

Review Articles

Mechanism of Action of OnabotulinumtoxinA in Chronic Migraine: A Narrative Review

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Objective.—To review the literature on the mechanism of action of onabotulinumtoxinA in chronic migraine.

Background.—OnabotulinumtoxinA is a chronic migraine preventive treatment that significantly reduces headache frequency. The traditional mechanism described for onabotulinumtoxinA – reducing muscle contractions – is insufficient to explain its efficacy in migraine, which is primarily a sensory neurological disease.

Methods.—A narrative literature review on the mechanism of action of onabotulinumtoxinA in chronic migraine.

Results.—Following injection into tissues, onabotulinumtoxinA inhibits soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE)-mediated vesicle trafficking by cleaving one of its essential proteins, soluble N-ethylmaleimide-sensitive fusion attachment protein (SNAP-25), which occurs in both motor and sensory nerves. OnabotulinumtoxinA inhibits regulated exocytosis of motor and sensory neurochemicals and proteins, as well as membrane insertion of peripheral receptors that convey pain from the periphery to the brain, because both processes are SNARE dependent. OnabotulinumtoxinA can decrease exocytosis of pro-inflammatory and excitatory neurotransmitters and neuropeptides such as substance P, calcitonin gene-related peptide, and glutamate from primary afferent fibers that transmit nociceptive pain and participate in the development of peripheral and central sensitization. OnabotulinumtoxinA also decreases the insertion of pain-sensitive ion channels such as transient receptor potential cation channel subfamily V member 1 (TRPV1) into the membranes of nociceptive neurons; this is likely enhanced in the sensitized neuron. For chronic migraine prevention, onabotulinumtoxinA is injected into 31–39 sites in 7 muscles of the head and neck. Sensory nerve endings of neurons whose cell bodies are located in trigeminal and cervical ganglia are distributed throughout the injected muscles, and are overactive in people with migraine. Through inhibition of these sensory nerve endings, onabotulinumtoxinA reduces the number of pain signals that reach the brain and consequently prevents activation and sensitization of central neurons postulated to be involved in migraine chronification.

Conclusion.—OnabotulinumtoxinA likely acts via sensory mechanisms to treat chronic migraine.

Key words: migraine, headache, botulinum, trigeminal system

Abbreviations: BoNTA botulinum toxin type A, CGRP calcitonin gene-related peptide, CNS central nervous system, FGFR3 fibroblast growth factor receptor 3, NAPs neurotoxin-associated proteins, NO nitric oxide, P2X3 purinergic receptor P2X ligand-gated ion channel 3, PACAP 38 pituitary adenylate cyclase-activating peptide-38, PSG polysialoganglioside, SNAP-25 soluble N-ethylmaleimide-sensitive fusion attachment protein, SNARE soluble N-ethylmaleimide-sensitive fusion attachment protein receptor, SV2 synaptic vesicle protein 2, TRPA1 transient

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receptor potential cation channel subfamily A member 1, TRPV1 transient receptor potential cation channel subfamily V member 1

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INTRODUCTION

Botulinum neurotoxin type A (BoNTA) is a potent inhibitor of muscle contraction that acts by preventing the release of acetylcholine at the neuromuscular junction. This property led to the development of an injectable formulation, commonly referred to as BOTOX (onabotulinumtoxinA), for the treatment of ocular conditions characterized by focal muscle overactivity, particularly blepharospasm and strabismus.^{1,2} Subsequently, the clinical use expanded and onabotulinumtoxinA became a first-line treatment for cervical dystonia and a treatment for upper and lower limb spasticity in adults³ and pediatrics. In clinical trials, treatment of cervical dystonia⁴⁻⁶ and spasticity⁷⁻⁹ with onabotulinumtoxinA reduced both muscle contractions and pain. The clinical use of onabotulinumtoxinA expanded to other conditions that involve abnormal muscle contractions.¹⁰ In the early 1990s, some patients described improvement in their migraine following treatment of facial lines with onabotulinumtoxinA.¹¹ Since migraine is primarily a sensory disease, these reports raised the possibility that onabotulinumtoxinA had an ability to block activation of nociceptive pathways. The literature on onabotulinumtoxinA has largely focused on its mechanism of action at the neuromuscular junction, and there is a gap in understanding how it may affect the sensory system as well.¹² Thus, this narrative literature review aims to summarize our current understanding of the mechanism of action for onabotulinumtoxinA for the treatment of chronic migraine.

In 2010, 2 double-blind placebo-controlled trials confirmed onabotulinumtoxinA's effectiveness for the prevention of headaches in chronic migraine

patients. In these trials, a migraine-specific injection paradigm (155-195 U, 31-39 injection sites in head and neck muscles, which correspond to areas innervated by sensory nerves) resulted in significant reduction of headache and migraine days per month compared to placebo (Table 1).¹³ These results led to the regulatory approval for chronic migraine in 2010, and lent credence to the idea that onabotulinumtoxinA treatment could modulate sensory neurons,¹⁴ which is the focus of this review.

ONABOTULINUMTOXINA MECHANISM OVERVIEW

OnabotulinumtoxinA contains 900-kDa BoNTA protein complex consisting of the 150-kDa botulinum neurotoxin and several nontoxic, neurotoxin-associated proteins (NAPs). The NAPs are thought to play a role in the pharmacologic actions of the neurotoxin, including structural stability of the neurotoxin,¹⁵ protection from proteolysis,¹⁶ and/or binding kinetics.¹⁷ OnabotulinumtoxinA acts on peripheral nerve terminals to interfere with specific events in the synaptic vesicle cycle. Briefly, at nerve terminals, synaptic vesicles undergo fusion to the cell membrane and are recycled. Vesicles containing neurotransmitters and neuropeptides destined for synaptic release undergo docking, priming, and fusion with the neuronal membrane.¹⁸ These steps require the crucial formation of the protein assembly SNARE complex (soluble N-ethylmaleimide-sensitive fusion-attachment protein receptor) (Fig. 1, top panel).¹⁹ Vesicular contents include small molecules in small synaptic vesicles (eg, acetylcholine and glutamate), or neuropeptides in large dense core vesicles (eg, calcitonin

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Table 1.—Efficacy of OnabotulinumtoxinA in the Treatment of Chronic Migraine†

| Variable‡ | OnabotulinumtoxinA (n = 688) | Placebo (n = 696) | Mean Intergroup Difference (95% Confidence Interval) | P Value |
|--|---------------------------------|-------------------|---|---------|
| Frequency of headache days§ | | | | |
| Baseline | 19.9 | 19.8 | 0.1 | .498 |
| Change from baseline | -8.4 | -6.6 | -1.8 (-2.52, -1.13) | <.001¶ |
| Frequency of migraine/probable migraine days | | | | |
| Baseline | 19.1 | 18.9 | 0.2 | .328 |
| Change from baseline | -8.2 | -6.2 | -2.0 (-2.67, -1.27) | <.001¶ |
| Total headache impact test-6 score | | | | |
| Baseline | 65.5 | 65.4 | 0.1 | .638 |
| Change from baseline | -4.8 | -2.4 | -2.4 (-3.11, -1.72) | <.001†† |

†Pooled results from 2 double-blind, randomized, controlled trials in which subjects were injected at baseline and 3 months.^{13,112}

‡Assessed at primary endpoint of 6 months.

§Primary efficacy variable.

¶Analysis of covariance.

††Wilcoxon rank-sum test.

gene-related peptide [CGRP], pituitary adenylate cyclase activating peptide 38 [PACAP 38], and Substance P). Large dense core vesicle cargo include proteins and receptors (eg, transient receptor potential cation channel subfamily V member 1 [TRPV1], transient receptor potential cation channel subfamily A member 1 [TRPA1], purinergic receptor P2X ligand-gated ion channel 3 [P2X3], etc.) whose insertion into the lipid bilayer of the synaptic membrane is critical for proper pain signaling.^{20,21} In some cases, vesicles fuse with the nerve terminal membrane through constitutive exocytosis,²² which is a housekeeping function. In other cases, fusion of synaptic vesicles with nerve terminal membrane is SNARE mediated. SNARE ability to regulate exocytosis is most commonly associated with electrical activity in the nerve. Synaptic vesicles that have fully fused with the membrane then undergo recycling and the process begins again.

The intraneuronal target for onabotulinumtoxinA is SNAP-25 (synaptosomal-associated protein-25 kDa), one of the SNARE proteins critical for vesicular fusion. Following injection, onabotulinumtoxinA is distributed to the extracellular space. When the neurotoxin encounters nerve terminals²³ the heavy chain of the botulinum neurotoxin binds with relatively low affinity to a polysialoganglioside (PSG), including GT1b (KD ~200 nM)²⁴⁻²⁶ (Fig. 1, bottom panel). A second receptor with greater affinity, synaptic vesicle protein 2 (SV2) (KD ~100 nM),²⁷⁻³¹ is a vesicle protein

that is exposed to the extracellular space during vesicular fusion.³² The heavy chain potentially binds to a higher-affinity receptor, fibroblast growth factor receptor 3 (FGFR3) (KD ~15 nM³³).

OnabotulinumtoxinA, bound to the receptors, is endocytosed, and once it enters the endosome, the light chain dissociates from the heavy chain and translocates into the intracellular cytosol where it specifically cleaves SNAP-25.³² The light chain's proteolytic cleavage of this essential component of the SNARE protein complex prevents the fusion of the synaptic vesicle to the inner surface of the cellular membrane. Impacted synaptic vesicles can neither release their contents into the synaptic cleft, nor deliver receptors or ion channels carried as cargo (eg, TRPV1, P2X3) into neuronal membranes. This latter effect is illustrated by onabotulinumtoxinA interfering with trafficking of thermoTRP channels.²² The downstream inhibitory effects depend on the target organ, whether it be nociceptors, motor, or autonomic nerves innervating skeletal or smooth muscle, or glands.

In the nerve terminal, the light chain endopeptidase escapes immediate degradation via specific interactions on the presynaptic terminal including the presence of a dileucine motif,³⁴ interactions with membrane-bound septins,³⁵ and specific deubiquinating enzymes,³⁶ and consequently, maintains persistent proteolytic cleavage of SNAP-25. OnabotulinumtoxinA-cleaved SNAP-25 can still form stable, although nonfunctional SNARE

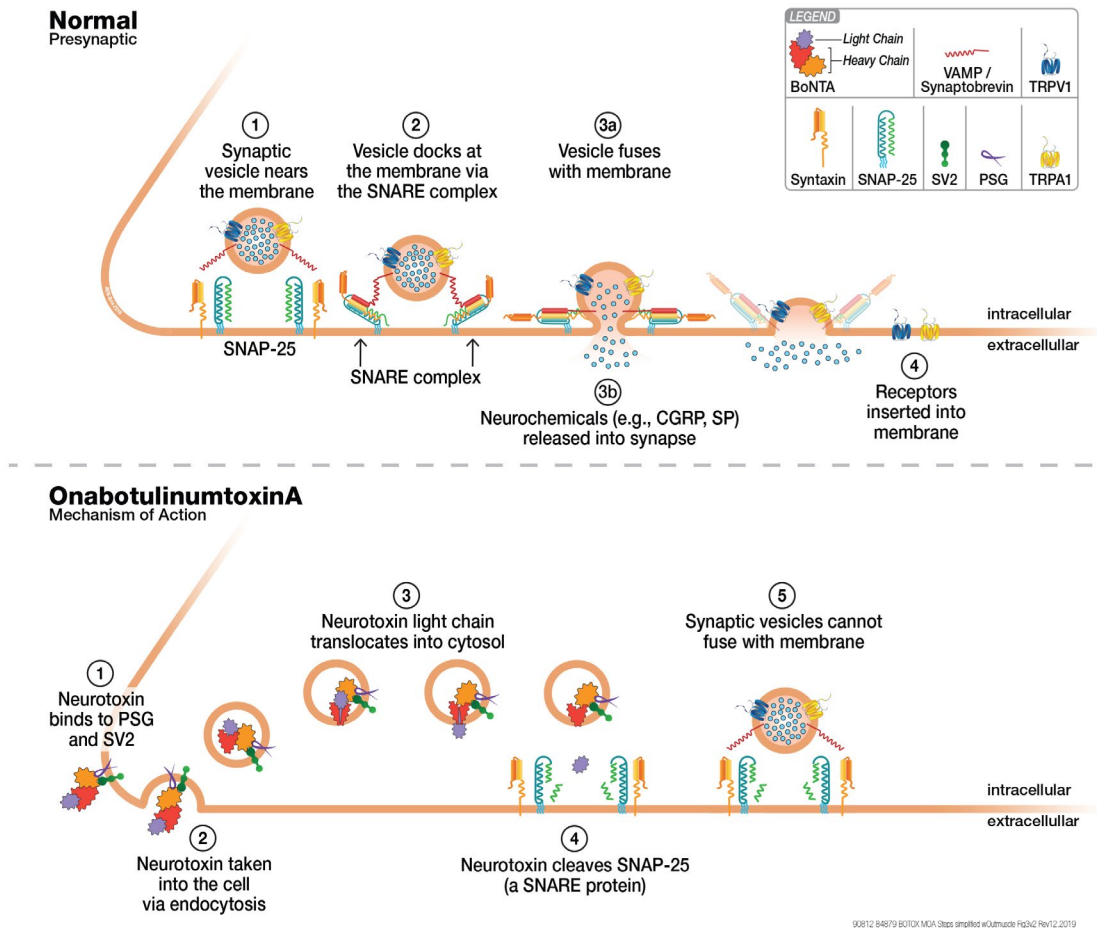


Fig. 1.—Mechanism of onabotulinumtoxinA at the synapse. The top panel shows fusion of large dense core synaptic vesicles with the nerve terminal membrane in the absence of onabotulinumtoxinA. By step 4, neurotransmitters contained in the synaptic vesicles are released into the synapse and receptors/ion channels are inserted into the nerve terminal membrane. The bottom panel shows the steps of onabotulinumtoxinA action at nerve terminals. The end result is that synaptic vesicles cannot fuse with the nerve terminal membrane, preventing release of neurotransmitters at the synapse, and inhibiting insertion of receptors/ion channels into the nerve terminal membrane.

complexes within neurons. These faulty complexes can have a relatively prolonged life within the synaptic terminal^{37,38} After exposure to BoNTA, cleaved SNAP-25 persisted beyond the latest timepoint, 80 days, in cultured spinal cord cells.³⁹ Together, these mechanisms (sustained proteolytic activity and prolonged faulty SNARE complexes) likely contribute to the long-acting, nerve/tissue-target-dependent effects of onabotulinumtoxinA. However, because the neuronal types studied in these preclinical experiments are not necessarily representative of mature motor nerves, and the experimental conditions diverge from the clinical situation, the translatability of the results to the clinical situation is unclear. Nevertheless, clinically, the effects of

onabotulinumtoxinA last approximately 3 to 4 months in motor nerves^{40,41} and 6 to 9 months in autonomic nerves.^{42,43} The onabotulinumtoxinA light chain is ultimately ubiquitinated³⁶ and neurotransmission is restored.⁴⁴ During recovery, the presence of sprouts in motor neurons⁴⁵ and their paucity in autonomic nerves⁴⁶ may also contribute to duration in specific nerve/tissue targets.

RATIONALE FOR ONABOTULINUMTOXINA FOR CHRONIC MIGRAINE TREATMENT

Sensory effects of onabotulinumtoxinA in migraine are supported by findings from preclinical studies, which established that BoNTA inhibits the release of neuropeptides such as substance P^{48,49} and CGRP⁵⁰

from primary sensory (first order) neurons. Sensory effects of onabotulinumtoxinA are also demonstrated in the formalin pain model, in which subcutaneous injection of onabotulinumtoxinA dose dependently inhibits the delayed pain response to formalin without affecting the acute pain response and without inducing muscle weakness.⁵¹ In clinical studies, there were early suggestions of a dissociation between pain and muscle relaxation in cervical dystonia, with some studies reporting more prevalent improvements in pain than muscle contractions.^{5,6} Additionally, a spasticity study that specifically examined the relationship between pain and muscle tone found only a weak correlation between them, consistent with the notion that onabotulinumtoxinA-associated improvements in muscle tone and pain are separate dimensions.⁴⁷ OnabotulinumtoxinA has also shown benefits in the treatment of other pain disorders, including painful diabetic neuropathy, a primary sensory disorder.⁵² The combination of these findings provides a clinical basis for understanding the sensory effects of onabotulinumtoxinA in chronic migraine and are further confirmed in the laboratory studies described in the subsequent section.

MIGRAINE PATHOPHYSIOLOGY AND ONABOTULINUMTOXINA MECHANISMS OF ACTION IN CHRONIC MIGRAINE PREVENTION

OnabotulinumtoxinA Inhibits Neurotransmitter and Neuropeptide Release.—The initiation of migraine pain occurs at the periphery when nociceptive neurons that innervate the dura and potentially the pia mater become active and release vasoactive and pro-inflammatory neuropeptides and neurotransmitters that further irritate them and mediate their prolonged activation.⁵⁸ The vasodilatory neuropeptides CGRP and PACAP-38, as well as the neurotransmitter nitric oxide (NO), are potent vasodilators involved in migraine pathophysiology.⁵⁹⁻⁶⁵

At the synaptic cleft, onabotulinumtoxinA attenuates the release of neuropeptides and neurotransmitters that activate and modulate receptors that have been implicated in migraine pathophysiology.^{48,50,66-69} This is supported by preclinical findings that show that onabotulinumtoxinA inhibits the release of glutamate,⁵¹ substance P,⁴⁹ and CGRP⁵⁰ from primary sensory (ie, first-order neurons in dorsal root and trigeminal

ganglia) nerve terminals.⁵¹ Regarding CGRP, recent reviews of its role in the headache phase of migraine⁷⁰⁻⁷² and the rationale behind the successful prevention of migraine with drugs that reduce its presence in the periphery⁷³ support the possibility that a part of onabotulinumtoxinA's mechanism of action in migraine prevention may involve the reduction of CGRP release from peripheral nerve terminals of meningeal and trigeminal nociceptors. Two lines of evidence support this possibility. The first is in vitro animal experiments showing that onabotulinumtoxinA inhibits the release of CGRP from sensory neurons.^{50,74} The second is a clinical study showing that onabotulinumtoxinA reduces interictal CGRP plasma levels in chronic migraine patients who are deemed treatment responders but not those deemed treatment nonresponders.⁷⁵

In cases in which chronic migraine is associated with chronic muscle tenderness, occipital allodynia,^{56,76,77} and altered expression of genes related to inflammation in the calvarial periosteum,^{56,76,77} extracranial injection of onabotulinumtoxinA may exert its effects through direct action on extracranial nerves (Fig. 2). However, extracranial injection of onabotulinumtoxinA also has a clear path to intracranial nerves,^{55,78} which may account for its effects on migraine headaches that originate intracranially. Functional evidence for these intracranial-to-extracranial and extracranial-to-intracranial pathways comes from the finding that extracranial administration of onabotulinumtoxinA inhibits responses of C- but not A δ -fibers to stimulation of their intracranial meningeal receptive fields with ligands of TRPV1 and TRPA1 channels.⁵⁷

The mechanism by which injection of onabotulinumtoxinA into extracranial muscles can affect intracranial neurons is still under investigation, and several possibilities exist, including effects of onabotulinumtoxinA on collateral branches of trigeminal axons that cross from the inside to the outside^{78,79} or cervical axons that cross from the outside to inside⁵⁵ of the skull via suture lines, emissary canals, and fissures, as demonstrated in rats^{55,78,79} and humans^{79,80} (Fig. 2). The mechanisms by which injections of onabotulinumtoxinA reduce activation along peripheral and central pathways, such as those that mediate migraine headache, include (1) increased threshold for nociceptive activation by reducing circulating levels of

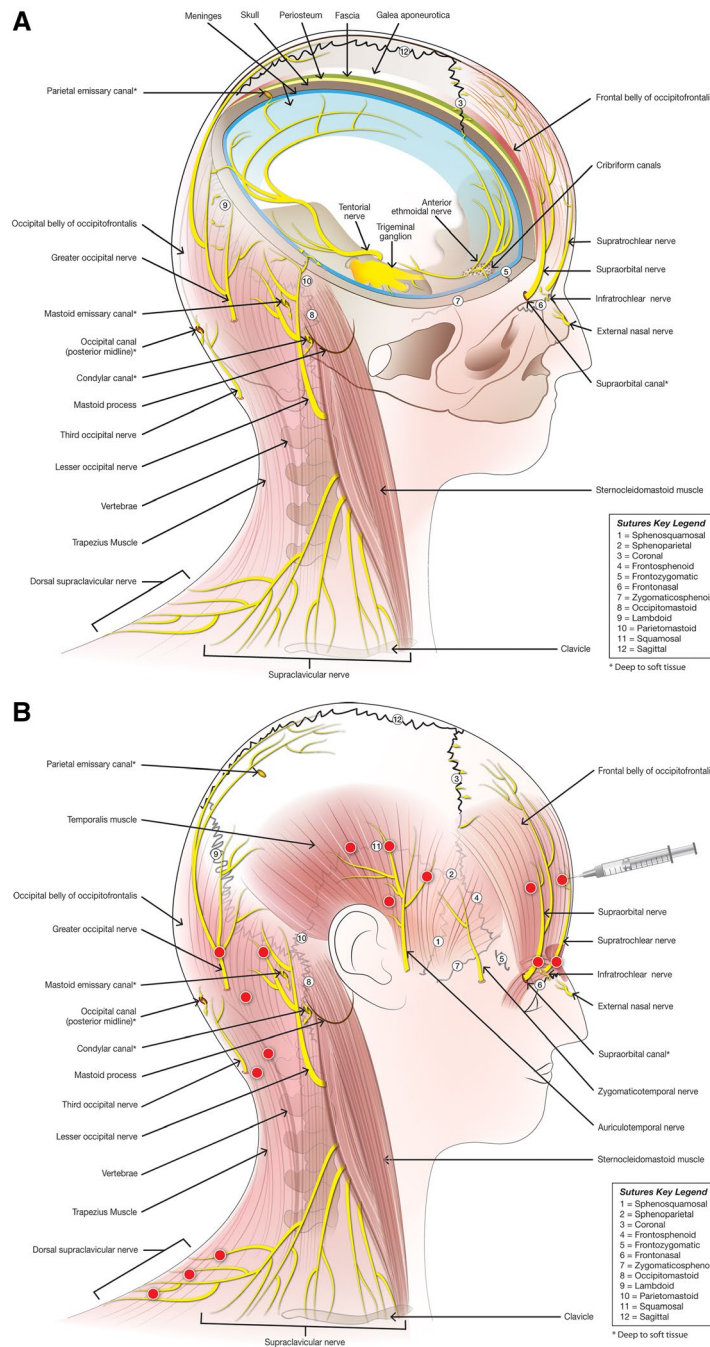


Fig. 2.—Neuroanatomy relevant to onabotulinumtoxinA injections sites. (A) Nerves originating from the trigeminal ganglion innervate intracranial structures and extend extracranially through cranial sutures. Spinal nerves originating from cervical dorsal root ganglia 2 and 3 innervate pericranial muscles and extend intracranially through cranial sutures, emissary canals, and fissures. (B) Extracranial injection sites correspond to anatomical region of extracranial nerves, many of which are adjacent to cranial sutures, emissary canals, and fissures.

neuropeptides (eg, CGRP) and neurotransmitters;^{75,81} (2) decreased TRPV1-immunoreactive neurons in the trigeminal ganglion following peripheral injections into the face;⁸² (3) reduced activation of dorsal horn

neurons^{83,84} and expression of NO synthase in the central nervous system (CNS) after injections of onabotulinumtoxinA into the intraplantar fascia and relevant muscles, respectively;⁸⁵ and (4) reduced numbers of

dendrites and synapses in central sensory processes, as exemplified in the hypoglossal nucleus after injection of onabotulinumtoxinA into the tongue,⁸⁶ which were also associated with changes in nucleolar and cell body shape. Given recent evidence against transsynaptic transfer of onabotulinumtoxinA,^{87,88} it is now believed that central sensitization, synaptic plasticity, and other CNS effects attributed to onabotulinumtoxinA are secondary to the decreased peripheral input.⁸⁹

OnabotulinumtoxinA Inhibits Ion Channel Insertion into Synaptic Membranes.—Migraine headache is commonly associated with throbbing and increased headache intensity caused by mild elevation in intracranial pressure due to coughing, sneezing, or bending over.⁹⁰⁻⁹³ These symptoms are believed to result from sensitization of nerve endings of first-order sensory neurons – a functional switch involving upregulation of pain-related ion channels on nociceptive nerve terminals and cell bodies, including TRPA1, TRPV1, and sodium channels. Repeated stimulation of trigeminal nerve endings and their eventual sensitization can lead to the development of central sensitization, ongoing pain, allodynia (pain caused by stimuli that do not normally evoke pain), and hyperalgesia (increased sensitivity to pain).^{94,95}

The effects of onabotulinumtoxinA on ionic channels expression in nociceptors have not been directly tested in people with migraine because the involved nerves are located in head and neck areas that are not readily accessible to biopsies. However, in patients with overactive bladder, onabotulinumtoxinA is injected directly into bladder muscle and submucosal area, which, given patients' consent, may be sampled for study. Epithelial cells in the urinary bladder express TRPV1 and P2X3 receptors, which are believed to be involved in conveying sensory information such as the urge to urinate.^{96,97} In suburothelial tissue obtained from patients with detrusor overactivity (a condition of overactive bladder), onabotulinumtoxinA significantly decreased and normalized the pretreatment elevated TRPV1 and P2X3 levels, and improved both clinical and urodynamic measures.⁹⁷ The decrease in P2X3 receptors and, to a lesser extent, TRPV1 receptors after onabotulinumtoxinA treatment were significantly correlated with improvements in sensations of urgency,

but not with changes in maximum detrusor pressure or the volume at which patients felt they could no longer delay urination. Along this line, in a capsaicin human pain model, subcutaneous administration of onabotulinumtoxinA to the forehead reduced capsaicin-induced pain intensity and duration, most likely through downregulation of TRPV1 receptors on unmyelinated c-fiber nociceptors,⁹⁸ and in a population of female patients with chronic migraine, a polymorphism in the TRPV1 gene was associated with a greater likelihood of response to onabotulinumtoxinA.⁹⁹

Selectivity of OnabotulinumtoxinA Effects.—The inhibitory effects of onabotulinumtoxinA on SNARE-mediated processes are not observed in all neurons. Outside the context of migraine, onabotulinumtoxinA does not give rise to local anesthesia,¹⁰⁰ suggesting that it does not interact with large-diameter myelinated axons carrying tactile information from the skin to the spinal cord. In the context of migraine, where the headache phase depends on activity in unmyelinated C- and thinly myelinated A δ -fibers in the dura, onabotulinumtoxinA appears to selectively inhibit activation and sensitization of the unmyelinated C- but not thinly myelinated A δ -fibers,¹⁰¹ as well as their activation by mustard oil and capsaicin⁵⁷ or cortical spreading depolarization/depression.¹⁰² The latter result is supported by the effectiveness of onabotulinumtoxinA in treating chronic migraine patients both with and without aura¹⁰³ (the former presumably related to cortical spreading depolarization/depression). As far as selectivity is concerned, a recent preclinical study found that another migraine medication, humanized CGRP monoclonal antibodies, inhibits A δ - but not C-type neurons in the trigeminal ganglion.¹⁰⁴ These preclinical findings as well as emerging clinical experience¹⁰⁵⁻¹⁰⁷ suggest the interesting possibility that a combination treatment that blocks both the C- (onabotulinumtoxinA) and the A δ - (CGRP monoclonal antibodies and CGRP receptor antagonists) meningeal nociceptors may be more effective than a monotherapy that blocks only one of these pathways. While these animal-based selectivities await additional confirmation in humans, the enigma of how onabotulinumtoxinA exerts its selective effects on different classes of sensory neurons remains unanswered.

RATIONALE FOR ONABOTULINUMTOXIN A INJECTION PARADIGM FOR CHRONIC MIGRAINE

For chronic migraine prevention, onabotulinumtoxin A is injected into 31-39 sites in 7 muscles of the head and neck.⁵³ The injection sites correlate closely with the sensory innervation of the face, scalp, and cervical region. These include the supratrochlear and supraorbital nerves, which travel through the corrugator, procerus, and frontalis muscles; the auriculotemporal and zygomaticotemporal nerves; the greater and lesser occipital nerves traveling along the occipitofrontalis complex to innervate the adjacent scalp; the third occipital nerve traveling through the cervical paraspinal muscles; and the supraclavicular nerves traveling through the trapezius (Fig. 2). Following intramuscular injection, onabotulinumtoxin A diffuses within the tissue to affect nerves within a circumscribed region.¹⁰⁸

The primary role of trigeminal and cervical neurons in migraine⁵⁴⁻⁵⁶ and the inhibition of SNARE-mediated processes by onabotulinumtoxin A are consistent with an inhibitory action of onabotulinumtoxin A on these nerves. SNARE-mediated processes in these nerve terminals include the vesicular release of inflammatory and nociceptive neuropeptides and neurotransmitters and the insertion of pain-encoding receptors into the membrane of unmyelinated c-fibers.⁵⁷

The aforementioned sensory effects of onabotulinumtoxin A suggest that it may also be useful for episodic migraine. Although several of the early randomized, controlled studies in episodic migraine showed an efficacy signal,^{109,110} they did not use the PREEMPT paradigm (ie, 31-39 injection sites in head and neck muscles) that was demonstrated to be effective in chronic migraine phase 3 studies. Thus, the efficacy and safety of onabotulinumtoxin A in episodic migraine has not been fully explored. Real-world evidence using the PREEMPT paradigm has demonstrated clinical benefit in patients with episodic migraine.¹¹¹

CONCLUSIONS

Mechanism of Action in the Synapse.—Although onabotulinumtoxin A is primarily known for its inhibition of muscle contraction, it is an effective treatment for the prevention of chronic migraine – a sensory neurological disease. The common basis

for these clinical outcomes is onabotulinumtoxin A inhibition of SNARE-mediated vesicle trafficking, which occurs in both motor and sensory nerves. Onabotulinumtoxin A inhibits regulated exocytosis of motor and sensory neurochemicals and proteins, as well as membrane insertion of peripheral receptors that convey pain from the periphery to the brain in pathological conditions such as chronic migraine because both processes are SNARE dependent (Fig. 1). Onabotulinumtoxin A can decrease exocytosis of pro-inflammatory and excitatory neurotransmitters and neuropeptides such as substance P, CGRP, and glutamate from primary afferent fibers that transmit nociceptive pain and participate in the development of peripheral and central sensitization. Onabotulinumtoxin A also decreases the insertion of pain-sensitive ion channels such as TRPV1 into the membranes of nociceptive neurons. Prolonged activation of sensory neurons is likely to increase insertion of TRPV1 channels into the membrane. In vivo studies have demonstrated that treatment reduced sensory neuron excitability and sensitization, consistent with increasing the pain threshold for migraine.

Mechanism of Action in Migraine.—The main sensory input to the face and head comes from the trigeminal nerve, which innervates muscles, meninges, and other tissues, with contributions from cervical and occipital nerves. Numerous pericranial injections of onabotulinumtoxin A are likely needed to target the vast projection regions of trigeminal and cervical nerves, in order to attenuate their overall input to central neurons, which appear to become sensitized and perpetuate chronic migraine when activated repeatedly or continuously by pain signals they receive from the periphery (Fig. 2). Through this antidromic influence, onabotulinumtoxin A injected into the periphery can reduce the number of pain signals that travel along sensory nerves from the dura to the spinal trigeminal nucleus, which indirectly prevents the development of hyperexcitability of spinal, brainstem, thalamic, and cortical neurons involved in migraine pathophysiology.

Beyond Headache.—Investigations into the mechanism of onabotulinumtoxin A action in chronic migraine and other conditions with prominent sensory components (eg, overactive bladder) have broadened

our understanding of its therapeutic benefit. In contemplating which, if any, other diseases may benefit from onabotulinumtoxinA treatment, it will be important to consider and be guided by the extent to which SNARE-mediated processes play a role in pathology.

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