Botulinum toxin

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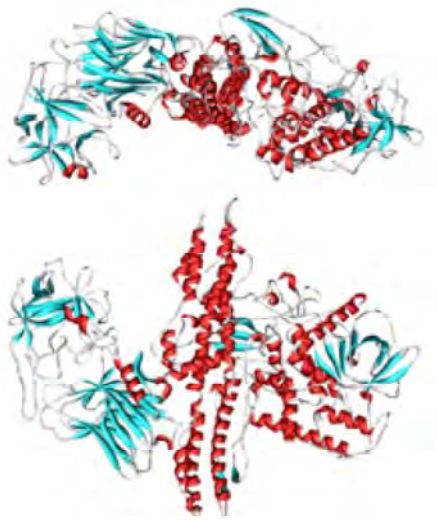
Botulinum toxin (**BTX**) is a neurotoxic protein produced by the bacterium *Clostridium botulinum* and related species.[1] Botulinum toxin causes the disease botulism; however, it is also used commercially in medicine, cosmetics, and research. There are seven types of botulinum toxin, named type A–G. Type A and B are capable of causing disease in humans, and are also used commercially and medically.[2] Types C–G are less common; types E and F can cause disease in humans, while the other types cause disease in other animals.[3] Botulinum toxin types A and B are used in medicine to treat various muscle spasms and diseases characterized by overactive muscle.

The U.S. Food and Drug Administration requires a boxed warning stating that when locally administered the toxin may spread from the injection site to other areas of the body, causing botulism. The warning was the result of deaths associated with its uses.[4][5] Infection with the bacterium may result in a potentially fatal disease called botulism. Botulinum is the most acutely lethal toxin known, with an estimated human median lethal dose (LD_{50}) of 1.3–2.1 ng/kg intravenously or intramuscularly and 10–13 ng/kg when inhaled.[6]

Botulinum toxin A



Clinical data

Routes of administration	IM (approved), SC, intradermal, into glands
ATC code	M03AX01 (WHO (http://www.whocc.no/atc_ddd_index/?code=M03AX01))

Legal status

Legal status	US: ℞-only

Identifiers

CAS Number	93384-43-1 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=93384-43-1) ✗
DrugBank	DB00083 (https://www.drugbank.ca/drugs/DB00083) ✗
ChemSpider	none

Chemical and physical data

Formula	$C_{6760}H_{10447}N_{1743}O_{2010}S_{32}$
Molar mass	150 kg/mol (150,000 g/mol)

✗✓ (what is this?) (verify)

Bontoxilysin

Identifiers

The commercial form is marketed under the brand names Botox, among others. Botox is made by Allergan.[7]

EC number	3.4.24.69 (http://www.chem.qmul.ac.uk/iubmb/enzyme/EC3/4/24/69.html)
	Databases
IntEnz	IntEnz view (http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&ec=3.4.24.69)
BRENDA	BRENDA entry (http://www.brenda-enzymes.org/enzyme.php?ecno=3.4.24.69)
ExPASy	NiceZyme view (http://www.expasy.org/enzyme/3.4.24.69)
KEGG	KEGG entry (http://www.genome.ad.jp/dbget-bin/www_bget?enzyme+3.4.24.69)
MetaCyc	metabolic pathway (http://biocyc.org/META/substring-search?type=NIL&object=3.4.24.69)
PRIAM	profile (http://priam.prabi.fr/cgi-bin/PRIAM_profiles_CurrentRelease.pl?EC=3.4.24.69)
PDB structures	RCSB PDB (http://www.rcsb.org/pdb/search/smartSubquery.do?smartSearchSubtype=EnzymeClassificationQuery&Enzyme_Classification=3.4.24.69) PDBe (http://www.ebi.ac.uk/pdbe/entry/search/index?ec_number:3.4.24.69) PDBsum (https://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/enzymes/GetPage.pl?ec_number=3.4.24.69)
Gene Ontology	AmiGO (http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?query=0006508&view=details) / EGO (https://www.ebi.ac.uk/ego/DisplayGoTerm?id=GO:0006508&format=normal)
	Search
PMC	articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&term=3.4.24.69%5BEC/RN%20Number%5D%20AND%20pubmed%20pmc%20local%5Bsb%5D)
PubMed	articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&term=3.4.24.69%5BEC/RN%20Number%5D)
NCBI	proteins (http://www.ncbi.nlm.nih.gov/protein?term=3.4.24.69%5BEC/RN%20Number%5D)

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Medical uses

Botulinum toxin is used to treat a number of problems.

Muscle spasticity

Botulinum toxin is used to treat a number of disorders characterized by overactive muscle movement, including post-stroke spasticity, post-spinal cord injury spasticity, spasms of the head and neck,[8] eyelid,[9] vagina,[10] limbs, jaw, and vocal cords.[11] Similarly, botulinum toxin is used to relax clenching of muscles, including those of the oesophagus,[12] jaw,[13] lower urinary tract and bladder,[14][15] or clenching of the anus which can exacerbate anal fissure.[16] It may also be used for improper eye alignment.[17]

Cosmetics

In cosmetic applications, botulinum toxin is considered safe and effective for reduction of facial wrinkles, especially in the uppermost third of the face.[18] Injection of botulinum toxin into the muscles under facial wrinkles causes relaxation of those muscles, resulting in the smoothing of the overlying

skin.[18] Smoothing of wrinkles is usually visible three days after treatment and is maximally visible two weeks following injection.[18] The treated muscles gradually regain function, and generally return to their former appearance three to four months after treatment.[18] Muscles can be treated repeatedly to maintain the smoothed appearance.[18]

Other

Botulinum toxin is also used to treat disorders of hyperactive nerves including excessive sweating,[19] neuropathic pain,[20] and some allergy symptoms.[11] In addition to these uses, botulinum toxin is being evaluated for use in treating chronic pain.[21]

Side effects

While botulinum toxin is generally considered safe in a clinical setting, there can be serious side effects from its use. Most commonly, botulinum toxin can be injected into the wrong muscle group or spread from the injection site, causing paralysis of unintended muscles.

Side effects from cosmetic use generally result from unintended paralysis of facial muscles. These include partial facial paralysis, muscle weakness, and trouble swallowing. Side effects are not limited to direct paralysis however, and can also include headaches, flu-like syndromes, and allergic reactions.[22] Just as cosmetic treatments only last a number of months, paralysis side-effects can have the same durations. At least in some cases, these effects are reported to dissipate in the weeks after treatment. Bruising at the site of injection is not a side effect of the toxin but rather of the mode of administration, and is reported as preventable if the clinician applies pressure to the injection site; when it occurs, it is reported in specific cases to last 7–11 days. When injecting the masseter muscle of the jaw, loss of muscle function can result in a loss or reduction of power to chew solid foods.[22]

Side effects from therapeutic use can be much more varied depending on the location of injection and the dose of toxin injected. In general, side effects from therapeutic use can be more serious than those that arise during cosmetic use. These can arise from paralysis of critical muscle groups and can include arrhythmia, heart attack, and in some cases seizures, respiratory arrest, and death.[22] Additionally, side effects which are common in cosmetic use are also common in therapeutic use, including trouble swallowing, muscle weakness, allergic reactions, and flu-like syndromes.[22]

In response to the occurrence of these side effects, in 2008 the U.S. FDA notified the public of the potential dangers of botulinum toxin as a therapeutic. Namely, they warned that the toxin can spread to areas distant from the site of injection and paralyze unintended muscle groups, especially when used for treating muscle spasticity in children treated for cerebral palsy.[4] In 2009, the FDA announced that boxed warnings would be added to available botulinum toxin products, warning of their ability to spread from the injection site.[5] Additionally, the FDA announced name changes to several botulinum toxin products, meant to emphasize that the products are not interchangeable and require different doses for proper use. Botox and Botox Cosmetic were renamed *onabotulinumtoxinA*, Myobloc was renamed *rimabotulinumtoxinB*, and Dysport name renamed *abobotulinumtoxinA*.[5] In conjunction with this, the

FDA issued a communication to health care professionals reiterating the new drug names and the approved uses for each.[23] A similar warning was issued by Health Canada in 2009, warning that botulinum toxin products can spread to other parts of the body.[24]

Role in disease

Botulinum toxin produced by *Clostridium botulinum* is the cause of botulism.[9] Humans most commonly ingest the toxin from eating improperly-canned foods in which *C. botulinum* has grown. However, the toxin can also be introduced through an infected wound. In infants, the bacteria can sometimes grow in the intestines and produce botulinum toxin within the intestine.[25] In all cases, the toxin can then spread, blocking nerves and muscle function. In severe cases, the toxin can block nerves controlling the respiratory system or heart, resulting in death.[1] Botulism can be difficult to diagnose, as it may appear similar to diseases such as Guillain–Barré syndrome, myasthenia gravis, and stroke. Other tests, such as brain scan and spinal fluid examination, may help to rule out other causes. If the symptoms of botulism are diagnosed early, various treatments can be administered. In an effort to remove contaminated food which remains in the gut, enemas or induced vomiting may be used.[26] For wound infections, infected material may be removed surgically.[26] Botulinum antitoxin is available and may be used to prevent the worsening of symptoms, though it will not reverse existing nerve damage. In severe cases, mechanical respiration may be used to support patients suffering from respiratory failure.[26] The nerve damage heals over time, generally over weeks to months.[3] With proper treatment, the case fatality rate for botulinum poisoning can be greatly reduced.[26]

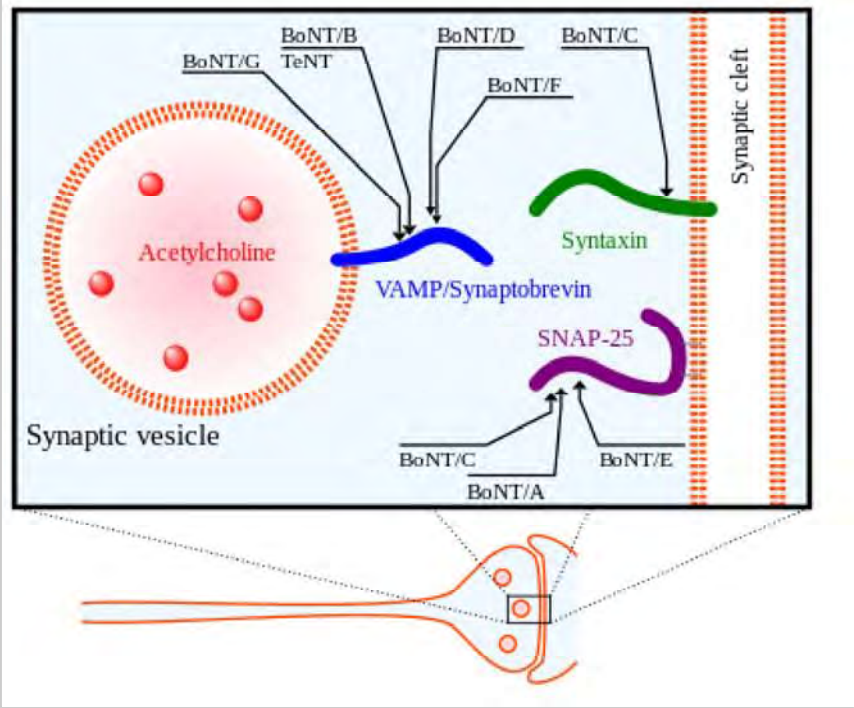
Two preparations of botulinum antitoxins are available for treatment of botulism. Trivalent (A,B,E) botulinum antitoxin is derived from equine sources using whole antibodies. The second antitoxin is Heptavalent (A,B,C,D,E,F,G) botulinum antitoxin, which is derived from equine antibodies which have been altered to make them less immunogenic. This antitoxin is effective against all known strains of botulism.

Mechanism of action

Botulinum toxin exerts its effect by cleaving key proteins required for nerve activation. First, the toxin binds specifically to nerves which use the neurotransmitter acetylcholine. Once bound to the nerve terminal, the neuron takes up the toxin into a vesicle. As the vesicle moves farther into the cell, it acidifies, activating a portion of the toxin which triggers it to push across the vesicle membrane and into the cell cytoplasm.[1] Once inside the cytoplasm, the toxin cleaves SNARE proteins preventing the cell from releasing vesicles of neurotransmitter. This stops nerve signaling, leading to paralysis.[1]

The toxin itself is released from the bacteria as a single-chain, then becomes activated when cleaved by its own proteases.[11] The active form consists cleaved a two-chain protein composed of a 100-kDa heavy chain polypeptide joined via disulfide bond to a 50-kDa light chain polypeptide.[28] The heavy chain contains domains with several functions: it has the domain responsible for binding specifically to presynaptic nerve terminals, as well as the domain responsible for mediating translocation of the light

chain into the cell cytoplasm as the vacuole acidifies.[1][28] The light chain is a zinc metalloprotease and is the active part of the toxin. It is translocated into the host cell cytoplasm where it cleaves the host protein SNAP-25, a member of the SNARE protein family which is responsible for fusion. The cleaved SNAP-25 is unable to mediate fusion of vesicles with the host cell membrane, thus preventing the release of the neurotransmitter acetylcholine from axon endings.[1] This blockage is slowly reversed as the toxin loses activity and the SNARE proteins are slowly regenerated by the affected cell.[1]



Target molecules of botulinum neurotoxin (abbreviated *BoNT*) and tetanus neurotoxin (*TeNT*), toxins acting inside the axon terminal.[27]

The seven toxin types (A-G) have different tertiary structures and sequence differences.[28][29] While the different toxin types all target members of the SNARE family, different toxin types target different SNARE family members.[27] The A, B, and E serotypes cause human botulism, with the activities of types A and B enduring longest *in vivo* (from several weeks to months).[28]

History

In 1820, Justinus Kerner, a small-town German medical officer and romantic poet, gave the first complete description of clinical botulism based on extensive clinical observations of so-called “sausage poisoning”.[30] Following experiments on animals and on himself, he concluded that the toxin acts by interrupting signal transmission in the somatic and autonomic motor systems, without affecting sensory signals or mental functions. He observed that the toxin develops under anaerobic conditions, and can be lethal in minute doses.[31] His prescience in suggesting that the toxin might be used therapeutically earned him recognition as the pioneer of modern botulinum toxin therapy.[32]

In 1895 (seventy-five years later), Émile van Ermengem, professor of bacteriology and a student of Robert Koch, correctly described *Clostridium botulinum* as the bacterial source of the toxin. Thirty-four attendees at a funeral were poisoned by eating partially salted ham, an extract of which was found to cause botulism-like paralysis in laboratory animals. Van Ermengem isolated and grew the bacterium, and described its toxin,[33] which was later purified by P Tessmer Snipe and Hermann Sommer.[34]

Over the next three decades, as food canning was approaching a billion dollar a year industry, botulism was becoming a public health hazard. Karl Friedrich Meyer, a prodigiously productive Swiss-American veterinary scientist (and supervisor of Alan B. Scott's mother's 1925 MA degree in bacteriology), created a center at the Hooper Foundation in San Francisco, where he developed techniques for growing the organism and extracting the toxin, and conversely, for preventing organism growth and toxin production, and inactivating the toxin by heating. The California canning industry was thereby preserved.

With the outbreak of World War II, weaponization of botulinum toxin was investigated at Fort Detrick in Maryland. Carl Lamanna and James Duff[35] developed the concentration and crystallization techniques that Edward J. Schantz used to create the first clinical product. When the Army's Chemical Corps was disbanded, Schantz moved to the Food Research Institute in Wisconsin, where he manufactured toxin for experimental use and generously provided it to the academic community.

The mechanism of botulinum toxin action – blocking the release from nerve endings of the neurotransmitter acetylcholine – was elucidated in the mid-1900s,[36] and remains an important research topic. Nearly all toxin treatments are based on this effect in various body tissues.

Eye muscle disorders

Ophthalmologists specializing in eye muscle disorders (strabismus) had developed the method of EMG-guided injection (using the electromyogram, the electrical signal from an activated muscle, to guide injection) of local anesthetics as a diagnostic technique for evaluating an individual muscle's contribution to an eye movement.[37] Because strabismus surgery frequently needed repeating, a search was undertaken for non-surgical, injection treatments using various anesthetics, alcohols, enzymes, enzyme blockers, and snake neurotoxins. Finally, inspired by Daniel Drachman's work with chicks at Johns Hopkins,[38] Alan B Scott and colleagues injected botulinum toxin into monkey extraocular muscles.[39] The result was remarkable: a few picograms induced paralysis that was confined to the target muscle, long in duration, and without side-effects.

After working out techniques for freeze-drying, buffering with albumin, and assuring sterility, potency, and safety, Scott applied to the FDA for investigational drug use, and began manufacturing botulinum type A neurotoxin in his San Francisco lab. He injected the first strabismus patients in 1977, reported its clinical utility in 1980,[40] and had soon trained hundreds of ophthalmologists in EMG-guided injection of the drug he named *Oculinum*™ ("eye aligner").

Strabismus is caused by imbalances in the actions of muscles that rotate the eyes, and can sometimes be relieved by weakening a muscle that pulls too strongly, or pulls against one that has been weakened by disease or trauma. Muscles weakened by toxin injection recover from paralysis after several months, so it might seem that injection would then need to be repeated. However, muscles adapt to the lengths at which they are chronically held,[41] so that if a paralyzed muscle is stretched by its antagonist, it grows longer, while the antagonist shortens, yielding a permanent effect. If there is good binocular vision, the brain mechanism of *motor fusion*, which aligns the eyes on a target visible to both, can stabilize the corrected alignment.

Other muscle disorders

By 1982, eye muscles had been injected for strabismus and nystagmus (jerky, involuntary eye movements), eyelid muscles for retraction and blepharospasm (sustained, involuntary contractions of muscles around the eye), facial muscles for hemifacial spasm, and limb muscles for dystonia (sustained muscle spasm), all as predicted in Scott's 1973 study.[39]

Scott also injected the first cases of torticollis (painful, spastic twisting of the neck), which were later published by Joseph Tsui of Vancouver.[42] But even a century and a half after Kerner's work, it was difficult for many to accept that the specificity and molecular tenacity that made ingested toxin so deadly also made it remarkably safe when injected directly into a target muscle, and no Bay Area neurology, orthopedic, or rehabilitation physician would try toxin for muscle contractures with stroke, dystonia, torticollis, or cerebral palsy. L Andrew Koman of Wake Forest University in North Carolina pioneered use of toxin to treat pediatric leg spasm in cerebral palsy.[43]

Patient groups quickly spread the word that there were now effective treatments for previously untreatable motility disorders such as blepharospasm, which can result in functional blindness despite an otherwise normal visual system. Torticollis patients discovered that their pain could be markedly reduced by toxin injection, motility increased, head position somewhat improved, even if tremor was not. In 1993, Scott, Pankaj Pasricha, and colleagues showed that botulinum toxin could be used for the treatment of achalasia, a spasm of the lower esophageal sphincter.[44] Spasmodic dysphonia (difficulty speaking), various gastroenteric and urinary sphincter spasms, muscle spasm in stroke, and many other muscle disorders, were also treated with botulinum toxin injection.

In January 2014, botulinum toxin was approved by UK's Medicines and Healthcare Products Regulatory Agency (MHRA) for treatment of restricted ankle motion due to lower limb spasticity associated with stroke in adults.[45]

On July 29, 2016, the U.S. Food and Drug Administration (FDA) approved abobotulinumtoxinA for injection for the treatment of lower limb spasticity in pediatric patients two years of age and older.[46] AbobotulinumtoxinA is the first and only FDA-approved botulinum toxin for the treatment of pediatric lower limb spasticity.

However, botulinum toxins have been used off-label for several pediatric conditions, including infantile esotropia.[47]

Supply problems

In 1986, Oculinum Inc, Scott's micromanufacturer and distributor of botulinum toxin, was unable to obtain product liability insurance, and could no longer supply the drug. As supplies became exhausted, patients who had come to rely on periodic injections became desperate. For 4 months, as liability issues were resolved, American blepharospasm patients traveled to Canadian eye centers for their injections.[48]

Based on data from thousands of patients collected by 240 investigators, under the 1983 US Orphan Drug Act, Scott got FDA approval in 1989 to market Oculinum for clinical use in the United States to treat adult strabismus and blepharospasm. Allergan served as the drug's distributor for almost 2 years, and in 1991 took over the licenses and changed the drug's name to Botox®.

Cosmetics

Richard Clark, a plastic surgeon from Sacramento (CA), was the first to document a cosmetic use for botulinum toxin. He treated facial asymmetry caused by unilateral facial nerve paralysis by injecting toxin into the non-paralyzed frontal muscle.[49]

Marrying ophthalmology to dermatology, Jean and Alistair Carruthers observed that blepharospasm patients who received injections around the eyes and upper face also enjoyed diminished facial glabellar lines ("frown lines" between the eyebrows), thereby initiating the highly-popular cosmetic use of the toxin.[50] Brin, and a group at Columbia University under Monte Keen made similar reports.[51] In 2002, following clinical trials, the FDA approved Botox Cosmetic, botulinum A toxin to temporarily improve the appearance of moderate-to-severe glabellar lines.[52] The FDA approved a fully *in vitro* assay for use in the stability and potency testing of Botox® in response to increasing public concern that LD50 testing was required for each batch sold in the market.[53][54]

Chronic pain

William Binder reported that patients who had cosmetic injections around the face reported relief from chronic headache.[55] This was initially thought to be an indirect effect of reduced muscle tension, but it is now known that the toxin inhibits release of peripheral nociceptive neurotransmitters, suppressing the central pain processing systems responsible for migraine headache.[56][57] In 2010, the FDA approved intramuscular botulinum toxin injections for prophylactic treatment of chronic migraine headache.

Society and culture

Economics

As of 2013, botulinum toxin injections are the most common cosmetic operation, with 6.3 million procedures in the United States, according to the American Society of Plastic Surgeons. Qualifications for Botox injectors vary by county, state and country. Botox cosmetic providers include dermatologists, plastic surgeons, aesthetic spa physicians, dentists, nurse practitioners, nurses and physician assistants.

The global market for botulinum toxin products, driven by their cosmetic applications, is forecast to reach $2.9 billion by 2018. The facial aesthetics market, of which they are a component, is forecast to reach $4.7 billion ($2 billion in the U.S.) in the same timeframe.[58]

Bioterrorism

Botulinum toxin has been recognized as a potential agent for use in bioterrorism.[59] It can be absorbed

through the eyes, mucous membranes, respiratory tract, or non-intact skin.[60]

The effects of botulinum toxin are different from those of nerve agents involved insofar in that botulism symptoms develop relatively slowly (over several days), while nerve agent effects are generally much more rapid and can be instantaneous. Evidence suggests that nerve exposure (simulated by injection of atropine and pralidoxime) will increase mortality by enhancing botulinum toxin's mechanism of toxicity.

With regard to detection, current protocols using NBC detection equipment (such as M-8 paper or the ICAM) will not indicate a "positive" when samples containing botulinum toxin are tested. To confirm a diagnosis of botulinum toxin poisoning, therapeutically or to provide evidence in death investigations, botulinum toxin may be quantitated by immunoassay of human biological fluids; serum levels of 12–24 mouse LD_{50} units per milliliter have been detected in poisoned patients.[61]

Brand names

Botulinum toxin A is marketed under the brand names Botox (marketed by Allergan), Dysport (marketed by Ipsen), and Xeomin (marketed by Merz Pharma). Botulinum toxin B is marketed under the brand name Myobloc (marketed by Solstice Neurosciences).

In the United States, botulinum toxin products are manufactured by a variety of companies, for both therapeutic and cosmetic use. Allergan, Inc., a principal U.S. supplier through their Botox products, reported in its company materials in 2011 that it could "supply the world's requirements for 25 indications approved by Government agencies around the world" with less than one gram of raw botulinum toxin.[62] Myobloc or Neurobloc, a botulinum toxin type B product, is produced by Solstice Neurosciences, a subsidiary of US WorldMeds. AbobotulinumtoxinA), a therapeutic formulation of the type A toxin manufactured by Galderma in the United Kingdom, is licensed for the treatment of focal dystonias and certain cosmetic uses in the U.S. and other countries.[23]

After the three primary U.S. manufacturers, there many reports of other sources of production. Xeomin, manufactured in Germany by Merz, is also available for both therapeutic and cosmetic use in the U.S.[63] Lanzhou Institute of Biological Products in China manufactures a BTX-A product; as of 2014 it was the only BTX-A approved in China.[63] BTX-A is also sold as Lantox and Prosigne on the global market.[64] Neuronox, a BTX-A product, was introduced by Medy-Tox Inc. of South Korea in 2009;[65] Neuronox is also marketed as Siax in the U.S.

Toxin production

Botulism toxins are produced by bacteria of the genus *Clostridium,* namely *Clostridium botulinum*, *C. butyricum, C. baratii* and *C. argentinense,*[66] which are widely distributed, including in soil and dust. As well, the bacteria can be found inside homes on floors, carpet, and countertops even after cleaning. Some food products such as honey can contain amounts of the bacteria.

Food-borne botulism results, indirectly, from ingestion of food contaminated with Clostridium spores, where exposure to an anaerobic environment allows the spores to germinate, after which the bacteria can multiply and produce toxin. Critically, *it is ingestion of toxin rather than spores or vegetative bacteria*

that causes botulism. Botulism is nevertheless known to be transmitted through canned foods not cooked correctly before canning or after can opening, and so is preventable. Infant botulism cases arise chiefly as a result of environmental exposure and are therefore more difficult to prevent. Infant botulism arising from consumption of honey can be prevented by eliminating honey from diets of children less than 12 months old.[67]

Therapeutic and weaponisable forms of the toxin are sourced from strains of *Clostriudium* where both the growth and toxin isolation are under specialized conditions.

Organism and toxin susceptibilities

Proper refrigeration at temperatures below 3 °C (38 °F) retards the growth of *Clostridium botulinum*. The organism is also susceptible to high salt, high oxygen, and low pH levels. The toxin itself is rapidly destroyed by heat, such as in thorough cooking.[68] The spores that produce the toxin are heat-tolerant and will survive boiling water for an extended period of time.[69]

The botulinum toxin is denatured and thus deactivated at temperatures greater than 80 °C (176 °F).[70] As a zinc metalloprotease (see below), the toxin's activity is also susceptible, post-exposure, to inhibition by protease inhibitors, e.g., zinc-coordinating hydroxamates.[28][71]

Research

Blepharospasm and strabismus

In the early 1980s, university-based ophthalmologists in the USA and Canada further refined the use of botulinum toxin as a therapeutic agent. By 1985, a scientific protocol of injection sites and dosage had been empirically determined for treatment of blepharospasm and strabismus.[72] Side effects in treatment of this condition were deemed to be rare, mild and treatable.[73] The beneficial effects of the injection lasted only 4–6 months. Thus, blepharospasm patients required re-injection two or three times a year.

In 1986, Scott's micromanufacturer and distributor of Botox was no longer able to supply the drug because of an inability to obtain product liability insurance. Patients became desperate, as supplies of Botox were gradually consumed, forcing him to abandon patients who would have been due for their next injection. For a period of four months, American blepharospasm patients had to arrange to have their injections performed by participating doctors at Canadian eye centers until the liability issues could be resolved.[48]

In December 1989, Botox, manufactured by Allergan, Inc., was approved by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients over 12 years old.[74]

Botox has not been approved for any pediatric use.[23] It has, however, been used off-label by physicians for several conditions. including spastic conditions in pediatric patients with cerebral palsy, a therapeutic course that has resulted in patient deaths.[23] In the case of treatment of infantile esotropia in patients younger than 12 years of age, several studies have yielded differing results.[47]

Cosmetic

The cosmetic effect of BTX-A on wrinkles was originally documented by a plastic surgeon from Sacramento, California, Richard Clark, and published in the journal *Plastic and Reconstructive Surgery* in 1989.[49] Canadian husband and wife ophthalmologist and dermatologist physicians, JD and JA Carruthers, were the first to publish a study on BTX-A for the treatment of glabellar frown lines in 1992.[50] Similar effects had reportedly been observed by a number of independent groups (Brin, and the Columbia University group under Monte Keen.[51]) After formal trials, on April 12, 2002, the FDA announced regulatory approval of botulinum toxin type A (Botox Cosmetic) to temporarily improve the appearance of moderate-to-severe frown lines between the eyebrows (glabellar lines).[52] Subsequently, cosmetic use of botulinum toxin type A has become widespread.[75] The results of Botox Cosmetic can last up to four months and may vary with each patient.[76] The US Food and Drug Administration approved an alternative product-safety testing method in response to increasing public concern that LD50 testing was required for each batch sold in the market.[53][54]

Upper motor neuron syndrome

BTX-A is now a common treatment for muscles affected by the upper motor neuron syndrome (UMNS), such as cerebral palsy, for muscles with an impaired ability to effectively lengthen. Muscles affected by UMNS frequently are limited by weakness, loss of reciprocal inhibition, decreased movement control and hypertonicity (including spasticity). In January 2014, Botulinum toxin was approved by UK's Medicines and Healthcare Products Regulatory Agency (MHRA) for the treatment of ankle disability due to lower limb spasticity associated with stroke in adults.[45] Joint motion may be restricted by severe muscle imbalance related to the syndrome, when some muscles are markedly hypertonic, and lack effective active lengthening. Injecting an overactive muscle to decrease its level of contraction can allow improved reciprocal motion, so improved ability to move and exercise.

Sweating

Khalaf Bushara and David Park were the first to demonstrate a nonmuscular use of BTX-A while treating patients with hemifacial spasm in England in 1993, showing that botulinum toxin injections inhibit sweating, and so are useful in treating hyperhidrosis (excessive sweating).[77] BTX-A has since been approved for the treatment of severe primary axillary hyperhidrosis (excessive underarm sweating of unknown cause), which cannot be managed by topical agents.[11][19]

Cervical dystonia

BTX-A is commonly used to treat cervical dystonia, but it can become ineffective after a time. Botulinum toxin type B (BTX-B) received FDA approval for treatment of cervical dystonia on December 21, 2000. Trade names for BTX-B are Myobloc in the United States, and Neurobloc in the European Union.[63]

Chronic migraine

Onabotulinumtoxin A (trade name Botox) received FDA approval for treatment of chronic migraines on October 15, 2010. The toxin is injected into the head and neck to treat these chronic headaches. Approval followed evidence presented to the agency from two studies funded by Allergan, Inc. showing a very slight improvement in incidence of chronic migraines for migraine sufferers undergoing the Botox treatment.[78][79]

Since then, several randomized control trials have shown botulinum toxin type A to improve headache symptoms and quality of life when used prophylactically for patients with chronic migraine[80] who exhibit headache characteristics consistent with: pressure perceived from outside source, shorter total duration of chronic migraines (<30 years), "detoxification" of patients with coexisting chronic daily headache due to medication overuse, and no current history of other preventive headache medications.[81]

See also

- Microbial toxins

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External links

- A Poison that can Heal (http://www.fda.gov/fdac/features/095_bot.html) from the U.S. Food and Drug Administration
- BotDB: extensive resources on BoNT structures, inhibitors, kinetics, and literature (http://botdb.abcc.ncifcrf.gov)
- A consumer sociological investigation of Botox Cosmetic's Rise (http://markus-giesler.com/publications/)