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**Passive Permeability: An Important Mechanism for Drug Absorption**

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How are drugs absorbed?

• By transporters only
• By passive diffusion only
• By both transporters and passive diffusion
• None of the above

* If your answer differs greatly from the choices above tell us in the chat!
Mechanisms of Drug Absorption

Passive permeability and transporter-mediated mechanisms coexist to impact drug absorption and disposition.

“Transporter-Only” Claim

- All transmembrane transport of drugs requires the use of transporters
- No passive diffusion through the bilayer occurs

“Transporter-only” claim ignores the basic scientific facts and is fundamentally flawed

- Experienced scientists in DMPK, Med Chem, Pharm Sci: minimal impact
- Can be misleading for students and less experienced scientists

Successful examples of applying the principles of passive permeability and transporter-mediated mechanisms in real-world drug discovery
Passive Permeability & Transporter-Mediated Mechanisms

**Passive Diffusion**
- Not dependent on substrate concentration, non-saturable, linear
- Not subject to inhibition / induction / drug-drug interactions
- Less structure specific: Log D, PSA, H-bonds, MW, rotatable bonds
- Less specific to tissue, cell-type, species

**Transporter**
- Dependent on substrate concentration, saturable, nonlinear
- Subject to inhibition / induction / drug-drug interactions
- More structure specific interactions between substrates and transporters
- Specific to tissue, cell-type, species


Saturable vs. Non-Saturable Mechanisms

- Transporter-mediated mechanisms are saturable at high concentrations and nonlinear with increasing concentrations
- Passive permeability is not saturable and linear with increasing concentrations
- Total (net) transport = passive + transporter

ADME Transporters in the Major Organs

- Transporters are tissue / membrane /directional specific
- P-gp/BCRP: apical membrane for most tissues
- OATP1B1/1B3: liver specific
- Expressions and activities of transporters can be species dependent
- An "universal transporter" doesn't exist

If “transporter-only”, an oral CNS drug would need specific transporters for each of the membranes in the gut, the liver and the brain. Expect high incidences of DDIs.

The Role of Passive Permeability in ADME

- Absorption
  - Oral absorption
- Distribution
  - Tissue exposure
  - Brain penetration
  - Target exposure
- Metabolism
  - Entry to hepatocytes
- Excretion
  - Hepatobiliary clearance
  - Renal clearance / reabsorption

ADME = Absorption, Distribution, Metabolism, Excretion
In Vitro Methods to Predict Human Intestine Passive Permeability

Passive permeability plays a major role in oral absorption

PAMPA = parallel artificial membrane permeability assay

Impact of Passive Permeability in Oral Absorption

High passive permeability leads high human intestinal absorption ($F_a$) when no solubility/dissolution restriction

Correlation between PAMPA and Rat Intestine Permeability

Passive permeability is insensitive to species. Enable direct translation of *in vitro* or animal data to humans with different physiology.


Cell Membrane Lipid Bilayer: Self-assembling Phospholipids

Hydrophilic polar head group

Fatty acid chains

Drug molecule

Water Molecules (polar)

Structured

Lipophilic

Structured Lipophilic phospholipid

Hydrophilic polar head group

Fatty acid chains

Drug molecule

Water Molecules (polar)
### Molecular Properties Govern Absorption by Passive Permeability

#### Oral Absorption
- Lipinski’s Rule of 5 (Ro5)
  - Poor absorption
    - HBD > 5 (OH and NH)
    - MW > 500
    - cLog P > 5
    - HBA > 10 (O and N)
- Veber’s Rules:
  - Good Bioavailability
    - Rotatable bonds < 10
    - PSA < 140 Å² or HB < 12

#### Brain Penetration
- CNS MPO > 4
  - cLogP
  - MW
  - TPSA
  - pKa
- CNS Rules
  - N+O < 5
  - ClogP-(N+O) > 0
  - PSA < 60-70
  - MW < 450
  - Log D 1-3
- Pardridge’s Rules
  - HB < 8-10
  - MW < 400-500
  - Non-acids

---


---

### Effect of PSA on Oral Absorption

![Graph showing effect of PSA on oral absorption](image)

**High fraction absorbed with low PSA (Polar Surface Area)**

**Size Penalty on Passive Permeability in bRO5 Space**

- Macrocyclic per-N-methylated peptides (no IMHB). AlogP 0-8, MW 800-1200
- Steep drop off of passive permeability with increasing size

C. R. Pye, et al., JMC, 2017, 60, 1665-1672

**Impact of Molecular Properties on Oral Absorption**

Compounds with high MW, rotatable bonds and PSA are rare as oral drugs

Cyclic Peptides to Increase Passive Permeability

- **Peptides:** poor membrane permeability, instability, injectables
  - H-bonds, charges, polar, low Log D
- **Cyclic peptide:** improved membrane permeability & stability, oral (CsA)
  - no charged termini, intramolecular H-bonds
  - Cyclosporin A: 4 intramolecular H-bonds, lipophilic side chains shield polarity, MW 1202, F 28%

![Cyclic Peptide Diagram]


---

**Audience Survey Question**

**ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT**

What are some effective strategies to INCREASE Passive Permeability? (select all that apply)

- Introduce intra-molecular hydrogen bonds
- Reduce polarity
- Reduce molecular weight
- Add carboxylic acid for brain penetration
- Reduce rotatable bonds

* If your answer differs greatly from the choices above tell us in the chat!
Strategies to Increase Passive Permeability

- Optimize lipophilicity
- Reduce hydrogen bonds
  - Introduce intra-molecular hydrogen bonds
- Reduce polarity
- Reduce molecular weight
- Reduce rotatable bonds
- Remove carboxylic acid for brain penetration
- Prodrug approach

HCV: Orally Bioavailable Cyclophilin Inhibitor Derived from the Sanglifehrin Macrocycle

R. M. Mackman, et al., JMC, 2018, 61, 9473-9399
Introduce Intramolecular Hydrogen Bonds to Increase Passive Permeability

Caco-2 $P_{\text{app}} = 2.2 \times 10^{-6}$ cm/s

Caco-2 $P_{\text{app}} = 17 \times 10^{-6}$ cm/s

R. M. Mackman, et al., JMC, 2018, 61, 9473-9399

Saturation of Transporters in the Intestine: Nonlinear PK

- Bosutinib: orally available TKI for leukemia, CYP3A & P-gp substrate
- Low doses (50-200 mg): super-proportional oral exposure - saturation of intestinal P-gp efflux
- High doses (200-600 mg): dose-proportional linear PK - passive absorption
- PBPK (SIMCYP-ADAM) modeling incorporates passive permeability, CYP3A metabolism and P-gp intestine efflux nicely captures PK and DDI
- If "transporter-only", expect to have much high frequencies of nonlinear PK – not reality

Passive Permeability in Brain Penetration

- Blood-brain barrier at the microvascular endothelial cells is a dynamic barrier made up of tight junctions, efflux transporters and drug metabolizing enzymes
- Most small molecule drugs cross the BBB by passive diffusion

Passive Permeability Through Blood Brain Barrier

- In silico
- In vitro (e.g., PAMPA-BBB)
- Combo (in silico + in vitro)

PBPK Model: Passive Permeability and Efflux

Passive Permeability Limited

\[ K_{puu} \approx 1 \]
Slow in
Slow out

Efflux Limited Brain Exposure

\[ K_{puu} < 1 \]
Fast in
Fast Out
~Steady-State

For two transporters, P-gp and BCRP

Models have been widely applied in drug discovery programs to identify successful CNS drug candidates

Passive Permeability in Hepatobiliary Clearance

Extended Clearance

\[ CL = (CL_{\text{met}} + CL_{\text{bile}}) \times \frac{(CL_{\text{pass}} + CL_{\text{uptake}})}{(CL_{\text{pass}} + CL_{\text{met}} + CL_{\text{bile}})} \]

Impact of Passive Permeability, Ionization and MW on Major Clearance Pathways - ECCS

Passive permeability plays an important role in defining major clearance mechanisms

M. Varma, et al, Pharm Res, 2015, 32, 3785-3802
Effects of Passive Permeability on Clearance and PK

Log $D_{7.4} = 1.8$
Hepatic clearance
Capacity-limited nonlinear PK

Log $D_{7.4} = 0.5$
Renal clearance of unchanged drug
Linear PK


Effects of Passive Permeability on Clearance Mechanisms

Renal Clearance
Metabolic Clearance

Smith et al., (1985) Drug Metabolism Reviews, 16, p365

chromone-2-carboxylic acid
PBPK Modeling of Enzyme- and Transporter-Mediated Clearance and Drug-Drug Interactions for Bosentan

Successfully model bosentan nonlinear PK, liver concentration and DDI


Renal Clearance

\[ \text{CL}_r = \text{GFR} \times f_{\text{ub}} + \text{CL}_{\text{sec}} - \text{CL}_{\text{reabs}} \]

Reabsorption: \( \text{CL}_r < \text{GFR} \times f_{\text{ub}} \)
Passive Permeability in Renal Clearance / Reabsorption

\[ \beta\text{-Blocker: Van de Waterbeemd et al., (2001)} \text{ J. Med. Chem, 44, p1313} \]

Passive Permeability in Renal Clearance

\[ \text{Prediction of renal clearance} \]
\[ \text{Prediction of crystal nephropathy} \]


Zhenhong Li, et al., Seminars in Nephrology, 2019, 39(2), 176-189
Zhenhong Li, et al., JMC, 2020, online

DDI between Cerivastatin and Gemfibrozil

- Cerivastatin (Baycol): approved 1997, withdrawn 2001, muscle weakness, 51 death, ~40% co-administrated with gemfibrozil (another cholesterol lowering drug)
- Cerivastatin: CYP2C8 and OATP1B substrate
- Gemfibrozil and glucuronide metabolite: potent CYP2C8 and OATP1B inhibitors

Inhibition / induction of enzymes and transporters can lead to DDI

Enzyme-transporter interplay can lead to increased magnitude of DDI

DDI Due to Enzyme and Transporter Inhibition

Extended Clearance

\[ CL = \frac{(CL_{\text{met}} + CL_{\text{bile}}) 	imes (CL_{\text{pass}} + CL_{\text{uptake}})}{(CL_{\text{pass}} + CL_{\text{met}} + CL_{\text{bile}})} \]

With Inhibitor

\[ CL_{\text{inh}} = \left( \frac{CL_{\text{met}}}{R_1} + \frac{CL_{\text{bile}}}{R_2} \right) \times \frac{(CL_{\text{pass}} + \frac{CL_{\text{uptake}}}{R_3})}{(CL_{\text{pass}} + \frac{CL_{\text{met}}}{R_1} + \frac{CL_{\text{bile}}}{R_2})} \]

Reversible inhibition in liver only

\[ R = 1 + \frac{[I]}{K_i} \]

[I] inhibitor concentration

\[ K_i \] inhibition constant
2018 was a record year for new drugs approved by the FDA with 59 total, how many of these were New Chemical Entries?

- About a quarter
- About half
- About three quarters
- All of them
- None of them

* If your answer differs greatly from the choices above tell us in the chat!

DDI of 2018 FDA Approved Drugs

- 42 New Chemical Entries (small molecules) approved in 2018 (59 total; 71%)
- 22 (52%) have label recommendations based on DDI evaluations
- CYP3A involved in the majority (72%) of all interactions
- Only three drug interactions with label recommendations were mediated mainly by transporters
- If “transporter-only” and no passive permeability, one would expect much higher incidences of transporter-mediated DDIs

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Precipitant</th>
<th>AUCR</th>
<th>Transporter</th>
<th>Label Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>elegolix</td>
<td>rifampin</td>
<td>5.58</td>
<td>OATP1B1</td>
<td>Contraindicated with strong OATP1B1 inhibitors.</td>
</tr>
<tr>
<td>baricitinib</td>
<td>probenecid</td>
<td>2.03</td>
<td>OAT3</td>
<td>Not recommended with strong OAT3 inhibitors.</td>
</tr>
<tr>
<td>talazoparib</td>
<td>P-gp inhibitors(^1)</td>
<td>1.45 (popPK)</td>
<td>P-gp</td>
<td>Reduce the dose of talazoparib with any of these P-gp inhibitors.</td>
</tr>
</tbody>
</table>

J. Yu, et al., 2019 ISSX poster
Conclusions

- Passive permeability: an important mechanism for drug absorption and disposition
  - Oral absorption
  - Brain penetration
  - Renal reabsorption
  - Defining major clearance pathways
  - Enzyme / transporter interplay – extended clearance, DDI

- “Transporter-only” claim is fundamentally flawed and misleading

- Passive permeability and transporters coexist to impact drug absorption and disposition

- Many successful drugs have been developed by using the design principles of passive permeability and transporters

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- Dennis Scott
- Dennis Smith (retired)
- David Tess
- Matt Troutman
- Susanna Tse
- Manthena Varma
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