Regulation of oligopeptide transporter PepT1 (SLC15A1) in disease and application in clinical nutrition

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Abstract

Many studies have demonstrated the di- and tripeptides is a major mechanism by which the digestion products of proteins are absorbed. The oligopeptide transporter PepT1 is localized to the brush-border membrane and mediates the absorption in mammalian intestine. Recently, regulations of PepT1 activity by a variety of pathological conditions have been studied. Critical illness, malnutrition and metabolic disorder could induce the modulation of protein and gene expressions of PepT1. We reviewed and analyzed by searching PubMed, google scholar database and reference literature to provide a theoretical basis for clinical nutrition support.

Keywords: oligopeptide transporter, PepT1, critical illness

1. Introduction

Studies have demonstrated the di- and tripeptides are major products from proteins are digested. Proteins are hydrolyzed in the intestines to small peptides, which are efficiently absorbed, intact, through specific transport mechanisms. Di- and tripeptides of the digestion products of proteins are absorbed through a proton-coupled oligopeptide transporters (POT) across the brush border are the major mechanism [1-7]. Four members in POT super family have been identified, which include PepT1 (SLC15A1), PepT2 (SLC15A2), PHT1 (SLC A4), and PHT2 (SLC A3). In humans, PepT1 expressed in the small intestine epithelium is involved in absorbing nutritional peptides [8, 9], and PepT2 expressed in the kidney plays an important role in reabsorption of peptide/mimetics [10]. Dietary proteins are converted into large peptides by gastric and pancreatic proteases in gastrointestinal lumen and further hydrolysis into 80% small peptides and 20% free amino acids by various peptidases in the brush border membrane of intestinal epithelium (Figure 1) [11]. Yoshihara et al studied the absorption of 100% free amino acids, 60% di-and tripeptides and 40% free amino acid mixture, 100% di- and tripeptides or lactalbumin. Absorption was evaluated by calculating the area under the curve of amino acid concentration in portal vein plasma of rats for 120 min after administration of each nitrogen source [12]. These results indicate the absorption was maximal upon administration of the nitrogen source when 60% di- and tripeptides and 40% free amino acid mixture were present (Figure 2).

PEPT1 is strongly expressed on the apical membrane of small intestinal enterocyte. Recently, regulations of PEPT1 activity by a variety of pathological conditions have been studied. This paper discusses the regulation of PepT1 expression for pathological conditions, to provide a theoretical basis for clinical nutrition support.

2. Bowel resection

Intestinal adaptation after massive bowel resection is by an increase intestinal wet weight villus height, crypt depth and absorption characteristics of the surface area of the structure. Functional characteristics of adaptation include an upregulation of NA+/Glucose cotransporters, Na+/H+ exchangers, and other enzymes involved in digestion and absorption [13, 14]. The overexpression of PEPT1 was observed, peaking at 2 weeks post-operation, with its levels declining to 12% at week 4. The ability of oligopeptide transport was correlated with the PepT1 levels [15]. PepT1 protein and mRNA are abundant in the small-bowel villus epithelial cells, but only small amounts of PepT1 mRNA are present in the proximal colon of rabbits [16]. Ziegler et al found the abundance of PepT1 mRNA in the colon of short-bowel syndrome patients was more than 5-fold that

in control subjects [17]. Short-bowel syndrome may Up-regulation of the expression of colonic PepT1 adapted to malabsorption of di-and tripeptides, independent of changes in the mucosal surface area.

3. Glutamine dipeptides promotes intestinal adaptation

Satoh et al used rats that underwent 80% proximal intestinal resection received a bolus supplement of glutamine (2.0 g/kg/day) + alanine (1.22 g/kg/day) mixture, alanyl-glutamine dipeptides (2.972/kg/day) to further evaluate the benefits. The result showed PepT1 mRNA increased 150% on the 5th postoperative day (POD). In the rats administered alanyl-glutamine, mucosal wet weight and protein content similarly increased with increasing villus height on the 7th POD. Enteral supplementation with alanyl-glutamine but not glutamine + alanine mixture promotes intestinal adaptation[18].

4. Traumatic brain injury

Traumatic brain injury (TBI) can induce significant damages of gut structure and impairment of barrier function. The villous height, crypt depth and surface area in jejunum decreases progressively with the time of brain injury. These changes occur rapidly as early as 3 hours following brain injury and lasts for more than 7 days with marked mucosal atrophy [19]. Hang et al used an everted sleeve of intestine which was securely incubated in Kreb's solution with radioactive dipeptide ((3) H-Gly-Sar, 10 microCi/mL) to measure the uptake and transport of PepT1 of small intestinal epithelial cells. The transport and uptake of dipeptide was significantly increased at 3 h post TBI, peaked at 12h and declined a bit at 24 h post TBI, and returned to the level of normal and control rats at 72 h and 7 days. Intestinal PepT1 expression could be up-regulated after TBI, and maintained the normal level under the condition of serious intestinal damage. Up-regulation of PepT1 may adaptively improve absorption of di- and tripeptides, independent of changes in the mucosal surface area [20].

5. Malnutrition

Nutritional status of patients with severe ill change rapidly. The effect on functional and molecular expressions of PepT1 was investigated. Intestinal villus atrophy through prolonged fasting was studied according to fasting animals. The PepT1 expression increases during metabolic fasting phases [21, 22]. Ogihara et al showed that 4 days of starvation markedly increased the PepT1 in the jejunum as examined by immunoblotting and image analysis of immunofluorescence [23]. The study demonstrated that starvation for 4 days and semistarvation for 10 days increased the PepT1 mRNA and protein in the rat jejunum [24].

The cell population of PepT1 is increased in starvation may explain that appeared in the results of studies performed in the earlier study. It was expected

to reduce the absorption of amino acids in human volunteers' jejunum and peptides after 14 days of hunger. In fact, the absorption of amino acids decreased, but surprisingly, the absorption of the peptide present in no significant change [25]. In summary, fasting, whether short-term or long-term, increases the PepT1 mRNA level, resulting in an increase in the population of the transporter in the brush-border membrane of the intestinal mucosa.

6. Diabetes

The study discussed of the Caco-2 cells has been shown that insulin upregulates PepT1 [26]. The other hand, Gangopadhyay et al studied the activity of PepT1 in the brush-border membrane vesicles prepared from the jejunum of diabetic rats disabled insulin for 96 h was determined. The results show the activity was significantly increased. The data show that uncontrolled diabetes has a corresponding increase in the abundance of mRNA encoding PepT1, and its molecular mechanism appears to be an increase in the stabilization of mRNA encoding Pept-1 [27]. These results indicate that, besides insulin, there are other factors that upregulate PepT1. This is also demonstrated involvement of multiple factors in upregulation of Pept-1. The PepT1 upregulation allows increased availability of substrates in diabetes.

7. Inflammatory Bowel Disease (IBD)

Some studied reported that intestinal bacteria secrete proinflammatory peptides. Among these peptides are n-formylated peptides. The evidence showed that PepT1-mediated transport of n-formyl peptides, such as the tripeptide N-formylmethionyl-leucyl-phenlalanine, l-Ala-gamma-d-Glu-meso-DAP, induces intestinal inflammation [28-30]. Merlin et al reported Pept-1 expression in the colon of patients with ulcerative colitis and Crohn's disease [31]. The mechanism is presumed to these patients' intestinal flora excessive secretion of inflammatory peptides. These substrates induce ectopic expression of PepT1.

Recent reports indicate soy-derived di- and tripeptides, a novel PepT1 substrate, which can inhibit the production of pro-inflammatory mediators in vitro in intestinal epithelial and immune cells, and reduce the severity of colitis in mice by down-regulating the expression of pro-inflammatory cytokines in the colon, suggesting that soy-derived di- and tripeptides may be promising for the treatment of IBD [32].

8. Burns

Small intestine is the major site of dietary protein absorption. Protein is important in severe burns and PepT1 plays an important role in the absorption of di/tripeptide. Ta et al showed the effects of transport and uptake of PepT1 in scalded rats were significantly decreased compared with controls [33]. Direct

appearance of blood supply in mesentery and intestine wall showed less blood supply. Sun et al proposed **b**lood supply to intestine and mesentery of rats was increased following injection of recombinant human growth hormone (rhGH). The effects of transport and uptake of PepT1 in scald rats were significantly increased [34].

9. Hyperthyroidism

Ashida et al to examine the effect of thyroid hormone status on PEPT1 in vivo. The results indicate that in hyperthyroid rats, the activity and expression of PEPT1 were decreased in the small intestine [35]. Kinetic analysis showed that the Vmax value for [14C]glycylsarcosine uptake was significantly decreased in hyperthyroid rats, whereas the Km value was not affected. The mean portal vein concentrations after intrajejunal administration of [14C]glycylsarcosine were also decreased in hyperthyroid rats.

10. Conclusion

It has been proposed that enteral feeding formulas containing small peptides are more efficacious and better tolerated than whole-protein formulas in critically ill patients. A randomized trial by Heimburger et al demonstrated During 10 days of feeding, the small-peptide diet produced slightly greater increases in serum rapid-synthesis proteins than did the whole-protein diet, especially between days 5 and 10. The clinical implications of this difference between the diets are unknown [36]. In conclusion, critically ill patients undergoing fasting and stress which resulting in mucosal atrophy. Patients start feeding often cannot digest well after resuscitation. Except hyperthyroidism, Up-regulation of PepT1 is in most critical ill. When critically ill patients after hemodynamic stability use formulas contain di-and tripeptides for 5 to 10 days for feeding may be a good choice. In addition the use of soy-derived di-and tripeptides formula for IBD can be considered.

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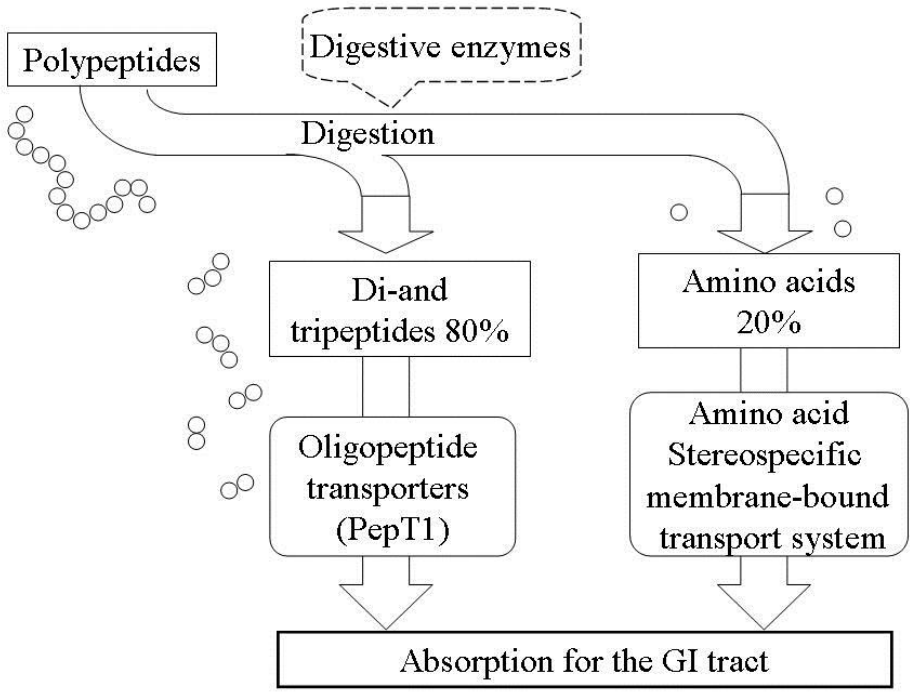

Figure 1: Dietary proteins are converted into large peptides by gastric and pancreatic proteases in gastrointestinal lumen and further hydrolysis into 80% small peptides and 20% free amino acids by various peptidases in the brush border membrane of intestinal epithelium.

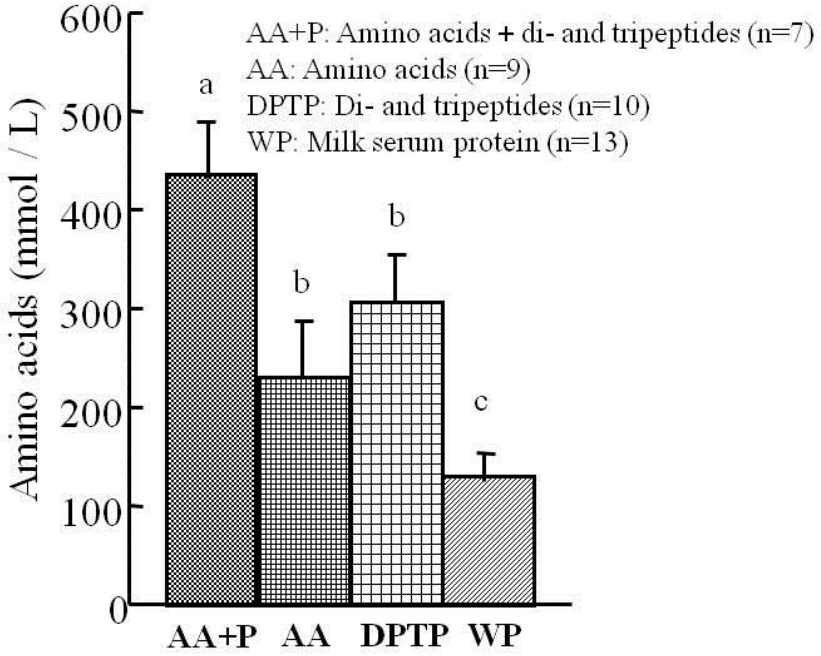

Figure 2: Coexistent effectiveness of peptides and amino acids. Amino acid concentration in portal vein plasma was evaluated for 120 min after administration of each nitrogen source. The vertical bars indicate the standard error of mean. Values not sharing common letters are significantly different ($p<0.05$).

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