DELIVERY OF PROTEINS: ROUTES OF ADMINISTRATION

Lecture 7

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The Oral Route of Administration

- Oral delivery of protein drugs would be preferable,because:

- ✓ it is patient friendly

- ✓ and no intervention by a healthcare professional is necessary to administer the drug.

The Oral Route of Administration

Protein oral bioavailability is usually very low

The two main reasons for this failure of uptake are:

(i) protein degradation in the gastrointestinal (GI) tract and

(ii) poor permeability of the wall of the GI tract in case of a passive transport process

The Oral Route of Administration

i. Protein degradation in the GI tract:

The human body has developed a very efficient system to break down proteins in our food to amino acids, or di- or tri-peptides. These building stones for body proteins are actively absorbed for use wherever necessary in the body. In the stomach pepsins, a family of aspartic proteases, are secreted. They are particularly active between pH 3 and 5 and lose activity at higher pH values. Pepsins are **endopeptidases** capable of cleaving peptide bonds distant from the ends of the peptide chain. They preferentially cleave peptide bonds between two hydrophobic amino acids. Other endopeptidases are active in the GI tract at neutral pH values, e.g., trypsin, chymotrypsin, and elastase. They have different peptide bond cleavage characteristics that more or less complement each other.

Exopeptidases, proteases degrading peptide chains from their ends, are present as well. Examples are carboxypeptidase A and B. In the GI lumen the proteins are cut into fragments that effectively further break down to amino acids, di- and tri-peptides by brush border and cytoplasmic proteases of the enterocytes.

The Oral Route of Administration

(ii) poor permeability:

High molecular weight molecules do not readily penetrate the intact and mature epithelial barrier if diffusion is the sole driving force for mass transfer. Their diffusion coefficient decreases with increasing molecule size. Proteins are no exception to this rule. Active transport of intact therapeutic recombinant proteins over the GI-epithelium has not been described yet.

The Oral Route of Administration

Conclusion:

The above analysis leads to the conclusion that nature, unfortunately, does not allow us to use the oral route of administration for therapeutic proteins if high (or at least constant) bioavailability is required.

The Oral Route of Administration

However, for the category of oral vaccines the above-mentioned hurdles of degradation and permeation are not necessarily prohibitive. For oral immunization, only a (small) fraction of the antigen (protein) has to reach its target site to elicit an immune response.

- The target cells are lymphocytes and
- antigen presenting accessory cells located in Peyer’s patches
- The B-lymphocyte population
- includes cells that produce secretory IgA antibodies

These Peyer’s patches are macroscopically identifiable follicular structures located in the wall of the GI tract. Peyer’s patches are overlaid with microfold (M) cells that separate the luminal contents from the lymphocytes. These M cells have little lysosomal degradation capacity and allow for antigen sampling by the underlying lymphocytes.

Moreover, mucus producing goblet cell density is reduced over Peyer’s patches. This reduces mucus production and facilitates access to the M cell surface for luminal contents. Attempts to improve antigen delivery via the Peyer’s patches and to enhance the immune response are made by using microspheres, liposomes or modified live vectors, such as attenuated bacteria and viruses

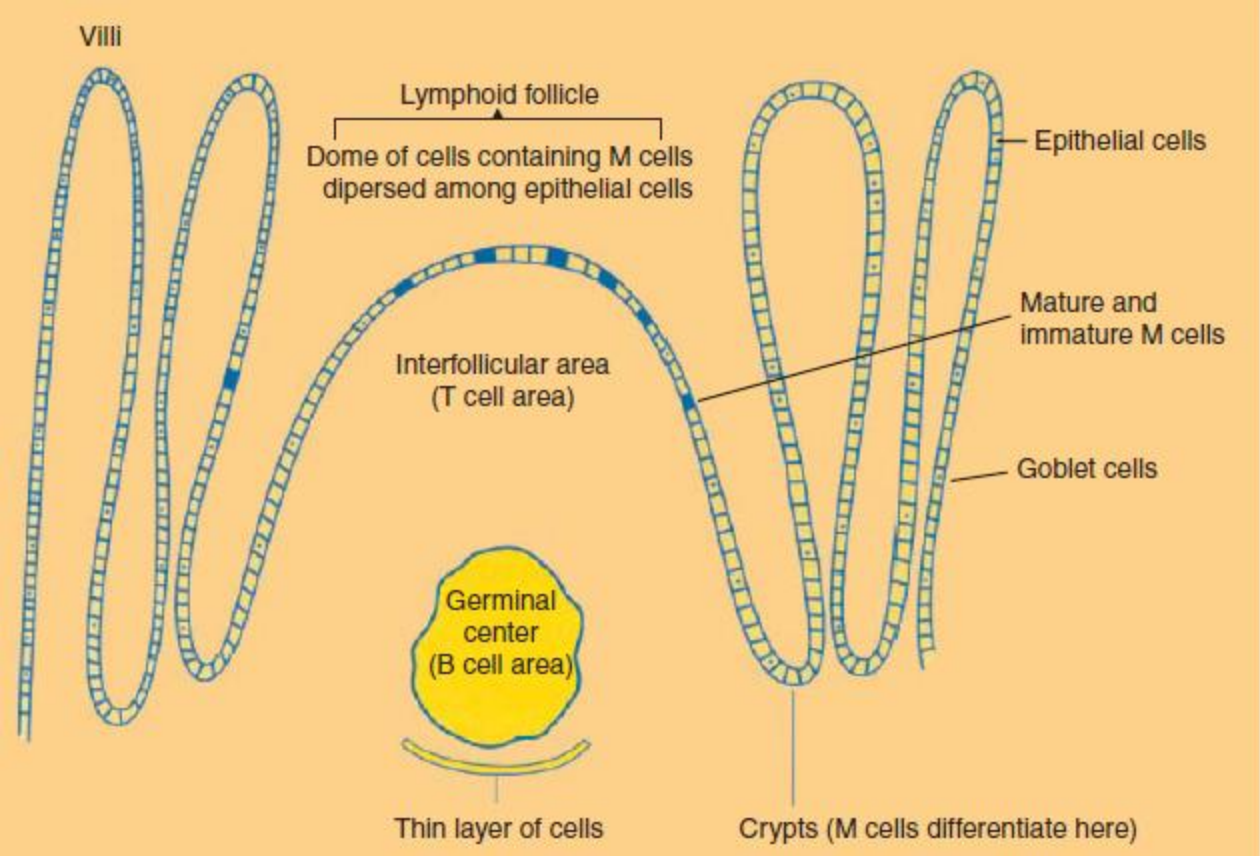


Figure 13 Schematic diagram of the structure of intestinal Peyer's patches. M cells within the follicle-associated epithelium are enlarged for emphasis. *Source*: Adapted from

Alternative Routes of Administration

Parenteral administration has disadvantages (needles, sterility, injection skills) compared to other possible routes. Therefore, systemic delivery of recombinant proteins by alternative routes of administration has been studied

extensively. The nose, lungs, rectum, oral cavity, and skin have been selected as potential sites of application.

The potential pros and cons for the different

relevant routes :The nasal, buccal, rectal, and transdermal routes are studied.

Alternative Routes of Administration

Nasal (Edman and Björk, 1992)

Advantage:
Easily accessible, fast uptake, proven track record with a number of "conventional" drugs, probably lower proteolytic activity than in the GI tract, avoidance of first pass effect, spatial containment of absorption enhancers is possible

Disadvantage:
Reproducibility (in particular under pathological conditions), safety (e.g., ciliary movement), low bioavailability for proteins

Pulmonary (Patton and Platz, 1992)

Advantage:
Relatively easy to access, fast uptake, proven track record with "conventional" drugs, substantial fractions of insulin are absorbed, lower proteolytic activity than in the GI tract, avoidance of hepatic first pass effect, spatial containment of absorption enhancers (?)

Disadvantage:
Reproducibility (in particular under pathological conditions, smokers/non-smokers), safety (e.g., immunogenicity), presence of macrophages in the lung with high affinity for particulates

Rectal (Zhou and Li Wan Po, 1991b)

Advantage:
Easily accessible, partial avoidance of hepatic first pass, probably lower proteolytic activity than in the upper parts of the GI tract, spatial containment of absorption enhancers is possible, proven track record with a number of "conventional" drugs

Disadvantage:
Low bioavailability for proteins

Buccal (Zhou and Li Wan Po, 1991b; Ho et al., 1992)

Advantage:
Easily accessible, avoidance of hepatic first pass, probably lower proteolytic activity than in the lower parts of the GI tract, spatial containment of absorption enhancers is possible, option to remove formulation if necessary

Disadvantage:
Low bioavailability of proteins, no proven track record yet (?)

Transdermal (Cullander and Guy, 1992)

Advantage:
Easily accessible, avoidance of hepatic first pass effect, removal of formulation if necessary is possible, spatial containment of absorption enhancers, proven track record with "conventional" drugs, sustained/controlled release possible

Disadvantage:
Low bioavailability of proteins

The first pulmonary insulin formulation was approved by FDA in January 2006 Uptake of insulin is faster than after a regular SC insulin injection (peak 5–60 minutes versus 60–180 minutes).

The fraction of insulin that is ultimately absorbed depends on: (i) the fraction of the inhaled/nebulized dose that is actually leaving the device, (ii) the fraction that is actually deposited in the lung, and (iii) the fraction that is being absorbed

In general, bioavailability is too low and varies too much! The pulmonary route may be the exception to this rule.

administered protein solutions with a wide range of molecular weights. Absorption was strongly protein dependent, with no clear relationship with its molecular weight.

Molecule	Mw kDa	No. of AA	Absolute bioavailability (%)
α-interferon	20	165	>56
PTH-84	9	84	>20
PTH-34	4.2	34	40
Calcitonin (human)	3.4	32	17
Calcitonin (salmon)	3.4	32	17
Glucagons	3.4	29	<1
Somatostatin	3.1	28	<1

Abbreviations: AA, number of amino acids; PTH, recombinant human parathyroid hormone.
Source: Adapted from Patton et al., 1994.

Table 5 Absolute bioavailability of a number of proteins

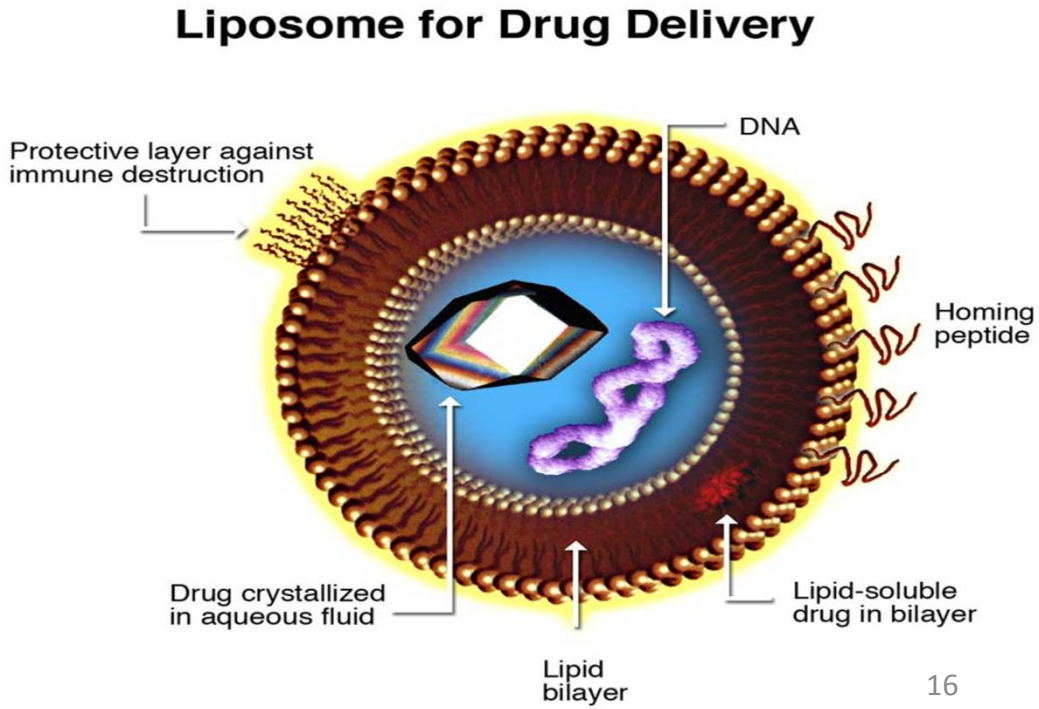
Approaches to enhance bioavailability of proteins

❑Increase the permeability of the absorption barrier:

- Addition of fatty acids/phospholipids, bile salts, enamine derivatives of phenylglycine, salicylate derivatives.

- Through iontophoresis

- By using liposomes



Approaches to enhance bioavailability of proteins

- Decrease peptidase activity at the site of absorption and along the “absorption route”: aprotinin, bacitracin, soybean tyrosine inhibitor.

- Enhance resistance against degradation by modification of the molecular structure.

- Prolongation of exposure time.

Molecule	No. of AA	Bioavailability (%)	
		Without glycocholate	With glycocholate
Glucagon	29	<1	70–90
Calcitonin	32	<1	15–20
Insulin	51	<1	10–30

Effect of glycocholate (absorption enhancer) on nasal bioavailability of some proteins and peptides