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# Delta opioid receptors in brain function and diseases

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## Abstract

Evidence that the delta opioid receptor (DOR) is an attractive target for the treatment of brain disorders has strengthened in recent years. This receptor is broadly expressed in the brain, binds endogenous opioid peptides, and shows as functional profile highly distinct from those of mu and kappa opioid receptors. Our knowledge of DOR function has enormously progressed from *in vivo* studies using pharmacological tools and genetic approaches. The important role of this receptor in reducing chronic pain has been extensively overviewed; therefore this review focuses on facets of delta receptor activity relevant to psychiatric and other neurological disorders. Beneficial effects of DOR agonists are now well established in the context of emotional responses and mood disorders. DOR activation also regulates drug reward, inhibitory controls and learning processes, but whether delta compounds may represent useful drugs in the treatment of drug abuse remains open. Epileptogenic and locomotor-stimulating effects of delta agonists appear drug-dependent, and the possibility of biased agonism at DOR for these effects is worthwhile further investigations to increase benefit/risk ratio of delta therapies. Neuroprotective effects of DOR activity represent a forthcoming research area. Future developments in DOR research will benefit from in-depth investigations of DOR function at cellular and circuit levels.

### Keywords

Delta opioid receptor; Knockout; Pharmacology; in vivo; pathology

## 1. Introduction

Mu, delta and kappa opioid receptors are G protein coupled receptors, which play a central role in pain control, and are key players in hedonic homeostasis, mood and well-being. The three receptors and their endogenous opioid peptides also regulate responses to stress, and a number of peripheral physiological functions including respiratory, gastrointestinal, endocrine and immune processes. Opioid receptors are highly homologous in sequence, and their crystal structure has been recently elucidated at high-resolution by X-Ray crystallography (Granier et al., 2012; Manglik et al., 2012; Wu et al., 2012). All three receptors inhibit neuronal activity, via reduced neuronal firing or lower transmitter release, and a main goal in opioid research is the identification of receptor-mediated signaling pathways that operate in vivo, to regulate physiology and behavior (Pradhan et al., 2012).



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In the past two decades, refinement of pharmacological tools and availability of genetic approaches have clarified the specific role of each opioid receptor in many aspects of opioid-related responses (Shippenberg et al., 2008; Gianoulakis, 2009; Sauriyal et al., 2011; Lutz & Kieffer, 2012; Gaveriaux-Ruff, 2013). Mu opioid receptors mediate both analgesic and addictive properties of clinically useful and abused opiates. Mu opioid receptor activation strongly inhibits severe pain, and is a major target for post-operative and cancer pain management (Zollner & Stein, 2007). Mu receptors are also central for reward processing (Le Merrer et al., 2009), representing a main factor in the initiation of addictive behaviors. Kappa opioid receptors also release pain (Chavkin, 2011) but oppose mu receptors in the regulation of hedonic homeostasis. The notion that kappa receptor blockade alleviates stress responses and depressive states is raising increasing interest (Shippenberg, 2009; Knoll & Carlezon, 2010).

Delta opioid receptors (also known as δ receptors, DORs or DOP receptors in the IUPHAR nomenclature) have emerged as an attractive target in many respects. In accordance with the rodent mRNA distribution, DOR in the human central nervous system is expressed in cortical regions and limbic structures such as hippocampus and amygdala, as well as basal ganglia and hypothalamus (Simonin et al., 1994; Peckys & Landwehrmeyer, 1999; Smith et al., 1999; Peng et al., 2012).

The development of highly selective delta opioid agonists and rapid progress in mouse mutagenesis approaches targeting the *Oprd1* gene (Filliol et al., 2000; Scherrer et al., 2006; Scherrer et al., 2009; Gaveriaux-Ruff et al., 2011) have set delta receptors as a model system for the analysis of G protein coupled receptor (GPCR) trafficking and biased signaling *in vivo*, and established this receptor as a promising target to treat chronic pain and mood disorders (Pradhan et al., 2011). The stimulation of delta opioid receptors strongly reduces pain, specifically under situations of persistent pain, and mechanisms of delta agonist analgesia have been extensively overviewed recently (Gaveriaux-Ruff & Kieffer, 2011). Here we will focus on non-nociceptive facets of delta receptor function, and summarize accumulating preclinical data supporting the key role of delta receptors in emotional processes (Tables 1 and 2), drug reward and addiction (Table 3), and other aspects of potential therapeutic relevance (Table 4). Both genetic approaches and behavioral pharmacology concur to support an implication of delta receptors in psychiatric and neurological disorders, and delta agonists have entered clinical trials (Table 5).

## 2. Delta opioid receptor and the control of emotional processes

Genetic studies have revealed a prominent role for DORs in emotional processing more than a decade ago. Knockout of the *Oprd1* gene, encoding DOR, led to higher anxiety-related responses and depressive-like behaviors (Filliol et al., 2000). This activity was clearly DOR-selective, since neither mu receptor knockout mice nor kappa receptor knockout mice showed a similar phenotype (Filliol et al., 2000). Mice deficient for *Penk* gene, encoding the pre-proenkephalin precursor, also showed increased levels of anxiety using a large number of experimental testing conditions (Konig et al., 1996; Ragnauth et al., 2001), suggesting that DOR/enkephalinergic systems exert control over anxiety-related behaviors. This was later supported by experiments performed in wild-type and mu receptor mutant mice, which both showed similar decreased levels of anxiety upon systemic administration of RB101, an enkephalinase inhibitor (Mas Nieto et al., 2005). Interestingly, over-expression of enkephalin by a virus approach in the amygdala potentiates the anxiolytic effect of benzodiazepines and this effect is abolished by systemic naltrindole (NTI) administration (Primeaux et al., 2006). Altogether therefore, genetic approaches have opened the way to explore DOR function in the areas of anxiety (Table 1) and depression (Table 2).

Pharmacological studies using both delta agonists and antagonists in rodents confirmed anxiolytic activity of the opioid tone mediated by DOR. As observed for knockout mice, receptor blockade by NTI administration, a selective DOR antagonist, increased anxiety-related behaviors in mice (Narita et al., 2006b) and rats (Saitoh et al., 2004; Saitoh et al., 2005; Perrine et al., 2006). DOR activation by selective agonists such as SNC80 (Saitoh et al., 2004; Perrine et al., 2006; Ambrose-Lanci et al., 2008), UFP-512 (Vergura et al., 2008) and ARM390 (Pradhan et al., 2010) decreased anxiety-related behaviors in most classical experimental paradigms (Table 1).

Regarding depressive states, and as predicted from knockout mice data, most currently existing DOR agonists (Pradhan et al., 2011) consistently decreased despair-like behaviors in a large number of tests (summarized in Table 2) in both mice (Saitoh et al., 2004; Naidu et al., 2007; Vergura et al., 2008) and rats (Jutkiewicz et al., 2005a; Jutkiewicz et al., 2005b; Torregrossa et al., 2006; Le Bourdonnec et al., 2008). Although no depression-related phenotype could be detected in animals lacking preproenkephalin (Bilkei-Gorzo et al., 2007), systemic administration of enkephalinase inhibitors had an antidepressant effect (Jutkiewicz et al., 2006b; Javelot et al., 2010). These studies suggest that the DOR/enkephalinergic system plays an important role in the control of depressive-like behaviors.

The circuitry of emotional processing has been extensively studied (LeDoux, 2000; Price & Drevets, 2012). Sensory information reaches cortical regions mostly through the thalamus and is integrated in limbic structures such as prefrontal cortex, hippocampus and amygdala. These brain areas, which attribute emotional value to internal and external stimuli show high DOR densities (Figure 1). Stereotaxic microinjection of several DOR agonists in the hippocampus (Solati et al., 2010), amygdala (Narita et al., 2006a; Randall-Thompson et al., 2010) and cingulate cortex (Narita et al., 2006b) reduced anxiety, and conversely, NTI administration at these brain sites increased levels of anxiety (Table 1). These data together suggest that DOR acting at the level of amygdala-cortico-hippocampal circuitry regulates emotional responses. Gene conditional approaches may be instrumental in the future to elucidate neural processes underlying DOR-controlled emotional responses at the cellular level.

## 3. Delta opioid receptor, reward and addiction

Drugs of abuse activate brain reward systems, and initially produce pleasurable effects. Repeated drug exposure may lead to loss of control over drug intake, and drug dependence. A well-accepted view describes drug abuse as a three-stage vicious circle involving intoxication/withdrawal/craving episodes (Koob & Volkow, 2010). Animal studies have demonstrated the development of altered reward processes and enhanced stress responses (Koob & Le Moal, 2008), the setting of aberrant learning mechanisms (Belin et al., 2009) and habitual behaviors (Barry J. Everitt et al., 2008), the disruption of self-control (Baler & Volkow, 2006) and the engagement of cue-induced relapse mechanisms (Pickens et al., 2011), which all contribute to maintaining drug use. All three opioid receptors are largely expressed in reward and associated neural circuits (Le Merrer et al., 2009; Koob & Volkow, 2010), which adapt to chronic drug exposure, and are involved in both recreational drug use (reward) and the many aspects of addictive behaviors.

Animal and human studies have clearly established that mu opioid receptors are essential to mediate rewarding properties of both natural stimuli and drugs of abuse, and that kappa receptors mediate dysphoria, particularly under stressful conditions (Lutz & Kieffer, 2012). The implication of DOR in drug reward is more complex and differs across drugs of abuse. Data from conditioned place preference (CPP) and self-administration (SA) experiments for four distinct classes of drugs of abuse are compiled in Table 3. Beyond drug reward, delta

receptors also contribute to the development of adaptations upon chronic drug exposure, mainly examined for morphine.

### 3.1 Morphine

DOR knockout mice showed decreased morphine-induced CPP in two studies (Chefer & Shippenberg, 2009; Le Merrer et al., 2011). However this effect was independent from rewarding properties of the drug, since mutant mice also exhibited decreased conditioned place aversion to lithium, as well as normal motivation to obtain morphine in a SA paradigm (David et al., 2008; Le Merrer et al., 2011). The association of stimuli that predict morphine administration was able to restore full expression of morphine CPP in these KO animals (Le Merrer et al., 2012). This set of experiments strongly suggests that DOR does not mediate morphine reward per se, but rather modulates learning processes in a place conditioning setting. Pharmacological studies using CPP experiments in rodents also support a role for DOR involvement in place conditioning paradigms (Suzuki et al., 1996; Shippenberg et al., 2009; Billa et al., 2010). A potential implication from all these data is that DOR may facilitate opiate-context association, which may be critical clinically in situations of context-induced relapse. A recent study, combining gene knockout and pharmacology, suggests that DOR is required to assign hedonic value to a reward-associated stimulus, a process that might influence motivation to get a reward (Laurent et al., 2012). The latter study, involving sucrose reward provides another indication for DOR-mediated associative processes.

Regarding chronic morphine effects, DOR knockout mice showed enhanced sensitization to locomotor effects of morphine (Chefer & Shippenberg, 2009), and pharmacological blockade of DOR by NTI (Chefer & Shippenberg, 2009) or naltriben (Billa et al., 2010) increased morphine-induced locomotor sensitization. Notably, morphine acts at mu opioid receptors in vivo (Contet et al., 2004) and does not directly activate DORs, as suggested by intact morphine analgesia (Y. Zhu et al., 1999; Scherrer et al., 2009) and reward (Table 3) in DOR knockout mice. Therefore the exact nature of delta-mu opioid receptor interactions in vivo and mechanisms underlying DOR-regulated chronic morphine effects remain to be clarified.

### 3.2 Ethanol

Pharmacological blockade of DOR systemically by NTI, naltriben or SORI-9409 decreased voluntary ethanol consumption (Nielsen et al., 2008; van Rijn & Whistler, 2009) and also cue-mediated drug seeking (Marinelli et al., 2009). Those studies suggested that DOR are likely involved in both rewarding properties of alcohol and learning processes responsible for the context-drug consumption association. Local administration of DOR antagonists into the ventral tegmental area (VTA) (Margolis et al., 2008), the dorsal striatum (Nielsen et al., 2012) or the central nucleus of the amygdala (Bie et al., 2009) also disrupted ethanol self-administration or ethanol-induced CPP. In accordance, systemic or local administration (dorsal striatum and paraventricular nucleus of the hypothalamus) of DOR agonists stimulated ethanol SA (Barson et al., 2010; van Rijn et al., 2010a; Nielsen et al., 2012). Therefore, pharmacology approaches concur to indicate that DOR activation at several brain sites, and overall, facilitates ethanol drinking in rodents.

Paradoxically, DOR knockout mice showed increased ethanol consumption in a two bottle choice test (SA paradigm) (Roberts et al., 2001). Because these mutant mice exhibit high levels of anxiety (Filliol et al., 2000), and ethanol SA reduced their innate high anxiety levels (Roberts et al., 2001), high voluntary ethanol intake in mutant mice may reflect a self-medication approach. No alcohol phenotype could be detected in animals lacking the *Penk* gene in two-bottle-choice and ethanol-induced conditioned place preference paradigms (Racz et al., 2008).

### 3.3 Psychostimulants

DOR knockout mice showed decreased nicotine-induced CPP and SA (Berrendero et al., 2012). Systemic DOR blockade by NTI produced a similar effect in rats and mice (Ismayilova & Shoaib, 2010; Berrendero et al., 2012), and also abolished amphetamine-induced CPP (Belkai et al., 2009). Endogenous DOR activity therefore seems to contribute to reinforcing properties of these two drugs, as for alcohol. NTI infused locally in the nucleus accumbens, VTA and amygdala had contrasting effects on cocaine SA (Ward & Roberts, 2007; Simmons & Self, 2009), suggesting differing roles of DORs at distinct brain sites of reward processing (Figure 1). Finally, a recent SNP study showed association between an *Oprd1* variant and cocaine addiction in the African American population (Crist et al., 2013), providing support for a role of DOR in psychostimulant dependence in humans.

In sum, both genetic and pharmacologic approaches suggest a regulatory role for DOR in drug intake, seeking and dependence, which vary depending on the drug and testing paradigm. DOR activity seems to facilitate alcohol and psychostimulant reward, but does not contribute to rewarding properties of morphine. Examination of reinforcing effects of cannabinoids showed no difference between DOR knockout and their control mice (Ghozland et al., 2002), and a contribution of DOR to cannabinoid reward has not been established. DORs are also involved in other aspects contributing to the development of drug abuse, including context learning and the development of tolerance (morphine), or the regulation of emotional responses (alcohol). The latter aspects may be critical in the development of therapeutic strategies. Indeed, targeting aspects of DOR function other than reward, which contribute to maintaining drug dependence, to the negative mood of protracted abstinence or to context-induced relapse, might be of particular interest. Finally, DOR was shown to regulate inhibitory controls in mice (Olmstead et al., 2009) and rats (Befort et al., 2011)**,** revealing yet another facet of DOR function in cognitive processes with potential implication in substance abuse disorders.

## 4. Delta opioid receptor and epileptic seizures

Early studies showed that the first developed non-peptidic DOR agonists, BW373U86 and SNC80 exhibit convulsive properties (Broom et al., 2002; Jutkiewicz et al., 2005b) and data are overviewed in Table 4. Convulsions induced by the agonists SNC80 are abolished both in DOR knockout mice and after pharmacological blockade of DOR with NTI (Jutkiewicz et al., 2005b). Notably, electroencephalographic and behavioral changes elicited by acute SNC80 administration remain brief and non-lethal as compared to those obtained with the reference seizurogenic GABA antagonist pentylenetetrazole (Jutkiewicz et al., 2006a). Mechanisms underlying DOR-mediated convulsions remain poorly understood, but likely relate to the neural circuitry involved in absence epilepsy (Jutkiewicz et al., 2006a).

SNC80-induced convulsions, but not anti-depressant effects, were greatly diminished when slowing the rate of administration (Jutkiewicz et al., 2005b), indicating a possible dissociation between proconvulsant and antidepressant activities of SNC80. Importantly also, recently developed delta agonists showed no detectable convulsing effects. ADL5859 in both rats and mice at doses up to 1000 mg/kg (p. o.) induced no seizures and no EEG disturbances (Le Bourdonnec et al., 2008), and a similar result was found for ADL5747 (Le Bourdonnec et al., 2009). Therefore the pro-epileptic activity of DOR seems agonist-dependent and opens the way to developing therapeutic compounds with a better benefit/risk profile. Whether this is a pharmacokinetics issue or another indication of biased-agonism at DOR *in vivo* (Pradhan et al., 2011) remains to be determined.

## 5. Delta opioid receptor and motor control

The DOR receptor is strongly expressed in the striatum (Figure 1) and the agonist SNC80 shows locomotor-stimulating properties (Fraser et al., 2000; Jutkiewicz et al., 2005a; Saitoh et al., 2011; Nozaki et al., 2012). On the other hand, DOR knockout mice showed hyperactivity in actimetry boxes (Filliol et al., 2000), and deficient striatal-dependent responses in a cross-maze assessing the hippocampal/striatal balance (Le Merrer et al., 2013). These data suggest a significant but complex implication of DOR in the regulation of motor activity and this facet of DOR function is of potential interest in diseases involving impaired motor control such as Parkinson ’s disease (PD). Indeed, DOR activation by the agonist UFP-512 at low dose increased locomotor coordination in a hemiparkinsonian rat model (Mabrouk et al., 2009), and had opposing effects at a high dose (Mabrouk et al., 2009). The antagonist NTI diminished abnormal movements classically described in the 6-OHDA model (Billet et al., 2012). More studies are necessary to understand DOR-mediated mechanisms regulating direct and indirect striatal output pathways.

Notably, recently developed DOR agonists do not show locomotor-activating properties (Svensson et al., 2003; Le Bourdonnec et al., 2008; Le Bourdonnec et al., 2009; Saitoh et al., 2011; Nozaki et al., 2012). Therefore, as for epileptic seizures, DOR-mediated locomotor effects appear agonist-dependent. Further investigations are required to define whether DOR agonist-mediated epileptic seizures and locomotor activity may share common neural circuitry and signaling pathway mechanisms.

## 6. Delta opioid receptor in hypoxia/ischemia

Hypoxic/ischemic conditions are characterized by reduced oxygen availability and trigger broad physiological alterations leading to cell death. The neuroprotective function of DOR activation has emerged recently, and offers interesting clinical perspectives for hypoxic/ischemic stress (Chao & Xia, 2010; Johnson & Turner, 2010). Beneficial effects of DOR activity deduced from *in vivo* models of hypoxia and ischemia are summarized in Table 4. Pharmacological studies showed that DOR activation by DADLE, a specific agonist, significantly increased neuronal survival in a model of asphyxia cardiac arrest, and that NTI opposed neuroprotective effects of hypoxic preconditioning in this model (Gao et al., 2010; Gao et al., 2012). DADLE also showed significant protective effects on astrocyte death in the hippocampus in another model of global ischemia (Duan et al., 2011). Studies in cell cultures suggested a critical role in ionic homeostasis in DOR-mediated neuroprotection (Chao et al., 2008; Chao et al., 2009). In a mitochondrial respiratory chain injury model, DOR activation protected neurons by decreasing pro-apoptotic factor expression levels like cytochrome c and caspase-3 (M. Zhu et al., 2009; M. Zhu et al., 2011). Altogether, these data strongly support a role for DOR to maintain cellular metabolic homeostasis and counteract detrimental effects of hypoxic/ischemic injury.

DOR may also minimize consequences of hypoxia on autonomic neural responses. In models of panic attack, CO2 exposure produces acute dyspnea. This response is alleviated by diazepam in wild-type but not DOR knockout mice, suggesting a role for DOR in diazepam-regulated respiratory responses (Borkowski et al., 2011). Also, low oxygen-evoked decrease in body temperature returned to normal levels more slowly upon DOR blockade by NTI (Scarpellini Cda et al., 2009). Altogether these data indicate that DOR agonists may be beneficial under ischemic conditions via multiple, direct and indirect, mechanisms.

## 7. Clinical perspectives

The pain-reducing (Gaveriaux-Ruff & Kieffer, 2011) and mood-enhancing (Tables 1 and 2) properties of delta opioid agonists in animal models have attracted lots of interest, and efforts are being developed to bring delta drugs to the clinic (Table 5). Several agonists are being tested for pain, including a number of indications in chronic pain patients. The AstraZeneca compound ADZ2327 went successfully through Phase II trials in patients with anxiety-associated major depressive disorder (NCT00759395) (Hudzik et al., 2011). Clinical trials with delta agonists are only at their beginning. Potential convulsant effects need to be carefully controlled, and whether delta agonists could be useful for neuroprotection or to treat Parkinson's disease will require additional validation from animal research.

With regard to drug design, the notion that DOR may heterodimerize with MOR, KOR, or another GPCR *in vivo* has fostered the development of dimer-specific drugs endowed with pharmacological properties distinct from agonists acting at DOR homomers (Panetta & Greenwood, 2008; van Rijn et al., 2010b; Costantino et al., 2012; Kleczkowska et al., 2013). Also, the recent demonstration of biased agonism at DOR *in vivo* may have clinical implications. The "biased agonism" concept (Galandrin et al., 2007; Kenakin, 2011), also referred to as functional selectivity, stems from the observation that distinct agonists acting at the same GPCR can engage different active receptor conformations and/or complexes with other GPCRs or intracellular effectors, leading to agonist-specific signaling responses. Opioid receptors were among the first GPCRs for which agonist-biased responses *in vivo* were demonstrated (Pradhan et al., 2012). The observation that delta opioid receptor agonists causing high (SNC80) or low (ARM00390) receptor internalization lead to distinct forms of tolerance (Pradhan et al., 2010) opens novel avenues towards drug design for therapeutic effects with limited side effects.

## 8. Concluding remarks

Delta opioid receptors and opioid peptides are broadly expressed across the brain. Our understanding of DOR function has tremendously progressed from *in vivo* studies using pharmacological tools and genetic approaches. Beneficial effects of DOR agonists are of a particular interest in the case of emotional responses and mood disorders. DOR regulates drug reward, and also plays a significant role in inhibitory controls and learning processes whose dysfunction contributes to the development of addiction. Whether delta compounds will represent useful drugs in addiction treatment remains open. DOR control over epileptic seizure mechanisms deserves further studies to enable the development of delta drugs with limited side effects. The neuroprotective role of DOR represents an emerging research field, with potential new opportunities for delta opioid drugs in the clinic. In the future, the development of improved delta drugs will also benefit from a better understanding of DOR function at distinct brain sites within neural circuits of emotion and cognition.

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## Abbreviations

**Amy** amygdala

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| **CA** | continuous access |
| **CeA** | central nucleus of the amygdala |
| **Cg** | cingulate cortex |
| **CPA** | conditioned place aversion |
| **CPP** | conditioned place preference |
| **Cpu** | caudate putamen nucleus |
| **Cx** | cortex |
| **DOR** | delta opioid receptor |
| **EEG** | electroencephalography |
| **Enk** | enkephalin |
| **FCx** | frontal cortex |
| **GPCR** | G protein coupled receptor |
| **Hipp** | hippocampus |
| **Hyp** | hypothalamus |
| **i.c.v** | intracerebroventricular |
| **i.p** | intraperitoneal |
| **i.v** | intraveneous |
| **IA** | intermittent access |
| **KO** | knockout |
| **Nacc** | nucleus accumbens |
| **NTI** | naltrindole |
| **OB** | olfactory bulb |
| **p.o** | pers os |
| **PR** | progressive ratio |
| **PVN** | paraventricular nucleus |
| **RS** | retrosplenial cortex |
| **s.c** | subcutaneous |
| **SA** | self-administration |
| **SC** | spinal cord |
| **th** | thalamus |
| **VTA** | ventral tegmental area |

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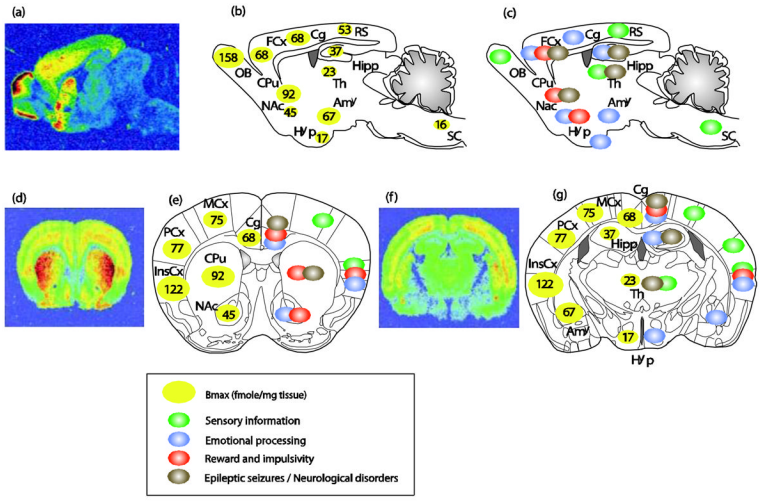


**Figure 1.**

Anatomical distribution of delta opioid receptors and relevant brain functions. Top panels, sagittal sections; bottom panels, coronal sections at 2 different anterio-posterior positions ((e) bregma 0.98mm; (g) bregma −1.46mm). **(a, d and f)** ([$^3$H]deltorphin ligand autoradiography reveals delta opioid receptor binding sites (courtesy of Ian Kitchen). **(b, e left part and g left part)** Quantification of DOR expression levels in fmole/mg of tissue (means from (Kitchen et al., 1997; Simonin et al., 1998; Slowe et al., 1999; Goody et al., 2002). DORs are particularly abundant in the OB, cortical regions (FCx, Cg, MCx, PCx and InsCx), amygdala and striatum (CPu and NAc). DORs are also expressed at moderate levels in the Hipp, RS, and at much lower level in Hyp, Th and SC. **(c, e right part and g right part)** Schematic representation of potential neural sites for DOR function. DORs are expressed in sensory regions (green circles), brain areas important for the regulation of anxiety and depression (blue circles adapted from (File et al., 2000; LeDoux, 2000; Cardinal et al., 2002; B. J. Everitt et al., 2003; Paulus & Stein, 2006; Rodrigues et al., 2009; Etkin et al., 2011; Gross & Canteras, 2012; Steenland et al., 2012)), brain sites for reward processing and inhibitory controls (red circles adapted from (Robbins & Everitt, 1996; Balleine & Dickinson, 1998; Kesner & Gilbert, 2007; Paton & Louie, 2012; Richard et al., 2012)) and areas relevant to epileptic seizures (grey circles adapted from (Andre et al., 1998; Brevard et al., 2006)). Abbreviations: Amy, Amygdala; Cg, Cingulate cortex; Cpu, Caudate Putamen; FCx, Frontal cortex; Hipp, Hippocampus; Hyp, Hypothalamus; InsCx, Insular cortex; MCx, Motor cortex; NAc, Nucleus Accumbens; OB, Olfactory Bulb; PCx, Parietal cortex; RS, Retrosplenial; SC, Spinal Cord; Th, Thalamus.

**Table 1**

Delta opioid receptor function in anxiety-related behavior control

| Approach | Model / compound | Test | Delta compound administration (route/dose) | Anxiety level (vs control) | References |
|---|---|---|---|---|---|
| **Genetic** | | | | | |
| | DOR KO mice | Elevated plus maze | | ↑ | (Filliol et al., 2000) |
| | | Light-dark box | | ↑ | (Filliol et al., 2000) |
| | | Open field | | ↔ | (Filliol et al., 2000) |
| | Enk KO mice | Open field | | ↑ | (Konig et al., 1996; Ragnauth et al., 2001) |
| | | Elevated O- maze | | ↑ | (Konig et al., 1996) |
| | | Resident- intruder test | | ↑ | (Konig et al., 1996) |
| | | Light-Dark Box | | ↑ | (Ragnauth et al., 2001) |
| | | Fear conditioning | | ↑ | (Ragnauth et al., 2001) |
| **Pharmacologic** | | | | | |
| | Rats / NTI | Elevated plus maze | s.c. (1, 3 or 5 mg/kg) | ↑ | (Saitoh et al., 2004; Saitoh et al., 2005; Perrine et al., 2006) |
| | | Elevated plus maze | local into Hipp (0.5, 1 or 2 μg/rat) | ↑ | (Solati et al., 2010) |
| | | Light-dark box | local into BLA (10 pmol/rat) | ↑ | (Narita et al., 2006a) |
| | Mice / NTI | Light-dark box | i.c.v. (1 nmol/mouse) | ↑ | (Narita et al., 2006a) |
| | | Light-dark box | s.c. (1 mg/kg) | ↑ | (Narita et al., 2006b) |
| | | Light-dark box | local into cingulate Cx (1 pmol/mouse) | ↑ | (Narita et al., 2006b) |
| | | Elevated plus maze | s.c. (1 mg/kg) | ↑ | (Narita et al., 2006b) |
| | | Elevated plus maze | local into cingulate Cx (1 pmol/mouse) | ↑ | (Narita et al., 2006b) |
| | Rats / SNC80 | Fear conditioning | s.c. (1 or 3 mg/kg) | ↓ | (Saitoh et al., 2004) |
| | | Elevated plus maze | s.c. (1–20 mg/kg) | ↓ | (Saitoh et al., 2004; Perrine et al., 2006) |
| | | Open field | s.c. (1 or 3 mg/kg) | ↔ | (Saitoh et al., 2004) |
| | | Defensive burying paradigm | s.c. (5 mg/kg) | ↓ | (Perrine et al., 2006) |
| | | Elevated O- maze | s.c. (5 mg/kg) | ↓ | (Ambrose-Lanci et al., 2010) |
| | Rats / DPDPE | Elevated plus maze | local into CeA (0.5 or 1.5 μg/μl; 1 μl/CeA) | ↓ | (Randall-Thompson et al., 2010) |
| | Mice / UFP-512 | Light-dark box | i.p. (1 mg/kg) | ↓ | (Vergura et al., 2008) |
| | | Elevated plus maze | i.p. (0.1 or 1 mg/kg) | ↓ | (Vergura et al., 2008) |
| | | Open field | i.p. (0.1 or 1 mg/kg) | ↔ | (Vergura et al., 2008) |

| Approach | Model / compound | Test | Delta compound administration (route/dose) | Anxiety level (vs control) | References |
|---|---|---|---|---|---|
| **Genetic** | | | | | |
| | Rats / Enkephalin | Elevated plus maze | local into Hipp (1, 2 or 5 μg/rat) | ↓ | (Solati et al., 2010) |
| | Mice / RB101 | Elevated O- maze | i.p. (80 mg/kg) | ↓ | (Mas Nieto et al., 2005) |
| | Rats / Opiorphin | Defensive burying paradigm | i.v. (1 mg/kg) | ↔ | (Javelot et al., 2010) |
| | Rats / AZD2327 | Modified geller-seifter conflict test | p.o. (0.5, 1 or 5 mg/kg) | ↓ | (Hudzik et al., 2011) |

**Table 2**

Delta opioid receptor function in depressive-like behavior control

| Approach | Model / compound | Test | Delta compound administration (dose/route) | Despair level (vs control) | References |
|---|---|---|---|---|---|
| **Genetic** | | | | | |
| | DOR KO mice | Forced swim test | | ↑ | (Filliol et al., 2000) |
| | | Motility conditioned suppression test | | ↔ | (Filliol et al., 2000) |
| | Enk KO mice | Forced swim test | | ↔ | (Bilkei-Gorzo et al., 2007) |
| | | Tail suspension test | | ↔ | (Bilkei-Gorzo et al., 2007) |
| **Pharmacologic** | | | | | |
| | Mice / NTI | Forced swim test | s.c. (1 or 3 mg/kg) | ↔ | (Saitoh et al., 2004) |
| | Rats / SNC80 | Forced swim test | s.c. (3.2, 10 or 32 mg/kg) | ↓ | (Jutkiewicz et al., 2005a; Jutkiewicz et al., 2005b) |
| | Mice / SNC80 | Forced swim test | s.c. (1 or 3 mg/kg) | ↓ | (Saitoh et al., 2004) |
| | Rats / DPDPE | Forced swim test | i.c.v. (155 nmol/rat) | ↓ | (Torregrossa et al., 2006) |
| | Rats / Deltorphin II | Forced swim test | i.c.v. (0.03 or 0.1 nmol/rat) | ↓ | (Torregrossa et al., 2006) |
| | Rats / JOM-13 | Forced swim test | i.v. (32 mg/kg) | ↓ | (Torregrossa et al., 2006) |
| | Mice / NIH 11082 | Tail suspension test | i.p. (16 or 32 mg/kg) | ↓ | (Naidu et al., 2007) |
| | Mice / UFP-512 | Forced swim test | i.p. (0.1 or 0.3 mg/kg) | ↓ | (Vergura et al., 2008) |
| | Rats / RB101 | Forced swim test | i.v. (32 mg/kg) | ↓ | (Jutkiewicz et al., 2006) |
| | Mice / RB101 | Forced swim test | i.p. (80 mg/kg) | ↓ | (Mas Nieto et al., 2005) |
| | | Motility conditioned suppression test | i.p. (80 mg/kg) | ↓ | (Mas Nieto et al., 2005) |
| | Rats / Opiorphin | Forced swim test | i.v. (1 mg/kg) | ↓ | (Javelot et al., 2010) |
| | Rats / AZD2327 | Learned helplessness | p.o. (1 or 10 mg/kg) | ↓ | (Hudzik et al., 2011) |
| | Mice / KNT-127 | Forced swim test | s.c. (0.1, 0.3 or 1 mg/kg) | ↓ | (Saitoh et al., 2011) |

**Table 3**

Delta opioid receptor function in reward and addiction

| Drug of abuse / approach | Model / compound | Test | Delta compound administration (dose/ route) | Behavioral level (vs control) | References |
|---|---|---|---|---|---|
| **Morphine** | | | | | |
| Genetic | DOR KO mice | CPP | | ↓ | (Chefer & Shippenberg, 2009; Le Merrer et al., 2011) |
| | | CPA (Lithium) | | ↓ | (Le Merrer et al., 2011) |
| | | SA | | ↔ | (Le Merrer et al., 2011) |
| | | SA | | ↔ | (David et al., 2008) |
| DOR antagonist | Mice / NTI | CPP | s.c. (0.3 mg/kg) | ↓ | (Chefer & Shippenberg, 2009) |
| | Rats / Naltriben | CPP | i.p. (1 mg/kg) | ↓ | (Billa et al., 2010) |
| DOR agonist | Mice / TAN-67 | CPP | s.c. (10 or 20 mg/kg) | ↑ | (Suzuki et al., 1996) |
| **Ethanol** | | | | | |
| Genetic | DOR KO mice | SA (Two bottle choice CA) | | ↑ | (Roberts et al., 2001) |
| | | Operant SA | | ↑ | (Roberts et al., 2001) |
| | Enk KO mice | SA (Two bottle choice CA) | | ↔ | (Racz et al., 2008) |
| DOR antagonist | Rats / NTI | Cue or context induced drug-seeking | i.p. (1, 5, 7.5 or 15 mg/kg) | ↓ | (Marinelli et al., 2009) |
| | | SA (Two bottle choice CA) | i.p. (5 or 10 mg/kg) | ↓ | (Nielsen et al., 2008) |
| | | CPP | intra-CeA (2 nM) | ↓ | (Bie et al., 2009) |
| | | SA (Two bottle choice IA) | intra-striatal (1 or 2 μg) | ↓ | (Nielsen et al., 2012) |
| | Mice / Naltriben | SA (Two bottle choice IA) | s.c. (6 or 10 mg/kg) | ↓ | (van Rijn & Whistler, 2009) |
| | Rats / TIPPΨ | SA (Two bottle choice CA) | intra-VTA (5 μM) | ↓ | (Margolis et al., 2008) |
| | Rats / S0RI-9409 | SA (Two bottle choice CA and IA) | i.p. (5, 15 or 30 mg/kg) | ↓ | (Nielsen et al., 2008) |
| DOR agonist | Rats / SNC80 | SA (Two bottle choice IA) | i.p. (20 mg/kg) | ↑ | (van Rijn et al., 2010) |
| | | | intra-striatal (5 ng) | ↑ | (Nielsen et al., 2012) |
| | Rats / DPDPE | SA (Two bottle choice CA) | intra-VTA (10 mM) | ↓ | (Margolis et al., 2008) |
| | Rats / DALA | SA (Two bottle choice IA) | intra-PVN (7.1 or 14.2 nM) | ↑ | (Barson et al., 2010) |
| **Cannabinoids** | | | | | |
| Genetic | DOR KO mice | CPP | | ↔ | (Ghozland et al., 2002) |
| **Nicotine** | | | | | |
| Genetic | DOR KO mice | Nicotine CPP | | ↓ | (Berrendero et al., 2012) |

| Drug of abuse / approach | Model / compound | Test | Delta compound administration (dose/ route) | Behavioral level (vs control) | References |
|---|---|---|---|---|---|
| | | Nicotine SA | | ↓ | (Berrendero et al., 2012) |
| DOR antagonist | Rats / NTI | Nicotine SA (0.03 mg/kg/infusion) | s.c. (0.3, 1 or 3 mg/kg) | Trend ↓ | (Ismayilova & Shoaib, 2010) |
| | Mice / NTI | Nicotine SA (30 μg/kg/infusion) | i.p. (5 mg/kg) | ↓ | (Berrendero et al., 2012) |
| **Psychostimulant** | | | | | |
| DOR antagonist | Mice / NTI | Amphetamine- induced CPP | s.c. (5 mg/kg) | ↓ | (Belkai et al., 2009) |
| | Rats / NTI | Cocaine SA (PR) (1.5 mg/kg/infusion) | intra-NAcc (5 nM/side) | ↓ | (Ward & Roberts, 2007) |
| | | | intra-VTA (5 nM/side) | ↑ | (Ward & Roberts, 2007) |
| | | | intra-amygdala (5 nM/side) | ↔ | (Ward & Roberts, 2007) |
| | Rats / NTI | Cocaine reinstatement | intra-NAcc (300, 1000 or 3000 ng/side) | ↔ | (Simmons & Self, 2009) |

**Table 4**

elta opioid receptor role in epileptic seizures, hypoxia/ischemia and parkinson disease

| Condition / pathology | Model / compound | Test / measures | Delta compound administration (dose/route) | Results | References |
|---|---|---|---|---|---|
| **Epileptic seizures** | | | | | |
| | DOR KO mice / | Ethological observations | s.c. (10–100 mg/kg) | DOR agonist- mediated seizures abolished | (Broom et al., 2002) |
| | Mice / SNC80 | Ethological observations | s.c. (10–100 mg/kg) | Seizures↑ | (Broom et al., 2002) |
| | Mice / BW373U86 | Ethological observations | s.c. (1–32 mg/kg) | Seizures↑ | (Broom et al., 2002) |
| | Rats / SNC80 | Ethological observations / EEG recording | s.c. or i.v. (1–100 mg/kg) | Seizures↑ | (Jutkiewicz et al., 2005a; Jutkiewicz et al., 2005b; Jutkiewicz et al., 2006a) |
| | Rats / NTI | Ethological observations of SNC80-induced convulsions | s.c. (0.1–10 mg/kg) | Seizures↑ | (Jutkiewicz et al., 2005b) |
| | Mice / KNT-127 | Ethological observations | s.c. (30 or 100 mg/kg) | No seizures | (Saitoh et al., 2011) |
| | Mice / RB101 | Ethological observations / EEG recording | i.v. (32 mg/kg) | No seizures | (Jutkiewicz et al., 2006b) |
| | Rats / ADL5859 | EEG recording | i.v. (10 or 30 mg/kg) | No seizures | (Le Bourdonnec et al., 2008) |
| | Rats / ADL5747 | EEG recording | i.v. (10 or 30 mg/kg) | No seizures | (Le Bourdonnec et al., 2009) |
| **Motor control** | | | | | |
| | Mice / SNC80 | Spontaneous locomotor activity | s.c. (1, 5 or 10 mg/kg) | ↑ | (Saitoh et al., 2011; Nozaki et al., 2012) |
| | Rats / SNC80 | Spontaneous locomotor activity | s.c. (3.2, 10 or 32 mg/kg) | ↑ | (Jutkiewicz et al., 2005a) |
| | Rats / RB101 | Spontaneous locomotor activity | i.v. (32 mg/kg) | ↑ | (Jutkiewicz et al., 2006b) |
| | Rats / $DV_L{}^2DA_L{}^5$Lanenk | Ethological observations | i.t. (0.1–30 μg) i.p. (0.1, 1 or 3 mg/kg) | ↔ | (Svensson et al., 2003) |
| | Mice / KNT-127 | Spontaneous locomotor activity | s.c. (1 or 10 mg/kg) | ↔ | (Saitoh et al., 2011) |
| | Mice / ADL5747 and ADL 5859 | Spontaneous locomotor activity | p.o. (10–300 mg/kg) | ↔ | (Nozaki et al., 2012) |
| | Rats / ADL5859 | Spontaneous locomotor activity | p.o. (up to 1000 mg/kg) | ↔ | (Le Bourdonnec et al., 2008) |
| | Rats / ADL5747 | Spontaneous locomotor activity | p.o. (30, 100 or 300 mg/kg) | ↔ | (Le Bourdonnec et al., 2009) |
| **Parkinson's disease** | | | | | |
| | Rats / UFP-512 | Hemiparkinsonian 6- OHDA-induced unilateral lesions / drag test-rotarod | i.p. (0.1–1000 μg/kg) | Low dose UFP-512 Motor coordination ↑ High dose UFP-512 Motor coordination ↑ | (Mabrouk et al., 2009) |

| Condition / pathology | Model / compound | Test / measures | Delta compound administration (dose/route) | Results | References |
|---|---|---|---|---|---|
| | Rats / DPDPE | Hemiparkinsonian 6- OHDA-induced unilateral lesions / ethological observation | i.c.v. (10 μg/5μl/rat) | Abnormal movements ↑ | (Billet et al., 2012) |
| | Rats / NTI | Hemiparkinsonian 6- OHDA-induced unilateral lesions / ethological observation | i.c.v. (10 μg/5μl/rat) | Abnormal movements ↓ | (Billet et al., 2012) |

## Table 5

Clinical trials targeting the delta opioid receptor

| Sponsor | Drug | Condition | Clinical Phase | References (ID) |
|---|---|---|---|---|
| **AstraZeneca** | AZD2327 | Anxious Major Depressive Disorder | 2 | NCT00759395 |
| **Cubist Pharmaceuticals** | ADL5859 | Acute Pain | 2 | NCT00993863 |
| **Cubist Pharmaceuticals; Pfizer** | ADL5859 | Osteoarthritis of the Knee | 2 | NCT00979953 |
| | ADL5747 | Osteoarthritis of the Knee | 2 | NCT00979953 |
| **Cubist Pharmaceuticals; Pfizer** | ADL5747 | Postherpetic Neuralgia | 2 | NCT01058642 |
| **Cubist Pharmaceuticals** | ADL5945 | Opioid-Induced Constipation | 2 | NCT01207427 |
| **Diamyd Inc** | NP2 | Intractable Pain | 2 | NCT01291901 |
| **Penn State University** | NP2 | Hepatocellular Cancer | 1 | NCT00706576 |
| | | Head and Neck Squamous Cell Carcinoma | 2 | NCT00905099 |