Skeletal muscle relaxants

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Learning objectives

By the end of this lecture, students should be able to:

- **Identify classification of skeletal muscle relaxants**
- **Describe the pharmacokinetics and dynamics of neuromuscular relaxants**
- **Recognize the clinical applications for neuromuscular blockers**
- **Know the different types of spasmolytics**
- **Describe the pharmacokinetics and dynamics of spasmolytic drugs**
- **Recognize the clinical applications for spasmolytic drugs**

Skeletal muscle relaxants

Are drugs used to induce skeletal muscle relaxation.

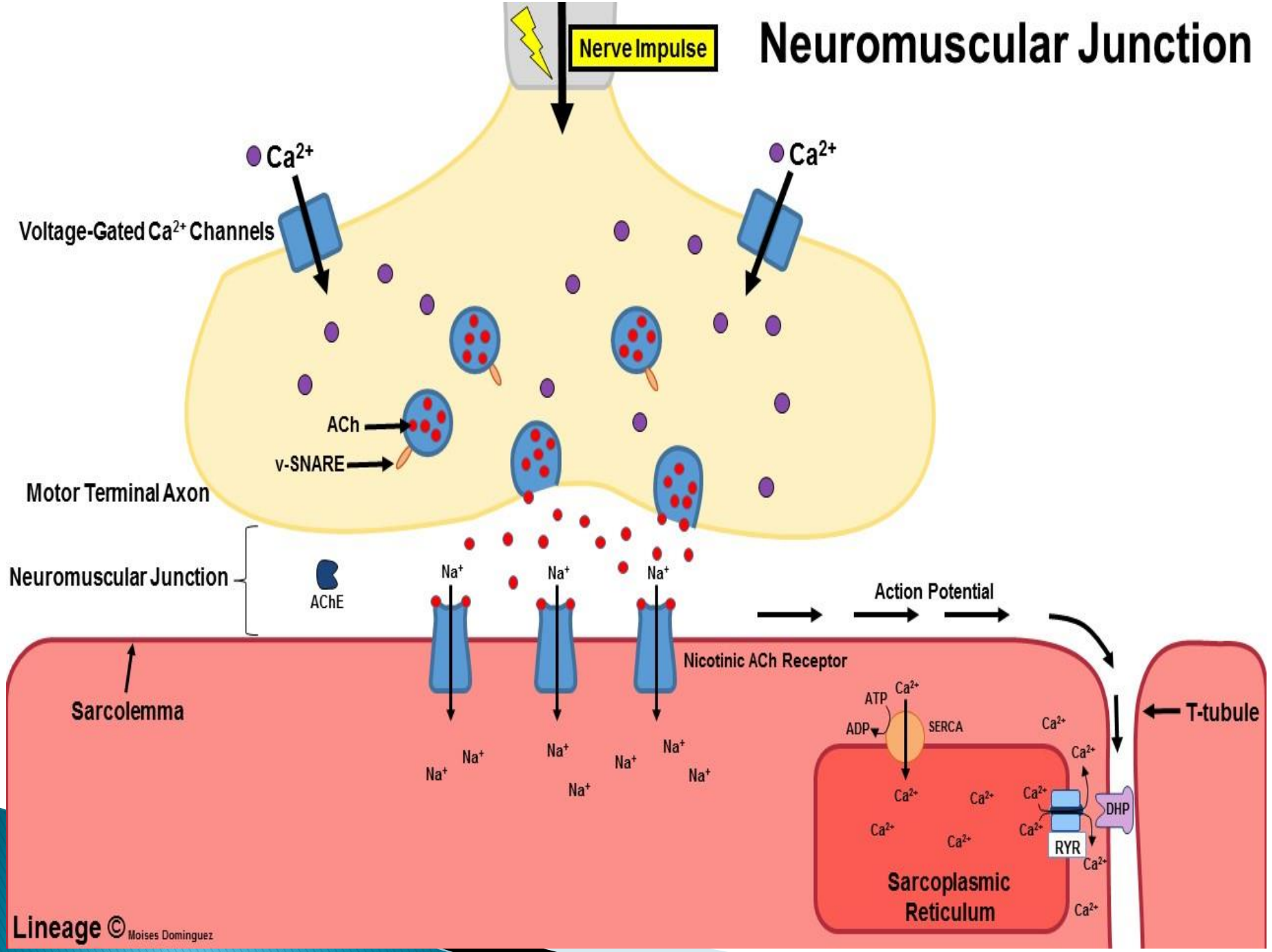
Classification of SKM relaxants

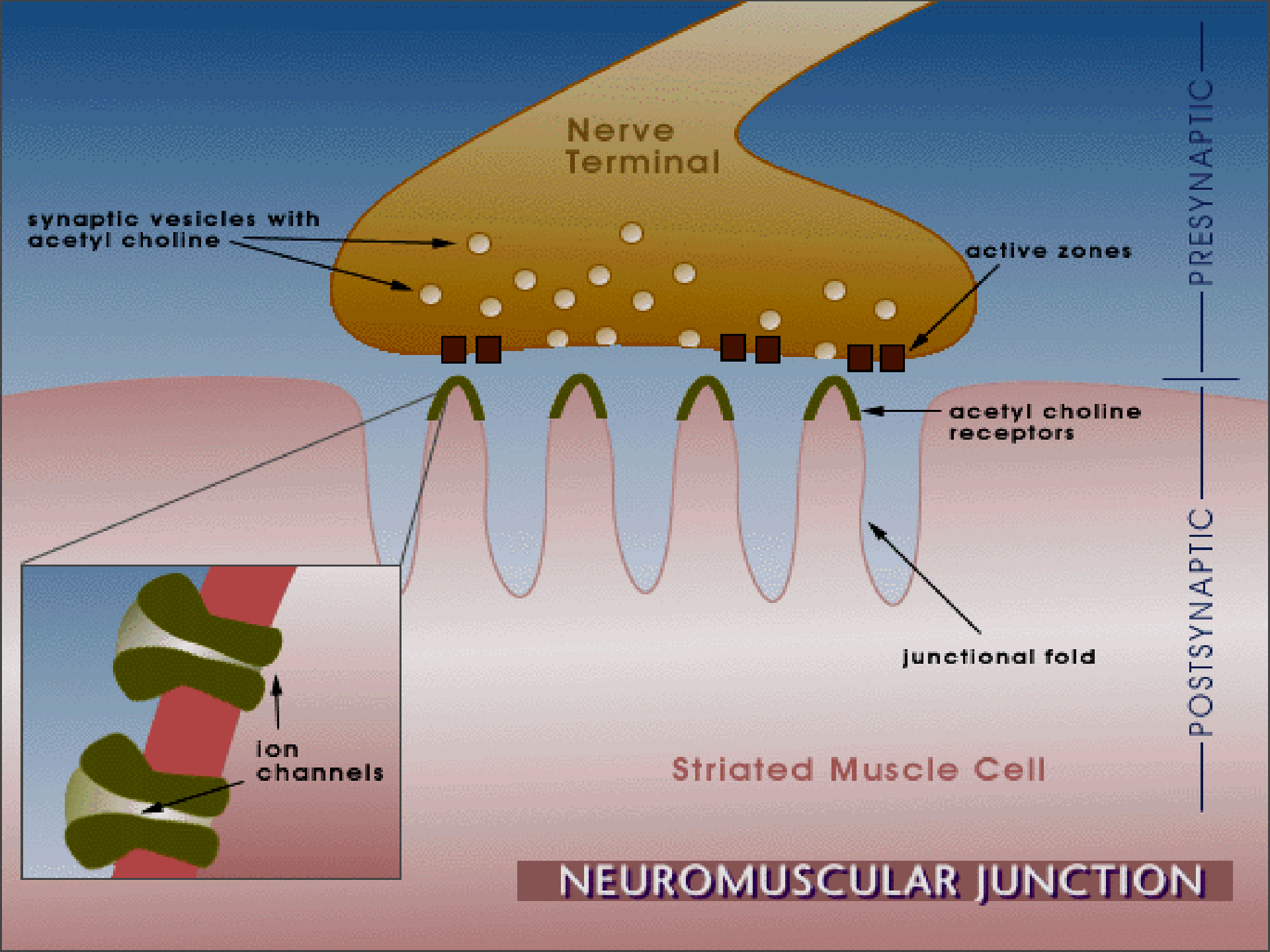
- **Peripherally acting skeletal muscle relaxants**
- **Centrally acting skeletal muscle relaxants e.g. Baclofen – Diazepam**
- **Direct acting skeletal muscle relaxants e.g. Dantrolene**

Peripherally acting SKM relaxants

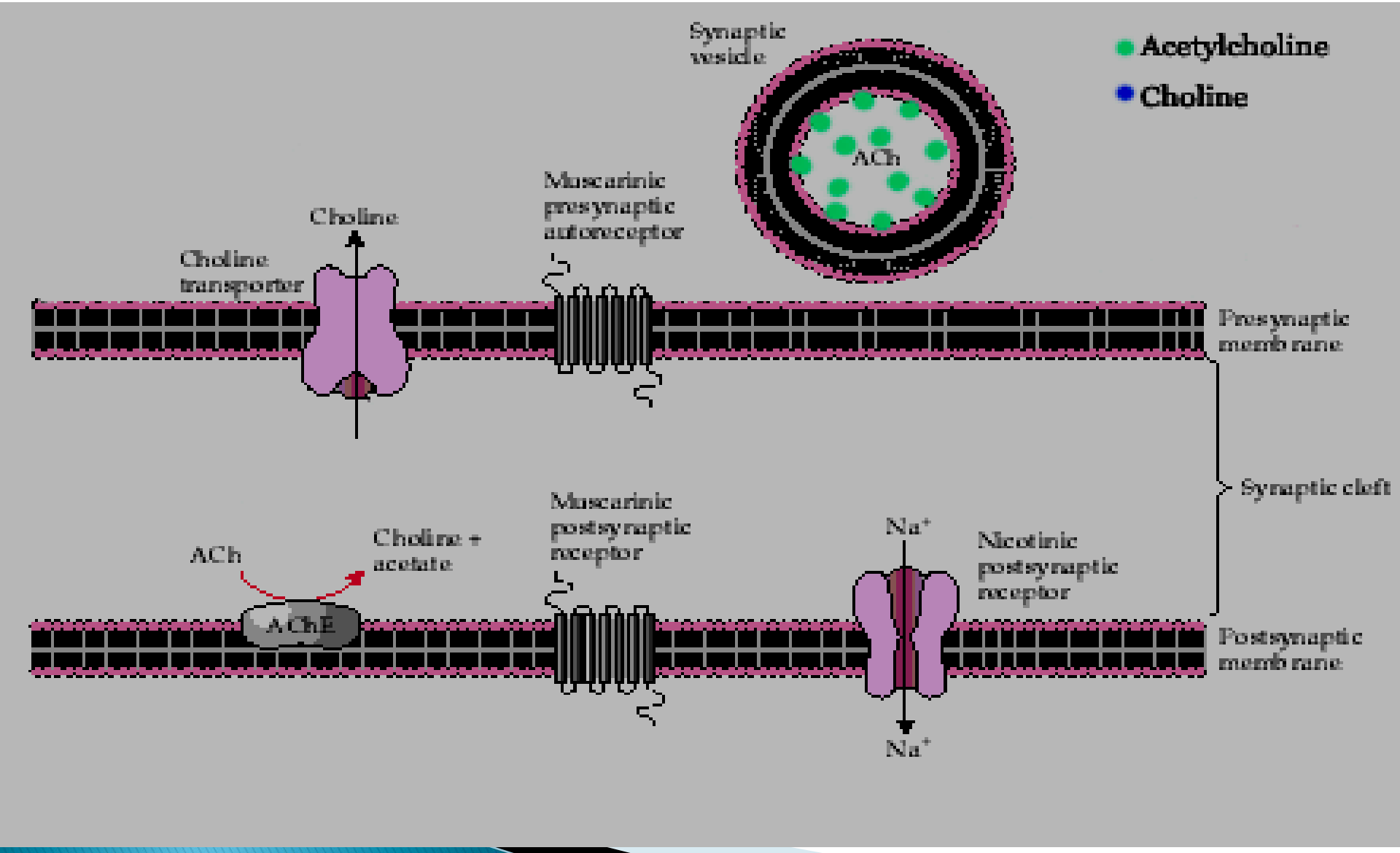
(Neuromuscular blockers)

Neuromuscular blockers act by blocking neuromuscular junction or motor end plate leading to skeletal muscle relaxation.


Neuromuscular Junction
Nerve Impulse
Ca2+
Ca2+
Voltage-Gated Ca2+ Channels
ACh
v-SNARE
Motor Terminal Axon
Neuromuscular Junction
AChE
Na+
Action Potential
Nicotinic ACh Receptor
Sarcolemma
T-tubule
ATP
ADP
SERCA
DHP
RYR
Sarcoplasmic Reticulum
Lineage © Moises Dominguez


Nerve Terminal
synaptic vesicles with acetyl choline
active zones
PRESYNAPTIC
acetyl choline receptors
POSTSYNAPTIC
junctional fold
ion channels
Striated Muscle Cell
NEUROMUSCULAR JUNCTION

Neuromuscular Junction



Classification of Peripherally SKM relaxants

According to mechanism of action, they are classified into:

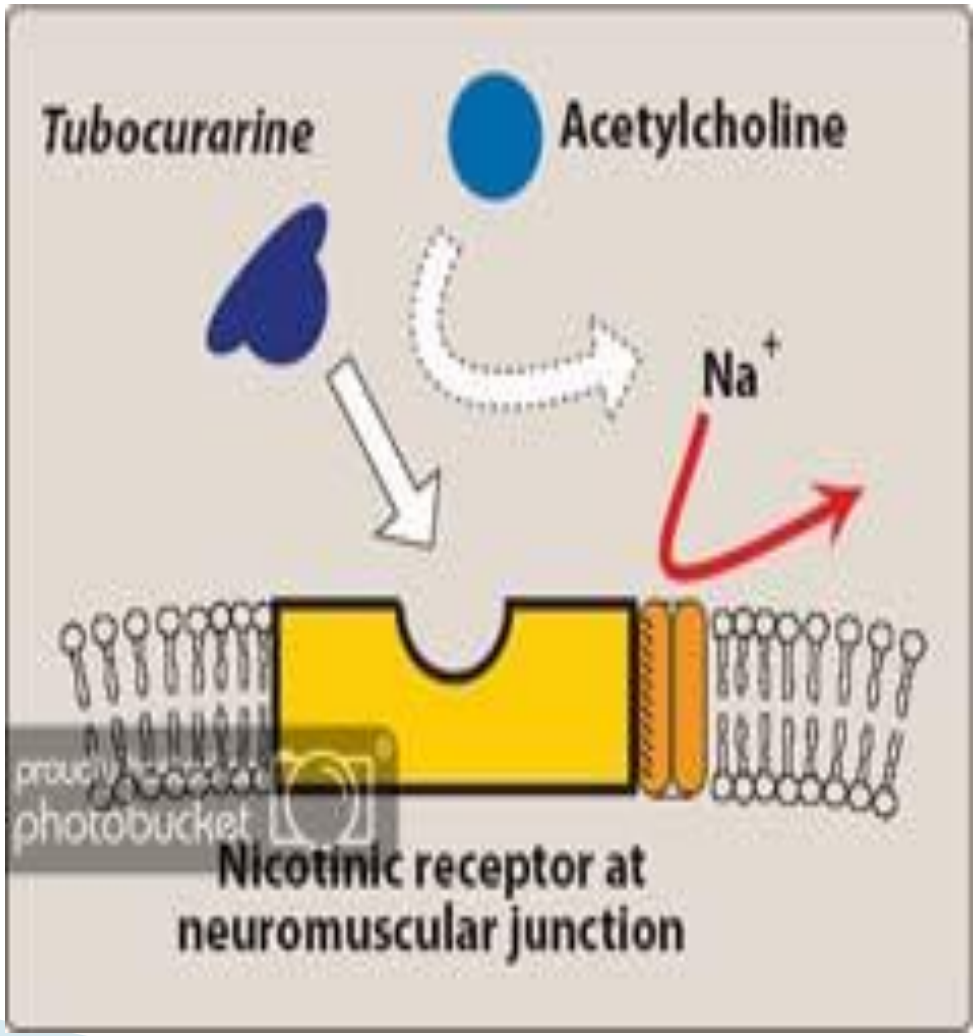
1. **Competitive neuromuscular blockers**
2. **Depolarizing neuromuscular blockers**

Competitive neuromuscular blockers

Mechanism of action:

- **Compete with Ach for the nicotinic receptors present in post junctional membrane of neuromuscular junction or motor end plate.**
- **No depolarization of post junctional membrane (non depolarizing).**
- **Action can be reversed by increasing Ach concentration.**

Competitive neuromuscular blockers



Competitive neuromuscular blockers

Have the common suffix curium or curonium

Classified according to duration of action into:

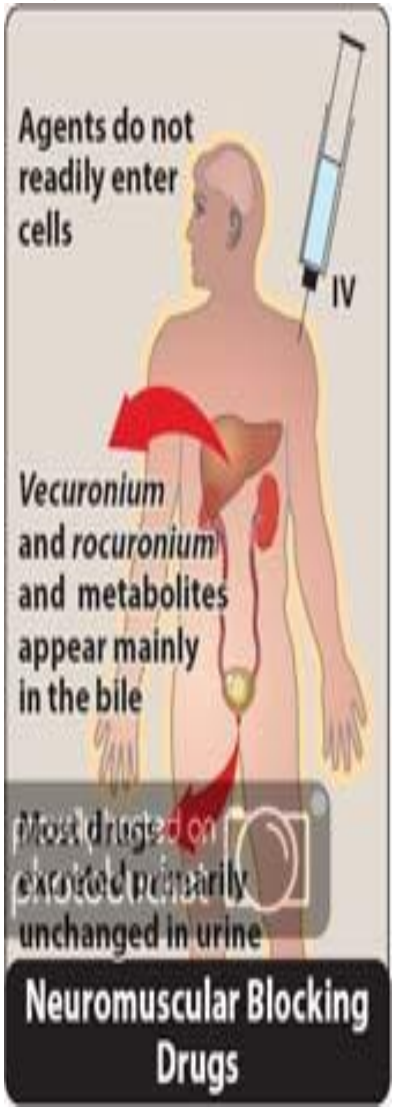
- ✓ Atracurium
- ✓ Mivacurium
- ✓ Pancuronium
- ✓ Vecuronium

Competitive Neuromuscular Blockers

- **Long acting**
  - **d-tubocurarine (prototype drug)**
  - Pancuronium
- **Intermediate acting**
  - Atracurium Vecuronium
- **Short acting**
  - Mivacurium

Pharmacokinetics of competitive neuromuscular blockers

- They are **polar compounds**
  - Inactive orally & taken parenterally
  - Do not cross BBB (no central action)
  - Do not cross placenta
- Metabolism depend upon kidney or liver



Except

Mivacurium

degraded by acetyl cholinesterase

Atracurium

spontaneous degradation in blood

Pharmacological actions of competitive NMBs:

- **Skeletal muscle relaxation.**

  Small rapidly contracting muscles of face and eyes
  fingers
  neck
  trunk muscle
  intercostal muscles
  diaphragm

  Recovery comes from **REVERSE MANNER** starting with diaphragm. Last is face and eyes

Pharmacological actions of competitive NMBs:

- Skeletal muscle relaxation.
- They produce different effects on CVS
- Some release **histamine and produce hypotension**
  - d-Tubocurarine
  - Atracurium
  - Mivacurium
- Others produce tachycardia (↑ H.R)
  - Pancuronium

d – Tubocurarine

- Long duration of action (1 - 2 h)
- Eliminated by kidney 60% - liver 40%.
- Not used clinically due to adverse effects:
- Histamine releaser leading to
  - Bronchospasm (constriction of bronchial smooth muscles).
  - Hypotension
  - Tachycardia
- More safer derivatives are now available

Atracurium

- As potent as curare
- Has intermediate duration of action (30 min).
- Liberate histamine → (Transient hypotension)
- Eliminated by non enzymatic chemical degradation in plasma *(spontaneous hydrolysis at body pH).*
- used in liver failure & kidney failure *(drug of choice).*
- Should be avoided in asthmatic patients **Why?**

Mivacurium

- Chemically related to atracurium
- Fast onset of action
- Has the shortest duration of action (15 min) of all competitive neuromuscular blockers.
- Metabolized by pseudo-cholinesterase.
- **Longer** duration in patient with liver disease or genetic **cholinesterase deficiency** or **malnutrition**.
- Transient hypotension (due to histamine release).

Pancuronium

- More potent than curare (6 times).
- Excreted by the kidney (80 %).
- Long duration of action.

Side effects:

- Hypertension, tachycardia
  - ↑ norepinephrine release from adrenergic nerve endings
  - Antimuscarinic action (block parasympathetic action).
    - Avoid in patient with coronary diseases.

Vecuronium

- More potent than tubocurarine (6 times).
- Metabolized mainly by liver and excreted in bile.
- Intermediate duration of action.
- **Advantages**
  - No histamine release.
  - No tachycardia.

Depolarizing Neuromuscular Blockers

Mechanism of action

- **combine with nicotinic receptors in post-junctional membrane of neuromuscular junction → initial depolarization of motor end plate → muscle twitching → persistent depolarization → Skeletal muscle relaxation**

Succinylcholine (suxamethonium)

Pharmacological Actions

Skeletal muscles: **twitching → relaxation**

Hyperkalemia: **Cardiac arrest.**

CVS: **arrhythmia**

Eye: ↑ **intraocular pressure** (due to contraction of extra-ocular muscle).

Pharmacokinetics

- Fast onset of action (1 min.).
- Short duration of action (5-10 min.).
- Metabolized by pseudo-cholinesterase in plasma
- Half life is prolonged in
  - Neonates
  - Elderly
  - Pseudo-cholinesterase deficiency (liver disease or malnutrition or genetic cholinesterase deficiency).

Side Effects

- Hyperkalemia
- CVS arrhythmia
- ↑ Intraocular pressure contraindicated in glaucoma
- Can produce malignant hyperthermia
- May cause succinylcholine apnea due to deficiency of pseudo-cholinesterase.

Malignant Hyperthermia

- Is a rare inherited condition that occurs upon administration of drugs as:
  - general anesthesia e.g. halothane
  - neuromuscular blockers e.g. succinylcholine
- Is an example of **Idiosyncrasy**
- Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic defect.
- ↑ Ca release, muscular rigidity, metabolic acidosis, tachycardia, and hyperpyrexia

Drug	Duration	Side effects	*Notes*
Tubocurarine	Long 1-2 h	Hypotension	# Renal failure
Pancuronium	Long 1-2 h	Tachycardia	# Renal failure
Atracurium	Short 30 min.	Transient hypotension Histamine release	Spontaneous degradation Used in liver and kidney failure
Vecuronium	Short 40 min.	Few side effects	# Liver failure
Mivacurium	Short 15 min.	Similar to atracurium	Metabolized by pseudocholinesterase # Choline esterase deficiency
Succinyl choline	Short 10 min.	Hyperkalemia Arrhythmia Increase IOP	# CVS Diseases # Glaucoma # Liver disease

Uses of neuromuscular blockers

- control convulsion → electroshock therapy in psychotic patients.
- Relieve of tetanus and epileptic convulsion.
- As adjuvant in general anesthesia to induce muscle relaxation
- Facilitate endotracheal intubation
- Orthopedic surgery.

Drugs and diseases that modify effects of neuromuscular blockers

- **Myasthenia gravis** increase the response to muscle relaxants.

- **Drugs** as **aminoglycosides** (e.g. streptomycin), magnesium sulphate, general anesthetics can potentiate or enhance the effect of neuromuscular blockers.

Spasmolytics

They reduce muscle spasm in spastic states

Baclofen:

- Centrally acting
- GABA agonist – acts on spinal cord.

Diazepam (Benzodiazepines):

- Centrally acting
- facilitate GABA action on CNS.

Dantrolene:

- direct action on skeletal muscles.

Uses of spasmolytics

They reduce muscle spasm in spastic states produced by neurological disorders as:

- Spinal cord injury
- Cerebral stroke
- Cerebral palsy

Dantrolene

Mechanism of action

- Acts directly on skeletal muscles.
- It interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum).
- It inhibits excitation-contraction coupling in the muscle fiber.
- Orally, IV, (t ½ = 8 - 9 h).
- **Used in the treatment of:**
  - Spastic states
  - Malignant hyperthermia