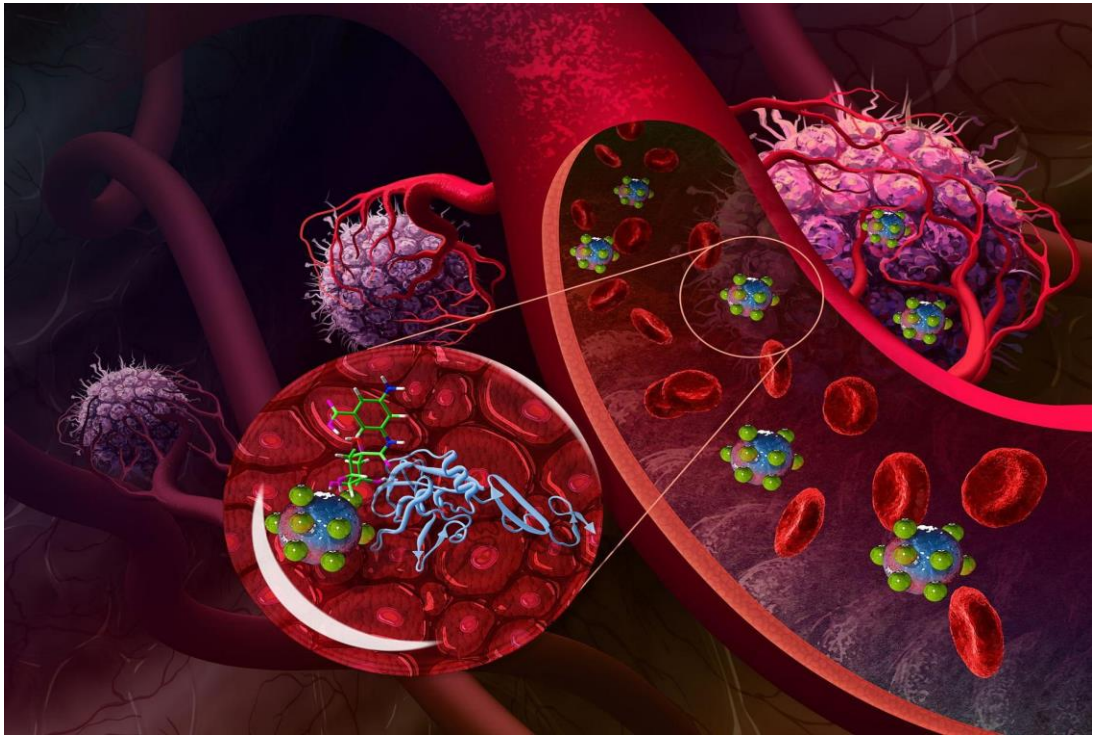
Organic Pharmaceutical Chemistry IV

Lec6: Drug targeting.



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Drug Targeting

- Recently, new therapies have been proposed which attempt the localization of prodrug activation enzymes into specific cancer cells prior to prodrug administration.

- <u>These new approaches are:</u>

  1. *Anti-body Directed Enzyme Prodrug Therapy (ADEPT)*
  2. *Gene Directed Enzyme Prodrug Therapy (GDEPT)*

Anti-body directed enzyme prodrug therapy (ADEPT)

- Enzymes that activate prodrugs can be directed to human xenografts by conjugating them to tumour selective monoclonal antibodies.

Anti-body directed enzyme prodrug therapy (ADEPT)

- An antitumor antibody is conjugated to an enzyme not normally present in extracellular fluid or on cell membranes and then these conjugates are localized in the tumour via IV infusion.

Anti-body directed enzyme prodrug therapy (ADEPT)

- In ADEPT procedure after allowing for the conjugate to clear from the blood, a prodrug is administered that is normally inert but is activated by the enzyme delivered to the tumour.

Gene directed enzyme prodrug therapy (GDEPT)

- Tumours have also been targeted with genes encoding prodrug-activating enzymes.
- This approach uses a viral vector e.g. retroviral vector or adenoviral vector to carry a prodrug-activating enzyme gene into both tumour and normal cells.

Gene directed enzyme prodrug therapy (GDEPT)

- By linking the foreign gene downstream of tumour-specific transcription units, tumour-specific expression of the foreign enzyme gene can be achieved.

Targeted prodrug design to optimize drug delivery

- Prodrug design can no longer be considered as just a chemical modification to solve problems associated with drugs.

- *Discuss this phrase.*

Targeted prodrug design to optimize drug delivery

- Prodrug design is becoming more elaborate in the development of efficient and selective drug delivery systems.
- The targeted prodrug approach is a promising strategy for precise and efficient drug delivery and the enhancement of therapeutic efficacy.

Targeted prodrug design

- Targeted prodrug design is based on the followings:

1. *Targeting specific enzymes.*
2. *Targeting specific membrane transporters.*

Prodrug Design Based on Targeting Enzymes

- In prodrug design, enzymes are recognized as prodrug-drug in vivo reconversion sites.

- <u>The enzyme-targeted prodrug approach has been used to improve:</u>

    i. *Oral drug absorption.*

    ii. *Site-specific drug delivery.*

Prodrug Design Based on Targeting Enzymes

- Colon-specific drug delivery has been designed by producing a polar promoiety with retarded intestinal absorption.

Examples on prodrug design based on targeting enzymes:

- ***Exaple1:***
- Glycosidase activity of the colonic microflora offers an opportunity to design ***a colon-specific drug delivery system.***

Examples on prodrug design based on targeting enzymes:

- Glycoside derivatives are hydrophilic and poorly absorbed from the small intestine, but once they reach the colon, they can be effectively cleaved by bacterial glycosidases to release the free drug.

Examples on prodrug design based on targeting enzymes:

- Glycosidic prodrug of Dexamethasone utilizing the activity of bacterial glycosidases has been reported.

Examples on prodrug design based on targeting enzymes:

- ***Exaple2:***

- Delivery of Dopamine to kidney in the form of its prodrug L-glutamyl dopa.

- Kidney possesses high concentration of L-glutamyl transpeptidase and L-amino acid decarboxylase enzymes.

Examples on prodrug design based on targeting enzymes:

- The prodrug is first cleaved by L-glutamyl transpeptidase producing L-dopa, which is converted to dopamine by L-amino acid decarboxylase.
- This leads to selective delivery of drug to kidney resulting in desired renal vasodilatation while avoiding systemic hypotension.

Prodrug Design Targeting Membrane Transporters

- This targeted prodrug approach uses transporters designed for facilitating membrane transport of polar nutrients such as amino acids and peptides.

- Targeting specific membrane transporters is particularly important when prodrugs are polar or charged.

Prodrug Design Targeting Membrane Transporters

- Intestinal epithelial transporters to facilitate the absorption of appropriately modified drugs have been proved to improve the bioavailability of poorly absorbed drug molecules.

- Prodrugs are designed to resemble the intestinal nutrients structurally and to be absorbed by specific carrier proteins.

- Many attempts have been made to improve drug absorption by targeting specific membrane transporters, including amino acids, peptides, and glucose transporters.

Peptide Transporter Associated Prodrug Therapy (PTAPT)

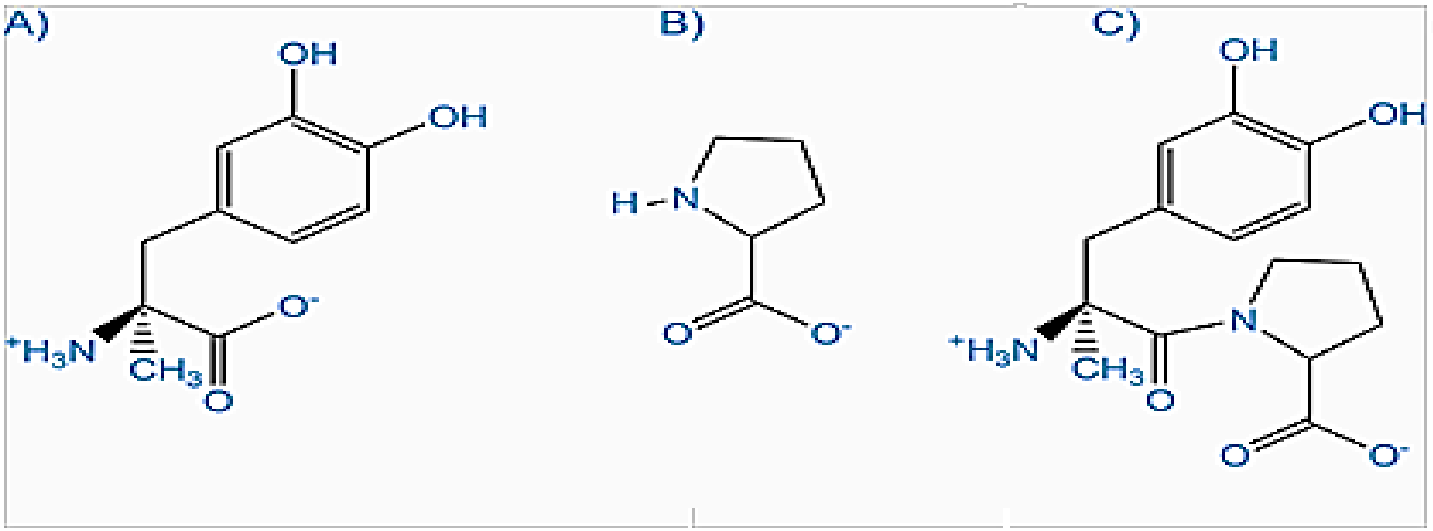
- Peptide transporters have broad substrate specificity and high capacity and are a good target for prodrug development to improve oral drug absorption.

- A polar drug with low membrane permeability through passive diffusion is converted into a prodrug that is absorbed via the peptide transporter into the mucosal cell.

- Following membrane transport, enzymes in the mucosal cell, blood, or liver hydrolyze the prodrug to release the active drug.

Peptide Transporter Associated Prodrug Therapy (PTAPT)

- This prodrug strategy has been effective for improving the membrane permeability and systemic availability of the polar μ-methyldopa through peptidyl derivative (μ-methyldopa-proline).



Structures of A) L-α-methyldopa, B) L-proline, and C) L-α-methyldopa-L-proline prodrug

Peptide Transporter Associated Prodrug Therapy (PTAPT)

- Recently the application of PTAPT is broadened to nonpeptidyl type prodrugs, such as amino acid ester prodrugs.
- For example: Several amino acid ester prodrugs of the nucleoside antiviral drugs Acyclovir and Azathioprine have been synthesized and examined for their intestinal absorption.

Peptide Transporter Associated Prodrug Therapy (PTAPT)

- These prodrugs have shown significant increase (3-10 folds) in intestinal absorption of their parent drugs via a peptide transporter mediated mechanism, even though they do not have a peptide bond in their structure.

Peptide Transporter Associated Prodrug Therapy (PTAPT)

- Following the membrane transport, these prodrugs were rapidly converted to the active drugs by intracellular hydrolysis.

Active targeting by Polymeric prodrug:

i. *Monoclonal antibodies.*
ii. *Lectins.*
iii. *Angiogenic vessels of tumor cells*.

Monoclonal antibodies:

- The monoclonal antibodies can be used as targeting group for coupling with the drug to increase the specific targeting of the prodrug on the tumor cells.

- These antibodies bind very specifically to tumor cells and this approach has been successfully used in cancer therapy.

- This approach minimizes nonspecific toxicity.

Monoclonal antibodies:

- Examples:

(a) Conjugate of plant toxins and antibodies, referred as immunotoxin is a very potent anti-tumor therapy.

(b) Tumor selective monoclonal antibody is covalently attached to an enzyme which converts nontoxic prodrug into potent cytotoxic drug after specific targeting at the tumor site.

Lectins:

- The sugar specific receptors present on the plasma membrane are called lectins and they have been characterized mainly on hepatocytes.

- Galactose specifically targets these lectins and this targeting seems to be an attractive approach for target specific drug delivery especially for treatment of liver diseases.

Lectins:

- Applications of targeted lectins:
  - ❑ *For treatment of liver diseases such as:*
    - ✓ Hepatitis.
    - ✓ Parasitic infections.
    - ✓ Liver metastasis.
- Drug delivery to macrophages (e.g. Kupffer cells) can be employed for targeted treatment of various malfunctions such as leishmaniasis.

Angiogenic vessels of tumor cells

- The endothelial cells in angiogenic vessels of tumors show increased expression of cell surface proteins.

- These proteins include receptors for vascular endothelial growth factor (VEGF) and integrin receptors.

Angiogenic vessels of tumor cells

- The peptides which specifically bind to these receptors can be used as targeting moiety for drug delivery such as RGD (arginine-glycine-aspartic acid) containing peptides that specifically bind with integrin receptors.

- The conjugation of RGD peptides and poly ethylene glycol (PEG) showed increased efficacy of drug against breast cancer.

References:

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