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REVIEW

Regulation profile of the intestinal peptide transporter 1 (PepT1)

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Abstract: The intestinal peptide transporter 1 (PepT1) was first identified in 1994. It plays a crucial role in the absorption of small peptides including not only >400 different dipeptides and 8,000 tripeptides digested from dietary proteins but also a repertoire of structurally related compounds and drugs. Owing to its critical role in the bioavailability of peptide-like drugs, such as the anti-cancer agents and anti-virus drug, PepT1 is increasingly becoming a striking prodrug-designing target. Therefore, the understanding of PepT1 gene regulation is of great importance both for dietary adaptation and for clinical drug treatment. After decades of research, it has been recognized that PepT1 could be regulated at the transcriptional and post-transcriptional levels by numerous factors. Therefore, the present review intends to summarize the progress made in the regulation of PepT1 and provide insights into the PepT1's potential in clinical aspects of nutritional and drug therapies.

Keywords: PepT1, dietary, regulation, transport activity, absorption, bioavailability

Introduction

The uptake and digestion of dietary proteins in the intestinal lumen are mainly in the form of free amino acids and small peptides. These free amino acids and small peptides absorbed are delivered to various tissues through the blood as resources for protein synthesis and energy metabolites.[1] While the free amino acids could be absorbed via several kinds of amino acid transporters located in the intestinal apical membrane, the di- and tripeptides could solely be transported by the oligopeptide transporter PepT1.[2]

PepT1 was first identified in 1994 as a small peptide transporter. The complementary DNA (cDNA) encoding the human PepT1 is 2,263 base pairs in length and has an open reading frame of 2,127 base pairs encoding 708 amino acids. However, the 3D structures of the proton-dependent peptide transporter remain elusive. Crystal structure analysis revealed that the high-capacity/low-affinity peptide transporter protein contains 12 putative membrane-spanning domains (TMD)[3] and a large extracellular domain (ECD) that is highly conserved within the mammalian homology.[4,5] The ECD of PepT1 consists of two immunoglobulin-like domains connected in tandem, which provides structural insight into the transport of mammalian peptides.[4]

PepT1, a prototypical member of the SLC15 family,[6] is mainly located on apical membranes of small intestinal epithelial cells. However, there are still controversies regarding PepT1's location in other tissues for a long while. Some studies reported that PepT1 can be expressed in tissues such as liver, pancreas and colon, while others proposed that the expression is only found in intestine.[7–13] In our opinion, these controversies may originate from the detection of only mRNA or protein level and lack of detailed region-specific analysis.

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Multiple assays revealed that PepT1 has an enormous range of substrates, including >400 different dipeptides and 8,000 tripeptides produced from the digestion of dietary or body proteins and a repertoire of structurally closely related compounds and drugs.[5,12,14] The influx of small peptides into intestinal epithelial cells is via inwardly directed proton electrochemical gradient, which is mediated by PepT1.[7,15] Considering its critical role in the absorption and bioavailability of numerous peptide-like drugs, such as the anticancer agents, bestatin, β-lactamantibiotics,[16] angiotensin-converting enzyme (ACE) inhibitors for hypertension,[17] anti-virus drug valacyclovir and L-DOPA-L-Phe,[18,19] PepT1 is increasingly becoming into a prodrug-designing target. Especially, some poorly absorbed drugs can be modified as peptidomimetic prodrugs targeting PepT1, so as to improve the membrane permeability. Therefore, detailed knowledge about the regulation of PepT1 may enhance its potential in clinical aspects of nutritional and drug therapies. The present review aimed to give an updated overview about the elementary knowledge on the factors modulating PepT1's expression and function. This information may be a useful application in pharmacological and clinical treatments.

Regulation by substrates

It was well accepted that one of the most possible regulators of function and/or expression of any transporter is its own substrates. This is true in case of PepT1; multiple studies have investigated this possibility and provided firm evidences as well. A study revealed that PepT1 could be upregulated in the transcriptional level by certain dipeptides produced from the dietary via directly stimulating the transcriptional activity of the PepT1 gene promoter.[20] Consistently, a subsequent study demonstrated an upregulation of PepT1 gene expression in human colon adenocarcinoma (Caco-2) cells after treatment with dipeptides such as Gly-Sar and Gly-Phe (chemically synthesized dipeptide).[21] In addition, Gly-Gln (a natural dipeptide) was also reported to be able to cause a threefold increase in the PepT1 mRNA level in the apical membrane of Caco-2 cells,[14] which is consistent with the research of Walker et al[22] that the V_{max} of Gly-Sar uptake increased ~1.64-fold after Caco-2 cells were treated with a peptide-rich medium. As Walker et al showed, the magnitude of functional increase in response to Gly-Gln may fully attribute to the increased expression of PepT1's mRNA and protein. Furthermore, the increase in the mRNA level was probably due to the enhanced PepT1 mRNA stability and the incremental transcription. Above all, the substrates have been firmly confirmed as regulators of PepT1 in the transcriptional level.

Regulation by proteins

It is well known that PepT1 cannot work alone under physiological conditions. The expression and activity may vary in response to several factors. In 2008, the post-transcriptional regulation of PepT1 caused by the postsynaptic density-95/disk-large/ZO-1 [PDZ] domain-containing protein (PDZK1) was first identified.[23] In this context, a significant decrease in the PepT1's location at the apical membrane of small intestinal epithelial cells was found in PDZK1 gene knockout mice, consistently, in Hek293/PDZK1 cells; both the PepT1 protein expression and the transport activity increased to ~1.7-fold without any change in the PepT1 mRNA level, which further clarified the post-transcriptional regulation by PDZK1. In 2012, Park et al suggested a strong inhibition effect of the aflavins on the transport of small peptides across Caco-2 cell monolayer via suppressing the AMPK-mediated PepT1 expression, which was consistent with previous reports that the apical PepT1 transport systems of Caco-2 cells can be regulated by AMP-activated protein kinase.[24] In addition, the AICAR (AMPK activator) has been shown to alter the peptide uptake in the small intestine model cell line Caco-2 cells.[25] Meanwhile, Coon et al[26] also investigated the effect of GIP on PepT1 and revealed that PepT1-mediated Gly-Sar absorption can be activated directly by GIP through the cAMP-dependent signaling pathway,[27,28] as far as the interaction between the AMP-activated protein kinase and PepT1 is clarified; further researches are still needed to identify the underlying molecular mechanisms. Of course, such post-transcriptional stimulation may also provide functional coupling of PepT1, just as proposed in the case of PepT1 and Na^+/H^+ exchanger (NHE3). It was reported that NHE3 located on apical membranes acted as PepT1's driving force via changing the H^+ gradient. In addition, the acid-loading activity of PepT1 and the requirement of the apical NHE3 activity for the recovery from the acid load have been clearly demonstrated by the use of a fluorescent reporter to monitor the intracellular pH changes. Furthermore, the functional coupling of PepT1 is evolutionarily conserved; the essential action of NHE3 in the mammalian enterocytes has already been established in the intestine of *Caenorhabditis elegans* by its ortholog NHX-2.[29–31]

In 2000, Fei et al described the cDNA structure and the promoter region of the mouse-Pept1; they proposed that the promoter region possesses three GC boxes that can bind to the transcription activator SP1.[32] Subsequently, Shimakura et al[33] cloned the human Pept1 promoter region and highlighted the direct interaction of Sp1 with the GC boxes in mammalian Pept1 expression. One year later, the same group

reported that Cdx2 can also regulate PepT1 transcription in concert with SP1 in mammals.[34] Another transcriptional regulation of PepT1 was reported in 2014; as reported, the transcriptional activity of PepT1 gene promoter can be stimulated directly via elevating Nrf2 binding with PepT1-ARE1 (a biologically active Nrf2 binding site within the PepT1 promoter),[35] and the endogenous PepT1 protein and mRNA abundance as well as transport activity are all enhanced via stimulating the Nrf2 pathway. All abovementioned explanation may provide new ideas in PepT1's protein regulations, and we can change the intake of nutrition and structurally related compounds via regulating these above proteins' level.

Regulation by hormones

Studies concerning the regulation of PepT1 by hormones are sparse. Evidences indicate that both insulin and epidermal growth factor (EGF) can be involved in the regulation of PepT1 even with different molecular mechanisms. Thamotharan et al hardly ever discovered changes in the PepT1 mRNA level in Caco-2 cells incubating with insulin, while the protein level of PepT1 in the apical membrane was increased. Following this, they proposed that insulin may regulate PepT1 via increasing the protein recruitment of the plasma membrane from the preformed cytoplasm pool. That is to say, although insulin cannot be found in the gut lumen, the peptide transport activity still can be regulated by binding to its receptor located in the basolateral membrane of the intestinal mucosal cells.[36]

Few years later, another study was performed to evaluate the role of EGF in PepT1's regulation; it proposed that a long-term incubation of EGF resulted in a cut down of PepT1's expression in both protein and mRNA levels in Caco-2 cells.[7,14] However, a following study demonstrated that short-term incubation with EGF may upregulate the PepT1's mRNA expression in enterocyte-like cells that express the specific small peptide transporter PepT1.[37] In other words, the effect of EGF appears paradoxical; to resolve this paradox, additional studies including different incubating times and diverse incubating doses need to be carried out.

Sun et al also evaluated the potential effect of recombinant human growth hormone (rhGH) on the human PepT1 expression. As a result of Caco-2 cells treated with rhGH, the dipeptide transport of PepT1 was upregulated greatly. In addition, it demonstrated that the remarkable increase in the PepT1 gene expression mostly attributed to the stimulation of PepT1 gene transcriptional activity.[38] In words, all of these three hormones act by combining with the tyrosine kinase receptor; the EGF and rhGH work via regulating the PepT1 gene expression, yet insulin acts by regulating protein recruitment. PepT1 can also be regulated by ghrelin (an orexigenic hormone). Liu et al[39] proposed that the uptake function of PepT1 can be upregulated by ghrelin, the small intestine epithelium of rats, and the expression of PepT1 both in the protein and mRNA levels was higher in ghrelin-treated group rats. This may be a transcriptional regulation even though the molecular mechanisms are still unclear.

Regulation by diseases

Intestinal diseases such as ulcerative colitis, Crohn's disease, diabetes and some cancer types may have effects on PepT1's expression. As already mentioned, insulin could regulate the protein expression of PepT1. Studies were also performed to investigate the expression of PepT1 in diabetes; the results showed that the protein expression of PepT1 was increased in uncontrolled diabetes without any change in gene transcription;[36] however, whether the abnormal expression of PepT1 in diabetes was caused by insulin or not still needs further research. Unlike diabetes, controversial findings exist in inflammatory bowel disease (IBD). To assess the association between PepT1 and IBD, Wuensch et al built IBD mouse models to analyze PepT1's expression during intestinal inflammation and studied the susceptibility of PepT1-deficient mice to experimental colitis. Eventually, they proposed that PepT1's expression level was decreased in the descending colon in both IBD patients and IBD mouse models.[9] However, this report contradicts with previous studies that proposed no expression of PepT1 in healthy colon but significant expression in inflamed colonic tissues in patients with IBD.[7,9,10,14,40,41] As has been mentioned, further investigation of PepT1's expression in patients with IBD is warranted. PepT1's abnormal expressions were also reported in tumors. As PepT1's critical role in intestinal inflammation, a recent study was performed to research if PepT1 could be involved in colitis-associated cancer development; it showed that PepT1 was highly expressed in colorectal tumor biopsy specimens, and mice with PepT1 overexpression had larger tumor sizes and increased tumor burdens compared with wild-type (WT) mice and PepT1-KO mice.[10] In addition, studies show that increasing peptide transport activity of PepT1 exists in the human fibrosarcoma cell HT1080, human pancreatic carcinoma cell AsPC-1, Capan-2, human colon cancer cell Caco-2, prostatic cancer cell PC-3, lung cancer cell A549, gastric cancer cell MKN45 and ovarian adenocarcinoma cell C13.[42–45] As is known to all, cancer cells are easy to be killed, but it is difficult to kill cancer cells without impairing the

normal physiological functions. If PepT1 can be a specific biomarker for carcinogenesis and tumor growth, it may have many useful applications in clinical treatments.

Regulation by pharmacological agents

Through decades of research, it has been recognized that PepT1 could be regulated by many pharmacological agents, such as floxuridine, gemcitabine and 5-fluorouracil. Studies revealed that when treated with 5-fluorouracil, both protein and mRNA levels for amino acid and glucose transporters were profoundly depressed, yet PepT1 conversely increased. It was proposed that the increasing of PepT1's expression and transport activity may be caused by stimulating the transcriptional activity of PepT1 directly rather than by changing the kinetic properties.[13] In our opinion, PepT1's high expression may affect the uptake of small peptides and then facilitate the proliferation of tumor and increase tumor burdens or even result in chemotherapy resistance. Further studies need to be carried out to confirm our hypothesis.

Likewise, another experiment was performed to investigate the effects of enrofloxacin and xylanase on PepT1, and the results showed that either treatment with enrofloxacin or xylanase leads to a significantly high expression of PepT1.[46,47] There are also studies that revealed that the transport activity of PepT1 can be altered directly by α2-adrenergic agonist clonidine via increasing the translocation of preformed cytoplasmic PepT1 to the apical membrane of Caco-2 cells.[48] Moreover, pentazocine, a selective σ1 ligand, was reported as a regulator of PepT1's expression in Caco-2 cells. Pentazocine can upregulate the mRNA level of PepT1, which leads to the increased protein level at the cell membrane, causing an increase in peptide transport activity eventually.[45] Simultaneously, an experiment has been performed to investigate if PepT1 can be affected by lipopolysaccharide (LPS), and in this context, the authors proposed that a significantly decrease in the abundance both in mRNA and protein levels was found after injecting rats with LPS.[49,50] Above all, even many pharmacological agents were mentioned; the molecular processes modifying PepT1's expression and transport property still need further discussion.

Summary

Within the past 2 decades, several factors that directly or indirectly influence the PepT1 on either the transcription level or the intracellular trafficking have been investigated.

Table 1 Overview of selected factors modulating the gene and/or protein expression and function of the intestinal peptide transporter PepT1

Modulator	Effect on PepT1	References
Substrates		
Dipeptides produced from the dietary	Modulates PepT1 promoter activity	20
Gly-Sar, Gly-Phe		21
Gly-Gln		14 and 22
Proteins		
PDZK1	Increases the PepT1 protein recruitment of the plasma membrane	23
AMPK	Modulates PepT1 protein expression and function	24 and 25
NHE3/NHX-2	Modulates PepT1 function via changing the intracellular pH	29–31
Transcription factors		
SP1	Binds to the PepT1 promoter and modulates the PepT1 transcription	32 and 33
Cdx2	Modulates PepT1 transcription in concert with SP1 and with butyrate in mammals	34
Nrf2	Modulates PepT1 promoter activity	35
Hormones		
Insulin	Increases the PepT1 protein recruitment of the plasma membrane	36
rhGH	Modulates PepT1 gene transcriptional activity	38
EGF	Modulates PepT1 gene transcriptional activity	7, 14 and 37
Ghrelinin	Modulates PepT1 protein expression and function	39
Pharmacological agents		
5-fluorouracil	Modulates PepT1 protein expression or function	13
Enrofloxacin and xylanase		46 and 47
Pentazocine		45
Clonidine		48
LPS		49 and 50
Others		
Salinity, development, diurnal rhythm, under acute undernutrition, etc.	Modulates PepT1 protein expression or function	51–56

Abbreviations: PepT1, peptide transporter 1; PDZK1, PDZ domain-containing protein; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; NHE3/NHX-2, Na^+/H^+ exchanger; rhGH, recombinant human growth hormone; EGF, epidermal growth factor; LPS, lipopolysaccharide.

For example, multiple studies revealed that the expression of PepT1 was increased under acute undernutrition on nutrient transport,[51,52] similar to results from a previous morphological study of the rat intestinal lining in relation to depletion of body stores during fasting and after refeeding. In this study, Habold et al proposed the major mechanisms of intestinal adaptation to fasting and refeeding and showed a remarkable increase in the apical PepT1 expression during both metabolic fasting phases. Additionally, they also revealed an upregulation of transporter expression along with the restoration of the villus structure and function when refeeding after both fasting phases.[53] Furthermore, there are also studies demonstrating that high-fat diet may upregulate the expression of PepT1.[21,54] Meanwhile, it was also reported that salinity, development and diurnal rhythm[55–57] could have effects on the function and/or expression of PepT1, although the pathways for the transmission of these signals is still unclear. These factors regulate PepT1 mainly via the following three ways: first, modifying PepT1's driving force via changing the H^+ gradient; second, regulating PepT1's amount via increasing the protein recruitment of the plasma membrane from the preformed cytoplasm pool and last, altering the transcription and stability of PepT1. Interestingly, the recent reporting of PepT1's 3D structure has opened up a fertile ground for exploring the molecular mechanisms of the regulation of PepT1.

To our knowledge, mammals absorb nitrogen via the uptake of small peptides in the gastrointestinal tract through PepT1. As far as clinical application is concerned, the knowledge of regulation of PepT1 has implications in studies of enteral nutrition and drug therapy. In this review, we tried to summarize the factors modulating the intestinal peptide transporter PepT1's expression and function so as to provide an exhaustive knowledge about the regulation of PepT1 (Table 1). As is well known to us, even the study of the proton-dependent peptide transporter PepT1 has achieved initial success; copious studies remain to be done. In-depth study of the 3D structure and factors affecting PepT1 activity and mechanisms of action, including gene promoter stimulation and post-transcriptional and translational mechanisms, can better utilize PepT1's unique biological property, so as to be applied in pharmacological and clinical treatments.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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