Update on Opioid and Analgesic Pharmacology

J. G. Bovill, MD, PhD, FCARCSI

One of the most remarkable advances in the past decade has been in unraveling the molecular processes in opioid pharmacology. There have also been substantial advances in our understanding of the mechanisms involved in the processing of nociceptive information. It has become obvious that this is a very complex process, involving multiple neuropeptides, neurotransmitters, and their respective receptors. These advances have led to exciting new developments in the management of acute and chronic pain. These advances will be surveyed in this review.

Opioids

The three classical opioid receptors—μ, δ, and κ—have recently been cloned and their nucleotide sequences characterized. The opioid receptors belong to the large superclass of G protein-coupled receptors, which all possess the same general structure: an extracellular amino-terminal region, seven transmembrane (TM) domains, and an intracellular carboxy-terminal tail structure. The endogenous ligands for the opioid receptors are the enkephalins, endorphins, and dynorphins, encoded by separate genes. These pentapeptides vary in their affinity for the opioid receptor, but none binds exclusively to one type. A new class of highly selective μ-selective endogenous peptides—the endomorphines—has recently been described. Endomorphin-1 and endomorphin-2 are tetrapeptides structurally unrelated to the other endogenous opioid peptides. Their distribution in the central nervous system mirrors that of the μ-opioid receptors, and they display extremely high affinity and selectivity for the μ receptor (1,2). Their affinity for μ receptor binding sites is more than 1000-fold greater than for δ or κ receptors, and they are thought to be the endogenous ligands for the μ receptor (2,3).

Although the endogenous opioids are analgesic, their clinical usefulness is severely limited by rapid biodegradation by peptidases. β-Endorphin is more resistant to enzymatic degradation than the smaller enkephalins, but it does not penetrate the blood-brain barrier. When injected intrathecally, it produces potent, long-lasting analgesia. Enkephalinase inhibitors are analgesic in animals, and mixed inhibitors of enkephalin-degrading enzymes are now undergoing preclinical trials (4).

The cloned opioid receptors are highly homologous, with 65% similarity in their amino acid sequence. The most divergent are the extracellular loops and amino- and carboxy-terminals. Opioid receptor ligands are bivalent, with one portion mediating signal transduction and the other determining receptor selectivity. These are referred to as the message and address regions, respectively. Signal transduction appears to involve the TM regions, whereas the function of the extracellular loops seems to be exclusion of ligands from the binding sites. The first extracellular loop of the μ- and δ-opioid receptors differ in only seven amino acids, the critical difference lying in one amino acid at position 108. Replacing lysine at this position in the δ receptor by asparagine allowed the receptor to bind the μ receptor ligand DAMGO with high affinity (5). The binding pocket of the receptor is formed by the spatial orientation of various amino acids in the different TM domains and extracellular loops. Antagonists cannot induce the conformational change needed for receptor activation. However, replacing a single amino acid, serine, by leucine in TM4 results in receptors at which antagonists display full agonist properties (6).

Activation of opioid receptors produces effects that are primarily inhibitory. Opioid agonists inhibit adenylyl cyclase (decreasing cyclic AMP production), close N-type voltage-operated calcium channels, and open calcium-dependent inwardly rectifying potassium channels (Fig. 1). This results in hyperpolarization and a reduction in neuronal excitability. Changes in intracellular Ca^{2+} influence the release of neurotransmitters and modulate the activity of protein kinases. In contrast to inhibitory activity, nanomolar concentrations of opioids can produce excitatory effects by activating excitatory G_s proteins (7). Antagonism of excitatory activity may underlie the observation that co-treatment with extremely low doses of an antagonist can markedly enhance the analgesic efficacy of opioid agonists (8). The administration of ultra-low doses of naloxone or nalmefene, a long-acting antagonist, significantly reduced morphine consumption by patients after surgery and decreased

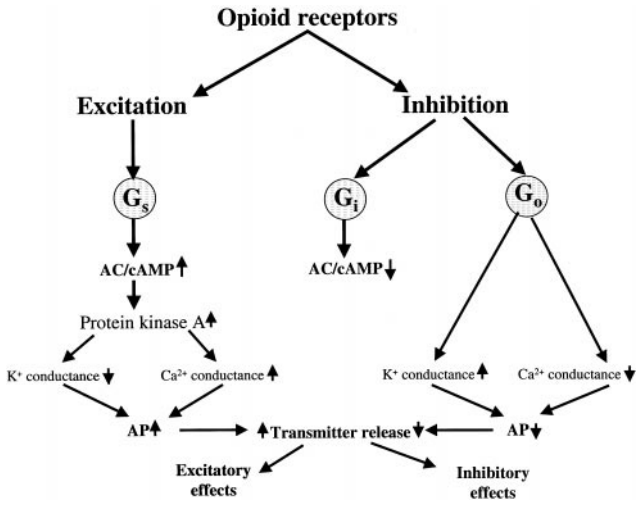

Figure 1. Opioid agonists in micromolar concentrations are primarily inhibitory, decreasing the activity of adenylyl cyclase (AC), intracellular cAMP, and the action potential (AP), resulting in neuronal hyperpolarization. In contrast, nanomolar concentrations cause the opposite effects, resulting in increased neuronal excitability.

the incidence of side effects such as emesis and pruritus (9,10).

Molecular Biology and Opioid Pharmacology

Cloning of the opioid receptors and other advances, including antisense technology, has produced spectacular advances in understanding the molecular pharmacology of opioids (11,12). Studies using mice deficient in the μ-opioid (MOR-1) receptor have shown that the μ receptor is essential for the analgesic and respiratory depressant properties of morphine. Antisense probes targeting exon 1 of the MOR-1 receptor gene blocked analgesia caused by morphine but not that by morphine-6β-glucuronide (M6G), heroin, or 6-acetylmorphine, suggesting that they might be acting on a splice variant of the μ receptor (13,14). Subsequent research using knock-out mice with disruptions of either the first or second coding exons of MOR-1 has provided further genetic evidence for a unique receptor site for M6G and heroin analgesia (15).

Although morphine and the fentanyl analogs are thought to activate the same μ receptor, the mechanisms involved may be dissimilar (16). The difference may be caused by the drugs binding at different locations on the receptor. Mutation of the aspartate amino acid at position 114 of the receptor to asparagine abolished receptor activation by morphine but had minimal effects on activation by the fentanyl analogs. This may partly explain the observation that patients with cancer-related pain refractory to morphine do not exhibit tolerance to fentanyl or sufentanil (17).

The Orphan Opioid Receptor

Soon after the cloning of the opioid receptors, several investigators reported the isolation of a protein with a structure typical of a G protein-coupled receptor. The new protein had approximately 65% homology to μ, δ, and κ receptors but did not bind classic peptide or nonpeptide opioid ligands. On structural grounds, it was classified as an opioid receptor and named "opioid receptor-like 1" (ORL1). It is also referred to as an orphan receptor because the endogenous ligand was unknown. The receptor has been identified in humans. ORL1 did not remain an orphan for long. A novel heptadecapeptide was identified as its endogenous ligand and named nociceptin (18) or orphanin FQ, because it is the endogenous ligand of the orphan receptor, and phenylalanine (F) and glutamine (Q) are the first and last amino acids of its primary sequence (19). The cellular responses evoked by nociceptin are similar to those of the classic opioid receptors. In animals, nociceptin produces a range of biological actions that differ from other opioids. It induces analgesia when administered intrathecally but causes hyperalgesia and reverses opioid-induced analgesia when given intracerebroventricularly. Nociceptin stimulates food intake, produces anxiolysis, and has a role in memory and central information processing.

The broad spectrum of pharmacological effects of nociceptin suggests multiple therapeutic applications for ORL1 receptor agonists and antagonists. The development of nonpeptide nociceptin antagonists will almost certainly result in new pharmacological tools for the management of pain, anxiety, and other pathological states (20). Of particular interest is that drugs interacting with the ORL1 receptor appear to be free of abuse potential.

New Opioids

A major side effect of current opioid agonists is respiratory depression. Opioids that interact with the κ receptor do not induce respiratory depression. Unfortunately, κ agonists produce a spectrum of side effects, including locomotor impairment, sedation, central nervous system disturbances, and diuresis. The first human study of a new mixed $\delta/\mu/\kappa$ opioid receptor agonist (DPI3290) has recently been reported (21). In animals, DPI3290 demonstrated strong analgesic activity with limited respiratory depression. The results of further investigations with this new opioid will be eagerly awaited. Another potent opioid, 14-methoxymetopon, induced no respiratory depression in dogs and caused less hypotension and bradycardia than sufentanil (22). This compound may be an agonist at μ and κ receptors. All its actions were reversed by naltrexone.

Transplantation of Opioid-Producing Cells

A novel approach to the management of cancer pain is transplantation of opioid-producing cells into the cerebrospinal fluid. Chromaffin cells of the adrenal medulla produce high levels of opioid peptides. In animals, adrenal medullary tissue or isolated chromaffin cell transplants into the spinal subarachnoid space produces potent and prolonged analgesia without neurotoxicity (23). The technique has been used in patients with intractable cancer pain after failure of systemic opioids, with significant improvement in pain and a reduction in systemic opioid requirements (24).

Opioids and Cannabinoids

There has been a recent resurgence of interest in the therapeutic applications of cannabis (25). Cannabis contains a large number of active compounds, cannabinoids, of which Δ^9-tetrahydrocannabinol is the main psychotropically active ingredient. Opioids and cannabinoids share several pharmacological effects, including analgesia, and there is evidence for functional links between the two systems (26–28). The combination of opioids and cannabinoids would therefore appear to offer potentially valuable therapeutic tools for the management of patients with acute and chronic pain.

Selective COX-2 Inhibitors

The nonsteroidal antiinflammatory analgesics (NSAIDs) produce their pharmacological effects by inhibition of the enzyme cyclooxygenase (COX), which catalyzes the synthesis of prostaglandins from arachidonic acid. Prostaglandins are involved in many homeostatic processes and are important mediators of inflammation. There are two COX isoenzymes: COX-1, the constitutive form; and COX-2, which is induced by exposure to mediators of inflammation. An important difference between COX-1 and COX-2 is the amino acid at position 523. COX-2 has a small valine at this position that allows access to a branched side channel by highly selective COX-2 inhibitors. The three-dimensional structure of COX-2 revealed by radiograph crystallography has been exploited in the design of drugs that allow them to fit into the active site of the COX-2 enzyme, but not onto the more cylindrical active site of COX-1.

Toxicity associated with NSAID therapy is largely caused by inhibition of COX-1, whereas therapeutic benefit derives from inhibition of COX-2. Compounds that selectively inhibit COX-2 are analgesic and antiinflammatory, with less of the gastric or renal toxicity normally associated with NSAIDs. Because only COX-1 is present in platelets, selective COX-2 inhibitors do not effect hemostasis. There is increasing evidence, however, that the distinction between the physiological and pathological roles of the two COX isoforms is becoming less tenable and that, indeed, their activities overlap to a considerable degree (29). COX-2 is constitutively expressed in neurones and gastric epithelial cells. It may be important in neural transmission and may play a crucial role in protecting the gastric mucosa from injury (30). Although the adverse renal effects of NSAIDs have largely been attributed to inhibition of COX-1, it is now recognized that COX-2 has a physiological role in renal homeostasis. COX-2 knock-out mice develop a progressive nephropathy as they age (31). To date, there is no firm evidence for adverse renal effects in humans with the presently available COX-2-selective NSAIDs. However, there is as yet only limited experience with these drugs, and caution is advised with their use in susceptible patients.

Although the highly selective COX-2 inhibitors may have limitations for long-term use, they may be useful for postoperative pain. In addition to analgesia, they suppress cytokine production and therefore may be useful in improving outcome after surgery and trauma. In the United States, the Food and Drug Administration has recently approved celecoxib and rofecoxib. These are respectively about 400 and 1000 times more selective for COX-2 than COX-1. Rofecoxib is available in Europe. Unfortunately, these newer drugs are not available in a parenteral formulation. Parecoxib, a new COX-2 inhibitor that can be given IV or IM, is currently undergoing clinical trials. When injectable, selective COX-2 inhibitors become available, they may well change our approach to the management of perioperative pain.

Ketamine

Ketamine has been used as an anesthetic for more than three decades. Its usefulness, however, has been limited by undesirable side effects. The mechanisms of its actions involve multiple receptors, including N-methyl-d-aspartate (NMDA) and non-NMDA glutamate receptors, as well as nicotinic and muscarinic cholinergic and opioid receptors (32). Much interest has focused on the noncompetitive binding to the NMDA receptor, which is thought to be mainly, but not exclusively, responsible for the anesthetic and analgesic effects of ketamine. The NMDA receptor is involved in a particular state of central nervous system sensitization known as wind-up, which is observed after repeated stimulation of dorsal horn C fibers. This has generated considerable interest in the role of ketamine in preemptive analgesia (33,34). Improved preemptive analgesia may be achieved by the combination of IV small-dose ketamine and epidural morphine (35). Epidural ketamine, in combination with morphine and a local

anesthetic, may contribute to preemptive analgesia when given before surgery. There are, however, concerns about the spinal toxicity of epidural ketamine. Small-dose ($<20\ \mu g \cdot kg^{-1} \cdot min^{-1}$) IV infusions of ketamine are effective for postoperative analgesia, with an opioid-sparing effect as large as 50% (36). The recent introduction of S(+)-ketamine will add to the renewed interest and application of this interesting drug.

Anticholinesterases

In the spinal cord, muscarinic cholinergic receptors are concentrated in the superficial layers of the dorsal horn of the spinal cord, where they are involved in the modulation of nociception. Muscarinic cholinergic agonists and cholinesterase inhibitors hold promise as nonopiate drugs for the treatment of acute and chronic pain. In volunteers, lumbar intrathecal neostigmine administration increases acetylcholine concentrations in cerebrospinal fluid and produces analgesia to noxious stimulation (37). There have been several reports of the effectiveness of intrathecal or epidural neostigmine, in combination with local anesthetics or opioids, for postoperative analgesia (38–40). Intraarticular neostigmine has also been successfully used for analgesia after knee surgery (41). A major side effect of spinal neostigmine is dose-related emesis.

Other Potential Analgesic Compounds

In addition to the drugs discussed above, many other substances are involved in the processes of nociception in the spinal cord and in the periphery (42). The neurokinin peptides substance P and neurokinin A are involved in the transmission and modulation of nociception. Clinical trials have begun with nonpeptide orally administered neurokinin receptor antagonists (42). In the dorsal horn of the spinal cord, somatostatin receptors are found in primary afferent terminals, spinal interneurons, and the axons from descending pathways. Clinical trials have been conducted with intrathecal somastatin or the synthetic somastatin analog, octreotide, in patients with cancer (42). Bradykinin and related peptides are implicated in inflammation and the induction of nociception and hyperalgesia. There has been considerable research in the past two decades to develop selective kinin receptor antagonists. The bradykinin B_1 receptor has become a target for pharmacological research, and it can be expected that B_1 antagonists will be developed for the management of pain and inflammation (43).

References

1. Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the μ-opiate receptor. Nature 1997;386:499–502.
2. Stone LS, Fairbanks CA, Laughlin TM, et al. Spinal analgesic actions of the new endogenous opioid peptides endomorphin-1 and -2. Neuroreport 1997;8:3131–5.
3. Goldberg IE, Rossi GC, Letchworth SR, et al. Pharmacological characterization of endomorphin-1 and endomorphin-2 in mouse brain. J Pharmacol Exp Ther 1998;286:1007–13.
4. Senokuchi K, Nakai H, Nagao Y, et al. New orally active enkephalinase inhibitors: their synthesis, biological activity, and analgesic properties. Bioorg Med Chem 1998;6:441–63.
5. Minami M, Nakagawa T, Seki T, et al. A single residue, Lys108, of the Δ-opioid receptor prevents the μ-opioid-selective ligand [D-Ala(2),N-MePhe(4),Gly-ol(5)]enkephalin from binding to the Δ-opioid receptor. Mol Pharmacol 1996;50:1413–22.
6. Claude PA, Wotta DR, Zhang XH, et al. Mutation of as conserved serine in TM4 of opioid receptors confers full agonist properties to classical antagonists. Proc Natl Acad Sci U S A 1996;93:5715–9.
7. Crain SM, Shen K-F. Opioids can evoke direct receptor-mediated excitatory effects on sensory neurones. Trends Pharmacol Sci 1990;11:77–81.
8. Crain SM, Shen K-F. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. Pain 2000;84:121–31.
9. Gan TJ, Ginsberg B, Glass PSA, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997;87:1075–81.
10. Joshi GP, Duffy L, Chehade J, et al. Effects of prophylactic nalmefene on the incidence of morphine-related side effects in patients receiving intravenous patient-controlled analgesia. Anesthesiology 1999;90:1007–11.
11. Keiffer BL. Opioids: first lessons from knockout mice. Trends Pharmacol Sci 1999;20:19–26.
12. Pasternak GW, Standifer KM. Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology. Trends Pharmacol Sci 1996;16:344–50.
13. Rossi GC, Pan Y-X, Brown GP, Pasternak GW. Antisense mapping the MOR-1 opioid receptor: evidence for alternative splicing and a novel morphine-6β-glucuronide receptor. FEBS Lett 1995;369:192–6.
14. Rossi GC, Brown GP, Leventhal L, et al. Novel receptor mechanisms for heroin and morphine-6β-glucuronide analgesia. Neurosci Lett 1996;216:1–4.
15. Schuller AGP, King MA, Zhang J, et al. Retention of heroin and morphine-6β-glucuronide analgesia in a new line of mice lacking exon 1 of MOR-1. Nat Neurosci 1999;2:151–6.
16. Bot G, Blake AD, Li S, Reisine T. Fentanyl and its analogs desensitize the cloned μ opioid receptor. J Pharmacol Exp Ther 1998;285:1207–18.
17. Paix A, Coleman A, Lees J, et al. Subcutaneous fentanyl and sufentanil infusion substitution for morphine tolerance in cancer pain management. Pain 1995;63:263–9.
18. Meunier J-M, Mollereau C, Toll L, et al. Isolation and structure of the endogenous agonist of the opioid receptor-like ORL1 receptor. Nature (London) 1995;377:532–5.
19. Reinscheid RK, Nothacker H-P, Bourson A, et al. Orphanin FQ: a neuropeptide that activates an opioid like G-protein-coupled receptor. Science 1995;270:792–4.
20. Darland T, Grandy DK. The orphanin/FQ system: an emerging target for the management of pain. Br J Anaesth 1998;81:29–37.
21. Somma J, Iselin Chavis I, Greenberg B, et al. Pharmacokinetics of DPI3290: a new opioid [abstract]. Anesthesiology 1999;91:A456.
22. Freye E, Schmidhammer H, Latasch L. 14-methoxymetopon, a potent opioid, induces no respiratory depression, less sedation, and less bradycardia than sufentanil in the dog. Anesth Analg 2000;90:1359–64.

23. Sagen J. Transplantation of opioid-producing cells. In: Stein C, ed. Opioids in pain control. Cambridge, England: Cambridge University Press, 1999:143–65.
24. Lazorthes Y, Sagen J, Sallerin B, et al. Human chromaffin cell graft into the CSF for cancer pain management: a prospective phase II clinical study. Pain 2000;87:19–32.
25. Sharpe P, Smith G. Cannabis: time for scientific evaluation of this ancient remedy. Anesth Analg 2000;90:237–40.
26. Manzanares J, Corchero J, Romero J, et al. Pharmacological and biochemical interactions between opioids and cannabinoids. Trends Pharmacol Sci 1999;20:287–94.
27. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement μ opioid antinociception by oral Δ^9-tetrahydrocannabinol: dose-response analysis and receptor identification. J Pharmacol Exp Ther 1999;289:859–67.
28. Welch SP, Eads M. Synergistic interactions between opioids and cannabinoid systems. Brain Res 1999;848:183–90.
29. Wallace JL. Selective COX-2 inhibitors: is the water becoming muddy? Trends Pharmacol Sci 1999;20:4–6.
30. Gretzer B, Ehrlich K, Maricic N, et al. Selective cyclo-oxygenase-2 inhibitors and their influence on the protective effect of a mild irritant in the rat stomach. Br J Pharmacol 1998;123:927–35.
31. Dinchuk JE, Car BD, Focht RJ, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. Nature. 1995;378:406–9.
32. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg 1998;87:1186–93.
33. Warncke T, Stubhaug A, Jørum E. Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. Pain 2000;86: 293–303.
34. Menigaux C, Fletcher D, Dupont X, et al. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg 2000;90:129–35.
35. Aida S, Yamakura T, Baba H, et al. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology 2000;92:1624–30.
36. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999;82: 111–25.
37. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine in humans. Anesthesiology 1995;82: 331–43.
38. Lauretti GR, Hood DD, Eisenach JC, et al. A multi-center study of intrathecal neostigmine for analgesia following vaginal hysterectomy. Anesthesiology 1998;89:913–8.
39. Nelson KE, D'Angelo R, Foss ML, et al. Intrathecal neostigmine and sufentanil for early labor analgesia. Anesthesiology 1999; 91:1293–8.
40. Lauretti GR, de Oliveira R, Reis MP, et al. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. Anesthesiology 1999;90: 1534–8.
41. Yang LC, Chen LM, Wang CJ, et al. Postoperative analgesia by neostigmine in patients undergoing knee arthroscopy. Anesthesiology 1998;88:334–9.
42. Dougherty PM, Staats PS. Intrathecal drug therapy for chronic pain. Anesthesiology 1999;91:1891–918.
43. Calixto JB, Cabrini DA, Ferreira J, Campos MM. Kinins in pain and inflammation. Pain 2000;87:1–5.