[0014] Typically, the botulinum toxin is administered to patients by carefully controlled injections of compositions containing botulinum toxin complex and albumin. However, there are several problems associated with this approach. Not only are the injections painful, but typically large subdermal wells of toxin are locally generated around the injection sites, in order to achieve the desired therapeutic or cosmetic effect. The botulinum toxin may migrate from these subdermal wells to cause unwanted paralysis in surrounding areas of the body. This problem is exacerbated when the area to be treated is large and many injections of toxin are required to treat the area. Moreover, because the injected toxin complexes contain non-toxin proteins and albumin that stabilize the botulinum toxin and increase the molecular weight of the toxin complex, the toxin complexes have a long half-life in the body and may cause an undesirable antigenic response in the patient. For example, some patients will, over time, develop an allergy to the albumin used as a stabilizer in current commercial formulations. Also, the toxin complexes may induce the immune system of the patient to form neutralizing antibodies, so that larger amounts of toxin are required in subsequent administrations to achieve the same effect. When this happens, subsequent injections must be carefully placed so that they do not release a large amount of toxin into the bloodstream of the patient, which could lead to fatal systemic poisoning, especially since the non-toxin proteins and albumin stabilize the botulinum toxin in blood.

[0015] In view of the drawbacks associated with current botulinum toxin formulations, it would be highly desirable to have an injectable botulinum toxin formulation that is efficacious and stable, but exhibits reduced antigenicity and a lower tendency to diffuse locally after injection. It would also be desirable to use such a botulinum toxin formulation for various therapeutic, aesthetic and/or cosmetic purposes.

SUMMARY

[0016] This disclosure provides injectable compositions comprising botulinum toxin non-covalently associated with a positively charged carrier molecule. In preferred examples, the compositions of the disclosure possess one or more advantages over conventional commercial botulinum toxin formulations, such as

BOTOX® or MYOBLOC®. For instance, in certain examples, the compositions may exhibit one or more advantages over conventional injectable botulinum formulations, including reduced antigenicity, a reduced tendency to undergo diffusion into surrounding tissue following injection, increased duration of clinical efficacy or enhanced potency relative to conventional botulinum toxin formulations, faster onset of clinical efficacy, and/or improved stability.

[0017] One example of this disclosure is the recognition that certain non-native molecules (i.e., molecules not found in botulinum toxin complexes obtained from *Clostridium botulinum* bacteria) can be added to botulinum toxin, botulinum toxin complexes, and in particular reduced botulinum toxin complexes (as defined herein), to improve toxin diffusion through tissues. The non-native molecules associate non-covalently with the toxin and act as penetration enhancers that improve the ability of the toxin to reach target structures after injection. Furthermore, the non-native molecules may increase the stability of the toxin prior to and after injection. By way of example, the penetration enhancers may be positively charged carriers, such as cationic peptides, which have no inherent botulinum-toxin-like activity and which also contain one or more protein transduction domains as described herein.

[0018] Another example of this disclosure is to provide a composition comprising botulinum toxin, a botulinum toxin complex (or a reduced protein botulinum toxin complex including just the 150 kD neurotoxin itself or the neurotoxin with some, but not all, of the native complex proteins) and a positively charged carrier.

[0019] The disclosure further relates to a method for producing a biologic effect by injecting an effective amount of the compositions of this disclosure to a subject or patient in need of such treatment. The biologic effect may include, for example, muscle paralysis, reduction of hypersecretion or sweating, treatment of neurologic pain or migraine headache, management of rhinitis or sinusitis, treatment of hyperactive bladder, reduction of muscle spasms, prevention or reduction of acne, reduction or enhancement of an immune response, reduction of wrinkles, or prevention or treatment of various other disorders.

[0019a] In one aspect, the disclosure provides a method of administering botulinum toxin to achieve a cosmetic effect to an individual in need thereof, the method comprising:

injecting an effective amount of a botulinum toxin composition into the individual to achieve a cosmetic effect,

wherein the botulinum toxin composition comprises

a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-$(K)_n$-GRKKRRQRRR, wherein n is selected from 10 to 23, and,

a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum toxin complex, reduced botulinum toxin complex, and botulinum toxin, and

a pharmaceutically acceptable diluent suitable for injection,

wherein the positively charged carrier is non-covalently associated with the botulinum toxin component.

[0019b] In one aspect, the disclosure provides use of a botulinum toxin composition in the manufacture of a medicament for achieving a therapeutic effect to an individual in need thereof, wherein the botulinum toxin composition comprises

a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-(K)n-GRKKRRQRRR, wherein n is selected from 10 to 23, and

a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum toxin complex, reduced botulinum toxin complex, and botulinum toxin, and

a pharmaceutically acceptable diluent suitable for injection,

wherein the positively charged carrier is non-covalently associated with the botulinum toxin component, and

wherein the therapeutic effect is reducing or enhancing immune response or reduction of a symptom associated with a disorder selected from the group consisting of muscle tension, muscle spasm, hemifacial spasm, adult onset spasmodic torticollis, anal fissure, blepharospasm, cerebral palsy, headaches, migraine headache, strabismus, temporomandibular joint disorder, neurologic pain, overactive bladder, rhinitis, sinusitis, acne, dystonia, dystonic contractions, hyperhidrosis, and hypersecretion of a gland controlled by the cholinergic nervous system.

[0019c] In one aspect, the disclosure provides use of a botulinum toxin composition in the manufacture of a medicament for reducing or preventing muscle spasm in an individual in need thereof,

wherein the botulinum toxin composition is to be injected into the individual, at an area affected by muscle spasm, to reduce or prevent said muscle spasm, wherein the botulinum toxin composition comprises a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-$(K)_n$-GRKKRRQRRR, wherein n is selected from 10 to 23, and, a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum toxin complex, reduced botulinum toxin complex, and botulinum toxin, and a pharmaceutically acceptable diluent suitable for injection;

wherein the positively charged carrier is non-covalently associated with the botulinum toxin component.

[0019d] In one aspect, the disclosure provides a sterile injectable composition for administration by injection to achieve a therapeutic or cosmetic effect in a subject in need thereof, the composition comprising:

a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum complex, a reduced botulinum toxin complex, and a botulinum toxin; and

a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-$(K)_n$-GRKKRRQRRR, wherein n is selected from 10 to 23;

wherein the botulinum toxin component is non-covalently associated with the positively charged carrier, and

a pharmaceutically or cosmeceutically acceptable diluent suitable for injection.

[0019e] In one aspect, the disclosure provides a syringe comprising:

a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum complex, a reduced botulinum toxin complex, and a botulinum toxin; and

a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-$(K)_n$-GRKKRRQRRR, wherein n is selected from 10 to 23;

wherein the botulinum toxin component is non-covalently associated with the positively charged carrier, and

a pharmaceutically or cosmeceutically acceptable diluent suitable for injection.

[0019f] In one aspect, the disclosure provides a reconstituted botulinum toxin composition comprising:

a botulinum toxin component present in an amount suitable for injection, the botulinum toxin component selected from the group consisting of a botulinum complex, a reduced botulinum toxin complex, and a botulinum toxin; and

a positively charged carrier comprising the amino acid sequence RKKRRQRRRG-$(K)_n$-GRKKRRQRRR, wherein n is selected from 10 to 23; and

a pharmaceutically acceptable aqueous liquid diluent, and

wherein the botulinum toxin component is non-covalently associated with the positively charged carrier.

[0020] This disclosure also provides kits for preparing formulations containing a botulinum toxin, a botulinum toxin complex, or a reduced protein botulinum toxin