ADRENOCEPTOR ACTIVATING DRUGS AND OTHER SYMPATHOMIMETICS

DEFINITION:
Sympathomimetics are drugs which partially or completely mimic the action of EPINEPHRINE (E) or NORADRENALINE (NE).

They can act:
- DIRECTLY - on the adrenergic receptors.
- INDIRECTLY - release CATECHOLAMINES (CA) from nerve endings.

The sympathomimetics include:
- the endogenous biogenic amines (NE, E, D, ISO)
- ephedrine and other vasoconstrictors
- bronchodilators
- CNS stimulants, anorexants

Their effects can be predicted from the knowledge of:
1. The type of adrenergic receptor with which they interact.
2. Their penetration or lack of penetration into the CNS.
3. Direct, indirect or mixed nature of their action.

BASIC PHARMACOLOGY OF SYMPATHOMIMETIC DRUGS

1. Identification of adrenoceptors

LANGLEY (1905), ERLICH (1913) receptor theory ("receptive substances")
AHRLQUIST (1948) α and β receptors

α receptors: NOREPINEPHRINE > EPINEPHRINE >>> ISOPROTERENOL
β receptors: ISOPROTERENOL > EPINEPHRINE > NOREPINEPHRINE

Receptor subtypes:
- β1, β2, β3: defined by their affinities for E or NE
- α1A, α1B, α2A, α2B
- NE > E
- E > NE
- NE > E

Effector:
- cAMP
- cAMP
- cAMP

α1 and α2: defined by their affinities for α receptor agonists and antagonists
Ca\(^{2+}\) influx ↑

Dopamine receptors - brain, splanchnic and renal vascular beds
D1 D2 D3 D4 D5
cAMP ↑ cAMP ↓ AMP ↓ cAMP ↓ cAMP ↑
K\(^+\) channel (Gi protein)

↑ K\(^+\) and Ca\(^{2+}\) channel
Relative selectivity of adrenoceptor agonists

\(\alpha\) agonists: PHENYLEPHRINE, METHOXAMINE \(\alpha_1 \gg \alpha_2 \gg \gg \gg \beta\)
CLONIDINE, M-NOREPINEPHRINE \(\alpha_2 > \alpha_1 \gg \gg \gg \beta\)
\(\alpha\) & \(\beta\) agonists: NOREPINEPHRINE \(\alpha_1 = \alpha_2; \ \beta_1 \gg \beta_2\)
EPINEPHRINE \(\alpha_1 = \alpha_2; \ \beta_1 = \beta_2\)
\(\beta\) agonists: ISOPROTERENOL \(\beta_1 = \beta_2 \gg \gg \gg \alpha\)
DOBUTAMINE \(\beta_1 > \beta_2 \gg \gg \alpha\)
TERBUTALINE, ALBUTEROL \(\beta_2 \gg \beta_1 \gg \gg \alpha\)

2. Molecular mechanisms of sympathomimetic action
\(\alpha\)-adrenoceptors

Identification: binding of radiolabeled compounds which have a high affinity for receptors, e.g.
\(\alpha_1\): PRAZOSIN, DIHYDROERGOCRPTINE
\(\alpha_2\): RAUWOLSCINE, YOHIMBINE

Effect of \(\alpha\)-adrenoceptor activation: Rise in cytosolic Ca\(^{2+}\) concentration
\(\alpha_1\): \(\alpha_1\) receptor \(\rightarrow G_q\) protein \(\rightarrow\) PLC-IP3/DG system \(\rightarrow\) release of Ca\(^{2+}\) from SR

Result: e.g. smooth muscle contraction

\(\alpha_2\): Inhibition of adenylate cyclase (Gi protein) \(\rightarrow\) cAMP\(\downarrow\) \(\rightarrow\) Ca\(^{2+}\) sequestration \(\downarrow\)
\(\rightarrow\) free Ca\(^{2+}\) \(\uparrow\).

Result: contraction

Differentiation between \(\alpha_1\) and \(\alpha_2\) receptors
- divergent tissue distribution and functions
- distinct biochemical effector mechanism
\(\alpha_1\) dominance for high frequency nerve stimulation and for high dose of NE
\(\alpha_2\) respond to low frequency stimulation, low dose of NE and circulating E
\(\alpha_1\) receptor activation (or agonists) \(\rightarrow\) rapid rise in blood pressure
\(\alpha_2\) receptor activation (postsynaptic) \(\rightarrow\) slower pressor response but more persistent
\(\alpha_2\) receptor activation (presynaptic) \(\rightarrow\) feedback inhibition of NE release
**β adrenoceptors**

Effect of β receptor activation (β1, β2 and β3)

- β activation → adenylate cyclase activity ↑ (Gs protein) → cAMP ↑

  **Myocardial cells:** cAMP ↑ → → Ca²⁺ influx ↑ → → contraction  
    → → Ca²⁺ sequestration ↑ → → relaxation

  **Smooth muscle cells:** cAMP ↑ → → inactivation of MLCK → → relaxation

  **Liver:** cAMP ↑ → → activation of glycogen phosphorylase

**Dopamine receptors**

- D1 receptor activation: cAMP ↑ → → smooth muscle relaxation
- D2 receptor activation: cAMP ↓ → → opening of K⁺ channel, Ca²⁺ influx ↓
### 3. Chemistry and Pharmacokinetics

**β-Phentolamine**

Catechol (ortho-dihydroxybenzene) + an amino group on the side chain

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**Substitutions:**

a.) **On the amino group**
- Increasing the size of the alkyl group → increased β and decreased α activity

b.) **On the benzene ring**
- Maximal α and β activity is found with CAs (R1 and R2 = OH)
- Absence the -OH at R1, the potency of drug decreases, e.g. PE << E
- Absence of one or two -OH increases bioavailability after oral administration (not attacked by COMT, found in gut and liver) and prolongs the duration of action.
- Absence of -OH groups increases lipid solubility → CNS stimulant effect

c.) **On the α carbon**
- Substitution blocks oxidation by MAO and prolongs the action
- α-methyl compounds displace CAs from storage sites (indirectly acting sympathomimetics, e.g. amphetamine)
ORGAN SYSTEM EFFECTS OF SYMPATHOMIMETIC DRUGS

1. Cardiovascular system
   a.) Blood vessels:  
   α receptor stimulation $\rightarrow$ vasoconstriction  
   β2 receptor stimulation $\rightarrow$ vasodilatation  

   VASCULAR RESISTANCE  
<table>
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<tr>
<th>Phenylephrine</th>
<th>Epinephrine</th>
<th>ISO</th>
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   -cutaneous, mucous membrane (α)  
   -skeletal muscle (α, β2)  
   -renal (α)  
   -splanchnic (α)  
   -TPR  
   -venous tone  
   CARDIAC  
   -contractility (β1, β2)  
   -heart rate (predominantly β1)  
   -stroke volume  
   -cardiac output  
   BLOOD PRESSURE  
   -MABP  
   -DABP  
   -SABP  
   -PULSE PRESSURE  

b.) Heart  
Mostly β1 receptors but β2 and α receptors have also been implicated  
**β receptor activation** $\rightarrow$ Ca$^{2+}$ influx $\rightarrow$ electrical and mechanical consequences  
+ chronotropic effect $\rightarrow$ increased pacemaker activity both normal (sinus) and abnormal (e.g. Purkinje fibres)  
+ dromotropic effect $\rightarrow$ increased conduction in the AV node, decreased refractory period  
+ inotropic effect $\rightarrow$ increased contractility, accelerated relaxation  
+ bathmotropic effect $\rightarrow$ increased excitability  

c.) Blood pressure (BP)  
* Explained by the effects of CAs on the heart, peripheral vascular resistance (TPR), and on the venous return  
* Pure α agonist (e.g. Phenylephrine) $\rightarrow$ TPR ↑ and venous tone↑ $\rightarrow$ BP ↑ (baroreceptor mediated increase in vagal tone HR ↓)  
* Pure β agonist (e.g. Isoproterenol) SABP ↑ and DABP ↓  
  ↓  ↓  
  ↓  ↓  
  β1 receptor stimulation $\rightarrow$ in the heart vascular beds $\rightarrow$ TPR ↓  
  increase in cardiac output (CO)
2. Eye
MYDRIASIS (radial pupillary dilator muscle of iris contains α receptors, α stimulation → → muscle contraction → → pupil dilates)
Slight decrease in accommodation (β stimulants relax the ciliary muscle)

3. Respiratory tract
Bronchial smooth muscle: β2 receptors; β activation → → bronchodilation
Upper respiratory tract mucosa: α receptors; α stimulants → → decongestion

4. Gastrointestinal tract
Both α and β stimulants → → relaxation of GIT smooth muscle
β receptor activation (smooth muscle cells) → → hyperpolarisation → → relaxation
α stimulants act indirectly; reduce presynaptically the release of acetylcholine

5. Genitourinary tract
Human uterus (α and β receptors). β2 receptor stimulation → → relaxation
Bladder base and urethral sphincter: α receptor → → contraction → → continence
Bladder wall: β2 receptors → → relaxation
Ejaculation is dependent upon normal α receptor activity

6. Exocrine glands
Salivary gland: increased secretion (mucinous rich saliva, poor in enzyme)
Apocrine sweat gland (eg. palms of hands): α stimulants → → sweat production↑
(non-thermoregulatory glands respond to psychotic stress, thermoregulatory sweat glands are regulated by ACH receptors)

7. Metabolic effects
Fat cells: β3 receptor activation → → increased lipolysis
Lipocytes: α receptor activation → → inhibited lipolysis (by decreasing cAMP)
Liver: β2 & α1 receptor activation → → glycogenolysis → → blood glucose ↑
Skeletal muscle: β1 receptor activation → → glycogenolysis → → lactate ↑
High dose of CAs causes metabolic acidosis

8. Endocrine function
Insulin secretion is stimulated by β1 and inhibited by α2 receptors
Renin secretion is stimulated by β1 and inhibited by α2 receptors

9. Other effects
Skeletal muscle: β2 receptor stimulation → → increased twitch tension in fast contracting muscles (white muscle) and reduced twitch in slow (red) muscles;
CNS: β2 receptor agonists cause tremor, shakiness, accompanied by fear and excitement
Mast cells: histamine release (eg. in lung tissues in response to anaphylactic challenge) is inhibited by CAs acting on β2 receptors
**SPECIFIC SYMPATHOMIMETIC DRUGS**

**A: CATECHOLAMINES**

**EPINEPHRINE (E, ADRENALINE)**  
(fight-or-flight response)

Acts on both α and β receptors. At low concentrations β effects, at high concentrations α effects predominate.

a.) **Effects on blood pressure**

- Low doses of E: MABP ↓ (β2 receptor stimulation → vasodilatation)
  - DABP ↓ because TPR ↓
- Large doses of E: MABP ↑ (α receptor stimulation → vasoconstriction)
  - SABP ↑ (β1 receptor stimulation → ventricular contraction ↑ → HR ↑)

b.) **Vascular effects**

  1. Decreased cutaneous blood flow (BF) (α)
  2. Increased BF to skeletal muscle (β2 - at low doses)
     - Decreased BF to skeletal muscles (α - at high doses)
  3. Increased hepatic BF, decreased splanchnic vascular resistance (β2)
  4. Increased renal vascular resistance → decreased renal BF
  5. Increased arterial and venous pulmonary pressure
  6. Increased coronary flow

c.) **Effects on the heart**

  1. Direct effect on the β1 receptors → contractility ↑, HR ↑ (or ↓)
  2. Increased stroke volume (SV) and cardiac output (CO)
  3. Increased arrhythmogenesis

d.) **Effect on smooth muscles**

  This depends on the predominant type of the receptor in the muscle

  1. GIT smooth muscle relaxation (α & β), sphincter contraction (α)
  2. Uterine contractions: inhibited (β2) or stimulated (α) depending on the menstrual phase or the state of gestation
  3. Bladder: detrusor relaxes (β2), trigone and sphincter contracts (α)
  4. Bronchial smooth muscle: relaxes (β2)

e.) **Metabolic effects**

  1. Increase in glucose and lactate production (liver and muscle glycogenolysis)
  2. Inhibition of insulin secretion (α)
  3. Increase in FFA (β3)
  4. Increase in oxygen consumption
NOREPINEPHRINE (NE, NORADRENALINE)
NE is almost equipotent to E in its action on β1 and α receptors but it has very little effect on β2 receptors
a.) NE increases SABP (β1) and DABP (α) by constricting vascular smooth muscle
b.) TPR ↑ → compensatory vagal reflex stimulation → HR ↓
c.) CO may actually maintained (increased venous return + inotropic effect)

Pharmacokinetics of Epinephrine and Norepinephrine
(1) Poor absorption following oral administration (rapid conjugation and oxidation)
(2) Slow absorption following subcutaneous administration → local vasoconstriction
(3) Inhaled solutions are used in the disease of respiratory tract
(4) They can be given intravenously (Caution! VF may occur)
(5) Metabolism in the liver (COMT and MAO); excretion in the urine

Therapeutic uses of Epinephrine and Norepinephrine
EPINEPHRINE
(1) to treat bronchospasm
(2) for relief hypersensitivity reactions (anaphylactic shock)
(3) to prolong the effect of local anaesthetics (infiltrative)
(4) to restore cardiac activity in cardiac arrest
(5) in glaucoma (facilitates aqueous drainage)

NOREPINEPHRINE for treating hypotension (when tissue perfusion is good)

Untoward effects of Epinephrine and Norepinephrine
Anxiety, headache, cerebral haemorrhage, cardiac arrhythmias, pulmonary hypertension

Preparations
Norepinephrine (Levophed) bitartarate, injection 1 mg/ml for iv. infusion
Ethyl-norepinephrine hydrochloride (Bronkephrine), 2 mg/ml for sc. or im. inj. to relieve bronchospasm
Epinephrine hydrochloride, inj. from 0.01 to 1 mg/ml, for nasal administration, 0.1 and 2 % solutions used in ophthalmology
Epinephrine bitartarate aerosols (Medihaler-Epi, Primatene Mist Suspension, etc.)
Epinephrine borate (Epinal, Eppy/N) 0.5 and 2 % ophthalmologic solutions
Dipivefrin hydrochloride (Propine) 0.1 % solution for the management of glaucoma
Epinephrine (ANAPEN) (inj. 0.3 mg) anaphylaxis (emergency syringe)
ISOPROTERENOL (ISO, ISOPRENALINE)

Potent ß receptor agonist (having a little effect on α receptors)
(1) Stimulates ß1 receptors in the heart → chronotropic and inotropic effect (SABP ↑)
(2) Stimulates ß2 receptors in vascular smooth muscle → vasodilatation → TPR ↓
   These effects lead to an increase in CO, associated with a fall in DABP & MABP
   in bronchial smooth muscle → bronchodilation
   in the uterus → uterus relaxation
(3) Stimulates ß3 receptors in fat cells → lipolysis → FFA ↑
(4) Stimulates insulin secretion

Pharmacokinetics of ISO
(1) ISO does not absorb orally
(2) It is easily absorbed when given parenterally or inhaled aerosol
(3) It is principally metabolised by COMT

Therapeutic use of ISO
Cardiac stimulant and bronchodilator. (Bradycardia with AV block, Torsade de pointes, sick-sinus syndrome test, etc.)

Untoward effects of ISO
(1) These are similar to the undesired effects of E
(2) Over-dosage can induce fatal VF
(3) Tolerance occurs with overuse as an antiasthmatic drug

DOPAMINE (DA)
The immediate metabolic precursor of NE
(1) Direct agonist on D1, D2 receptors, ß1 and α receptors
   D1 receptor stimulation (low dose of DA) reduces arterial resistance in mesenteric, renal, cerebral and coronary vascular beds → increased BF to these areas
   (D1 receptors are not blocked by α or ß blocking drugs, they can be inhibited by Haloperidol and Phenothiazine)
   Presynaptic D2 receptor stimulation inhibits NE release from nerve endings
   ß1 receptor stimulation (medium dose of DA) → increased contractility and HR
   α receptor stimulation (high dose of DA) → TPR ↑
(2) Transmitter in the CNS

The pharmacokinetic properties of DA resemble to those of NE and E

Therapeutic uses of DA
(1) Cardiogenic and septic shock
(2) Chronic refractory congestive heart failure

Untoward effects
(1) Over-dosage → excessive sympathomimetic activity
(2) Anginal pain, arrhythmias, nausea, hypertension

Preparation
Dopamine hydrochloride (Intropin, Dopastat) iv. infusion 2 to 5 µg/kg/min
**DOBUTAMINE (DOBUTREX)**
It is a relatively β1 selective synthetic CA. Inotropic action > chronotropic effect.
It does not act on D1 receptors.
1. It is not absorbed when given orally
2. It has a short half-life (< 2 min)
3. It is usually used in intravenous infusion (2.5 to 10 µg/kg/min)
4. It is used in AMI with CHF, and after coronary bypass surgery

**B: NON-CATECHOLAMINES**

**PHENYLEPHRINE**
Pure α receptor agonist, with long duration of action (not inactivated by COMT)
1. Direct acting sympathomimetic, its effects are similar to those of NE but less potent
2. Vasoconstriction, BP ↑, reflex bradycardia occur after parenteral administration

**Therapeutic uses**
1. nasal decongestant
2. pressor agent
3. local vasoconstrictor - as 10 % ophthalmic solution
   - as an adjunct for use of LA
4. for relief of paroxysmal atrial tachycardia

**Untoward effects**
1. Large doses → ventricular arrhythmias (e.g. after systemic absorption), AMI
2. Rebound nasal congestion may occur after chronic use

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**Preparation**

**Phenylephrine hydrochloride** (Neo-Synephrine), 10 mg/ml injection for vasoconstriction, 0.125-1 % solution for nasal application
COLDREX, NEO-CITRAN (phenylephrine, paracetamol, ascorbic acid) – common cold
VIBROCIL, OTRIVIN (phenylephrine + H1 blocker) – rhinitis, common cold

**METHOXAMINE** (Methoxamine hydrochloride, Vasoxyl)
1. Its pharmacologic actions are similar to those of Phenylephrine
2. Predominantly it is a directly acting α receptor agonist → prolonged increase in BP, vagal-mediated bradycardia
3. Weak CNS stimulator
4. It is used in hypotensive states (20 mg/ml) and paroxysmal atrial tachycardia

**EPHEDRINE**

**Pharmacologic actions**
1. Mixed acting agonist - it has both direct and indirect actions
   - INDIRECT agonist → releases NE and competes with NE for vesicular uptake, but
   - it also stimulates directly the adrenoceptors
2. Following iv. administration its action is similar to that of E, but
   a.) the pressure response occurs more slowly and lasts longer
   b.) its potency is much more less than that of E
3. It causes CNS stimulation → insomnia, nervousness, nausea, agitation
4. Tachyphylaxis occurs with repeated administration
Pharmacokinetics
(1) It is absorbed when taken orally
(2) It is resistant to COMT and MAO → prolonged action

Therapeutic use
(1) In the treatment of bronchial asthma
(2) As a nasal decongestant
(3) As a pressor agent in spinal anaesthesia
(4) As a mydriatic

Untoward effects
(1) Similar to the undesired effects of E
(2) CNS effects may occur
(3) It must be used with caution in patent with cardiovascular diseases

Preparations
Ephedrine sulphate (Vatronal) 25 and 50 mg capsules, 0.5 % nose drops, 25 and 50 mg/kg injection for vasoconstriction

XYLOMETAZOLINE, OXYMETAZOLINE and NAPHASOLINE
(1) Direct acting α agonists, used as nasal decongestants.
(2) Following continuous use they may induce chronic rhinitis (rebound swelling)
(3) Systemic effects: hypertension, dizziness, palpitation, CNS stimulation

Xylometazoline hydrochloride (Otrivin) 0.05 and 0.1 % nose drops
Oxymetazoline hydrochloride (Afrin) 0.025 and 0.05 % nose drops,
0.025 % eye drops
Naphasoline hydrochloride (Privine) 0.05 % nose drops.
Side effects: drowsiness, coma in children and rebound nasal congestion.
Tetrahydrozoline hydrochloride (Murine) 0.05 and 0.1 % nose drops

Combination with antihistamines:
Phenylpropanolamine hydrochloride 25-75 mg tablets and capsules
Pseudoephedrine hydrochloride (Sudaphed) 30 and 60 mg tablets, 120 mg capsules
Pseudoephedrine sulphate (Afrinol) 120 mg tablets
L-Desoxyephedrine (Vicks) for inhalation
AMPHETAMINES

**AMPHETAMINE** is a phenylisopropylamine (no OH group on the ring)

**Pharmacologic effects**

1. It acts indirectly by releasing NE
2. Potent CNS stimulant (d form > l form)
3. It depresses appetite (feeding centre, lateral hypothalamus)
4. It increases metabolism

**Therapeutic use**

1. Narcolepsy
2. Hyperkinetic syndrome in children
3. Control of obesity (Caution! ABUSE)

**Untoward effects**

1. Tolerance (1-2 weeks) develops, both psychic and physical dependence occur. Large doses → toxic psychosis, prolonged use → mental depression and fatigue
2. CNS stimulation: restlessness, insomnia
3. Cardiovascular stimulation: tachycardia, hypertension
4. Mydriasis, dry mouth

**Contraindicated:** In patients with cardiovascular disease, in those receiving Guanethidine and MAO inhibitors

Treatment of toxic symptoms: Acidification of the urine by ammonium chloride, Chlorpromazine at CNS symptoms

**Preparations**

**Amphetamine sulphate** 5 and 10 mg tablets

**Dextroamphetamine sulphate** (Dexedrine) 5 and 10 mg tablets, anorexants

METHAMPHETAMINE is related chemically to both Amphetamine and Ephedrine. It is a mixed acting agonist.

**CNS stimulating effect:** Amphetamine = Methamphetamine

**Pressor effect:** Methamphetamine > Ephedrine

**Therapeutic use:** narcolepsy

**Methamphetamine hydrochloride** (Desoxyn) 5-15 mg tablets

**Hydroxyamphetamine** - mixed acting agonist, it lacks CNS effect

**Therapeutic use:** as mydriatic, decongestant, pressor agent

**Mephentermine** sulfate (Wyamine) - mixed acting agonist, it lacks CNS effects

**Therapeutic use:** in hypotensive states, 15 and 30 mg/ml injection

**Metaraminol** bitartarate (Aramine) is a mixed acting sympathomimetics. It has little effect on the CNS. **Therapeutic use:** in hypotensive states, 10 mg/ml injection

**Phenmetrazine** hydrochloride (Preludin) anorexant, 75 mg tablets

**Phentermine** hydrochloride (Fastin) anorexant, 8-37.5 mg tablets

**Fenfluramine** hydrochloride (Pondimin) anorexant, 20 mg tablets

**MAZINDOL** (Sanorex, Mazanor) anorexant, 1 and 2 mg tablets
C: RECEPTOR SELECTIVE SYMPATHOMIMETIC DRUGS

1. α2 receptor selective drugs: CLONIDINE, GUANFACINE, GUANABENZ
   They are potent centrally acting antihypertensive drugs

2. β receptor selective drugs (separation of β1 and β2 effects)
   (1) β1 receptor selective drugs: DOBUTAMINE, PRENARTEROL
      They increase CO without changes in HR. Tolerance can develop.
      Use: Congestive heart failure
   (2) β2 receptor selective drugs: in asthma therapy and uterus relaxants
      a.) β2 receptor stimulating bronchodilators → bronchial smooth muscle
         relaxation with slight effect on cardiac β1 receptors
         Therapeutic uses: Bronchial asthma, bronchospasm
         Caution in patients with cardiovascular disease, hyperthyroidism
         Preparations: Metaproterenol sulfate (Alupent, Metaprel), solution, tablets
         Terbutaline sulfate (Brethine), aerosol, injection, tablets
         Albuterol (Proventil, Ventolin), aerosol, tablets
         Bitolterol mesylate (Tornalate), aerosol
      b.) β2 receptor stimulating uterus relaxants → to avoid premature labour
         Preparations: Ritodrine hydrochloride (Yutopar) 10 mg tablets
         Adverse effects: tachycardia, tremor
         Contraindications: eclampsia, cardiovascular disease, hyperthyroidism

CLINICAL PHARMACOLOGY OF SYMPATHOMIMETIC DRUGS

1. Cardiovascular applications
   a.) HYPOTENSION (volume contraction, cardiac arrhythmias, adverse reactions
       after antihypertensive therapy, infection). Sympathomimetics may be used in
       hypotensive emergency to preserve cerebral and coronary blood flow
       DRUGS: Direct acting α agonists: NE, Phenylephrine, Methoxamine
   b.) SHOCK - critical reduction in perfusion of vital organs, hypotension, oliguria,
       metabolic acidosis, altered mental state. Progress to death.
       THERAPY: volume replacement and treatment of underlying disease
           (vasoconstrictor or vasodilator therapy)
   c.) CARDIOGENIC SHOCK - usually due to massive myocardial infarction
       THERAPY: fluid replacement, optimize tissue blood flow rather than blood
       pressure. Dopamine, Dobutamine in intravenous infusion.
   d.) PAROXYSMAL TACHYCARDIA - Phenylephrine, Methoxamine
   e.) HEART BLOCK - Isoproterenol, Epinephrine (in cardiac arrest),
   f.) CONGESTIVE HEART FAILURE - Dobutamine, Dopexamine, Prenarterol

2. Conditions in which blood flow is to be reduced
   α receptor stimulation is desired:
   In surgery for achieving haemostasis Epinephrine, Cocaine
   Reducing diffusion of LAs Epinephrine
   Reducing mucous membrane congestion Phenylephrine, Oxymetazoline,
   (e.g. hay fever, common cold) Xylometazoline
3. Respiratory applications
Bronchial asthma - selective β2 agonists

4. Anaphylaxis - anaphylactic shock and related hypersensitivity reactions affect both respiratory and cardiovascular systems.
SYMPTOMS: bronchospasm, mucous membrane congestion, angioedema, collapse
THERAPY: Rapid subcutaneous injection of Epinephrine, Glucocorticoids, Antihistamines

5. Ophthalmic applications
Phenylephrine - mydriatic, decongestant
Epinephrine - glaucoma (intraocular pressure and humour formation ↓, humour outflow ↑)

6. Genitourinary applications - β2 selective agonists relax pregnant uterus
DRUGS: Ritodrine, Terbutaline

7. CNS applications - Amphetamine-like drugs → euphoric effect
USE: narcolepsy, hyperkinetic syndrome in children

Biosynthesis of catecholamines

TYROSINE

DOPA

DOPAMINE

TYRAMINE

DOPAMINE

OCTOPAMINE

EPIPHINE

NOREPINEPHRINE

EPINEPHRINE

TYROSINE → tyrosine hydroxylase → DOPA

DOPA → decarboxylase → DOPAMINE

DOPAMINE → D β H hydroxylase → epinephrine

DOPAMINE → D β H hydroxylase → tyramine

DOPAMINE → D β H hydroxylase → octopamine

TYROSINE → L-amino-acid decarboxylase → DOPA

DOPAMINE → N-methyl transferase → EPIPHINE

DOPAMINE → N-methyl transferase → NOREPINEPHRINE

DOPAMINE → N-methyl transferase → EPINEPHRINE

TYROSINE → tyrosine hydroxylase → DOPA

DOPA → decarboxylase → DOPAMINE

DOPAMINE → D β H hydroxylase → epinephrine

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DOPAMINE → N-methyl transferase → EPINEPHRINE
Metabolism of catecholamines

EPINEPHRINE → NOREPINEPHRINE → DOPAMINE

DIOXYMANDELIC ACID

DIHYDROPHENYLACETIC ACID

3-METHOXYTYRAMINE

HOMOVALLINIC ACID

3-METHOXY-4 HYDROXYPHENYLGLYCOL (MHPG)

3-METHOXY-4-HYDROXYMANDELIC ACID (VMA)

NORADRENALINE

DOBUTAMINE

ISOPROTERENOL

CLONIDINE

FORSKOLIN

Gd

β

Gα

Gβ

Gγ

ATP

TEOPHYLLINE

AMRINONE

PDE

5’AMP

cAMP

PROTEIN KINASE A

Ca++

PROTEIN KINASE C

DG

IP3

IP2

IP

PIP

PI

PLC

Ca++

SER

cellular response

G = guanine nucleotide protein
C = adenylyl cyclase
PIP2 = phosphatidyl-inositol bisphosphate
IP3 = inositol triphosphate
IP2 = inositol phosphate
IP = phosphatidyl inositol
PLC = phospholipase C