Neurotoxins

- toxins that affect Ion Channels and Membrane Potential
- toxins that affect vesicular release
- toxins that block neuromuscular transmission (acetylcholine and its receptors)

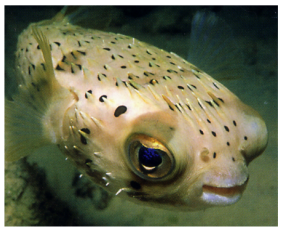
Toxins that affect Ion Channels and Action Potential

TTX (Tetrodotoxin)
blocks voltage-gated Na+ channels

TEA (Tetraethylammonium)
blocks voltage-gated K+ channels

Batrachotoxin opens Na+ channels, causing persistent depolarization

Tetrodotoxin -- blocks voltage-gated Na+ channels



1 pufferfish/30 humans

Weight-for-weight, tetrodotoxin is ten times as deadly as the venom of the many-banded krait of Southeast Asia. It is 10 to 100 times as lethal as black widow spider venom (depending upon the species) when administered to mice, and more than 10,000 times deadlier than cyanide. It has the same toxicity as saxitoxin which causes paralytic shellfish poisoning ([both TTX and saxitoxin block the Na+ channel - and both are found in the tissues of pufferfish])

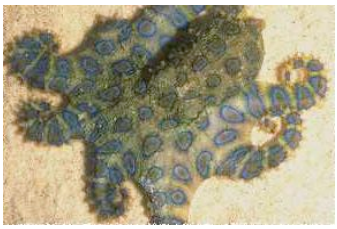
The first recorded [European] cases of tetrodotoxin poisoning were from the logs of Captain James Cook. He recorded his crew eating some local tropic fish (pufferfish), then feeding the remains to the pigs kept on board. The crew experienced numbness and shortness of breath, while the pigs were all found dead the next morning. In hindsight, it is clear that the crew received a mild dose of tetrodotoxin, while the pigs ate the pufferfish body parts that contain most of the toxin, thus killing them.

The toxin was first isolated and named in 1909 by Japanese scientist Dr. Yoshizumi Tahara.

Cutting Fugu http://www.youtube.com/watch?v=WBc8e7fkc6E

Inflating Pufferfish http://www.youtube.com/watch?v=DftYU1GTDhw

http://ngm.nationalgeographic.com/ngm/0505/feature1/multimedia3.html



- Puffer fish grown in culture do not produce tetrodotoxin until they are fed tissues from a toxin producing fish.
- The blue-ringed octopus found in Australian waters accumulates tetrodotoxin in a special salivary gland and infuses its prey with toxin by bite. This octopus contains tetrodotoxin-producing bacteria.
- Xanthid crabs collected from the same waters contain tetrodotoxin and paralytic shellfish toxin.

http://www.chm.bris.ac.uk/motm/ttx/ttx.htm

Batrachotoxin -- opens Na+ channels, causing persistent depolarization

1 frog / 50 humans

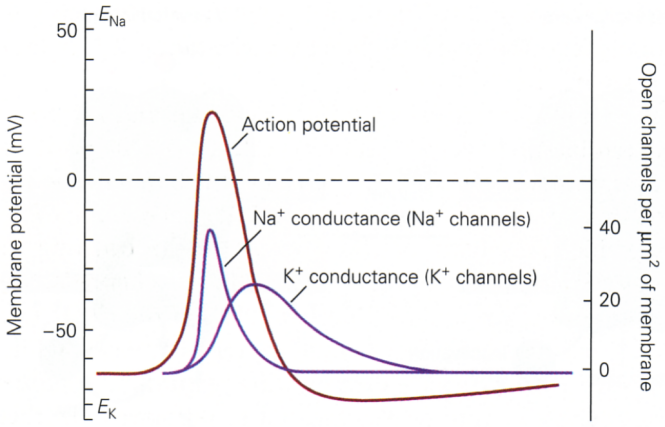
Phyllobates terribilis, or the **Golden Poison Frog**

Pitohui bird from Papua New Guinea, also toxic

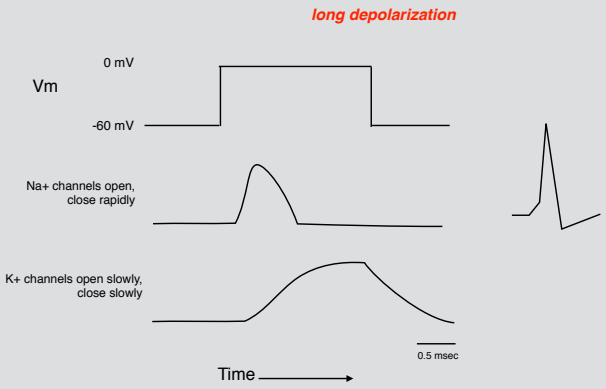
Melyrid beetles produce the batrachotoxin, are eaten by birds and frogs

http://www.chm.bris.ac.uk/motm/batrachotoxin/batrah.htm

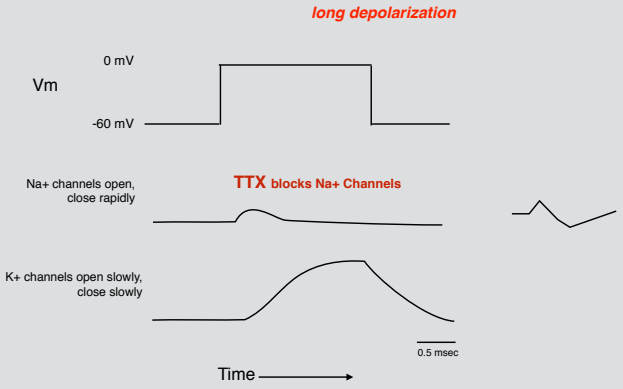
Action potential: Na+ and K+ channels open



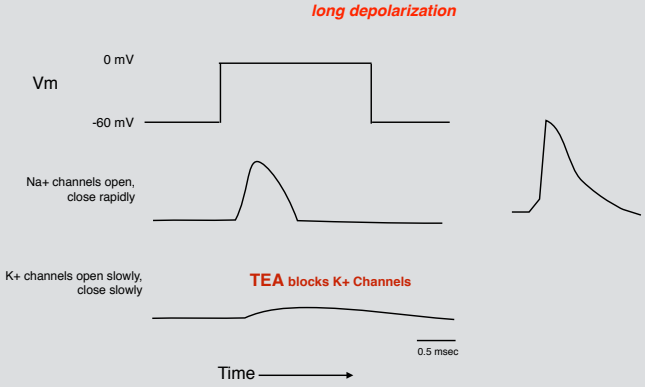
Na+ and K+ channels respond differently to depolarization



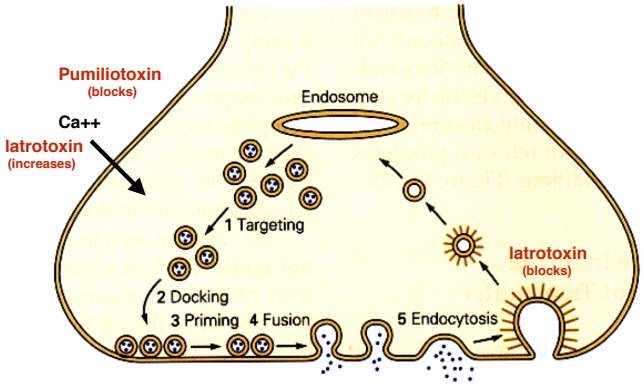
Na+ and K+ channels respond differently to depolarization



Na+ and K+ channels respond differently to depolarization



Toxins affecting Synaptic Vesicle Cycle



Poison Dart Frogs

Pumiliotoxin (pumilio = dwarf)
Block Ca++ channels, so prevents vesicular release
(1000x weaker than Batrachotoxins)

Blue Poison Dart frog Dendrobates azureus at Bristol Zoo, Bristol, England. Photographed by Adrian Pingstone in September 2005 and released to the public domain. Yellow-banded Poison Dart frog Dendrobates leucomelas at Bristol Z

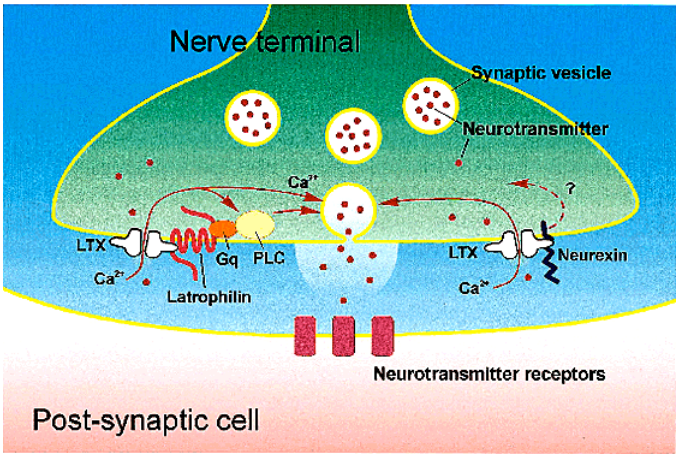
Black Widow Spider Venom (latrotoxin)

(Latrodectus
= secret-biting)

A black widow spider bite gives the appearance of a target, with a pale area surrounded by a red ring. Severe muscle pain and cramps may develop in the first two hours. Severe cramps are usually first felt in the back, shoulders, abdomen and thighs. Other symptoms include weakness, sweating, headache, anxiety, itching, nausea, vomiting, difficult breathing and increased blood pressure. Young children, the elderly and those with high blood pressure are at highest risk of developing symptoms from a black widow spider bite.

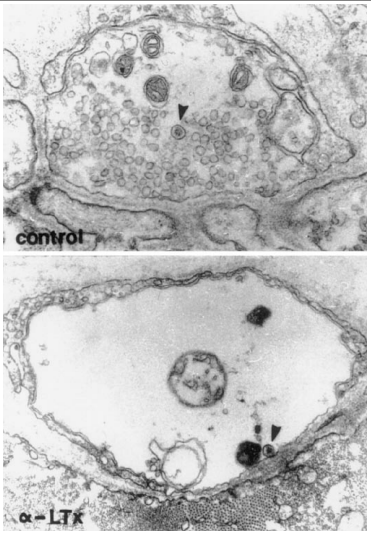
www.doacs.state.fl.us/.../ venomousspiders.html

Black Widow Spider Venom (latrotoxin)



latrotoxin (LTX) forms Ca++ pore in presynaptic membrane, causing massive vesicular release

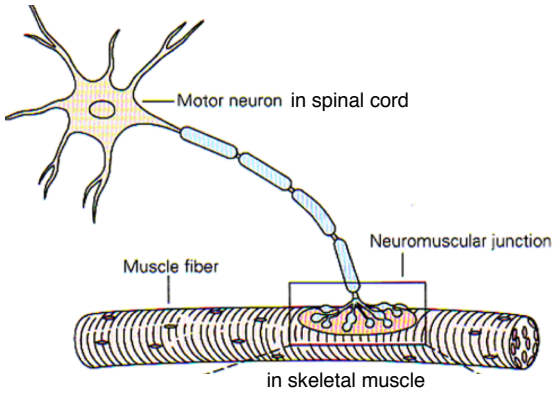
http://www.nature.com/nsmb/journal/v7/n1/full/nsb0100_3.html

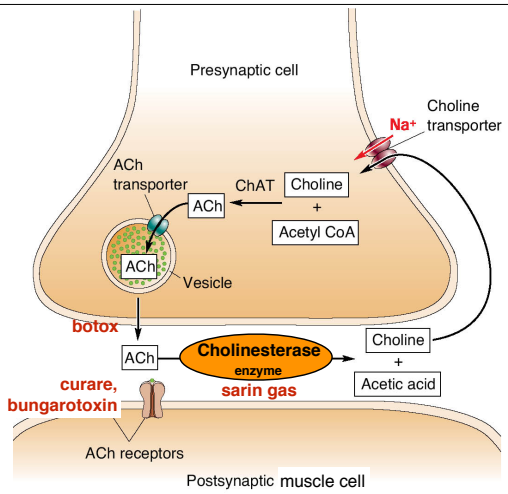


Frog neuromuscular junction treated with latrotoxin (LTX). Exposure to high amounts of toxin for hours causes a massive release of small synaptic vesicles. This results in an enlargement of the plasmalemma and a total depletion of the neurotransmitter containing vesicles, but not of the large dense-core vesicles containing neuropep- tides (arrow).

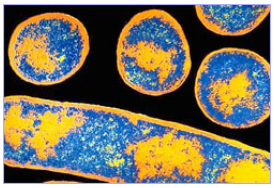
Schiavo, Giampietro, Michela Matteoli, and Cesare Montecucco. Neurotoxins Affecting Neuroexocytosis. Physiol. Rev. 80: 717–766, 2000.

Cholinergic Neuromuscular Junction as Model for transmission of Action Potential





Botox -- Clostridium botulinum



http://www.dbtechno.com/health/2008/01/19/canned-beans-recalled-due-to-botulism-contamination/

http://nabc.ksu.edu/content/factsheets/category/Botulism

Blocks release of Acetylcholine from motor neuron.

Symptoms include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth and muscle weakness. Treatment may include antitoxins, intensive medical care or surgery of infected wounds. if left untreated, botulism can temporarily paralyze your arms, legs, trunk, and the muscles that help you breathe. The paralysis usually improves slowly over several weeks. People who develop severe botulism experience breathing failure and paralysis and need to be put on ventilators (breathing machines) (NIH website)

"botulus" = home-fermented sausage

Botulism, a serious but relatively rare disease, is caused by an extremely potent toxin produced by the bacterium Clostridium botulinum. C. botulinum is an anaerobic, gram-positive, spore-forming bacterium that most commonly affects wild fowl and poultry, cattle, horses, and some species of fish.

Although the incidence of botulism is relatively low in humans (~ 9 outbreaks of foodborne botulism per year with and average of 2.4 cases per outbreak), the disease is of considerable concern because of its high infectivity and high mortality rate (untreated). Only a few nanograms of toxin can cause human illness. And, in the 962 recorded botulism outbreaks in humans (2,320 cases) in the U.S. from 1899 to 1990, there have been 1,036 deaths.

Acetylecholine (ACh) receptor toxins

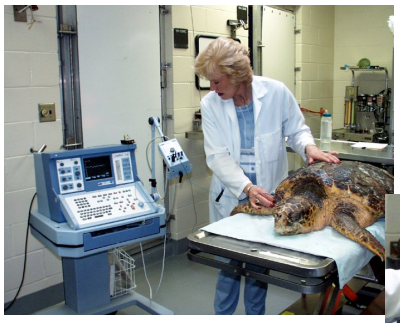
curare - plant toxin; binds weakly to ACh receptor

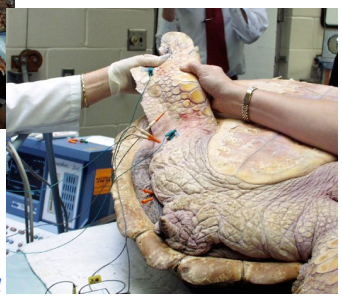
a-bungarotoxin - snake venom; binds tightly to ACh receptor

mysathenia gravis - autoimmune disease; immune system attacks ACh receptors

sarin nerve gas - blocks acetylcholinesterase, raises ACh levels

Hard to record muscle action potentials in paralyzed patients





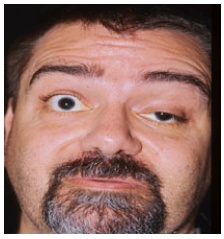
http://www.vetmed.ufl.edu/college/departments/sacs/research/LoggerheadSeaTurtleEpizooticinFlorida.html

Curare -- Acetylcholine Receptor Blocker

Strychnos Toxifera by Koehler 1887

During 1811-1812 Sir Benjamin Collins Brody (1783-1862) experimented with curare [4] He was the first to show that curare does not kill the animal and the recovery is complete if the animal's respiration is maintained artificially. In 1825 Charles Waterton (1783-1865) (who gained fame by riding a captured alligator) described a classical experiment in which he kept a curarized she-ass alive by artificial ventilation with a bellows through a tracheostomy.[5] Waterton is also credited with bringing curare to Europe.[6] Robert Hermann Schomburgk, who was a trained botanist, identified the vine as one of the Strychnos species and gave it the now accepted name Strychnos toxifera.[7]

Disease of Neuromuscular Junction: Myasthenia Gravis



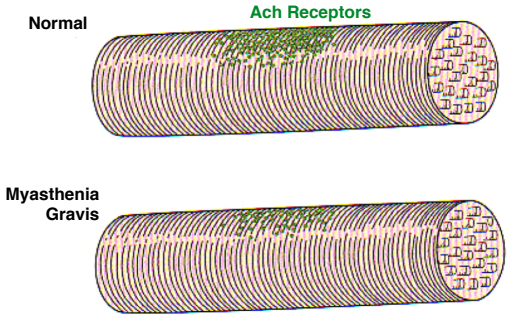
Symptoms

The most common symptoms of MG relate to weakness of the muscles that lift up the lid (ptosis) or move the eyes (double vision). MG can affect muscles anywhere in the body including those of swallowing or even breathing. Shortness of breath or difficulty swallowing may be very serious symptoms of MG and must be brought to your doctor's attention immediately. MG does not produce pain or numbness. If pain is present there must be something else going on and you need to tell your doctor.

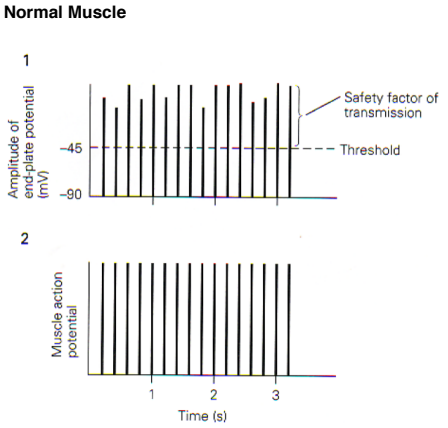
www.beverlyhillsneurology.com

http://meds.queensu.ca/medicine/oph/patients/myastheniagravis.shtml

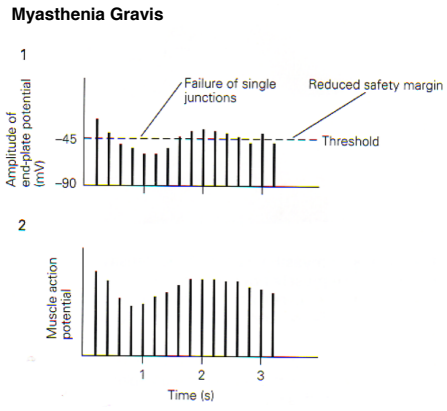
Disease of Neuromuscular Junction: Myasthenia Gravis



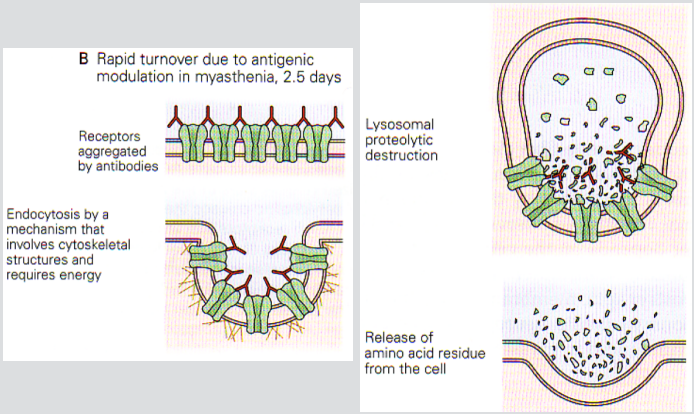
Neuromuscular EPSPs (Endplate Potentials) in MG



Endplate Potentials in MG



Autoimmune attack on ACh Receptors



Sarin Nerve Gas -- cholinesterase inhibitor

news.bbc.co.uk/ 1/hi/uk/413827.stm

Initial symptoms usually include intense sweating, runny nose and twitching of muscles. The pupils of the eyes constrict, dimming sight and causing other visual difficulties. If enough sarin is inhaled or absorbed, a victim quickly develops tightness of the chest and begins gasping for breath. The heart rate slows and the blood pressure can drop to dangerous levels. Sarin also can cause nausea and vomiting, abdominal cramps, diarrhea, headache, drowsiness, convulsions and coma.

Summary of Toxins

TTX (tetrodotoxin) - blocks voltage-gated Na+ channels

TEA (tetraethylammonium) - blocks voltage-gated K+ channels

batrachotoxin - opens Na+ channels, causing persistent depolarization

pumiliotoxin - blocks Ca++ channels so blocks vesicular release

latrotoxin - forms Ca++ channel, so causes vesicular release; also blocks endocytosis of membrane

botulinum (botox) - blocks acetylcholine release

curare, alpha-bungarotoxin - antagonists of nicotinic acetylcholine receptor

mysathenia gravis - autoimmune disease; immune system attacks ACh receptors

sarin nerve gas - blocks acetylcholinesterase, raises ACh levels