^1-acetyltransferase formed a complex on the plasma membrane which might suggest of involvement of these proteins in the export of acetylated PA. However, further study has shown that SLC3A2 can import Put at a low tissue PA content indicating bidirectional functionality of this transporter (Uemura et al. 2010). In addition, it has been demonstrated that the diamine was transported into the gastrointestinal tissues by a caveolin-1- and nitric oxide synthase 2-dependent mechanism. This mechanism has been considered as one of the putative models of PA accumulation and sequestration into vesicles in mammalian cells (Poulin et al. 2011).

SLC12A8A/CCC9a

SLC12A8 is a gene that encodes for solute carrier family 12 (sodium/potassium/chloride transporters) member 8 protein and it is also referred as the cation chloride co-transporters 9 (CCC9) (Daigle et al. 2009). This gene has a role in susceptibility to German psoriasis vulgaris (Huffmeier et al. 2005) and it can also promote PA and amino acid transport in mammalian cells (Aouida et al. 2010; Friauf et al. 2011). Daigle et al. (2009) discovered that SLC12A8 comes in multiple splice variants and one of them was referred as SLC12A8A/CCC9a. In addition, Daigle and colleagues have found that if SLC12A8A variant is expressed in HEK293 cells, the plasma membrane of these cells can accept PA and amino acids as substrates and facilitate their transport. They have also concluded that PA influx was increased through acute induction of SLC12A8A expression in HEK293 cells. This transport was an ion insensitive carrier system specifically, for Na^+, K^+ or Cl^- (Daigle et al. 2009).

SLC22A16/OCT6/CT2/Flipt2

SLC22A16 is a member of solute carrier transporter family 22 and it has also described as OCT6, carnitine transporter 2 (CT2) or Fly-like putative transporter 2 (Flipt2) (Okabe et al. 2005). Studies have suggested a primary role of this transporter in the import of doxorubicin, which is a widely used anticancer drug (Okabe et al. 2005), in addition to its role in the PA transport in several cell lines (Aouida et al. 2010). OCT6 has a limited distribution in human tissue; however, a very strong expression has been detected in testis (Koepsell et al. 2007). Bleomycin-A5 (BLM-A5) is a PA analogue which contains a Spd moiety and it has been investigated as a substrate for OCT6 transporter (Aouida et al. 2010). Human testicular (NT2/D1) cells, which highly express the SLC22A16 variant, were extremely sensitive to BLM-A5. However, human colon carcinoma HCT116 cells and human breast cancer MCF-7 cells were highly resistant to the same analogue, because the former cell line is devoid of the permease, whilst the latter cell line shows a weak express of the variant (Aouida et al. 2010). As a result, Aouida and colleagues have concluded that OCT6 can mediate BLM-A5 and PA uptake.

ABC superfamily

Transporters of this superfamily play a substantial role in the disposition of natural molecules and drugs in the human body. These transporters depend on adenosine-5-triphosphate (ATP) hydrolysis to exert their actions (Petzinger and Geyer 2006). Nowadays, they have a direct impact on the pharmacological properties of most of drugs in use because they can influence drug toxicity, interaction, side effects, excretion, metabolism and bioavailability (Calcagno et al. 2006; Schinkel and Jonker 2012). ABC transporters are expressed in many tissues such as small intestine, liver and brain and in addition to their expression in diverse tumour cells can lead to anticancer resistance (Mizuno and Sugiyama 2002; Takano et al. 2006; Baguley 2010).

Although there are many isoforms in this superfamily, for example, multidrug resistance P-glycoprotein (P-gp/MDR1), multidrug resistance proteins and breast cancer resistance protein; to our knowledge, PA transport by the ABC superfamily has not been fully investigated. In our laboratory, we have preliminary evidence that there might be a relationship between PA export and one member of this superfamily encoded by ABCB1 gene, and it is referred as MDR1. We have found that in the presence of three independent MDR1 inhibitors, the cytotoxicity of a Spd conjugate was enhanced when compared to controls (Abdulhussein and Wallace, unpublished work). Furthermore, the concentration of the Spd conjugate inside the treated cells was higher than in controls indicating that MDR1 inhibitors might decrease the export of the conjugate from cells. Although further investigation is required, this transporter protein might be a component part of the PTS.

In conclusion, MTs have significant effects on drug disposition and response. Whilst major research has been carried out on the SLC members, it seems that both superfamilies should be considered in terms of PA transport. Our studies on DDIs at the transporter level have suggested that Spd and/or polyamine conjugates might be a substrate for OCT1 and MDR1 transporters although further research is required. With the recent recommendations of the International Transporter Consortium concerning of the clinical development of new molecular entity (NME), as well as to the guidelines issued by the Food and Drug

Administration and European Medicines Agency (Zhang et al. 2009; Giacomini et al. 2010), we would expect that any prospective PA-related NME will be investigated at the transporter level. These investigations will improve our knowledge regarding PA transport by the MTs and it might also assist to understand the complete picture of the PTS.

Conflict of interest The authors declare that they have no conflict of interest.

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