

## DISTRIBUTION OF XENOBIOTICS

- I. GENERAL PRINCIPLES
- II. CNS DISTRIBUTION
- III. MATERNAL-FETAL DISTRIBUTION
- IV. DISTRIBUTION INTO BREAST MILK

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## I. GENERAL PRINCIPLES

### *Distribution:*

The reversible transfer of xenobiotics from one location in the body to another

### A. Extent of Distribution

#### Determined by:

- partitioning across various membranes
- binding to tissue components
- binding to blood components (RBC, plasma protein)
- physiological volumes

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### Extracellular

<u>Vascular</u>	<u>Extravascular</u>	<u>Intracellular</u>
3 L	9 L	28 L
4% BW	13% BW	41% BW

### Components of Total Body Water

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**How can we measure the extent of distribution?**

*Apparent volume of distribution ( $V_d$ )*

$$V_d = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

**VOLUME OF DISTRIBUTION FOR SOME DRUGS**

<u>DRUG</u>	<u>Vd (L)</u>
cocaine	140
clonazepam	210
amitriptyline	1050
amiodarone	~5000

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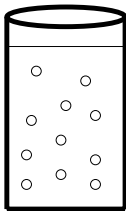
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What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10 \text{ mg}}{10 \text{ mg/L}} = 1L$$

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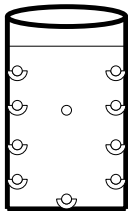
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What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10 \text{ mg}}{1 \text{ mg/L}} = 10L$$

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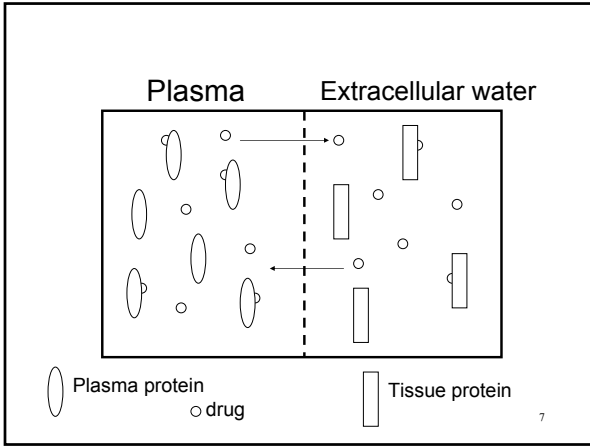
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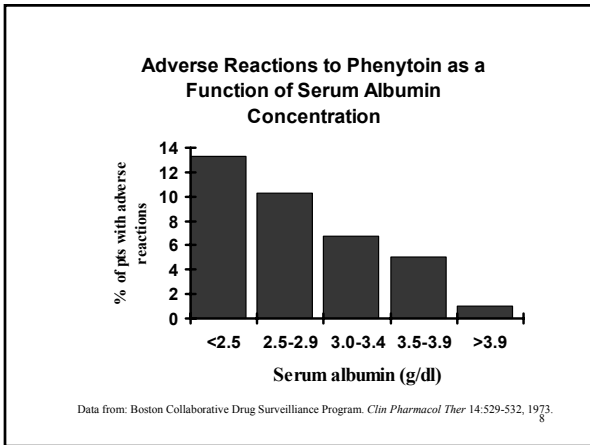
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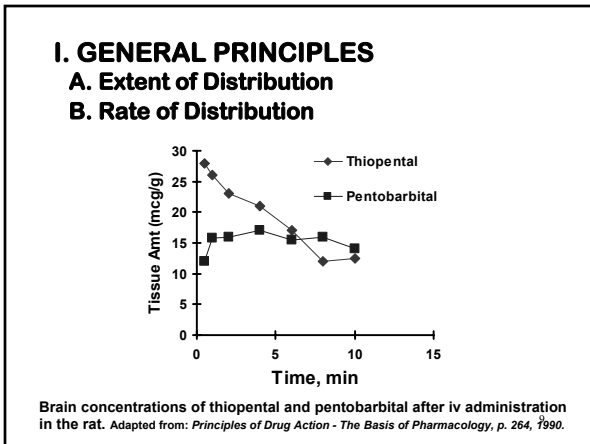
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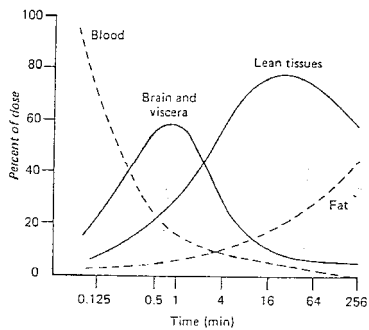
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Time course of thiopental in blood and tissues after intravenous administration.

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## II. CNS DISTRIBUTION

Three compartments in the CNS:

- blood
- brain
- cerebrospinal fluid (CSF)

Three anatomical barriers

- blood-brain barrier
- blood-CSF barrier
- CSF-brain barrier

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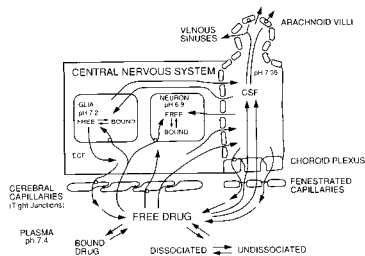


Fig. 3-24. Pathways of drug entry, distribution, and exit from the central nervous system. Drugs may enter and exit by passive diffusion of the undissociated (nonionized) form or by transport of the dissociated (ionized) form. Transport is indicated by open circles with arrows in membranes of various cells. ECF denotes the brain interstitial fluid (extracellular fluid). Bulk flow of CSF is indicated by arrows extending out of the brain interstitial fluid to the CSF and into the venous sinuses. (From Woodbury<sup>12</sup> with permission.)

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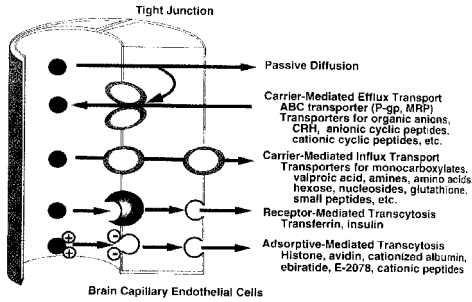
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## Mechanisms of Blood-Brain Barrier Biotransport



From: Tsuji A. Specific mechanisms for transporting drugs into brain, In: *The Blood-Brain Barrier and Drug Delivery to the CNS*. Begely DJ, Bradbury MW, Kreuter J. Marcel Dekker, New York, 2000.

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## Transport Systems for the CNS

### *Carrier-Mediated*

glucose, amino acids, lactic acid, thyroid hormone  
nucleosides

### *Receptor-Mediated*

angiotensin II, insulin, transferrin

### *Plasma Protein-Mediated*

corticosteroids, androgens, propranolol, estradiol  
bupivacaine

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**Means by which xenobiotics may gain entry to the CNS:**

- appropriate physiochemical properties
- utilize an existing transport
- direct administration into the CNS
- disruption of the blood-brain barrier

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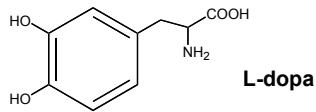
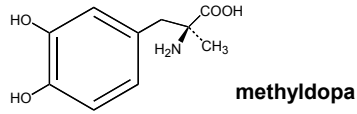
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**Effect of co-administration of methyl dopa and neutral amino acids on brain methyl dopa content in rats.**

From: Markovitz DC, Fernstrom JD. *Science* 197:1014-1015, 1977.



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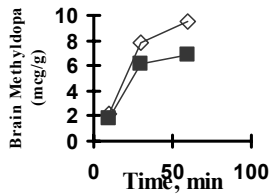
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**Effect of co-administration of methyl dopa and neutral amino acids on brain methyl dopa content in rats.**

From: Markovitz DC, Fernstrom JD. *Science* 197:1014-1015, 1977.

- ◇ Control
- + Neutral Amino Acids



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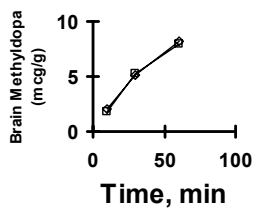
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**Effect of co-administration of methyl dopa and neutral amino acids on brain methyl dopa content in rats.**

From: Markovitz DC, Fernstrom JD. *Science* 197:1014-1015, 1977.

- ◇ Control
- + Acidic Amino Acids



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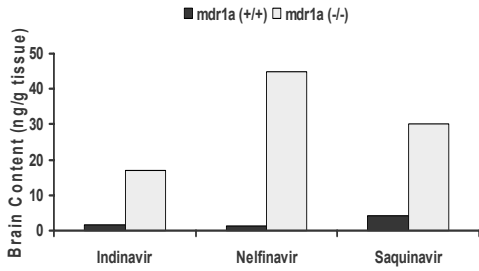
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**Role of P-glycoprotein determining brain content of protease inhibitors.** Data from: Kim et al. *J Clin Invest* 101:289-294, 1998.




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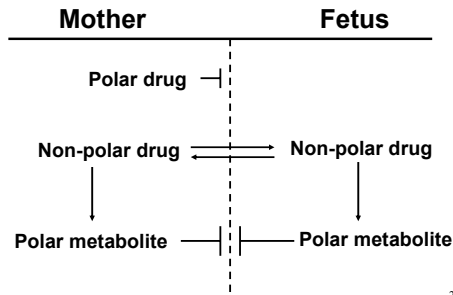
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**III. MATERNAL-FETAL DISTRIBUTION**




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**Maternal and Fetal Concentrations of Tubocurarine and Thiopental After IV Maternal Administration in Humans.** Data from: Cohen EN. *Anesth Analg* 41:122, 1962.

Time	Tubocurarine		Thiopental	
	Maternal	Fetal	Maternal	Fetal
5	3.0	0.0	8.5	5.5
6	3.2	0.0	8.0	3.5
9	1.1	0.1	4.8	2.5
11	2.1	0.1	2.0	1.2

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**Factors that may influence placental transfer**

<u>Factor</u>	<u>Effect</u>
Placental blood flow	increased delivery of drug to placental membrane
Molecular size of drug	decreased transfer as size increases <i>impermeable to drugs MW&gt;1000</i> <i>permeable to drugs MW&lt;600</i>
Lipid solubility of drug	increased transfer as lipid solubility increases
pKa of drug	ion trapping on either side

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**IV. DISTRIBUTION INTO BREAST MILK**

$$M/P = \frac{f_p^{un} f_p}{f_m^{un} f_m (S/M)}$$

**M/P** - milk to plasma concentration ratio  
**S/M** - skim to whole milk concentration ratio  
**f<sub>p</sub>** - unbound fraction in plasma  
**f<sub>m</sub>** - unbound fraction in milk  
**f<sup>un</sup>** - unionized fraction in respective fluid

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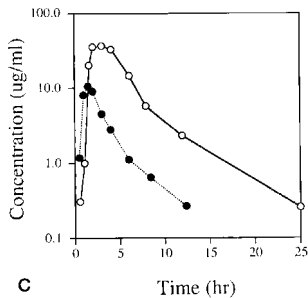
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**C** Concentration-time profile for cimetidine in serum (●) and breast milk (○) after a single dose in a lactating female. Reproduced from *Clin Pharmacol Ther* 58:548-555, 1995.

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