Chapter 12
The Opioid System in Levodopa-Induced Dyskinesia

Tom H. Johnston, Paula Ravenscroft, and Michael P. Hill

Abstract A wealth of evidence underlies the pivotal role of opioidergic neurotransmission in both normal and pathological basal ganglia function. Accompanying the development and expression of levodopa-induced dyskinesia (LID), following long-term dopamine replacement therapy in Parkinson's disease (PD), are myriad changes in both opioid receptor levels as well as the stoichiometry and processing of endogenous opioid peptides. Notably, in both patients and animal models of PD, dopamine denervation and chronic levodopa therapy are associated with an enhancement of basal ganglia opioid transmission. Whether this and other alterations are wholly causative or compensatory remains to be fully elucidated. Nevertheless, such observations have formed the basis for utilizing a variety of small molecules and other potential therapies to modulate the opioid system for the treatment of motor complications in PD. This chapter will provide an overview of the opioid system and describe both preclinical and clinical studies concerning the role of opioids in LID. New insights such as the role of receptor dimerization and potential role for biased ligands are also reviewed.

Keywords Opioid • PPE-B • Levodopa • Dyskinesia • Motor complications

The Endogenous Opioid System

The first description of a related group of endogenous opioid peptides, the enkephalins, and their structures was reported by Hughes and colleagues [1]. Other endogenous opioids were quickly discovered including dynorphin and β-endorphin [2–5]. All these peptides share the enkephalin sequence (Tyr-Gly-Gly-Phe-Leu or

T.H. Johnston PhD (✉) • P. Ravenscroft, PhD
Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, Krembil Discovery Tower, 60 Leonard Avenue, Room 8KD-402, Toronto, ON M5T 2S8, Canada
e-mail: tom.johnston@uhnresearch.ca

M.P. Hill, PhD
Toronto Western Research Institute, Krembil Discovery Tower, 60 Leonard Avenue, Room 8KD-402, Toronto, ON M5T 2S8, Canada

S.H. Fox, J.M. Brotchie (eds.), *Levodopa-Induced Dyskinesia in Parkinson's Disease*, DOI 10.1007/978-1-4471-6503-3_12

Tyr-Gly-Gly-Phe-Met) at the N-terminus, with differing extensions at the C-terminus. Subsequently, another set of endogenous peptides with opioidergic properties, the endomorphins, were discovered and were found to be distinct from the classic opioid peptides in that they were highly μ-opioid receptor selective and did not contain the enkephalin sequence [6]. A further opioid-like peptide that has similarities to dynorphin A [7] was discovered independently by two groups and termed orphanin FQ by one [8] and nociceptin by the other [9].

Opioid Peptide Precursors

Enkephalins are pentapeptides, produced from the proteolysis of the polypeptide precursor molecule preproenkephalin-A (PPE-A), which contains six copies of methionine-enkephalin (met-enkephalin) and one copy of leucine-enkephalin (leu-enkephalin) [10, 11]. Dynorphins are produced from the proteolysis of preproenkephalin B (PPE-B, also known as preprodynorphin), which also contains sequences for leu-enkephalin, α-neoendorphin, and β-neoendorphin [12–15]. In addition, preproopiomelanocortin contains sequences for β-endorphin [16]. Nociceptin/Orphanin FQ (N/OFQ) is derived from prepronociceptin and is found almost exclusively in the CNS [17]. No precursor for the endomorphins has been found to date.

Opioid Receptors

The existence of opioid receptors was first demonstrated in 1973 by a number of groups [18–20], and around 20 years later molecular sequencing and cloning studies confirmed the existence of three distinct classes; μ-, δ-, and κ- [21–23]. Each class displays at least two pharmacological subtypes in vivo (reviewed in [24]). Opioid receptors, as well as other G-protein-coupled receptors, exist in oligomeric complexes [25, 26]. Homo-oligomerization of μ-, δ-, and κ-opioid receptors has been demonstrated, suggesting a critical functional role for receptor–receptor interactions. Of more interest perhaps is the phenomenon of hetero-oligomerization. Hetero-dimerization between δ- and κ-opioid receptors was the first opioid receptor complex identified and was shown to display novel pharmacology [27]. Hetero-dimerization between δ- and μ-opioid receptors has been extensively documented [28, 29], and recently a selective ligand was identified for this complex [30]. It has also been shown that the endogenous opioids endomorphin-1 and leu-enkephalin have a higher affinity for the μ–δ complex than either receptor alone [31]. Thus, specifically targeting opioid hetero-oligomers may open up new opportunities for therapeutic development. To add to the complexity, at least 31 splice variants of the μ-opioid receptor have been isolated from mice, 16 from rats, and 19 from humans (reviewed in:[32]). The endogenous opioid peptides have different degrees of selectivity for opioid receptors. Leu-enkephalin and

Table 12.1 Mammalian endogenous opioid ligands and receptors

Precursor	Endogenous peptide	Opioid receptor selectivity
Preproenkephalin-A	Met-enkephalin	δ-opioid receptor
	Leu-enkephalin	δ-opioid receptor
Preproenkephalin-B	Dynorphin A	κ-opioid receptor
	Dynorphin B	κ-opioid receptor
	Leu-enkephalin	δ-opioid receptor
	α-neoendorphin	κ-opioid receptor
	β-neoendorphin	κ-opioid receptor
Preproopioimelanocortin	β-endorphin	μ-opioid receptor
No precursor discovered	Endomorphin-1	μ-opioid receptor
	Endomorphin-2	μ-opioid receptor
Prepronociceptin	N/OFQ	N/OFQ receptor

met-enkephalin are predominantly endogenous ligands of the δ-opioid receptor [33], β-endorphin, and the endomorphins predominantly bind to the μ-opioid receptor [6, 34, 35], whereas the dynorphins and neoendorphins act mainly via the κ-opioid receptor [36]. N/OFQ binds to the nociceptin receptor (also referred to as the orphanin FQ receptor) [17]. The nociceptin receptor has a high degree of homology to other opioid receptors, but the classic endogenous opioids exhibit little or no affinity for it [37]. A summary of key endogenous opioids and their preferred target receptor is described in Table 12.1.

Opioid receptors are distributed throughout the structures of the basal ganglia and the distribution is relatively conserved across species. The distribution of opioid receptor mRNA and opioid receptor binding sites in the rat CNS has been reviewed by Mansour et al. [38]. There is a high correlation between μ-opioid receptor mRNA expression and binding in the clusters and patches of the striatum and nucleus accumbens and pallidal complex [38, 39], suggesting local receptor synthesis. δ-Opioid receptor mRNA and binding is also highly correlated in the striatum, nucleus accumbens, and globus pallidus [39, 40]. While mRNA and binding of κ-opioid receptors are highly correlated in the striatum and nucleus accumbens, there are differences in the substantia nigra pars compacta and ventral tegmental area which may be due to receptor transport [39]. The subthalamic nucleus also contains high levels of κ-opioid receptors [41].

Changes to the Opioid System in PD and LID

Many studies in both rodent [42–63] and nonhuman primate [64–72] models of Parkinson's disease have consistently demonstrated increased striatal PPE-A mRNA expression compared to normal control animals. Similarly, studies in PD patients show the same pattern of increase in striatal PPE-A mRNA expression [73–75].

Conversely, rodent [46, 47, 49, 51, 52, 60, 76–78] and nonhuman primate [66–68, 79] models of PD show reduced striatal PPE-B mRNA expression. It has also been demonstrated that prepronociceptin is increased in the substantia nigra in rodent models of PD [80–83]. Following repeated D_1/D_2 dopamine receptor stimulation in rodents, striatal PPE-A mRNA is either further elevated compared to that in the parkinsonian state or remains the same, while PPE-B mRNA levels are elevated [46–48, 50, 52, 57, 59, 63, 76, 78, 84–90]. The same pattern is seen in nonhuman primate models of PD [65–68, 70, 91–94] and in PD patients [73–75]. In contrast to the number of studies looking at precursor expression, relatively few studies have looked at the expression of the opioid peptides being produced from these precursors. However, a recent study in MPTP-lesioned nonhuman primates demonstrated significant elevations in met- and leu-enkephalin in the putamen and external segment of the globus pallidus [66]. Elevated levels of N/OFQ have also been demonstrated in the CSF of PD patients [95]. Recent studies have looked at the levels of opioid peptides in rat [87, 96] and nonhuman primate [66] models of LID. The rodent studies used the sensitive technique of matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) that allows comprehensive detection of multiple molecular species in a single tissue section. They found elevated levels of the PPE-B derived peptides, dynorphin B and α-neoendorphin, in the dorsolateral striatum [87] and substantia nigra [96] of severely dyskinetic rats compared with mildly dyskinetic or non-dyskinetic rats. A similar elevation in the PPE-B derived peptide, dynorphin A, has been seen in dyskinetic nonhuman primates [66]. Changes in receptor levels and receptor signaling in PD and dyskinetic states have been extensively reviewed by Huot and colleagues [97] and are summarized in Table 12.2.

Potential of Selective vs. Nonselective Classical Opioid Receptor Therapies

The plethora of changes in basal ganglia function such as underactivity of output nuclei (i.e., internal segment of the globus pallidus and substantia nigra pars reticulata) likely represent key mechanisms underlying dyskinesia in PD (reviewed in [98]).

Table 12.2 Changes to opioid receptor levels and receptor signaling in PD and dyskinetic states

μ-receptor levels are reduced in the striatum and GPi of dyskinetic NHPs killed in the ON state
μ-receptor-mediated signaling is overactive in the striatum and GPi of MPTP-lesioned NHPs killed in the ON state
δ-receptor levels are unchanged in the striatum of dyskinetic NHPs killed in the ON state
δ-receptor-mediated signaling is overactive in the striatum of MPTP-lesioned NHPs killed in the ON state
κ-receptor levels are reduced in the GPe and GPi of dyskinetic NHPs killed in the ON state
κ-receptor-mediated signaling is overactive in the caudate nucleus and motor cortex of MPTP-lesioned NHPs killed in the ON state

Adapted from: Huot et al. [97]

Concomitantly, a substantial preclinical literature has implicated aberrant opioid transmission in the expression of LID. As discussed, these include the classic observations of increases in the synthesis of basal ganglia PPE-B and associated opioid peptides in animal models of LID and in *postmortem* tissue from dyskinetic PD patients [46, 74, 75, 91, 99, 100]. Additionally, functional imaging studies using positron emission tomography showed that PD patients with LID displayed heightened opioid transmission [101]. Such observations have lent support to the hypothesis that antagonism of opioid transmission, in the first instance using the approach of nonselective receptor subtype blockade, might be associated with anti-dyskinetic actions. Indeed, the nonselective opioid receptor antagonist naloxone was shown to alleviate established abnormal involuntary movements (AIMs), a correlate of dyskinesia seen in PD patients, in the 6-OHDA-lesioned rat model of PD [102], but was alternately proven both ineffective [103] and effective [104] at reducing LID in the MPTP-lesioned macaque. Responses to another nonselective opioid antagonist, naltrexone, were also ambivalent showing an alleviation of established LID evident in the MPTP-lesioned marmoset [92] while lacking effect on, or even exacerbating, LID in the macaque [105–108]. The lackluster display of benefit attributed to use of non-subtype-selective blockade was borne out in clinical studies examining both naloxone [109] and naltrexone [110, 111] in which either a total absence of, or only modest, anti-dyskinetic benefit was revealed. Such lack of clear anti-dyskinetic actions possibly reflects the interaction of non-subtype-selective ligands with multiple opioid receptors, which might provide competing pro- and anti-dyskinetic effect. Strikingly, recent advanced mass spectrometry studies have for the first time afforded insight into the exact nature of the PPE-B-derived opioid peptide species generated in the dyskinetic state that could shed light on why generalized blockade of all opioid actions likely represents too blunt a therapeutic strategy. Thus, the aforementioned MALDI-TOF-based imaging in nigral and striatal tissues of levodopa-treated, 6-OHDA-lesioned rats has revealed a strong positive correlation between AIMs severity and levels of the PPE-B derived peptides, dynorphin B and α-neoendorphin. Of note, these dyskinesia-associated peptides were not those with the highest affinity to κ-opioid receptors, but also activate μ- and δ-opioid receptors [87, 96]. Such data provide compelling evidence that enhanced activation of non-κ-opioid receptors by select peptide products of PPE-B may contribute to the development of dyskinesia after chronic levodopa therapy. In keeping with heightened activity of μ-opioid function, the selective μ-opioid receptor antagonists cyprodime and ADL5510 both alleviated LID in the MPTP-lesioned nonhuman primate, without affecting levodopa anti-parkinsonian efficacy [92, 105]. Likewise, and in agreement with hyperactive δ-opioid receptor-mediated transmission in dyskinesia, the δ-opioid receptor antagonist naltrindole reduced LID in the MPTP-lesioned nonhuman primate, also without affecting levodopa anti-parkinsonian efficacy [92]. While earlier studies remain pertinent in suggesting overactivity of κ-opioid-mediated signaling in LID (based on elevated PPE-B-heightened expression), as being a key element in the generation of LID, the more recent MALDI data described perhaps temper this assertion. Indeed, behavioral studies in which κ-opioid receptors were blocked with nor-binaltorphimine (*nor*-BNI) showed no reduction in LID in the MPTP-lesioned nonhuman primate [92]. Conversely,

stimulation of κ-opioid receptors with U50,488 reduced established AIMs in the 6-OHDA-lesioned rat and dyskinesia in the MPTP-lesioned squirrel monkey, though at the expense of impairing levodopa anti-parkinsonian action [112]. In addition, TRK-820, a selective κ-opioid receptor agonist, effectively ameliorated levodopa-induced AIMs in the 6-OHDA-lesioned rat, an effect which was blocked by prior treatment with *nor*-BNI [113]. Thus, the lack of clear efficacy of non-subtype selective opioid receptor antagonists may reflect that any anti-dyskinetic benefit conferred by blocking μ- and δ-opioid receptors may be offset by blockade of κ-opioid receptors. If the failure of non-subtype selective opioid antagonists to alleviate LID in clinical trials is indeed due to their blockade of κ-opioid receptors, and if the anti-dyskinetic efficacy of the non-subtype selective opioid agonists is primarily mediated via an agonist effect at κ-opioid receptors, then selective stimulation of these receptors may yet represent a promising anti-dyskinetic target. Any κ-opioid agonist-based strategy will of course have considerable challenges to overcome in dealing with the dysphorogenicity implicit with this class of compound [114].

The optimal balance of opioid receptor stimulation and blockade with which to achieve peak anti-dyskinetic effect has yet to be fully elucidated. Indeed, an alternative explanation for the rise in levels of PPE-B and derived opioid peptides observed in striatal tissue from dyskinetic patients or animal models, is as a compensatory response to prolonged levodopa therapy and onset of dyskinesia rather than a direct causative event (reviewed in: [115]). Evidence to support this alternate hypothesis is no less compelling. Thus, nonselective stimulation of opioid receptors with meperidine alleviated LID in the MPTP-lesioned nonhuman primate [103] while not affecting the anti-parkinsonian action of levodopa. Likewise, morphine alleviated established LID as well as dyskinesia elicited by selective stimulation of either D_1 or D_2 dopamine receptors in the MPTP-lesioned nonhuman primate [116] and showed efficacy in a small open-label clinical report [117]. Given the anti-dyskinetic actions afforded by selective κ-opioid agonists, it is fair to assume that at least part of the benefit exhibited by morphine and meperidine as nonselective agonists is exerted via activity at this receptor. The obvious challenges of advancing an opioid agonist for this indication aside, the potential benefit of a selective μ-opioid agonist would be interesting to see although similar mood-altering side effects to those observed with κ-opioid selective agonists have been reported for μ-opioid agonist-based approaches [118]. It can however be said with certainty that stimulation of the δ-opioid receptor is unlikely to underlie such effects. In the untreated parkinsonian state (prior to advent of dopamine replacement therapy), δ-opioid receptor agonists can provide robust anti-parkinsonian effects. In both haloperidol-administered rats and MPTP-lesioned nonhuman primates, the selective δ-opioid receptor agonist, SNC80, reversed all parkinsonian deficits [119]. While δ-opioid receptor agonists have considerable potential as anti-parkinsonian agents, their use in more advanced patients, where dyskinesia has already emerged, may be limited. Thus, in MPTP-lesioned nonhuman primates with established levodopa-induced dyskinesia, δ-opioid agonists elicit dyskinesia even as monotherapy and exacerbate dyskinesia if given in combination with levodopa [120].

Recent work has examined both agonist and antagonist effects at the nociceptin/orphanin FQ (N/OFQ) receptor as a strategy to alleviate LID. Systemic administration

of J-113397, an N/OFQ receptor antagonist, enhanced the anti-parkinsonian actions of low-dose levodopa in 6-OHDA-lesioned rats [121] but worsened established LID in the MPTP-lesioned nonhuman primate [122]. Conversely, both native N/OFQ peptide and a synthetic N/OFQ agonist, Ro 65–6570, given via intracerebroventricular injection reduced established AIMs in the 6-OHDA-lesioned rat and, given systemically to MPTP-lesioned nonhuman primates, Ro 65–6570 significantly reduced established LID without compromising the anti-parkinsonian benefit of levodopa [123].

New Avenues in Therapeutic Development

Given the multiplicity of effects, both positive and negative, offered by modulation of the opioid system in PD and LID, a combination approach that simultaneously yields the best of multiple strategies may be of value. The concept of opioid ligands with "agonist/antagonist" properties is hardly new, having been described several decades ago for pentazocine and related compounds [124]. Recent work has identified single chemical entities with dual δ-opioid receptor agonist and μ-opioid antagonist (DAMA) characteristics [125]. Such compounds, with inherent anti-parkinsonian actions (mediated via actions at the δ-opioid receptor) also, via μ-opioid receptor blockade, have the potential to suppress both the development of dyskinesia in early disease, when given as monotherapy, and its expression, when combined with levodopa, in later stages of the disease. A similar strategy centered on dual-actions of a single compound at the κ- and μ-opioid receptors has also recently been promulgated [126]. Specifically, nalbuphine, a semisynthetic opioid used clinically as an analgesic, with activity as both a weak μ-opioid receptor antagonist and a κ-opioid receptor partial agonist, has been shown to ameliorate established dyskinesia in MPTP-lesioned nonhuman primates without worsening parkinsonian symptoms. This strategy offers the combined anti-dyskinetic potential of both μ-opioid antagonism and κ-opioid agonism reportedly using sub-analgesic doses of nalbuphine below those at which any propensity for side effects relating to κ-opioid receptor stimulation (dysphoria and loss of anti-parkinsonian action) might compromise therapeutic benefit.

Avoidance of such psychotomimetic effects and other opioid agonist-related complications such as the development of tolerance with chronic administration [127] would represent a considerable advance on current therapies. Possible solutions to these issues may be forthcoming with some profound advances in the fundamental understanding of GPCR biology witnessed over the last decade. Chief among these may be the recognition that in addition to the classical repertoire of agonists and antagonists which activate or inactivate the entirety of a receptor's signaling network, "biased" ligands can selectively activate a subset of the signaling pathways available to that receptor by a particular ligand [128, 129]. For instance, a newly developed κ-opioid receptor agonist, 6′-guanidinonaltrindole, was shown to display bias toward the activation of signaling through non-β-arrestin

2 pathways [130, 131], a mechanism associated with the loss of dysphoria [132]. Such preferential signaling that avoids β-arrestin engagement is also being explored in the context of enhancing δ-opioid receptor agonist strategies in an attempt to limit seizure activity associated with "classical" agonists such as SNC80 [133]. Separation of seizure and locomotor effects may however be challenging. For example, some of the newer δ-opioid receptor agonists such as ADL5747 and ADL5859, while showing a lack of seizure activity at doses associated with analgesia, also show a total lack of SNC80-like anti-parkinsonian effect [134]. Future therapeutic development may also take into consideration discovery of yet another class of new opioid receptor ligands, those, as discussed earlier, with the capacity to selectively bind to, and activate, heteromeric opioid receptors, rather than either receptor expressed in monomeric form [30].

Conclusion

It is clear that opioidergic neurotransmission is significantly altered in Parkinson's disease and levodopa-induced dyskinesia. Current data suggest that the elevated level of opioids derived from PPE-B plays the most prominent role in dyskinesia expression following long-term dopamine replacement therapy. The most promising target explored to date appears to be the μ-opioid receptor where selective antagonists afford anti-dyskinetic activity without compromising the anti-parkinsonian benefit of levodopa. However, new avenues that utilize compounds with combined opioid agonist and antagonist properties, biased ligands, in particular κ-opioid agonists lacking β-arrestin activity or those selective for opioid receptor heterodimers, may provide novel strategies in the treatment of levodopa-induced dyskinesia.

References

1. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature. 1975;258(5536):577–80.
2. Birdsall NJ, Hulme EC. C fragment of lipotropin has a high affinity for brain opiate receptors. Nature. 1976;260(5554):793–5.
3. Cox BM, Opheim KE, Teschemacher H, Goldstein A. A peptide-like substance from pituitary that acts like morphine. 2. Purification and properties. Life Sci. 1975;16(12):1777–82.
4. Goldstein A. Opioid peptides endorphins in pituitary and brain. Science. 1976;193(4258):1081–6.
5. Li CH, Chung D, Doneen BA. Isolation, characterization and opiate activity of beta-endorphin from human pituitary glands. Biochem Biophys Res Commun. 1976;72(4):1542–7.
6. Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. Nature. 1997;386(6624):499–502.
7. Meunier JC. Nociceptin/orphanin FQ and the opioid receptor-like ORL1 receptor. Eur J Pharmacol. 1997;340(1):1–15.

8. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, et al. Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science. 1995;270(5237):792–4.
9. Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, et al. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature. 1995;377(6549):532–5.
10. Rosen H, Douglass J, Herbert E. Isolation and characterization of the rat proenkephalin gene. J Biol Chem. 1984;259(22):14309–13.
11. Noda M, Teranishi Y, Takahashi H, Toyosato M, Notake M, Nakanishi S, et al. Isolation and structural organization of the human preproenkephalin gene. Nature. 1982;297(5865):431–4.
12. Hughes J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. Brain Res. 1975;88(2):295–308.
13. Civelli O, Douglass J, Goldstein A, Herbert E. Sequence and expression of the rat prodynorphin gene. Proc Natl Acad Sci U S A. 1985;82(12):4291–5.
14. Horikawa S, Takai T, Toyosato M, Takahashi H, Noda M, Kakidani H, et al. Isolation and structural organization of the human preproenkephalin B gene. Nature. 1983;306(5943):611–4.
15. Seizinger BR, Grimm C, Hollt V, Herz A. Evidence for a selective processing of proenkephalin B into different opioid peptide forms in particular regions of rat brain and pituitary. J Neurochem. 1984;42(2):447–57.
16. Chretien M, Benjannet S, Gossard F, Gianoulakis C, Crine P, Lis M, et al. From beta-lipotropin to beta-endorphin and 'pro-opio-melanocortin'. Can J Biochem. 1979;57(9):1111–21.
17. Mollereau C, Simons MJ, Soularue P, Liners F, Vassart G, Meunier JC, et al. Structure, tissue distribution, and chromosomal localization of the prepronociceptin gene. Proc Natl Acad Sci U S A. 1996;93(16):8666–70.
18. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. Science. 1973;179(4077):1011–4.
19. Simon EJ, Hiller JM, Edelman I. Stereospecific binding of the potent narcotic analgesic (3H) Etorphine to rat-brain homogenate. Proc Natl Acad Sci U S A. 1973;70(7):1947–9.
20. Terenius L. Stereospecific interaction between narcotic analgesics and a synaptic plasm a membrane fraction of rat cerebral cortex. Acta Pharmacol Toxicol (Copenh). 1973;32(3):317–20.
21. Evans CJ, Keith Jr DE, Morrison H, Magendzo K, Edwards RH. Cloning of a delta opioid receptor by functional expression. Science. 1992;258(5090):1952–5.
22. Yasuda K, Raynor K, Kong H, Breder CD, Takeda J, Reisine T, et al. Cloning and functional comparison of kappa and delta opioid receptors from mouse brain. Proc Natl Acad Sci U S A. 1993;90(14):6736–40.
23. Zastawny RL, George SR, Nguyen T, Cheng R, Tsatsos J, Briones-Urbina R, et al. Cloning, characterization, and distribution of a mu-opioid receptor in rat brain. J Neurochem. 1994;62(6):2099–105.
24. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol. 2006;147 Suppl 1:S153–62.
25. Bouvier M. Oligomerization of G-protein-coupled transmitter receptors. Nat Rev Neurosci. 2001;2(4):274–86.
26. Gomes I, Jordan BA, Gupta A, Rios C, Trapaidze N, Devi LA. G protein coupled receptor dimerization: implications in modulating receptor function. J Mol Med. 2001;79(5–6):226–42.
27. Jordan BA, Devi LA. G-protein-coupled receptor heterodimerization modulates receptor function. Nature. 1999;399(6737):697–700.
28. Traynor JR, Elliott J. delta-Opioid receptor subtypes and cross-talk with mu-receptors. Trends Pharmacol Sci. 1993;14(3):84–6.
29. Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, et al. Crystal structure of the micro-opioid receptor bound to a morphinan antagonist. Nature. 2012;485(7398):321–6.

30. Gomes I, Fujita W, Gupta A, Saldanha SA, Negri A, Pinello CE, et al. Identification of a mu-delta opioid receptor heteromer-biased agonist with antinociceptive activity. Proc Natl Acad Sci U S A. 2013;110(29):12072–7.
31. George SR, Fan T, Xie Z, Tse R, Tam V, Varghese G, et al. Oligomerization of mu- and delta-opioid receptors. Generation of novel functional properties. J Biol Chem. 2000;275(34):26128–35.
32. Pasternak GW. Opioids and their receptors: are we there yet? Neuropharmacology. 2014;76(Pt B):198–203.
33. Quock RM, Burkey TH, Varga E, Hosohata Y, Hosohata K, Cowell SM, et al. The delta-opioid receptor: molecular pharmacology, signal transduction, and the determination of drug efficacy. Pharmacol Rev. 1999;51(3):503–32.
34. Wang JB, Imai Y, Eppler CM, Gregor P, Spivak CE, Uhl GR. mu opiate receptor: cDNA cloning and expression. Proc Natl Acad Sci U S A. 1993;90(21):10230–4.
35. Fichna J, Janecka A, Costentin J, Do Rego JC. The endomorphin system and its evolving neurophysiological role. Pharmacol Rev. 2007;59(1):88–123.
36. Chavkin C, James IF, Goldstein A. Dynorphin is a specific endogenous ligand of the kappa opioid receptor. Science. 1982;215(4531):413–5.
37. Henderson G, McKnight AT. The orphan opioid receptor and its endogenous ligand–nociceptin/orphanin FQ. Trends Pharmacol Sci. 1997;18(8):293–300.
38. Mansour A, Fox CA, Burke S, Akil H, Watson SJ. Immunohistochemical localization of the cloned mu opioid receptor in the rat CNS. J Chem Neuroanat. 1995;8(4):283–305.
39. Mansour A, Fox CA, Burke S, Meng F, Thompson RC, Akil H, et al. Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in situ hybridization study. J Comp Neurol. 1994;350(3):412–38.
40. Mansour A, Thompson RC, Akil H, Watson SJ. Delta opioid receptor mRNA distribution in the brain: comparison to delta receptor binding and proenkephalin mRNA. J Chem Neuroanat. 1993;6(6):351–62.
41. Zhu J, Chen C, Xue JC, Kunapuli S, DeRiel JK, Liu-Chen LY. Cloning of a human kappa opioid receptor from the brain. Life Sci. 1995;56(9):L201–7.
42. Angulo JA. Involvement of dopamine D1 and D2 receptors in the regulation of proenkephalin mRNA abundance in the striatum and accumbens of the rat brain. J Neurochem. 1992;58(3):1104–9.
43. Angulo JA, Cadet JL, Woolley CS, Suber F, McEwen BS. Effect of chronic typical and atypical neuroleptic treatment on proenkephalin mRNA levels in the striatum and nucleus accumbens of the rat. J Neurochem. 1990;54(6):1889–94.
44. Angulo JA, Christoph GR, Manning RW, Burkhart BA, Davis LG. Reduction of dopamine receptor activity differentially alters striatal neuropeptide mRNA levels. Adv Exp Med Biol. 1987;221:385–91.
45. Angulo JA, Davis LG, Burkhart BA, Christoph GR. Reduction of striatal dopaminergic neurotransmission elevates striatal proenkephalin mRNA. Eur J Pharmacol. 1986;130(3):341–3.
46. Duty S, Brotchie JM. Enhancement of the behavioral response to apomorphine administration following repeated treatment in the 6-hydroxydopamine-lesioned rat is temporally correlated with a rise in striatal preproenkephalin-B, but not preproenkephalin-A, gene expression. Exp Neurol. 1997;144(2):423–32.
47. Duty S, Henry B, Crossman AR, Brotchie JM. Topographical organization of opioid peptide precursor gene expression following repeated apomorphine treatment in the 6-hydroxydopamine-lesioned rat. Exp Neurol. 1998;150(2):223–34.
48. Engber TM, Susel Z, Kuo S, Gerfen CR, Chase TN. Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats. Brain Res. 1991;552(1):113–8.
49. Gerfen CR, McGinty JF, Young 3rd WS. Dopamine differentially regulates dynorphin, substance P, and enkephalin expression in striatal neurons: in situ hybridization histochemical analysis. J Neurosci. 1991;11(4):1016–31.

50. Granata R, Wenning GK, Jolkkonen J, Jenner P, Marsden CD. Effect of repeated administration of dopamine agonists on striatal neuropeptide mRNA expression in rats with a unilateral nigral 6-hydroxydopamine lesion. J Neural Transm. 1996;103(3):249–60.
51. Harrison MB, Kumar S, Hubbard CA, Trugman JM. Early changes in neuropeptide mRNA expression in the striatum following reserpine treatment. Exp Neurol. 2001;167(2):321–8.
52. Henry B, Crossman AR, Brotchie JM. Effect of repeated L-DOPA, bromocriptine, or lisuride administration on preproenkephalin-A and preproenkephalin-B mRNA levels in the striatum of the 6-hydroxydopamine-lesioned rat. Exp Neurol. 1999;155(2):204–20.
53. Hong JS, Yang HY, Gillin JC, Costa E. Effects of long-term administration of antipsychotic drugs on enkephalinergic neurons. Adv Biochem Psychopharmacol. 1980;24:223–32.
54. Jaber M, Fournier MC, Bloch B. Reserpine treatment stimulates enkephalin and D2 dopamine receptor gene expression in the rat striatum. Brain Res Mol Brain Res. 1992;15(3–4):189–94.
55. Jaber M, Normand E, Bloch B. Effect of reserpine treatment on enkephalin mRNA level in the rat striatum: an in situ hybridization study. Brain Res Mol Brain Res. 1995;32(1):156–60.
56. Jaber M, Tison F, Fournier MC, Bloch B. Differential influence of haloperidol and sulpiride on dopamine receptors and peptide mRNA levels in the rat striatum and pituitary. Brain Res Mol Brain Res. 1994;23(1–2):14–20.
57. Salin P, Dziewczapolski G, Gershanik OS, Nieoullon A, Raisman-Vozari R. Differential regional effects of long-term L-DOPA treatment on preproenkephalin and preprotachykinin gene expression in the striatum of 6-hydroxydopamine-lesioned rat. Brain Res Mol Brain Res. 1997;47(1–2):311–21.
58. Tang F, Costa E, Schwartz JP. Increase of proenkephalin mRNA and enkephalin content of rat striatum after daily injection of haloperidol for 2 to 3 weeks. Proc Natl Acad Sci U S A. 1983;80(12):3841–4.
59. Taylor MD, De Ceballos ML, Rose S, Jenner P, Marsden CD. Effects of a unilateral 6-hydroxydopamine lesion and prolonged L-3,4-dihydroxyphenylalanine treatment on peptidergic systems in rat basal ganglia. Eur J Pharmacol. 1992;219(2):183–92.
60. Voorn P, Docter GJ, Jongen-Relo AL, Jonker AJ. Rostrocaudal subregional differences in the response of enkephalin, dynorphin and substance P synthesis in rat nucleus accumbens to dopamine depletion. Eur J Neurosci. 1994;6(3):486–96.
61. Voorn P, Roest G, Groenewegen HJ. Increase of enkephalin and decrease of substance P immunoreactivity in the dorsal and ventral striatum of the rat after midbrain 6-hydroxydopamine lesions. Brain Res. 1987;412(2):391–6.
62. Young 3rd WS, Bonner TI, Brann MR. Mesencephalic dopamine neurons regulate the expression of neuropeptide mRNAs in the rat forebrain. Proc Natl Acad Sci U S A. 1986;83(24):9827–31.
63. Zeng BY, Jolkkonen J, Jenner P, Marsden CD. Chronic L-DOPA treatment differentially regulates gene expression of glutamate decarboxylase, preproenkephalin and preprotachykinin in the striatum of 6-hydroxydopamine-lesioned rat. Neuroscience. 1995;66(1):19–28.
64. Asselin MC, Soghomonian JJ, Cote PY, Parent A. Striatal changes in preproenkephalin mRNA levels in parkinsonian monkeys. Neuroreport. 1994;5(16):2137–40.
65. Bezard E, Ravenscroft P, Gross CE, Crossman AR, Brotchie JM. Upregulation of striatal preproenkephalin gene expression occurs before the appearance of parkinsonian signs in 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine monkeys. Neurobiol Dis. 2001;8(2):343–50.
66. Bourdenx M, Nilsson A, Wadensten H, Falth M, Li Q, Crossman AR, et al. Abnormal structure-specific peptide transmission and processing in a primate model of Parkinson's disease and l-DOPA-induced dyskinesia. Neurobiol Dis. 2014;62:307–12.
67. Herrero MT, Augood SJ, Hirsch EC, Javoy-Agid F, Luquin MR, Agid Y, et al. Effects of L-DOPA on preproenkephalin and preprotachykinin gene expression in the MPTP-treated monkey striatum. Neuroscience. 1995;68(4):1189–98.

68. Jolkkonen J, Jenner P, Marsden CD. L-DOPA reverses altered gene expression of substance P but not enkephalin in the caudate-putamen of common marmosets treated with MPTP. Brain Res Mol Brain Res. 1995;32(2):297–307.
69. Lavoie B, Parent A, Bedard PJ. Effects of dopamine denervation on striatal peptide expression in parkinsonian monkeys. Can J Neurol Sci. 1991;18(3 Suppl):373–5.
70. Morissette M, Goulet M, Soghomonian JJ, Blanchet PJ, Calon F, Bedard PJ, et al. Preproenkephalin mRNA expression in the caudate-putamen of MPTP monkeys after chronic treatment with the D2 agonist U91356A in continuous or intermittent mode of administration: comparison with L-DOPA therapy. Brain Res Mol Brain Res. 1997;49(1–2):55–62.
71. Morissette M, Grondin R, Goulet M, Bedard PJ, Di Paolo T. Differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists. J Neurochem. 1999;72(2):682–92.
72. Quik M, Police S, Langston JW, Di Monte DA. Increases in striatal preproenkephalin gene expression are associated with nigrostriatal damage but not L-DOPA-induced dyskinesias in the squirrel monkey. Neuroscience. 2002;113(1):213–20.
73. Calon F, Birdi S, Rajput AH, Hornykiewicz O, Bedard PJ, Di Paolo T. Increase of preproenkephalin mRNA levels in the putamen of Parkinson disease patients with levodopa-induced dyskinesias. J Neuropathol Exp Neurol. 2002;61(2):186–96.
74. Henry B, Duty S, Fox SH, Crossman AR, Brotchie JM. Increased striatal pre-proenkephalin B expression is associated with dyskinesia in Parkinson's disease. Exp Neurol. 2003;183(2):458–68.
75. Nisbet AP, Foster OJ, Kingsbury A, Eve DJ, Daniel SE, Marsden CD, et al. Preproenkephalin and preprotachykinin messenger RNA expression in normal human basal ganglia and in Parkinson's disease. Neuroscience. 1995;66(2):361–76.
76. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma Jr FJ, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science. 1990;250(4986):1429–32.
77. Jiang HK, McGinty JF, Hong JS. Differential modulation of striatonigral dynorphin and enkephalin by dopamine receptor subtypes. Brain Res. 1990;507(1):57–64.
78. Li SJ, Jiang HK, Stachowiak MS, Hudson PM, Owyang V, Nanry K, et al. Influence of nigrostriatal dopaminergic tone on the biosynthesis of dynorphin and enkephalin in rat striatum. Brain Res Mol Brain Res. 1990;8(3):219–25.
79. Parent A, Asselin MC, Cote PY. Dopaminergic regulation of peptide gene expression in the striatum of normal and parkinsonian monkeys. Adv Neurol. 1996;69:73–7.
80. Gouty S, Brown JM, Rosenberger J, Cox BM. MPTP treatment increases expression of prepro-nociceptin/orphanin FQ mRNA in a subset of substantia nigra reticulata neurons. Neuroscience. 2010;169(1):269–78.
81. Marti M, Mela F, Fantin M, Zucchini S, Brown JM, Witta J, et al. Blockade of nociceptin/orphanin FQ transmission attenuates symptoms and neurodegeneration associated with Parkinson's disease. J Neurosci. 2005;25(42):9591–601.
82. Norton CS, Neal CR, Kumar S, Akil H, Watson SJ. Nociceptin/orphanin FQ and opioid receptor-like receptor mRNA expression in dopamine systems. J Comp Neurol. 2002;444(4):358–68.
83. Di Benedetto M, Cavina C, D'Addario C, Leoni G, Candeletti S, Cox BM, et al. Alterations of N/OFQ and NOP receptor gene expression in the substantia nigra and caudate putamen of MPP+ and 6-OHDA lesioned rats. Neuropharmacology. 2009;56(4):761–7.
84. Andersson M, Hilbertson A, Cenci MA. Striatal fosB expression is causally linked with l-DOPA-induced abnormal involuntary movements and the associated upregulation of striatal prodynorphin mRNA in a rat model of Parkinson's disease. Neurobiol Dis. 1999;6(6):461–74.
85. Bronstein DM, Ye H, Pennypacker KR, Hudson PM, Hong JS. Role of a 35 kDa fos-related antigen (FRA) in the long-term induction of striatal dynorphin expression in the 6-hydroxydopamine lesioned rat. Brain Res Mol Brain Res. 1994;23(3):191–203.

86. Cenci MA, Lee CS, Bjorklund A. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. Eur J Neurosci. 1998;10(8):2694–706.
87. Hanrieder J, Ljungdahl A, Falth M, Mammo SE, Bergquist J, Andersson M. L-DOPA-induced dyskinesia is associated with regional increase of striatal dynorphin peptides as elucidated by imaging mass spectrometry. Mol Cell Proteomics. 2011;10(10):M111 009308.
88. Lundblad M, Picconi B, Lindgren H, Cenci MA. A model of L-DOPA-induced dyskinesia in 6-hydroxydopamine lesioned mice: relation to motor and cellular parameters of nigrostriatal function. Neurobiol Dis. 2004;16(1):110–23.
89. van de Witte SV, Drukarch B, Stoof JC, Voorn P. Priming with L-DOPA differently affects dynorphin and substance P mRNA levels in the striatum of 6-hydroxydopamine-lesioned rats after challenge with dopamine D1-receptor agonist. Brain Res Mol Brain Res. 1998;61(1–2):219–23.
90. Winkler C, Kirik D, Bjorklund A, Cenci MA. L-DOPA-induced dyskinesia in the intrastriatal 6-hydroxydopamine model of parkinson's disease: relation to motor and cellular parameters of nigrostriatal function. Neurobiol Dis. 2002;10(2):165–86.
91. Aubert I, Guigoni C, Li Q, Dovero S, Bioulac BH, Gross CE, et al. Enhanced preproenkephalin-B-derived opioid transmission in striatum and subthalamic nucleus converges upon globus pallidus internalis in L-3,4-dihydroxyphenylalanine-induced dyskinesia. Biol Psychiatry. 2007;61(7):836–44.
92. Henry B, Fox SH, Crossman AR, Brotchie JM. Mu- and delta-opioid receptor antagonists reduce levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. Exp Neurol. 2001;171(1):139–46.
93. Tamim MK, Samadi P, Morissette M, Gregoire L, Ouattara B, Levesque D, et al. Effect of non-dopaminergic drug treatment on Levodopa induced dyskinesias in MPTP monkeys: common implication of striatal neuropeptides. Neuropharmacology. 2010;58(1):286–96.
94. Tel BC, Zeng BY, Cannizzaro C, Pearce RK, Rose S, Jenner P. Alterations in striatal neuropeptide mRNA produced by repeated administration of L-DOPA, ropinirole or bromocriptine correlate with dyskinesia induction in MPTP-treated common marmosets. Neuroscience. 2002;115(4):1047–58.
95. Marti M, Sarubbo S, Latini F, Cavallo M, Eleopra R, Biguzzi S, et al. Brain interstitial nociceptin/orphanin FQ levels are elevated in Parkinson's disease. Mov Disord. 2010;25(11):1723–32.
96. Ljungdahl A, Hanrieder J, Falth M, Bergquist J, Andersson M. Imaging mass spectrometry reveals elevated nigral levels of dynorphin neuropeptides in L-DOPA-induced dyskinesia in rat model of Parkinson's disease. PLoS One. 2011;6(9):e25653.
97. Huot P, Johnston TH, Koprich JB, Fox SH, Brotchie JM. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. Pharmacol Rev. 2013;65(1):171–222.
98. Bezard E, Brotchie JM, Gross CE. Pathophysiology of levodopa-induced dyskinesia: potential for new therapies. Nat Rev Neurosci. 2001;2(8):577–88.
99. Maneuf YP, Mitchell IJ, Crossman AR, Brotchie JM. On the role of enkephalin cotransmission in the GABAergic striatal efferents to the globus pallidus. Exp Neurol. 1994;125(1):65–71.
100. de Ceballos ML, Fernandez A, Jenner P, Marsden CD. Parallel alterations in Met-enkephalin and substance P levels in medial globus pallidus in Parkinson's disease patients. Neurosci Lett. 1993;160(2):163–6.
101. Piccini P, Weeks RA, Brooks DJ. Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-induced dyskinesias. Ann Neurol. 1997;42(5):720–6.
102. Lundblad M, Andersson M, Winkler C, Kirik D, Wierup N, Cenci MA. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. Eur J Neurosci. 2002;15(1):120–32.
103. Gomez-Mancilla B, Bedard PJ. Effect of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. Clin Neuropharmacol. 1993;16(5):418–27.

104. Klintenberg R, Svenningsson P, Gunne L, Andren PE. Naloxone reduces levodopa-induced dyskinesias and apomorphine-induced rotations in primate models of parkinsonism. J Neural Transm. 2002;109(10):1295–307.
105. Koprich JB, Fox SH, Johnston TH, Goodman A, Le Bourdonnec B, Dolle RE, et al. The selective mu-opioid receptor antagonist adl5510 reduces levodopa-induced dyskinesia without affecting antiparkinsonian action in mptp-lesioned macaque model of Parkinson's disease. Mov Disord. 2011;26(7):1225–33.
106. Samadi P, Gregoire L, Bedard PJ. Opioid antagonists increase the dyskinetic response to dopaminergic agents in parkinsonian monkeys: interaction between dopamine and opioid systems. Neuropharmacology. 2003;45(7):954–63.
107. Samadi P, Gregoire L, Hadj Tahar A, Di Paolo T, Rouillard C, Bedard PJ. Naltrexone in the short-term decreases antiparkinsonian response to l-Dopa and in the long-term increases dyskinesias in drug-naive parkinsonian monkeys. Neuropharmacology. 2005;49(2):165–73.
108. Samadi P, Gregoire L, Rouillard C, Bedard PJ. Dyskinesias occur in response to saline and naltrexone alone after priming with combination of dopaminergic agents and naltrexone in the MPTP parkinsonian monkeys. Neurobiol Dis. 2005;19(1–2):266–72.
109. Fox S, Silverdale M, Kellett M, Davies R, Steiger M, Fletcher N, et al. Non-subtype-selective opioid receptor antagonism in treatment of levodopa-induced motor complications in Parkinson's disease. Mov Disord. 2004;19(5):554–60.
110. Manson AJ, Katzenschlager R, Hobart J, Lees AJ. High dose naltrexone for dyskinesias induced by levodopa. J Neurol Neurosurg Psychiatry. 2001;70(4):554–6.
111. Rascol O, Fabre N, Blin O, Poulik J, Sabatini U, Senard JM, et al. Naltrexone, an opiate antagonist, fails to modify motor symptoms in patients with Parkinson's disease. Mov Disord. 1994;9(4):437–40.
112. Cox H, Togasaki DM, Chen L, Langston JW, Di Monte DA, Quik M. The selective kappa-opioid receptor agonist U50,488 reduces L-dopa-induced dyskinesias but worsens parkinsonism in MPTP-treated primates. Exp Neurol. 2007;205(1):101–7.
113. Ikeda K, Yoshikawa S, Kurokawa T, Yuzawa N, Nakao K, Mochizuki H. TRK-820, a selective kappa opioid receptor agonist, could effectively ameliorate L-DOPA-induced dyskinesia symptoms in a rat model of Parkinson's disease. Eur J Pharmacol. 2009;620(1–3):42–8.
114. Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. J Neurosci. 2008;28(2):407–14.
115. Samadi P, Bedard PJ, Rouillard C. Opioids and motor complications in Parkinson's disease. Trends Pharmacol Sci. 2006;27(10):512–7.
116. Samadi P, Gregoire L, Bedard PJ. The opioid agonist morphine decreases the dyskinetic response to dopaminergic agents in parkinsonian monkeys. Neurobiol Dis. 2004;16(1):246–53.
117. Berg D, Becker G, Reiners K. Reduction of dyskinesia and induction of akinesia induced by morphine in two parkinsonian patients with severe sciatica. J Neural Transm. 1999;106(7–8):725–8.
118. Wagner KJ, Valet M, Kochs EF, Kriner M, Tolle TR, Sprenger T. The mu-opioid receptor agonist remifentanil induces acute dysphoria irrespective of its analgesic properties. J Psychopharmacol. 2010;24(3):355–61.
119. Hille CJ, Fox SH, Maneuf YP, Crossman AR, Brotchie JM. Antiparkinsonian action of a delta opioid agonist in rodent and primate models of Parkinson's disease. Exp Neurol. 2001;172(1):189–98.
120. Johnston TH, Fox SH, Gomez-Ramirez J, Lee J, Brotchie JM, editors. Anti-parkinsonian effects of delta opioid receptor stimulation are accompanied by dystonia in MPTP-lesioned non-human primates previously treated with L-DOPA. 8th International Congress of Parkinson's Disease and Movement Disorders. Rome: Movement Disorder Society; 2004.
121. Marti M, Trapella C, Viaro R, Morari M. The nociceptin/orphanin FQ receptor antagonist J-113397 and L-DOPA additively attenuate experimental parkinsonism through overinhibition of the nigrothalamic pathway. J Neurosci. 2007;27(6):1297–307.

122. Visanji NP, de Bie RM, Johnston TH, McCreary AC, Brotchie JM, Fox SH. The nociceptin/orphanin FQ (NOP) receptor antagonist J-113397 enhances the effects of levodopa in the MPTP-lesioned nonhuman primate model of Parkinson's disease. Mov Disord. 2008;23(13):1922–5.
123. Marti M, Rodi D, Li Q, Guerrini R, Fasano S, Morella I, et al. Nociceptin/orphanin FQ receptor agonists attenuate L-DOPA-induced dyskinesias. J Neurosci. 2012;32(46):16106–19.
124. Martin WR. History and development of mixed opioid agonists, partial agonists and antagonists. Br J Clin Pharmacol. 1979;7 Suppl 3:273S–9.
125. Chang KJ, Pendergast W, Holt J. Method of treating parkinson's disease with diarylmethylpiperazine compounds exhibiting delta receptor agonist activity. Google Patents; 2007.
126. Braithwaite S, Mouradian M, Voronkov M. Method of treating dyskinesia. Google Patents; 2012.
127. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10(4):537–51.
128. Kenakin T. Functional selectivity through protean and biased agonism: who steers the ship? Mol Pharmacol. 2007;72(6):1393–401.
129. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. Nat Rev Drug Discov. 2013;12(3):205–16.
130. Schmid CL, Streicher JM, Groer CE, Munro TA, Zhou L, Bohn LM. Functional selectivity of 6′-guanidinonaltrindole (6′-GNTI) at kappa-opioid receptors in striatal neurons. J Biol Chem. 2013;288(31):22387–98.
131. Zhou L, Lovell KM, Frankowski KJ, Slauson SR, Phillips AM, Streicher JM, et al. Development of functionally selective, small molecule agonists at kappa opioid receptors. J Biol Chem. 2013;288(51):36703–16.
132. Bruchas MR, Land BB, Aita M, Xu M, Barot SK, Li S, et al. Stress-induced p38 mitogen-activated protein kinase activation mediates kappa-opioid-dependent dysphoria. J Neurosci. 2007;27(43):11614–23.
133. Bausch SB, Garland JP, Yamada J. The delta opioid receptor agonist, SNC80, has complex, dose-dependent effects on pilocarpine-induced seizures in Sprague-Dawley rats. Brain Res. 2005;1045(1–2):38–44.
134. Nozaki C, Le Bourdonnec B, Reiss D, Windh RT, Little PJ, Dolle RE, et al. delta-Opioid mechanisms for ADL5747 and ADL5859 effects in mice: analgesia, locomotion, and receptor internalization. J Pharmacol Exp Ther. 2012;342(3):799–807.