Principles of pharmacodynamics

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Table of content

- Definition of pharmacodynamics
- Mechanisms of drug action
- Type of drugs-receptor interaction
- Tachyphylaxis, desensitization and tolerance
- Dose-response curves
Describes the effects of drugs on the body
Mechanisms of drug action

A. Dependent on physicochemical properties

Antacids neutralizes gastric acid
Dicobalt edetate chelates cyanide ions
Sugammadex selectively chelates rocuronium

B. Action on enzymes, voltage-gated ion channels and receptors
B. Drug action on enzymes, voltage-gated ion channels and receptors

1. Enzymes

Most drugs that interact with enzymes are inhibitors.

Enzyme inhibition may be:
- Competitive (edrophonium for anticholinesterase)
- Non-competitive or irreversible (aspirin for cyclooxygenase and omeprazole for Na/H ATPase)
B. Drug action on enzymes, voltage-gated ion channels and receptors

2. Voltage-gated ion channels

Involved in conduction of electrical impulses associated with excitable tissues in muscle and nerve.
Several drugs block these ion channels:
- **Local anaesthetics** act by inhibiting Na channels in nerve membrane.
- Several **anticonvulsants** block similar channels in the brain.
- **Calcium channel blocking agents** act on vascular smooth muscle ion channel.
- **Antiarrhythmic agents** block myocardial ion channels.
B. Drug action on enzymes, voltage-gated ion channels and receptors

3. Receptors

A drug acting at a R may have an effect (agonist), prevent the action of a natural ligand (inhibitor) or reduce a constitutive effect of a R (inverse agonist)

3 classes of R depending on mechanism of action:
1. Altered ion permeability: ion channels
2. Production of intermediate messenger
3. Regulation of genes transcription
3. Receptors

1. Altered ion permeability: ion channels

- Ligand binding causes a conformational change in the structure of this membrane protein complex allowing the channel to open and so increasing the permeability of the membrane to certain ions

- 3 ligand-gated ion channel families:
  1. The pentameric family (nicotinic Ach, GABAa, 5-HT3)
  2. Ionotropic glutamate (NMDA)
  3. Ionotropic purinergic receptor
3. Receptors

1. Altered ion permeability: ion channels
3. Receptors

2. Production of intermediate messenger

- There are several membrane-bound systems that transduce a ligand-generated signal presented on one side of the cell membrane into an intracellular signal transmitted by intermediate messengers

- The most common is the G-protein coupled R system (GPCR system)

  - GPCR binds a ligand on its extracellular side and the resultant conformational change increases the likelihood of coupling with a particular type of G-protein resulting in activation of intermediate messenger at the expense of GTP breakdown
3. Receptors

2. Production of intermediate messenger
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- G-protein coupled Receptor and G-proteins
  - Ratio of G-protein to GPCR is about 100 to 1, allowing signal amplification
  - Adenylyl cyclase catalyzes the formation of cAMP, which acts as a final common pathway for a number of extracellular stimuli
2. Production of intermediate messenger

- G-protein coupled Receptor and G-proteins

  - cAMP formed under the regulation of the G-protein is broken down by the action of the phosphodiesterases. PDE inhibitors prevent breakdown of cAMP so that intracellular levels rise

  - Positive inotropy is possible by either increasing cAMP levels (with B-adrenergic agonist or a non-adrenergic inotrope such as glucagon) or by reducing the breakdown of cAMP (with PDE III inhibitor such as milrinone)
2. Production of intermediate messenger

- Membrane guanylyl cyclase
  - Atrial natriuretic peptide mediate their actions via membrane-bound receptors with intrinsic guanylyl cyclase activity. As a result, cGMP levels increase and it acts as secondary messenger by phosphorylation of intracellular enzymes.
  - Nitric oxide exert its effects by increasing the levels of intracellular cGMP by stimulating a cytosolic guanylyl cyclase.
2. Production of intermediate messenger

- Membrane tyrosine kinase
  - Insulin and growth factor act through the tyrosine kinase system
  - Activation of tyrosine kinase at the inner surface of the cell, catalyses phosphorylation of target proteins via ATP
  - Typically minutes to hours
3. Regulation of gene transcription

- Steroids and thyroid hormones act through intracellular receptors to modify the expression of DNA and RNA.

- The lipid-soluble agonist passes through the cell membrane to interact with the nuclear receptor, leading to alteration of DNA transcription.

- Typically up to several hours.
3. Regulation of genes transcription

3 Regulation of gene transcription. Receptors are sited within the cell membrane or the nucleus.
Down and up-regulation of receptors

- **Downregulation**: Chronic stimulation (e.g. asthmatics taking β2-adrenergic receptor agonists) results in a decreased number of receptors.

- **Upregulation**: Understimulation (e.g. following spinal cord injury) leads to an increased number of receptors.
2 properties of a drug that determine the nature of its pharmacological effect are affinity and intrinsic activity

- **Affinity**: refers to how well or avidly a drug binds to its receptor. Is determined by the $K_d$ or $K_a$ of the drug.

- **Intrinsic activity (IA)** or efficacy refers to the magnitude of effect the drug has once bound. IA takes a value between 0 and 1, although inverse agonists can have an IA between -1 and 0.
Type of drugs-receptor interaction

- Agonist: has significant receptor affinity and full intrinsic activity ($IA = 1$)

- Antagonist: significant receptor affinity but no intrinsic activity ($IA = 0$)

- Partial agonist: significant receptor affinity but only fractional intrinsic activity ($0 < IA < 1$)

- Inverse agonist: can be full or partial ($-1 < IA < 0$)
Type of drugs-receptor interaction

Full agonists

- Drugs able to generate a maximal response from a receptor
- They have, not only high affinity, but also high IA
- The potency of the drug is determined by its $K_d$: the lower $K_d$ the higher the potency
- For many drugs, the ED50 corresponds to the $K_d$
Type of drugs-receptor interaction

Partial agonists

- IA less than 1, with a submaximal effect
- They failed to achieve a maximal effect, even in very high dose (with full receptor occupancy)
- They may act as either agonists or antagonists depending on circumstances
- If used alone, they are agonists
- If used with low dose of full agonist, they produce additive effects, but switches to competitive antagonism as the dose increases
Type of drugs-receptor interaction

Inverse agonists

- Inverse agonists bind to these receptors and greatly reduce the incidence of the active conformation responsible for this constitutive activity, as a result inverse agonists appear to exert an opposite effect to the agonist.

- Inverse agonist will favour a shift of equilibrium toward inactive receptors whereas a competitive antagonist binds equally to active and inactive receptors and simply prevents the agonist from binding.
Type of drugs-receptor interaction

Antagonists

- Antagonists have affinity but no intrinsic activity
- Their binding may be reversible (competitive or non-competitive) or irreversible

- Competitive antagonists

  The effect of the antagonist may be overcome by increasing the concentration of the agonist – the two molecules are competing for the same receptor and the relative amounts of each (combined with affinity) determine the ratios of receptor occupation
Competitive antagonists

- In the presence of a competitive inhibitor the log (dose) versus response curve is shifted to the right along the x-axis

- Examples:
  - Non-depolarizing muscle relaxants competing with acetylcholine for cholinergic binding sites at the nicotinic receptor of the neuromuscular junction
  - B-blockers competing with dobutamine at Beta-adrenergic receptor sites in the heart
Non-competitive antagonists

- Do not bind to the same site as the agonist
- Their antagonism results from preventing receptor activation through conformational distortion
- Their action cannot be overcome by increasing the concentration of an agonist

Examples:

- Ketamine at NMDA receptors in CNS
Non-competitive antagonists

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Allosteric modulation of receptor binding

- Some drugs can bind to sites distant from the agonist receptor site and still alter the binding characteristics of the agonist.

- They may either reduce or increase the activity of a given dose of agonist without having any discernible effects of their own.

- Examples:
  - Positive allosteric modulator effect of benzodiazepines on the activity of GABA at the GABA receptor complex.
Irreversible antagonists

- May either bind irreversibly to the same site as the agonist or at a distant site
- Increasing agonists concentration will not overcome the blockade
- Examples
  - Phenoxybenzamine irreversibly binds to and antagonizes the effects of catecholamines at alfa-adrenoceptors
  - Aspirin irreversibly inhibits the COX-1 enzyme in platelets
Tachyphylaxis, desensitization and tolerance

- **Tachyphylaxis**
  - Rapid decrease in response to repeated doses over a short time period
  - Most common mechanism is the decrease of stores of a transmitter before resynthesis can take place
  - Example: diminishing response to repeated doses of ephedrine, an indirectly acting sympathomimetic amine, caused by the depletion of noradrenaline
Tachyphylaxis, desensitization and tolerance

- Desensitization
  - Chronic loss of response over a longer period and may be caused by a structural change in receptors morphology or by an absolute loss of receptor numbers
  
- Example
  - Loss of Beta-adrenergic receptors from the heart in the continued presence of adrenaline or dobutamine
Tachyphylaxis, desensitization and tolerance

Tolerance

- Refers to the phenomenon where larger doses are required to produce the same pharmacological effect.

- Occurs in chronic opioid use or abuse; may be a reduction of R density or a reduction of R affinity.

- Also occurs if nitrates are continuously given for prolonged periods, as the sulphydryl groups on vascular smooth muscle become depleted – need for drug holiday of a few hours.
Dose-response curves

Normal agonist dose-response curve, which is hyperbolic
If curve plotted using a log scale for dose is used, the classical sigmoid shape is produced.
- A and B are full agonists; B is less potent than A
- C is a partial agonist that is unable to produce a maximal response
Competitive inhibition. Note the parallel shift to the right in the presence of competitive inhibitor, with preservation of maximum response. DR represents dose-ratio.
- **Non-competitive inhibition.** In the presence of the non-competitive inhibitor the curve is not shifted to the right, but the maximum obtainable response is reduced.
- $K_D$ is the dissociation constant and is unaltered by the inhibitor.
Partial agonist acting as competitive inhibitor. In this scenario A is a full agonist; C is a partial agonist. The dotted line, A + C, shows the dose-response curve for A in the presence of a sub-maximal dose of C. At low concentration of A the combination results in a greater effect than with A alone but as the dose of A is increased there comes a point at which the effect of A + C is less than with A alone. There is a point in which the only way A can increase the response is by competing for receptors occupied by C. C therefore appears to act as a competitive inhibitor.
Fig. 55 Dose–response curves (see text)
THANKS!

Any questions?

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