drugs or NSAIDs), opioids, and co-analgesics (e.g. gabapentin), pain continues to afflict millions of individuals in the US alone and remains a profound burden to patients, health care, and business.

[0005] Oxytocin has been shown to reduce pain, in particular chronic pain, associated with the trigeminal nerve, such as trigeminal neuralgia and migraine headache. Human clinical trials have demonstrated efficacy of intranasal oxytocin in treating migraine headache. However, these trials have shown that the latency to analgesia caused by nasal oxytocin is around 2 hours, with the maximal analgesic effect not occurring until about 4 hours after dosing. Thus, there exists a need for an oxytocin peptide formulation capable of faster on-set of the analgesic effect.

SUMMARY

[0006] Provided are methods and compositions comprising an oxytocin peptide and a magnesium salt for treating pain via craniofacial mucosal administration (e.g., intranasal administration). The methods and magnesium containing oxytocin peptide formulations described herein provide faster, stronger and longer lasting analgesic effect compared to oxytocin alone.

[0007] Disclosed is a method for treating pain comprising administering to a subject in need thereof an effective dose of an oxytocin peptide and a magnesium salt, wherein co-administration of the oxytocin peptide and the magnesium salt produces a synergistic analgesia. The oxytocin peptide and the magnesium salt may be co-administered concurrently or sequentially. In some embodiments, the oxytocin peptide is administered concurrently with the magnesium salt either in the same unit dose or in separate unit doses or formulations. In some embodiments, the oxytocin peptide and the magnesium salt are administered sequentially. For example, the oxytocin peptide is administered at a time period after administration of the magnesium salt. In some embodiments, the subject is a human.

[0008] The oxytocin peptide and the magnesium salt may be administered via the same route or different routes to a subject in need thereof. In some embodiments, the oxytocin peptide is administered via craniofacial mucosal administration (e.g., nasal, buccal, sublingual or ocular administration). In one embodiment, the oxytocin peptide and the magnesium salt are both administered intranasally in the same formulation.

[0009] In some embodiments, the oxytocin peptide is human oxytocin consisting of Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly (SEQ. ID NO:1). In some embodiments, the effective dose of the oxytocin peptide is about 0.5 μg to about 2000 μg, preferably about 8 μg to about 1000 μg, more

preferably about 15 μg to about 120 μg. In some embodiments, the effective dose of the magnesium salt administered provides about 50 μg to about 68 mg of magnesium, preferably about 50 μg to about 34 mg of magnesium, more preferably about 1 mg to about 3 mg of magnesium. In some embodiments, the magnesium salt comprises magnesium citrate and/or magnesium chloride administered in an amount to provide about 50 μg to about 68 mg of magnesium, or about 50 μg to about 34 mg of magnesium, or about 1 mg to about 3 mg of magnesium. In some embodiments, the magnesium salt is magnesium citrate or magnesium chloride administered in an amount to provide about 50 μg to about 68 mg of magnesium, or about 50 μg to about 34 mg of magnesium, or about 1 mg to about 3 mg of magnesium. In some embodiments, the effective dose of the magnesium salt is about 0.48 mg to about 600 mg of magnesium citrate, preferably about 0.48 mg to about 300 mg of magnesium citrate, more preferably about 10 mg to about 30 mg of magnesium citrate. In some embodiments, the effective dose of the oxytocin peptide and the magnesium salt comprises about 0.5 μg to about 2000 μg, or about 15 μg to about 120 μg (e.g., about 66 μg) of the oxytocin peptide administered in an aqueous solution containing about 1% to about 25% (preferably about 10% to about 14%, e.g. about 12 %) (w/v) magnesium citrate. In some embodiments, the effective dose of the oxytocin peptide and the magnesium salt comprises about 0.5 μg to about 2000 μg, or about 15 μg to about 120 μg (e.g., about 60 μg or about 66 μg) of the oxytocin peptide administered in an aqueous solution containing about 0.11% to about 2.8% (preferably about 1.1% to about 1.6%, e.g. about 1.36 %) (w/v) magnesium.

[0010] In some embodiments, the pain treatable by the method includes any pain treatable by oxytocin peptide, such as orofacial and craniofacial (e.g., headache pain), neck pain (e.g. occipital neuralgia), shoulder pain, or pain in the upper extremities. In some embodiments, the pain is a chronic pain, acute pain, or episodic pain. In some embodiments, the pain is a head or facial pain. In some embodiments, the pain is a trigeminal nerve-associated pain. In some embodiments, the pain is a migraine headache. In some embodiments, the pain is a cervical nerve-associated pain.

[0011] In one embodiment, the invention provides a method for treating migraine headache comprising administering (e.g., intranasally) to a subject in need thereof an effective dose of an oxytocin peptide and a magnesium salt, wherein co-administration of the oxytocin peptide and the magnesium salt produces a synergistic analgesia.

[0012] Disclosed is a magnesium-containing oxytocin peptide formulation and uses thereof in the treatment of pain. In one aspect, there is provided a composition comprising an oxytocin peptide and a magnesium salt, wherein the composition is contained in a device for craniofacial mucosal administration, and wherein the molar ratio between the oxytocin peptide in the composition and the magnesium ions in the composition is between about 1:800 and about 1:30000. Thus, provided is a composition comprising an oxytocin peptide and a magnesium salt, wherein the oxytocin peptide and the magnesium salt are in an amount that produces a synergistic analgesia when used in the

treatment of pain. In some embodiments, the oxytocin peptide is human oxytocin consisting of Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly (SEQ. ID NO:1). In some embodiments, the magnesium salt comprises magnesium citrate and/or magnesium chloride. In some embodiments, the magnesium salt comprises magnesium citrate and magnesium chloride. In some embodiments, the magnesium salt is magnesium citrate or magnesium chloride. In some embodiments, the composition is a liquid formulation comprising between about 0.01 mg/mL and about 16 mg/mL (preferably between about 0.1 mg/mL and about 2 mg/mL, more preferably between about 0.15 mg/mL and about 1.5 mg/mL, or about 0.33 mg/mL) of the oxytocin peptide. In some embodiments, the composition is a liquid formulation comprising the magnesium salt in an amount to provide between about 1 mg/mL and about 30 mg/mL (or between about 5 mg/mL and about 30 mg/mL, between about 10 mg/mL and about 30 mg/mL, preferably between about 11 mg/mL and about 15 mg/mL, or about 13 mg/mL, or about 12 mg/mL) of magnesium. In some embodiments, the composition further comprises one or more excipients, vehicles, emulsifiers, stabilizers, preservatives, mucosal adhesives, antibacterial agents, buffers, and/or other additives. In some embodiments, the composition has a pH of about 2 to about 7 (preferably about 4.5). In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[0013] In some embodiments, provided is a pharmaceutical composition comprising an oxytocin peptide and a magnesium salt, and a pharmaceutically acceptable carrier, wherein the oxytocin peptide and the magnesium salt are in an amount that produces a synergistic analgesia when used in the treatment of pain.

[0013a] In another aspect, there is provided use of a composition described herein and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating pain.

[0014] In some embodiments, the composition is adapted for craniofacial mucosal administration (e.g., nasal, buccal, sublingual or ocular administration). In some embodiments, the composition is adapted for intranasal administration, which may further comprise a device for intranasal administration, such as a nasal pump apparatus, e.g., a nasal pump apparatus comprising a reservoir bottle attached to an aerosolizer. In some embodiments, the nasal pump apparatus comprises one of more of the following: (i) a filter for preventing back flow, (ii) a metal-free fluid path, and (iii) a plastic material stable to gamma-radiation. In some embodiments, the nasal pump apparatus provides a metered dose (e.g., about 50 to about 150 μL per spray, or about 50 μL per spray). Therefore, in another aspect, there is provided use of an effective dose of the composition described herein in the manufacture of a medicament for treating pain in a subject in need thereof, wherein the pain is a head or facial pain, a neck pain, a shoulder pain, or a pain in the upper extremities, wherein the oxytocin peptide is formulated to be administered via craniofacial mucosal administration.

[0015] Also provided is a method for treating pain in a subject in need thereof comprising intranasally administering to a subject in need thereof an effective dose of a magnesium-containing oxytocin peptide formulation described herein.

[0016] Further provided is a magnesium-containing oxytocin peptide formulation described herein for use in a method of treating pain in a subject in need thereof. Also provided is a use of

a magnesium-containing oxytocin peptide formulation described herein in the manufacture of a medicament for the treatment of pain.

[0017] Also provided is a kit comprising a magnesium-containing oxytocin peptide formulation described herein contained in a device for intranasal administration such as a nasal pump apparatus and suitable packaging. The kit may further comprise instructions for administering the magnesium-containing oxytocin peptide formulation in a subject in need thereof. In another aspect, there is provided a kit comprising the composition described herein and a packaging.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. **1**. Effect of magnesium chloride or magnesium lactate in a rat model of facial thermal nociception. Rats were treated with saline, 15% magnesium chloride or 1% magnesium lactate, and withdrawal response latency was measured just prior to treatment and at 1, 2 and 3 hours post-treatment.

[0019] FIG. **2**. Dose-dependence of analgesic effect of nasal application of magnesium citrate in a rat model of facial thermal nociception. Rats were treated with 3, 6, 10, or 12% magnesium citrate, and withdrawal response latency was measured just prior to treatment and at 15, 30, 45, 60, 120, 180, 240, and 300 min post-treatment.

[0020] FIG. **3**. Dose-dependence of analgesic effect of nasal application of oxytocin in a rat model of facial thermal nociception. Rats were treated with 1, 4, or 8 μg oxytocin, and withdrawal response latency was measured just prior to treatment and at 15, 30, 45, 60, 120, 180, 240, and 300 min post-treatment.

[0021] FIG. **4**A. Analgesic effects of nasal application of 1 μg oxytocin in a 6% magnesium citrate solution. Difference in response latency at 15, 30, 45, 60, 120, 180, 240, and 300 min post-treatment was determined for 1 μg oxytocin alone, 6% magnesium citrate alone, calculated additive effect of 1 μg oxytocin in 6% magnesium citrate solution, and actual application of 1 μg oxytocin in 6% magnesium citrate solution.

[0022] FIG. **4**B, **4**C, and **4**D. Analgesic effects of nasal application of 1μg oxytocin in a 3, 6, or 12% magnesium citrate solution. Difference in response latency at 45 min post-treatment was determined for oxytocin alone, magnesium citrate alone, calculated additive effect of oxytocin in magnesium citrate solution, and actual application of oxytocin in magnesium citrate solution.

[0023] FIG. **5**. Analgesic effects of nasal application of 4 μg oxytocin in a 6% magnesium citrate solution. Difference in response latency at 120 min post-treatment was determined for 4 μg oxytocin alone, 6% magnesium citrate alone, calculated additive effect of 4 μg oxytocin in

CLAIMS

What is claimed is:

1. A composition comprising an oxytocin peptide and a magnesium salt, wherein the composition is contained in a device for craniofacial mucosal administration, and wherein the molar ratio between the oxytocin peptide in the composition and the magnesium ions in the composition is between about 1:800 and about 1:30000.

2. The composition of claim 1, wherein the oxytocin peptide is human oxytocin (SEQ ID NO:1).

3. The composition of claim 1, wherein the composition is a liquid formulation comprising between about 0.01 mg/mL and about 16 mg/mL of the oxytocin peptide.

4. The composition of claim 3, wherein the liquid formulation comprising between about 0.15 mg/mL and about 1.5 mg/mL of the oxytocin peptide.

5. The composition of claim 1, wherein the composition is a liquid formulation comprising the magnesium salt in an amount to provide between about 3 mg/mL and about 30 mg/mL of magnesium.

6. The composition of claim 5, wherein the liquid formulation comprising between about 11 mg/mL and about 15 mg/mL of magnesium.

7. The composition of claim 1, further comprises one or more excipients, vehicles, emulsifiers, stabilizers, preservatives, mucosal adhesives, antibacterial agents, buffers, and/or other additives.

8. The composition of claim 1, wherein the composition has a pH of about 4.5.

9. The composition of claim 1, wherein the composition is contained in a device for intranasal administration.

10. The composition of claim 9, wherein the device for intranasal administration is a nasal pump apparatus comprising a reservoir bottle attached to a pump actuator or a reservoir bottle attached to an aerosolizer.

11. Use of the composition of claim 1 and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating pain.

12. A kit comprising the composition of claim 1 and a packaging.

13. The composition of claim 1, wherein the molar ratio between the oxytocin peptide in the composition and the magnesium ions in the composition is between about 1:800 and about 1:20000.

14. Use of an effective dose of the composition of claim 1 in the manufacture of a medicament for treating pain in a subject in need thereof, wherein the pain is a head or facial pain, a neck pain, a shoulder pain, or a pain in the upper extremities, wherein the oxytocin peptide is formulated to be administered via craniofacial mucosal administration.

15. The use of claim 14, wherein the oxytocin peptide is formulated to be administered via intranasal administration.

16. The use of claim 14, wherein the effective dose of the oxytocin peptide is about 0.5 μg to about 2000 μg.

17. The use of claim 14, wherein the effective dose of the magnesium salt provides about 50 μg to about 68 mg of magnesium.

18. The use of claim 14, wherein the effective dose of the oxytocin peptide and the magnesium salt comprises about 15 μg to about 120 μg of the oxytocin peptide administered in an aqueous solution containing about 1.1% to about 1.6% (w/v) of magnesium.

19. The use of claim 14, wherein the effective dose of the oxytocin peptide and the magnesium salt comprises about 66 μg of the oxytocin peptide administered in an aqueous solution containing about 1.36% magnesium.

20. The use of claim 14, wherein the pain is a chronic pain, an acute pain, or an episodic pain.

21. The use of claim 14, wherein the pain is a trigeminal nerve-associated pain or a cervical nerve-associated pain.

22. The use of claim 14, wherein the pain is a migraine headache.

23. The use of claim 14, wherein the oxytocin peptide is human oxytocin (SEQ ID NO:1).

24. The use of claim 14, wherein the molar ratio between the dose of the oxytocin peptide to be administered and the dose of magnesium ions to be administered is between about 1:800 and 1:20000.