Tetanospasmin and the Pathogenesis of Tetanus
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Introduction
Tetanus is a disease which is characterized by painful skeletal muscle contractions (Mayo Clinic 2010). Awareness of the disease is thought to have begun around the fifth century BCE (Linnenbrink and McMichael, 2006). In the year 1889, the Japanese bacteriologist Kitasato Shibasaburo isolated the microorganism responsible for the disease, Clostridium tetani (Encyclopedia Britannica). This bacterium, C. tetani, is an anaerobic bacillus which produces spores (CDC). C. tetani releases two different exotoxins: tetanolysin and tetanosin (ibid). Although the function of tetanolysin is not entirely known, studies show that the neurotoxin tetanosin causes clinical symptoms of tetanus (ibid). However, the mechanisms of tetanosin are not fully known, and continue to be researched. The focus of this paper will be on tetanosin in tetanus to better understand the pathogenesis of this prevalent and unfortunate disease.

Tetanus

Tetanosin is characterized by muscle spasms of the back, chest, neck, and abdominal muscles. However, the first spasms to occur are usually located in the muscles of the jaw. In some cases, opisthotonos (back arching) can occur, as can tetany (sudden contractions that have the potential to lead to bone fractures and muscle tears.) Other symptoms include fever, sweating, and trouble swallowing (HealthGuide: The New York Times)

Tetanus is preventable, and can be avoided by taking the combined DTP vaccine (diphtheria, pertussis and tetanus), which offers defense for about ten years after administration (HealthGuide: The New York Times).

Tetanus was identified as a disease centuries ago. Though once an extremely devastating illness, the CDC reports that only 233 cases of tetanus were identified in the United States between the years of 2001-2008. Of these cases, the fatality rate was about thirteen percent. As evidenced in the graph below, the decline in cases of tetanus is due primarily to the use of antitoxin and vaccine. Additionally, the subtype neonatal tetanus has been almost completely eradicated (CDC 2011).

The Effect of Tetanosin on the Nervous System
Tetanosin, or tetanus toxin, is made in a low oxygen environment by C. tetani, an anaerobic bacterium that functions by producing terminal spores (Sirisoo, Damak, and Mirshafiey, 2009). These spores are extremely robust, and can endure adverse conditions (such as high temperatures) for reasonably long periods of time (Taylor 2006). Along with tetanosin, a second toxin is also manufactured by the spores; tetanolysin is involved in erythrocyte lysing and tissue damage (Linnenbrink and McMichael, 2006).

C. tetani enters the body through ulcers, burns, some types of surgery, or other types of wounds (Binz and Rummel, 2009). The low oxygen environment of a wound provides the optimal conditions for production of tetanus toxin. The bacilli will release TeNT (tetanus neurotoxin) into circulation (Binz and Rummel, 2009). TeNT, in its inactive form, is a 150 kDa polyepitide unit. This peptide is cleaved into a heavy chain (about 100 kDa) and a light chain (about 50 kDa) (Sirisoo, Namaki, and Mirshafiey, 2009). The two chains are linked only by a disulfide bridge (Linnenbrink and McMichael, 2006). The heavy chain aids in binding and entering the target cell locally (Binz and Rummel, 2009). The toxins are sent to the central nervous system by the process of retrograde transport, at an approximate rate of 200 mm/day (Linnenbrink and McMichael, 2006). The C terminus of the heavy chains selectively binds to specific gangliosides on the surface of nerves. These gangliosides are sialidase sensitive disialogangliosides (Binz, Rummel and Namaki, 2009). The N terminus is thought to become integrated into the target cell membrane, eventually creating a channel through which the light chain can travel (Binz and Rummel, 2009). Once the toxins reach inhibitory neurons in the spinal cord and brain, the light chain acts as a protease that cuts specific peptide bonds in synaptobrevin (a protein associated with the membrane of synaptic vesicles.) More specifically, synaptobrevin aids in merging the membranes of the vesicle with the postsynaptic cell membrane (acts as a SNARE). By this process, TeNT prohibits the release of inhibitory neurotransmitters, specifically glycine and gamma-amino butyric acid (GABA) (Binz and Rummel, 2009). By preventing the release of these inhibitory neurotransmitters by the interneurons, acetylcholine will continue to be released into the neuromuscular junction, and will prevent the relaxation of muscles (Sirisoo, Namaki, and Mirshafiey, 2009). Once muscles are prevented from relaxation, muscle tone and muscle rigidity intensify. Additionally, the classic muscle spasms will ensue (Taylor 2006). Unfortunately, this blocking is irreversible, and new axons are required in order to recover from the effects of the toxin (Linnenbrink and McMichael, 2006).

Effective methods to control the muscular rigidity and spasms induced by tetanosin include sedation and neuromuscular blocking agents (Cook et al. 2001). Both methods counter the function of acetylcholine in order to reduce symptoms characteristic of tetanus.

One method of sedation utilizes the psychoactive drug benzodiazepine to express muscular relaxant properties (Firth et al. 2011). Benzodiazepine enhances the effect of the GABAA receptor (ibid). In tetanus patients, benzodiazepine counters TeNT’s inhibition of the GABAA receptor, which leads to its subsequent neurotransmission of GABA (Cook et al. 2011). GABA is then released in the neuromuscular junction and regulates neuronal excitability. GABA’s inhibitory nature thus controls the hyper-activity of acetylcholine by TeNT and induces muscular relaxation. Another anesthetic commonly used to treat tetanus is propofol (Firth et al. 2011). Propofol also acts to potentiate the GABAA receptor while concurrently blocking sodium channels (Namakian and Hempnings, 1997). Its injection augments the activity of inhibitory neurotransmission (Firth et al. 2011). Both benzodiazepine and propofol effectively relax the muscle spasms and rigidity that characterize tetanus. Possible side effects of sedation include low blood pressure and tachycardia (Cook et al. 2001).

Neuromuscular blocking agents are also effective in controlling muscular spasms with the accompaniment of ventilation support (Cook et al. 2001). A non-depolarizing neuromuscular blocking agent pancuronium acts to antagonize acetylcholine by competing for cholinergic receptors at the motor end plate (Sigma-Aldrich). Pancuronium is subsequently able to reduce the effects of acetylcholine and inhibit muscular relaxant qualities (ibid). Other neuromuscular blocking agents, such as vecuronium, are successful in treating tetanus (Firth et al. 2011). Although pancuronium is more potent at an equal dose, the latter lacks the cardiovascular side effects pancuronium elicits (ibid). Overall side effects of neuromuscular agents include the progression of tachycardia and hypertension (ibid).

Significance of Findings
This investigation of the effect of tetanosin specifically offers a way of comprehensively understanding the pathogenesis of Tetanus. In result, these findings may lead to additional prevention methods that can potentially decrease the prevalence of the disease. According to Figure 1, the continual decline in reported cases of tetanus in the United States, gives hope to a future of complete eradication of the disease. Understanding the biochemistry of the mechanism of tetanosin entrance and attack of the host, gives insight into ways this synthesis can be stopped and therefore prevented. Further studies can explore the implications of how tetanosin and tetanosin work together in order to cause tetanus. The involvement of both toxins as a unit may give potential insight into further prevention procedures. Specifically looking at the biochemistry of how diseases in general attack a host, offers significant findings into inhibiting the invasion.