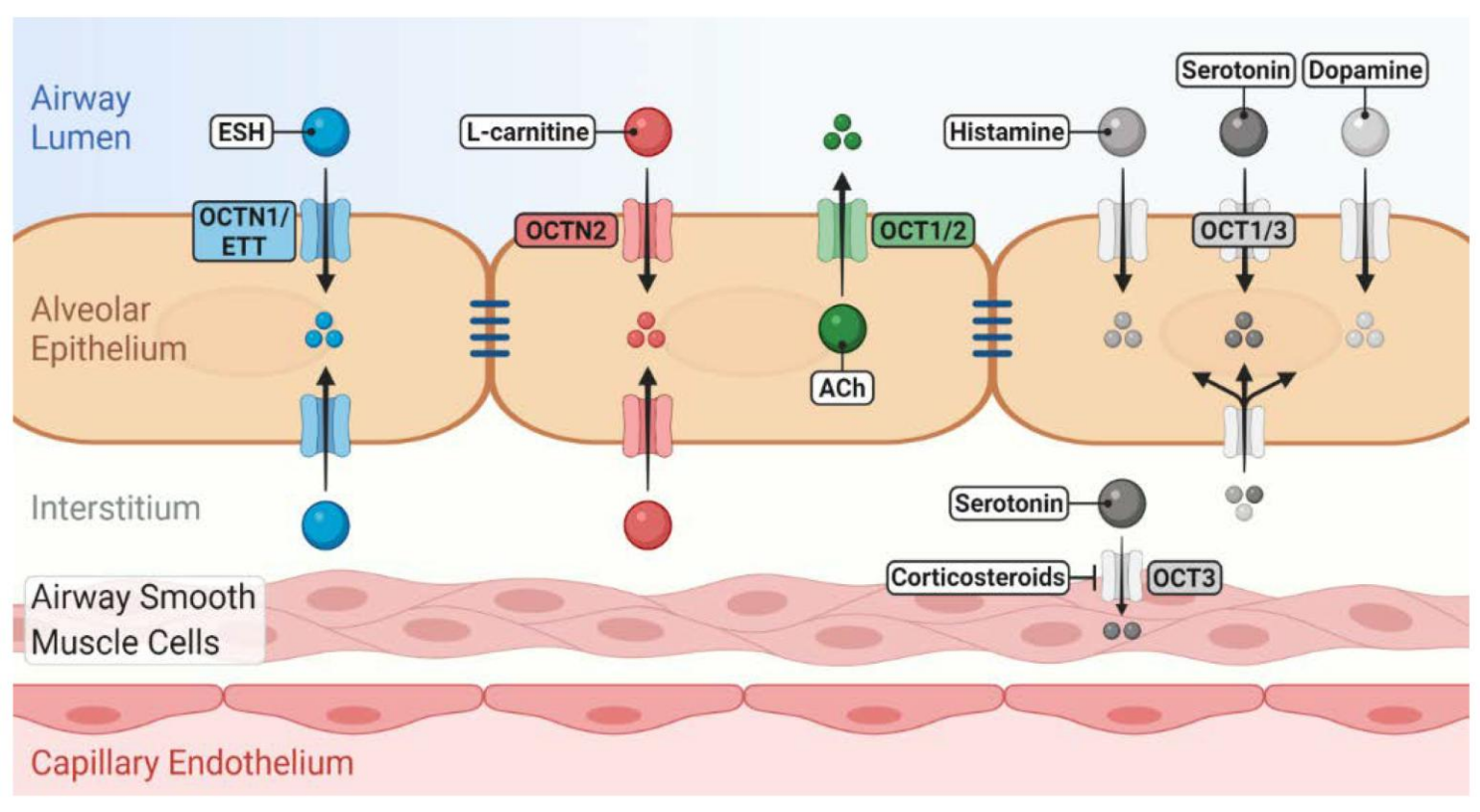
Organic cation transporters



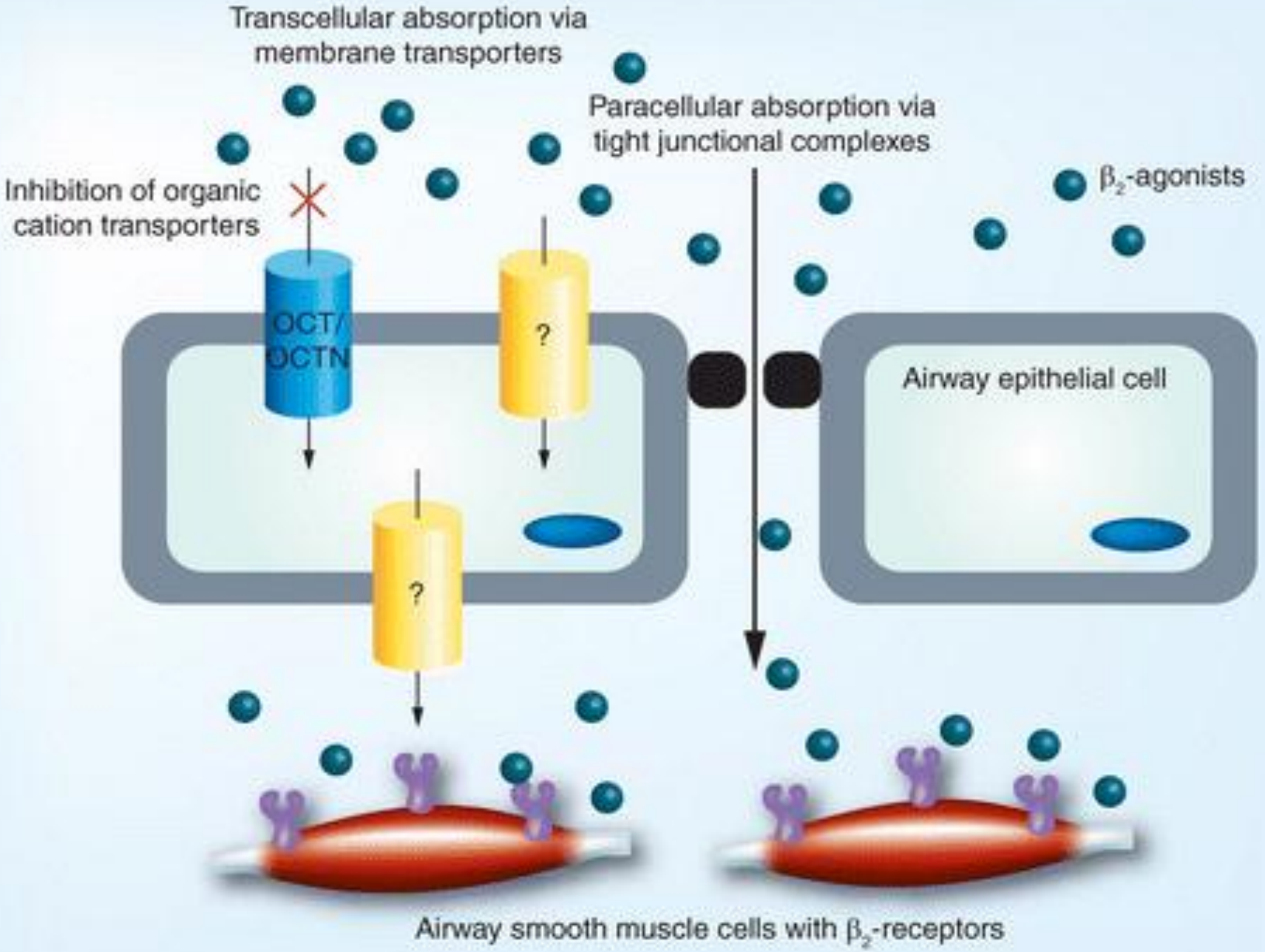
Dr. Shashi Kiran Misra
School of Pharmaceutical Sciences

1. Organic Anion Transporters (OAT, SLCO, OATP)

- Ionic agents generally exhibit low passive membrane permeability, resulting in their poor bioavailability.
- An organic anion-transporter is a membrane transport protein or 'transporter' that transports organic anions across the cell membrane.
- These are present in the lipid bilayer of the cell membrane. OATs belong to the Solute Carrier Family (SLC), more specifically the Solute Carrier Organic Anion (SLCO) gene subfamily.

2. Organic Cation Transporters (OCT, OCTN)

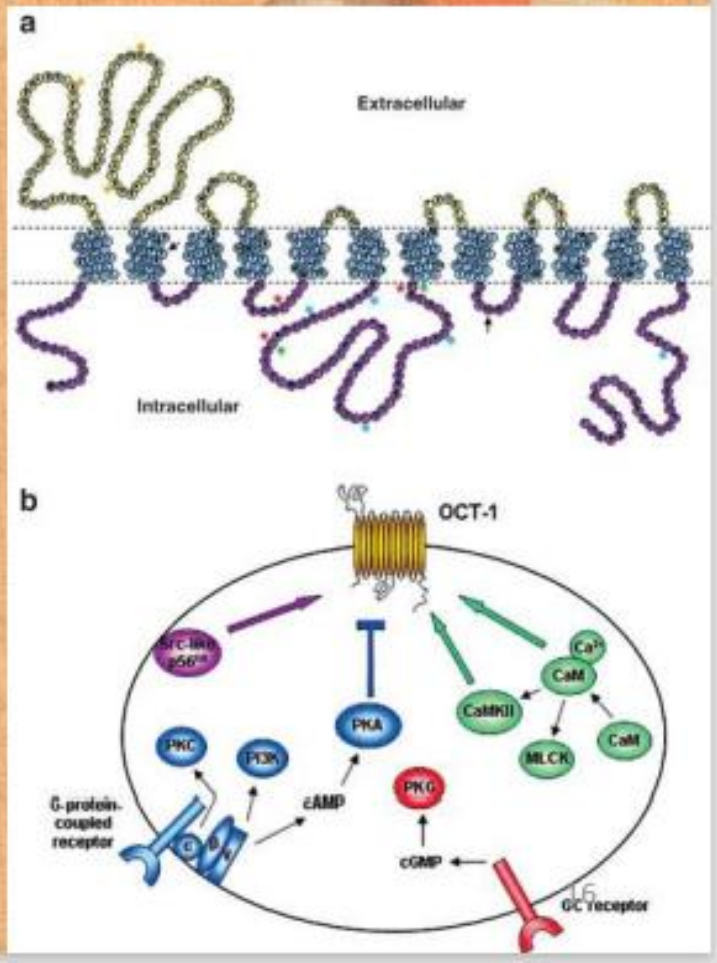
- An organic Cation transport protein mediates the transport of organic cations, zwitterions and anions across the cell membrane. These proteins are members of the solute carrier family, subfamily 22.
- Topology characteristics are similar as OATs.
- They have two distinct subfamilies i.e. OCT and OCTN both of them having multiple species.



- OCT1-3, are polyspecific transporters capable of transporting wide range of organic cations like tetraethylammonium (TEA) and *N*-methylquinine, 1-methyl-4-phenylpyridium (MPP+), antiviral, metformin monoamine neurotransmitters acetylcholine, dopamine, serotonin, histamine, choline etc.
- Physiological compounds such as creatinine, guanidine, and thiamine.
- Pharmaceuticals like desipramine, an antidepressant cimetidine, acyclovir, ganicyclovir and α Blocker Prazosin.
- Members of the OCTN subfamily have differential abilities to interact with a variety of organic cation drugs, as well as carnitine.

- OCTs translocate organic cations and compounds in an electrogenic manner (i.e. producing a change in the electrical potential of a cell).
- Na^+ ions and H^+ independent.
- Driving force is provided by substrate concentration gradient and the membrane potential.

- OCTs isoforms are mainly expressed in liver or kidney.
- To a lesser extent in heart, skeletal muscles, placenta, prostrate and small intestine.
- OSTNs were also detected in intetestinal enterocytes.

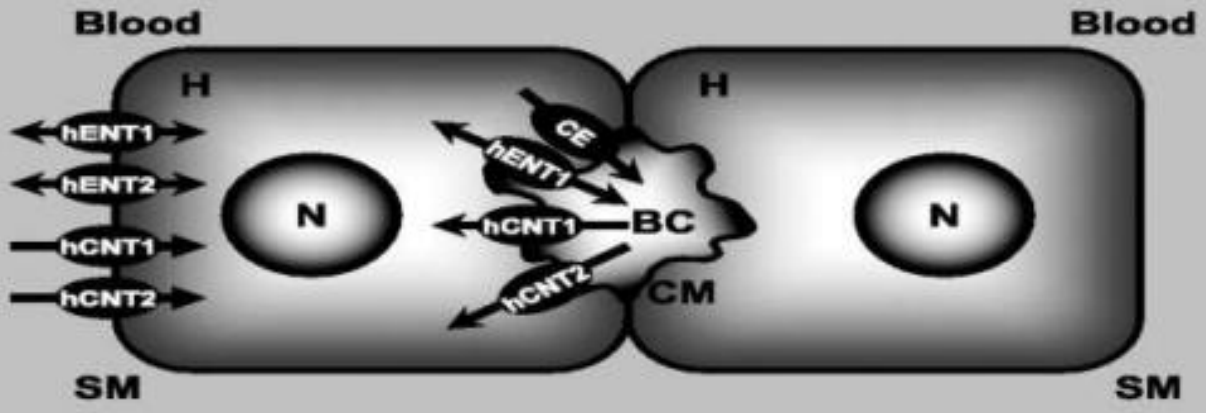


- The regulation of OCTs is associated with phosphorylation / dephosphorylation of the transporters.
- A gender dependent difference was also observed in a study in rats.
- Another study showed OCTs level gradually increase from infants to adults.

Nucleoside Transporters (CNT, ENT)

- Nucleosides are the ribosylated precursors of purine and pyrimidine nucleotides, these not only help in cellular energy and signal transduction in the form of their phosphorylated analogs (e.g., ATP and cAMP, respectively), but also have other physiological functions.
- E.g. cardiac and vascular effects, adenosine act as a neuromodulator, inhibit lipolysis in fat cells and act as an anti-inflammatory.

- The cellular transport of nucleosides is mediated by two distinct families the high affinity, concentrative nucleoside transporters (CNT; SLC28) and the low affinity, equilibrative nucleoside transporters (ENT; SLC29).
- These transporter have distinguished structural features and transport mechanisms.



Concentrative Nucleoside Transporter (CNT)

- CNT consists of three subtypes CNT1-CNT3.
- These are comprised of 13 putative TMD and exhibits several protein kinase C phosphorylation sites.
- They have wide range of substrate specificities e.g. pyrimidine nucleotides, purine adenosine, uridine and purine nucleotides.
- Pharmaceutical compounds include nucleoside analogs e.g zidovudine, lamivudine, cytidine cladrabine etc.

- CNT expression has been shown in small intestine, kideny, liver, heart, brain, placenta, pancreas, skeletal muscle, colon, rectum mammary gland, bone marrow, trachea prostrate and testis.
- CNT family is sodium dependent and works through an active symport mechanism.

Impact of Intestinal Transporters on Bioavailability

- The interplay of various transporter protein mechanisms along with transport by parallel pathways can significantly impact on the overall bioavailability of a compound.
- Drug transporters play an important role in intestinal drug absorption and secretion, and can be major determinants of oral bioavailability.
- Transporters exhibit affinity for an extraordinary range of compounds and provide great insight for advancing the field of rational drug design.

- By understanding the substrate specificity, transport mechanism, and expression profile of transporters, efficient intestinal absorption may be made feasible by strategies including appropriately modifying either the structural recognition elements of NCEs or through rational formulation design to tailor optimized drug delivery.