Opioid binding sites were first demonstrated experimentally in 1973, almost 20 years after their existence was originally hypothesized [1]. Shortly after, in their classic pharmacological studies on chronic spinal dogs, Martin and colleagues provided definitive evidence of multiple opioid receptors, which they named (after the drugs used in their studies), mu (morphine), kappa (ketocyclazocine) and sigma (SKF 10047, N-allylnormetazocine) [2]. In 1977, Lord and colleagues discovered a binding site in the isolated mouse vas deferens with high affinity for enkephalins and named it the delta (deferens) receptor [3].

Only mu, delta and kappa receptors are currently recognized as opioid receptors and some of their characteristics are summarized in table I. They differ in function, distribution and affinity for various ligands, although considerable overlap exists and all three mediate analgesia. There are three structurally related groups of naturally occurring opioid peptides present in the mammalian CNS that bind to opioid receptors, β-endorphin, dynorphin-related peptides and the enkephalins. The dynorphins and enkephalins appear to be the endogenous ligands for kappa and delta receptors respectively, although whether β-endorphin or even morphine itself is the endogenous ligand for the mu receptor remains speculative [4]. The sigma receptor is a high affinity binding site for phencyclidine and related compounds. It is not an opioid receptor because sigma receptor-mediated effects are not reversed by high concentrations of opioid antagonists such as naloxone [5]. Opioid receptor-mediated analgesia is not a simple on/off phenomenon but exhibits considerable functional plasticity. This is seen peripherally at the site of injury and centrally within the dorsal column of the spinal cord. Peripheral activation of (silent) opioid receptors may occur by endogenous ligands synthesized and released by immune cells infiltrating inflammatory tissue [19]. Opioid receptors exist on the peripheral end of primary afferent neurones and their activation may either directly decrease neurotransmission or inhibit the release of excitatory neurotransmitters, such as substance P, and there is clinical evidence in support of a peripheral role [20]. Similarly, opioid receptor-mediated inhibition of C fibres may occur by endogenous ligands synthesized and released by immune cells infiltrating inflammatory tissue [19].

The primary effect of opioid receptor activation is reduction in neurotransmission [12]. This occurs largely by presynaptic inhibition of neurotransmitter release, although postsynaptic inhibition of evoked activity may occur also. The intracellular biochemical events of opioid receptor occupancy are now reasonably well established and it appears that it is increased potassium conductance (leading to hyperpolarization), calcium channel inactivation, or both, that produce an immediate reduction in neurotransmitter release [13]. Opioid receptor-mediated inhibition of adenylate cyclase is not responsible for an immediate effect but may have a delayed effect, possibly via reduction in cAMP-responsive neuropeptide genes and reduction of neuropeptide mRNA concentrations [14]. In addition to the general inhibitory effects of opioids, excitatory effects have been observed in vivo and in vitro. For example, Kaysen, Besson and Guibaud demonstrated in an arthritic rat model of persistent pain that very low doses of morphine produce paradoxical hyperalgesia and increased doses analgesia; both effects can be reversed by naloxone [15]. Furthermore, electrophysiological studies have shown that low doses of opioids prolong the action potential by either decreasing potassium or increasing calcium conductance [16]. In addition, opioid receptor-mediated stimulation of adenylate cyclase [17] and phospholipase C [18] has been demonstrated. Physiological roles for these excitatory effects remain speculative but they may represent an early warning system of noxious stimuli at certain critical sensory neurones or account for side effects of opioid analgesics, such as pruritus and euphoria.

Opioid receptor-mediated analgesia is not a simple on/off phenomenon but exhibits considerable functional plasticity. This is seen peripherally at the site of injury and centrally within the dorsal column of the spinal cord. Peripheral activation of (silent) opioid receptors may occur by endogenous ligands synthesized and released by immune cells infiltrating inflammatory tissue [19]. Opioid receptors exist on the peripheral end of primary afferent neurones and their activation may either directly decrease neurotransmission or inhibit the release of excitatory neurotransmitters, such as substance P, and there is clinical evidence in support of a peripheral role [20]. Similarly, opioid receptor-mediated inhibition of C or Aβ fibre-evoked dorsal horn neuronal activity is considerably greater after inflammation. The mechanism of this is unclear but activation of descending noradrenergic systems may be involved [21]. These results confirm previously published data from studies examining the behavioural response of rats exposed to intrathecal opioids after carrageenan-induced inflammation [22].

Recently, interest has focused on the use of kappa receptor agonists as mediators of analgesia as they do not exhibit the side effects characteristic of mu agonists, for example respiratory depression and...
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Table 1. Characteristics of mu (μ), delta (δ) and kappa (κ) opioid receptors. Apart from morphine, fentanyl, naloxone and enadoline (currently undergoing clinical trials), the agonists and antagonists illustrated are restricted to the laboratory. They are important because their introduction helped considerably the characterization of the various receptor subtypes.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Mu</th>
<th>Delta</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous ligand</td>
<td>β-endorphin?</td>
<td>Enkephalin</td>
<td>Dynorphin</td>
</tr>
<tr>
<td>Exogenous agonist</td>
<td>Morphine, fentanyl, DAMGO</td>
<td>DPDPE, DSLET</td>
<td>Endoline, U50,488H, U69,593</td>
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<tr>
<td>Antagonist</td>
<td>naloxonazine, CTP</td>
<td>Naltrexone</td>
<td>NorBNI</td>
</tr>
<tr>
<td>Cloned</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Subtypes</td>
<td>μ1,2</td>
<td>δ1,2</td>
<td>κ1,2,3</td>
</tr>
<tr>
<td>Adenylate cyclase</td>
<td>Inactivates</td>
<td>Inactivates</td>
<td>Inactivates</td>
</tr>
<tr>
<td>Voltage-dependent function</td>
<td>Increases</td>
<td>Increases</td>
<td>Increases</td>
</tr>
<tr>
<td>Potassium channel conductance</td>
<td>Analgesia, depression, constipation</td>
<td>Analgesia, respiratory depression</td>
<td>Analgesia, diuresis, depression</td>
</tr>
</tbody>
</table>

constipation [23]. Unfortunately they are associated with dysphoria and diuresis which may limit their use. In addition, animal studies reveal that high intensity painful stimuli are resistant to the analgesic effect of kappa agonists. Although the role of kappa agonists in the management of acute and chronic pain remains to be determined, the recent introduction of several kappa agonists (e.g. enadoline [24]) into clinical trials [personal communication, Dr J.C. Hunter, Parke Davis Research Centre, Cambridge] will provide further information.

An enormous amount of information has been generated in the past 20 years concerning the opioid receptor. As far as clinical anaesthetists are concerned, the “holy grail” of profound analgesia without significant side effects has yet to be realized. However, the important recent advances outlined above allow us to be cautiously optimistic. Although our knowledge of opioid receptor pharmacology is far from complete, it is a rapidly expanding field and certainly has an exciting future.

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REFERENCES


