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Botulinum Toxin : A Wonder for ENT Problems

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Abstract

Botulinum toxin is a neurotoxin produced by clostridium botulinum. Toxin are classified into type A-G, type A toxin being the most common commercially available type. The toxin act at the neuromuscular junction and prevent the action of acetylcholine in the junction thus cause paralysis of the involved muscle. This principle of the toxin has been used in the medical practice to treat many diseases, similarly the toxin has role in various ENT diseases.

Keyword: Botulinum toxin, mechanism of action, medical uses , role in Otolaryngology

Introduction

Botulinum toxin is a neurotoxic protein produced by the anaerobic spore forming organism called Clostridium botulinum and related species [1]. The toxin types are classified as A, B,C,D,E,F and G. Human botulism has been described with the strains of clostridium botulinum that produce toxin types A, B,and E. Less frequently, cases involving type F toxin produced by C. Baratii and toxin type E produced by C. Butyricum have been published [2].

It is also produced commercially for medical, cosmetic, and research use. There are two main type botulinum toxin type A and botulinum toxin type B which have been extensively studied and available commercially [3]. Botulinium neurotoxin consists of a heavy chain and a light chain linked together by a single disulfide bond. It is synthesised as a relatively inactive single chain polypeptide with a molecular mass of approximately 150 kd. It is activated when the polypeptide chain is proteolytically cleaved into the 100kd heavy chain and the 50 kd light chain [4]. The heavy chain binds to specific receptor at the presynaptic nerve terminal. There are probably different receptors for the binding of the different serotypes. The toxic domain is the light chain [5].

Mechanism of action

When the motor neuron action potential depolarizes the axon terminal, acetylcholine is released from the cytosol into the synaptic cleft. This acetylcholine release is performed by a transport protein chain, the soluble N-ethylmaleimide- sensitive factor attachment protein receptor (SNARE) complex. When botulinium toxin (BT) is injected into a target tissue the heavy chain of the botulinum neurotoxin binds to glycoprotein structures specifically found on cholinergic nerve terminals. This specific docking is the reason for BT's high selectivity for cholinergic synapses. After internalization, the light chain of the botulinum toxin binds with high specificity to the SNARE protein complex(Fig 1) [4]. The target proteins vary amongst the BT serotypes. BT-A cleaves synaptosomal associated protein of 25kda (SNAP-25). BT-B cleave vesicle associated membrane protein (VAMP), also known as synaptobrevin II. The light chain's proteolytic cleavage of the SNARE protein complex prevents the docking of the acetylcholine vesicle on the inner surface of the cellular membrane and results in blockage of vesicle fusion. When the target tissue is a muscle, paralysis by chemical denervation occurs. When the target tissue is an exocrine gland, the glandular secretion is blocked. The inhibition of the acetylcholine exocytosis by BT is terminated by restoration of the SNARE protein complex turnover. Axonal sprouting and endplate elongation occurs, but is believed to be a transient phenominon not responsible for the termination of BT effect [3].

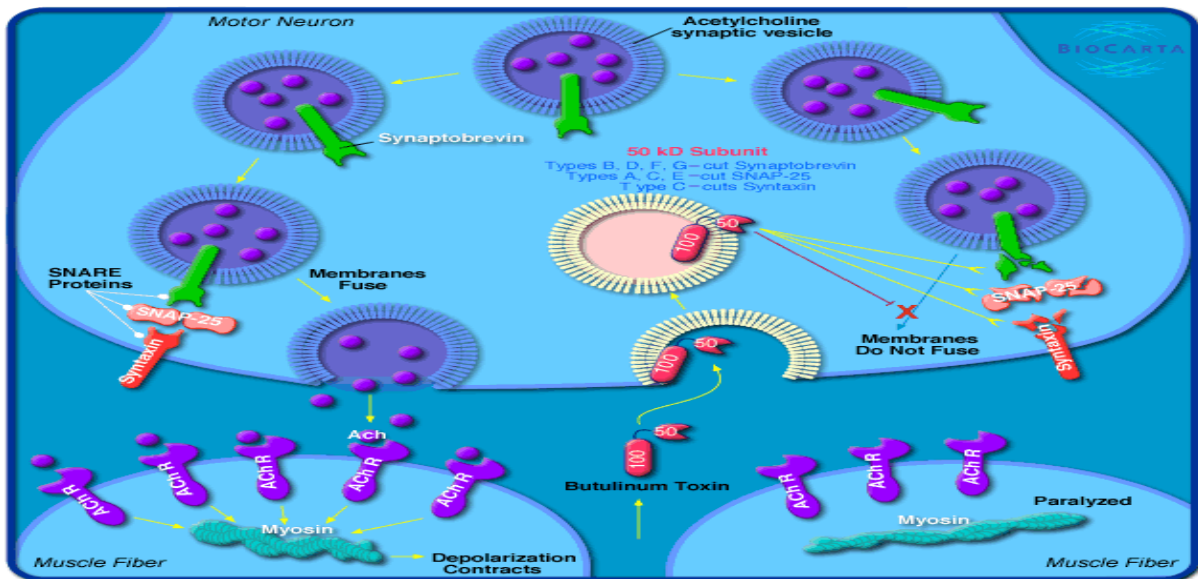


Fig :1 Action of Botulinum toxin at the neuromuscular junction

Uses of botulinum toxin in Otolaryngology

Botulinum toxin is used for a number of medical problems. When injected in small amounts into a striated muscle, paralysis occurs after 2-5 days and lasts for a period of three to four months before it starts to gradually wear off [3]. It is used in the treatment of spasms and dystonias. various uses in otolaryngology are

- **Facial Movement Disorders, Esthetic Use of BTX**

Dyskinesia like hemifacial spasm, blepharospasm, synkinesis, or Meige syndrome (combination of blepharospasm and oromandibular dystonia) are the most common facial indications of BTX applications in otorhinolaryngology.

Hemifacial spasm is an ‘overactivity’ of mimic muscles of one half of the face, and is mostly caused by a contact between the root entry zone of the facial nerve and a vessel close to the brainstem. Also tumors or inflammations are able to cause a hemifacial spasm.

Therapy includes the subcutaneous injection of all hyperkinetic muscles as the orbicularis oculi muscle, the glabella, the frontalis muscle, the orbicularis oris muscle, the mentalis and depressor labii inferioris muscles, and the zygomatic and risorius muscles. In cases of a spastic entropion, BTX injections into the lower eyelid musculature are also a helpful option.

Concerning the use of BTX in mimic muscles, its use in the esthetic medicine gained more

importance. Lower eyelid wrinkles, bunny lines, drooping nasal tip, perioral wrinkles, masseter hypertrophy, drooping mouth corners, dimpled chin, platysmal bands, and décolleté wrinkles can be treated. Reducing the innervation level of certain areas of mimic muscles leads to a straightening of wrinkles in this area of the face and to a ‘younger facial expression’[5].

- **Laryngeal Dystonia**

Dystonic laryngeal movements can cause spasmodic dysphonia. The main form shows adduction of the vocal folds (>90%) with a staccato voice interruption of pressed quality. Only some show abduction of the vocal folds with a breathy voice and a feeling of dyspnea because of air loss through the open glottis.

BTA is the treatment of choice. In the adductor type, the vocalis muscle and the thyroarytenoid muscle are the goal to inject, and in the abductor type, the cricoarytenoideus posterior muscle is injected. Different ways to reach the region are possible: transorally in local or general anesthesia and transcutaneously with electromyography.

Side effects can involve local pain, a breathy voice, and dysphagia. Some rare indications are the granuloma of the arytenoid cartilage and a synechia of the posterior commissure.

As other rare indications in the larynx BTX have been used to weaken the abducting muscles of the larynx in multiple sclerosis, to prevent resynechia after dissection, to reduce phonation with the false vocal folds, and to influence stuttering [5].

- **Gustatory Sweating (GS)**

Gustatory sweating (GS) is a well-known sequela after parotid gland surgery. GS does not only occur after parotid gland surgery but also, e.g. after trauma, infections, or central nervous diseases.

BTX injections has become the ‘first-line treatment’ in GS. Other forms of hyperhidrosis are also were treated using BTX injections. Before BTX treatment, patients are asked to eat

an apple to provoke sweating during Minor's test. So the area of pathological sweating can exactly be identified. Preferred method is a subdivision of the affected area in small boxes to ensure a treatment of the whole sweating area. After a few days, the affected area is dry when patients eat or chew [5].

- **Sialorrhea**

There is evidence that BTX injections can successfully reduce the saliva flow in patients with drooling caused by different reasons. This is an important treatment option for adults and children suffering from this problem. The technique used is the ultrasound-guided injection of BTX into the parotid and submandibular glands.

In otorhinolaryngology, bi- and unilateral applications of BTX have proven success in swallowing problems after tumor surgery with aspiration of saliva or the inability to swallow saliva. In disturbances of wound healing after extended laser resections of laryngeal tumors, it can improve wound healing [5].

- **BTX to Reduce Sweating in Patients with Hearing Aids, Active Middle Ear, and Cochlear Implants**

Sweating in the temporal and occipital skin region may be a serious problem for patients with hearing aids, active middle ear implants, or cochlear implants. Affected patients often report about the impossibility to use their hearing aids or their speech processor and sometimes complain about a complete loss of function of their device.

In this context, the use of BTX is of great practical relevance. BTX can reduce sweating by intracutaneous injections. BTX injections are suitable to improve complaints caused by sweating in patients with hearing aids, active middle ear implants, and cochlear implants [5].

- **BTX to Reduce Rhinorrhea**

Chronic rhinitis is a common condition affecting over 20% of the population. Nasal hypersecretion due to allergic or idiopathic rhinitis (in former times 'vasomotor rhinitis') can often not be treated sufficiently by conventional medication. Since most of the nasal glands

are innervated by acetylcholine, an anticholinergic drug like BTX should have an effect on nasal hypersecretion. BTX has been injected into the nasal mucosa or applied minimally invasive by sponges in patients with nasal hypersecretion with a reduction in rhinorrhea lasting for about 4–12 weeks [5].

- **Facial Pain, Headache**

Several studies exist that deal with BTX applications in pain syndromes of the head and neck region, and there is some evidence that BTX is effective in the treatment of chronic migraine and other types of headache. Recently, the treatment of trigeminal neuralgia also has been demonstrated [5].

- **Fistulas**

Early fistulas of the parotid gland tend to close spontaneously, but during their existence they evoke clinical symptoms like a continuous loss of saliva through the fistula. Permanent fistulas need revision surgery in nearly all cases to be closed; in rare cases radiotherapy is the last alternative. Early or permanent fistulas of the parotid glands themselves or in other regions of the head and neck after surgery (e.g. after laryngectomy) can be treated with BTX. In patients who developed a fistula after laryngectomy BTX injections into the salivary glands help to improve the wound healing, the closure of the fistula, and the complaints of the patients [5].

- **Flaps/Reconstructive Surgery**

Oncological head and neck surgery often leads to tissue defects that have to be closed after removing, e.g. a big tumor. To reach a good functional result after surgery, different flaps are suitable to close these defects. Saliva is an aggressive agent prohibiting an uncomplicated wound healing and this is of relevance, e.g. in free flaps covering defects in the oral cavity. BTX injections into the salivary glands improve the ambience for the wound healing by reducing the amount of saliva [5].

- **Stenosis of Stensen Duct.**

After trauma or infections, a stenosis of Stensen duct leads to complaints that are based on a

stasis of the saliva flow, resulting in pain, swelling, and infections of the affected gland. In cases of stenosis of Stensen duct, in which sialendoscopic treatment is not successful, a reduction in the saliva production of the affected gland by BTX injections can be helpful [5].

- **Additional Treatment of Dysphagia**

A number of patients with neurological diseases suffer from dysphagia because of a discoordinated relaxation of the upper esophageal sphincter (UES) (cricopharyngeal achalasia). They often suffer from silent aspiration. In these cases, we inject BTX into the cricopharyngeal muscle to open the UES. Often this treatment is combined with additional BTX injections into the salivary glands (parotid gland, submandibular gland) in patients who have a lot of saliva, because the exclusive relaxation of the upper esophagus sphincter is in many cases not sufficient to reach total recovery [5].

- **Improvement in Wound Healing**

Injuries in the head and neck region may lead to unesthetic scars in the face. During early surgical treatment, it is of great importance to consider the special situation in the face (relaxed skin tension lines). Besides, the circumstances for an unproblematic wound healing can be improved using BTX injections [5].

- **Dysphagia**

Dysphagia may have many causes. In some cases, the physiological relaxation of the UES is disturbed during swallowing. In other cases, the opening of the lower esophageal sphincter (LES) is disturbed (achalasia). For achalasia, BTX injections into musculature of the distal esophagus can be performed as one therapeutically method instead of surgery as the established first-line treatment. In cases of a disturbed UES function, we inject BTX into the cricopharyngeal muscle using instruments for microlaryngoscopy [5].

- **Tinnitus, Autophonia**

An objective clicking tinnitus can be caused by a palatal myoclonus. It is a rare neurological disorder characterized by involuntary movements of the soft palate musculature. Conventional medical treatments with anxiolytics, antidepressants, and anticonvulsants have

limited efficacy so that BTX is injected electromyographically controlled. The salpingopharyngeus and tensor veli palatini muscles are the goal of injection. In autophonia due to a malfunction of the muscles around the eustachian tube (tensor and levator veli palatini muscles and salpingopharyngeus muscle), BTX has been injected in these muscles. Autophonia disappeared and tympanic ventilation normalized [5].

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