Pharmacokinetics
Pharmacology = Study of the effects of a drug on behavior
Pharmacokinetics = Study of the ‘fate’/‘movement’ of substances administered to the body

Other Routes of administration
- Intraperitoneal - Fast indirect access to brain
  - Intrarectal - Slow, bypass the stomach
  - Nasal, eye
  - Intracerebral - Bypass the BBB
  - Intra(cerebro) ventricular - Bypass the BBB, global effect, emergency
- FDA considers 111 routes of administrations as valid

Kinetics of absorption = Study of the effects on some specific brain areas
- Movement through the BBB
- Lipid-soluble (heroin) substances pass the BBB
- Water-soluble (morphine) substances do not
- Rush vs. sustained
- Inactivation vs. excretion

Effectiveness: Dose-response curve
- If the effect was proportional to the amount of drugs: linear curve
  - Most drugs: non-linear curve
- At some point dosage effectiveness curve flat lines and has a max effect
  - Can’t take more to increase the effect
**Effectiveness: Affinity**

- Drugs may have the same end-results, but may vary in effectiveness
- Different sites of action:
  - Morphine:
    - Analgesic
    - Inhibits pain-perception neurons
  - Aspirin
    - Analgesic
    - Suppress 'chemical signal' from damaged cells to the nervous system
- Different affinity
  - Drug binds to receptors
- **Affinity** = strength of binding

**Margin of safety**
- Drugs have multiple effects at different concentrations
- 'good effect' - pain goes away
- 'bad' effect - heart rate and breathing decrease and the more you take the more it decreases
- Want a large margin of safety

**Therapeutic Index**
- TI measure of drug safety
- Ratio between lethal dose and effective dose for 50% of animals
- Therapeutic Index = LD$_{50}$/ED$_{50}$
- Want lethal dose to be large and effective dose to be small
- Want a large therapeutic index
  - Valium (tranquilizer, anxiety reducer): TI=$\sim$100
    - 100 will kill you
  - Barbiturate (anesthesia, anticonvulsants): TI=$\sim$3
    - Requires measurements in blood and monitoring
    - 3 will kill you

► **Dose-Response Curves for the Analgesic and Depressant Effects of Morphine**
**Drug misuse/abuse**

- What kinds of long term effects do drugs have?
  - Effect decreases with repeated (prolonged) use
    - **Tolerance**: need more drugs. Compensatory mechanism counteracting the effect of a drug
      - E.g. decrease in affinity, decrease in receptor numbers
    - **Withdrawal** symptoms: compensatory mechanisms alone, does the opposite of what the drug is supposed to do (behavioral/emotional effects)
  - Effect increases with repeated (prolonged) use
    - **Sensitization**
      - Antidepressants: need time to be effective
  - Effect can be psychological: **Placebo effect**
    - Used mainly in research
    - E.g. control for anxiety (human)
    - E.g. control for the effect of drug administration (animals)
  - Drug reinforcing effect depends on environment
    - Nicotine and cues
      - Cue (stress)

- How do drugs work? Agonists, antagonists
  - An **agonist** has the same postsynaptic effects as a particular neurotransmitter (i.e. it opens receptors)
  - An **antagonist** has different postsynaptic effects than a particular neurotransmitter (i.e. it closes receptors)
    - Direct agonist/antagonist (competitive binding)
      - Competes with neurotransmitter molecules
    - Indirect agonist/antagonist (noncompetitive binding)
      - Does not compete with neurotransmitter molecules
  - Drugs can interfere with reuptake and degradation

**Agonists and Antagonists**

- **Agonists**: Drugs that occupy receptors and activate them.
- **Antagonists**: Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.

![Diagram of drug action](image)
Neurotransmitters

- Goal of neurotransmitter release:
  - Postsynaptic potentials (EPSP/IPSPs)
- The main families of neurotransmitters
  - Amino acids
    - **Glutamate (Glu, Glutamic Acid)**
      - Synthesis
        - From proteins in food
      - Found where?
        - Everywhere in CNS
      - Receptors
        - Always excitatory
        - Ionotrophic for Na⁺ (AMPA, Kainate)
        - Ionotrophic for Na⁺ and Ca²⁺ (NMDA)
        - Metabotropic glutamate receptor
      - Psychopharmacology
        - NMDA involved in learning and memory
        - AP5 blocks the glutamate binding site on NMDA receptors
        - Alcohol blocks NMDA receptors
        - PCP (angel dust) blocks NMDA and blocks calcium entry in the cell
          - Hallucination and aggression
          - Also animal model for schizophrenia
        - Too much glutamate binding results in **excito-toxicity** (cell death)
    - **GABA**
      - Synthesis
        - From glutamate
          - Glu ----> GAD ----> GABA
      - Found where?
        - Everywhere in CNS
      - Receptors
        - Always inhibitory
        - Ionotrophic for Cl⁻ (GABA_A)
        - Metabotropic for K⁺ (GABA_B)
          - Exists presynaptically (**autoreceptor**)
      - Psychopharmacology
        - Controls spread of excitation (epilepsy, seizures)
        - Muscimol opens, and bicuculline blocks GABA_A
        - Benzodiazepines (anxiolytics, sleep promoters, seizure reducers) open GABA_A
          - Valium = diazepam, Librium
        - GABA_A is blocked by picrotoxin (convulsions)
        - Barbiturates (low doses = anesthesia, higher dose = respiratory arrest, low TI) open GABA_A
        - Gama-HydroxyButyrate (GHB, 'date-rape drug'): GABA agonist
    - **Glycine**
      - Synthesis
- Found in sugar cane
- Endogenous production unknown
  - Non essential (can be synthesized by body, no need for external source)
- Found where?
  - Mainly: spinal cord
- Receptors
  - Always inhibitory
  - Inotropic for Cl⁻
- Psychopharmacology
  - Prevents excessive muscle contraction
  - Tetanus: bacteria produces a chemical that blocks glycine release
  - Strychnine blocks the glycine receptor (convulsion and death)
    - Used for animal control

Properties of some major neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>Postsynaptic cleft</th>
<th>Precursors</th>
<th>A. Small molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ach (Acetylcholine)</td>
<td>Excitatory</td>
<td>Choline + Acetyl CoA</td>
<td>Gasmic acid</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Excitatory</td>
<td>Glutamine</td>
<td>Aescine</td>
</tr>
<tr>
<td>GABA</td>
<td>Inhibitory</td>
<td>Glutamate</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Glycine</td>
<td>Inhibitory</td>
<td>Serine</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Both excitatory and inhibitory</td>
<td>Tyrosine</td>
<td>Cocaine</td>
</tr>
<tr>
<td>• Epinephrine</td>
<td></td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td>• Norepinephrine</td>
<td></td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td>• Dopamine</td>
<td></td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>Inhibitory (mostly) excitatory</td>
<td>Tryptophan</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Histamine</td>
<td>Excitatory</td>
<td>Histidine</td>
<td>Cocaine</td>
</tr>
<tr>
<td>ATP</td>
<td>Excitatory</td>
<td>ADP</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>Both excitatory and inhibitory</td>
<td>Amino acids</td>
<td>Cocaine</td>
</tr>
</tbody>
</table>

B. Large molecules

- Neuropeptides (Substance P, Endorphins, Insulin, Glucagon etc)