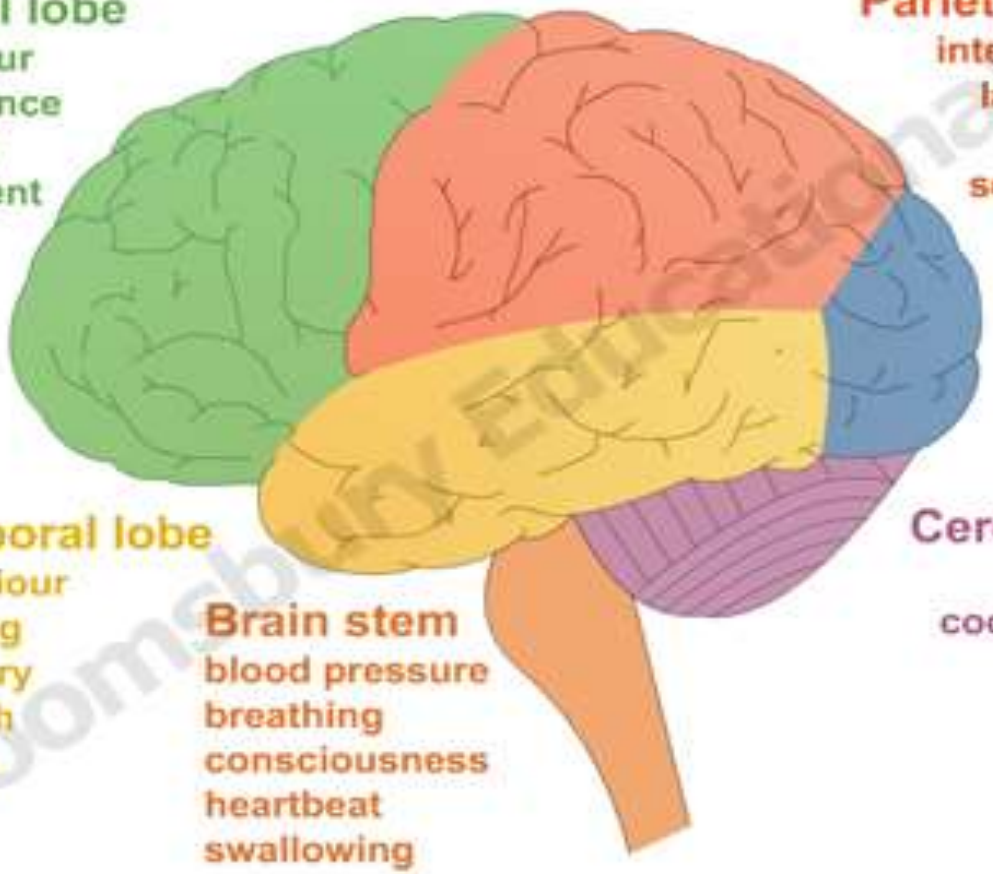
Drug Delivery to Brain and Targeting of Drugs to Brain

Dr.R.L.C.SASIDHAR

Associate Professor, CHIPS

Functions of the brain



Pascalis Spyrou

Introduction

- The CNS is the most dynamic expression of the harmonious co-ordination found in the human beings.
- Brain is the important part of CNS.
- Certain diseases that attack brain mainly arise from local or peripheral physiological disorders.
- Ex: Epilepsy, Parkinson's disease etc.
- Some are caused by brain infections.

Ex: **Encephalitis**, is an acute inflammation of the brain.

Meningitis. is an inflammation of the membranes that surround the brain and spinal cord . Meningitis is most commonly caused by infections with various pathogens, examples of which are *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Factors that Influence Uptake and Distribution of Drug into Brain

- Blood flow.
- Binding of proteins in blood plasma.
- Clearance from blood.
- Metabolism.

- Drugs that are effective against diseases in CNS should reach the brain by passing through blood brain barrier.
- The major challenge to CNS drug delivery is the blood-brain barrier (BBB), which limits the access of drugs to the brain substance.
- BBB is formed by complex system of endothelial cells, astroglia, pericytes and basal lamina.
- The BBB is the rate limiting factor in the permeation of drug into brain and also influences the steady state distribution.

Barriers in Brain drug delivery

1) Blood-Brain Barrier (BBB)

- Build up by endothelial cells of the brain capillaries
- Protects brain from foreign and toxic substances as well as neurotransmitters and hormone

2) Blood-CSF Barrier (BCSFB)

- Formed by the epithelia of the choroid plexus and the circumventricular organs
- More permeable than BBB

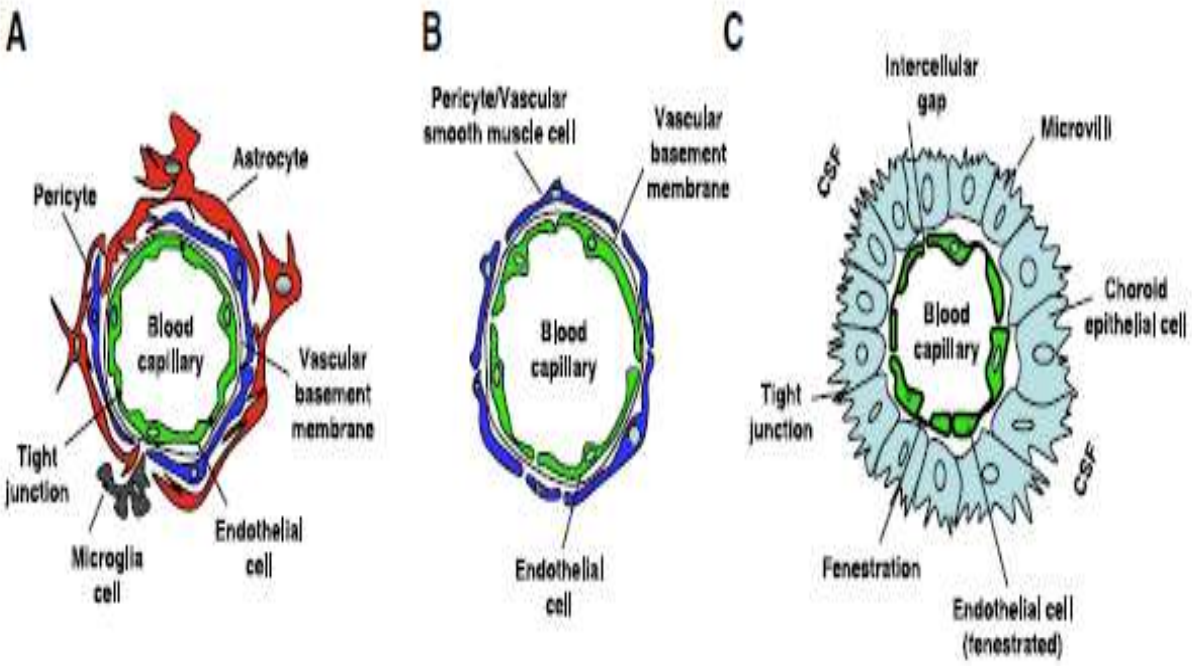
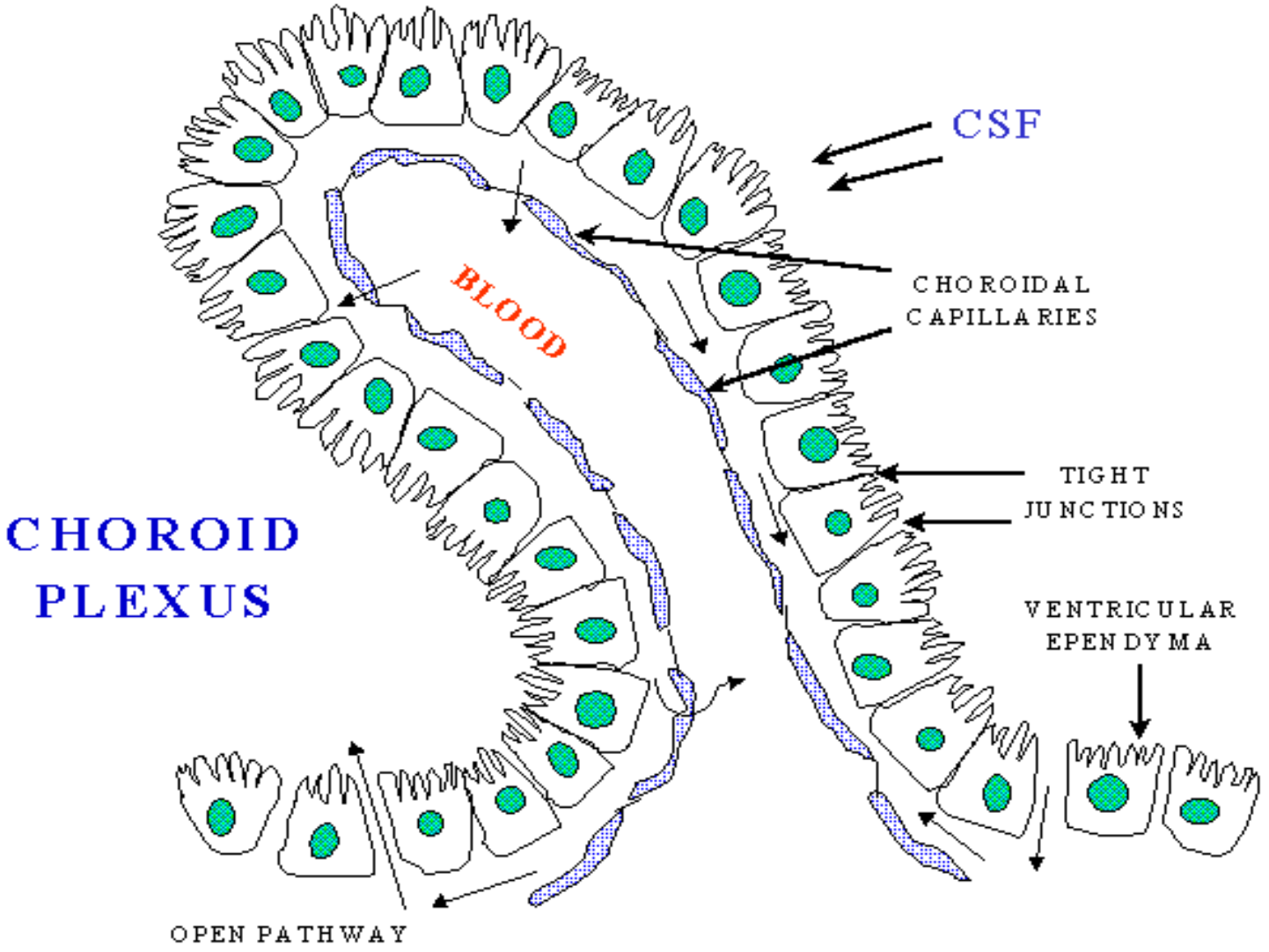


Fig . NO. 1 Structure of

A. Blood brain barrier
B. Peripheral capillaries
C. B-CSF barrier

- The brain micro vessel endothelial cell (BMEC) that form the BBB, display important morphological characteristics such as the presence of tight junctions between the cells, the absence of fenestrations that together help to restrict the passage of compounds from the blood into the extra cellular environment of the brain.
- This barrier permits the exchange of essential gases and nutrients between the bloodstream and the brain, while blocking larger entities such as microbes, immune cells and most drugs from entering.


CSF
BLOOD
CHOROIDAL
CAPILLARIES
TIGHT
JUNCTIONS
CHOROID
PLEXUS
VENTRICULAR
EPENDYMA
OPEN PATHWAY

Mechanism of transporting drugs into brain

- Permeation of compounds across BBB depends on their lipophilicity.
- Some drugs like VINCRISTINE, VINBLASTINE although highly lipophilic, the permeation of these drugs across BBB is very slow.
- This indicates the existence of multiple mechanisms of drug transport through BBB.

VARIOUS BBB TRANSPORT MECHANISMS

1. **Active efflux transport by p-glycoprotein at BBB.**

- PGP at BBB is important for limiting access of endogenous and exogenous toxic agents.

- Pharmacological opening of BBB by inhibition of PGP function leads to increased uptake of some drugs like Anti-Cancer drugs.

2. **Carrier mediated BBB transport of drugs**

- Mono carboxylic acid transport systems

  Ex: lactate, pyruvate.
- Amine transporters

  Ex: Endogenous hydrophilic amine choline.
- Neutral amino acid transport system for drugs like leucine, l-dopa, gabapentin.
- Basic amino acid transport system for lysine.
- Beta amino acid transport system for beta-Alanine.

3. Transport of peptide across BBB

- Peptides are generally relatively large hydrophilic and unstable. So specific delivery strategy is employed.

Carrier Mediated Transport of Peptides

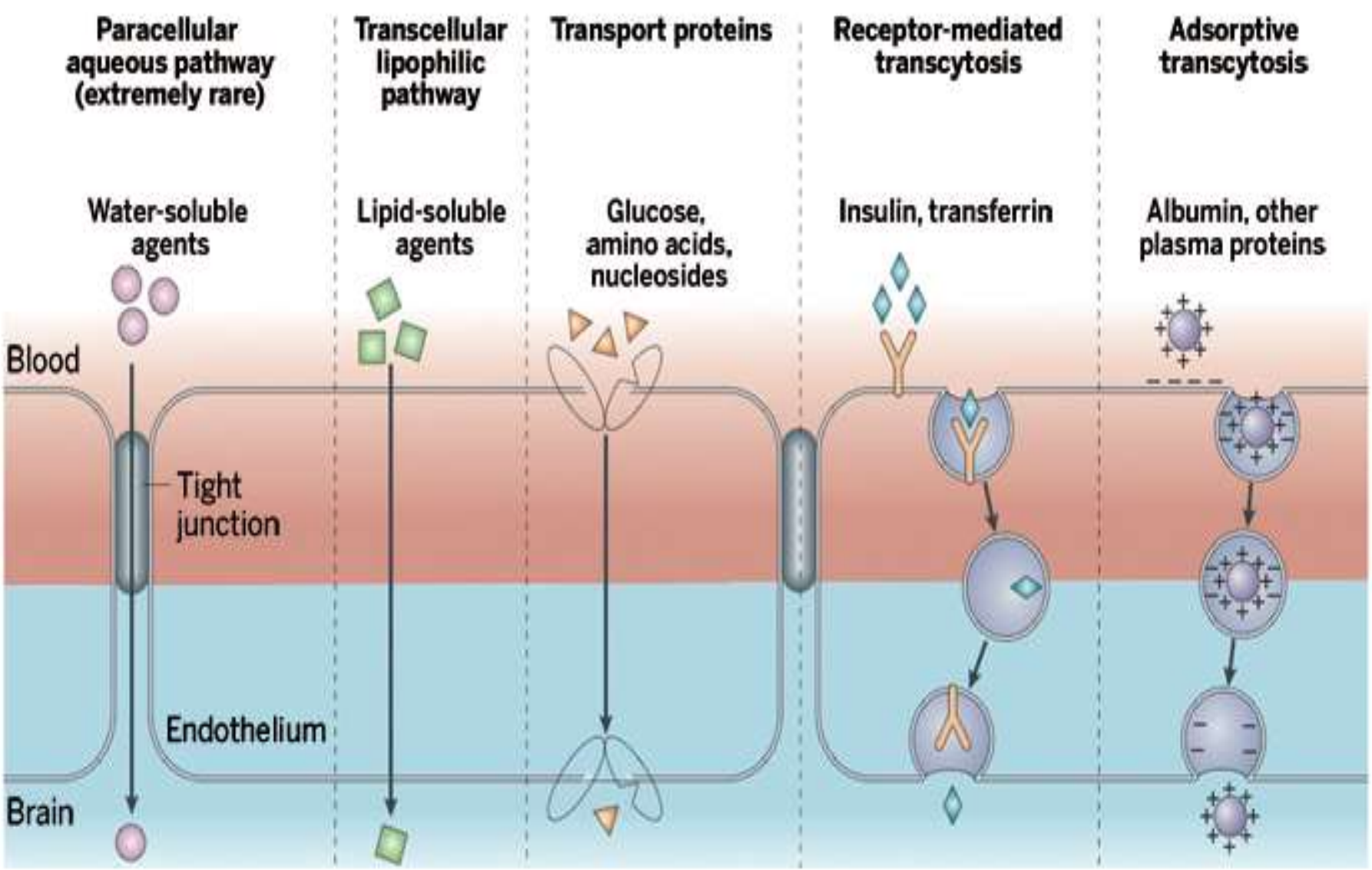
- It is suitable for small Di and Tri peptides.

Adsorptive Mediated Endocytosis

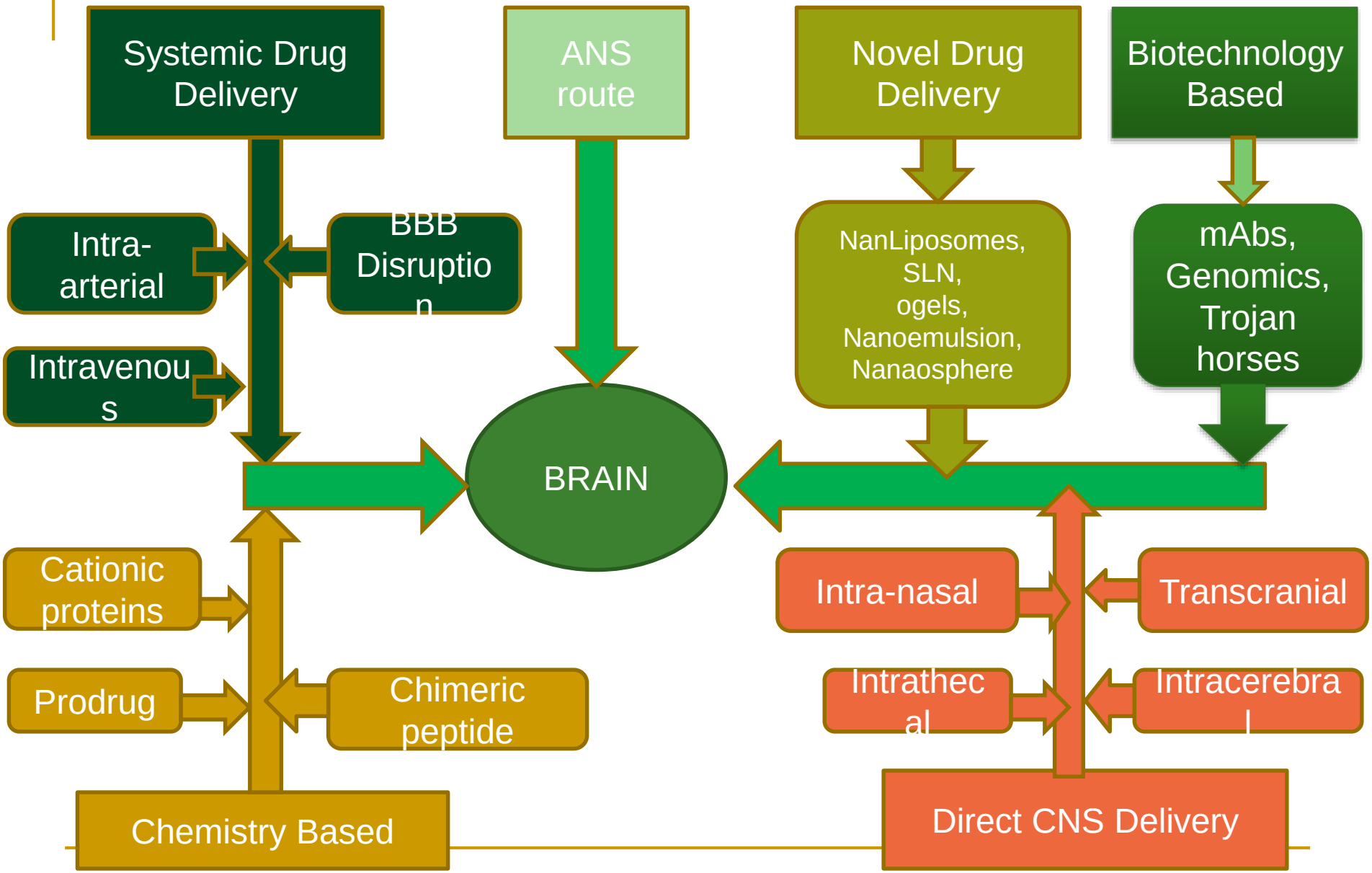
- It is triggered by electrostatic interaction between a positively charged peptide and negatively charged plasma membrane surface region.

4. Efflux transport system for drugs

- It is expressed at luminal and for albuminal membranes of basal capillary endothelial cells which restricts accumulation of some drugs.
- PGP is one such Efflux transporter.


Paracellular aqueous pathway (extremely rare)
Transcellular lipophilic pathway
Transport proteins
Receptor-mediated transcytosis
Adsorptive transcytosis
Water-soluble agents
Lipid-soluble agents
Glucose, amino acids, nucleosides
Insulin, transferrin
Albumin, other plasma proteins
Blood
Tight junction
Endothelium
Brain

Approaches for Brain Drug Delivery



OVERVIEW OF DIFFERENT APPROACHES OF BRAIN TARGETING

Pathways for drug administration into Brain

- BBB
- Nasal route

  Ex: Vitamin B12, Apomorphine, Analgesics Anti migraine drugs etc…
- Intra cerebroventricular administration: surgical implantation.

  Ex: water soluble Anti Cancer drugs, Morphine.

Strategies for brain delivery of drug

INVASIVE	PHYSIOLOGICAL	PHARMACOLOGICAL
BBB disruption	Pseudonutrients	Liposome
Intracerebral Implants	ligand binding proteins	Nanoparticles
	Chimeric Peptides	Chemical Drug Delivery

Intra nasal drug delivery

- After nasal delivery drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation by Tran cellular and Para cellular passive absorption, carrier-mediated transport, and absorption through trancytosis.
- When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur.

Invasive Delivery Strategies

- Invasive approach to drug delivery require surgical intervention. This includes the methods that physically bypass the BBB by direct delivery into CSF.

1. Drug delivery based on BBB disruption.

   This method involves temporary physiochemical disruption of endothelial cells.

Intraventricular / Intrathecaldelivery

- Here using a plastic reservoir which implanted subcutaneously in the scalp and connected to the ventricles within the brain by an outlet catheter. Drug injection into the CSF is a suitable strategy for sites close to the ventricles only.

- Hyper Osmolar Barrier Opening

  It is used for delivery of small molecular weight cytostatic agents to brain tumors.

Mechanisms:

- Endothelial cell shrinkage.
- Disruption of tight junctions.
- Vasodilation by osmotic shift.

Biochemical barrier opening

- BBB opening may also be achieved by receptor mediated mechanisms.
- Vasoactive compounds such as prostaglandins, serotonin, histamine, bradykinin induce BBB leakage.
- Effects of bradykinin are more pronounced on blood tumor barrier than normal BBB.

2.Physiological Delivery Strategies

- Drug treatments of chronic degenerative disorders will require long term therapy.
- This implies a need to develop a non invasive approach for brain delivery via systemic route.

1. Receptor mediated uptake:

   This involves transport of peptides and proteins at BBB.

   The overall process is designated as transcytosis and is composed of binding to a luminal plasma membrane receptor, Endocytosis, transfer through endothelial cytoplasm.

2. Absorptive mediated uptake of lecithins and cationic peptides/proteins

- A mechanism of brain uptake related to receptor-mediated transcytosis operates for cationic peptides/proteins and some lecithins.

- Initial binding to luminal plasma membrane is mediated by electrostatic interactions with anionic sites or by specific interaction with sugar residues [absorptive mediated transcytosis]

3. Drug delivery trough chimeric peptides

these are generated by linking a drug that lacks transport at BBB to a vector.

binding of vector at luminal membrane of brain capillary endothelial cells initiates receptor mediated or adsorptive mediated transcytosis.

Chemical Delivery Systems

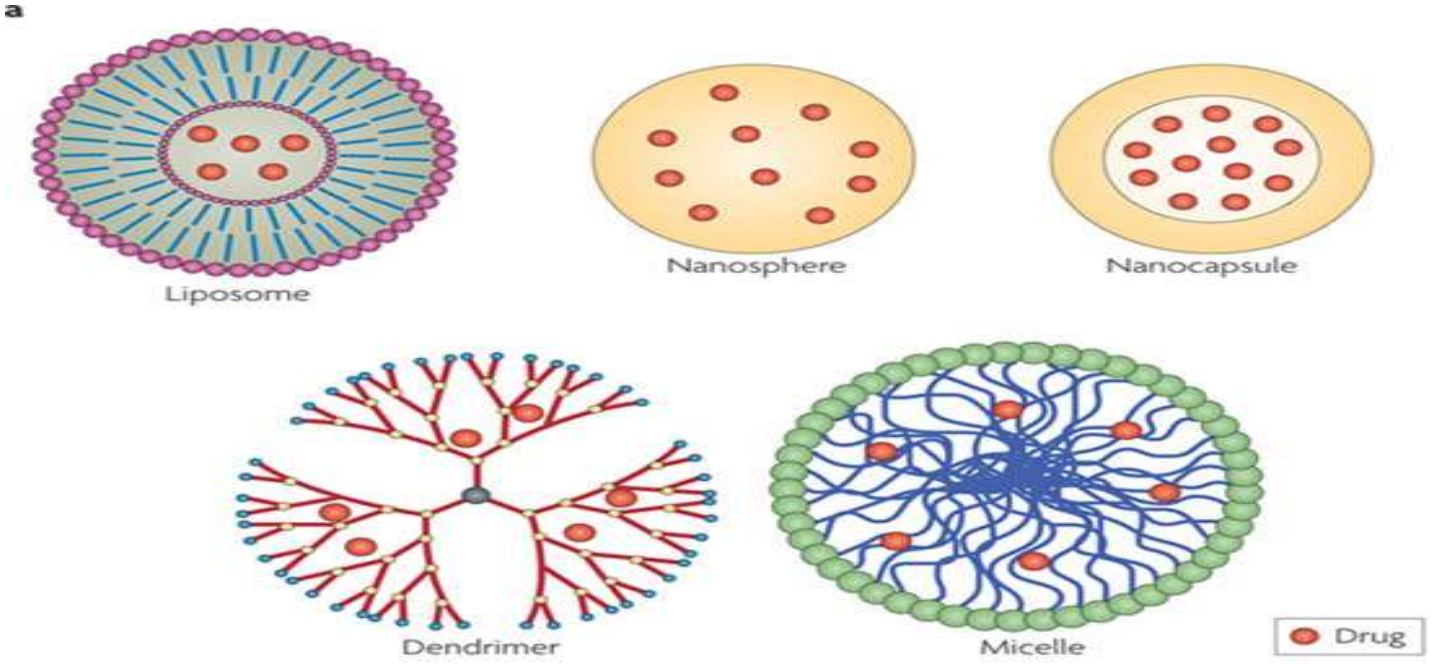
- Brain targeted chemical delivery systems represent a rational drug design approach that exploits sequential metabolism not only to deliver but also to target drugs to their site of action.

- By localizing drugs at desired site of action one can reduce toxicity and increase treatment efficacy.

- The use of redox chemical system for drug targeting to brain is of great significance for two categories of drugs.

    1. Which do not cross BBB at all.
    2. The drugs that readily penetrate BBB.

PHARMACOLOGICAL STRATEGIES



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NANOPARTICLES

Nanoparticles are solid colloidal particles ranging in size 1-1000nm.

- They consist of macromolecular materials in which the active principle is dissolved, entrapped or encapsulated.
- Drugs may be bound inform of a solid solution or dispersion or be adsorbed to the surface or chemically attached.
- Poly (butylcyanoacrylate) nanoparticles represent the only nanoparticles that were so far successfully used for the in vivo delivery of drugs to the brain.
- The first drug that was de-livered to the brain using nanoparticles was the hexapeptidedalargin

Mechanisms of Nanoparticles mediated transport.

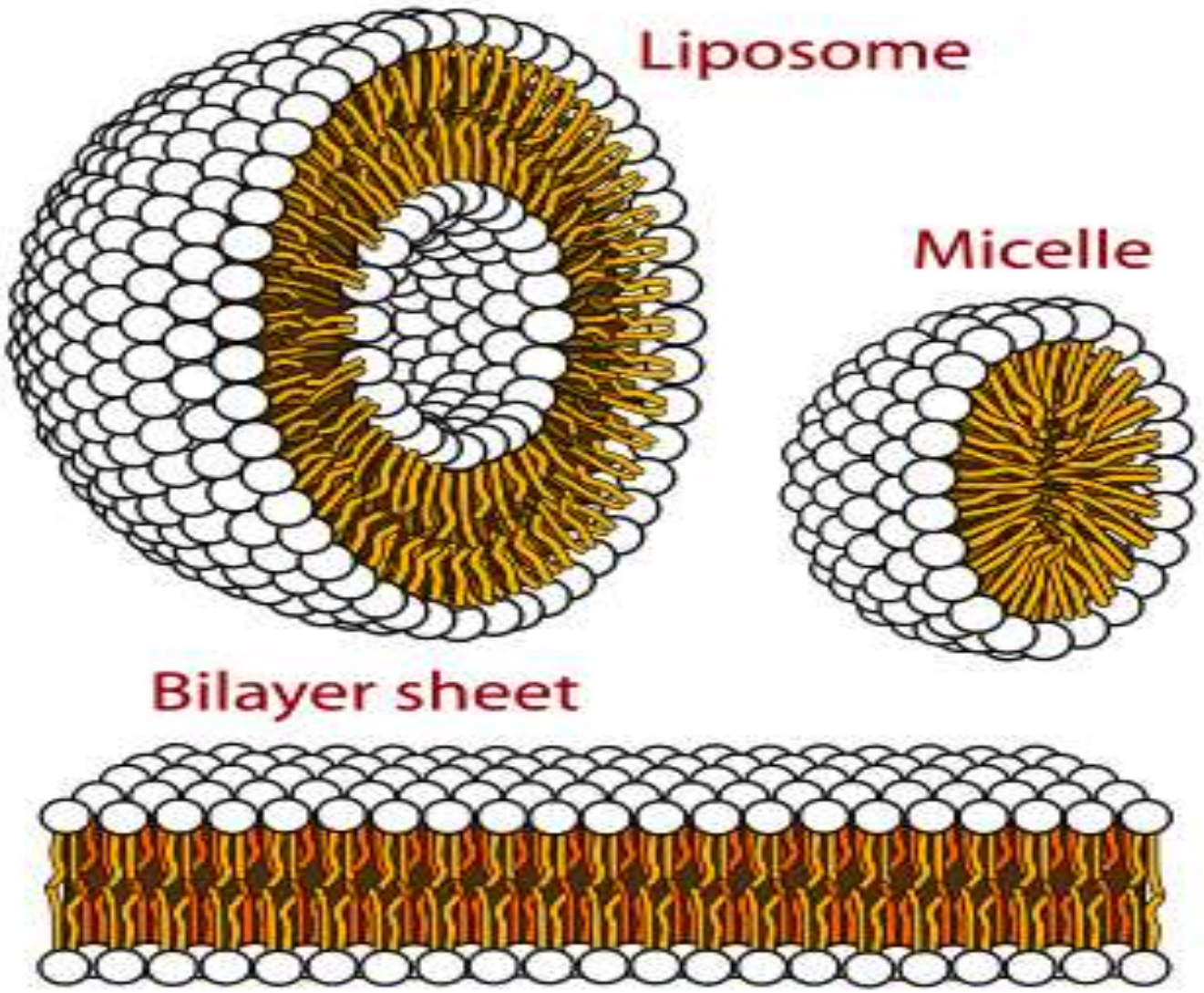
1. Adhesion of Nanoparticles to brain blood vessel walls.
2. Fluidization of endothelium by surfactants
3. Opening of tight junctions of endothelium
4. Endocytosis by the brain blood vessel endothelial cells.
5. Blockage of p-glycoprotein in the brain cells.

- Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine.
- The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers.
- The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

Liposomes

- Liposomes are lipid vesicles that offer an advantage of targeting the drug to the tissues.
- Liposomes are biocompatible, non-toxic and biodegradable which offer possibility of carrying hydrophilic, hydrophobic and amphoteric molecules.
- They can act as carriers for drugs, enzymes, proteins, anticancer substances etc…
- These modify therapeutic profile of selected anitumor drugs in favorable manner by reducing toxicity.

- In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell.
- In the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released.
- Liposomal delivery systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to target them to specific diseased tissues.


Liposome
Micelle
Bilayer sheet

Monocytes:

- The unusual ability of Monocytes to cross BBB makes it possible to consider these cells to transport agents into CNS.

- Monocytes express certain receptors on their membrane which are involved in receptor mediated Endocytosis upon interaction with suitable ligands.

Recent advances

- Cationic Liposomes were developed and these were found to undergo absorptive mediated Endocytosis into cells.

- The addition of sulfatide to liposome composition improves their ability to penetrate BBB.

- Prolonged circulation of Liposomes is achieved by insertion of gangliosides or PEG derivatised lipids within the bi layer of Liposomes.

In vivo techniques for assessing pharmacokinetics of drugs targeted to brain

- The various in vivo techniques include

1. Brain uptake index.
2. Brain efflux index.
3. Brain perfusion.
4. Unit impulse method.
5. Micro dialysis.

- The brain uptake index (BUI), as originally described and refined by Oldendorf. The BUI employs a rapid bolus injection of radiolabeled test and reference substances into the common carotid artery of anesthetized animals (e.g., in the rat 0.2 ml in less than 0.5 s).
- After the 1- to 2-s passage time through the brain capillaries, brain uptake is measured as the single pass extraction, E, by brain tissue sampling after decapitation, which is performed within 5-15 s.
- A second reference substance is co injected, which does not penetrate the BBB, to correct for the fraction of the bolus remaining in the vascular lumen at the time of brain sampling (about 2%).
- Suitable combinations of radioisotopes must be available to allow for double or triple isotope counting of the tracers in injectate and brain tissue, respectively. The calculation of BUI (as percentage) is defined by the equation:

$$BUI = 100[(E_{test} - E_{refv})] E_{refp}$$

- where E_{test} is the brain extraction of the unknown test substance, E_{refV} is the apparent extraction of a vascular marker (non permeant reference) and E_{refP} is the extraction of the permeant reference.

IN SITU BRAIN PERFUSION.

- A major approach to measure brain penetration in whole animals has been brain perfusion method of Takasatu and colleagues, which measures the rate of entry across brain endothelium *in situ*.
- Unlike earlier methods, such as the brain uptake index, which is mostly suitable for fast BBB-penetrating compounds, the brain perfusion method can be used for both slow and fast brain-penetrating compounds.
- The method utilizes catheterization of the common carotid artery in the anesthetized rat, together with ligation of the external carotid artery.
- The brain is then perfused via the internal carotid using an oxygenated physiological saline buffer containing the test substance.
- Once perfusion is complete, the brain is removed for analysis and uptake (volume of distribution, Vd) determined according to the following equation:

$$V_d = \text{tissue concentration} / \text{perfusate concentration}$$

- With a constant concentration of the test compound during the perfusion over time, t, the rate of compound transfer (K_{in}) can be determined according to the following equation:

$$K_{in} = V_d / t$$

- *In situ* perfusion therefore provides a kinetic measure of the uptake of a compound into brain.

Micro Dialysis

- Intracerebral micro dialysis is particularly suitable for estimating extra cellular unbound drug concentration.
- The kinetics of unbound drug in blood is known Intracerebral micro dialysis can be used to characterize drug transport across BBB under various conditions.
- Intracerebral dialysis involves the implantation of a micro dialysis probe into brain.

Advantages:

It provides samples obtained from multiple time points from an individual animal.

Disadvantage:

It involves an implantation of probe which may cause tissue trauma.

DRUG	MECHANISM OF TRANSPORT	USE OF DRUG
GLUCOSE MANNOSE	HEXOSE TRANSPORT SYSTEM	SOURSE OF CARBOHYDRATE IN PARENTERAL NUTRITION
FLUOROURACIL RANIMUSTIN	PHARMACOLOGICAL OPENING OF BBB BY INHIBITION OF PGP	ANTICANCER
ROVASTATIN	MONO CARBOXYLIC ACID TRANSPORT SYSTEM	TREATMENT OF HYPER LIPIDAEMIAS
EBIRATIDE	ADSORPTIVE MEDIATED ENDOCYTOSIS	ALZHEIMERS DISEASE
ß-LACTAM ANTIBIOTICS	OLIGOPEPTIDE TRANSPORTERS[PEP T1, PEP T2]	ANTIBIOTIC
PHENYL ALANINE	NEUTRAL AMINO ACID TRANSPORT SYSTEM	DIETARY SUPPLEMENT
ASPARATE	ACIDIC AMINO ACID TRANSPORT SYSTEM	DIETARY SUPPLEMENT

Thank you