Toxicokinetics: Absorption, Distribution, and Excretion

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Section A

How Do Chemicals Reach Their Molecular Target?

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Toxic Action and Toxic Effect

- The **toxic action of a chemical** is a consequence of the physical/chemical interaction of the active form of that chemical with a molecular target within the living organism.

- The magnitude of the **toxic effect** will be a function of the concentration of altered molecular targets.
  - This is related to the concentration of the active form of the toxicant (biologically effective dose) at the site where the molecular targets are located.
Xenobiotics Cross Membranes to Reach Targets

Environment → Mucosa or skin → Interstitial fluid → Capillary membrane → Plasma → Capillary membrane → Interstitial fluid → Target cell membrane → Interstitial fluid → Subcellular organelle membrane → Intraorganelle fluid (mitochondria, lysosome, nucleus)
How Do Chemicals Cross Membranes?

- The absorption, distribution, and excretion of xenobiotics involves them passing through various cell and organ membranes.
- This occurs through various transport mechanisms.
Factors Affecting Membrane Transport of Chemicals

- Molecular weight/shape
- Charge
- Lipid solubility
- Membrane composition
- Membrane thickness
Transport Mechanisms

- Simple diffusion
- Facilitated diffusion (passive mediated)
- Active transport
- Pinocytosis/receptor-mediated uptake
- Filtration
Different Types of Transport

Non-electrolytes and un-ionized form of weak acids and weak bases

Molecules of varying sizes

Diffusion

Filtration & bulk flow

Endocytosis

Ion-pair

Facilitated or active

Drug-carrier complex
Characteristics of Simple Diffusion

- Transport proceeds in the direction of the electrochemical potential (concentration) gradient—unionized form
- Transport is not saturable even at high concentration gradients
- No structural specificity
- No energy requirement
- Inherently symmetrical transport
Both passive-mediated (*facilitated*) and active-mediated transport involve the use of carrier proteins.
Characteristics of Facilitated Transport

- Transport proceeds in the direction of the electrochemical potential (concentration) gradient

- The process is saturable at high concentration gradients
  - That is, there is a maximum rate of transport

- Structural specificity (specific inhibitors)

- No energy requirements

- Inherently *symmetrical* transport
Characteristics of Active-Mediated Transport

- Transport can proceed against an electrochemical potential (concentration) gradient

- The process is saturable at high concentration gradients

- Structural specificity

- Requires cellular energy

- *Asymmetrical* transport
Examples: Chemical Toxicity and Active Transport

- The herbicide *paraquat*, which targets alveolar type II cells in the lung

- *MPTP* toxicity results in Parkinson’s disease
  - A result of being selectively toxic to dopamine neurons in the substantia nigra of the brain
  - *MPTP* is metabolized to *MPP+* in the CNS
  - *MPP+* is taken up and accumulates in dopamine neurons
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Pinocytosis and Phagocytosis

Pinocytosis
- Cell membrane
- Pinocytosis channel
- Pinocytic vessels

Phagocytosis
- Pseudopod
Filtration

- Transport of solutes (dissolved materials) as a consequence of bulk flow of fluid (aqueous) phase

- Glomerulus of kidney is a good example of a major site where filtration occurs