Lecture 1 Notes – Welcome to Pharmacology

What is Pharmacology?

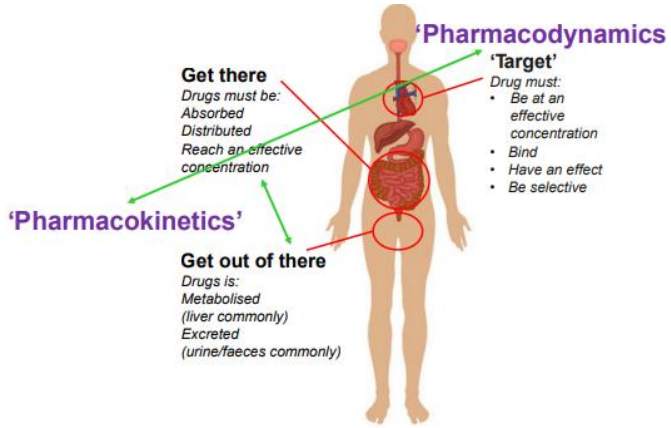
- A multidisciplinary biomedical science linking together chemistry, pathology and physiology
- A biomedical science that quantifies the effect of drugs on isolated tissues
- A biomedical science that studies drug action
- A biomedical science that encompasses toxicology
- a '*branch of science concerned with drugs and their actions'*

History of Pharmacology – Key Principles

- *Hippocrates (5th Century BCE):* Established 'Risk vs Reward' when choosing to create/utilise drugs
- *Paracelsus (16th Century):* "All things (drugs) are poison, and nothing is without poison; only the DOSE permits something to be poisonous i.e. 'Dose determines effect'
- *Erlich (20th Century): "for chemotherapy the principle is true that corpora non agunt nisi fixate* → 'Drugs bind molecular targets'

What Makes a Safe and Effective Drug?

- **Pharmacokinetics =** the branch of pharmacology concerned with the movement of drugs within the body.
- **Pharmacodynamics =** the branch of pharmacology concerned with the effects of drugs and the mechanism of their action



What is a drug?

- Chemical that affects physiological function in a specific way
    - **Present in the body (used for cellular communication)**
        - Hormones, neurotransmitters, second messengers
        - Antibodies, genes
    - **Not normally found in the body**
        - Synthetic or naturally occurring e.g. Atropine from Atropa Belladonna (dilate pupils to 'look more attractive')

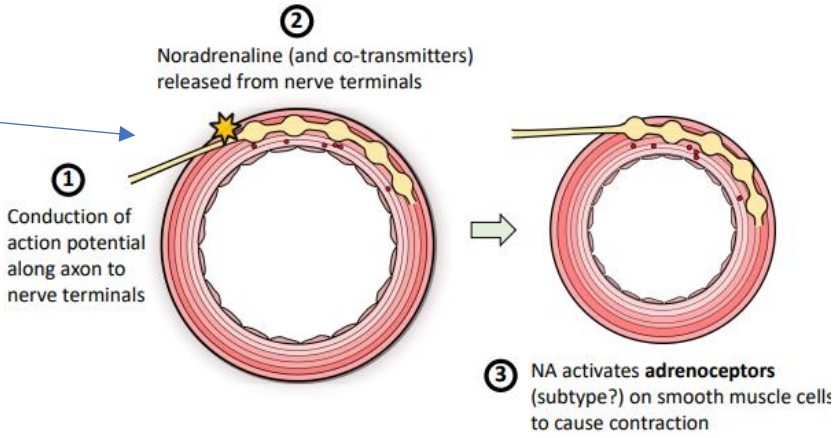
Drug names – most marketed drugs have both a TRADE name and a GENERIC name i.e. Ventolin (trade) is salbutamol (generic) or Prozac (trade) is fluoxetine (generic)

Additional notes

- Peptide drugs injected – oral would be digested in stomach (e.g. insulin)
- '-Statins' are cholesterol lowering drugs; inhibit a particular enzyme in the liver

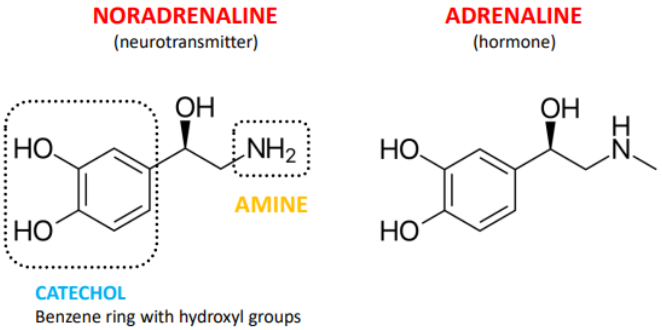
Lecture 6 Notes – Adrenergic Pharmacology

Sympathetic Nerve-Mediated Responses in Peripheral Tissues



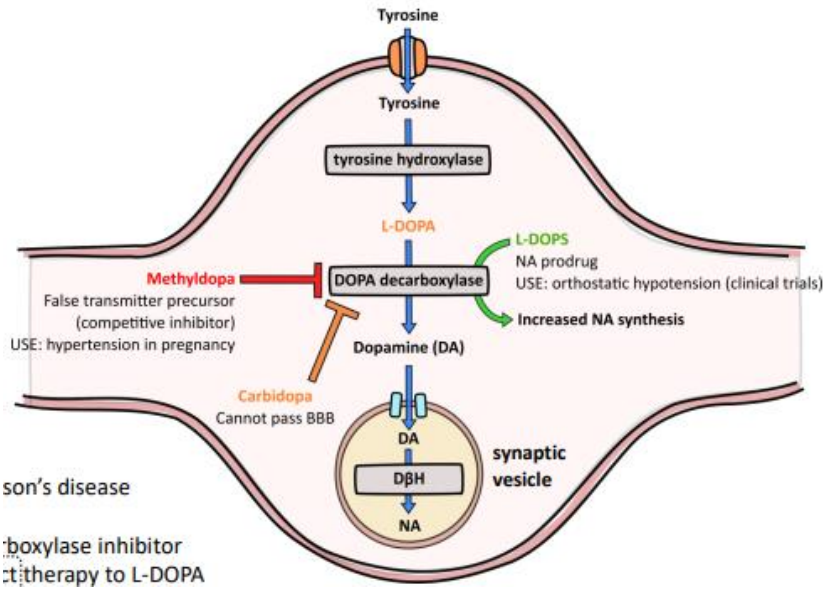
Key Adrenergic Mediators

- Noradrenaline (NA): a neurotransmitter
- Adrenaline: a hormone
- Have similar but not identical pharmacological properties
- Adrenergic mediators are **CATECHOL**AMINES



Catecholamine Synthesis (In sympathetic nerve terminals)

- Tyrosine – tyrosine hydroxylase – L-DOPA – DOPA decarboxylase – Dopamine (DA) – (INTO SYNAPTIC VESICLE) – DA – DbetaH – NA
  - **Methyldopa** and
  - **L-DOPS** are drugs that act on DOPA decarboxylase
  - So does **Carbidopa** (cannot pass BBB)



Lecture 10 Notes – Human Variability in Drug Responses – Pharmacogenetics

Differences in terms

- **Pharmacogenetics:** studies variability in drug responses that relate to genetic differences
- **Pharmacogenomics:** utilisation of global genomic technologies (gene expression profiling etc.) to serve pharmacogenetic aims

Other related terms

- **Toxicogenomics:** how genetic variation contributes to drug toxicity
- **Ethnopharmacology:** the study of variable drug responses that relate to ethnic differences

Why is all this important:

- Adverse drug reactions (ADRs):
    - Costly to patient, costly to healthcare system
- Lack of drug efficacy in some patients
- Economic issues:
    - Withdrawal of drugs pre- or post- marketing due to ADRs or lack of efficacy
    - Huge costs to pharmaceutical industry

From where does variability arise?

- DNA polymorphisms
    - Germ line mutation (inherited)
    - Somatic mutations (cancers, mostly)
    - Often single nucleotide polymorphisms (SNPs) – although other mutation also exist
- Epigenetics
    - Also important, but currently less well examined

How does this variation change phenotype/drug responsivity?

- Change in protein structure and/or function
    - Direct
    - Alternative splicing
- Change in gene transcription and hence quantity of protein produced
    - Promoter region polymorphisms etc

Detection of polymorphisms

- Many methods have been developed for the detection of polymorphisms.
    - DNA sequencing for original identification of polymorphism.
    - This time consuming/expensive?
- If SNP known, high throughput systems have been developed – 'microarrays'

Skeletal muscle relaxant: suxamethonium

- Suxamethonium (active) –(Plasma (pseudo/butyryl) cholinesterase) → inactive

Lecture 13 Notes – How do we Know if it Works? The Evolution of Medical Therapies

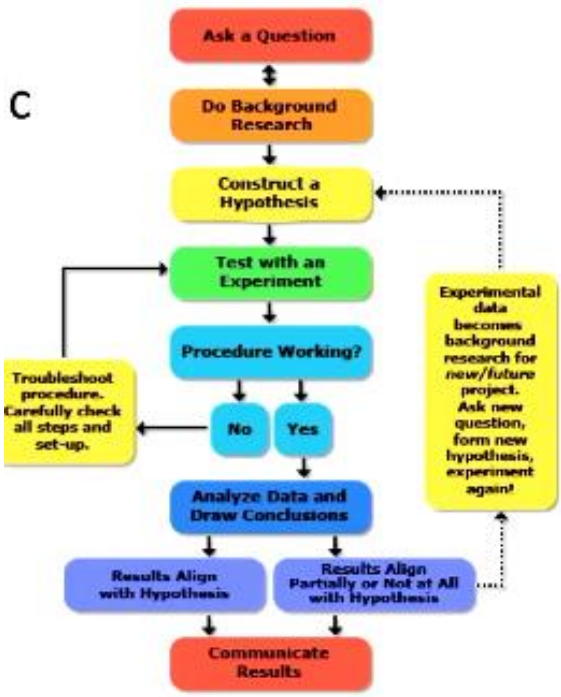
Spirits as cause of disease

- Illness or disease caused by evil spirits or as punishment
- Trepanning/trephining, oldest known surgical procedure
    - Drill through skull to dura mater to 'release the bad spirits'
    - Popular up until 18th century

How has history influenced our present day 'scientific process of investigation'?

- Hippocrates – do no harm in treatment
- Paracelsus – 'dose determines effect' (EFFICACY)
- Plant-based medicines

The Scientific Process



The Evidence Pyramid

- Case report: is something that is published about a single person i.e. something unusual
- Case series: is about a patient
- 'Studies' have larger number of individuals, with a known outcome, looking for causation
    - E.g. looking at lung cancer – smokers vs non-smokers, individual backgrounds, place of work, other factors etc.
- Randomised Controlled Double Blind Studies: experimental study involving intervention amongst groups
    - gold-standard for human-based clinical evidence
- Systematic Reviews and Meta-analyses: statistical evaluation of multiple, for example, clinical trials

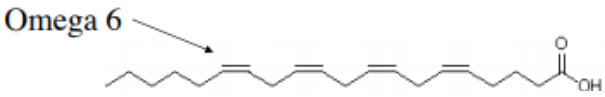
Clinical trial history

- **1747 –** James Lind
    - 12 patients; 6 groups
    - Scurvy
    - Oranges and lemons

Lecture 14 Notes – Bioactive Lipids as Therapeutic Targets

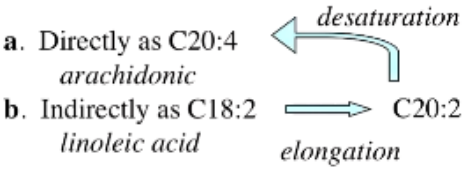
Arachidonic acid (AA)

- A precursor for biologically active lipids
- Sterified in membranes
- 20 carbons long, 4 double bonds
- An 'Omega 6'
    - Double bonds are 6 carbons away from methyl end



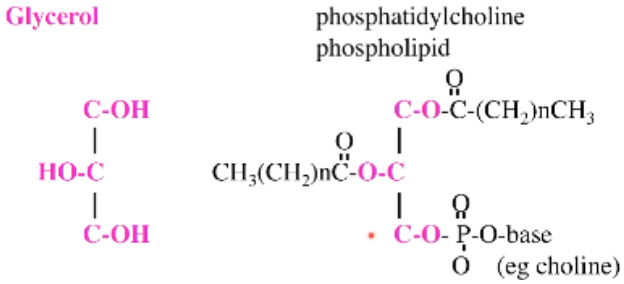
Where does arachidonic acid come from?

- Poly-unsaturated fatty acids (PUFA)
- Diet – usually dominated by omega-6 PUFAs
- Transported bound to plasma proteins
    - Keep them away from enzymes that would convert them to bioactive compounds
- Very little "free" either extra- or intra-cellularly
- Deep sea fish enriched in omega-3:
    - Alpha-linolenic (C18:3) and eicosapentaenoic (C20:5)
        - Reduce production of active arachidonic acid metabolites



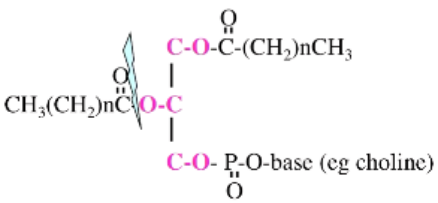
Where does arachidonic acid go?

- Stored esterified in membrane phospholipids
    - PM
    - Nuclear membrane



How is arachidonic acid released from membranes?

- **Phospholipase A_2** =
    - Activated by INCREASE in INTRAcellular calcium
    - Releases arachidonic acid from membrane – now available to particular enzymes in the cell its been liberated from
- Many snake venoms contain phospholipase A_2 in large amounts



What happens next?

- Metabolism to eicosanoids – biologically active metabolites of arachidonic acid
- The type(s) of eicosanoid depends on the cell type
- Metabolism depends on phenotype
- Two types of cyclo-oxygenase expressed in all cells (Cyclo-oxygenase introduces oxygen, then electrons)
    - Constitutive (COX-1) is usually more prominent; physiological prostaglandins (PGs)
        - 'House-keeper' – keeps epithelium in good conditions; keep gastric mucosa free of ulcers

Lecture 20 Notes – Drugs in CV System (1): Heart

CV System

- Major functions:
  - Transport and distribute essential substances
  - Remove by-products of metabolism
  - Humoral (hormone) communication
  - Regulation of body temp.

Components of CV system

- Pump (heart) which propels blood to:
  - 1st lungs for O2/CO2 exchange (pulmonary circulation) via right atrium/ventricle; then
  - 2nd all other tissues of the body (systemic circulation) via left atrium/ventricle
- Distributing tubes (arteries/arterioles)
  - High pressure system (17% blood vol.)
- Collecting tubes (veins/venules)
  - Low pressure system
  - Reservoir (70% blood vol.)
- Extensive system of thin vessels (capillaries) for rapid exchange between tissues and vascular channels
  - NOT targeted by any drugs as no nerve innervation/smooth muscle

Components of BP

- BP = CO x TPR
  - TPR – tonic Symp. Nervous system control
  - Humoral control: e.g. Adrenaline, Angiotensin II
  - Local control: particular vascular bed may release nitrous oxide or prostacyclin (relax or constrict)

Sites of BP regulation

- Heart (BP depends on HR and SV)
- Arteries (TPR – is the after load on the left heart) (BP depends on HR)
- Veins
- Kidney – regulates intravascular fluid volume

Control of HR

- **Symp:** Increased sympathetic activity → NA release → B1 receptor (in SA node) → Increase HR - chronotropic effect (in SA node)
- **Adrenal Gland:** Increase circulating adrenaline → ADR → B1 receptor → Increase HR (in SA node)
- **Para. (Vagal outflow):** Increased para. → ACH → M2 → Decreased HR (in SA)