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Clinical relevance of intestinal peptide uptake

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Abstract

AIM: To determine available information on an independent peptide transporter 1 (PepT1) and its potential relevance to treatment, this evaluation was completed.

METHODS: Fully published English language literature articles sourced through PubMed related to protein digestion and absorption, specifically human peptide and amino acid transport, were accessed and reviewed. Papers from 1970 to the present, with particular emphasis on the past decade, were examined. In addition, abstracted information translated to English in PubMed was also included. Finally, studies and reviews relevant to nutrient or drug uptake, particularly in human intestine were included for evaluation. This work represents a summary of all of these studies with particular reference to peptide transporter mediated assimilation of nutrients and pharmacologically active medications.

RESULTS: Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein. A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent PepT1. A number of "peptide-mimetic" pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be attenuated with orally-administered anti-inflammatory tripeptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

CONCLUSION: Further evaluation of the role of this transporter in treatment of intestinal disorders, including inflammatory bowel disease is needed.

Key words: Dietary peptides; Peptide transport; Peptide transporter 1; Intestinal inflammation; Drug absorption; Bacterial peptides

Core tip: Intestinal uptake of intact di-peptides and tri-peptides occurs by an independent epithelial transport process for protein assimilation. This carrier may also be used to absorb specific drugs and bacterial peptide products that may result in inflammatory disease.

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INTRODUCTION

Protein digestion and absorption in humans depends on initial enzymatic hydrolysis in the stomach and proximal small intestine. The hydrolytic products include oligopeptides and amino acids that ultimately undergo small intestinal uptake into the portal vein. A critical step in this overall uptake process involves a transmembrane protein [peptide transporter 1 (PepT1)], located in the brush border that can transport nutrient peptides into the enterocyte[1-3]. In addition, studies have also demonstrated that PepT1 is able to transport some pharmaceutical agents along with bacterial by-products from the intestinal lumen that may trigger an ongoing and persistent inflammatory intestinal mucosal response.

MATERIALS AND METHODS

Fully published English language literature articles sourced through PubMed related to protein digestion and absorption, specifically human peptide and amino acid transport, were accessed and reviewed. Papers from 1970 to the present, with particular emphasis on the past decade, were examined. In addition, abstracted information translated to English in PubMed was also included. Finally, studies and reviews relevant to nutrient or drug uptake, particularly in human intestine were included for evaluation. This work represents a summary of all of these studies with particular reference to peptide transporter mediated assimilation of nutrients and pharmacologically active medications.

RESULTS

Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein. A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent PepT1. A number of "peptide-mimetic" pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be attenuated with orally-administered anti-inflammatory tripeptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

DISCUSSION

Gastric and pancreatic phases

Critical nutrients derived from digested protein are absorbed in the intestinal tract, specifically amino acids and peptides, during health as well as during disease. Normally, gastric and pancreatic enzymes initiate hydrolysis of dietary and other luminal proteins from endogenous sources. As a result of this initial hydrolytic phase, an array of free amino acids and different oligopeptides of variable length appear in the small intestinal lumen. Information on human protein digestion and absorption has been previously reviewed and updated[1-3].

Intestinal phase

Protein digestion studied in human volunteers using long intestinal tubes showed that infused bovine serum albumin appeared to be completely hydrolyzed before the distal ileum[4]. A host of brush border microvillus membrane transport proteins are located in the intestinal epithelial cell resulting in the uptake of specific substrates into the enterocyte. These transporters are specialized membrane proteins that can recognize, bind and translocate a specific substrate or multiple different substrates across the brush border membrane into the epithelial cell. In addition, other transport proteins involved in this process have been detected and characterized to a limited extent on the basolateral membrane. Most free amino acids that present on the luminal or apical surface of the epithelial cell are transported by both brush border and basolateral membranes into the portal venous blood. A number of brush border membrane amino acid carriers, linked to different ions, have been defined that result in transport of basic, neutral and anionic amino acids. For oligopeptides, however, different cellular transport routes are evident.

Peptide uptake

For both di-peptides and tri-peptides, a separate membrane protein, PepT1, is present that appears to have very broad substrate capacity and, theoretically, it is believed, could transport all possible di-peptides and tri-peptides into the epithelial cell[5]. For 20 different amino acids, a total of 400 di-peptides and 8000 tri-peptides have been enumerated. For those peptides that consist of 4 or more amino acids, brush border enzymes must first hydrolyze each of these to free amino acids, di-peptides and tri-peptides. Then, substrate uptake into the epithelial cell follows. Once inside the epithelial cell, cytoplasmic enzymes hydrolyze these di-peptides and tri-peptides further into free amino acids for transport into the portal venous blood. Most oligopeptidases are aminopeptidases, acting to

remove an amino acid residue from the amino-terminus of the peptide. Peptide chain length determines the location of hydrolysis with longer peptides hydrolyzed at the brush border and di-peptides and tri-peptides mainly in the cytoplasm[6]. A number of other brush border and cytoplasmic peptidases are present. In particular, proline-containing oligopeptides are poorly hydrolyzed by most peptidases, yet are very important for assimilation of many normal dietary proteins with a high proline content (*e.g.,* gliadin). Proline-specific dipeptidases are also located in the brush border membrane and cytoplasmic portion of the cell and these serve to hydrolyze most proline-containing peptides (*e.g.,* dipeptidyl aminopeptidase Ⅳ)[7]. Particularly important was the early observation that amino acids infused into human intestine in peptide form are more readily absorbed than if infused into the intestinal lumen as free amino acids[8]. Some peptides, particularly in other non-human mammalian species, are incompletely hydrolyzed and may be transported out of enterocytes into the circulation, likely by a novel peptide transporter located in the baso-lateral membrane of the epithelial cell[9,10]. Other routes of uptake into the enterocyte have been hypothesized to exist[5]. For example, so-called "cell penetrating peptides" may carry peptides into the cell, either by direct penetration through the apical membrane or associated with endocytosis. Finally, enhanced permeability of the tight junctions between epithelial cells may result in increased paracellular uptake.

PepT1

The peptide transporters are part of a proton-coupled oligopeptide transporter superfamily, or peptide transporter family[10,11]. PepT1 (or SLC15) has several transmembrane domains and acts as a cotransporter with hydrogen ions (H^{+ion})[12]. After uptake of di-peptides or tri-peptides along with H^{+ion} into the enterocyte, H^{+ion} is then removed from the cell through the sodium-hydrogen (Na^{+ion}/H^{+ion}) exchanger on the brush border membrane in exchange for Na^{+ion}. The Na^{+ion} is then moved out of the cell by a Na^{+ion}/K^{+ion} ATPase pump on the basolateral membrane where 3 Na^{+ion} are transported out of the cell and 2 K^{+ion} are transported into the cell causing the epithelial intra-cellular electrochemical gradient to normalize.

Tissue and cellular distribution studies have also located this carrier protein in intestinal and renal brush border membranes along with lysosomal membranes. Interestingly, most PepT1 activity is located in the proximal small intestine (specifically, duodenum and jejunum), but some activity exists in other intestinal sites, including the ileum and colon. As little dietary protein actually normally reaches the distal portions of the intestine, some investigators have suggested that endogenous proteins might serve as proteolytic substrates for intestinal microflora, particularly in the colon. In addition, a transcription factor, CDX2, that appears to play important roles in proliferation, differentiation and maturation of epithelial cells, has been shown to specifically regulate this enterocyte brush border membrane transporter, PepT1[13].

The transporter has been cloned from several mammalian species, including humans, with a size estimated to be about 708 amino acids[14]. Of particular clinical importance, PepT1 may accept other non-nutrients for uptake, including pharmaceutical agents that have similar structural characteristics and actually mimic peptide substrates. These "peptide-mimetic" therapeutic agents include some antibiotics like cephalosporins and penicillins, some anti-viral agents (*e.g.,* acyclovir, ganciclovir) and inhibitors of angiotensin-converting enzyme. Each may undergo uptake across the intestinal epithelial cell through the PepT1 transporter[15-17]. Important molecular insights into proton coupled peptide transporters have resulted from evaluation of crystal structures of bacterial transporters combined with some biochemical studies of transport, including use of genetically modified animals have recently been reviewed[18,19].

Peptide transporter regulation

A number of factors may serve to regulate PepT1, including altered dietary intake[20,21]. For example, increased expression of PepT1 may be caused by an increased quantity of dietary protein, as well as the specific amino acid composition of the dietary protein. Behavioral changes may also affect expression of the transporter. In particular, a diurnal rhythm in PepT1 expression may occur due to feeding behavior, increasing at night in some mammalian species that tend to be nocturnal feeders[22,23], a pattern abolished by fasting or imposed daytime feeding[24]. Increased expression of PepT1 during food deprivation or starvation may also occur, particularly with mucosal changes and reduced intestinal surface area associated with long-term parenteral feeding. Developmental factors also play a role in alteration of transporter expression, especially at the time following birth with suckling of a high protein milk diet and then the post-weaning phase with a shift from milk to solid food[25].

Peptide transporter in disease

PepT1 expression persists with intestinal disease, even with severe mucosal damage. Normally, PepT1 is expressed to only a limited extent in the colon compared to the small intestine[26]. In the short bowel syndrome, PepT1 expression is increased in the colon, possibly serving to conserve amino acids[27]. Similar changes have been reported in the colon of patients with inflammatory bowel diseases[28]. As a result of PepT1 up-regulation associated with the inflammatory process, dipeptides and tripeptides from bacteria in the colonic lumen may be transported by PepT1 into epithelial cells. Some of these bacterial peptides include N-formylmethionyl-leucyl-phenylalanine, a

tripeptide from Escherichia coli, muramyl dipeptide (MDP), found in the cell walls of gram negative and gram positive bacteria, and L-Ala-(γ)-D-Glu-meso-diaminopimelic acid (Tri-DAP), a cell wall byproduct of gram negative bacteria. After uptake into the intestinal cell, the NF-κB pathway is activated while downstream pro-inflammatory cytokine and chemokine production are enhanced. Some bacterial peptides probably also gain access by a paracellular pathway. Added studies demonstrate that Tri-DAP transport is mediated by PepT1 expressed intestinal epithelial cells, but not in cells that did not express PepT1[29]. In the lamina propria of intestinal mucosa, these bacterial peptides may then be taken up by macrophages causing up-regulation of major histocompatibility class I molecules and increased cytokine and chemokine production, further contributing to the inflammatory process[30]. Others have reported that colonic expression of the PepT1 was down-regulated during intestinal inflammation[31]. Interestingly, PepT1 may play an important interactive role with receptors of the innate immune system to eliminate pathogens[32]. For example, ligands specific for members of the nucleotide-binding oligomerization domain (NOD) family of receptors, specifically NOD 1 and NOD 2 present in cytoplasm, may be transported by PepT1. Activation of NOD leads to NF-κB activation. A linkage with NOD mutations and risk of Crohn's disease has been reported[33-35]. In addition, recent studies suggest that PepT1 polymorphisms may be associated with development of inflammatory bowel disease in some Scandanavian populations[36]. Recently, cellular and molecular mechanism underlying NOD 2 risk-associated polymorphisms in Crohn's disease have been reviewed[37]. Finally, a specific tri-peptide (Lys-Pro-Val) or KPV has anti-inflammatory activities that may be transported by PepT1 and cause inhibition of NF-κB activation[38]. KPV encapsulated in polysaccharide for release primarily in the colon may reduce inflammatory mucosal changes[39]. Similarly, a PepT1-transportable soy tripeptide VPY reduced intestinal inflammation, suggesting its use as a possible treatment for inflammatory bowel disease[40].

Recently, it has been hypothesized that different microbial genomes within the intestinal tract may play a role in the immune response in several inflammatory diseases[41]. Further clinically-relevant studies focused on the human intestinal microbiome and the potential role of PepT1 are needed.

COMMENTS

Background

Assimilation of dietary protein in humans involves gastric and pancreatic enzyme hydrolysis to luminal oligopeptides and free amino acids. During the ensuing intestinal phase, these hydrolytic products are transported into the epithelial cell and, eventually, the portal vein.

Research frontiers

A critical component of this process is the uptake of intact di-peptides and tri-peptides by an independent peptide transporter transmembrane protein, peptide transporter 1 (PepT1). In recent years, a number of "peptide-mimetic" pharmaceutical agents may also be transported through this carrier, important for uptake of different antibiotics, antiviral agents and angiotensin-converting enzyme inhibitors. In addition, specific peptide products of intestinal bacteria may also be transported by PepT1, with initiation and persistence of an immune response including increased cytokine production and associated intestinal inflammatory changes. Interestingly, these inflammatory changes may also be attenuated with orally-administered anti-inflammatory tri-peptides administered as site-specific nanoparticles and taken up by this PepT1 transport protein.

Innovations and breakthroughs

Further evaluation of the role of this transmembrane transport protein, PepT1, in transport of pharmaceutical agents is needed. This may provide novel approaches to treatment, particularly for intestinal disorders. In particular, use of agents that employ this peptide transporter to permit access into intestinal cells may have a special role in inflammatory bowel disease treatment.

Applications

From a practical perspective, use of agents that particularly localize to the intestinal mucosal cells might have an important role in localization of treatment regimens rather than use of current systemically-applied pharmaceutical or biological agents.

Terminology

The PepT1 transporter is a special transmembrane intestinal transport protein located in the microvillus membrane. Its role as a nutrient transporter, specifically for di-peptides and tri-peptides is well established. However, in recent years, its role in uptake of several pharmaceutical agents has become apparent, including its potential relevance for management of inflammatory intestinal disorders.

Peer-review

Conceptually, the peer reviewers have raised the important linkage of this peptide transporter and the modern "metagenomic revolution" that should further our understanding of intestinal, particularly inflammatory, disorders. Added studies are also needed that explore these intestinal uptake processes and role of this PepT1 transporter in the developing human intestinal tract, particularly in fetal and neonatal settings.

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