The Neurotransmitters

Principles of Psychopharmacology

• Psychopharmacology
  ◦ study of the effects of a drug on behavior

• Pharmacokinetics
  ◦ study of the 'fate' or 'movement' of substances administered to the body
    ▪ administration
    ▪ absorption
      • entering the body, or a body compartment (brain)
    ▪ distribution
      • being carried to specific target organs (blood)
    ▪ metabolism
      • being broken down by enzymes
    ▪ excretion

Routes of Administration

• Intravenous
  ◦ fast, precise, direct access to the brain
    ▪ drugs of abuse (heroin), adrenaline

• Intraperitoneal (abdomen)
  ◦ fast, indirect access to the brain
    ▪ chemotherapy

• Intramuscular
  ◦ slower (capillaries), direct access
    ▪ vaccines, antibiotics

• Subcutaneous (skin)
  ◦ slow absorption (fat tissue), indirect
    ▪ insulin

• Oral
  ◦ easy, delayed (has to go through the stomach/intestines and liver)
    ▪ aspirin

• Sublingual (under the tongue)
  ◦ easy (for humans), bypasses digestive system, capillaries of the tongue
    ▪ steroids, cardiovascular (hypertension, vasodilator)

• Intrarectal
  ◦ slow, bypass the stomach
    ▪ suppositories

• Inhalation
  ◦ fast, easy, requires volatile substances
    ▪ nasal, decongestant, drugs of abuse, asthma

• Topical administration
  ◦ fast, local (skin, mucous)
    ▪ nasal, eye (herpes, glaucoma) and ear drops

• Intracerebral
  ◦ bypass the Blood Brain Barrier, local (specific brain area), mostly research

• Intra(Cerebro)Ventricular
  ◦ bypass the BBB, global effect, emergency

• FDA considers 111 routes of administration as valid
  ◦ epidural, intracardiac, transdermal
Kinetics of Absorption
- Study of the effects on some specific brain areas, movement through the BBB
- Lipid-soluble (e.g. heroin) substances pass the BBB, water-soluble substances (e.g. morphine) do not

Effectiveness
- Dose-Response curve
  - if the effect was proportional to the amount of drugs: linear curve
    - most drugs are non-linear
- Affinity and sites of actions
  - drugs may have the same end-results, but may vary in effectiveness/sites of action
  - different sites of action
    - morphine
      - analgesic: inhibits pain-perception neurons
    - aspirin
      - suppress 'chemical signal' from damaged cells to the nervous system
  - different affinity (strength of the binding)
    - drug binds to receptors

Margin of Safety
- Drugs have multiple effects at different concentrations
  - morphine

Therapeutic Index
- Measure of drug safety, overdose danger
  - LD50/ED50
    - lethal dose for 50% of the animals
    - effective dose for 50% of the animals
    - high TI is 'better', risk of overdose is smaller
      - valium (tranquilizer, anxiety reducer)
        - TI = 100
      - barbiturate (anesthesia, anticonvulsant)
        - TI = 3

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
      - decrease in affinity, decrease in receptor numbers
    - withdrawal symptoms
      - compensatory mechanism alone
      - opposite behavioral/emotional effects
        - euphoric drug withdrawal causes depression
  - effect increases with repeated use: sensitization
    - antidepressants: need time to be effective
  - effect can be psychological: placebo effect
    - used mainly in research
      - control for anxiety (human)
control for the effect of drug administration (animals)
• drug reinforcing effect depends on environment
  ‣ nicotine and cues
• rat experiments find nicotine reinforcement to be low alone
• with combination of nicotine and visual cues, rate of nicotine use increases
  ‣ other smokers around for humans, environmental cues

How do Drugs Work?
• Agonists
  ‣ an agonist has the same postsynaptic effects as a particular neurotransmitter (it opens/closes receptors)
• Antagonists
  ‣ an agonist opposes or inhibits the effects of a particular neurotransmitter
• Competitive binding
  ‣ direct agonist/antagonist competes with neurotransmitters
• Noncompetitive binding
  ‣ indirect agonist/antagonist does not compete with neurotransmitters
• Drugs can interfere with reuptake and degradation

Neurotransmitters
• Goal of neurotransmitter release
  ‣ postsynaptic potentials (EPSP/IPSP)
• Transmitter ID card
  ‣ pathway of release
  ‣ receptors
  ‣ disease/behavior and action of prescription drugs
• The main families of neurotransmitters
  ‣ Amino acids
    ‣ Glutamate
    ‣ GABA
    ‣ Glycine
  ‣ Acetylcholine (ACh)
  ‣ Monoamines
    ‣ Catecholamines
      ‣ Dopamine
      ‣ Norepinephrine
      ‣ Epinephrine
    ‣ Serotonin
    ‣ Histamine
  ‣ Neuropeptides
  ‣ other (lipids, nucleosides, soluble gases)
Amino Acids

**Glutamate (Glu, Glutamic acid)**
- believed to be the first neurotransmitters to have evolved
- synthesis
  - from proteins in food
- found where
  - everywhere in the CNS
- receptors
  - always excitatory
  - ionotropic for Na+ (AMPA, Kainate)
  - ionotropic for Na+ and Ca2+ (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 calcium entry in the cell
    - hallucination and aggression, animal models for schizophrenia
  - too much glutamate binding results in **excito-toxicity** (cell death)

**GABA**
- synthesis
  - from Glutamate
- found where
  - everywhere in the CNS
- receptors
  - always inhibitory
  - ionotropic for Cl- (GABAa)
  - metabotropic for K+ (GABAb), exists presynaptically (autoreceptor)
- psychopharmacology
  - controls spread of excitation (epilepsy, seizures)
  - Muscimol opens, and Bicuculline blocks GABAa
  - Benzodiazepines (anxiolytics, sleep promoters, seizure reducers) open GABAa
    - valium= Diazepam, Librium
  - GABAa is blocked by picrotoxin (convulsions)
  - Barbiturates (low doses= anesthesia, higher dose = respiratory arrest, low TI) open GABAa
  - Gamma-HydroxyButyrate (GHB, 'date rape drug'), GABA agonist

**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 spinal cord
- receptors
  - always inhibitory
  - ionotropic for Cl-
- psychopharmacology
  - prevents excessive muscle contraction
  - Tetanus: bacteria produces a chemical that blocks Glycine release
  - Strychnine blocks the Glycine receptor (convulsions and death), used for animal control