Adrenoceptor -activating & other sympathomimetic drugs
• Three Neurotransmitters of Sympathetic Nervous System
• NE, E, DA
• Adrenoceptor agonists
• Sympathomimetics :
  – Directly acting
  – Indirectly acting
  – Mixed action
1. **SYNTHESIS OF NOREPINEPHRINE**
   - Hydroxylation of tyrosine is the rate-limiting step.
   - Tyrosine $\rightarrow$ DOPA $\rightarrow$ Dopamine
   - Urine $\rightarrow$ Inactive metabolites

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.

**INTRACELLULAR RESPONSE**

**SYNTHETIC SPACE**

**SYNAPsic vesicle**

**Presynaptic receptor**

**Catechol-O-methyltransferase (COMT)**

**Inactive metabolites**

**Urine**

**Ca^{2+}**
# Alpha receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>G-protein</th>
<th>Second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Postsynaptic: Vascular smooth ms, skin, MM, dilator pupillae, salivary glands, prostate, trigone &amp; sphincter of UB; Vas deferens, &amp; Sem Vesicles</td>
<td>Gq</td>
<td>↑IP3, ↑DAG</td>
</tr>
<tr>
<td>α2</td>
<td>Presynaptic: adr / cholinergic N.terminals., platelets, pancreatic cells, CNS</td>
<td>Gi</td>
<td>↓c AMP</td>
</tr>
</tbody>
</table>
FIGURE 9-1  Activation of α₁ responses. Stimulation of α₁ receptors by catecholamines leads to the activation of a Gₜₐ coupling protein. The activated α subunit (αₐ*) of this G protein activates the effector, phospholipase C, which leads to the release of IP₃ (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol) from phosphatidylinositol 4,5-bisphosphate (PtdIns 4,5P₂). IP₃ stimulates the release of sequestered stores of calcium, leading to an increased concentration of cytoplasmic Ca²⁺. Ca²⁺ may then activate Ca²⁺-dependent protein kinases, which in turn phosphorylate their substrates. DAG activates protein kinase C (PKC). GTP, guanosine triphosphate; GDP, guanosine diphosphate. See text for additional effects of α₁-receptor activation.
Beta receptors

- $\beta_1$: Heart, JGA
- $\beta_2$: Respiratory, Uterine, VSM, Skeletal Ms, Liver
- $\beta_3$: Fat cells
- All stimulate increased C-AMP

- **Dopamine Receptors**
  - D1: $\uparrow$ cAMP
  - D2: $\downarrow$ cAMP
  - D3 $\downarrow$ cAMP
  - D4 $\downarrow$ cAMP, D5 $\uparrow$ cAMP
FIGURE 9–2 Activation and inhibition of adenylyl cyclase by agonists that bind to catecholamine receptors. Binding to β adrenoceptors stimulates adenylyl cyclase by activating the stimulatory G protein, Gs, which leads to the dissociation of its α subunit charged with GTP. This activated αs subunit directly activates adenylyl cyclase, resulting in an increased rate of synthesis of cAMP. Alpha₂-adrenoceptor ligands inhibit adenylyl cyclase by causing dissociation of the inhibitory G protein, Gi, into its subunits; i.e., an activated αi subunit charged with GTP and a βγ unit. The mechanism by which these subunits inhibit adenylyl cyclase is uncertain. cAMP binds to the regulatory subunit (R) of cAMP-dependent protein kinase, leading to the liberation of active catalytic subunits (C) that phosphorylate specific protein substrates and modify their activity. These catalytic units also phosphorylate the cAMP response element binding protein (CREB), which modifies gene expression. See text for other actions of β and α₂ adrenoceptors.
<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Most vascular smooth muscle</td>
<td>Contracts (↑ vascular resistance)</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contracts (mydriasis)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Contracts (erects hair)</td>
</tr>
<tr>
<td></td>
<td>Liver (in some species, eg, rat)</td>
<td>Stimulates glycogenolysis</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibits transmitter release</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Stimulates aggregation</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contracts</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibits lipolysis</td>
</tr>
<tr>
<td></td>
<td>Pancreatic $\beta$ (B) cells</td>
<td>Inhibits insulin release</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Heart</td>
<td>Stimulates rate and force</td>
</tr>
<tr>
<td></td>
<td>Juxtaglomerular cells of kidney</td>
<td>Stimulates renin release</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Airways, uterine, and vascular smooth muscle</td>
<td>Relaxes</td>
</tr>
<tr>
<td></td>
<td>Liver (human)</td>
<td>Stimulates glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Pancreatic $\beta$ (B) cells</td>
<td>Stimulates insulin release</td>
</tr>
<tr>
<td></td>
<td>Somatic motor neuron terminals (voluntary muscle)</td>
<td>Causes tremor</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Stimulates rate and force</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>Fat cells</td>
<td>Stimulates lipolysis</td>
</tr>
<tr>
<td>Dopamine, ($D_1$)</td>
<td>Renal and other splanchnic blood vessels</td>
<td>Dilates (↓ resistance)</td>
</tr>
<tr>
<td>Dopamine$_2$, ($D_3$)</td>
<td>Nerve terminals</td>
<td>Inhibits adenylyl cyclase</td>
</tr>
</tbody>
</table>
ADRENOCEPTORS

\[ \alpha_1 \]
- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

\[ \alpha_2 \]
- Inhibition of norepinephrine release
- Inhibition of acetylcholine release
- Inhibition of insulin release

\[ \beta_1 \]
- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

\[ \beta_2 \]
- Vasodilation
- Slightly decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis
- Increased release of glucagon
- Relaxed uterine smooth muscle
Receptor regulation

- Desensitization /Tolerance/ Refractoriness
- Tachyphylaxis
Classification: MOA

Adrenergic Agonists

- Direct-acting
  - Selective
    - Phenylepinephrine
    - Clonidine
    - Dobutamine
    - Terbutaline
  - Non-selective
    - Epinephrine
    - Norepinephrine
    - Oxymetazoline
    - Isoprenaline

- Mixed acting
  - ephedrine

- Indirect Acting
  - Releasing agent
    - Amphetamine
    - Tyramine
  - Uptake inhibitor
    - Cocaine
  - MAO inhibitors & COMT inhibitors
    - Selegiline
    - Entacapone
Classification: MOA

- **Direct acting**
  - Epinephrine, Norepinephrine, Isoprenaline, dopamine, dobutamine (Catecholamines)
  - Salbutamol, terbutaline, phenylephrine, clonidine, methoxamine …..

- **Indirect-acting**
  - Amphetamine, Cocaine, Tyramine

- **Mixed action**
  - Ephedrine, pseudoephedrine
Phenylethylamine is the parent compound from which sympathomimetic drugs are derived. It consists of a benzene ring with an ethylamine side chain. The modification of phenylethylamine changes the affinity of the drugs for receptors, the intrinsic ability, and pharmacokinetics.
PK and SAR

- Subst. by OH- gp at C 3 & 4 yields catecholamines
- Chem str – determines activity at various receptors and also PK properties
  Catecholamines –
  - High potency ,
  - Rapid inactivation,
  - not absorbed orally ,
  - Poor CNS penetration
Phenylethylamine and some important catecholamines. Catechol is shown for reference.
<table>
<thead>
<tr>
<th>Relative selectivity of adrenoceptor agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Alpha agonists</strong></td>
</tr>
<tr>
<td>• Phenylephrine, methoxamine: selective $\alpha_1$</td>
</tr>
<tr>
<td>• Clonidine, $\alpha_2$</td>
</tr>
<tr>
<td>• <strong>Beta agonists</strong></td>
</tr>
<tr>
<td>• Dobutamine : $\beta_1$</td>
</tr>
<tr>
<td>Isoprenaline : $\beta_1 = \beta_2$</td>
</tr>
<tr>
<td>• Salbutamol, terbutaline, ritodrine : $\beta_2$</td>
</tr>
<tr>
<td>• <strong>Mixed alpha &amp; beta agonists</strong></td>
</tr>
<tr>
<td>• Norepinehrine : $\alpha_1 = \alpha_2$, $\beta_1 &gt;&gt; \beta_2$</td>
</tr>
<tr>
<td>• Epinephrine : $\alpha_1 = \alpha_2$, $\beta_1 = \beta_2$</td>
</tr>
<tr>
<td>• <strong>Dopamine agonists</strong></td>
</tr>
<tr>
<td>• Dopamine : $D1=D2 &gt;&gt; \beta &gt;&gt; \alpha$</td>
</tr>
</tbody>
</table>
Effects of sympathomimetic drugs on organ systems

- CVS: 1) Blood vessels
  2) Heart
  3) BP
- Eye
- Respiratory
- GIT
- GU
- Metabolic effects
$\alpha_1 + \beta_1$ effect

$\beta_2$ effect

$\alpha$ blocker

$\beta_2$ effect (low doses)

$\beta$ blocker
Eye

- Mydriasis: $\alpha_1$
- $\alpha_1$ vasoconst of ciliary vesels--$\downarrow$ aqueo form.
- $\alpha_2$: $\downarrow$ aqueo form. d/t $\downarrow$ secretory activity of ciliary epith
- $\beta_2$: enhanced secretory activity of ciliary epith. Facilitation of trabecular flow.
- Overall aqueous form $\downarrow$ & outflow facilitated.
Glaucoma

- characterized by increased intraocular pressure and excavation and atrophy of the optic nerve; produces defects in the visual field and may result in blindness.
- Adrenergic agonists: Used topically- dipivefrine
- Other agents for glaucoma
Respiratory Tract

- Bronchial smooth muscle contains $\beta_2$ receptors that cause bronchodilation.
- The blood vessels of the respiratory tract mucosa contains $\alpha$ receptors;
- The decongestant action of adrenoceptor stimulants is clinically useful.
Catecholamines:

- High potency,
- Rapid inactivation,
- not absorbed orally,
- Poor CNS penetration.
Endogenous Catecholamines

- **Epinephrine:** (Adrenaline)
- **Uses:** Anaphylactic Shock: 0.5ml of 1:1000 IM - life saving,
- Bronchospasm,
- As vasoconstrictor: locally , with Local Anaesthetics
- Glaucoma, Cardiac arrest,
- A/E: HT ---cerebral hrage, ppt angina, palpitations , arrhythmias, CNS : tremors , anxiety
Endogenous Catecholamines....

- **DI:** Halothane, MAOI s
- **CI:** hyperthyroidism, angina, HT,
- **Norepinephrine:**
- **Dopamine:** IV Infusion: Dose dependent effects
- **Uses:** Shock d/t MI, trauma, surgery;
- **CHF** –
- correct hypovolemia before adm.
- **A/E:** N, V, tachycardia, HT
Dopamine

- DA is a non–selective adrenergic agonist, which acts either directly on DA – receptors in addition to $\beta_1$ - adrenergic receptors or indirectly by releasing NE
- It is given parenterally only (not orally)
- $T_{1/2} = 3 – 5$ min
- Metabolized by either
  - Converted to NE in adrenergic neurons or
  - By MAO in the Liver
• Clinical Uses :
  – In small dose of DA (2-5ug / Kg / min by I.V infusion) Renal dose:
    • It will stimulate DA–receptors
      – It will cause vasodilatation (VD) in:
        » Renal vascular bed
        » Cerebral vascular bed
        » Coronary vascular bed
        » Mesenteric vascular bed

Therefore, it is useful in treatment of shock to save these vital organs from hypoxia
– **In medium dose**: (5-10ug/Kg/min by I.V infusion)
  
  Cardiac dose
  
  • It will stimulate $\beta_1$ – receptors to cause increase HR, CO and BP

– **In high dose of DA** (> 10ug / Kg / min by I.V infusion)

  • It will stimulate $\alpha_1$ receptors (direct + Via release of NE) to cause VC leading to increase BP and decrease organ perfusion

So, the high dose of DA is not recommended in shock.
Shock

- is a complex acute cardiovascular syndrome that results in a critical reduction in perfusion of vital tissues, and usually associated with hypotension, oliguria.
- The major mechanisms are hypovolemia, cardiac insufficiency, and altered vascular resistance.
- sympathomimetic drugs have been used in the treatment of all forms of shock.
Types of shock

- Hypovolamic shock
- Septic shock
- Anaphylactic shock
- Neurogenic shock
- Cardiogenic shock
Synthetic CA

• **Isoprenaline**: - in heart blocks

• **Dobutamine**: $\beta_1$ - more selective inotropic than chronotropic acn.

• **Use**: as iv inf in CHF, cardiogenic shock

• **A/E**: sharp incr in BP & HR, ppt angina
Dobutamine:

- It is direct acting $\beta_1$ – selective agonist (only)
- $T1/2 = 10 – 15\text{ min}$
- is metabolized in the liver by oxidative deamination
- causes increases in CO with minimal effect on HR.
- less arrhythmogenic effects than dopamine
- Uses: Inotropic agent for Heart Failure; in septic and cardiogenic shock.
α1 selective agonists

- Phenylephrine: oral nasal decongestant, mydriatic
- Midodrine: oral prodrug for postural hypotension
- Naphazoline, Oxymetazoline, Xylometazoline – nasal decongestants
- PPA: withdrawn
- OTC medications – caution in HT, cardiac, elderly males
α2 selective agonists

- **Clonidine**: Acts centrally on VMC - ↓BP & HR. Oral BA 100%. TTS also,
  - Use: HT, Opioid/alcohol withdrawal, PAM, diarrhoea in DM, menopausal hot flushes,
  - A/E: rebound HT after abrupt withdrawal, dry mouth, sedation, nasal stuffiness, constipation
  - Apraclonidine, Brimonidene –topically in glaucoma
β 2 –Selective agonists

• **Salbutamol, Terbutaline**: Bronchodilators - short-acting, Oral and inhalational- MDI useful
• **Formetrol, Salmeterol**: long-acting
• **Ritodrine**
• **A/E**: 


Indirectly acting sympathomimetics

Amphetamine

- It is non-selective adrenergic agonist, non-catecholamine
  - Acts mainly, indirectly via enhancing NE release and DA.
  - given orally
  - s lipid–soluble well absorbed from GIT, penetrates CNS
  - $t_{1/2} = 45 – 60$ min
  - metabolized in the liver
Indirectly acting sympathomimetics

- **Amphetamine**: CNS effects
  - stimulates cortical regions & RAS & resp C. – Induces wakefulness, alertness, less fatiguability—highly abused.
  - CVS: HT, tachy, arrhythmias in large doses.
  - Anorexia d/t supp of hypoth feeding center, but tolerance develops.
  - A/E: restlessness, tremors, irritability, insomnia, euphoria, hallucin, palpitation, headache, dry mouth, anorexia, abd cramps. Psychological dependence on prolonged use, tolerance to anorexic effect.
Indirectly acting sympathomimetics

- Use: narcolepsy, ADHD (now better drugs)
- Methylphenidate—mild CNS stimulant—more can on mental fnc
- Use: Narcolepsy, ADHD
- Modafinil: central alpha 1 R + GABA, glutamate, serotonergic R: Narcolepsy, ADHD
Mixed action agents: Ephedrine

- It is non selective adrenergic agonist
- It directly acts on the receptors ($\alpha, \beta_1, \text{and} \beta_2$)
  - AND indirectly by releasing NE
  - PK almost similar to amphetamine
  - Causes tachyphylaxis, but no addiction
  - Like amphetamine, it is CNS and respiratory stimulants.
  - does not suppress the appetite
Mixed action agents…

- Ephedrine, Psuedoephedrine, *Phenyl propranolamine*, α & β agonist + enhances release of NE
- Tachyphylaxis
- S/E: CNS
  - Insomnia
  - Restlessness
  - Confusion
  - Irritability
  - Anxiety
  - Loss of appetite, Hypertension
Clinical applications of Sympathomimetic drugs

- Hypotension
- Shock
- In Heart Failure
- Alongwith local anesthetic for minor surgery: Adrenaline
  - Decrease bleeding
  - Prevent spread of local anesthetic into systemic circulation
- In bronchial asthma
- As nasal decongestants
- In cardiac arrest
- For mydriasis
- In Glaucoma
- For delaying of labour
- In ADHD
- For narcolepsy
<table>
<thead>
<tr>
<th>CATECHOLAMINES</th>
<th>NONCATECHOLAMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Rapid onset of action</td>
<td>Compared to catecholamines:</td>
</tr>
<tr>
<td>● Brief duration of action</td>
<td>● Longer duration of action</td>
</tr>
<tr>
<td>● Not administered orally</td>
<td>● All can be administered orally</td>
</tr>
<tr>
<td>● Do not penetrate the blood-brain barrier</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>TCRR</th>
<th>RECEPTOR SPECIFICITY</th>
<th>THERAPEUTIC USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>$\alpha_1$, $\alpha_2$ $\beta_1$, $\beta_2$</td>
<td>Acute asthma</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>$\alpha_1$, $\alpha_2$ $\beta_1$</td>
<td>Treatment of shock</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>$\beta_1$, $\beta_2$</td>
<td>As a cardiac stimulant</td>
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<tr>
<td>Dopamine</td>
<td>Dopaminergic $\alpha_1$, $\beta_1$</td>
<td>Treatment of shock</td>
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<td>Treatment of congestive heart failure</td>
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<tr>
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<td>Raise blood pressure</td>
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<td>As a nasal decongestant</td>
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<td></td>
<td>Raise blood pressure</td>
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<tr>
<td>Methoxamine</td>
<td>$\alpha_1$</td>
<td>Treatment of supraventricular tachycardia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>$\alpha_2$</td>
<td>Treatment of hypertension</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>$\beta_2 &gt; \beta_1$</td>
<td>Treatment of bronchospasm and asthma</td>
</tr>
<tr>
<td>Albuterol</td>
<td>$\beta_2$</td>
<td>Treatment of bronchospasm (short acting)</td>
</tr>
<tr>
<td>Piritetol</td>
<td>$\beta_2$</td>
<td>Treatment of bronchospasm (long acting)</td>
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<td>Terbutaline</td>
<td>$\beta_2$</td>
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<tr>
<td>Salmeterol</td>
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<tr>
<td>Formoterol</td>
<td>$\alpha$, $\beta$, CNS</td>
<td>As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and appetite control</td>
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<td>Pseudoephedrine</td>
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