SKELETAL MUSCLE RELAXANTS

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Definition

- **Skeletal muscle relaxants** are drugs that act peripherally at neuromuscular junction/ muscle fiber itself or centrally in the cerebrospinal axis to reduce muscle tone and /or cause paralysis.

- **Drugs that affect skeletal muscle function fall into two major groups:**

  1. **Neuromuscular blocking drugs**
  2. **Spasmolytics**

Neuromuscular Junction

- With the arrival of an **action potential** at **motor nerve terminal**, influx of Ca, and release of **acetylcholine (ACh)**
- **ACh** diffuses across synaptic cleft to **nicotinic receptor** located on the **motor end plate**
- Combination of Ach with receptor causes opening of **Na and K channels**
- **Na moves inside** producing **depolarisation** of **motor end plate membrane**
- **Muscle contraction** is then initiated by **excitation-contraction coupling**

The Neuromuscular Junction

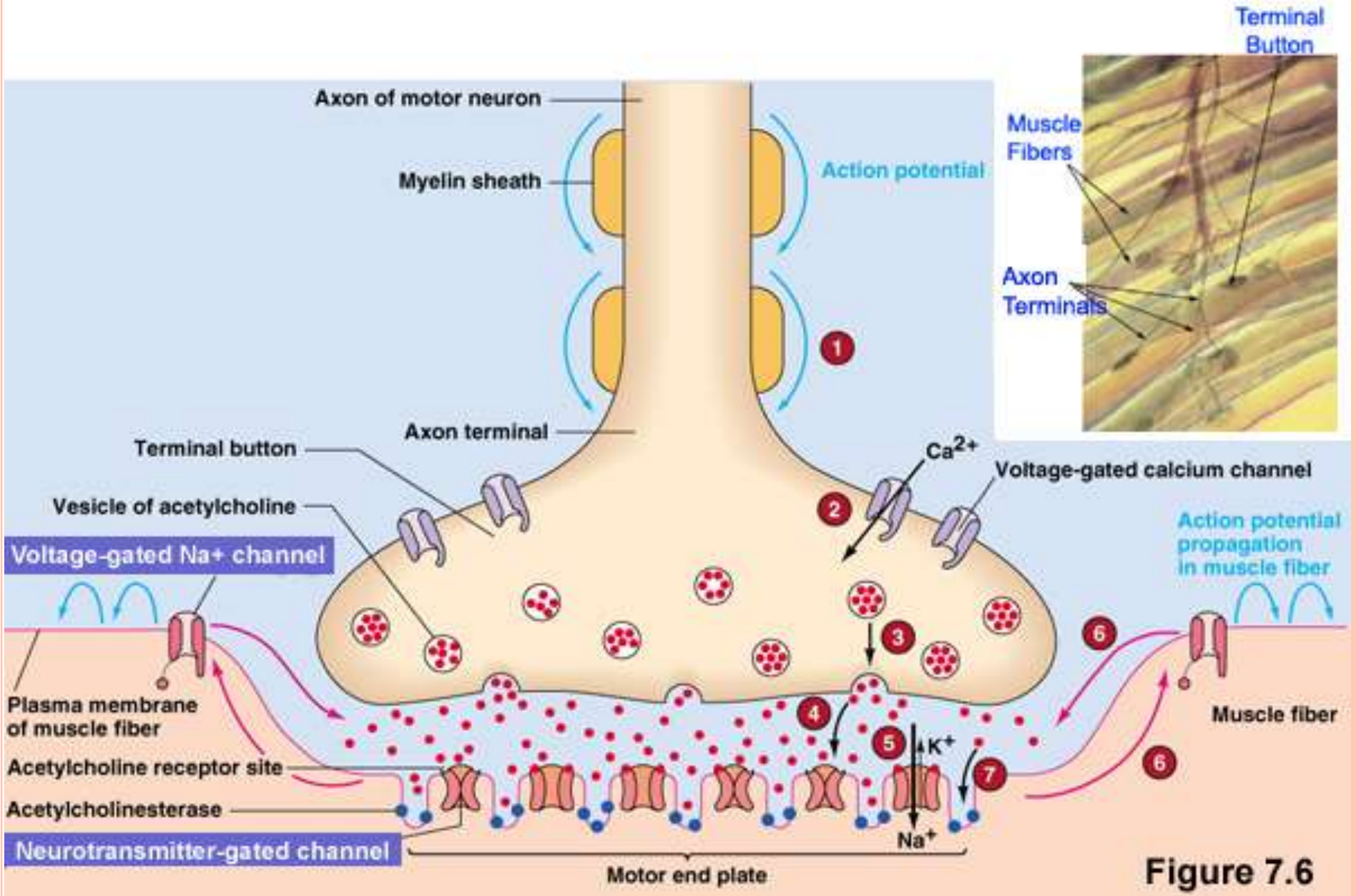


Figure 7.6

- The released **Ach is quickly removed by enzymatic destruction** by **acetylcholinesterase (splits Ach into choline and acetate),** and thereby **terminates action of Ach**

- **Skeletal muscle relaxation and paralysis** occur from interruption of function at several sites including:
  - **The motor end plate**
  - **Central nervous system**
  - **Contractile apparatus**

1. Neuromuscular blocking drugs

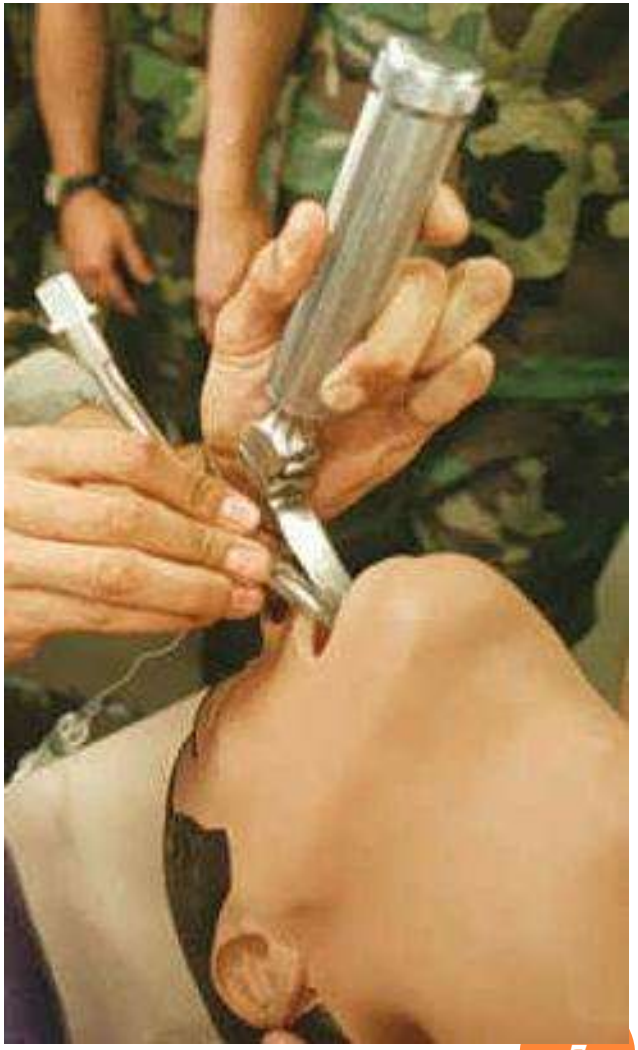
- **Cite of action:** interfere with cholinergic transmission at neuromuscular end plate

- All of **neuromuscular blocking drugs** are **highly polar** & **inactive when administered by mouth**

- **They are always administered intravenously (i.v.)**

Therapeutic uses

1. **To provide muscle relaxation during surgery** (adjuvant to anesthesia)
2. They relax **vocal cords** & facilitate **tracheal intubation**



3. **Intensive care units (ICU)**

- Because neuromuscular block **may paralyse muscles required for breathing**, **mechanical ventilation** should be available

Neuromuscular blocking drugs

A. Competitive (non-depolarising blocking drugs):

- Constitute the majority of clinically-relevant neuromuscular blockers
- These drugs are **competitive antagonists of Ach**
- They bind to nicotinic receptors, **prevent access of Ach to its receptors** & **prevent depolarisation**, the result is **flaccid paralysis**

A. Competitive (non-depolarising blocking drugs):

- **Two major families of competitive antagonists:**

1. Isoquinoline derivatives:

- Atracurium
- Tubocurarine
- Cisatracurium
- Mivacurium

2. Steroid derivatives

- Pancuronium
- Vecuronium
- Pipecuronium
- Rocuronium

- Non-depolarising blocking drug is chosen according to its:

1. Onset of effect

2.Duration of action:

- Short-acting (15-30 min), mivacurium

- Intermediate-acting (30-40 min), atracurium

- Long-acting (60-120 min), pancuronium

3. Side-effects

-Isoquinoline derivatives (except cisatracurium) are associated with **histamine release** which can cause **flushing, hypotension, tachycardia & bronchospasm**

-Steroid muscle relaxants are not associated with histamine release

-Non-depolarising muscle relaxants **have a slower onset of action** than suxamethonium

1. Atracurium:

- Short to intermediate duration of action
- It undergoes **non-enzymatic metabolism** which is **independent of liver & kidney function**
- Thus it is used **in patients with hepatic or renal impairment**

2. Pancuronium

- Has a long duration of action
- Is often used in patients receiving long-term mechanical ventilation in intensive care units

Reversal of non-depolarising blocking drugs:

- Reversal of this type can be achieved with **cholinesterase inhibitor** drugs, such as **neostigmine**

- **Prevents destruction of Ach by cholinestarase**, allowing **accumulation of Ach at nerve endings & reduce competitive effect blocking agents**

- Neostigmine is given **intravenously**

- It acts in **4 minutes** & lasts for **30 minutes**

B. Depolarising blocking drugs:

- **Succinylcholine (Suxamethonium)** is the only drug used clinically
- Act by depolarising the end plate, similar to Ach, except that it produces a longer effect

Mechanism of action

- **Phase I (depolarising phase):**

  - **Suxamethonium** reacts with nicotinic receptor & causes **depolarisation** of end plate

  - This in turn **spreads & depolarises adjacent membranes**, causing **generalised disorganised contractions** of muscle motor units **(transient muscle fasciculations)**

-Because Suxamethonium is not metabolised effectively at the synapse

-The membrane remains depolarised & unresponsive to additional impulses

- **Phase II (desensitising phase):**

-With continued exposure to Suxamethonium, initial end plate depolarisation decreases & membrane becomes repolarised

- Despite this repolarisation, membrane cannot easily be depolarised again (it is desensitised), this causes flaccid paralysis

- Suxamethonium has:
  - Most rapid onset (30 seconds)
  - Shortest duration of action (5-10 minutes)

- Tracheal intubation is possible in less than 60 seconds & total paralysis lasts up to 4 minutes
- Suxamethonium is destroyed by plasma cholinesterase

- Repeated injections of **Suxamethonium** can cause **bradycardia & ventricular arrest** due to **activation of cholinoreceptors in heart** & can be prevented by **atropine**

Side effects:

1. Hyperkalemia:

- Suxamethonium depolarisation causes a release of K from muscle
- This a problem only if patient's plasma K is already high, e.g. acute renal failure
- In patients with spinal cord injuries & those with major burns, suxamethonium may cause a release of K, sufficient to cause cardiac arrest

2. Muscle pain:

- Is an important **postoperative complaint** in patients who have received succinylcholine

-This is due to secondary damage produced in muscle by unsynchronised contractions of adjacent muscle fibers just before paralysis

-Suxamethonium should be given after anesthesia because paralysis is usually preceded by painful muscle fasciculation

3. Apnea:

-in patients who are deficients to plasma cholinesterse

2. Spasmolytics

- **Spasticity** is disorder of motor system especially CNS, certain muscles are continuously contracted
- It is associated with a variety of neurologic conditions: **cerebral palsy, multiple sclerosis & stroke**
- **Spasmolytics** are called **centrally acting muscle relaxants**
- Spasmolytics are used to reduce spasticity by:

- Either enhancing level of inhibition or reducing level of excitation that motor neuron receives
- Interfering directly with skeletal muscle excitation-contraction coupling

1. Diazepam:

- Benzodiazepines facilitate action of γ-aminobutyric acid (GABA) in CNS
  - It acts at all $GABA_A$ synapses
  - It can be used in patients with muscle spasm of any origin, including local muscle trauma
  - It produces sedation in most patients at doses required to reduce muscle tone

2.Baclofen:

- It acts as GABA agonist at $GABA_B$ receptors

-Activation of receptors in brain by baclofen results in hyperpolarisation

-This hyperpolarisation serve a presynaptic inhibitory function, by reducing Ca influx, to reduce release of excitatory neurotransmittors in both brain & spinal cord

- Baclofen is at least as effective as diazepam in reducing spasticity & causes much less sedation

- It dose not reduce general muscle strength as much as dantrolene

- Rapidly & completely absorbed after oral use half-life of 3-4 hours

- Dosage 15 mg twice daily, increasing to 100 mg daily

3. Dantrolene:

- It reduces skeletal muscle strength by **interfering with excitation-contraction coupling in muscle fiber**

- The normal contractile response involves **release of Ca from its stores in sarcoplasmic reticulum**

-**Ryanodine receptor** mediates **release of Ca**

- Ca brings interaction of **actin with myosin & initiates muscle contraction**

Cite of action:

- Binds to ryanodine receptor & decreasing intracellular Ca concentration
- half-life is **8 hours**
- Treatment begun with **25 mg daily**, increasing to **100 mg four times daily**
- Major adverse effects are **generalised muscle weakness & sedation**

4. Tizanidine:

- Is a newly introduced alpha$_2$-adrenocptor agonist
- It is indicated for spasticity associated with multiple sclerosis or spinal cord injury

Drugs used for acute local muscle spasm

Orphenadrine, metaxalone, cyclobenzabine

-They relieve **acute temporary muscle spasm caused by trauma or strain**

- Most act as sedative at level of **spinal cord or brain stem**