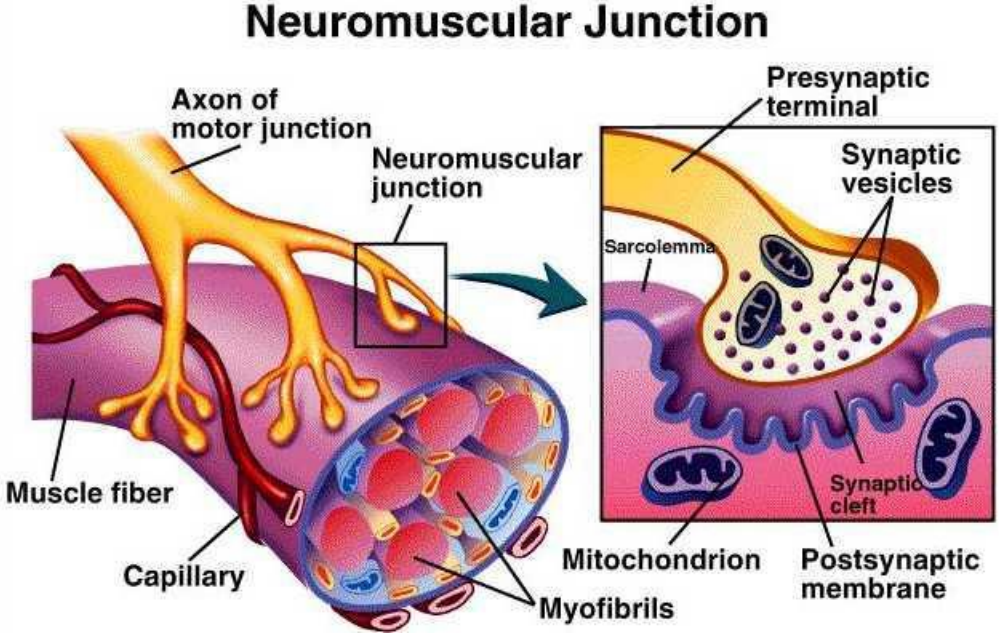
NEUROMUSCULAR BLOCKADE

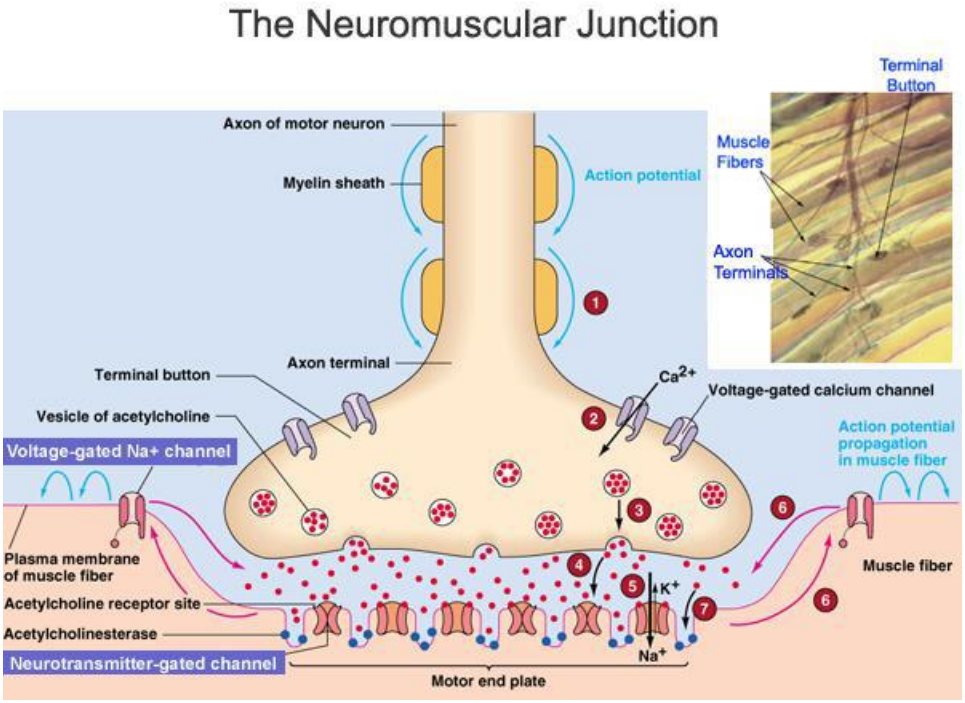
Physiology of neuromuscular junction:

Acetylcholine (ACh) is the neurotransmitter at the neuromuscular junction that released from pre-synaptic nerve endings on passage of a nerve terminal. When a nerve impulse (action potential) arrived, the storage vesicles are transferred to the active zones on the edge of the axonal membrane and release the ACh by the depolarizing of the nerve terminal. Entry of Ca^{+2} ions into the nerve terminal is a necessary part of this process.

The active sites of release are located directly opposite the nicotinic ACh receptors on the junctional folds of the post-synaptic membrane lying on the muscle surface.



Each nicotinic ACh receptor consists of 5 subunits, two of which, the alpha, are identical, activation of the receptor requires both two alpha sites to be occupied producing a structural change in the receptors complex that opens channel running between the receptors for a very short period (about 1 ms), this allows movement of cations such Na_{+}, K_{+}, Ca_{+2} and Mg_{+2} along their concentration gradients. The main change is influx of Na_{+} ions and followed by efflux of K_{+} ions (this process is the end-plate current). The current lowers the trans-membrane potential of the end-plate region sufficient to depolarize it and generate a muscle potential sufficiently to allow muscle contraction.



Depolarizing and non depolarizing muscle relaxants

Muscle relaxants (Neuromuscular blocking agents) are drugs used to produce relaxation and paralyses to the skeletal muscles. These agents are divided into two classes: Depolarizing and Non-depolarizing (competitive) muscle relaxants, the depolarizing muscle relaxant alters the structural conformity of the post-synaptic ACh receptor and produce an initial depolarization preventing further action potentials passing down the ion channels and that how the muscle become flaccid, while the non-depolarizing muscle relaxant competes with the neurotransmitter (ACh) at the site, preventing its binding and so leading to muscle relaxation.

Note: There are two types of ACh receptors, Nicotinic and muscurinic, the type of receptors in which located in the neuromuscular junction and responsible to skeletal muscle contraction are the nicotinic receptors, neuromuscular blocking agents (muscle relaxants) acts on these receptors. While the muscarinic receptors have another functions such as (secretion from salivary glands and stomach, slowing heart rate, reducing contractile force of atrium, bronchoconstriction and increasing lung secretion, increasing gastrointestinal motility, and inducing emesis).

Depolarizing muscle relaxants

Succinylcholine (Suxamethonium).. Scoline®:

The only depolarizing muscle relaxant now available in clinical practice. It is comparable to two molecules of ACh linked together, they have the capacity to cling to each of the alpha units of the post-synaptic ACh receptor altering its structural conformation and opening the ion channel, but for a longer period than does a molecule of ACh, administration of succinylcholine therefore results in an initial depolarization and muscle contraction termed fasciculation, at this effect persists, however, further action potentials cannot pass down the ion channels and the muscle become flaccid.

The dose of succinylcholine necessary for tracheal intubation in adults is 1 – 1.5 mg / kg, this dose produces profound block within 1 minute. The drug is metabolized predominantly in the plasma by the enzyme plasma cholinesterase at a very rapid rate. Recovery from neuromuscular block may start to occur within 3 minutes and complete within 12 – 15 minutes. The use of anticholinesterase such as neostigmine, which would inhibit such enzyme activity, is contraindicated. About 10% of the drug is excreted in the urine, there is a very little metabolism in the liver although some breakdown by non-specific esterases occurs in the plasma.

If plasma cholinesterase is structurally abnormal because of inherited factors, or if its concentration is reduced by acquired factors, then the duration of the drug may be altered significantly.

Side effects and clinical considerations of succinylcholine:

1) Cardiovascular instability:

a) Bradycardia: with administrating of low doses, administration of second bolus and when administrating to children: Intravenous atropine (0.4 mg in adults, 0.02 mg/kg in children) is normally given as a prophylaxis to children prior to the first and subsequent doses, and *usually* before a second dose of succinylcholine is given to adults.

b) Tachycardia: with higher doses.

c) Increased or decreased blood pressure.

2) Hyperkalaemia: It can be life-threatening in patients with preexisting hyperkalemia. The increase in potassium in patients with burn injury, massive trauma, neurological disorders, and several other conditions can be large and catastrophic.

3) Prolonged Paralysis (scoline apnea): patients with reduced levels of normal pseudocholinesterase may have a longer than normal duration of action, whereas patients with atypical pseudocholinesterase will experience markedly prolonged paralysis.

4) Fasciculations: The onset of paralysis by succinylcholine is usually signaled by visible motor unit contractions called fasciculations.

5) Muscle pain: Perioperative use of nonsteroidal anti-inflammatory drugs and benzodiazepines may reduce the incidence and severity of it.

6) Masseter muscle rigidity: Succinylcholine transiently increases muscle tone in the masseter muscles. Some difficulty may initially be encountered in opening the mouth because of incomplete relaxation of the jaw. A marked increase in tone preventing laryngoscopy is abnormal and can be a premonitory sign of malignant hyperthermia.

7) Malignant hyperthermia: Succinylcholine is a potent triggering agent in patients susceptible to malignant hyperthermia.

8) Generalized contractions: Patients afflicted with myotonia may develop myoclonus after administration of succinylcholine.

9) Increased intraocular pressure: Extraocular muscle differs from other striated muscle in that it has multiple motor end-plates on each cell.

10) Increased intragastric pressure: Abdominal wall muscle fasciculations increase intragastric pressure, which is offset by an increase in lower esophageal sphincter tone.

11) Increased intracranial pressure: slight increases in cerebral blood flow and intracranial pressure in some patients.

12) Histamine release: Slight histamine release may be observed in some patients.

Non-depolarizing (competitive) muscle relaxants

Unlike succinylcholine, these drugs do not alter the structural conformity of the post-synaptic ACh receptor and therefore do not produce an initial contraction. Instead, they compete with the neurotransmitter (ACh) at the site, binding reversibly to one or both the two alpha subunits of the nicotinic ACh receptors, whenever these are not occupied by ACh. The end-plate potential produced in the presence of a non-depolarizing agent is therefore smaller, it does not reach the threshold necessary to initiate a propagating action potential to initiate a muscle contraction.

Metabolism of neuromuscular blocking agents is not thought to occur at the neuromuscular junction. By the end of surgery, the end-plate concentration of the relaxant is decreasing as the drug diffuses down a concentration gradient into the plasma, from which it is cleared, thus more receptors are stimulated by the neurotransmitter allowing recovery from block, an anticholinesterase given at this time increases the half life of ACh at the neuromuscular junction facilitating recovery.

Examples of non-depolarizing muscle relaxants:

1) Tubocurarine (Tubarine®):

It has marked propensity to produce histamine release and thus hypotension with possibly a compensatory tachycardia. In large doses it may also produce ganglion blockade which potentiates these cardiovascular effects. It is excreted unchanged through the kidney with some biliary excretion.

2) Gallamine (Flaxidil®):

It is crosses the placenta to a significant degree and should not be used in obstetric practice. It is excreted almost by the kidney thus it should not be used in patients with renal impairment. Gallamine increases pulse rate and arterial pressure.

3) Atracurium (Tracurium®):

Atracurium breaks down spontaneously at varying temperature and PH in a process called "Hofmann degradation phenomenon". The Hofmann degradation may be considered as a safety net risk patient with impaired liver or renal function. Atracurium causes histamine release but less than tubocurarine.

4) Cisatracurium:
Is similar to atracurium bat has longer time of action and less release of histamine.
5) Pancuronium (pavulon®):
It doesn't produce histamine release. About 60% of a dose of the drug is excreted unchanged through the kidney. It is also decetylated in the liver.
6) Vecuronium (Norcuron®):
Rarely produce histamine release. It is excreted through the kidney (30%), and undergoes hepatic decetylation.
7) Rocuronium (Esmeron®):

It stimulates little histamine release or cardiovascular disturbance. The drug is excreted unchanged in the urine and in the bile.

Table

This table shows the intubating dose when tracheal intubation should be possible and time required to achieves it and time when 20-25% recovery when anticholinestrase may be used reliably to reverse residual block produced for each one of non-depolarizing muscle relaxants that have been mentioned: Drug	**Dose required**	**Time required** (seconds)	**Time when 20-25% recovery (minutes)**
Atracurium	**0.5 mg/kg**	**110**	**43**
Cisatracurium	**0.1 – 0.15 mg/kg**	**110**	**60**
Pancuronium	**0.08 – 0.1 mg/kg**	**220**	**75**
Vecuronium	**0.1 mg/kg**	**180**	**33**
Rocuronium	**0.6 mg/kg**	**75**	**33**