BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology

Course Code : BM35C7

Unit-2

Pharmacology of Peripheral Nervous System - Part 3

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Guest Lecturer

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LOCAL ANESTHETICS

Local anesthetic

- Cocaine, was serendipitously discovered late 19th century.
- Cocaine - leaves of the coca shrub (Erythroxylon coca).
- For centuries, Andean natives have chewed an alkali extract of these leaves for its stimulatory and euphoric actions.
- When, in 1860, ALBERT NIEMANN isolated cocaine, he tasted his newly isolated compound, noted that it numbed his tongue, and a new era began.
- Sigmund Freud studied cocaine's physiological actions, and Carl Koller introduced cocaine into clinical practice in 1884 as a topical anesthetic for ophthalmological surgery.

Local anesthetic (LA)

- Topical application or local injection cause reversible
- Loss of sensory perception, pain, in a restricted area
- Block generation and conduction of nerve impulse
- Sensory but also motor impulses are interrupted

  when a LA is applied to a mixed nerve

  resulting in muscular paralysis

  loss of autonomic control as well

CLASSIFICATION

Injectable anaesthetic

Low potency, short duration

- Procaine
- Chloroprocaine

Intermediate potency and duration

- Lidocaine (Lignocaine)
- Prilocaine

High potency, long duration

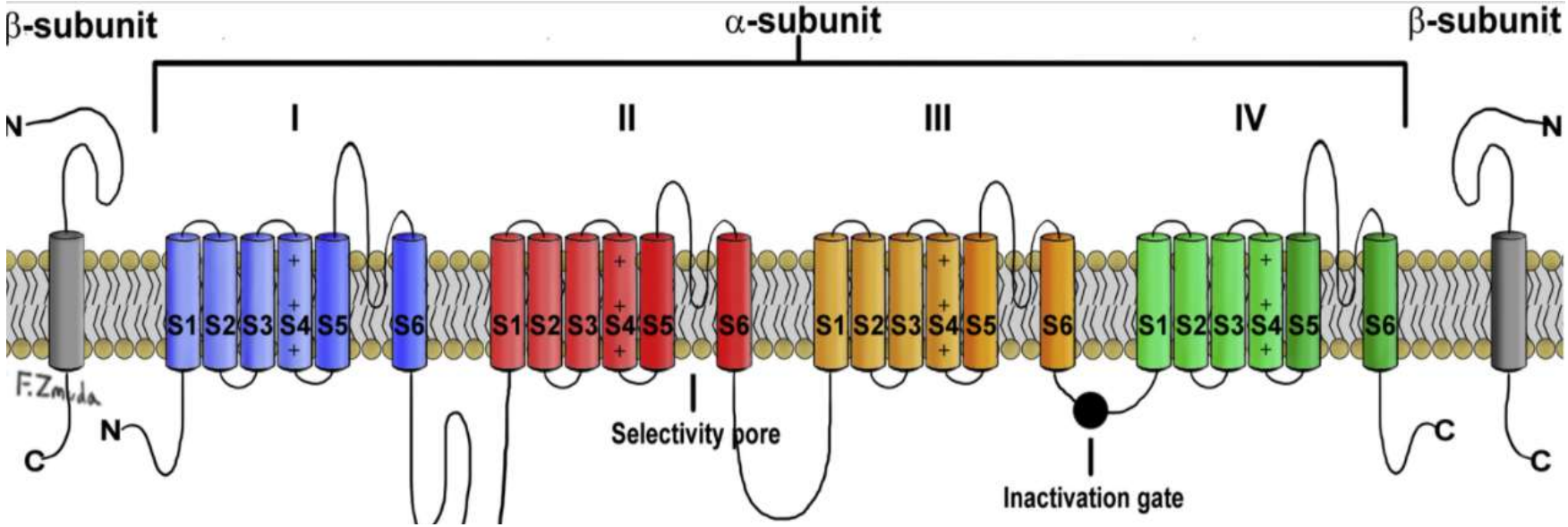
- Tetracaine (Amethocaine)
- Bupivacaine
- Ropivacaine
- Dibucaine (Cinchocaine)

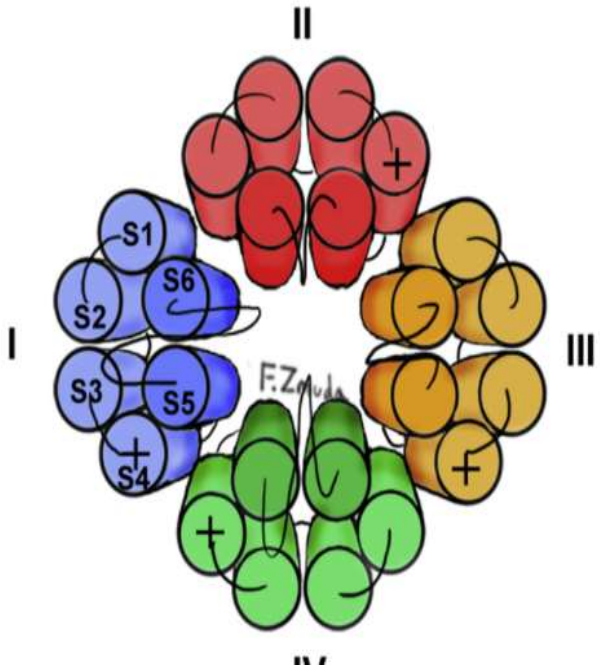
Surface anaesthetic

Soluble	*Insoluble*
Cocaine	Benzocaine
Lidocaine	Butylaminobenzoate (Butamben)
Tetracaine	
Benoxinate	Oxethazaine

	General anaesthesia	*Local anaesthesia*
1. Site of action	CNS	Peripheral nerves
2. Area of body involved	Whole body	Restricted area
3. Consciousness	Lost	Unaltered
4. Care of vital functions	Essential	Usually not needed
5. Physiological trespass	High	Low
6. Poor health patient	Risky	Safer
7. Use in non-cooperative patient	Possible	Not possible
8. Major surgery	Preferred	Cannot be used
9. Minor surgery	Not preferred	Preferred

- Neuronal Na+ channel is a 300 KD glycoprotein (Alpha and beta)
- Na+ selective pore within its **4 HOMOLOGOUS DOMAINS (I TO IV),** each domain has 6 membrane spanning helical segments (S1 to S6) connected alternately by intracellular and extracellular loops.
- The wall of the pore is formed by all four **S5-S6 segments**, while the short non helical loops connecting S5-S6 on the extracellular surface fold into the pore and serve as the **ACTIVATION GATE**.
- Voltage sensors located in the **S4 segments** move vertically on depolarization and **open the activation gate by allosteric conformational change.**
- A few msec later, the short **INTRACELLULAR LOOP** connecting domains **III and IV** folds into the inner mouth of the pore **INACTIVATING THE CHANNEL**.
- The LA receptor is located in the **S6** segment of domain **IV.**
- Channel activation either transforms the LA receptor to a higher affinity conformation.


β-subunit
α-subunit
β-subunit
I
II
III
IV
N
N
C
C
S1 S2 S3 S4 S5 S6
S1 S2 S3 S4 S5 S6
S1 S2 S3 S4 S5 S6
S1 S2 S3 S4 S5 S6
Selectivity pore
Inactivation gate


II
I
III
S1
S6
S2
S3
S5
S4

Na+ channel has an **activation gate ('m' gate)** near its extracellular

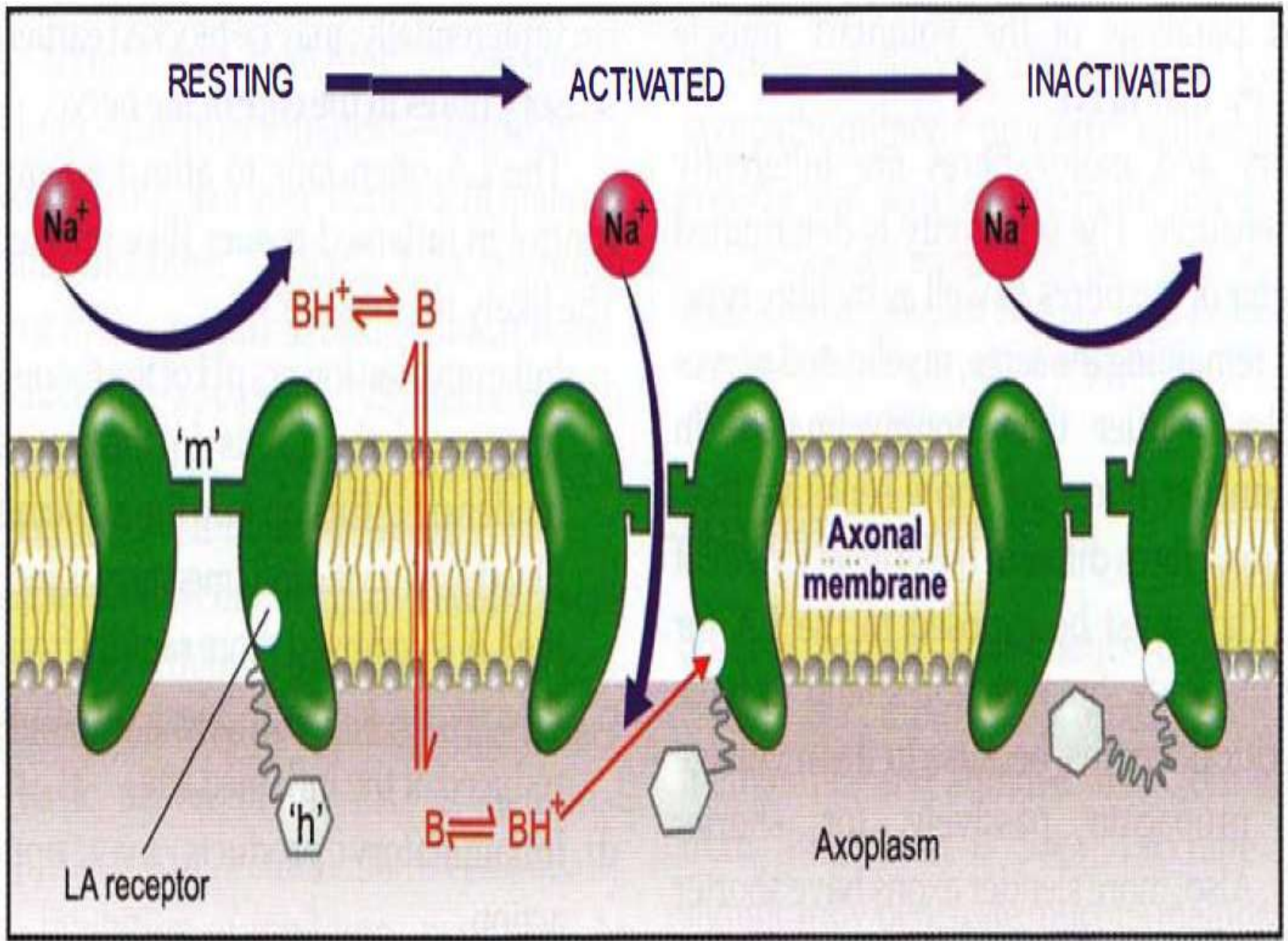
Inactivation gate ('h' gate) at the intracellular

In the resting state the activation gate is **Closed.**

Threshold depolarization of the membrane **Opens** the activation gate allowing Na+ ions to flow in along the concentration gradient.

Within a few msec, the inactivation gate **Closes** and ion flow ceases.

The channel recovers to the Resting State in a time-dependent manner.


RESTING
ACTIVATED
INACTIVATED
Na+
Na+
Na+
BH+ ⇌ B
'm'
'h'
B ⇌ BH+
Axonal membrane
LA receptor
Axoplasm

Local anaesthetic (LA) receptor

- Located within the channel in its intracellular half.
- The LA traverses the membrane in its **UNIONIZED LIPOPHILIC FROM** (B), reionizes in the axoplasm and approaches the LA receptor through the intracellular mouth of the channel.
- Cationic form (BH+) of the LA binds to the receptor.
- The receptor has higher affinity LA in the activated state
- Stabilizes the channel in the inactive state
- **Thus reduces the probability of channel opening.**

Pharmacological Action

The clinically used LAs have no / minimal local irritant action

BLOCK

sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse and receptors

i.e. structures which function through increased Na+ permeability.

They also reduce release of acetylcholine from motor nerve endings.

- LA act prevent the generation and the conduction of nerve impulses.

- Local anesthetics block conduction by **decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane.**

- This action of local anesthetics is due to their direct interaction with voltage-gated Na+ channels.

- **CNS:** At high doses or on inadvertent i.v. they decrease automaticity, excitability, contractility, conductivity and increase effective refractory period (ERP).

- **CVS:** All LAs are capable of producing a sequence of stimulation followed by depression.

C.N.S.

- All LAs are capable of producing a sequence of stimulation followed by depression.
- **Cocaine -euphoria-excitement-mental confusion-restlessness-tremor - twitching of muscles- convulsions-unconsciousness-respiratory depression--death, in a dose-dependent manner.**
- **Procaine and other synthetic LAs** are much less potent in this regard
- **Lidocaine,** on the contrary, can initially cause drowsiness and lethargy, but higher doses produce excitation followed by depression

Absorption, fate and excretion:

- Local anaesthetics are **not absorbed from unbroken skin.**
- Absorption is more rapid from the **trachea than from the pharynx**
- When used by infiltration, the absorption can be retarded by combining it with a **vasoconstrictor agent like adrenaline.** (1:50,000 to 1:200,000):
- Esters and are metabolised by **hydrolysis in both the liver and plasma**.
- The amide-like LA such as lignocaine are **dealkylated by the liver.**

- The LA often fails to afford adequate pain control in inflamed tissues (like infected tooth).

➢ Inflammation **lowers pH** of the tissue-greater fraction of the LA is in the ionized form hindering diffusion into the axolemma.

➢ **Blood flow increased** the LA is removed more rapidly from the site.

➢ Effectiveness of **Adr injected with the LA** is reduced

➢ **Inflammatory products** may oppose LA action.

Topical Anesthesia

- Anesthesia of mucous membranes of the **nose, mouth, throat, tracheobronchial tree, esophagus, and genitourinary tract**
- Direct application of aqueous solutions of salts LA
- By suspension of the poorly soluble local anesthetics.

Surface anaesthesia

Amethocaine

(Eye, throat, urethra, rectum and skin)

Benzocaine and lidocaine hydrochloride

(All purpose except for eye)

Dibucaine

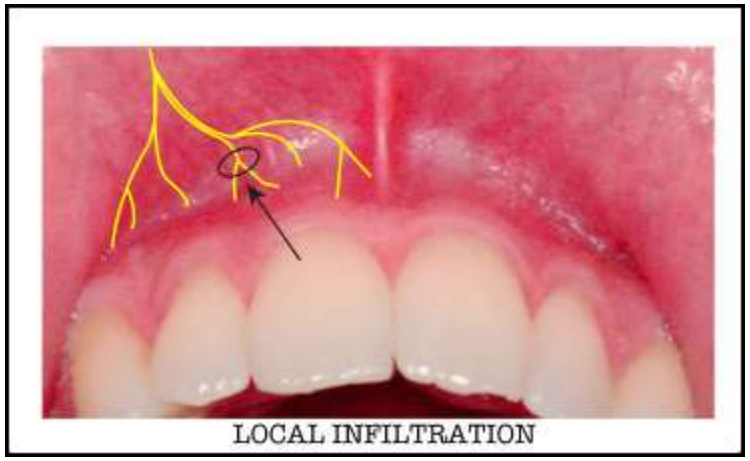
(ear, rectum skin)

Proparacaine and tetracaine

(Exclusively for the eye)

Infiltration anesthesia

- **The nerve endings are anaesthetised by their** direct exposure drug.
- The drug is infiltrated subcutaneously.
- Procaine 2% and lignocaine 2%
- They are mixed with adrenaline (1:200,000)prolong action.



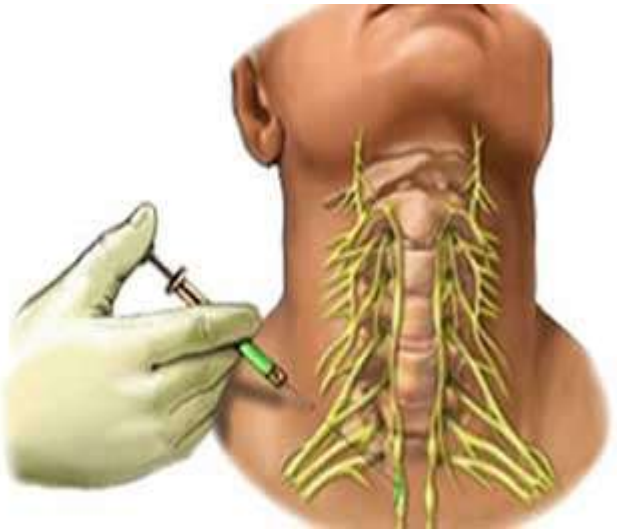
Nerve Block Anesthesia

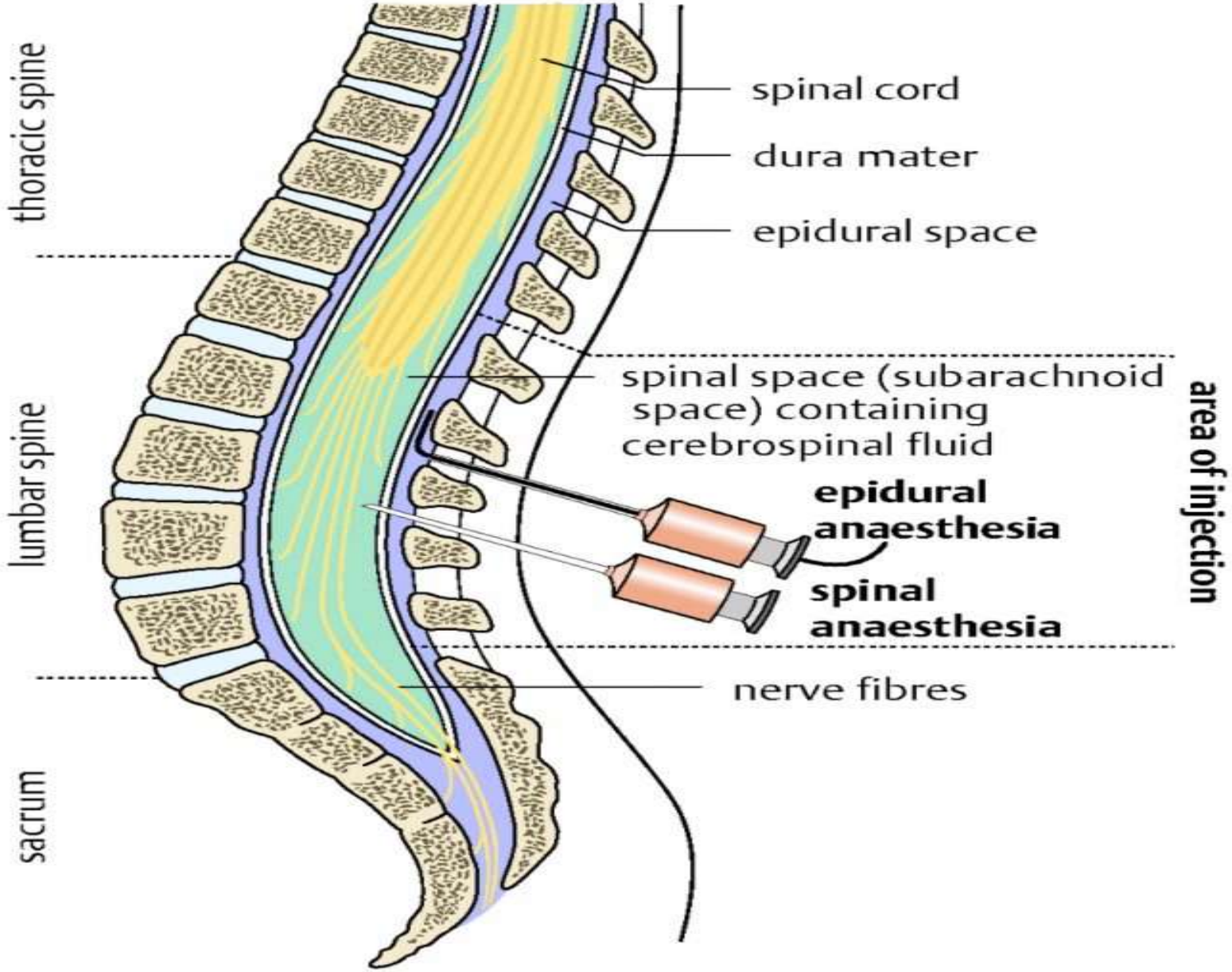
- Injection of a solution of a local anesthetic into or about individual peripheral nerves or nerve plexuses produces even greater areas of anesthesia than do the techniques already described.
- Blockade of mixed peripheral nerves and nerve plexuses also usually anesthetizes somatic motor nerves, producing skeletal muscle relaxation, which is essential for some surgical procedure

Nerve block or conduction block

Injected very close to the nerve

e.g. brachial plexus.




thoracic spine
lumbar spine
sacrum
spinal cord
dura mater
epidural space
spinal space (subarachnoid space) containing cerebrospinal fluid
epidural anaesthesia
spinal anaesthesia
nerve fibres
area of injection

Spinal anaesthesia

- Inj. into the **subarachnoid space.**
- Its level in the space is adjusted by using solutions with higher (hyperbaric) or lower (hypobaric) specific gravity than that of CSF, as vehicles.
- **‘heavy’** by adding dextrose or **‘light’** by adding saline.
- Lignocaine and bupivacaine
- Injected outside the **dura**, **epidural anaesthesia.**
- **A**naesthetic is restricted to a specific region

Acute ADR

(a) Allergic reactions.

(b)Activation of sympathetic nervous system produces vasoconstriction, an acute rise in **BP, tachycardia** and a predisposition to **acute myocardial infarction**, **ventricular arrhythmias** and **convulsions.** It may also result in **mydriasis, hyperglycemia and hyperthermia**.

(c) **Since it is metabolised by plasma and liver cholinesterases,** people with deficiency of these enzymes (liver disease), infants, pregnant women and old persons are at greater **risk of cocaine toxicity.**

Chronic ADR

- **Sexual dysfunction**
- **Anorexia,** disturbances of sensation and emotion, hallucinations and insanity are observed in cocaine addicts.
- Cocaine when used by pregnant women may cause **prematurity, intrauterine growth retardation and microcephaly.**
- It has teratogenic effects on brain development.
- It can cause neurological symptoms including **sudden death** in the newborn.

PROCAINE

- It is the **diethyl aminoethyl ester of para aminobenzoic acid.**
- It is nonirritant and as effective as cocaine as a local anaesthetic, but is much less toxic.
- It is a vasodilator.
- Its disadvantages are that it is **poorly absorbed from the mucous membranes and,** therefore, has no topical use.
- It is rapidly **hydrolysed by esterases in the plasma and liver** and is partly excreted in the urine, conjugated with glucuronic acid and glycine.

LIGNOCAINE (Lidocaine)

This is the most commonly employed local anaesthetic.

It is stable, can be stored for a **long time at room temperature** and can be autoclaved.

It has a **quick onset of action** and a **high degree of penetration.**

Its toxicity is similar to that of other LA

It is also an excellent surface anaesthetic.

Skeletal muscle relaxants

- Help to reduce **unwanted spasm or spasticity** without interfering with consciousness and normal voluntary movements
- They have important application in various **neurological or painful musculo-skeletal disorders.**
- They are also valuable, **during surgery for achieving satisfactory muscle relaxation.**

- Spasticity is due to **increase in skeletal muscle tone associated with decrease in muscle power**
- Due to damage to the **corticomoto-neuronic pathways as in cerebral palsy**, **multiple sclerosis**, CNS injury or stroke.
- **Spasm, involuntary contraction of** a muscle or group of muscles, usually accompanied by pain and limited function.

Neuromuscular blocking agents

Nondepolarizing (Competitive) blockers

Long acting

d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium

Intermediate acting

Vecuronium, Atracurium, Cisatracurium, Rocuronium, Rapacuronium

Short acting

Mivacurium

Depolarizing blockers

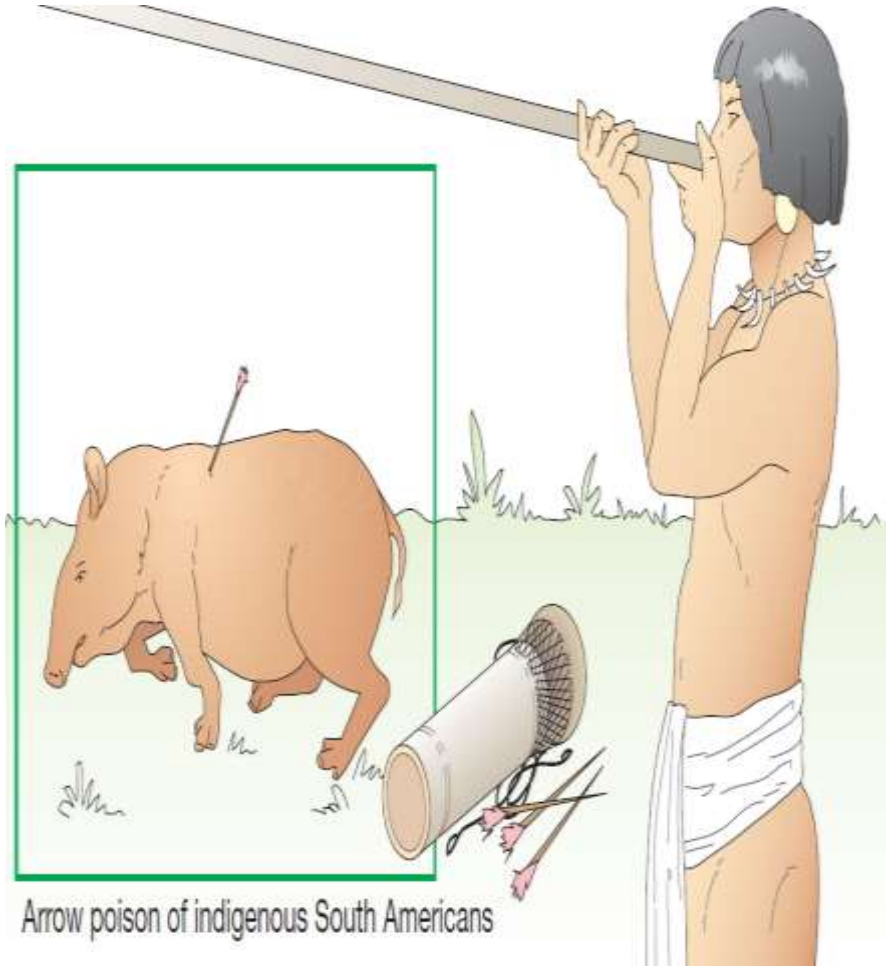
Succinylcholine, Decamethonium

Directly acting agents

Dantrolene sodium Quinine

CURARE

- South American tribals as **arrow poison** for game hunting.
- The animals got paralysed even if not killed by the arrow.
- Natural sources of curare are **Strychnos toxifera, Chondrodendron tomentosum** and related plants.

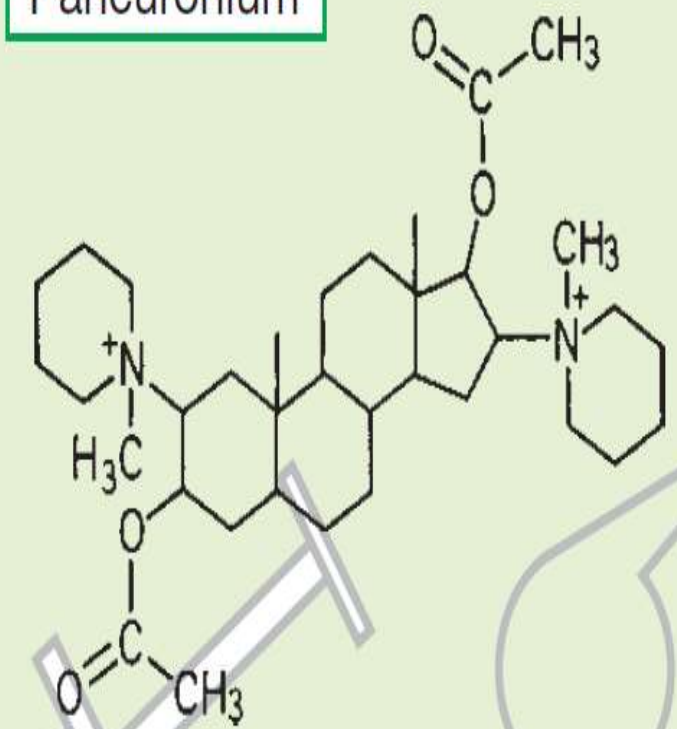


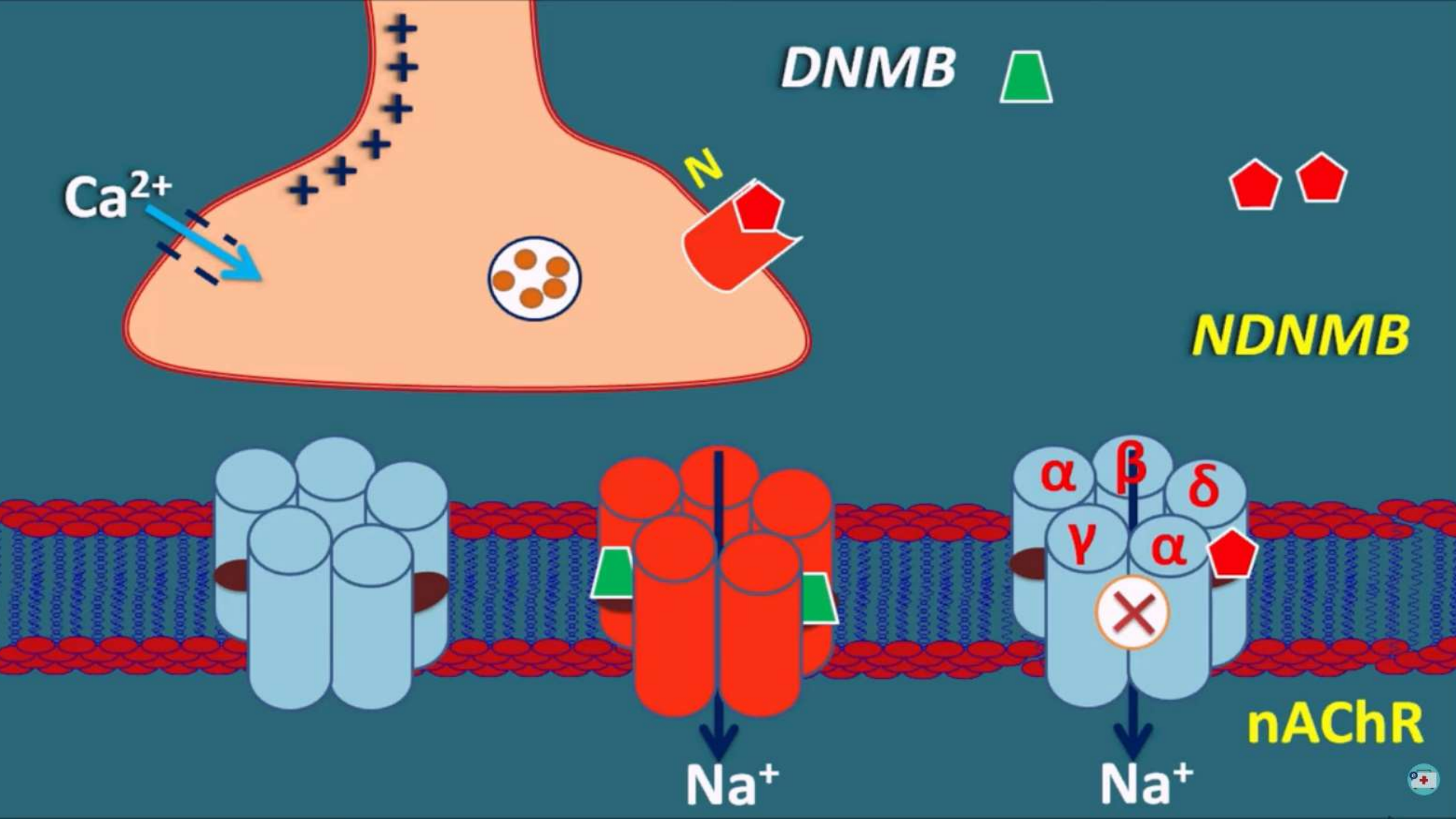
Arrow poison of indigenous South Americans

d-Tubocurarine

(no enteral absorption)

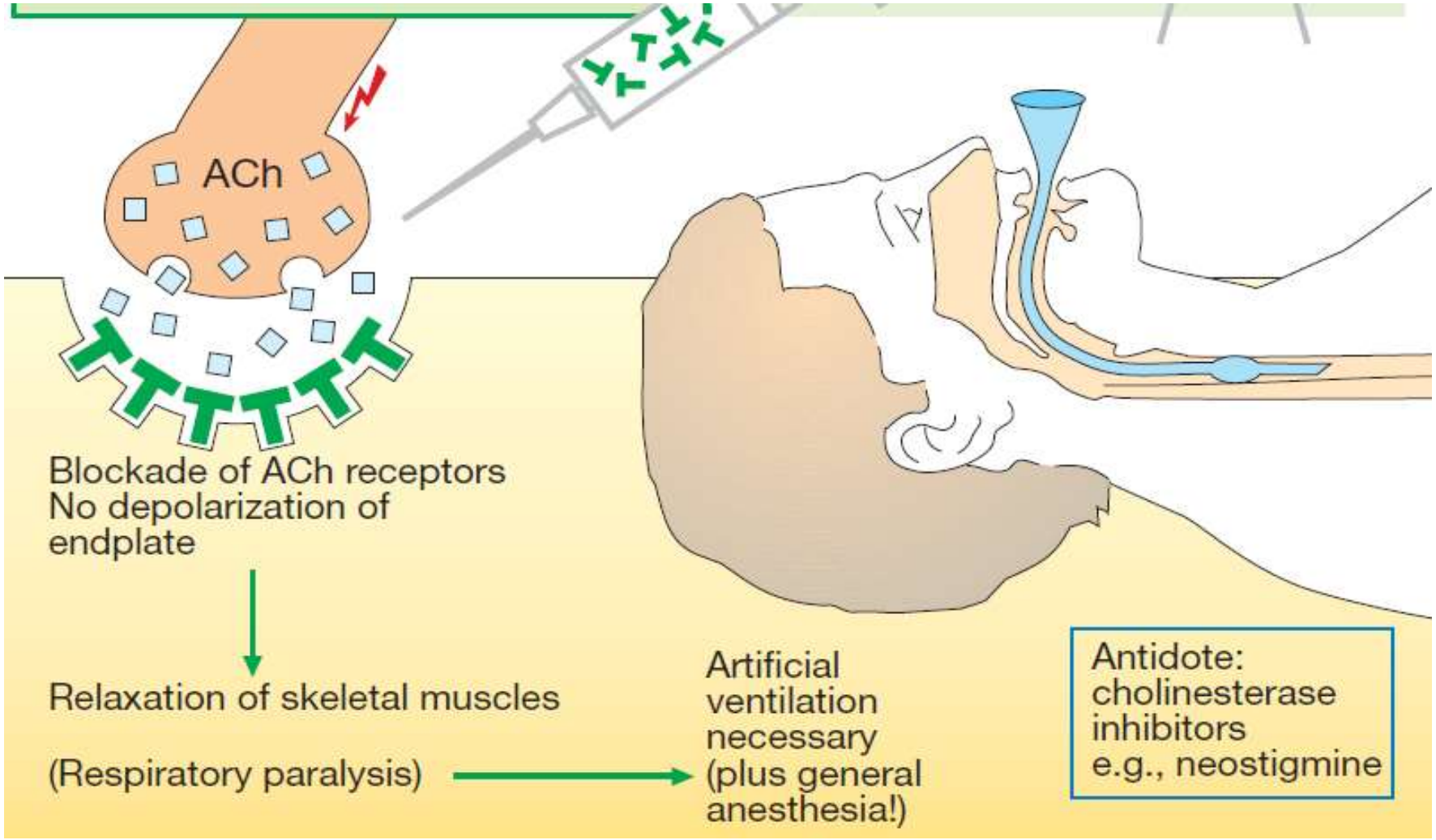
Pancuronium




DNMB
N
Ca2+
NDNMB
α
β
δ
γ
α
nAChR
Na+
Na+

- ACh released from motor nerve endings is not able to combine with its receptors to generate end plate potential (EPP).
- When EPP falls critical level it is unable to trigger muscle action potential (MAP) and muscle fails to contract in response to nerve impulse.
- **Curare like drugs enter the Na+ channels** and **directly block them to produce more intense noncompetitive neuromuscular block** that is only partly reversed by **neostigmine**

Non-depolarizing muscle relaxants



Competitive Blockers

- Block prejunctional nicotinic receptors located on motor nerve endings.
- Since activation of these receptors by ACh normally facilitates mobilization of additional quanta of ACh from the axon to the motor nerve endings, their blockade contributes to depression of neuromuscular transmission.
- Accordingly, the competitive blockers exhibit the 'fade' phenomenon
- i.e. twitch responses during partial block are progressively depressed on repetitive stimulation.

Competitive Blockers

Do not dissociate rapidly from the Receptor

↓

induce prolonged partial depolarization

↓

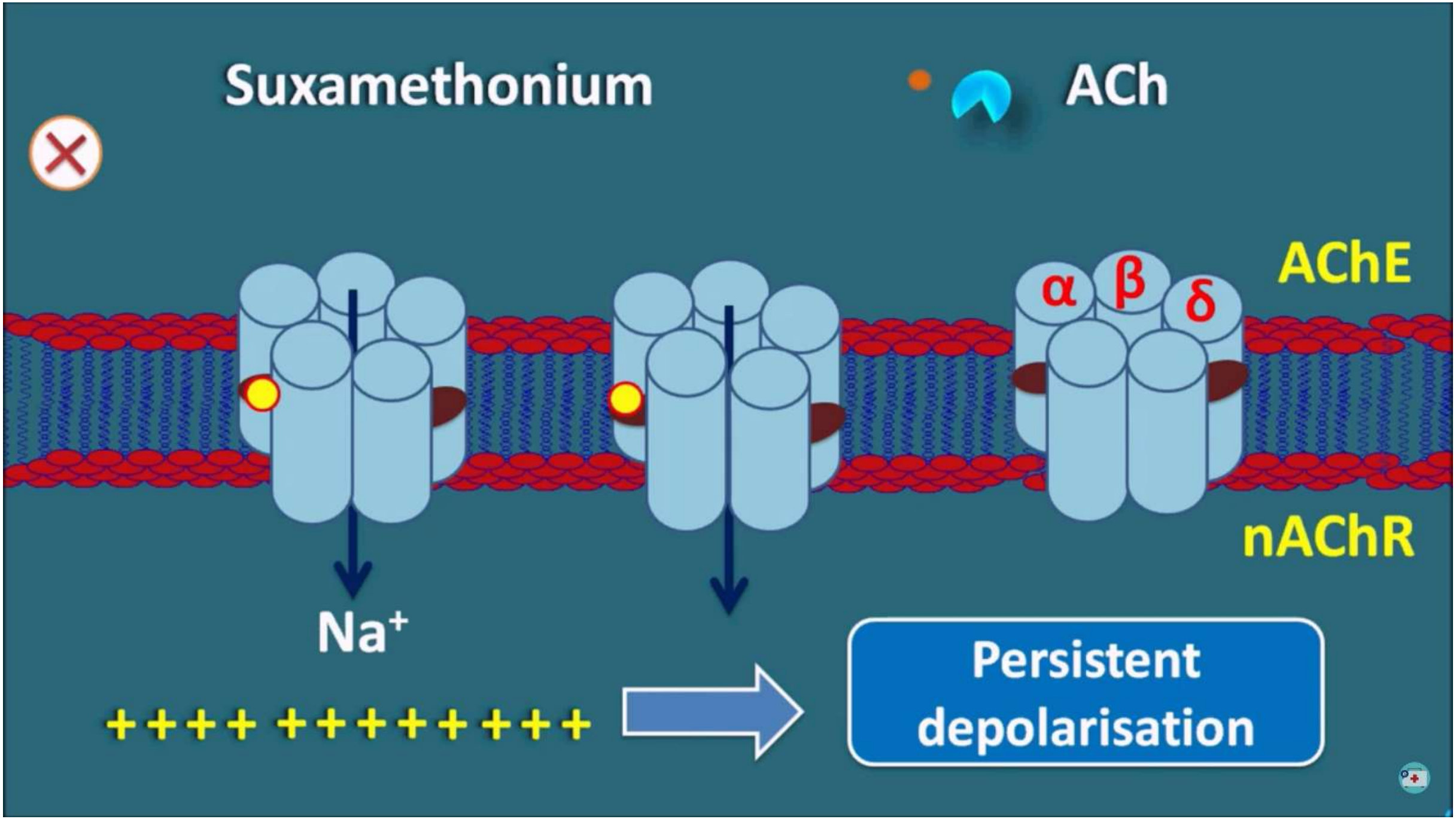
Na + channels get inactivated

↓

ACh released from motor nerve endings is unable to generate propagated MAP

↓

flaccid paralysis in mammals.


Suxamethonium
ACh
AChE
α
β
δ
nAChR
Na+
++++ +++++++++
Persistent depolarisation

Skeletal muscles

I.V inj nondepolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis.

Fingers, Extraocular, hands, feet-arm, leg, neck, face, trunk, intercostal muscles, diaphragm, respiration stops

RS:

d-TC releases histamine from mast cells.

Bronchospasm and increased respiratory secretions

C.V.S.

d-Tubocurarine produces significant fall in BP.

(a) ganglionic blockade

(b) histamine release

(c) reduced venous return-a result of paralysis of limb and respiratory muscles

Prolonged administration of SCh - Cardiac arrhythmias

- **G.I.T.**

  The ganglion blocking activity - Postoperative

  paralytic ileus after abdominal operations.
- **C.N.S.**

  All neuromuscular blockers are quaternary compounds-do not cross blood-brain barrier.

Pharmacokinetics

- i.v.,
- Muscles with higher blood flow receive more
- Redistribution to non-muscular tissues plays a significant role in the termination of surgical grade muscle relaxation,
- The duration of action is directly dependent on the elimination
- Metabolized in the plasma/liver
- Excreted in urine as well as in bile.

INTERACTIONS

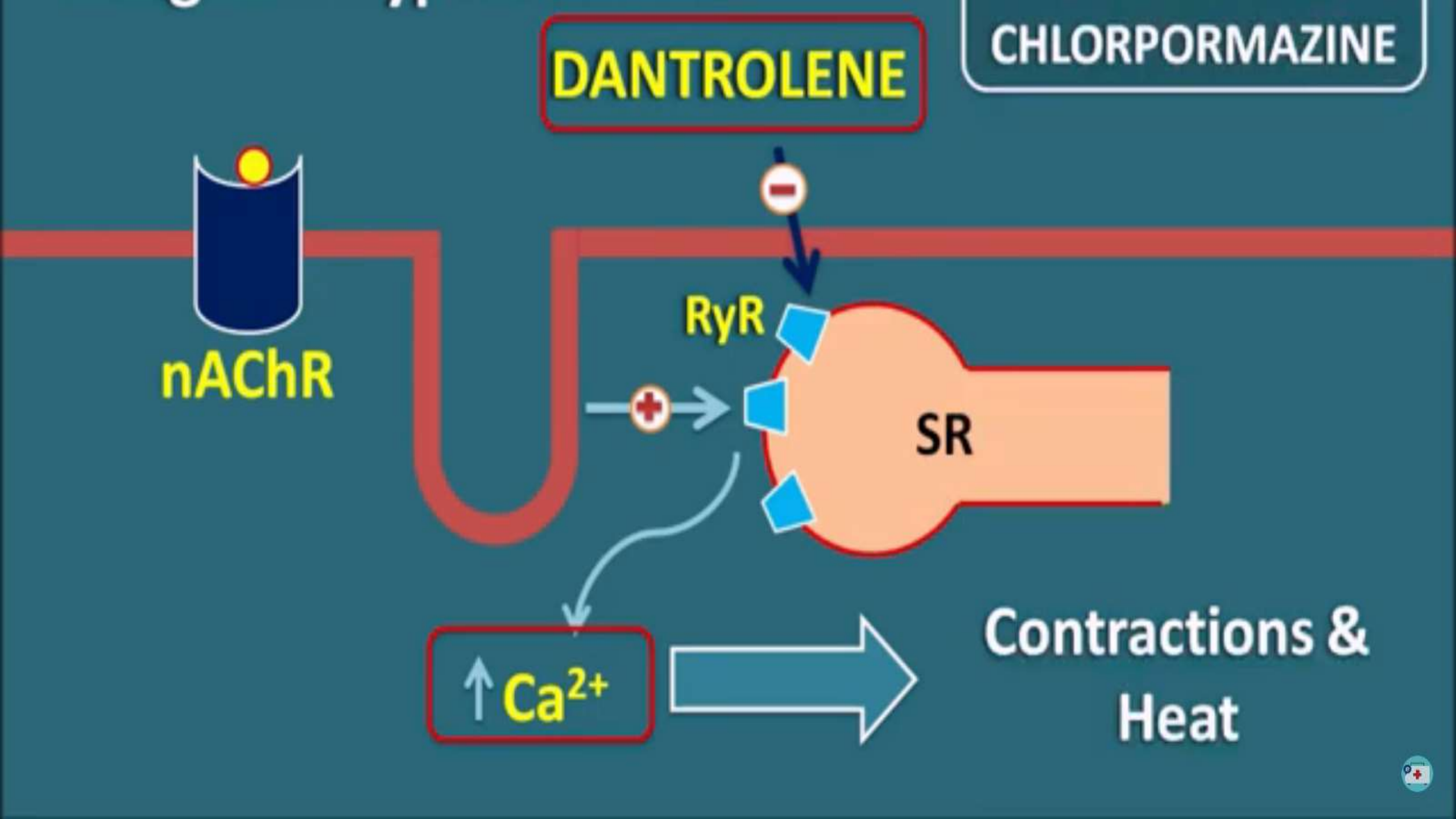
- Thiopentone sodium
- General anaesthetics
- Anticholinesterases
- Antibiotics
- Calcium channel blockers
- Diuretics
- Diazepam, propranolol and quinidine

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene acts on the **RyR (Ryanodine Receptor)**

Calcium channels in the sarcoplasmic reticulum of skeletal muscles

Prevents their depolarization triggered opening.


DANTROLENE
CHLORPORMAZINE
nAChR
RyR
SR
↑Ca2+
Contractions &
Heat

USES

- **Reduce reflex muscle contraction** in the region undergoing surgery, and assist maintenance of controlled ventilation during anaesthesia.
- Abdominal and thoracic surgery, intubation and endoscopies, orthopedic manipulations, etc.
- **SCh** - endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocations, and to treat laryngospasm.

- Used orally dantrolene (25-100 mg QID) reduces spasticity in upper motor neurone disorders, **hemiplegia, paraplegia, cerebral palsy and multiple sclerosis.**
- Given **orally,** it is incompletely (about 1/3rd) absorbed and is largely **metabolised in the liver.**
- It can also be given IV. Dose: **25 mg/d**, increased weekly to a maximum of **100 mg bid or qid**

Adverse effects

- **Muscular weakness** is the dose limiting side effect.
- **Sedation, malaise, light headedness**
- Troublesome **diarrhoea**
- Long term use **liver toxicity**

Centrally acting muscle relaxants

- Cause **muscular relaxation without loss of consciousness.**
- CNS like **cortex, brain stem and spinal cord.**
- Depression of polysynaptic spinal and supraspinal reflexes, especially of the reticular system, controlling the muscle tone

- **Antispastic agents:**

  Prescribed for conditions such as cerebral palsy and multiple sclerosis:

  Diazepam, Baclofen, Dantrolene.

- **Antispasmodic agents:**

  Prescribed for musculoskeletal conditions

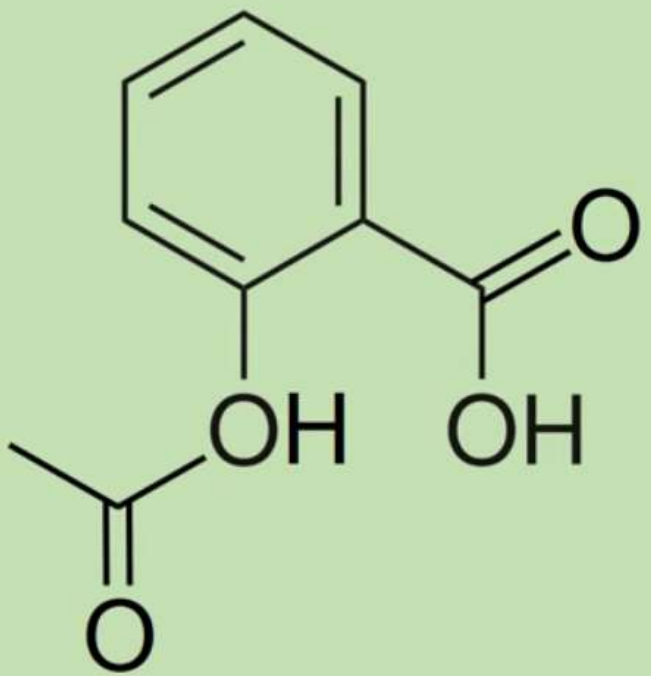
  Cyclobenzaprine, Tizanidine, Diazepam, Metaxalone, Methocarbamol, Orphenadrine, Carisoprodol, Chlorzoxazone.

BACLOFEN

- **This compound, beta-4 (chlorophenyl) - gamma aminobutyric acid,**
- Is structurally related to inhibitory neurotransmitter, GABA.
- It is a selective **GABA B receptor agonist**, mainly acting, on **presynaptic receptors in the spinal cord** rather than on post synaptic GABA B receptors.
- It depresses the reflexes by **reducing the calcium influx** and thereby prevents **release of excitatory neurotransmitters**.

Analgesic, Antipyretic and Anti-inflammatory actions

Charles Frédéric Gerhardt
First Scientist to Make
Aspirin (in 1853)



Acetylsalicylic Acid
(Aspirin)

Felix Hoffmann
First Scientist to Make
Pure Aspirin (in 1897)

- Willow bark (Salix alba) had been used for many centuries.
- Salicylic acid was prepared by hydrolysis of the bitter glycoside obtained from this plant.
- Sodium salicylate was used for fever and pain in 1875; Led to the introduction of acetylsalicylic acid (aspirin) in 1899.
- Phenacetin and antipyrine were also produced at that time.
- The next major advance was the development of phenylbutazone in 1949 having antiinflammatory activity almost comparable to corticosteroids.
- The term Nonsteroidal Antiinflammatory Drug (NSAID) was coined to designate such drugs. Indomethacin was introduced in 1963

Analgesic, Antipyretic and Antiinflammatory actions

- In contrast to morphine they do not depress CNS, do not produce physical dependence, have no abuse liability and are weaker analgesics (except for inflammatory pain).
- They are also called nonnarcotic, nonopioid or aspirin-like analgesics.
- They act primarily on peripheral pain mechanisms, but also in the CNS to raise pain threshold.
- They are more commonly employed and many are over-the counter drugs

CLASSIFICATION

A. *Nonselective COX inhibitors (traditional NSAIDs)*

1. *Salicylates*: Aspirin.
2. *Propionic acid derivatives*: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. *Anthranilic acid derivative*: Mephenamic acid.
4. *Aryl-acetic acid derivatives*: Diclofenac, Aceclofenac.
5. *Oxicam derivatives*: Piroxicam, Tenoxicam.
6. *Pyrrolo-pyrrole derivative*: Ketorolac.
7. *Indole derivative*: Indomethacin.
8. *Pyrazolone derivatives*: Phenylbutazone, Oxyphenbutazone.

B. *Preferential COX-2 inhibitors*

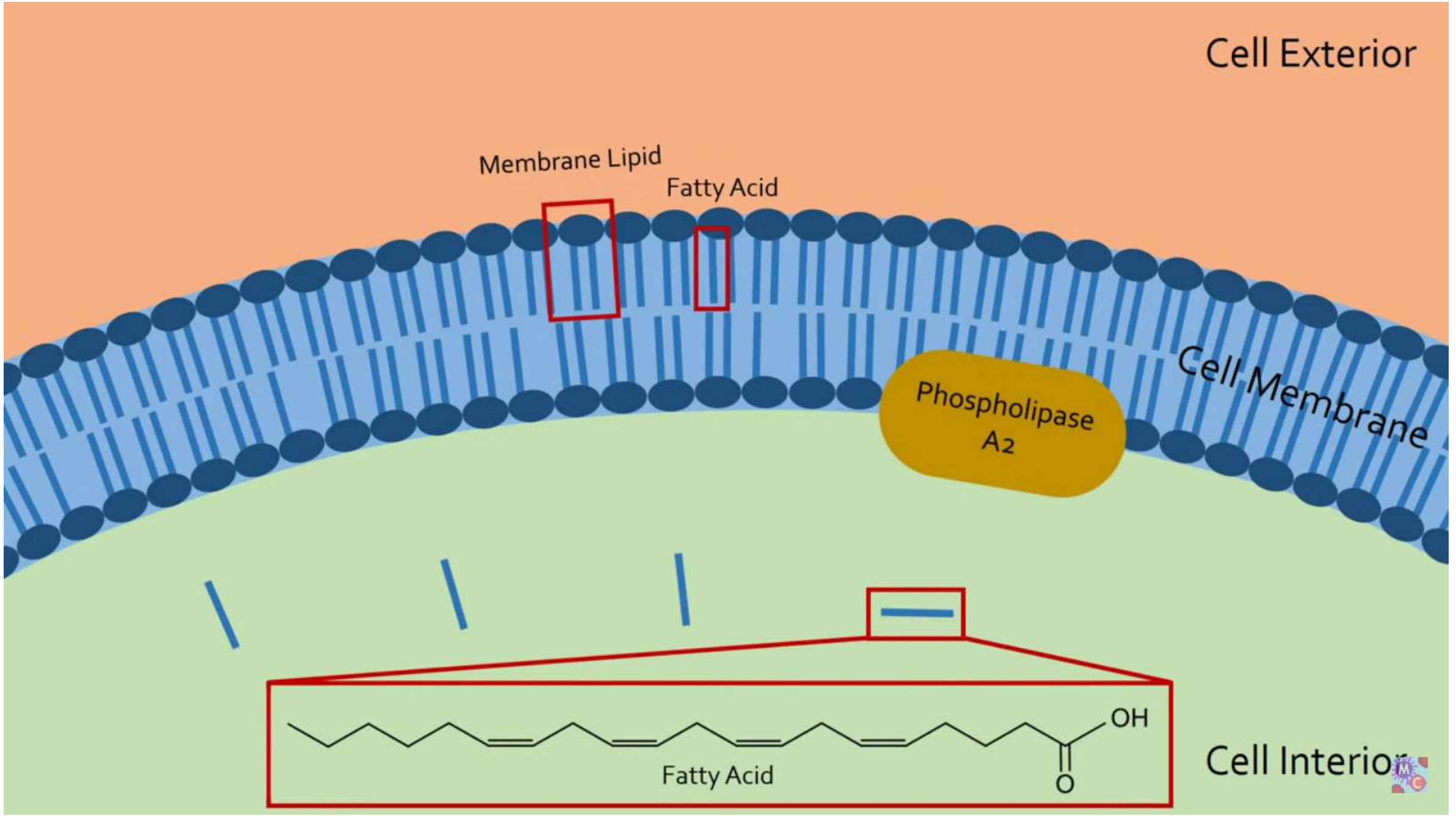
Nimesulide, Meloxicam, Nabumetone.

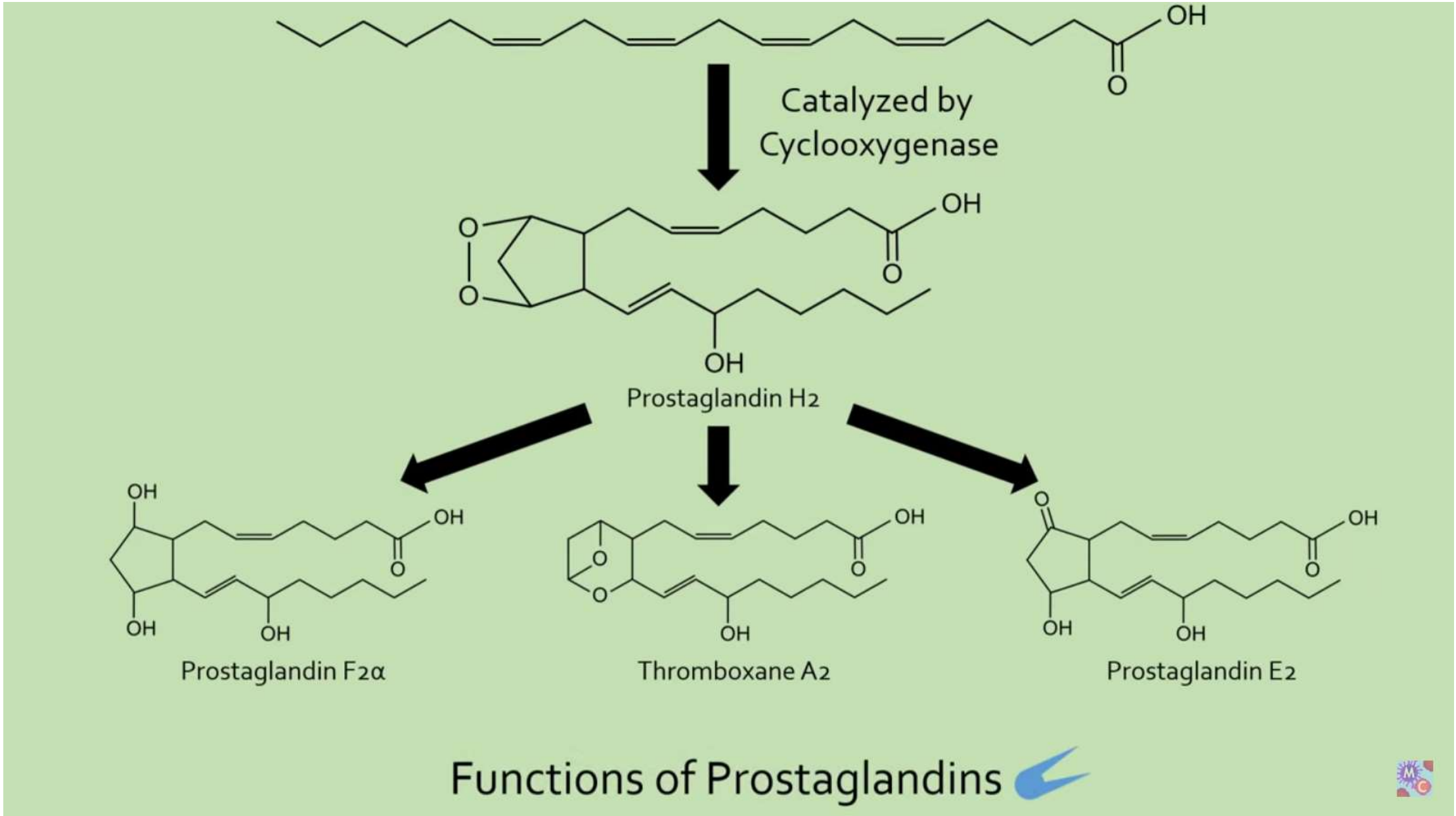
C. *Selective COX-2 inhibitors*

Celecoxib, Etoricoxib, Parecoxib.

D. *Analgesic- antipyretics with poor antiinflammatory action*

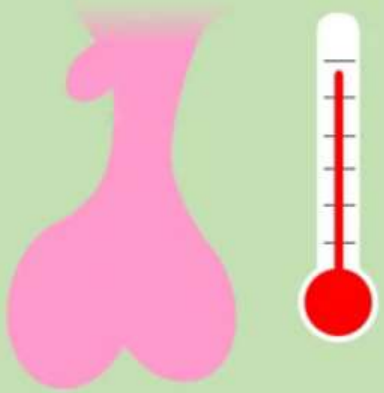
1. *Paraaminophenol derivative*: Paracetamol (Acetaminophen).
2. *Pyrazolone derivatives*: Metamizol (Dipyrone), Propiphenazone.
3. *Benzoxazocine derivative*: Nefopam.


Cell Exterior
Membrane Lipid
Fatty Acid
Phospholipase A2
Cell Membrane
OH
O
Fatty Acid
Cell Interior



Functions of Prostaglandins

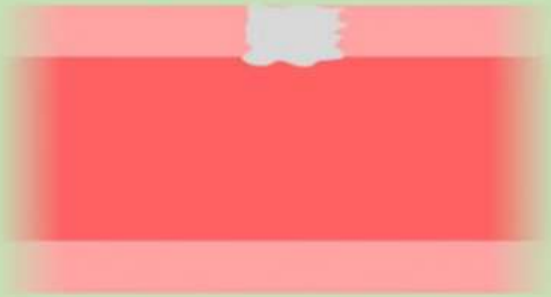
Functions of Prostaglandins



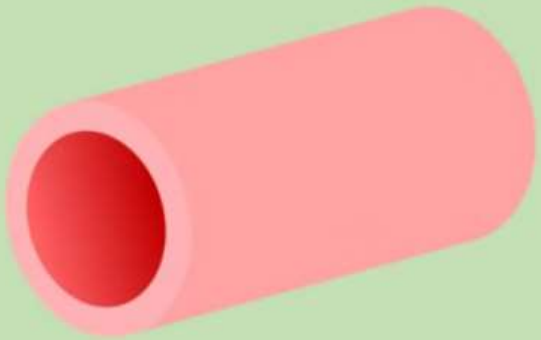
Stimulate Hypothalamus to Increase Body Temperature

Stimulate Immune Cells to Cause Inflammation

Sensitize Nerves to Pain



Initiate Blood Clotting



Constrict or Dilate Blood Vessels

Produce Protective Mucous in Stomach

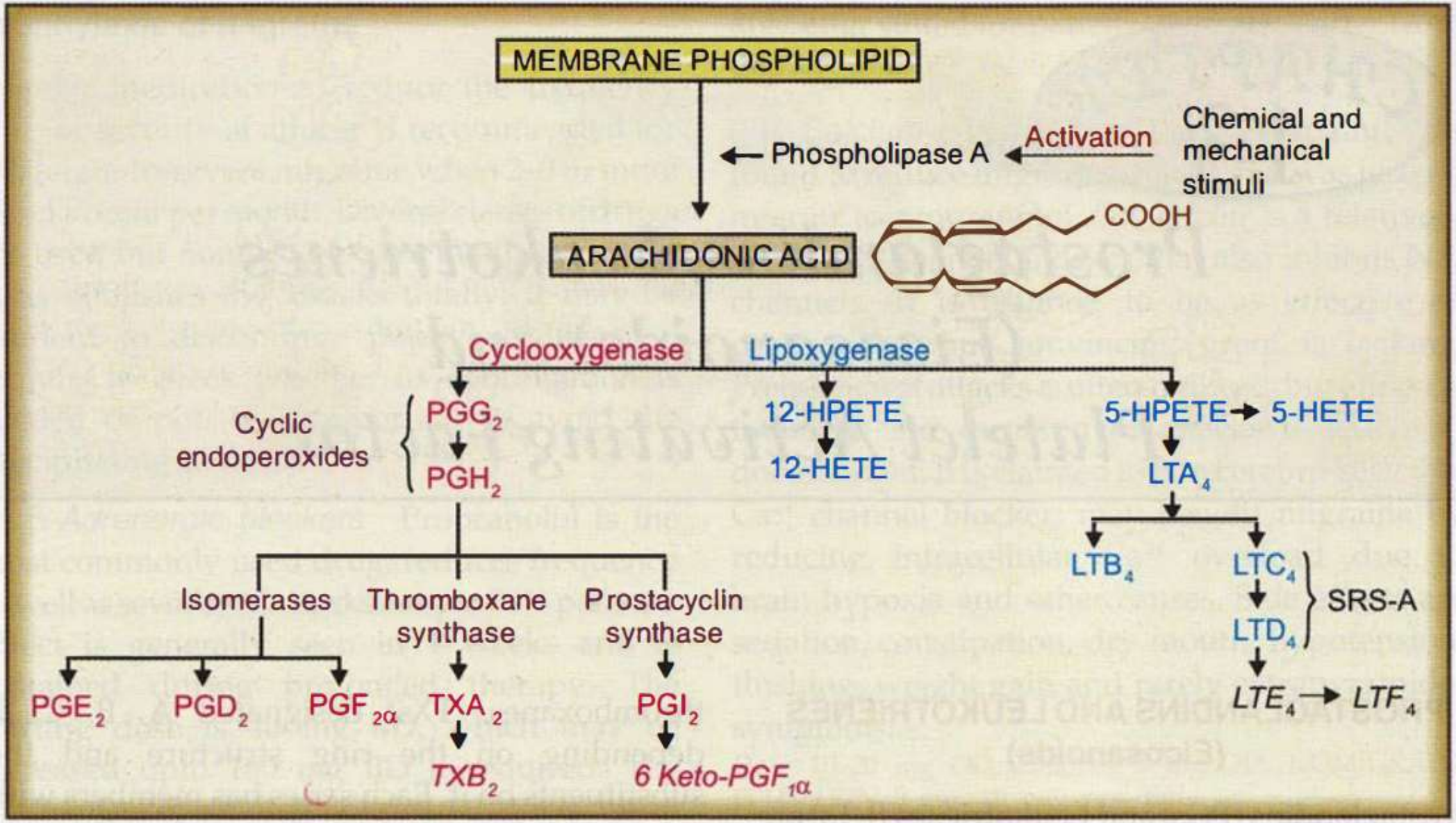


Fig. 13.1: Biosynthesis of prostaglandins (PG) and leukotrienes (LT). Less active metabolites are shown in italics TX—Thromboxane, PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid); HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow reacting substance of anaphylaxis

- Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids that are released from cell membrane phospholipids.
- They are the major lipid derived autacoids
- Chemically, PGs may be considered to be derivatives of prostanoic acid, though prostanoic acid does not naturally occur in the body.
- In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/ penta enoic acids.
- Therefore, they can be collectively called eicosanoids

- Prostaglandins, prostacyclin (PG 12) and thromboxane A2 (TXA2) are produced from arachidonic acid by the enzyme cyclooxygenase
- (which exists in a constitutive (COX-I) and an inducible (COX-2) isoforms; the former 'house keeping' functions, while the latter, is induced by cytokines at the site of inflammation
- PGs locally which mediate many of the inflammatory changes.
- However, COX-2 is constitutively present at some sites in brain and in juxtaglomerular cells: may serve physiological role at these sites.
- Most NSAIDs inhibit COX-l and COX-2 nonselectively, but now some selective COX-2 inhibitors have been produced

Anti-inflammatory

- NSAIDs is considered to be inhibition of PG synthesis at the site of injury.
- The antiinflammatory potency of different compounds corresponds with their potency to inhibit COX.
- Nimesulide is a potent relatively weak COX inhibitor.
- PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines, etc.
- Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages, and there are many targets for antiinflammatory action.

- Activated endothelial cells express adhesion molecules (ECAM-I, ICAM-I) on their surface and play a key role in directing circulating leucocytes to the site of inflammation (chemotaxis).
- Inflammatory cells express selectins and integrins.
- Certain NSAIDs may act by additional mechanisms including inhibition of expression/ activity of some of these molecules and generation of superoxide/ other free radicals.
- Growth factors like GM-CSF, IL-6 and lymphocyte transformation factors may also be affected.
- Stabilization of leucocyte lysosomal membrane and antagonism of certain actions of kinins may be contributing to NSAID action.

Aspirin Prevents Production of Prostaglandins

1971

John R. Vane

Bengt I. Samuelsson

Sune K. Bergström

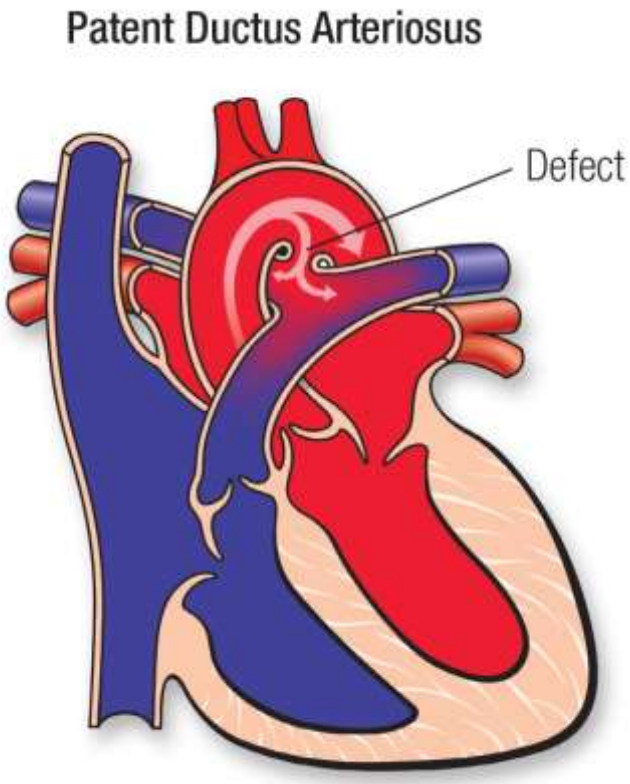
1982 Nobel Prize in Physiology or Medicine

Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme.

Beneficial actions due to PG synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyresis
- Antiinflammatory
- Antithrombotic
- Closure of ductus arteriosus in newborn

- The ductus arteriosus is **a normal fetal artery connecting the main body artery (aorta) and the main lung artery (pulmonary artery)**. The ductus allows blood to detour away from the lungs before birth.
- After birth, the opening is no longer needed and it usually narrows and closes within the first few days of life.



Ductus arteriosus closure

- During foetal circulation ductus arteriosus is kept patent by local elaboration of PGE2 and PGI2.
- Unknown mechanisms switch off this synthesis at birth and the ductus closes.
- When this fails to occur, small doses of indomethacin or aspirin bring about closure in majority of cases within a few hours by inhibiting PG production.
- Administration of NSAIDs in late pregnancy has been found to promote premature closure of ductus in some cases.
- Prescribing of NSAIDs near term should be avoided.

Parturition

- Sudden spurt of PG synthesis by uterus probably triggers labour and facilitates its progression.
- Accordingly, NSAIDs have the potential to delay and retard labour.
- However, labour can occur in the absence of PGs.

Gastric mucosal damage

- Gastric pain, mucosal erosion/ulceration and blood loss are produced
- Inhibition of COX-l mediated synthesis of gastroprotective PGs (PGE2I PGI2) is clearly involved, **though local action inducing back diffusion of H+ ions in gastric mucosa also plays a role**.
- Deficiency of PGs reduces mucus and HC03- secrection, tends to enhance acid secretion and may promote mucosal ischaemia.

NSAIDs produce renal effects

- COX-1 dependent impairment of renal blood flow and reduction of g.f.r. --- can worsen renal insufficiency.
- Juxtaglomerular COX-2 dependent Na+ and water retention.
- Ability to cause papillary necrosis on habitual intake.

Dysmenorrhoea

- Involvement of PGs in dysmenorrhoea has been clearly demonstrated: **level of PGs in menstrual flow, endometrial biopsy and that of PGF2a metabolite in circulation are raised in dysmenorrhoeic women.**
- Intermittent ischaemia of the myometrium is probably responsible for menstrual cramps.
- NSAIDs lower uterine PG levels-afford excellent relief in 60-70% and partial relief

Antiplatelet aggregation

- NSAIDs inhibit synthesis of both proaggregatory (TXA2) and antiaggregatory (PGI2) prostanoids, but effect on **platelet TXA2 (COX-I generated) predominates**
- Therapeutic doses of most NSAIDs inhibit platelet aggregation: bleeding time is prolonged.
- Small doses are therefore able to exert antithrombotic effect for several days.
- Risk of surgical bleeding is enhanced.

PHARMACOKINETICS

- Aspirin is absorbed from the stomach and small intestines.
- Higher pH also favours ionization, thus decreasing the diffusible form.
- Aspirin is rapidly deacetylated in the gut wall, liver, plasma
- It is -80% bound to plasma proteins and has a volume of distribution - 0.17 L/kg.
- It slowly enters brain but freely crosses placenta.
- Both aspirin and salicylic acid are conjugated in liver with glycine salicyluric acid (major pathway); and with glucuronic acid.
- Excreted by glomerular filtration as well as tubular secretion.

SELECTIVE COX-2 INHIBITORS (Coxibs)

- Highly selective COX-2 inhibitors have been introduced
- They cause little gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than with traditional NSAIDs.
- They do not depress TXA2 production by platelets (COX-I dependent)
- Do not inhibit platelet aggregation or prolong bleeding time, but reduce PGI2 production by vascular endothelium.

Celecoxib

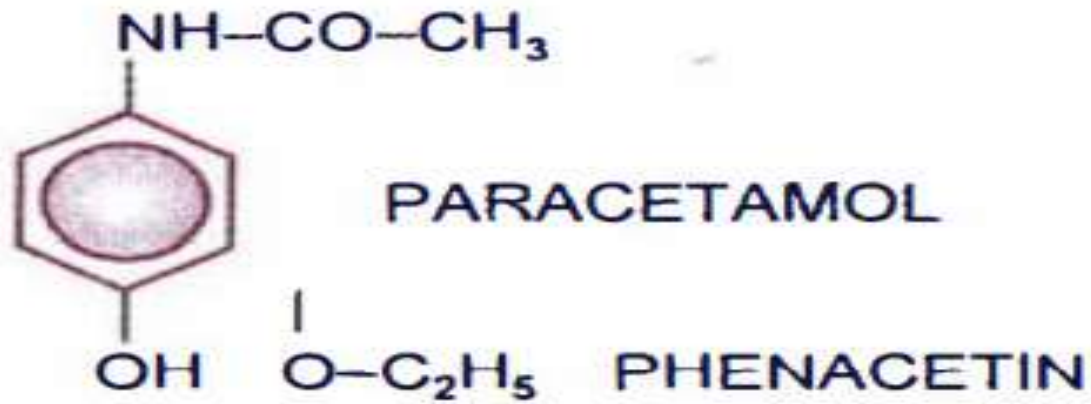
- The COX-2 selectivity of celecoxib is modest (6-20 fold).
- It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential.
- Without affecting COX-1 activity in gastroduodenal mucosa
- Platelet aggregation in response to collagen exposure remained intact
- serum TXB2 leveis were not reduced.
- Tolerability of celecoxib is better than traditional NSAIDs,
- Abdominal pain, dyspepsia and mild diarrhoea are the common side effects.
- Rashes, edema and a small rise in BP

- Celecoxib is slowly absorbed
- 97% plasma protein bound
- Metabolized primarily by CYP2C9 with a t1/2 of -10 hours.
- It is approved for use in Osteo and rheumatoid arthritis in a dose of 100-200 mg

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but is now banned because it was implicated in analgesic abuse nephropathy.

Paracetamol (*acetaminophen*) the deethylated active metabolite of phenacetin, was also introduced in the last century but has come into common use only since 1950.



Actions

- The central analgesic action of paracetamol is like aspirin
- Weak peripheral antiinflammatory component.
- Analgesic action of aspirin and paracetamol is additive.
- Paracetamol is a good and promptly acting antipyretic.
- It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain.

Acute paracetamol poisoning

- It occurs especially in small children who have low hepatic glucuronide conjugating ability.
- If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur.
- Fatality is common with > 250 mg/kg.
- Treatment If the patient is brought early, vomiting should be induced or gastric lavage done.
- **Activated charcoal** is given orally or through the tube to prevent further absorption. Other supportive measures, as needed, should be taken. **Specific: N-acetylcysteine**

Pharmacokinetics

- Paracetamol is well absorbed orally
- Only about 1/ 4th is protein bound in plasma and it is uniformly distributed in the body.
- Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are excreted rapidly in urine.
- Plasma tl/2h is 2-3 hours. Effects after an oral dose last for 3-5 hours

Antipyresis

- NSAIDs reduce body temperature in fever, but do not cause hypothermia in normothermic individuals.
- Fever during infection is produced through the generation of pyrogens including, ILs, TNFa, interferons which induce PGE2 production in hypothalamus-raise its temperature set point.
- NSAlDs block the action of pyrogens but not that of PGE2 injected into the hypothalamus.
- The isoform present at this site appears to be COX-2 (possibly COX-3 also).
- However, fever can occur through non-PG mediated mechanisms as well.

Analgesia

- PGs induce hyperalgesia
- NSAIDs block the pain sensitizing mechanism induced by bradykinin, TNFa, interleukins (ILs) and other algesic substances.
- They are, therefore, more effective against inflammation associated pain.

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Acknowledgement

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