[0005] Opioid drugs are commonly used to relieve moderate to severe pain. However, their usefulness is limited by tolerance and dependence that normally develop with chronic treatment. Opioid drugs such as morphine can be addictive and are associated with significant and potentially fatal side effects such as respiratory depression in addition to sedation and mental alteration, constipation, nausea, exaggerated pain sensitivity, hormonal disturbances, and alteration of the immune system.

[0006] Despite a wide range of available medical treatments, pain continues to afflict millions of individuals in the US alone and remains a profound burden to patients, health care, and business. New methods are required for increasing the efficacy of intervention and reducing the side effects associated with pain management in the clinical setting.

SUMMARY

[0007] Disclosed are methods and compositions for treatment of pain by craniofacial mucosal administration of an NOP agonist, for example, intranasal administration of nociceptin/orphanin FQ (N/OFQ).

[0007a] In one aspect, there is provided use of an NOP agonist that is a non-opioid molecule for the manufacture of a medicament for the treatment of pain via craniofacial mucosal administration, provided the medicament does not contain an oxytocin peptide.

[0008] The disclosure also provides a method for the treatment of pain comprising administering to an individual in need thereof an effective dose of an NOP agonist via craniofacial mucosal administration. In some embodiments, the treatment comprises treatment of a trigeminal pain, a somatic pain, a neuropathic pain, a procedural pain or a visceral pain. In some embodiments, the treatment comprises treatment of an acute pain or a chronic pain. In some embodiments, the pain is a craniofacial pain or a head pain. In some embodiments, the craniofacial pain or the head pain is caused by temporomandibular joint disorder (TMJ), migraine or trigeminal neuralgia. In some embodiments, the craniofacial mucosal administration comprises intranasal administration, buccal administration, sublingual administration or conjunctival administration. In a particular embodiment, the mucosal administration is intranasal administration. In some embodiments, the NOP agonist is administered to the lower two thirds of the nasal cavity. In some embodiments, the NOP agonist is administered to the upper third of the nasal cavity. In some embodiments, the NOP agonist is administered specifically to reach both the lower two thirds and the upper third of the nasal cavity. In some embodiments, the NOP agonist is administered via buccal or sublingual administration. In some embodiments, the NOP agonist is administered via conjunctival administration or via other tissues around the eye. In a particular embodiment, the NOP agonist is N/OFQ. In some embodiments, any of the methods may further comprise

administering to the individual in need thereof at least one additional active agent, wherein the additional active agent is administered before, after or simultaneously with administration of the NOP agonist. In some embodiments, the methods may further comprise administering to the individual in need thereof at least two additional active agents, wherein each of the additional active agents is administered independently before, after or simultaneously with administration of the NOP agonist.

[0009] The disclosure further provides a method for the treatment of pain comprising administering to an individual in need thereof an effective dose of an non-opioid analgesic peptide via craniofacial mucosal administration, wherein said administration results in a global analgesic effect. In some embodiments, the treatment comprises alleviation of pain. In some embodiments, the treatment comprises prevention of pain. In some embodiments, the craniofacial mucosal administration comprises intranasal administration, buccal administration, sublingual administration or conjunctival administration. In a particular embodiment, the craniofacial mucosal administration is intranasal administration.

[0010] Also disclosed is a method for the treatment of pain comprising administering to an individual in need thereof an effective dose of N/OFQ via intranasal administration. In some embodiments, the unit dose of the N/OFQ administered is about 0.2 mg to about 5000 mg. In some embodiments, the administration results in reduction of a pain rating on the VAS of 30% or more.

[0011] Further disclosed are methods for the treatment or prevention of migraine headache pain or the treatment of migraine comprising administering to an individual in need thereof an effective dose of an NOP agonist wherein the NOP agonist is administered via craniofacial mucosal administration, e.g. intranasal administration. In some embodiments, the treatment comprises treating one or more symptoms associated with migraine such as nausea, photophobia and phonophobia. In some embodiments, the migraine is a migraine without aura, a migraine with aura or a migraine with aura but without headache. In a particular embodiment, the method for the treatment of migraine comprises administering to an individual in need thereof an effective dose of N/OFQ via intranasal administration.

[0012] Pharmaceutical compositions comprising an analgesic compound (e.g. a non-opioid analgesic peptide, an NOP agonist or N/OFQ) and methods for administrating such compositions via craniofacial mucosal administration (e.g. intranasal administration, buccal administration, sublingual administration or conjunctival administration) are also provided. As are kits comprising the pharmaceutical compositions and optionally a device for

administration. The pharmaceutical composition may further comprise one or more pharmaceutically acceptable excipients, adjuvants, diluents or stabilizers. In some embodiments, the pharmaceutical composition or the kits may include one or more additional active agents such as at least one additional analgesic agent, a vasoconstrictor, at least one protease inhibitor and/or at least one absorption enhancer.

[0013] Also disclosed is the use of an analgesic compound (e.g. a non-opioid analgesic peptide, an NOP agonist or N/OFQ) or a pharmaceutical composition comprising an analgesic compound (e.g. a non-opioid analgesic peptide, an NOP agonist or N/OFQ) for the manufacture of a medicament for the treatment of pain via craniofacial mucosal administration (e.g. intranasal administration). Also provided is an analgesic compound (e.g. a non-opioid analgesic peptide, an NOP agonist or N/OFQ) for use in the treatment of pain via craniofacial mucosal administration (e.g. intranasal administration).

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 shows A-delta cheek withdrawal latencies in response to noxious heat: *i.n.* Nociceptin (0.2mg/kg, 1.0 mg/kg, and 5.0 mg/kg) vs. *i.v.* Nociceptin (5.0 mg/kg) vs. *i.m.* Morphine (0.25 mg/kg) vs. *i.m.* Saline. Data are presented as the mean ± 1 SEM. (n = 6 Rats/group).

[0015] Figure 2 shows C-fiber cheek withdrawal latencies in response to noxious heat: *i.n.* Nociceptin (0.2mg/kg, 1.0 mg/kg, and 5.0 mg/kg) vs. *i.v.* Nociceptin (5.0 mg/kg) vs. *i.m.* Morphine (0.25mg/kg) vs. *i.m.* Saline. Data are presented as the mean ± 1 SEM. (n = 6 Rats/group).

[0016] Figure 3 shows A-delta paw withdrawal latencies in response to noxious heat: *i.n.* Nociceptin (0.2 mg/kg, 5.0 mg/kg) vs. *i.v.* Nociceptin (5.0 mg/kg) vs. *i.m.* Morphine (0.25 mg/kg) vs. *i.m.* Saline. Data are presented as the mean ± 1 SEM. (n = 6 rats/group).

[0017] Figure 4 shows C-fiber paw withdrawal latencies in response to noxious heat: *i.n.* Nociceptin (0.2 mg/kg, 5.0 mg/kg) vs. *i.v.* Nociceptin (5.0 mg/kg) vs. *i.m.* Morphine (0.25mg/kg) vs. *i.m.* Saline. Data are presented as the mean ± 1 SEM. (n = 6 Rats/group).

[0018] Figure 5 shows A-delta cheek withdrawal latencies in response to noxious heat: subcutaneous Nociceptin Antagonist (10.0mg/kg) plus *i.n.* Nociceptin (5.0mg/kg) vs. subcutaneous Saline plus *i.n.* Nociceptin (5.0mg/kg). Data are presented as the mean ± 1 SEM. (n= 3 rats/group).

CLAIMS

What is claimed is:

1. Use of an NOP agonist that is a non-opioid molecule for the manufacture of a medicament for the treatment of pain via craniofacial mucosal administration, provided the medicament does not contain an oxytocin peptide.

2. The use according to claim 1, wherein said treatment comprises treatment of a trigeminal pain, a somatic pain, a neuropathic pain or a visceral pain.

3. The use according to claim 1, wherein said treatment comprises treatment of a somatic pain, a neuropathic pain or a visceral pain.

4. The use according to claim 1, wherein said treatment comprises treatment of an acute pain or a chronic pain.

5. The use according to any one of claims 1-4, wherein the pain is a craniofacial pain or a head pain.

6. The use according to claim 5, wherein the craniofacial pain or the head pain is caused by temporomandibular joint disorder (TMJ), migraine or trigeminal neuralgia.

7. The use according to any one of claims 1-6, wherein the craniofacial mucosal administration comprises intranasal administration, buccal administration, sublingual administration or conjunctival administration.

8. The use according to claim 7, wherein the mucosal administration is intranasal administration.

9. The use according to any one of claims 1-8, wherein the NOP agonist is a peptide NOP agonist.

10. The use according to any one of claims 1-9, wherein the NOP agonist is N/OFQ.

11. The use according to any one of claims 1-10, wherein the individual in need thereof is to be administered at least one or at least two additional active agent, wherein the additional active agent is to be administered before, after or simultaneously with administration of the NOP agonist.

12. The use according to claim 11, in which the active agents are to be administered consisting of the NOP agonist and one or two additional active agent(s).

13. The use according to claim 11 or 12, wherein the additional active agent is selected from the group consisting of non-peptide opioids, opioid and opioid-like peptides and their analogs, NMDA-receptor antagonists, sodium channel blockers, calcium channel blockers, adrenergic antagonists, gabaergic agonists, glycine agonists, cholinergic agonists, adrenergic agonists, epinephrine, anticonvulsants, Rho kinase inhibitors, PKC inhibitors, p38-MAP kinase inhibitors, ATP receptor blockers, endothelin receptor blockers, pro-inflammatory cytokine, chemokine, interleukin and tumor necrosis factor blockers, pro-inflammatory cytokines, tricyclic antidepressants, serotonergic antagonists, serotonergic agonists, NSAIDs and COXIBs, acetaminophen; analgesic peptides, toxins, TRP channel agonists and antagonists, cannabanoids, antagonists of pro-nociceptive peptide neurotransmitter receptors CGRP1 and CGRP2, antagonists of pro-nociceptive peptide neurotransmitter receptor NK1, antagonists of pro-nociceptive peptide neurotransmitter receptor NK2, antagonists of pro-nociceptive peptide neurotransmitter receptor Y1-5, antagonists of pro-nociceptive peptide neurotransmitter receptors VPAC2, VPAC1 and PAC1, antagonists of pro-nociceptive peptide neurotransmitter receptors Gall-3 or GalR1-3, agonists or antagonists of vasopressin, corticotropin releasing hormone (CRH), growth hormone releasing hormone (GHRH), luteinizing hormone releasing hormone (LHRH), somatostatin growth hormone release inhibiting hormone, thyrotropin releasing hormone (TRH), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), pancreatic polypeptide, peptide tyrosine-tyrosine, glucogen-like peptide-1 (GLP-1), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), brain natriuretic peptide, cholecystokinin (CCK), islet amyloid polypeptide (IAPP) or amylin, melanin concentrating hormone (MCH),

melanocortins (ACTH, α-MSH and others), neuropeptide FF (F8Fa), neurotensin, parathyroid hormone related protein, calcitonin, Agouti gene-related protein (AGRP), cocaine and amphetamine regulated transcript (CART)/peptide, 5-HT-moduline, hypocretins/orexins, nocistatin, prolactin releasing peptide, secretoneurin, urocortin and derivatives and analogues thereof.

14. The use according to any one of claims 1-13, wherein the NOP agonist is to be administered as a pharmaceutical composition.

15. The use according to claim 14,
(a) wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients, adjuvants, diluents or stabilizers; and/or
(b) wherein the pharmaceutical composition further comprises at least one protease inhibitor and/or at least one absorption enhancer.

16. The use according to claim 1, wherein the pain is migraine headache pain and wherein the medicament is to be administered via intranasal administration, provided that the NOP agonist is not co-administered with an oxytocin peptide.

17. The use according to claim 10 or claim 16 wherein the NOP agonist is N/OFQ and the unit dose of the N/OFQ administered is 0.2 mg to 5000 mg.

18. The use according to any one of claims 1-17, wherein the administration results in reduction of a pain rating on the VAS of 30% or more.