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Extended Abstract

Journal of Computational Methods in Molecular Design, 2021 **ISSN 2231-3176**
https://www.scholarsresearchlibrary.com/journals/journal-of-computational-methods-in-molecular-design/

Functional and expression profiles exploring molecular changes to the renal cotransporters PEPT1 and PEPT2 due to ageing

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Renal PEPT1 and PEPT2 cotransporters play an important role in the balance of circulating body oligopeptides and certain peptide like drugs. The reduction in renal functions associated with ageing can affect reabsorption/ excretion balance. Several studies report the importance of adjusting protein intake and optimizing drug dosages for individuals with compromised renal function to avoid adverse reactions. We aim to comprehensively investigate age related changes of PEPT co-transporters at gene, protein and functional level in two important regions of the kidney superficial cortex and outer medulla. A standard method is used to isolate brush border membrane vesicles (BBMV) and outer medulla membrane vesicles (OMMV) from the kidneys of young, middle-aged and old Wistar rats. Different biomolecular techniques are used to determine age-related changes of PEPT cotransporters from different angles: conventional and real-time RT-qPCR are utilized for characterizing the gene expressions; chemiluminescent Western blotting and Immunohistofluorescence are used for relatively quantifying and localizing the protein expressions; fluorescence-based methods were developed to measure the transport activity across BBMV and OMMV. The protein expression of PEPT1 was not only increased in BBMV from old rats, but PEPT1 also appeared in OMMV from middle-aged and old rats. SLC15A1 gene expression in the renal cortex increased in middle-aged group. PEPT2 protein expression was not only increased with ageing, but PEPT2 also was found in BBMV from middleaged and old groups. SLC15A2 gene expression in the renal outer medulla increased in the old group. These changes in the localization and expression profile of PEPT1 and PEPT2 could explain the changes of the transport activity in BBMV and OMMV. These findings provide novel insights which would be useful for maintaining protein nutrition and optimizing the delivery of some peptidomimetic drugs in elderly individuals. Mammalian peptide transporters (PEPT1 and PEPT2) play a pivotal role in the absorption of small peptides from the intestine and kidney, respectively, and in the disposition and targeting of peptide or mimetic drugs. However, there are few reports on the molecular basis of their regulation, especially in the young. The aim of this study was to determine the developmental expression of intestinal and renal oligopeptide transporters in rats from embryonic to adult ages. Intestinal segments were collected (i.e. duodenum, jejunum, ileum, and colon) along with whole kidney, and their mRNA and protein levels were measured. Expression levels of PEPT1 were maximal 3-5 d after birth in the duodenum, jejunum, and ileum, and then declined rapidly. Expression was increased transiently at d 24, most notably in the ileum. Adult protein levels were approximately 70% of that observed on d 3-5. Significant PEPT1 expression was observed in colon during the first week of life, but levels were undetectable shortly thereafter through adulthood. PEPT1 and PEPT2 expression is less regulated in rat kidney and more pronounced in older animals. Peptide transporters were also present as early as d 20 of fetal life for all tissues tested. These results are unique in providing the developmental expression of peptide transporter mRNA and protein in distinct regions of the small intestine, colon, and kidney in rat. Our findings suggest that intestinal expression of PEPT1 is induced postpartum, possibly by suckling, and again at the time of weaning, and that the colon may participate in peptide transport early in life. The H^+-coupled transporter, peptide transporter 1 (PepT1), is responsible for the uptake of dietary di- and tripeptides in the intestine. Using an in vivo continuously perfused gut loop model in Yucatan miniature pigs, we measured dipeptide disappearance from four 10 cm segments placed at equidistant sites along the length of the small intestine. Pigs were studied at 1, 2, 3 (suckling) and 6 weeks (post-weaning) postnatal age. Transport capability across the PepT1 transporter was assessed by measuring the disappearance of ^{3}H-glycylsarcosine; real-time RT-PCR was also used to quantify PepT1 mRNA. Each of the regions of intestine studied demonstrated the capacity for dipeptide transport. There were no differences among age groups in transport rates measured in the most proximal intestine segment. Transport of ^{3}H-glycylsarcosine was significantly higher in the ileal section in the youngest age group (1 week) compared with the other the suckling groups; however, all suckling piglet groups demonstrated lower ileal transport compared with the post-weaned pigs. Colonic PepT1 mRNA was maximal in the earliest weeks of development and decreased to its lowest point by week 6. These results suggest that peptide transport in the small intestine may be of importance during the first week of suckling and again with diet transition following weaning. Intestinal inflammation is characterized by epithelial disruption, leading to loss of barrier function and the recruitment of immune cells, including neutrophils. Although the mechanisms are not yet completely understood, interactions between environmental and immunological factors are thought to be critical in the initiation and progression of intestinal inflammation. In recent years, it has become apparent that the di/tripeptide transporter PepT1 may play an important role in the pathogenesis of such inflammation. In healthy individuals, PepT1 is primarily expressed in the small intestine and transports di/tripeptides for metabolic purposes. However, during chronic inflammation such as that associated with inflammatory bowel disease, PepT1 expression is upregulated in the colon, wherein the protein is normally expressed either minimally or not at all. Several recent studies have shown that PepT1 binds to and transports various bacterial di/tripeptides into colon cells, leading to activation of downstream proinflammatory responses via peptide interactions with innate immune receptors. In the present review, we examine the relationship between colonic PepT1-mediated peptide transport in the colon and activation of innate immune responses during disease.

Bottom Note: *This work is partly presented at EuroScicon congress on Biochemistry, Molecular Biology & Allergy* October 11 - 12, 2018 Amsterdam, Netherlands