Botulinum and Pain Relief

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Abstract

While the term “neurotoxins” inherently has a connotation of harm and danger, their targeting mechanism plays an important role in pain relief. This paper takes a deeper look into a major neurotoxin - botulinum, one of the most poisonous chemical compounds. By blocking acetylcholine, a neurotransmitter that facilitates communication between nerve endings and smooth muscle, botulinum has found popularity for cosmetic usage but more importantly muscle pain relief. However, new research has shown that it may be able to affect other neurotransmitters to provide a more direct effect.

Introduction

From the products we use to the air we breathe, neurotoxins can be found everywhere. Common examples include lead, ethanol, tetanus toxin, and even essential molecules like glutamate and nitric oxide. Neurotoxins, as opposed to neurotoxicants, are naturally occurring chemicals that result in the alteration of normal neuronal activity or neurotoxicity. More specifically, they can cause cell and tissue death, disrupt signal pathways and metabolic processes, and have been linked to neurodegenerative disorders like Alzheimer’s and Parkinson’s disease. It is important to note, however, that neurotoxins are not intrinsically toxic (Spencer & Lien, 2014). It is only when exposed to an extremely high concentration that negative consequences can occur. This characteristic of neurotoxins makes them especially useful in drug manufacturing.

What is Botulinum?

Botulinum is a toxin produced by a bacteria known as Clostridium botulism and can be commonly found in soil, water, and the intestines of certain animals. Unfortunately, this toxin is extremely deadly when ingested or when it comes in contact with open wounds, resulting in botulism. Botulism results in muscle paralysis that can in turn lead to the weakening of muscles, blurry vision, difficulty swallowing, and more. What makes this illness so dangerous is the spreading of paralysis to the extremities and even respiratory muscles.

More specifically, these symptoms can be attributed to the toxin targeting neuromuscular junctions to inhibit the release of acetylcholine. Acetylcholine is a neurotransmitter that controls muscle contraction and voluntary movement. Through an irreversible process, BoNT binds to the presynaptic membrane and severs the SNARE protein complex that connects the vesicles containing acetylcholine to the membrane (Nigam & Nigam, 2010). With acetylcholine unable to bind to the postsynaptic receptors, an action potential is never fired. In other words, the message to contract the target muscle is temporarily stopped, thereby inhibiting bodily movement.

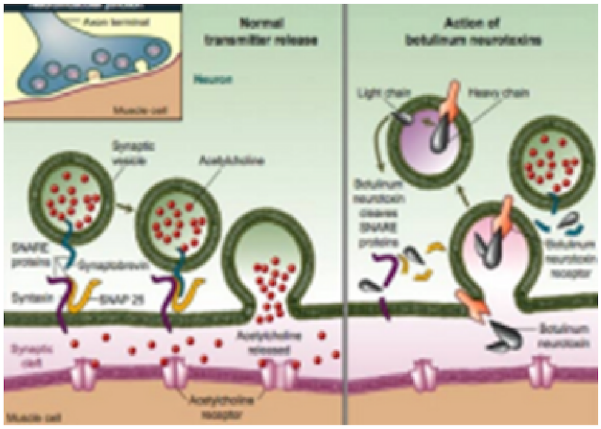

Fig. 1. Comparison of normal acetylcholine release versus the action of BoTN-A on the presynaptic neuron (“Novel Compound”, 2018).

In recent years, scientists have realized that this same mechanism can be manipulated to give the illusion of youth. This process starts with purifying the toxin or removing any bacterial cell components. It is then using 0.0073 nanograms of this pure neurotoxin that one unit of BOTOX is created. Once injected into the desired muscle, the lack of muscle contractions help prevent the formation of wrinkles. Fortunately, since these injections contain such a small amount of toxin, they can block nerve communication and temporarily paralyze the area without causing botulism.

Given botulinum’s ability to interrupt the transmission of signals, it can disrupt abnormal muscle and pain signals and thus act as a pain killer. In fact, the toxin is commonly used for a series of conditions like excessive sweating, lazy eye, tight muscles, chronic migraines, and muscle spasms.

Indirect Pain Relief

The most common mechanism of botulinum-induced pain relief is temporarily stopping the muscle spasm-pain cycle by blocking acetylcholine. In fact, intramuscular injections can reduce arthritis-induced pain, spasticity (stiffness in muscles), dystonia (uncontrollable muscle contraction), muscle tension, and more.

As such they are commonly used, to reduce symptoms of stroke, cerebral palsy, and MS patients (Davis & Barnes, 2000). This is especially important given the lack of effective and affordable pain treatment. In fact, many oral medications, anti-inflammatory and narcotics alike, have several harmful side effects. On the other hand, botulinum injections tend to have milder and reversible side-effects, if any.

Direct Pain Relief

A more recent discovery, however, is BoTN-A's ability to directly relieve pain. While the exact mechanism is unclear, past research has shown that BoTN-A may suppress other neurotransmitters and neuropeptides (chemical messengers that are made up of amino acids and released by neurons) in addition to acetylcholine. This includes glutamate, substance P, and CGRP. Uncoincidentally, these neurotransmitters are found in high concentrations along the nociceptive pathway and tend to be released when the body is experiencing pain.

The nociceptive pathway refers to the pain pathway. A vital component of this pathway is C fibers. These fibers transmit feelings of itch, burning pain, and temperature from receptors in the skin/joints/muscles to the brain. As seen in Figure 2., these fibers do so by releasing neurotransmitters like glutamate, substance P, and CGRP.

For instance, increased levels of glutamate is associated with migraines and fibromyalgia (muscle pain and tenderness throughout the body) (Bittencourt et al., 2014). Fortunately, in both mice and human studies, BoTN-A injections have been shown to directly suppress the secretion of these messengers in a similar fashion to the suppression of acetylcholine release. Once the neurotransmitters are blocked, the individual no longer feels pain.

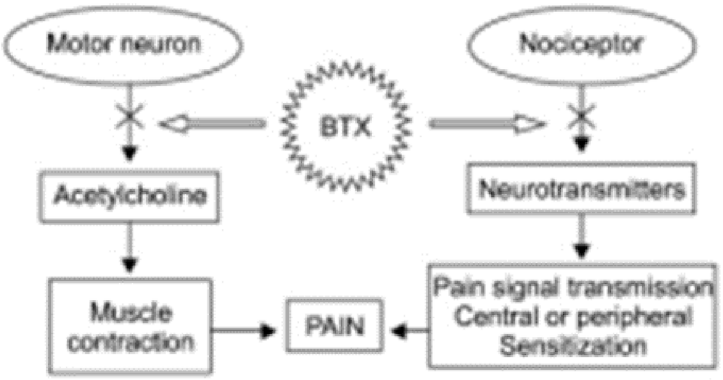

Fig. 2. BoTN-A caused inhibition of both acetylcholine and neurotransmitters released from nociceptors aid in the reduction of pain (Sim, 2011)

Additionally, studies have found that the toxin may also directly effect glial cells - non-neuronal cells that provide structural and functional support to neurons. Glial cells can be further divided into astrocytes, which primarily controls the brain's metabolism and homeostasis, microglia which function as immune cells, oligodendrocytes which mainly make myelin and more.

While it continues to be debated whether they primarily interact with microglia or astrocytes, scientists do know that BoTN-A can reduce inflammation and pain caused by touch or temperature stimuli via glial cells (Feng et al., 2021). This highlights the need for continued research on the true mechanism of botulinum toxin.

Current Research

Using toxins as drugs brings up many challenges. As discussed earlier, neurotoxins in high concentrations cause a number of problems, making it vital to inject precise doses. However, there is a lack of standardized dosing guidelines as research continues to search for the most effective drug and concentration.

Additionally, research by Dr. Bomba-Warczak and colleagues has shown that contrary to previous findings, the botulinum toxin may spread from the injected site. They believe that while some of the toxin acts on the intended area, a fraction of the toxin travels to other neurons which may increase the risk of harm. This brings up the question of whether desired effects for both cosmetics and pain may be in part due to the movement of the toxin. To answer this, they hope to genetically modify Clostridium bacteria and potentially find a safer way to ensure paralysis in a localized area (Tennenbaum, 2016). On the other hand, this ability to travel into the central nervous system may have benefits to science. In particular, it may be used to develop drugs against viral infections that can cross the blood-brain barrier.

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