

PASSAGE OF XENOBIOTICS ACROSS BIOLOGICAL MEMBRANES

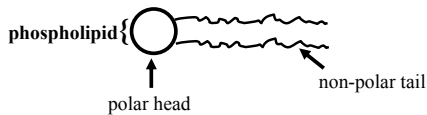
I. PHYSICOCHEMICAL DETERMINANTS OF THE PASSAGE OF XENOBIOTICS ACROSS BIOLOGICAL MEMBRANES

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A. Membrane Characteristics

1. Membrane Composition

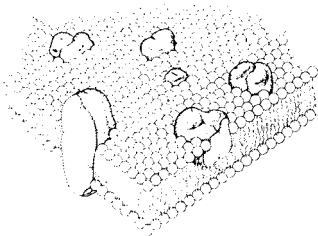
<i>Membrane Type</i>	<i>Phospholipid</i>	<i>Protein</i>
General	40%	60%
Inner mitochondrial	20-25%	75-80%
Myelin	75%	25%



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A. Membrane Characteristics

1. Membrane Composition 2. Membrane Structure



Fluid-mosaic model of Singer and Nicholson (*Science* 175:720-731, 1972)

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A. Membrane Characteristics

B. Drug Characteristics

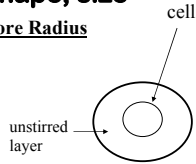
- molecular weight, shape, size

<u>Tissue</u>	<u>Estimated Pore Radius</u>
jejunem	7.5 A
ileum	3.5A

- lipid solubility

- ionization

- solubility in unstirred layer around cell

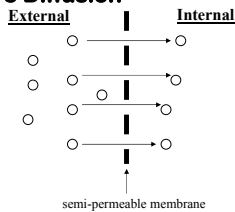


II. MECHANISMS OF BIOTRANSPORT

Biotransport

The translocation of a solute from one side of a biological barrier to the other side in the intact form.

A. Passive Diffusion



Fick's Law of Diffusion

$$\frac{dQ}{dt} = \left(\frac{DAK_p}{h} \right) (C_1 - C_2)$$

dQ/dt - rate of diffusion D - diffusion coefficient
 A - surface area of membrane K_p - partition coefficient
 h - membrane thickness

$C_1 - C_2$ = concentration difference for solute





Generally, $C_1 >> C_2$

ABSORPTION FROM RAT STOMACH AND SMALL INTESTINE

<u>Drug</u>	<u>% absorbed in 1 hr from stomach</u>	<u>% absorbed in 10 min from small intestine</u>
phenobarbital	17	52
pentobarbital	24	55
promethazine	0	38
ehtanol	38	64

Data from: Magnussen MP. *Acta Pharmacol Toxicol* 26:130, 1968.

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<u>Structure</u>	<u>Increase in Surface (relative to cylinder)</u>	<u>Surface Area sq cm</u>
simple cylinder 	1	3,300
Folds of Kerckring 	3	10,000
Villi 	30	100,000
Microvilli 	600	2,000,000

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COMPARISON OF BARBITURATE ABSORPTION FROM RAT COLON

<u>Barbiturate</u>	<u>Kp</u>	<u>% Absorbed</u>
barbital	0.7	12
phenobarbital	4.8	20
pentobarbital	28	30
secobarbital	51	40

Data from: Schanker LS. *J Pharmacol Exp Ther* 123:81, 1958.

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EFFECT OF pH ON INTESTINAL ABSORPTION IN THE ISOLATED RAT SMALL INTESTINE

	pKa	% absorbed at			
		pH 4	pH 5	pH 7	pH 8
Acids					
5-nitrosalicylic	2.3	40	27	0	0
salicylic	3.0	64	35	30	10
acetylsalicylic	3.5	41	27	---	---
benzoic	4.2	62	36	35	5
Bases					
aniline	4.6	40	48	58	61
aminopyrine	5.0	21	35	48	52
quinine	8.4	9	11	41	54

Data from: Schanker LS, *J Pharmacol Exp Ther* 123:81, 1958.

$$\frac{dQ}{dt} = \left(\frac{DAK_p}{h} \right) (C_1 - C_2)$$

Since D , K_p , and h are constant for a given drug/membrane; and given that $C_1 \gg C_2$:

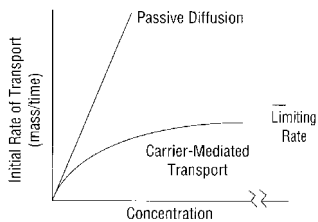
$$\frac{dQ}{dt} = PC_1$$

Where P - permeability constant

II. MECHANISMS OF BIOTRANSPORT

A. Passive Diffusion

B. Carrier-Mediated Biotransport



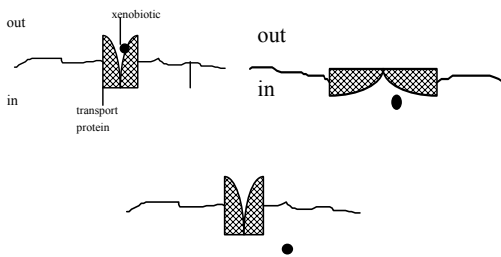
CHARACTERISTICS OF CARRIER-MEDIATED TRANSPORT

Facilitated Diffusion Active Transport

Movement against a concentration gradient	no	yes
Utilization of energy	no	yes
Exhibits saturation	yes	yes
Example substances	riboflavin, Vit B12	5-flurouracil

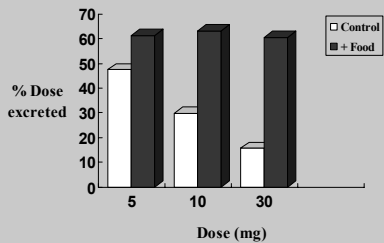
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Proposed Model for Carrier-Mediated Transport



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Effect of Food on the Absorption of Riboflavin



Data from: Levy G, Jusko WJ. *J Pharm Sci* 55:285-289, 1966.

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Membrane Transporters and Their Substrates

Transporter	Substrates
Amino acid transporters	baclofen, cyclosporin, L-dopa, gabapentin, methyldopa
Peptide transporters (hPEPT1, HPT1)	β -lactam antibiotics, ACE inhibitors, cephalexin, cyclosporin, methyldopa
Nucleoside transporters (CNT1, CNT2)	zidovudine, zalcitabine, dipyridamole
Organic anion transporters (OATP1, OATP3, OATP8)	ceftriaxone, benzoic acid, methotrexate, pravastatin
Organic cation transporters (OCT1, OCT2)	thiamine, desipramine, quinidine, midazolam, verapamil
Bile acid transporters (IBAT/ISBT)	chlorambucil, thyroxine

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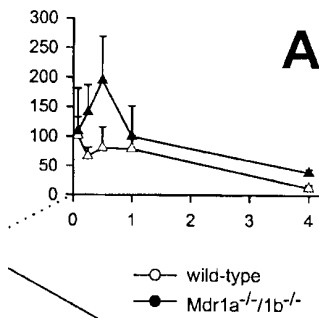
II. MECHANISMS OF BIOTRANSPORT

- A. Passive Diffusion
- B. Carrier-Mediated Biotransport
- C. Cellular Efflux

Key ABC Efflux Transporters

P-glycoprotein: *MDR1 (ABCB1)*
 Multidrug Resistance Protein: *MRP1 (ABCC1)*
 Breast Cancer Resistance Protein: *BCRP (ABCG2)*

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Plasma levels of saquinavir versus time after oral administration in wild type (open circles) and *Mdr1a*^{-/-}/*1b*^{-/-} mice. From: Huisman MT, et al. P-glycoprotein limits oral availability, brain and fetal penetration of saquinavir even with high doses of ritonavir. *Mol Pharmacol* 59:806-813, 2001

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