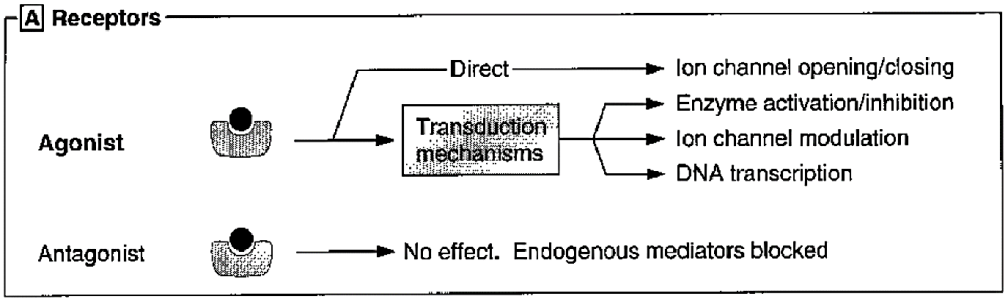
» Drug Targets 1: Protein Targets for Drug Action

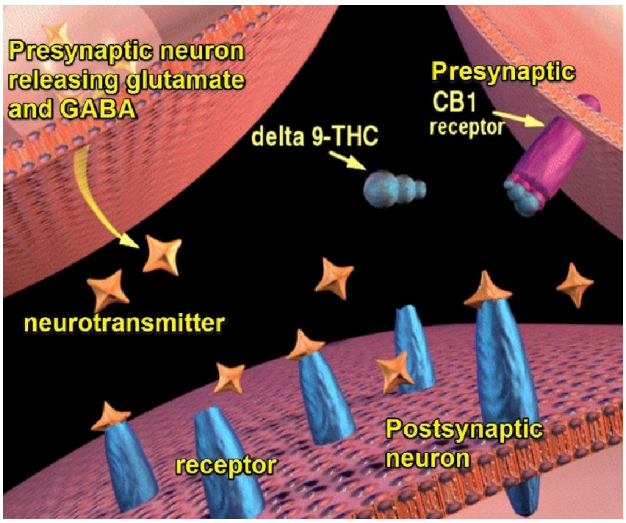
- Protein targets for drug action: **RICE**
  1. Receptors
  2. Ion channels
  3. Carriers
  4. Enzymes

Receptors

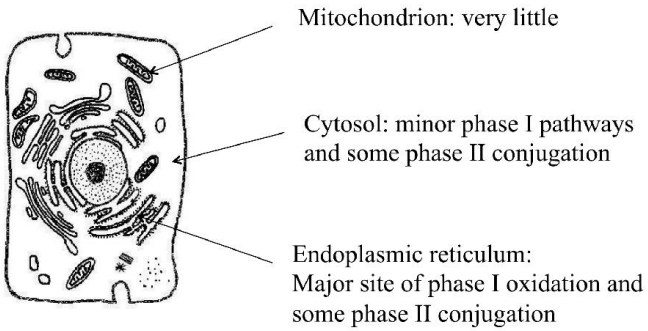
- Proteins found in the cell membrane
- Responsible for receiving chemical information from hormones, transmitters, cytokines and growth factors.



- Cannabis: **CB1 receptor** (cannabinoid receptor type 1)
  - Cannabis is the most widely used illicit drug in the world.
  - The main psychoactive constituent (cannabinoid) is **Δ^9-THC**.
    - Δ^9-THC binds to CB1 receptors in the brain, producing classical cannabinoid effects (euphoria, anxiety, memory impairment and appetite stimulation).
  - Mechanism of action:
    - This is a synapse containing the endogenous cannabinoid system. The CNS contains CB1 receptors and endogenous mediators (endocannabinoids) such as anandamide and 2-AG. These endocannabinoids are physiological ligands for the cannabinoid receptors.
    - Glutamate acts on glutamate receptor proteins in the postsynaptic membrane, and is responsible for 'activating' a person.
      - **Glutamate is the main excitatory neurotransmitter**. It depolarises neurons by increasing membrane Na^+ conductance.
    - The presynaptic CB1 receptors are autoreceptors – i.e. this system modulates the release of other neurotransmitters.
      - Δ^9-THC mimics the endogenous mediator anandamide by binding to CB1 receptors and inhibiting the release of glutamate (presynaptic inhibition).
    - This reduces 'activation' of a person and produces a calming effect.



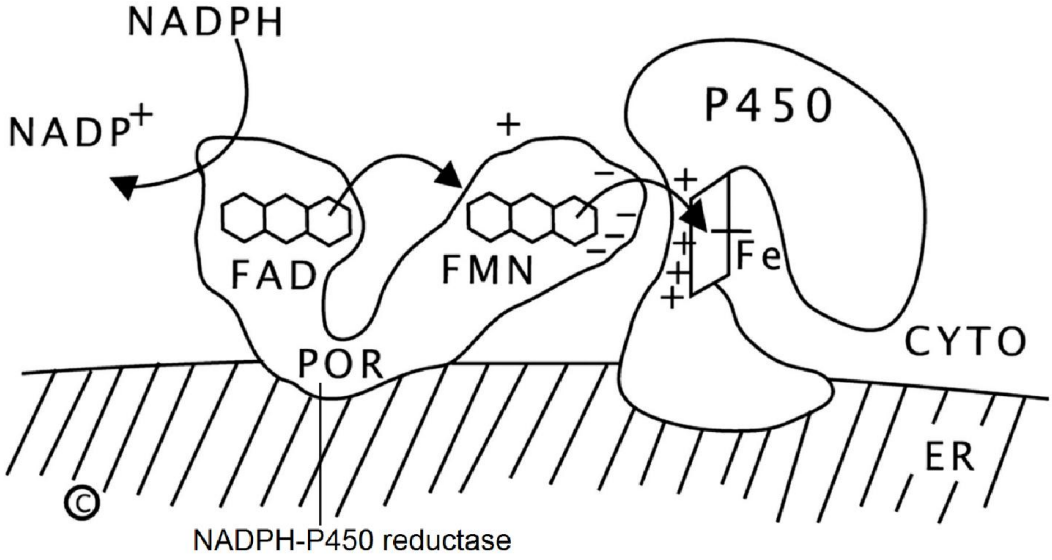
- Sites of biotransformation in the cell:



- Phase I reactions:
  - Chemical conversion of a lipophilic chemical into a more polar analogue.
  - Inclusion of a new functional group (usually by oxidation, reduction or hydrolysis), which is subject to phase II metabolism.
    - Example: Oxidation of the O-ethyl group in phenacetin produces a phenol, with ~10 fold decrease in lipophilicity.

Cytochromes P450

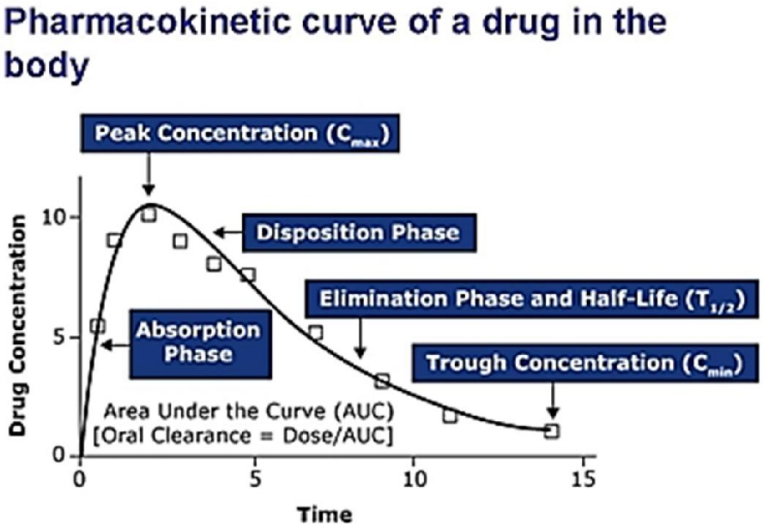
- **P450** (aka **CYP**) is the major class of phase I biotransformation enzymes.
- Unlike most enzymes, **P450s are multifunctional enzymes that act on diverse substrates**, including the xenobiotics and endobiotics to which we are exposed.
  - **P450s have low substrate specificity** – can accommodate a wide range of substrates.
  - However, there are still some drugs and chemicals that are oxidised by a single P450.
- Factors that affect P450 activities can markedly affect drug elimination.
- Components of the Phase I P450 System: Lipophilic xenobiotics and endobiotics are oxidised by cytochromes P450s.



  - **P450 enzyme**
    - Site of oxygen activation (activated oxygen inserted into substrate)
  - **NADPH**
    - Source of electrons that drives activation of oxygen.
  - The cofactor **NADPH-P450 reductase**
    - Transfers electron from NADPH to P450 enzyme.
  - **Membrane phospholipid**
    - To reproduce the environment within the endoplasmic reticulum.
- Characteristic P450 Reactions:
  - Drugs often form several metabolites because they contain more than one substituent that can be oxidised.

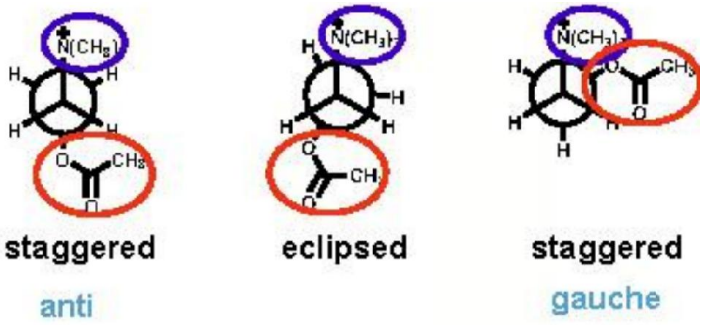
Pharmacokinetic Parameters

- After absorption, a drug builds up effective serum concentrations, but is also converted to forms that are more readily eliminated.
- The characteristics of these processes are described by a series of pharmacokinetic parameters.



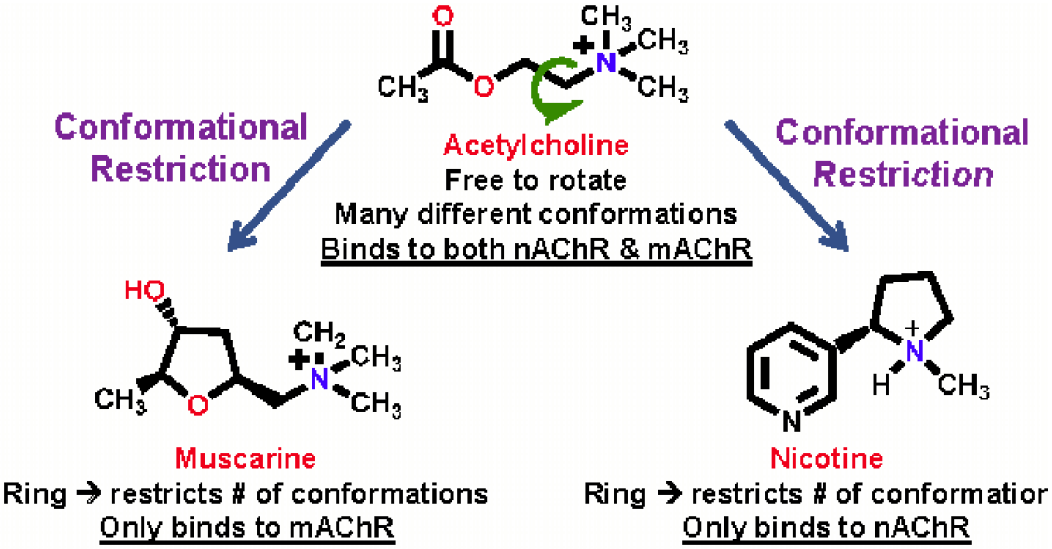
Pharmacokinetic Parameter	Definition
C_{max} (µg/mL)	• **Peak plasma concentration (C_p)** – Usually following an oral dose • Reflects drug disposition in terms of bioavailability and distribution
T_{max} (h)	• **Time taken to reach C_{max}**
C_{min} (µg/mL)	• **Trough C_p** at the end of the dosing interval (before the next dose is given)
Clearance (L/h)	• **Volume of plasma cleared of the drug per unit time** • Measure of efficiency of drug elimination – Irreversible elimination from circulation – One-way elimination (sweat, urine, etc.) and/or metabolic conversion • At a given IV dose rate, clearance is the sole parameter determining steady state $[drug]_{plasma}$
Volume of distribution (L or L/kg)	• $\mathbf{V_d = \frac{dose\ (g)}{initial\ plasma\ concentration,\ C_0\ (g/L)}}$ • Relates amount of drug in body to $[drug]_{plasma}$ • Measure of extent of distribution – The higher the V_d, the greater the proportion of drug that is distributed outside the blood stream • V_d is not a real volume; it is the apparent volume into which the drug appears to distribute to achieve the measured C_0 • Used to calculate loading dose (initial dose required to achieve a given C_p) – Back-calculated from $[drug]_{plasma}$ following given dose
Half-life (h)	• **Time to halve drug amount in body** – Duration of action following single dose • Determined by clearance (CL) and V_d – $t_{1/2} = 0.693 \times \frac{V_d}{CL}$ • Clearance follows first order kinetics (mostly exponential) – $C_t = C_0 \times e^{-kt}$ – Doubling the dose only increases duration by one half-life
AUC_{0-x} (µg·h/mL)	• **Area under concentration-time curve**

Flexibility of ACh



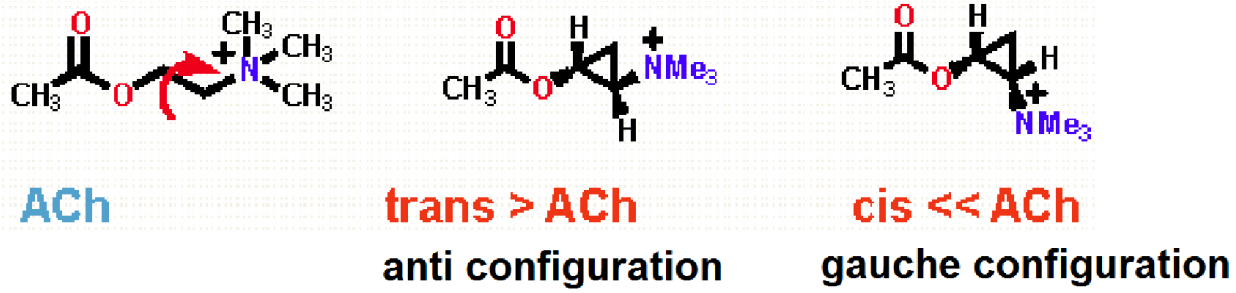
- Staggered conformation much more energetically stable than eclipsed.
- Staggered gauche conformation more stable than staggered anti because of stabilising intramolecular interaction between negative dipole of ester group and positive quaternary nitrogen.
  - Pulls energy of gauche conformer below energy of anti conformer.

Selectivity of Muscarine and Nicotine



Muscarinic Agonists

- Rotational flexibility about C-C bond can be restricted by installing cyclopropane rings.
- Trans and cis isomers interconvert the position of the quaternary amine.
  - Trans (but not cis) isomer is a much more potent agonist than ACh at the mAChR.
    - Depends on whether N^+Me_3 and OAc groups are closer to anti than gauche configurations.



» S-A Relationships for Cholinergic Drugs 2

Acetylcholinesterase Inhibitors

- Compounds which inhibit the activity of AChE cause a build up in the concentration of ACh in the synaptic cleft, which can result in an overstimulation of the cholinergic receptors in the PNS and CNS.
- Acetylcholinesterase inhibitors have toxic and therapeutic uses.