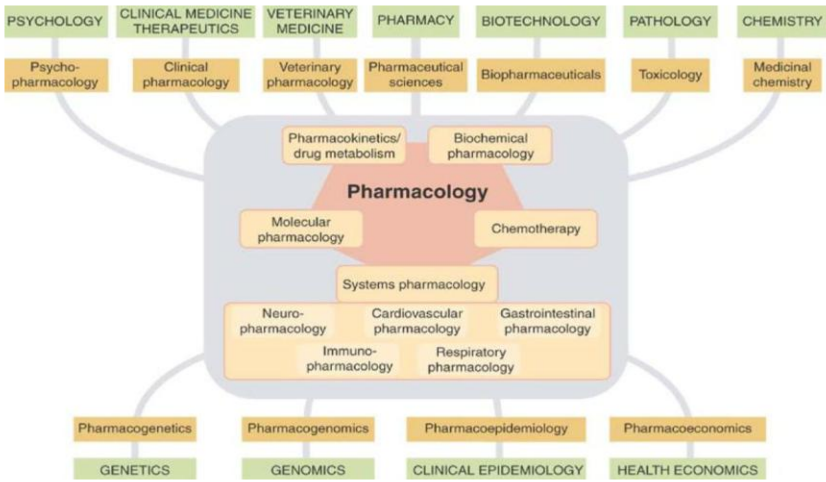
Clinical Pharmacology (400981) Study Notes – Semester 2, 2011

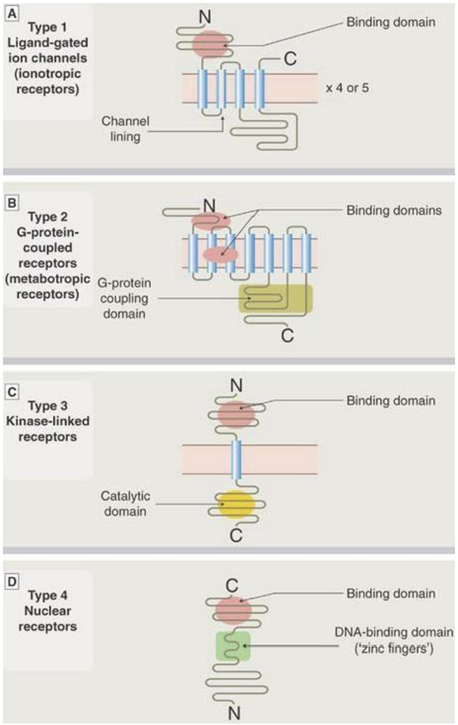
Week 1 – Introduction to Pharmacology



- A *drug* is chemical substance with a known structure which produces a biological effect. *Pharmacology* is the study of drugs (effects/impacts) on the human body; *clinical pharmacology* is the study of substances used to prevent, diagnose & treat disease. *Toxicology* deals with the undesirable effects of drugs.
- Many *subdivisions,* **e.g. Pharmacogentics & Pharmacogenomics studies genetics & use of genetic information respectively.**
- Use of substances to cure diseases is as old as human race, **e.g. Opium Poppy (*Papaver Somniferum*) used for pain management, Fox Glove (*Digitalis spp*.) used for heart disease & Ginkgo (*Ginkgo Biloba*) used for dementia**
- History:
  - *The Age of Natural Substances:* therapeutic agents were plants/plant extracts, **e.g. traditional Chinese medicine**
  - *The Age of Synthetic Agents:* last 150-200 years; 20th century modern chemistry/chemical technology – mass production of synthetic drugs
  - *The Age of Biotechnology:* last 30-40 years; genetically modified micro-organisms in production of various endogenous (made from within) proteins/peptides (recombinant DNA technology – incorporate DNA into bacteria) & gene therapy/manipulation (modify molecular structure)
- *Source of Drugs:*
  - *Micro-organisms:* fungi used as source of antibiotics
  - *Plants:* Opium Poppy
  - *Humans & other animals:* adrenaline
  - *Minerals:* iodine, iron products
  - *Laboratories:* synthesised products, **e.g. beta-blocker**
- *Drug Names:*
  - *Chemical Name:* description of drug's chemical composition & molecular structure; important to medical chemists but too long/difficult to remember for clinicians
  - *Approved (Generic)/Non-Proprietary Name:* given by manufacturer & approved by drug regulatory authority, **e.g. amoxycillin derived from chemical name amino-hydroxybenzylpenicillin.**
  - *Proprietary (Brand) Name:* invented by manufacturer to market drug, **e.g. Amoxil for amoxycillin.** Problems: 1 drug can potentially have unlimited no. of brand names, practically impossible to remember/use all of them, brand names vary internationally,

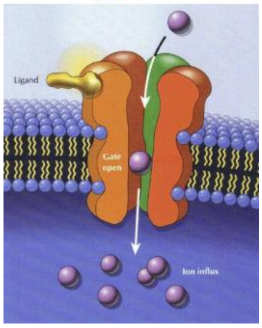
brand names for very different drugs sound similar leading to prescription mistakes. This encourages prescribers to use generic instead of brand names.

Week 1 & Week 2 - Pharmacodynamics



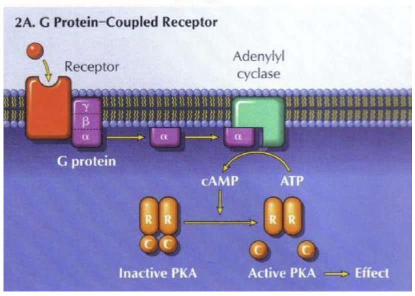
- Study of the mechanism of drug action on living tissue; response of tissues to specific chemical agents
- Drugs act on 4 main types of proteins (regulatory proteins) which mediate the actions of hormones, neurotransmitters & autocoids; drugs work by chemical & physical action.
  - *Receptors:* complex macromolecules to which endogenous mediators (**e.g. hormones**) bind & initiate changes in cellular function. Most receptors are embedded in cell membranes & less are found inside the cell. To reach *intracellular receptors*, drugs must be *lipid-soluble* to pass through the cell membrane. All receptors that exist have a physiological role; no receptors had been specifically allocated for drugs. 4 main types of receptors:
    - *Type 1 Ligand-Gated Ion Channels:* coupled directly to ion channels & their activation leads to ion channel opening & movement of certain ions through the cell membrane. Depending on type of ion channel, ionic movement causes changes in resting membrane potential in form of depolarisation/hyperpolarisation. Response time: very fast (milliseconds), **e.g. nicotinic receptors, GABA & some serotin receptors**

Type I



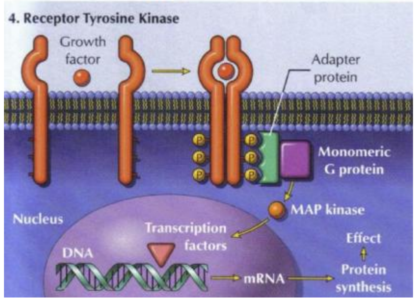
    - *Type 2 G-Protein-Coupled Receptors:* coupled to various *second messengers* such as cyclic monophosphate (cAMP) via membrane bound G-proteins. Second messengers may produce several intracellular changes: *ion channel modulation* (effect on resting membrane potential or muscle contractility via regulating Ca^{2+} entry), *activation of certain enzymes & release of Ca^{2+} from intracellular stores* located in *endoplasmic reticulum* (Ca^{2+} control many important intracellular processes). Response time slower than Type 1 (seconds), **e.g. muscarinic receptors & noradrenergic receptors.** Signal Amplification: effect of G-protein coupled receptors doesn't occur linearly; instead it's significantly amplified. Single drug molecule binds to receptor→ activates up to 100 G-proteins→ each G-protein activates 1 *adenylyl cyclise molecule*→ produces up to 1000 cAMP molecules→ each cAMP activates 1 *protein kinase*→ activate upon 1000's of substrate molecules (other enzymes)→ cAMP is quickly broken down by phosphodiesterase.

Type 2

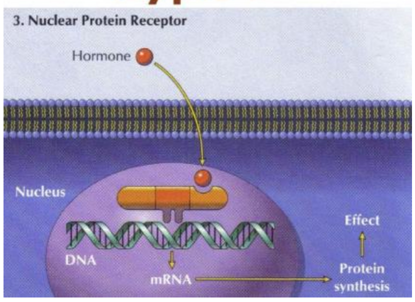


- *Type 3 Kinase-Linked Receptors:* are directly linked to *kinase enzymes* which cause alterations of gene transcription hence *protein synthesis*. Response time slow (hours), **e.g. epidermal growth hormones, atrial natriuretic peptide & nerve growth factor.**
- *Type 4 Nuclear Receptors:* only receptors located inside cell (*cytoplasm or nucleus*). After formation, *drug-receptor complex* interacts with *nuclear DNA* & cellular effects are produced due to gene activation & ↑ protein synthesis. Response time similar to that of Type 3 (hours), **e.g. steroid hormones & drugs (very lipid soluble compounds) act on such receptors.**

Type 3



Type 4



- *Enzymes:* interaction between drugs & cellular enzymes. Drugs may act in form of *competitive & non-competitive inhibition*:
  - *Competitive:* drug act as substrate similar to reversibly blocking enzyme's active site & inhibit the biochemical process, **e.g. all *angiotensin converting enzyme (ACE – vasoconstrictor) inhibitors* used in management of HTN & heart failure.**
  - *Non-Competitive:* drug forms irreversible bond with enzyme relatively permanently blocking its function, **e.g. aspirin on *cyclo-oxygenase* that control formation of *inflammatory mediator's prostaglandin*.** Many anticancer drugs inhibit enzymes involved in nucleic acid synthesis suppressing cell division.

Examples	Receptor	Enzyme	Ion channel	Carrier system
Aspirin reducing formation of prostaglandins from arachidonic acid		✓		
Local anaesthetics reducing generation and conduction of nerve impulses			✓	
Antidepressant Aropax reducing uptake of serotonin in the synaptic end bulb				✓
Antihypertensive Renitec reducing conversion of angiotensin I into angiotensin II		✓		
Antihypertensive Adalat relaxing blood vessel smooth muscles by reducing calcium entry			✓	
Weight-loss drug Xenical reducing lipid absorption from the gut		✓		
Drug digoxin used in management of heart failure				✓
Drug Aricept increasing CNS acetylcholine activity in Alzheimer's disease		✓		
Antispasmodic drug Buscopan relieving crampy abdominal pain	✓			
Drug Dimetapp used in form of spray as nasal decongestant - vasoconstriction	✓			
Diuretic drug Lasix increasing elimination of electrolytes and water in urine				✓
Drug Losec used in management of peptic ulcer and gastric reflux				✓
Drug Viramune used in management of HIV infection		✓		
Anticoagulant warfarin used in prevention of venous thrombosis		✓		

- *Carrier Molecules (Active Transport Systems):* Ions & other large molecules require active (energy-consuming) carriers (pumps) to move across cell membrane when they aren't lipid soluble enough & when they are moving against their concentration gradient. If the movement of molecules by carrier-mediated transporter is in same direction (*symporter*) & opposite direction (*antiporter*). Drug may interfere & inhibit activity of such systems, **e.g. antidepressants inhibit re-uptake of noradrenalin or serotin into the nerve terminals after synaptic transmission→ ↑ effect on postsynaptic receptors as it remains in synapt for longer period of time**
- *Ion Channels: Voltage-Gated & Ligand-Gated Ion Channels* also serve as direct targets for drug action. Most common interaction type involves physical blocking of channel by frug molecule→ prevents transfer of ions across cell membrane, **e.g. calcium**

channel blocking drugs that block calcium channels in the heart & smooth muscle reducing their capability & local anaesthetics block sodium channels & generation/transmission of sensory impulses.

- *Drugs that work by simple Chemical Action:* few drugs; basic inorganic compounds or none-complex organic compounds, **e.g. magnesium hydroxide (antacid; base substance) in treatment of peptic ulcer (acidic environment).**
- *Drugs that work by Physical Action:* few drugs; act by a purely physical mechanism, **e.g. drugs that act on osmosis – osmotic laxatives & diuretics (↑ osmotic pressure in lumen of intestines).**
- *Receptors – Drug Receptor Binding:* most drugs produce their effects by binding to various target protein molecules. These bonds are reversible (not permanent; only rarely the bond is irreversible via strong covalent bonds) & occur via *electrostatic forces* **such as hydrogen bonds &** *weak electrostatic forces* ***such as van der Waals forces.*** Strength & duration of bonding depends on no. of such bonds which depends on a drug's shape/molecular size & whether it has a complimentary fit to target. Chemical structure & electrical charge also effects bonding.
- *Receptors – Factors Affecting Receptor Occupancy by Drugs:* pharmaceutical response is proportional to receptor occupancy (no. of receptors to which drug molecules adhere to). Receptor occupancy depends on:
  - *Drug Concentration:* depends on dose. Concentration is the key to finding target (increasing dose).
  - *Receptor Concentration:* usually constant but may change
  - *Drug Affinity:* tendency of drug to bind to a receptor; although it is random (random binding) – no actual attraction, travel throughout body until target is found. Affinity is seen after binding (after good fit) – difficult to dislodge after binding because of the good fit – this is affinity. The longer the drug stays, the stronger the affinity, but doesn't stay forever (or would be permanent). Drug doesn't leave; when conditions are sufficient – the drug is pushed out – thus, the better the fit (the more appropriate the molecular/chemical structure), the less likelihood that the drug will leave. Drug with high affinity will achieve a large degree of receptor saturation at low concentrations
- *Agonist:* compounds that bind & activate receptors; mimic action of endogenous agonists (mediators). Produce effect when bonding.
  - *Full Agonists:* compounds that produce largest response that can be produced by that drug in high concentration (maximal response)
  - *Partial Agonists:* compounds that can only produce a sub-maximal response
  - The difference between *full & partial agonists* lies in the r/ship b/w occupancy & response. Full agonists have high efficacy; partial agonists have median efficacy (how effective effect is after binding)