**Basics of Pharmacology**

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**What is pharmacology?**

- Pharmacology may be defined as the study of the effects of drugs on the function of living systems
- **Pharmacodynamics**
  - The mechanism(s) of action of a drug
    - What the drug does to the body
- **Pharmacokinetics**
  - How the drug moves in the body
    - What the body does to the drug

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**What is a drug?**

- Chemical substance of known structure, which when administered produces a response
- Conventional low-molecular-weight organic molecules
- Biopharmaceuticals or bioproducts
  - Proteins produced by genetic engineering of cells
    - Insulin, growth hormone
  - A rapidly increasing number of monoclonal antibodies
    (used in cancer, autoimmune diseases…)
  - Enzymes

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**How drugs act: general principles**

- In disease, normal physiological functions may become disturbed and alteration/normalization of those functions is often beneficial
- Most drugs either activate or inhibit physiological functions of the body
- Drugs may modulate normal message flow/“communication” at various levels
  - Between organs/tissues
  - Between cells (neurotransmission)
  - At the intracellular level (affecting signalling pathways)

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**Transmission of messages in the body**

- Nerve conduction/neurotransmitters
- Hormones
- Local mediators
- Intracellular signalling cascades

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**Ions mediate excitation and inhibition of cells**

- $Ca^{2+}$ or $Na^+$ in = Excitation
- $K^+$ out or $Cl^-$ in = Inhibition
Function of synapse
1. Action potential arrives in presynaptic terminus
2. Release of neurotransmitter
3. Neurotransmitter diffuses across synaptic gap
4. Neurotransmitter binds to postsynaptic receptor
5. Activation or inhibition of target cell
6. Inactivation of neurotransmitter

Synapses as drug targets
1. Propagation of impulse
2. Formation and release of neurotransmitter
3. Postsynaptic receptors
4. Presynaptic receptors
5. Enzymatic inactivation of neurotransmitter
6. Reuptake of neurotransmitter

Neurotransmitters and receptor classification

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor names and subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D (subtypes 1-5: D₁-D₅)</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Alpha (subtypes 1 &amp; 2: alpha₁-α₂); beta (subtypes 1-3: beta₁-β₃)</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT (subtypes 1-7: HT₁-HT₇)</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Muscarine (subtypes 1-5); Nicotine</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA, AMPA, kainate, mGluR1-8</td>
</tr>
<tr>
<td>GABA</td>
<td>GABA (subtypes A-C: GABAₐ, GABAₐ, GABAₐ)</td>
</tr>
<tr>
<td>Opioid peptides</td>
<td>Mu, delta, kappa</td>
</tr>
<tr>
<td>Histamine</td>
<td>H (subtypes 1 &amp; 2: H₁, H₂)</td>
</tr>
</tbody>
</table>

Hormones as therapies

- Thyroxin
- Glucocorticoids
- Insulin
- Oestrogens

Local mediators
- Cells release substances which modulate the function of neighbouring cells
- Inflammatory cells are one source of such substances
- Examples of substances include prostaglandins, which affect inflammatory reaction and body temperature

Signalling inside cells
- Activation of cell membrane receptors modulates levels of intracellular signalling factors known as second messengers
- Examples of second messengers include cyclic AMP, cyclic GMP, Ca²⁺
- Some drugs (e.g. Viagra) modulate the level of second messengers directly (i.e. not via cell surface receptors)
Insulin increases blood glucose transporter

"A drug will not work unless it is bound"
Paul Ehrlich
(Distinguished German physician 1854-1915)

Drug targets
• The effect of most drugs results from their binding with a macromolecule within the body
• This macromolecule is the target molecule
• Many target molecules are proteins and therefore also called target proteins

Drug target molecules
• Four main kinds of proteins are commonly involved as primary drug targets
  – Physiological receptors
  – Ion channels
  – Enzymes
  – Transporter molecules
• There are other targets such as
  – Nucleotides
  – Cytokines and other messengers

Physiological receptor families

1. G protein-coupled receptors (GPCRs)
2. Ion channel-gated ion channels
3. Enzyme-linked receptors
4. Nuclear receptors
Ligand-gated ion channel receptors
- Ligand-receptor binding causes the ion channel to open
- Different channels are permeable to different ions (Na\(^+\), K\(^+\), Ca\(^{2+}\) or Cl\(^-\))
- Examples:
  - GABA\(_A\) receptors
  - nicotinic receptors
  - NMDA-receptors
- Action evident in milliseconds

G-protein-coupled receptors
- The most common target for drugs
- Multiple receptor subfamilies
- Ligand binding “activates” G-protein, which further affects the activity of target enzyme or ion channels
- Action evident in seconds

Enzyme-linked receptors
- Receptor is linked to enzyme
- Ligand binding activates intracellular enzyme
- Like insulin receptor, actions in minutes-hours

Enzyme (or kinase) receptor
Nuclear receptors
- Ligand penetrates cell membrane and binds to soluble receptor inside cell
- Ligand-receptor complex moves to nucleus and affects activation of genes and protein synthesis
- Examples: oestrogens, corticosteroids
- Actions in hours

Drug target proteins
- Alternatives to physiological receptors as primary drug targets
  - Ion channels (direct effects)
  - Enzymes
  - Transporter molecules

Direct effects on ion channels
- Two main families of ion channels
  - Ligand-gated ion channels - physiological receptors
  - Voltage-sensitive ion channels, which are activated by change in voltage, e.g. in nerve conduction, smooth muscle contraction
- Drugs can directly block the channels
  - Local anaesthetics, e.g. lidocaine
  - Calcium channel blockers in cardiovascular medicine
- Drugs may affect recovery from activation
  - Many antiepileptics
  - Arrhythmia drugs

Ion channels as direct drug targets
- Normal function
- Inhibition

Enzymes as direct drug targets
- Only few enzymes are direct targets for current drugs

Transporters as direct drug targets
- Transporters carry molecules through lipid membranes
- Many neurotransmitters and other messengers are taken up by cells
Transporters as direct drug targets

- Antidepressants inhibit the transporters which carry serotonin and/or noradrenaline back to presynaptic neurones

From target molecule binding to therapeutic response

- Binding of the drug to the target molecule
- Modulation of target molecule function
- Modulation of cellular function
- Modulation of organ function
- Therapeutic response

Drug-target interaction

- A drug has to bind to its target molecule in order to initiate the cascade of reactions leading to a therapeutic response
- Important terms related to drug binding to target molecule/receptor and response
  - Affinity and potency
  - Competitive and non-competitive binding
  - Agonist, antagonist, response
  - Efficacy, maximal response
  - Specificity, selectivity

Antibodies as binding molecules

- Many biological drugs are antibodies which are produced in cell cultures
- Antibodies
  - normally formed by the immune system against bacterial and virus particles
- Antibodies can be targeted against other proteins such as cytokines, receptors and enzymes
- Increasing numbers of new drugs are monoclonal antibodies (Mab)

Other examples of target molecules and mechanism of drugs

- Nucleotides
  - Antibiotics and cytostats
- Precursor molecules for endogenous compounds
  - L-dopa used in Parkinson’s disease
- Antibodies against various targets

From target protein binding to therapeutic response
Affinity and potency

- **Affinity** indicates how strongly a drug occupies its receptors
  - High affinity = low concentrations occupy receptors → lower doses are needed
  - Low affinity = high concentrations needed to occupy receptors → higher doses are needed
- **High potency** means that the drug has high affinity for the receptor and that low doses are sufficient for an effect

Competitive and non-competitive binding

- **Competitive or reversible binding**
  - Ligands have very short-lasting binding to the target molecule → ligands are competing for the same binding site → competitive or reversible binding
  - Non-competitive or irreversible binding
    - Ligand has very long-lasting binding to the target molecule → therefore other ligands cannot compete for binding → non-competitive or irreversible binding

Receptor agonists and antagonists

- Agonists bind to and activate receptors, producing a similar response as endogenous agonists
- Antagonists bind to the receptor but do not activate them
  - In a physiological system antagonists have opposite effects to agonists
  - Antagonists inhibit the agonist response if an agonist or endogenous ligand is present
  - Antagonists do not produce a response if no agonist or endogenous ligand is present

Drug-receptor interactions

- **Agonist**
  - Binding is governed by affinity
  - Activation leads to response
  - \( A + R \rightarrow AR \rightarrow AR^* \rightarrow \text{RESPONSE} \)

- **Antagonist**
  - \( B + R \rightarrow BR \rightarrow \text{NO RESPONSE} \)

Partial agonist

- Partial agonist (blue) binds to the receptor but causes lesser maximal response than a full agonist (red)
- Full agonist: Large stimulus at cellular level → Large effect
- Partial agonist: Small stimulus at cellular level → Small effect
Response to beta-blocker and adrenaline

Rest Exercise “Exercise” and Beta-blocker Rest and adrenaline

Agonist dose-response curve in the presence of a competitive antagonist

Dose of Drug A (mg)

Efficacy: maximal response

- Efficacy refers to the size of the maximal response to a drug
- After maximal response is achieved higher doses increase only side-effects

Drug specificity

- Drugs with high specificity either (a) bind only to their target receptors or (b) bind to those receptors with at least 100-fold more affinity than to any other receptors
- Non-specific drugs bind also to other receptors with similar affinity as their target receptors
- Unspecific binding to non-target receptors may cause side-effects

Dose

- Right dose is crucial in drug treatment
- Dose too low: only placebo effect
  - Receptors are not occupied by drug at target tissue
- Right dose: therapeutic response
  - Receptors are occupied by drug at target tissue
- Overdose: side-effects, poisoning?
  - Excessive number of target receptors occupied by drug
  - Unspecific binding of drug to non-target receptors

ED$_{50}$ and EC$_{50}$

Cumulative frequency of responders

Percentage of responders

Dose or plasma concentration
Reasons for variability in therapeutic response

- Age
- Size
- Gender
- Genes
- Diseases
- Food, other drugs

Drugs and time to response

- Mechanism of action affects how fast a therapeutic response appears
  - Pain killers (opioids and NSAIDs)
    - Effects typically emerge rapidly
  - Immunosuppressants
    - Slow onset of effect on inflammatory pain
- Some drugs require adaptive responses before therapeutic effect is seen
  - Antidepressant effects emerge after ~3 weeks delay

Risk-benefit evaluation!

Therapeutic window of morphine

Margin of safety

- Margin of safety indicates how much therapeutic dose may be increased without serious side-effects

Number needed to treat (NNT)

- NNT is more sophisticated measure of risk-benefit analysis
- NNT is the number of patients who need to be treated in order for one to show beneficial effect
Vascular smooth muscle cell-drug targets?

Drug targets
1. Postsynaptic receptor
2. Presynaptic autoreceptor
3. Aminetransporter
4. Enzymes
5. Precursor
6. Ion channels

Synapse

Neurotransmitters and receptors in autonomic nervous system?

Muscle

Ion channels can be regulated in various way by drugs

Ion channel receptors
GPCR
Nuclear receptors indirectly
Direct channel block
Allosteric modulation