Adverse effects and contraindications:

1. Sedation and extrapyramidal and psychogenic depression that can lead to suicide.
    - ❖ Reserpine must be discontinued at first sign of depression and the drug should never be given to patients with a history of depression.
2. Nasal stuffiness.
3. Exacerbation of peptic ulcer disease.

(3) Guanethidine

Site and mechanism of action:

- Via uptake-1, guanethidine enters the peripheral adrenergic neurons and stored by the storage granules.
- Stimulation of adrenergic neurons release guanethidine instead of NE.
- Finally, guanethidine depletes the stores of NE with impairment of the function of the adrenergic neurons.
- The drug doesn't pass the blood-brain barrier and have no CNS effects.

Pharmacological actions:

1. Vasodilatation and bradycardia give rise to marked reduction in the blood pressure with the possibility of orthostatic hypotension.
2. Nasal stuffiness, salt & water retention and increased GI motility & secretion.

Therapeutic uses: Treatment of moderate & severe degree hypertension as well as in the control of hypertensive crises.

Adverse effects:

1. Postural hypotension,bradycardia, salt & water retention.
2. Increased GIT secretion & motility (activation of peptic ulcer, diarrhea).

Interaction with other drugs:

The antihypertensive effect of guanethidine could be antagonized by drugs that:

- Inhibit neuronal reuptake e.g. Tricyclic antidepressants and Cocaine
- Indirectly acting sympathomimetics (Amphetamine, Ephedrine, Phenylpropanolamine. etc.).

Alpha-adrenoceptor Antagonists

- Stimulation of α_1 adrenoceptor → contraction of arterial and venous smooth muscle.
- Stimulation of α_2 adrenoceptor → suppressing sympathetic outflow, facilitating platelet aggregation, inhibiting the release of norepinephrine and acetylcholine from nerve endings.

Classification of α-drenoceptor antagonists:

Nonselective (block α_1 & α_2)	Selective α_1 blockers	Selective α_2 blockers	α- & β-blockers
Ergot alkaloids Phenoxybenzamine Phentolamine Tolazoline	Prazosin Terazosin Doxazosin Tamsulosin	Yohimbine	Labetalol Carvedilol

Pharmacological Properties:

CVS:

- α_1 blockers inhibit vasoconstriction induced by endogenous catecholamines or administration of sympathomimetics. The result is a decrease in peripheral resistance and a fall in blood pressure.
- Alpha blockers prevent the pressor effects of α agonists (e.g. Phenylephrine).
- In case of agonists with both α and β_2 effects (e.g. epinephrine), α-blockers convert a pressor to a depressor response. This change in response is called **epinephrine reversal.**

Selective α_2 antagonists such as yohimbine can increase sympathetic outflow and release of NE from nerve endings with rise in blood pressure.

Other actions: α_1 receptors block in the base of the bladder and the prostate decreases resistance to the flow of urine.

I] Non-selective α blockers

(1) Ergot alkaloids

Ergot is a fungus "Claviceps purpurea" that grows parasitically on rye grains. Ergot alkaloids are the hydroalcoholic extract of the fungus.

Pharmacological properties:

1- Direct vasoconstrictor effect.
2- α adrenergic blocking effect.
3- Uterine stimulant (oxytocic) effect.
4- Dopaminergic stimulant effect (nausea & vomiting, inhibition of prolactin & growth hormone secretion and anti-parkinsonian effect).

Compounds isolated from the ergot extract:

1- **Ergotamine:** ***vasoconstrictor*** with moderate α-blocking effect and uterine stimulant effect.
2- **Ergometrine:** ***potent uterine stimulant effect*** together with moderate vasoconstrictor and α-blocking effect.
3- **Ergotoxine:** ***marked α-blocking effect*** with moderate vasoconstrictor & uterine stimulant effects.

N.B. The vasoconstrictor effect of the above mentioned compounds is induced by partial agonist activity on both α adrenergic and 5-HT_2 receptors

Modifications in the structure of the above compounds give more efficient drugs:

1. Dihydro-ergotamine: vasoconstrictor with minimal dopaminergic & α-blocking effects.
2. Dihydro-ergotoxine: potent α-blocking effect.
3. Methyl-ergometrine: more potent uterine stimulant while dopaminergic effect is attenuated.

Therapeutic uses:

1. Migraine headache: Ergotamine orally, alone or in combination with caffeine (cafergot), can be used for ***acute attacks*** of migraine headache.
   - Dihydro-ergotamine IV or IM can be used.
   - They are better to be started as early as possible (during aura).
2. Senile dementia: Dihydro-ergotoxine [increases cerebral blood flow].
3. Postpartum hemorrhage: Methyl-ergometrine.
4. To suppress prolactin & growth hormone secretion: Bromocriptine is used.
5. Parkinsonism: Bromocriptine is used.

Contraindications:

- Except for bromocriptine, all other drugs are contraindicated during pregnancy.
- Ergotamine, dihydro-ergotamine, ergometrine and methyl-ergometrine are contraindicated in hypertension, coronary heart disease and peripheral vascular diseases.

(2) Phenoxybenzamine

Phenoxybenzamine blocks α_1 and α_2 adrenergic receptors ***irreversibly***. The only way the body can overcome this block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, its actions last about 24 hours.

Pharmacological properties:

1. Vasodilatation causing a progressive decrease in peripheral resistance.
2. Tachycardia ***due to*** reflex sympathetic nerve stimulation and enhanced release of norepinephrine (because of α_2-blockade) that stimulates β_1 receptors in the heart.
3. Blockade of histamine, serotonin and muscarinic receptors.

Therapeutic uses: Treatment of ***pheochromocytoma*** either for:

- Preoperative preparation of the patient for surgery.
- Life-long management of the disease in patients with inoperable cases.
- Treatment of hypertensive emergency of pheochromocytoma.

Adverse effects:

1. Postural hypotension with reflex tachycardia and other arrhythmias.
2. Nasal stuffiness.
3. Inhibition of ejaculation because of impaired smooth muscle contraction in the vas deferens and ejaculatory ducts.

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(3) Phentolamine & Tolazoline

- Competitive α-blockers.
- Block 5-HT receptors and causes release of histamine from mast cells.
- Stimulate GIT and enhance gastric acid secretion.
- Tolazoline is less potent than phentolamine.

Therapeutic uses:

Phentolamine:

1- Short-term control of hypertensive crises due to:
   - Pheochromocytoma.
   - Abrupt withdrawal of Clonidine.
   - Ingestion of tyramine-containing foods during the use of nonselective MAO inhibitors.

2- To inhibit tissue necrosis caused by extravasation of α-agonist drugs.

Tolazoline:

1- Treatment of pulmonary hypertension of the newborn.

2- To visualize distal peripheral vessels during arteriography.

Toxicity and adverse effects:

1. Hypotension.
2. Tachycardia, cardiac arrhythmias, and ischemic cardiac events, including myocardial infarction.
3. Gastrointestinal stimulation may result in abdominal pain, nausea, and exacerbation of peptic ulcer.

N.B. Phentolamine should be used with particular caution in patients with coronary artery disease or a history of peptic ulcer.

II] Alpha-1 selective blockers

Prazosin

Mechanism of action:

- Highly selective for α_1 receptors. This may explain the relative absence of tachycardia compared with that of Phentolamine and Phenoxybenzamine.
- It also inhibits phosphodiestrase enzymes responsible for degradation of cAMP, and cGMP, both produce vasodilatation. cAMP could produce tachycardia, which could be counteracted by cGMP (produce bradycardia), the net effect is vasodilatation with little tachycardia.

Therapeutic uses:

- Essential hypertension especially if associated with benign prostatic hyperplasia (BPH), it is given as 1-4 mg twice daily.
- Effective in the management of hypertension urgency 1 mg ever 1-2 hours until controlled.
- Its half-life is about 3 hours.

Adverse Effects:

1- **First-dose phenomenon** (marked postural "orthostatic" hypotension and syncope).
   - Usually is seen 30 to 90 min after the initial dose and with a rapid increase in dose.
   - This can be minimized by limiting the initial dose to 1 mg at bedtime and increasing the dosage slowly and by introducing additional antihypertensive drugs cautiously.

2- **Non-specific adverse effects** such as headache, dizziness, drowsiness, and nausea.

- **Terazosin:** is effective in hypertension and in urinary symptoms due to benign prostatic hyperplasia (BPH). Its half-life is 9–12 hours. It is given in dose of 1- 4 mg ***once daily.***
- **Doxazosin:** is efficacious in the treatment of hypertension and BPH. It has a longer half-life of about 22 hours. It is the ***longest acting*** of these drugs. It is given in dose of 1- 4 mg once daily.
- **Tamsulosin:** is used in ***BPH if not associated with hypertension.*** The drug has higher affinity for **α_{1A} receptors** present is the prostatic capsule & prostatic urethra than for the vascular α_{1B} subtype. Thus it produces relaxation of prostate and prostatic urethra without significant effect on blood pressure.

III] Alpha-2 selective blockers

Yohimbine

- Yohimbine is a selective competitive α_2 blocker.
- It has been used as a sexual stimulant and in the treatment of erectile dysfunction.
- However, its use to treat these conditions is ***not recommended*** due to lack of demonstrated efficacy.
- Yohimbine works at the level of the CNS to increase sympathetic outflow to the periphery.

Beta Adrenoceptor Antagonists

Drugs which could block the β adrenergic receptor are called β adrenergic receptor antagonists (β blockers).

Classification of β-blockers:

- **First generation:** (Non-selective β blockers)
  - Propranolol, timolol, sotalol, pindolol, nadolol
- **Second generation:** (β_1Selective blockers)
  - Acebutolol, **metoprolol, esmolol, bisoprolol, atenolol.**
- **Third generation:** β blockers with additional mechanisms of vasodilatation e.g. carvedilol

Drug	Block			NO production	β_2-receptor agonism	Ca^{2+} entry blockade	K^+ channel opening	Inhibition of neuronal uptake of NE	Antioxidant activity
	β_1	β_2	α_1						
Betaxolol	++					++			
Bevantolol	++		++			++			
Bopindolol	++	++		++	++				
Bucindolol	++	++	++						
Carteolol	++	++		++	++				
Carvedilol	++	++	++			++			++
Celiprolol	++			++	++				
Labetalol	++	++	++					++	
Nebivolol*	++			++					
Nipradilol	++	++	++	++					
Tilisolol	++	++					++		

*The ***most selective*** β_1-antagonist.

- Bucindolol and Carvedilol have β_3-adrenoceptor blocking effect.

- **Some β blockers have intrinsic sympathetic activity "ISA" or partial agonists:**
  - Oxyprenolol, pindolol and acebutolol.
  - ISA prevent profound bradycardia or negative inotropy in a resting heart.

- **Some β blockers have membrane-stabilizing properties** (e.g. propranolol), or increase the effective refractory period of the heart (e.g. sotalol).
  - ❖ These actions share in their anti-arrhythmic effect.
- **Water soluble β-blockers (long $t_{1/2}$ & contraindicated in renal impairment)**
  - ❖ Atenolol and nadolol.

Pharmacokinetics of β blockers:

Absorption:

- β-blockers are well-absorbed after oral administration, except esmolol is not absorbed orally.

Bioavailability:

- Propranolol undergoes extensive hepatic 1st pass metabolism; its bioavailability is low.
- Bioavailability is moderate for most β-blockers.
- Betaxolol, penbutolol, pindolol, and sotalol have high bioavailability.

Distribution and elimination:

- Propranolol is quite lipophilic and readily crosses the blood-brain barrier.
- Most β-blockers have half-lives in the range of 3-10 hours.
- **Esmolol** is rapidly hydrolyzed by red cell ***esterases*** and has a half-life of approximately 10 minutes.
- Propranolol and metoprolol are extensively metabolized by the liver CYP_{450} 2D6. Their elimination is prolonged in the presence of liver disease, diminished hepatic blood flow, or hepatic enzyme inhibition.
- Nadolol and atenolol are excreted unchanged in the urine. Their half-lives are prolonged in renal failure.
- Nadolol has the longest half-life (up to 24 hours).

Pharmacological/Pharmacokinetic properties of β blockers:

Drug	Membrane-stabilizing properties	Intrinsic agonist activity	Lipid solubility	Absorption (%)	Oral bioavailability (%)	$t_{1/2}$ (hours)
Non-selective β-blockers: First generation						
Nadolol	0	0	Low	30	30-50	20-24
Penbutolol	0	+	High	~100	~100	~5
Pindolol	+	+++	Low	>95	~100	3-4
Propranolol	++	0	High	<90	30	3-5
Timolol	0	0	Low to moderate	90	75	4
β_1-blockers: Second generation						
Acebutolol	+	+	Low	90	20-60	3-4
Atenolol	0	0	Low	90	50-60	6-7
Bisoprolol	0	0	Low	90	80	9-12
Esmolol	0	0	Low	NA	NA	0.15
Metoprolol	0	0	Moderate	~100	40-50	3-7
Non-selective β-blockers with additional actions: Third generation						
Carteolol	0	++	Low	85	85	6
Carvedilol	++	0	Moderate	>90	~30	7-10
Labetalol	+	+	Low	>90	~33	3-4
β_1-blockers with additional actions: Third generation						
Betaxolol	+	0	Moderate	>90	~80	15
Celiprolol	0	+	Low	~74	30-70	5
Nebivolol	0	0	Low	Variable	Variable	11-30

NA: Not Absorbed

Pharmacological actions:

I. Cardiovascular system:

- **Heart:** β-blockers decrease all cardiac properties:
  - They decrease the automaticity.
  - They slow conduction in the atria and in the AV node.

- They decrease myocardial contractility.
- They decrease heart rate.

❖ **Coronary blood flow:**

- β-blockers decrease myocardial oxygen consumption by reduction of the heart rate and myocardial contractility.
- This effect improves the relationship between cardiac oxygen supply and demand.

❖ **Vascular system:**

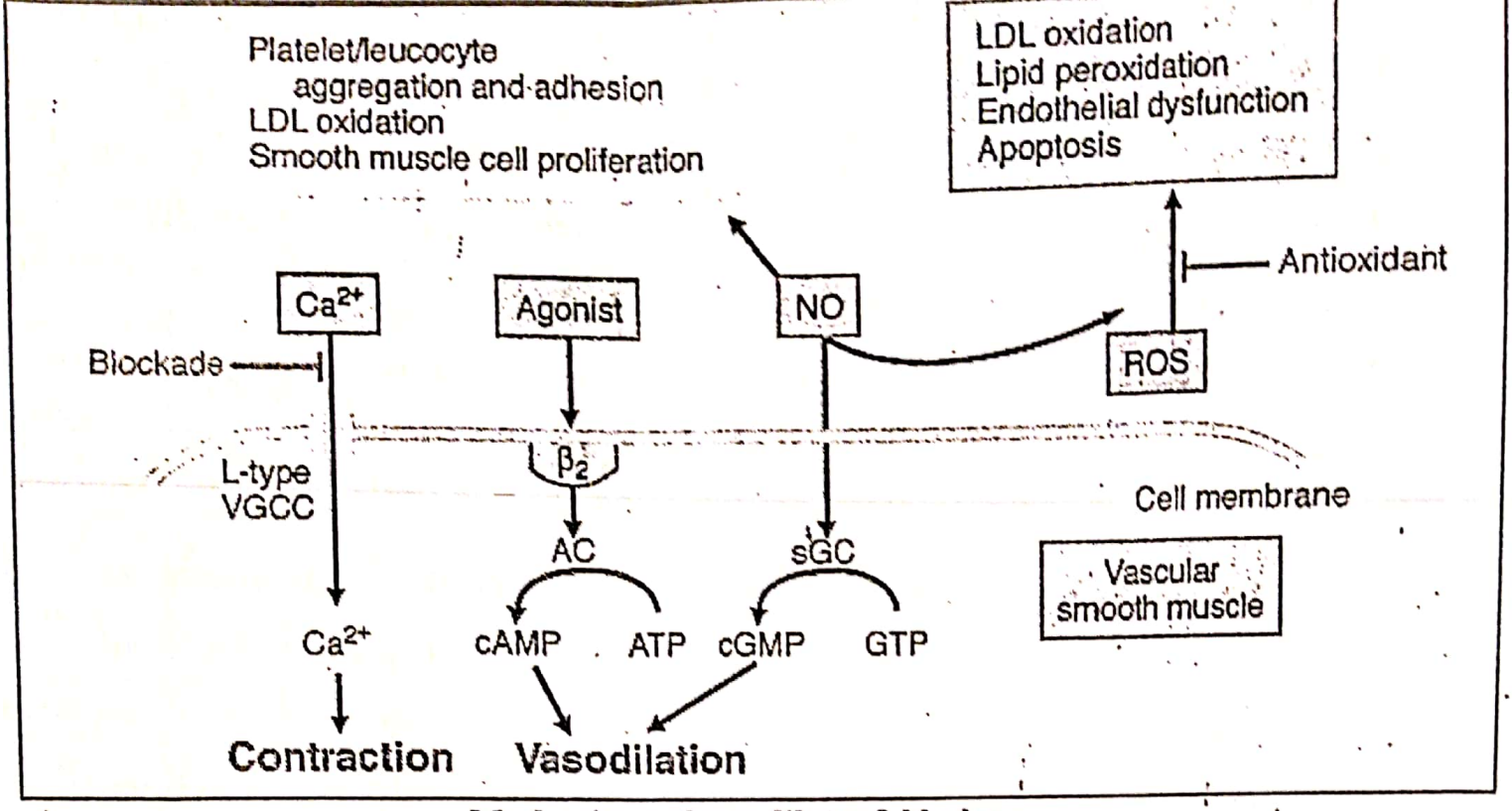
- Beta blockers reduce cardiac output → reflex sympathetic stimulation → initial rise in peripheral resistance from α-receptor-mediated vasoconstriction with no β_2-mediated vasodilatation due to their block.
- However, with long-term use of β-blockers, total peripheral resistance returns to initial values.
- β-blockers have antihypertensive action but, do not cause a reduction in blood pressure in patients with normal blood pressure.

❖ **The mechanisms of antihypertensive action:**

1. Reduction of the cardiac output.
2. Inhibition of renin release.
3. Inhibition of NE release from the sympathetic neurons due to block of presynaptic β receptors on adrenergic neurons.
4. Resetting of the baroreceptors.
5. Reduction of the sympathetic outflow centrally.
6. Increase vasodilator prostaglandins.

Drugs with additional vasodilator mechanisms:

- **α_1 receptor antagonism:** Labetalol & carvedilol.
- **β_2 receptor agonism:** Celiprolol.
- **Calcium channel block:** Carvedilol & betaxolol.
- **Nitric oxide production:** Nebivolol & carteolol.



Mechanisms of vasodilator β-blockers

II. Pulmonary system:

- Nonselective β-blockers block β_2 receptors in bronchial smooth muscle. This usually has little effect on pulmonary function in normal individuals.
- In patients with asthma or COPD, life-threatening bronchoconstriction can occur.
- Although $\beta_1$selective antagonists or antagonists with intrinsic sympathomimetic activity (partial agonists) are less likely to increase airway resistance in patients with asthma, these drugs should be used only with great caution in these cases.

III. Metabolic effects:

- Nonselective β-blockers may delay recovery from hypoglycemia in insulin-dependent diabetics and mask the tachycardia [warning sign] that is typically seen with hypoglycemia.
- Increase triglycerides and decrease HDL. β_1 selective blockers and those with "ISA" may cause less of an effect on lipid metabolism.
- Beta blockers inhibit K^+ influx into skeletal muscles that occurs with sympathetic activation.

IV. Other Effects: β blockers prevent catecholamines-induced tremors.

Therapeutic uses of β blockers:

I. Cardiovascular diseases:

1. **Hypertension:** Alone mild degree hypertension and in combination with other drugs to control moderate and severe degree hypertension.
2. **Angina pectoris:** Prophylaxis of angina due to coronary atherosclerosis. However, these drugs are may worsen vasospastic angina.
3. **Acute myocardial infarction** and in the prevention of recurrence.
4. **Supraventricular arrhythmia.**
5. **Heart Failure:**
   - Small doses of *metoprolol, bisoprolol, and carvedilol* reduce mortality in selected patients with chronic heart failure.
   - This may be due to their beneficial effects on myocardial remodeling and in decreasing the risk of sudden death.
6. **Hypertrophic obstructive cardiomyopathy:** β blockers slow ventricular ejection and decreased outflow resistance.
7. **Medical management of acute dissecting aortic aneurysm:** β blockers decrease the rate of development of systolic pressure.

II. Non-cardiovascular diseases:

1. **Prophylaxis of migraine:** These drugs are not useful for treatment of acute attacks of migraine.
2. **Essential tremors:** As sympathetic activity may enhance skeletal muscle tremors.
3. **Glaucoma:** Topically administered β blockers decrease "IOP" by decreasing the rate of production of aqueous humor by the ciliary body.
4. **Esophageal varices:** Prevent bleeding from esophageal varices in patients with portal hypertension.
5. **Hyperthyroidism:** β-blockers prevent the excessive catecholamine activity especially on the heart. Propranolol can inhibit de-iodinase enzyme that convert T4 to T3 and has been used extensively in patients with thyroid storm.

Adverse effects:

I. Cardiovascular system:

1- β-blockers exacerbate heart failure in patients with compensated heart failure.

2- Bradycardia may progress to life-threatening partial or complete heart block.

3- Symptoms of peripheral vascular disease may worsen.

4- Abrupt discontinuation of β blockers after long-term treatment can exacerbate angina and may increase the risk of sudden death.

- This may due to upregulation of β_1 receptors. Such enhanced sensitivity can be attenuated by tapering the dose of β-blockers for several weeks before discontinuation.

II. Central nervous system:

- Fatigue, sleep disturbances (including insomnia and nightmares), and depression may occur especially with the use of lipophilic β-blockers.

III. Pulmonary function:

- In patients with bronchial asthma or chronic obstructive lung disease, a life-threatening bronchospasm may occur.
- Drugs with selectivity for β_1 receptors or those with "ISA" at β_2 receptors may be somewhat less likely to induce bronchospasm. However, the selectivity of current β-blockers is lost with increasing the dose.
- Consequently, these drugs should be avoided in patients with asthma.

VI. Metabolism:

1- β-blockers may blunt recognition and delay recovery from insulin-induced hypoglycemia.

2- β-blockers cause an increased concentration of plasma triglycerides and decrease the concentration of HDL-Cholesterol.

Drug interactions:

Pharmacokinetic interactions:

1- Aluminum salts, cholestyramine, and colestipol may decrease the absorption of β-blockers.

2- Drugs such as phenytoin, rifampicin, and phenobarbital (enzyme inducers) decrease plasma concentrations of β-blockers that are metabolized extensively (e.g. propranolol).

3- Cimetidine and hydralazine (enzyme inhibitors) may have the reverse effect.

4- β-blockers can impair the clearance of lidocaine. Its clearance by the liver is flow-dependant and beta blockers decrease the portal blood flow.

Pharmacodynamic interactions:

1- Ca^{2+}-channel blockers (e.g. verapamil) and β blockers have additive effects on the cardiac conducting system and myocardium and may progress to heart failure and heart block.

2- Additive effects on blood pressure between β-blockers and other antihypertensive agents.

3- The antihypertensive effects of β-blockers could be opposed by indomethacin and other non-steroidal anti-inflammatory drugs due to reduction of prostaglandin production.

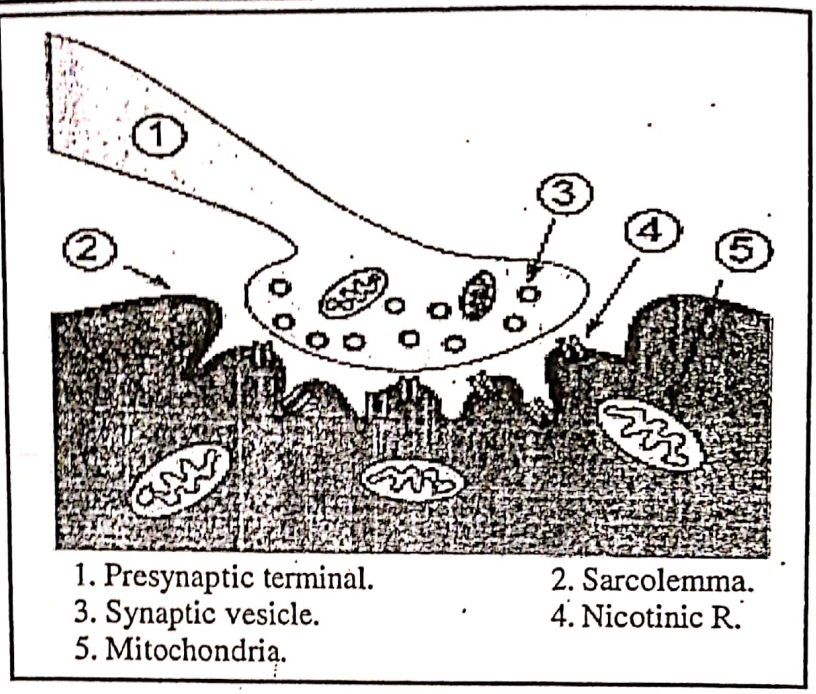
Overdose: Hypotension, bradycardia and seizures may occur.

- Bradycardia should be treated with ***atropine***, but a ***cardiac pacemaker*** is often required.
- ***Glucagon*** has positive chronotropic and inotropic effects on the heart that are independent of interactions with β receptors, so useful in some patients.

Skeletal Muscle Relaxants

The neuromuscular junction (NMJ):

It is the region of contact between the muscle & the somatic nerve supplying it. It is called motor end plate. In the motor end plate there are nicotinic receptors & acetylcholine is their transmitter.



1. Presynaptic terminal. 2. Sarcolemma.
3. Synaptic vesicle. 4. Nicotinic R.
5. Mitochondria.

Classification of skeletal muscle relaxants

1- **Neuromuscular blockers (NMBs):** These drugs are clinically useful to relax skeletal muscles, act on nicotinic receptors in NMJ and lack CNS activity.

2- **Spasmolytic drugs:** used to decrease skeletal muscle spasm. They include:

   A. ***Centrally acting (on CNS)*** e.g. mephenesin & baclofen, are used in painful conditions e.g. chronic back pain or injury. They do not affect voluntary activity.

   B. Direct or peripherally acting (on skeletal muscles) e.g. dantrolene.

3- **Drugs that decrease acetylcholine at nerve terminals:**

   A. Inhibitors of ACh synthesis: hemicolinium, triethylcholine.

   B. Inhibitors of ACh release: local anesthetics as procaine, excess Mg^{+2} and lack of Ca^{+2}.

   C. Inhibitors of ACh storage e.g. vesamicol.

   N.B. Hemicholinium & vesamicol are experimental tools only.