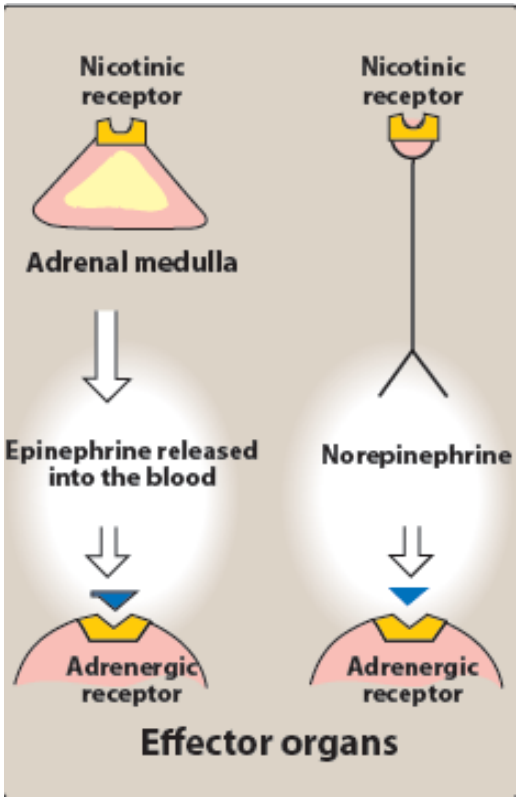
Adrenergic Drugs

Adrenergic agonists

- Adrenrgic agonists; sympathomimetics: drugs that activate adrenoceptors
  (Receptors stimulated by norepinephrine or epinephrine)

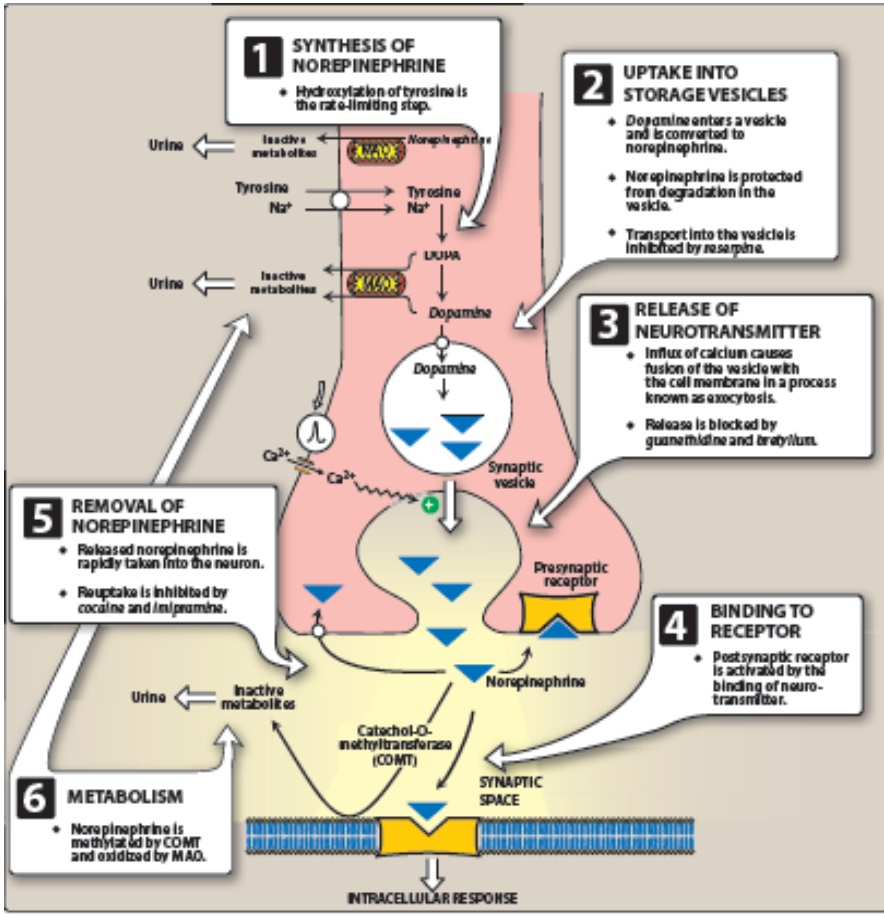


Adrenergic neurons

- Adrenergic neurons release NE as the primary neurotransmitter
- Adrenal medulla NE is converted to epinephrine, they are both stored and released upon stimulation in the ratio of 80% epinephrine and 20% NE
- Found in the CNS and sympathetic nervous system
- Adrenergic receptors located presynaptically on the neuron or postsynaptically on the effector organ are the sites of action of adrenergic drugs

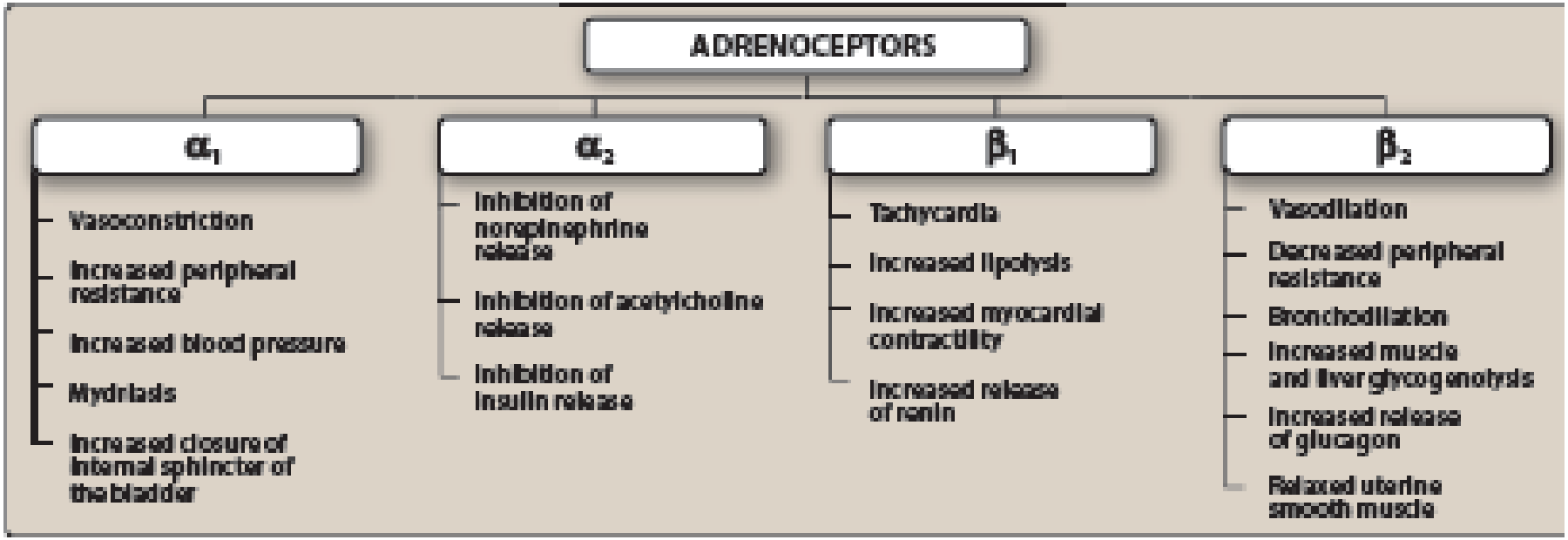
Neurotransmission at adrenergic neurons

1. Synthesis of norepinephrine
2. Storage of NE in vesicles
3. Release of NE
4. Binding to receptors
5. Removal of NE
6. Metabolism by the enzymes Catechol O-methyltransferase (COMT) and monoamine oxidase (MAO)



Adrenergic receptors (Adrenoceptors)

- α_1
  - Present on postsynaptic membranes of effector organs
  - Constriction of smooth muscle, vasoconstriction, increased blood pressure, total peripheral resistance
  - Subdivided to α_{1A}, α_{1B}, α_{1C}, and α_{1D}
- α_2
  - Located on presynaptic nerve endings
  - Stimulated α_2 cause feedback inhibition of NE release
  - Subdivided to α_{2A}, α_{2B} and α_{2C}
- β_1 (Heart, Kidney)
  - Tachycardia, Increased myocardial contractility, Renin release
- β_2 (Bronchi, blood vessels, uterus)
  - Vasodilation, Bronchodilation, Relax uterine smooth muscles
- β_3


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
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

- Desensetization of adrenoceptors: Reduction in the responsiveness of these receptors due to prolonged exposure to catecholamines (NE and epinephrine)
- Mechanisms for desentization
  - Sequestration of the reseptors, so they are not available for binding
  - Downregulation of receptors by destruction or decreased synthesis
  - Inability to couple to G protein

Sympathomimetic Agents

- These drugs exert their effects via direct stimulation of the adrenergic receptors (α_1, α_2, β_1, β_2) leading to a wide-range of pharmacological effects.

- Endogenous sympathomimetic drugs include:

Epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine.

- Catecholamines: Sympathomimetic amines

(NE, epinephrine, dopamine and isoprotrenol)

Highly potent in stimulating adrenergic receptors

Rapidly inactivated by COMT and MAO

Poor CNS penetration

- Non catecholamine adrenergic agonists have longer duration of action

Direct acting adrenergic agonists

- Epinephrine
- Norepinephrine
- Isoprotrenol
- Dopamine
- Dobutamine
- Oxymetazoline
- Phenylphrine
- Clonidine
- Metaprotrenol
- Albuterol and terbutaline
- Saleterol and formoterol

Direct acting adrenergic agonists

- Epinephrine
  - Commonly used in therapy
  - Strengthens the contractility of myocardium (β1) (positive inotrpic effect)
  - Increases the rate of contraction (β1) (positive chronotropic effect)
  - Increase cardiac output (β1)
  - Promotes renin release, increase blood pressure (β1 on kidney)
  - Constriction of arterioles (α_1)
  - Dilation of vessels going to liver and skeletal muscles (β2)
  - Bronchodilation (β2)
  - Hyperglycemia (β2 in liver)

Epinephrine

- Therapeutic uses
  - Bronchospasm, emergency for acute asthma
  - Anaphylactic shock
  - Cardiac arrest
  - Anesthetics, to increase the duration of local anesthesia (vasoconstriction)
- Pharmacokinetics
  - Rapidly metabolized by COMT and MAO
  - Administered IV for emergencies
  - Can be administered IM or SC but not oral
- Adverse effects:
  - cardiac arrhythmia
  - CNS effects: anxiety, tremor.

Norepinephrine

- Acts mostly on α receptors
- Effects
  - Vasoconstriction (α1 effect)
  - Increase total peripheral resistance
  - Increase blood pressure
  - Reflex bradycardia due to stimulation of baroreceptor
- Therapeutic uses
  - Shock, NE increases peripheral resistance and blood pressure
- Administered IV
- Adverse effects: similar to epinephrine

Isoprotrenol

- β1 and β2 agonist, nonselective, rarely used
- Increase heart rate and force of contraction, increasing cardiac output
- Used to stimulate the heart in emergencies (atrioventricular (AV) block or cardiac arrest)
- Adverse effects: similar to epinephrine

Dopamine

- Activates α and β receptors
- A neurotransmitter that occurs naturally in the CNS and adrenal medulla
- Increases heart rate and force of contraction

(positive chronotropic and inotropic effects)

- Rapidly metabolized by MAO and COMT
- Used for
  - Shock treatment
  - Hypotension
  - Severe congestive heart failure
- Adverse effects
  - Hypertension
  - Arrhythmia

Direct acting adrenergic agonists

- Dobutamine
  - β1 agonist
  - Increases cardiac rate and output
  - Uses:
    - Increase cardiac output in acut congestive hear failuer
    - For inotropic support after cardiac surgery
  - Adverse effects:
    - Similar to epinephrine

Direct acting adrenergic agonists

- Oxymetazoline
  - Stimulates α_1 and α_2 receptors
  - Used locally in the eye or nose as a vasoconstrictor
  - Mechanism: Directly stimulates α receptors on blood vessels in nasal mucosa and conjunctiva to reduce blood flow and decrease congestion
  - Found in many over the counter short-term nasal spray decongestants
  - Found in opthalmic solution for relief of redness of the eye
  - Rebound congestion and tolerance can occur with long term use

Direct acting adrenergic agonists

- Phenylphrine
  - Stimulates α_1 receptors
  - Vasoconstrictor
  - Used in opthalmic solutions for mydriasis
  - Used as nasal decongestant
  - Can be used to raise blood pressure and to terminate episodes of supraventricular tachycardia

Direct acting adrenergic agonists

- Clonidine
  - α_2 agonist
  - Used in essential hypertension to lower blood pressure because of its action in the CNS
  - Acts centrally to inhibit sympathetic activity and outflow to periphery
  - Side effects
    - Lethargy
    - Sedation
  - Abrupt discontinuation leads to rebound hypertension

Direct acting adrenergic agonists

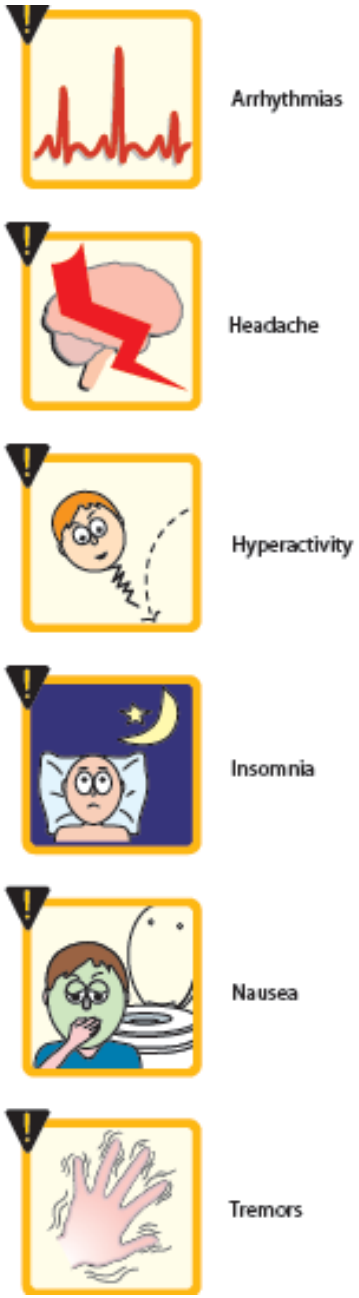
- Albuterol and terbutaline
  - β2 agonists
  - Used as bronchodilators, administered by a metered dose inhaler
  - Terbutaline is used as uterine relaxant to suppress premature labor (off label use)
  - Side effects:
    - Tremor
    - Restlessness
- Salmeterol and formoterol
  - β2 agonists
  - Long acting bronchodilators, administered by a metered dose inhaler

Indirect acting adrenergic agonists

- Inhibit reuptake of norepinephrine or cause norepinephrine release from presynaptic terminal
- Amphetamine
  - CNS stimulant
  - Can increase blood pressure by stimulation of α_1 and β_1 receptors
  - Used in hyperactivity of children, narcolepsy
- Cocaine:
  - Inhibits reuptake of norepinephrine
  - CNS stimulant

- Cocaine
  - Highly addictive
  - Blocks reuptake of epinephrine, serotonin and dopamine into presynaptic terminals
  - Prolongs the peripheral and central actions of these neurotransmitters
  - Dopaminergic effects in the brain's pleasure system (limbic system) produce the euphoria associated with cocaine

Adverse effects of adrenergic agonists



Mixed action adrenergic agonists

- Induce the release of norepinephrine from presynaptic terminals and activate adrenergic receptors on the postsynaptic membrane
- Ephedrine and pseudoephedrine
  - Release stored NE from nerve endings and directly stimulate α and β receptors
- Pseudoephedrine is used orally to treat nasal and sinus congestion

Adrenergic antagonists, adrenergic blockers, sympatholytics: bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects.

These drugs bind to receptors reversibly or irreversibly and prevent the activation of receptors by epinephrine and norepinephrine.

α-Adrenergic blockers

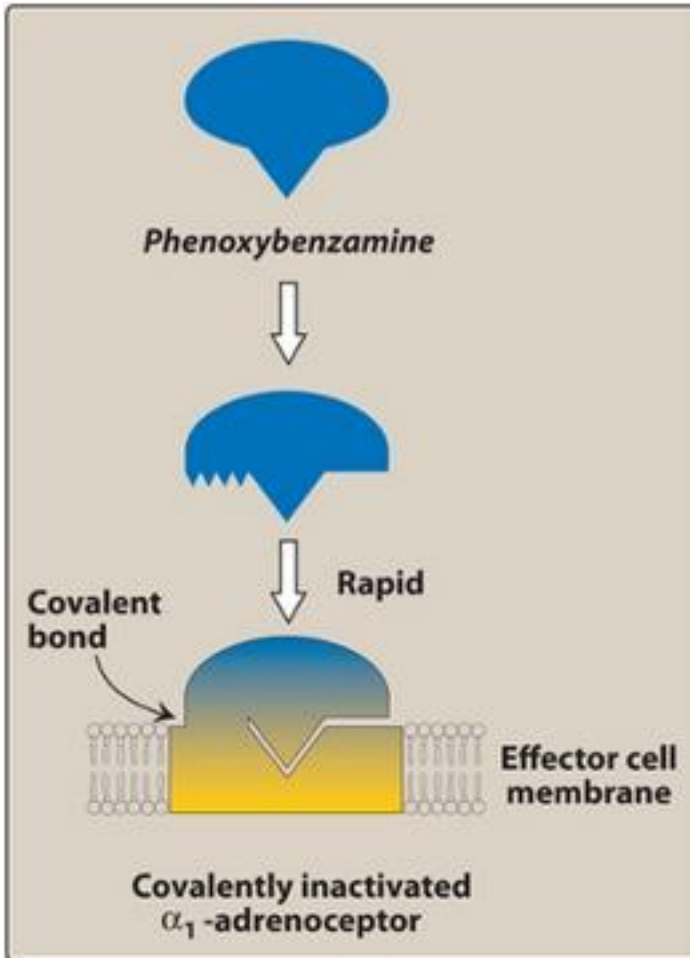
- Affect blood pressure
- Blocking α-receptors reduces the sympathetic tone of the blood vessels decreasing the peripheral vascular resistance
- Lowered blood pressure induces reflex tachycardia

α-Blockers

- Alfuzosin
- Doxazosin
- Phenoxybenzamine
- Phentolamine
- Prazosin
- Tamsulosin
- Terazosin
- Yohimbine

Phenoxybenzamine

- Nonselective, binds to α_1 and α_2
- The block is irreversible and noncompetetive, to overcome the block, the body has to synthesize adrenoceptors (requires a day or longer)



Phenoxybenzamine

- Actions
  - Prevents vasoconstriction of peripheral blood vessels by endogenous cathecholamines
  - Reflex tachycardia occurs
  - α_2 receptors are also blocked causing increased cardiac output
  - Phenoxybenzamine use for hypertension was discontinued because it was unsuccessful in maintaining lower blood pressure due to blockade of α_2 and α_1 receptors

Phenoxybenzamine

- Uses:
  - Treatment of pheochromocytoma (a catecholamine secreting tumor of cells derived from adrenal medulla)
  - Used for Raynaud's disease and frostbite

- Adverse effects
  - Postural hypotension
  - Nasal stuffiness
  - Nausea and vomiting

Phentolamine

- Competitively blocks α_1 and α_2 receptors
- Causes reflex tachycardia
- Used for pheochromocytoma (adrenal medulla tumor)
- Adverse effects
  - Postural hypotension
  - Arrhythmia

Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

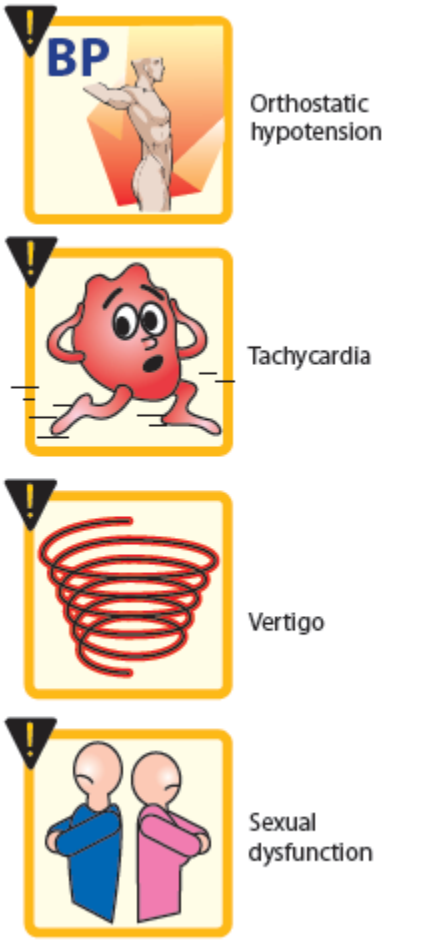
- Selective competitive blockers of α_1 receptors
- Prazosin, terazosin and doxazosin are useful for treating hypertension
- Tamsulosin and alfuzosin are indicated for benign prostatic hypertrophy (BPH)
- Effects
  - Decrease peripheral vascular resistance by causing relaxation of arterial and venous smooth muscle
  - Cause minimal change in cardiac output
  - Can cause first dose syncope (fainting)
    - First dose administered should be adjusted to 1/3 the regular dose, or given at bedtime

Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

- Uses:
  - Congestive heart failure, by dilating the arteries and veins these drugs reduce the preload and the afterload leading to increased cardiac output and reduction of pulmonary congestion
  - Prazosin, terazosin and doxazosin are useful for treating hypertension due to blockade of α_1 receptors
  - Tamsulosin (selectivity for α_1 on prostate) and alfuzosin are indicated for benign prostatic hypertrophy (BPH) because the blockade of α-receptors decreases the smooth muscle tone of the bladder neck and prostate and improves urine flow

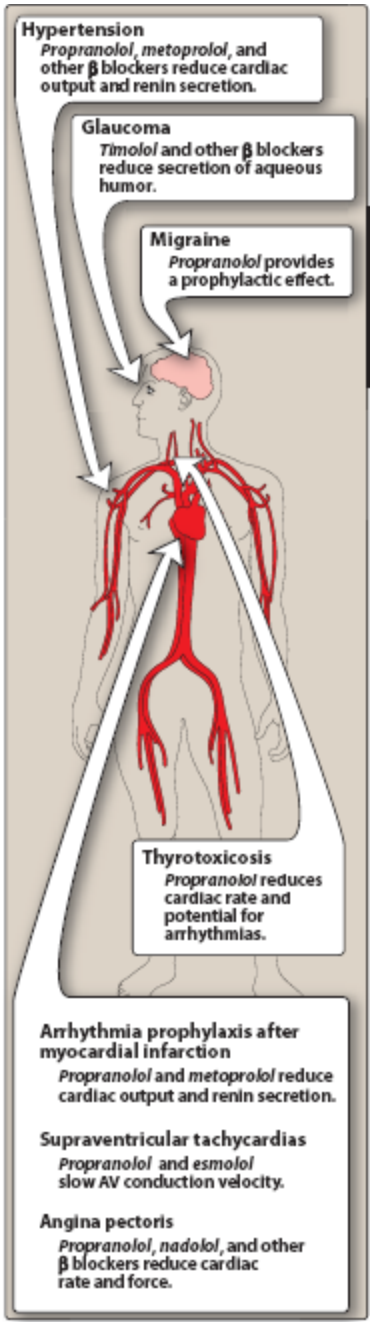
Prazosin, terazosin, doxazosin, tamsulosin and alfuzosin

- Adverse effects
  - Dizziness
  - Lack of energy
  - Orthostatic hypotension
  - Tachycardia
  - Inhibition of ejaculation due to blockade of α-receptors in the ejaculatory ducts



β-Adrenergic blockers

- Uses
  - Hypertension
  - Angina
  - Cardiac arrhythmias
  - Myocardial infarction
  - Congestive heart failure



Propranolol

- Non selective β antagonist (blocks β1 and β2)
- Reduces cardiac output and heart rate
- Reduces blood pressure
- Causes bronchoconstriction (β2)
- Uses
  - Hypertension
  - Hyperthyroidism
  - Migraine
  - Angina
  - Myocardial infarction
- Adverse effects
  - Bronchoconstriction
  - Arrhythmia

Timolol and Nadolol

- Non selective β-antagonists
- More potent than propranolol
- Nadolol has a very long duration of action
- Timolol is used topically for glaucoma
  - Inhibits aqueous humor production

Acebutolol, atenolol, metoprolol, bisoprolol, esmolol

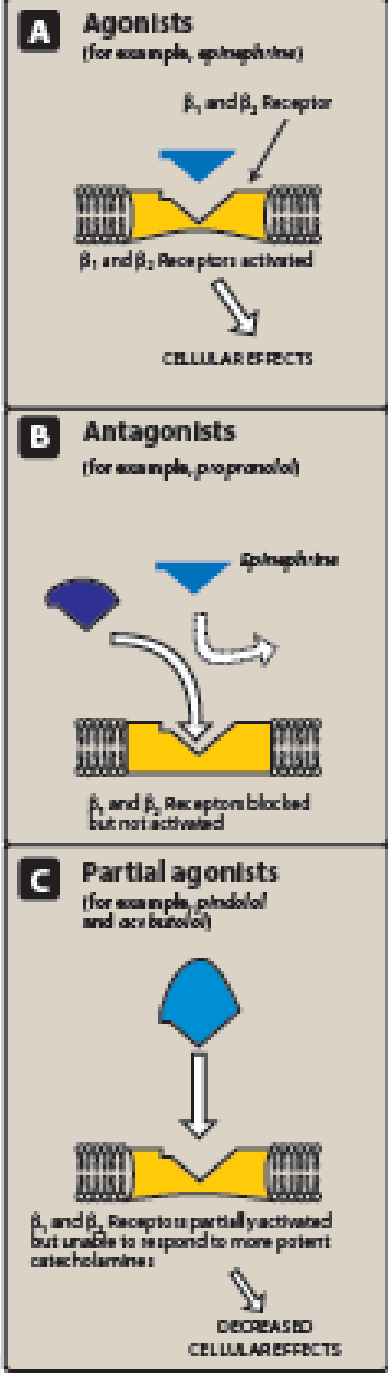
- Selective β1 antagonists
- Cardioselective (at low doses)
- No β2 antagonism (no bronchoconstriction)
- Little effect on peripheral resistance
- Therapeutic use
  - Hypertension (to lower blood pressure)
  - Angina (increase exercise tolerance)

Acebutolol and pindolol

- Antagonists with partial agonist activity
- Have intrinsic sympathomimetic activity
- Acebutolol is β1 selective antagonist
- Pindolol is non selective β-blocker
- Used for hypertensive patients with moderate bradycardia because they cause less heart rate decrease

Labetalol and carvedilol

- Antagonists of both α and β
  - Block α_1 receptors causing peripheral vasodilation and reducing blood pressure
- Used for hypertension
- Labetalol can be used in pregnancy-induced hypertension
- Intravenous labetalol can be used for hypertensive emergencies
- Adverse effects:
  - Orthostatic hypotension


A
Agonists
(for example, epinephrine)
β1 and β2 Receptor
β1 and β2 Receptors activated
CELLULAR EFFECTS
B
Antagonists
(for example, propranolol)
Epinephrine
β1 and β2 Receptors blocked
but not activated
C
Partial agonists
(for example, pindolol
and acebutolol)
β1 and β2 Receptor is partially activated
but unable to respond to more potent
catecholamines
DECREASED
CELLULAR EFFECTS

Adverse Effects of β-blockers:

- In patients with AV conduction defects, β_1 blockers may cause life-threatening bradyarrhythmias.
- Abrupt discontinuation of long-term β_1 blockers use in angina can exacerbate angina and may increase risk of sudden heart attack.
- β_2 receptor blockade can worsen bronchoconstriction in asthmatic populations.
  - β_1-selective blockers or non-selective β blockers with partial β_2 agonism produce less bronchoconstriction than non-selective β blockers.

Drugs affecting neurotransmitter release or reuptake

- Reserpine
  - Blocks the transport of the biogenic amines norepinephrine, dopamine and serotonin from the cytoplasm into storage vesicles in adrenergic nerves
  - Causes depletion of biogenic amines
  - Impairs sympathetic function
  - Long duration of action
- Guanethidine
  - Blocks the release of stored norepinephrine
  - Causes orthostatic hypotension