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Pharmacological traits of delta opioid receptors: pitfalls or opportunities?

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Abstract

Delta opioid receptors (DORs) have been considered as a potential target to relieve pain as well as treat depression and anxiety disorders, and are known to modulate other physiological responses, including ethanol and food consumption. A small number of DOR selective drugs are in clinical trials, but no DOR selective drugs have been approved by the Federal Drug Administration and some candidates have failed in phase II clinical trials, highlighting current difficulties producing effective delta opioid based therapies. Recent studies have provided new insights into the pharmacology of the DOR, which is often complex and at times paradoxical. This review will discuss the existing literature focusing on four aspects: 1) Two DOR subtypes have been postulated based on differences in pharmacological effects of existing DOR-selective ligands 2) DORs are expressed ubiquitously throughout the body and central nervous system and are, thus, positioned to play a role in a multitude of diseases. 3) DOR expression is often dynamic, with many reports of increased expression during exposure to chronic stimuli, such as stress, inflammation, neuropathy, morphine, or changes in endogenous opioid tone. 4) A large structural variety in DOR ligands implies potential different mechanisms of activating the receptor. These combined features of DOR pharmacology illustrate the potential benefit of designing tailored or biased DOR ligands.

Keywords

opioid receptor; GPCR; trafficking; localization; drug; alcohol; depression; anxiety; allodynia

1. Introduction

Opioids are some of the earliest drugs used medicinally, with utility dating back thousands of years to the use of opium. Opioid based mixtures continued to be used for centuries without a proper understanding of the mechanism of action. It was not until the beginning of the 19th century that some of the active analgesic alkaloids, like morphine and codeine, were isolated from opium. This was followed a century later, in the midst of the Second World War, with the synthesis of the first synthetic opiates (Brownstein 1993). By this time, receptor theory had become reasonably well established (Maehle et al. 2002) and in 1973 binding studies with radiolabeled opioids performed by Pert, Snyder, Terenius and Simon suggested the existence of multiple different opioid receptors with distinct distribution patterns (Kuhar et al. 1973; Pert and Snyder 1973; Simon et al. 1973; Terenius 1973) and see Simon et al for review (Simon and Hiller 1978)). This hypothesis was further supported

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by the isolation of endogenous opioids (Cox et al. 1976; Goldstein 1976; Goldstein et al. 1979; Hughes et al. 1975). Using morphine and ketacyclazocine Martin et al proposed the existence of kappa (KOR) and mu (MOR) opioid receptors (Martin et al. 1976) and, a year later, the delta opioid receptor (DOR) was proposed based on the preference of leu-enkephalin to bind to receptors in the mouse vas deferens (Lord et al. 1977). These studies were soon followed by the cloning of the genes encoding the endogenous opioids pro-opiomelanocortin (Nakanishi et al. 1979), preproenkephalin (Noda et al. 1982) and prodynorphin genes (Civelli et al. 1985), and subsequently the cloning of the genes for the receptors, DOR (Evans et al. 1992; Kieffer et al. 1992), MOR (Chen et al. 1993; Thompson et al. 1993; Wang et al. 1993) and KOR (Li et al. 1993; Meng et al. 1993; Minami et al. 1993).

DOR subtypes

Prior to the cloning of the DOR gene, several studies reported ambiguous DOR pharmacology (Negri et al. 1991b; Vaughn et al. 1990; Xu et al. 1991). Some of these studies proposed the existence of an “uncomplexed” DOR and a DOR that was “complexed” with the MOR. These DOR subtypes were labeled DORcx, the DOR in complex with MOR, and DORncx, the non-complexed DOR (Rothman et al. 1992a; Rothman et al. 1992b; Rothman et al. 1991). New DOR selective ligands were also identified and synthesized and several groups classified them into two classes, whereby agonists of one class would not produce cross-tolerance to an agonist of the other class (Mattia et al. 1991). The existence of more than one class of DOR was further supported by observations that antagonist(s) from one class could not block the effects of an agonist from the other class (Mika et al. 2001; Sofuoglu et al. 1991; Sofuoglu et al. 1993; Thorat and Hammond 1997).

These findings led investigators to propose the existence of two distinct DOR subtypes, DOR1 and DOR2. Based mostly on pharmacological studies of cross tolerance and selective antagonism, some DOR ligands were classified as DOR1-selective (DPDPE, TAN67, DALCE and BNTX) and other as DOR2-selective (Deltorphan II, DSLET, Naltriben and 5'NTII). However, the underlying molecular mechanisms responsible for this subtype classification is poorly understood (Dietis et al. 2011), especially once it was clear there was only a single DOR gene and unlike for the MOR (Pasternak 2004), splice variants were much less apparent (Gaveriaux-Ruff et al. 1997). Also it has proven difficult to recapitulate DOR subtype specific pharmacology in vitro in cells expressing only DOR (Parkhill and Bidlack 2002). This suggests that the subtypes only appear post-translational at the protein-level, rather than at the gene-level. This would agree, for example, with the observation that protein-protein interactions between the DOR and MOR contribute to subtype pharmacology. Another option is that simultaneous blockade or stimulation of DORs and MORs that are expressed in the same brain circuit, but not necessarily in the same neuron, could produce a pharmacological effect distinct from ligands that only occupy DORs, and not MORs. For the latter hypothesis to be true one would expect to see a clear difference in DOR/MOR selectivity ratio between the DOR subtypes. However, it does not appear that DOR1 selective ligands display higher MOR affinity compared to DOR2 selective ligands (Table 1), which would argue against the “circuitry” hypothesis.

DOR selective ligands

There is a large structural variety in compounds that have moderate to high affinity for the DOR (Figure 1). Endogenous opioids have been isolated from humans (e.g. Met- and Leu-enkephalin) as well as from other species such as frogs (e.g. deltorphin I and II) (Erspermer et al. 1989) snake venom (Picolo and Cury 2004) and spinach (Yang et al. 2003). Some of these peptides have served as template or have been derivatized to create more selective, potent and/or stable peptidic ligands that are less prone to enzymatic degradation, such as

[D-Ala², D-Leu⁵]-Enkephalin (DADLE), D-Ser²-Leu-Enkephalin-Thr⁶ (DSLET), [d-Pen², d-Pen⁵]-Enkephalin (DPDPE) and the tetrapeptide JOM-13 (David et al. 1982; Kosterlitz et al. 1980; Mosberg et al. 1983; Mosberg and Kroona 1992). A major concern with these compounds from a therapeutic point of view is their poor ability to cross the blood brain barrier, although some reports have suggested the existence of pumps that can transport DPDPE and deltorphin II across the blood brain barrier (Fiori et al. 1997; Williams et al. 1996). For that reason, numerous small non-peptidic, DOR-selective alkaloids have been developed. Some of these compounds are morphinan derivatives (BNTX, NTI, SoRI-9409), whereas others use different alkaloid scaffolds such as diarylmethylpiperazines (SNC80, ARM1000390, AZD2327) (Calderon 2011), isoquinoline (TAN-67, KNT-127), spiro (ADL5747) and diarylmethylenepiperidine (JNJ-39204880). More recently, bi-functional and bivalent ligands (Ananthan 2006; Fujita et al. 2004; Harvey et al. 2012) have been designed that have affinity for DOR as well as for MOR including KSK-103 (Miyamoto et al. 1993a; Purington et al. 2011), MDAN (Daniels et al. 2005), L2 and L4 (Harvey et al. 2012). The bivalent ligands have been designed in part to test the hypothesis that DORs heterodimerize with MORs to form an opioid receptor target with unique functionality (Abdelhamid et al. 1991; Gendron et al. 2007b; Gomes et al. 2004; van Rijn et al. 2012b; van Rijn and Whistler 2009). The bi-functional ligands would fit the hypothesis that ligands acting on DOR and MOR can produce a unique functional response that is different from selective DOR or MOR ligands.

DOR subtypes—As mentioned in the introduction, complex pharmacological observations that could not be reconciled by a single DOR have led to the proposed existence of multiple DOR subtypes (DOR1 and DOR2). Yet, despite that numerous new DOR selective compounds have been synthesized, none of these DOR compounds have been classified as DOR1 or DOR2 beyond those mentioned in the introduction. Additionally, little research is currently performed that is specifically designed to understand the basis of the two subtypes. The potential of DOR agonists to act on different targets has become more interesting due to findings by us and others that subtype-selective DOR ligands can have opposing behavioral effects. More specifically, the DOR2 selective *antagonist* NTB reduces ethanol intake (Krishnan-Sarin et al. 1995; van Rijn and Whistler 2009), yet a DOR1 *agonist* TAN-67 also decreases ethanol intake (van Rijn and Whistler 2009), and a DOR agonist SNC80, increases both ethanol intake (Nielsen et al. 2012; van Rijn et al. 2010) and ethanol lever pressing (Platt and Bano 2011). The differential effects on ethanol intake of these compounds were further supported by findings that these two DOR subtype selective agonists also modulate ethanol preference in opposite directions. Specifically, TAN-67 increases ethanol place preference (Matsuzawa et al. 1998; van Rijn et al. 2012a), whereas SNC80 decreases ethanol place preference (van Rijn et al. 2012a). The place preference data would suggest that a DOR1 agonist reduces ethanol intake by increasing the reinforcing effect of ethanol, whereas SNC80 increases ethanol intake by reducing ethanol reinforcement learning. This is in sharp contrast with the opioid antagonist naltrexone, which decreases ethanol place preference as well as ethanol intake (Le et al. 1993; Middaugh and Bandy 2000; Phillips et al. 1997; van Rijn and Whistler 2009), suggesting that TAN-67, SNC80 and naltrexone affect ethanol related behavior in three different ways.

We and others have provided evidence suggesting certain DOR subtype selective ligands require the presence of both DOR and MOR to be effective (Gendron et al. 2007b; van Rijn et al. 2012b) for example in relation to ethanol intake (van Rijn and Whistler 2009). Studies have shown that DOR can directly interact with MOR to form a DOR-MOR heteromer (George et al. 2000; Gomes et al. 2000). This DOR-MOR heteromer has the ability to activate signal transduction properties different from DOR monomers/homomers (Hasbi et

al. 2007; Rozenfeld and Devi 2007). Thus heteromerization of DORs with MORs can be responsible for the differential effects observed with DOR subtype-selective ligands.

DOR subtype selectivity appears to play an important role in the ability of DOR ligands to induce or suppress coughing. The DOR1 antagonist BNTX is an antitussive (Kamei et al. 1994b), whereas the DOR1 agonist DPDPE inhibited the antitussive effects of MOR agonists morphine and DAMGO (Kamei et al. 1991). Conversely, the DOR2 agonist deltorphin II enhanced the antitussive responses of DAMGO (Kamei et al. 1993b). The selective DOR agonist SB 227122 reduced citric acid induced coughing in guinea pigs (Kotzer et al. 2000), suggesting that SB 227122 may activate DOR2. The effect of SB 227122 was blocked by the DOR antagonist SB 244525, which by itself had no effect on coughing (Kotzer et al. 2000). It is currently not known if SB 244525 has DOR subtype selectivity. And while the non-subtype-selective DOR antagonist NTI functioned as antitussive (Kamei et al. 1993a), this may rather be caused by its effects on KOR at high enough concentrations. To avoid any off target effects, antagonists with improved selectivity for DOR over KOR and MOR have been developed and these drugs: TRK-850 [(5*R*,9*R*,13*S*,14*S*)-17-cyclopropylmethyl-6,7-didehydro-4,5-epoxy-5',6'-dihydro-3-methoxy-4'-*H*-pyrrolo[3,2,1-*ij*]quinolino[2',1':6,7]morphinan-14-ol methanesulfonate] (Sakami et al. 2008b), and the more metabolically stable TRK-851 (Sakami et al. 2008a) show strong antitussive effects. Being antagonists, side effects such as respiratory depression and dependence may be less of an issue with these drugs. A recent paper showed the presence of an antitussive alkaloid, kopsinine, with DOR affinity in *Kopsia Hainanensis* (Tan et al. 2010). Kopsinine, however, most likely acted as an agonist, and therefore may have a worse side effect profile than a non-selective DOR or DOR1-selective antagonist. Currently, no studies have investigated if the DOR1-selective antitussive effects require the presence of MORs, which could hint at the target being a DOR-MOR heteromer.

There also appears to be subtype selectivity in the ability of DOR ligands to reduce physical dependence on morphine, as the DOR1 antagonists DALCE (Miyamoto et al. 1994) and BNTX (Suzuki et al. 1997) do not reduce precipitated withdrawal symptoms as effectively as DOR2 antagonists (Miyamoto et al. 1993a). Inhibition of DOR with DOR-(Chefer and Shippenberg 2009; Suzuki et al. 1994), DOR1- (Suzuki et al. 1994) and DOR2-selective (Billa et al. 2010; Suzuki et al. 1994) antagonists has also been shown to block morphine place preference acquisition. The DOR1 agonist TAN-67 enhances morphine conditioned place preference (Suzuki et al. 1996), yet a DOR2 antagonists prevents sensitized morphine place preference (Shippenberg et al. 2009) and can precipitate morphine withdrawal (Miyamoto et al. 1993b), suggesting that both DOR subtypes modulate aspects of the reinforcing effects and physical dependence inducing properties of morphine—and that they may do so in opposite directions. This complexity is also observed in studies that show that endogenous opioids that produce antinociception (Kim et al. 2003; Vanderah et al. 1992) when released after cold water swim stress can be blocked by a DOR2 antagonist (5'NTII) but not a DOR1 antagonist (DALCE) (Vanderah et al. 1992).

Differences in expression levels and localization of DOR subtypes within certain brain circuits complicate assessing the subtype selectivity of DOR selective ligands. Whereas the DOR agonist SNC80 produces anxiolytic-like effects in both naïve and ethanol withdrawn mice, the DOR1 agonist TAN-67 reduces anxiety-like behavior only in mice that have consumed ethanol (van Rijn et al. 2010), suggesting an emergence of DOR1s in ethanol withdrawn mice. Similarly the DOR2 antagonist NTB, but not the DOR1 antagonist BNTX, increases anxiety-like behavior (Saitoh et al. 2005). Yet, microinjection of the DOR1 agonist DPDPE in the central nucleus of the amygdala decreases anxiety (Randall-Thompson et al. 2010) in naïve mice. Similarly anxiolytic-like effects for the DOR1 agonist KNT-127 have been reported in rats (Saitoh et al. 2012). This suggests that location and expression level of

DOR1 and DOR2s may affect anxiety-like behavior to different extents, such that it becomes difficult to determine whether the effects of a systemically injected DOR-subtype selective compound is mediated by only that subtype. It is important to note that several DOR ligands including both DOR1 and DOR2 subtype-selective agonists (Pakarinen et al. 1995; Ukai et al. 1997) disrupt learning (Le Merrer et al. 2013), although less than scopolamine (Jutkiewicz et al. 2003), a muscarinic antagonist known to impair learning. Thus it is conceivable that a systemically injected DOR agonist at a dose where it affects learning, may influence task performance when measuring for example responses in place preference (Le Merrer et al. 2012), elevated plus maze or forced swim paradigms. This is particularly important to consider when an agonist response changes between local and systemic administration.

Selectively targeting a single DOR subtype could potentially reduce side effects, or at least display a different side effect profile. For example, Saitoh et al demonstrated that the DOR1 agonist KNT-127 has a lower potency to induce convulsion than SNC80 (Saitoh et al. 2011). The DOR1 agonists TAN-67 and DPDPE did not induce seizures themselves (Tortella et al. 1984; Yajima et al. 2000), whereas the DOR2 agonist deltorphin II does (Capasso and Cavallo 2005; Di Giannuario et al. 2001). DOR1- but not DOR2-selective ligands modulate the ability of the antiepileptic drug zonisamide to alleviate Parkinson's symptoms (Yamamura et al. 2009). A small number of studies have investigated the role of DOR subtypes on immune responses; a DOR1 agonist can activate granulocytes and immunocytes (Stefano et al. 1992), whereas only a DOR2, but not a DOR1 agonist can suppress splenic immune responses (Rahim et al. 2001). However, it appears that DOR subtype selectivity plays less of an important role for some other potential DOR-mediated side effects. Many DOR1- and DOR2-subtype selective agonists (DPDPE (Charron et al. 2008; Lasukova et al. 2009; Yang et al. 2011), SNC-121 (Patel et al. 2006), Eribis peptide 94 (Karlsson et al. 2011), fentanyl isothiocyanate [FIT] (Gross et al. 2005), BW373U86 (Peart et al. 2011), TAN-67 (Guo et al. 2005), ARD-353 (Watson et al. 2006), deltorphin II (Maslov et al. 2010a) have cardioprotective abilities. While a study by Maslov et al suggested that only the DOR2 selective deltorphin II, but not DPDPE, reduced infarct size (Maslov et al. 2010b), these differences may relate to experimental procedures (e.g. duration of occlusion, reperfusion). Thus it appears that there are indications such as ethanol use, seizure and cough that react differently to DOR1- than to DOR2-subtype-selective ligands (Table 2), as well as physiological responses that do not show DOR-subtype selectivity. While DOR selective therapies have not yet been approved by the Federal Drug Administration, several DOR agonists are in clinical trials for treatment of neuropathic/inflammatory pain, as well as anxiety/depression and as antitussive.

DOR expression and potential role in (patho)physiology—Early studies using in situ hybridization and autoradiography revealed that the delta opioid receptor and its cognate endogenous opioids are widely expressed throughout the human body and central nervous system (Dilts and Kalivas 1990; Goodman et al. 1980; Harlan et al. 1987; Mansour et al. 1994; Mansour et al. 1987; Shivers et al. 1986). The production of a transgenic mouse line expressing a DOR fused to a green fluorescent protein (DOR-eGFP) has provided further confirmation for the ubiquitous nature of DOR expression (Erbs et al. 2012; Faget et al. 2012; Poole et al. 2011; Scherrer et al. 2006) and seems to match localization patterns of DORs produced by immunohistochemistry (Cahill et al. 2001a). This is significant as an often recurring issue for DOR expression studies is antibody specificity (Chabot-Dore et al. 2008; Scherrer et al. 2009). It is important to note that the mRNA and protein expression as well as cellular localization and trafficking pattern of DOR-eGFP deviates from the wild-type receptor (Scherrer et al. 2006; Wang et al. 2008). This would limit the DOR-eGFP mice use to regional localization studies, and may make it harder to draw conclusions with regard

to cellular localization and redistribution after chronic stimulation if not additionally confirmed in wild-type mice.

Like MORs, DORs are expressed in pain circuits, both in supraspinal (Le Merrer et al. 2009) and spinal regions (Onofrio and Yaksh 1983), although, there may be some differences in the types of nociception the DOR is involved in (Scherrer et al. 2009; van Rijn et al. 2012b), compared to MOR, DORs are not as abundantly expressed in midbrain regions such as the periaqueductal grey (Pradhan et al. 2011). Often DOR mediated antinociception is observed in models of chronic pain, such as chronic inflammation or neuroconstriction (Cahill et al. 2003; Holdridge and Cahill 2007; Kabli and Cahill 2007; Zhang et al. 2006b). However, also in naïve mice DOR agonists can produce potent mechanical antinociception (Ochi et al. 1999; Scherrer et al. 2009; van Rijn et al. 2012b), an effect that has been attributed to DOR expression in peripheral NaV1.8-positive primary nociceptive neurons (Gaveriaux-Ruff et al. 2011).

The DOR is expressed in regions commonly associated with depression and mood disorders. These include the hippocampus, nucleus accumbens and frontal cortex which are associated with motor and motivational control (Tejedor-Real et al. 1998). DORs are also expressed in brain regions implicated in stress: the amygdala, locus coeruleus (Alvira-Botero and Garzon 2006; Scherrer et al. 2006) and regions of the hypothalamus where they are co-localized with stress hormones (Williams and Milner 2011) and can regulate corticotropin releasing hormone release (Williams and Milner 2011). The antitussive effects of opioids, including DOR selective opioids stems from actions in the CNS but also in part, from the localization of opioid receptors on sensory nerve fibers in the vagus nerve in the lung (Belvisi and Hele 2009).

Current research has revealed potential roles for DORs in neurodegenerative diseases. For example decreased expression of DORs was observed in putamen and amygdaloid regions of Alzheimer patients (Barg et al. 1993; Hiller et al. 1987; Mathieu-Kia et al. 2001; Rinne et al. 1993). Endogenous opioids acting on DORs can inhibit long term potentiation, a form of cellular memory, in the dentate gyrus of the hippocampus (Xie and Lewis 1995), a brain region well known for its role in memory formation (Neves et al. 2008). Thus DOR selective opioids may serve a role in preventing or treating Alzheimer's disease. Parkinson's disease is another neurodegenerative disease, caused by a loss of dopaminergic neurons in the substantia nigra, leading to a lack of muscle movement control due to the inability for the neurons to properly relay signals (Davie 2008). DOR selective ligands may be of therapeutic benefit for Parkinson's Disease considering that DORs are expressed in parts of the basal ganglia (Mansour et al. 1987; Scherrer et al. 2006) and several DOR agonists are reported to induce hyperlocomotion when administered systemically (Perrine et al. 2006), intracerebroventricularly, or into the nucleus accumbens (Churchill et al. 1995; Havemann et al. 1983; Ingman et al. 2003; Katsuura and Taha 2010; Kelley et al. 1996; Michael-Titus et al. 1989; Michael-Titus et al. 1990; Mickley et al. 1990; Mizoguchi et al. 1996; Murray and Cowan 1990; Negri et al. 1991a; Ukai et al. 1989).

Expression of DORs on cardiac myocytes (Ventura et al. 1989) has made these receptors interesting targets to study ischemia and stroke. In particular DOR agonists may protect against ischemic injury (For review see (Johnson and Turner 2010; Schultz and Gross 2001)). Recent studies have suggested a role for DORs in human immunodeficiency virus (HIV) infection. It has been shown that DORs are expressed on T-cells (Carr et al. 1988), which play a key role in HIV infection, and that the DOR agonists SNC80 and deltorphin inhibit the infection rate of HIV into T-cell derived jurkat cells (Sharp et al. 1998). The observation that DOR expression is upregulated in human peripheral blood lymphocytes after stimulation with phytohaemagglutinin (Sharp et al. 2001), which proliferates these cells

to activated T-like cells (O'Donovan et al. 1995) increases its functional relevance as potential (co-)therapy of HIV infection.

The expression of DORs in certain brain areas may explain some side effects commonly observed with opioid receptor targeted therapeutics in lab animals and humans. For example DORs have been identified in several brain regions involved in sleep, including the ventral division of the reticular oral pontine nucleus (Alvira-Botero and Garzon 2006) as well as in the nucleus of the solitary tract of the brain stem (Reinoso-Barbero and de Andres 1995). The expression of these DORs could account for some of the somnolence side effects commonly observed during opioid therapies (Cherny et al. 2001; Swegle and Logemann 2006). DORs are also reported to be expressed in respiratory centers of the brain stem (Alheid and McCrimmon 2008; Sales et al. 1985; Stasinopoulos et al. 2000) (dorsal and ventral respiratory group of the medulla oblongata and pontine respiratory group in the rostral pons), and several DOR agonists (SNC80 (Szeto et al. 1999), DSLET (Morin-Surun et al. 1984), DPDPE (Johnson et al. 2008; Szeto et al. 1999), deltorphin II (Szeto et al. 1999) and DADLE (Johnson et al. 2008; Pazos and Florez 1983; 1984)) have been reported to modulate respiration.

Using DOR-eGFP knock-in mice, DORs have been identified on submucosal and myenteric neurons (Poole et al. 2011), and it is known that DOR selective compounds can modulate GI motility and transit (Broccardo and Improta 1992b; Broccardo et al. 1998; Chamouard et al. 1994; Negri et al. 1999), potentially leading to constipation or diarrhea. Besides affecting GI motility, opioid receptors including DORs have also been implicated in renal function (Holt et al. 2005; Sezen et al. 1998). It is thought that these effects can be attributed to stimulation of peripheral opioid receptors on kidney cells by enkephalins released from the parasympathetic ganglia (de Groat and Kawatani 1989) as well as effects mediated by DORs in the paraventricular and hypothalamic supraoptic nuclei (Tsushima et al. 1993).

DOR dynamic expression—An intriguing aspect of DOR pharmacology is that while the receptor is ubiquitously expressed, many studies have reported instances of dynamic changes in DOR expression and localization, in particular translocation of DORs from large dense core vesicles to the cell surface (Zhang et al. 2006b). During certain chronic conditions the functional activity of DORs is increased as evidenced by findings that DOR-selective agonists become more potent and efficacious under conditions of inflammatory pain, chronic opioid use, chronic ethanol consumption and repeated stress (Cahill et al. 2007; Cahill et al. 2003; Cahill et al. 2001b; Commons 2003; Kabli and Cahill 2007; van Rijn et al. 2012b; Zhang et al. 2006b) (Table 3). Induction of inflammation and neuropathy causes a cellular redistribution of DORs (Cahill et al. 2003; Kabli and Cahill 2007). Chronic morphine has been shown to increase DOR expression in several areas of the central nervous system (Bie et al. 2010; Cahill et al. 2001b; Hack et al. 2005; Lucido et al. 2005; Ma et al. 2006), including the central nucleus of the amygdala (Chieng and Christie 2009), where the DORs could play a role in opioid withdrawal anxiety.

Several studies have recently investigated the role of DORs on ethanol intake. Both in vitro and in vivo studies suggest that ethanol exposure modulates DOR expression levels. For example, DORs are upregulated in neuroblastoma cell culture exposed to ethanol (Charness et al. 1986). Increased [³H]DPDPE binding was observed after ethanol exposure in several brain regions including the prefrontal cortex, the nucleus accumbens, different areas of the striatum and the substantia nigra pars reticulata (Mendez et al. 2004). Moreover, DOR function is enhanced in the central nucleus of the amygdala (Bie et al. 2009a), ventral tegmental area (Margolis et al. 2008), striatum (Nielsen et al. 2012) and spinal cord (van Rijn et al. 2012b) after long term ethanol consumption. Yet, functional DORs may already be present in naïve animals based on GTPγS activation studies in several brain regions

including, cortex (Nielsen et al. 2012) hippocampus, cerebellum and colliculus (Saland et al. 2004) as well as cAMP inhibition studies in striatum (Shen et al. 1997) and electrophysiology performed in the central nucleus of the amygdala (Kang-Park et al. 2007). Margolis and co-workers found that rats that consume large amounts of ethanol are in general more anxious and express fewer functional DORs in the ventral tegmental area (Margolis et al. 2008). Interestingly, ethanol exposure increases GTP γ S activation by the DOR1 agonist TAN-67, but not the DOR2 agonist SNC80 in rat spinal cord (Nielsen et al. 2012). Similarly, it has been reported that obese-diabetic (ob/ob) mice have increased binding of the DOR1 agonist DPDPE in their extensor digitorum longus, and that DPDPE, but not the DOR2 agonist deltorphin II, increases glucose transport in these mice (Evans et al. 2001).

Stress appears to play a strong role in DOR expression. During stress the body does not only release stress hormones such as corticotropin releasing hormone, but it also releases endogenous opioids/enkephalins (Amir et al. 1980; Kalivas and Abhold 1987), suggesting that DORs may be part of a negative feedback system. Indeed, in already stressed mice, DPDPE drastically reduces the response to future stress (Hebb et al. 2005). In rats, foot-shock stress specifically enhances postsynaptic DOR activity in dopaminergic neurons of the ventral tegmental area (Margolis et al. 2011). Stress induced by exposure to cold water in a forced swim paradigm has been reported to cause a cellular redistribution of DORs (Commons 2003). Similarly, stress induced by housing condition or social rank also affects DOR activity (Pohorecky et al. 1999). Downregulation of DORs has been observed in rats that have been sleep deprived by placing them on a small platform surrounded by water. This downregulation may occur due to endocytosis and degradation of DORs after activation by endogenous enkephalins, released by the stressful event. However, it is also possible that this is an adaptation designed to induce alertness and wakefulness (Fadda et al. 1991). Indeed, naltrindole increases wakefulness (Moss et al. 1993), suggesting that activation of DORs by endogenous opioids or exogenous opioids (Reinoso-Barbero and de Andres 1995) induce sleep.

There have been several reports that suggest increases of DOR activity and expression in intestinal tissue by inflammatory stress (Wade et al.). Shook et al found that while DPDPE did not inhibit transit in naïve mice it reduced castor oil induced diarrhea (Shook et al. 1989), which could suggest that castor oil enhances DOR activity. Similarly, diarrhea caused by croton oil induced intestinal inflammation potentiated DOR agonist inhibition of GI transit (Pol et al. 1994). Collectively, these studies indicate that the type and duration of stress affect the expression level of DORs and thus may influence the efficacy of DOR-selective ligands.

While most studies on DOR expression level were performed in rodent and other animal models, some data in humans suggest similar plasticity in DOR expression levels. Human studies have found increases in DOR selective (Madar et al. 1997) opioid PET radioligand binding after an epileptic seizure. Antibodies (Krajnik et al. 2010), RT-PCR (Schreiber et al. 1998) and PET (Madar et al. 2007) studies of human lung carcinoma cells revealed higher expression of DORs compared to normal healthy lung tissue.

3. Future prospects for the development of DOR selective drug treatments

DOR subtypes

Our hypothesis of DOR subtypes, from the overarching literature is that the observation of DOR subtype-selective effect can not simply be explained by invoking the existence of two DOR targets. Instead, we believe that the types of response a DOR-selective ligand will produce strongly depend on the site of action and the presence of other receptors, MOR in

particular. In some cases an effect that may have been attributed to a DOR subtype may actually be binding of that ligand to MORs or another receptor as it turns out that the drug is still active in DOR KO mice (He and Lee 1998; Matthes et al. 1998; Scherrer et al. 2004; van Rijn et al. 2012b; Zhu et al. 1999). In some cases the effect may be mediated by a combined effect of the DOR subtype-selective ligand to a target that requires both DOR and MOR (Gendron et al. 2007b; van Rijn et al. 2012b; van Rijn and Whistler 2009). Sometimes, both DOR1 and DOR2 subtype-selective drugs act on the same target (Wild et al. 1993). In other cases this may be attributed to biased agonism or differences in receptor trafficking (Pradhan et al. 2010). It is important to realize that for example a “DOR2 selective” ligand such as deltorphin II can act on MOR in spinal cord neurons mediating thermal pain, but on DOR-MORs in neurons mediating mechanical pain (van Rijn et al. 2012b), and on DORs in yet another region (Hosohata et al. 2000). Similarly, in our ethanol studies we propose that SNC80 acts like a DOR2 agonist as its effect is the opposite of a DOR2 antagonist (van Rijn and Whistler 2009). This is in line with some other studies that found SNC80 effects only to be influenced by NTB, but not BNTX (Baker and Meert 2002; Rawls et al. 2005; Saitoh et al. 2005). Yet other studies have found SNC80 being blocked by both BNTX and NTB (Pacheco et al. 2005), or only BNTX, thus suggesting DOR1 agonism (Zhu et al. 2009). This complexity, when better understood, can provide an incredible opportunity to tailor drugs to produce the proper response for a specific indication. The aforementioned large structural diversity of DOR selective drugs that have been designed so far holds promise for the development of tailored DOR drugs for selective therapies.

Peripheral vs Central effects

Since some of the effects of DOR selective ligands arise from activation of DORs located in the periphery, such as cardiac, mucosal and lung tissue, rather than the central nervous system, this should facilitate the development of peripherally restricted (e.g. peptides, hydrophilic ligands or quarternary nitrogen containing ligands) DOR selective ligands. These drugs could potentially be used as anti-tussive, to reduce constipation or to protect against ischemic injury, with reduced risk of central nervous system side effects.

Transient DOR expression

As summarized in this review, cellular redistribution of DORs and increases in the efficacy of DOR selective drugs have been observed after chronic inflammation, neuropathy, opioid exposure, ethanol exposure, stress, ischemia and potentially cancer and obesity (Table 3). It is important to investigate the exact triggers and mechanisms for the cellular redistribution of DORs and how selectively this occurs. Recent studies have provided detailed information on the redistribution of DORs from large dense core vesicles and the proposed mechanisms (Bao et al. 2003; Bie et al. 2010; Guan et al. 2005; Zhang et al. 2006b). Yet several questions remain to be answered satisfactorily: How long does the cellular redistribution of DORs last? How region-specific is this cellular translocation and how much does this depend on the event that triggers the redistribution? What is the role of the plasma enkephalin tone during the redistribution? In other words, does stress change cellular compartmentalization of DORs throughout cells in the body, whereas a local event such as castor oil exposure, only redistribute DORs in cells along the gastro-intestinal tract? If DORs are translocated only in a specific region this would allow for selective treatment of the disorders and a reduced liability of side effects. On the other hand if DORs are translocated in cells throughout the body, rather than in only a subpopulation, it may for example be possible to first eliminate peripheral DORs by administration of a peripherally restricted DOR agonist with a strong internalization profile, which should eliminate those DORs, as DORs are targeted for degradation (Whistler et al. 2002). Subsequently a DOR agonist with a low internalization profile, such as ARM1000390 (Pradhan et al. 2009) could be administered to treat a central nervous system disorder without major side effects in the

periphery. Conditional DOR and preproenkephalin knockout mice could be useful in addressing temporal and mechanistic aspects of DOR translocation. Another tool that may assist in answering some of these questions is the availability of fluorescent DOR ligands (Arttamangkul et al. 2000; Balboni et al. 2004; Chen et al. 2005; Korlipara et al. 1997; Kshirsagar et al. 1998; Morinville et al. 2004a). A better understanding of the DOR pharmacology (i.e. subtype and expression level of DORs) within a certain circuit may also lead to design and synthesis of better/more (subtype-) selective fluorescent DOR probes and PET ligands (Clayson et al. 2001; Elmore et al. 2011) to investigate DOR function specifically within this circuit.

Sex and age differences

The realization of the versatility of DORs as potential drug target should spur on more investigations of the effects of DOR selective effects in females, as currently the majority of research has been performed in males (Craft 2003; Dahan et al. 2008). It is known that gender differences exist for the pharmacological effects of KOR selective drugs (Rasakham and Liu-Chen 2011). Recent studies suggest some sex differences, that result in changes in potency and efficacy may also exist for DOR selective ligands (Dahan et al. 2008; Saloman et al. 2011; Wilson et al. 2002). Additionally, DOR expression level changes during development (Zhu et al. 1998) and in areas such as the dorsal striatum DOR expression may decline with age (Nielsen et al. 2012). Therefore it will be important to understand the contribution of age and gender to an already complex DOR pharmacology.

Ongoing and future clinical trials

A small number of DOR selective drugs have recently entered clinical trials. AZD2327 is currently in phase II clinical trials for treatment of anxious major depressive disorder, both as a potential anti-depressant and anxiolytic. ALD5859 and ALD5747 have completed phase II clinical trials for the treatment of osteoarthritic knee pain, post-herpetic neuralgia and acute dental pain after third molar extraction, but failed to show significant effects to warrant further clinical investigations. TRK-851 may be close to entering clinical trials for the treatment of persistent cough (Nagase and Fujii 2011; Sakami et al. 2008a).

In summary, the wide spread distribution of DORs throughout the body allows it to be a factor in the etiology of many diseases. The existence of conditional and global DOR and preproenkephalin knockout mice as well as a large library of selective DOR ligands has been of great help to dissect the role of DORs in different diseases. The recent development of optogenetic tools may be used to study the effect of neuronal signal transduction of DOR expressing neurons, which combined with retrograde labeling could establish more detailed information on the networks in which DORs are playing a role. The large effort in synthesizing structurally diverse DOR selective drugs gives DORs a great potential for translational research. It will be interesting to follow the current DOR selective drugs through their clinical trials and the hope is that they will pave the way for initiating more clinical trials with other DOR selective drugs for multiple difference indications.

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Figure 1.
Overview of a variety of selective delta-opioid receptor agonists and antagonists.

Table 1

Binding affinities for the delta and mu opioid receptor for a selection of DOR1, DOR2, and DOR-selective ligands.

	Ligand	DOR	MOR	Selectivity	[3H]DOR	[3H]MOR	Ref [‡]
Delta1	TAN-67	0.647	775	1197	[3H]NTI	[3H]CTOP	[1]
	DPDPE	14	>1000	>71	[3H]NTI	[3H]DAMGO	[2]
	BNTX	0.66	18	27.3	[3H]NTI	[3H]DAMGO	[2]
	DALCE	4.1	55	13.4	[3H]DPDPE	[3H]DAMGO	[3]
Delta2	SNC80	0.181	3900	21547	[3H]DPDPE	[3H]DAMGO	[4]
	Naltriben	0.013	12	923	[3H]NTI	[3H]DAMGO	[2]
	DeltorphanII	3.3	>1000	>303	[3H]NTI	[3H]DAMGO	[2]
	DSLET	4.8	39	8.1	[3H]NTI	[3H]DAMGO	[2]
	5'NTII	5.9	ND	NA	[3H]DPDPE	NA	[5]
Delta	ADL5859	0.84	>10000	>11904	[3H]DPN	[3H]DPN	[6]
	TIPPpsi	0.308	3230	10487	[3H]DSLET	[3H]DAMGO	[7]
	ARM390	0.87	3800	4367	[125I]Delt II	[125I]FK33824	[8]
	NTI	0.02	64	3200	[3H]NTI	[3H]DAMGO	[2]
	AZD2327	0.49	770	1571	[125I]Delt II	[125I]FK33824	[9]
	JNJ	2	1191	595	[3H]DPDPE	[3H]DAMGO	[10]
	SB235863	4.81	906	188	[3H]DADLE	[3H]DAMGO	[11]
	ICI174,864	193	24700	128	[3H]DADLE	[3H]DAMGO	[7]
	SOr9409	2.2	51	23	[3H]DADLE	[3H]DAMGO	[12]
	DADLE	0.74	16	21	[3H]NTI	[3H]DAMGO	[2]
	Leu-Enkephalin	4	3.4	0.9	[3H]NTI	[3H]DAMGO	[2]
	Biphalin	2.6	1.4	0.5	[3H]DPDPE	[3H]CTOP	[13]
	Met-Enkephalin	1.7	0.65	0.4	[3H]NTI	[3H]DAMGO	[2]

(ND = not determined, NA = not applicable)

[‡]Reference: [1] (Knapp et al. 1995), [2] (Raynor et al. 1994), [3] (Bowen et al. 1987), [4] (Knapp et al. 1996), [5] (Portoghese et al. 1992), [6] (Le Bourdonnec et al. 2008), [7] (Schiller 2004), [8] (Wei et al. 2000), [9] (Hudzik et al. 2011), [10] (Codd et al. 2009), [11] (Petrillo et al. 2003), [12] (Xu et al. 2001), [13] (Misicka et al. 1997)

Table 2

Schematic overview of the physiological effects of delta opioid receptor subtype-selective agonists and antagonists. (NE = no effect).

Physiological effect	Agonist	Antagonist	References [‡]
Anxiety-like behavior	$\delta_1 \downarrow, \delta_2 \downarrow$	δ_1 NE, $\delta_2 \uparrow$	[1–5]
Ethanol consumption	$\delta_1 \downarrow, \delta_2 \uparrow$	$\delta_2 \downarrow$	[3, 6–8]
Ethanol place preference	$\delta_1 \uparrow, \delta_2 \downarrow$	$\delta \downarrow$	[9, 10]
Cough	$\delta_1 \uparrow, \delta_2 \downarrow$	$\delta_1 \downarrow$	[11–13]
Seizure threshold	δ_1 NE/ $\uparrow$, $\delta_2 \downarrow$	-	[14–19]
Locomotion	$\delta_2 \uparrow$	-	[20, 21]
HIV infection	$\delta_2 \downarrow$	-	[22]
Morphine dependence	-	δ_1 NE, $\delta_2 \downarrow$	[23–26]
Intestinal motility	$\delta_1 \downarrow, \delta_2 \downarrow$	-	[27–32]
Depression-like behavior	$\delta_1 \downarrow, \delta_2 \downarrow$	-	[16, 33]
Ischemic injury	$\delta_1 \downarrow, \delta_2 \downarrow$	-	[34–39]
Hyperalgesia	$\delta_1 \downarrow, \delta_2 \downarrow$	-	[40–46]
Memory	$\delta_1 \downarrow, \delta_2 \downarrow$	-	[47, 48]

[‡][1] (van Rijn et al. 2010), [2] (Saitoh et al. 2005) [3], (Margolis et al. 2008), [4] (Sugiyama et al. 2012), [5] (Randall-Thompson et al. 2010), [6] (Krishnan-Sarin et al. 1995) [7] (van Rijn and Whistler 2009), [8] (Matsuzawa et al. 1998), [9] (Bie et al. 2009a), [10] (van Rijn et al. 2012a), [11] (Kamei et al. 1994b), [12] (Kamei et al. 1993b), [13] (Kamei et al. 1991), [14] (Tortella et al. 1984), [15] (Tortella et al. 1988), [16] (Saitoh et al. 2011), [17] (Yajima et al. 2000), [18] (Di Giannuario et al. 2001), [19] (Capasso and Cavallo 2005), [20] (Mizoguchi et al. 1996), [21] (Fraser et al. 2000b), [22] (Sharp et al. 1998), [23] (Miyamoto et al. 1994), [24] (Miyamoto et al. 1993a), [25] (Miyamoto et al. 1993b), [26] (Suzuki et al. 1997), [27] (Broccardo and Improta 1992b), [28] (Broccardo and Improta 1992a), [29] (Krevsky et al. 1991), [30] (Fox-Threlkeld et al. 1994), [31] (Pairet and Ruckebusch 1984), [32] (Shook et al. 1989), [33] (Torregrossa et al. 2006), [34] (Charron et al. 2008), [35] (Maslov et al. 2010b), [36] (Maslov et al. 2010a), [37] (Guo et al. 2005), [38] (Yang et al. 2011), [39] (Lasukova et al. 2009), [40] (Stewart and Hammond 1994), [41] (Mika et al. 2001), [42] (Taiwo and Levine 1991), [43] (Fraser et al. 2000a), [44] (Hurley and Hammond 2000), [45] (Cahill et al. 2003), [46] (Holdridge and Cahill 2007), [47] (Ukai et al. 1997), [48] (Castellano and Pavone 1985)

Table 3

Overview of conditions for which changes in DOR expression or function or potency of DOR ligands have been reported.

Increased DOR expression, potency and/or function	References [‡]
Chronic opioid exposure	[1–13]
(Chronic) inflammation	[14–22]
Alcohol (withdrawal)	[23–29]
Stress	[30–33]
Cancer	[34–36]
Obesity/diabetes	[37–39]
Hypoxia (preconditioning)	[40,41]
Neuropathy	[42]
Fibromyalgia	[43]
Seizure	[44]
Failing heart	[45]

[‡][1] (Cahill et al. 2001b), [2] (Morinville et al. 2003), [3] (Ma et al. 2006), [4] (Bie et al. 2009b), [5] (Chieng and Christie 2009), [6] (Lucido et al. 2005), [7] (Morinville et al. 2004a), [8] (Hack et al. 2005), [9] (Lesscher et al. 2003), [10] (Hyytia et al. 1999), [11] (Khotib et al. 2004), [12] (Bie et al. 2010), [13] (Zhang and Pan 2010), [14] (Cahill et al. 2003), [15] (Codd et al. 2009), [16] (Morinville et al. 2004b), [17] (Gendron et al. 2007b), [18] (Gendron et al. 2007a), [19] (Pol et al. 1994), [20] (Shook et al. 1989), [21] (Wade et al.), [22] (Hurley and Hammond 2000), [23] (van Rijn et al. 2010), [24] (van Rijn et al. 2012b), [25] (Margolis et al. 2008), [26] (Bie et al. 2009a), [27] (Nielsen et al. 2012), [28] (Charness et al. 1986), [29] (Mendez et al. 2004), [30] (Margolis et al. 2011), [31] (Commons 2003), [32] (Hebb et al. 2005), [33] (Pohorecky et al. 1999), [34] (Krajnik et al. 2010), [35] (Madar et al. 2007), [36] (Schreiber et al. 1998), [37] (Evans et al. 2001), [38] (Kamei et al. 1997), [39] (Kamei et al. 1994a), [40] (Zhang et al. 2006a), [41] (Ma et al. 2005), [42] (Kabli and Cahill 2007), [43] (Salemi et al. 2007), [44] (Madar et al. 1997), [45] (Bolte et al. 2009)