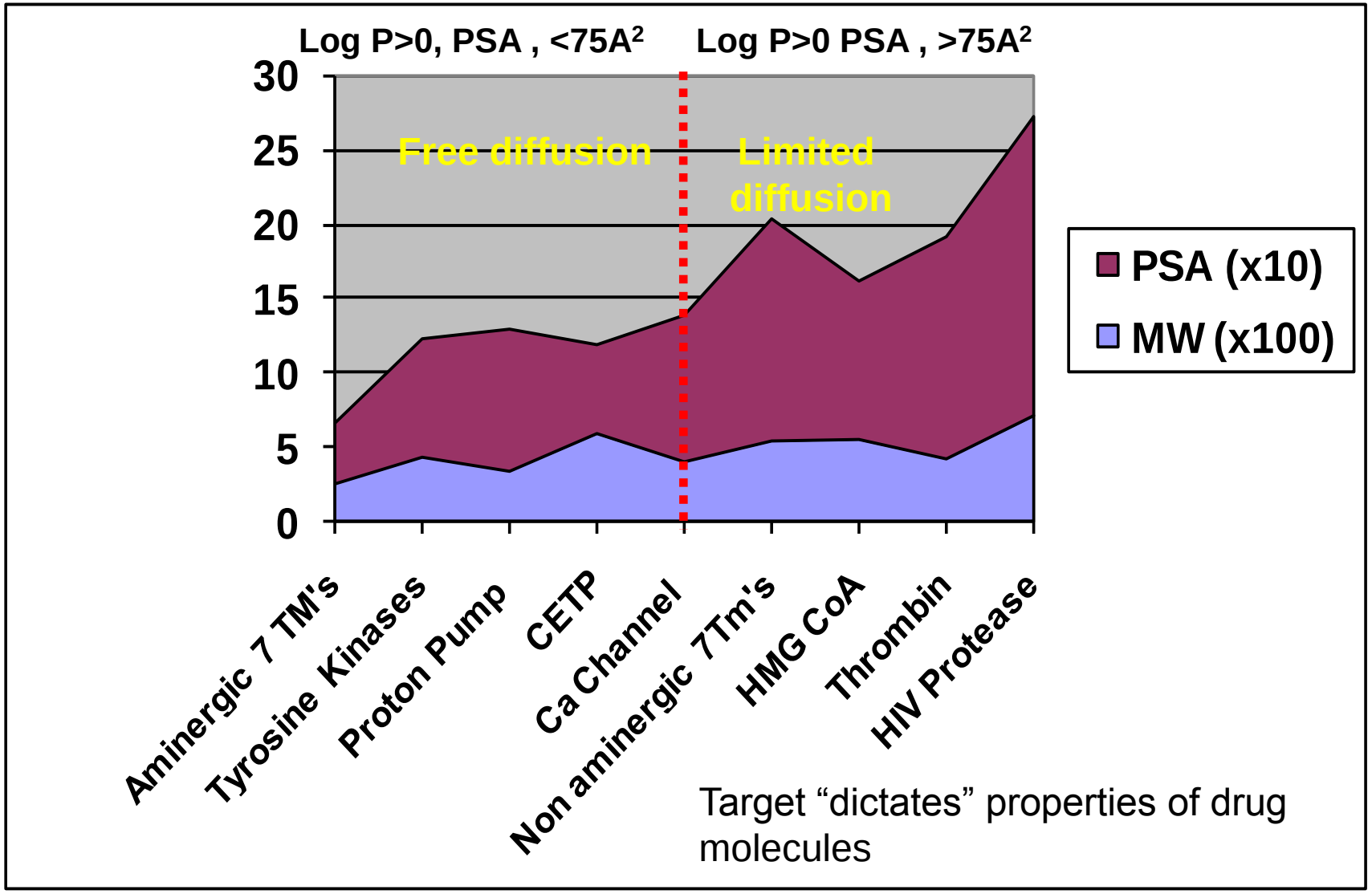
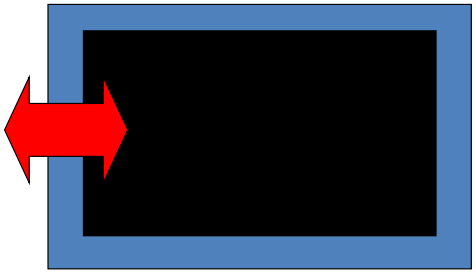
Lipoidal permeability central to drug ADME

Major barriers to drug discovery: dogma surrounding plasma protein binding and tissue concentration

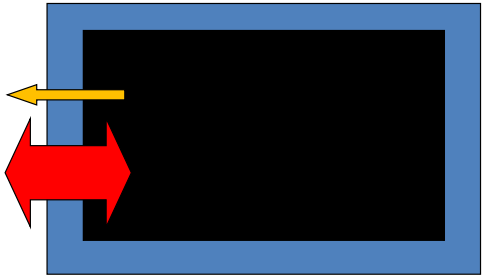
Lipoidal permeability of typical antagonists / inhibitors



Drugs move across membranes by lipoidal diffusion as a common mechanism



Transport v. passive diffusion
High lipoidal permeability: small impact of transporter



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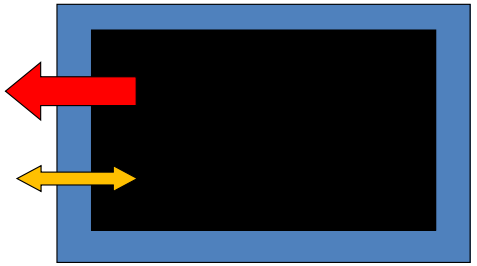
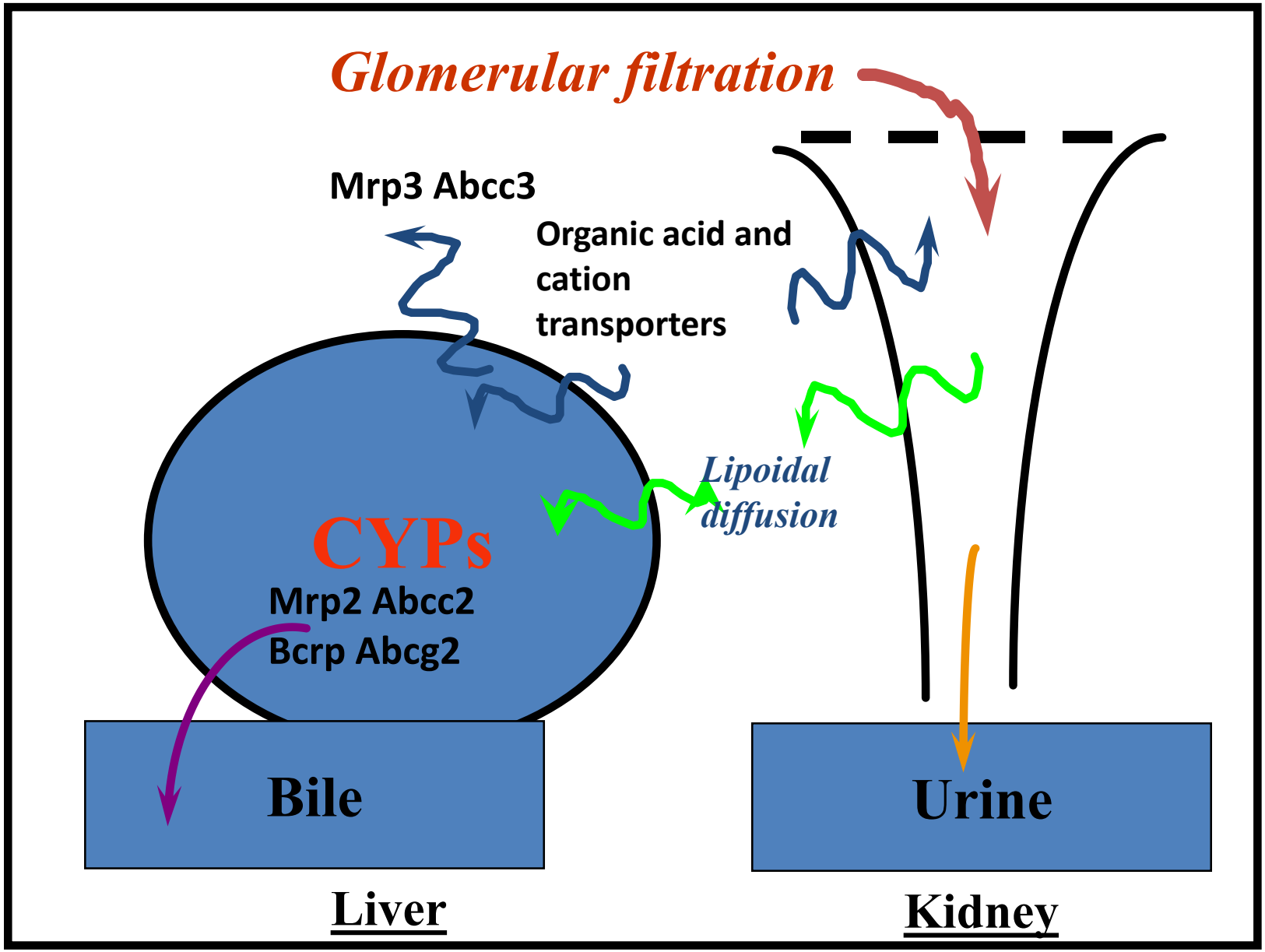



Glomerular filtration
Mrp3 Abcc3
Organic acid and cation transporters
Lipoidal diffusion
CYPs
Mrp2 Abcc2
Bcrp Abcg2
Bile
Urine
Liver
Kidney

Lipoidal Permeability: pivotal to ADME fate

Permeability	Low	Medium	High
PSA/LogP	**High (low log D or P)**	**Medium (PSA>75A^2)**	**Low PSA<75A^2)**
Absorption	**Low (*aliskeran*) unless MWt less than 250 daltons and absorbed by paracellular route *(atenolol)***	**Variable. Influenced by permeability and transporters *(nelfinavir)***	**High via transcellular route *(propranolol*)**
Bioavailability	**As for absorption**	**As for absorption and metabolism**	**Variable. Influenced by metabolism**
Clearance	**Renal or Biliary (possible transporter involvement)**	**Transporters and metabolism**	**Metabolism**

AQUEOUS CONCENTRATIONS AND TARGET ACCESS ?

Example drugs, which are all lipid permeable, have identical TBW and unbound plasma concentrations: total access to all drug targets

	Drug	pKa	Log D	PSA	fu	Vd L/Kg	Vd(u) L/kg
Vd <TBW Due to albumin binding in plasma and extravascular fluid	Indomethacin	3.9 acid	0.7	68.5	0.004	0.29	72
	Ketoprofen	4.2 acid	0.2	54.4	0.008	0.15	19
Vd =TBW Due to low binding	Fluconazole	-	0.5	71.8	0.87	0.7	0.8
	Diazepam	-	2.8	32.7	0.013	1.1	84
Vd > TBW Due to phospholipid binding in tissues	Fluoxetine	10.5 basic	1.4	21.3	0.06	35	583

Sampling for these drugs has included CSF, synovial fluid, vaginal fluid and saliva apart from plasma. In addition PET scanning is available on related molecules. The unbound concentrations which interact with proteins and trigger pharmacodynamic effects are identical unbound drug concentrations in the circulation.

Unbound plasma concentrations are not determined by plasma protein binding.

- **AUCu = Fabs . Fgut . Dose / Clint**
- **Cav(u)= Fabs . Fgut . (Dose / Clint) / T**

Fu does not determine AUCu or Cav(u)

- AUCu or Cav(u) determined by :

Fraction absorbed

Fraction escaping gut metabolism

Dose

Intrinsic clearance

Blood Assay or in vitro assay with protein. Why protein binding alters *in vitro* potency but is irrelevant *in vivo*.

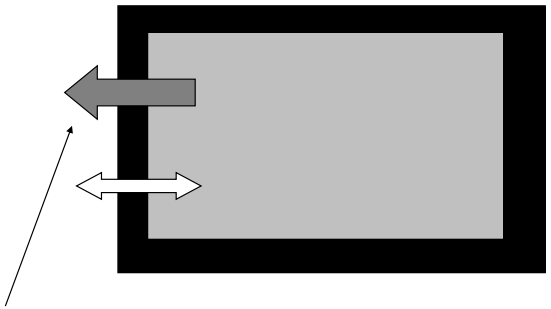
Intrinsic Potency (nM)	fu	Blood assay potency (nM)
1	0.1	10
1	1	1

In vivo

fu	Vd (L/kg)	Cp(total) nM	Cp (free) nM	Cl (total) ml/min/kg	Cl (free) ml/min/kg	T1/2 (hours)
0.1	1	10	1	1	10	11.5
1	10	1	1	10	10	11.5

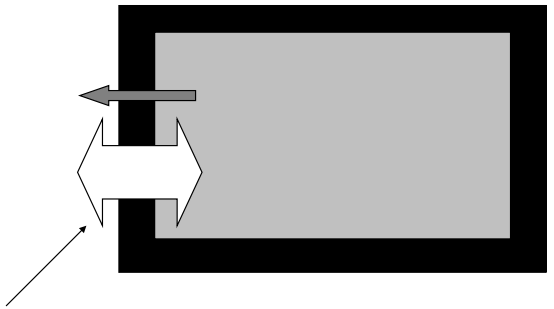
Certain conditions can accumulate free concentrations of drugs

Transport v. passive diffusion
Low permeability: large impact of transporter
Log D > 0 and PSA > $75A^2$



Transporter rate exceeds intrinsic permeability

Transport v. passive diffusion
High permeability: small impact of transporter
Log D > 0 and PSA < $75A^2$



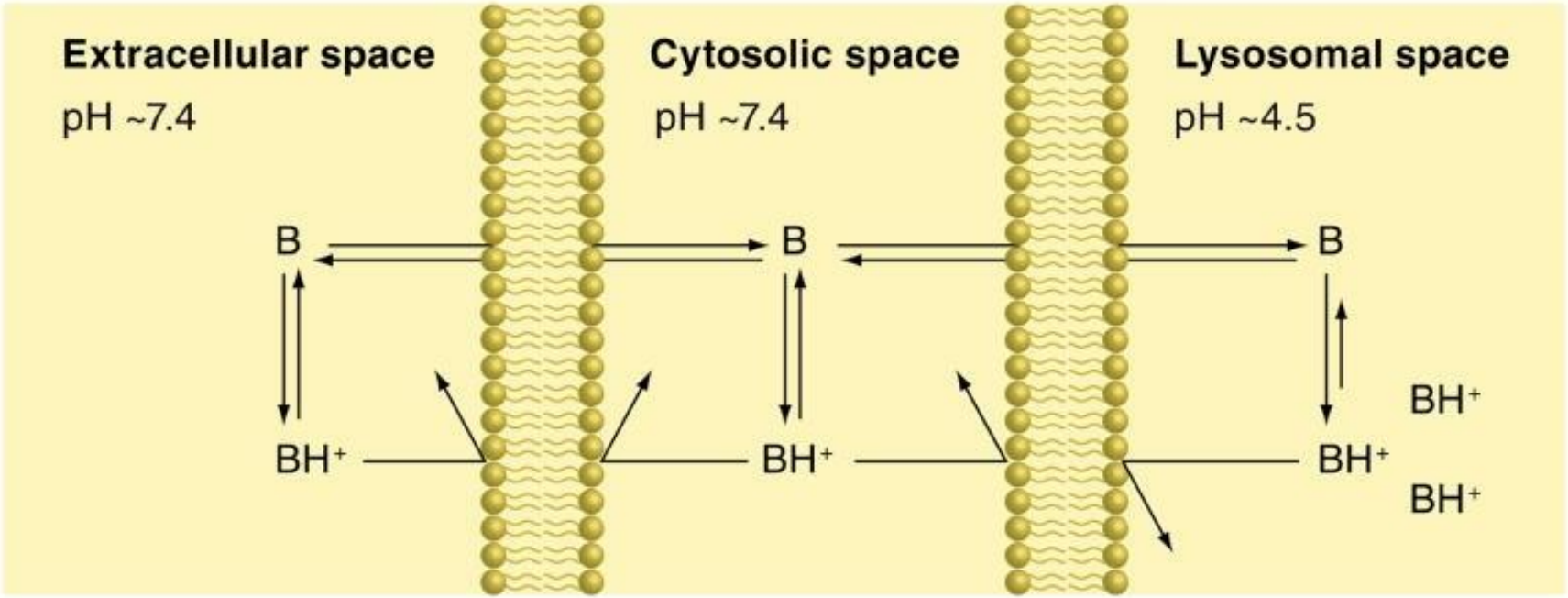
Intrinsic permeability exceeds transporter rate

Anionic transport into hepatocytes (Paine, et al., 2008).

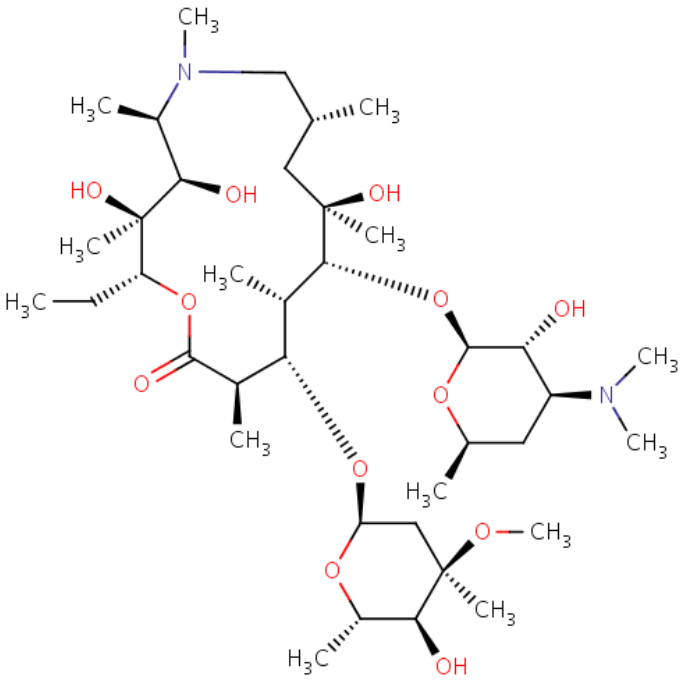
	Log P	pKa	PSA	HBD	Relative rate of transport	Accumulation ratio
Indomethacin	4.3	4.5	68	1	+++	3
Atorvastatin	5.7	4.33	115	3	++	18
Cerivastatin	4.1	4.05	100	3	++	8

Lysosomes

- Internal pH of around 5 (cf 7.4) to allow acidic hydrolases to act.
- For a monobasic compound with pKa above 6 log D lowered 2 units between cytosol and lysosome. For a dibasic compound lowered 4 units.



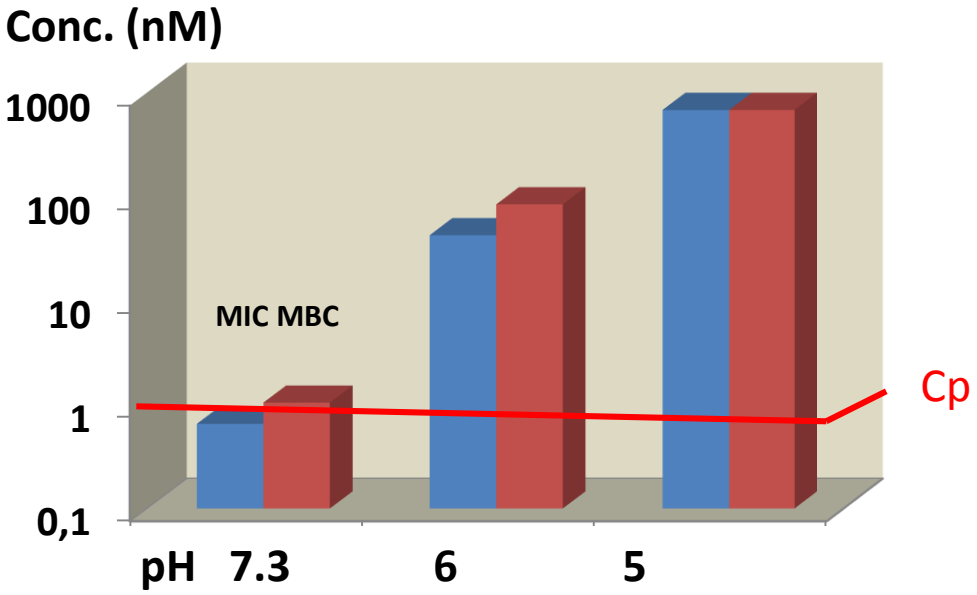
Azithromycin



Lemaire et al. Antimicobial Agents and Chemotherapy, 47, 2283, 2003

Accumulation into macrophages (lysosome rich cells) 40 – 50 fold

But active drug may not be the protonated form! Azithromycin MICs , MBCs much higher at low pHs



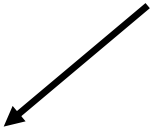
Key Points

- High lipoidal permeability drugs have identical unbound concentration in TBW.
- Apparent accumulation is membrane binding in tissues.
- PPB not important *in vivo.*
- Less lipoidal permeable drugs can be excluded (brain) or accumulated (liver) in certain tissues
- Lyosomal accumulation may not be active drug.

Pharmacokinetics and oral drugs

Benet, L. Z. & Hoener, B.-A. Clin. Pharmacol. Ther. 71, 115-121 (2002).

- **Cl= Q . fu .Clint / Q + fu . Clint (well stirred model)**
- **AUC = F . Dose / Cl**



- **Foral = Fabs . Fgut . Fhep**
- **Fhep = Q / Q + fu . Clint**

- **AUC = Fabs . Fgut . (Q / Q + fu . Clint) . Dose / Q . Fu .Clint / Q + fu . Clint**

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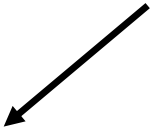

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Fraction unbound moved from left to right

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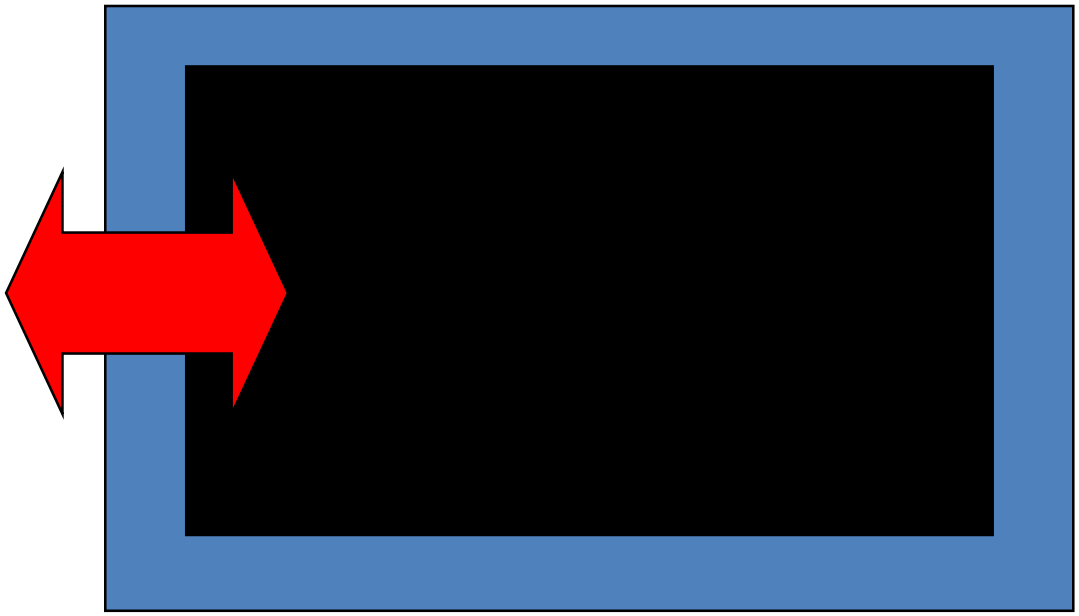

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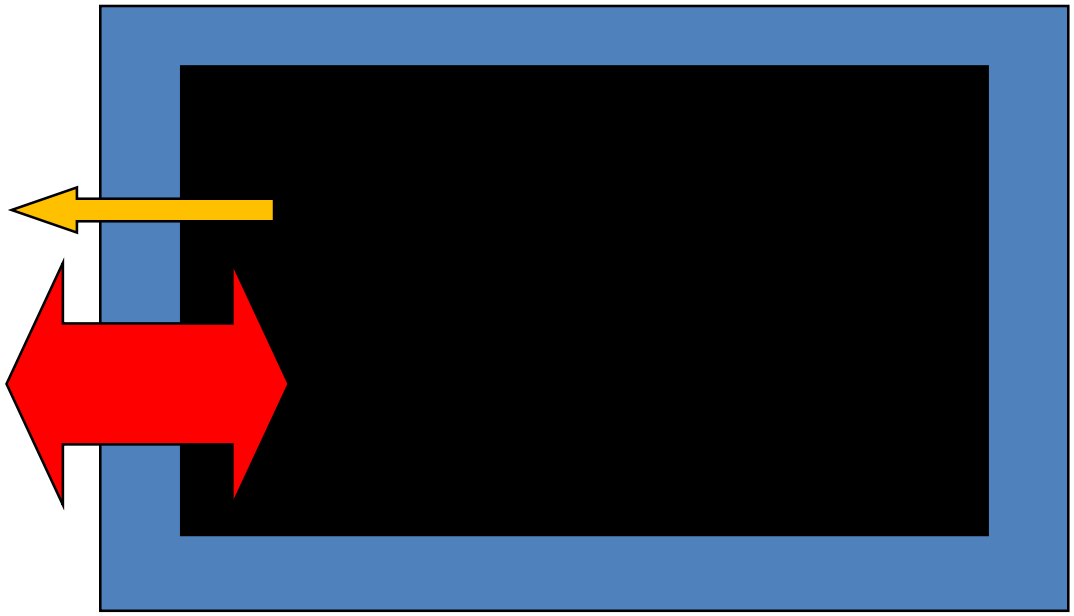

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