1) Roles of adipose tissue and the blood-brain barrier

Adipose tissue provides a non-polar environment and is a site of accumulation for lipophilic drugs. It can act as a reservoir for slow release into the body. Lipophilicity is measured as the '**partition coefficient'.**

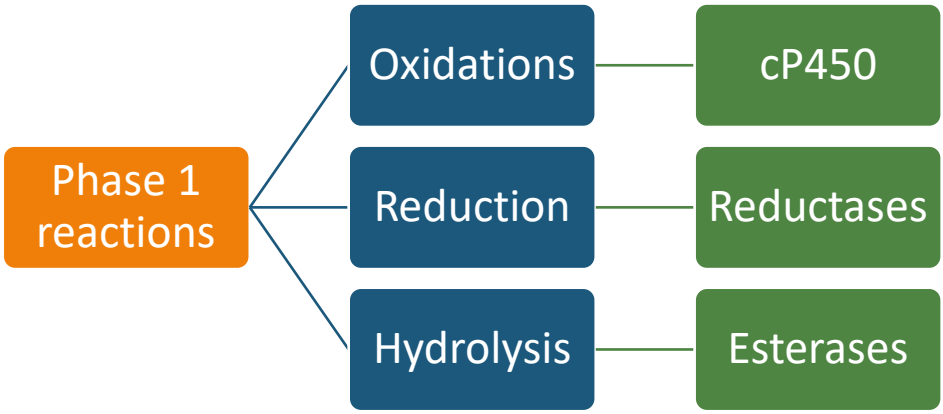
For drugs to enter the CNS, they must be very lipophilic or be a substrate for specific transporter. Transporters are also used to remove drugs from the brain. E.g. MRP's (multi-drug resistance proteins) are non-selective drug transporters and are also found in the GIT and liver.

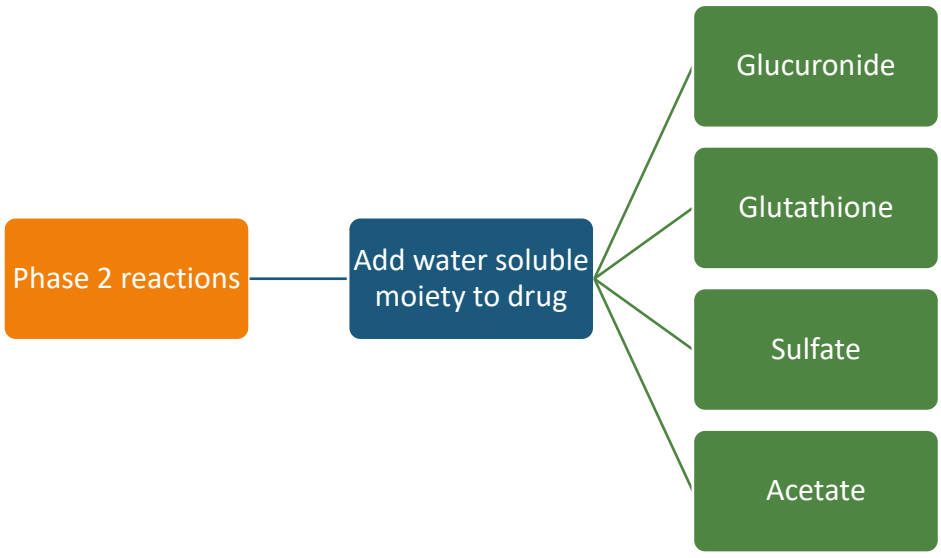
1 LECTURE 7: METABOLISM

The purpose of metabolism of xenobiotics (foreign compounds) is to increase the rate of excretion and decrease likely toxicity. Generally, the metabolite is; more polar (hydrophilic), more rapidly excreted, has less pharmacological activity and less toxicity.

1) Understand the difference between phase 1 and phase 2 metabolism

There are two major types of enzymatic reactions





- Increase in HR and contractility and vasoconstriction (orthostatic reflex)
- Can lead to orthostatic hypotension

Transmitters & Receptors

Noradrenaline and adrenaline act on adrenergic receptors (GPCR). These are divided into two main types: α-receptors mediate excitatory effects of sympathomimetic amines, whereas inhibitory effects are generally mediated by β-receptors. Exceptions are smooth muscle of the gut and the heart.

Receptor	2nd Messenger	Effects	Use
α1	Gq- IP3/DAG	**Smooth muscle contraction**: Vasoconstriction in viscera Dilate pupils Close GI sphincters	Agonists: nasal decongestants Antagonists: treatment of hypertension
β1	Gs- cAMP	**Heart**: Increase frequency, contractility, conduction at AV node	Agonists increase cardiac contractility. Problem: dysarrythmia
β2	Gs- cAMP	**Smooth muscle relaxation**: Vasodilation in skeletal muscle Decrease GI motility Dilate bronchi	Agonists used for asthma.

Sympathetic nerves originate in the thoracic-lumbar sections of the spinal cord and synapse in paravertebral ganglia or prevertebral ganglia in the adrenal medulla. Preganglionic neurons release ACh onto nACHR on the post-ganglionic neurons. Post-ganglionic neurons release NA onto various adrenergic receptors on the end organs.

Adrenaline vs Noradrenaline and Peripheral Resistance

- NA acts mainly on a receptors (no relaxation of smooth muscle)
- A acts on all adrenergic receptors

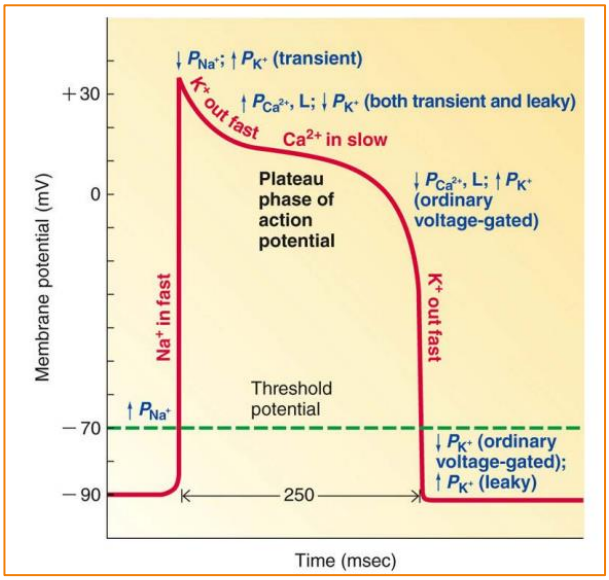
When adrenaline is administered vasodilation predominates resulting in slightly decreased peripheral resistance which increasing heart rate, contractile force and blood pressure.

Three main drug clasess

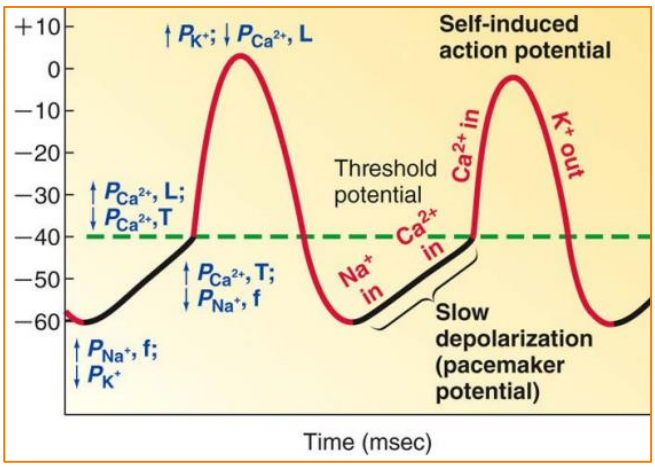
1) Sympathomimetic drugs
    - Agonist at a1, b1, b2 receptors
    - A and NA, little receptor selectivity
2) Sympatholytic drugs
    - Antagonists at a1, b1, b2 receptors
    - A2 agonists
        - MOA: blocks NA release by reducing cAMP and inhibition of Ca channels

2 LECTURE 19: DYSRHYTHMIAS & ANTI-DYSRHYTHMIC DRUGS 1

1) Pacemaker generates wave of signals to contract
2) Signals are delayed at AV node
3) Signals pass to heart apex
4) Signals spread throughout ventricles



- Low resting potential due to leaky K channels
- Na channels open transiently and are rapidly inactivated
- There is sustained plateau phase with Ca prolonged influx
- Outward K currents repolarize myocyt



- Autorhythmic cells lack a RP
- Slow depolarization due to a funny Na channel that opens at negative membrane potential

Pacemaker cells in different parts of the heart fire spontaneous action potentials at difference rates. SA=70-80/min, AV=40-60/min, His/Purkinje=20-40/min. Non-SA autorhythmic cells are **latent pacemakers.**

Parasympathetic activity decreases HR, sympathetic increases HR.

Dysrythmias can be classified according to

- Site of origin
- Whether HR is increased or decreased
- Tachyarrhythmias: atrial fibrillation, SV tachycardia, ventricular tachycardia and ventricular fibrillation
- Bradyarrythmias: heart block and asystolic arrest

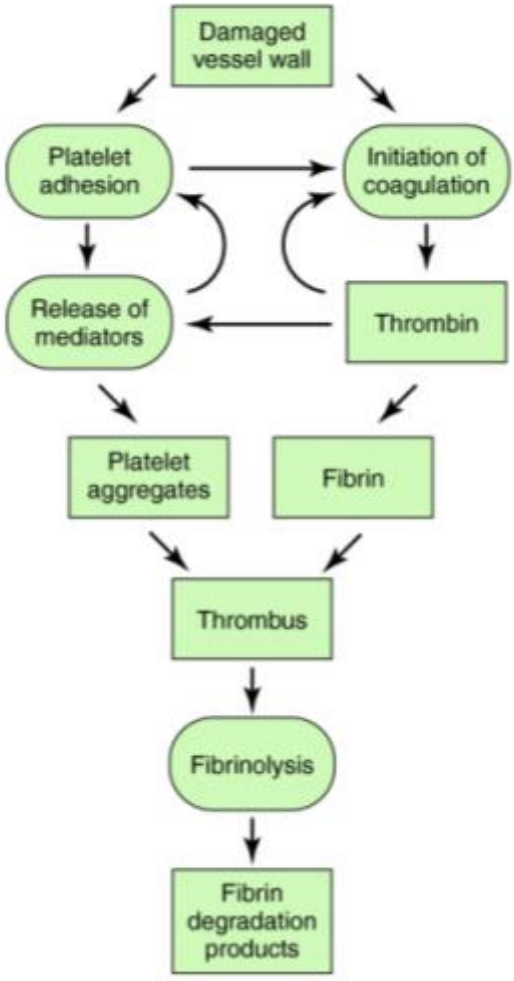
Ectopic Focus: an excitable group of cells that causes a premature heart beat outside the normally functioning SA node.

- Encouraged by sympathetic activity and partial depolarization (ischemia, hypoxia)

3 LECTURE 21: HAEMOSTASIS

Haemostasis: the stopping of blood loss from damaged vessels and protect against haemorrhage.

- Vasoconstriction
- platelet adhesion to the exposed tissue + Platelet activation to form a haemostatic plug = platelet plug
- Reinforcement of plug by fibrin (coagulation)



Thrombosis= haemostasis in the wrong place → formation of plug in absence of bleeding

Predisposing factors include;

- Injury to vessel wall (rupture of plaque)
- Altered blood flow (e.g. legs in sitting)
- Increased coagulability of blood

Venous thrombi = red clots, mainly erythrocytes and fibrin

Arterial thrombi= white clots, mainly platelet aggregates. Often atherosclerosis

1) Platelets adhere to and are activated by exposed collagen at the site of vessel injury
2) Activated platelets release ADP and thromboxane A2
3) Activate passing by platelets
4) Newly activated platelets aggregate onto growing plug → release more activating chemicals
5) Normal endothelium release prostacyclin and NO which inhibit platelet aggregation → confined to site of injury

Antiplatelet agents reduce platelet aggregation and arterial thrombosis. Used in patients with acute MI or high risk of MI. Combining different classes leads to a synergistic effect but increases the risk of bleeding.

Arachidonic acid is released from membrane phospholipids by PL A2. AA→ series of biologically active metabolites (eicosanoid). Three major pathways for eicosanoid production involve **cyclooxygenases (COX), lipoxygenases, epoxygenases.**