The Delta Opioid Receptor in Pain Control

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Abstract

Nowadays, the delta opioid receptor (DOPr) represents a promising target for the treatment of chronic pain and emotional disorders. Despite the fact that they produce limited antinociceptive effects in healthy animals and in most acute pain models, DOPr agonists have shown efficacy in various chronic pain models. In this chapter, we review the progresses that have been made over the last decades in understanding the role played by DOPr in the control of pain. More specifically, the distribution of DOPr within the central nervous system and along pain pathways is presented. We also summarize the literature supporting a role for DOPr in acute, tonic, and chronic pain models, as well as the mechanisms regulating its activity under specific conditions. Finally, novel compounds that have make their way to clinical trials are discussed.

Keywords

Analgesia • Antinociception • Delta opioid receptor • Pain • Pain pathways

1 The Opioid System

While opium has been used for centuries, the endogenous opioid system was only discovered in the mid-1970s. Two pentapeptides named methionine- and leucine-enkephalin were first identified and characterized by Hughes and colleagues in 1975 (Hughes et al. 1975). Rapidly thereafter, endorphin (Li and Chung 1976; Loh et al. 1976) and dynorphin (Goldstein et al. 1979) were also discovered. More recently, an opioid-like peptide named nociceptin/orphanin was also identified (Meunier et al. 1995; Reinscheid et al. 1995). The endogenous opioid/opioid-like ligands are derived from four distinct precursors, namely proenkephalin, pro-opiomelanocortin (POMC), prodynorphin, and pronociceptin/orphanin. The synthesis of the opioid peptides therefore depends on the activity of endo- or carboxypeptidases (for more details on the discovery of the opioid peptides, see Akil et al. 1998; Darland et al. 1998; Snyder and Pasternak 2003).

Opioid peptides bind to three major receptor subtypes, namely mu (MOPr), delta (DOPr), and kappa (KOPr) opioid receptors. These receptors are, respectively, encoded by the *oprm1*, *oprd1*, and *oprk1* genes. The opioid-like peptide nociceptin/orphanin rather binds to the opioid-like receptor called Orphanin FQ/nociceptin receptor (NOPr). All four receptors belong to the superfamily of G protein-coupled receptors (GPCRs) and exhibit a high sequence homology in their protein structure and genomic organization (Kieffer and Gaveriaux-Ruff 2002; Stevens 2009).

Opioids (and opioid receptors) are particularly well known for their important effects in controlling pain. However, opioids are also involved in reward, addiction, neuroprotection, and many other physiological processes such as respiration, gastrointestinal motility, as well as in the endocrine and the immune systems (for reviews, see Kieffer and Gaveriaux-Ruff 2002; Kieffer and Evans 2009; Pradhan

et al. 2011; Sauriyal et al. 2011; Chu Sin Chung and Kieffer 2013; Lutz and Kieffer 2013; Gendron et al. 2015). Indeed, MOPr agonists are widely prescribed for the management of pain, although their pronounced unwanted effects (constipation, respiratory depression, sedation, tolerance) often limit their usage (McQuay 1999; Al-Hasani and Bruchas 2011). By contrast, DOPr agonists also produce pain relief but they were shown to have fewer unwanted effects than MOPr agonists (Dondio et al. 2001; Petrillo et al. 2003; Gallantine and Meert 2005) and do not induce tolerance in various animal models (Dondio et al. 2001; Mika et al. 2001; Beaudry et al. 2009). DOPr agonists therefore appear as a good and promising alternative for the treatment of chronic pain (Pradhan et al. 2011). It is worth noting that DOPr agonists also have anxiolytic, anti-depressive, analgesic, and cardio- and neuroprotective effects (Pradhan et al. 2011; Headrick et al. 2015).

In this chapter, we will discuss the role and the functions of DOPr in pain control. In particular, we will describe the distribution of DOPr along the pain pathways and summarize the literature supporting a role for DOPr in the treatment of pain. An overview of novel compounds and their effects in clinical trials will also be provided.

2 The Delta Opioid Receptor: A One-of-a-Kind

2.1 Cloning of DOPr

In 1992, two distinct groups successfully identified an opioid binding site from NG108-15 cells (Evans et al. 1992; Kieffer et al. 1992). Using similar approaches, both groups concomitantly cloned the mouse DOPr by creating a random cDNA library from the RNA of these cells. The cloning of MOPr and KOPr followed soon afterward (Chen et al. 1993; Meng et al. 1993; Minami et al. 1993; Wang et al. 1993).

Oprd1, the gene encoding DOPr, was identified and its chromosomal localization determined. In humans, *oprd1* is located in the distal part of the short arm of chromosome 1. Interestingly, although they share a similar genomic structure and a high sequence homology (Zaki et al. 1996; Chaturvedi et al. 2000), genes encoding MOPr and KOPr are found on different chromosomes, namely in the long arm of chromosomes 6 and 8, respectively (Befort et al. 1994; Wang et al. 1994; Yasuda et al. 1994). The detailed structure of *oprd1* and its translational and epigenetic regulation have been recently reviewed elsewhere (Wei and Loh 2011; Gendron et al. 2016).

2.2 DOPr Structure and Signaling

As a member of the GPCR superfamily, DOPr contains seven hydrophobic transmembrane domains connected by intra- and extracellular loops. DOPr also possesses N- and C-terminal tails, respectively, at its extra- and intracellular ends.

The crystal structures of all three opioid receptors have been recently resolved (Granier et al. 2012; Manglik et al. 2012; Wu et al. 2012). The structures revealed a well-conserved amino acid backbone among the three receptors in the lower part of the binding pocket, a region important for the recognition of the morphinan group. This portion of the binding pocket interacts with the "message segment" of the ligand which is responsible for its efficacy. The upper part of the binding pocket is, however, divergent among the three receptors and its interaction with the distinct "address" segment of the ligand is responsible for receptor selectivity (Granier et al. 2012). DOPr was also found to contain a sodium allosteric binding site regulating biased signaling and constitutive activity (Fenalti et al. 2014).

As MOPr and KOPr, DOPr interacts with numerous proteins and signaling partners (Gendron et al. 2016). When activated, conformational changes within the receptor and its transmembrane domains are leading to the activation of multiple signaling pathways. In particular, the G protein subunits $G\alpha_{i/o}$ and $G\beta\gamma$ dissociate from each other and act on various intracellular effectors. The activation of the G protein modifies the activity of calcium (*P*/*Q*-, *N*- and *L*-type) and potassium channels (G protein gated inwardly rectifying potassium, Kir3) and inhibits adenylyl cyclase activity (reducing the level of intracellular cAMP). These events produce a decrease in neuronal excitability and modifications of gene expression (Kieffer and Evans 2009; Al-Hasani and Bruchas 2011; Gendron et al. 2016). Following agonist stimulation, DOPr also undergoes rapid phosphorylation by G protein-regulated kinases (GRKs). Phosphorylation of DOPr on its C-terminal tail by GRKs is followed by the recruitment of β-arrestins and internalization of the receptor via clathrin-coated vesicles (endocytosis). After internalization, GPCRs are either recycled back to the plasma membrane or undergo degradation (Bie and Pan 2007). While MOPr is mainly recycled back to the plasma membrane, DOPr was shown to be primarily degraded through the lysosomal pathway (Tsao and von Zastrow 2000; Finn and Whistler 2001; Whistler et al. 2002). Several motifs within the receptor are involved in controlling this process. In particular, specific interactions with distinct sorting proteins are routing DOPr either to the degradation or to the recycling pathways. As an example, the Na+/H+ exchanger regulatory factor (NHERF), also called ERM-binding phosphoprotein 50 (EBP50), and the *N*-ethylmaleimide sensitive factor (NSF) were found to be important for the recycling of DOPr (Heydorn et al. 2004; Bie et al. 2010). By contrast, GPCR associated sorting protein (GASP) and sorting nexin-1 (SNX-1) were shown to sort the receptor to the degradation pathway. The C-terminal tail of DOPr seems to have a high affinity for GASP and SNX-1 (Whistler et al. 2002; Heydorn et al. 2004; Simonin et al. 2004). Indeed, swapping the C-terminal tail of DOPr with that of MOPr was shown to shift the fate of the receptor from the degradation toward the recycling pathway (Whistler et al. 2002). Similarly, GASP inactivation was shown to reduce the amount of DOPr in lysosomal compartments and to inhibit its downregulation following agonist stimulation (Whistler et al. 2002).

2.3 DOPr Expression and Distribution

The expression of DOPrs in the mammalian central nervous system has been widely investigated. Precisely, the distribution of DOPr mRNA and binding sites was studied by in situ hybridization, autoradiography, and/or immunohistochemistry (Mansour et al. 1987, 1993, 1994; Sharif and Hughes 1989; George et al. 1994; Cahill et al. 2001a; Pradhan and Clarke 2005; Peng et al. 2012). In mice, the expression of the opioid receptors begins at early developmental stages in the CNS and in peripheral tissues (Zhu et al. 1998). MOPr and KOPr mRNA were, respectively, detected in basal ganglia and midbrain as early as at embryonic stage E11.5. By contrast, the expression of DOPr mRNA only begins at E13.5 in the pons and the hypothalamus. Compared to MOPr and KOPr, DOPr remains restricted within a few brain regions including the caudate–putamen, the olfactory tubercle, and the parabrachial nucleus until late in the development. In dorsal root ganglia (DRGs), DOPr mRNA was detected as early as the embryonic stage E12.5 while it only appears at E15.5 in the ventral part of the spinal cord. Surprisingly, the expression of DOPr mRNA in the mouse dorsal horn of the spinal cord only appears at E17.5 (Zhu et al. 1998).

Although opioid binding sites have been observed by autoradiography in the developing embryo (Kent et al. 1981), specific binding for DOPr has not been observed in rodents before the second week after birth (McDowell and Kitchen 1986; Negri et al. 1997). However, DPDPE-induced GTPγS binding was reported in the caudate–putamen at E12.5 and at E17.5 in the pons and the hypothalamus, suggesting the existence of functional DOPrs at these stages, at least in mice (Nitsche and Pintar 2003).

In the adults, the three opioid receptors are not evenly distributed throughout the CNS, suggesting that they have distinct physiological roles (for reviews see Mansour et al. 1995; Le Merrer et al. 2009). Whereas MOPrs are widely distributed in the brain with an enrichment in the thalamus, striatum, interpeduncular complex, habenula, cortex, superior and inferior colliculi, DOPrs are mainly expressed in distinct areas of the forebrain, predominantly in the olfactory tubercle, cerebral cortex, amygdala, nucleus accumbens, and striatum (Fig. 1a, b). KOPrs are mainly found in the cortex, olfactory tubercle, striatum, nucleus accumbens, hypothalamus, amygdala, and periaqueductal gray (PAG) (Mansour et al. 1987; Sharif and Hughes 1989; Slowe et al. 1999). Interestingly, in the areas where the three receptors were found, their cellular distribution often differs. This is exemplified in the striatum, where DOPr and KOPr are diffusely distributed while MOPrs are expressed in patch-like clusters (Mansour et al. 1987).

Of a particular interest for this chapter, DOPrs are known to be largely expressed along the pain pathways in all animal species studied to date, including humans. DOPrs are indeed present in primary afferents (i.e., DRGs), in the spinal cord, as well as in important structures along the ascending and descending pain pathways (Fig. 1). Among these structures, it is worth noting that DOPr is expressed in the PAG, the rostro-ventral medulla (RVM), the cerebral cortex, and the amygdala (Mansour et al. 1994, 1995; Cahill et al. 2001a; Mennicken et al. 2003; Poulin et al.

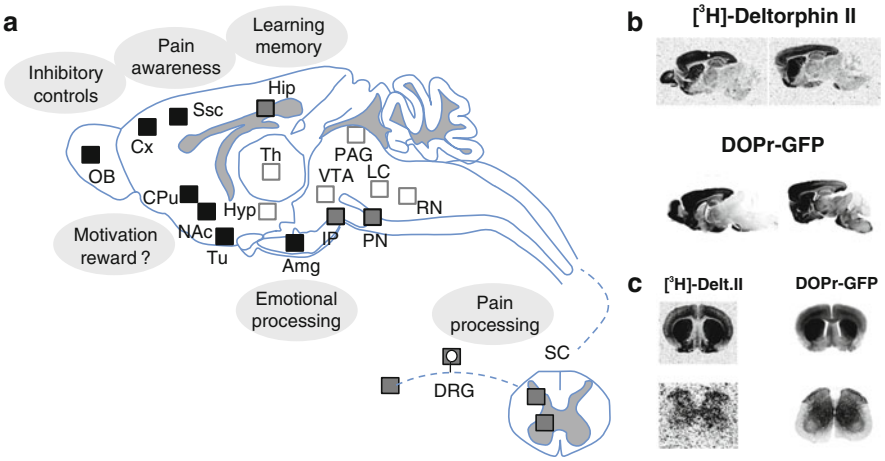

Fig. 1 DOPr distribution and functions in the central nervous system. (**a**) Schematic representation of DOPr binding sites and presumed functions in the central nervous system (CNS). DOPrs are highly expressed in the rostral part of the brain (*black squares*), especially in the olfactory bulb, cortex, striatum, and amygdala suggesting a role in pain processing and awareness, in emotional disorders (depression and anxiety), in addiction and impulsivity. Moderate (*grey squares*) to weak (*open squares*) expression of DOPr is also observed throughout the caudal part of the brain, including the spinal cord and the DRGs. (**b**, **c**) Representative photomicrographs showing a similar pattern of expression between DOPr binding sites labeled with [^{3}H]-Deltorphin II and DOPr immunofluorescence from DOPr-GFP knock-in mice (modified with permission from Pradhan et al. 2011; Bardoni et al. 2014)

2006; Peng et al. 2012). Interestingly, the distribution of DOPr in the spinal cord – and possibly in other structures as well – significantly differs among species. In the rodent spinal cord (mice and rats), DOPr is diffusely distributed in the gray matter (Sharif and Hughes 1989; Arvidsson et al. 1995; Mennicken et al. 2003) (Fig. 2). In monkeys, although DOPr binding sites are also found in all lamina of the spinal cord, a higher density of binding could be observed in the superficial lamina. Most interestingly, DOPr binding sites are restricted to the superficial lamina as well as in the Clark's column in the human spinal cord (Mennicken et al. 2003) (Fig. 2). The fact that the DOPr transcript is virtually absent in the human spinal cord (Fig. 2) suggests that DOPr binding sites are exclusively present on presynaptic primary afferent axon terminals. These observations strongly advise for a specialization of DOPr toward the pain pathways in higher species. For instance, the intrathecal injection of DOPr agonists in various acute and chronic pain models has been shown to produce antinociception, supporting a role for DOPr in pain.

The exact distribution of DOPr in primary afferents remains a matter of controversy and most certainly differs among species. While DOPr was commonly shown to be expressed in all three types of DRG neurons (Dado et al. 1993; Mansour et al. 1994; Ji et al. 1995; Minami et al. 1995; Zhang et al. 1998; Wang and Wessendorf 2001; Mennicken et al. 2003; Gendron et al. 2006), in DOPr-GFP knock-in mice

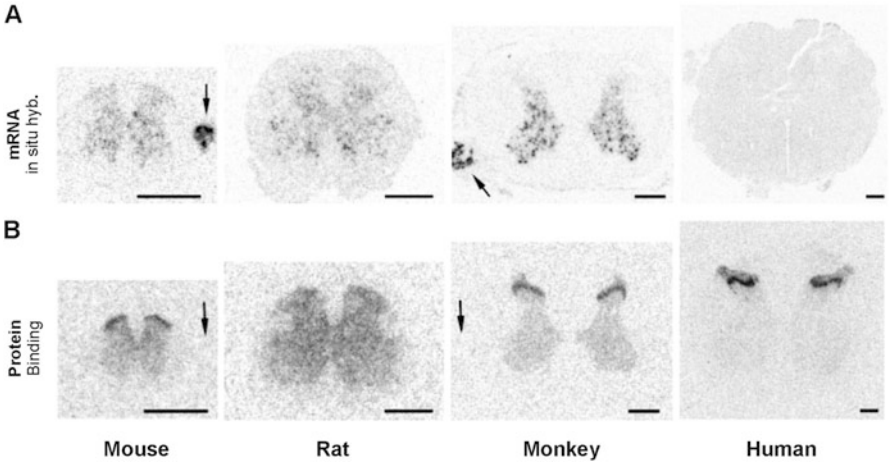

Fig. 2 Phylogenetic changes in DOPr expression in spinal cord and DRGs. Representative photomicrographs illustrating (**A**) DOPr mRNA expression (in situ hybridization) and (**B**) [^{125}I]-Deltorphin labeled DOPr binding sites in spinal cord and DRGs of mice, rats, monkeys, and humans (modified with permission from Mennicken et al. 2003)

DOPr was rather found to be primarily expressed in large myelinated non-peptidergic neurons and around hair follicles supporting a role in the perception of mechanical stimuli and light touch (Bardoni et al. 2014). These observations support the fact that MOPr and DOPr were, respectively, shown to specifically inhibit thermal and mechanical pain (Scherrer et al. 2009). This is, however, in sharp contrast with the work of others. Firstly, DOPr has often been found in substance P-containing neurons by a number of independent groups, and with different experimental approaches (Guan et al. 2005; Zhang et al. 2006, 2010; Riedl et al. 2009; Wang et al. 2010; Zhao et al. 2011). In particular, a role for an interaction between DOPr and preprotachykinin A (the precursor for substance P) in the targeting of DOPr to the cell surface through the regulated secretory pathway has been described (Guan et al. 2005). DOPr was indeed found to be present in large dense core vesicles (LDCV) containing substance P (Guan et al. 2005; Zhao et al. 2011). The presence of DOPr in substance P-containing neurons was also confirmed by single-cell RT-PCR (Wang et al. 2010). Also contrasting with the work cited above is the fact that the activation of DOPr by various agonists and in different animal models of pain was not only found to inhibit noxious mechanical stimuli but also heat-induced pain (Tables 1 and 2).

For a GPCR, DOPr was found to have an uncommon subcellular location. Indeed, under normal conditions DOPr was found to be retained in the cytoplasm, in association with intracellular compartments (Pasquini et al. 1992; Arvidsson et al. 1995; Cheng et al. 1995, 1997; Zhang et al. 1998; Cahill et al. 2001a; Commons et al. 2001; Wang and Pickel 2001) (Fig. 3a). Interestingly, it was observed that the density of cell surface DOPr can be increased under certain conditions such as in chronic pain models, or following prolonged morphine

Table 1 Acute pain modulation by DOPr agonists

Type	Test	Agonist	Effective doses (route of administration)	Animal species	References
Thermal pain	Tail flick	Deltorphin II	2.5–5 μg (i.t.)	Mouse	Dubois and Gendron (2010)
	Tail flick (warm water)	SNC80	104 nmol (i.c.v.) 69 nmol (i.t.) 57 mg/kg (i.p.)	Mouse	Bilsky et al. (1995)
	Tail flick (light beam)	SB-235863	100–300 mg/kg (p.o.) no effect	Rat	Petrillo et al. (2003)
		Deltorphin II	30–45–60 nmol (i.c.v.)	Rat	Fraser et al. (2000a)
		SNC80	200–300–400 nmol (i.c.v.)	Rat	Fraser et al. (2000a)
	Tail flick	SNC80	80 mg/kg (s.c.) no effect	Rat	Gallantine and Meert (2005)
		DPDPE	20 μg no effect Intra-RVM Intra-PAG	Rat	Rossi et al. (1994)
		Deltorphin II	20 μg Intra-RVM Intra-PAG	Rat	Rossi et al. (1994)
	Hot plate	Deltorphin II	10 μg (i.t.)	Rat	Cahill et al. (2001b)
		SNC80	100 nmol (i.c.v.)	Mouse	Bilsky et al. (1995)
		SB-235863	No effect (p.o.)	Rat	Petrillo et al. (2003)
	Hargreaves test	SNC80	No effect at 200 μg (i.t.)	Rat	Kouchek et al. (2013)
		Deltorphin II	No effect at 50 μg (i.pl.)	Rat	Kabli and Cahill (2007)
Mechanical pain	Von Frey test	SNC80	No effect (10 mg/kg, i.p.)	Mouse	Pradhan et al. (2013)
	Paw pressure	Deltorphin II	EC80 60 nmol (i.c.v.)	Rat	Fraser et al. (2000b)
		SNC80	EC80 400 nmol (i.c.v.)	Rat	Fraser et al. (2000b)
Chemical pain	Capsaicin	Deltorphin II	10 μg (i.t.)	Rat	Beaudry et al. (2011)
	Capsaicin (tail thermal hypersensitivity)	SNC80	1–10 mg/kg (s.c.)	Monkey	Brandt et al. (2001)
	Capsaicin (mechanical)	DPDPE	10–100–300 μg (i.m.)	Rat	Saloman et al. (2011)
	Prostaglandin E2	SNC80	3.2 mg/kg (s.c.)	Monkey	Brandt et al. (2001)

(continued)

Table 1 (continued)

Type	Test	Agonist	Effective doses (route of administration)	Animal species	References
	Formalin	Deltorphin II	10 μg (i.t.)	Rat	Beaudry et al. (2011)
		Deltorphin II	5 μg (i.t.)	Mouse	Morinville et al. (2003)
		Deltorphin II	ED50 7.7 μg/phase I and 32.4 μg/phase II (i.t.)	Rat	Cahill et al. (2001b)
		Deltorphin II	20 nmol (i.t.) 100 nmol (ipl)	Rat	Bilsky et al. (1996b)
		Deltorphin II	1–10 μg (i.t.)	Rat	Pradhan et al. (2006)
		SNC80	200 μg (i.t.)	Rat	Kouchek et al. (2013)
		Deltorphin II	50 μg (ipl)	Rat	Kabli and Cahill (2007)
		SNC80	11–44–111 nmol (ipl)	Rat	Obara et al. (2009)
		DSLET	14–42–70 nmol (ipl)	Rat	Obara et al. (2009)
		KNT-127	3 mg/kg (s.c.)	Mouse	Saitoh et al. (2011)
		SNC80	3 μmol/kg (i.v.)	Mouse	Barn et al. (2001)
	Acetic acid	KNT-127	3 mg/kg (s.c.)	Mouse	Saitoh et al. (2011)
		SNC80	10 mg/kg (s.c.)	Rat	Gallantine and Meert (2005)

treatment (Cahill et al. 2001a, 2003; Commons 2003; Morinville et al. 2003, 2004; Lucido et al. 2005; Gendron et al. 2006) (Fig. 3b, c). Since it is not the purpose of this chapter, the distinct mechanisms involved in the regulation of DOPr trafficking will not be discussed here. This topic has, however, recently been extensively reviewed elsewhere (Gendron et al. 2016). Simply, it should be kept in mind that the subcellular localization of DOPr and the possibility to increase its density at the cell surface could explain why DOPr agonists are more potent under certain conditions than in control/naïve animals.

Table 2 Chronic pain modulation by DOPr agonists

Type	Test	Agonist	Effective doses (route of administration)	Animal species	References
Inflammatory CFA	*Thermal pain*				
	Hargreaves Plantar test	Deltorphin II	1–3–10 μg (i.t.)	Rat	Cahill et al. (2003), Gendron et al. (2007a), and Beaudry et al. (2009, 2015b)
		Deltorphin II	1–2.5 μg (i.t.)	Mouse	Gendron et al. (2007b), Beaudry et al. (2009, 2015b), and Dubois and Gendron (2010)
		DPDPE Deltorphin II	50 nM (i.t.)	Mouse	Qiu et al. (2000)
		Deltorphin II	3–10–30–60 nmol (i.c.v.)	Rat	Fraser et al. (2000a)
		SNC80	100–300 nmol (i.c.v.)	Rat	Fraser et al. (2000a)
		SB-235863	30–70 mg/kg (s.c.)	Rat	Beaudry et al. (2009)
		SNC80	40 mg/kg (s.c.)	Rat	Gallantine and Meert (2005)
		SNC80	10 mg/kg (s.c.)	Mouse	Gaveriaux-Ruff et al. (2008)
		DPDPE	77.4–154.8 nmol (ipl)	Mouse	Hervera et al. (2009)
	Tail flick	SNC80	3.2 mg/kg (s.c.)	Monkey	Brandt et al. (2001)
	Mechanical pain				
	Von Frey filament	Deltorphin II	10–30 μg (i.t.)	Rat	Otis et al. (2011)
		SNC80	10 mg/kg (i.p.)	Mouse	Pradhan et al. (2013)
		SNC80	10 mg/kg (s.c.)	Mouse	Gaveriaux-Ruff et al. (2008)
	Paw pressure test (Randall–Stiletto)	DPDPE	10–100 μg (ipl)	Rat	Zhou et al. (1998)
Carrageenan	*Thermal pain*				
	Hargreaves Plantar test	SB-235863	10 mg/kg (p.o.)	Rat	Petrillo et al. (2003)
		Deltorphin II	10 μg (i.t.)	Rat	Stewart and Hammond (1994)

(continued)

Table 2 (continued)

Type	Test	Agonist	Effective doses (route of administration)	Animal species	References
		DPDPE	30 μg (i.t.)	Rat	Stewart and Hammond (1994)
	Mechanical pain				
	Von Frey filament	SNC80	200 μg (i.t.)	Rat	Kouchek et al. (2013)
Cancer pain	*Mechanical pain*				
	Von Frey filament	Deltorphin II	3–10–30 μg (i.t.)	Rat	Otis et al. (2011)
		DVal Ala-E	1.3 mg/kg (i.p.)	Mouse	Brainin-Mattos et al. (2006)
		SNC80	10 nmol (ipl)	Mouse	Ye et al. (2012)
	Thermal pain				
	Unilateral hotplate test	DPDPE	30 μg (peritumoral)	Mouse	Baamonde et al. (2005)
Diabetic neuropathy	Tail flick	TAN-67	ED50 ~6 μg (i.c.v.)	Mouse	Kamei et al. (1997b)
	Formalin	TAN67	30 mg/kg (s.c.)	Mouse	Kamei et al. (1997a)
Neuropathic pain	*Thermal pain*				
	Hargreaves Plantar test	DSLET	111 nmol (ipl)	Rat	Obara et al. (2009)
		SNC80	111 nmol (ipl)	Rat	Obara et al. (2009)
		SB-235863	10 mg/kg (p.o.)	Rat	Petrillo et al. (2003)
	Noxious thermal stimuli (paw)	Deltorphin II	10 μg (i.t.)	Rat	Holdridge and Cahill (2007)
	Tail flick (cold allodynia)	Deltorphin II	15–25 μg (i.t.)	Rat	Mika et al. (2001)
	Tail flick (heat and cold stimuli)	Deltorphin II	1.5–15–25 μg (i.t.)	Rat	Mika et al. (2001)
	Tail flick (cold allodynia)	DPDPE	25 μg (i.t.)	Rat	Mika et al. (2001)
	Tail flick (heat and cold stimuli)	DPDPE	5–25 μg (i.t.)	Rat	Mika et al. (2001)
	Acetone application	DPDPE	20 μg intra-PAG	Rat	Sohn et al. (2000)
	Mechanical pain				
	Von Frey filament	Deltorphin II	10–15–30 μg (i.t.)	Rat	Holdridge and Cahill (2007)

(continued)

Table 2 (continued)

Type	Test	Agonist	Effective doses (route of administration)	Animal species	References
		Deltorphin II	50 μg (ipl)	Rat	Kabli and Cahill (2007)
		SNC80	22–66–111 nmol (ipl)	Rat	Obara et al. (2009)
		DSLET	22–56–111 nmol (ipl)	Rat	Obara et al. (2009)
		DPDPE	20 μg intra-PAG	Rat	Sohn et al. (2000)
		BUBU	1.5–6 mg/kg (i.v.)	Rat	Desmeules et al. (1993)

ipl intraplantar, *s.c.* subcutaneous, *i.t.* intrathecal, *i.m.* intramuscular, *i.c.v.* intracerebroventricular, *i.p.* intraperitoneal, *p.o.* perorally, *i.v.* intravenous

3 DOPr and Pain Modulation

The analgesic efficacy of DOPr agonists was widely investigated using pharmacological and genetic approaches. Before describing the effects of DOPr agonists in acute and chronic pain models, it is worth noting that mice deficient for DOPr (DOPr knockout mice) did not show any significant change in pain perception following acute noxious stimuli (thermal, mechanical, or chemical stimuli) (Zhu et al. 1999; Filliol et al. 2000). However, sensitivity to thermal and mechanical stimuli is increased in inflammatory and neuropathic pain models in DOPr knockout mice (Nadal et al. 2006; Gaveriaux-Ruff et al. 2008). These observations therefore suggest that a constitutive tone of endogenous opioid release acting on DOPr would prevent exacerbation of chronic pain. This hypothesis is supported by the fact that the selective ablation of DOPr in NaV1.8 sensory neurons increases chronic pain (Gaveriaux-Ruff et al. 2011).

3.1 DOPr-Mediated Analgesia in Acute Pain Models

Agonists acting at DOPr are known to produce antinociception (Gaveriaux-Ruff and Kieffer 2011). Although first evidence for DOPr-mediated antinociception was provided in the early 1980s (Brantl et al. 1982), the lack of highly selective DOPr ligands prevented a clear demonstration of the physiological effects of this receptor. A pioneer study used [2-D-penicillamine, 5-D-penicillamine]enkephalin (DPDPE), a highly selective DOPr agonist (Mosberg et al. 1983), and confirmed that DOPr could mediate antinociception in the hot plate test (Porreca et al. 1984). Although their antinociceptive effects have been commonly reported thereafter, it is generally accepted that DOPr agonists, no matter the route of administration, only have weak

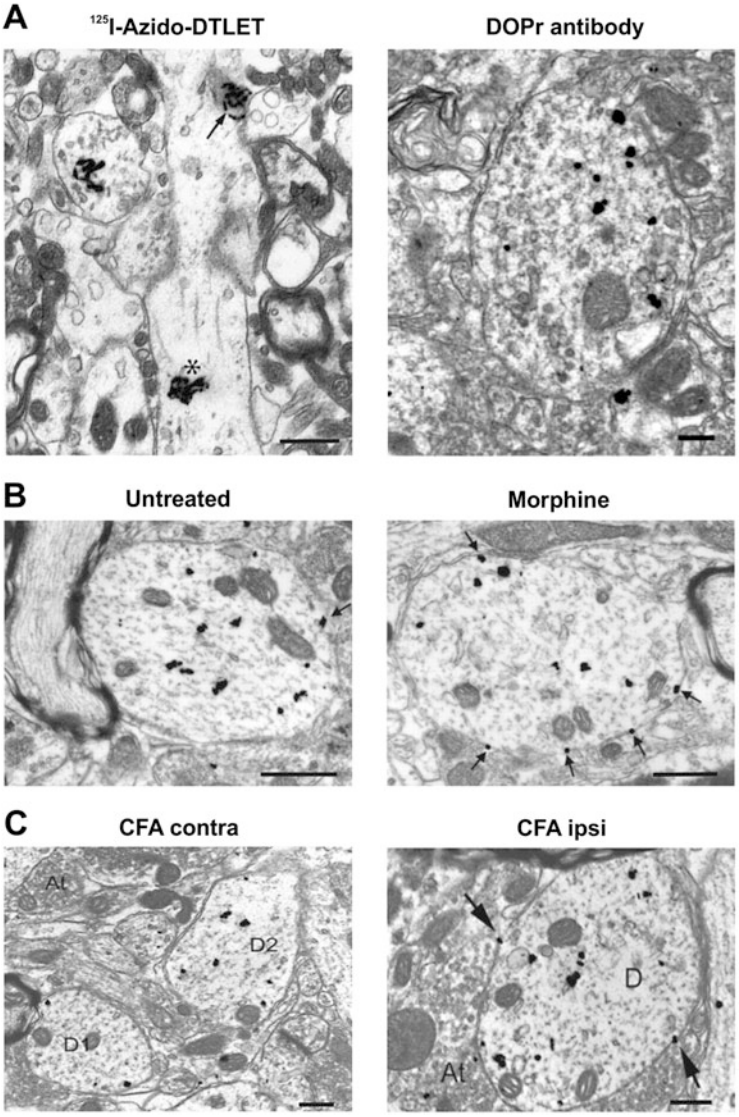

Fig. 3 Enhancement of DOPr expression at the plasma membrane of neurons under inflammatory or chronic morphine conditions. (**a**) Intracellular localization of DOPr in the neostriatum labeled with [^{125}I]-Azido-DTLET (a DOPr selective agonist, *left panel*) or by a DOPr antibody directed against the 3–17 segment (*left panel*) in untreated animals. (**b**, **c**) Electron microscopy of immunolabeled DOPr in the superficial laminae of lumbar spinal cord dorsal horn in animals treated with morphine (**b**, *right panel*) or in the CFA pain model (**c**, *right panel*) showing an increase in immunogold particles associated with the plasma membrane (adapted with permission from Pasquini et al. 1992; Cahill et al. 2001b, 2003, Lucido et al. 2005)

or no antinociceptive effects when healthy animals are tested with routinely used acute pain tests (e.g., tail flick and hot plate tests). Indeed, DOPr agonists seem to have only modest antinociceptive effects in acute pain models when compared to MOPr agonists. As an example, the i.c.v. administration of [D-Ala2, *N*-methyl-Phe4, Gly5-ol]enkephalin (DAMGO; a selective MOPr agonist) produced a more profound analgesia than DPDPE in the hot plate test (Porreca et al. 1984). Similarly, DAMGO was also shown to reduce mechanical nociception by 80% at a dose of 0.2 nmol (i.c.v.) in the paw pressure test while doses of 60 and 400 nmol of the DOPr agonists Deltorphin II and SNC80, respectively, were needed to produce similar effects (Fraser et al. 2000b). Table 1 summarizes the DOPr-mediated antinociceptive effects in acute pain tests.

3.1.1 Regulation of DOPr by MOPr in Healthy Animals

As described above, the antinociceptive effects of centrally administered DOPr agonists are generally weak. However, it was demonstrated that morphine or other MOPr agonists can potentiate the analgesic effects of spinally administered DOPr agonists (Cahill et al. 2001b; Morinville et al. 2003; Gendron et al. 2007a). The cellular mechanisms involved in the potentiation of DOPr functions are unclear. However, it was noted that the administration of morphine induces a translocation of DOPr to the plasma membrane in DRG (Gendron et al. 2006), spinal cord (Cahill et al. 2001b; Morinville et al. 2003; Gendron et al. 2007a), and central gray neurons (Lucido et al. 2005; see also Fig. 3b). As of to date, the exact mechanisms involved in this process have not been totally unveiled. We do know, however, that it involves MOPr as these effects are completely abolished in MOPr knockout animals (Morinville et al. 2003). In the PAG, morphine also increases the DOPr-mediated presynaptic inhibition of GABAergic synaptic currents (Hack et al. 2005). Both MOPr and β-arrestin 2 have been shown to be important for the upregulation of DOPr functions in the PAG (Hack et al. 2005). A more recent study also suggests that morphine induces a cdk5-mediated phosphorylation of the threonine 161 residue located in the second intracellular loop of DOPr (Xie et al. 2009). Phosphorylation of this residue by cdk5 would indeed increase the membrane expression of DOPr and, ultimately, enhance the antinociceptive effects of DOPr agonists in morphine-treated animals (Beaudry et al. 2015b). The phosphorylation of DOPr by cdk5 was further hypothesized to disrupt the formation of the MOPr-DOPr heterodimer (Xie et al. 2009). This is consistent with the observations made by others who show that chronic morphine treatment potentiates MOPr and DOPr heterodimerization throughout the CNS including areas involved in pain processing and in the DRGs (Gupta et al. 2010). It was further demonstrated that a mixture of the MOPr agonist methadone and the DOPr antagonist naltriben can stabilize DOPr at the cell surface in a heterodimer form preventing its endocytosis and therefore avoiding degradation (Milan-Lobo and Whistler 2011; Milan-Lobo et al. 2013).

3.2 DOPr-Mediated Analgesia in Acute Inflammatory Pain Models

By contrast to their minor effects in acute pain tests, DOPr agonists were found to be more efficient at alleviating acute inflammatory pain. Formalin- and capsaicin-induced pain behaviors are indeed efficiently inhibited following DOPr activation (Bilsky et al. 1996b; Cahill et al. 2001b; Morinville et al. 2003; Pradhan et al. 2006; Beaudry et al. 2011). As an example, the intrathecal administration of Deltorphin II was shown to significantly reduce the typical biphasic nociceptive response induced by formalin as well as the spontaneous pain-like behaviors – licking, biting, and flinching – induced by capsaicin. These effects were completely antagonized by the DOPr selective antagonist naltrindole, therefore supporting a role for DOPr (Bilsky et al. 1996b; Cahill et al. 2001b; Morinville et al. 2003; Pradhan et al. 2006; Beaudry et al. 2011). At the spinal level, DOPr-mediated analgesia was shown to involve an inhibition of substance P release (Beaudry et al. 2011; Kouchek et al. 2013). Substance P is produced in peptidergic C fibers and released upon activation of these neurons by peripheral noxious stimuli (Cao et al. 1998). As revealed by an inhibition of c-fos expression, the intrathecal administration of Deltorphin II or SNC80 reduces the activation of spinal neurons (Beaudry et al. 2011; Kouchek et al. 2013). Activation of DOPr in the spinal cord also prevents substance P release and blocks NK1 internalization in the superficial lamina of the lumbar dorsal horn induced by intraplantar formalin and capsaicin (Beaudry et al. 2011; Kouchek et al. 2013).

The systemic administration of DOPr agonists also produces antinociception in response to chemical stimuli (Barn et al. 2001; Brandt et al. 2001; Saitoh et al. 2011; Saloman et al. 2011). In primates, thermal hypersensitivity induced by capsaicin and prostaglandin E2 was completely reversed following subcutaneous administration of SNC80 (Brandt et al. 2001). KNT127 and SNC80 were also found to inhibit the biphasic nociceptive response induced by formalin as well as the acetic acid induced abdominal constrictions in mice (Barn et al. 2001; Saitoh et al. 2011).

Beside their central mechanism of actions, DOPr agonists also produce analgesia via receptors expressed in the periphery (Stein et al. 2001). The intraplantar administration of Deltorphin II, SNC80, and DSLET was shown to effectively suppress formalin-induced pain behaviors in rodents (Bilsky et al. 1996b; Kabli and Cahill 2007; Obara et al. 2009). This antinociceptive effect was completely reversed by intraplantar treatment with the DOPr antagonist naltrindole or by a pretreatment with DOPr antisense oligodeoxynucleotides (Bilsky et al. 1996a, b). Again, DOPr agonists had no significant effect on thermal or mechanical nociceptive thresholds under normal conditions (Bilsky et al. 1996b; Kabli and Cahill 2007; Obara et al. 2009).

3.2.1 Regulation of DOPr in Acute Inflammatory Pain

A recent study by Doyle Brackley and collaborators has provided mechanistic insights for the lack of efficacy of peripheral DOPr agonists in naïve animals.

They indeed observed that peripheral DOPr expressed on sensory nerves is constitutively desensitized by a GRK2-dependent mechanism. They found that under basal conditions GRK2 is constitutively associated with DOPr, therefore preventing its coupling to G proteins or other signaling partners. The knockdown of GRK2 was found to be sufficient to increase peripheral DOPr-mediated analgesia. Interestingly, in inflamed tissues PKC activation leads to RKIP phosphorylation which in turn sequesters GRK2. In this model, the sequestering of GRK2 "awakens" DOPr in sensory neurons and increases the analgesic effects of peripheral DOPr agonists (Brackley et al. 2016).

3.3 DOPr-Mediated Analgesia in Chronic Pain Models

The antinociceptive effects of various DOPr agonists in animal models of chronic pain are summarized in Table 2. In general, the efficacy and the potency of DOPr agonists at producing antinociception in chronic pain models are more important, when compared to acute pain models. Overall, the observations made in preclinical models of chronic pain suggest that DOPr agonists efficiently inhibit inflammatory, neuropathic, diabetic, as well as cancer pain. Interestingly, recent observations also support a role for DOPr in the treatment of migraine.

3.3.1 DOPr in Inflammatory Pain Models

Complete Freund's adjuvant (CFA) and carrageenan are commonly used to induce inflammation or as rodent models of arthritis (Klareskog 1989; Hansra et al. 2000). In these inflammatory pain models, spinal DOPr activation was shown to alleviate hyperalgesia (Hylden et al. 1991; Stewart and Hammond 1994; Qiu et al. 2000). In the CFA model of inflammation, Deltorphin II is effective at reducing both thermal hyperalgesia and mechanical allodynia in a dose-dependent manner (Cahill et al. 2003; Gendron et al. 2007a, b; Beaudry et al. 2009, 2015a; Dubois and Gendron 2010; Otis et al. 2011). The effects of Deltorphin II are DOPr-mediated since they are completely antagonized by DOPr selective antagonists. Interestingly, Deltorphin II has no analgesic effect on the uninflamed paw, supporting a lack of effects in healthy tissues (Cahill et al. 2003; Gendron et al. 2007a; Beaudry et al. 2009; Dubois and Gendron 2010; Otis et al. 2011). Indeed, in these chronic pain models, DOPr agonists commonly display a leftward shift of their dose-response effects when compared to dose-response curves in healthy animals.

The enhancement of DOPr analgesic potency in inflammatory pain models is thought to be the result of an increase in DOPr expression at the plasma membrane of spinal neurons. As stated above, the subcellular distribution of DOPr in the lumbar dorsal horn, as assessed by electron microscopy, revealed a predominant localization of the receptor within the intracellular compartments of neurons (Fig. 3b, c). However, following some inflammatory/pain state, an increase in DOPr distribution at the plasma membrane was seen in the ipsilateral lumbar spinal cord and the DRG neurons (Cahill et al. 2003; Gendron et al. 2006) (see also Fig. 3c). Studies based on fluorescent ligand internalization (used as a tool to

evaluate the density of membrane receptors) further revealed an increased level of internalization in the lumbar spinal cord and in small and medium DRG neurons in inflamed animals, thus supporting an upregulation of DOPr at the neuronal plasmalemma (Gendron et al. 2006, 2007a). Again, the mechanisms involved in this process are still unclear. As for the morphine-induced regulation of DOPr, CFA-induced inflammation requires MOPr to increase the membrane density of DOPr and the antinociceptive effects of DOPr agonists (Cahill et al. 2003; Gendron et al. 2007b). Similarly, the inhibition of cdk5-induced phosphorylation of DOPr prevents the enhancement of DOPr-mediated analgesia (Beaudry et al. 2015b). However, if an interaction between DOPr and preprotachykinin A appears to be essential for the membrane expression of DOPr in non-treated mice, the upregulation of DOPr function in the CFA model was shown to be independent of substance P (Dubois and Gendron 2010).

Centrally administered (i.c.v.) DOPr agonists also produce analgesia in the CFA model of inflammatory pain. SNC-80 and Deltorphin II were shown to increase the time to paw withdrawal in response to a thermal stimulus (Hargreaves test) (Fraser et al. 2000a). The potency of centrally administered DOPr agonists was also found to be improved in animals with persistent inflammation when compared to healthy animals. Indeed, the effective i.c.v. dose of SNC80 and Deltorphin II required to produce antihyperalgesic effect in the rat CFA model of inflammation is three times lower than that needed to induce analgesia to thermal stimulus in acute pain models (Fraser et al. 2000a). Other groups have also demonstrated an involvement of DOPr in the descending pain pathways. In fact, DOPr activation in supraspinal sites such as the RVM and PAG was found to produce analgesia in various animal models of chronic pain (for review, see Bie and Pan 2007). As an example, microinjection of Deltorphin II into the RVM was shown to dose-dependently reverse thermal hyperalgesia in CFA-treated rats (Hurley and Hammond 2000).

Activation of peripheral DOPr produces antinociception under pathological pain conditions. DPDPE, when administered in the periphery, produces antinociception in CFA and neuropathic pain models (Zhou et al. 1998; Hervera et al. 2009; Obara et al. 2009). Following inflammation, opioid receptors were shown to be upregulated in primary afferents in which they are highly transported toward the free nerve endings in the periphery. As a consequence, the potency of peripheral opioid agonists in mediating analgesia is enhanced. The low pH in the inflamed tissues is also thought to facilitating ligand/receptor coupling (for reviews, see Stein et al. 2001; Stein and Lang 2009). The local administration of the DOPr agonist SNC80 was also shown to dose-dependently reduce the mechanical hyperalgesia induced by the subcutaneous injection of prostaglandin E2 in the hindpaw (Pacheco and Duarte 2005). DOPr-induced analgesia in the periphery is thought to be mediated by the nitric oxide/cGMP pathway. Indeed, in the CFA model of inflammation the nitric oxide donor NOC-18 potentiates the antihyperalgesic effect of DPDPE (Hervera et al. 2009). Nitric oxide synthase or guanylate cyclase inhibitors also prevent the SNC80-mediated analgesia in the prostaglandin E2 pain model (Pacheco and Duarte 2005). Interestingly, the intraplantar administration of glibenclamide and tolbutamide, two ATP-sensitive K+ channel blockers, was

shown to reduce the analgesia produced by the local administration of SNC80, suggesting that the antinociceptive effect of this compound is specifically mediated by ATP-sensitive K+ channels (Pacheco and Duarte 2005).

3.3.2 DOPr in Neuropathic Pain Models

As reported in Table 2, DOPr agonists are also efficient at alleviating neuropathic pain in various preclinical models. The intrathecal administration of DPDPE or Deltorphin II was shown to significantly relieve allodynia and hyperalgesia in the sciatic nerve ligation model (Mika et al. 2001; Holdridge and Cahill 2007). DPDPE injected into the ventral PAG also effectively reduces mechanical and thermal allodynia in a neuropathic pain model where both the tibial and sural nerves are completely cut (Sohn et al. 2000). In other nerve injury models, peripherally administered DOPr agonists also produce anti-allodynic effects (Kabli and Cahill 2007; Obara et al. 2009). In the peripheral nerve injury model, the increased analgesic effects of DOPr agonists may be the consequence of a higher level of DOPr expression or as a relocalization of DOPr at the cell surface (Kabli and Cahill 2007; Obara et al. 2009).

3.3.3 DOPr in Diabetic Neuropathy

Diabetic neuropathy represents another disease in which DOPr agonists may be used to reduce pain. For instance, the non-peptide TAN-67 was found to produce a dose-dependent antinociception in the mouse tail flick assay when administered i.c.v. (Kamei et al. 1997b). In diabetic mice, an increase in the endogenous tone of the spinal DOPr system was demonstrated. Indeed, in these mice, the inflammatory phase of the formalin test is greatly reduced, an effect reversed by naltrindole (Kamei et al. 1997a).

3.3.4 DOPr in Bone Cancer Pain

Although it has a unique set of characteristics, bone cancer-induced pain includes an important neuropathic component (Honore et al. 2000). It is therefore not surprising to see that DOPr agonists are effective in bone cancer models. In a rat model of metastatic bone cancer-induced pain (Dore-Savard et al. 2010), the intrathecal administration of Deltorphin II was shown to dose-dependently reverse mechanical allodynia, an effect completely blocked by a pretreatment with the DOPr antagonist naltrindole (Otis et al. 2011). The intraperitoneal administration of [dVal(L)2,Ala(L)5]E, another selective DOPr agonist, also produces analgesia in a mouse model of bone cancer-induced pain (Brainin-Mattos et al. 2006). The analgesic effect of DOPr was also demonstrated in mice bearing a tibial osteosarcoma (Baamonde et al. 2005). In this model the peritumoral injection of DPDPE induced a naltrindole-sensitive increase in the paw thermal withdrawal latencies (Baamonde et al. 2005). Similarly, DOPr activation alleviates mechanical hypersensitivity in an orthotopic mouse oral cancer model (Ye et al. 2012). In humans coping with cancer pain, intrathecally administered DADLE, a DOPr-preferred agonist, has also been shown to produce analgesia, even in patients who had

developed tolerance to morphine (Onofrio and Yaksh 1983; Moulin et al. 1985; Krames et al. 1986).

3.3.5 DOPr Agonists in Trigeminal and Migraine Pain Models

DOPr appears to play a crucial role in the modulation of trigeminal pain. In rodents and humans, DOPr mRNA can be found in small-, medium-, and large-sized trigeminal ganglia neurons (Mennicken et al. 2003). In the trigeminal nucleus caudalis (Sp5C), a structure involved in modulating and processing somatosensory and nociceptive inputs originating from the orofacial region, DOPr binding sites have a more widespread distribution in rodents than humans. In humans, DOPr binding sites are confined to the superficial laminae of the Sp5C (Mennicken et al. 2003; Ichikawa et al. 2005). Supporting a role for DOPr in trigeminal pain, the activation of peripheral DOPrs was found to attenuate the capsaicin-induced mechanical hypersensitivity in the masseter muscle via the activation of GIRK channels in rats (Saloman et al. 2011; Chung et al. 2014). The activation of DOPr with low doses of DPDPE was also found to reduce substance P release from Sp5C slices, a hallmark of opioid-mediated analgesia (Suarez-Roca and Maixner 1992). Yet, the systemic administration of Deltorphin II produces a pronounced inhibition of C fiber-evoked responses in wide dynamic range neurons of the Sp5C (Wang et al. 1996). Under inflammatory conditions, DOPr-mediated trigeminal analgesia is also enhanced. As measured by a reduction in CGRP release and adenylate cyclase activity, a pretreatment with bradykinin increases the potency of DPDPE to inhibit the activity of trigeminal nociceptors (Patwardhan et al. 2005). In trigeminal nociceptors, this effect is concomitant to an increase of cell surface DOPr (Patwardhan et al. 2005).

In patients unresponsive to classical treatments, opioids acting on MOPrs are often prescribed to treat severe cases of migraine headaches[1] (for review see Becker 2015). In some cases, however, extensive treatments with opioids can lead to an exacerbation of the frequency and the intensity of migraine episodes in addition to interfere with other migraine therapies (Bigal and Lipton 2008; Bigal et al. 2008; Ansari and Kouti 2016). Recent reports revealed a promising therapeutic potential for DOPr in alleviating migraine headaches (Charles and Pradhan 2016). In an animal model of migraine induced by nitroglycerine (NTG), DOPr activation efficiently reduces thermal hyperalgesia and mechanical allodynia, two symptoms often observed in humans coping with migraine (Pradhan et al. 2014). In this model, the antinociceptive effect of SNC80 is similar to that obtained with sumatriptan, a classical serotonergic receptor (5-HT_{1B} and 5-HT_{1D}) agonist used to treat migraine headaches. SNC80 was also found to be efficient in reducing the aversive state

[1]Migraine is the most common and disabling neurological disorder that occurs as recurrent, pulsatile, episodic headaches with or without aura. It is thought to be the result of trigeminal nerve activation leading to distension in cerebral and meningeal blood vessels. The cortical spreading depression (CSD) is defined as a slowly propagated wave of depolarization originating from the occipital to the frontal part of the brain which is followed by a suppression of brain activity (Goadsby et al. 2009; Olesen et al. 2009).

evoked by NTG in the conditioned place preference test, further supporting a role for DOPr in alleviating migraine headaches (Pradhan et al. 2014). These observations are supported by the fact that cortical spreading depression events (CSD; a phenomenon thought to be responsible for the occurrence of migraine with aura, Charles and Baca 2013) evoked by KCl were reduced by the systemic administration of SNC80 (Pradhan et al. 2014).

4 Novel Compounds and Clinical Trials

DOPr is commonly considered as a potential target for the development of novel therapies for the management of chronic pain and emotional disorders (Pradhan et al. 2011). One of the major challenges in the development of novel DOPr agonists for the clinic is the propensity of such ligands to induce nonlethal convulsions at analgesic doses (Comer et al. 1993; Dykstra et al. 1993; Pakarinen et al. 1995; Broom et al. 2002a, b; Chung et al. 2015). Still, a few drugs targeting DOPr have been moved to clinical trials. ADL5747 and ADL5859 are two orally bioavailable compounds (Le Bourdonnec et al. 2008, 2009) that were tested in small cohorts of patients. These compounds, which are devoid of pro-convulsive actions in preclinical models, have indeed been tested for acute (NCT00993863) and chronic (NCT00979953) pain management in Phase 2 clinical trials. Unfortunately, none of the compounds were more effective than the placebo in patients suffering from osteoarthritic pain.

More recently, it was proposed that DOPr-induced seizures are mediated by the activation of the β-arrestin 2 pathway. Exploiting the concept of biased ligands, Trevena, Inc. has developed a novel orally available DOPr-selective compound with a robust bias toward the G protein signaling pathway. This is to say that the compound has virtually no ability to recruit β-arrestin 2 but still activates G proteins with high efficiency. The preclinical evaluation of TRV250 is promising for the treatment of migraine headaches. TRV250 was found to preserve the analgesic properties of common DOPr agonists without producing seizures (http://www.trevenainc.com/TRV250.php).

Although this was not thoroughly covered in this chapter, one should note that DOPr can form dimers or interact with other GPCRs (reviewed in Gendron et al. 2016). Because of their unique pharmacology, GPCR dimers represent a novel class of targets for the development of new drugs and/or therapies (Fujita et al. 2014, 2015). One such target is the MOPr-DOPr heteromer (Fujita et al. 2015). A library screening for this target led to the identification of CYM51010, a selective MOPr-DOPr agonist (Gomes et al. 2013). In the tail flick test, CYM51010 was found to produce antinociception without inducing tolerance (Gomes et al. 2013). This target is thought to induce analgesia without causing the common unwanted effects associated with opioids (Fujita et al. 2015). Bivalent ligands designed to have a high affinity for MOPr and DOPr or KOPr and DOPr were found to exhibit good analgesic properties. Compounds targeting MOPr and DOPr such as L2, L4 (Harvey et al. 2012), MDAN (Daniels et al. 2005b), or RV-JIM-C3 (Podolsky

et al. 2013) as well as compounds targeting KOPr and DOPr such as KDAN-18 (Daniels et al. 2005a) and KDN-21 (Bhushan et al. 2004) were found to produce robust analgesia with no apparent signs of tolerance, physical dependence, or sedation (Daniels et al. 2005b; Ansonoff et al. 2010; Podolsky et al. 2013). Two such bivalent ligands targeting MOPr and DOPr are currently in clinical trials. Compound 51 and MuDelta (both acting as MOPr agonist and DOPr antagonist) completed clinical trials in patients suffering from irritable bowel syndrome (Breslin et al. 2012; Wade et al. 2012). The MuDelta was approved recently by the US authorities to be commercialized under the name of Eluxadoline (Garnock-Jones 2015). This compound proved to be efficient in relieving abdominal pain symptoms and diarrhea (Garnock-Jones 2015; Lembo et al. 2016).

5 Conclusion

DOPr represents a promising therapeutic target for the treatment of chronic pain and emotional disorders. Although DOPr agonists produce only weak analgesic effects in healthy animals and in acute pain models, numerous groups have previously described an increase in their analgesic potency in chronic pain models (e.g., inflammatory, neuropathic, and bone cancer-induced pain models). Interestingly, the increased analgesic effects of DOPr agonists are paralleled by a translocation of DOPr from the intracellular compartments to the plasma membrane of spinal cord and DRG neurons.

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References

Akil H, Owens C, Gutstein H, Taylor L, Curran E, Watson S (1998) Endogenous opioids: overview and current issues. Drug Alcohol Depend 51:127–140

Al-Hasani R, Bruchas MR (2011) Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology 115:1363–1381

Ansari H, Kouti L (2016) Drug interaction and serotonin toxicity with opioid use: another reason to avoid opioids in headache and migraine treatment. Curr Pain Headache Rep 20:50

Ansonoff MA, Portoghese PS, Pintar JE (2010) Consequences of opioid receptor mutation on actions of univalent and bivalent kappa and delta ligands. Psychopharmacology 210:161–168

Arvidsson U, Dado RJ, Riedl M, Lee JH, Law PY, Loh HH, Elde R, Wessendorf MW (1995) Delta-opioid receptor immunoreactivity: distribution in brainstem and spinal cord, and relationship to biogenic amines and enkephalin. J Neurosci 15:1215–1235

Baamonde A, Lastra A, Juarez L, Garcia V, Hidalgo A, Menendez L (2005) Effects of the local administration of selective mu-, delta-and kappa-opioid receptor agonists on osteosarcoma-induced hyperalgesia. Naunyn Schmiedebergs Arch Pharmacol 372:213–219

Bardoni R, Tawfik VL, Wang D, Francois A, Solorzano C, Shuster SA, Choudhury P, Betelli C, Cassidy C, Smith K, de Nooij JC, Mennicken F, O'Donnell D, Kieffer BL, Woodbury CJ, Basbaum AI, MacDermott AB, Scherrer G (2014) Delta opioid receptors presynaptically regulate cutaneous mechanosensory neuron input to the spinal cord dorsal horn. Neuron 81:1312–1327

Barn DR, Caulfield WL, Cottney J, McGurk K, Morphy JR, Rankovic Z, Roberts B (2001) Parallel synthesis and biological activity of a new class of high affinity and selective delta-opioid ligand. Bioorg Med Chem 9:2609–2624

Beaudry H, Proteau-Gagne A, Li S, Dory Y, Chavkin C, Gendron L (2009) Differential noxious and motor tolerance of chronic delta opioid receptor agonists in rodents. Neuroscience 161:381–391

Beaudry H, Dubois D, Gendron L (2011) Activation of spinal mu- and delta-opioid receptors potently inhibits substance P release induced by peripheral noxious stimuli. J Neurosci 31:13068–13077

Beaudry H, Gendron L, Moron JA (2015a) Implication of delta opioid receptor subtype 2 but not delta opioid receptor subtype 1 in the development of morphine analgesic tolerance in a rat model of chronic inflammatory pain. Eur J Neurosci 41:901–907

Beaudry H, Mercier-Blais AA, Delaygue C, Lavoie C, Parent JL, Neugebauer W, Gendron L (2015b) Regulation of mu and delta opioid receptor functions: involvement of cyclin-dependent kinase 5. Br J Pharmacol 172:2573–2587

Becker WJ (2015) Acute migraine treatment in adults. Headache 55:778–793

Befort K, Mattei MG, Roeckel N, Kieffer B (1994) Chromosomal localization of the delta opioid receptor gene to human 1p34.3-p36.1 and mouse 4D bands by in situ hybridization. Genomics 20:143–145

Bhushan RG, Sharma SK, Xie Z, Daniels DJ, Portoghese PS (2004) A bivalent ligand (KDN-21) reveals spinal delta and kappa opioid receptors are organized as heterodimers that give rise to delta(1) and kappa(2) phenotypes. Selective targeting of delta-kappa heterodimers. J Med Chem 47:2969–2972

Bie B, Pan ZZ (2007) Trafficking of central opioid receptors and descending pain inhibition. Mol Pain 3:37

Bie B, Zhang Z, Cai YQ, Zhu W, Zhang Y, Dai J, Lowenstein CJ, Weinman EJ, Pan ZZ (2010) Nerve growth factor-regulated emergence of functional delta-opioid receptors. J Neurosci 30:5617–5628

Bigal ME, Lipton RB (2008) Excessive acute migraine medication use and migraine progression. Neurology 71:1821–1828

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168

Bilsky EJ, Calderon SN, Wang T, Bernstein RN, Davis P, Hruby VJ, McNutt RW, Rothman RB, Rice KC, Porreca F (1995) SNC 80, a selective, nonpeptidic and systemically active opioid delta agonist. J Pharmacol Exp Ther 273:359–366

Bilsky EJ, Bernstein RN, Hruby VJ, Rothman RB, Lai J, Porreca F (1996a) Characterization of antinociception to opioid receptor selective agonists after antisense oligodeoxynucleotide-mediated "knock-down" of opioid receptor in vivo. J Pharmacol Exp Ther 277:491–501

Bilsky EJ, Wang T, Lai J, Porreca F (1996b) Selective blockade of peripheral delta opioid agonist induced antinociception by intrathecal administration of delta receptor antisense oligo-deoxynucleotide. Neurosci Lett 220:155–158

Brackley AD, Gomez R, Akopian AN, Henry MA, Jeske NA (2016) GRK2 constitutively governs peripheral delta opioid receptor activity. Cell Rep 16:2686–2698

Brainin-Mattos J, Smith ND, Malkmus S, Rew Y, Goodman M, Taulane J, Yaksh TL (2006) Cancer-related bone pain is attenuated by a systemically available delta-opioid receptor agonist. Pain 122:174–181

Brandt MR, Furness MS, Mello NK, Rice KC, Negus SS (2001) Antinociceptive effects of delta-opioid agonists in Rhesus monkeys: effects on chemically induced thermal hypersensitivity. J Pharmacol Exp Ther 296:939–946

Brantl V, Pfeiffer A, Herz A, Henschen A, Lottspeich F (1982) Antinociceptive potencies of beta-casomorphin analogs as compared to their affinities towards mu and delta opiate receptor sites in brain and periphery. Peptides 3:793–797

Breslin HJ, Diamond CJ, Kavash RW, Cai C, Dyatkin AB, Miskowski TA, Zhang SP, Wade PR, Hornby PJ, He W (2012) Identification of a dual delta OR antagonist/mu OR agonist as a potential therapeutic for diarrhea-predominant irritable bowel syndrome (IBS-d). Bioorg Med Chem Lett 22:4869–4872

Broom DC, Jutkiewicz EM, Folk JE, Traynor JR, Rice KC, Woods JH (2002a) Convulsant activity of a non-peptidic delta-opioid receptor agonist is not required for its antidepressant-like effects in Sprague-Dawley rats. Psychopharmacology 164:42–48

Broom DC, Nitsche JF, Pintar JE, Rice KC, Woods JH, Traynor JR (2002b) Comparison of receptor mechanisms and efficacy requirements for delta-agonist-induced convulsive activity and antinociception in mice. J Pharmacol Exp Ther 303:723–729

Cahill CM, McClellan KA, Morinville A, Hoffert C, Hubatsch D, O'Donnell D, Beaudet A (2001a) Immunohistochemical distribution of delta opioid receptors in the rat central nervous system: evidence for somatodendritic labeling and antigen-specific cellular compartmentalization. J Comp Neurol 440:65–84

Cahill CM, Morinville A, Lee MC, Vincent JP, Collier B, Beaudet A (2001b) Prolonged morphine treatment targets delta opioid receptors to neuronal plasma membranes and enhances delta-mediated antinociception. J Neurosci 21:7598–7607

Cahill CM, Morinville A, Hoffert C, O'Donnell D, Beaudet A (2003) Up-regulation and trafficking of delta opioid receptor in a model of chronic inflammation: implications for pain control. Pain 101:199–208

Cao YQ, Mantyh PW, Carlson EJ, Gillespie AM, Epstein CJ, Basbaum AI (1998) Primary afferent tachykinins are required to experience moderate to intense pain. Nature 392:390–394

Charles AC, Baca SM (2013) Cortical spreading depression and migraine. Nat Rev Neurol 9:637–644

Charles A, Pradhan AA (2016) Delta-opioid receptors as targets for migraine therapy. Curr Opin Neurol 29:314–319

Chaturvedi K, Christoffers KH, Singh K, Howells RD (2000) Structure and regulation of opioid receptors. Biopolymers 55:334–346

Chen Y, Mestek A, Liu J, Hurley JA, Yu L (1993) Molecular cloning and functional expression of a mu-opioid receptor from rat brain. Mol Pharmacol 44:8–12

Cheng PY, Svingos AL, Wang H, Clarke CL, Jenab S, Beczkowska IW, Inturrisi CE, Pickel VM (1995) Ultrastructural immunolabeling shows prominent presynaptic vesicular localization of delta-opioid receptor within both enkephalin- and nonenkephalin-containing axon terminals in the superficial layers of the rat cervical spinal cord. J Neurosci 15:5976–5988

Cheng PY, Liu-Chen LY, Pickel VM (1997) Dual ultrastructural immunocytochemical labeling of mu and delta opioid receptors in the superficial layers of the rat cervical spinal cord. Brain Res 778:367–380

Chu Sin Chung P, Kieffer BL (2013) Delta opioid receptors in brain function and diseases. Pharmacol Ther 140:112–120

Chung MK, Cho YS, Bae YC, Lee J, Zhang X, Ro JY (2014) Peripheral G protein-coupled inwardly rectifying potassium channels are involved in delta-opioid receptor-mediated anti-hyperalgesia in rat masseter muscle. Eur J Pain 18:29–38

Chung PC, Boehrer A, Stephan A, Matifas A, Scherrer G, Darcq E, Befort K, Kieffer BL (2015) Delta opioid receptors expressed in forebrain GABAergic neurons are responsible for SNC80-induced seizures. Behav Brain Res 278:429–434

Comer SD, Hoenicke EM, Sable AI, McNutt RW, Chang KJ, De Costa BR, Mosberg HI, Woods JH (1993) Convulsive effects of systemic administration of the delta opioid agonist BW373U86 in mice. J Pharmacol Exp Ther 267:888–895

Commons KG (2003) Translocation of presynaptic delta opioid receptors in the ventrolateral periaqueductal gray after swim stress. J Comp Neurol 464:197–207

Commons KG, Beck SG, Rudoy C, Van Bockstaele EJ (2001) Anatomical evidence for presynaptic modulation by the delta opioid receptor in the ventrolateral periaqueductal gray of the rat. J Comp Neurol 430:200–208

Dado RJ, Law PY, Loh HH, Elde R (1993) Immunofluorescent identification of a delta (delta)-opioid receptor on primary afferent nerve terminals. Neuroreport 5:341–344

Daniels DJ, Kulkarni A, Xie Z, Bhushan RG, Portoghese PS (2005a) A bivalent ligand (KDAN-18) containing delta-antagonist and kappa-agonist pharmacophores bridges delta2 and kappa1 opioid receptor phenotypes. J Med Chem 48:1713–1716

Daniels DJ, Lenard NR, Etienne CL, Law PY, Roerig SC, Portoghese PS (2005b) Opioid-induced tolerance and dependence in mice is modulated by the distance between pharmacophores in a bivalent ligand series. Proc Natl Acad Sci U S A 102:19208–19213

Darland T, Heinricher MM, Grandy DK (1998) Orphanin FQ/nociceptin: a role in pain and analgesia, but so much more. Trends Neurosci 21:215–221

Desmeules JA, Kayser V, Gacel G, Guilbaud G, Roques BP (1993) The highly selective delta agonist BUBU induces an analgesic effect in normal and arthritic rat and this action is not affected by repeated administration of low doses of morphine. Brain Res 611:243–248

Dondio G, Ronzoni S, Farina C, Graziani D, Parini C, Petrillo P, Giardina GA (2001) Selective delta opioid receptor agonists for inflammatory and neuropathic pain. Farmaco 56:117–119

Dore-Savard L, Otis V, Belleville K, Lemire M, Archambault M, Tremblay L, Beaudoin JF, Beaudet N, Lecomte R, Lepage M, Gendron L, Sarret P (2010) Behavioral, medical imaging and histopathological features of a new rat model of bone cancer pain. PLoS One 5:e13774

Dubois D, Gendron L (2010) Delta opioid receptor-mediated analgesia is not altered in preprotachykinin A knockout mice. Eur J Neurosci 32:1921–1929

Dykstra LA, Schoenbaum GM, Yarbrough J, McNutt R, Chang KJ (1993) A novel delta opioid agonist, BW373U86, in squirrel monkeys responding under a schedule of shock titration. J Pharmacol Exp Ther 267:875–882

Evans CJ, Keith DE Jr, Morrison H, Magendzo K, Edwards RH (1992) Cloning of a delta opioid receptor by functional expression. Science 258:1952–1955

Fenalti G, Giguere PM, Katritch V, Huang XP, Thompson AA, Cherezov V, Roth BL, Stevens RC (2014) Molecular control of delta-opioid receptor signalling. Nature 506:191–196

Filliol D, Ghozland S, Chluba J, Martin M, Matthes HW, Simonin F, Befort K, Gaveriaux-Ruff C, Dierich A, LeMeur M, Valverde O, Maldonado R, Kieffer BL (2000) Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat Genet 25:195–200

Finn AK, Whistler JL (2001) Endocytosis of the mu opioid receptor reduces tolerance and a cellular hallmark of opiate withdrawal. Neuron 32:829–839

Fraser GL, Gaudreau GA, Clarke PB, Menard DP, Perkins MN (2000a) Antihyperalgesic effects of delta opioid agonists in a rat model of chronic inflammation. Br J Pharmacol 129:1668–1672

Fraser GL, Holmgren J, Clarke PB, Wahlestedt C (2000b) Antisense inhibition of delta-opioid receptor gene function in vivo by peptide nucleic acids. Mol Pharmacol 57:725–731

Fujita W, Gomes I, Devi LA (2014) Revolution in GPCR signalling: opioid receptor heteromers as novel therapeutic targets: IUPHAR review 10. Br J Pharmacol 171:4155–4176

Fujita W, Gomes I, Devi LA (2015) Heteromers of mu-delta opioid receptors: new pharmacology and novel therapeutic possibilities. Br J Pharmacol 172:375–387

Gallantine EL, Meert TF (2005) A comparison of the antinociceptive and adverse effects of the mu-opioid agonist morphine and the delta-opioid agonist SNC80. Basic Clin Pharmacol Toxicol 97:39–51

Garnock-Jones KP (2015) Eluxadoline: first global approval. Drugs 75:1305–1310

Gaveriaux-Ruff C, Kieffer BL (2011) Delta opioid receptor analgesia: recent contributions from pharmacology and molecular approaches. Behav Pharmacol 22:405–414
Gaveriaux-Ruff C, Karchewski LA, Hever X, Matifas A, Kieffer BL (2008) Inflammatory pain is enhanced in delta opioid receptor-knockout mice. Eur J Neurosci 27:2558–2567
Gaveriaux-Ruff C, Nozaki C, Nadal X, Hever XC, Weibel R, Matifas A, Reiss D, Filliol D, Nassar MA, Wood JN, Maldonado R, Kieffer BL (2011) Genetic ablation of delta opioid receptors in nociceptive sensory neurons increases chronic pain and abolishes opioid analgesia. Pain 152:1238–1248
Gendron L, Lucido AL, Mennicken F, O'Donnell D, Vincent JP, Stroh T, Beaudet A (2006) Morphine and pain-related stimuli enhance cell surface availability of somatic delta-opioid receptors in rat dorsal root ganglia. J Neurosci 26:953–962
Gendron L, Esdaile MJ, Mennicken F, Pan H, O'Donnell D, Vincent J-P, Devi LA, Cahill CM, Stroh T, Beaudet A (2007a) Morphine priming in rats with chronic inflammation reveals a dichotomy between antihyperalgesic and antinociceptive properties of deltorphin. Neuroscience 144:263–274
Gendron L, Pintar JE, Chavkin C (2007b) Essential role of mu opioid receptor in the regulation of delta opioid receptor-mediated antihyperalgesia. Neuroscience 150:807–817
Gendron L, Mittal N, Beaudry H, Walwyn W (2015) Recent advances on the delta opioid receptor: from trafficking to function. Br J Pharmacol 172:403–419
Gendron L, Cahill CM, von Zastrow M, Schiller PW, Pineyro G (2016) Molecular pharmacology of delta-opioid receptors. Pharmacol Rev 68:631–700
George SR, Zastawny RL, Briones-Urbina R, Cheng R, Nguyen T, Heiber M, Kouvelas A, Chan AS, O'Dowd BF (1994) Distinct distributions of mu, delta and kappa opioid receptor mRNA in rat brain. Biochem Biophys Res Commun 205:1438–1444
Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR (2009) Neurobiology of migraine. Neuroscience 161:327–341
Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L (1979) Dynorphin-(1-13), an extraordinarily potent opioid peptide. Proc Natl Acad Sci U S A 76:6666–6670
Gomes I, Fujita W, Gupta A, Saldanha SA, Negri A, Pinello CE, Eberhart C, Roberts E, Filizola M, Hodder P, Devi LA (2013) Identification of a mu-delta opioid receptor heteromer-biased agonist with antinociceptive activity. Proc Natl Acad Sci U S A 110:12072–12077
Granier S, Manglik A, Kruse AC, Kobilka TS, Thian FS, Weis WI, Kobilka BK (2012) Structure of the delta-opioid receptor bound to naltrindole. Nature 485:400–404
Guan JS, Xu ZZ, Gao H, He SQ, Ma GQ, Sun T, Wang LH, Zhang ZN, Lena I, Kitchen I, Elde R, Zimmer A, He C, Pei G, Bao L, Zhang X (2005) Interaction with vesicle luminal protachykinin regulates surface expression of delta-opioid receptors and opioid analgesia. Cell 122:619–631
Gupta A, Mulder J, Gomes I, Rozenfeld R, Bushlin I, Ong E, Lim M, Maillet E, Junek M, Cahill CM, Harkany T, Devi LA (2010) Increased abundance of opioid receptor heteromers after chronic morphine administration. Sci Signal 3:ra54
Hack SP, Bagley EE, Chieng BC, Christie MJ (2005) Induction of delta-opioid receptor function in the midbrain after chronic morphine treatment. J Neurosci 25:3192–3198
Hansra P, Moran EL, Fornasier VL, Bogoch ER (2000) Carrageenan-induced arthritis in the rat. Inflammation 24:141–155
Harvey JH, Long DH, England PM, Whistler JL (2012) Tuned-affinity bivalent ligands for the characterization of opioid receptor heteromers. ACS Med Chem Lett 3:640–644
Headrick JP, See Hoe LE, Du Toit EF, Peart JN (2015) Opioid receptors and cardioprotection – 'opioidergic conditioning' of the heart. Br J Pharmacol 172:2026–2050
Hervera A, Leanez S, Negrete R, Pol O (2009) The peripheral administration of a nitric oxide donor potentiates the local antinociceptive effects of a DOR agonist during chronic inflammatory pain in mice. Naunyn Schmiedebergs Arch Pharmacol 380:345–352
Heydorn A, Sondergaard BP, Ersboll B, Holst B, Nielsen FC, Haft CR, Whistler J, Schwartz TW (2004) A library of 7TM receptor C-terminal tails. Interactions with the proposed post-endocytic sorting proteins ERM-binding phosphoprotein 50 (EBP50), N-ethylmaleimide-

sensitive factor (NSF), sorting nexin 1 (SNX1), and G protein-coupled receptor-associated sorting protein (GASP). J Biol Chem 279:54291–54303

Holdridge SV, Cahill CM (2007) Spinal administration of a delta opioid receptor agonist attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. Eur J Pain 11:685–693

Honore P, Rogers SD, Schwei MJ, Salak-Johnson JL, Luger NM, Sabino MC, Clohisy DR, Mantyh PW (2000) Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 98:585–598

Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR (1975) Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature 258:577–580

Hurley RW, Hammond DL (2000) The analgesic effects of supraspinal mu and delta opioid receptor agonists are potentiated during persistent inflammation. J Neurosci 20:1249–1259

Hylden JL, Thomas DA, Iadarola MJ, Nahin RL, Dubner R (1991) Spinal opioid analgesic effects are enhanced in a model of unilateral inflammation/hyperalgesia: possible involvement of noradrenergic mechanisms. Eur J Pharmacol 194:135–143

Ichikawa H, Schulz S, Hollt V, Sugimoto T (2005) Delta-opioid receptor-immunoreactive neurons in the rat cranial sensory ganglia. Brain Res 1043:225–230

Ji RR, Zhang Q, Law PY, Low HH, Elde R, Hokfelt T (1995) Expression of mu-, delta-, and kappa-opioid receptor-like immunoreactivities in rat dorsal root ganglia after carrageenan-induced inflammation. J Neurosci 15:8156–8166

Kabli N, Cahill CM (2007) Anti-allodynic effects of peripheral delta opioid receptors in neuropathic pain. Pain 127:84–93

Kamei J, Kashiwazaki T, Hitosugi H, Nagase H (1997a) The role of spinal delta1-opioid receptors in inhibiting the formalin-induced nociceptive response in diabetic mice. Eur J Pharmacol 326:31–36

Kamei J, Kawai K, Mizusuna A, Saitoh A, Morita K, Narita M, Tseng LF, Nagase H (1997b) Supraspinal delta 1-opioid receptor-mediated antinociceptive properties of (-)-TAN-67 in diabetic mice. Eur J Pharmacol 322:27–30

Kent JL, Pert CB, Herkenham M (1981) Ontogeny of opiate receptors in rat forebrain: visualization by in vitro autoradiography. Brain Res 254:487–504

Kieffer BL, Evans CJ (2009) Opioid receptors: from binding sites to visible molecules in vivo. Neuropharmacology 56(Suppl 1):205–212

Kieffer BL, Gaveriaux-Ruff C (2002) Exploring the opioid system by gene knockout. Prog Neurobiol 66:285–306

Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG (1992) The delta-opioid receptor: isolation of a cDNA by expression cloning and pharmacological characterization. Proc Natl Acad Sci U S A 89:12048–12052

Klareskog L (1989) What can we learn about rheumatoid arthritis from animal models? Springer Semin Immunopathol 11:315–333

Kouchek M, Takasusuki T, Terashima T, Yaksh TL, Xu Q (2013) Effects of intrathecal SNC80, a delta receptor ligand, on nociceptive threshold and dorsal horn substance p release. J Pharmacol Exp Ther 347:258–264

Krames ES, Wilkie DJ, Gershow J (1986) Intrathecal D-Ala2-D-Leu5-enkephalin (DADL) restores analgesia in a patient analgetically tolerant to intrathecal morphine sulfate. Pain 24:205–209

Le Bourdonnec B, Windh RT, Ajello CW, Leister LK, Gu M, Chu GH, Tuthill PA, Barker WM, Koblish M, Wiant DD, Graczyk TM, Belanger S, Cassel JA, Feschenko MS, Brogdon BL, Smith SA, Christ DD, Derelanko MJ, Kutz S, Little PJ, DeHaven RN, DeHaven-Hudkins DL, Dolle RE (2008) Potent, orally bioavailable delta opioid receptor agonists for the treatment of pain: discovery of N,N-diethyl-4-(5-hydroxyspiro[chromene-2,4'-piperidine]-4-yl)benzamide (ADL5859). J Med Chem 51:5893–5896

Le Bourdonnec B, Windh RT, Leister LK, Zhou QJ, Ajello CW, Gu M, Chu GH, Tuthill PA, Barker WM, Koblish M, Wiant DD, Graczyk TM, Belanger S, Cassel JA, Feschenko MS, Brogdon BL, Smith SA, Derelanko MJ, Kutz S, Little PJ, DeHaven RN, DeHaven-Hudkins DL, Dolle RE (2009) Spirocyclic delta opioid receptor agonists for the treatment of pain: discovery of N,N-diethyl-3-hydroxy-4-(spiro[chromene-2,4′-piperidine]-4-yl) benzamide (ADL5747). J Med Chem 52:5685–5702

Le Merrer J, Becker JA, Befort K, Kieffer BL (2009) Reward processing by the opioid system in the brain. Physiol Rev 89:1379–1412

Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, Davenport JM, McIntyre G, Lopez R, Turner L, Covington PS (2016) Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 374:242–253

Li CH, Chung D (1976) Isolation and structure of an untriakontapeptide with opiate activity from camel pituitary glands. Proc Natl Acad Sci U S A 73:1145–1148

Loh HH, Tseng LF, Wei E, Li CH (1976) beta-endorphin is a potent analgesic agent. Proc Natl Acad Sci U S A 73:2895–2898

Lucido AL, Morinville A, Gendron L, Stroh T, Beaudet A (2005) Prolonged morphine treatment selectively increases membrane recruitment of delta-opioid receptors in mouse basal ganglia. J Mol Neurosci 25:207–214

Lutz PE, Kieffer BL (2013) Opioid receptors: distinct roles in mood disorders. Trends Neurosci 36:195–206

Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S (2012) Crystal structure of the micro-opioid receptor bound to a morphinan antagonist. Nature 485:321–326

Mansour A, Khachaturian H, Lewis ME, Akil H, Watson SJ (1987) Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain and midbrain. J Neurosci 7:2445–2464

Mansour A, Thompson RC, Akil H, Watson SJ (1993) Delta opioid receptor mRNA distribution in the brain: comparison to delta receptor binding and proenkephalin mRNA. J Chem Neuroanat 6:351–362

Mansour A, Fox CA, Burke S, Meng F, Thompson RC, Akil H, Watson SJ (1994) Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in situ hybridization study. J Comp Neurol 350:412–438

Mansour A, Fox CA, Akil H, Watson SJ (1995) Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. Trends Neurosci 18:22–29

McDowell J, Kitchen I (1986) Ontogenesis of delta-opioid receptors in rat brain using [3H] [D-Pen2,D-Pen5]enkephalin as a binding ligand. Eur J Pharmacol 128:287–289

McQuay H (1999) Opioids in pain management. Lancet 353:2229–2232

Meng F, Xie GX, Thompson RC, Mansour A, Goldstein A, Watson SJ, Akil H (1993) Cloning and pharmacological characterization of a rat kappa opioid receptor. Proc Natl Acad Sci U S A 90:9954–9958

Mennicken F, Zhang J, Hoffert C, Ahmad S, Beaudet A, O'Donnell D (2003) Phylogenetic changes in the expression of delta opioid receptors in spinal cord and dorsal root ganglia. J Comp Neurol 465:349–360

Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, Butour JL, Guillemot JC, Ferrara P, Monsarrat B et al (1995) Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature 377:532–535

Mika J, Przewlocki R, Przewlocka B (2001) The role of delta-opioid receptor subtypes in neuropathic pain. Eur J Pharmacol 415:31–37

Milan-Lobo L, Whistler JL (2011) Heteromerization of the mu- and delta-opioid receptors produces ligand-biased antagonism and alters mu-receptor trafficking. J Pharmacol Exp Ther 337:868–875

Milan-Lobo L, Enquist J, van Rijn RM, Whistler JL (2013) Anti-analgesic effect of the mu/delta opioid receptor heteromer revealed by ligand-biased antagonism. PLoS One 8:e58362

Minami M, Toya T, Katao Y, Maekawa K, Nakamura S, Onogi T, Kaneko S, Satoh M (1993) Cloning and expression of a cDNA for the rat kappa-opioid receptor. FEBS Lett 329:291–295

Minami M, Maekawa K, Yabuuchi K, Satoh M (1995) Double in situ hybridization study on coexistence of mu-, delta- and kappa-opioid receptor mRNAs with preprotachykinin A mRNA in the rat dorsal root ganglia. Brain Res Mol Brain Res 30:203–210

Morinville A, Cahill CM, Esdaile MJ, Aibak H, Collier B, Kieffer BL, Beaudet A (2003) Regulation of delta-opioid receptor trafficking via mu-opioid receptor stimulation: evidence from mu-opioid receptor knock-out mice. J Neurosci 23:4888–4898

Morinville A, Cahill CM, Aibak H, Rymar VV, Pradhan A, Hoffert C, Mennicken F, Stroh T, Sadikot AF, O'Donnell D, Clarke PB, Collier B, Henry JL, Vincent JP, Beaudet A (2004) Morphine-induced changes in delta opioid receptor trafficking are linked to somatosensory processing in the rat spinal cord. J Neurosci 24:5549–5559

Mosberg HI, Hurst R, Hruby VJ, Gee K, Yamamura HI, Galligan JJ, Burks TF (1983) Bis-penicillamine enkephalins possess highly improved specificity toward delta opioid receptors. Proc Natl Acad Sci U S A 80:5871–5874

Moulin DE, Max MB, Kaiko RF, Inturrisi CE, Maggard J, Yaksh TL, Foley KM (1985) The analgesic efficacy of intrathecal D-Ala2-D-Leu5-enkephalin in cancer patients with chronic pain. Pain 23:213–221

Nadal X, Banos JE, Kieffer BL, Maldonado R (2006) Neuropathic pain is enhanced in delta-opioid receptor knockout mice. Eur J Neurosci 23:830–834

Negri L, Severini C, Lattanzi R, Potenza RL, Melchiorri P (1997) Postnatal development of delta-opioid receptor subtypes in mice. Br J Pharmacol 120:989–994

Nitsche JF, Pintar JE (2003) Opioid receptor-induced GTPgamma35S binding during mouse development. Dev Biol 253:99–108

Obara I, Parkitna JR, Korostynski M, Makuch W, Kaminska D, Przewlocka B, Przewlocki R (2009) Local peripheral opioid effects and expression of opioid genes in the spinal cord and dorsal root ganglia in neuropathic and inflammatory pain. Pain 141:283–291

Olesen J, Burstein R, Ashina M, Tfelt-Hansen P (2009) Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol 8:679–690

Onofrio BM, Yaksh TL (1983) Intrathecal delta-receptor ligand produces analgesia in man. Lancet 1:1386–1387

Otis V, Sarret P, Gendron L (2011) Spinal activation of delta opioid receptors alleviates cancer-related bone pain. Neuroscience 183:221–229

Pacheco DF, Duarte ID (2005) Delta-opioid receptor agonist SNC80 induces peripheral antinociception via activation of ATP-sensitive K+ channels. Eur J Pharmacol 512:23–28

Pakarinen ED, Woods JH, Moerschbaecher JM (1995) Repeated acquisition of behavioral chains in squirrel monkeys: comparisons of a mu, kappa and delta opioid agonist. J Pharmacol Exp Ther 272:552–559

Pasquini F, Bochet P, Garbay-Jaureguiberry C, Roques BP, Rossier J, Beaudet A (1992) Electron microscopic localization of photoaffinity-labelled delta opioid receptors in the neostriatum of the rat. J Comp Neurol 326:229–244

Patwardhan AM, Berg KA, Akopain AN, Jeske NA, Gamper N, Clarke WP, Hargreaves KM (2005) Bradykinin-induced functional competence and trafficking of the delta-opioid receptor in trigeminal nociceptors. J Neurosci 25:8825–8832

Peng J, Sarkar S, Chang SL (2012) Opioid receptor expression in human brain and peripheral tissues using absolute quantitative real-time RT-PCR. Drug Alcohol Depend 124:223–228

Petrillo P, Angelici O, Bingham S, Ficalora G, Garnier M, Zaratin PF, Petrone G, Pozzi O, Sbacchi M, Stean TO, Upton N, Dondio GM, Scheideler MA (2003) Evidence for a selective role of the delta-opioid agonist [8R-(4bS*,8aalpha,8abeta, 12bbeta)]7,10-dimethyl-1-methoxy-11-(2-methylpropyl)oxycarbonyl 5,6,7,8,12,12b-hexahydro-(9H)-4,8-methanobenzofuro[3,2-e] pyrrolo[2,3-g]isoquinoli ne hydrochloride (SB-235863) in blocking hyperalgesia associated with inflammatory and neuropathic pain responses. J Pharmacol Exp Ther 307:1079–1089

Podolsky AT, Sandweiss A, Hu J, Bilsky EJ, Cain JP, Kumirov VK, Lee YS, Hruby VJ, Vardanyan RS, Vanderah TW (2013) Novel fentanyl-based dual mu/delta-opioid agonists for the treatment of acute and chronic pain. Life Sci 93:1010–1016

Porreca F, Mosberg HI, Hurst R, Hruby VJ, Burks TF (1984) Roles of mu, delta and kappa opioid receptors in spinal and supraspinal mediation of gastrointestinal transit effects and hot-plate analgesia in the mouse. J Pharmacol Exp Ther 230:341–348

Poulin JF, Chevalier B, Laforest S, Drolet G (2006) Enkephalinergic afferents of the centromedial amygdala in the rat. J Comp Neurol 496:859–876

Pradhan AA, Clarke PB (2005) Comparison between delta-opioid receptor functional response and autoradiographic labeling in rat brain and spinal cord. J Comp Neurol 481:416–426

Pradhan AA, Siau C, Constantin A, Clarke PB (2006) Chronic morphine administration results in tolerance to delta opioid receptor-mediated antinociception. Neuroscience 141:947–954

Pradhan AA, Befort K, Nozaki C, Gaveriaux-Ruff C, Kieffer BL (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. Trends Pharmacol Sci 32:581–590

Pradhan A, Smith M, McGuire B, Evans C, Walwyn W (2013) Chronic inflammatory injury results in increased coupling of delta opioid receptors to voltage-gated Ca^{2+} channels. Mol Pain 9:8

Pradhan AA, Smith ML, McGuire B, Tarash I, Evans CJ, Charles A (2014) Characterization of a novel model of chronic migraine. Pain 155:269–274

Qiu C, Sora I, Ren K, Uhl G, Dubner R (2000) Enhanced delta-opioid receptor-mediated antinociception in mu-opioid receptor-deficient mice. Eur J Pharmacol 387:163–169

Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, Grandy DK, Langen H, Monsma FJ Jr, Civelli O (1995) Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science 270:792–794

Riedl MS, Schnell SA, Overland AC, Chabot-Dore AJ, Taylor AM, Ribeiro-da-Silva A, Elde RP, Wilcox GL, Stone LS (2009) Coexpression of alpha 2A-adrenergic and delta-opioid receptors in substance P-containing terminals in rat dorsal horn. J Comp Neurol 513:385–398

Rossi GC, Pasternak GW, Bodnar RJ (1994) Mu and delta opioid synergy between the periaqueductal gray and the rostro-ventral medulla. Brain Res 665:85–93

Saitoh A, Sugiyama A, Nemoto T, Fujii H, Wada K, Oka J, Nagase H, Yamada M (2011) The novel delta opioid receptor agonist KNT-127 produces antidepressant-like and antinociceptive effects in mice without producing convulsions. Behav Brain Res 223:271–279

Saloman JL, Niu KY, Ro JY (2011) Activation of peripheral delta-opioid receptors leads to anti-hyperalgesic responses in the masseter muscle of male and female rats. Neuroscience 190:379–385

Sauriyal DS, Jaggi AS, Singh N (2011) Extending pharmacological spectrum of opioids beyond analgesia: multifunctional aspects in different pathophysiological states. Neuropeptides 45:175–188

Scherrer G, Imamachi N, Cao YQ, Contet C, Mennicken F, O'Donnell D, Kieffer BL, Basbaum AI (2009) Dissociation of the opioid receptor mechanisms that control mechanical and heat pain. Cell 137:1148–1159

Sharif NA, Hughes J (1989) Discrete mapping of brain Mu and delta opioid receptors using selective peptides: quantitative autoradiography, species differences and comparison with kappa receptors. Peptides 10:499–522

Simonin F, Karcher P, Boeuf JJ, Matifas A, Kieffer BL (2004) Identification of a novel family of G protein-coupled receptor associated sorting proteins. J Neurochem 89:766–775

Slowe SJ, Simonin F, Kieffer B, Kitchen I (1999) Quantitative autoradiography of mu-,delta- and kappa1 opioid receptors in kappa-opioid receptor knockout mice. Brain Res 818:335–345

Snyder SH, Pasternak GW (2003) Historical review: opioid receptors. Trends Pharmacol Sci 24:198–205

Sohn JH, Lee BH, Park SH, Ryu JW, Kim BO, Park YG (2000) Microinjection of opiates into the periaqueductal gray matter attenuates neuropathic pain symptoms in rats. Neuroreport 11:1413–1416

Stein C, Lang LJ (2009) Peripheral mechanisms of opioid analgesia. Curr Opin Pharmacol 9:3–8

Stein C, Machelska H, Binder W, Schafer M (2001) Peripheral opioid analgesia. Curr Opin Pharmacol 1:62–65

Stevens CW (2009) The evolution of vertebrate opioid receptors. Front Biosci (Landmark Ed) 14:1247–1269

Stewart PE, Hammond DL (1994) Activation of spinal delta-1 or delta-2 opioid receptors reduces carrageenan-induced hyperalgesia in the rat. J Pharmacol Exp Ther 268:701–708

Suarez-Roca H, Maixner W (1992) Delta-opioid-receptor activation by [D-Pen2,D-Pen5]enkephalin and morphine inhibits substance P release from trigeminal nucleus slices. Eur J Pharmacol 229:1–7

Tsao PI, von Zastrow M (2000) Type-specific sorting of G protein-coupled receptors after endocytosis. J Biol Chem 275:11130–11140

Wade PR, Palmer JM, McKenney S, Kenigs V, Chevalier K, Moore BA, Mabus JR, Saunders PR, Wallace NH, Schneider CR, Kimball ES, Breslin HJ, He W, Hornby PJ (2012) Modulation of gastrointestinal function by MuDelta, a mixed micro opioid receptor agonist/ micro opioid receptor antagonist. Br J Pharmacol 167:1111–1125

Wang H, Pickel VM (2001) Preferential cytoplasmic localization of delta-opioid receptors in rat striatal patches: comparison with plasmalemmal mu-opioid receptors. J Neurosci 21:3242–3250

Wang H, Wessendorf MW (2001) Equal proportions of small and large DRG neurons express opioid receptor mRNAs. J Comp Neurol 429:590–600

Wang JB, Imai Y, Eppler CM, Gregor P, Spivak CE, Uhl GR (1993) mu opiate receptor: cDNA cloning and expression. Proc Natl Acad Sci U S A 90:10230–10234

Wang JB, Johnson PS, Persico AM, Hawkins AL, Griffin CA, Uhl GR (1994) Human mu opiate receptor. cDNA and genomic clones, pharmacologic characterization and chromosomal assignment. FEBS Lett 338:217–222

Wang XM, Yan JQ, Zhang KM, Mokha SS (1996) Role of opioid receptors (mu, delta 1, delta 2) in modulating responses of nociceptive neurons in the superficial and deeper dorsal horn of the medulla (trigeminal nucleus caudalis) in the rat. Brain Res 739:235–243

Wang HB, Zhao B, Zhong YQ, Li KC, Li ZY, Wang Q, Lu YJ, Zhang ZN, He SQ, Zheng HC, Wu SX, Hokfelt TG, Bao L, Zhang X (2010) Coexpression of delta- and mu-opioid receptors in nociceptive sensory neurons. Proc Natl Acad Sci U S A 107:13117–13122

Wei LN, Loh HH (2011) Transcriptional and epigenetic regulation of opioid receptor genes: present and future. Annu Rev Pharmacol Toxicol 51:75–97

Whistler JL, Enquist J, Marley A, Fong J, Gladher F, Tsuruda P, Murray SR, Von Zastrow M (2002) Modulation of postendocytic sorting of G protein-coupled receptors. Science 297:615–620

Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E, Liu W, Thompson AA, Huang XP, Carroll FI, Mascarella SW, Westkaemper RB, Mosier PD, Roth BL, Cherezov V, Stevens RC (2012) Structure of the human kappa-opioid receptor in complex with JDTic. Nature 485:327–332

Xie WY, He Y, Yang YR, Li YF, Kang K, Xing BM, Wang Y (2009) Disruption of Cdk5-associated phosphorylation of residue threonine-161 of the delta-opioid receptor: impaired receptor function and attenuated morphine antinociceptive tolerance. J Neurosci 29:3551–3564

Yasuda K, Espinosa R 3rd, Takeda J, Le Beau MM, Bell GI (1994) Localization of the kappa opioid receptor gene to human chromosome band 8q11.2. Genomics 19:596–597

Ye Y, Dang D, Viet CT, Dolan JC, Schmidt BL (2012) Analgesia targeting IB4-positive neurons in cancer-induced mechanical hypersensitivity. J Pain 13:524–531

Zaki PA, Bilsky EJ, Vanderah TW, Lai J, Evans CJ, Porreca F (1996) Opioid receptor types and subtypes: the delta receptor as a model. Annu Rev Pharmacol Toxicol 36:379–401

Zhang X, Bao L, Arvidsson U, Elde R, Hokfelt T (1998) Localization and regulation of the delta-opioid receptor in dorsal root ganglia and spinal cord of the rat and monkey: evidence for association with the membrane of large dense-core vesicles. Neuroscience 82:1225–1242

Zhang X, Bao L, Guan JS (2006) Role of delivery and trafficking of delta-opioid peptide receptors in opioid analgesia and tolerance. Trends Pharmacol Sci 27:324–329

Zhang X, Bao L, Ma GQ (2010) Sorting of neuropeptides and neuropeptide receptors into secretory pathways. Prog Neurobiol 90:276–283

Zhao B, Wang HB, Lu YJ, Hu JW, Bao L, Zhang X (2011) Transport of receptors, receptor signaling complexes and ion channels via neuropeptide-secretory vesicles. Cell Res 21:741–753

Zhou L, Zhang Q, Stein C, Schafer M (1998) Contribution of opioid receptors on primary afferent versus sympathetic neurons to peripheral opioid analgesia. J Pharmacol Exp Ther 286:1000–1006

Zhu Y, Hsu MS, Pintar JE (1998) Developmental expression of the mu, kappa, and delta opioid receptor mRNAs in mouse. J Neurosci 18:2538–2549

Zhu Y, King MA, Schuller AG, Nitsche JF, Reidl M, Elde RP, Unterwald E, Pasternak GW, Pintar JE (1999) Retention of supraspinal delta-like analgesia and loss of morphine tolerance in delta opioid receptor knockout mice. Neuron 24:243–252