ADRENERGIC AND ANTI-ADRENERGIC DRUGS

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SYMPATHETIC NERVOUS SYSTEM

Fight or flight response results in:

1. Increased BP
2. Increased blood flow to brain, heart and skeletal muscles
3. Increased muscle glycogen for energy
4. Increased rate of coagulation
5. Pupil dilation
ADRENERGIC RECEPTORS

- Alpha—A1 and A2
- Beta—B1, B2, B3
- Dopamine—subsets D1-5
REVIEW OF FUNCTIONS OF SYMPATHETIC NERVOUS SYSTEM RECEPTORS

- Alpha 1—smooth muscle contraction
- Alpha 2-negative feedback causes less norepinephrine to be released so BP is reduced
- Beta 1—increased heart rate
- Beta 2—bronchodilation
- Beta 3—actual site for lipolysis
MECHANISMS OF ACTION AND EFFECTS OF ADRENERGIC DRUGS

- Direct adrenergic drug action
- Affects postsynaptic alpha 1 and beta receptors on target effector organs
- Examples: epinephrine, Isuprel, norepinephrine, phenylephrine
2. Indirect adrenergic drug action occurs by stimulation of postsynaptic alpha 1, beta 1 and beta 2 receptors. Cause release of norepinephrine into the synapse of nerve endings or prevent reuptake of norepinephrine. Examples include cocaine and TCAs.
3. mixed action. Combination of direct and indirect receptor stimulation

Examples are ephedrine and pseudoephedrine
Stimulation of alpha 2 receptors in CNS is useful in decreasing BP

Most body tissues have both alpha and beta receptors

Effect occurs secondary to receptor activated and number of receptors in the particular body tissue
Some drugs act on both receptors--dopamine
Some are selective--Isuprel
INDICATIONS FOR USE

- Emergency drugs in treatment of acute cardiovascular, respiratory and allergic disorders
- In children, epinephrine may be used to treat bronchospasm due to asthma or allergic reactions
- Phenylephrine may be used to treat sinus congestion
INDICATIONS OF ADRENERGICS CONT.

- Stokes Adams
- Shock
- Inhibition of uterine contractions
- For vasoconstrictive and hemostatic purposes
CONTRAINDICATIONS TO USE OF ADRENERGICS

- Cardiac dysrhythmias, angina pectoris
- Hypertension
- Hyperthyroidism
- Cerebrovascular disease
- Distal areas with a single blood supply such as fingers, toes, nose and ears
- Renal impairment use caution
INDIVIDUAL ADRENERGIC DRUGS

- *Epinephrine*—prototype
- Effects include: increased BP, increased heart rate, relaxation of bronchial smooth muscle, vasoconstriction in peripheral blood vessels
BIOSYNTHESIS OF DOPAMINE, NOREPINEPHRINE AND EPINEPHRINE (CATECHOLAMINES)

- The amino acid **tyrosine** is transported into the sympathetic nerve axon.
- Tyrosine (Tyr) is converted to **DOPA** by tyrosine hydroxylase (rate-limiting step for NE synthesis).
- DOPA is converted to **dopamine** (DA) by DOPA decarboxylase.
- Dopamine is transported into vesicles then converted to norepinephrine (NE) by **dopamine β-hydroxylase** (DBH); transport into the vesicle.
BIOSYNTHESIS OF DOPAMINE, NOREPINEPHRINE AND EPINEPHRINE (CATECHOLAMINE)

L-Tyrosine

 tyrosine hydroxylase (tetrahydrobiopterin, O₂)

L-DOPA

DOPA decarboxylase (pyridoxal phosphate)

Dopamine

Dopamine β-hydroxylase (Ascorbate, O₂)

Norepinephrine

phenylethanolamine N-methyltransferase (S-adenosylmethionine)

Epinephrine
ADRENERGIC OR CATECHOLAMINE TRANSMISSION

Steps involved in cholinergic transmission

• Synthesis of norepinephrine
• Storage of norepinephrine into vesicle
• Release
• Binding by receptor
• Removal of norepinephrine/reuptake
• Metabolism
The amino acid **tyrosine** is transported into the sympathetic nerve axon.

- Tyrosine (Tyr) is converted to **DOPA** by tyrosine hydroxylase (rate-limiting step for NE synthesis).
- DOPA is converted to **dopamine (DA)** by DOPA decarboxylase.
- Dopamine is transported into vesicles then converted to norepinephrine (NE) by dopamine β-hydroxylase (DBH); transport into the vesicle.
- An action potential traveling down the axon depolarizes the membrane and causes **calcium** to enter the axon.
ADRENERGIC OR CATECHOLAMINE TRANSMISSION

- Increased intracellular calcium causes the vesicles to migrate to the axonal membrane and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space.
- The NE binds to the postjunctional receptor and stimulates the effector organ response.
1. SYNTHESIS OF NOREPINEPHRINE
   - Hydroxylation of tyrosine is the rate-limiting step.

2. UPTAKE INTO STORAGE VESICLES
   - Dopamine enters a vesicle and is converted to norepinephrine.
   - Norepinephrine is protected from degradation in the vesicle.
   - Transport into the vesicle is inhibited by reserpine.

3. RELEASE OF NEUROTRANSMITTER
   - Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
   - Release is blocked by guanethidine and bretylium.

4. BINDING TO RECEPTOR
   - Postsynaptic receptor is activated by the binding of neurotransmitter.

5. REMOVAL OF NOREPINEPHRINE
   - Released norepinephrine is rapidly taken into the neuron.
   - Reuptake is inhibited by cocaine and imipramine.

6. METABOLISM
   - Norepinephrine is methylated by COMT and oxidized by MAO.

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INTRACELLULAR RESPONSE

Urine ← Inactive metabolites

Presynaptic receptor

Catechol-O-methyltransferase (COMT)

SYNAPTIC SPACE

Urine ← Inactive metabolites

INTRACELLULAR RESPONSE
METABOLISM OF CATECHOLAMINE

NE (and epinephrine) is metabolized by catechol-O-methytransferase (COMT) and monoamine oxidase (MAO). The final product of these pathways is vanillylmandelic acid (VMA).
METABOLISM OF NOREPINEPHRINE

Norepinephrine

\[ \text{COMT} \]

\[ \text{1) MAO} \]
\[ \text{2) Aldehyde Dehydrogenase} \]

3,4-Dihydroxymandelic Acid

\[ \text{COMT} \]

\[ \text{1) MAO} \]
\[ \text{2) Aldehyde Dehydrogenase} \]

3-Methoxy-4-hydroxymandelic acid (Vanillylmandelic acid; VMA)

Normetanephrine
Norepinephrine $\xrightarrow{COMT}$ Normetanephrine

$\downarrow$ MAO

Dihydroxymandelic acid $\xrightarrow{COMT}$ Vanillylmandelic acid (VMA)

$\uparrow$ MAO

Epinephrine $\xrightarrow{COMT}$ Metanephrine

MAO = monoamine oxidase
COMT = catechol-O-methyltransferase
REGULATION OF NE RELEASE

NE acts on alpha 2 Autoreceptor and inhibit adenylate cyclase. Thus cAMP conc. Suppression of Ca- channel which inhibit exocytosis
Drug can be classified
- According to pharmacological action
- According to chemical nature
- According to M/A
1. Vasoconstriction
   + Adrenaline/epinephrine
   + Noradrenaline/Norepinephrine

2. Vasodilator
   + Dopamine
   + Isoprenaline

3. Bronchodilator
   + Sulbutamol
   + Terbutaline

4. CNS Stimulant
   + Amphetamine
   + Methylamphetamine
ACCORDING TO CHEMICAL NATURE

- Catecholamine
  - Adrenaline
  - Noradrenaline
  - Dopamine
- Non- catecholamine
  - Amphetamine
  - Tyramine
According to M/A

Direct acting
- clonidine
- Dopamine
- Dobutamine
- Epinephrine
- norepinephrine

Indirect acting
- Ephedrine

Mixed
- Amphetamine
- Tyramine
CLASSIFICATION

Adrenergic Drugs

Direct Acting

Epinephrine

Nor-epinephrine

Dopamine

α-agonists

β-agonists

Indirect Acting

Natural Compounds

Synthetic compounds

Releasers

Uptake Inhibitors

MAO Inhibitors
DIRECT ACTING (NATURAL COMPOUNDS)

These include;

- Epinephrine
- Nor-epinephrine
- Dopamine

- If these catecholamines are released from nerve fibers, these are called neurotransmitters.
- If released from glands, these are called as hormones.
- If released from the outside, these are called as drugs.
DIRECT ACTING (SYNTHETIC COMPOUNDS)

**α-agonists**
- Phenylephrine, Methoxyline (stimulate α-1 receptors)
- Clonidine, Detomedine, Xylezene (stimulate α-2 receptors)

**β-agonists**
- Isoprotalenol (stimulate β-1 & β-2 receptors)
- Dobutamine (stimulate β-1 receptors)
- Terbutalin, Sulbutamol, Clenbutarol (stimulate β-2 receptors)
INDIRECT ACTING

Releasers
Tyremine
Amphetamine
Ephidrine

Uptake inhibitors
Cocaine
Triphenylamine

MAO inhibitors
Isocarboxazid
Phenelzine
Iproclozide
Procarbazine
Hydralazine and Phenoxypropazine
Direct-acting agonists:
These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone epinephrine from the adrenal medulla.
These enhance release of Nor-epinephrine from the endings.

These drugs block and reverse the activity of **nor-epinephrine transporter (NET)**. NET is a transport protein present on surface of some cells that clears adrenaline and nor-adrenaline from the extracellular space and into the cells, thus terminating the signaling effect.

By inhibiting the enzyme monoamine oxidase.
**MECHANISM OF ACTION (MIXED)**

Mixed-action agonists: They have the capacity both to stimulate adrenoceptors directly and to release norepinephrine from the adrenergic neuron.
PHARMACOLOGICAL ACTION (ADRENALINE & NE)

- Eye
- CVS (Heart & B.V)
- Respiratory system
- Gastro intestinal tract
- Urinary bladder
- kidney
- Central Nervous System
- Liver
- pancreas
PHARMACOLOGICAL ACTION

Effects on eye:
Adrenaline binds with $\alpha_1$ receptor, cause contraction of pupillae muscle, increase outflow of aqueous humor, decrease IOP, relief glucoma
On CVS:
- **Heart**: increase BP
- **On blood vessel:**
  - **Low dose Adrenaline**: binds with $\beta_2$ receptor
  - On large artery and vessel of skeletal muscles, increase cAMP, cause vasodilation and decrease BP
  - **Usual dose of Adrenaline**: binds with $\alpha_2$
    - Receptor on arteriole, pre-capillary sphincter, mucous membrane, renal tissue
    - Increase DAG, IP$_3$ & Ca++ influx
    - Increase PR
    - Increase BP
PHARMACOLOGICAL ACTION

Lungs:
- Bronchodilatation

GIT:
Relaxation of GI smooth muscle & contraction of sphincter constipation

Urinary bladder:
Relaxation of detrusor muscle of urinary bladder and contraction of sphincter urine retention
PHARMACOLOGICAL ACTION

Kidney:
Increase renin secretion $\rightarrow$ angiotansin II
salt & water retention $\leftarrow$ renal vasoconstriction

Increase BP
Liver:
Increase glycogenolysis & gluconeogenesis →
Increase blood glucose.

Pancreas:
α2 receptor → decrease insulin secretion
β2 receptor → increase insulin secretion

CNS:
Mild restlessness, insomnia, tremor, euphoria
INDICATION

- **Anaphylactic shock**
- **CVS application:**
  - Cardiogenic shock: dopamine / Dobutamine
  - Cardiac arrest: Adrenaline
  - Heart block: Isoprenaline
  - Heart failure: Dobutamine
- **Respiratory application:**
  - Severe acute bronchial asthma: sulbutamol
  - As nasal decongestant: oxymetazoline (local)
  - Ephedrine (systemic)
ANAPHYLACTIC SHOCK

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes a number of symptoms including an itchy rash, throat swelling, and low blood pressure. Common causes include insect bites/stings, foods, and medications. On a pathophysiologic level, anaphylaxis is caused by the release of mediators from certain types of white blood cells triggered either by immunologic or non-immunologic mechanisms.
Clinical feature:
Bronchospasm
Hypotension
Allergic reaction

General management:
- Should stop the drug immediately
- Patient should be kept in supine position with elevated leg.
- Respiratory resuscitation.
- Monitoring the BP.
Role of adrenaline in anaphylactic shock:
In anaphylactic shock there is rupture of basophil and mast cell membrane and subsequently massive release of Histamine which causes
- Bronchoconstriction
- Hypotension

- Adrenaline causes elevation of BP by binding with \( \alpha_1 \) – receptor
- prevent bronchoconstriction by binding \( \beta_2 \) receptor
ADVERSE EFFECT

- Hypertension
- Tremor
- Insomnia
- Retention of urine
- Constipation
- May cause dyslipidaemia
- hyperglycaemia
Epinephrine

- Increased glucose, lactate, and fatty acids in the blood due to metabolic effects
- Increased leukocyte and increased coagulation
- Inhibition of insulin secretion
**EPINEPHRINE**

- Affects both alpha and beta receptors
- Usual doses, beta adrenergic effects on heart and vascular smooth muscle will predominate; high doses, alpha adrenergic effects will predominate
- Drug of choice for bronchospasm and laryngeal edema of anaphylaxis
EPINEPHRINE

- Excellent for cardiac stimulant and vasoconstrictive effects in cardiac arrest
- Added to local anesthetic
- May be given IV, inhalation, topically
- Not PO
EPINEPHRINE

- Physiologic antagonist to histamine
- Those on beta blockers may need larger doses
- Drug of choice in PEA. Vasopressin has now become drug of choice in ventricular tachycardia
- Single dose of Vasopressin, 40 units IV
OTHER ADRENERGICS

- Ephedrine is a mixed acting adrenergic drug. Stimulates alpha and beta receptors. Longer lasting than epinephrine.
- See in Primatene mist
PSEUDOPHED

- Used for bronchodilating and nasal decongestant effects
ISUPREL (ISOPROTERENOL)

- Synthetic catecholamine that acts on beta 1 and 2 receptors
- Stimulates heart, dilates blood vessels in skeletal muscle and causes bronchodilation
- No alpha stimulation
- Used in heart blocks (when pacemaker not available) and as a bronchodilator
NEOSYNEPHRINE (PHENYLEPHRINE)

- Pure alpha
- Decreases CO and renal perfusion
- No B1 or B2 effects
- Longer lasting than epinephrine
- Can cause a reflex bradycardia
- Useful as a mydriatic
TOXICITY OF ADRENERGICS IN CRITICALLY ILL PATIENTS

- Affects renal perfusion
- Can induce cardiac dysrhythmias
- Increases myocardial oxygen consumption
- May decrease perfusion of liver
- Tissue necrosis with extravasation
TOXICITY

- Do not give epinephrine and Isuprel at same time or within 4 hours of each other. Could result in serious dysrhythmias.
FUNCTIONS OF ADRENOCEPTORS

**α₁**
- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

**α₂**
- Inhibition of norepinephrine release
- Inhibition of acetylcholine release
- Inhibition of insulin release

**β₁**
- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

**β₂**
- Vasodilation
- Slightly decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis
- Increased release of glucagon
- Relaxed uterine smooth muscle
ANTI-ADRENERGICS

- Sympatholytic
- Block or decrease the effects of sympathetic nerve stimulation, endogenous catecholamines and adrenergic drugs
ANTIADRENERGIC S—MECHANISMS OF ACTION AND EFFECTS

- Can occur by blocking alpha 1 receptors postsynaptically
- Or by stimulation presynaptic alpha 2 receptors. Results in return of norepinephrine to presynaptic site. Activates alpha 2 resulting in negative feedback. Decreases release of additional norepinephrine.
Alpha-Adrenergic Agonists and Blocking Agents

- Alpha 2 agonists inhibit release of norepinephrine in brain; thus, decrease effects on entire body
- Results in decrease of BP
- Also affects pancreatic islet cells, thus some suppression of insulin secretion
ALPHA 1 ADRENERGIC BLOCKING AGENTS

- Act on skin, mucosa, intestines, lungs and kidneys to prevent vasoconstriction
- Effects: dilation of arterioles and veins, decreased blood pressure, pupillary constriction, and increased motility of GI tract
May activate reflexes that oppose fall in BP such as fluid retention and increased heart rate

Can prevent alpha medicated contraction of smooth muscle in nonvascular tissues

Thus, useful in treating BPH as inhibit contraction of muscles in prostate and bladder
ALPHA 1 ANTAGONISTS

- Minipress (prazosin)—prototype.
- Hytrin (terazosin) and Cardura (doxazosin)—both are longer acting than Minipress.
**Flomax (tamsulosin).** Used in BPH. Produces smooth muscle relaxation of prostate gland and bladder neck. Minimal orthostatic hypotension.

**Priscoline (tolaxoline) used for vasospastic disorders.** Pulmonary hypertension in newborns. Can be given sub Q, IM or IV.
**ALPHA 2 AGONISTS**

- Catapres (clonidine). PO or patch.
- Tenex (guanfacine)
- Aldomet (methyldopa). Can give IV. Caution in renal and hepatic impairment.
BETA ADRENERGIC BLOCKING MEDICATIONS

- Prevent receptors from responding to sympathetic nerve impulses, catecholamines and beta adrenergic drugs.
EFFECTS OF BETA BLOCKING DRUGS

- Decreased heart rate
- Decreased force of contraction
- Decreased CO
- Slow cardiac conduction
- Decreased automaticity of ectopic pacemakers
EFFECTS OF BETA BLOCKING DRUGS

- Decreased renin secretion from kidneys
- Decreased BP
- Bronchoconstriction
- Less effective metabolism of glucose. May result in more pronounced hypoglycemia and early s/s of hypoglycemia may be blocker (tachycardia)
EFFECTS OF BETA BLOCKING AGENTS

- Decreased production of aqueous humor in eye
- May increase VLDL and decrease HDL
- Diminished portal pressure in clients with cirrhosis
INDICATIONS FOR USE

- Alpha 1 blocking agents are used for tx of hypertension, BPH, in vasospastic disorders, and in persistent pulmonary hypertension in the newborn
- May be useful in treating pheochromocytoma
- May be used in Raynaud’s or frostbite to enhance blood flow
REGITINE (PHENTOLAMINE)

- Used for extravasation of potent vasoconstrictors (dopamine, norepinephrine) into subcutaneous tissues
**INDICATIONS FOR USE**

- Alpha 2 agonists are used for hypertension—Catapres
- Epidural route for severe pain in cancer
- Investigationally for anger management, alcohol withdrawal, postmenopausal hot flashes, ADHD, in opioid withdrawal and as adjunct in anesthesia
Mainly for cardiovascular disorders (angina, dysrhythmias, hypertension, MI and glaucoma)

In angina, beta blockers decrease myocardial oxygen consumption by decreasing rate, BP and contractility. Slow conduction both in SA node and AV node.
BETA BLOCKERS

- Possibly work by inhibition of renin, decreasing cardiac output and by decreasing sympathetic stimulation
- May worsen condition of heart failure as are negative inotropes
- May reduce risk of “sudden death”
BETA BLOCKERS

- Decrease remodeling seen in heart failure
- In glaucoma, reduce intraocular pressure by binding to beta-adrenergic receptors in ciliary body, thus decrease formation of aqueous humor
Inderal (propranolol) is prototype
Useful in treatment of hypertension, dysrhythmias, angina pectoris, MI
Useful in pheochromocytoma in conjunction with alpha blockers (counter catecholamine release)
migraines
BETA BLOCKERS

- In cirrhosis, Inderal may decrease the incidence of bleeding esophageal varices
- Used to be contraindicated in heart failure, now are standard
- Known to reduce sudden death
- Often given with ACEIs
- Indications include: htn, angina, prevention of MI
Acetutolol, atenolol, betaxolol, esmolol, and metoprolol are relatively cardioselective.

These agents lose cardioselectivity at higher doses as most organs have both beta 1 and beta 2 receptors.

Byetta is a new agent that is cardioselective.
NON-RECEPTOR SELECTIVITY

- Carteolol, levobunolol, metipranolol, nadolol, propranolol, sotalol and timolol are all non-selective.
- Can cause bronchoconstriction, peripheral vasoconstriction and interference with glycogenolysis.
COMBINATION SELECTIVITY

- Labetalol and carvedilol (Coreg) block alpha 1 receptors to cause vasodilation and beta 1 and beta 2 receptors which affect heart and lungs.
- Both alpha and beta properties contribute to antihypertensive effects.
- May cause less bradycardia but more postural hypotension.
- Less reflex tachycardia.
INTRINSIC SYMPATHOMIMETIC ACTIVITY

- Have chemical structure similar to that of catecholamines
- Block some beta receptors and stimulate others
- Cause less bradycardia
- Agents include: Sectral (acebutolol), Cartrol (carteolol), Levatol (penbutolol) and Visken (pindolol)
SPECIFIC CONDITIONS-ALPHA AGONISTS AND ANTAGONISTS

- In tx for BPH, patient should be evaluated for prostate cancer
- With alpha 2 agonists, sudden cessation can cause rebound BP elevation
- With alpha 1 blockers, first dose syncope may occur from hypotension. Give low starting dose and at hs. May also cause reflex tachycardia and fluid retention.
SPECIFIC CONDITIONS-BETA BLOCKERS

- With significant bradycardia, may need med with ISA such as pindolol and penbutolol
- Patient with asthma, cardioselectivity is preferred
- For MI, start as soon as patient is hemodynamically stable
SPECIAL CONDITIONS—BETA BLOCKERS

- Should be discontinued gradually. Long term blockade results in increase receptor sensitivity to epinephrine and norepinephrine. Can result in severe hypertension. Taper 1-2 weeks.
ETHNIC CONSIDERATIONS

- Monotherapy in African Americans is less effective than in Caucasians.
- Trandate (labetalol) with both alpha and beta effects has been shown to be more effective in this population than Inderal, Toprol or timolol.