Skeletal muscle relaxants

Classification

- **Peripherally acting (Neuromuscular blockers).**
- **Centrally acting Sk. M. relaxants**
  - **Baclofen - Diazepam**
- **Direct acting Sk. M. relaxants.**
  - **Dantrolene**

Peripherally acting

A) Presynaptic neuromuscular blockers

1) Inhibit Ach synthesis

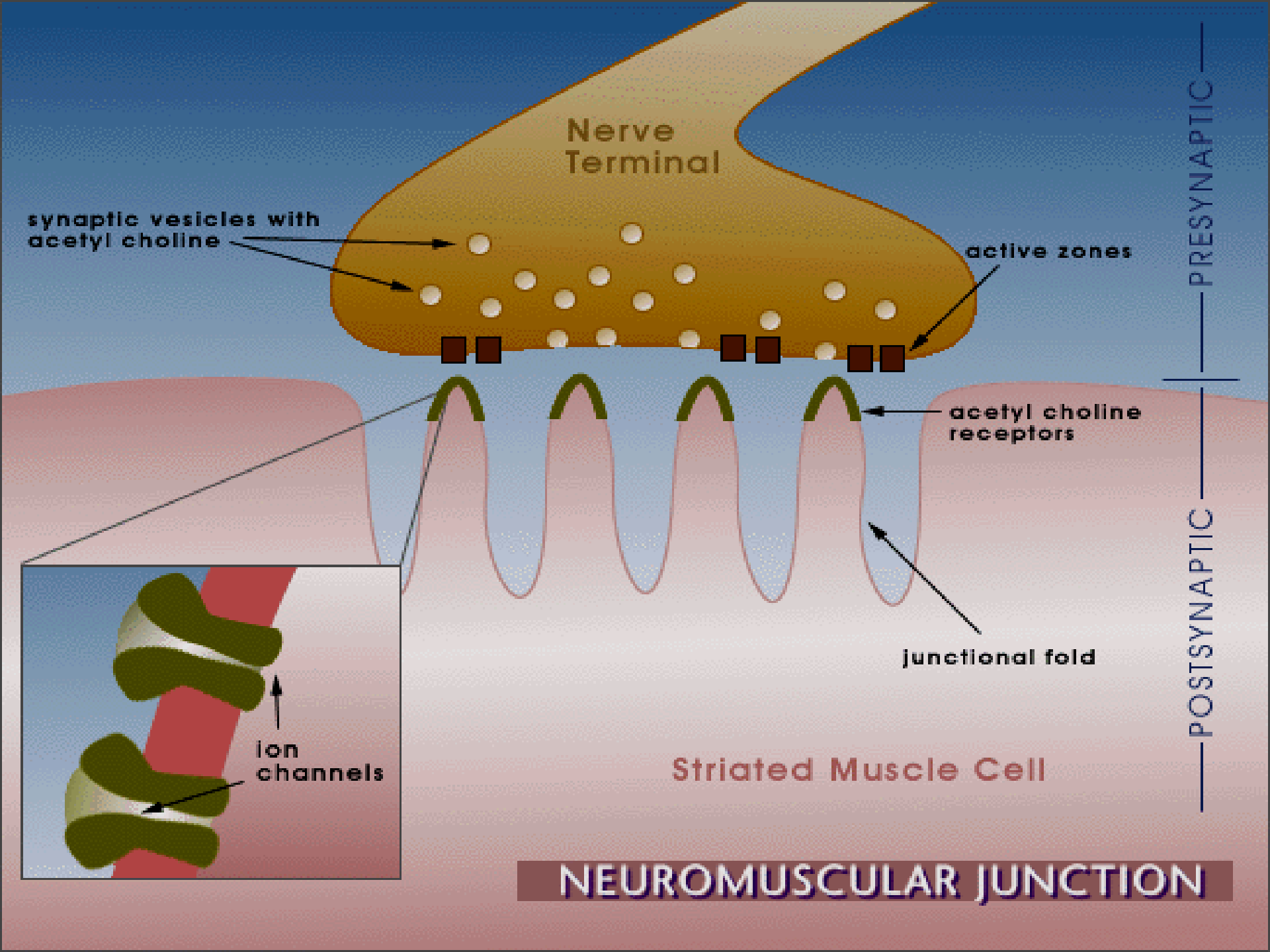
Triethylacholine - hemicholinium

2) Inhibit Ach release

Mg, aminoglycosides, botulinum toxin,

B) Postsynaptic neuromuscular blockers

1) Competitive (non depolarizing blockers)
2) Depolarizing blockers


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

Postsynaptic Neuromuscular Blockers

Competitive NM blockers

- d-tubocurarine
- Gallamine
- Atracurium
- Pancuronium
- Vecuronium

Depolarizing NM blockers

- Succinylcholine (suxamethonium)

Uses of NMB blockers

- control convulsion → electroshock therapy in psychotic patient .
- Relieve of tetanus and epileptic convulsion.
- facilitate endoscopy
- As adjuvant in general anesthesia to induce muscle relaxation
- orthopedic surgery.

Competitive NM blockers

Mechanism of Action

- competitive antagonists: compete with Ach at the Nicotinic receptors of NMJ.
- No depolarization of postjunctional membrane.
- Cholinesterase inhibitors can reverse blockade (Neostigmine).

Pharmacokinetics

- They are polar comp.
  - inactive orally &taken parenterally.
  - No cross placenta & CNS
- Metabolism depend upon kidney or liver EXCEPT

atracurium - mivacurium (cholinesterase).

Pharmacological actions

- **Skeletal muscle relaxation.**

- **CVS**

Hypotension (Histamine release)	**↑ H.R**
d.Tubocurarine	**Gallamine**
Mivacurium	**Pancuronium**
Atracurium	

Gallamine (Flaxedil)

- Less potent than curare (1/5).
- Metabolized mainly by kidney 100% # in renal failure
- Long duration of action.
- Tachycardia due to :
  - Atropine like action.
  - Release of NA from adrenergic nerve endings.

d – Tubocurarine

- More potent than gallamine

- Long duration of action (1 - 2 hr.)
- Eliminated by kidney 60% - liver 40%.
- Histamine releaser
  - Bronchospasm
  - Hypotension
- Blocks autonomic ganglia (Hypotension)

Atracurium

- As potent as curare (1.5)
- Has intermediate duration of action (30 min).
- Eliminated by non enzymatic chemical degradation in plasma (Spontaneous hydrolysis at body pH).
- used in liver failure & kidney failure (drug of choice).
- Liberate histamine → (Transient hypotension).
- No effect on muscarinic receptor nor ganglia .

Mivacurium

- Chemically related to atracurium
- Metabolized by pseudo cholinesterases.
- Fast onset of action
- Short duration of action (15 min).
- Transient hypotension (histamine release).
- Longer duration in patient with liver disease or genetic cholinesterase deficiency.

Pancuronium

- More potent than curare (6 times).
- Excreted by the kidney (80 %).
- Long duration of action.
- Tachycardia
  - Antimuscarinic action
  - ↑ NE release from adrenergic nerve endings.

Vecuronium

- More potent than tubocurarine (6 times).
- Metabolized mainly by liver.
- Intermediate duration of action.
- Has few side effects.
  - No histamine release.
  - No ganglion block.
  - No antimuscarinic action.

Depolarizing Neuromuscular Blockers

Mechanism of Action

Phase I (Depolarizing)

- combine with nicotinic receptors → depolarization of motor end plate → initial muscle twitching → Persistent depolarization → paralysis.

- Phase I block is augmented not reversed by anticholinestrases.

Phase II (Desensitization Block)

- Continuous exposure to succinylcholine → depolarization decreases and the membrane become repolarized, but the membrane cannot be depolarized by Ach as long as succinylcholine present → desensitization of the membrane.
- This phase reversed by anticholinesterase.

Succinylcholine (suxamethonium)

Pharmacological Actions

1. **SK. muscle :** fasciculation → spastic paralysis.
2. **Hyperkalemia :** Cardiac arrest.
3. **Eye :** ↑ intraocular pressure.
4. **GIT :** ↑ intragastric pressure → regurgitation of gastric content to esophagus.
5. **CVS :** arrhythmia

Pharmacokinetics

- Short onset of action (1 min.).
- Short duration of action (5-10 min.).
- Destroyed by pseudocholinesterase

Side Effects

- Hyperkalemia.
- CVS arrhythmia (Bradycardia, extrasystol and cardiac arrest).
- ↑ IOP # glaucoma
- Malignant hyperthermia.
- Succinylcholine apnea due to ?
  - liver disease (neonates – elderly).
  - Malnutrition
  - Organophosphorous poisoning.

Drug	Duration	Side effects	*Notes*
Tubocurarine	Long (1 h)	Hypotension	# Renal failure
Gallamine	Long	Tachycardia Muscarinic antagonist	Renal excretion # Renal failure
Pancuronium	Long	Tachycardia Antimuscarinic action	# Renal failure
Vecuronium	short	Few side effects	# Liver failure
Atracurium	short	•Transient hypotension •Histamine release	•Spontaneous degradation •Used in liver and kidney failure
Cisatracurium		Less histamine release	

Mivacurium	**Short**		• **Similar to atracurium** • **Metabolized by plasma choline esterases** • **# Choline esterase deficiency**
Suxamethonium	**Short**	**Hyperkalemia** **Arrhythmia** **Increase IOP**	**CVS Diseases** **Glaucoma** **Liver disease**

Drug	Speed of onset	Duration of action	Main side-effects	Notes
Tubocurarine	Slow (>5 min)	Long (1–2 h)	Hypotension (ganglion block plus histamine release) Bronchoconstriction (histamine release)	Plant alkaloid, now rarely used **Alcuronium** is a semisynthetic derivative with similar properties but fewer side-effects
Gallamine	Slow	Long	Tachycardia (muscarinic antagonist)	100% renal excretion; therefore, to be avoided in patients with poor renal function The first synthetic alternative to tubocurarine, now rarely used
Pancuronium	Intermediate (2–3 min)	Long	Slight tachycardia. No hypotension	The first steroid-based compound. Better side-effect profile than tubocurarine. Widely used **Pipecuronium** is similar
Vecuronium	Intermediate	Intermediate (30–40 min)	Few side-effects	Widely used. Occasionally causes prolonged paralysis, probably owing to active metaboli **Rocuronium** is similar, with faster onset
Atracurium	Intermediate	Intermediate (<30 min)	Transient hypotension (histamine release)	Unusual mechanism of elimination (spontaneous non-enzymic chemical degradation in plasma). Degradation slowed by acidosis Widely used **Doxacurium** is chemically similar but stable in plasma, giving it long duration of action **Cisatracurium** is the pure isomeric constituent of atracurium, similar but with

Mivacurium	Fast (~2 min)	Short (~15 min)	Transient hypotension (histamine release)	New drug, chemically similar to atracurium but rapidly inactivated by plasma cholinesterase (therefore, longer acting in patients with liver disease or with genetic cholinesterase deficiency (see p. 153)
Suxamethonium	Fast	Short (~10 min)	Bradycardia (muscarinic agonist effect) Cardiac dysrhythmias (increased plasma K^+ concentration—avoid in patients with burns or severe trauma) Raised intraocular pressure (nicotinic agonist effect on extraocular muscles) Postoperative muscle pain	Acts by depolarisation of endplate (nicotinic agonist effect)—the only drug of this type still in use Paralysis is preceded by transient muscle fasciculations Short duration of action owing to hydrolysis by plasma cholinesterase (prolonged action in patients with liver disease or genetic deficiency of plasma cholinesterase) Used for brief procedures (e.g. tracheal intubation, electroconvulsive shock therapy). Rocuronium has similar speed of onset and recovery with fewer unwanted effects

Spasmolytics

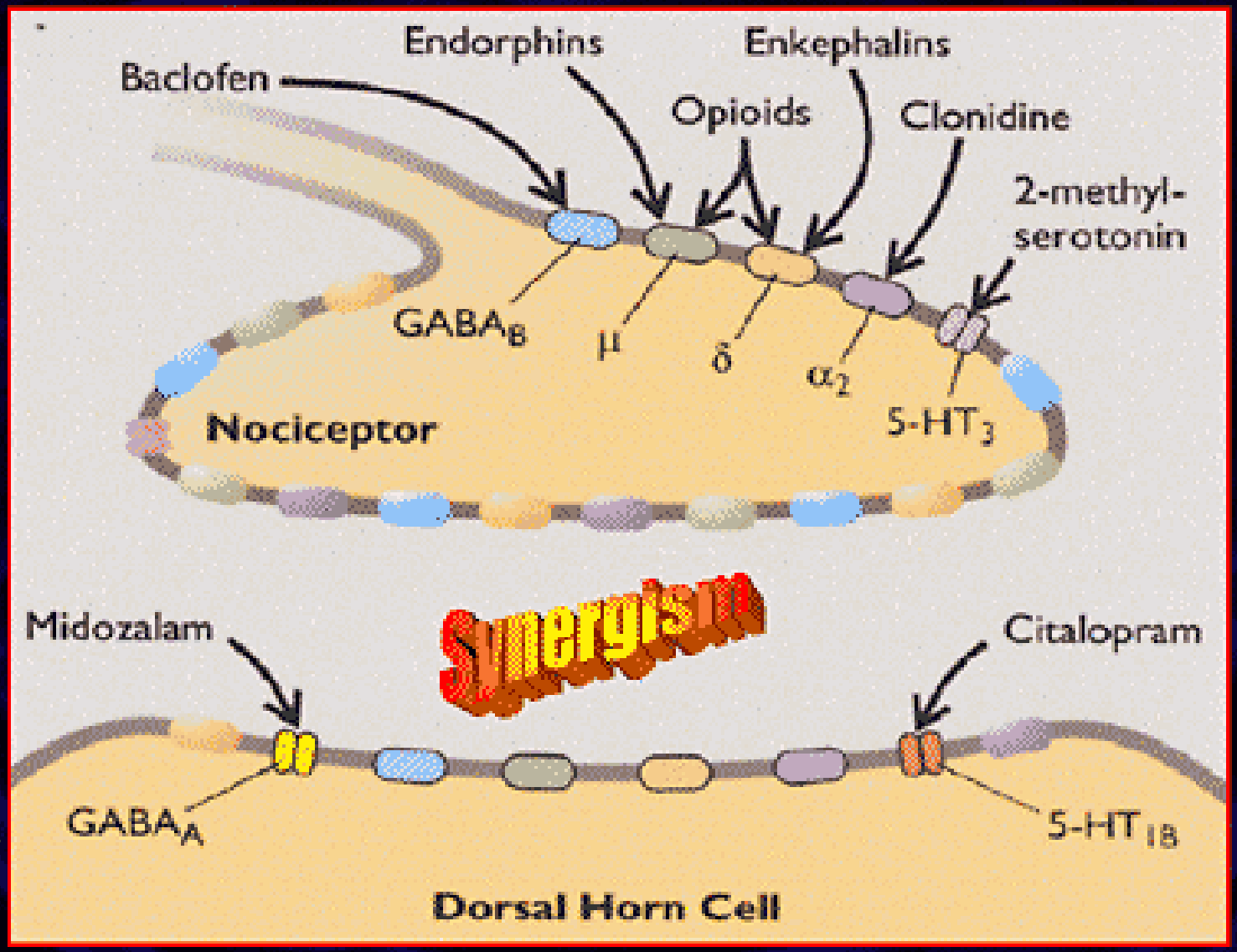
Baclofen:

Centrally acting (GABA agonist –Sp. cord).

Diazepam (Benzodiazepines):

Centrally acting (facilitate GABA action on Sp. Cord & CNS).

Dantrolene: direct action on sk. muscles.



Courtesy of Daniel Brookoff, MD, PhD *University of Tennessee; Memphis TN USA*

Uses of spasmolytics

reduce muscle spasm in

- Spinal cord injury
- Stroke
- Cerebral palsy

Dantrolene

Mechanism of Action

1. It interferes with the release of calcium from its stores in sk. muscles (**sarcoplasmic reticulum**).
2. It inhibits excitation-contraction coupling in the muscle fiber.

Uses

Malignant Hyperthermia.

Spastic states.

IV, orally t ½ = 8 - 9 hrs.

Malignant hyperthermia

- **Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic defect .**
- **Sensitive to some drugs**
  - **general anesthesia e.g. halothane**
  - **neuromuscular blockers e.g. suxamethonium**
- **↑ Ca release, intense muscle spasm, rise in Temp**