The Neurotransmitters (drugs)

**Pharmacokinetics**
Psychopharmacology: Study of the effects of a drug on behavior
Pharmacokinetics: Study of the ‘fate’/movement’ of substances administered to the body

**Five Stages of the movement of the drug:** from administration to absorption.
- Administration
- Absorption: Entering the body, or a body compartment (e.g. brain)
- Distribution: Being carried to specific target organs (e.g. blood)
- Metabolism: Being broken down by enzymes
- Excretion

**Routes of Administration**

**Intravenous:** fast, precise, direct access to brain. (within a minute, depending on the drug you have access)
- E.g. drug of abuse, adrenaline

**Intraperitoneal:** fast, indirect access to brain because the drug has to be absorbed by the organs there
- E.g. chemotherapy (cancer)

**Intramuscular (Inside the muscles typically the butt, shoulder):** slower (capillaries), direct access
- E.g. vaccines, antibiotics

**Subcutaneous:** Slow absorption (fat tissue), indirect
- E.g. Insulin

**Oral:** easy, delayed (has to go through intestines/stomach and liver).
- E.g. aspirin, Tylenol

**Sublingual:** under the tongue, easy (for humans) Bypass the digestive system and go straight to the blood. Capillaries of the tongue
- E.g. steroids, cardiovascular (hypertension)

**Intrarectal:** Slow, bypass the stomach (some drugs get broken down by the acids therefore don’t like to be digested)
- E.g. suppositories

**Inhalation** fast, easy, requires volatile substances
- E.g. Nasal decongestant, drugs of abuse (MJ), Asthma

**Topical administration:** fast, local (skin, mucous)
- E.g. nasal, eye (herpes, glaucoma)/ear drops

**Intracerebral:** Put in the brain drugs that are usually blocked by blood brain barrier. Bypass the BBB, local, (specific brain area), mostly research

**Intra(cerebro)ventricular:** Bypass the BBB, global effect, emergency, also used in research

FDA considers 111 routes of administrations as valid
Other examples are: Epidural, intracardiac, transdermal (patch)
**Kinetics of Absorption**
- Study of the effect on some specific brain areas. Movement through BBB.
- Lipid soluble (e.g. heroine) substances pass the BBB. Water soluble substances (e.g. morphine) do not.

**Effectiveness: Dose-Response Curve (fig. 4.2)**
**Dosage on x-axis, effect on y-axis**
If the effect was proportional to the amount of drugs: *Linear curve*
Most drugs: Non-linear Curve, after a certain point increasing dosage does not help, but may produce more side effects

**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: Suppress ‘chemical signal’ from damaged cells to the nervous system

**Different Affinity:**
- Drugs bind to receptors
  - Affinity=Strength of binding

**Margin of Safety**
Drugs have multiple effects at different concentrations:
- Morphine Fig. 4.3
Too much morphine will slow done heart rate and breathing that is a ‘bad effect’ it’s undesirable
Low margin of safety is not good, you need a high margin of safety (meaning you need to take 25 aspirins to get to that level of ‘bad effect’)

**Therapeutic Index:**
**TI:** Measure of drug safety
= $\frac{LD_{50}}{ED_{50}}$
‘LD’ =Lethal Dose: for 50% of the animals
‘ED’ =Effective Dose’: for 50% of the animals
Valium (tranquilizer, anxiety reducer): TI= ~100
You need to take 100 pills for 50% to die
Barbiturate (anesthesia, anticonvulsants): TI= ~3. (3 pills will kill you) Requires measurement sin the blood and monitoring (Typically done in hospital settings)
Higher TI the better, it will take more pills to kill you. The higher TI, the safer the drug.

**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 mechanism alone. Opposite behavioral/emotional effects. e.g. Euphoria <-> Depression

**Sensitization**: Effect increases with repeated (prolonged) use
  - E.g. Antidepressants: need time to be effective

Effect can be psychological: **Placebo effect**
- Used mainly in research
  - E.g. Control for anxiety (human), control for the effect of drug administration (animals)

Drug reinforcing effect depends on environment: Nicotine and cues (environmental, social)
  - Nicotine itself is not reinforcing, it’s the cues that are

**How do drugs work? Agonists, antagonists**
An agonist has the same postsynaptic effects as a particular neurotransmitter (i.e. it opens receptors)
  - **Competitive agonist**: Binds to receptor at the same site as a neurotransmitter and opens it

Drugs can interfere with reuptake and degradation
- Reuptake: reuptake inhibitor → Antidepressants (agonist)
- Deactivating Enzymes: e.g. prevent enzymatic degradation (not destroying, more molecules, more binding so it’s an agonist)

**Neurotransmitters**
Goal of neurotransmitter release: Post-Synaptic Potentials (EPSP/IPSP)
Transmitter ID Card:
  - Synthesis and destruction
  - Pathway of release
  - Receptors
  - Disease + Action of prescription release

**The Main Families of Neurotransmitters**
**Amino Acids**:
  - Glutamate, GABA, Glycine
**Acetylcholine (Ach)** no family
**Monoamines**:
  - Catecholamines:
Amino Acids

Glutamate (Glu, Glutamic Acid)

**Synthesis:** From proteins in food

**Found where?** In the CNS

**Receptors:** Always Excitatory
- Ionotropic for Na+ (AMPA, Kainate)
- Ionotropic for Na+ and Ca 2+ (NMDA)
- Metabotropic glutamate receptor

**Psychopharmacology:**
- NMDA involved in learning and memory
- AP5 blocks the glutamate-binding site on NMDA receptors (antagonist)
- *Alcohol* blocks NMDA receptors (antagonist)
- PCP (angel dust) blocks NMDA and blocks the calcium entry in the cell Hallucination and aggression. Also, animal model for schizophrenia
- Too much glutamate binding results in excite-toxicity (cell death)

GABA

**Synthesis:** From Glutamate

**Found Where?** Everywhere in the CNS

**Receptors:** Always inhibitory
- Ionotropic for Cl- (GABA\(_a\))
- Metabotropic for K+ (GABA\(_b\)). Exists presynaptically (autoreceptor)

**Psychopharmacology:**
- Controls spread of excitation (epilepsy, seizures)
- Muscimol open, and bicuculline blocks GABA\(_a\) (agonist)
- *Benzodiazepines* (anxiolytics, sleep promoters, seizure reducers) open GABA\(_a\) example: valium = diazepam, Librium (agonist)
- GABA\(_a\) is blocked by picrotoxin (convulsions)
- Barbituates (low doses = anesthesia, higher dose = respiratory arrest, Low TI) open GABA\(_a\)
  - Gamma-HydroxyButyrate (GHB, ‘date rape drug’) GABA agonist

Figure 4.12

Glycine

**Synthesis:** Found in sugar cane

Endogenous production unknown. *Non essential* (can be synthesized by the body, no need for external source)
**Found Where?** Mainly in the spinal cord

**Receptors:**
- Always inhibitory
- Ionotropic for Cl-

**Psychopharmacology:**
- Prevents excessive muscle contraction
- Tetanus: bacteria produces a chemical that blocks Glycine release
- Strychnine blocks Glycine receptor (convulsion and death. Used for animal control)

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**If there were a quiz…**

1. Agonists are drugs that bind to receptors and open them (T)
2. The margin of safety is measured: As the distance between two dose-response curves (Good vs. bad)
3. A competitive agonist is: (B) A drug that binds to a receptor at the same site as a neurotransmitter and opens it
4. Intravenous drug administration has slow and diffuse effects: (F)