The Synapse: Intercollegiate science magazine

Volume 1 | Issue 0 Article 10

12-1-2011

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By Ksenia Vlasov

Humans are gigantic and incredibly complex organisms. However, what keeps us alive, functional, and sane are the interactions between a handful of chemicals. One class of these compunds are neurotransmitters, chemicals responsible for communication between specialized nerve cells, or neurons, of the body and the brain. Neurotransmitters are packaged into vesicles in one neuron and released into the synaptic cleft, the space between two neurons, where they can bind onto receptors on the plasma membrane of the adjacent neuron. From cell to cell, vital information about our external environment and internal states is conducted to and from the brain within seconds. One such neurotransmitter is acetylcholine (Ach), which is involved in activating muscles connected to the peripheral nervous system (all nerves that are not in your brain or spinal cord). Many foreign chemicals can overstimulate or inhibit the Ach system and upset its delicate balance. Interfering with any step in the process of Ach release or metabolism can cause rather unpleasant effects, ranging from muscle weakness to fatal paralysis.

Recently, a toxin known as succinylcholine was reportedly used in the high profile assassination of a senior Hamas commander in Dubai. Often described as the "perfect poison", it has a low lethal dose and nigh undetectable metabolites. Succinylcholine is a special kind of Ach agonist, which means that it competes with Ach to bind to specialized receptors and also causes long-term depolarization of the cell. This process is known as a depolarization block and occurs specifically at the nicotinic Ach receptor. Basically, succinylcholine desensitizes the Ach receptor to stimulation if it is present in the synapse for a long time. The receptor is kept perpetually open, letting more and more positive charge into the cell and keeping it constantly depolarized. Unable to return to its baseline voltage, the postsynaptic cell is simply unable to fire another action potential (the electrical signal that lets the neuron know that it's time to release more Ach). Eventually the receptor stops responding altogether to any molecule that binds to it, including Ach, and you go from having muscle twitches to full on paralysis. Succinylcholine is the only depolarization blocking agonist that is used clinically. Trauma surgeons and anesthesiologists commonly administer this drug prior to endotracheal intubation because it has the fastest onset (about 30 seconds) and the shortest duration (a few minutes) of any paralytic, making it highly useful in emergency situations.

While some drugs can amplify the effects of Ach by directly binding to its receptors, other drugs affect the function of its breakdown enzyme,

AchEsterase (or AChE). Physostigmine, a toxin that comes from the Nigerian Calabar bean, has profound effects on the central nervous system (brain and spinal cord) by blocking AChE altogether, keeping hordes of un-degraded Ach free to float around in the synaptic cleft. This leads to over-stimulation of the Ach receptor. Poisoning can lead to confusion, hallucinations, convulsions, coma, and potentially death. In the 19th century, missionaries in West Africa discovered several villages that used this toxin during trials for witchcraft. If the defendant was able to either regurgitate the poisonous bean or walk ten feet after swallowing one, he was considered innocent. Of course, most did neither, were charged guilty, and died a horrible death. The shaman judges had no way of studying receptors or any of the biological mechanisms behind the effects of this toxin, so the "diagnostic factor" was the degree of salivation in the mouth of the accused. The hypothesis was that a guilty person would produce less saliva and be unable to vomit and save themselves. Since Ach is now known to also stimulate secretion in the salivary glands, this idea may not have been as arbitrary as it sounds (though the logical connection between salivation and guilt is of course debatable). The British tried pretty hard to put an end to this practice, eventually outlawing it in the mid 1800's.

By now you've probably picked up on the theme of "neurotoxins that mess with the Ach system are a little terrifying." Allow me to introduce the Botulinum toxin. Instead of mimicking acetylcholine, it interferes with the transport and release of Ach into the synaptic cleft. The toxin attacks a fusion protein (syntaxin, synaptobrevin, or SNAP-25) and prevents the vesicles full of Ach from anchoring to the plasma membrane of the presynaptic neuron and releasing the neurotransmitter into the synaptic cleft. As we have already seen, a lack of Ach at the neuromuscular junction can lead

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to paralysis. Botulinum happens to be one of the deadliest toxins ever discovered. The lethal dose for humans is about 0.3 micrograms, depending on the means of administration — as a textbook states it, "one gram (equivalent to the weight of three aspirin tablets) is enough to kill over 3 million individuals." If a person accidentally ingests food contaminated with germinating spores of the bacteria *Clostridium botulinum*, they may get botulism poisoning, which manifests as blurred vision, speech impediment, muscle weakness, and can be fatal if the muscles in the diaphragm are paralyzed. Perhaps the most interesting fact about this toxin lies in its more common name: Botox. Purified botulinum toxin type A can be used to treat disorders such as strabismus (crossed eyes), excessive underarm sweating, chronic migraines, and of course, wrinkles. A Botox injection into specific facial muscles causes localized paralysis that lasts a couple months and is used by many people for cosmetic purposes to make skin appear smoother and younger.

The border between health and disease is thin, only guarded from unwanted visitors by plasma membranes, receptors, channels, pumps, and obsessively patrolling tiny molecules. Seven billion highly complex, intelligent beings can still be completely incapacitated by a microscopic chemical produced by a single cell organism. With the addition of a functional group here or there, one molecule can be made to seamlessly mimic an endogenous chemical. These undercover toxins can use our own cellular mechanisms to throw this entire finely tuned and inherently fragile system into complete disarray without the brain's knowledge or permission. This is humbling to say the least, yet learning more about how these toxins infiltrate the body is essential for understanding how the brain operates under normal circumstances and, most importantly, allows us to use them in a controlled manner to mend the system when it goes awry.