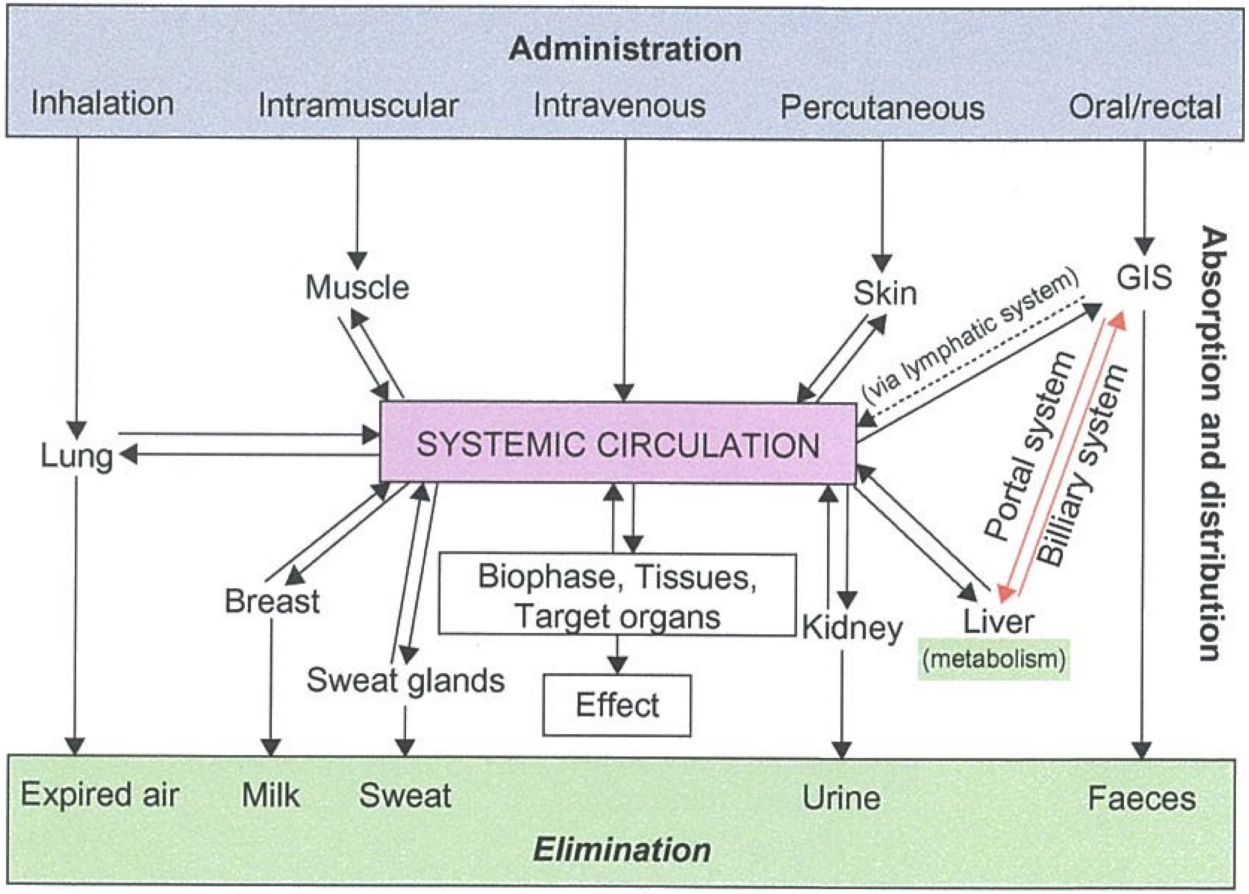
Medicinal Chemistry: An Overview

Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/04/07	Strategies for Discovering Lead Compounds
7	2016/04/17	Structure-Activity Relationships
8	2016/04/25	Spatial Organization, Receptor Mapping, and Molecular Modeling
9	2016/05/02	Pharmacokinetic Properties
10	2016/05/09	Legal and Economic Aspects of Drug Development

Pharmacokinetics

Pharmacokinetics involves studying the concentrations of a drug in different parts of the organism as a function of time. The drug concentrations are determined by the administered dose, the rate and extent of absorption, distribution, and elimination.



Passage of Drugs Through Biological Barriers

The passage of a drug through the body may involve traveling through the cells (transcellular drug transport) or through intercellular gaps (paracellular drug transport)

Transcellular drug transport

A drug has to traverse the cell membrane for it to get to its intracellular target. The main mechanisms by which a drug passes through the cell membrane are;

passive diffusion: movement of molecules from a region of higher concentration to a region of lower concentration. Lipid molecules can easily penetrate the cell membrane.

carrier-mediated processes: transmembrane protein mediated processes operating either passively or actively. Influx and efflux transporters.

vesicular transport: formation of a cavity around a particle (large proteins) to give a vesicle or vacuole, which is used for endocytosis, exocytosis or transcytosis.

Paracellular drug transport

Passage of drugs through cell junctions initiated by passive diffusion or filtration caused by hydrostatic pressure gradient across the cell layer. There is a wide variation between different barriers to drug transport. For instance, the endothelium of glomerular capillaries is abundant in intercellular pores while the endothelial cells of brain capillaries are impervious.

Drug Administration Routes

Parenteral routes

intravenous bolus (i.v.): direct injection into circulatory system resulting in total and immediate bioavailability.

intravenous infusion (i.v.): slow and constant rate injection thus accurate controlling plasma drug levels.

intramuscular injection (IM): easier than i.v. injection but rates of absorption depends on muscle group.

subcutaneous injection (s.c.): relatively slow absorption which depend on local blood flow.

Enteral routes

buccal or sublingual (SL) drug delivery: no first-pass effects, but only useful for small lipophilic molecules.

oral drug delivery: safest and easiest route drug administration.

rectal drug delivery: variable absorption from suppository but reliable absorption from enema (solution).

Other routes

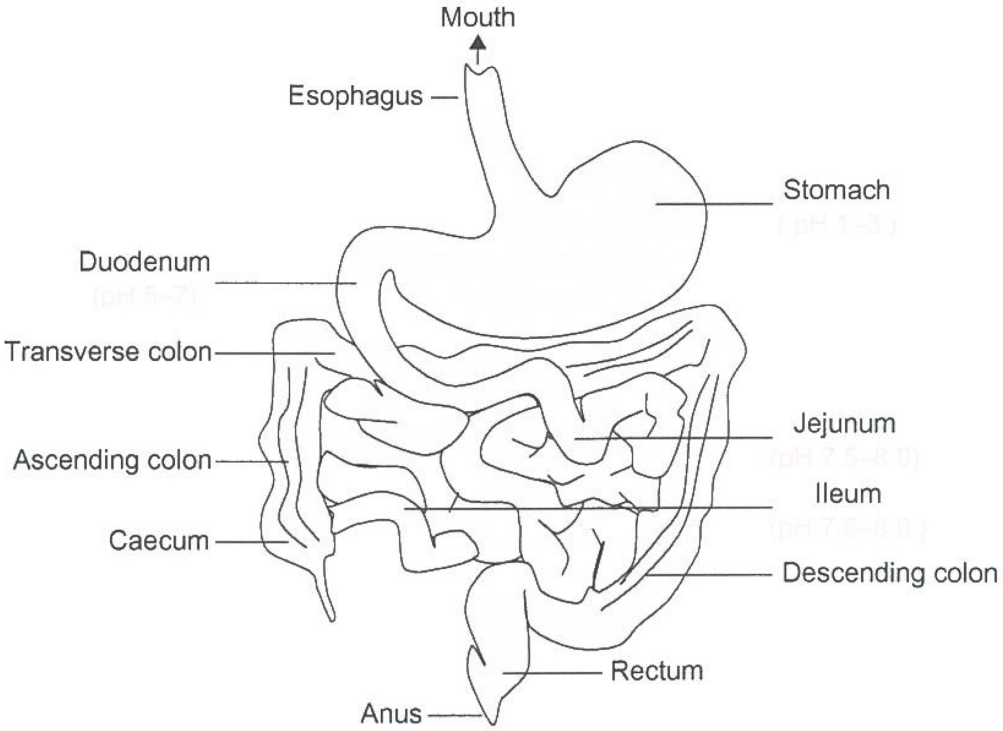
transdermal/percutaneous drug delivery: liver first-pass metabolism is avoided, and easy use (e.g., patches).

intranasal drug delivery: good for the delivery of peptides.

pulmonary drug delivery: mainly used for local effects.

Drug Absorption (Oral Route)

Drug adsorption refers to the passage of drug from its administered site to the circulatory system.



Factors controlling the rate and extent of absorption after oral administration include:

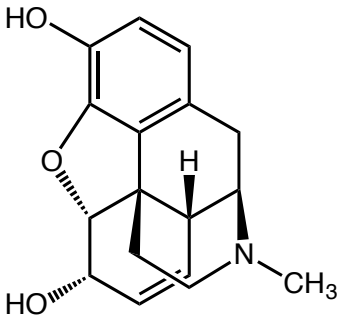
1) drug dosage form
2) GI (gastrointestinal) motility and gastric emptying
3) GI permeability to the drug
4) perfusion of the GI tract
5) the first pass effect

Drug Distribution

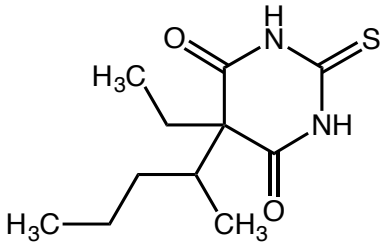
The transportation of drug molecules to their site of action and to other tissues that cause side effects is performed by the blood plasma. The rate and degree of distribution in cells depend on:

1) Plasma binding proteins such as albumin (bind to acidic drugs), α_1-acid glycoprotein (bind to basic drugs), and lipoproteins, immunoglobulins, and erythrocytes.

2) Drug accumulation due to high affinity for a specific tissue. For example, molecules with high fat/water partition coefficients accumulate in body fat. However, most drugs have low fat/water partition coefficients.



Morphine



Thiopentone

	Morphine	Thiopentone
fat/water partition coefficient	0.4	10

Low blood supply to body fat also limits accumulation of drugs in body fat.

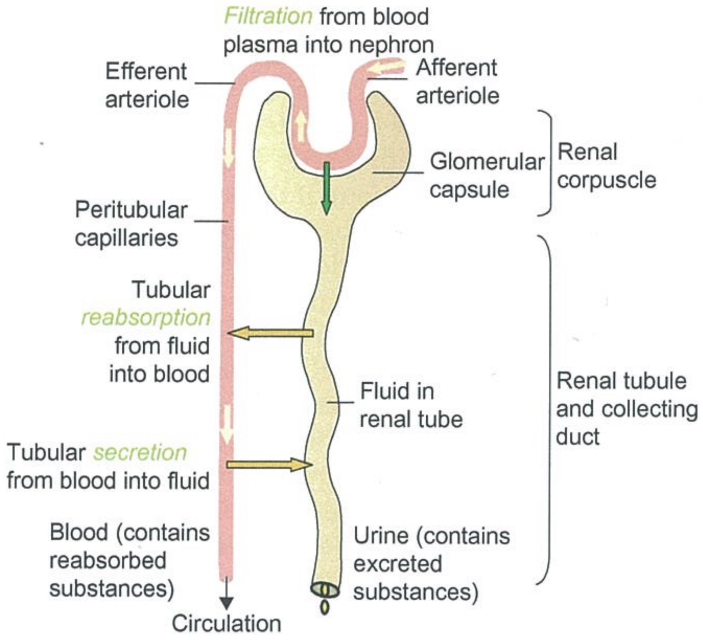
3) The blood–brain barrier limits the delivery of drugs to the brain. The barrier is made up of brain capillary endothelial cells that are sealed together by tight junctions surrounded by a large amount of astrocytes.

Drug Elimination

This is the irreversible removal of drugs from the body by excretion and biotransformation.

Excretion

1) Renal excretion: includes glomerular filtration, tubular reabsorption, and active tubular secretion, all performed by the kidneys, where 20% of the total body blood flow goes.



2) Biliary excretion by the liver may contain polar drugs

Biotransformation: This occurs in two phases. Phase I involves oxidation, reduction or hydrolysis of the parent drug by cytochrome P450 enzymes located in the endoplasmic reticulum of tissues. The phase I products may be more toxic than the parent drug. Phase II entails conjugation of the reactive group in the parent molecule or those in the product of phase I, in the cytoplasm. Phase II products are usually pharmacologically inactive.

Pharmacokinetic Variations

1) Genetic factors: genetic polymorphism affects ADME.

2) Age: renal excretion is less efficient in neonates and elderly people. For example, rate of glomerular filtration in the newborn is about 20% of the rate in adults.

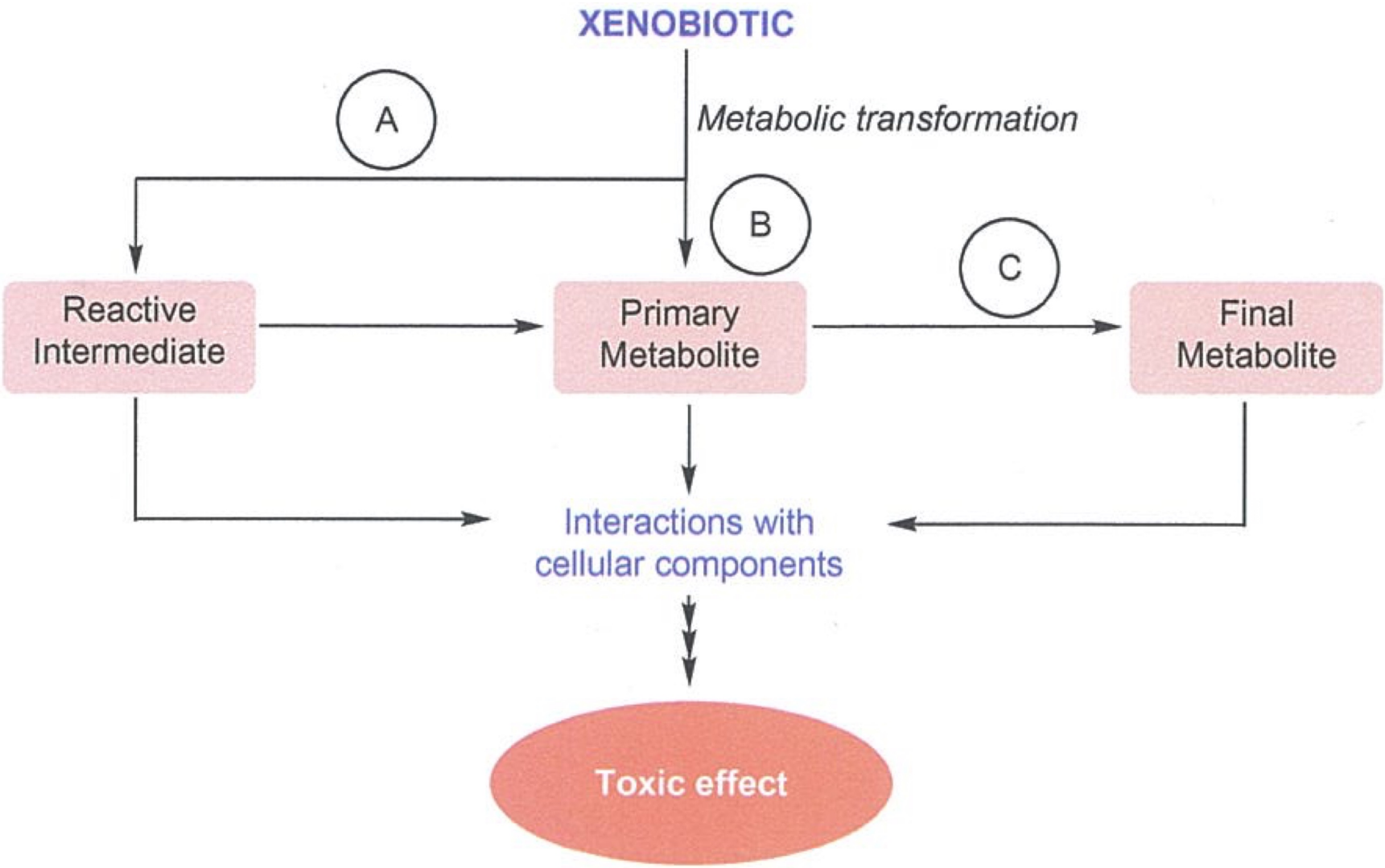
3) Drug Interactions: GI absorption of drugs is affected by drugs that affect GI motility. Drugs that lower blood flow can reduce absorption.

4) Disease state: inefficient functioning of the liver or kidneys leads to toxicity. Hypothermia significantly reduces the clearance of drugs.

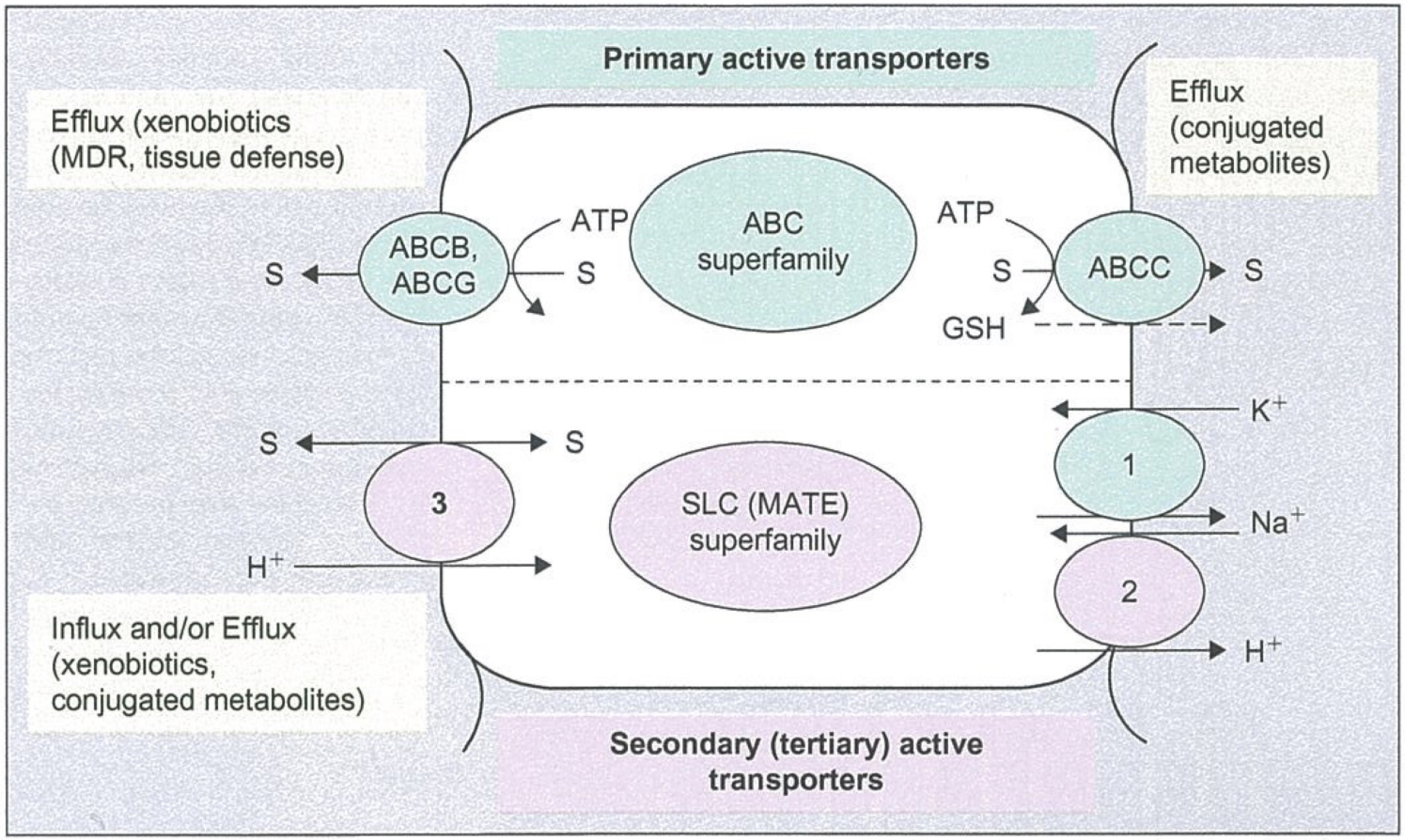
5) Pregnancy: increased glomerular filtration leads to increased renal elimination of drugs.

Drug Toxicity

Drug toxicity is the result of the harmful actions of chemicals on a living organism.



Active Transport

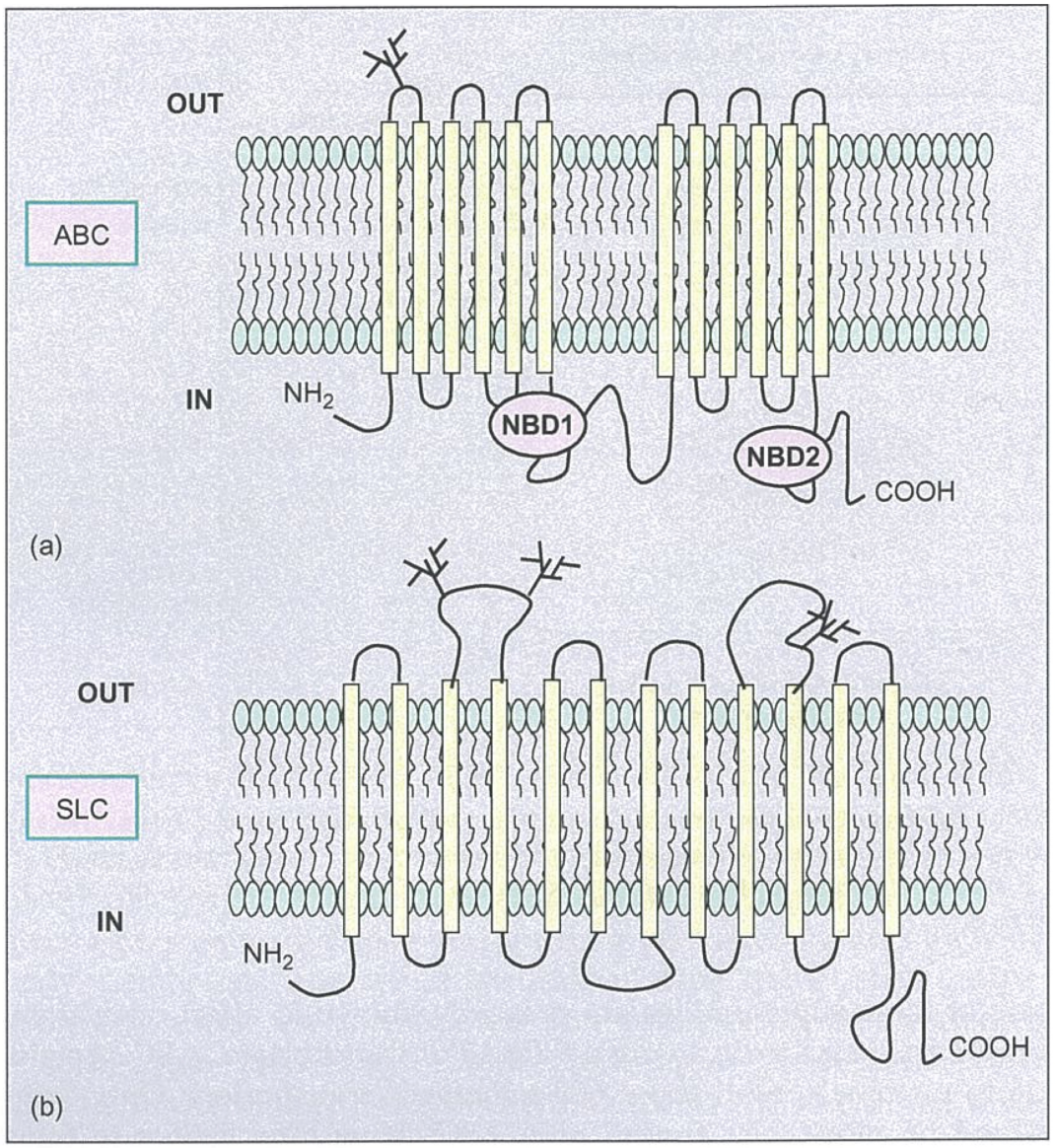


Modes of active transport

Primary active transporters: only need ATP hydrolysis by ion pumps (ATPases) or GSH co-transport for substrate (S) transport.

Secondary (tertiary) active transporters: require a voltage and/or ion gradient to transport both solutes and ions. Can be classified as uniporters, symporters, and antiporters.

Basic Structure of the Active Drug Transporters



- Usually have twelve α-helical structured transmembrane domains (TMDs) linked by amino acid sequences
- The external loop amino acids are usually *N*-glycosylated while the internal loop amino acids are phosphorylated.
- ABC transporters have between 1200–1,500 residues and a mass of 140–190 kDa while the SLC and MATE transporters have 300–800 residues and a mass of 40–90 kDa

Distribution and Properties of Transporters in Tissues

1) All the plasma membranes of the different types of human tissues and their organelles all have transporters.

2) The apical and basolateral membranes of plasm membranes have different populations of transporters.

3) Efflux and influx transporters regulate the quantities of xenobiotic reaching the enzyme's binding sites or the rate at which metabolites are eliminated.

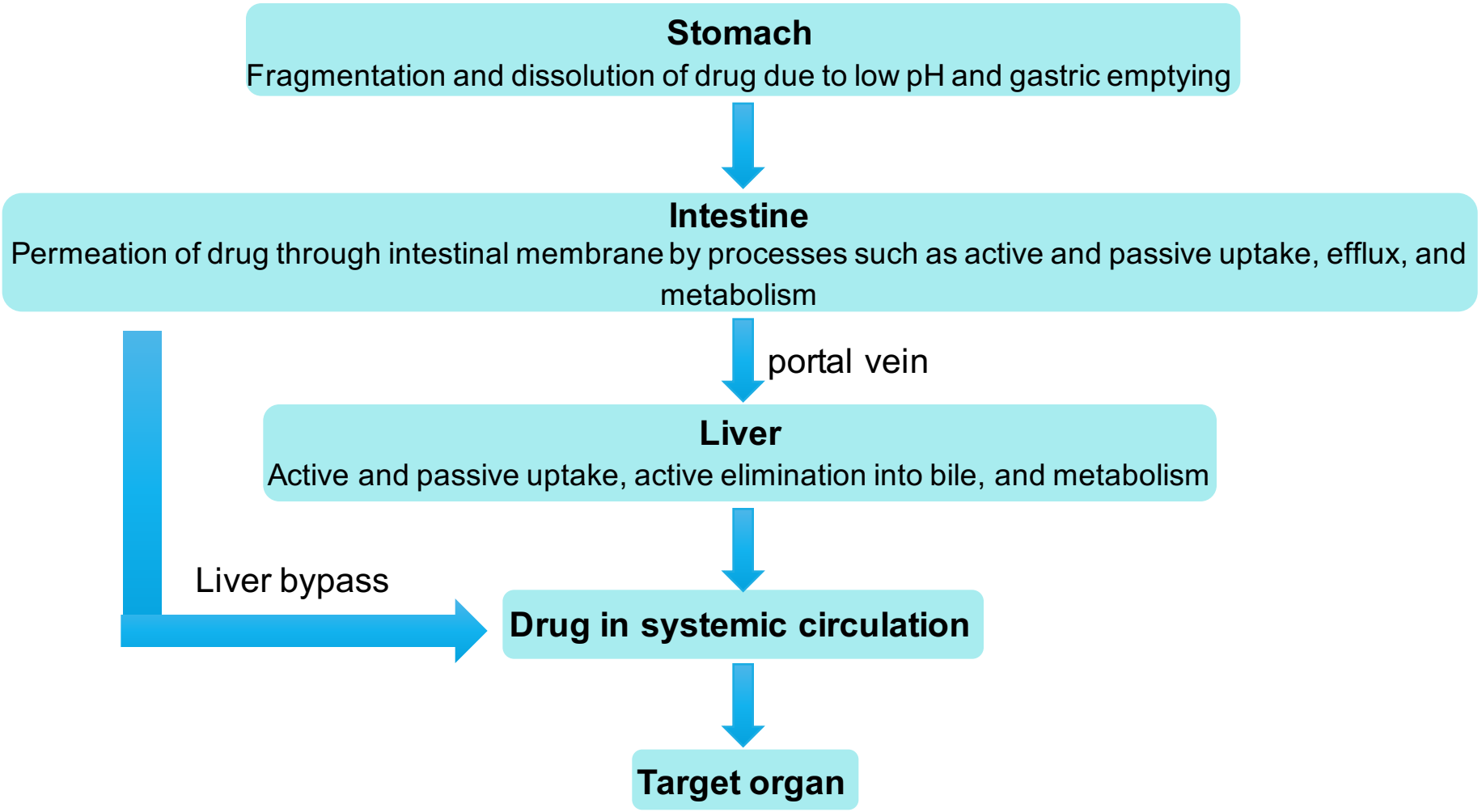
4) The substrate specificity of transporters is very broad.

5) Transport kinetics and variability.

Oral Bioavailability

Of all the sold drugs, about 60% are used orally.

Oral bioavailability (F) = F_a x F_g x F_h F_a = fraction absorbed, F_g = fraction escaping first-pass elimination, F_h = fraction escaping hepatic elimination



Fasinu *et al. Biopharm. Drug Dispos.* **2011**, *32,* 185–209.

Enhancement of Oral Bioavailability

1) Solubility: around 60 µg/ml (pH 11)[1] determined by presence of polar and ionizable groups, melting point.

2) Permeability: reduce number of ionization and hydrogen bond groups, molecular weight between 300 –400 Da, logP of 2–3[2,3] for passive diffusion.

3) Metabolic stability: use halogens to block positions that are metabolically unstable. Significant differences metabolism occur across species.

4) Structural rigidity.

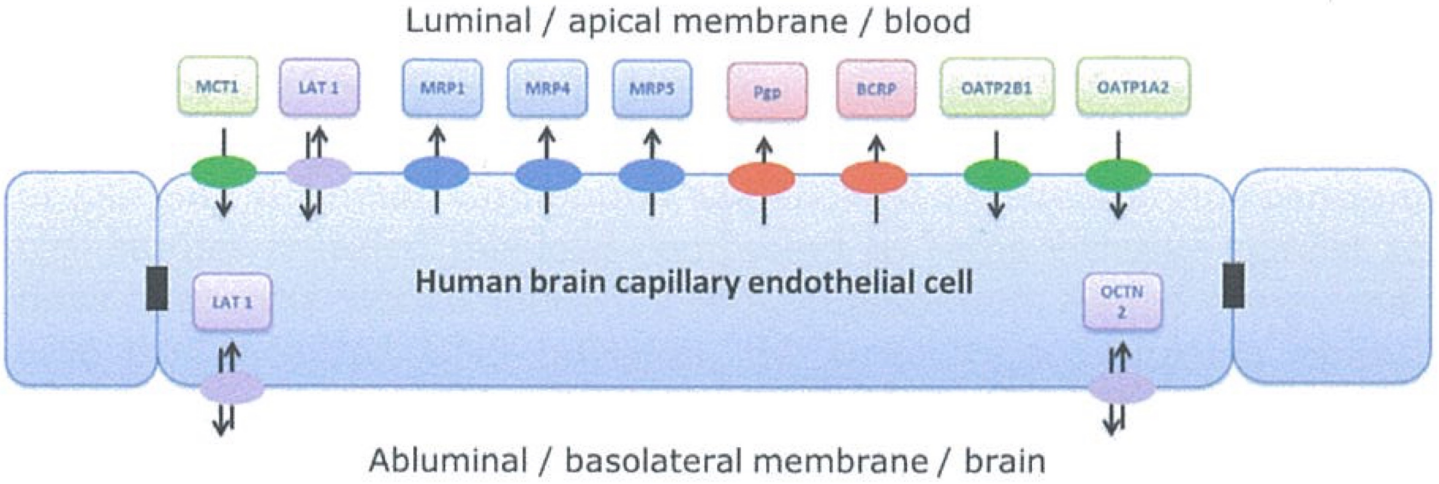
5) Transporter based strategies.

6) Prodrugs.

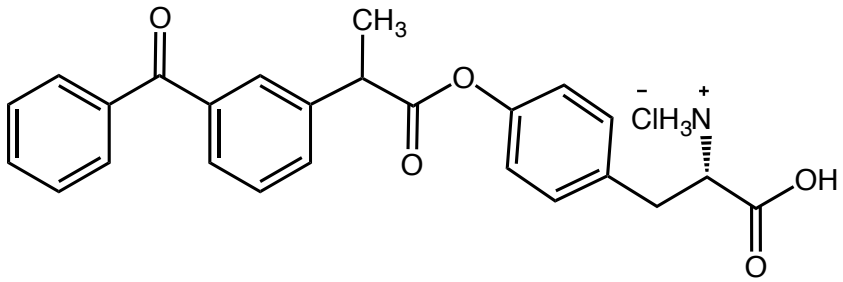
1) Kerns *et al. Curr. Drug. Metab.* **2008**, *9,* 879–885. 2) Di, L. and Kerns E. H. *Curr. Opin. Chem. Biol.* **2003**, *7,* 402–408. 3) Thomas *et al. Expert Opin. Drug. Meta. Toxicol.* **2006**, *2,* 591–608.

Enhancement of Brain Penetration

The blood-brain barrier is made up capillary endothelial cells that are linked by very tight junctions. Embedded in the cells are transporters, which move polar compounds across the barrier.



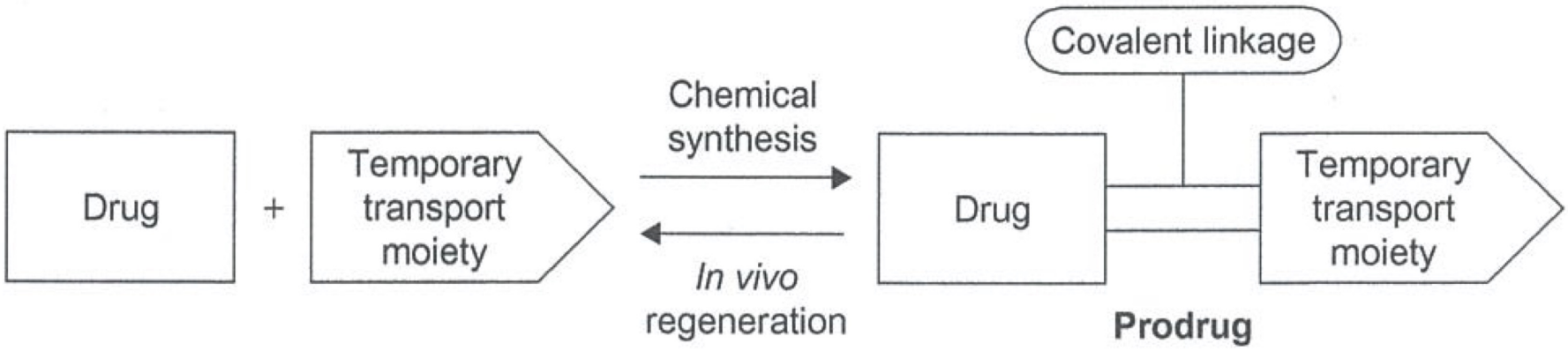
1) logP: a measure of the degree of lipophilicity of the molecule (2–4).
2) pKa: a measure of the extent of acidity of a molecule (6.1–10.5).
3) Hydrogen bond donor: 0–1, molecular weight between 300 –400 Da, logP of 2–3[2,3] for passive diffusion.
4) P-gp liability: P-gp is the main efflux pump in the brain.
5) Prodrugs: The conjugation of ketoprofen to L-tyrosine, a substrate for the LAT1 transporter, enabled an active brain uptake.



Gynther *et al. J. Med. Chem.* **2008**, *51*, 932–936.

Prodrugs

Prodrugs are compounds that pharmacologically inert but converted by enzymes or chemical action to the active form of the drug at or near their target site.



1) A covalent bond is usually used to connect the drug substance and the transport moiety.

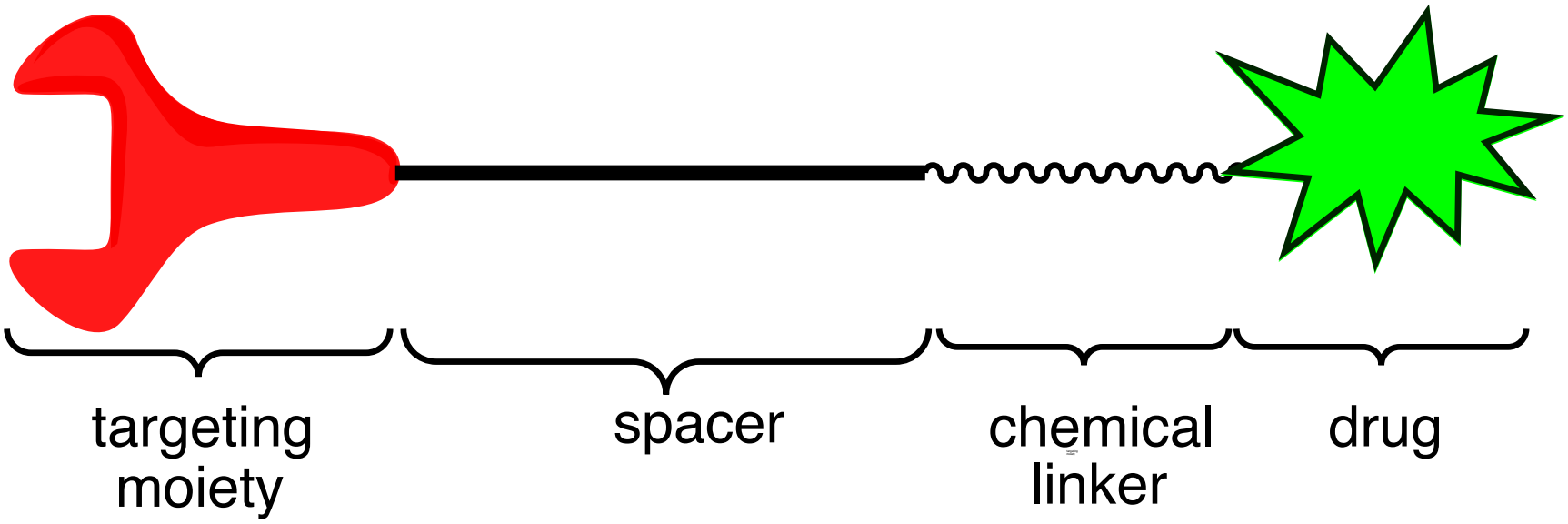
2) The prodrug should be inactive or less active than the parent compound.

3) In vivo cleavage of the linkage between the prodrug and the parent compound.

4) Nontoxic nature of both the prodrug and transport moiety.

5) Fast release of the drug.

Design of Prodrug



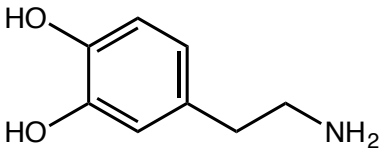
1) Site-directed drug delivery: tissue-specific transporters or cell surface receptors transport the prodrug or conjugate to the target cells/tissues.

2) Site-specific drug release: despite its whole body distribution, the prodrug is activated only in target cell by local enzymes.

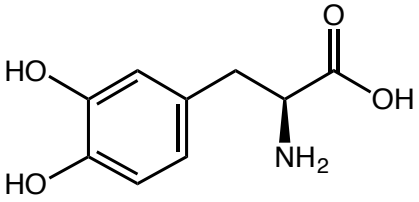
Site-Directed Drug Delivery

1) Tumor delivery: using the arginine-glycine-aspartic acid to target the integrin $\alpha_1\beta_3$, an heterodimeric transmembrane glycoprotein involved in cell-to-cell and cell-to-extracellular matrix interactions. Integrin $\alpha_1\beta_3$ are overexpressed on poliferating endothelial cells and breast, glioma, melanoma, prostrate tumor tissues, but absent pre-existing endothelial cells and normal tissues.

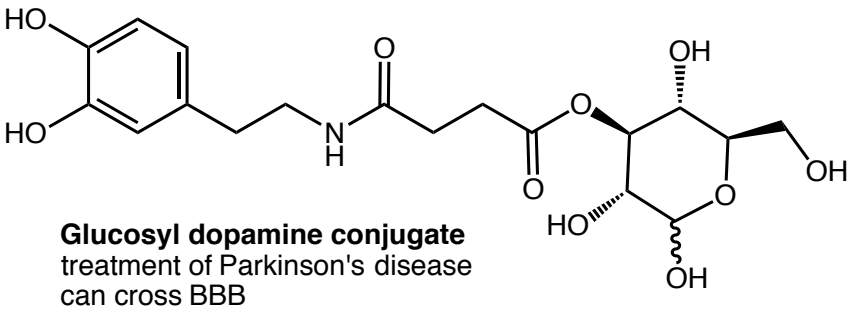
2) Brain delivery: glucosyl dopamine conjugate penetrates the BBB by GLUT1.



Dopamine
cannot cross BBB



L-Dopa
treatment of Parkinson's disease
can cross BBB
decarboxylated in the brain to give dopamine
conversion to dopamine in peripherial tissues
leads to unwanted side effects



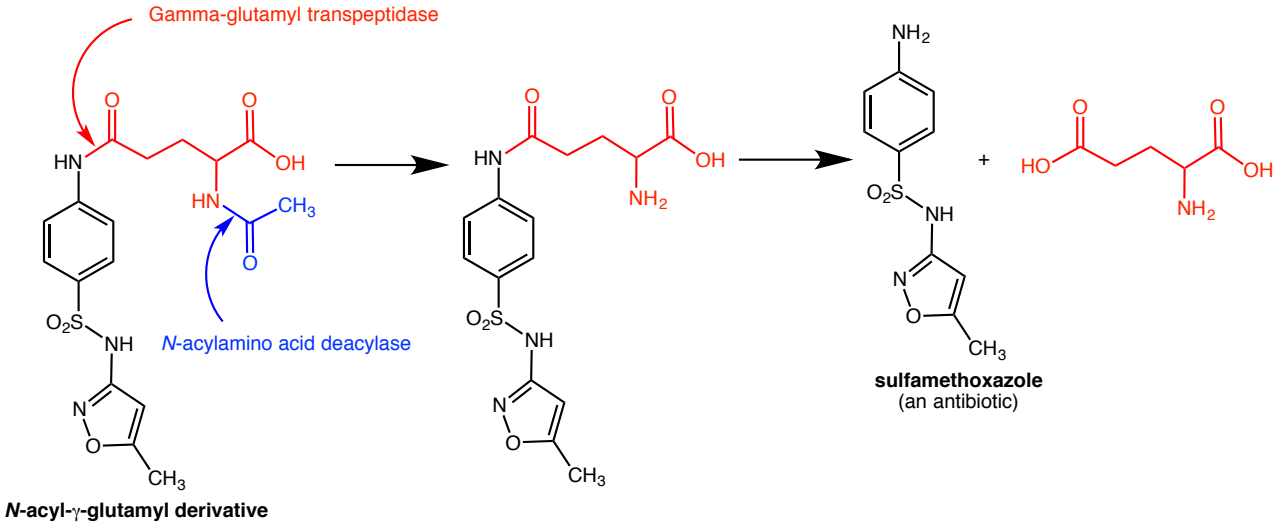
Glucosyl dopamine conjugate
treatment of Parkinson's disease
can cross BBB
decarboxylated in the brain to give dopamine

Dalpiaz *et. al. Inter. J. Pharm.* **2007**, *336*, 133–139.

3) Site-directed of drug delivery to the eyes, kidney, and livers are also known.

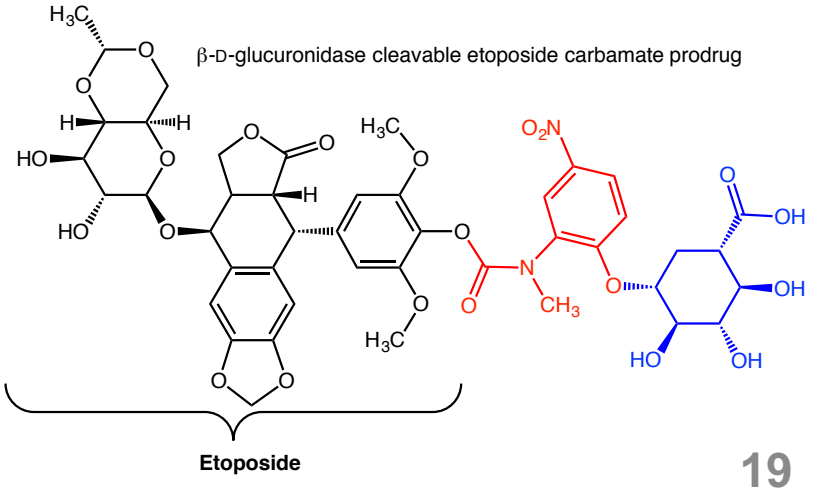
Site-Specific Drug Release

1) Kidney delivery: the high concentration of gamma-glutamyl transpeptidase and *N*-acylamino acid deacylase in the kidney enables kidney selective accumulation of sulfamethoxazole.

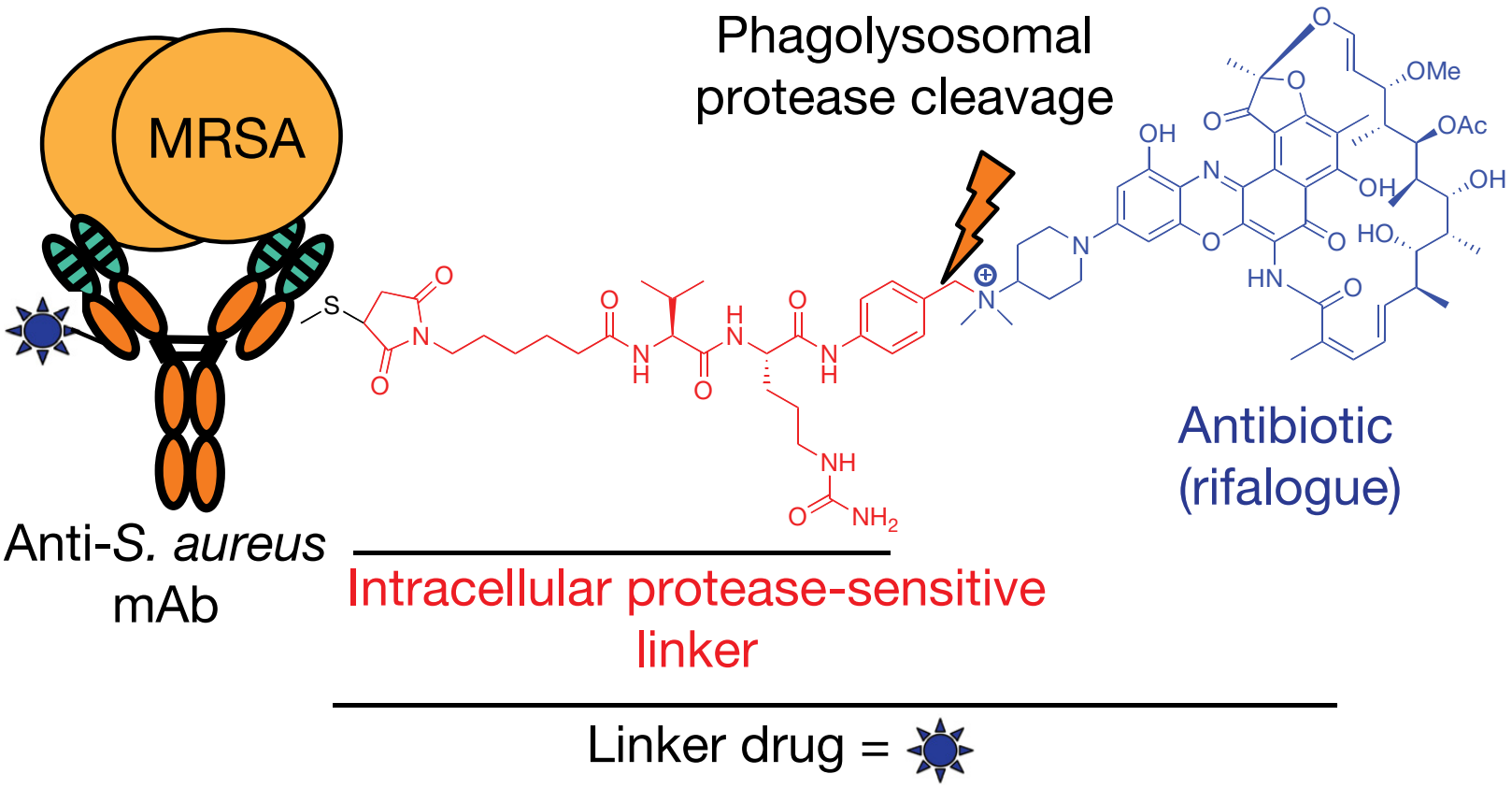


Orlowski *et. al. Inter. J. Pharmacol. Exp. Ther.* **1979**, *212*, 167–172.

2) Release in tumor sites: release of high local concentration of β-D-glucuronidase by necrotic tumors allows for the release of the drug near the tumor cells.



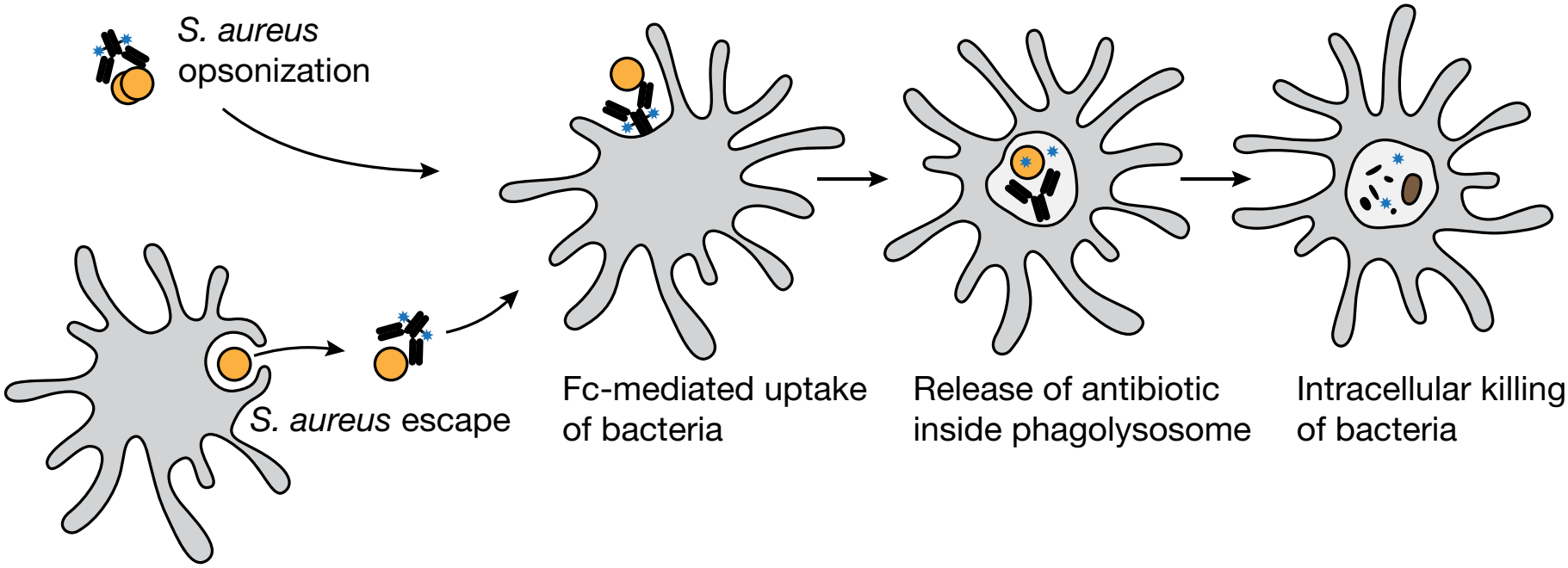
Antibody-Antibiotic Conjugate (AAC) Design



- ✓ The efficacious antibiotic is joined to the anti-*S. aureus* antibody by a cathepsin-cleavable linker.
- ✓ The AAC does not diffuse into the cell.
- ✓ The AAC has no antibacterial activity when bound to the planktonic *S. aureus*.

Mariathasan *et. al. Nature* **2015**, *527*, 523−528.

Mechanism of Action of the AAC



Thousands of AACs can bind to a single bacterium resulting in the delivery of adequate concentration of the unconjugated antibiotic in the phagosome.

Mariathasan *et. al. Nature* **2015**, *527*, 523−528.

Drug Solubility in Water

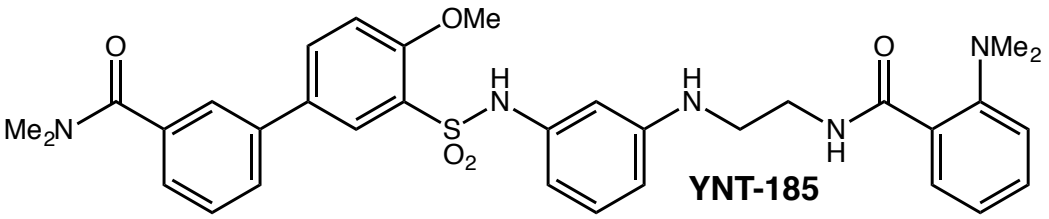
The challenge of solubilizing a drug in water is rarely a problem during *in vitro* testing. However, solubility can be an obstacle during *in vivo* testing, especially during toxicological studies in animals.

Parenteral route: administration of drug anywhere in the body except the mouth and alimentary canal, in an injectable form.

Oral route: administration of drug through the mouth in a form that allows for fast dissolution and absorption.

Ways of Improving Drug Solubility in Water

1) Salt formation: usually 10 mg/mL for parenteral products and about 1 mg/mL for oral products.

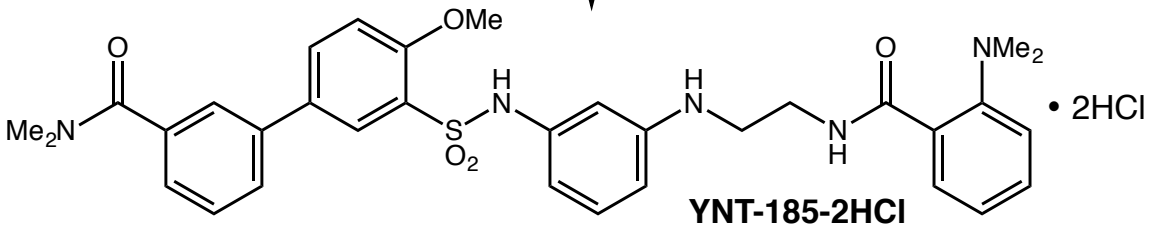


YNT-185

OX2R: EC_{50} = 0.028 μM
OX1R: EC_{50} = 2.750 μM

low solubility

10% HCl-methanol
methanol
rt



YNT-185-2HCl

water-soluble (1.3 M in saline)

Nagase and coworkers *J. Med. Chem.* **2015**, *58*, 7931−7937.

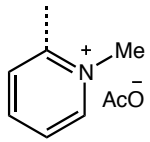
2) Covalent attachment of solubilizing functional groups such as carboxylic acid (−CO_2H), alcohol (−OH), sulfonic acid (−SO_3H), and phosphate (PO_3H_2).

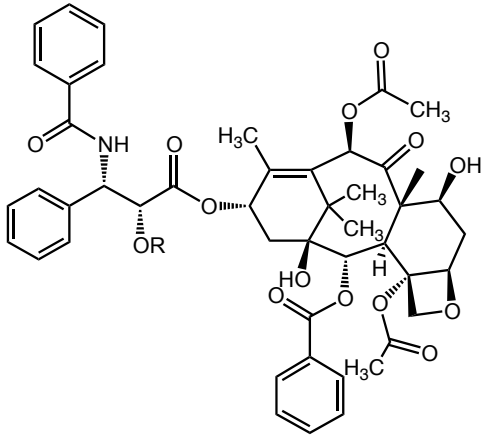
Ways of Improving Drug Solubility in Water

1) Complexation with cyclodextrins, calixarenes, and cucurbiturils

Cyclodextrins p-Sulfonatocalixarenes Cucurbiturils

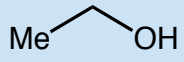
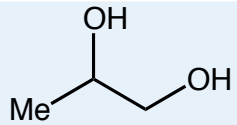
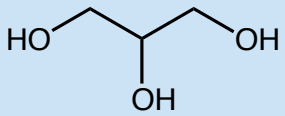
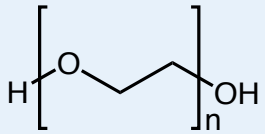
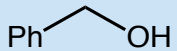
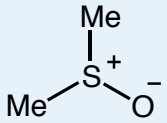
2) Prodrug approach

R	Water solubility (mg/mL)
H	< 0.004
	1.4



Drug Solubility Using Water-Cosolvent Systems

Cosolvency is the addition of water-miscible solvents to an aqueous systems. Cosolvents are used in 13% of FDA-approved parenteral products.

Solvent	Molecular Structure	Usage
Ethanol 96%		Moderately hemolytic cosolvent in injectables, up to 25%; used in oral dosage forms
1,2-Propanediol (propylene glycol)		In injectables up to 70%, low hemolytic effect. Used in oral dosage forms.
Glycerol		In injectables up to 30%, low hemolytic effect. Used in oral dosage forms.
Polyethylene glycol PEG 200: n = 4; PEG 400: n = 8-9 PEG 600: n = 12-14 PEG 4000: n = 68-84		Used In injectables and oral dosage forms. Can be used undiluted even for subcutaneous administration without tissue damage.
Benzyl alcohol		Used In injectables up to 4%; used for its preservative and local anesthetic activity. Limited miscibility with water.
Dimethylsulfoxide		Not in humans.

Composition of Cosolvent-Solubilized Drugs

	Component	Amount
(1) Librium® for i.m. injection		**in 2 ml**
In 5-ml dry filled ampoule:	chlordiazepoxide · HCl	100 mg
In 2-ml solvent ampoule:	maleic acid	1.6 %
buffering agent	NaOH	to adjust pH
solvents		
– solvent and surfactant	polysorbate 80	1.5 %
– solvent and preservative	benzyl alcohol	4 %
– solvents	propylene glycol	20 %
	water	to volume
(2) Bactrim® solution for i.v. infusion		**in 5 ml**
Active substances	trimethoprim	80 mg
	sulfamethoxazole	400 mg
Preservative	benzyl alcohol	1 %
Preservative	ethanolamine	0.3 %
Antioxidant	sodium metabisulfite	0.1 %
Solvents	propylene glycol	40 %
	ethanol	10 %
	water	to volume
(3) Ativan® for i.m. injection		**in 1 ml**
Active substance	lorazepam	2 or 4 mg
solvent	PEG 400	0.18 ml
solvent and preservative	benzyl alcohol	2%
solvent	propylene glycol	to volume

The drug substance is provided as a dry powder because limited stability in solution.

Two cosolvents accounting for 50% of the total volume.

Water-free mixture of “cosolvents”.

The formulation of has to be devised such that the dilution of the drug solution by aqueous body fluids during administration does cause precipitation during injection.

Summary

A comprehensive understanding of what the body does to a drug from the site of administration to the sites of elimination is essential for the drug's efficacy.

Next Lecture, 2016/05/09

Legal and Economic Aspects of Drug Development