Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2016; 8(1): 104-107

ISSN- 0975 1556

Review Article

Role of T-Type Amino Acid Transporter TAT1 (S1C 16a 10) in Aromatic Amino Acid Homeostasis

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Available Online: 31st December, 2015

ABSTRACT

TAT1 (T-type amino acid transporter 1), also known as SLC16A10 (solute carrier family 16, member 10), aromatic amino acid transporter 1, MCT10 (mono carboxylate transporter 10) or PRO0813, is a 515 amino acid protein that belongs to the monocarboxylate porter family. It is a uniporter, which is a Na+-independent transporter of aromatic amino acids (AAA) such as tryptophan, tyrosine, and phenylalanine across plasma membranes .It is highly expressed in skeletal muscle and kidney, found in low levels in heart, placenta, spleen , thymus , small intestine and liver epithelial cells. The gene encoding TAT1 maps to human chromosome 6, which contains170 million base pairs and comprises nearly 6% of the human genome. Its role in aminoacid homeostasis has been investigated using TAT1 defective mice (tat1(-/-). These mice show no gross phenotype or neurological defect however there is increased plasma, muscle and kidney AAA concentration under both normal and high protein diet, although this concentration remains normal in the liver. A major aromatic aminoaciduria and a smaller urinary loss of all substrates were revealed under a high protein diet suggesting an epithelial transport defect. Thus this indicates that uniporter TAT1 is required to equilibrate the concentration of AAAs across specific membranes by enabling the hepatocyte to function as a sink and also facilitates the release of AAAs across the basolateral membrane of small intestine and proximal kidney tubule epithelial cells thereby controlling the extracellular AAAs concentration.

Keywords: TAT1 (T-type amino acid transporter-1), AAA (aromatic amino acid), tat 1-/- (tat 1 defective mice)

INTRODUCTION

It is certain that transporters like Na^+ K^+ ATPase, H^+ K^+ ATPase, SGLT, and GLUT with respect to food absorption like carbohydrates, proteins, fats, vitamins and electrolytes is well known. Information on transporters for amino acid absorption is meagre. Some other transport channels are studied because their mutation and dysfunction may lead to certain diseases, example cystic fibrosis where there is a mutation in the CFTR chloride channels. The reason for some transporters being studied extensively is because they are expressed abundantly in the tissues and easily accessible to experimentation. However, there are very few studies that carried out in certain transporters though it is essential for the success and survival of the organism because of their low level expression in mixed cell population and probably located on the membrane that is difficult to work. One among them is system T. The importance of such a transporter system is often under investigated and overlooked due to difficulty in performing the experiments.

TAT 1

TAT is a Na^+ and Cl^- independent low affinity uniporter of the aromatic amino acid tryptophan, tyrosine and phenyl alanine, plus L-Dopa and derivatives. It was originally described as a transporter in human erythrocyte[1]. Its function has been described in hepatocyte, intestine, placenta and pre-implantation conceptuses. Its C-DNA has been isolated from rat, mouse and human and named as TAT1 (T-type amino acid transporter 1)[2-5]. It is almost similar to the thyroid hormone transporter MCT1-4 with respect to amino acid sequence and is thus categorised as the tenth member of solute carrier family 16. (SLC 16 A10) .It also exhibits sequence similarity (~30% identity at the amino acid level) to H^+/monocarboxylate transporters[2]. However the distribution of TAT 1 mRNA varies between species. It is broadly found in small intestine, colon, kidney, liver, skeletal muscle, placenta, heart, spleen, thymus, prostrate and pancreas. Thus, this broad tissue distribution suggests its key role in physiological function. It is been found basically in the basolateral membrane of small intestine, proximal tubule of kidney and liver[2-4]. The physiological roles of this transport protein were studied using knock out rodent model[6]. This acts as a uniporter amino acid influx in the kidney and small intestine. The tat 1-/- mice had increased plasma aromatic amino aciduria. This identifies that TAT 1 plays a key role in controlling whole body aromatic aminoacid homeostasis by mediating influx into hepatocyte, the major site of aromatic amino acid metabolism. Also it is known to mediate basolateral efflux of the aromatic amino acid (AAA) from renal filtrate[6] and therefore deficiency of this transport protein leads to an increase in AAA levels in the kidney and aminoaciduria. In the gut it is known to mediate the basolateral release of AAA from the diet. Further, an interesting concept was

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seen in animals which were fed on high protein diet, where in the neutral amino acid substrates for the amino acid exchanger system lat 2/4 f 2 hc were lost in the urine, indicating that TAT 1functions in co-operation with lat2/4f2hc to maximize amino acid reabsorption under normal circumstances. However tat 1-/- mice grow and reproduce normally suggesting that the loss of this transport protein alone does not cause any obvious disease phenotype though it is a precursor of serotonin, nicotinic acid, catecholamine and thyroid hormones precursor. This informs that it forms a part of functional network of amino acid transporters to optimise epithelial activity. Thus the disease phenotype and redundancy may appear only with ageing, dietary restriction specific stresses or following mutation of multiple transporters in iminoglyciuria[7]. Thus tat1-/- mice, displays increased plasma, muscle and kidney AAA concentration under both normal and high protein diet, although its concentration remains normal in liver. Food containing dietary proteins as well as endogenous proteins is finally hydrolysed in the human GIT to tripeptides, dipeptides and individual amino acids (AA). These are later taken up by the cells of small intestine[8] where they are further metabolized into single AAs.Ultimately they enter into portal circulation, thereby influencing the rate of AA appearance in plasma[9, 10]. Thus, it is important to note that the amount of free AAs transported daily from enterocytes into circulation is much larger than the free AA pool of plasma and extracellular space suggesting that their uptake into tissue is critical for maintaining extracellular AA homeostasis[9]. Later in the cells of different organs, AAs then serve as building blocks for the synthesis of structural and functional proteins or is used for cellular metabolism or is used as signalling molecule[11,10]. Thus amino acid transfer across plasma membrane play a crucial role in AA homeostasis and defect in this transportation may lead to several diseases[11,12]. LAT 2-4F2hc (SLC 7a8) and y^+ LAT 1-4F2hc (SLC 7a7) antiporters are the best AA transporters found in the small intestine and proximal kidney tubule. They perform directional transport of all their substrate AAs across the membrane thereby mediating a directional flux[13-17]. LAT 2-4F2hC defective mouse presented with a mild increase in neutral AAs in plasma and a corresponding minor aminoaciduria[18]. However AAAs were not elevated in the plasma of LAT 2 null mice, suggesting that another AA transporter played a dominant role here ; possibly the T-type AAA transport TAT1 (SLC 16a 10), which was found slightly up regulated in the kidneys of these mice. Later this was molecularly identified and characterised by Endon and his co workers in the year 2001[3]. Studies using Xenopus laevis oocyte expression system, revealed that TAT 1 mediates facilitated diffusion pathway of AAAs L-Phe, L-Try and L-Tyr[6] Also, it is shown to co localise in the kidney proximal tubule[19], basolateral membrane of small intestine enterocytes and in the sinusoidal membrane of previous hepatocytes[6]. Also studies using polymerase chain reaction (PCR) reveals the presence of this protein in brain and muscle[6]. Further AAAs transported by TAT 1 such as L-Trp and L Tyro are known to be precursors of serotonin, catecholamines and thyroid hormones. Thus, the absence of TAT 1 transporter potentially affects neurotransmitter and thyroid hormone availability leading to neurological disorders[20]. Although TAT 1 does not play a role in the normal development and fertility of mice, few studies does reveal that it plays an important role on body AA homeostasis. It is indeed well known that the accumulation of AAs as a result of high protein is counteracted by an increase in the metabolism in the liver[21].Thus liver plays a major role as a metabolic organ for AAAs catabolism[22,23] and thus liver failure can cause an increase in AAAs in plasma[23]. This leads to a decrease of BCAA's /AAA's ratio and a consecutive increase of AAA uptake into the brain which has suggested to be one of the main causes of hepatic encephalopathy[24,25]. Further an increase is also reflected in skeletal muscle [20] suggesting that TAT1 is not necessary for the AAA equilibrium between plasma and this compartment. In contrast, the intracellular AAA values in the liver of tat-/- mice were normal suggesting that liver functions as a sink for the AAA catabolism and thereby sets their concentration and controls their body homeostasis. AAA's play an important role in the brain function. An increased or decreased level of this AA impairs the brain cell function as in case of liver cell failure in hepatic encephalopathy. A study by Uchida et al[26] showed that dietary restriction of α- Trp is known to alter emotional response to stress and increased locomotor activity. However recent studies have proved that there is no co relation between L-Trp depletion, central serotomic reduction and affective behavioural changes[27]. However, studies reveal that, there are no gross functional consequences like hepatic encephalopathy or behavioural disorder in tat-/- mice, proving that AAA concentration was found to be normal as the tat1 is not expressed in mouse blood brain barrier[28]. Also studies suggest that lack of TAT1 do not have a major impact on the function of thyroid hormone, although this transporter was known to involve in the diffusion of T3 and T4[29]. Indeed, recent investigation from Heike Hener laboratory confirms that thyroid hormone metabolism is not altered in TAT1 null mice. Further TAT1 is expressed in placental barrier that can be dispensed in the laboratory conditions[30]. However, tat-/- fetus develop normally and that the female mice were fertile even. It is seen that after birth these mice maintain the capacity to absorb AA from nutritional sources, indicating that intestinal AA absorption and basolateral efflux of AAA's from enterocyte is possible even in the absence of TAT1. This suggest that paracellular transport could have compensated for tat 1 abent mice under normal diet. Thus studies prove that tat 1-/-mice under high protein diet show a massive loss of AAAs and more discrete loss of all substrates AAs of the neutral exchanger Lat2-4f2hc in the urine. This aminoaciduria explains the maximal transport capacity for these AAs excreted in kidney proximal tubule and reveals the role of TAT1 for epithelial AA transport. However, under normal protein diet the aminoacid transport rate is near the maximum. The spill over of AA occurs only on high protein diet. Interestingly, the loss of L-Phen in the urine was lower than that of L-Tyr and L- Trp, and this is due to the ability of another

basolateral uniporter to transport L-Phe. Indeed, Lat 4 (Slc 43a2) is a localized in the basolateral membrane of proximal kidney tubule cells and of small intestine enterocytes. This was first described by Bodoy et al in 2005 and is shown to mediate the facilitated diffusion of BCAAs, L-Met and L-Trp. The presence of this uniporter for essential AAs and its selectivity might explain the differential urinary AAA pattern observed in tat1-/- mice. Further, LAT 4 could to a large extent compensate for the absence of TAT1 in kidney and intestine and thus explain the mild phenotype of tat1-/-mice. The lack of LAT 4 in liver explains the fact in the absence of tat1 expression the liver cannot function as a sink for AAAs[31]. Further, in vivo micro-SPECT/CT and ex-vivo everted gut sac experiment in tat1-/- mice showed accumulation of AAAs tracers inside the epithelial cells and this is attributed to substantial residual permeability of the small intestinal epithelium that explains the normal growth of these mice. This residual permeability is due to Lat4 and probably a paracellualar transport aswell[32,33]. A defect in tat 1 has been predicted to be cause of blue diaper syndrome[2,6,11]. This syndrome was discovered by Drummond and his co-workers in 1964 and is known to be caused by an excess of unabsorbed L-Trp in the intestinal tract[34].

SUMMARY

TAT1 exerts a major homeostatic function by equilibrating the concentration of AAAs between plasma and hepatocyte, where the AAAs are catabolized. Tat1-/-mice confirmed that a complex machinery of AA transporters functionally co operate for the absorption and distribution of dietary AAs. Absences of TAT1 becomes evident only under high protein diet, when the transport capacity of the kidney is exceeded leading to a massive aromatic and neutral aminoaciduria thereby contributing to the disturbance in AA plasma homeostasis. However, this is compensated by basolateral transporter LAT 4 (Slc43a2) to some extent. This in particular drives the export function of the exchangers Lat2-4 F2hC and y+ Lat1-4f2hc in small intestine and kidney proximal tubule.

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