Skeletal Muscle Relaxants-2

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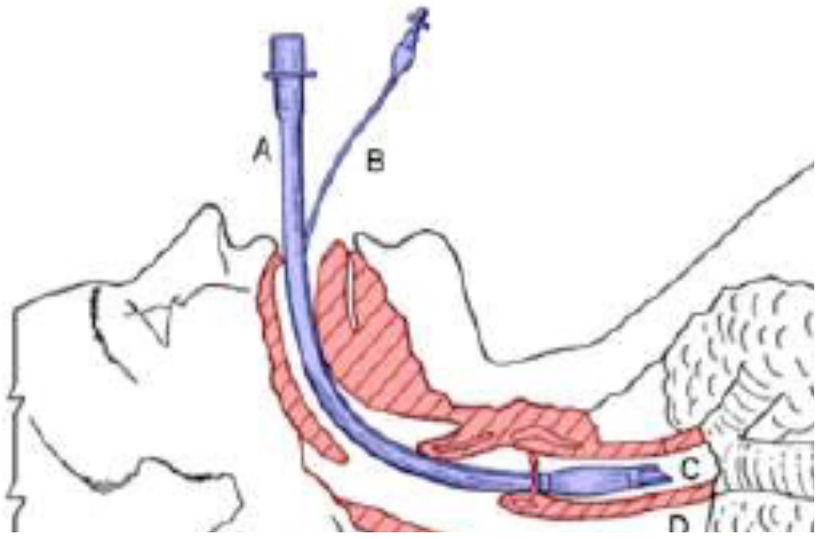
Why are Skeletal muscle relaxants important clinically



History

Classification

Skeletal muscle relaxants

Centrally acting
- Diazepam and other benzodiazepines
- Methocarbamol
- Chlorzoxazone
- Tizanidine
- Baclofen
- Gabapentin

Peripherally acting

Drugs acting at NMJ

Depolarizing blockers
- Succinylcholine
- Decamethonium

Non-depolarizing blockers (Competitive blockers)
- d-TC
- Pancuronium
- Doxacurium
- Pipecuronium

} Long acting

- Vecuronium
- Atracurium
- Rocuronium

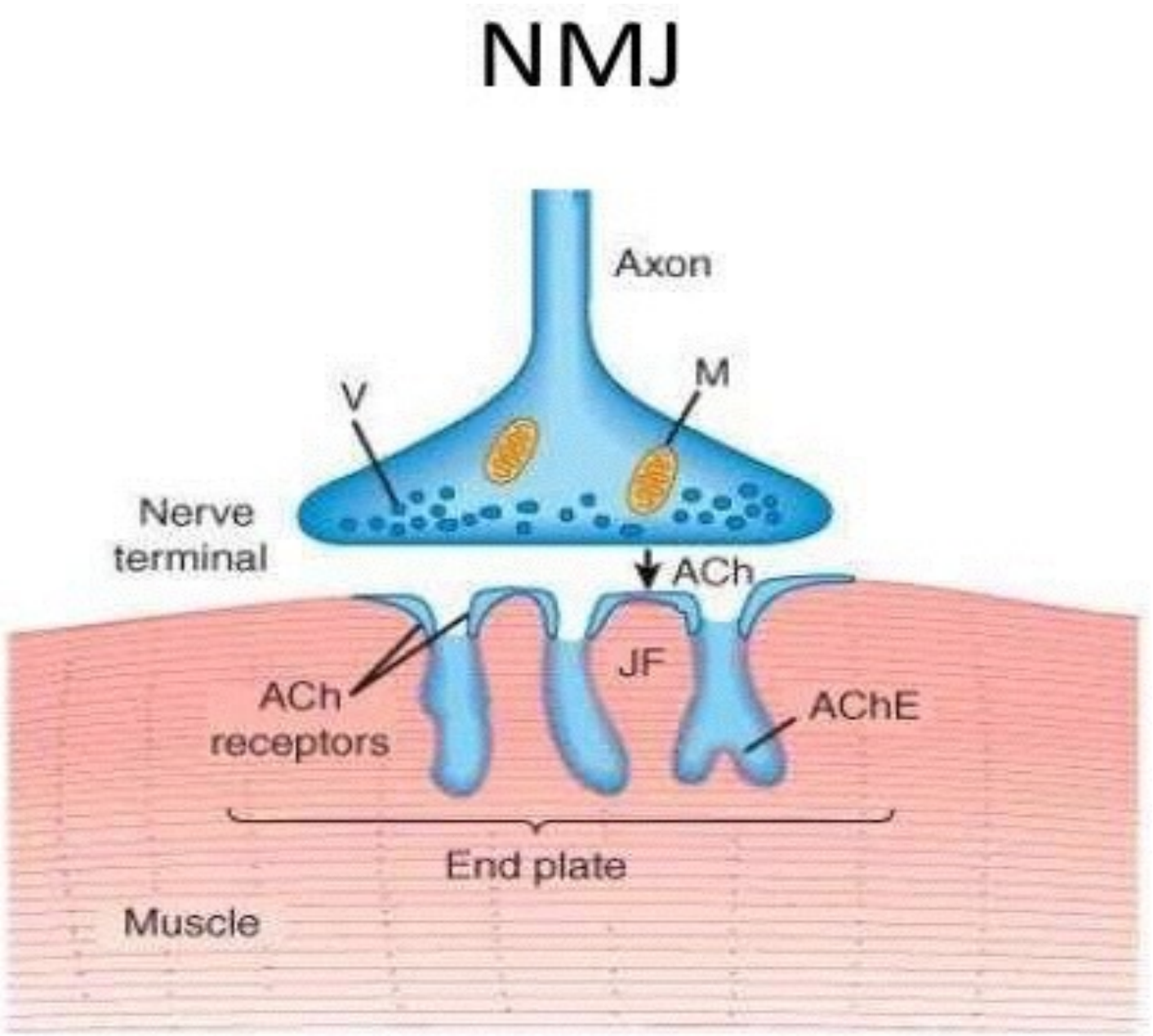
} Intermediate acting

- Mivacurium — Short acting

Drugs directly acting on skeletal muscle
- Dantrolene

Others
- Botulinum toxin A

Neuromuscular Junction (NMJ)



Physiology of Skeletal Muscle Contraction

Motor nerve impulse

↓

Release of acetylcholine

↓

Binds with N_M receptors at NMJ

↓

Depolarization and development of end-plate potential (EPP) at motor end plate (Mainly due to influx of Na^+)

↓

Muscle-action potential (MAP) – Contraction of skeletal muscle

↓

ACh is rapidly inactivated by cholinesterase leading to repolarization

↓

Muscle is ready for a fresh nerve impulse

Peripherally acting: Neuromuscular Blockers

- **Depolarizing Blockers** – mimic the action of acetylcholine (ACh)
  - Agonists
  - Succinylcholine (SCh) is the only drug used clinically

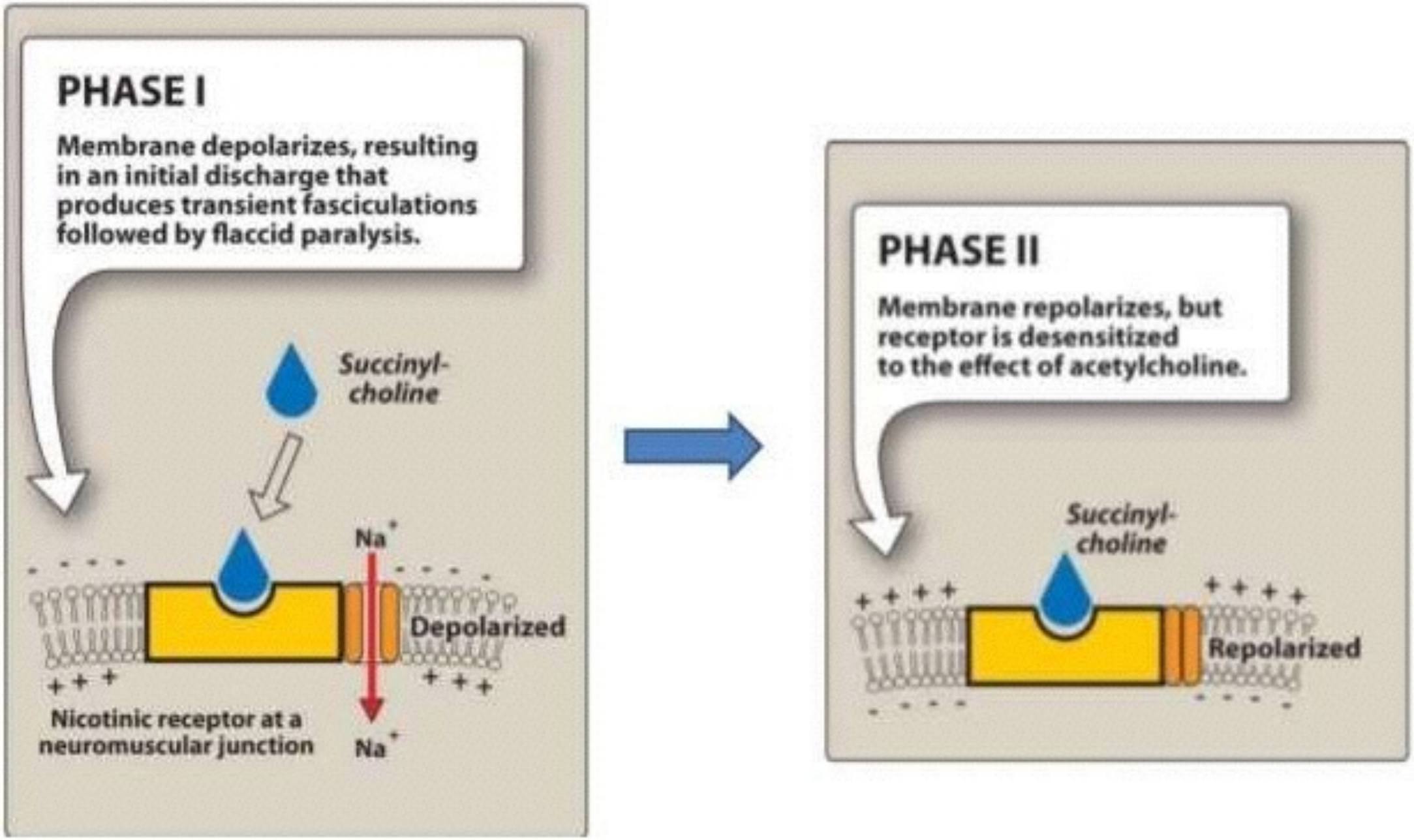
- **Non-Depolarizing** – interferes with the action of ACh
  - Competitive Blockers (Antagonist)
  - Further divided into short, intermediate and long acting non- depolarizing drugs

Succinylcholine acts on the Nicotinic receptors of the muscles, stimulates them and ultimately cause their relaxation.

➢ This process occur in two phases :

- Phase I: During Phase I (depolarizing phase), they cause muscular fasciculations while they are depolarizing the muscle fibers.

- Phase II: After sufficient depolarization has occurred, phase II (desensitized phase) sets and the muscle is no longer responsive to Ach released by the nerve endings.


PHASE I
Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.
Succinyl-choline
Na+
Depolarized
Nicotinic receptor at a neuromuscular junction
Na+
PHASE II
Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.
Succinyl-choline
Repolarized

Succinylcholine

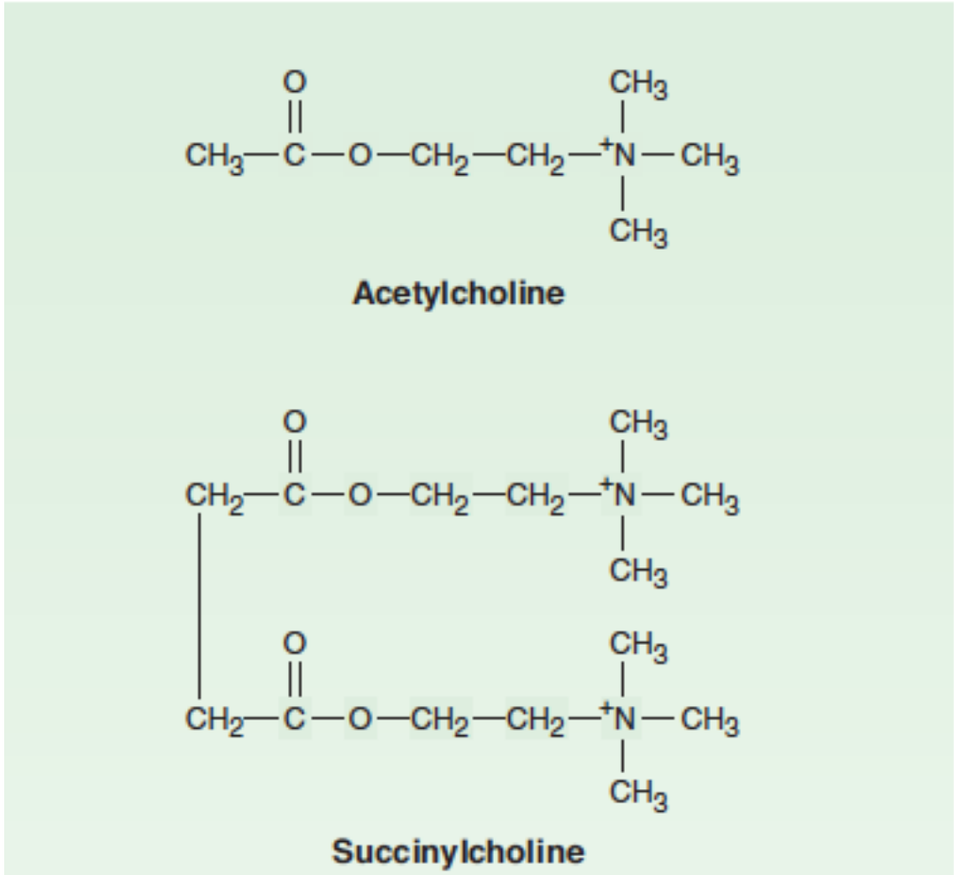
Advantages:

- Most commonly used for Tracheal intubation
- Rapid onset (1-2 min)
- Good intubation conditions – relax jaw, separated vocal chords with immobility, no diaphargmatic movements
- Short duration of action (5-10 minutes)
- Dose 1-1.5mg/kg
- Used as continous infusion occasionally

Disadvantages:

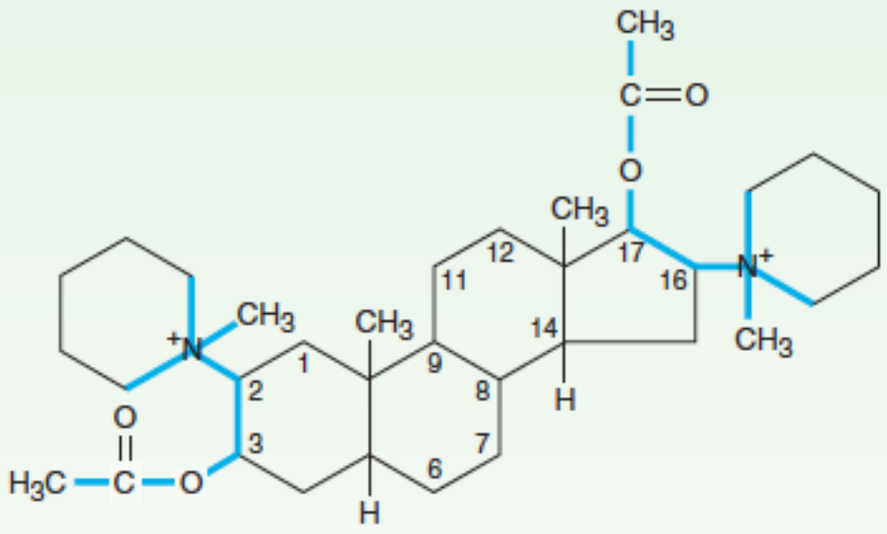
- Cardiovascular: unpredictable BP, heart rate and arrhythmias
- Fasciculation
- Muscle pain
- Increased intraocular pressure
- Increased intracranial pressure
- Hyperkelemia: k+ efflux from muscles, life threatening in Cardiac Heart Failure, patient with diuretics etc

Chemistry & PK



Acetylcholine

Succinylcholine



Pancuronium

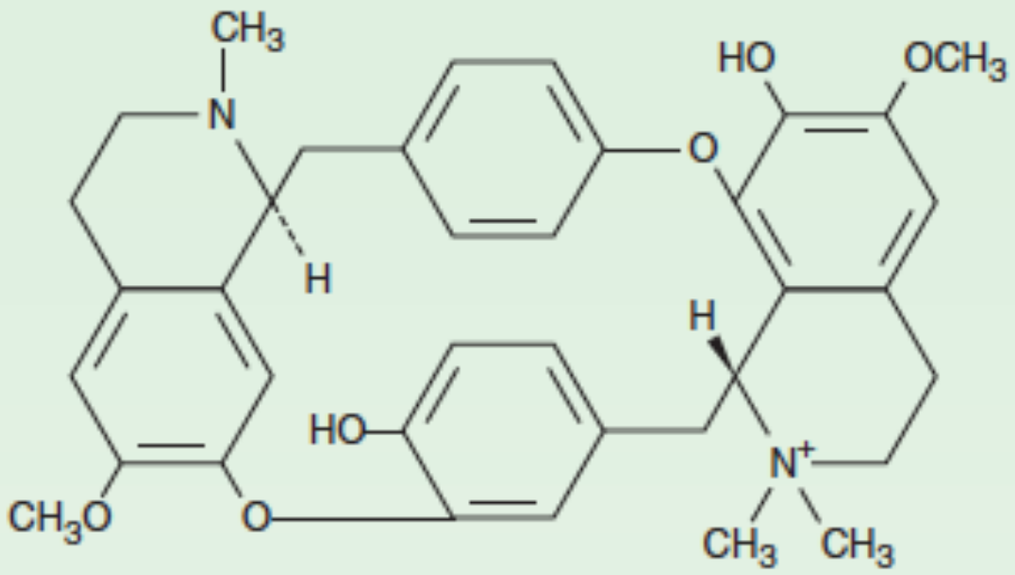
Non-Depolarising Drugs

- Competitive Blockers having no intrinsic activity (antagonist)
- These are of 3 types based on their activity:
  - *Long Acting :* d-TC, Pancuronium, Pipecuronium, Gallamine (Kidney Excretion)
  - *Intermediate :* Vecuronium, Rocuronium, Atracuronium (eliminated by liver)
  - *Short Acting :* Mivacuronium, Ropcacuronium (inactivated by plasma cholinesterase)

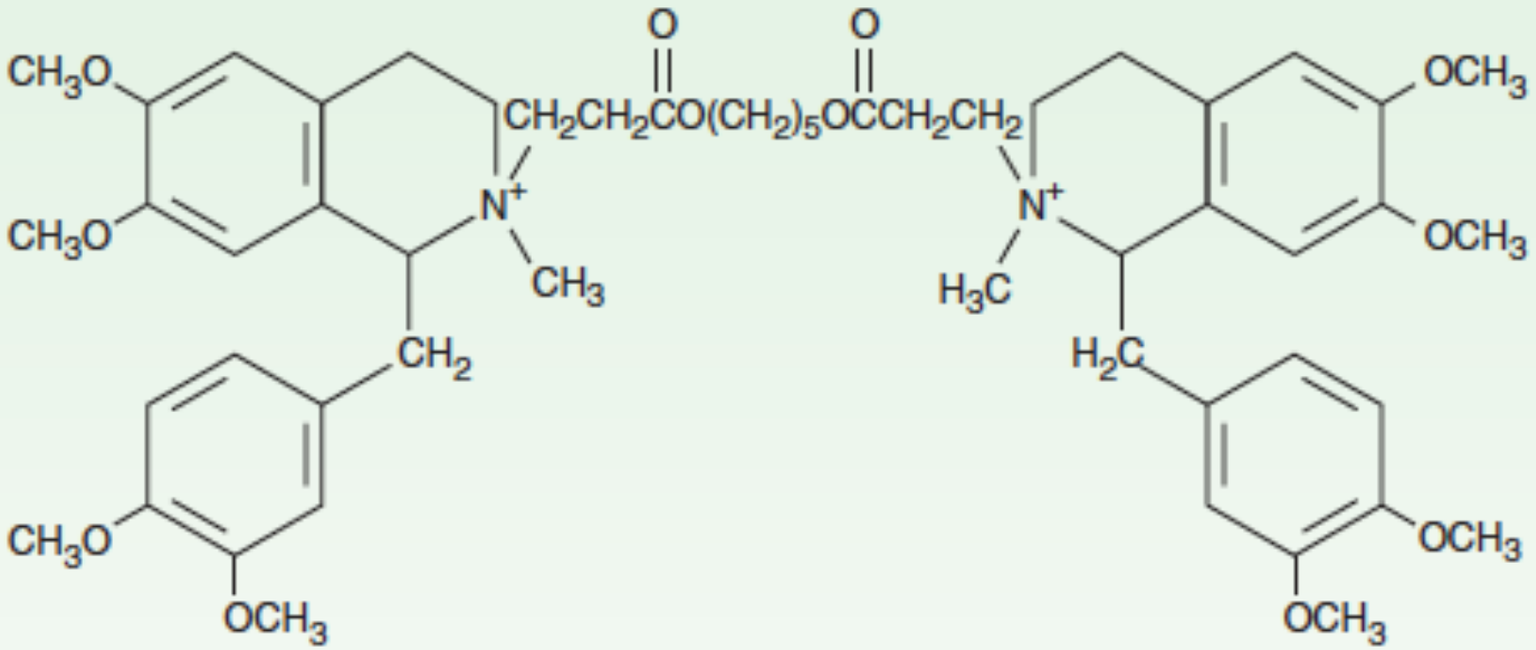
Pharmacokinetics of N_m blockers

- Polar quaternary compound - Not absorbed orally, do not cross cell membranes, Blood Brain Barrier or placental barrier

- low Volume of distribution – always given intravenously or rarely intramuscular



Tubocurarine



Atracurium

Structures of two isoquinoline neuromuscular blocking drugs. These agents are nondepolarizing muscle relaxants.

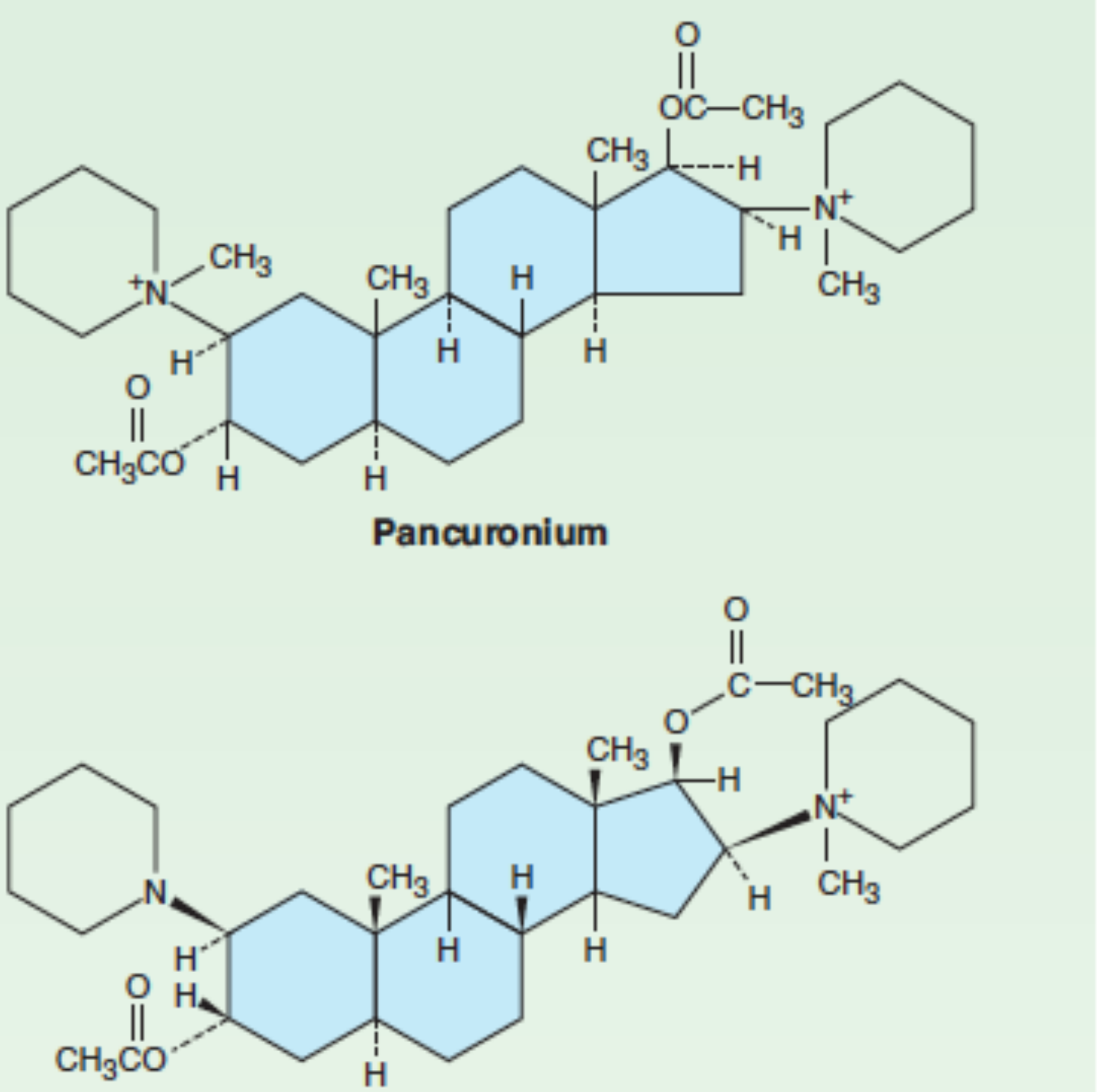
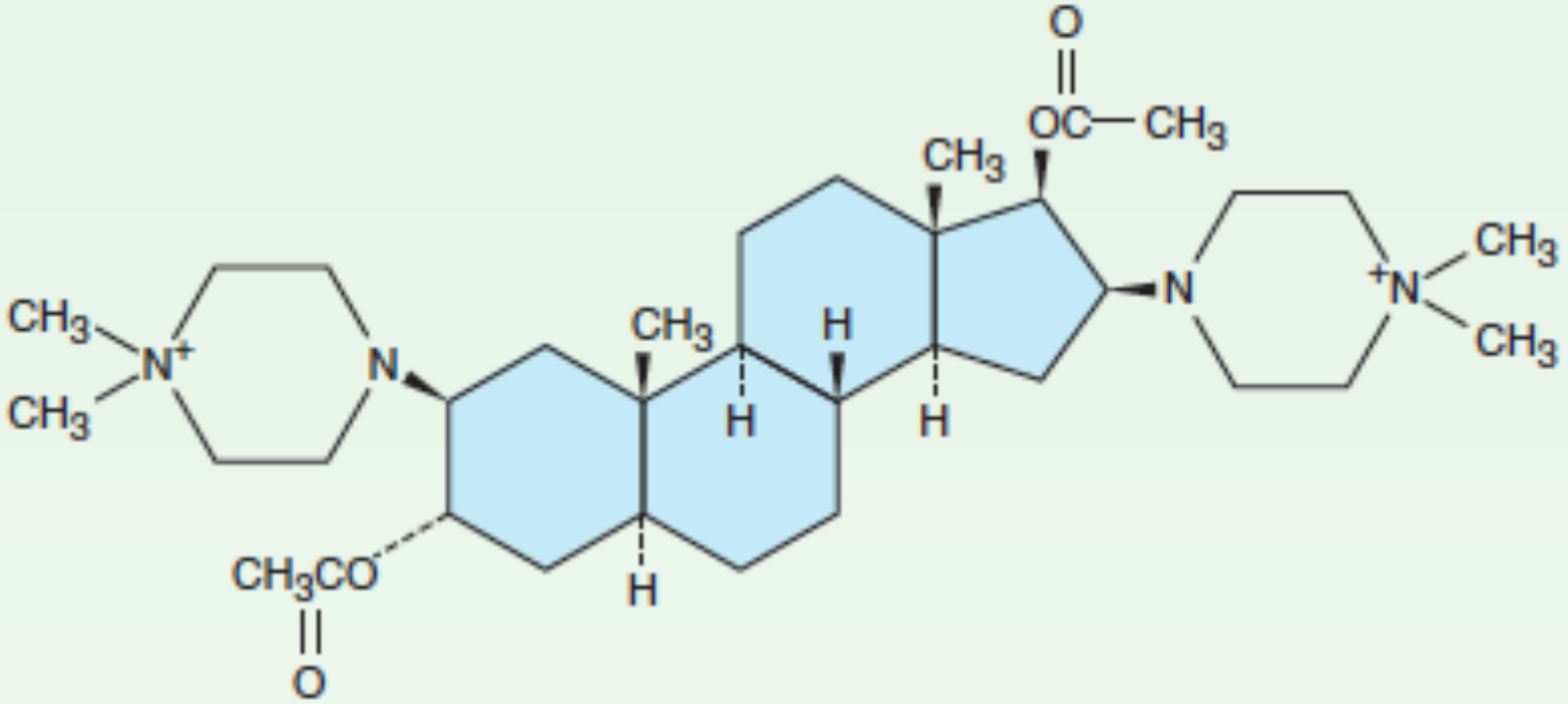
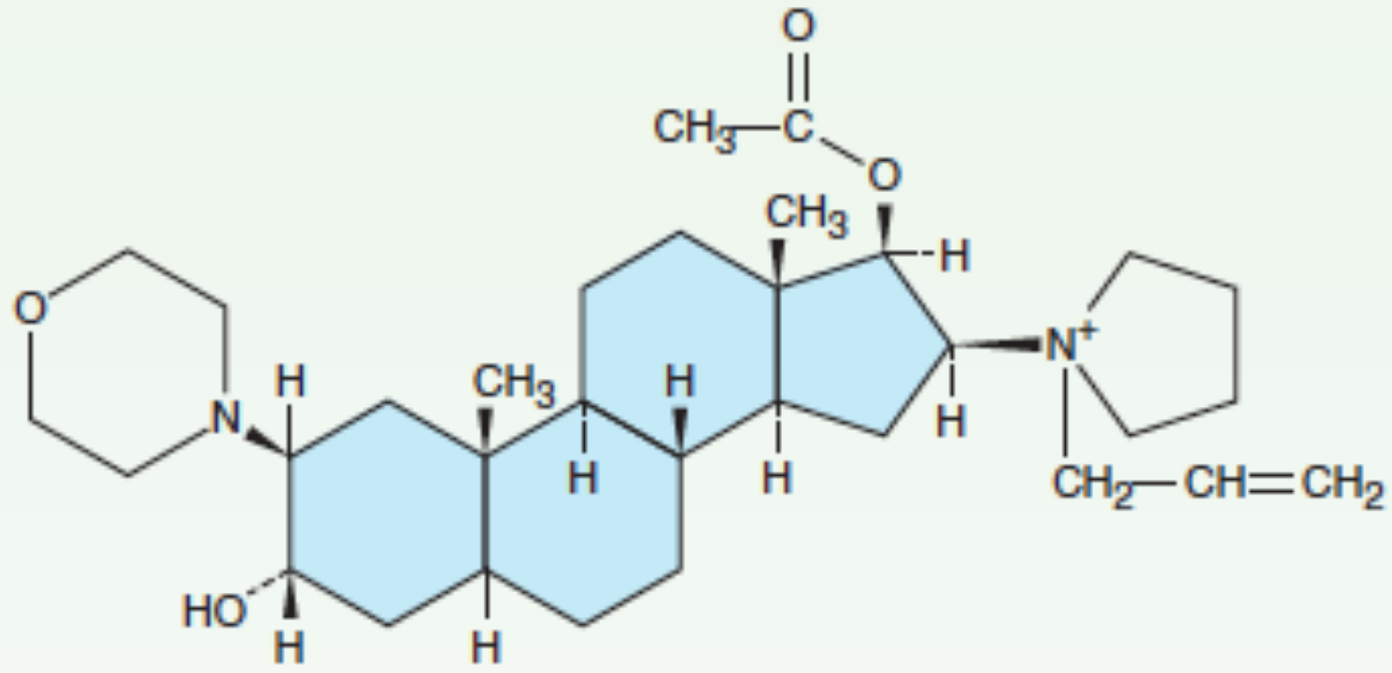


FIGURE 27–5 Structures of steroid neuromuscular blocking drugs (steroid nucleus in color). These agents are all nondepolarizing muscle relaxants.



Pipecuronium



Rocuronium

FIGURE 27–5 Structures of steroid neuromuscular blocking drugs (steroid nucleus in color). These agents are all nondepolarizing muscle relaxants.

Effects of Non-depolarizing blockers

- **Low Doses**:
  - Competitive antagonists of ACh
  - Action reversed by ACh ecterase inhibitors
- **Large Doses**:
  - Ion Channel is blocked
  - More weakness of neuromuscular transmission
  - Action could not be reversed by ACh esterase inhibitors
- **Other actions**:
  - Can block pre-junctional Na_+ channels and interfere with mobilization of ACh at nerve endings

Non-depolarizing Drug: d-Tubocurarine

- 1st agent to undergo clinical investigation
- purified curare – *Chondodendrom tomentosum*
- ED_{95}= 0.5mg/kg
- undergoes minimal metabolism- is excreted
  - 10% in urine
  - 45% in bile
- excretion impaired in Renal Failure

CVS Effects:

- hypotension frequently even at doses < ED_{95}
- histamine released (skin flushing frequently)
- autonomic ganglionic blockade- manifests as hypotension

Clinical Use:

- long duration of action(60 to 120 mins) and CVS effects restricted its use
- used as “precurarization”

Non-depolarizing Drugs

- Gallamine
  - Less potent than curare
  - Tachycardia
- D-Tubocurarine
  - 1-2 hr duration of action
  - Histamine releaser (Brochospasm, hypotension)
  - Blocks autonomic ganglia (Hypotension)
- Atracurium
  - Rapid recovery
  - Safe in hepatic & renal impairment
  - Spontaneous inactivation to laudanosine (seizures)

Non-depolarizing Drugs

- Mivacurium
  - Metabolized by pseudocholinesterase
  - Fast onset and short duration
- Pencuronium
  - Long duration of action
  - Tachycardia
- Vecuronium
  - Intermediate duration of action
  - Fewer side effects (no histamine release, no ganglion blockade, no antimuscarinic action)

Difference between the competitive and depolarisinng muscle blocker

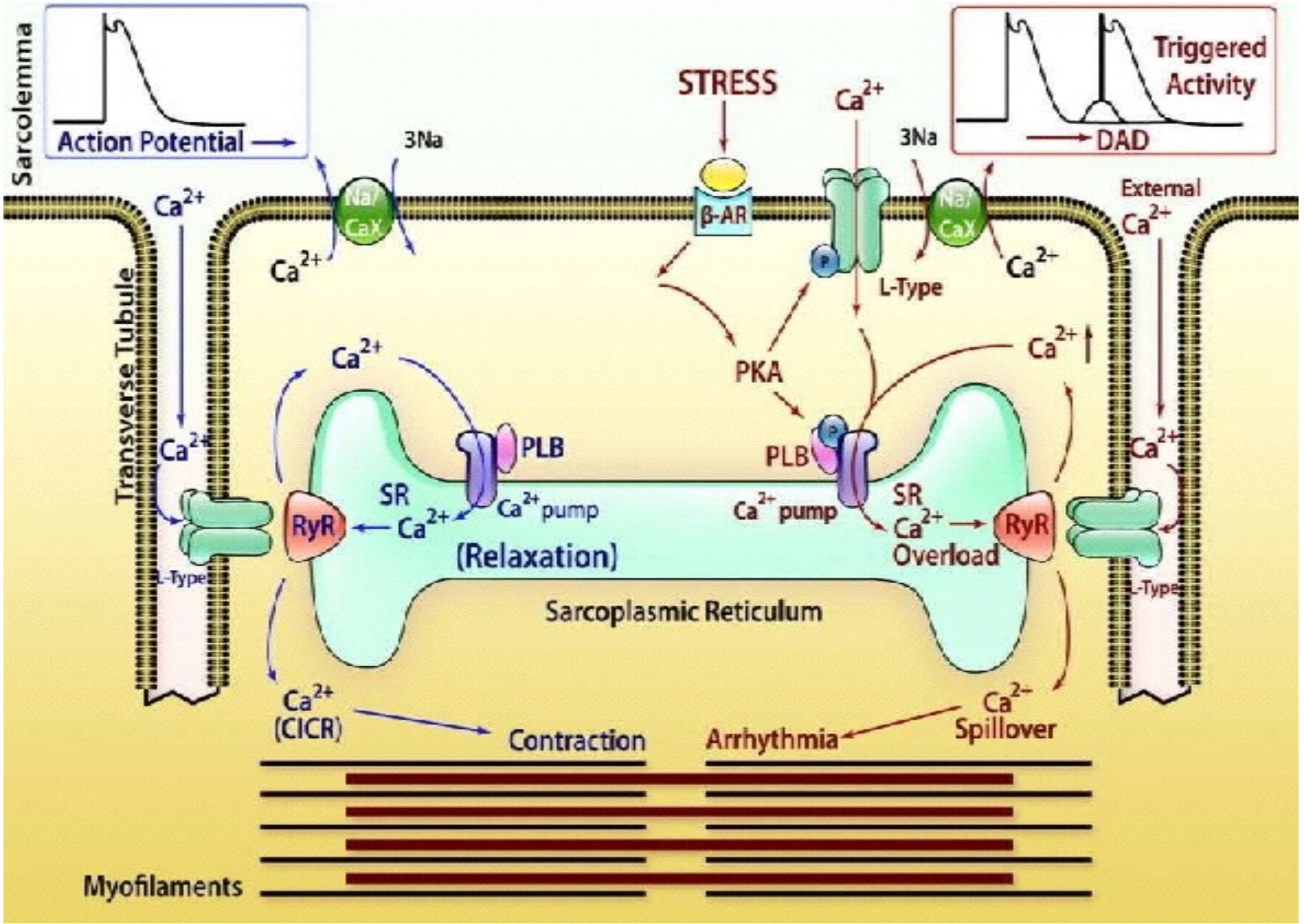
parameter	D tubocurarine	Succinylcholine
Blockade type	Competitive blockade	Depolarising blockade
Type of relaxation	Flaccid paralysis	Fasciculation followed by paralysis
Neostigmine addition +	antagonism	Potentiation
Effect of other neuromuscular blocking drug	Decreased effect	Increases effect
Histamine release	++ release	negligible
Serum k+ level	No change	Hyperkalemia
Pharmocogenetic variation	nil	pesudocholinesterase
Cardiac M2 receptor	No effect	stimulate (bradycardia)

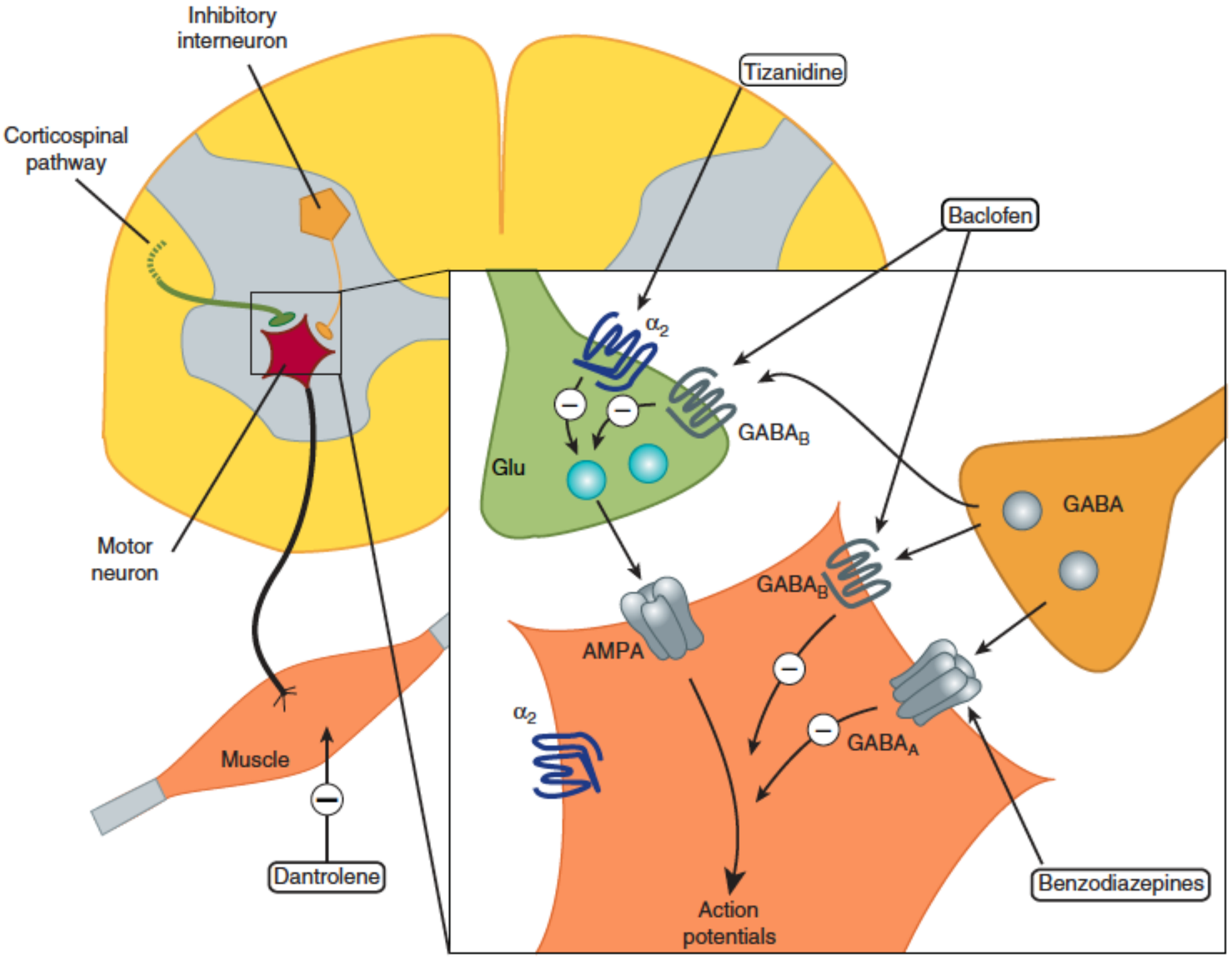
Other Actions of N_m Blockers

- Automic ganglia:
  - Partial blockage of ganglia (Nm type of receptor)
  - Results in fall in BP and tachycardia
- Histamine release:
  - Hypotension
  - Bronchospasm, excess bronchial and salivary secretion
- Cardiovascular: Fall in BP due to
  - Ganglion blockage, histamine release and reduced venous return
  - Succinylcholine may cause cardiac arrhythmias
- GIT: Paralytic ileus

Directly acting relaxants - Dantrolene

- Different from neuromuscular blockers, no action on neuromuscular transmission
- Mechanism of Action: Ryanodine receptors (RyR) calcium channels – prevents depolarization – no intracellular release of Ca_{++}
- Absorbed orally, penetrate brain and produces sedation, metabolized in liver, excreted in kidney. $T_{1/2}$ 8-12 hrs
- Dose: 25-100mg - 4 times daily
- Uses: Upper Motor Neuron disorders – paraplegia, hemiplegia, cerebral palsy and malignant hyperthermia (drug of choice 2.5-4 mg/kg)
- Adverse effects – Sedation, malaise, light headedness, muscular weakness, diarrhoea and hepatotoxicity


Sarcolemma
Action Potential
Triggered Activity
DAD
STRESS
Ca^{2+}
3Na
Na/CaX
β-AR
P
L-Type
External
Ca^{2+}
Transverse Tubule
PKA
PLB
SR
Ca^{2+} pump
RyR
(Relaxation)
Ca^{2+} Overload
Sarcoplasmic Reticulum
Ca^{2+} (CICR)
Contraction
Arrhythmia
Ca^{2+} Spillover
Myofilaments


Inhibitory interneuron
Tizanidine
Corticospinal pathway
Baclofen
α_2
$GABA_B$
Glu
GABA
$GABA_B$
AMPA
α_2
$GABA_A$
Motor neuron
Muscle
Dantrolene
Action potentials
Benzodiazepines