PHRM20001

Pharmacology: How Drugs Work

H1 Comprehensive Subject Notes

Contents

Agonists

Pharmacological principles of pharmacodynamics

- Pharmacodynamics describes what drug do to the body, explaining both the mechanism of action AND dose-response relationship

Understand and compare the following drug properties between agonists

- **Affinity**
  - Measure of attraction of a ligand for its biological target (the strength of binding)
  - Quantified by the equilibrium dissociation constant (KA); **lower KA = higher affinity**
  - **Binding strength**: determined by the forces of attraction, receptor concentration, and ligand binding

- **Efficacy**
  - The ability of a bound ligand to activate a receptor
  - Full agonists induce **maximum activation**
  - Antagonists have **no efficacy**
  - **Emax** - maximal response/effect that a drug can product

	Agonist	**Partial Agonist**	**Antagonist**
	Full activation	Submaximal (partial) activation	No activation
Affinity	✓	✓	✓
Efficacy	✓✓	✓	-

- **Potency**
  - The drug concentration required to elicit a given effect.
  - Measured by **EC50;** the drug concentration that elicits a 50% response
    - To calculate EC50: logEC50 at 50% of Emax; convert the log and find EC50.
  - **Lower EC50 = higher potency (most leftward curve)**
  - A drug needs to have a relatively high affinity and efficacy to have a high potency

Appreciate that tissue responses to drugs are dependent on receptor expression

- The tissue response depends on receptor expression
- Variability in receptor density affects the Emax achievable by a drug

Recognise the pharmacological utility of different types of agonists

- **Full agonist:** maximum therapeutic effect, used when a complete response is desired
- **Partial agonist:** useful when a lower response is desired to reduce effects
  - **Salbutamol** (β2-adrenoceptors) treats asthma with minimal desensitisation
  - **Sumatriptan** treats migraines, minimising risk of heart attack
  - **Buprenorphine** (μ-opioid receptors) provides pain relief with reduced euphoric and addictive side effects, as well as less respiratory depression.

Adrenergic Pharmacology

NA synthesis, storage, release, reuptake and metabolism.

- Catecholamine synthesis in nerve terminals **(noradrenaline)**
  - Precursor of NA is L-tyrosine
  - L-tyrosine is transported in to nerve terminal through tyrosine transporter
  - L-tyrosine undergoes hydroxylation by tyrosine hydroxylase to produce L-DOPA
  - L-DOPA is converted by DOPA decarboxylase to dopamine
  - Dopamine is transported into synaptic vesicle via VMAT
  - In the synaptic vesicle, DA -> NA via Dopamine-beta-hydroxylase
  - Arrival of action potential leads to vesicular fusion and NA is released into synapse
  - L-tyrosine -> L-DOPA -> Dopamine -> Noradrenaline
- Storage of catecholamine is important!
- Ensures release of neurotransmitters is regulated, release of neurotransmitters only occurs following depolarisation of the synthetic varicosity
- When they are stored, they are protected from metabolism

- Catecholamine synthesis in chromaffin cells **(adrenaline)**
  - NA -> A
  - Chromaffin cells in adrenal medulla
  - NA is converted to Adrenaline via PNMT
  - Adrenaline is stored in neurosecretory granule and released into circulation following activation of nicotinic receptors
  - Postganglionic sympathetic neuron innervates chromaffin cells releasing Ach binding to nicotinic receptors causing it to release adrenaline into circulation
  - L-tyrosine -> L-DOPA -> Dopamine -> Noradrenaline -> Adrenaline

Drugs targeting neurotransmitter synthesis and storage

- L-DOPA and carbidopa
- L-DOPA increases dopamine synthesis; crosses the blood brain barrier
  - Treats Parkinson's disease (insufficient release of DA)
  - L-DOPA is taken up by both central and peripheral terminals involved in catecholamine synthesis
  - Production of dopamine in the periphery causes side effects
- Carbidopa is a DOPA decarboxylase inhibitor that doesn't cross the BBB
  - Carbidopa inhibits L-DOPA periphery side effects.
  - Maximises effectiveness by increasing amount of L-DOPA that is able to get to CNS as opposed to PNS.

- Reserpine
- VMAT inhibitor that prevents synthesis of NA.
  - *Reserpine* prevents the transportation of dopamine into the synaptic vesicle.

- **Nicotinic antagonist**
  - D-tubocurarine is a competitive nicotinic reversible antagonist
  - Selective in NMJ (N1), but non-selective at high concentrations
  - Used in anaesthesia to induce muscle paralysis
  - Hexamethonium is a nicotinic antagonist selective for N2
  - Used to manage hypertension by blocking autonomic ganglia

Summary of autonomic and somatic receptor subtypes

Receptor type	Subtype	Location	Signal pathway	Effect	Physiological context
Alpha	α1	Vascular smooth muscle	Gαq → PLC → ↑ IP3/DAG → ↑ Ca^{2+}	Vasoconstriction, smooth muscle contraction	Diverts blood flow to essential organs
	α2	SAMPLE	SAMPLE	SAMPLE	SAMPLE
Beta	β1	SAMPLE	SAMPLE	SAMPLE	SAMPLE
	β2	SAMPLE	SAMPLE	SAMPLE	SAMPLE
Muscarinic	M2	SAMPLE	SAMPLE	SAMPLE	SAMPLE
	M3	SAMPLE	SAMPLE	SAMPLE	SAMPLE
Nicotinic	N1	SAMPLE	SAMPLE	SAMPLE	SAMPLE
	N2	Autonomic ganglia	Ligand-gated ion channels → Na^{+} influx → Depolarization	Transmits signals between preganglionic and postganglionic neurons in sympathetic and parasympathetic ganglia	Autonomic regulation of involuntary functions such as heart rate, digestion, respiration

- Adenylate cyclase (AC) converts ATP to cAMP
- In **smooth** muscle - increased cAMP causes **relaxation**
  - cAMP activates PKA which phosphorylates and inhibits MLC-K which is critical for contraction
- In **cardiac** muscle - increased cAMP causes **contraction**
  - cAMP activates PKA which phosphorylates cardiac proteins that result in increased calcium pumped into the SR, thus strengthening each heartbeat.

Pharmacokinetics

Administration routes

- Drugs can be given to act locally or systemically
- **Local administration**: drug acts at or near the site of administration
  - Access to limited tissues, minimal side effects
- **Systemic administration**: drug enters bloodstream to access target
  - Oral administration
    - Most common and convenient
    - Subject to **first pass metabolism** in the liver; less drug reaches target
  - Intravenous administration

Eicosanoids

Describe how eicosanoids are generated with particular emphasis upon the key roles played by the enzymes PLA2, cyclooxygenase and lipoxygenase.

- PLA2 is activated by stimuli such as inflammatory signals and mechanical damage to cells.
- PLA2 releases arachidonic acid from the phospholipid bilayer of the cell membrane.
- Once arachidonic acid (AA) is free, it can be converted to eicosanoids by two pathways:
    - **Cyclo-oxygenase enzymes (COX)**
        - COX converts AA to **prostanoids;** prostaglandin **and** thromboxane
        - **Prostaglandin** is involved in inflammation, pain, and fever
        - **Thromboxane** is involved in platelet aggregation
    - **Lipoxygenase (LOX)**
        - LOX converts AA to leukotrienes
        - **Leukotrienes** are important mediators in allergic responses and inflammation

Major actions of prostaglandins and leukotrienes in the body.

- **Prostaglandin (PGE2)**
    - Transmits **pain** signals
    - Induces **fever**; inflammation -> neutrophil activation -> cytokines -> PGE2 enters hypothalamus and raises temperature
    - **Inflammation**
        - Vasodilatation (causes redness and heat)
        - Increases vascular permeability
        - Influences release of inflammatory cytokines (promotes chemotaxis)
    - **Gastric protection**: secretes mucus and decreases HCl production
    - Increases **renal blood flow** and increases **excretion of water and sodium**
    - Uterine contractions; **induces labour**
- **Thromboxane (TXA2)**
    - Promote **platelet aggregation**
    - **Vasoconstriction**
    - Causes blood clots and limits blood flow
- **Leukotrienes**
    - **SMC contraction:** bronchoconstriction (pathophysiology of allergic responses and asthma)
    - **Increases vascular permeability**
    - **Chemotaxis**, contributing to oedema and inflammation

Major features of the inflammatory response and the role that eicosanoids play in it.

- **Redness** - caused by increased blood flow due to vasodilatation (histamine, bradykinin, PGE2)
- **Heat** - increased blood flow and local elevation of temperature
- **Swelling** - increased vascular permeability; oedema (leukotrienes, histamine, and a bit of PGE2, bradykinin)