

Nociceptin/orphanin FQ receptor ligands and translational challenges: focus on cebranopadol as an innovative analgesic.

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Abstract

Opioids are characterized as classical (μ , δ , and κ) along with the non-classical nociceptin/orphanin FQ (N/OFQ) receptor or NOP. Targeting NOP has therapeutic indications in control of the cardiovascular and respiratory system along with control of micturition and a profile as an antidepressant; in all of these indications there is translational human data. Opioids such as morphine and fentanyl (activating the μ receptor) are the mainstay of pain treatment in the perioperative period, despite a challenging side effect profile. Opioids in general have poor efficacy in neuropathic pains. Moreover, longer term use is associated with tolerance. There is good evidence for an interaction between opioid receptors and co-activation can reduce side effects without compromising analgesia; this is particularly true for μ and NOP co-activation. Recent pharmaceutical development has produced a mixed opioid/NOP agonist cebranopadol. This new chemical entity is effective in animal models of nociceptive and neuropathic pain with greater efficacy in the latter. In these animal models there is little evidence for respiratory depression and tolerance (compared to morphine) only develops after substantial treatment periods. There is now early phase clinical development in diabetic neuropathy, cancer pain and low back pain where cebranopadol displays significant efficacy. In 1996 N/OFQ was formally identified with an innovative analgesic profile, ~20 years later, cebranopadol as a clinical ligand is advancing through the human trials process.

Keywords: opioids, NOP receptor ligands, cebranopadol, pain, analgesia

Introduction

The neuropeptide nociceptin/orphanin FQ (N/OFQ)^{1,2} has been identified as the endogenous ligand of the opioid receptor like 1 receptor now referred to as N/OFQ peptide receptor (NOP). N/OFQ as well as the NOP receptor display high structural homology with peptides and receptors of the opioid family. In addition, the NOP receptor is a 7TM receptor coupled with G_i proteins thus its transduction mechanisms are similar to those of classical opioid receptors e.g. reduction of cAMP levels, stimulation of potassium currents and inhibition of calcium conductance³. Despite these similarities the pharmacological profile of the NOP receptor is completely distinct from that of classical opioid receptors; for instance the action of N/OFQ (as well as those of selective NOP agonists) are resistant to naloxone the universal opioid receptor antagonist (for a detailed analysis of the NOP pharmacological profile see⁴)

The NOP receptor and the N/OFQ prepropeptide (ppN/OFQ) are widely expressed in the central and peripheral nervous system; accordingly N/OFQ via selective stimulation of the NOP receptor controls several biological functions including pain transmission, locomotor activity, stress and anxiety, emotional states, learning and memory, food intake, drug reward, gastrointestinal, cardiovascular and immune functions, the cough and micturition reflex³. This broad spectrum of actions stimulated the interest of academic and industrial researchers and generated a large panel of NOP receptor ligands useful for target validation studies (see Table 1). Among NOP peptide ligands the partial agonist SER100 (alias ZP120⁵) the full agonist Rec 0438 (alias UFP-112⁶) and the antagonist UFP-101⁷ are worthy of mention. As far as NOP non peptide ligands are concerned, the most well used compounds are the agonists Ro 65-6570⁸, Ro 64-6198⁹, MCOPPB¹⁰, and AT-403¹¹ and the antagonists J-113397¹², SB-612111¹³, and C-24¹⁴. Moreover, crystal structure of the NOP receptor in complex with the two latter compounds has been recently solved^{15 16}. The availability of these structures may be used in the future for the rational structure based design of innovative NOP ligands. In parallel, genetic models have been developed for investigating the biology of the N/OFQ-NOP receptor system including mice¹⁷ and rats^{18, 19} knockout for the NOP receptor gene (NOP(-/-)), mice knockout for the ppN/OFQ gene²⁰, and more recently mice knockin for the NOP-eGFP fusoprotein in place of the native NOP²¹. Based on a large body of evidence coming from preclinical studies performed using the above tools, NOP receptor agonists have been proposed as innovative drugs for treating anxiety, drug abuse, cough, and urinary incontinence^{3, 22, 23}, while NOP selective antagonists as novel treatments for Parkinson disease²⁴ and depression²⁵

(see Table 2). For some of these indications of NOP ligands preclinical findings were confirmed by clinical studies that are briefly described in the following section.

NOP receptor ligands and potential therapeutic indications (non-pain studies)

i) Cardiovascular dysfunction - The NOP partial agonist SER100 has been designed and tested in preclinical studies as an aquaretic ^{26 27}. The compound also elicits hypotensive and vasorelaxant actions that are more pronounced in spontaneously hypertensive rats ²⁸. SER100 displayed an acceptable safety profile in patients with isolated systolic hypertension and produced significant lowering of systolic blood pressure ²⁹. This proof of concept study generated encouraging results for the further development of NOP receptor (partial) agonists for the treatment of hypertension.

ii) Micturition - A series of preclinical studies reviewed in ³⁰ demonstrated that N/OFQ elicits profound inhibitory effects on the micturition reflex in rats. Based on this evidence the effects of N/OFQ were evaluated in patients suffering from overactive bladder. A first proof of concept study ³¹, a second randomized, placebo controlled, double blind study ³², and a third study in which 1 mg N/OFQ for 10 days was given intravesically once a day for 10 days ³³ demonstrated a large increase in mean bladder capacity and volume threshold for the appearance of detrusor hyperreflexia only in patients assigned to the N/OFQ group. Interestingly, recent findings demonstrated that NOP receptor expression in nerve fibres within the bladder suburothelium is increased by several fold in detrusor overactivity patient specimens ³⁴. Thus these findings strongly support the use of NOP receptor agonists as a therapeutic approach for controlling detrusor overactivity incontinence.

With the aim of increasing N/OFQ potency and duration of action different chemical modifications were combined in the same molecule generating Rec 0438 ⁶. Rodent studies reviewed in ³⁵ demonstrated that Rec 0438 behaves as potent and selective NOP agonist and is able to mimic in vivo N/OFQ actions producing longer lasting effects. This has been confirmed in a series of experiments performed in Recordati laboratories (P Angelico, personal communication) in rats where Rec 0438 produced a dose dependent and SB-612111 sensitive increase of the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition.. A Phase I clinical study with Rec 0438 was recently completed in normal subjects as well as in patients with an overactive bladder, demonstrating that intravesical infusion of Rec 0438 is well tolerated and there is no leakage to the systemic circulation. A Phase II study is now ongoing; if the

encouraging results obtained with N/OFQ are confirmed with Rec 0438 a novel possibly well tolerated and highly effective option will be soon available for treating these patients.

iii) Respiratory system and cough - N/OFQ has a potential role to play in the aetiopathogenesis of asthma where its immunomodulatory and bronchodilatory actions in an animal model of asthma offer advantages over beta-adrenergic agonist and steroid combinations. The animal data perfectly match observational studies in ex vivo human tissue and tissues samples^{36 37}. Use of nebulized N/OFQ is an interesting possible indication. N/OFQ demonstrated antitussive effects in experimental cough models in Guinea pigs and cats via selective stimulation of the NOP receptor³⁸. With the aim of identifying a drug like molecule for this indication, Schering-Plough researchers developed a large series of non-peptide NOP agonists³⁹⁻⁴² and SCH 486757 was selected for further development. After oral administration, SCH 486757 dose-dependently suppressed cough in guinea pigs and cats⁴³. SCH 486757 was also evaluated in patients with subacute cough in comparison with placebo and codeine. However there were no significant changes in average cough severity scores from baseline to treatment either between SCH 486757 and placebo or between codeine and placebo. There were some hints of possible limited antitussive efficacy with SCH 486757 but the dose used was limited by its tendency to produce somnolence⁴⁴. Development of NOP receptor agonists as antitussive agents can only advance after finding molecules with a therapeutic window larger than SCH 486757. It is worthy of mention at this regard that are now several non peptide NOP agonists (such as MCOPPB and AT-403) available that are more potent and much more selective than SCH 486757 (see¹¹ for a direct comparison of the basic pharmacological profile of these molecules).

iv) Antidepressant actions - In the mouse forced swimming test, NOP receptor antagonists produced antidepressant like effects⁴⁵. This initial finding was later confirmed using different antagonists, animal species, and behavioral assays. Converging evidence has been obtained in genetic studies since NOP(-/-) mice and rats displayed an antidepressant like phenotype²⁵. More recent studies investigating lipopolysaccharide induced depression⁴⁶ and learned helplessness⁴⁷ in mice confirmed previous findings and further corroborated the antidepressant like activity of NOP antagonists. Researchers at Eli Lilly discovered the potent and selective NOP receptor antagonist LY2940094⁴⁸ that displayed antidepressant-like behavioral effects in the forced-swimming test in mice, an effect absent in NOP(-/-) animals⁴⁹. This compound was used in a proof of concept, double-blind, placebo-controlled trial that evaluated its therapeutic potential as a novel oral medication for the treatment of patients with major depressive disorder. Once daily oral dosing of

LY2940094 at 40 mg for 8 weeks vs placebo provided evidence for an antidepressant effect based on the change from baseline to week 8 in the GRID-Hamilton Depression Rating Scale-17 item total score. LY2940094 was safe and well tolerated⁵⁰. Preclinical findings were confirmed by this first human data providing evidence that blockade of NOP receptor signaling represents a promising strategy for the treatment of depression.

NOP receptor ligands and pain

As far as pain transmission is concerned the effects of N/OFQ and NOP selective agonists are complex depending on multiple factors including: i) dose, at very low doses (pmol range) intrathecal N/OFQ facilitates pain transmission in the spinal cord while at higher doses (nmol range) robust antinociceptive effects have been consistently reported; ii) site of action, in rodents N/OFQ elicits antinociceptive effects both after local and spinal injection while intracerebroventricular N/OFQ promotes a pronociceptive action and is able to counteract the analgesic effect of opioid drugs such as morphine; iii) animal species, as mentioned before at supraspinal level N/OFQ has a pronociceptive action in mice and rats, however recent evidence⁵¹ demonstrated that in non-human primates an antinociceptive effect is measured in response to supraspinal N/OFQ; iv) pain modality, non-peptide NOP agonists (e.g. Ro 65-6570) given systemically do not affect nociceptive pain while they display antinociceptive effects in models of inflammatory and neuropathic pain (for related references see^{52, 4, 53}). This complex picture clearly made the development of selective NOP agonists as analgesics difficult. However, consistent results have been reported in the literature regarding the analgesic potential associated to the simultaneous activation of NOP and opioid (particularly mu) receptors. In rodents spinal N/OFQ increased systemic and spinal morphine analgesia^{54, 55}. Moreover, isobolographic analysis demonstrates a supraadditive interaction between NOP and mu activation at the spinal level in the rat chronic constriction injury model⁵⁵ and subthreshold doses of morphine and Ro 64-6198 elicited robust analgesic effects in the mouse hot plate test when given together⁵⁶. These rodent findings were confirmed and corroborated by studies performed in non-human primates where spinal N/OFQ⁵⁷ or Rec 0438⁵⁸ strongly potentiated morphine analgesia and systemic NOP and opioid receptor agonists produced supraditive analgesic effects⁵⁹. Collectively this evidence strongly suggests that mixed NOP/opioid receptor agonists may have therapeutic potential as novel analgesics. Some compounds with the above pharmacological profile have been reported in the literature including the peptides [Dmt¹]N/OFQ(1-13)-NH₂⁶⁰ and its tetrameric derivative PWT-[Dmt¹]N/OFQ(1-13)⁶¹, DeNo (a dermorphin-N/OFQ chimeric peptide)⁶² and some non-peptide compounds SR16435,

SR16507, and SR14150 (reviewed in ⁴) that display variable potency and efficacy at NOP and mu receptors. Moreover, BU08028 is a buprenorphine derivative that displayed high affinity for NOP and opioid receptors ⁶³. After spinal administration in mice BU08028 was more potent than morphine in attenuating nerve injury-induced tactile allodynia and inflammation-induced thermal hyperalgesia; antagonist experiments demonstrated the involvement of NOP and opioid receptors in the action of BU08028 ⁶⁴. BU08028 has also been evaluated in non-human primates where after systemic administration it produced a dose dependent and long-lasting antinociceptive and antiallodynic effects. These effects were blocked by both mu and NOP receptor antagonists. Importantly, BU08028 at antinociceptive doses did not cause respiratory depression and did not promote physical dependence ⁶⁵. Collectively these findings provide a strong rationale for mixed NOP/opioid receptor agonists as analgesic drugs.

Cebranopadol preclinical studies

In order to identify and optimize novel compounds acting as mixed NOP/opioid selective agonists a large series of structure activity studies were performed by Grunenthal researchers ^{66, 67}. These efforts led to the identification of cebranopadol (trans-6' -fluoro-4' -9' -dihydro-N,N-dimethyl-4-phenyl-spiro[cyclohexane-1,1' (3' H)-pyrano[3,4-b]indol]-4-amine, see chemical structure in Figure 1). An alternative, robust and easy method for the synthesis of cebranopadol has also been recently reported in literature ⁶⁸.

In receptor binding studies cebranopadol displayed high affinity for NOP (0.9 nM) and opioid (0.7, 2.6, and 18 nM for mu, kappa and delta, respectively) receptors. In agonist stimulated [³⁵S]GTPγS binding experiments cebranopadol displayed high potency and efficacy at NOP and mu receptor while it showed reduced potency at the delta and reduced potency and efficacy at the kappa receptors ⁶⁹. This basic pharmacological profile has been confirmed in an independent study performed measuring calcium mobilization in cells co-expressing NOP or classical opioid receptors and chimeric G proteins ⁷⁰. The same study also evaluated the ability of cebranopadol to promote NOP and mu receptor interaction with G protein and β-arrestin2. This study demonstrated that cebranopadol behaves as a biased agonist toward G protein; the degree of the bias was modest for the mu receptor while very large for the NOP receptor ⁷⁰. G protein biased agonism (see box 1) is clearly an advantageous feature for a mu receptor ligand; in studies performed in β-arrestin2 knockout mice the analgesic properties of morphine are strongly associated with G protein

dependent signaling ⁷¹ while tolerance liability ⁷², respiratory depression and constipation ⁷³ are more dependent on β -arrestin2. This suggests that mu receptor agonists biased toward G protein may be developed as safer analgesics ⁷⁴. Preclinical ⁷⁵ and clinical findings ^{76 77 78} recently obtained with the G protein biased agonist oliceridine (alias TRV130) seem to confirm this proposal. In contrast, the possible biological implications of the large G protein bias displayed by cebranopadol at NOP receptors is at present unknown. Indeed, functional selectivity studies in the NOP receptor field are still in their infancy ^{79 80 11 81}; thus further investigations e.g. evaluation of the actions of N/OFQ and NOP selective ligands in mice knockout for β -arrestin2 and discovery and testing of NOP ligands with large bias toward G protein and toward β -arrestin2 are needed to understand the possible role of functional selectivity in the development of NOP agonists as analgesics.

The pharmacokinetic parameters of cebranopadol in rats have been investigated in detail (see table 3 in ⁶⁹). Cebranopadol was extensively distributed with a half-life of 4.5 h; its oral bioavailability was of 13–23%. Cebranopadol displayed dose-dependent and potent antinociceptive effects both when given per os and intravenously in models of nociceptive, inflammatory and neuropathic pain in mice and rats ^{67, 69}. Compared to morphine, cebranopadol was more than 100 fold more potent and produced longer lasting effects ^{67, 69}. These results were confirmed in other laboratories ⁷⁰ and extended to chemotherapy-induced neuropathic pain ⁸², Freund's adjuvant induced arthritic pain ⁸³, and to painful conditions of the trigeminal territory ⁸⁴. Importantly the antinociceptive action of cebranopadol are due to the simultaneous activation of NOP and opioid receptors as consistently demonstrated in antagonist studies. Both naloxone and NOP selective antagonists (J-113397 ^{69 83}, or SB-612111 ⁷⁰) were able to counteract the effects of cebranopadol.

Interestingly, when compared to morphine, that displayed similar potency in various assays, cebranopadol was more potent in models of chronic neuropathic than acute nociceptive pain ⁶⁹. This has been confirmed by Rizzi et al where fentanyl displayed similar potency in the tail withdrawal and formalin test, the NOP selective agonist Ro 65-6570 was active in the latter but not the former assay, and cebranopadol was active in both the assays but was approximately 10 fold more potent in the formalin test ⁷⁰. Collectively these findings are in line with previous results briefly discussed in the introduction suggesting that NOP receptor agonists are much more efficacious in models of inflammatory and neuropathic pain than nociceptive pain (also reviewed in ^{53 4}). This may be explained, at least in part, by an upregulation of NOP receptors in dorsal root ganglia ^{85, 86} and nerve fibres ³⁴ which has been reported during neuropathic and inflammatory conditions.

A separate study investigated the site of action of cebranopadol; experiments performed in different models of chronic neuropathic pain demonstrated that cebranopadol exerts potent and efficacious antihyperalgesic, antiallodynic, and antinociceptive effects after local/peripheral, spinal, and supraspinal administration ⁸⁷.

These initial studies demonstrated that cebranopadol not only promoted highly potent and efficacious analgesic effects in various pain models but also displayed a favorable side effect profile. Cebranopadol did not modify animal performance in the rotarod test, even at doses several fold higher than its maximal analgesic dose ^{69, 70} while a small but consistent reduction of animal performance on the rod was already measurable at maximal analgesic doses of morphine ⁶⁹. Disruption of motor behavior is a typical feature of selective NOP agonists at full doses and for this reason the dose response curve to Ro 65-6570 in the formalin assay could not be completed ⁷⁰. Thus in terms of ratio between disruption of motor activity and analgesic doses, cebranopadol is not only superior to NOP selective agonists but also to classical opioid drugs. Another dose limiting and potentially life-threatening acute side effect of opioids is respiratory depression. This has been investigated in detail in a recent study in which antinociceptive and respiratory depressant effects of cebranopadol and fentanyl were compared in rats ⁸⁸. At maximally effective analgesic doses, cebranopadol did not produce significant effects on arterial carbon dioxide tension while the ratio of fentanyl potencies for increasing carbon dioxide tension and for analgesic effects were less than 3. Importantly, the NOP antagonist J-113397 potentiated the respiratory depressant effects of cebranopadol that were, as expected, fully sensitive to naloxone ⁸⁸. These findings suggest that NOP activation by cebranopadol counteracts mu receptor dependent respiratory depression making the therapeutic index (in terms of analgesia vs respiratory depression) larger for cebranopadol than for the mu selective agonist fentanyl.

Among the issues associated with the use of opioid drugs in chronic pain, analgesic tolerance and the development of physical dependence are perhaps the most important. As far as tolerance is concerned, it is worthy of note that 26 days were needed to obtain complete tolerance to the analgesic action of cebranopadol while under the same experimental conditions an equieffective dose of morphine became completely inactive after only 11 days of treatment ⁶⁹. The reasons underlying the reduced tolerance liability of cebranopadol are far from obvious. It can be speculated that, since tolerance is a function of the amount of receptor stimulation and since the analgesic action of cebranopadol derives from the activation of two different receptors (NOP and the mu), is somewhat expected that tolerance liability of cebranopadol is lower than that of morphine whose

analgesic effects solely depends on mu receptor activation. However it should be borne in mind that NOP receptor signaling may play a role in controlling the development and/or expression of tolerance to the analgesic action of opioid drugs and at this regard conflicting results have been reported in the literature. A single study reported beneficial effects of NOP receptor stimulation on morphine tolerance⁸⁹ while several studies reported beneficial effects of NOP receptor blockade^{13, 90-93}. Clearly further studies are needed to understand the mechanism(s) responsible for the reduced tolerance liability of the analgesic action of cebranopadol. As far as physical dependence is concerned, this aspect has been specifically evaluated in a recent study⁹⁴. In a naloxone-precipitated withdrawal assay, mice treated with morphine within the analgesic dose range displayed clear withdrawal symptoms while animals treated with cebranopadol (even exceeding the analgesic dose range) showed very little withdrawal symptoms. Similar results were obtained in rats both investigating spontaneous and naloxone-precipitated withdrawal⁹⁴. These results suggest a lower potential of cebranopadol to produce physical dependence in rodents than morphine and the authors of the study speculated that this may derive from the ability of cebranopadol to stimulate the NOP receptor. This is certainly an attractive hypothesis that should be validated experimentally by testing cebranopadol in similar experiments in the absence and presence of selective NOP receptor antagonists and/or in wild type and NOP(-/-) mice or rats.

Finally, very recent studies^{95 96} demonstrated that cebranopadol is worthy of development as treatment for drug addiction. Cebranopadol prevented cocaine self-administration, escalation of intake and reinstatement in rats. Importantly this action of cebranopadol derives from its ability to simultaneously activate NOP and mu receptors being prevented only by the coadministration of SB-612111 (NOP antagonist) and naltrexone (opioid antagonist).

Cebranopadol clinical studies

As previously discussed in an editorial in this journal⁹⁷, cebranopadol is now in clinical development for analgesic indications. According to a clinicaltrial.org search performed at the end of 2017, 9 studies on cebranopadol have been completed in patients suffering from different painful conditions including diabetic polyneuropathy (3), bunionectomy, cronic low back pain, osteoarthritis of the knee (2), and cancer (2); some of these are outlined in Table 3. The following section summarizes the published information relative to these trials.

The basic pharmacokinetic properties of cebranopadol were assessed in phase I and phase II clinical trials ⁹⁸. After oral administration, cebranopadol displayed a late time to reach maximum plasma concentration (4-6 h), a long half-life (14-15 h), and a terminal phase half-life in the range of 62-96 h. After multiple once-daily dosing in patients, an operational half-life of 24 h was calculated. In summary, cebranopadol displayed basic pharmacokinetic features compatible with a once-daily regimen that is a convenient treatment option for patients with chronic pain ⁹⁸, this is an advantage over the commonly used analgesics in this patient population.

A phase 1 clinical trial was performed aimed at the quantification of cebranopadol respiratory effects in healthy subjects ⁹⁹. 0.6 mg of cebranopadol per os induced typical opioid-like effects including miosis, analgesia, and respiratory depression. However, compared to its analgesic effects the respiratory depression induced by cebranopadol was moderate and short lasting. This is in line with preclinical studies that demonstrated in receptor antagonist experiments a protective role of NOP receptor stimulation on mu receptor induced respiratory depression ⁸⁸. Thus these findings suggest that compared to classical opioid drugs cebranopadol has lower propensity to depress respiratory function.

Christoph et al ¹⁰⁰ conducted the first phase II, randomized, double-blind, placebo- and active-controlled trial, evaluating the analgesic efficacy, safety, and tolerability of cebranopadol in patients with low back pain. This is a common pain phenotype with both nociceptive and neuropathic components fitting well with the pre-clinical profile described above. Patients were treated for 14 weeks with cebranopadol (0.2, 0.4, or 0.6 mg) once daily, tapentadol (200 mg) twice daily, or placebo. Cebranopadol and tapentadol demonstrated analgesic efficacy, with statistically significant and clinically relevant improvements over placebo. Beneficial effects of cebranopadol were also reported regarding physical functioning and sleep disturbance. Cebranopadol treatment was safe, with higher doses leading to higher treatment discontinuations mostly during the 2 week titration phase. The incidence rate of most frequently reported adverse events (constipation, dizziness, fatigue, hyperhidrosis, nausea, vomiting, and somnolence) during maintenance phase was $\leq 10\%$. Interestingly and in line with preclinical findings ⁹⁴, discontinuation of cebranopadol after 14 weeks of treatment was not followed by clear withdrawal symptoms and only few cases of mild to moderate withdrawal symptoms were reported. Therefore, slow tapering off of the cebranopadol treatment seems not required. This study demonstrated that cebranopadol is a new drug candidate for the treatment of patients with low back pain. Moreover, further studies aimed at optimizing the

titration scheme to find the optimal dose for each patient may probably contribute to increase cebranopadol tolerability.

From the clinical trials register it is possible to extract some highlight data in (i) diabetic neuropathy and (ii) cancer pain. In patients with diabetic neuropathy 0.6 mg of cebranopadol produced significant analgesia when compared to placebo. In cancer pain 0.2-1 mg of cebranopadol (by patient titration) produced significant analgesia (CORAL trial). This study was extended to 26 week safety (CORAL XT); side effect profile of a typical opioid was reported.

Conclusions

Current opioid based analgesic options are effectively limited to activation of mu receptors with drugs such as morphine, fentanyl or with pharmacokinetic advantage; remifentanyl. Despite their utility there are a wide range of side effects including respiratory depression and the induction of tolerance. Tolerance can lead to a vicious circle of dose escalation and increasing side effects. In the ~20 year period since formal identification of N/OFQ as the endogenous ligand for the NOP receptor and a role in pain processing, data confirming interaction with mu are emerging. Indeed, activation of NOP and mu receptors produces analgesia at the expense of reduced side effects. This evidence coming from animal experiments has been confirmed in the first generation clinical studies with cebranopadol. Clearly further clinical investigation is needed to firmly establish the place in therapy of mixed NOP/opioid agonists as innovative analgesics. It is however worthy of mention that in just two decades the research work in the field of N/OFQ-NOP receptor system has been translated into significant clinical development, with cebranopadol, and important indications in particularly challenging pains like those of neuropathic origin.

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Table 1. NOP receptor ligands

compound name	chemical nature	pharmacological activity	references
N/OAQ	peptide	endogenous agonist	1, 2
Rec 0438	peptide	full agonist	6
Ro 65-6570	non peptide	full agonist	8
Ro 64-6198	non peptide	full agonist	9
MCOPPB	non peptide	full agonist	10
AT-403	non peptide	full agonist	11
SER 100	peptide	partial agonist	5
UFP-101	peptide	antagonist	7
J-113397	non peptide	antagonist	12
SB-612111	non peptide	antagonist	13
C-24	non peptide	antagonist	14
LY2940094	non peptide	antagonist	⁴⁸

Table 2. Therapeutic indications for NOP ligands

Therapeutic indication	NOP ligand	Pivotal study/review	Clinical evidence
anxiety	agonists	101	no
drug abuse	agonists	102 103	no
cough	agonists	104	yes ⁴⁴
overactive bladder	agonists	30	yes ³¹⁻³³
hypertension	partial agonists	28	yes ²⁹
depression	antagonists	25, 45	yes ⁵⁰
Parkinson disease	antagonists	105	no
memory deficits	antagonists	106	no
pain	mixed NOP/opioid agonists	69	yes ¹⁰⁰

Table 3: Significant clinical trial information.

Trial	Started;CTR entry	Pain type	#Patients	Primary End Point	Secondary End Point
KF6005/08	27/9/13;27/4/16	Neuropathic-Diabetes	314	Pain Int vs Placebo Cebranopadol 600µg ¹ SIGNIFICANT	None
KF6005/07	29/10/13;30/9/16	Cancer	200	Morphine rescue Cebranopadol 200-1000µg by patient titration ² SIGNIFICANT	#Patients with relevant pain reduction Similar # to Morphine group (no stats)
KF6005/09	18/12/13;29/1/17	Cancer – 26w safety patients completed 6005/07	76	Incidence TEAE 64/76 (no stats)	(i) Intensity TEAE 42%-serious;83%-non serious ³ (ii) Change baseline pain NRS 0.8 (0=no pain; no stats)
KF6005/06	30/11/12;25/2/16	Chronic low back	637	(i) Change baseline pain NRS Cebranopadol 200/400/600µg Vs Placebo ⁴ ALL SIGNIFICANT	None

TEAE

¹, Diabetes trial – opioid typical AE. Cebranopadol 600/Placebo group 6.5/3.2 and 84/69% incidence serious and non-serious AE.

², Cancer trial – tumour progression and opioid typical AE. Cebranopadol/Morph group 21.5/18.0 and 80/79% incidence serious and non-serious AE.

³, Cancer trial – death, tumour progression and opioid typical AE.

⁴, Back pain trial – opioid typical AE. Cebranopadol 600/Placebo group 1.6/1.6 and 90/63.5% incidence serious and non-serious AE.

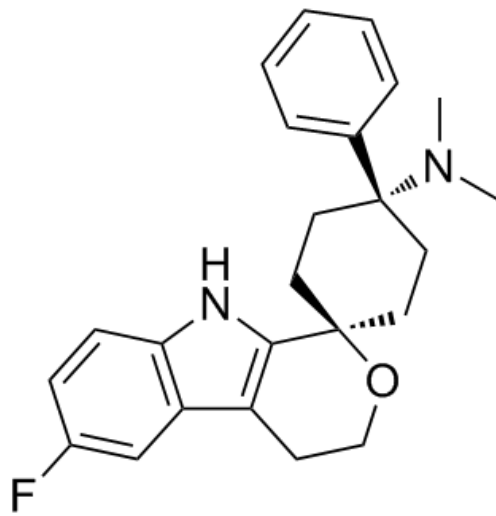


Figure 1, chemical structure of cebranopadol.

Box-1: Functional selectivity or biased agonism

Receptor selectivity is particularly important in drug design and as a concept simply describes the propensity of a ligand to bind exclusively to the desired target; a ligand with 100 fold selectivity will produce off target effects at 100x the dose required for its therapeutic indication. In other words receptor selectivity indicates the ability of a synthetic ligand to discriminate some of the biological actions of a receptor family based on the receptor type involved. In the past more effective and/or better tolerated drugs have been generated by identifying highly selective receptor ligands i.e. β_1 selective antagonists, β_2 selective agonists, H_2 selective antagonists, and so on. Recent findings indicated that receptors may signal via activation of different effectors, i.e. G proteins and arrestins, and that synthetic agonists for a given receptor may display different ability to stimulate one effector pathway (e.g. G protein) vs the other (e.g. arrestin). Functional selectivity also known as biased agonism describes the propensity of an agonist to promote signaling via selective activation of one signaling pathway. Thus in the future more effective and/or better tolerated drugs can be generated not only based on the receptor type involved (receptor selectivity) but also by selecting only some specific pathways among those associated to the activation of that specific receptor type (functional selectivity). To give a practical example, as mentioned in the text, there is a large and elegant set of experimental evidence to indicate that the analgesic response to opioids depends on mu receptor / G protein signaling while some important side effects of these drugs (respiratory depression, constipation, tolerance) mainly depend on mu receptor / arrestin signaling (see the following scheme). Thus mu receptor agonists biased toward G protein might maintain the analgesic effects of opioids but display reduced respiratory depression, constipation and tolerance liability therefore acting as safer analgesics.

