REGULATION OF BLOOD PRESSURE

• The sympathetic adrenergic nervous system plays a major role in the regulation of arterial pressure. Activation of these nerves to the heart increases the heart rate (positive chronotropy), contractility (positive inotropy) and velocity of electrical impulse conduction (positive dromotropy).

• Minute-to-minute control of arterial blood pressure is achieved when small pressure changes are linked to reflex alterations in autonomic nerve activity.

• Sensory nerve endings embedded in the wall of the carotid sinus and aortic arch (BARORECEPTORS) are activated by wall stretch when arterial pressure increases.

• This leads within a few seconds to an increase in vagal activity and a reduction in sympathetic activity.
Sympatholytic drugs can block the sympathetic adrenergic system at three different levels.

1. **Peripheral sympatholytic drugs** such as alpha-adrenoceptor and beta-adrenoceptor antagonists block the influence of NA at the effector organ (heart or blood vessel).

2. **Ganglionic blockers** block impulse transmission at the sympathetic ganglia.

3. Drugs that block sympathetic activity within the brain are called **centrally acting sympatholytic drugs**.
NORADRENALINE and ADRENERGIC RECEPTORS

PERIPHERAL AND CENTRAL EFFECTS

\( \alpha_1 \)

- Smooth muscle contraction, mydriasis, vasoconstriction in the skin, mucosa and abdominal viscera & sphincter contraction of the GI tract and urinary bladder
- Favors wakefulness (locus coeruleus)

\( \alpha_2 \)

- Smooth muscle mixed effects, noradrenaline inhibition, platelet activation; pancreatic insulin release inhibition;
- Blood pressure control (baroceptors/NTS);
- Increases sleepfulness (locus coeruleus);
- Stimulates hunger;

\( \beta_1 \)

- Positive chronotropic, dromotropic and inotropic effect; activates the RAAS on iuxta-glomerular cells

\( \beta_2, 3 \)

- Smooth muscle relaxation in the GI tract; promotes relaxation of detrusor muscle in the bladder;
- Enhances lipolysis in the liver
- takes part to mood control
- Favors satiety
THE NORADRENERGIC SYNAPSE
CENTRAL SYMPATHOLYTICS

Centrally acting sympatholytics block sympathetic activity by binding to and **activating alpha\(_2\) (\(\alpha_2\))-adrenoceptors**. This reduces sympathetic outflow to the heart thereby decreasing cardiac output by decreasing heart rate and contractility. Reduced sympathetic output to the vasculature **decreases sympathetic vascular tone** (which causes vasodilation) and **reduced systemic vascular resistance** (which decreases arterial pressure).

- Clonidine
- Guanabenz
- Guanfacine
- \(\alpha\)-Methyldopa
- Moxonidine
- Rilmenidine
CENTRAL ALPHA-2 AGONISTS

CLONIDINE (Catapresan®)
Selective agonist for α2 adrenergic receptors

PHARMACOKINETICS
Administration: Oral, transdermal
Urgency/emergency fl. 0,15 mg IM or IV (diluted in 10 ml NaCl 0,9% and injected in 10 min.)

Absorbance: oral bioavailability > 90%
Distribution: peak effect < 3 h; half-time 6-12 h
Metabolism: Liver 30-50%
Excretion: Kidney

- The antihypertensive effect is reached at plasma concentrations between about 0.2 to 2.0 ng/mL in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.
- **Following oral administration**, about 40 to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Neither food nor the race of the patient influences the pharmacokinetics of Clonidine.
- **Following intravenous administration**, Clonidine displays biphasic disposition with a distribution half-life of about 20 minutes and an elimination half-life ranging from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function.
- Clonidine crosses the placental barrier.
CENTRAL ALPHA-2 AGONISTS

CLONIDINE  (Catapresan®)
Selectiv agonist for $\alpha_2$ adrenergic receptors

MEDICAL USE:

• As **antihypertensive** drug, to treat hypertension
• As **mild sedative**, used as premedication before surgery or procedures
• It may be used to **ease withdrawal symptoms** associated with the long-term use of narcotics, alcohol, benzodiazepine and nicotine (smoking). It can alleviate opioid withdrawal symptoms by reducing the sympathetic nervous system response such as tachycardia and hypertension, as well as reducing sweating, hot and cold flashes, and general restlessness.
• Clonidine can also be used for **migraine headaches and hot flashes** associated with menopause.
• In the US, clonidine has been approved in 2010 for the treatment of **attention deficit hyperactivity disorder (ADHD)**, alone or with stimulants, for pediatric patients aged 6–17 years.
• **Brimonidine**, a less lipophylic derivate, is used for lowering eye pressure in patients with open-angle glaucoma or increased pressure in the eye (**ocular hypertension**).
CENTRAL ALPHA-2 AGONISTS

CLONIDINE (Catapresan®)

ADVERSE REACTIONS:
Most adverse effects are mild, appear to be dose-related, and tend to diminish with continued therapy. The most frequent are

- dry mouth, drowsiness, dizziness, constipation and sedation.

Less frequent adverse experiences include:

- **Body As A Whole**: Fatigue, fever, headache, pallor, weakness and withdrawal syndrome.
- **Cardiovascular**: Bradycardia, congestive heart failure, electrocardiographic abnormalities, orthostatic symptoms, palpitations, Raynaud’s phenomenon, syncope, and tachycardia.
- **Central Nervous System**: Agitation, anxiety, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.
- **Dermatological**: Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.
- **Gastrointestinal**: Abdominal pain, anorexia, constipation, hepatitis, nausea and vomiting.
- **Genitourinary**: Decreased sexual activity, erectile dysfunction, loss of libido, urinary retention.
- **Hematologic**: Thrombocytopenia
- **Metabolic**: Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, weight gain.
- **Musculoskeletal**: Leg cramps and muscle or joint pain.
- **Oro-otolaryngeal**: Dryness of the nasal mucosa.
- **Ophthalmological**: Accommodation disorder, blurred vision, decreased lacrimation, and dryness of eyes.
CLONIDINE (Catapresan®)

WARNINGS:

Withdrawal:
Sudden cessation of Clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma (Hypertension rebound effect).

The likelihood of such reactions appears to be greater after administration of higher doses

When discontinuing therapy with Clonidine, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

Intravenous administration:
Clonidine must be infused slowly to avoid peripheral effects (stimulation of vascular post-synaptic α2-receptors) which may transiently increase blood pressure levels.
α-METHYL-DOPA

It is a prodrug. In contrast to clonidine, α-methylldopa does not directly reduce BP but first requires conversion to α-methylnorepinephrine in the central nervous system, which, in turn, leads to activation of central α2-ARs and inhibition of sympathetic outflow. Although once a mainstay of antihypertensive therapy, α-methyl-dopa is currently used mainly in pregnant women with hypertension because of lack of teratogenicity or fetal side effects.

RESERPINE

Natural alcaloid (*Rauwolfia serpentina*). Unlike sympatholytic drugs, reserpine reduces BP by depleting NA stores in the peripheral postganglionic sympathetic nerve terminals without reducing central sympathetic discharge. This progressive depletion of NA availability explains its long-lasting effects despite its short half-life. At higher doses it has been associated with significant side effects, including nasal stuffiness, peptic ulcer disease, and depression.

METYROSINE

Metyrosine blocks the activity of tyrosine hydroxylase, the enzyme converting tyrosine to DOPA. Therefore is a whole catecholamine synthesis inhibitor. It may be used either as a pretreatment before surgery or for the long-term treatment of symptoms associated with pheochromocytoma.
GANGLIONIC BLOCKERS

They inhibit transmission between preganglionic and postganglionic neurons in the autonomic nervous system, by acting as a **nicotinic receptor antagonists**. Because they block both the parasympathetic and sympathetic nervous system, their effect depends upon the dominant tone in the organ system. Ganglionic blockers are still used in some emergency situations, such as aortic dissection or autonomic dysreflexia.

**TRIMETAPHAN** can be administered by intravenous infusion and has a very sort half-life

### ALPHA-ADRENERGIC RECEPTOR BLOCKERS

- **NON SELECTIVE**
  - **PHENOXYBENZAMINE**  
    (irreversible, slower onset and a longer-lasting effect)
  - **PHENTOLAMINE**  
    (reversible, rapid and transient effect)
  - **TOLAZOLINE**  
    (mostly used in veterinary)

Their primary application is for the control of hypertensive emergencies, most notably due to pheochromocytoma

- **SELECTIVE α1-ANTAGONISTS**
  - **ALFUZOSIN, DOXAZOSIN, PRAZOSIN , TAMSULOSIN, TERAZOSIN, SILODOSIN**
SELECTIVE $\alpha_1$-ANTAGONISTS

They bind selectively to alpha-1 receptors, and therefore interfere with the ability of cathecolamines to provoke alpha-mediated response (in the vasculature, in the eye, in the nose, at bladder level).

PHARMACOKINETICS

**PRAZOSIN**: short half-life (2-3 hours); liver metabolism; kidney excretion
**TERAZOSIN**: 12 hours half-life; duration 18 hours; liver metabolism; kidney excretion
**DOXAZOSIN**: 20 hours half-life; duration 36 hours; liver metabolism; kidney excretion

THERAPEUTIC USE

- **Hypertension** (in association with diuretics and beta-blockers)
- **Benign prostatic hyperplasia** (**TAMSULOSIN** in association with FINASTERIDE - 5$\alpha$-reductase inhibitor, to reduce prostatic volume)
- **Vasospasm** in pz with Raynaud’s disease
- $\alpha$-blockers can also be used to treat **anxiety and panic disorders**, such as generalized anxiety disorder, panic disorder, or posttraumatic stress disorder (PTSD).

SIDE EFFECTS
Orthostatic hypotension, baroreceptor-mediated reflex, tachycardia, impotence, stuffed nose, miosis.
BETA BLOCKERS

“The greatest breakthrough when it comes to pharmaceuticals against heart illness since the discovery of digitalis 200 years ago”

The Nobel Committee, in recognition of the work of Sir James Black (1988)

These drugs have high affinity for β-adrenergic receptors.
They may bind to all β-adrenergic receptors or bind selectively to β1 receptors.
They may act as competitive antagonists or partial receptor agonists.
β-ADRENERGIC RECEPTOR LOCALIZATION AND RELATIVE PHYSIOLOGICAL FUNCTION

- Uterus relaxation
- Arterial vasodilation
- Airways relaxation
- Renin release
- Lipolysis
- Insulin secretion
- Glycogenolysis
- Gluconeogenesis and glycogenolysis
- Increase automatism, heart rate, contraction

Catecholamines

- β₁
- β₂
- β₂
- β₂
- β₂
- β₁
- β₁
- β₂
- β₂
- β₂
- β₂
- β₁
- β₁
- β₃
- β₁
- β₃

Human organ images with receptor localization:
- Uterus
- Arterial vasodilation
- Airways relaxation
- Renin release
- Aqueous humor secretion
- Lipolysis
- Insulin secretion
- Glycogenolysis
- Gluconeogenesis and glycogenolysis
BETA BLOCKERS

Beta-adrenoceptor blocking drugs

Non-selective

- β₁ β₂

Nadolol
Propranolol
Timolol
Sotalol
Tertalolol

Selective

- β₁

Atenolol
Esmolol
Metoprolol
Bisoprolol
Betaxolol
Bevantolol

Acebutolol (Practolol)
Celiprolol

With α-blocking activity

Labetalol
Bucindolol
Carvedilol

With vasodilatant properties

Nebivolol
BETA BLOCKERS with I.S.A.

Beta blockers with intrinsic sympathomimetic activity (ISA) can exert a low level agonistic activity, in any case much lower than that exerted by endogenous cathecolamines (partial agonists). Thus, even if they are able to reduce heart rate under effort, the resting heart rate is not affected.

Heart rate
Percent change

\[ \beta_{1/2} \] Pindolol (+ISA)
\[ \beta_1 \] Practolol (+ISA)
\[ \beta_1 \] Acebutolol (+ISA)
\[ \beta_{1/2} \] Propranolol (-ISA)
\[ \beta_1 \] Atenolol (-ISA)
NON SELECTIVE BETA-BLOCKERS

Propranolol
Nadolol
Timolol

Proteina G Adenilato-ciclasi
ATP AMPc

β1

β2

Vascular smooth muscle cells contraction
peripheral resistence

Airway resistance

Inhibition glicogenolisis
Reduced hypoglicemic response

Heart rate
Contractility
A-V conductance
renin release
aqueous humor secretion

Bisoprolol

Atenolol
Metoprolol

β1 BLOCKERS
PHARMACOKINETICS

- **Propranolol**
  - min
  - hepatic metabolism (~100%)
  - high first passage effect
  - high interindividual variability
  - short half-life
  - low bioavailability (10-50%)
  - high plasma protein drug binding
  - cross BBB

- **Alprenolol**
  - lipophylic

- **Oxprenolol**
  - max

- **Metoprolol**
  - min
  - prevalent kidney excretion (60-100%)
  - low gastro-intestinal absorption
  - longer half-life
  - reduced interindividual variability
  - low plasma protein drug binding

**Other beta-blockers**
- Nadolol
- Celiprolol
- Sotalol
- Atenolol
THERAPEUTIC USES

Cardiovascular uses

- Hypertension
- Congestive Heart Failure
- Angina pectoris
- AMI secondary prevention
- Cardiac arrhythmias
- Cardiac hypertrophy

Non-cardiovascular uses

- Hypertroidism
- Anxiety
- Glaucoma
- Migraine

ß-BLOCKING EFFECTS

1. Negative chronotropic
2. Negative dromotropic
3. Anti-arrhythmic
4. Negative inotropic
5. Anti-ischemic

Interacting drugs

- Nodal depression by
  - Verapamil
  - Diltiazem
  - Digoxin
  - Amiodarone

- Other negative inotropes
  - CCBs
  - Anti-arrhythmics
  - Anesthetics

Opie 2012
Beta-blockers lower systemic blood pressure mainly by reducing cardiac output. At the beginning of treatment, blockade of beta-receptors in the vessels may slightly increase peripheral resistance and mask systemic effects. Overtime, the heart effect prevails.

These drugs have been past-recommended as first-line therapy for hypertension (HTN). At present, benefits have been overshadowed by their side-effect profile (sexual dysfunction, fatigue, depression, metabolic abnormalities). For hypertension treatment, beta-blockers are indicated if:

- **intolerance or contraindication to ACE-I/ARBs**
- **increased sympathetic drive-HTN with tachycardia**
- **tense young patients**
- **post AMI**
HYPERTENSION

- Atenolol
  - Most commonly used
  - Selective β-1 blocker
  - Low lipid solubility.
  - Does not cross BBB- CNS ADR are less
  - Longer duration of action, OD dosing

- Metoprolol
  - Cardioselective Beta 1 blocker
  - Can be used in Diabetics with HTN, CHF

- Nebivolol
  - Highly selective β1 blocker
  - Nitric oxide release, vasodilatation
  - Use: Hypertension
  - Dose - 2.5 mg OD

- Labetolol
  - 3rd generation
  - Alpha -1 blocker
  - β -1 blocker
  - Partial agonist β -2 (Vasodilation, Bronchodilation)

Uses:
- Hypertensive emergencies
- Pheochromocytoma
- Pregnancy induced hypertension
Beta-blockers induce bradycardia, thus increasing coronary blood flow and decreasing myocardial oxygen demand. Protect from cathecolamine myocyte toxicity. Suppress ventricular arrhythmias. Help suppressing RAAS activity.

In addition, beta-blocker administration seem to induce upregulation of β receptors and improve β₂-antiapoptotic signaling, reduce the hyperphosphorylation of Ca²⁺-release channels from sarcoplasmic reticulum and thereby normalize their function.
CONGESTIVE HEART FAILURE

β blocker in CHF - proper patient selection:

- mild to moderate (NYHA class II, III) cases of dilated cardiomyopathy with systolic dysfunction
- No place in decompensated patients.
- Stopped during an episode of acute heart failure
- Starting dose - very low - then titrated upward

Carvedilol

- Alpha 1, β1, β2 blocker
- Anti oxidant property
- Inhibits free radical induced lipid peroxidation, vascular smooth muscle mitogenesis
- Use: cardioprotective in CHF Hypertension
Anti-anginal drugs prevent attacks of angina by **decreasing myocardial oxygen consumption** (by lowering heart rate, blood pressure, myocardial loading, or myocardial contractility) and/or by **increasing myocardial oxygen supply** (by increasing coronary blood flow).

Beta blockers reduce myocardial oxygen consumption by competitive inhibition of beta-adrenoceptors, which lowers heart rate, blood pressure, and myocardial contractility. The bradycardia prolongs diastole, thereby increasing the period of maximal coronary blood flow.
ANGINA PECTORIS

- Combined with nitrates for chronic prophylaxis

- Cardioselective-
  - Metoprolol 25-100 mg
  - Atenolol 25-100 mg

- Abrupt withdrawal - precipitate Angina / MI - up regulation of beta receptors

- Contraindicated in Prinzmetal's angina

Celiprolol
- Selective β1 blocker
- Weak β2 agonistic activity
- Nitric oxide release, vasodilatation
- No deleterious effects on lipid profile
- Safe in asthmatics
- Hypertension, Angina
- Dose: 200mg OD - 400mg OD
MYOCARDIAL INFARCTION

- Myocardial infarction occurs when myocardial ischemia, a diminished blood supply to the heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death.

a. Myocardial salvage during evolution of MI

- **β** blockers-
  1. limit infarct size by reducing oxygen consumption, prevents re-infarction
  2. prevent arrhythmias including ventricular fibrillation

- **Not given if**-
  - Heart rate < 60/min
  - Systolic BP < 90 mm Hg
  - PR interval > 0.24 sec
  - LVF

- Within 4-6 hrs Metoprolol- 5 mg i.v every 5 mins – 3 doses
- Metoprolol 25–50 mg orally every 6 h

b. Secondary prophylaxis of MI:

- Decrease subsequent mortality by 20%.
  1. By preventing re-infarction
  2. By preventing sudden ventricular fibrillation at the second attack of MI

- **β**- 1 selective antagonist – Atenolol, Carvedilol
Beta-blockers are classified as Class II anti-arrhythmics. They act by blocking the effects of catecholamines at the $\beta_1$-adrenergic receptors, thereby decreasing sympathetic activity on the heart. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node. Class II agents include atenolol, esmolol, propranolol, and metoprolol.
ARRHYTHMIAS

Esmolol

- Intravenous
- It has been used to terminate:
  - Paroxysmal supraventricular tachycardia
  - Episodic atrial fibrillation or flutter
  - Adrenergically mediated arrhythmia
  - Pheochromocytoma
  - Arrhythmia during anaesthesia
  - Intra-operative, post-operative hypertension
  - In early treatment of myocardial infarction

- Acebutolol - 20–40 mg
- Propranolol - 40–80 mg

- Sotalol
  - Additional K channel blocking
  - Class III anti-arrhythmic
OTHER CARDIOVASCULAR USES OF BETA-BLOCKERS

DISSECTING AORTIC ANEURYSM

- Intravenous Propranolol, Metoprolol-maintain heart rate of approximately 60 beats/min

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

- Subaortic region is hypertrophic
- Forceful contraction of this region under sympathetic stimulation (exercise, emotion) increases outflow resistance

MITRAL VALVE PROLAPSE
NON CARDIOVASCULAR USES OF BETA-BLOCKERS

HYPERTHYROIDISM

- Thyroxine

Up regulation of β-1 receptors in myocardium

Tachycardia, palpitations

- T 4 → T 3

Beta-blockers can be used:

(i) with carbimazole or radiiodine
(ii) with iodide preoperatively
(iii) Thyroid storm (thyrotoxic crisis): emergency

Propranolol- 1-2 mg slow i.v. → 40-80 mg orally
NON CARDIOVASCULAR USES OF BETA-BLOCKERS

GLAUCOMA

- Decrease aqueous secretion
- chronic simple (wide angle) glaucoma

Timolol

- Non-selective
- Action is smooth, well sustained
- Effect on i.o.t. persists for 2-3 weeks following discontinuation

- Dose – 0.25% drops BD

Levobunolol- Long duration, OD
Non cardioselective beta blockers, such as propranolol or nadolol are the usual choice; however, cardioselective agents, such as atenolol and metoprolol also may be used. **Labetalol** is a non cardioselective beta-adrenergic blocker and selective alpha-adrenergic blocker that has been shown to be effective in controlling hypertension associated with pheochromocytoma. However, it has also been associated with paradoxic episodes of hypertension thought to be secondary to incomplete alpha blockade. Thus, its use in the preoperative treatment of patients with pheochromocytoma is controversial.
NON CARDIOVASCULAR USES OF BETA-BLOCKERS

MIGRAINE

• Prophylaxis
• severe migraine
• Propranolol
  - most effective drug
  - reduces frequency, severity of attacks- in 70% patients
    - Effect seen in 4 weeks
  -Dose- 40 mg BD to 160 mg BD
• Others- timolol, metoprolol, atenolol

Headaches

| Sinus: pain is behind browbone and/or cheekbones | Cluster: pain is in and around one eye | Tension: pain is like a band squeezing the head | Migraine: pain, nausea and visual changes are typical of classic form |
ANXIETY

- Stage fright, Nervousness, panic
- Propranolol- 10-20 mg BD
ALCOHOL WITHDRAWAL

Non-cardiovascular uses of beta-blockers

- Oesophageal variceal bleeding and portal hypertension

-Nadolol + isosorbide mononitrate
1. Asthma, COPD
2. Prinzmetal's angina
3. Bradycardia
   Heart Block
   Acute decompensated heart failure
4. Peripheral Vascular disease
ADVERSE EFFECTS OF BETA-BLOCKERS

1. Adverse Lipid profile-
   - total TG and LDL-cholesterol increase
   - HDL-cholesterol falls.
   - Cardioselective β blockers - little/no deleterious effect on blood lipids

2. Fatigue and reduced exercise capacity

3. CNS side effects
   - sleep disturbance, bad dreams, sexual dysfunction

4. Hypoglycemia
   - Masks sympathetic symptoms of hypoglycemia

5. Rebound Hypertension
   - Chronic therapy → up regulation of Beta receptors
   - sudden withdrawal → rebound hypertension
   - Gradually tapered and Withdrawn