Review

Development of Delta Opioid Peptides as Nonaddicting Analgesics

Rao S. Rapaka\textsuperscript{1,3} and Frank Porreca\textsuperscript{2}

Although much effort has been devoted to opioid research since the identification of enkephalins, understanding of the physiological importance and mechanisms of action of endogenous opioids lags behind understanding of opiate alkaloids such as morphine. In recent years, several novel approaches have been refined with promise for the successful development of the long-awaited nonaddicting analgesics that act at the opioid delta receptor. The present communication reviews these efforts.

KEY WORDS: delta opioid peptides; nonaddicting analgesics; drug development; peptide drugs.

INTRODUCTION

Nearly 15 years after the initial euphoria associated with the discovery of the endogenous opioids (1), the immediate promise of novel therapeutic agents derived from these substances has yet to be fulfilled, and many pharmaceutical companies have canceled their long-standing opioid research programs. Does such pessimism reflect the realities of the development of peptides as drugs, or is there still cause to envision useful compounds emerging from the initial discovery of endogenous opioids? Recent developments in the synthesis of peptide analogues, peptidomimetics, and nonpeptides suggest that abandoning the effort for novel applications of opioid peptides is premature. Indeed, it would be gratifying if peptides could be developed as drugs because of their unique properties. Opioid peptides will be unique therapeutic agents (2) when compared to opiates for the following reasons.

1. It is anticipated that peptide analogues of enkephalins and related peptides will not be able to cross the placenta because of degradation by placental enzymes and, hence, could serve as obstetric medications, providing analgesia for the mother without exposing the fetus (3,4). Thus, peptides that degrade during their placental passage could be superior to the commonly used opiates (meperidine).

Further, the opioid delta receptor cannot be demonstrated in human fetal brain tissue. Thus, unlike mu and kappa opioids, delta agonists offer an additional level of safety for the fetus.

2. On metabolic degradation, peptides will be hydrolyzed to their constituent amino acids, and the metabolic end products, unlike the opiates, are polar, easily eliminated from the body, and unlikely to cause liver or kidney damage.

3. From the drug design aspects, peptides offer special advantages. As peptides are made up of subunits, amino acid residues, virtually an unlimited number of analogues can be synthesized. As peptides are conformationally labile, the three-dimensional architecture of the peptides can be altered by incorporating various structural modifications (such as unnatural amino acids, N-methyl substituents, peptide bond replacements, formation of cyclic structure, etc.) to achieve a desired pharmacophoric conformation. Thus, manipulation of three dimensional structure to obtain a desired bioactivity is easier with opioid peptides than with structurally rigid opiates.

4. Peptides are endogenous. They serve as better models for studies on biosynthesis and conformation. As peptides are polar molecules, solution studies can be performed in different solvents and with different ions to understand the effects of solvents, etc., on conformation. In addition, techniques for peptide synthesis have been simplified and are automated (solid phase method).

5. Peptide agonists for the opioid delta receptor are likely to have decreased dependence/abuse liability and lower reinforcing efficacy.

6. Peptide agonists for the opioid delta receptor do not demonstrate significant analgesic cross-tolerance to opiates acting at the mu receptor such as morphine; thus, they are likely to be useful pain relievers in patients undergoing prolonged therapy or high-dose treatments with mu opiates (5).

Hence, design of biologically active peptides as analgesics would be highly desirable.

BACKGROUND

Efforts to gain insight into the pharmacological rele-
vance of the various opioid receptor types have been especially hampered by the lack of stability of the endogenous opioid peptides. Thus, it was not possible to simply inject these peptide substances and measure a robust pharmacological response. This situation has delayed clear understanding of the relevance and potential therapeutic importance of the opioid delta receptor. This opioid receptor was postulated on the basis of rank order of potency of enkephalins and opiate alkaloids in two classical bioassays exclusively used by Hans Kosterlitz (Aberdeen, Scotland) and his colleagues, the guinea pig isolated ileum (GPI) and the mouse isolated vas deferens (MVD) (6). It was suggested that a new receptor type was present in the MVD and termed the delta receptor after the d in deferens (6). Later, this receptor was identified using radioligand binding approaches in nervous tissue (7).

Administration of the endogenous ligands of the receptor, [Leu] and [Met]enkephalin, produces a few measurable actions. The reason for the relative inactivity of these substances is thought to be due to the rapid degradation of these simple, short, straight-chain peptides by endopetidases present throughout the body (8). Attempts to circumvent this problem generally have involved the incorporation of unnatural D-amino acids along the peptide sequence. Unfortunately, the modification of the peptide backbone changed the selective activity at the delta receptor and possible cross-reactivity at other receptor types (i.e., the mu and kappa receptors) (for reviews see Refs. 9–13).

A variety of approaches has been used to overcome the concern of cross-reactivity at other receptor subtypes of stabilized enkephalin analogues (13). One of the most successful of these approaches has involved the stabilization of the peptide molecule in a conformation which prefers the desired receptor by incorporation of conformational restrictions (14). This approach has been exploited by Victor Hruby (Tucson, Arizona) and Henry Mosberg (Ann Arbor, Michigan) as well as by the group of Peter Schiller (Montreal, Canada) (see Ref. 15) and others. The introduction of conformational restrictions such as unnatural bulky synthetic amino acids and techniques of cyclization of the peptide chain has resulted in the synthesis of highly selective peptides such as [D-Pen] and [D-Pen]enkephalin (DPDPE) (16). The introduction of this peptide in 1983 provided the first tool for investigating the opioid delta receptor. An equally important development occurred at about the same time when the group at ICI (Macclesfield, U.K.) introduced the first highly selective delta receptor antagonist, ICI 174,864 (17). With these tools, opioid researchers could finally begin to study the pharmacological importance and potential physiological involvement of delta receptors.

DIRECT INVOLVEMENT OF OPIOID DELTA RECEPTORS IN ANTIINOCICEPTION

Initial studies were done with the highly selective cyclic delta agonist, DPDPE in the rat (18) and in the mouse (19). These studies showed that central (intracerebroventricular, icv) administration of this compound produced effective analgesia in the hot-plate test in the rat and in the hot-plate and tail-flick tests in the mouse. In addition, unlike mu agonists, over the effective analgesic dose range and higher, DPDPE did not inhibit propulsion of contents along the gastrointestinal tract. In contrast, agonists at the opioid mu receptor were shown to produce both analgesia and inhibition of intestinal motility. Thus, it was concluded that cerebral delta receptors could be activated to produce analgesia and that these receptors were not involved in the central regulation of gastrointestinal motility.

The concept that supraspinal delta receptors could be implicated in the direct production of analgesia was met with a good deal of skepticism, mainly because of the fact that although the ligand studied was highly delta selective, the possibility still existed that it produced its effects through cross-reactivity at the mu receptor. Additionally, it had long been accepted that substances that produced opiate-like analgesia within the brain did so by actions at the mu receptor, a view that was reinforced by noting the strong correlation between clinically effective analgesic doses of mu agonists and activity in the guinea pig isolated ileum. Confirmation of the possible involvement of the delta receptor in antinociceptive processes was important because of the potential therapeutic implications of a novel class of substantially nonaddicting analgesic drugs.

Efforts to establish firmly the possibility of delta receptor involvement in analgesia focused on a series of studies emphasizing the use of DPDPE in conjunction with the highly selective delta antagonist, ICI 174,864 (20), and antagonists at the mu opioid receptor such as beta-funaltrexamine (beta-FNA) (21) and naloxomazine (22–24). The concern of DPDPE action at opioid kappa receptors was minimal since this agonist had no measurable affinity for the kappa receptor in radioligand binding assays (16,25,26) or in the rabbit vas deferens (27), a bioassay for opioid kappa receptors (28).

Using the mouse tail-flick test, icv DPDPE produced analgesia which was blocked in a dose-related fashion by ICI 174,864 (29). The doses of ICI 174,864 needed to antagonize the analgesic actions of icv. DPDPE were not themselves analgesic and did not antagonize the analgesic actions of morphine or of [D-Ala², NMePhe⁴, Gly-ol]enkephalin, DAMGO (29), a highly selective mu receptor agonist (30). Further, no cross-tolerance could be demonstrated between morphine and DPDPE following icv administration in the mouse. The demonstration of differential antagonism using a delta antagonist, ICI 174,864, provided strong evidence for the independent participation of delta receptors in the production of analgesia at supraspinal levels. Additional evidence stemmed from studies with mu receptor antagonists such as beta-FNA and naloxomazine. In mice pretreated with beta-FNA, the morphine and DAMGO dose–response lines were displaced significantly to the right, indicating blockade of mu receptors. In contrast, the analgesic dose–response line of DPDPE was totally unchanged in these beta-FNA-pretreated mice (31). Furthermore, while ICI 174,864 could not antagonize the analgesic effects of morphine in control mice, this delta antagonist was able to antagonize morphine in beta-FNA-pretreated mice (31). This finding suggested that when mu receptors were blocked, morphine produced its analgesic actions by acting at other available receptors, such as the delta receptor. The demonstration that morphine could produce analgesia at sites other than the