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Commentary
On subclasses of opioid analgesics

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Abstract

Background:

The history of discovery of analgesic drugs has followed a trajectory from original serendipitous discovery of plant-derived substances to laboratory creation of customized molecules that are intentionally designed to interact with specific receptors of neurotransmitters involved in either the transmission of the pain signal or the attenuation of such a signal. The drugs most recently developed have been designed to provide incremental greater separation between pain relief and adverse effects. The result has been drugs that have individualized pharmacodynamic and pharmacokinetic characteristics that represent specific advances in basic science and translate into unique clinical profiles. Several of the drugs include non-opioid components. They retain some of the features of opioids, but have distinct clinical characteristics that differentiate them from traditional opioids. Thus they defy simple classification as opioids.

Scope:

A summary is provided of the development of the modern view of multi-mechanistic pain and its treatment using analgesics that have multi-mechanisms of action (consisting of both opioid and non-opioid components). Descriptions of examples of such current analgesics and of those that have pharmacokinetic characteristics that result in atypical opioid clinical profiles are given.

Findings:

By serendipity or design, several current strong analgesics have opioid components of action, but have an additional non-opioid mechanism of action or some pharmacokinetic feature that gives them an atypical opioid clinical profile and renders them not easily classified as classical opioids.

Conclusion:

An appreciation that there are now opioid analgesics that differentiate from classical opioids in ways that defy their simplistic classification as opioids suggests that recognition of subclasses of opioid analgesics would be more accurate scientifically and would be more informative for healthcare providers and regulators. This would likely lead to positive outcomes for the clinical use and regulatory control of the current drugs, and provide direction/strategy for the discovery of new drugs.

Introduction

The original opiate strong analgesics, including morphine and codeine, are extracts of the opium poppy *Papaver somniferum*, so it is tempting to assume that any drug that has any component of similar mechanism of action must have identical characteristics. However, it is now known that there are other plants that have evolved opioid-like analgesics (e.g., the mitragynines) that produce opioid-like analgesia, but with a greater separation between therapeutic efficacy and some adverse effects[1]. It is therefore reasonable to expect that modern drug discovery, as Nature, could design molecules with properties more complex than the simple opiates.

Methods: source of information

The author was a team leader in analgesics drug discovery, conducted preclinical studies on novel analgesics, and serves on advisory boards related to development of analgesic drugs. The material herein is known from first-hand experience and is supplemented by literature (PubMed) searches of the specific opioids mentioned as examples. Additional papers were identified from the reference lists of retrieved publications.

Review and analysis

Prior to 1986, pain management as a goal independent of the cure of the underlying medical condition was in its infancy and not yet emerged as a healthcare discipline[2]. Opioids were legal, but severely restricted in many countries and legal, but not culturally well accepted, in others[3–8]. The introduction of the WHO stepwise approach ('ladder') in 1986 offered a simple and conservative treatment algorithm for pain control. It was based on the level of pain (e.g., mild, moderate, or severe) and all opioids were classified as either weak or strong. Although of great benefit at the time[9], hallmark advances in knowledge about pain[10] have revealed that pain is multi-mechanistic – and therefore that it is most effective to treat pain by matching the analgesic's mechanism of action with the pain's underlying (patho)physiology[11–13].

The earliest modern understanding of opioid pharmacology emerged in the 1970s with the discovery of opioid receptors and the endogenous opiate-like compounds (opioids), and their involvement with afferent pain-transmitting pathways[14]. For the subsequent several decades, synthetic opioids were explicitly designed to mimic the natural opiates and, therefore, excluding some minor differences in preference for the opioid receptor subtypes (μ, δ, and κ), were all basically the same. During this period, it was not unreasonable to think of opioids as a 'class' of analgesics, with only nuances of differences in clinical attributes. However, recent years have given rise to four major changes in the way that pain – and analgesia – is perceived:

(1) Discovery that in addition to the previously known afferent ('ascending') pain-transmission pathways there are powerful non-opioid efferent ('descending') pain-modulatory pathways[15,16]. The neurotransmitters of these pathways are monoamines (e.g., norepinephrine and serotonin).
(2) Discovery of transporter proteins, e.g., the ABC transporter P-glycoprotein 1 (P-gp) (*mdrl1*) and the organic ion transporter (OAT), which determine the brain–plasma concentration gradient, and differentially increase or decrease BBB (blood brain barrier) passage of individual opioid analgesics[17].
(3) Many pains involve more than one physiological process, so treatment using analgesics of only one mechanism results in sub-optimal pain relief and, if the dose is raised in an attempt to 'chase' the pain, unnecessary adverse effects. Therefore, there are advantages to multi-mechanistic (opioid plus non-opioid) agents[12].
(4) Consolidation of the well known facts that endogenous opioid peptides bind to different sites on opioid receptors than do exogenous opioid ligands[18] and that subsets of G proteins differentially mediate analgesic (antinociceptive) effects of different opioids[19] into the new construct of 'biased agonism' in second messenger transduction[20].

That these advances argue against the lumping of modern analgesics into the same clinical class is illustrated by the following examples.

The importance of BBB mechanisms

Loperamide

Loperamide (e.g., Imodium*) is used clinically to treat diarrhea. Although it has very high binding affinity and intrinsic activity (as measured by GTPγS binding) at opioid receptors, the efflux transporter P-gp prevents brain accumulation of loperamide or its metabolite *N*-desmethyl-loperamide, thereby preventing expression of its central opioid effects[21]. This is demonstrated by loperamide-induced effects revealed after inhibition of P-gp using quinidine or in P-gp knockout (KO) rats[22].

Oxycodone

At the opposite extreme is oxycodone, which displays an entirely different clinical and abuse profile. Surprisingly, oxycodone's binding affinity to opioid receptors is an order of magnitude less than morphine's[23] (oxycodone's metabolites contribute little to its analgesic effect due either to low plasma levels, e.g., oxymorphone, or to poor BBB penetration, e.g., noroxycodone, noroxymorphone). However, oxycodone is actively transported into brain by OCT (organic ion transporter)[24], resulting in greater oxycodone concentration in the brain than in plasma (about two-fold)[25], which is the opposite of morphine and other opioids. This differentiation likely contributes to oxycodone's appeal as a drug of abuse.

Thus, the central nervous system activity and the abuse potential of three seemingly similar opioids are dramatically different due to exclusion, inhibition, or enhancement of passage into the brain (loperamide, morphine, and oxycodone, respectively).

*Imodium is a registered trade name of McNEIL-PPC, Inc (Ft Washington, PA).

The importance of multi-mechanisms

Buprenorphine

Buprenorphine is an example of an opioid analgesic that produces analgesia through a combination of mechanisms. It was first synthesized in the late 1960s as an analog of the poppy-derived opiate thebaine and possesses high binding affinity for opioid receptors[26,27], including those in the human brain[28]. Buprenorphine shares some of the general preclinical[29] and clinical attributes of traditional opioids such as morphine and fentanyl[30], but differs by having slow receptor dissociation kinetics, a biphasic (bell or inverted U shaped) dose–response relation in some animal models[31,32] and a ceiling effect on respiratory depression in humans[33]. In agreement with early findings that morphine and buprenorphine induce analgesia through some shared, but some distinct, signal transduction mechanisms[34], significant differences have been found[35,36]: supraspinal (intracerebroventricular) administration of naloxone or PTX (pertussis toxin) attenuates the antinociception induced by morphine and fentanyl, but not by buprenorphine; in contrast, supraspinal G_z-antisense does not alter morphine- or fentanyl-induced antinociception, but it reduces buprenorphine-induced antinociception, and supraspinal okadaic acid produces a mixed low-dose attenuation, high-dose enhancement of buprenorphine-induced antinociception, whereas it has no effect on morphine- or fentanyl-induced antinociception. Overall, the results suggest the existence of a novel non-opioid supraspinal naloxone-, PTX-, and NOP (nociceptin/orphanin FQ peptide)-insensitive, G_z- and Ser/Thr-sensitive component to buprenorphine's mechanism of analgesic action, and thus provide mechanistic explanation for buprenorphine's unique preclinical and clinical profiles. Describing it as no different from a conventional opioid would be inaccurate.

Tramadol

Should tramadol be classified as an opioid? There is no simple yes or no answer to this question. An esteemed researcher, who isolated the enkephalins and was one of the pioneers of opioid pharmacology, emphatically told this author that it should not be (CPDD College on Problems of Drug Dependence meeting, Florida 1991). Based on animal and human studies, tramadol has been shown to produce its analgesic effect through two mechanisms[37]. One of the two mechanisms involves weak binding affinity for μ-opioid receptors, which is estimated to be about 6000 times lower than the binding affinity of morphine and about the same affinity as dextromethorphan. Tramadol's O-desmethyl metabolite (M1) binds to μ-opioid receptors with greater affinity than does the parent compound and it is presumably responsible for the opioid component. However, in most animal tests and in human clinical tests, the analgesic effect of tramadol is only partially blocked (<50%) by the opioid antagonist naloxone, suggesting that there is a significant contribution of a non-opioid mechanism[37]. The non-opioid component of analgesic mechanism of analgesic action is related to inhibition of the neuronal reuptake of norepinephrine and 5-HT. Neuronal reuptake of these monoamines is associated with analgesia[38]. Tramadol might also have some peripheral or anti-inflammatory action. There are reports that tramadol analgesia can be produced in the periphery via activation of singular opioid receptors and that such analgesic effects might be particularly prominent in painful inflammatory conditions[39]. In osteoarthritis, the concentration of tramadol in synovial fluid is more than half its plasma concentration and significantly reduces the amount of substance P[40]. It has been suggested that reduced substance P in the joint space could be due to an opioid agonist action at peripheral opioid receptors on 1° sensory afferents within the joint (an action more prominent in inflammatory conditions) or to monoamine action, since norepinephrine inhibits secretion of proinflammatory mediators in the synovial tissue of patients with inflammatory conditions like osteoarthritis.

In addition to the individual contributions made by the opioid and non-opioid components, there is an interaction between the two mechanisms of action. Specifically, the (+) enantiomer of tramadol binds to μ-opioid receptors and inhibits the neuronal reuptake of 5-HT more potently than does the (−) enantiomer, whereas the (−) enantiomer inhibits neuronal reuptake of norepinephrine more potently than does the (+) enantiomer. Each enantiomer individually produces centrally mediated (spinal) antinociception and, in several tests, the combination of the enantiomers is more potent than either enantiomer alone – that is, the mechanisms of action interact synergistically in inhibiting pain[41]. Importantly, the interaction is less than synergistic, or even less than additive, in several tests of side-effects. Thus, the clinical profile of tramadol results from the fortuitous combinations and interactions of its component parts. It is this duality of mechanism of analgesic action that forms the basis of tramadol's clinical attributes. The co-existence of both opioid and non-opioid mechanisms of tramadol sends competing and conflicting messages to the brain of drug abusers. That is, it is simultaneously inhibitory (the opioid component) and excitatory (the non-opioid component), which reduces 'liking'[42].

Tapentadol

The 3-D molecular shape of tapentadol is very different from that of tramadol, which manifests itself in the different pharmacological profiles of the two analgesics. The preference of the pentyl chain in tapentadol compared

with analogs containing the hexyl chain was not predictable by *in silico* tools and does not fit conventional opioid structure–activity relationships. The chemical distinction from tramadol results in reduced molecular complexity and stronger CNS functional activity that is primarily derived from its two intrinsically synergistic mechanisms of analgesic action. Unlike tramadol, tapentadol is a single molecule, with no analgesically active metabolites. Although it has lower binding affinity at opioid receptors, the functional activity of tapentadol in the agonist-stimulated GTPγS binding assay in cells recombinantly expressing human μ-opioid receptors is significantly higher[43,44]. The contribution of noradrenergic activity and the lack of relevant serotonergic activity has been demonstrated in a number of animal pain models[45]. A recent study demonstrated that tapentadol's two mechanisms of action show a pronounced intrinsic synergy with respect to antinociceptive activity[46]. Indirect evidence was also obtained for an intrinsic antihyperalgesic synergy in a spinal nerve ligation (neuropathic) model. Tapentadol is thus the only drug for which two mechanisms of analgesic action have been demonstrated to produce synergistic analgesic effect within a single molecule. The synergistic interaction between tapentadol's mechanisms of analgesic action, and the lack of synergistic interaction on gastrointestinal transit[47] produces better analgesic efficacy with better gastrointestinal tolerability[48–50]. The novel features of tapentadol's mechanism of action have led several authors to suggest that tapentadol should be considered in a new pharmacological class of drugs[51].

Cebranopadol

It is increasingly appreciated that most pain is multimechanistic and is best treated by complementary multimechanistic mechanisms of action, and this concept is now beginning to be applied as a general drug discovery principle of 'designed multiple ligands'[52,53], and this approach was used in the design of tapentadol. Cebranopadol is a new analgesic that combines agonist action at opioid receptors and also at NOP receptors[54]. The NOP agonist action is credited with contributing to cebranopadol's antihypersensitive effect. Development of analgesic tolerance in a neuropathic pain (chronic constriction injury) model is delayed compared with an equianalgesic dose of morphine and, unlike morphine, cebranopadol does not disrupt either respiration or motor coordination at doses within the analgesic dose range. If these properties are confirmed in clinical trials, cebranopadol, through its combined agonism at NOP and opioid receptors, would represent yet another subclass of opioid analgesics.

Enkephalinase inhibitors

Although not direct-acting opioids, the pharmacologic effects of inhibitors of the enzymes that degrade the endogenous opioids (e.g., enkephalins) produce effects that mimic those of exogenous opioids, since the opioid drugs bind to the receptors that transduce the effects of the endogenous opioids. The pentapeptide enkephalins are inactivated by two membrane-bound Zn-metallopeptidases: neprilysin, which cleaves the Gly^3-Phe^4 bond, and aminopeptidase N, which releases the *N*-terminal Tyr. Inhibition of encephalin degradation increases the extracellular concentrations and half-life of the endogenous opioids released in response to a noxious stimulus. Previously, such inhibitors had only poor oral activity, but dual inhibitors with improved oral bioavailability have been reported[55]. These should be considered as a subclass of indirect-acting opioids.

Summary and perspective

With the recent advances in the understanding of multi-mechanistic pain physiology and in design of analgesic drugs that target these multiple mechanisms with multi-mechanistic mechanisms of action, the categorization of all analgesics that have any component of opioid mechanism of action into the same class is anachronistic. It is not possible to fit the examples of loperamide, oxycodone, tramadol, tapentadol, cebranopadol, and enkephalinase inhibitors into the same clinical class. Recognition of subclasses of opioids seems warranted scientifically, and beneficial to healthcare providers, payers, and regulators.

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References

1. Raffa RB, Beckett JR, Brahmbhatt VN, et al. Orally active opioid compounds from a non-poppy source. J Med Chem 2013;56:4840-8
2. Meldrum M. The ladder and the clock: cancer pain and public policy at the end of the twentieth century. J Pain Symptom Manage 2005;29:41-54
3. Bennett DS, Carr DB. Opiophobia as a barrier to the treatment of pain. J Pain Palliat Care Pharmacother 2002;16:105-9
4. Weissman DE, Gordon D, Bidar-Sielaff S. Cultural aspects of pain management. J Palliat Med 2004;7:715-16
5. Thota RS, Jain P, Bakshi SG, Dhanve CN. Opioid-prescribing practices in chronic cancer pain in a tertiary care pain clinic. Indian J Palliat Care 2011;17:222-6
6. Paice JA, Toy C, Shott S. Barriers to cancer pain relief: fear of tolerance and addiction. J Pain Symptom Manage 1998;16:1-9
7. Davis MP, Walsh D. Epidemiology of cancer pain and factors influencing poor pain control. Am J Hosp Palliat Care 2004;21:137-42
8. Ziegler SJ, Lovrich Jr NP. Pain relief, prescription drugs, and prosecution: a four-state survey of chief prosecutors. J Law Med Ethics 2003;31:75-100
9. Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. Ann Oncol 2005;16(Suppl 4):iv132-5
10. Bonica JJ. History of pain concepts and pain therapy. Mt Sinai J Med 1991;58:191-202
11. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharm Ther 2001;26:257-64
12. Raffa RB, Clark-Vetri R, Tallarida RJ, Wertheimer AI. Combination strategies for pain management. Expert Opin Pharmacother 2003;4:1697-708
13. Pergolizzi J. Chronic pain – moving from symptom control to mechanism-based treatment. Curr Med Res Opin 2011;27:2079-80
14. Snyder SH, Pasternak GW. Historical review: opioid receptors. Trends Pharmacol Sci 2003;24:198-205
15. Millan MJ. Descending control of pain. Prog Neurobiol 2002;66:355-474
16. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. J Clin Invest 2010;120:3779-87
17. Mercer SL, Coop A. Opioid analgesics and P-glycoprotein efflux transporters: a potential systems-level contribution to analgesic tolerance. Curr Top Med Chem 2011;11:1157-64
18. Xue JC, Chen C, Zhu J, et al. Differential binding domains of peptide and non-peptide ligands in the cloned rat kappa opioid receptor. J Biol Chem 1994;269:30195-9
19. Raffa RB, Martinez RP, Connelly CD. G-protein antisense oligodeoxyribonucleotides and mu-opioid supraspinal antinociception. Eur J Pharmacol 1994;258:R5-7
20. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. Nat Rev Drug Discov 2013;12:205-16
21. Kalvass JC, Olson ER, Cassidy MP, et al. Pharmacokinetics and pharmacodynamics of seven opioids in P-glycoprotein-competent mice: assessment of unbound brain EC50,u and correlation of in vitro, preclinical, and clinical data. J Pharmacol Exp Ther 2007;323:346-55
22. Zamek-Gliszczynski MJ, Bedwell DW, Bao JQ, Higgins JW. Characterization of SAGE Mdr1a (P-gp), Bcrp, and Mrp2 knockout rats using loperamide, paclitaxel, sulfasalazine, and carboxydichlorofluorescein pharmacokinetics. Drug Metab Dispos 2012;40:1825-33
23. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011;59:385-90
24. Okura T, Hattori A, Takano Y, et al. Involvement of the pyrilamine transporter, a putative organic cation transporter, in blood-brain barrier transport of oxycodone. Drug Metab Dispos 2008;36:2005-13
25. Lalovic B, Kharasch E, Hoffer C, et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461-79
26. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. J Pharmacol Exp Ther 2001;297:688-95
27. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol 2004;2:395-402
28. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 2003;28:2000-9
29. Cowan A. Buprenorphine: new pharmacological aspects. Int J Clin Pract Suppl 2003;133:3-8, discussion 23-4
30. Budd K, Raffa RB (eds). Buprenorphine – The Unique Opioid Analgesic. Stuttgart–New York: Thieme, 2005
31. Christoph T, Kogel B, Schiene K, et al. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. Eur J Pharmacol 2005;507:87-98
32. Raffa RB, Ding Z. Examination of the preclinical antinociceptive efficacy of buprenorphine and its designation as full- or partial-agonist. Acute Pain 2007;9:145-52
33. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth 2006;96:627-32
34. Wheeler-Aceto H, Cowan A. Buprenorphine and morphine cause antinociception by different transduction mechanisms. Eur J Pharmacol 1991;195:411-13
35. Ding Z, Raffa RB. Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine. Br J Pharmacol 2009;157:831-43
36. Tallarida RJ, Cowan A, Raffa RB. On deriving the dose–effect relation of an unknown second component: an example using buprenorphine preclinical data. Drug Alcohol Depend 2010;109:126-9
37. Raffa RB, Friderichs E. The basic science aspect of tramadol hydrochloride. Pain Reviews 1996;3:249-71
38. Nakajima K, Obata H, Iriuchijima N, Saito S. An increase in spinal cord noradrenaline is a major contributor to the antihyperalgesic effect of antidepressants after peripheral nerve injury in the rat. Pain 2012;153:990-7
39. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995;332:1685-90
40. Bianchi M, Broggini M, Balzarini P, et al. Effects of tramadol on synovial fluid concentrations of substance P and interleukin-6 in patients with knee osteoarthritis: comparison with paracetamol. Int Immunopharmacol 2003;3:1901-8
41. Raffa RB, Friderichs E, Reimann W, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. J Pharmacol Exp Ther 1993;267:331-40
42. Stoops WW, Lofwall MR, Nuzzo PA, et al. Pharmacodynamic profile of tramadol in humans: influence of naltrexone pretreatment. Psychopharmacology (Berl) 2012;223:427-38
43. Tzschentke TM, Christoph T, Kogel B, et al. (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007;323:265-76
44. Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. Naunyn Schmiedebergs Arch Pharmacol 2000;362:116-21
45. Schröder W, Vry JD, Tzschentke TM, et al. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. Eur J Pain 2010;14:814-21
46. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J Pharmacol Exp Ther 2011;337:312-20
47. Cowan A, Raffa RB, Tallarida CS, et al. Lack of synergistic interaction between the two mechanisms of action of tapentadol in gastrointestinal transit. Eur J Pain 2014. Epub ahead of print. DOI 10.1002/j.1532-2149.2014.00461.x

48. Hartrick C, Van Hove I, Stegmann JU, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. Clin Ther 2009;31:260-71
49. Daniels S, Casson E, Stegmann JU, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. Curr Med Res Opin 2009;25:1551-61
50. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig 2010;30:489-505
51. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? Eur J Pain 2010;14:781-3
52. Morphy R, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. Drug Discov Today 2004;9:641-51
53. Zimmermann GR, Lehar J, Keith CT. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discov Today 2007;12:34-42
54. Linz K, Christoph T, Tzschentke TM, et al. Cebranopadol: a novel potent analgesic nociceptin/orphanin FQ peptide and opioid receptor agonist. J Pharmacol Exp Ther 2014;349:535-48
55. Poras H, Bonnard E, Dange E, et al. New orally active dual enkephalinase inhibitors (DENKIs) for central and peripheral pain treatment. J Med Chem 2014;57:5748-63

