**The Future Of Opioid Analgesics**

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**PROLOGUE**

The opioid analgesics represent an important class of agents for the treatment of severe clinical pain, but many effects often limit their usefulness. This manuscript will discuss recent findings in opioid pharmacology, and how medicinal chemists may be able to utilize these findings of novel opioid analgesics with reduced undesired effects. As such, the manuscript serves as an example of integrating medicinal chemistry, pharmaceutical chemistry, and pharmacology, and relating them to the clinical problems associated with effective pain management.

**INTRODUCTION**

The development of effective medications for the management of chronic pain remains a major focus of pharmaceutical research (1). Although the opioid (narcotic) analgesics such as morphine 1 have proven very useful, serious undesired effects often leads to under medication in clinical settings (2). The undesired effects associated with morphine include respiratory depression, tolerance, constipation, dependence, and nausea. Respiratory depression is the major cause of fatalities through illicit opioid use (generally with diacetylmorphine or heroin 2(3), but such events can be generally controlled with therapeutic opiates through close observation in a clinical setting.

The constipatory effects of morphine have been known for many years, and have proved beneficial through its use as an antidiarrheal agent. However, in a clinical setting, constipation remains a major undesired effect, and the pain associated with constipation has been described as often being worse than the pain the morphine is treating. Indeed, in extreme cases, the constipation can be life-threatening (4). These facts are the main reasons why chronic pain is often under medicated with morphine (5).

Obviously, the development of novel analgesic medications lacking such delirious effects would prove extremely useful for physicians treating terminal cancer pain, and this manuscript will discuss the potential approaches which can be taken by medicinal chemists in the design of agents with a reduced profile of undesired effects. This manuscript does not attempt to present a comprehensive account of the known medicinal chemistry and pharmacology of opioids, but how such knowledge could be applied to the discovery of new agents. Excellent reviews of opioid structure activity relationships are available from previous issues of this Journal (6,7) and else-where (8,9).

**OPIOID RECEPTORS**

The discovery of nalorphine 3 as an antagonist of morphine while still being an analgesic in animal models, was the first indication that the opioids may interact with more than one type of opioid receptor (10). Indeed, Martin postulated that the opioid system comprises three subtypes of receptors, namely mu, kappa, and sigma (11). However, it is now accepted that the sigma system is non-opioid due to the effects of sigma agonists not being reversed by the universal opioid antagonist, naloxone (12). Work on the endogenous ligands by Lord, uncovered a further class of opioid receptors, namely delta opioid receptors (6). These three well established opioid receptors (mu, kappa, delta) have been cloned (13), and form part of the family of seven transmembrane G-protein coupled receptors. Models of the opioid receptors have been developed, and together with point mutation and receptor chimera studies, have yielded invaluable information as to how ligands interact with the receptors at a molecular level (7).

Such studies may be anticipated to aid in the development of novel selective ligands; however, as the undesired effects of opioids occur through the same mechanism of activation of the receptors as does the desired analgesic effects, their value in developing new medications lacking undesired effects has yet to be shown.

A significant breakthrough in the understanding of the mechanism of action of the opioids came with the observation of the oligomerization (or dimerization) of the opioid receptors, and the findings that receptor activation is associated, in part, with direct interactions between receptors (14). In fact, experiments suggest that manipulation of receptor oligomerization show far greater promise of yielding ligands with reduced levels of undesired effects (14). It has been demonstrated that the pharmacological profile of opioid receptor dimers possess a different pharmacological profile to the receptor monomers, and that the pharmacological suggestion of opioid receptor subtypes of mu, kappa, and delta receptors may be due to the presence of receptor dimers. For example, a heterodimer between kappa and delta receptors has been shown to possess the pharmacological profile of the proposed kappa-2 subtype (14). Further studies to develop models of the dimmers (15), will aid in the design of ligands with novel pharmacological profiles that impact dimerization. While the success of such an approach cannot be predicted at present, it is anticipated that such ligands may possess decreased levels of undesired effects.

A related receptor (orphanin, ORL1) was recently discovered and shows high homology to the traditional opioid receptors. ORL1 is now often treated as a fourth subtype of opioid receptors, but it should be remembered that the effects of agonists at ORL1 are not reversed with the universal opioid antagonist naloxone. Reviews of ORL1 can be found elsewhere (16).

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KAPPA- AND DELTA-MEDIATED ANALGESIA
The discovery of the kappa and delta opioid receptors was a major breakthrough for opioid research. The fact that agonists at the two receptors give rise to analgesia in animal models without the traditional undesired effects, suggested that agonists acting at one of the receptors may provide a new medication for the treatment of severe pain. Unfortunately, it was discovered that kappa agonists possess an unacceptable undesired effect of their own, namely dysphoria (17) which significantly reduces the promise of kappa agonists to treat severe pain. Importantly, delta agonists appear to have few undesired effects (18), but are not able to treat the same level of pain as mu and kappa mediated analgesics.

FUTURE APPROACHES
As can be seen from the above, centrally acting kappa and delta agonists do not represent candidates for development into agents for the effective treatment of severe pain. Thus, for the treatment of severe pain attention has turned back to mu mediated analgesia, with attempts to control the undesired effects. Research in the area of kappa and delta mediated analgesics have focused on the treatment of less severe pain via peripheral opioid receptors, thus removing the undesired dysphoric central effects of kappa agonists (17). The section below will briefly discuss the currently accepted structure-activity relationships (SAR) of each class of ligands, and then discuss possible approaches open to medicinal chemists to develop agonists at all three receptors into clinically useful analgesics.

Mu Receptor Ligands
Many of the undesired effects of mu agonists are controlled well in the clinic, but as stated above, constipation remains a major problem. Indeed, the rapid build-up of constipation often has been reported as a reason for physicians under medicating chronic pain. This section will review chemical approaches towards the development of mu opioid medications with decreased constipatory effects. Morphine 1 is the prototypical mu agonist, although it is known to interact with all three opioid receptors (6). Much of the early structural modifications to morphine were evaluated in whole animal assays which predominantly measured central mu agonism, and thus the majority of the SAR of the opioids is mu SAR. In the morphinan-based opioids, the effect of the N-substituent dominates the efficacy at mu. N-Methyl and N-phenethyl tend to be mu agonists, whereas N-allyl (such as in nalorphine 3) and N-cyclopropyl methyl tend to be mu antagonists (8). As the natural opiates possess an N-methyl substituent, many of the drugs currently used also contain this substituent, such as oxycodone 4. A variety of other structural classes also interact with mu receptors (8), including the extremely potent orvinol class of ligands, such as buprenorphine 5 and etorphine 6. Interestingly, although a wide range of mu agonist ligands have been developed with a wide variety of different carbon-nitrogen skeletons, all give rise to the undesired effect of constipation.

Mu Agonists
Constipation is known to be primarily due to interaction of mu agonists with mu receptors in the periphery, specifically the GI tract, whereas the analgesic effect is primarily due to interactions with central opioid receptors (19). Thus, the development of peripherally selective mu antagonists could potentially antagonize the constipatory effects, yet not affect the central analgesic effects of morphine if coadministered.

As discussed above, an N-cyclopropylmethyl in the opioids tends to give rise to mu antagonism, and naltrexone 7 is a prototypical example. Naltroxene acts as an antagonist at mu receptors both centrally and in the periphery, but conversion to the quaternary salt 8 limits its central availability by increasing hydrophilicity, and therefore reducing its ability to cross the lipophilic blood-brain barrier. As naltroxene interacts with the mu receptor in a protonated form, it was considered that the charged quaternary amine may similarly interact with the receptor. Studies with 8, known as methylnaltroxene, have shown that upon methylation antagonist activity is retained, and it has shown great promise in reducing the occurrences of constipation in various clinical trials (20). Unfortunately, metabolic N-demethylation of 8 back to the centrally active naltrexone has been suggested (21), and may limit the long-term utility of 8, as antagonism of the central analgesic effects may result. Recent studies have also focused on the novel peripherally selective mu antagonist ADL8-2698 9 which cannot be metabolized to a centrally active mu antagonist (22). Compound 9 exists in the charged zwitterionic form, thus limiting access into the CNS. Fewer studies have been performed with 9 than with 8, but initial results suggest that 9 possesses the expected profile of reducing the constipatory effects of morphine (22).

Even though metabolism may be a problem with 8, the concept of antagonizing just peripheral receptors has been demonstrated, and suggests that mu antagonists that cannot be metabolized into centrally active compounds (such as 9) have the potential to make a major impact in the treatment of terminal cancer pain.

Kappa Receptor Ligands
Although the N-substituent of morphinans dominates the efficacy at mu receptors, this is not the case for kappa where the effect of the N-substituent cannot be predicted (6). Indeed, the observations made for nalorphine 3 are due to the fact that it possesses a profile of mu antagonism and kappa agonism. The design of selective kappa ligands remains a focus of many research groups, and few selective morphinan-based selective kappa ligands are known. Ketocyclazine 10 is the prototypical
kappa agonist, but it displays poor selectivity as do other benzomorphan based kappa agonists (6). A major breakthrough in kappa opioid agonist ligands came with the discovery of the arylacetamides, U50, 488 11 and U69, 593 12, non-morphinan based ligands which display excellent selectivity and efficacy at kappa receptors (6).

Attempts to correlate the structures of this class of ligands with the morphinan skeleton have yielded little success, implying that they bind to different, but overlapping areas of the kappa receptor. Though many studies were performed with the aim of developing the arylacetamides into clinically useful analgesics, none were ever brought to the clinic due to severe dysphoric effects occurring through central kappa receptors.

All kappa ligands of the arylacetamide class demonstrate agonist activity (6), adding further weight to the suggestion that they bind differently to the kappa receptor than the morphinan-based ligands. This is evidenced by kappa antagonists that have been developed by Portoghese through the introduction of additional basic nitrongs onto the morphinan skeleton to give norBNI 13 and GNTI 14. Such kappa antagonists were the subject of a recent review (7), and modeling studies have suggested that the basic nitrogen interacts with specific residues in the receptor, but their low kappa selectivity leaves this area a fertile ground for further studies.

**Kappa Agonists**

The main reason for the poor potential therapeutic profile of kappa is due to the dysphoric effects which occur through a central mechanism of action. However there is growing evidence that agonists at peripheral kappa receptors could treat certain pain conditions, such as hyperalgesia, an increased sensitivity to stimuli which are not generally noxious (23). Studies have concentrated on restricting access of the arylacetamides into the CNS, through both increasing and decreasing the lipophilicity (24). The trifluoromethyl substituted arylacetamide 15 would be expected to possess high lipophilicity, and indeed shows far greater peripheral analgesia than central analgesia in rodents. In a complementary fashion, the sulfon-amido substituted 16 would be expected to possess low lipophilicity (high hydrophilicity), and this compound shows promise as a local anesthetic agent. Such agents are in early stages of development, but obviously show great promise in

**Delta Receptor Ligands**

In a similar fashion to kappa ligands, selective delta agonists based on the morphinan skeleton have proved difficult to develop. Indeed, until the early 1990s the effects of delta agonists in vivo were almost entirely due to studies with peptidic ligands. The development of the highly delta selective diarylmethylpiperazines, BW373U86 17 and SNC80 18 was a major advance in this area (25). The skeletons are non-morphinan and they possess SAR quite different to morphinan-based opioids. Although a phenolic group in morphinans is generally considered essential for high affinity to opioid receptors, SNC80 18 contains no such group, yet retains very high affinity for delta opioid receptors. Studies utilizing SNC80 18 have shown that delta agonists have few undesired effects (18), but do not treat the same level of pain as mu and kappa agonists, and thus probably do not have the potential to be developed into useful agents for the treatment of severe clinical pain.

The prototypical class of delta antagonists are the indolo-morphinans, such as naltrindole 19 (25). This class of compounds all possess an aromatic ring (or similar lipophilic group) attached to the C-ring of the opioids. The introduction of the aromatic ring causes an increase in delta affinity, and a decrease in both mu and kappa affinity, giving rise to the observed delta selectivity. Many attempts have been made to increase the selectivity of the indolomorphinans (25), but attempts to increase the efficacy (to give agonists) have been generally unimpressive, with even the N-methyl derivative 20 displaying partial delta agonism in vitro and delta antagonism in vivo (25).

The fact that the indolomorphinans tend to display antagonism, and the diarylmethylpiperazines tend to display agonism, led to modeling studies to determine what, if any, structural overlap there is between the two series of ligands. Once an overlap has been determined, the incorporation of the relevant functional groups from one series into the other may be expected lead to changes in efficacy. Two conflicting overlaps have been suggested by Dondio (25) and Coop (26). Dondio has suggested that the oxygenated aromatic ring, terminal basic nitrogen, and benzamide groups of the diarylmethylpiperazines correspond to the oxygenated aromatic ring, basic nitrogen, and indole group of the indolomorphinans, respectively (25). In contrast, Coop has shown that the distances between these groups is quite different between the two classes, and that in the pharmacologically relevant protonated forms, such an overlap places the protons in very different orientations (26). It is obvious that further receptor-based molecular modeling is required to determine the merits of each hypothesis.

**Delta Opioids**

As stated above, the potential for the development of delta agonists into clinically useful agents for the treatment of severe clinical pain (18).
pain appears slim. However, recent pharmacological findings have suggested that delta antagonists may prove extremely useful in an indirect fashion. It has been shown that coadministration of the delta antagonist naltrindole together with morphine causes a slower build-up of tolerance to morphine, as compared to administration of morphine alone. The development of tolerance in the clinical setting causes ever-increasing doses of morphine to be administered in order to treat severe pain. Complicating the situation is that the development of tolerance to peripheral effects appears to occur more slowly than to the central effects (27), as there is a great increase in constipatory effects. The benefit of adding a delta antagonist is that the increasing doses of mu agonist are not required, thus greatly reducing the constipatory effects. However, the administration of two drugs is far from ideal due to differential metabolism and distribution leading to the conclusion that a ligand with a dual profile of mu agonism and delta antagonism could be the ideal analgesic. Evidence supporting this hypothesis has been demonstrated by Schiller (28), who showed that a peptidic ligand with such a dual profile possesses potent analgesic actions, without any development of tolerance. However, it should be noted that peptidic drugs are limited due to poor metabolic stability and penetration across the blood-brain barrier. Studies with non-peptides have been limited due to the unavailability of ligands with such a profile, but Ananthan recently disclosed morphinan 21 (29), which appears to possess the desired profile, but the low potency of 21 makes firm conclusions difficult. This compound possesses an aromatic ring similar to the selective delta antagonist naltrindole (19), but the chlorine substituted ring is in a different plane relative to the pyridine ring. Naltrindole possesses a fused indole ring, where both aromatic rings are in the same plane. This suggests that two non-planar aromatic rings attached to the morphinan skeleton may give rise to morphine antagonism, but not to the loss of mu affinity seen with the planar rings in naltrindole.

In order to design a potent analgesic ligand with such a profile of mu agonism and delta antagonism, further information concerning the structural requirements for obtaining both mu agonism and delta antagonism in the morphinan-based ligands is required. The importance of determining the differences between the delta antagonist naltrindole and the delta agonist diayllylmethylperazines is thus underscored. Modeling studies to determine the important group conferring low delta efficacy in naltrindole are thus required, and the group incorporated into a ligand which would be expected to possess high mu efficacy.

SUMMARY
There are several avenues available for the development of novel opioid analgesics lacking the undesired effects of traditional mu-mediated analgesics such as morphine. Success will depend on multidisciplinary research incorporating medicinal chemistry, molecular modeling, and pharmacology. In addition, further findings in the area of receptor oligomerization will generate further targets for potential utilization in the development of improved opioid mediated analgesics.

References