



Topical botulinum toxin to treat hyperhidrosis? No sweat!

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Summary Palmar, plantar and axillary hyperhidrosis, though benign, may be burdensome and occupationally restrictive, even hazardous. Treatment modalities range from topical antiperspirants, iontophoresis, systemic medications such as anticholinergics and benzodiazepines and injections of botulinum toxin, to thoracic sympathectomy. Intradermal injections of botulinum toxin (BTX), though effective, are painful especially when multiple injections are required. Iontophoretic administration of BTX has been described, the BTX entering the eccrine sweat glands via the sweat pores and through the sweat ducts. We postulate that BTX can be administered topically, either unassisted or assisted by application of an electrical gradient, low-frequency ultrasound or excipients such as dimethylsulfoxide. We examine the rationale and feasibility for such a treatment modality and route of administration. © 2006 Elsevier Ltd. All rights reserved.

Introduction

Hyperhidrosis, a condition characterized by excessive sweating, can be generalized or focal. When generalized, it usually occurs in association with an infectious, endocrine or neurologic disorder [1]. Focal hyperhidrosis is idiopathic, and occurs in otherwise-healthy individuals, affecting the palms, soles or axillae [1]. A recent survey of 150,000 households in the United States estimated the overall prevalence at 2.8%, with the highest

rate in the 25–64 age group [2]. Focal hyperhidrosis is a benign, socially rather than medically burdensome condition, associated with a decreased quality of life [3]. In extreme cases, it can result in social isolation or occupational disability [4].

Pathophysiology

The pathophysiology of hyperhidrosis is poorly understood. Sweat is produced by the eccrine, apocrine and apoecrine sweat glands of the body. Eccrine sweat glands produce an odourless, clear fluid, whose main function is the regulation of body temperature. Apocrine sweat glands are scent glands, confined to the axillary and urogenital

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regions, that produce odoriferous secretions. Mixed or apoeccrine sweat glands, are mainly found in the axillary and perianal regions [5]. Eccrine sweat glands are innervated by cholinergic fibers from the sympathetic nervous system. The function of apocrine sweat glands is mainly mediated through hormones. Eccrine sweat glands are responsible for focal hyperhidrosis. Eccrine sweat glands are most densely located in the forehead and soles of the feet, followed by the palms and cheeks [1,5].

The sweat glands of patients with focal hyperhidrosis have not been shown to differ in structure, size or number from normal [1]. Instead, the condition is thought to represent a complex dysfunction of the autonomic nervous system, involving both the sympathetic and parasympathetic pathways [1].

Current treatment modalities

The current treatments for focal hyperhidrosis vary in efficacy, duration of effect, side effects, cost, ease of administration and performance. These are summarized in Table 1. Therapy can be divided into medical (topical, iontophoresis, intradermal injections, systemic) and surgical options.

Hypothesis: using *topical* botulinum toxin (BTX) to treat hyperhidrosis

Intradermal injections of botulinum toxin (BTX) are the best-studied treatment to date for focal hyperhidrosis [1]. Though effective, intradermal injections of botulinum toxin are very painful and often require the use of topical [6], vibrational [7] or regional anesthesia [1,8] for patient comfort. Kavanagh et al. have described the successful iontophoresis of BTX to treat palmar hyperhidrosis in two patients [9]. We hypothesize that BTX can be administered topically, without the need for iontophoresis. If topical application works, then BTX can be prepared in an inert vehicle and applied as a cream or gel and the effective, painless treatment of hyperhidrosis will be possible.

BTX: mode of action

BTX is derived from the exotoxin of *Clostridium botulinum*. It comprises a light and heavy chain, linked by a disulphide bond. Commercially available BTX contains complexing proteins that stabilize the preparation [10]. After gaining access into target tissues, BTX is internalized after the

heavy chain binds to glycoprotein receptors on cholinergic nerve terminals [11,12]. The light chain of BTX then binds with high specificity to the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) protein complex, after which it proteolytically cleaves target proteins, which normally serve to allow the docking of the acetylcholine-containing vesicles to the inner surface of the synaptic membrane (Fig. 1). This chemical denervation is terminated when SNARE protein complex turnover is restored [11,13]. BTX has been described to have a duration of action of up to 2 years in treating focal hyperhidrosis [14].

BTX without needles

Although usually injected, either intramuscularly, intradermally or subcutaneously, BTX can be administered without needles. Systemic botulism has been described to occur after the ingestion of contaminated canned food, as well as by the inhalation of intranasal BTX [13].

Focal hyperhidrosis has been successfully treated in two patients by iontophoresis of BTX. It is believed that BTX can traverse the sweat ducts (Fig. 2) which open onto the surface [9,15], hence it can be directly delivered to the eccrine sweat glands.

Topical administration of BTX

Topically administered drugs may be absorbed by: (1) penetration of the cutaneous layer, e.g. testosterone [16] and estradiol [17] or (2) transport via the sweat pores, e.g. acetylcholine or lidocaine [1]. Topically-administered BTX would reach target eccrine glands via the latter method. The palmar glabrous skin has the highest density of sweat pores [18], making it eminently suitable for topical BTX treatment. Intuitively, (1) pore size and (2) osmotic gradient would be directly proportional to rate of absorption of BTX, whereas (3) size of the molecule would bear an inverse relationship. Application of an electrical gradient (iontophoresis), or low-frequency ultrasound (sonophoresis) [19], can also positively influence transport of BTX into the sweat glands.

How can BTX be topically administered to treat focal hyperhidrosis?

Topical administration of BTX can be unassisted (i.e. without external influences) or assisted. In

Table 1 Current therapeutic modalities for focal hyperhidrosis [1]

Technique	What technique entails	Mechanism of action	Ease of administration or performance	Efficacy	Duration of benefit	Side effects	Cost/disadvantages
<i>Medical</i> Aluminium chloride	20–25% Aluminium chloride solution applied topically (palm/sole/axillae) every 24–48 h	Mechanical obstruction of eccrine gland or atrophy of secretory cells	Easy	Improvement within 3 weeks	Short-term. Benefit disappears with cessation of treatment (within 48 h)	Localized burning, stinging and irritation (33% of patients)	Inexpensive/messy
Iontophoresis	Placing hands/feet in a shallow container of water, through which an electric current is passed	Postulated obstruction of duct by charged particle or disruption of eccrine gland secretion by charged particle	Fairly easy, but requires 30–40 min per treatment, 4X/week for at least 6–10 treatments before benefit	No large randomized controlled trials. 80–100% efficient in uncontrolled trials	Medium-term (months)	Erythema, vesicles, burning, tingling, acrocyanosis and edema	Fairly inexpensive/time consuming. Contraindicated in pregnant women or those with pacemakers
Intradermal botulinum toxin	Injection (palms, soles, axillae) with botulinum toxin intradermally (up to 100 U and 20 injection sites per palm)	Inhibits release of acetylcholine from (presynaptic) sympathetic nerves	Fairly easy	Very effective	Medium-term (months)	Transient intrinsic muscle weakness, compensatory hyperhidrosis	Expensive/painful
Anticholinergic medications	Ingestion of oral anticholinergic medications	Inhibition of synaptic acetylcholine and interruption of neuroglandular signalling	Easy	Fairly effective	Short-term. Benefit disappears with cessation of treatment	Dry mouth, blurred vision, urinary retention, constipation and tachycardia	Inexpensive/Limited by side effects (systemic)
<i>Surgical</i> Endoscopic thoracic sympathectomy	Destruction of the sympathetic ganglia by excision, clamping, transection or ablation with cauterly or laser	Sympathetic denervation	Difficult. Requires skilled surgeon	Very effective	Long-term (years)	Compensatory hyperhidrosis, gustatory sweating, phantom sweating, neuralgia, Horner's syndrome, hemo/pneumothorax	Expensive/operator-dependent

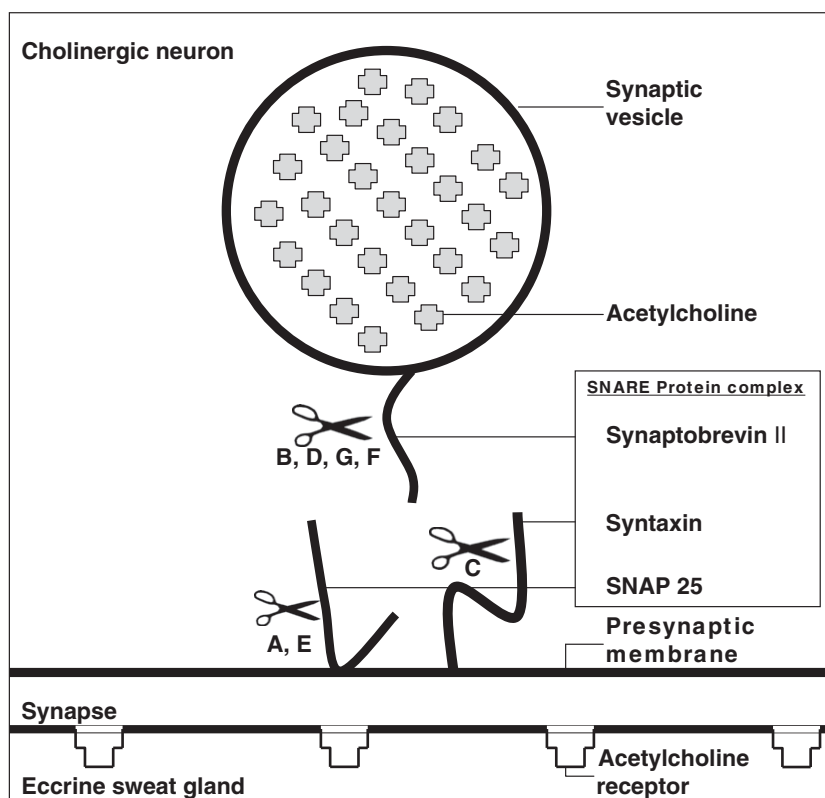


Figure 1 Action of Botulinum toxin at the presynaptic neuroglandular terminal. The scissors indicate cleavage sites of the various Botulinum exotoxins (indicated in bold below) [7].

the former technique, the hyperhidrotic hand (or foot) can be immersed in a shallow container of BTX reconstituted in normal saline. Factors that are likely to influence the success of this method of administration include: (1) concentration, (2) temperature of the solution and (3) size of the sweat pores. In order to ensure large sweat pore size, it may be necessary to warm the surface of the palm or sole first (e.g. with a heat lamp).

Assisted techniques of application of BTX include the application of a small electrical current (iontophoresis), low-frequency ultrasound (sonophoresis), or the use of excipients such as dimethyl sulfoxide in the diluent to increase absorptive properties.

Recently, Benecke et al. have described efficacy of Xeomin, a form of BTX free of complexing proteins [20]. This smaller molecule of BTX may allow greater absorption of the toxin through the sweat pores. It may well be that the light chain of BTX, which is the active component of the molecule that cleaves the SNARE proteins, may be all that is required to decrease eccrine secretion. Therefore, it is possible that formulations containing only the light chain of

botulinum toxin (reconstituted in gel or cream form), may be all that is required to treat hyperhidrosis in the future.

Summary

Focal hyperhidrosis, which is a social rather than medical burden, may effectively be treated by multiple intradermal injections of BTX. This procedure is painful, and physicians have resorted to local as well as regional anesthesia in an effort to ameliorate the pain. Iontophoresis of BTX has been successful in two patients. BTX is thought to enter the eccrine sweat glands via the sweat pores, traversing the sweat duct. It is possible that application of low-frequency ultrasound may likewise be useful in increasing the rate at which BTX enters the sweat gland, and that the osmotic gradient alone may achieve this. The development of BTX, free of complexing proteins (resulting in a smaller molecule), may allow this technique for treating focal hyperhidrosis to become a reality.

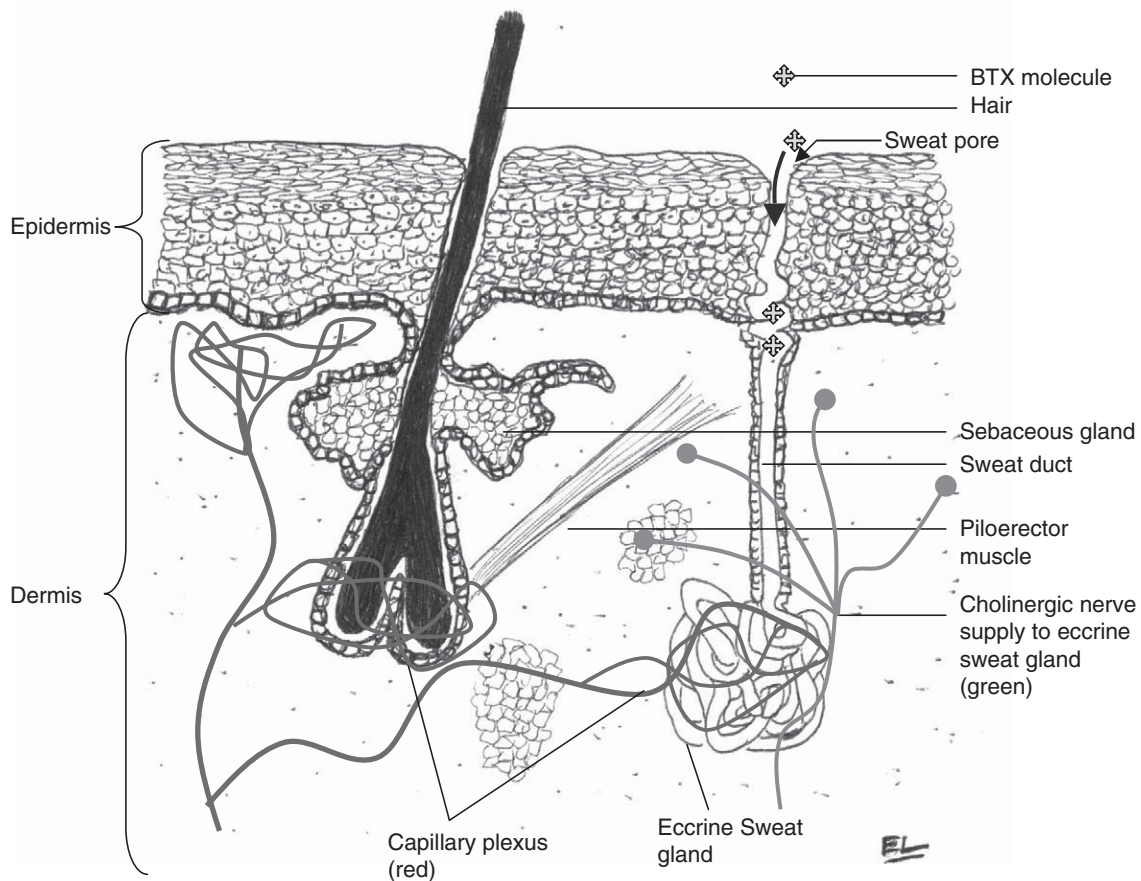


Figure 2 Cross section of skin showing uptake of BTX molecule into sweat gland via sweat duct.

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