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Oral delivery of anti-diabetes therapeutics using cell penetrating and transcytosing peptide strategies

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ABSTRACT

Oral delivery of insulin and other anti-diabetic peptides is inhibited by low intestinal absorption caused by the poor permeability across cellular membranes and the susceptibility to enzymatic degradation in the gastrointestinal tract. Cell-penetrating peptides (CPPs) have been investigated for a number of years as oral absorption enhancers for hydrophilic macromolecules by electrostatic or covalent conjugation on in conjunction with nanotechnology. Endogenous cellular uptake mechanisms present in the intestine can be exploited by engineering peptide conjugates that transcytose; entering cells by endocytosis and leaving by exocytosis. Efficiently delivering hydrophilic and sensitive peptide drugs to safely transverse the digestive barrier with no effect on gut physiology using remains a key driver for formulation research. Here we review the use of CPP and transcytosis peptide approaches, their modification and use in delivering anti-diabetic peptides (with the primary example of Insulin and engineered homologues) by direct oral administration to treat diabetes and associated metabolic disorders.

1. Introduction

Recent advances in biotechnology and molecular engineering have led to the development and manufacture of an increasing number of new therapeutic proteins/peptides, especially those modifying natural variants of hormones that control glucose homeostasis. Formidable obstacles exist to achieve effective oral delivery of proteinaceous molecules; including low stability, poor absorption, and lack of lipophilicity resulting in low permeation through intestinal and interstitial tissues (Fig. 1). Along with rapid inactivation/degradation by gastrointestinal (GI) enzymes the bioavailability and therapeutic efficacy of such therapeutics is severely compromised (Fig. 2) [1,2].

The prerequisite steps needed for oral absorption of peptides, digestive transit (in stomach, GI fluids, and residence time in absorption window), the crossing biological intestinal barriers (by diffusion, paracellular or transcellular transport) and ultimately the routing (portal route or systemic exposure) of the therapeutic to the site of action are all important in engineering such therapies (Fig. 3). Each of these steps is associated with a particular type of barrier (chemical, biochemical or physical) that restricts peptide drug entry into the systemic circulation. It is therefore a major focus of this field to promote the permeation of such barriers without affecting their important role as barriers against toxins and pathogens exiting the digestive system.

In recent years several novel peptide delivery strategies have emerged for overcoming the problems of biopharmaceutical instability associated with proteins/peptide, thereby improving productivity and reducing metabolism of peptide drugs along with alternative routes of administration. For oral delivery penetration enhancers such as cell penetrating peptides [CPPs], protease inhibitors, polymeric or mucoadhesive carriers, and chemical modification are beginning to increase the bioactivity of these therapeutics to functional levels. Other routes including mucosal (through nasal spray, sublingual or pulmonary delivery), transdermal (patches) and improved controlled release parenteral routes (s.c., i.m. or i.v) will all be important in future efforts especially in the antidiabetic peptide field.

This review will focus on various CPP and transcytosing peptides based technologies that have been applied for improving the delivery and bioavailability of anti-diabetic peptides by the oral route. These approaches could however be readily adapted to other administration routes as there also require the ability to effectively transverse biological barriers (Fig. 4).

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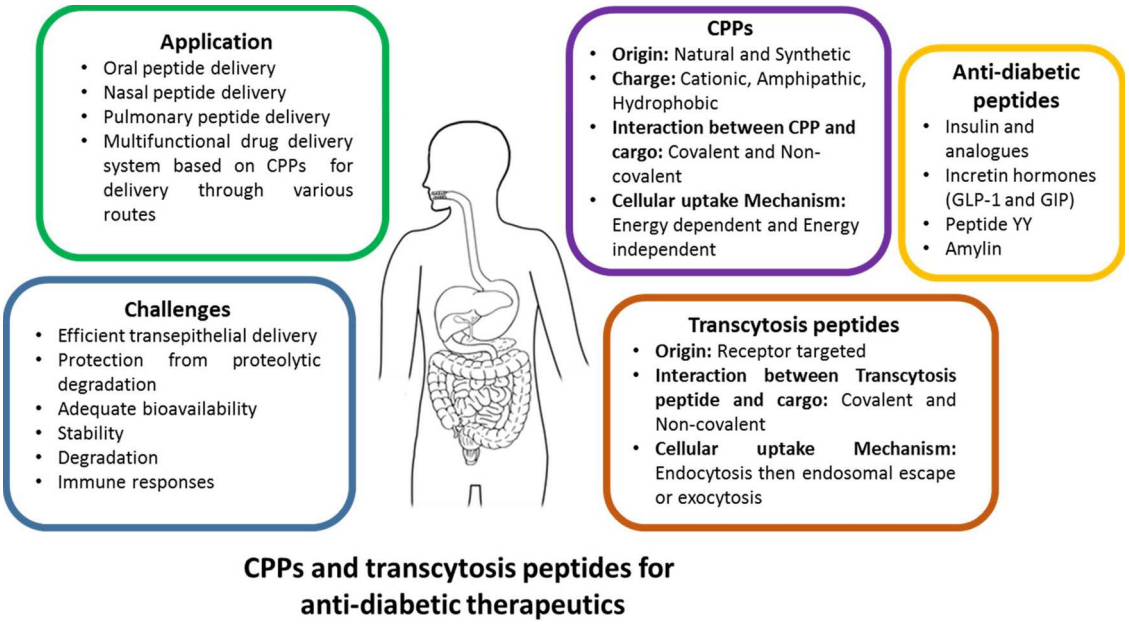

Fig. 1. Schematic of Anti-diabetic peptide application and challenges in oral delivery. Cell penetrating peptides (CPPs) and transcytosis peptide strategy origin and mechanisms are also detailed as are the anti-diabetic peptides that have been formulated in these strategies.

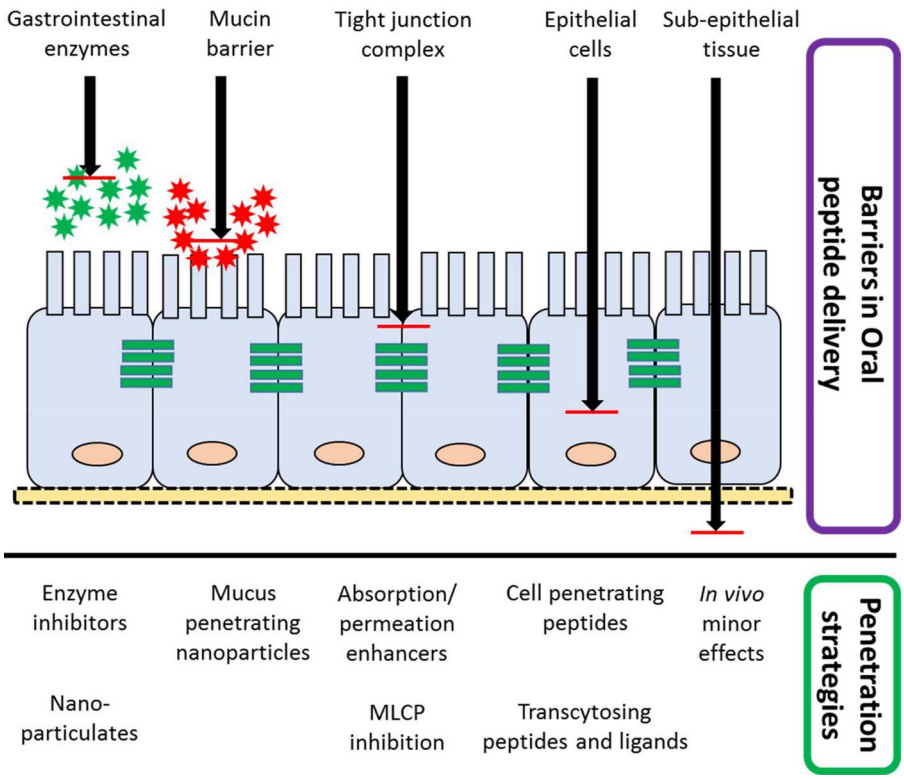

Fig. 2. Gastrointestinal barriers in oral delivery of peptides include; gastrointestinal enzymes, mucin barrier, Tight junction (TJ) complexes and intestinal tissue barriers particularly by epithelial and sub-epithelial tissues. For overcoming these various physiological barriers different strategies could be employed as shown in figure including the use of enzyme inhibitors, nanoparticles, absorption/permeation enhancers, MLCP inhibition, CPPs and transcytosing peptides.

2. Cell penetrating peptides (CPPs)

During the past two decades, protein transduction domains (PTDs) or cell penetrating peptides (CPPs) have emerged as powerful *trans*-epithelial vectors for the efficient intracellular delivery of large variety of cargoes through the biological membranes. These are also termed as membrane translocation sequences or Trojan peptides [3–5]. CPPs are relatively small functional carrier peptides, typically cationic or amphipathic with 5–30 amino acids, water soluble, and can be isolated from naturally existing proteins, modified or designed de novo [6,7]. They are capable of entering cells in a non-invasive manner without disrupting cell membrane integrity compared to some standard traditional techniques such as microinjection and electroporation, therefore they are considered safe and highly efficient [8].

Since their discovery, more than 100 CPPs having variable amino acids in sequence (5 − > 30) have been identified that can efficiently internalize into plant, mammalian and bacterial cell membranes, thereby mediating the transport of a large number of biologically active drug molecules, drug delivery vectors and cargoes. CPPs have successfully delivered a large variety of drugs inside cells, such as proteins,