Zaporizhzhia State Medical University
Pharmacology Department

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:

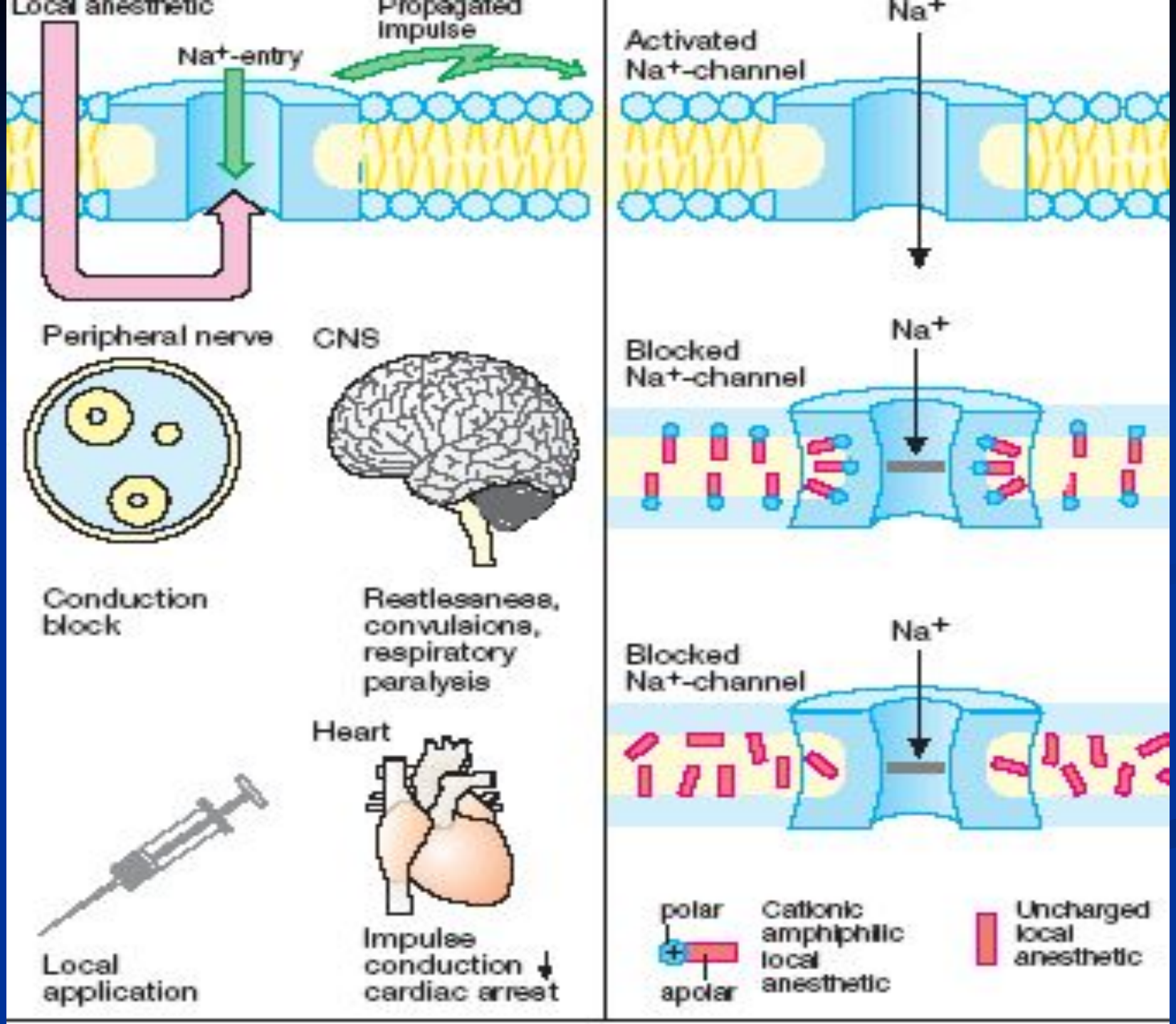
Anaesthetesine

Dicaine

Novocaine

2. Amides: Lidocaine, Trimecaine,

Ultracaine, Bupivacaine


Local anesthetic
Propagated impulse
Na+-entry
Activated Na+-channel
Na+
Peripheral nerve
CNS
Blocked Na+-channel
Na+
Conduction block
Restlessness, convulsions, respiratory paralysis
Heart
Blocked Na+-channel
Na+
Local application
Impulse conduction ↓ cardiac arrest
polar
apolar
Cationic amphiphilic local anesthetic
Uncharged local anesthetic

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.

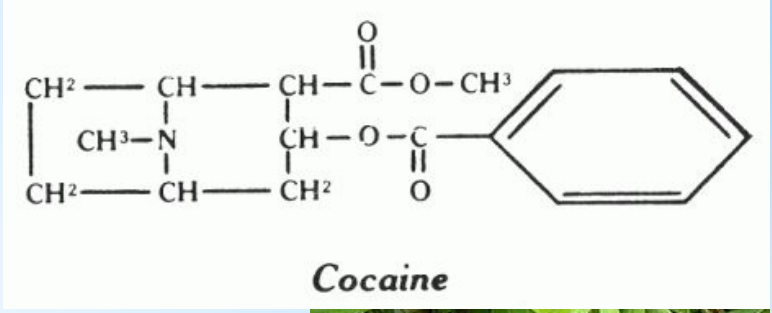
Premedication with *Diazepam* IM 0.5% solution 2 ml provides prophylaxis against seizures.

Cocaine blockades:

Noradrenaline

Serotonin

Dopamine



Cocaine

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**

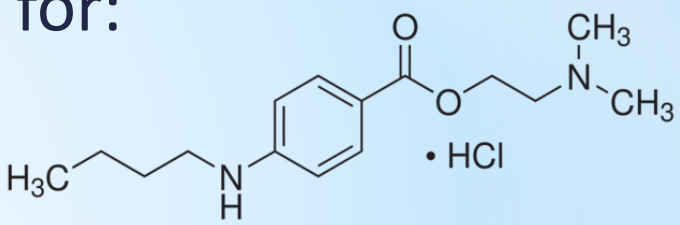
Adverse Effects of COCAINE:

1. **Anxiety Reactions:**

   BP, HR, Sweating, Paranoia.

2. **Depression Reactions**
3. **Heart Disease**
4. **Nasal Septum Necrosis**

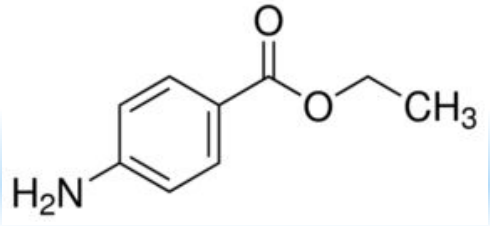
Dicaine (*Tetracaine*) is used topically for:



· Eye Mucous Anesthesia

· Throat Mucous Anesthesia

Anaesthesine (*Benzocaine*) –

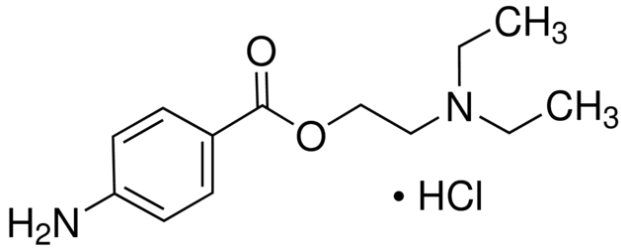


Externally: in powder, paste, ointment – on affected skin

PO: in tablets - to treat GIT disorders

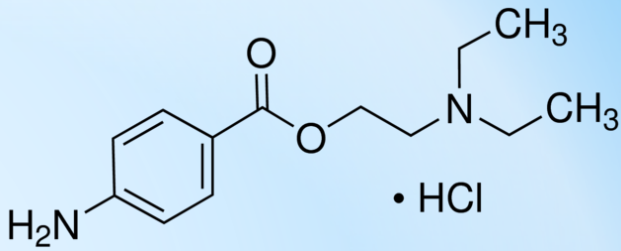
PR: in suppositories – for Fissures of Rectum and Hemorrhoid

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

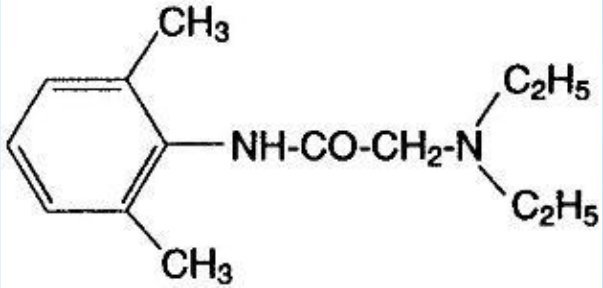
For intraspinal anesthesia:

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 **=>**

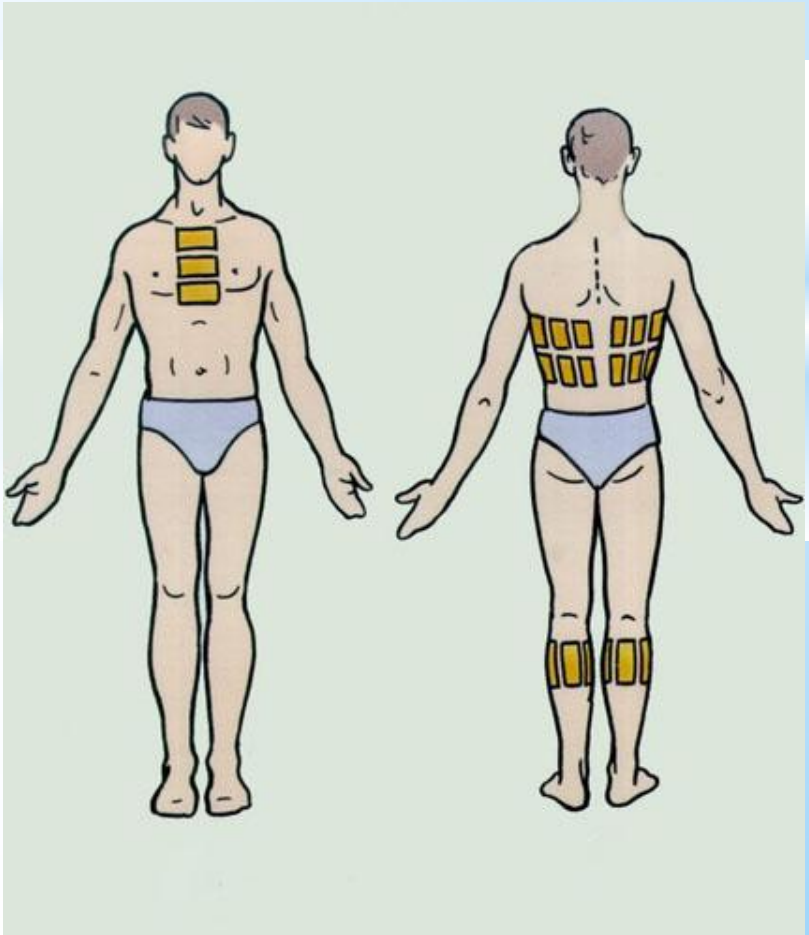
=> Inflammatory Process Shifts from **Deeper Area** to the **Surface**.

· **Reflex action**

· **Liberation of**

Morphine-like substances

in the CNS – **Encephalins** 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:

M_1 – Gastric Parietal Cells

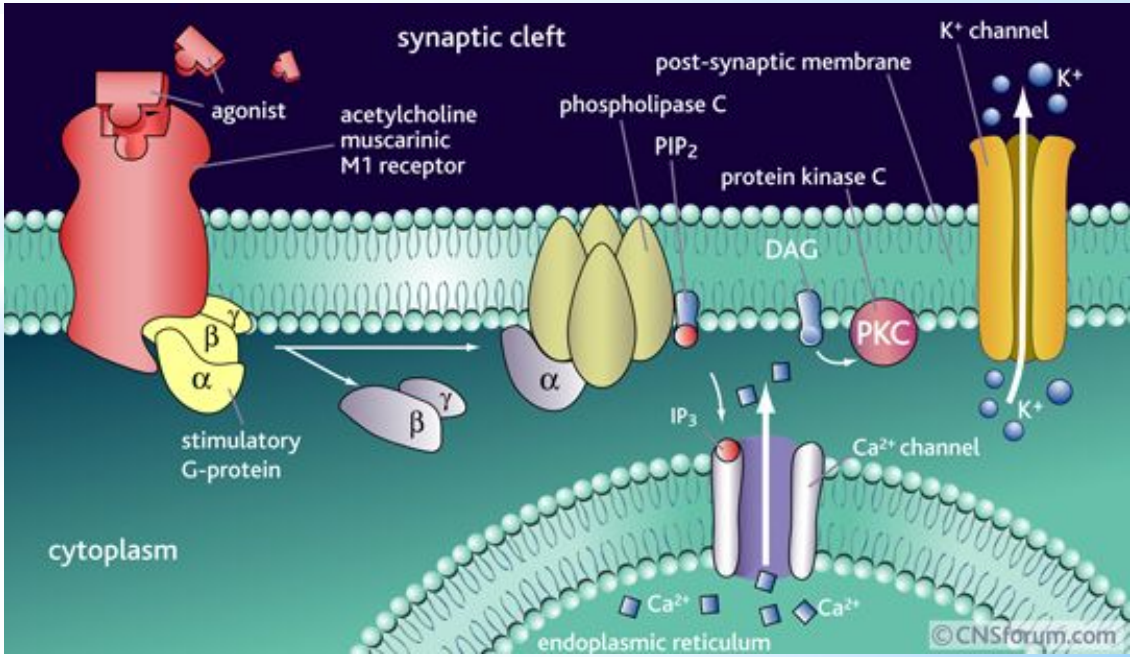
Vegetative Ganglia, CNS

M_2 – HEART

M_3 – 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

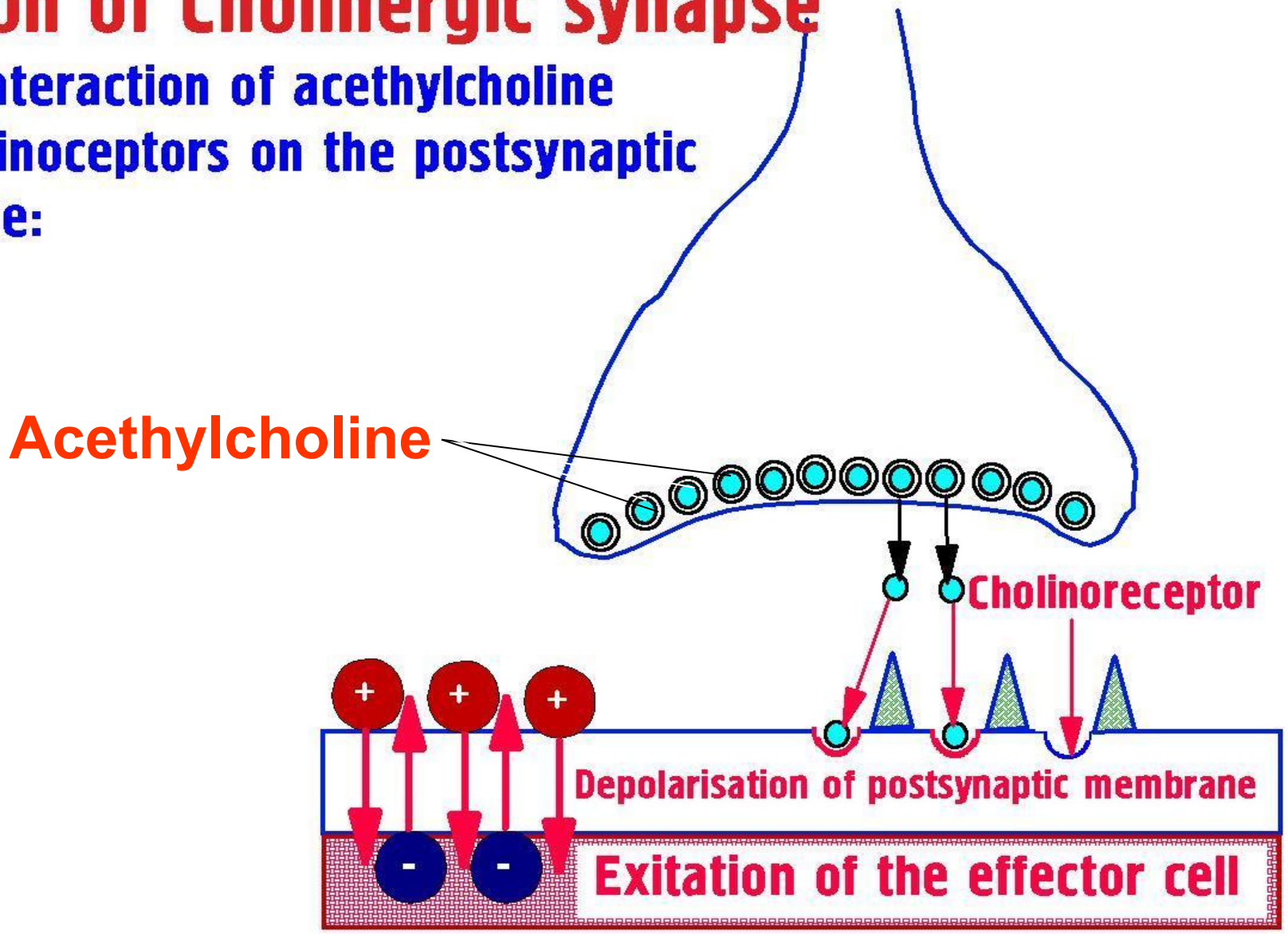
- Proserin (*Neostigmine*)
- Oxazyl
- Pyridostigmine

→ Quaternary Amines

2. Irreversible Action: Armine

Function of Cholinergic synapse

Interaction of acethylcholine with cholinoceptors on the postsynaptic membrane:



Stimulation **M_1** and **M_3** Receptors => **Stimulating Action**:

the Receptor interacts with a G_s Protein =>

Activation of **Phospholipase C** =>

Hydrolysis of **PIP_2** => **DAG** + **IP_3**

IP_3 => Ca^{2+}

PIP_2 – *Phosphatidyl-Inositol-bis-Phosphate*

DAG - *Diacylglycerol*

IP_3 - *Inositol-tris-Phosphate*

Stimulation of **M_2 Receptors** **=> Inhibiting Action**:

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

=> **Adenyl Cyclase Inhibition** =>

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

↓ Heart Rate

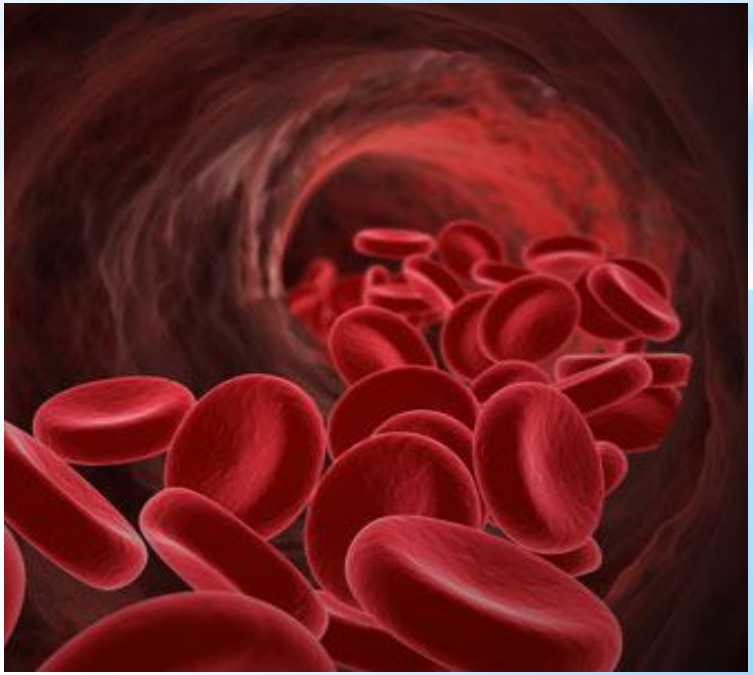
↓ Force of Heart Contraction

Stimulation of M_3 Receptors in the Blood Vessels => VASODILATION

Mechanism:

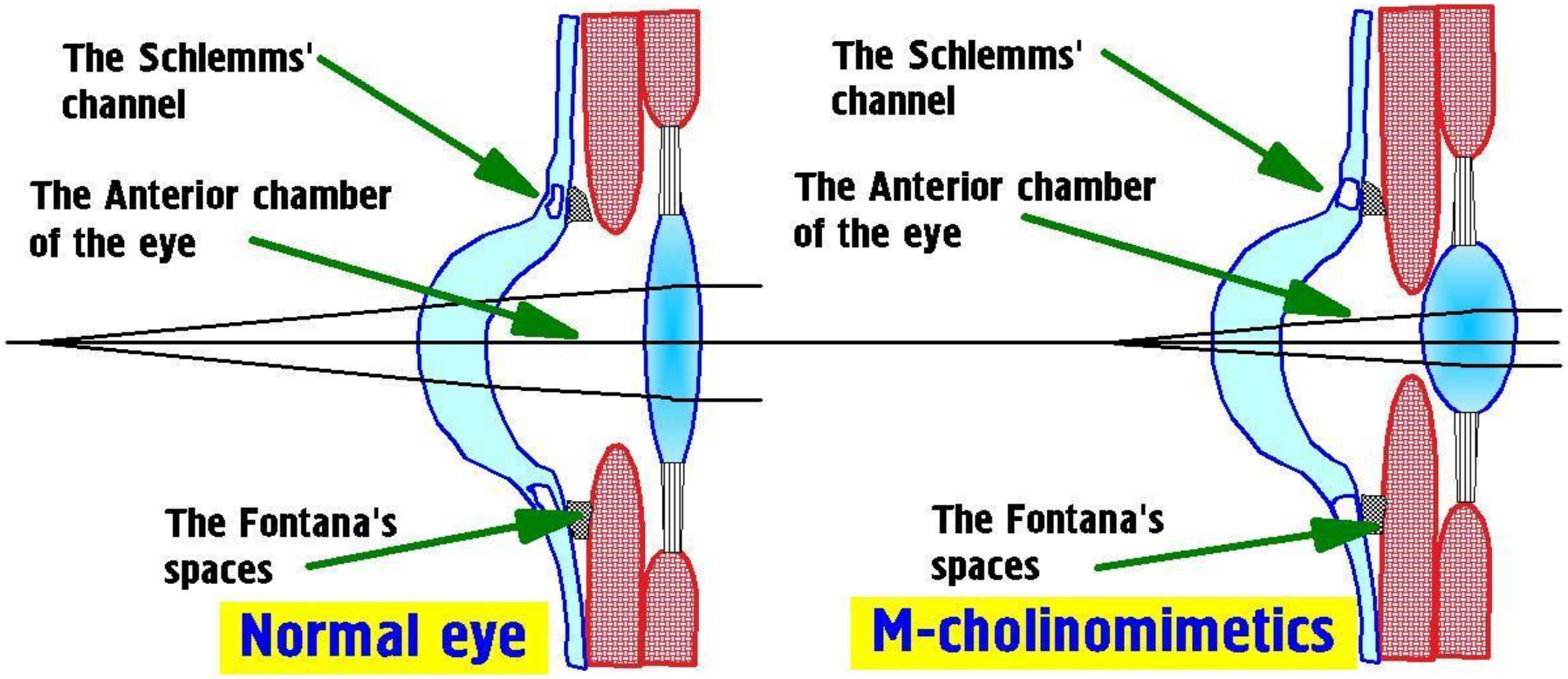
PIP_2 => DAG + IP_3 => □ Ca^{2+} =>

=> **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** =>

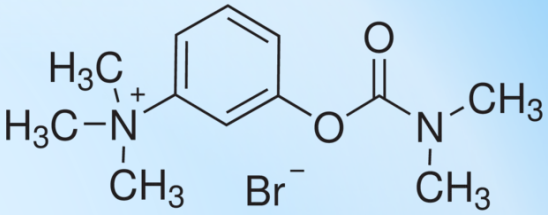
=> a **Resistance** to **Depolarization** and **Flaccid Paralysis**.

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***) – aerozol

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

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 alcaloids with M-cholinoblocking activity:
  - psycho-motor exitement, 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.

Treatmwent includes administration of

Antidotes - Anticholinesterase Agents:

PROSERINE (Neostigmine)

Galanthamine

Physostigmine

Atropa Belladonna

Hyoscuamus 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. Sulfer-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 paralises in neurology - MELLICTINE.

► Side effects:

→ non-depolarizing drugs - hypotension;

→ depolarizing drugs - hypertension, tachicardia.

Treatment of overdosage:

→ non-depolarisating drugs - cholinesterase inhibitors;

→ depolarisating drugs - blood transfusion (contains the pseudo cholinesterase, which destroys a drug).


Thank You
for Your Attention!