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Central N/OFQ-NOP Receptor System in Pain Modulation

Norikazu Kiguchi, **Huiping Ding**, and **Mei-Chuan Ko**[1]

Department of Physiology & Pharmacology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Abstract

It has been two decades since the peptide, nociceptin/orphanin FQ (N/OFQ), and its cognate (NOP) receptor were discovered. Although NOP receptor activation causes a similar pattern of intracellular actions as mu opioid (MOP) receptors, NOP receptor-mediated pain modulation in rodents are more complicated than MOP receptor activation. In this review, we highlight the functional evidence of spinal, supraspinal, and systemic actions of NOP receptor agonists for regulating pain. In rodents, effects of the N/OFQ-NOP receptor system in spinal and supraspinal sites for modulating pain are bidirectional depending on the doses, assays, and pain modalities. The net effect of systemically administered NOP receptor agonists may depend on relative contribution of spinal and supraspinal actions of the N/OFQ-NOP receptor signaling in rodents under different pain states. In stark contrast, NOP receptor agonists produce only antinociception and antihypersensitivity in spinal and supraspinal regions of nonhuman primates regardless of doses and assays. More importantly, NOP receptor agonists and a few bifunctional NOP/MOP receptor agonists do not exhibit reinforcing effects (abuse liability), respiratory depression, itch pruritus, nor do they delay the gastrointestinal transit function (constipation) in nonhuman primates. Depending upon their intrinsic efficacies for activating NOP and MOP receptors, bifunctional NOP/MOP receptor agonists warrant additional investigation in primates regarding their side effect profiles. Nevertheless, NOP receptor-related agonists display a much wider therapeutic window as compared to that of MOP receptor agonists in primates. Both selective NOP receptor agonists and bifunctional NOP/MOP receptor agonists hold a great potential as effective and safe analgesics without typical opioid-associated side effects in humans.

Keywords

Analgesics; Bifunctional ligands; Neuropathic pain; NOP receptor; Opioids; Primate; Rodent; Spinal cord; Supraspinal regions; Translational research

1. Introduction

After the cloning of delta- (Evans, Keith, Morrison, Magendzo, & Edwards, 1992; Kieffer, Befort, Gaveriaux-Ruff, & Hirth, 1992), kappa- (Yasuda et al., 1993), and mu- (Chen,

[1]Corresponding author: Mei-Chuan Ko, Ph.D., Department of Physiology & Pharmacology, Wake Forest University School of Medicine, 205 NRC, Medical Center Boulevard, Winston-Salem, NC 27157, USA. mko@wakehealth.edu (M.C. Ko).

Conflict of Interest

N.K. and H.D. declare that there is no conflict of interest.

Mestek, Liu, Hurley, & Yu, 1993) opioid receptors (DOP, KOP, and MOP receptors, respectively), several groups of scientists in 1994 identified a G-protein coupled receptor with high homology to opioid receptors and this receptor was named opioid receptor like 1 (ORL1) (Bunzow et al., 1994; Fukuda et al., 1994; Mollereau et al., 1994; Nishi, Takeshima, Mori, Nakagawara, & Takeuchi, 1994; Wang et al., 1994). Subsequently, an endogenous haptadecapeptide (FGGFTGARKSARKLANQ) selective for ORL1 was discovered independently by two groups. This peptide was named “nociceptin” by one group based on its ability to elicit hyperalgesia following supraspinal administration in mice (Meunier et al., 1995). The other group named this same peptide as “orphanin FQ” based on the recognition of ORL1 and its first and last amino acid residues (Reinscheid et al., 1995). After the identification of nociceptin/orphanin FQ (N/OFQ), the ORL1 was renamed N/OFQ peptide (NOP) receptor based on the nomenclature guidelines recommended by the International Union of Basic and Clinical Pharmacology (Cox, Christie, Devi, Toll, & Traynor, 2015).

1.1. Characteristics of N/OFQ and the NOP receptor

N/OFQ is derived from a precursor prepro-N/OFQ (ppN/OFQ), which is encoded on chromosome 8p21 in humans (Mollereau et al., 1996), and the sequence of ppN/OFQ gene has similar structural features to precursors of classical opioid peptides, such as prepro-enkephalin, -dynorphin, and -opiomelanocortin (Sundstrom, Dreborg, & Larhammar, 2010). The amino acid sequence of ppN/OFQ is highly conserved across several animal species, and ppN/OFQ and N/OFQ are widely distributed in the peripheral and central nervous system (CNS) of both rodents and primates. In particular, N/OFQ is provided by interneurons in numerous areas of the brain (Neal, Mansour, Reinscheid, Nothacker, Civelli, & Watson, 1999b; Peluso, LaForge, Matthes, Kreek, Kieffer, & Gaveriaux-Ruff, 1998; Witta, Palkovits, Rosenberger, & Cox, 2004), suggesting its multiple effects on brain function. N/OFQ is also expressed in the dorsal horn and ventral horn of the spinal cord which integrate sensory processing (Neal et al., 1999b).

On the other hand, NOP receptor gene is encoded on chromosome 20 in humans (Lambert, 2008; Sundstrom et al., 2010), and its primary structure is also highly conserved across mammalians (Calo & Guerrini, 2013). According to several biochemical studies and 3-dimensional crystal structure analysis, positions of amino acid residues configuring the binding pocket of NOP receptor differ from those of DOP, KOP, and MOP receptors (Granier et al., 2012; Manglik et al., 2012; Thompson et al., 2012; Wu et al., 2012). Consequentially, the hydrophobic and hydrophilic parts of the binding pockets of the NOP receptor and other opioid receptors are different. These atomic details of ligand-receptor recognition explain marked differences in the binding selectivity of corresponding ligands in spite of high sequence homology between the NOP receptor and classical opioid receptors (Calo & Guerrini, 2013; Calo, Guerrini, Rizzi, Salvadori, & Regoli, 2000; Schröder, Lambert, Ko, & Koch, 2014). Like N/OFQ, the NOP receptor is abundant in multiple brain areas and spinal cord (Berthele et al., 2003; Neal et al., 1999a), indicating that the N/OFQ-NOP receptor system plays a fundamental role in regulating several functions including pain.

1.2. Cellular actions of the N/OFQ-NOP receptor system

Similar to classical opioid receptors (i.e., DOP, KOP, and MOP receptors), NOP receptor is coupled to pertussis toxin-sensitive Gi/o proteins, which inhibit adenylate cyclase and voltage-gated calcium channels and activate inward potassium channels (Hawes, Graziano, & Lambert, 2000; Ma, Cheng, Fan, Cai, Jiang, & Pei, 1997; Margas, Sedeek, & Ruiz-Velasco, 2008). These cellular events following NOP receptor activation reduce synaptic transmission, by either reducing neurotransmitter release *via* presynaptically-located NOP receptors, or inhibiting neuronal excitability *via* postsynaptically-located NOP receptors (Connor, Vaughan, Chieng, & Christie, 1996; Connor, Yeo, & Henderson, 1996; Knoflach, Reinscheid, Civelli, & Kemp, 1996). Indeed, NOP receptor activation has been shown to inhibit the release of a variety of neurotransmitters (e.g., glutamate, GABA, substance P, noradrenaline) in the CNS (Nicol et al., 1998; Nicol, Lambert, Rowbotham, Smart, & McKnight, 1996; Schlicker & Morari, 2000). Although NOP receptor activation induces a similar pattern of intracellular events as MOP, DOP, and KOP receptors, NOP receptor-mediated effects on pain modulation are more complicated than MOP receptor activation. Depending on the administration routes and animal species, NOP receptor activation could potentially lead to either pronociceptive or antinociceptive effect (Schröder et al., 2014). In this review, we highlight the functional evidence of central N/OFQ-NOP receptor system for regulating pain processing. In specific, we discuss the pharmacological evidence of spinal and supraspinal NOP receptor activation and integrated outcomes from systemic administration of NOP receptor-related ligands between rodents and nonhuman primates. Accumulated evidence strongly supports the therapeutic potential of NOP receptor-related agonists as effective and safe analgesics in primates.

2. Spinal actions of the N/OFQ-NOP receptor system

2.1. Spinal actions of NOP receptor agonists in rodent models of acute pain

Since the NOP receptor is present at central pain-processing pathways (Anton, Fein, To, Li, Silberstein, & Evans, 1996; Mollereau & Mouledous, 2000; Neal et al., 1999a), several groups of researchers have investigated the function of spinal N/OFQ-NOP receptor system in pain modulation. In rodents, several lines of evidence demonstrate that intrathecal administration of N/OFQ at nanomole doses produced antinociceptive effects in the rodent tail-flick test (King, Rossi, Chang, Williams, & Pasternak, 1997; Xu, Hao, & Wiesenfeld-Hallin, 1996). Intrathecal N/OFQ also had antinociceptive effects in the formalin-induced pain behaviors (Erb, Liebel, Tegeder, Zeilhofer, Brune, & Geisslinger, 1997; Yamamoto, Nozaki-Taguchi, & Kimura, 1997a), and potentiated morphine-induced antinociception (Tian et al., 1997). Through chemical modifications of N/OFQ by increasing its agonist potency and decreasing its peptidase sensitivity, a NOP receptor agonist, UFP-112 (Arduin et al., 2007), exhibited antinociceptive effects with higher potency and longer duration than N/OFQ in mice (Calo et al., 2011; Rizzi et al., 2007). Nevertheless, lower femtomole doses of intrathecal N/OFQ caused pain-like behaviors in mice, suggesting biphasic actions of N/OFQ (Inoue et al., 1999; Sakurada et al., 1999). Except for lower doses, higher doses of intrathecal N/OFQ might inhibit the excitatory glutamatergic transmission *via* presynaptic and postsynaptic NOP receptor activation, leading to spinal analgesia (Le Cudennec, Suaudeau, & Costentin, 2002). Additionally, N/OFQ inhibited action potentials in cultured

spinal cord based on the firing of both C- and A-fibers (Faber, Chambers, Evans, & Henderson, 1996), and C-fiber-evoked excitation of dorsal horn neurons (Stanfa, Chapman, Kerr, & Dickenson, 1996).

2.2. Spinal actions of NOP receptor agonists in rodent models of chronic pain

Spinal NOP receptor activation exerted potent and efficacious antihyperalgesic and antiallodynic effects in rodents under chronic pain. For example, intrathecal N/OFQ inhibited carrageenan- and complete Freund's adjuvant (CFA)-induced thermal hyperalgesia in rats (Chen & Sommer, 2007; Hao, Xu, Wiesenfeld-Hallin, & Xu, 1998; Yamamoto, Nozaki-Taguchi, & Kimura, 1997b). In addition, intrathecal N/OFQ attenuated thermal hyperalgesia and mechanical allodynia in rats under neuropathic pain caused by chronic constriction injury (CCI) or spinal nerve ligation (SNL) (Corradini, Briscini, Ongini, & Bertorelli, 2001; Courteix, Coudore-Civiale, Privat, Pelissier, Eschalier, & Fialip, 2004; Yamamoto & Nozaki-Taguchi, 1997). Interestingly, pre-emptive administration of N/OFQ delayed the development of chronic pain induced by CCI (Yamamoto, Ohtori, & Chiba, 2000). Similar to N/OFQ, a selective non-peptidic NOP receptor agonist, Ro64-6198, inhibited mechanical and cold allodynia derived from CCI, without affecting pain threshold in naïve rats (Obara, Przewlocki, & Przewlocka, 2005). Furthermore, intrathecal N/OFQ attenuated mechanical hyperalgesia in diabetic rats and was more potent in producing antinociceptive effects in diabetic mice as compared to naive mice (Courteix et al., 2004; Kamei, Ohsawa, Kashiwazaki, & Nagase, 1999). These NOP receptor agonist-induced antihyperalgesic and antiallodynic effects might be at least in part explained by an up-regulation of the NOP receptors in the spinal cord under these painful conditions. In fact, expression of N/OFQ and the NOP receptor were up-regulated in the dorsal horn of rats under carrageenan- and CFA-induced inflammation, respectively (Jia, Linden, Serie, & Seybold, 1998; Rosen, Lundeberg, Bytner, & Nylander, 2000). Importantly, the NOP receptor was also up-regulated in the dorsal horn of rats with CCI (Briscini, Corradini, Ongini, & Bertorelli, 2002) and the inhibitory effect of N/OFQ on spinal wide dynamic range neurons was enhanced in rats under neuropathic pain (Sotgiu, Bellomi, & Biella, 2004).

2.3. Spinal actions of NOP receptor agonists in primate pain models

According to the radioligand binding assay, the NOP receptor is widely distributed in the spinal cord of nonhuman primates (Bridge, Wainwright, Reilly, & Oliver, 2003). Unlike findings in rodents, intrathecal administration of N/OFQ over a wide range from femtomole to nanomole doses only produced antinociceptive effects without eliciting pronociceptive responses in a monkey thermal nociceptive assay, and these effects can be reversed by a NOP receptor antagonist (Ko & Naughton, 2009; Ko, Wei, Woods, & Kennedy, 2006). Although NOP receptors are expressed in neural substrates involved in pain processing in rodents and primates (Berthele et al., 2003; Bridge et al., 2003; Neal et al., 199a), there is no anatomical study to directly compare the distribution of NOP receptors in different populations of neurons. It is important to further investigate the nature of nociceptive neurons expressing NOP receptors and determine if they have different properties for releasing pain-inhibiting and -eliciting neuropeptides between rodents and primates. Using an innovative chemical approach, peptide welding technology (PWT), different

tetrabranched derivatives of N/OFQ has been generated and PWT-N/OFQ derivatives behaved as high-affinity, potent and selective full NOP receptor agonists (Rizzi et al., 2014). In particular, PWT2-N/OFQ was 40-fold more potent and produced an extremely long-lasting inhibitory effect than the natural peptide N/OFQ in mice (Rizzi et al., 2014). More importantly, this largely increased potency and improved duration of action exhibited by PWT2-N/OFQ can be translated from rodents to primates. Intrathecal administration of PWT2-N/OFQ potently produced full antinociceptive effects lasted for more than 24 hours in monkeys (Rizzi et al., 2015). Under similar experimental conditions, PWT2-N/OFQ (0.3–3 nmol) is approximately 30-fold more potent than N/OFQ (10–100 nmol) and the duration of antinociceptive action of PWT2-N/OFQ (~24 hours) is 10-fold longer than that of N/OFQ (~2.5 hours) in primates (Ding et al., 2015b; Ko et al., 2006; Rizzi et al., 2015). It is worth noting that among all agonists selective for opioid receptor subtypes, NOP receptor agonists are the only class of drugs that are able to change the nociceptive threshold of primates without side effects commonly caused by MOP receptor agonists (Lin & Ko, 2013).

Although the analgesic efficacy of spinal NOP receptor agonists in patients under neuropathic pain is unknown, intrathecal UFP-112 was 10 times more potent than morphine in attenuating acute pain and capsaicin-induced thermal allodynia in monkeys (Hu, Calo, Guerrini, & Ko, 2010). Capsaicin evokes pain by activating the transient receptor potential vanilloid type 1, which has been implicated in the transduction of diverse pain modalities including diabetic neuropathy (Aykanat, Gentgall, Briggs, Williams, Yap, & Rolan, 2012; Szolcsanyi & Sandor, 2012). It has been used in both humans and nonhuman primates to investigate pain mechanisms and explore novel pharmacological interventions (Butelman, Harris, & Kreek, 2004; Eisenach, Hood, Curry, & Tong, 1997; Park, Max, Robinovitz, Gracely, & Bennett, 1995). Given full antiallodynic effects of intrathecal UFP-112 in primates, NOP receptor agonists hold a great potential for clinical use as strong analgesics. In addition, carrageenan-induced thermal hyperalgesia has been developed as an inflammatory pain model in nonhuman primates to assess the analgesic efficacy of opioids and non-steroidal anti-inflammatory drugs (Sukhtankar, Lee, Rice, & Ko, 2014). Unlike classical opioid peptides such as β-endorphin and enkephalins, intrathecal N/OFQ completely inhibited carrageenan-induced hyperalgesia without eliciting itch scratching in monkeys (Lee & Ko, 2015). These findings collectively demonstrate that spinal NOP receptor activation produces antinociceptive and antihypersensitive effects across different pain modalities in nonhuman primates. The promising therapeutic profile of NOP receptor agonists in primates encourages further development of this class of drugs as spinal analgesics.

3. Supraspinal actions of the N/OFQ-NOP receptor system

3.1. Supraspinal actions of NOP receptor agonists in rodent models of acute pain

The NOP receptor is abundant in supraspinal areas, such as thalamus, hypothalamus, locus coeruleus, periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), which modulate ascending and descending pain pathways (Civelli, 2008; Heinricher, McGaraughty, & Grandy, 1997; Mollereau & Mouledous, 2000; Neal et al., 1999a). Supraspinal actions of the N/OFQ-NOP receptor system are complicated, as supraspinal NOP receptor activation

produces opposite effects on pain processing depending on the pain state and species. Initial studies reported that intracerebroventricular (i.c.v.) administration of N/OFQ produced hyperalgesia in the mouse hot plate and tail flick tests (Meunier et al., 1995; Reinscheid et al., 1995) and i.c.v. N/OFQ counteracted morphine-induced antinociception in the rodent tail flick test (King, Chang, & Pasternak, 1998; Tian et al., 1997). In addition, a peptidic analogue of N/OFQ, [Phe$^1\psi$(CH_2-NH)Gly^2]N/OFQ-(1–13)-NH_2 (Butour, Moisand, Mollereau, & Meunier, 1998; Grisel, Farrier, Wilson, & Mogil, 1998), also elicited pronociceptive effects after i.c.v. administration in mice and rats, and inhibited morphine-induced antinociception in the mouse tail withdrawal assay (Calo et al., 1998; Wang, Zhu, Cao, & Wu, 1999b). Although exact mechanisms of NOP receptor agonist-induced pronociceptive effects are unclear, it is hypothesized that two types of neurons (ON cells and OFF cells) in the RVM, which regulate descending inhibition of pain, might be differentially regulated by the NOP receptor. Firing of ON cells induces enhanced and prolonged nociception, whereas excitation of OFF cells leads to antinociception. ON cells are normally dominant through tonic inhibition of OFF cells via GABA-dependent mechanisms (Fields, 2004). Analgesia is produced by MOP receptor-dependent inhibition of ON cells, followed by excitation of OFF cells (Heinricher, Morgan, Tortorici, & Fields, 1994). In contrast, supraspinal NOP receptor ligands may directly inhibit OFF cells and induce anti-opioid action and subsequent pronociceptive effects (Heinricher et al., 1997). On the other hand, i.c.v. administration of a highly selective peptidic NOP receptor antagonist, [Nphe^1, Arg^{14}, Lys^{15}]N/OFQ-NH^2 (UFP-101) (Calo et al., 2005; McDonald, Calo, Guerrini, & Lambert, 2003), exerted antinociceptive effects in the mouse formalin test (Rizzi et al., 2006). These findings suggest that supraspinal N/OFQ-NOP receptor system might be constitutively pronociceptive in rodent models of acute pain.

3.2. Supraspinal actions of NOP receptor agonists in rodent models of chronic pain

Based on the limited literature, supraspinal actions of NOP receptor agonists in rodents under chronic pain have mixed results depending on pain modalities. Following i.c.v. administration, a NOP receptor agonist, [Phe$^1\psi$(CH_2-NH)Gly^2]N/OFQ-(1–13)-NH_2, caused hyperalgesia and inhibited morphine-induced antihyperalgesia in rats with CFA-induced inflammation (Bertorelli, Corradini, Rafiq, Tupper, Calo, & Ongini, 1999). Conversely, microinjection of a NOP receptor antagonist, UFP-101, into ventrolateral PAG (vlPAG) reversed carrageenan-induced mechanical allodynia in rats (Scoto, Arico, Iemolo, Ronsisvalle, & Parenti, 2009). Therefore, in rodent models of inflammatory pain, supraspinal N/OFQ-NOP receptor system seems to elicit pronociceptive effects.

After i.c.v. administration, highly selective non-peptidic NOP receptor agonists, GRT-TA2210 and Ro65-6570 (Hashiba et al., 2001; Linz, Christoph, Schiene, Koch, & Englberger, 2013), attenuated CCI-induced allodynia (Linz et al., 2013; Schiene, Christoph, Kogel, & Tzschentke, 2013). In contrast, microinjection of a NOP receptor antagonist UFP-101 into vlPAG attenuated CCI-induced tactile allodynia in rats (Scoto et al., 2009). It is currently unknown how NOP receptor agonists and antagonists, administered at different neuroanatomical sites in brain can result in similar antiallodynic effects. It is plausible to detect different drug actions derived from a brain subregion (e.g., vlPAG) versus an integrated outcome from the entire supraspinal region following i.c.v. administration.

Clearly, additional antagonist studies using the supraspinal, not microinjection, delivery route will provide a general functional profile of supraspinal N/OFQ-NOP receptor system in rodents under neuropathic pain.

Although some reports demonstrate that up-regulation of either N/OFQ or the NOP receptor under chronic pain conditions, their correlations with functional evidence of NOP receptor ligands has not been fully characterized. For example, NOP receptor positive cells in the PAG and RVM were increased, while N/OFQ was increased in cingulate cortex, but not PAG and RVM, in rats under CCI (Ma, Xie, Dong, Wang, & Wu, 2005; Rosen et al., 2000). Furthermore, N/OFQ expression was up-regulated in the PAG at a later period in SNL rats (Sun, Wang, Zhao, Chang, & Han, 2001). The direction of pain modulation *via* supraspinal N/OFQ-NOP receptor system might be changed along with temporal up-regulation and functional plasticity of the NOP receptor henceforth (Schröder et al., 2014). Influence of chronic pain state (e.g., inflammatory versus neuropathic pain) on the function of descending inhibitory pathways in supraspinal areas warrants further investigation with region-specific and i.c.v. administration of NOP receptor agonists and antagonists. It is noteworthy that actual analgesic profile and relative therapeutic index in humans will likely be related to the integrated effect of either intrathecal/epidural or oral/systemic administration, since local brain or i.c.v. administration is not widely used in clinical practice.

3.3. Supraspinal actions of N/OFQ in a primate model of acute pain

With improved surgical techniques, a recent study has established an intrathecal catheterization procedure by placing the catheter tip in the cisterna magna of rhesus monkeys, thus allowing practical supraspinal administration (Ding et al., 2015b). Unlike supraspinal N/OFQ-induced pronociception in rodents, intracisternal administration of N/OFQ dose-dependently produced antinociceptive effects which were reversed by a NOP receptor antagonist J-113397 in monkeys (Ding et al., 2015b). For comparison, intracisternal substance P and morphine produced hyperalgesia and antinociception, respectively, in the same group of monkeys. Furthermore, intracisternal N/OFQ did not produce anti-morphine actions in these nonhuman primates (Ding et al., 2015b). These findings provide distinct functional profiles of supraspinal N/OFQ-NOP receptor system between rodents and primates. More importantly, this intrathecal catheter implantation not only documents the functional role of central N/OFQ-NOP receptor system for pain inhibition, but also illustrates how we can study supraspinal neuropeptides' pain-eliciting or pain-inhibiting effects in awake, behaving primates.

4. Systemic actions of the N/OFQ-NOP receptor system

4.1. Systemic actions of NOP receptor agonists in rodent models of acute pain

As mentioned above, the involvement of N/OFQ-NOP receptor system in nociceptive processing is multimodal depending upon pain modalities and routes of administration in rodents. Effects of systemically administered NOP receptor agonists depend on the integration of peripheral, spinal, and supraspinal sties of action. Early studies show that systemic administration of a non-peptidic NOP receptor agonist Ro64-6198 did not produce

antinociceptive effects in the mouse and rat tail flick tests, nor in the mouse tail immersion test (Dautzenberg et al., 2001; Jenck et al., 2000; Kotlinska, Wichmann, Rafalski, Talarek, Dylag, & Silberring, 2003). This net effect of systemic Ro64-6198 could be integrated from spinal antinociceptive action and supraspinal pronociceptive action of the N/OFQ-NOP receptor signaling. There is only one study showing that systemic Ro64-6198 produced antinociceptive effects in the mouse hot plate test (Reiss, Wichmann, Tekeshima, Kieffer, & Ouagazzal, 2008). However, systemic Ro64-6198 increased pain sensitivity in the mouse tail flick test by supraspinally inhibiting stress-induced analgesia (Reiss et al., 2008). Overall, systemic administration of selective NOP receptor agonists does not produce a robust analgesic profile in rodent acute pain models.

4.2. Systemic actions of NOP receptor agonists in rodent models of chronic pain

Unlike their analgesic efficacy against acute pain, systemic administration of NOP receptor agonists exhibited antihyperalgesic effects in rodents under inflammatory pain. Systemic GRT-TA2210 and Ro65-6570 attenuated CFA-induced inflammatory pain in rats without disrupting locomotor activity (Linz et al., 2013; Schiene et al., 2013). Moreover, a non-peptidic NOP receptor agonist, SCH 221510 (Varty et al., 2008), produced antihypersensitive effects on trinitrobenzene sulfonic acid-induced inflammatory pain (Sobczak et al., 2014; Sobczak, Salaga, Storr, & Fichna, 2013). These pharmacological findings agree with the functional studies from either ppN/OFQ or NOP receptor knockout mice that displayed normal sensitivity to acute pain, but showed increased inflammatory hyperalgesia (Depner, Reinscheid, Takeshima, Brune, & Zeilhofer, 2003). In addition, systemic Ro65-6570 also produced antihyperalgesic and antiallodynic effects in both mice and rats under neuropathic pain without locomotor side effects (Schiene et al., 2013). These findings collectively support the therapeutic potential of systemic NOP receptor agonists as analgesics in rodent models of chronic pain. The analgesic efficacy of systemic NOP receptor agonists in rodents under chronic pain may depend on the functional plasticity of the N/OFQ-NOP receptor system across spinal and supraspinal regions (Schröder et al., 2014).

4.3. Systemic actions of NOP receptor agonists in primate pain models

Contrary to their pain modality-dependent efficacy in rodent models, systemic administration of NOP receptor agonists has generally produced analgesic effects across different nonhuman primate models. Following subcutaneous administration, Ro64-6198 dose-dependently produced antinociceptive effects against an acute thermal nociceptive stimulus in monkeys (Ko, Woods, Fantegrossi, Galuska, Wichmann, & Prinssen, 2009; Lin & Ko, 2013). As mentioned above, capsaicin-induced allodynia has been used in both nonhuman primates and humans to distinguish strong analgesics (Butelman et al., 2004; Eisenach et al., 1997; Park et al., 1995). Crucially, systemic Ro64-6198 potently inhibited capsaicin-induced thermal allodynia in monkeys (Ko et al., 2009). In addition, systemic Ro64-6198 potently attenuated carrageenan-induced hyperalgesia in the monkey inflammatory pain model (Sukhtankar et al., 2014). Importantly, just like Ro64-6198, another NOP receptor agonist with different chemical structure, SCH 221510 (Varty et al., 2008), produced antinociceptive and antihypersensitive efficacy against acute pain, capsaicin-induced allodynia and carrageenan-induced hyperalgesia in monkeys following

systemic administration (Cremeans, Gruley, Kyle, & Ko, 2012; Wladischkin, Dysko, Collins, Ko, Winger, & Ko, 2012). These findings strongly indicate that NOP receptor agonists may be effective for treating pain derived from different nociceptive origins in humans.

5. Therapeutic potential of NOP receptor-related agonists as analgesics

5.1. Development of bifunctional NOP/MOP receptor agonists

In the early stage of developing NOP receptor-related ligands as analgesics, the effort was mainly focused on NOP receptor antagonists due to central NOP receptor-mediated pronociception and anti-opioid actions, and NOP receptor antagonist-induced antihyperalgesia in rodent pain models (Lutfy et al., 2003; Meunier et al., 1995; Mogil, Grisel, Reinscheid, Civelli, Belknap, & Grandy, 1996; Reinscheid et al., 1995). For example, pretreatment with a NOP receptor antagonist J-113397 potentiated antinociceptive effects of buprenorphine in mice, indicating that NOP receptor activation compromised buprenorphine-induced antinociception (Lutfy et al., 2003). However, J-113397 did not enhance buprenorphine-induced antinociception in monkeys. Instead, NOP receptor agonists, Ro64-6198 and SCH 221510, produced synergistic antinociception with buprenorphine without eliciting other side effects in monkeys (Cremeans et al., 2012). This antinociceptive synergism by co-activation of both NOP and MOP receptors not only occurs following systemic administration, but also exists in the spinal cord (Courteix et al., 2004; Hu et al., 2010; Ko & Naughton, 2009). Mounting evidence in the past few years indicates that central N/OFQ-NOP receptor signaling does not function opposing the effects of MOP receptor agonists, especially in primates (Ding et al., 2015b; Ko & Naughton, 2009). More importantly, ligands with agonist actions on both NOP and MOP receptors (i.e., *bifunctional NOP/MOP receptor agonists*) may represent effective and safe analgesics as they have a wider therapeutic window and a slower development of tolerance to analgesic efficacy (Lin & Ko, 2013).

Medicinal chemists have developed several series of NOP receptor-related ligands with different efficacies on NOP and MOP receptors for distinct therapeutic applications (Calo & Guerrini, 2013; Husbands, 2013; Journigan, Polgar, Khroyan, & Zaveri, 2014; Kumar et al., 2014; Schunk et al., 2014; Toll, 2013; Zaveri, Jiang, Olsen, Polgar, & Toll, 2013). Table 1 highlights several mixed NOP/MOP receptor agonists, [Dmt^1]N/OFQ(1–13)-NH_2 (Molinari et al., 2013), SR14150 (Spagnolo et al., 2008), SR16435 (Khroyan, Polgar, Jiang, Zaveri, & Toll, 2009), SR16835 (Toll, Khroyan, Polgar, Jiang, Olsen, & Zaveri, 2009), and BU08028 (Khroyan, Polgar, Cami-Kobeci, Husbands, Zaveri, & Toll, 2011a), in terms of their antinociceptive and antihypersensitive actions. Generally, systemic administration of these mixed NOP/MOP receptor agonists effectively blocked hyperalgesia and allodynia in rodent models of chronic pain. However, antagonist studies do not elucidate the contribution of spinal versus supraspinal NOP and MOP receptors in these antihypersensitive effects by systemic NOP/MOP receptor agonists. On the other hand, intrathecal administration of mixed NOP/MOP receptor agonists, SR16435 and BU08028, attenuated nerve injury-induced tactile allodynia and inflammation-associated thermal hyperalgesia more potently than selective NOP or MOP receptor agonists in mice (Sukhtankar, Zaveri, Husbands, & Ko,

2013). In addition, repeated intrathecal administration of SR16435 showed a delayed development of tolerance to antiallodynic effects as compared to a MOP receptor agonist (Sukhtankar et al., 2013). This delayed tolerance development could be attributed to the consequence of repeated co-activation of NOP and MOP receptors, i.e., a synergistic action with a larger reservoir for both receptor populations (Lin & Ko, 2013).

It is worth noting that cebranopadol, the first NOP and opioid receptor agonist, is currently in clinical development for the treatment of severe chronic pain (Salat, Jakubowska, & Kulig, 2015). Cebranopadol binds with nanomolar affinity to the NOP receptor and classical opioid receptors, and it has nearly full agonist activity at human NOP, MOP, and DOP receptors and partial agonist activity at the KOP receptor, based on the [^{35}S]GTPγS binding assay (Linz et al., 2014). Across diverse rodent models of acute and chronic pain, cebranopadol displayed highly potent (i.e., ED50 values: 0.5–5 μg/kg by intravenous route) and efficacious antinociceptive and antihypersensitive effects. Interestingly, antihypersensitive effects of cebranopadol could be partially blocked by either the NOP receptor antagonist J-113397 or the MOP receptor-preferring antagonist naloxone (Linz et al., 2014). More importantly, at equianalgesic doses, cebranopadol showed a delayed development of analgesic tolerance as compared to morphine, and its analgesic doses did not disrupt motor coordination in rats (Linz et al., 2014). Cebranopadol has been registered for several clinical trials and both scientific and medical care communities are earnestly waiting for the outcomes of these trials.

5.2. Lack of major side effects commonly associated with MOP receptor agonists

Based on the current literature, selective NOP receptor agonists display a much wider therapeutic window as compared to that of MOP receptor agonists in primates (Lin & Ko, 2013). Only at a dose that is approximately 100-fold higher than its antihyperalgesic dose, systemic Ro64-6198 produced sedative effects in monkeys (Podlesnik, Ko, Winger, Wichmann, Prinssen, & Woods, 2011; Sukhtankar et al., 2014). Across a wide analgesic dose range, NOP receptor agonists do not produce reinforcing effects (abuse liability), respiratory depression, itch pruritus, nor do they delay the gastrointestinal transit function (constipation potential) (Cremeans et al., 2012; Ko et al., 2009; Sukhtankar et al., 2014; Wladischkin et al., 2012). These side effects are commonly associated with clinically used opioid analgesics. In the past few decades, research on classical opioid receptors, i.e., MOP, DOP, and KOP receptors, has expanded our understanding of how opioid drugs act, but could not shed light on the discovering of a new generation of opioid analgesics without MOP receptor agonist-associated side effects (Corbett, Henderson, McKnight, & Paterson, 2006). Research on selective NOP receptor agonists in primates in the past 10 years has opened a new avenue for developing effective and safe analgesics with fewer side effects (Lin & Ko, 2013; Schröder et al., 2014).

Emerging evidence indicates that mixed NOP/MOP receptor agonists also display a promising therapeutic profile as analgesics in primates. As mentioned above, such agonists exhibited improved potency and delayed development of analgesic tolerance (Linz et al., 2014; Sukhtankar et al., 2013). For instance, BU08028 is a recently developed buprenorphine analog which has binding affinity (i.e., Ki: 1–10 nM) for the NOP and

classical opioid receptors. However, this ligand only has detectable efficacy on both NOP and MOP receptors, i.e., 20–40% stimulation by the [^{35}S]GTPγS binding assay (Khroyan et al., 2011a). This mixed NOP/MOP receptor agonist produced morphine-comparable maximal antinociception which was reversed equally by both NOP and MOP receptor antagonists in the monkey thermal nociceptive assays (Ding et al., 2015a). More importantly, unlike buprenorphine, BU08028 did not produce reinforcing effects in the monkey drug self-administration assay. At doses within and 10-fold higher than the antinociceptive dose range, BU08028 did not compromise physiological functions including respiratory and cardiovascular activities in monkeys (Ding et al., 2015a). These recent findings strongly support the therapeutic potential of bifunctional NOP/MOP receptor agonists as innovative analgesics in primates.

Among newly developed NOP receptor-related agonists, there are differential intrinsic efficacies (i.e., from low, mid, to full efficacy) for activating both NOP and MOP receptors (Calo & Guerrini, 2013; Husbands, 2013; Journigan et al., 2014; Khroyan et al., 2011a; Schunk et al., 2014). Some ligands may produce reinforcing effects and/or respiratory depression if their efficacy on the MOP receptor is not low enough. Given the species differences in the pharmacological profiles of NOP and MOP receptor-related ligands between rodents and primates (Lin & Ko, 2013; Schröder et al., 2014), it is important to study the side effect profiles (e.g., abuse liability, respiratory depression, and physical dependence) of these ligands in awake, behaving monkeys. Such studies will validate the therapeutic profiles of systemic bifunctional NOP/MOP receptor agonists and help identify candidate ligands as a translational bridge for their therapeutic applications in humans.

6. Conclusion

Taken together, functional profiles of central NOP receptor activation are different between rodents and primates. In rodents, antinociceptive and antihypersensitive actions of the N/OFQ-NOP receptor system in spinal and supraspinal areas are bidirectional depending on the doses, assays, and pain modalities. In stark contrast, NOP receptor-related ligands, i.e., both selective NOP receptor agonists and mixed NOP/MOP receptor agonists, produced only antinociception and antihypersensitivity in primates regardless of doses and assays applied. Most importantly, spinal administration of NOP receptor-related agonists exhibited analgesic efficacy across different rodent and primate pain models. Depending upon their intrinsic efficacies for activating NOP and MOP receptors, mixed NOP/MOP receptor agonists warrant additional investigation in primates regarding their side effect profiles. Effects of acute and chronic administration of such ligands will determine their tolerability and facilitate the development of candidate ligands as a new generation of analgesics in humans.

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Abbreviations

BU08028	(2*S*)-2-[(5*R*,6*R*,7*R*,14*S*)-*N*-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylpentan-2-ol
CCI	chronic constriction injury
CFA	complete Freund's adjuvant
CNS	central nervous system
DOP	delta-opioid peptide
GABA	gamma aminobutyric acid
GTPγS	guanosine 5'-*O*-(3-thio)triphosphate
i.c.v.	intracerebroventricular
KOP	kappa-opioid peptide
MOP	mu-opioid peptide
N/OFQ	nociceptin/orphanin FQ
NOP	N/OFQ peptide
ORL1	opioid receptor like 1
PAG	periaqueductal gray
ppN/OFQ	prepro-N/OFQ
PWT	peptide welding technology
Ro64-6198	(1*S*,3*aS*)-8-(2,3,3*a*,4,5,6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one
Ro65-6570	8-acenaphthen-1-yl-phenyl-1,3,8-triaza-spiro[4,5]decan-4-one
RVM	rostral ventromedial medulla
SCH 221510	8-[bis(2-methylphenyl)-methyl]-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol
SNL	spinal nerve ligation
SR14150	1-(1-Cyclooctylpiperidin-4-yl)-indolin-2-one
SR16435	1-(1-(bicyclo[3.3.1]nonan-9-yl)piperidin-4-yl)indolin-2-one

SR16835	1-(1-(2,3,3*a*,4,5,6-hexahydro-1*H*-phenalen-1-yl)piperidinl-4-yl)-indolin-2-one
UFP-101	[Nphe^{1}, Arg^{14}, Lys^{15}]N/OFQ-NH$_2$
UFP-112	[(pF)Phe^{4},Aib^{7},Arg^{14},Lys^{15}]N/OFQ-NH$_2$
vlPAG	ventrolateral PAG

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Table 1

Multiple effects of NOP receptor-related ligands on regulating pain processing.

NOP receptor-related ligands	Findings in rodents	Findings in primates
NOP Receptor Agonists (Peptides)		
N/OFQ	Spinal, Acute pain ↓ (Xu et al., 1996) (Erb et al., 1997) (King et al., 1997) (Yamamoto et al., 1997a) Spinal, Acute pain ↑ (Inoue et al., 1999) (Sakurada et al., 1999) Spinal, Inflammatory pain ↓ (Yamamoto et al., 1997b) (Hao et al., 1998) (Chen & Sommer, 2007) Spinal, Neuropathic pain ↓ (Yamamoto & Nozaki-Taguchi, 1997) (Corradini et al., 2001) (Courteix et al., 2004) Supraspinal, Acute pain ↑ (Meunier et al., 1995) (Reinscheid et al., 1995) Supraspinal, Inflammatory pain ↑ (Zhu et al., 1997) (Wang et al., 1999a)	Spinal, Acute pain ↓ (Ko et al., 2006) (Ko & Naughton, 2009) Supraspinal, Acute pain ↓ (Ding et al., 2015b)
[Phe$^1\psi$(CH$_2$-NH)Gly^2]N/OFQ-(1–13)-NH$_2$	Supraspinal, Acute pain ↑ (Calo et al., 1998) (Wang et al., 1999b) Supraspinal, Inflammatory pain ↑ (Bertorelli et al., 1999)	
UFP-112	Spinal, Acute pain ↓ (Rizzi et al., 2007) (Calo et al., 2011)	Spinal, Acute pain ↓ (Hu et al., 2010) Spinal, Capsaicin-induced allodynia ↓ (Hu et al., 2010)
PWT2-N/OFQ	Spinal, Acute pain ↓ (Rizzi et al., 2015) Spinal, Neuropathic pain ↓ (Rizzi et al., 2015)	Spinal, Acute pain ↓ (Rizzi et al., 2015)
NOP Receptor Agonists (Non-peptides)		
Ro64-6198	Spinal, Neuropathic pain ↓ (Obara et al., 2005) Systemic, Acute pain ↓ (Reiss et al., 2008) Systemic, Acute pain ↑ (Reiss et al., 2008)	Systemic, Acute pain ↓ (Ko et al., 2009) Systemic, Inflammatory pain ↓ (Sukhtankar et al., 2014) Systemic, Capsaicin-induced allodynia ↓ (Ko et al., 2009)
Ro65-6570	Supraspinal, Neuropathic pain ↓ (Schiene et al., 2013) Systemic, Inflammatory pain ↓	

NOP receptor-related ligands	Findings in rodents	Findings in primates
	(Schiene et al., 2013) Supraspinal, Neuropathic pain ↓ (Schiene et al., 2013)	
GRT-TA2210	Supraspinal, Neuropathic pain ↓ (Linz et al., 2013) Systemic, Inflammatory pain ↓ (Linz et al., 2013) `	
SCH 221510	Systemic, Inflammatory pain ↓ (Sobczak et al., 2013) (Sobczak et al., 2014)	Systemic, Acute pain ↓ (Cremeans et al., 2012) Systemic, Inflammatory pain ↓ (Wladischkin et al., 2012) Systemic, Capsaicin-induced allodynia ↓ (Wladischkin et al., 2012)
NOP Receptor Antagonist		
UFP-101	Supraspinal, Acute pain ↓ (Rizzi et al., 2006) Supraspinal, Inflammatory pain ↓ (Scoto et al., 2009) Supraspinal, Neuropathic pain ↓ (Scoto et al., 2009)	
Mixed NOP/MOP Receptor Agonists		
[Dmt[1]]N/OFQ(1–13)-NH_2	Spinal, Acute pain ↓ (Calo et al., 2012)	Spinal, Acute pain ↓ (Molinari et al., 2013)
SR16435	Spinal, Inflammatory pain ↓ (Sukhtankar et al., 2013) Spinal, Neuropathic pain ↓ (Sukhtankar et al., 2013) Systemic, Acute pain ↓ (Khroyan et al., 2009)	
SR14150	Systemic, Neuropathic pain ↓ (Khroyan et al., 2011b)	
SR16835	Systemic, Neuropathic pain ↓ (Khroyan et al., 2011b)	
BU08028	Spinal, Inflammatory pain ↓ (Sukhtankar et al., 2013) Spinal, Neuropathic pain ↓ (Sukhtankar et al., 2013) Systemic, Acute pain ↓ (Khroyan et al., 2011a)	Systemic, Acute pain ↓ (Ding et al., 2015a) Systemic, Capsaicin-induced allodynia ↓ (Ding et al., 2015a)
Cebranopadol	Systemic, Acute pain ↓ (Linz et al., 2014) Systemic, Inflammatory pain ↓ (Linz et al., 2014) Systemic, Neuropathic pain ↓	

NOP receptor-related ligands	Findings in rodents	Findings in primates
	(Linz et al., 2014)	

↓, antinociception or antihypersensitivity; ↑, pronociception or hypersensitivity