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Delta opioid receptor analgesia: recent contributions from pharmacology and molecular approaches

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Abstract

Delta opioid receptors represent a promising target for the development of novel analgesics. A number of tools have been developed recently that have significantly improved our knowledge of delta receptor function in pain control. These include several novel delta agonists with potent analgesic properties, as well as genetic mouse models with targeted mutations in the delta opioid receptor gene. Also, recent findings have further documented the regulation of delta receptor function at cellular level, which impacts on the pain-reducing activity of the receptor. These regulatory mechanisms occur at transcriptional and post-translational levels, along agonist-induced receptor activation, signaling and trafficking, or in interaction with other receptors and neuromodulatory systems. All these tools for *in vivo* research, as well as proposed mechanisms at molecular level, have tremendously increased our understanding of delta receptor physiology, and contribute to designing innovative strategies for the treatment of chronic pain and other diseases such as mood disorders.

Keywords

delta opioid receptor; analgesia; pain; mouse genetic model; rat; regulation; mechanism

Introduction

Morphine and other related opiates are potent analgesics widely used for pain treatment. These compounds act on opioid receptors to inhibit pain transmission and perception. The three opioid receptors, mu, delta and kappa receptors, are transmembrane G-proteins coupled receptors encoded by *Oprm1*, *Oprd1* and *Oprk1* genes, respectively (Kieffer & Gaveriaux-Ruff, 2002; Stevens, 2009). Opioid receptors are activated endogenously by the opioid peptides enkephalins, beta-endorphin and dynorphins processed from large precursor proteins encoded by *Penk*, *Pomc* and *Pdyn* genes (Akil *et al.*, 1998). The opioid system plays a central role in pain control, as well as in reward (Mendez & Morales-Mulia, 2008;

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(1) (Obara *et al.*, 2009), (3) (Bilsky *et al.*, 1995., 1996),(Kabli & Cahill, 2007), (4) (Pacheco & Duarte, 2005),(Obara *et al.*, 2009), (Joseph & Levine, 2010),(Gaveriaux-Ruff *et al.*, 2011); (5) (Stein *et al.*, 1989), (Zhou *et al.*, 1998), (Hervera *et al.*, 2009., 2010); (6) (Bilsky *et al.*, 1996),(Cahill *et al.*, 2001, 2003), (Mika *et al.*, 2001), (Pradhan *et al.*, 2006), (Gendron *et al.*, 2007a,b), (Holdridge & Cahill, 2007), (Beaudry *et al.*, 2009), (Dubois & Gendron, 2010),(Otis *et al.*, 2011); (7) (Pacheco & Duarte, 2005), (Scherrer *et al.*, 2009); (8) (Fraser *et al.*, 2000); (9) (Hurley & Hammond, 2000); (10) (Kawaraguchi *et al.*, 2004); (11) (Baamonde *et al.*, 2005), (Mika *et al.*, 2001); (12) (Ma *et al.*, 2006); (13) (Kamei *et al.*, 1997) ; (14) (Barn *et al.*, 2001; Brandt *et al.*, 2001; Gallantine & Meert, 2005; Gaveriaux-Ruff *et al.*, 2008; Pradhan *et al.*, 2009., 2010).. (15) (Barn *et al.*, 2001) ; (16) (Beaudry *et al.*, 2009; Petrillo *et al.*, 2003) ; (17) (Brainin-Mattos *et al.*, 2006) ; (18) (Pradhan *et al.*, 2009., 2010) ; (19) (Aceto *et al.*, 2007) ; (20) (Le Bourdonnec *et al.*, 2008) ; (21) (Le Bourdonnec *et al.*, 2009) ; (22) (Codd *et al.*, 2010) ; (23) (Jones *et al.*, 2009)

Rodriguez-Arias *et al.*, 2010; Shippenberg *et al.*, 2008) and neuroptoection (Chao & Xia, 2010; Johnson & Turner, 2010). In addition this system regulates a number of physiological functions that include respiration and gastrointestinal transit, as well as endocrine and immune systems (Kieffer & Gaveriaux-Ruff, 2002; Sauriyal *et al.,* 2010).

Since the initial molecular cloning (Evans *et al.*, 1992; Kieffer *et al.*, 1992), a number of tools have been developed enabling better understanding of delta receptor function in nociception and pain. Research on delta opioid analgesia has benefited from a series of novel agonists that extend the panel of pharmacological tools available to study delta receptors in pain control. Mouse genetic models have been created, that harbor targeted mutations of the receptor. These mice represent unique tools for assessing both the endogenous pain-reducing delta tone and the implication of delta receptors in the actions of opioid as well as non-opioid analgesics. These tools will be presented here, together with novel mechanisms for the development of therapeutics strategies targeting the delta opioid receptor.

In addition, there was tremendous progress in understanding how delta receptor expression and activity are regulated, and these mechanisms heavily contribute to delta analgesia. Receptor regulation takes place at different levels, including genomic and transcriptional controls in the nucleus, post-translational events in the cytoplasm and endoplasmic reticulum, interaction of delta receptors with other receptors at the cell membrane, and processes that follow delta receptor activation within the cell, and these aspects will be discussed.

Altogether, delta opioid receptor research represents a very active field of investigation, with about 1000 publications within the last five years. This review therefore cannot be exhaustive and only recent reviews or publications are cited.

Delta opioid analgesia: from early pharmacology to novel agonists

In early opioid pharmacology, two peptidic agonists DPDPE ([2-D-penicillamin, 5-D-penicillamin]-enkephalin) (Mosberg *et al.*, 1983) and deltorphin (Kreil *et al.*, 1989) were most frequently used to study delta receptor function in pain control (Chang *et al.*, 2004). However, their peptidic nature prevented their use by systemic administration *in vivo*. Later, the non-peptidic agonists BW373U86 and SNC80 (Bilsky *et al.*, 1995; Chang *et al.*, 2004), and the antagonist naltrindole (Portoghese *et al.*, 1988) (Chang *et al.*, 2004) proved to be more stable ligands *in vivo* to investigate delta receptor-mediated analgesia.

The identification of several novel delta agonists has further broadened the repertoire of molecules available to study delta receptors *in vivo* (Pradhan *et al.*, 2011; Vanderah, 2010). Over the past decade, SB-235863 (Petrillo *et al.*, 2003), DValAla-Enk (Brainin-Mattos *et al.*, 2006), NIH 11082 (Aceto *et al.*, 2007), AR-M100390 (Pradhan *et al.*, 2009), ADL5859 (Le Bourdonnec *et al.*, 2008), ADL5747 (Le Bourdonnec *et al.*, 2009), JNJ-20788560 (Codd *et al.*, 2009), compound 8e (Jones *et al.*, 2009) and KNT-127 (Saitoh *et al.,* 2011) have been developed as analgesics in preclinical models. Table 1 summarizes the analgesic effects of these novel agonists in several pain models, as well as analgesic effects of previously described reference molecules such as DPDPE, DSLET, deltorphin, SNC80 or Tan-67. Altogether, the data cited in Table 1 indicate that delta receptor activation diminishes chronic pain in the three mouse, rat and monkey species. Table 1 also shows that several distinct chronic pain models are sensitive to delta agonists, including inflammatory, neuropathic, cancer and diabetic pain. Moreover, delta receptor activation reduces hypersensitivity in heat, cold and mechanical modalities. Altogether, delta opioid agonists efficiently decrease chronic pain in many preclinical models and clinical trials will validate their translational potential to patients.

Mouse genetic models to study delta receptor function *in vivo*

Delta opioid receptor knockout mice

A major step for understanding delta receptor function was the generation of mice with a targeted inactivation of the *Oprd1* gene, or delta receptor knockout mice (Filliol *et al.*, 2000) (Zhu *et al.,* 1999). A prime finding with these mutant mice was the discovery that delta receptors plays a critical role in the control of emotional responses (Filliol *et al.*, 2000), revealing anxiolytic and antidepressant activities of the receptor that were further confirmed by the pharmacology (Pradhan *et al.*, 2011) (Jutkiewicz, 2006; Noble & Roques, 2007) (Javelot *et al., 2010*). This mouse line represents a unique genetic tool to assess both the influence of endogenous delta receptor tone on pain physiology, and the *in vivo* selectivity of known or new delta agonists.

Delta receptor knockout mice showed no change or only subtle alterations in their sensitivity to acute pain (Contet *et al.*, 2006; Filliol *et al.*, 2000; Gaveriaux-Ruff *et al.*, 2008; Martin *et al.*, 2003; Nadal *et al.*, 2006; Pradhan *et al.*, 2011) and stress-induced analgesia developed normally (Contet *et al.*, 2006). Interestingly however, delta receptor knockout mice showed augmented neuropathic and inflammatory pain (Gaveriaux-Ruff *et al.*, 2008; Nadal *et al.*, 2006), suggesting that endogenous delta opioid activity alleviates chronic pain. Altogether, data from the genetic approach are in agreement with the notion that delta agonists barely modulate acute nociception, but are most efficient under conditions of persistent pain (see below). SNC80-induced analgesia was abolished in delta receptor knockout animals in a model of inflammatory hyperalgesia induced by Complete Freund's Adjuvant (Gaveriaux-Ruff *et al.*, 2008). These data confirmed the *in vivo* selectivity of the compound previously proposed by the pharmacology (Chang *et al.*, 2004).

Interestingly, chronic treatment with tricyclic antidepressants, which produce anti-allodynic effects in a neuropathic pain model, was ineffective in delta receptor knockout mice (Benbouzid *et al.*, 2008). These data revealed the implication of delta receptors in the analgesic effects of tricyclic anti-depressants, likely downstream from aminergic transporter systems. The implication of endogenous opioid mechanisms in this particular activity of anti-depressant drugs was specifically mediated by delta receptors, since the compounds were fully effective in mu receptor knockout animals (Bohren *et al.*, 2010). Along this line, anti-allodynia induced by chronic beta2-agonists was blocked by the delta receptor antagonist naltrindole (Yalcin *et al.,* 2010) suggesting an interaction between beta2-adrenergic and delta receptor systems. In the future, delta receptor knockout mice may help to reveal the interaction of delta receptor with other receptor systems in pain control.

Conditional knockout mice lacking delta opioid receptors in Nav1.8 nociceptive neurons

Under chronic pain, delta receptor activation produces analgesia at different sites within nociceptive circuits. Delta agonists are effective when administered systemically, intrathecally, intracerebroventricularly, or into the rostral ventromedial medulla or Nucleus Raphe Magnus (Figure 1). A potent analgesia was also obtained at the periphery where nociceptive processing is initiated, and opioid receptors of the peripheral nervous system are proposed as therapeutic targets to limit the centrally-mediated adverse effects of opiates. First trials have been promising (Stein *et al.*, 1990) and the field of peripheral opioid receptors has gained importance lately (Hua & Cabot, 2010; Stein *et al.*, 2009).

To inactivate genes specifically in nociceptive primary afferents, a conditional knockout strategy has been reported for the cannabinoid CB1 receptor (Agarwal *et al.*, 2007) and Nav1.7 channel (Nassar *et al.*, 2004). The approach was based on the Cre-Lox system and used a mouse line expressing Cre recombinase in $Nav1.8^{+}$ sensory neurons that include unmyelinated C and thinly myelinated Ad nociceptive neurons. The same driver Cre line

was used recently to inactivate *Oprd1* in these neurons and examine whether peripheral delta receptors contribute to pain control (Gaveriaux-Ruff *et al.*, 2011). In conditional knockout mutants, analgesia induced by intraperitoneal SNC80 treatment was abolished under both inflammatory and neuropathic conditions, revealing the essential role of peripheral delta receptors in systemic delta opioid analgesia. These peripheral receptors are not necessarily sufficient to produce the full analgesic response, since delta receptors expressed in peripheral non-Nav1.8 DRG neurons, at the level of spinal cord or in the brain (Ossipov *et al.*, 2010) may also participate in systemic delta analgesia. The results nevertheless support the notion that developing peripherally-acting delta agonists is a feasible strategy for the design of novel effective analgesics devoid of centrally-mediated side effects.

Knock-in mice expressing a functional green fluorescent delta opioid receptor

A unique genetic mouse model was developed, in order to investigate the distribution of delta receptors throughout the nervous system, and the link between receptor localization at a subcellular level and receptor function *in vivo*. In these mice, endogenous delta receptors are replaced by delta receptors in fusion with green fluorescent protein (DOR-eGFP) using a knock-in strategy (Scherrer *et al.*, 2006). DOR-eGFP mice express fully functional delta receptors, which are directly visible *in vivo*. Fluorescent delta receptors are expressed in DRGs, spinal cord and brain (Scherrer *et al.*, 2006, 2009,), with profiles in accordance with results from *in situ* hybridization (Mansour *et al.*, 1995; Mennicken *et al.*, 2003) and ligand binding autoradiography (Goody *et al.*, 2002). In models of inflammatory pain, DOR-eGFP mice respond to delta agonist-induced analgesia as control wild-type mice (Pradhan *et al.*, 2009., 2010). These animals have been instrumental in deciphering differential internalizing properties of the two delta agonists SNC80 and AR-M100390 throughout the nervous system *in vivo*, and elucidating short-and long-term consequences of ligand-biased receptor trafficking on analgesic responses (see details below and (Pradhan *et al.*, 2009., 2010).

Delta receptor expression and function are regulated at different levels within the cell

A major factor contributing to delta opioid analgesia is the expression level of the receptor protein at the cell surface of neurons, and at the different sites of the pain-processing pathways. Variations in receptor density may result from sequence variations within the *Oprd1* gene, transcriptional regulation, post-translational events or receptor trafficking to and from the plasma membrane.

Genetic variability

Sequence variants within the *Oprd1* gene may influence delta receptor expression across individuals, and may contribute to inter-individual differences in responses to delta drugs (Lotsch & Geisslinger, 2011). In the human gene, several single nucleotide polymorphisms (SNP) have been identified (Kim *et al.*, 2006). The T80G variant in exon 1, occurring at an allele frequency of 0.08, leads to a Phe27Cys substitution in the extracellular N-terminal domain, and has been associated with pain sensitivity (Kim *et al.*, 2006). In heterologous expression systems, the Cys27 variant showed lower maturation efficiency, increased accumulation of receptor precursors in pre-Golgi compartment and faster constitutive internalization (Leskela *et al.*, 2009). Other human SNP variants showed no association with pain sensitivity (Huang *et al.*, 2008; Kim *et al.*, 2006; Zhang *et al.*, 2010). In the mouse *Oprd1* gene, polymorphism was identified in mice selectively bred for high and low stress-induced analgesia, and later shown to differ also in basal nociception and opioid analgesia. In this study, three polymorphic sites were detected in the *Oprd1* coding region (Sacharczuk *et al.*, 2010). Among these, the C320T transition resulted in an A107V substitution in the first extracellular loop of the delta receptor protein. The C320T decreased SNC80-induced

analgesia in thermal pain tests. Altogether, the identification of natural genetic variants affecting extracellular domains of the delta receptor and altering pain perception, opens the possibility of inter-individual variability in responses to delta agonists.

Transcriptional regulation

Pathological situations like chronic pain, inflammation and nerve damage were shown to induce transcriptional regulation of the delta receptor that may impact on receptor activity. Transcription factors binding to *Oprd1* promoter sequences and regulating gene expression, as well as epigenetic aspects, have recently been reviewed extensively (Wei & Loh, 2011). Regulation at the transcriptional level of delta receptor expression was investigated in several models of chronic pain and appears highly variable depending on a series of factors including (i) the pain model, (ii) the receptor localization (brain, spinal cord, DRG, sciatic nerve or skin), (iii) time points considered after pain initiation, (iv) the animal strain (Herradon *et al.*, 2008) and (v) the technique used for detecting receptor expression. Data are summarized in Table 2. In the different models of inflammatory pain, no change, up-regulation or down-regulation of delta receptor mRNA levels were reported. In models of neuropathic pain also, several regulation patterns were observed and together the data indicate that regulation at transcriptional level may be detectable in specific pain situations, and likely impact on delta receptor protein levels (Table 2). Most expression studies were performed at the level of DRG and spinal cord. Delta receptor activity, as measured by agonist-induced G protein activation, was also altered in the cingulate cortex and amygdala under conditions of inflammatory and neuropathic pain (Narita *et al.*, 2006a,b). This particular regulation in the central nervous system was suggested to contribute to chronic pain-induced emotional dysfunction (Narita *et al.*, 2006a,b). Finally, delta receptor expression was highly increased under two clinical pain conditions, in the skin of fibromyalgia patients (Salemi *et al.*, 2007) as well as in hypertrophic scars (Cheng *et al.*, 2008). Collectively the data show that delta receptor expression is regulated under experimental chronic pain, and more investigations in pain patients are needed to correlate findings in animal models with clinical situations.

Post-translation regulation

A third level of regulation occurs post-translationally in receptor protein maturation and transport. Mechanisms for delta receptor folding and integration into membranes were investigated using heterologous expression systems. Tuusa et al. (2010) recently showed that delta receptor biogenesis is regulated early after translation at the level of endoplasmic reticulum by the molecular chaperone calnexin and the sarcoendoplasmic reticulum calcium ATPase SERCA2b in a calcium and ATP dependent manner. Delta receptor targeting from the endoplasmic reticulum to the cell surface was further proposed to require the golgi chaperone receptor transport protein 4 RTP4. *In vitro* experiments showed that this protein participates in folding of delta-mu receptor heterodimers, enhancing the trafficking of delta-mu receptor complexes from the Golgi apparatus to the cell surface and decreasing the expression of delta monomers (Decaillot *et al.*, 2008). Future experiments will determine whether these processes occur *in vivo.*

Receptor activity at the cell surface

Receptor activity is also modulated at the plasma membrane, via interactions with other membrane proteins. In particular, delta receptors may associate with other GPCRs to form heterodimers or larger heteromers at the cell surface. Based on several approaches and criteria used to define potential GPCR heterodimers (see (Massotte, 2010), delta receptors have been proposed to interact with GPCRs implicated in pain control, including mu and kappa opioid receptors (Gupta *et al.*, 2010; Kabli *et al.*, 2010; van Rijn *et al.,* 2010), CB1 cannabinoid receptors (see Bushlin *et al.,* 2010) and alpha2-adrenergic receptors (see van

Rijn *et al., 2010*). Delta receptors may also interact with chemokine receptors (Parenty *et al.*, 2008; Pello *et al.*, 2008) with potential consequences on inflammation, including inflammatory pain (Chen *et al.*, 2007). These studies, mainly performed in heterologous cell recombinant systems, show new pharmacological properties for delta receptor-GPCR heterodimers (reviews (Bushlin *et al.*, 2010; Rozenfeld & Devi, 2010; van Rijn *et al.,* 2010). Opioid receptor heterodimers may also be involved in the activities of bi-functional opioid drugs investigated as novel classes of analgesics (Ansonoff *et al.*, 2010; Schiller, 2010).

Receptor activation and intracellular effectors

Finally, receptor density and activity at the cell surface is tightly regulated by intracellular effectors, which engage the receptor into both signaling and trafficking processes upon activation. The best-known signaling effectors of the delta receptor are inhibitory heterotrimeric Gi/o proteins, which further modulate ion channels and second messengers leading ultimately to reduced neuronal activity (Williams *et al.*, 2001). In addition to signaling, agonist binding to the receptor also induces phosphorylation, internalization, trafficking and redistribution of the receptor, and these events represent key mechanisms for the regulation of receptor activity (Cahill *et al.*, 2007; Ritter & Hall, 2009). Unlike the mu opioid receptor, which rapidly recycles to the cell surface, delta receptors are targeted towards lysosomal degradation (Pradhan *et al.*, 2009) via the Endosomal Sorting Complex Required for Transport (ESCRT) machinery, using ubiquitination-dependent or independent mechanisms (Henry *et al.,* 2010). Other factors upstream of the ESCRT pathway also contribute to delta receptor proteolysis, including G protein-coupled receptor Associated Sorting Proteins (GASPs) shown to interact with the delta receptor (Abu-Helo & Simonin, 2010; Moser *et al.,* 2010).

The link between agonist-induced internalization, downregulation and *in vivo* function of delta receptors was investigated using the DOR-eGFP mouse model (Pradhan *et al.*, 2009., 2010). Data indicated that a single injection of a high- (SNC80) and a low (AR-M100390)-internalizing compound to DOR-eGFP mice produced equally efficient analgesia in a model of inflammatory pain. SNC80 also concomitantly induced receptor internalization throughout the nervous system, accompanied by G-protein uncoupling and acute behavioral desensitization, such that a second drug injection was inefficient. Receptor desensitization was transient and receptor responsiveness returned to basal levels after one day. In contrast, AR-M100390 induced none of the regulatory responses, since no internalization, G-protein uncoupling or acute desensitization were detectable (Pradhan *et al.,* 2009). Interestingly further chronic treatment with the two agonists both induced the development of tolerance, but the expression of tolerance differed. The high-internalizing agonist (SNC80) induced generalized tolerance, so that all agonist effects were blunted in chronically-treated mice, and the low-internalizing agonist (AR-M100390) produced a partial tolerance that was restricted to analgesic responses, while anxiolytic or locomotor effects of delta agonists remained intact (Pradhan *et al.*, 2010). This set of data is in accordance with previous *in vitro* studies showing ligand-specific conformational changes of the delta receptor (Audet *et al.*, 2008) and definitely establish the *in vivo* relevance of delta receptor ligand-biased agonism in drug efficacy. The critical consequences of biased agonism at the delta receptor add further physiological support to the rapidly growing field of functional selectivity at GPCRs (Bosier & Hermans, 2007; Galandrin *et al.*, 2007; Mailman, 2007; Vaidehi & Kenakin 2010; Zheng *et al.,* 2010) and may be considered for the development of effective therapeutic drugs.

Functional interactions between delta and other neuromodulatory systems

An active research field is the elucidation of respective contributions of mu and delta receptors in nociceptive processing, particularly to control heat and mechanical pain

modalities (Basbaum *et al.*, 2009; Scherrer *et al.*, 2009; Woolf, 2009)**,** and the identification of molecular and cellular mechanisms underlying functional interactions between the two receptors. Interactions may occur either at cellular or systems levels within nociceptive pathways. This has been extensively discussed in the past (Kieffer, 1999; Smith & Lee, 2003; Zaki *et al.*, 1996) and more recent anatomical analysis has provided evidence for potential interactions at the cellular level *in vivo*. Data from *in situ* mRNA hybridization (Mansour *et al.*, 1995; Mennicken *et al.*, 2003; Wang & Wessendorf, 2001), the analysis of DOR-eGFP mice (Scherrer *et al.*, 2009), and local pharmacology in peripheral neurons (Joseph & Levine, 2010) suggest that mu and delta receptors may be co-localized in a limited number of peripheral nociceptor neurons. This co-expression opens the possibility for within-cell functional interactions in primary nociceptive processing, which may occur between receptors or their downstream signaling pathways. Delta and mu receptor co-localization in the dorsal spinal cord remains debated (Overland *et al.*, 2009; Scherrer *et al.*, 2009; Wang *et al.,* 2010).

A large array of evidence indicates that delta receptor function is increased either after chronic morphine or under conditions of chronic pain. A suggested common basis for this phenomenon lies in the observation of increased delta receptor density at the cell surface in both cases, leading to higher number of receptors available for activation (Bie & Pan, 2007; Cahill *et al.*, 2007; Morgan *et al.*, 2009; Schramm & Honda, 2010). In the case of chronic morphine, the enhancement of delta receptor function likely involves a functional link between mu receptor activation and delta receptors, whose mechanism remains open (see above). In situations of persistent pain, other mechanisms involving bradykinin (Patwardhan *et al.*, 2005), protease activated receptor-2 (Patwardhan *et al.*, 2006), arachidonic acid (Rowan *et al.*, 2009) and nerve growth Factor (Bie *et al.*, 2010) have been shown to augment delta receptor activity. Collectively, interactions between delta receptors and several other opioid or non-opioid receptor systems have been reported to influence delta opioid analgesia, and a great diversityof GPCRs involved pain control (Pan *et al.*, 2008; Stone & Molliver, 2009) may potentially interact with, or modulate, delta receptor analgesic activity.

Conclusion

The field of delta opioid receptor analgesia has benefited from recent contributions in pharmacology, molecular and cellular approaches. Novel selective delta agonists with potent *in vivo* activities are now available to strengthen approaches targeting delta receptors. The field of delta receptors and pain control may also benefit from the development of animal models more closely related to clinical pain (Finley *et al.*, 2008). In particular the evaluation of delta receptor activity in spontaneous pain and in the emotional or affective dimensions of pain (King *et al.*, 2009; Minami, 2009) may provide new elements for the development of delta receptor-based therapeutic strategies.

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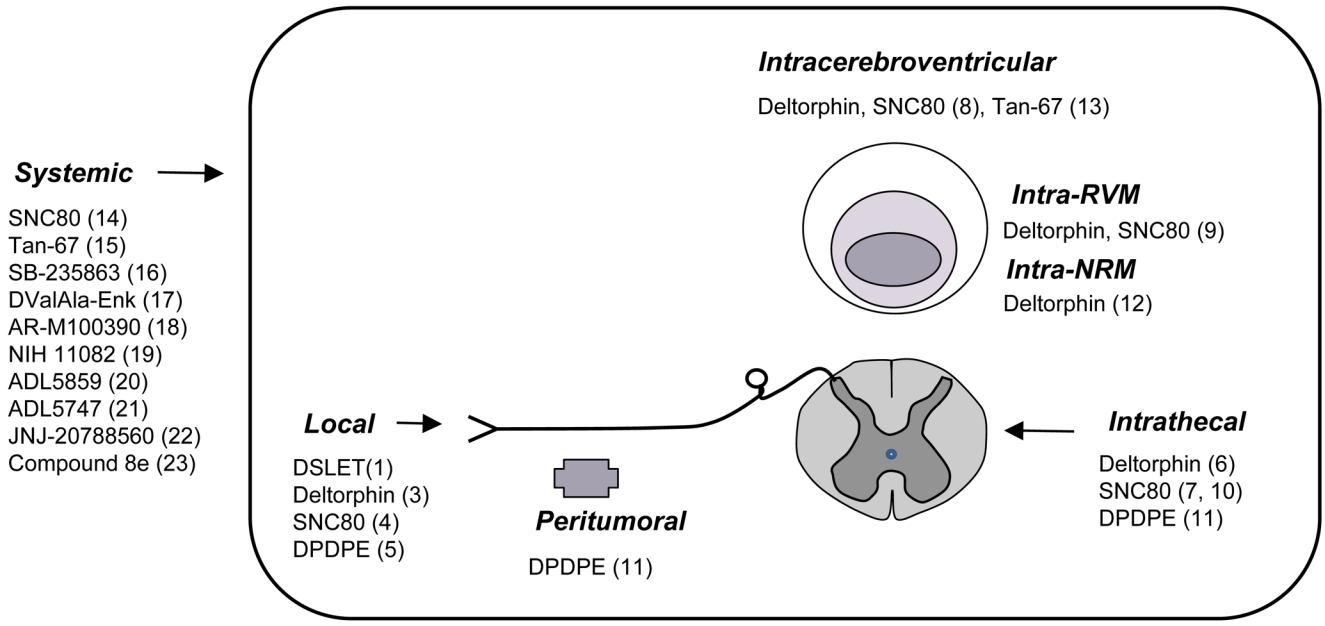

Figure 1.

Sites for delta opioid analgesia. This scheme summarizes sites where delta agonist administration induces analgesia in animal models of chronic pain (see table1). *Abbreviations: DPDPE, (D-Pen2, D-Pen5)-enkephalin; DSLET, (D-Ser2,Leu5)-enkephalin; NRM, Nucleus Raphe Magnus ; RVM, Rostroventral medulla

Table 1

Analgesic effects of delta opioid agonists

Agonist	Pain model#	Species	Pain Modality	Reference
DPDPE [*]/ DSLET	Formalin	Rat		(Obara *et al.*, 2009)
	Capsaicin	Rat		(Saloman *et al.*, 2011)
	Inflammatory	Rat	M [*]	(Stein *et al.*, 1989)
		Mouse	H [*]	(Hervera *et al.*, 2009)
		Rat	M	(Zhou *et al.*, 1998)
	Neuropathic	Mouse	H, M, C [*]	(Hervera *et al.*, 2010)
		Rat	H, M	(Obara *et al.*, 2009)
		Rat	C	(Mika *et al.*, 2001)
	Cancer	Mouse	H	(Baamonde *et al.*, 2005)
Deltorphin	Formalin	Mouse		(Morinville *et al.*, 2003)
		Rat		(Bilsky *et al.*, 1996)
		Rat		(Cahill *et al.*, 2001)
		Rat		(Pradhan *et al.*, 2006)
	Inflammatory	Rat	H	(Fraser *et al.*, 2000)
		Rat	H	(Hurley & Hammond, 2000)
		Rat	H	(Cahill *et al.*, 2003)
		Rat	H	(Gendron *et al.*, 2007a)
		Rat	M	(Otis *et al.*, 2011)
		Rat	H	(Beaudry *et al.*, 2009)
		Mouse	H	(Gendron *et al.*, 2007b)
		Mouse	H	(Dubois & Gendron)
	Neuropathic	Rat	C	(Mika *et al.*, 2001)
		Rat	M, C	(Holdridge & Cahill, 2007)
		Rat	M	(Kabli & Cahill, 2007)
	Cancer	Rat	M	(Otis *et al.*, 2011)
SNC80	Formalin	Mouse		(Barn *et al.*, 2001)
		Rat		(Obara *et al.*, 2009)
	GDNF hyperalgesia	Rat	M	(Joseph & Levine)
	NGF hyperalgesia	Rat	M	(Joseph & Levine)
	PGE2 hyperalgesia	Monkey	H	(Brandt *et al.*, 2001)
		Rat	M	(Pacheco & Duarte, 2005)
	Dynorphin A allodynia	Rat	M	(Kawaraguchi *et al.*, 2004)
	Inflammatory	Monkey	H	(Brandt *et al.*, 2001)
		Rat	H	(Fraser *et al.*, 2000)
		Rat	M	(Cao *et al.*, 2001)
		Rat	H	(Gallantine & Meert, 2005)
		Mouse	H	(Gendron *et al.*, 2007b)
		Mouse	H, M	(Gaveriaux-Ruff *et al.*, 2008)

Agonist	Pain model#	Species	Pain Modality	Reference
		Mouse	H, M	(Pradhan *et al.*, 2009; Pradhan *et al.*, 2010)
	Neuropathic	Mouse	M	(Scherrer *et al.*, 2009)
		Monkey	H	(Brandt *et al.*, 2001)
		Mouse	M	(Scherrer *et al.*, 2009)
		Mouse	H, M	(Gaveriaux-Ruff *et al.*, 2011)
		Rat	H, M	(Obara *et al.*, 2009)
Tan-67	Formalin	Mouse		(Barn *et al.*, 2001)
	Diabetes	Mouse	H	(Kamei *et al.*, 1997)
SB-235863	Inflammatory	Rat	H	(Petrillo *et al.*, 2003)
		Rat	H	(Beaudry *et al.*, 2009)
	Neuropathic	Rat	H	(Petrillo *et al.*, 2003)
DValAla-Enk	Cancer	Mouse	M	(Brainin-Mattos *et al.*, 2006)
AR-M100390	Inflammatory	Mouse	H, M	(Pradhan *et al.*, 2009)
		Mouse	H, M	(Pradhan *et al.*, 2010)
NIH 11082	Inflammatory	Rat	M	(Aceto *et al.*, 2007)
ADL5859	Inflammatory	Rat	M	(Le Bourdonnec *et al.*, 2008)
ADL5747	Inflammatory	Rat	M	(Le Bourdonnec *et al.*, 2009)
JNJ-20788560	Inflammatory	Rat	H	(Codd *et al.*, 2010)
Compound 8e	Inflammatory	Rat	n.i.	(Jones *et al.*, 2009)
KNT-127	Formalin	Mouse		(Saitoh *et al.*, 2011)

[#]Visceral pain was induced by intraperitoneal acetic acid injection; inflammatory pain by injection of Complete Freund's Adjuvant (CFA) , zymosan, yeast, or carrageenan ; neuropathic pain was induced by sciatic nerve or spinal nerve ligation; cancer pain by injection of NCTC 2472 osteosarcoma cells,

[*]Abbreviations: C, cold: DPDPE, (D-Pen2, D-Pen5)-enkephalin; DSLET, (D-Ser2,Leu5)-enkephalin; GDNF Glial cell line-derived neurotrophic factor; H, heat; M mechanical; NGF, nerve growth factor; PGE2, prostaglandin-E2

Table 2

Changes in delta opioid receptor expression in chronic pain models

Pain model	Species	Time and region/cell type examined	mRNA or protein - technique	Change	Reference
Inflammatory pain					
CFA * into paw	rat	DRG *	mRNA Q-RT-PCR *	No	(Gendron *et al.*, 2006)
CFA into paw	rat	DRG	mRNA Q-RT-PCR	No	(Puehler *et al.*, 2004)
CFA into paw	rat	DRG	Protein immunohistochemistry	No	(Brack *et al.*, 2004)
CFA into paw	rat	DRG	Protein immunohistochemistry	Down	(Zhang *et al.*, 1998)
CFA into paw	rat	Spinal cord	mRNA Q-RT-PCR	No	(Obara *et al.*, 2009)
CFA into paw	rat	Spinal cord	mRNA ISH * Protein Western blot	Up	(Cahill *et al.*, 2003)
CFA into paw	rat	Spinal cord	mRNA ISH	No	(Maekawa *et al.*, 1996)
CFA into paw	rat	Spinal cord	Protein radioligand binding	No	(Millan *et al.*, 1988)
CFA into paw	mouse	DRG	mRNA Q-RT-PCR	Up	(Gaveriaux-Ruff *et al.*, 2011)
Carrageenan into paw	rat	DRG	Protein immunohistochemistry	Down	(Ji *et al.*, 1995)
		Spinal cord		Down	
CFA into tail	rat	Spinal cord	mRNA Q-RT-PCR	Up	(Calza *et al.*, 2000)
CFA into joint	rat	Thalamus, reticular nucleus	mRNA ISH	Down	(Neto *et al.*, 2008)
		Brainstem, dorsal reticular nucleus		Down	
		Brainstem, parvocellular reticular nucleus		Up	
CFA into joint	rat	Spinal cord	Protein radioligand binding	Up	(Besse *et al.*, 1992b)
Incision - post-operative	mouse	DRG	mRNA Q-RT-PCR	Down	(Cabanero *et al.*, 2009)
		Spinal cord		Down	
Intestinal, croton oil	mouse	Spinal cord	mRNA Q-RT-PCR	Up	(Pol *et al.*, 2003)
			Protein Western blot		
		Whole gut		Up	
		Brain		No	
Neuropathic pain					
CCI *	rat	DRG Spinal cord	mRNA Q-RT-PCR	Down No	(Obara *et al.*, 2009)
CCI	rat	DRG	mRNA Q-RT-PCR	Down	(Herradon *et al.*, 2008)
		Spinal cord		No	
CCI	rat	Spinal cord	Protein immunohistochemistry	Down	(Tseng *et al.*, 2008)

Pain model	Species	Time and region/cell type examined	mRNA or protein - technique	Change	Reference
CCI	rat	Spinal cord	Protein western blot	No	(Holdridge & Cahill, 2007)
CCI, Spinal NL *	rat	Spinal cord	Protein immunohistochemistry	Down	(Stone *et al.*, 2004)
CCI	rat	Spinal cord	Protein radioligand binding	Down	(Stevens *et al.*, 1991)
CCI	rat	Spinal cord	Protein radioligand binding	Down	(Besse *et al.*, 1992a)
CCI	mouse	DRG	mRNA Q-RT-PCR	Down	(Hervera *et al.*, 2010)
		Spinal cord		No	
Cuff	rat	DRG	Protein western blot	Up	(Kabli & Cahill, 2007)
pSNL *	mouse	DRG	mRNA Q-RT-PCR	No	(Gaveriaux-Ruff *et al.*, 2011)
pSNL	mouse	DRG & spinal cord	mRNA Q-RT-PCR	No	(Pol *et al.*, 2006)
Multiple sclerosis					
TMEV * infection	mouse	Spinal cord	mRNA Q-RT-PCR	Down	(Lynch *et al.*, 2008)

*Abbreviations: CCI, chronic constriciton injury; CFA, Complete Freund's Adjuvant; DRG, dorsal root ganglion; ISH, In Situ hybridization; NL, nerve ligation; pSNL, partial sciatic nerve ligation; Q-RT-PCR, quantitative reverse transcriptase-PCR; TMEV, Theiler's murine encephalomyelitis virus