Skeletal muscle relaxants

Classification

- **Peripherally acting (Neuromuscular blockers).**
- **Centrally acting skeletal muscle relaxants**

  e.g. Baclofen - Diazepam
- **Direct acting skeletal muscle relaxants**

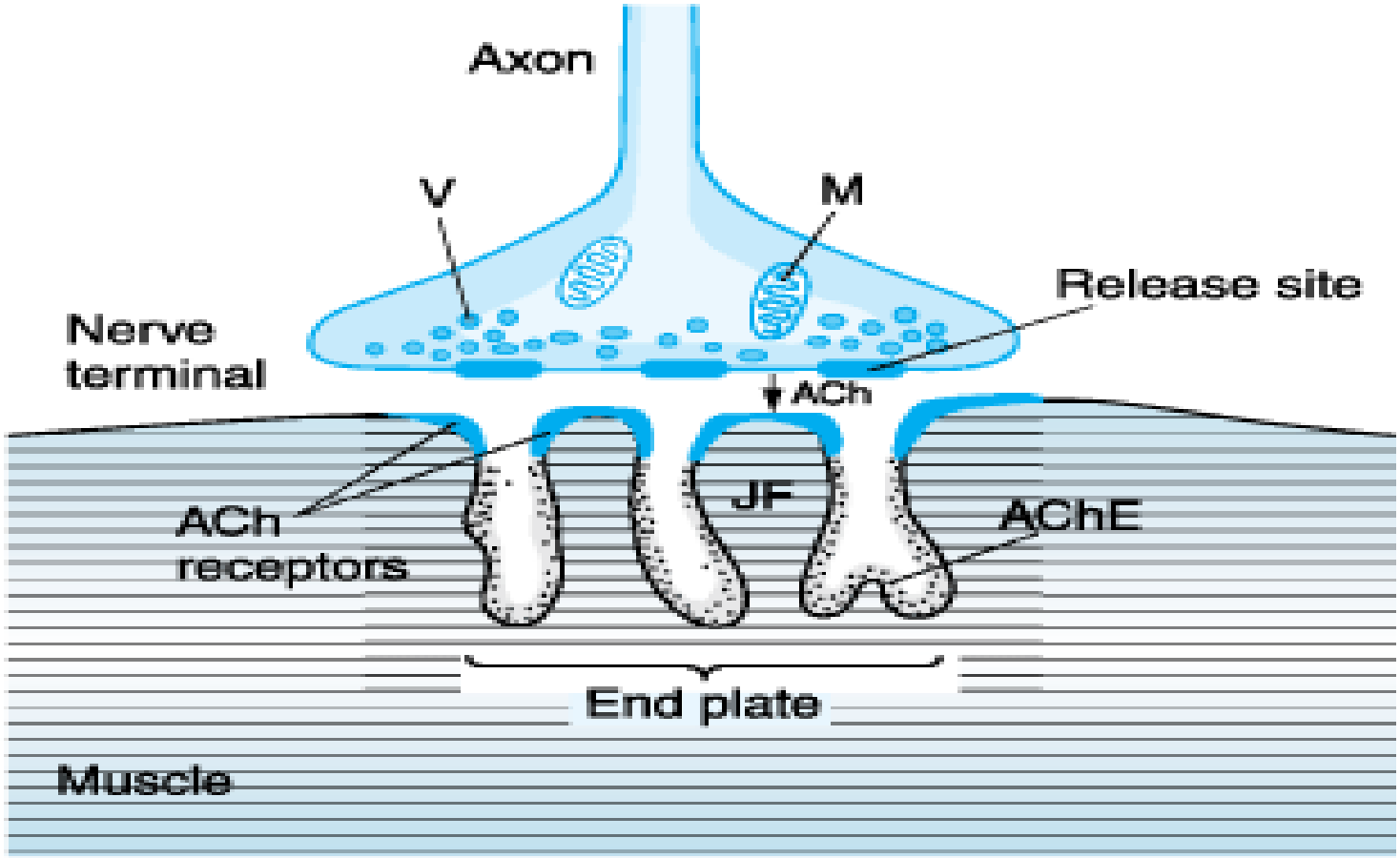
  e.g. Dantrolene

Neuromuscular blockers

Classification:

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

Depolarizing muscle relaxants act as acetylcholine (ACh) receptor agonists, whereas nondepolarizing muscle relaxants function as competitive antagonists.



Source: Morgan GE, Mikhail MS, Murray MJ: *Clinical Anesthesiology*, 4th Edition: http://www.accessmedicine.com

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.

Neuromuscular Blockers

Competitive (Nondepolarizing) NM blockers

- **d-tubocurarine (prototype)**
- **Atracurium**
- **Mivacurium**
- **Pancuronium**
- **Vecuronium**

VP-ATM

Depolarizing NM blockers

- **Succinylcholine**

Competitive NM blockers

Mechanism of Action

- **Are competitive antagonists for Ach at the nicotinic receptors present in postjunctional membrane of motor end plate.**
- **No depolarization of postjunctional membrane.**
- **Cholinesterase inhibitors can reverse blockade (Neostigmine).**

Pharmacokinetics

- **They are polar compounds**
  - **inactive orally & taken parenterally**
  - **Do not cross placenta & CNS**
- **Elimination depend upon kidney or liver Except**
  - **Mivacurium *(degraded by acetylcholinesterase enzyme)***
  - **Atracurium *(spontaneous degradation)***

Pharmacological actions:

- **Skeletal muscle relaxation.**
- **They produce different effects on CVS**
- **Some release histamine and produce hypotension**
  - **d.Tubocurarine (not used clinically)**
  - **Atracurium**
  - **Mivacurium**
- **Others produce tachycardia (↑ H.R)**
  - **Pancuronium**

d – Tubocurarine

- **Prototype skeletal muscle relaxant (first muscle relaxant used clinically) .**
- **Not used now clinically due to adverse effects**
- **Histamine releaser**
  - **Bronchospasm**
  - **Hypotension**
- **Blocks autonomic ganglia *(Hypotension)***
- **More safer derivatives are now available.**

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 *(drug of choice).*
- Liberate histamine → (Transient hypotension), bronchospasm.
- Anti-histamine pretreatment may prevent these side effects.
- No effect on muscarinic receptor nor ganglia .

Atracuriam should be avoided in asthma patients b/c it causes bronchospasm due to histamine release.

Mivacurium

- **Chemically related to atracurium**
- **Fast onset of action**
- **Metabolized by pseudo cholinesterases.**
- **Shortest duration of action of all the nondepolarzing drugs (15 min).**
- **Longer duration in patient with liver disease or genetic cholinesterase deficiency.**
- **Transient hypotension (histamine release, similar to atracurium).**

Mivacuriuam induced prolonged muscle paralysis can be reversed by acetycholinesterase inhibitors such as endrophonium,

acetycholinesterase inhibitors increase the Ach level in NMJ and displace Mivacuriam from nicotinic receptors in NMJ.

Pancuronium

- More potent than curare (6 times).
- metabolized in liver and excretion is renal (80 %).
- Long duration of action (metabolic products have some NM blocking activities).
- Tachycardia
  - Antimuscarinic action *(atropine like effects)*
  - Blocks muscarinic receptor in SA node
  - ↑ NE release from adrenergic nerve endings.
  - Avoid in patient with coronary diseases.

Vecuronium

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

Table 9–6. A Summary of the Pharmacology of Nondepolarizing Muscle Relaxants

Relaxant	Chemical Structure[1]	Metabolism	Primary Excretion	Onset[2]	Duration[3]	Histamine Release[4]	Vagal Blockade[5]
Atracurium	B	+++	Insignificant	++	++	+	0
Cisatracurium	B	+++	Insignificant	++	++	0	0
Mivacurium	B	+++	Insignificant	++	+	+	0
Doxacurium	B	Insignificant	Renal	+	+++	0	0
Pancuronium	S	+	Renal	++	+++	0	++
Pipecuronium	S	+	Renal	++	+++	0	0
Vecuronium	S	+	Biliary	++	++	0	0
Rocuronium	S	Insignificant	Biliary	+++	++	0	+

[1]B, benzylisoquinolone; S, steroidal.

[2]Onset: +, slow; ++, moderately rapid; +++, rapid.

[3]Duration: +, short; ++, intermediate; +++, long.

[4]Histamine release: 0, no effect; +, slight effect; ++, moderate effect; +++, marked effect.

[5]Vagal blockade: 0, no effect; +, slight effect; ++, moderate effect.

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

Depolarizing Neuromuscular Blockers

Mechanism of Action

Phase I (Depolarizing)

- **combine and activates nicotinic receptors → depolarization of motor end plate → initial muscle twitching →**

- **Phase II: Persistent depolarization → paralysis (Phase II clinically resembeles non-depolarizing muscle relaxants .**

Succinylcholine (suxamethonium)

Pharmacological Actions (due to depolarization of muscle)

1. **SK. muscle : fasciculation → spastic paralysis.**
2. **Hyperkalemia (due to sk muscle contraction) : Cardiac arrest.**
3. **Eye : ↑ intraocular pressure (depolarization and contraction of extraocular muscle.**
4. **GIT :↑ intragastric pressure → regurgitation of gastric content to esophagus.**
5. **CVS : arrhythmia**

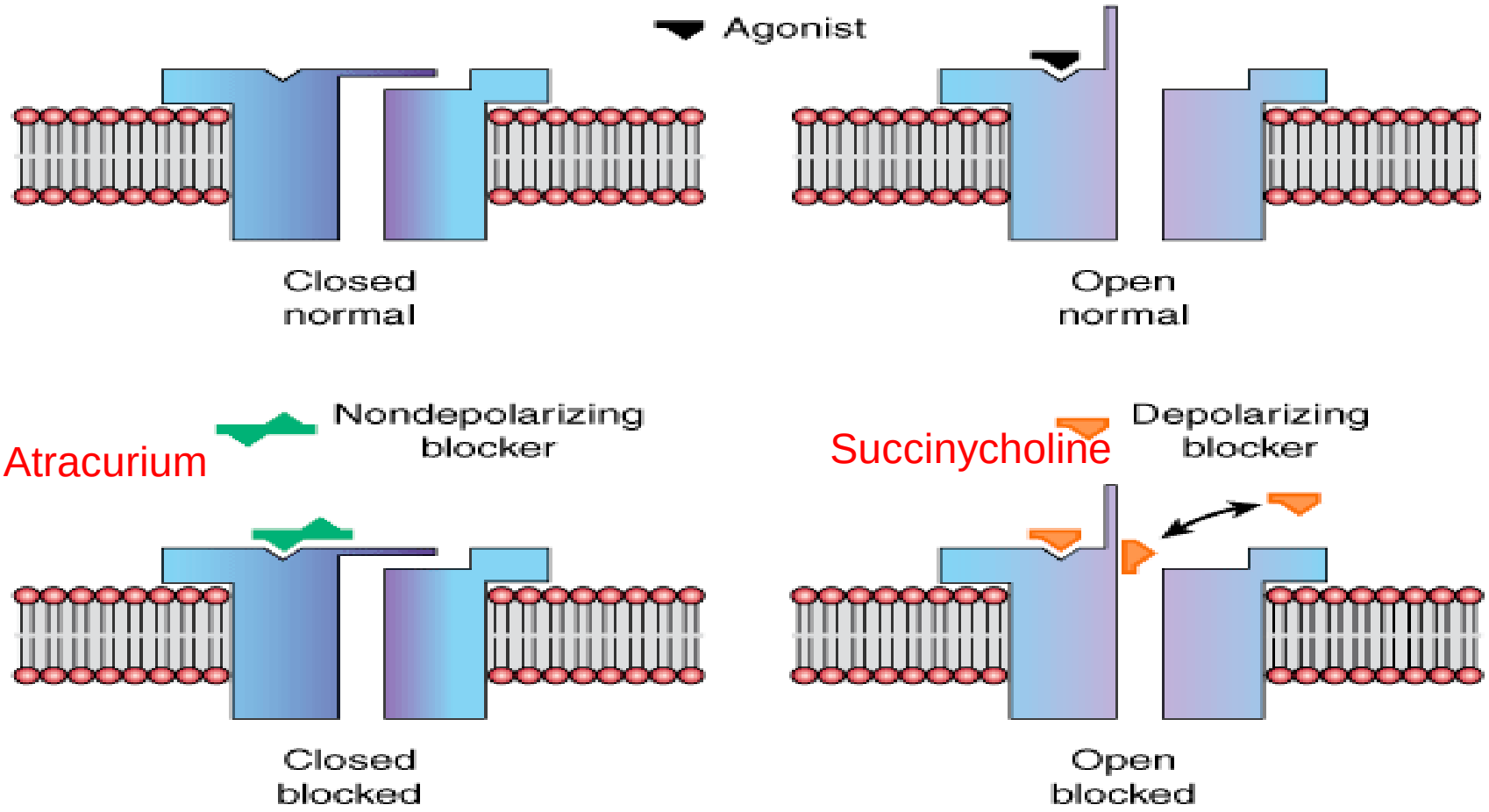
Pharmacokinetics

- **Short onset of action (1 min.).**
- **Short duration of action (5-10 min.).**
- **Destroyed by pseudocholinesterase**
- **Half life is prolonged in**
  - **Neonates**
  - **Elderly**
  - **Pseudcholinesterase deficiency**

Side Effects

- **Hyperkalemia**
- **CVS arrhythmia**
- **↑ IOP # glaucoma**
- **Can produce malignant hyperthermia**
- **May cause succinylcholine apnea due to deficiency of pseudocholinesterase by:**
  - **liver disease**
  - **Malnutrition**
  - **Organophosphorous poisoning (acetylcholinesterase inhibition).**

Mechanism of non-depolarizing and depolarizings muscle relaxants



e.g Atracurium

Succinycholine

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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, severe rise in body temperature**

Dantrolene

Mechanism of Action

- **It interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum).**

- **It inhibits excitation-contraction coupling in the muscle fiber.**
- Calcium is released from the sarcoplasmic reticulum via a calcium channel, called the **ryanodine receptor (RyR) channel and dantrolene blocks the opening of these channels.**

Uses :Malignant Hyperthermia. And Spastic states.

given IV, orally .

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.**
- **Used in treatment of malignant hyperthermia**

Uses of spasmolytics

They reduce muscle spasm in spastic states produced by :

- **Spinal cord injury**
- **Stroke**
- **Cerebral palsy**

Drugs and diseases that modify NM blockers effects

- **Aminoglycosides (e.g streptomycin) enhances the effects of NM blockers.**
- **Cholinesterase inhibitors may enhance the effect of depolarizing relaxants but decrease the effect of nondepolarzing relaxants.**
- **Disease states such as mysthania gravis and parkinson modify the response to muscle relaxants.**
- **Magnesium sulphate may antagonize the effect of muscle relaxants.**