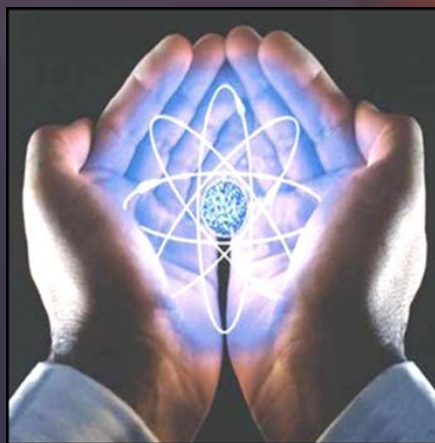


Lecture №2

**Drugs Affecting
the Afferent and Efferent Nervous System.
Cholinergic Drugs.**

Lecturer: Associate Professor Irene Borysovna Samura



LOCAL (*REGIONAL*) ANAESTHETICS

1. For Terminal (*Superficial*) Anaesthesia:

Cocaine

Anaesthesine (Benzocaine)

Dicaine (Tetracaine)

Pyromecaine

2. For Infiltration, Conductive and Intraspinal Anaesthesia:

Novocaine

Trimecaine

Ultracaine

Bupivacaine

3. For all kinds of Anaesthesia:

Lidocaine



According to the Chemical structure:

1. Esters of aromatic acids:

Natural Esters: **Cocaine**

Derivatives of PABA:

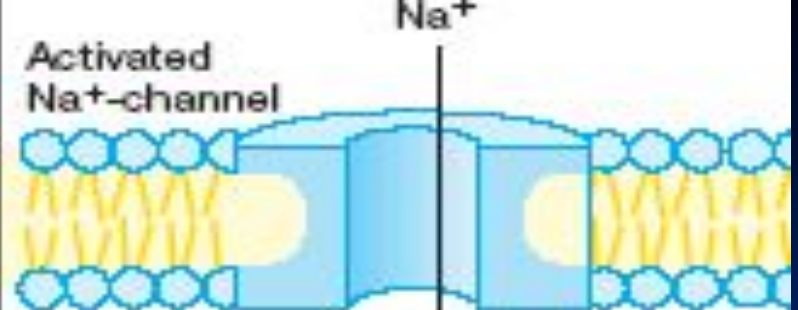
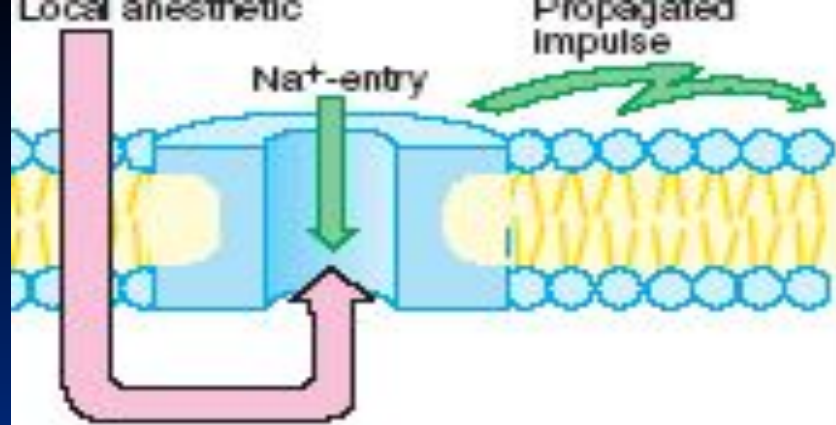
Anaesthesine

Dicaine

Novocaine

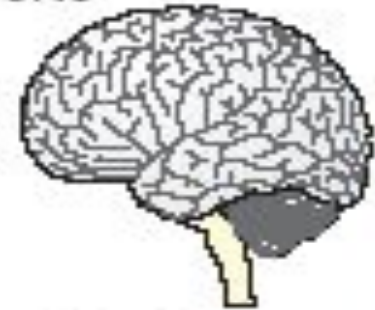
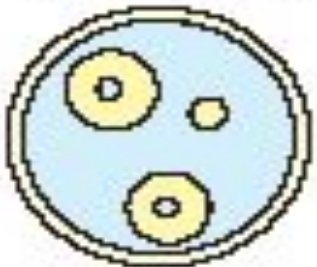
2. Amides: **Lidocaine, Trimecaine,**

Ultracaine, Bupivacaine



Peripheral nerve

CNS



Blocked Na+ channel

Na+



Conduction block

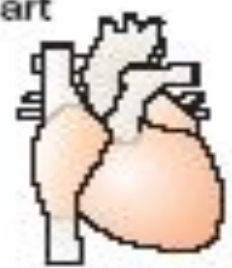
Restlessness, convulsions, respiratory paralysis

Blocked Na+ channel

Na+



Heart



Local application

Impulse conduction ↓ cardiac arrest



LAs are Weak Bases.

In order that **a drug** manifests its **action** it must occur **hydrolysis** and **liberation** of **lipid dissoluble base** that occurs in **Alkaline Medium** only .

Normally in Tissues **pH = 7.35 - 7.4**

In Focus of Inflammation **pH = 5.0 - 6.0**

LAs do not manifest their activity

in Inflamed Tissues since

Salt Hydrolysis does not occur in **Acid Medium**.

+ Vasoconstrictor

Adrenaline hydrochloride 0.1% - 1 drop in 2-10 ml

↓ the rate of absorption =>

- Systemic Toxicity
- the Duration of Action.

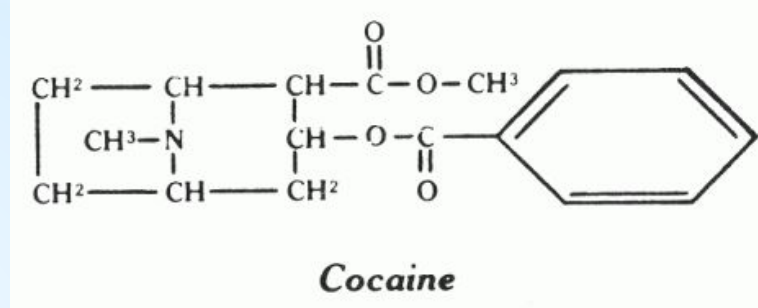
Premedication with *Diazepam* IM 0.5% solution 2 ml
provides prophylaxis against seizures.

Cocaine blockades:

Noradrenaline

Serotonin

Dopamine



reuptake into the Presynaptic Terminals.

□ **Dopamine** in brain's **Pleasure System** (limbic system) =>
=> **Euphoria**.

Chronic Intake of **Cocaine** => Depletes **DOPAMINE** =>

=> the **Vicious Cycle** of Craving for Cocaine



COCAINE:

- ★ POTENTIATES the action of *Noradrenaline*
- ★ the «**FIGHT OR FLIGHT**» SYNDROME of

ADRENAL STIMULATION:

- Tachycardia
- Hypertension
- Pupillary Dilation
- Peripheral Vasoconstriction

Adverse Effects of COCAINE:

1. Anxiety Reactions:

BP, HR, Sweating, Paranoia.

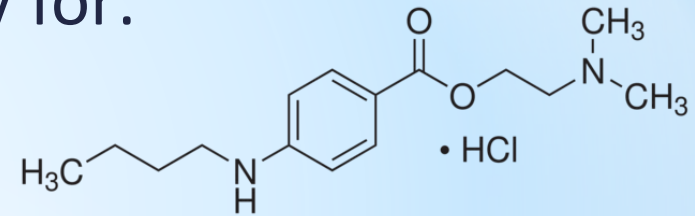
2. Depression Reactions

3. Heart Disease

4. Nasal Septum Necrosis

Dicaine (*Tetracaine*) is used topically for:

- Eye Mucous Anesthesia
- Throat Mucous Anesthesia



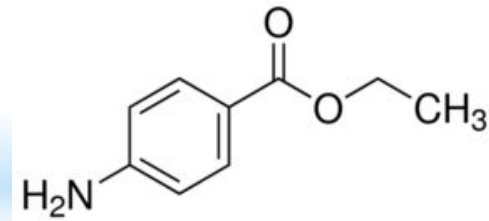
Anaesthesia (*Benzocaine*) –

Externally: in powder, paste, ointment –
on affected skin

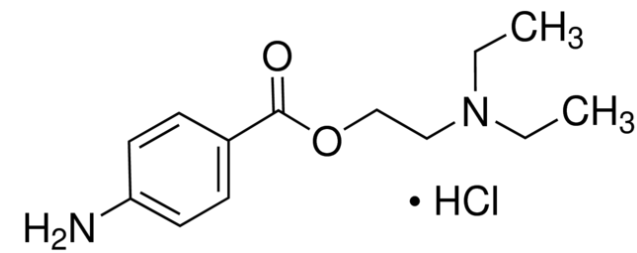
PO: in tablets - to treat GIT disorders

PR: in suppositories –

for Fissures of Rectum and Hemorrhoid

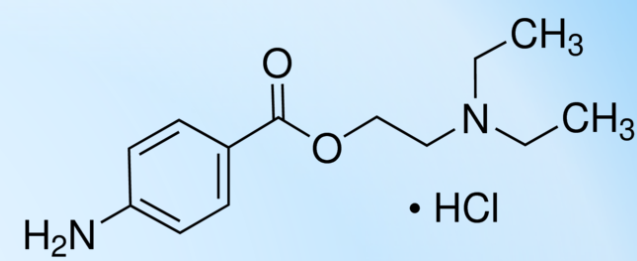


Novocaine => System Effects :



- ↓ Acetylcholine Formation
- Block of the Vegetative Ganglions

- Spasmolytic Properties
- ↓ Excitability of Myocardium and Motor Zones of the Cerebral Cortex



For infiltration anesthesia:

Novocaine 0.25-0.5% - 200-1000 ml

For conductive anesthesia:

Novocaine 1-2% - 20-25 ml

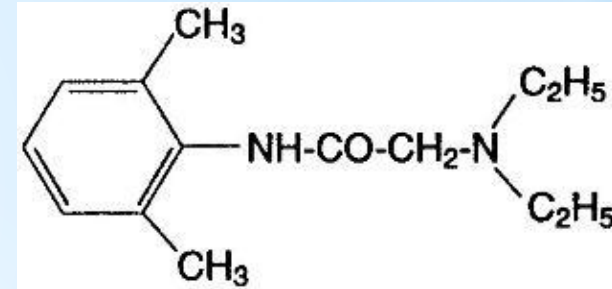
For intraspinal anesthesia:

Novocaine 5% - 2-3 ml



Lidocaine (amp 2%-10 ml; 10%-2 ml) -

a Local Anesthetic and
Ventricular Antiarrhythmic



- *Suppresses Automaticity*
- *Shortens the Effective Refractory Period* and *Action Potential Duration*
- the Drug of choice to treat *Ventricular Tachycardia* and *Fibrillation*

Astringents

1. Organic Compounds:

Tannin

Tannalbin

Oak Bark [*Cortex Quercus*]

Grass of st. Johns wort [*Herba Hyperici*]

Leaves of Salvia

Flowers of Chamomile

2. Inorganic Compounds:

Bismuth subcitrate [DE-NOL]

Silver nitrate

Zinc oxide

Lead acetate

Aluminum hydroxide

Almagel, Maalox

Magnesium hydroxide /oxide

Range of **SHMIDEBERG**:

Pb, Al, Bi, **Zn** Cu, Ag, Hg

Left Part - forms **Dense Albuminates** -
=> Protective Anti-Inflammatory Action

Right one forms **Friable Albuminates** –
in **High** concentration => **Cell Necrosis** -
CAUTERIZING action

In **Small** concentration =>
ASTRINGENT action

3. GASTROPROTECTORS

Colloidal bismuth subcitrate (De-nol)

Bismuth subsalicylate

Sucralfate

Almagel

Covering agents:

Mucus from Starch

Seeds of Flax

ADSORBENTS:

TALC

WHITE CLAY (*Bolus Alba*)

ACTIVATED CHARCOAL

IRRITATING AGENTS:

MUSTARD PLASTER

MENTHOL

VALIDOL

TURPENTINE OIL REFINED

AMMONIA SOLUTION

Mustard plaster

- **Distracting action: Inflammation Zone** on the skin =>
=> **Inflammatory Process Shifts** from **Deeper Area** to
the **Surface**.

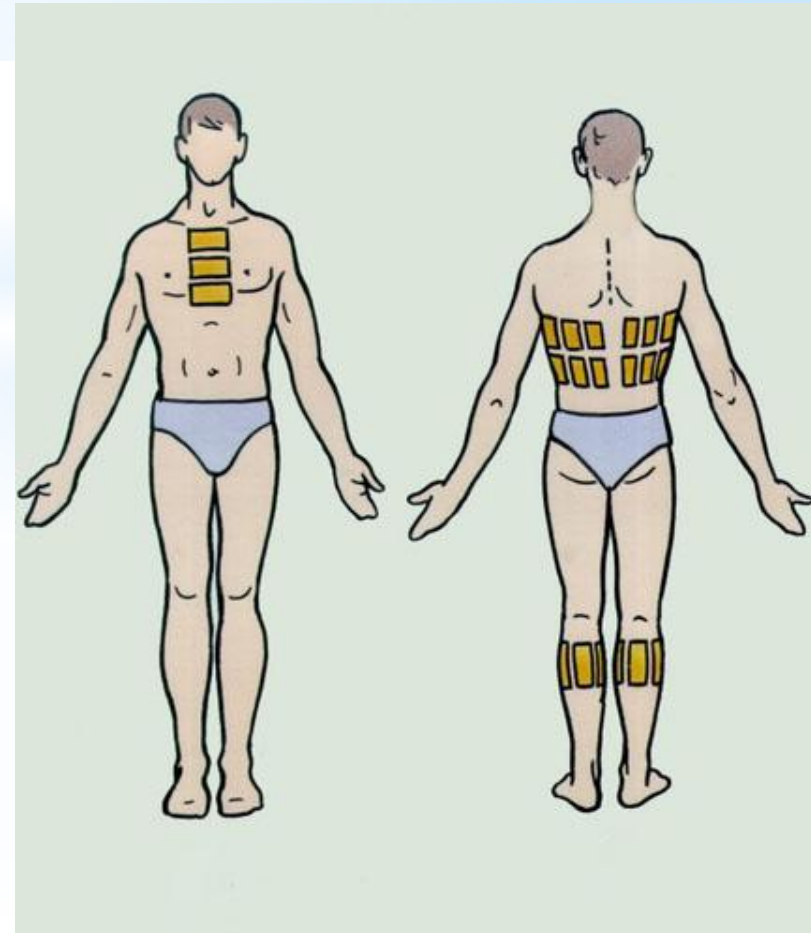
- **Reflex action**

- **Liberation of**

Morphine-like substances

in the CNS – **Enkephalins** and

Endorphins.



Validol – 25–30% Menthol solution

in Menthol Ether of Isovalerianic acid

- ★ Calming action on the CNS
- ★ Reflex Action => **Vasodilation**

Mechanism of Action:

Stimulation of **Cold Receptors** of the Tongue =>

=> Reflex **Vasodilatation** of Coronary Vessels

Clinical Uses:

- Acute Angina Pectoris, Neurosis,
- Sea and Air Sickness - as Antiemetic Agent

Cholinergic Drugs

Location of **Muscarinic M-Receptors**:

M₁ – Gastric Parietal Cells

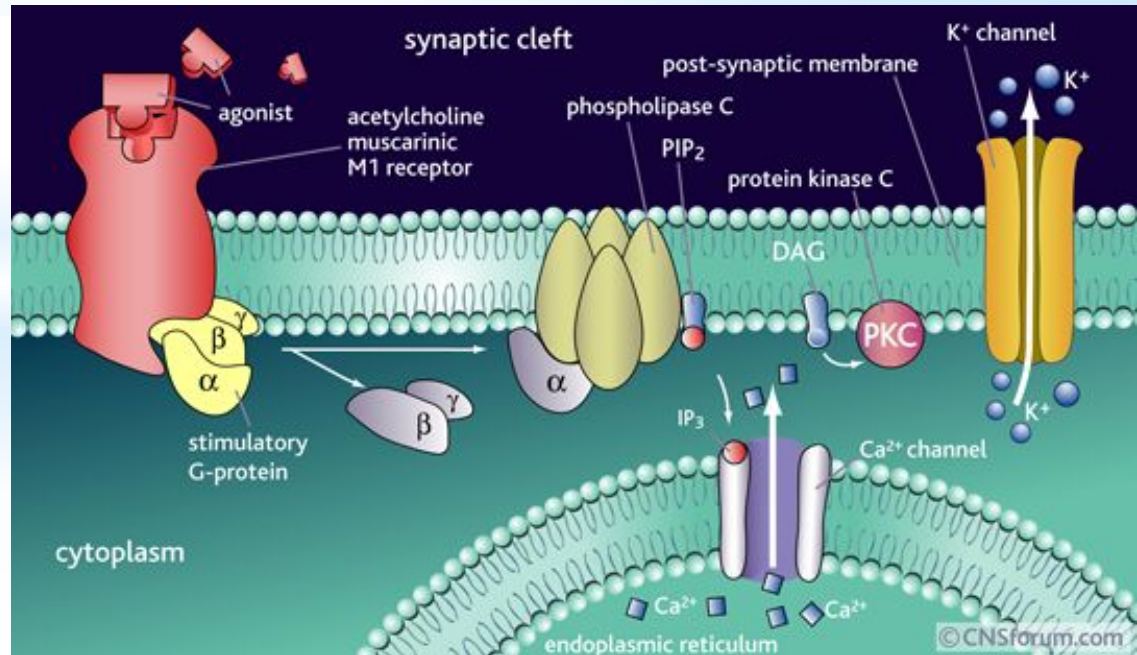
Vegetative Ganglia, CNS

M₂ – HEART

M₃ – Smooth Muscle

Exocrine Glands

Endothelium



Location of Nicotinic N-receptors:

N neuronal: (N_n)

- CNS

- **AUTONOMIC GANGLIA**

ADRENAL MEDULLA

N muscular: (N_m)

- **NEURO-MUSCULAR JUNCTIONS**

Cholinergic Drugs

I. M,N-cholinergic Agents of Direct Action:

1. M, N- Cholinomimetics:

Acetylcholine - powder

Carbacholine – 1% solution - 10 ml

2. M, N- Cholinoblockers:

Cyclodol – Tab. 0.001 g

Norakin – Tab. 2 mg

Amyzyl - Tab. 1 mg

Spasmolytin – powder

II. Anticholinesterase Agents:-

M, N - Cholinomimetics of Indirect action

1. Reversible Action:

Physostigmine

Galantamine

Tertiary Amines



Proserin (*Neostigmine*)

Oxazyl

Quaternary Amines



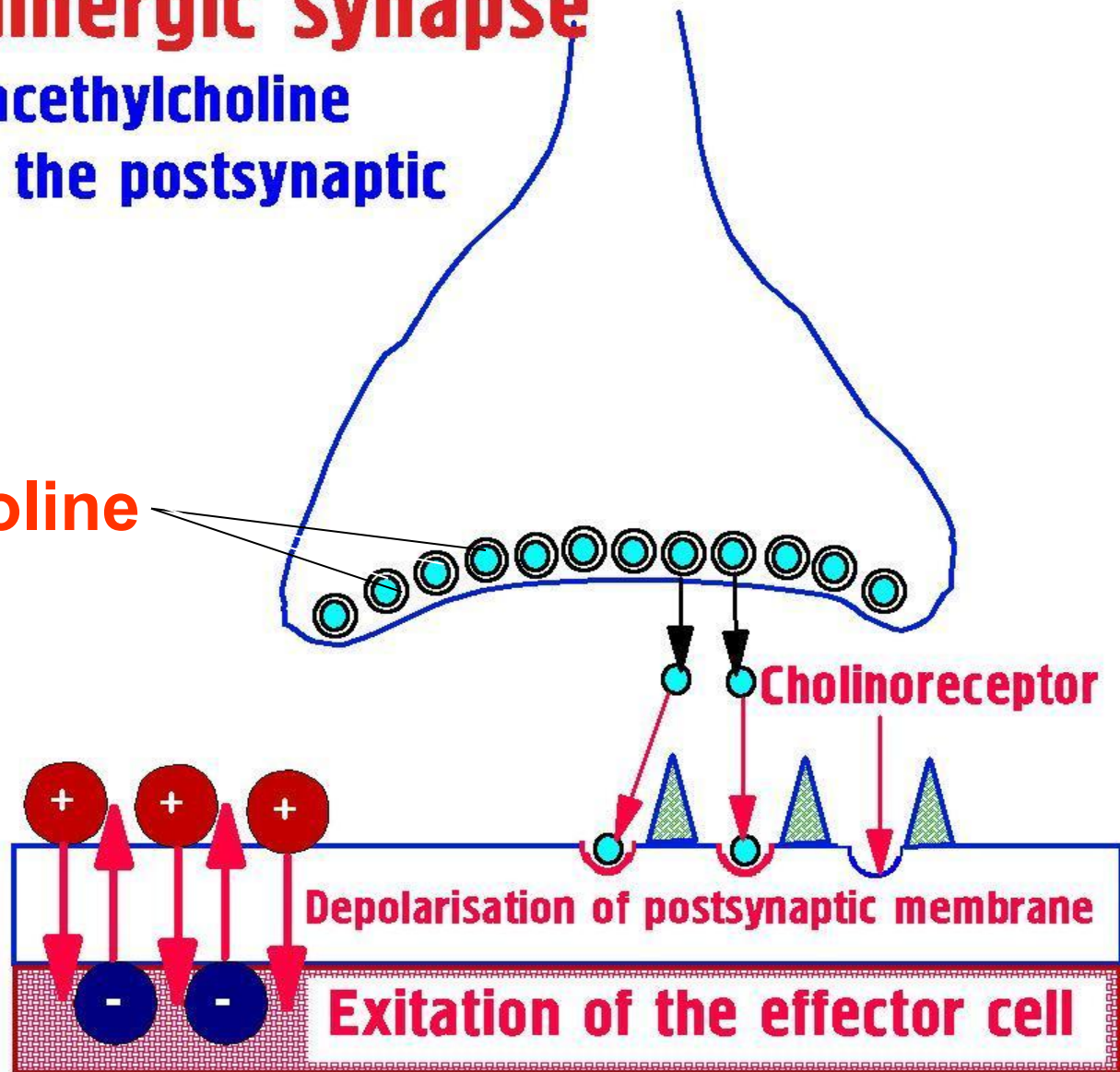
Pyridostigmine

2. Irreversible Action: Armine

Function of Cholinergic synapse

Interaction of acetylcholine with cholinceptors on the postsynaptic membrane:

Acetylcholine



Stimulation **M₁** and **M₃** Receptors => **Stimulating Action:**

the Receptor interacts with a **G_s Protein** =>

Activation of **Phospholipase C** =>

Hydrolysis of **PIP₂** => **DAG + IP₃**

IP₃ => \square **Ca²⁺**

PIP₂ – *Phosphatidyl-Inositol-bis-Phosphate*

DAG - *Diacylglycerol*

IP₃ - *Inositol-tris-Phosphate*

Stimulation of **M₂ Receptors** => **Inhibiting Action:**

the Receptor interacts with **G_{inhibitory}**-Protein =>

=> **Adenyl Cyclase Inhibition** =>

=> **□ cAMP** and **□ K⁺ Conductance** :

↓ Heart Rate

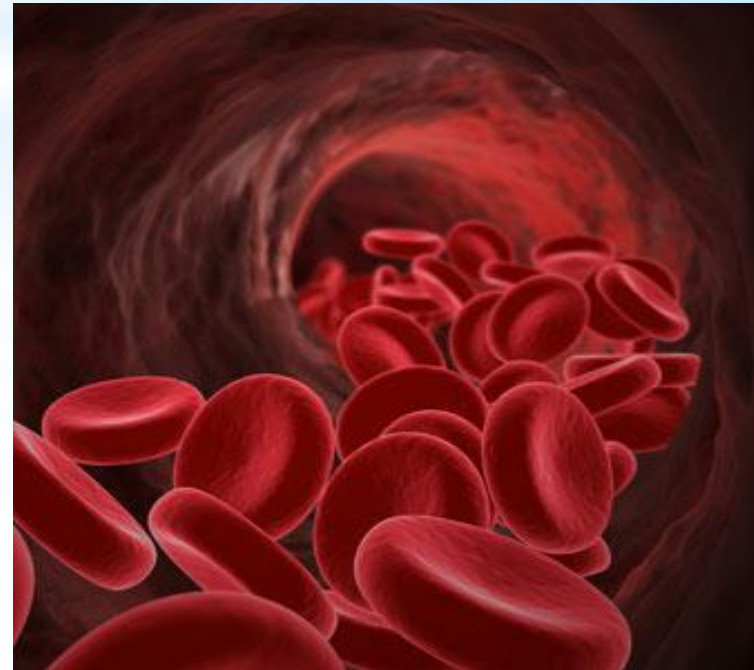
↓ Force of Heart Contraction

Stimulation of M_3 Receptors in the Blood Vessels \Rightarrow VASODILATION

Mechanism:

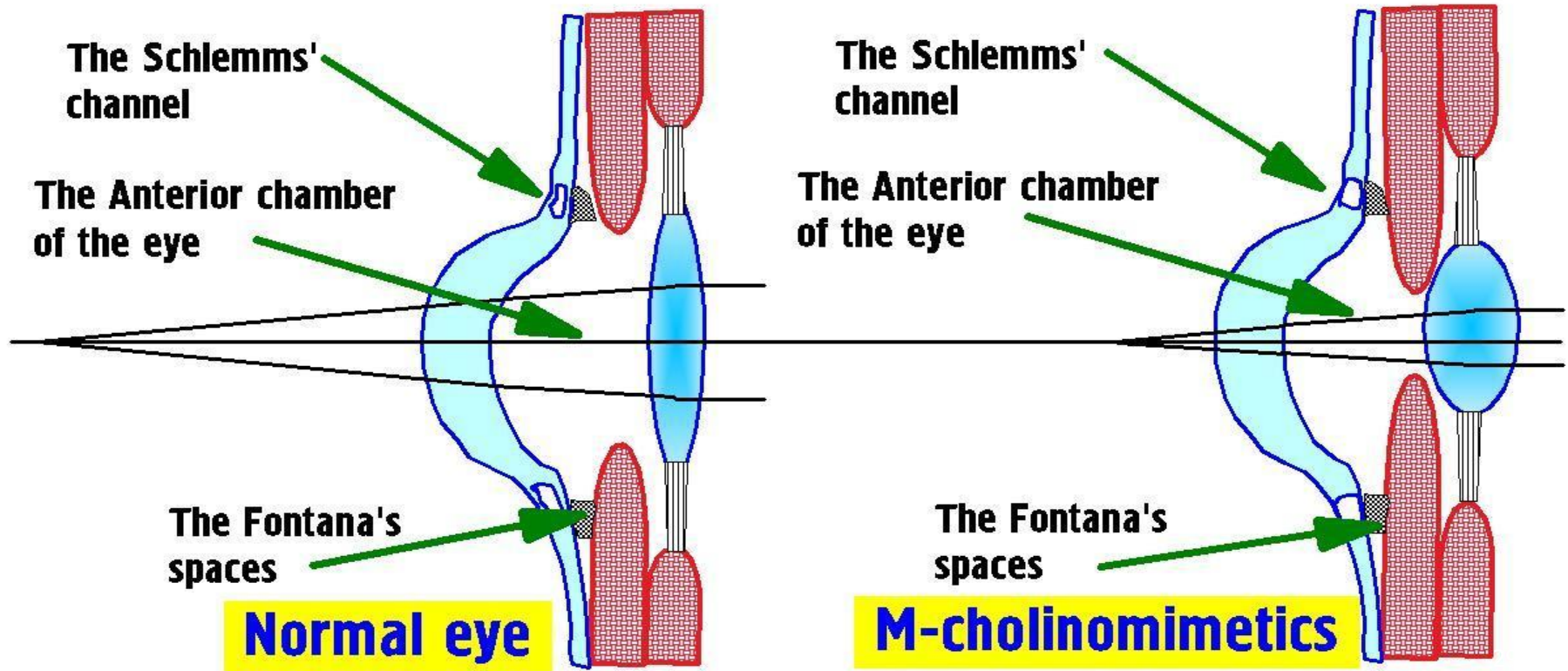
$PIP_2 \Rightarrow DAG + IP_3 \Rightarrow \square Ca^{2+} \Rightarrow$
 \Rightarrow **Nitric Oxide [NO]** formation

from **Arginine**
in the Endothelial Cells



► **Contraction of the circular muscle of the iris:**

Opening of Schlemms' channel and Fontana's spaces: increase of liquor outflow from the anterior chamber of the eye - therapeutic effect in glaucoma (decrease of intraocular pressure)



Stimulation of N - Receptors

Phase I: The opening of the **Na⁺ channel** => **Depolarization** and **Stimulating Effects**.

Phase II: The continued binding *renders the receptor incapable* of transmitting of further impulses and to **Blocking N- Receptor Action**.

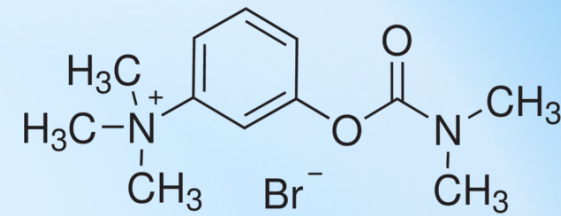
The Na⁺ channel closes or is blocked =>
=> a **Resistance to Depolarization** and **Flaccid Paralysis**.

Proserin (*Neostigmine*)– Polar Compound => does not enter **the CNS**.

Pharmacologic Effects:

- Pupil Contraction and Spasm of Accommodation
- ↑ Smooth Muscle Tonus of the Bronchi and other Internal Organs
- ↑ Secretion of the Bronchial, Digestive and Sweat Glands
- **Heart**: Bradycardia, ↓BP, Depression of Conductivity and Automatism
- **Dilation** of the **Pelvic Organs** and **Skeletal Muscles Vessels**
- ↑ **Adrenaline** Discharging
- Improvement of **Neuromuscular Transmission**

Clinical uses of Proserine:



- Myasthenia Gravis
- Glaucoma
- Intestines, Urinary, Gall Bladder Atonia
- Flaccid Paresis and Paralysis
- as Antidote in Myorelaxants and M-Cholinoblocker Poisonings

Galantamine - the alkaloid from the roots of Snowdrop – *Galanthus Woronowi*

- Penetrates into the **CNS**
- Produces **local irritative action** -
it is not used as eye drops!!

Clinical use:

- Myasthenia
- Intestines, Urinary and Gall Bladder Atonia
- **Flaccid Paresis** and **Paralysis**
- as Antidote in **myorelaxants** and **M-blockers** poisonings

Reactivators of Acetylcholinesterase:

Alloxim (*amp. 0.075 g*)

Dipiroxime (*amp. 15%-1 ml*)

Isonitrosin (*amp. 40%-3 ml*)

Special Antidotes

in Acute and Chronic poisoning with:

- Anticholinesterase Agents
- Phosphoorganic compounds:

Chlorophos, Carbophos et al.

Central M,N-Cholinoblockers:

CYCLODOL

NORAKIN

Clinical use: Parkinson's Disease
Parkinsonism

Adverse effects:

Dry Mouth, Blurred Vision, «sandy eyes»,
Tachycardia, Constipation,
Progressive Deterioration of Memory

M – CHOLINOMIMETICS

Pilocarpine – 1%-10 ml, Tab. 5 mg (0.005 g)

Aceclidine – amp. 0.2%-1ml, 3% ointment

Pilocarpine - stimulates **M-receptors** of
the Sphincter Muscles of Iris => **Miosis**

□ Intraocular Pressure

Spasm of Accommodation

Clinical Use: Glaucoma, Xerostomia

Overdose with Pilocarpine

Taking **100 mg** PO is considered fatal

Muscarinic symptoms:

Nausea, Vomiting, Diarrhea, Bronchospasm,
Involuntary Defecation and Urination,
□Bronchial and Salivary Secretions,
Respiratory Depression, Flushing,
Bradycardia, Cardiac arrest.

Treatment:

Atropine - 0.5-1 mg SC or IV

Adrenaline - 0.3-1 mg SC or IV

Lavage, then Activated Charcoal and Cathartics,
Support Respiratory and Cardiovascular System.

M - Cholinoblockers

Atropine sulfate – amp. 0,1%-1 ml

Scopolamine – amp. 0.05%-1 ml

Platyphyllin – amp. 0.2%-1 ml

Methacin – amp. 0.1%-1 ml

Ipratropium bromide (*Atrovent*) – aerosol

Pirenzepine (*Gastrozepin*) – amp. 0.5%-2 ml, Tab. 0.05

Clinical Uses of Cholinoblockers

- Hypersecretory Conditions: *Atropine sulfate, Scopolamine, Platyphyllin, Pirenzepine*
- Sinus bradycardia and AV-blockade: *Atropine*
- Preoperative use: *Atropine, Platyphyllin, Methacin*
- Motion sickness: *Scopolamine (Tab. "Aeronum")*
- Bronchospasm, Bronchial Asthma:
Ipratropium bromide

M-Cholinoblockers

Symptoms of poisoning:

► by atropine or by the plants containing it or another alkaloids with M-cholinoblocking activity:

- psycho-motor excitement, delirium, hallucinations;
- significant dilation of pupils;
- tachycardia;
- dryness and hyperemia of the skin, increase of body temperature, dryness in the mouth, impairment of swallowing, hoarse voice.

Treatment includes administration of

Antidotes - Anticholinesterase Agents:

PROSERINE (Neostigmine)

Galanthamine

Physostigmine



Atropa Belladonna



Hyoscyamus niger

N - Cholinomimetics:

Nicorette – *Chewing Tab. 2 mg and 4 mg*

Cytiton – *amp. 0.15%-1 ml*

Lobeline – *amp. 1%-1 ml*

Nicorette – exerts nicotine-replacement action.

Clinical uses:

Nicotinic abstinence at refusal from smoking

Adverse effects:

Dizziness, Hypersalivation,

Erosive-ulcerous Defeats of GIT,

Arrhythmias, Allergic Reactions.

Lobeline and Cytiton-

- **Respiratory stimulants** with **reflector type** of action

Mechanism of action: drugs stimulate **N-receptors** in **autonomic ganglia** and **carotid sinus**, which is accompanied by **Excitement** of **Respiratory, Vasomotor** and other Centers of Oblongatal Brain.

Clinical Use: Reflector Respiratory Arrest

(poisoning with Carbon Oxide, Inspiration of Irritating agents).

Ganglioblockers

1. The Quaternary Ammonium Compounds:

Benzohexonium

Pentamin

Hygronium

2. The Tertiary Ammonium Compounds:

Pirilen

Pachycarpine

3. Sulfur-containing agent - Arfonad

Myorelaxants

1. Non-depolarizing type:

Tubocurarine

Diplacin

Anatruxonium

Pipecuronium (*Arduan*)

Mellictin

2. Depolarizing type: Dythiline

3. Mix type: Dioxonium

Myorelaxation drugs (Skeletal Muscle Relaxants)

Indications for use:

- Surgical operations.
- Trachea intubation.
- Reposition of bone fragments, dislocations of joints.
- Urgent treatment of convulsions in tetanus, electroconvulsant therapy, poisoning by strychnine.
- Spastic paralyses in neurology - **MELLICTINE**.

▶ Side effects:

- **non-depolarizing drugs** - hypotension;
- **depolarizing drugs** - hypertension, tachicardia.

Treatment of overdose:

- **non-depolarising drugs** - cholinesterase inhibitors;
- **depolarising drugs** - blood transfusion (**contains the pseudo cholinesterase, which destroys a drug**).



**Thank You
for Your Attention!**

