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Opioid receptors in analgesic drug design – the past, present and future

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Abstract

Pain is a common phenomenon that is expressed due to external tissue injury or innate physiological dysfunction. While everyone has experienced pain in some form or the other, over 40% of all Americans visited the clinic due to chronic pain each year according to the American Pain Society. In spite of certain deleterious side effects, such as, respiratory depression, tolerance, and addictive potential, opioids have remained the drugs of choice for the treatment of pain. This review provides a brief snapshot of the past, and ongoing, research in the opioid field, to generate potent analgesics without the debilitating side effects.

Opioid receptors and their ligands – a brief history

It has been known for over five millennia that the alkaloids obtained from the juice of opium poppy seeds proffered analgesic and euphoric properties[1]. The various ligands in the opium alkaloid cocktail were termed 'opiates', of which morphine is the major component[2]. Decades of concerted research have expanded the list of compounds that have similar pharmacological effects, and the armamentarium as a whole is designated as 'opioid' ligands[1,2]. Even with the advent of several classes of analgesic drugs, opioids agonists such as, morphine and codeine are the analgesics of choice to treat pain in the clinic.

The major problems with managing pain using morphine are respiratory depression, tolerance, constipation, and physical dependence associated with its use. In 1929, it was proposed that making structural modifications to the morphine scaffold would result in a molecule devoid of the side effects while retaining its more salutary attributes[3,4]. Unfortunately, none of the synthetic molecules showed any reduction in addictive potential. This was a considerable blow to the opioid field as the prevailing thought at the time was that it would be impossible for a non-morphine scaffold to have potent analgesic properties. Hence, the discovery that the rather simple piperidine, meperidine, could also elicit potent analgesic effects was a departure that revitalized the field[4]. In time, other analgesics such as methadone, fentanyl, morphinans and benzomorphans were synthesized. However, the ideal opioid that would produce potent analgesia without deleterious side effects remained elusive.

By the early 1950s, structure-activity relationship (SAR) studies with the prevailing opioid ligands suggested that ligand structure, size and shape were all important for analgesic activity. This led Beckett and Casy to first propose a unique opioid receptor that followed the lock and key mechanism to interact with opioids[5]. To simplify their hypothesis, they proposed that all opioids adopt a morphine-like structure within the receptor, which allowed for the similarity of activity for a diverse group of molecules. However, there were several anomalies that did not fit such a structurally rigid receptor[1,4].

In an effort to address the inconsistencies in the Beckett and Casy model, Portoghese suggested an alternate hypothesis in 1965[6]. Again using SAR, he showed that parallel changes of the N-substituent of rigid scaffolds (morphine, morphinan or benzomorphan) produced similar effects on the analgesic activity. This suggested that the rigid parent structures were all interacting with the active

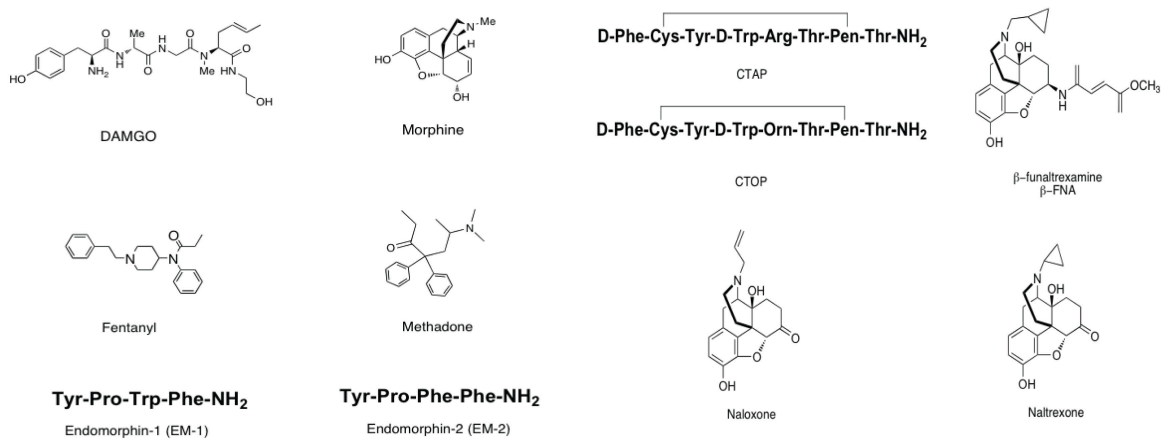

Figure 1. Selective ligands for mu opioid receptors

site in a simi[1]lar fashion. However, for non-rigid scaffolds (methadone, meperidine, etc) similar modification did not produce parallel changes in activity indicating the rigid and non-rigid molecules were binding differently to the opioid receptor. This was hence called the bimodal binding model of opioids. A prescient interpretation by Portoghese was that instead of different modes of interaction with the same active site, the data also indicated the possible existence of multiple opioid receptors[6].

Around the same time, Goldstein and colleagues also used structural determinants in opioids to propose the existence of a unique opioid receptor[7]. As the radioligand binding assays gained prevalence[8], three independent laboratories simultaneously described the first opioid receptor sites in rat brain membranes[9-11]. Shortly thereafter, Hughes and coworkers[12] isolated the first endogenous opiate-like factors, methionine enkephalin (Met-enkephalin) and leucine enkephalin (Leu-enkephalin). The discovery of the biological aspects of the opioid system was well underway.

To add to the initial suggestion by Portoghese[6] that the diversity in opioid ligand structure would require multiple opioid receptor sites, the experiments by Martin and coworkers[13-16] in dogs led to suggestion of mu (μ), kappa (κ) and sigma (σ) opioid receptors. The activity of sigma receptors is not naloxone-reversible and these receptors are no longer considered as opioid receptors[17]. An observation that the mouse vas deferens showed greater affinity for enkephalins than morphine led to the suggestion of the delta (δ) opioid receptor[18]. Two studies by Cuatrecasas and colleagues showed the existence of the enkephalin-preferring delta site in the brain, and they attempted to describe opioid receptor distribution in various brain regions[19,20]. However, to perform such detailed analyses it was paramount to develop ligands selective for the various suggested opioid receptors types (Fig 1-3).

Selective opioid ligands

The development of high specific activity tritiated ligands in the 1970s and 1980s opened up the field for receptor characterization and localization studies. After the discovery of enkephalins, synthetic efforts were centered on making substitutions that would render stability towards hydrolysis by enkephalinase [21]. These efforts led to the synthesis of the enkephalin analogs, DADLE and DSLET, that were shown to be delta-selective peptides[18-21] (Fig 2). However, they still had affinity for mu receptors. The synthesis of conformationally restricted bis-pencillamine enkephalins afforded the highly delta-selective analog DPDPE[22].

The isolation of the endogenous linear heptapeptides from frog skin extracts led to the discovery of deltorphins[23,24]. The first ligand that was isolated had the sequence: Tyr-D-Met-Phe-His-Leu-Met-Asp-NH2. Two more peptides were later reported that had D-Alanine as the second

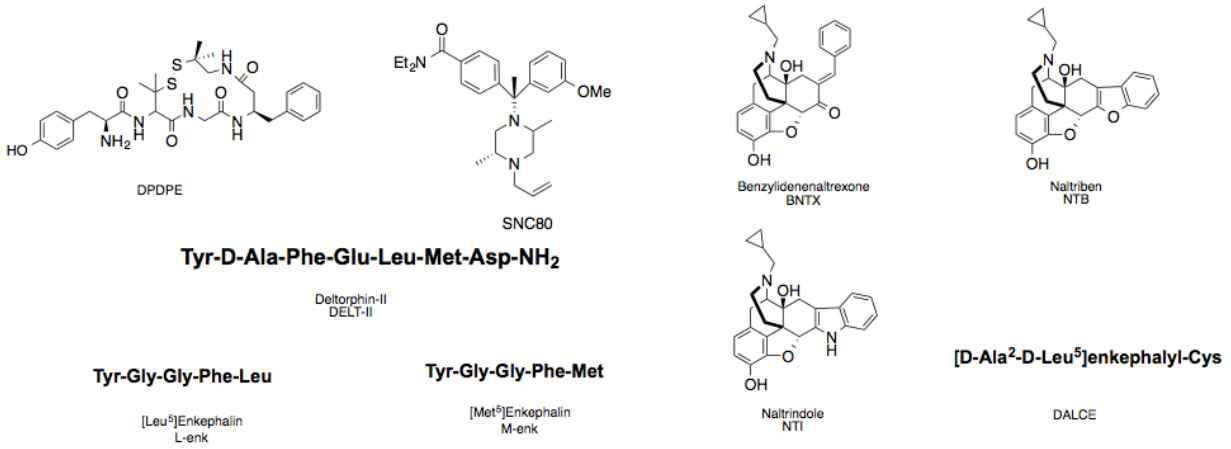

Figure 2. Selective ligands for delta opioid receptors

residue, with either aspartate or glutamate residue in position 4, and were named [D-Ala^2]-deltorphin I (DELT-I) and II (DELT-II), respectively. These linear peptides showed the highest affinity for delta receptors compared to any of the ligands at the time. Indeed, the two [D-Ala^2] deltorphins had ~200-fold greater affinity for delta receptors than DPDPE.

For kappa receptors (Fig 3), ethylketocyclazocine (EKC, Fig 1.5) stood as the prototypic ligand throughout the 1970s. However, Von Voightlander and colleagues used binding and in vivo behavioral procedures to show that the benzeneacetamide, U50,488, is a kappa ligand with greater selectivity[25]. They showed that U50,488 displaced [^{3}H]EKC and the displacement was not blocked by high doses of dihydromorphine. In addition, U50,488 did not produce cross-tolerance to morphine tolerance suggesting that U50,488 was mediating its effects via a non-mu opioid receptor. pA_2 studies with naloxone further implicated the involvement of kappa receptors in the activity of U50,488 and bremazocine.

At the time, there still wasn't a highly selective tritiated ligand available for kappa receptors. The introduction of [^{3}H]U69593, an analog of U50,488, provided the opportunity to determine the distribution and expression levels of kappa receptors in various tissues[26]. U69395 was shown to be 484-fold more selective at kappa, when compared with mu or delta receptors, making it the most selective kappa ligand. This study also showed that bremazocine was less selective and could bind to all the three opioid receptors. Thus, in early studies, morphine [27,28] and [D-Ala^2-MePhe^4-Glyol^5] enkephalin (DAMGO; [21,29]) have been described and used widely as selective ligands for mu receptors, DADLE, D-Pen^{5}D-Pen^{5}enkephalin (DPDPE; [22]) and deltorphin-II (DELT-II) [30,31] for delta receptors, and EKC, U69593 [26,32], and bremazocine [32] for kappa receptors.

Early attempts to tackle morphine's adverse effects in the clinic: Mixed agonist-antagonist ligands

The development of tolerance, physical dependence, and respiratory depression are the major side effects associated with morphine pharmacotherapy. The design of improved ligands with reduced deleterious effects and efforts to elucidate mechanisms that lead to tolerance and dependence remain a major focus of opioid research. Nalorphine was an early opioid antagonist that was used in the clinic for opioid overdose. However, Lasagna and coworkers were surprised to observe that nalorphine could produce potent analgesic activity by itself[33]. Since nalorphine was shown to reverse morphine-induced withdrawal, it was deemed that a mixture of kappa agonist opioid with mu antagonist properties would be a preferred opioid analgesic. The hypothesis was

that μ antagonism would ensure that the ligand would mitigate mu opioid side effects like respiratory depression, tolerance, and dependence, while the kappa agonism would confer the antinociceptive ability[2]. With this premise a number of kappa agonist/mu antagonist ligands were developed.

Pentazocine, a benzomorphan-derived analgesic, was one of the first drugs in this class that was initially considered to have the right attributes and was used extensively in the clinic[33,34]. Depending on the route of administration, pentazocine was considered to be one-half to one-fifth as potent as morphine[35-38]. Pentazocine could attenuate abstinence syndrome in patients dependent on low-dose morphine (30 mg/kg), but not at higher doses of morphine. Indeed, pentazocine has been shown to precipitate withdrawal-like syndrome in morphine-addicted patients which may be due to its mu antagonistic activity[39]. Pentazocine has also been shown to precipitate physical dependence, and naloxone administration in these patients can produce moderate withdrawal symptoms[39,40]. In addition, pentazocine can also produce dysphoric and psychotomimetic effects that limited its use[39,41-43]. It was also contraindicated in patients with coronary problems[44].

Nalbuphine is a noroxymorphone analogue that shows effects that are very much like pentazocine. However, nalbuphine has been shown to produce substantially fewer psychotomimetic effects[45]. In postoperative pain management, nalbuphine was equipotent to morphine, but at least 3 to 5-fold more potent than pentazocine. Physical dependence was observed only with chronic administration of ~200 mg of nalbuphine per day. Interestingly, nalbuphine did not produce any abstinence syndrome in morphine-dependent patients, unlike naloxone[46].

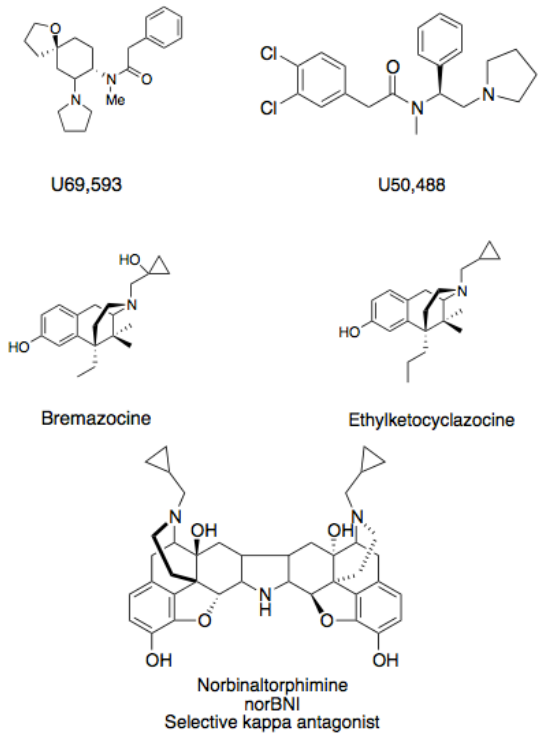

Figure 3. Selective ligands for kappa opioid receptors

Butorphanol is an opioid ligand of the morphinan class of compounds and has been used extensively in the clinic. Butorphanol produces pharmacological effects that are also very much like pentazocine. By the intramuscular route of administration, butorphanol has been found to be >15-fold more potent than pentazocine and 5-8 times more potent than morphine[47-51]. Similar difference in potency was also observed when both morphine and butorphanol were administered by the intravenous route[52]. Butorphanol was reported to be fast acting with limited side effects. Indeed, psychotomimetic effects were only observed in patients who had a history of using narcotic drugs which suggested that these effects may represent mild withdrawal syndrome[53].

In spite of the largely favorable pharmacological profile (limited tolerance and abuse potential when compared with morphine) of the above analgesics, the psychotomimetic and dysphoric effects made them eventually unpopular in the clinic. Indeed, even today, the

issue of limiting the abuse potential of opioids remains the central focus of most opioid investigators.

Opioid antagonists

The introduction of naloxone as a potent narcotic antagonist remains a watershed moment in the history of opioid research[54,55]. It is a potent and non-selective opioid antagonist that has been used so often that those ligands whose effects are not naloxone-reversible are not considered to act via opioid receptors. It has been most useful in the clinic as an antidote for narcotic overdose and has helped save many lives. Even though naltrexone was more potent than naloxone, the lack of intrinsic activity has helped naloxone remain as the prototypic opioid antagonist[56] (Fig 1).

The elucidation of effects of the different opioid receptors was greatly facilitated by the synthesis of selective opioid antagonists. In the early 1980s, Portoghese and coworkers described the synthesis, pharmacological properties, and mechanism of action of β-funaltrexamine (β-FNA) as an affinity label for mu opioid receptors[57-60]. β-FNA produced long-acting and irreversible antagonism of mu agonists in the guinea pig ileum (GPI) preparation, mouse vas deferens (MVD), and in vivo[59,60]. Indeed, β-FNA produced long-acting antagonism of morphine, even 120 hrs after i.c.v. or s.c. administration in mice. Interestingly, β-FNA produced short-acting agonism that was reversible and was attributed to activity at kappa receptors[58].

In search of a reversible antagonist for mu opioid receptors, Hruby and colleagues developed D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2 (CTOP) and D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP), cyclic derivatives of somatostatin, as highly selective mu ligands[61,62] (Fig 1). They attributed the mu selectivity by determining the ability of CTOP in displacing [^{3}H]naloxone and [^{3}H]DPDPE. The results showed that CTOP displaced [^{3}H]naloxone ~ 4,829-fold greater than [^{3}H]DPDPE. In 1994, CTOP was shown to be highly selective for the cloned mu opioid receptor[63].

A major step in the quest to develop selective antagonists for kappa receptors occurred with the discovery of TENA, a bivalent ligand containing two naltrexone-derived pharmacophores tethered by a spacer of 10 atoms[64]. Portoghese and colleagues reported that shorter spacers promoted greater selectivity for kappa receptors, while increased spacer length promoted mu selectivity[65]. With this in mind, bivalent ligands with short spacers were developed. Pyrrole ring was chosen as a spacer to conformationally restrict the orientation of the molecule in an effort to facilitate better binding to the kappa receptors. This led to the development of norbinaltorphimine (norBNI, Fig 3) that possessed the highest affinity and selectivity for kappa receptors. Indeed, even with the synthesis of several other kappa selective antagonists, to date norBNI has remained the standard kappa antagonist in opioid research[66,67].

A few years before the synthesis of norBNI, the "message-address concept" was proposed by Schwyzer as a way to reconcile peptide ligand selectivity for receptors[68]. Based on specific sequence identifiers in opioid peptides, this model was shown to be applicable to non-peptide opioid ligands as well[69,70]. For instance, it was suggested that adding Phe-Leu to mu ligands conferred delta selectivity[71]. This was used as the design strategy to convert naltrexone into a non-peptide delta antagonist. It was hypothesized that the benzene ring in Phe^4 of Leu-enkephalin will need to be incorporated into the morphinan core of naltrexone via a rigid spacer. While a pyrrole ring was chosen as the spacer for synthetic ease, it led to the development of the prototypic delta antagonist, naltrindole (NTI, Fig 2)[72]. NTI was 240-fold more selective for delta receptors than naltrexone, giving credence to the incorporation of the delta address-mimic into a non-selective ligand. Using a furan ring instead of the pyrrole led to the synthesis of naltriben (NTB, Fig 2)[73] which is less potent, but with greater affinity than NTI.

Genetic receptors vs pharmacological receptors

For years investigators had been piecing together the complex physiological effects of opioid receptors with the help of ligands. However, given that most ligands are not specific for a single receptor, it was near impossible to determine the receptor effects in isolation. The advent of molecular biology changed this scenario when two groups independently cloned the delta opioid receptor[74,75]. Within a couple of years other investigators cloned the kappa[76] and mu opioid[77,78] receptors and genetically mapped the gene sequences to specific chromosomal locations[79-81].

The studies showed that opioid receptors are class A members of the G protein coupled-receptor (GPCR) superfamily. The general GPCR structure consists of seven transmembrane (7TM) domains linked by three alternating intracellular and extracellular loops. There is high amino acid homology (~60%) within the opioid receptor family that constitutes a group of four receptor types: MOP (mu), DOP (delta), KOP (kappa) and ORL-1 (nociceptin)[82]. Though ORL-1 was originally placed within the opioid family due to sequence homology, it is not known to interact with any of the non-selective opioid ligands and produces downstream effects that are unlike the other three opioid receptors. We have, therefore, focused our research efforts on the mu, kappa and delta opioid receptors.

Most of the homology between the opioid receptors occurs in the TM domains, intracellular loops and in the C-terminus[17]. However, it was surprising that all the cloning studies pointed to just three different gene products when the literature at the time suggested the existence of three mu (μ_1, μ_2, μ_3), two delta (δ_1 and δ_2), and three kappa (κ_1, κ_2 and $\kappa 3$) receptor subtypes based on distinctive pharmacological effects.

Opioid receptor subtypes

In the early 1990s, several reports emerged that showed that the delta opioid agonists, DPDPE and deltorphin II (DELT-II), were inhibited to different extents by delta antagonists[83-85]. For instance, it was shown that the DALCE and BNTX selectively inhibited DPDPE, but not DELT-II. On the other hand NTB selectively antagonized DELT-II, but did not antagonize DPDPE. This led to the postulation of two distinct delta subtypes: δ_1 which is selective for DPDPE and BNTX, and δ_2 which is selective for DELT-II and NTB.

Genetic manipulation of delta receptors revealed tissue specific effects of ligands targeting delta opioid receptors. Using antisense oligos that were administered intrathecally (i.t.), Pasternak and colleagues showed that the spinal activity of both DPDPE (δ_1) and DELT-II (δ_2) was completely abolished[86]. However, Bilsky and coworkers showed that the antisense molecules inhibited the antinociceptive activity of DELT-II ($\delta 2$), but not DPDPE ($\delta 1$), when administered supraspinally[87]. In both studies the effects of DAMGO (μ) or U69,593 (κ) were unaffected by the delta-selective oligos.

Since molecular cloning only identified a single gene for the delta receptor, it was speculated that different splice variants could lead to the expression of the δ_1 and δ_2 receptor subtypes. There are three exons contained in the delta receptor gene, which prompted Pasternak and coworkers to design oligonucleotides for all the three exons to gain a comprehensive understanding of delta receptor expression[88]. In all, five oligonucleotides were designed. All the oligos inhibited the antinociception of DPDPE and DELT-II when administered i.t. However, while the antinociception mediated by DELT-II was abolished by i.c.v. administration of all the oligos, only oligos targeting exon 3 attenuated the i.c.v. activity of DPDPE. This led to the suggestion that δ_1 and δ_2 are distinct receptors that are expressed due to splice variants that contain either all three exons (δ_2), or only the 3rd exon (δ_1). While the study had tremendous implications, no such splice variants have been isolated to date.

One of the criticisms of antisense oligo methods is that the level of knockdown is rarely homogenous across all the cells in the tissue of interest. This can lead to challenges in interpretation, as some tissues may be more permeable to both the oligos and ligands than

other tissues. To get around this problem, knockout mouse models were developed that allowed for the entire genes to be abolished. In an ineteresting study, Pintar and coworkers developed a delta knockout (DORKO) mouse model and studied the antinociceptive activity of the two subtype selective ligands, DPDPE and DELT-II[89]. In these knockout animals, neither [^{3}H]DPDPE or [^{3}H]DELT-II showed any binding in the brain. In addition, the spinal activity of both ligands was attenuated. In contrast to the antisense studies, the supraspinal antinociceptive activity of both DPDPE and DELT-II remained intact. The authors summarized that the lack of binding indicated that both δ_1 and δ_2 were expressed by the same δ receptor gene, but the supraspinal activity of these ligands was mediated by delta-like receptor that is different from the cloned delta receptor.

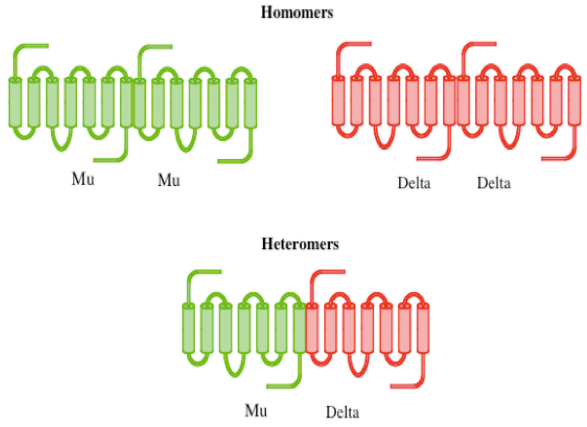

Figure 4. An illustration for the concept of receptor oligomerization. When two similar receptors form a complex, it is termed a homomer while dissimilar receptors oligomerize to form heteromers.

But this interpretation has several inconsistencies. The authors suggest that the supraspinal activity of these ligands is mediated by a delta-like receptor[89]. However, they also showed that there was no binding of the tritiated ligands in the brain. If there was a different receptor that was mediating the antinocieption, the authors should have still observed residual binding in the brain. In other words, if the ligands are not binding to any receptor in the brain, where is the supraspinal activity coming from?

Several studies also suggested pharmacological subtypes for kappa opioid receptors[90-93]. Such an idea stemmed from the fact that benzenomorphan ligands like bremazocine consistently showed greater amount of binding than arylacetamide ligands[90]. The receptors that arylacetamides bound were considered κ_1, while the residual binding for bremazocine that was observed in the presence of excess δ, μ and κ_1 selective ligands was considered to be κ_2. However, genetic knockout studies suggested that bremazocine is a non-selective opioid ligand that binds all three opioid receptors. In a sequential knockout study by Simonin and colleagues[90] in mu, delta, double mu/delta, and triple mu/kappa/delta knockout animals, [^{3}H]bremazocine binding was shown to represent 68% from mu, 27% from delta and only 14.5% from kappa receptor genes. Indeed all of the labeling due to [^{3}H]bremazocine was abolished in the triple knockout mice. Thus, the putative κ_2 receptor, for which bremazocine has been considered to be the prototype agonist, may just stem from the simultaneous occupancy of all the three receptors.

While there have also been suggestions for the existence of multiple mu opioid receptor subtypes[94], as in the case of delta and kappa receptors, there is little genetic evidence to support it. Though numerous mu opioid splice variants have been isolated, further studies are needed to elucidate their importance in modulating physiological and pharmacological effects.

Oligomerization of opioid receptors – a game changer

There is an additional consideration that had been consistently gaining ground to explain the evidence for pharmacological receptor subtypes. Even in the early 1980s, independent studies by Portoghese and Rothman groups suggested the possibility of adjacent and interacting opioid receptors that

are organized as complexes[65,95]. For instance, Portoghese and coworkers showed that bivalent ligands containing two pharmacophores separated by variable length spacer, can occupy proximal receptor active sites[64,65] in the Guinea pig ileum (GPI) and mouse vas deferens (MVD). Studies by Vaught et al., suggested that mu and delta receptors interact in the spinal cord and promote distinct downstream effects[96]. In addition, Rothman and colleagues showed that mu and delta ligands antagonized each other non-competitively at low doses, suggesting a level of allosteric coupling between mu and delta opioid receptors[97-99]. These provocative results, led to further experimentation and the concept of oligomerization of opioid receptors gained traction.

Experimental evidence for opioid oligomers

To better appreciate the concept of receptor oligomerization, it would be helpful to visualize the simplest minimal functional unit, a dimer. When two similar receptors form a complex, we have a homogenous complex or a 'homomer', and the complexation of two different receptors is termed a 'heteromer'[97] (Fig 4). In the case of opioid receptors, the groups of Devi and George were instrumental in elucidating the various opioid homomers and heteromers. Devi and colleagues isolated homomers of delta[98], kappa[99], mu opioid receptors[100,101] and later, the kappa-delta heteromer[102], one of the first GPCR heteromers to have been isolated. The mu-delta heteromer was subsequently identified by the research groups of both Devi and George[100,103]. Finally, Sadee and coworkers utilized bioluminescence resonance energy transfer (BRET) to show that all the opioid receptors can associate to form homomers and heteromers[104], thus providing independent evidence using a different experimental technique.

Ligands targeting opioid receptor heteromers – the future?

When we take note of the fact that most GPCRs can exist as monomeric units and be functionally active, the most intriguing aspect of receptor oligomerization is the functional and physiological outcome of the resultant 'meta'-receptor. An obvious progression of this idea is the possibility that ligands targeting such oligomers may have novel pharmacological effects that can lead to tantalizing therapeutic discoveries. Again, the work of the Portoghese group has provided the first examples of ligands targeting opioid receptor heteromers and has been reviewed previously[105].

Delta opioid receptors have been shown to modulate some of the side effects produced by mu opioid agonists. For instance, the administration of the delta antagonist naltrindole (NTI)[106], delta receptor antisense knockdown [107] and delta receptor knockout [108] have shown attenuated tolerance and dependence due to the treatment of morphine. Given the fact that mu and delta opioid receptors oligomerize to form heteromers[100,103], Portoghese and colleagues synthesized a series of MDAN bivalent ligands that contain mu agonist and delta antagonist pharmacophores tethered via spacers of varying length[109]. While the ligands with shorter spacers produced tolerance and physical dependence, the 21-atom spacer bivalent ligand was reported to produce potent antinociception devoid of tolerance, physical dependence, or place preference,[109,110]. This study suggested that MDAN-21 was bridging the active sites of adjacent mu and delta protomers within a mu-delta heteromer leading to the lack of deleterious side effects.

An effort to develop ligands for kappa-delta heteromers led to the identification of 6'-GNTI[111] that selectively activates kappa-delta heteromers in HEK-293 cells and produces antinociception in mice only when administered intrathecally (i.t.), but not intracerebroventricularly (i.c.v.). These data suggested the tissue-specific expression of kappa-delta heteromers in the spinal cord of mice. The study where Wessendorf and coworkers showed that kappa and delta receptors are extensively colocalized in the rodent spinal cord[112] provides independent support for the possibility of such tissue-specifc expression.

Recently, we reported on the discovery of N-Naphthoyl-β-naltrexamine (NNTA), a ligand that selectively activates mu-kappa opioid receptor heteromers with binding affinities in the sub-picomolar range[113]. NNTA produced antinociception intracerebroventricularly (i.c.v.), but was ~100-fold more potent in the spinal cord. Significantly, NNTA did not produce any physical dependence or place preference in mice suggesting that targeting mu-kappa heteromers may produce analgesics devoid of those side effects.

Conclusions

In spite of concerted efforts to develop new analgesics, opioids still remain the drugs of choice in the clinic. However, the deleterious side effects such as tolerance, physical dependence, and respiratory depression lead to complications during therapy. As discussed in the review, historically there have been several attempts to reduce these side effects with little to no success. The discovery that opioid receptors, and other GPCRs, can form higher order complexes suggests novel permutations of molecular and physiological effects that can be exploited using selective ligands. Indeed, the discovery that ligands targeting mu-delta and mu-kappa receptors can produce potent antinociception without tolerance, dependence or place preference show considerable promise towards developing therapeutics that will revolutionize pain treatments. Only time will tell if it is the desired mountain peak, or the proverbial abysmal cliff at the end of this path.

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Figure Legends

Fig 1. Selective ligands for mu opioid receptors

Fig 2. Selective ligands for delta opioid receptors

Fig 3. Selective ligands for kappa opioid receptors

Fig 4. An illustration for the concept of receptor oligomerization. When two similar receptors form a complex, it is termed a homomer while dissimilar receptors oligomerize to form heteromers.

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