ADRENOCEPTOR AGONISTS AND ANTAGONISTS

(BIOMED IV CLASS)

BIETE LUNDAU LUKE

Mclinpharm , Bpharm ,DipPharm

ADRENOCEPTOR AGONISTS

- Adrenoceptor agonists are a large group of drugs with diverse pharmacological action making them suitable for treatment of a wide spectrum of clinical conditions ranging from cardiovascular emergencies to common colds

- While some of these drugs exert their effects on multiple organ systems, others target a specific organ

- These drugs mimic the effect of sympathetic nervous system and hence they are also called **sympathomimetic** drugs

Classification of Adrenoceptor Agonists

1. Direct – Acting Adrenoceptor agonists

a) Catecholamines

b) Non - catecholamines

2. Indirect-Acting Adrenoceptor Agonists

3. Mixed-Acting Adrenoceptor Agonists

1. **Direct – Acting adrenoceptor agonists**

   i. **Catecholamines (DNIED) – Read as DeNIED**

Catecholamines are produced in the medulla of the adrenal gland (which are natural). Synthetic catecholamines mimic the actions of the naturally occurring ones.

a) Dobutamine
b) Dopamine
c) Epinephrine
d) Isoproterenol
e) Norepinephrine

ii. Non catecholamines (CAPAMO - BCD) OR **(CAMP – ABCD)**

a) Albuterol (Salbutamol)
b) Apraclonidine
c) Clonidine
d) Midodrine
e) Oxymetazoline
f) Phenylephrine
g) Brimonidine
h) Dexmedetomidine

Oxymetazoline, Brimonidine, Dexmedetomidine, Clonidine and **Apraclonidine** are under another division called **Imidazoline drugs**, due to their chemical structures **(OABCD-** Order in which they perform similar functions; O binds a_1 while rest a_2**)**

2. Indirect – Acting adrenoceptor agonists

- Amphetamine
- Cocaine
- Tyramine

3. Mixed – Acting Adrenoceptor agonists

- Ephedrine
- Pseudoephedrine

Adrenoceptors

- There are two main types of adrenoceptors i.e. α and β with their subtypes whose classification was done based on the relative potency of agonists in different tissues

- Epinephrine and norepinephrine are more potent than isoproterenol at adrenoceptors in smooth muscles and these were designated as α – adrenoceptors

- Isoproterenol is more potent than epinephrine and norepinephrine at adrenoceptors in cardiac tissues and these were called β – adrenoceptors

Alpha adrenoceptors

- Stimulation of α_1 receptors mediates contraction of vascular smooth muscle, iris dilator muscle, muscle in the lower urinary tract (bladder, urethra, prostate)

- Activation of the α_2 receptors in the sympathetic neurons lead to feedback inhibition of norepinephrine release from nerve terminals
- a_2 receptors are also found in the platelet, ocular, adipose, intestinal, hepatic, renal and endocrine tissue
- In the pancreas they mediate the inhibition of insulin secretion that occurs when the sympathetic nervous system is activated
- In platelets a_2 mediate platelet aggregation.
- a_2 specific to insulin inhibition, norepinephrine inhibition and platelet aggregation. = **PIN (mnemonic)**

Beta adrenoceptors

- Activation of β_1 receptors produces cardiac stimulation leading to positive chronotropy (increased heart rate), a positive inotropy (increased contractility), positive dromotropy (increased cardiac conduction velocity)
- Activation of β_1 receptors also increases renin secretion from renal juxtaglomerular cells
- B_2 adrenoceptors mediate relaxation of bronchial, uterine, and vascular smooth muscle; and also potassium uptake in the skeletal muscle
- Whereas epinephrine and norepinephrine are equally potent on β_1 adrenoceptors in cardiac tissue, epinephrine is more potent on β_2 in smooth muscle
- B_3 adrenoceptors is the most recent characterized one known to mediate lipolysis, thermogenesis in skeletal muscle, uterine relaxation

Dopamine receptors

- These are activated by dopamine and not other adrenergic receptor agonists
- D_1 receptors mediate vascular smooth muscle relaxation
- D_2 receptors modulate neurotransmitter release
- Dopamine activates D_1 receptors, β_1 receptors and α receptors
- Unlike other catecholamines, dopamine also stimulates the release of norepinephrine from sympathetic neurons upon its binding to D_2 receptors
- For this reason, dopamine is both a direct acting and an indirect acting receptor agonist

A comparison of affinity for specific adrenoceptors

Adrenoceptor agonist	Affinity for adrenoceptor
Norepinephrine	$\alpha_1 = \alpha_2$; $\beta_1 > \beta_2$
Epinephrine	$\alpha_1 = \alpha_2$; $\beta_1 = \beta_2$
Isoproterenol	$B_1 = \beta_2 >> \alpha$
Dopamine	$D_1 > \beta_1 > \alpha$
Dobutamine	$\beta_1 = \beta_2 >> \alpha$

- Isoproterenol and dobutamine have similar proportions of potency

Direct Acting adrenoceptor agonists

Catecholamines

- The naturally occurring catecholamines are norepinephrine, an endogenous sympathetic neurotransmitter, epinephrine the principal hormone of the adrenal medulla
- Dopamine is another neurotransmitter and a precursor to norepinephrine and epinephrine
- Synthetic catecholamines include isoproterenol and dobutamine

Chemistry and pharmacokinetics

- They contain the catechol moiety and an ethylamine side chain
- They are rapidly inactivated by monoamine oxidase (MAO) and Catecho-O-methyltransferase (COMT), enzymes found in the gut, liver and other tissues
- For this reason, these drugs have low bioavailability and short plasma half lives and must be administered parenterally when systemic action is required like in management of anaphylactic shock

Indications for catecholamines

- Catecholamine are used to treat several types of shock

- Shock is a condition in which circulation to vital organs is profoundly reduced as a result of inadequate blood volume (hypovolemic shock), inadequate cardiac function (cardiogenic shock) or inadequate vasomotor tone (neurogenic and septic shock)

- Septic shock is associated with massive vasodilation secondary to the production of toxins by microrganisms and it is sometimes called warm shock to distinguish it from the others where patients' extremities are usually cold due to inadequate blood flow

- Anaphylactic shock results from severe immediate hypersensitivity reactions and usually manifests by hypotension and difficult breathing caused by bronchoconstriction

Approaches to use of vasopressors

- Catecholamine drugs that increase blood pressure are called vasopressors

- These are used to treat shock when organ function is impaired because mean arterial blood pressure is less than 60mm Hg or simply the BP being less than 90/60 mm Hg

- It is always important to correct hypovolemia by administering intravenous (I.V) fluids before giving vasopressors because vasopressors will not be effective when hypovolemia is present e.g., dextran

Dopamine

- Used to treat septic or cardiogenic shock when patients remain hypotensive despite adequate fluid administration
- Low dose (2mg/kg) is used first and then titrated to achieve the desired blood pressure
- Though low doses of dopamine have been found to increase urine output by augmenting renal blood flow in normal subjects, evidence shows that these low doses are usually not effective in preventing and treating acute renal failure
- The most effective means of protecting the kidneys in patients with shock is the maintenance of mean arterial pressure greater than 60 mm Hg with I.V fluids and adequate doses of vasopressors

Norepinephrine

- As a potent vasoconstrictor, it is used to treat septic shock
- It is also given to patients with cardiogenic shock when the response to dopamine is inadequate or is accompanied by tachycardia
- Norepinephrine is also used to treat hypotension caused by decreased peripheral resistance like in persons who have received excessive doses of vasodilator drugs, like the cholinergic agonists

Epinephrine

- Epinephrine is the treatment of choice for anaphylaxis
- By producing bronchodilation and increasing blood pressure, epinephrine counteracts the effects of histamine and other mediators released from mast cell and basophils during immediate hypersensitivity reactions
- Used as a vasoconstrictor to **reduce bleeding during surgery** and **to prolong the action of local anesthetics** by retarding their absorption into general circulation
- Epinephrine is also used as cardiac stimulant in the treatment of **cardiac arrest** and **ventricular fibrillation**

Isoproterenol

- Used to treat **refractory tachycardia** (tachycardia once treated but recurring) and **atrioventricular block**(recurrent sudden attacks of unconsciousness caused by impaired conduction of the impulse that regulates the heartbeat)

- Although used in treatment of asthma, selective β_2 receptor agonists like salbutamol, terbutaline, salmetelol are more preferred as they do not increase the heart rate as much as isoproterenol

Dobutamine

- Dobutamine is a cardiac stimulant (Inotropic agent) that also produces vasodilation

- Used as (1)**cardiac stimulant during heart surgery** (2)in the **short term management of acute heart failure** and (3)**cardiogenic shock**

- It is routinely used in treating septic shock because its vasodilator effect further reduces vascular resistance and blood pressure

Non-catecholamines

- These do not have the catechol moiety neither are they substrates for the COMT and some of them are resistant to MAO degradation

Phenylephrine

Mechanism and effects

- Phenylephrine activates α_1 adrenoceptors and causes smooth muscle contraction which produces vasoconstriction and increases vascular resistance and blood pressure

- Ocular administration of phenylephrine leads to contraction of the iris dilator muscle and dilatation of the pupil (Mydriasis)

Indications of Phenylephrine

- Used as nasal decongestant in patients with **viral rhinitis** caused by different subtypes of rhinovirus (condition commonly called common cold)
- Also used in **allergic rhinitis**, an inflammation by histamine released from mast cells during allergic reaction
- The drug's vasoconstrictive effect on the nasal mucosa reduces nasal congestion and mucus secretion thereby, opening the nasal passage and facilitating easiness of breath
- Phenylephrine is also used in **allergic conjunctivitis (red eye)**, an inflammation of the eye associated to **hay fever** (seasonal rhinitis resulting from an allergic reaction to pollen)or other allergies
- When administered intravenously, phenylephrine is used to treat forms of **hypotension** and **shock caused by decreased peripheral resistance**

Midodrine

- Forms an active metabolite that selectively activates α_1-adrenoceptors in arteriolar and venous circulation
- This leads to increase in diastolic and systolic pressure in standing, sitting and supine position
- The drug is used to treat postural (orthostatic) hypotension in person impaired by the condition e.g. patients with severe diabetic autonomic neuropathy
- Hypertension in supine position is the known adverse effect

Salbutamol (Albuterol), Pirbuterol, Terbutaline

- These are known β_2 – adrenoceptor agonists that can be given by inhalation, with salbutamol and terbutaline being available as oral medication while terbutaline is available for injection by cAMP pathway through adenylyl cyclase

Mechanism and indication

- β_2 – adrenoceptor agonists cause smooth muscle relaxation in several tissues resulting in bronchodilation and hence these drugs being beneficial in the management of asthma and chronic obstructive lung disease

- Also used off lable as tocolytics in the management of pre term (Premature) labour which is labour before the 37th week of gestation

- The tocolytic effect relaxes the uterus and maintains pregnancy for 24 – 48hours the period enough to have corticosteroid, like betamethasone, administered to prevent neonatal respiratory distress
- Can also be used to transport a mother who is in labour pain to a distant delivery facility. For this purpose, indomethacin, oxytocin antagonists and nifedipine can also be used

- Tachycardia, muscle tremors and nervousness are known adverse effects of salbutamol and other selective β_2 – adrenoceptor agonists

Imidazoline Drugs

- These compounds activate α - adrenergic and imidazoline receptors and mostly administred by topical ocular or nasal route

Mechanism and indications

1. Oxymetazoline, **Xylometazoline**

- Together with similar drugs activate α_1 receptors and cause vasoconstriction and hence its use as nasal or ocular decongestant

- Because of increasing blood pressure, oxymetazoline should not be taken by hypertensive patients

- Topical nasal decongestant should not be used for more than 3 – 5 days to avoid nasal rebound which comes about due to vasoconstriction and tissue ischaemia

2. Brimonidine and **apraclonidine**

- Activate α_2 in the ciliary body and reduce aqueous humor secretion by reducing adenylyl cyclase and consequent reduction of cAMP

- Used to prevent short term elevation of intraocular pressure after cataract surgery

3. Clonidine and dexmedetomidine

- These activate α_2 and imidazoline receptors in the CNS and leads to reduction to sympathetic outflow in the medulla
- Clonidine is used in the treatment of hypertension
- Also used to facilitate abstinence from opioids in persons being treated for substance abuse
- Activation of is responsible for sedation and analgesic effects of clonidine and dexmedetomidine and hence these drugs are used as adjunct to anaesthesia during surgical procedure with an addition property of preventing shivering

Indirect acting adrenoceptor agonists

Amphetamine and Tyramine

- Have high solubility and increase synaptic concentration of norepinephrine in the central and peripheral nervous system and causes vasoconstriction

- Tyramine is naturally occurring found in food like bananas, cheese which metabolized by MAO and may thus be absorbed in patients receiving MAO inhibitors for depression and may cause exaggerated sympathetic effect

Cocaine

- A plant alkaloid which acts as local anesthetic and also stimulates sympathetic system by preventing norepinephrine re uptake at both peripheral and central synapses

- Cocaine also blocks the re uptake of dopamine leading to its effects and vulnerability for abuse

- Its sympathetic effects also appears to be responsible for the severe hypertension and cardiac damage that may occur in people who abuse cocaine

Mixed Acting Adrenoceptor Agonists

- These are drugs which act both as direct and indirect mechanism e.g. ephedrine, pseudoephedrine and dopamine
- They indirectly increase synaptic concentration of norepinephrine like amphetamines

Ephedrine and Pseudoephedrine

- Ephedrine is naturally occurring compound obtained plant of the genus *Ephedra* which is also called ma huang
- Ephedrine is well absorbed from the gut and has sufficient lipid solubility to enter CNS
- Ephedrine is relatively resistant to metabolism by COMT and hence it long duration of action. It causes bronchodilation and is used to treat **asthma** and **bronchitis**.

- Pseudoephedrine, an isomer to ephedrine used as nasal decongestant to treat colds and allergies

- Availability of pseudoephedrine is now restricted in many countries because of its newfound use in illegal making of methamphetamines for illicit sale and use

Mechanism and indications of Ephedrine and Pseudoephedrine

- Ephedrine and the related drugs activate α and β adrenoceptors
- Stimulation of α_1 causes vasoconstriction and thus making them useful as nasal decongestants in treatment of viral and allergic conjunctivitis
- Activation of β adrenoceptors leads bronchodilation but selective β_2 adrenoceptor agonists are more safe and effective for this purpose
- Tachycardia and increased blood pressure are known adverse effects of ephedrine and pseudoephedrine

ADRENOCEPTOR ANTAGONISTS

Overview on adrenoceptor Antagonists

- Excessive sympathetic nervous system activity causes a number of diseases including common cardiovascular disorders such as hypertension, angina pectoris and cardiac arrhythmias

- Drugs that reduce sympathetic activity are called **sympatholytics** and can be used in the management of diseases such as cardiovascular diseases and other diseases like glaucoma, migraine headache and urinary obstruction
- Adrenoceptor antagonists block α and β adrenoceptors or both and their therapeutic effects are almost entirely caused on α_1 and β_1

- Blockade of α_1 relaxes the smooth muscles in tissues innervated by the sympathetic nervous system where as blockade of β_1 reduces the sympathetic stimulation of the heart

- Blockade of α_2 and β_2 adrenoceptors is responsible for many of the side effects of these drugs and hence drugs selective to α_1 and β_1 have been developed in an effort to avoid these adverse effects

Classification of Adrenoceptor Antagonists

1. Alpha – Adrenoceptor Antagonists

i. Non selective α - blockers

a) Phenoxybenzamine
b) Phentolamine

ii. Selective α_1 – blockers

Selectivity lesson: Ala! Don't talk about silly people. It's a sin!! Relax!!!

a) Doxazosin
b) Tamsulosin
c) Alfuzosin
d) Silodosin
e) Prazosin

2. Beta Adrenoceptor Antagonists

Bcoz Non-proprietary teams pay nerds. LOL

i. Non selective β – blockers (PRO TI PI NAD)

a) Propranolol
b) Timolol
c) Pindolol
d) Nadolol

ii. Selective β1 – blockers (ES MET ACE ATE)

B1 always expresses my anger

a) Atenolol
b) Esmolol
c) Metoprolol
d) Acebutolol

3. α - and β – Adrenoceptor Antagonists

a) Carvedilol
b) Labetalol

α - Adrenoceptor Antagonists

Non selective α Blockers

- These block both α_1 and α_2 adrenoceptors
- Phenoxybenzamine is a non competitive antagonist while Phentolamine is a competitive antagonist

Phenoxybenzamine

- Administered orally and undergoes non enzymatic chemical transformation to an active metabolite

Effects and indication

- Lowers vascular resistance and lowers both supine and standing blood pressure
- Used to treat hypertensive episodes in patients with pheochromocytoma (a vascular tumor of the adrenal gland; hypersecretion of epinephrine results in intermittent or sustained hypertension)

Phentolamine

- Structurally related to oxymetazoline and other drugs within the imidazoline group

Mechanism, effect and indication

- Phentolamine is a competitive adrenoceptor antagonist that produces vasodilation, decreases vascular resistance and decreases blood pressure
- It is used in the treatment of acute hypertensive episodes caused by α - adrenoceptor agonists
- Accidental injection of a finger with an epinephrine may result in local vasoconstriction, ischemia and necrosis and phentolamine can be used to treat this condition
- Phentolamine and other non selective α - blockers are not used in treating chronic hypertension as they can cause reflex tachycardia, headache, and nasal congestion

Selective α1- Antagonists

- These selectively antagonize α_1-adrenoceptors and they include alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, telazosin

Pharmacokinetics

- Administered orally and undergo varying amounts of first pass and systemic circulation

Mechanism, effects and indications

- These α_1- blockers relax vascular and other smooth muscles including those of the urinary bladder, urethra and prostate

- Because they produce vasodilation and reduce blood pressure, they are used to treat essential hypertension

- Quite helpful in treating lower urinary tract symptoms associated with benign prostatic hyperplasia (frequency, urgency, nocturia)

Further sub categorization of specific selective α_1- Antagonists

- Most common adverse effects include hypotension, dizziness and sedation
- **P**razosin, **t**erazosin and **d**oxazosin (**PTD - BOTH**) are used for treatment of hypertension and to relieve lower urinary tract symptoms
- It is worth noting that terazosin and doxazosin have a longer half life than prazosin
- On the other hand, alfuzosin, silodosin and tamsulosin (SAT) are more uro-selective that lower urinary tract symptoms without as much hypotension, dizziness and sedation like the other drugs

β-Adrenoceptor Antagonists

Non selective β-blockers

- In addition to blocking β_1-adrenoceptors in the heart tissue, they block β_2 in smooth muscle, liver and other tissues
- Examples include propranolol, nadolol, pindolol and timolol

Pharmacokinetics

- The β-Adrenoceptor Antagonists are structural analogues of β-Adrenoceptor Antagonists, all of which can be administered orally while propranolol is also administered parenterally

Mechanisms and effects

- Non selective β-blockers competitively block the effects of norepinephrine and other adrenoceptor agonists at β_1 and β_2 – adrenoceptors while some of them exhibit intrinsic sympathomimetic activity and membrane stabilizing (local anesthetic) activity

Specific properties

- Comparing the drugs; propranolol, nadolol, pindolol and timolol some specific properties are found with individual drugs
- Pindolol is found to have intrinsic sympathomimetic activity or partial agonist activity which enables it to exert a weak agonist effect on β – adrenoceptors
- Although **propranolol** and **pindolol (PP-STABILIZE)** have membrane stabilizing effects (Local anesthetic activity), nadolol and timolol **(NaT)**do not
- This membrane stabilizing activity causes the blockage of sodium channels in nerves and heart tissue thereby slowing conduction velocity
- Propranolol the first β-blocker approved (Prototype) for clinical use is distinguished by its high lipid solubility and CNS penetration and hence a higher incidence of side effects such as headache, psychosis, nightmares, sleep disturbances, vertigo, visual disturbance

Indications Non selective β-blockers

Pindolol

- Approved for hypertension treatment

Propranolol

- Treatment of hypertension, angina pectoris and cardiac arrhythmias
- Prevention of migraine headaches
- as adjunctive therapy in treatment of acute thyrotoxicosis, acute myocardial infarction and pheochromocytoma

Nadolol

- Treatment of hypertension, angina pectoris and prevention of migraine headache

Timolol

- Administered orally for treatment of hypertension, to reduce risk of death in patients with acute myocardial infarction and prevention of migraine headache

- Ocular topical application for treatment of glaucoma and is suitable because it does not have local anesthetic effect and hence cannot anesthetize the cornea when instilled into the eye

Selective β_1-blockers

- These have a greater affinity for β_1 than for β_2 adrenoceptors and because β_1 are primarily located in the cardiac tissue, β_1-blockers are also known as cardio selective β-blockers
- Examples are acebutolol, atenolol, esmolol and metoprolol
- Comparing with non selective β-blockers, selective β_1-blockers produce less bronchoconstriction and other mediated effects
- Their selectivity for β_1 adrenoceptors is not absolute and therefore, blockade of β_2-receptors increases with dose and hence β_1 should be used with caution in patients with asthma

NB: with the last point in mind, it is important to appreciate that cardio selectivity is not the same as cardio specificity

Specific properties and indications for selective β1-blockers

Acebutolol

- Administered orally for treatment of hypertension and cardiac arrhythmias

Atenolol

- Shows less variability in its oral absorption than do other β – blockers and is largely excreted unchanged in the urine and has lower lipid solubility
- Administered orally for treatment of hypertension, angina pectoris and acute myocardial infarction

Esmolol

- Has shorter half life compared to others β – blockers and is administered intravenously for treatment of hypertension and acute supraventricular tachycardia when these occur during surgery

Metoprolol

- Used to treat hypertension, angina pectoris and acute myocardial infarction

- Administered orally or parenterally and is extensively metabolized by CYP450 enzymes before undergoing renal excretion

Other β_1- selective antagonists

- These include bisoprolol and betaxolol

- Both of these drugs are administered orally for treatment of hypertension

- Topical application of betaxolol also reduces aqueous humour secretion while producing negligible systemic β-adrenoceptors and hence it is used in treatment of chronic open angle glaucoma

α and β – Adrenoceptor Antagonists

- These block both α and β adrenoceptors and they include carvedilol and labetalol

Carvedilol

- Carvedilol blocks β_1, β_2 and α_1 adrenoceptors and also possesses antioxidant activity
- Each of these properties offer the cardioprotective effect

Antioxidant effects of carvedilol

- Inhibition of lipid peroxidation in myocardial membranes
- Scavenging of free radicals
- Prevention of neutrophil release of O_2
- Additionally carvedilol has antiapoptotic effect which helps prevent myocyte death and reduce infarct size in persons with myocardial ischaemia

Indications of carvedilol

- Carvedilol is therefore referred to as third generation β-blockers and neurohumoral antagonists and its value in treating myocardial infarction has been established

- Carvedilol is used in management of hypertension

Labetalol

- This is a non selective β blocker and selective α_1 blocker that is primarily used in the treatment of hypertension

- Labetalol decreases heart rate and cardiac output as a result of β_1-adrenoceptor blockade and it reduces peripheral vascular resistance as a result of α_1-adrenoceptor blockade

END