PHARMACOKINETICS: Distribution (p.1)

As absorption continues, gradually distribution occurs
It takes time for drug to reach RSs

Transportation of drug molecules into bloodstream
One minute = circulation turnover rate
Plasma concentration is of drug is proportional to concentration at RSs
Extracellular fluids + blood plasma (a pool of solvent for drug)
Tissue affinities
1. blood proteins (e.g. albumin, globulins), drug binding
protein binding, protein bound drugs
e.g. chlorpromazine 90%, diazepam 99%
Most psychotropic drugs bind extensively
Implications for dose levels
can manipulate protein binding
Note: people with impaired kidney/liver function often have reduced levels of plasma proteins...implication

2. tissues rich in blood supply

3. tissues high in water content

4. tissues high in fat (fat cells, poor blood supply)
Pentothal (thiopental) vs. Nembutal (pentobarbital)
Marijuana (THC) vs. ethanol (ETOH)

Non-ionized, lipid soluble drugs do pass through BBB and into CNS
Ionized drugs or non-ionized water soluble drugs (non-lipid soluble) drugs do not pass through BBB and into CNS
PHARMACOKINETICS: Distribution (p.2)

Leaving the CNS
Lipid soluble, non-ionized drugs leave via the capillaries/veins and via the choroids plexus (arachnoid granulations --- into cerebrospinal fluid/CSF --- into veins/superior sagital sinus)

Note: the BBB is not an absolute (impermeable) barrier
Nor is it invariable….its permeability can change
e.g. penicillin, meningitis/encephalitis, fevers, tumors, concussion, age

“Drug reservoirs” – plasma proteins
   cellular reservoirs (esp. muscle & fat tissue)

Termination of drug effect: via redistribution

Summary to this point:
1. Once a drug has been absorbed & reaches the blood stream, it is distributed to tissue of body (incl. CNS & RSs on neurons)
2. Drugs can be deposited in fat & muscle cells (which act as drug reservoirs), which may even have more drug stored in them than the bloodstream is carrying
3. Blood plasma/serum level of the drug is thus not an absolutely accurate measure of the total body concentration of the drug; None-the-less, this level is used by convention/convenience
4. Distribution is a two phase process: An initial distribution to organs with rich blood supply (kidney, liver, heart, lungs brain), followed by distribution to other tissues with less rich blood supply (fat, muscles, bone, bladder) which especially act as longer term drug reservoirs
5. The so-called “single-compartment” model assumes that drug is evenly distributed throughout the body (not really true) and that this takes about 1 to 3 times through the circulatory system (at rate of one cycle per minute)
PHARMACOKINETICS: Distribution (p.3)

Summary to this point (cont.)

6. Ultimately large amounts of a drug can accumulate in these tissue reservoirs of fat/muscle, esp. in person with large amounts of such tissues
   Note: distribution to and storage in tissue reservoirs explains why one still may see drug effects on behavior long after the drug has been D/C’d and even after 1 to 5 drug ½-lives have occurred

7. **Protein binding** to proteins in the bloodstream provides another drug reservoir, as only the unbound drug molecules can cross cell membranes; bound drug molecules are chemically inactive until such time as they unbind again, and can leave plasma to then find their way to a RS
   Note: most psychotropic drugs bind extensively to plasma proteins
   Note: “serum drug levels” include both bound & unbound molecules

**Placental transfer**