PHARMACODYNAMICS

(BIOMED IV CLASS)

BIETE LUNDAU LUKE

DipPharm, Bpharm, Mclinpharm

INTRODUCTION

- This involves the study of the action of the drugs on the body
- It focuses on the detailed mechanism of action by which drugs produce their pharmacological effects
- This starts with the binding of the drug to its target receptor or enzyme, followed by the signal transduction pathway by which the receptor activates the second messenger molecules and ends with the final intracellular process altered by the impact of the drug
- Pharmacodynamics provides the scientific basis for the selection and use of drugs to counteract or reverse pathophysiological changes caused by disease or trauma

NATURE OF DRUG RECEPTORS

- Drug receptors are specific cellular macromolecules which may be metabolic or regulatory enzymes or coenzymes, proteins or glycoproteins associated with transport mechanism
- Drugs produce their effect by interacting with specific receptors
- Most ligands(drugs or neurotransmitters) bind to protein molecules
- It is worthy noting though that some agents act directly on DNA or lipid membranes

Types of receptors

- The largest family of drug receptors is that of the G protein coupled – receptors (GPCRs)
- They contain four extracellular, seven transmembrane and four intracellular domains
- The extracellular and to a lesser extent the transmembrane domains are responsible for binding and selectivity while the intracellular domain mediates the receptor interaction with its effector molecule
- A number of ligands inhibit the function of specific enzymes either competitively or non competitively
- A ligand that binds to the same active catalytic site as the endogenous substrate is called a competitive inhibitor
- A ligand that binds on different sites of the enzyme which leads to the change of the shape of the molecule thereby, leading to the reduction in catalytic effect is called a noncompetitive inhibitor

Receptor classification

- Drug receptors are classified according to a number of properties such as;

i. Drug specificity
ii. Tissue location
iii. Primary amino acid sequence

- For example, based on their affinity for norepinephrine, epinephrine and other agents, adrenoceptors were initially divided into two namely α(alpha) and β(beta) receptors

- The development of specific antagonists subsequently confirmed the distinction between these two adrenoceptors

- These two receptors were later divided into subtypes based on differences on agonist potency, tissue distribution and varying effects

Orphan receptors

- These are receptor like proteins predicted from the human genome for which an endogenous ligand is not identified

- These orphan receptor are of great interest to pharmaceutical companies as they act as targets for drug development

Family of receptors

- Families of receptors are grouped according to their sequence similarity using bioinformatics with the barking of results from both the in vivo and in vitro studies

- Generally, each type of receptor corresponds to a single, unique gene with subtypes of receptors arising from different transcripts of the same gene

DRUG RECEPTOR INTERACTIONS

- For a cellular response to be effected, a drug should bind to a receptor
- In most cases, drugs bind to their receptors by forming hydrogen, ionic or hydrophobic (van der Waals) bonds with a receptor site
- In a few cases, drugs form relatively permanent covalent bonds with specific receptors e.g. antineoplastic drugs binding to DNA, drugs irreversibly inhibit the enzyme cholinesterase
- These weak bonds are reversible and enable the drug to dissociate as the tissue of the drug dissociate
- Stereospecificity is often exhibited as drugs bind to receptors making it possible for only one of the stereoisomers (enantiomers e.g. D – isoproterenol, L- isoproterenol, L - propranolol) to form a three point attachment

Drug receptor affinity

- The tendency of a drug to combine with its receptor is called **affinity**
- This is the measure of the strength of the drug – receptor complex
- According to the **law of mass action**, the number of receptors (R) occupied by a drug depends on the drug concentration (D) and the drug – receptor association and dissociation rate constants (k_1 and k_2)
- The ratio of the two constants is K_D which represents the drug concentration required to saturate 50% of the receptors
- The lower the K_D is, the greater is the drug's affinity for the receptor
- The receptor affinity of the drug is the primary determinant of a drug potency

SIGNAL TRANSDUCTION

- This describes the pathway from ligand binding to conformational changes in the receptor, receptor interaction with effector molecules and downstream molecules
- These downstream molecules are called second messengers
- This cascade of receptor mediated biochemical events ultimately leads to a physiological effect

G protein coupled receptors

- The signal transduction pathway for GPCRs is well studied and understood
- These receptors constitute a super family of receptors for many endogenous ligands and drugs including receptors for acetylcholine, epinephrine, histamine, opioids and serotonin
- The G proteins has three subunits known as G_{α}, G_{β}, G_{γ}
- Ga G alpha further has subunits i.e. one being a stimulating ($G_{\alpha s}$)type and the being other for inhibiting ($G_{\alpha i}$) type, each determining a specific cellular response
- The $G_{\alpha s}$ increases adenyl cyclase activity and thereby stimulating the production of cyclic adenosine monophosphate (cAMP) while $G_{\alpha i}$ does the opposite
- Another G protein $G_{\alpha q}$ activates phospholipase C which leads to the formation of inositol triphosphate (IP_3) and diacylglycerol (DAG) which leads to the accumulation of Calcium ions in the cell

The second messengers

- cAMP, IP3, DAG and calcium ions are second messengers which activate or inhibit unique cellular enzymes in each target cells

- cAMP activates a number of tissue specific cAMP dependent protein kinases e.g. protein kinase A is activated by the increase in cAMP produced by epinephrine binding to β_2 - adrenoceptor in the muscle

- IP3 and DAG evoke the release of calcium from intracellular storage sites and thereby, augmenting calcium mediated processes such as muscle contraction, glandular secretion, neurotransmitter release

Ligand - gated ion channels

- These are a large class of membrane proteins that share similar subunits structure and are assembled in tetrametric or pentametric structures
- Drugs that bind to ligand – gated ion channels alter the conductance of ions through the channel protein
- There are no second messengers directly activated by the drug binding to a ligand gated ion channels
- However, the resulting changes in the intracellular ion concentrations may regulate other enzyme signaling cascades

Other receptors

1. Membrane – bound enzymes

- Membrane bound enzymes also serve as receptors e.g.

a). Guanylate cyclase – this is the target for atrial natriuretic factor (ANF)

- Binding of ANF produces direct activation of guanalyl cyclase and increase of intracellular cyclic guanosine monosphosphate (cGMP)

b). Tyrosine kinase

- A large number of ligands activate the receptors including epidermal growth factor, nerve growth factor and insulin

Nuclear receptors

- There are two types of nuclear receptors i.e.

Type I nuclear receptors

- This includes targets for sex hormones (androgen, oestrogen, progesterone), glucocorticoid and mineralcorticoid

- Steroid receptors are located inside the cell

Type II nuclear receptors

- These include receptors for non steroid ligands including thyroid hormone, vitamin A and D receptors and retinoid receptors

- These receptors are already present in the nucleus and are activated by the ligand entering the nucleus through the nucleus pores

EFFICACY

- Efficacy is the ability of the drug to initiate a cellular effect or intrinsic activity
- Intrinsic being the effect likely to be seen when the endogenous ligand bind to the receptor
- Efficacy is not directly related to receptor affinity and differs among many drugs that bind to a receptor to initiate a signal transduction

Agonists and antagonists

AGONISTS

- these are drugs that have both the receptor affinity and efficacy e.g. salbutamol is beta 2 - adrenoceptor agonist

ANTAGONISTS

- These are drugs which only have receptor affinity but lack efficacy e.g. propranolol is a beta receptor antagonist (blocker)

- These prevent the action of agonists and inverse agonists by occupying the binding sites

- Both agonists and antagonists have common components for receptor affinity but only agonists have a structure required for efficacy

Three types of agonists

Full agonists

- These produce a maximum response obtainable in a tissue and thus have high efficacy

Partial agonists

- These produce a submaximal response
- May also act as antagonists in the presence of full agonists by preventing the full agonist from binding the receptor to exert the maximal benefit

Inverse agonists

- Also called negative agonists which work by reducing the signal transduction unlike full agonists which increase signal transduction
- Gamma amino butyric acid (GABA) is an example of inverse agonist

Types of antagonists

Competitive antagonists

- Bind to the same receptor sites as the agonist but are reversibly bound
- The effects of competitive antagonists are surmountable if the dose of the agonist is increased sufficiently

Non competitive antagonists

- Block the agonist site irreversibly usually by forming a covalent bond
- The effects of the non competitive antagonists cannot be overcome or surmountable by the increased doses of agonists

Receptor regulation

- Receptors can undergo dynamic changes in their density (number per cell) and their affinity for drugs and other ligands
- Continous exposure of receptors to agonists can desensitize receptors
- Short term effect of agonists exposure is called **desensitization** or **tachyphylaxis**
- The long term exposure to agonists can through internalization and regulation of receptor gene lead to reduction in receptors and this is called **down – regulation**
- In contrast, continuous exposure to antagonists initially can increase the response of the receptor, the phenomena called **supersensitivity**
- Chronic exposure to antagonists will eventually lead to increase in the number of receptors on the membrane via **up - regulation**

Drug tolerance

- **Drug tolerance** is seen when the same dose of drug is given repeatedly loses its effect to an extent where greater doses are needed to achieve the previously obtained effect
- Receptor down-regulation is often responsible for **pharmacodynamic** tolerance
- On the other hand, **pharmacokinetic** tolerance is caused by increased drug elimination usually resulting from upregulation of enzymes that metabolise the drug
- Some diseases also alter the number of receptors e.g. myasthenia gravis an autoimmune disease in which antibodies destroy nicotinic receptors

DRUG RESPONSE RELATIOSHIP

- Dose response relationship is the relationship between the concentration of the drug at the receptor sites and the magnitude of the response

- Depending on the study, the relationship can be described in terms of graded (Continous) or quantal (all or none) response

Potency

- This is the characteristic of a drug action for comparing different pharmacological agents (The extent of the pharmacological activity/effect)
- It is usually expressed in terms of median effective dose(ED50) which is the dose that produces 50% of the maximum response
- The potency of a drug varies inversely with ED50 of a drug so that a drug with ED50 of 4mg will be 20 times more potent than a drug with ED50 of 40mg
- Potency is largely determined by the affinity of a drug because drugs with greater affinity will require a lower dose to occupy 50% of the functional receptors

A recap and contextualizing efficacy

- The maximum response produced by the drug is known as its efficacy
- A full agonist has maximum efficacy where as a partial agonist less than maximal efficacy
- An antagonist by definition has no efficacy in this sense but can be an effective medication e.g. beta blockers used in the treatment of hypertension

END