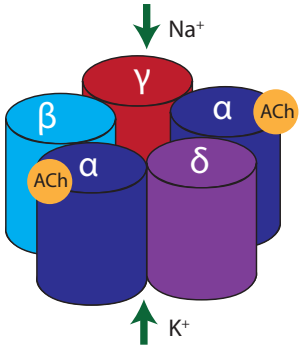
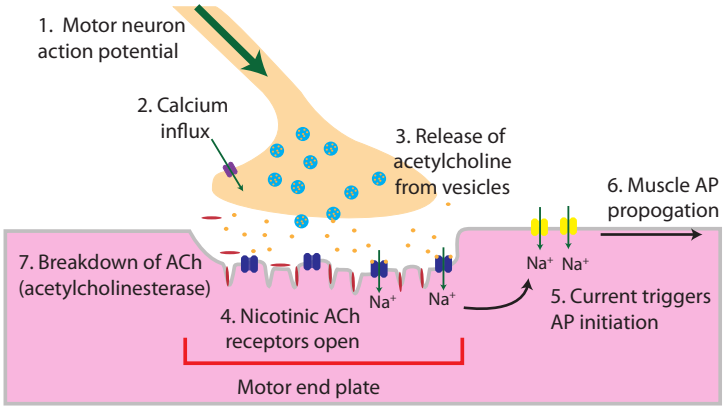
NEUROMUSCULAR JUNCTION

Nicotinic acetylcholine receptor

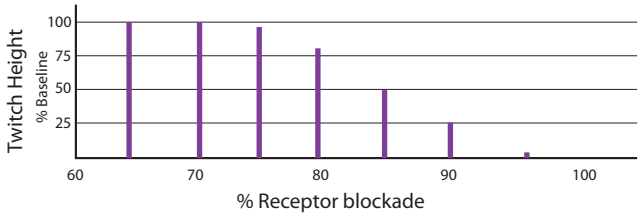
The receptor channel complex consists of five subunits, all of which contribute to forming the pore. When two molecules of acetylcholine bind to portions of the alpha-subunits exposed to the membrane surface, the receptor channel changes conformation. This opens the pore in the portion of the channel embedded in the lipid bilayer, and both K^+ and Na^+ flow through the open channel down their electrochemical gradient. As each open it generates a miniature end plate potential. These summate until the threshold potential is reached trigger AP initiation at which point voltage gated Na^+ are opened causing a rapid depolarisation, leading to the propogation of an action potential across the muscle surface. On reaching the T tubule system, Ca^{++} is released from the sarcoplasmic reticulum which initiates muscle contraction.



Neuromuscular junction physiology



Single twitch stimulation muscle relaxants are monitored by examining the effect they have on muscle contraction following stimulation of the relevant nerve. Nerve stimulators generate a supramaximal stimulus (60-80 mA) for 0.1 msec. Single twitch stimulation is the simplest form of neurostimulation and requires a baseline twitch height for it to reveal useful information. There will be no reduction in twitch height until 75% of NMJ have been occupied by a muscle relaxant. The diagram adjacent shows a representation of single twitch stimulation. Other modalities include train of four, double burst stimulation, tetanic stimulation and post tetanic potentiation and count.



Pharamacology of neuromuscular blockers are classified in by whether they act by directly depolarising the nicotinic receptors at the neuromuscular junction (suxamethonium) or by blocking the depolarising action of acetylcholine at the neuromuscular junction. The non depolarising muscle relaxants may be further categorised by either their chemical structure -amino steroids (vecuronium, rocuronium, pancuronium) or isoquinolones (atracurium, cisatracurium) or their duration of action into short, medium and long.

Suxamethonium is the most commonly used depolarising neuromuscular blocking agent. It is commonly used because of its rapid onset of neuromuscular block or paralysis (60-90sec) and short duration of action. Pharmaceutical is formulated as a colourless solution containing 50mg/ml in a 2ml vial. It is stable for only four weeks of stored at room temperature. Pharmacodynamics Sux mimics the action of ACh by attaching to the nicotinic ACh receptor and causing membrane depolarisation. Because its hydrolysing enzyme (plasma or pseudo-cholinesterase) is not present at the NMJ its duration of action is longer than that of ACh. The persistent depolarisation renders voltage sensitive sodium channels within 1-2mm of the receptor inactive. This area of electrical inexcitability prevents the transmission of further action potenials resulting in muscle relaxation. Clinically this is characterised by a desynchronised depolarisation (fasiculations) followed by relaxation. Pharmacokinetics Because of the plasma and pseudo-cholinesterase much of the IV dose is hydrolysed prior to reaching the NMJ, with as little as 20% of the dose reaching the NMJ. It is typically given in relatively high doses (usually 1mg/kg) with respect to its ED_{95} (effective dose where 95% of people are paralysed) which is 0.3-0.6 mg/kg. Metabolism; following hydrolysation it forms a weakly active metabolite which is further metabolised by the plasma esterases. It has a very short half life of several minutes (when patient is homozygous for the normal Eu gene). Side effects and issues are significant. Arrhythmias may occur via stimulation of the muscarinic receptors in the SA/AV nodes (leading to bradycardia). Hyperkalaemia may occur transiently due to the rapid efflux of potassium out of the cells during depolarisation. In some patient populations this can lead to serious issues. Burns patients, and patients with neuromuscular disorders, paraplegia, and those with already elevated K (renal failure) may develop a severe hyperkalaemia precipitating cardiac arrest. Myalgias are common likely secondary to the fasciculations, this is typically in young females. Intra-occular pressure IOP rises by about 10mmHg (normal baseline is 10-15mmHg). This can be offset by thiopentone. Sux makes a significant proportion of the anaphylaxis observed in muscle relaxants. There are also two adverse drug effects with a known genetic basis. The first is malignant hyperthermia. It is a rare autosomal dominant condition (1:200000) related to an abnormal ryanodine receptor on the sarcoplasmic reticulum (which triggers Ca release) resulting in excessive Ca release leading to rigidity, excessive activity requires ++ ATP which leads to heat and lactate production, ultimately leading to muscle breakdown and hyperkalaemia. Treatment is with aggressive cooling and dantrolene which binds to ryanodine receptors and stops release of Ca. The second genetic condition predisposes to abnormal plasma esterases. 96% of the population has a normal Eu:Eu gene and they metabolise sux quickly, 4% are heterozygotes Eu:other leading to a prolonged block of up to 10 mins. A very small number (less than 1:3000) do not have an Eu gene (eg Ef:Ef or Ea:Ef)) and they may take several hours to recover.

Non depolarising muscle relaxants non depolarising agents inhibit the actions of ACh at the NMJ by binding competitively to the alpha subunit of the nicotinic ACh receptor on the post junctional membrane. There is a wide safety margin at the NMJ to ensure muscle contraction, so more than 70% of receptors need to be occupied by muscle relaxant before neuromuscular blockade can be detected by a peripheral nerve stimulator. All have small volumes of distribution, other characteristics are below.

	Vecuronium	Rocuronium	Pancuronium	Atracurium	Cisatracurium
Chemical Structure	Aminosteroid	Aminosteroid	Aminosteroid	Isoquinolone	Isoquinolone (isomer of atrac)
Presentation	Powder for reconstitution 10mg diluted in 5ml water	Colourless solution 50mg in 5ml	Colourless solution 4mg in 2ml	Colourless solution 10mg/ml stored at 4°	Colourless solution 2 or 5mg/ml stored at 4°
ED_{95} mg/kg and intubating dose	0.05 / 0.1mg/kg	0.3-0.4 / 0.6mg/kg	0.06-0.07 / 0.1 mg/kg	0.25 0.5mg/kg	0.05 / 0.2 mg/kg
Speed of onset	Medium	Rapid	Medium	Medium	Medium
Duration of Action	Intermediate (45-90 mins)	Intermediate (45-70)	Long (60-120)	Intermediate (30-45)	Intermediate (40-75)
Protien binding (%)	10	10	20-60	15	15
Metabolism	liver by deacetylation active metab but short $t_{1/2}$	minimal metabolism	liver by deacetylation active metab	Ester hydrolysis, Hofmann (degrades at pH 7.4)	Hofmann elimination, then hydrolysis of the products
Excretion	80% unchanged Urine 30% : Bile 70%	95% unchanged Urine 40% : Bile 60%	70% unchanged Urine 80% : Bile 20%	95% metabolised independent renal/liver fn	95% metabolised independent renal/liver fn
Cardiovascular	none or bradycardia	none	tachycardia	none, slight histamine	none

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