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Review article

Delivery aspects of small peptides and substrates for peptide transporters ☆

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Abstract

The present summary highlight chemical strategies applied to improve plasma half-lives and oral bioavailability of peptidic drugs as well as view on intestinal and pancreatic peptidase mediated degradation of peptidic drugs. In general chemical strategies used to increase the oral bioavailability of peptidic drugs consisting of more than three amino acids is disappointing. On the other hand chemical approaches to stabilize peptidic drugs against metabolism seem promising for increasing plasma half-lives of parental peptidic drugs as well as for increasing oral bioavailability of di/tripeptidomimetics and dipeptidyl pro-moieties targeting peptide transporters.

Keywords: Proteolytic enzymes; Exopeptidases; Intestinal peptide transporters; Amide bond replacement; Peptides; Drug delivery; Prodrugs

1. Introduction

A number of peptides have therapeutic potential as drugs in treatment of a variety of diseases. They are, however, susceptible to rapid inactivation by exopeptidases and proteolytic enzymes distributed throughout the body. Chemical stabilization strategies have been successfully applied to increase plasma half-lives of parenterally administered peptidic drugs. Similar strategies have been suggested for increasing bioavailabilities of oral administered peptidic drugs. Whereas increasing bioavailability of peptidic drugs by chemical stabilization seems to be less successful strategies for peptides consisting of more than three amino acids, the approach seems promising for di/tripeptidic drugs and pro-moieties targeted the intestinal peptide transporter PEPT1. The aim of the present summary is to highlight on pancreatic and intestinal peptidases, i.e. exopeptidases and proteolytic enzymes, as well as view on chemical strategies applied to increase plasma half-lives and increase oral bioavailability of peptidic drugs and pro-moieties. Furthermore, to give a short status on the approach utilizing peptidyl bond replacement to stabilize dipeptidyl pro-moieties targeted PEPT1.

2. Intestinal digestive/absorptive process of peptides

Exogenic peptides are generally rapidly metabolised within the intestinal tract by pancreatic and intestinal proteolytic enzymes to form smaller peptides, di/tripeptides and amino acids [1,2]. Even though endocytotic uptake of peptides is described, it is generally believed that larger peptides have almost restricted entrance into enterocytes. In contrast, large amounts of amino acids and di/tripeptides are transported across the mucosal enterocytic membrane by amino acid and peptide transporters. Intestinal nutrient transporters including peptide and amino acid transporters have recently been reviewed elsewhere [3]. Most di/tripeptides are believed to be hydrolysed within the enterocytes by various enzymes; for dipeptides by enzymes such as cytosolic non-specific dipeptidase and Xaa-His dipeptidase [1,2]. Examples of enzymes involved in the pancreatic/intestinal digestive process of peptides are summarized in Table 1. These enzymes as well as transporters and the physiology of the gastrointestinal tract

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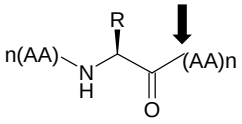
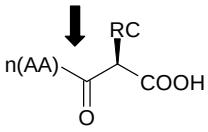
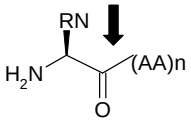
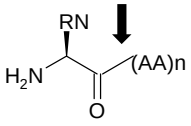
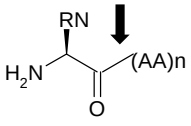
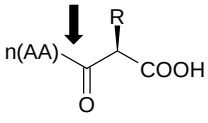
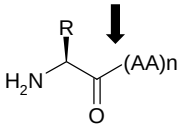
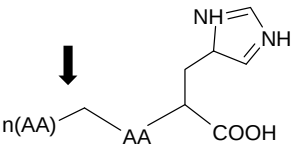
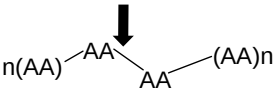
Table 1
Intestinal and pancreatic enzymes found in *Homo sapiens* involved in digestion of peptides/proteins. (AA)*n*: *n* amino acids

Peptidyl bond	IUBMB nomenclature, recommended name, tissue and gene: GO ontology number	Released AA and peptides
 R1: aromatic	EC 3.4.21.1 chymotrypsin, secreted in pancreas as chymotrysinogen activated by trypsin, endopeptidase, GO: 0004263	Cleave at C-terminal at aromatic AA. Small peptides
 R3: aromatic	EC 3.4.17.1, carboxypeptidase A, secreted in pancreas. Exopeptidase, GO: 0004182	Prefer aromatic AA in C-terminal. Tyr, Trp, Phe and small peptides. (Little or no activation with -Asp, -Glu, -Arg, -Lys, or -Pro)
 R1: preferment Ala	EC.11.2, membrane alanyl aminopeptidase, luminal enterocytic membrane, GO: 0004179	Neutral amino acids, Ser, Cys, Gly, Ala, Gln, Asn, Leu, Val and small peptides
 R1: preferment Cys	EC 3.4.11.3, cysteine aminopeptidase, secreted by pancreas. Exopeptidase. No GO number known	Neutral amino acids, Ser, Cys, Gly, Ala, Gln, Asn, Leu, Val and small peptides
 R1: preferently Leu	EC 3.4.11.1, leucyl aminopeptidase, secreted by pancreas. Exopeptidase, GO: 004178	Neutral amino acids, Ser, Cys, Gly, Ala, Gln, Asn, Leu, Val and small peptides
 R3: cationic	EC 3.4.17.2, carboxypeptidase B, secreted in pancreas. Exopeptidase GO: 0050425	Cationic amino acids, Lys, Arg and small peptides
 R1: cationic	EC 3.4.21.4, trypsin, secreted as trypsinogen in pancreas, exopeptidase, GO: 0004295	
	EC 3.4.13.18, cytosolic non-specific dipeptidase, cytosolic in enterocytes, GO: 0042315	Pro Anionic AA Glu, Asp Cationic and neutral AA (see above)
	EC.3.4.13.3, Xaa-His dipeptidase, cytosolic in enterocytes as well as secreted by pancreas. Exopeptidase, GO number not known	AA-His
	EC. 3.4.21.36, pancreatic elastase, secreted in pancreas as proelastase, GO: 0008125	Small peptides