OPIOID RECEPTORS AND THEIR RELEVANCE TO ANAESTHESIA

B. J. PLEUVRY

The therapeutic entities which have been derived from the constituents of opium, the dried exudate of the incised capsule of the opium poppy, have probably spawned more scientific publications than any other drug group. The observations that only the laevorotatory isomer of morphine, the active constituent of opium, was active and that most opioid analgesic drugs had similarities in structure, prompted Beckett and Casey to propose a tentative structure for an opioid receptor [4]. Since then our understanding of opioid pharmacology has progressed steadily with the notable highs of the discovery of the endogenous ligands to the opioid receptor [37] and the overwhelming evidence of multiple opioid receptors first noted by Martin and colleagues [56]. The anaesthetist uses morphine and its derivatives most commonly as analgesics for moderate to severe pain. With adjustment of dose and route of administration, opioids may perform this function with the minimum of side effects, which may range from the uncomfortable (itching, nausea and vomiting) to the life-threatening (respiratory depression). Chronic use of opioids may also lead to tolerance and physical dependence. It is worth re-emphasizing the theme which runs through most recent reviews of any aspect of opioid activity: “It was hoped that the development of opioid agonists selective for a particular opioid receptor subtype might separate the useful actions of opioids from the rest, and result in a therapeutic breakthrough. This breakthrough has not occurred!” What then, is the relevance of the subdivisions of opioid receptors to the anaesthetist?

OPIOID RECEPTORS: EVIDENCE FROM SELECTIVE LIGANDS

The different profiles of activities of morphine, ketocyclazocine and N-allyl-norcyclazocine (SKF 10,047) in the chronic spinal dog prompted the first well founded suggestion that subdivisions of opioid receptors might exist [56]. The first two (μ for morphine and κ for ketocyclazocine) mediate analgesia, which is generalized for the n agonist but spinal for the κ agonist. No cross tolerance exists between them. The third, σ for SKF, did not mediate analgesia and has subsequently been associated with the psychotomimetic activity of opioids. The next receptor to be described was the δ receptor [54] for which the endogenous opioid peptide leu-enkephalin showed selectivity. Originally this receptor was not associated with analgesic activity, but as we shall see later, this is not the case. The final receptor to be described (ε) is still an enigma. In a few, very specific situations, β endorphin appears to have agonist activity at opioid receptors which is not shared with morphine but which is antagonized by κ agonists [90]. Whether or not this represents a unique receptor (ε) or a lack of spare μ receptors at these β endorphin sensitive sites [61] is open to debate.

Further subdivisions of opioid receptors have been suggested based on selective ligand binding (table I).

μ receptors

The subdivision of μ receptors into μ1 and μ2 is based on the detection of two affinity states for the receptor [67] and on the selectivity of a single antagonist, naloxonazine [29], for the higher affinity state (μ1). Meptazinol was claimed to be a selective μ1 agonist but the intrinsic cholinomimetic activity of this compound clouded its pharmacology [5]. In contrast, morphine has greater selectivity for the low affinity site (μ2), while the opioid peptides and morphine have similar affinities for the μ1 site [39]. Published articles are polarized into those who do not accept a subdivision of μ receptors and, therefore, do not mention them, and those who treat their existence as an established fact.

δ receptors

Several lines of evidence support a subdivision of δ receptors. Two highly selective δ agonists have been described. Both the synthetic peptide [D-Pen², D-Pen⁵] enkephalin [62] and [D-Ala²] deltorphin II, isolated from frog skin [47], bind with high affinity to δ receptors and exhibit analgesic activity in animal models [41]. This analgesic activity is antagonized

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by the selective δ antagonist ICI 174,864, but not by the selective μ antagonist, β-funaltrexamine. However, there is no cross tolerance between the analgesic activity of these two compounds in mice [57], suggesting that they do not interact with identical receptors. Furthermore, each drug may be selectively antagonized by one of two novel δ receptor antagonists (table I) [42]. Additionally, these two agonists appear to activate different signal transduction mechanisms (see below). There is some evidence [32] that μ and δ receptors may exist in two forms, complexed together and non-complexed. If this is true, it could explain some of the observations regarding subdivisions of μ and δ receptors discussed above. The functionally coupled μ-δ receptor is sensitive to β-funaltrexamine, but not naloxonazine, which is believed to be selective for μ₁ receptors.

κ receptors

Binding selectivity studies have produced evidence of three subdivisions of κ receptors. Both κ₁ and κ₂ receptors appear to have selective agonists, (5a,7a,8b)–(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)-de-8-yl] benzenacetamide (U69,593) for κ₁ receptors [92] and naloxone benzoylhydrazone (NalBzoH) for κ₂ receptors [9, 11]. The highly selective κ₁ receptor antagonist nor-binaltorphimine [82], has poor affinity for the κ₂ site. It has been suggested that the first drug used to antagonize morphine-induced respiratory depression, nalorphine, may exert its intrinsic analgesic activity via this κ₂ site [69]. The κ₂ site is characterized more by what does not bind to it rather than what does (i.e. it is insensitive to U69,593 and NalBzoH). Nock and co-workers [63] also described a U69,593 and NalBzoH insensitive binding site for the κ agonist ethylketocyclazocine. It was concluded that this might be the β endorphin specific receptor, the ε receptor! Perhaps κ₁ and κ₂ are the same receptor! However, there are still no selective ligands for this binding site as β endorphin binds to μ, δ, κ₁ and κ₂/ε sites [9].

σ receptors

The original σ receptor ligand SKF 10,047, was found to bind to both the PCP (1-(1-phenylcyclohexyl)piperidine, commonly known as phencyclidine or “angel dust”) receptor and the σ receptor. The rank order of potency for binding to these two receptors differs: benzomorphans have greater affinity than PCP at the σ site and vice versa at the PCP site [74]. The PCP receptor is now known to be present in the ion channel gated by the N-methyl-D-aspartate receptor [52] whilst the σ receptor has been proposed to have two subtypes, σ₁ and σ₂ [73]. σ ligands, such as (+)-pentazocine, dextromethorphan and SKF 10,047, have much greater affinity for σ₁ than σ₂ receptors. (-)-Pentazocine and many anti-psychotic drugs are non-selective ligands at σ receptors and naloxone is inactive [85]. For this last reason, σ receptors are no longer classified as opioid receptors.

SIGNAL TRANSDUCTION MECHANISMS

Several of the opioid receptors have been solubilized and purified, but details of their primary structure, at least of those that may mediate analgesic activity, await elucidation [53]. It is hoped that this information will be available by the time this review is published. For the present, only indirect pointers to the nature of the opioid receptors may be used. Indicators predict that most of the opioid receptors characterized so far are members of the guanine nucleotide binding protein (G protein)-coupled receptor super family. Guanine nucleotides, particularly guanosine triphosphate (GTP), decrease specifically agonist binding to the μ, δ and κ opioid receptors and opioid agonists stimulate GTPase activity. In addition, in the presence of sodium, guanine nucleotides discriminate effectively between agonist and antagonist binding: the agonist binding is unaffected by GTP concentrations. These findings are characteristic of G protein-coupled

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<tr>
<th>Receptor</th>
<th>Subtype</th>
<th>Agonist</th>
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<tbody>
<tr>
<td>μ</td>
<td>μ₁</td>
<td>Meptazinol</td>
<td>Naloxonazine</td>
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<td>μ₂</td>
<td>Morphine = opioid peptides</td>
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<tr>
<td>δ</td>
<td>δ₁</td>
<td>[D-Pen² D-Pen⁵] enkephalin</td>
<td>β-Funaltrexamine†, cypriidine†</td>
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<tr>
<td></td>
<td>δ₂</td>
<td>[D-Ala³] deltorphin II</td>
<td>[D-Ala³][Leu⁶]Cyp⁵] enkephalin (DALCE), Naltrexone-S-ISO-isothiocyanate (SNTII)</td>
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<tr>
<td>κ</td>
<td>κ₁</td>
<td>U69,593</td>
<td>Naltrindole-f, ICI 174,864†</td>
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<td></td>
<td>κ₂ (ε?)</td>
<td>NalBzoH</td>
<td>Nor-binaltorphimine</td>
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<td>σ</td>
<td>PCP</td>
<td>Phencyclidine &gt; benzomorphans</td>
<td>Haloperidol†, (+) pentazocine†</td>
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<tr>
<td></td>
<td>σ₁</td>
<td>(+) Pentazocine, benzomorphans† &gt; phencyclidine†</td>
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†No selectivity for receptor subtypes; ‡agonist/antagonist status is controversial [85]. ICI 174,864 = N,N-diallyl-Trp-γ-aminosuberic acid-γ-aminosuberic acid-γ-Leu OH
receptors. GTP sensitivity is also seen with $\sigma_1$ receptors, but not with $\sigma_2$ receptors [73]. G proteins are heterotrimers, that is consisting of three different subunits, designated $\alpha$, $\beta$ and $\gamma$ in order of decreasing molecular weight. The $\alpha$ subunit binds the guanine nucleotides and differences in this subunit are used to identify different G proteins. The $G_\mu$ notation was used originally to designate a G protein which stimulated (s) adenylyl cyclase and $G_\delta$, a G protein which inhibited (i) this enzyme. Eventually this method of classification will change as more G proteins are identified and the heterogeneous character of the presently described G proteins is elucidated (e.g. $G_\alpha$ has at least three forms).

Two toxins, cholera and pertussis, are known to catalyse covalent modifications (adenosine diphosphate (ADP) ribosylation) of the $\alpha$ subunit. Cholera toxin has selectivity for the $\alpha$ subunit of the stimulatory $G_s$ protein, causing persistent activation [25]. This induces persistent activation of adenylyl cyclase in, for example, the intestinal epithelium, which leads to copious intestinal secretions, characteristic of the disease [75]. Pertussis toxin, on the other hand, causes ribosylation of $G_i$ and other G proteins, but not $G_s$ proteins. Pertussis toxin modifies the ability of the $G$ protein to bind to the receptor and thus prevents its activity [25]. How this causes the symptoms of pertussis is less clearcut and may reflect the heterogeneity of $G_i$ proteins alluded to above.

In some, but not all systems, opioid agonists have been shown to inhibit adenylyl cyclase. This effect is also GTP sensitive and is blocked by pertussis toxin. These findings are consistent throughout the literature and demonstrate that opioid receptors (the evidence is greater for $\mu$ and $\delta$ than $\kappa$) inhibit adenylyl cyclase via a $G_i$ protein [10]. Pertussis toxin reduces morphine-induced analgesia when injected intraventricularly [66] and intrathecally [34], thus implicating $G_i$, or at least a pertussis sensitive G protein, in this action. Similarly, $G_i$ protein activation has been implicated in the place preference properties of morphine [80].

Cholera toxin, which activates $G_\alpha$, also prevents the analgesic action of morphine, indicating the complex circuitry involved in pain and analgesia [7]. There is some evidence that direct activation of $G_\alpha$ proteins may be involved in the excitatory actions of opioids [13]. Uncovering of these excitatory effects by pertussis toxin has been offered as an explanation of the observation that, while pertussis toxin attenuates opioid-induced analgesia, it enhances lethality [59]. However, no direct evidence was offered as to the cause of death in these animals, although naloxone was preventative, suggesting involvement of opioid receptors.

Whether or not adenylyl cyclase is implicated as a second messenger in all opioid activity is debatable. G proteins are, as quoted so descriptively by many reviewers, promiscuous. They may interact directly with ion channels, as well as with several other second messenger systems, such as guanylyl cyclase, phospholipase C–inositol phosphate, phospholipase A2, etc. The involvement of some of these other systems with opioid activity is suggested from a number of sources. In the locus coeruleus, the response to agonist-$\mu$ receptor interaction is activation of potassium conductance via a G protein with no other detectable second messenger system involved [46]. Both $\mu$ and $\delta$ receptors appear to be associated with the opening of potassium channels, whilst $\kappa$ receptors are associated with the closure of calcium channels [14], at least when inhibitory activity is recorded. To date, potassium channels are the most diverse group of ion channels investigated. At least 13 major types exist and several subtypes exist within each group [20]. Glibenclamide, believed to be a selective blocker for the ATP sensitive potassium channels in the CNS [2], antagonizes morphine-induced analgesia, whilst tetraethylammonium and quinine, which block other types of potassium channels [2], antagonizes potassium channel opener pinacidil, potentiates potassium analgesia in the rat [84]. Using ligands selective for the proposed $\delta_1$ and $\delta_2$ receptors discussed above, Wild and colleagues [89] found that $\delta_2$-induced analgesia was antagonized by glibenclamide and not tetraethylammonium (TEA) whilst $\delta_1$ agonist was antagonized by TEA and not glibenclamide. It would be logical that, if some $\mu$ and $\delta$ receptors are complexed (as outlined above), they should be the ones linked to the same effector system (i.e. the glibenclamide-sensitive potassium channel). Agonists at $\kappa$ receptors, which are believed to act through calcium channels, were unaffected by either of the potassium channel blocking drugs discussed above. Four types of calcium channels have been described, L, N, T and P. The L channel, which is blocked by calcium antagonists, such as nifedipine, is particularly important in smooth muscle and cardiac muscle contraction and is located in some neurons. However, it is the N channels, which have been identified only in neurons and appear to participate in neurotransmitter release, which are selectively inhibited by the $\kappa$ agonist, dynorphin A.
Only a proportion of N channels are sensitive to \( \kappa \) agonists.

Nitric oxide is synthesized by certain mammalian cells, including brain cells, as a biological messenger molecule which activates guanylyl cyclase. The role of this in the central nervous system is unknown, but addition of the nitric oxide precursor L-arginine, potentiates \( \beta \) endorphin-induced analgesia (or antinoceptive), whilst NO-nitro-L-arginine, an inhibitor of nitric oxide production, prevents \( \beta \) endorphin-induced analgesia [83]. There is also some suggestion that a nitric oxide–cyclic GMP signalling pathway is involved in peripheral analgesia [18], but whether or not this is important for the peripheral activity of opioids (discussed below) is unclear (fig. 1).

It is particularly ironic that the only opioid binding protein which has been cloned and sequenced at the time of writing is not a G protein-coupled receptor. Its amino acid sequence places it in the immunoglobulin super family, which includes the interleukin-6 receptor [53]. This binding protein may be relevant to the activities of opioid agonists on the immune response, which has been reviewed by Sibinga and Goldstein [76].

FUNCTIONAL RELEVANCE OF OPIOID RECEPTORS

As mentioned above, the most important pharmacological property of opioid drugs is analgesic activity. It is now apparent that opioids exert this effect supraspinally, at the level of the brain stem, spinally by inhibiting nociceptive input, and peripherally when pain is produced by inflammation or a sympathetic pain syndrome.

Supraspinal injections of \( \mu \), \( \kappa \) and \( \delta \) agonists produce naloxone-sensitive analgesia. However, in most instances, activation of \( \mu \) receptors may explain the analgesic activity observed [14]. However, there is evidence that analgesia occurs through activation of \( \delta \) receptors [33]. The independent supraspinal analgesic activity of \( \kappa \) receptor activation is uncertain and all shades of opinion may be found in the literature [14, 49, 60]. While the role of \( \mu \) receptors in supraspinal analgesia is accepted unequivocally by most authors, the exact mechanism by which this effect is achieved is exceedingly murky. There is contradictory evidence that morphine both enhances and inhibits descending inhibitory control of spinal nociceptive pathways (e.g. [1, 15, 24, 26]). Authors on both sides of the divide have produced interesting hypotheses as to how their findings might explain observations concerning the analgesic action of morphine. However, few address the problem as to why these studies produce opposing views.

The observation that opioids cause analgesia at a spinal site has led to increasing use of extradural or spinal administration of opioids for pain relief [22]. The maximum pain relief achieved by this route is less than that achieved when there is some spread of the drug to supraspinal sites, although this spread is accompanied by an inevitable increase in side effects, such as respiratory depression. Some drugs, such as pethidine and fentanyl, possess additional local anaesthetic activity [71] and this may increase their ability to produce pain relief via the spinal or extradural route [27]. It is most likely that the spinal analgesic activity of opioids is mediated via \( \mu \) receptors, as these make up the largest proportion of receptors in the spinal cord. These receptors are found close to the C-fibre terminals in lamina 1 and in the substantia gelatinosa. In addition, all clinically used opioids have significant \( \mu \) receptor activity. Naloxonazine does not antagonize the analgesic activity of \( \mu \) agonists in the spinal cord, although it does antagonize supraspinal \( \mu \)-induced analgesia. This could indicate that \( \mu \) receptors mediate spinal analgesia, whilst supraspinal analgesia is \( \mu \)-mediated [68]. However, both \( \mu \) and \( \delta \) receptor selective agonists inhibit C-fibre activity: this effect is sensitive to selective receptor antagonists [70]. Very small doses of \( \mu \) agonists actually enhance C-fibre activity: this effect is not shared by \( \delta \) agonists [16]. This may be a result of activation of \( G \) proteins (see above). It has been suggested that this enhancement of C-fibre activity may account for the itching seen after spinal opioid injections in man [14].

Synergy between the spinal antinoceptive actions of \( \mu \) and \( \delta \) agonists has been reported by several groups [16, 59, 65]. Thus enhanced analgesic efficacy of spinal opioids may be obtained by combining drugs with \( \mu \) and \( \delta \) receptor activity. As with the supraspinal site, the role of \( \kappa \) receptor activation in the production of analgesia is controversial. While drugs with \( \kappa \) agonist activity produce analgesia at the spinal level, many possess activity at other receptors, both opioid and non-opioid, which could explain their action. For example, trans-3,4-dichloro-N-methyl-N-[(2 pyrrolidinyl)-cyclohexyl] benzene acetamide (U50,488H) has been used as a selective \( \kappa \) agonist, but it has been shown to have non-opioid analgesic effects in vivo [31]. In addition, the \( \kappa \) antagonist, nor-binaltorphimine, which shows good selectivity for \( \kappa \) receptors in vitro, requires large doses and prolonged exposure to be effective in vivo and may not discriminate between \( \mu \) and \( \kappa \) receptors [6]. Some studies have even shown an anti-analgesic action of dynorphin A, a proposed endogenous ligand at \( \kappa \) receptors [23].

Powerful analgesic effects in inflammatory pain may be obtained with opioids acting at peripheral receptors. Early experiments failed to demonstrate unequivocally that these receptors were truly opioid in nature, as antagonist reversibility was questionable [21]. Subsequently, evidence was produced demonstrating that these peripheral effects were stereospecific and naloxone sensitive, suggesting true opioid receptors. The use of selective agonists and antagonists also suggested that these receptors had characteristics resembling \( \mu \), \( \delta \) and \( \kappa \) receptors [78]. Inflammatory mediators, such as prostaglandin E2 (PGE2), activate adenylyl cyclase via a stimulatory G protein causing nociceptor sensitization. Activation of \( \mu \) receptors switch off this process via \( G \), and thus prevent nociceptor sensitization [50]. Prevention of PGE2 hyperalgesia is not a property shared by \( \delta \) and \( \kappa \) agonists, but they can prevent bradykinin-induced hyperalgesia. Bradykinin induces the release of nociceptor sensitizing agents, including the pros-
tanos, from postganglionic sympathetic nerves, thus it is thought that \( \delta \) and \( \kappa \) receptors mediating peripheral analgesia are situated on the sympathetic nerves and prevent the release of noxious mediators [81]. These interesting observations prompted a study which resulted in the successful use of morphine injected intra-articularly for pain relief after arthroscopic knee surgery [77], and may mean the more extensive use of peripherally applied opioids [3]. Indeed reports on the benefits of intra-articular morphine are beginning to appear in the anaesthetic literature [44].

Although a significant proportion of the discussion above has concentrated on the possible roles of \( \delta \) and \( \kappa \) receptors in opioid-induced analgesia, it must be emphasized that the main analgesic component in the activity of presently available opioids is mediated via the \( \mu \) receptor.

**IN Volvement of Other Neurotransmitter Systems**

Pain pathways and their modulation involve many neurotransmitters in addition to the endogenous opioids. In the recent past, particular attention has been focused on the roles of the excitatory amino acids, noradrenaline and cholecystokinin, in pain pathways and in modulation of opioid analgesic activity (table II).

**Amino acids**

The excitatory amino acids, glutamate and aspartate, combine with at least five subtypes of receptor, known as N-methyl-D-aspartate (NMDA), \( \alpha \)-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) (previously quisqualate), kainate, L-2-amino-4-phosphonobutyrate (L-AP4) and metabotropic [87]. These receptors are named after selective agonists. The NMDA receptor has been characterized the best and is known to be part of a ligand-gated ion channel.

Both glutamate and NMDA produce analgesia when injected into the periaqueductal grey matter and this effect is not naloxone sensitive. However, the competitive NMDA antagonist, \((-\)\)-2-amino-7-phosphonoheptanoate (\((-\)\)-AP-7), antagonized the actions of both morphine and NMDA at this site [40]. It was concluded that morphine inhibited neurones containing NMDA receptors. Systemic administration of the non-competitive NMDA receptor channel complex antagonist, MK 801 (dizocilpine), also reduced morphine-induced analgesia [51]. In the nucleus raphae magnus, long lasting opioid-induced analgesia was not inhibited by NMDA antagonists, but was reduced by a selective quisqualate/kainate receptor antagonist, indicating the involvement of non-NMDA receptors at this site [72]. In contrast, NMDA receptors have also been implicated in increases in nociceptive responsiveness, that is amplification of noxious inputs. Prior administration of opioids prevents this hyper-responsiveness [14]. It would appear that the co-administration of opioids and NMDA antagonists may be useful or harmful, depending on the characteristics of the pain being treated! Inhibitory amino acids may also have a role in opioid analgesia as intrathecal midazolam potentiates morphine in doses which are without effect when injected alone [91]. In addition, there are clear links between opioid receptors and GABA\(_A\) disinhibition of interneurones [19].

**Monoamines**

Over the past few years, there has been increasing interest in the potential use in anaesthesia of drugs acting at alpha\(_2\) adrenoceptors [58]. Agonists at alpha\(_2\) receptors, such as dexmedetomidine, have both sedative and analgesic activity and reduce the dose requirements for i.v. and inhalation anaesthetics and opioid drugs. There is clear synergy between opioids and alpha\(_2\) agonist analgesia and in some experimental situations, dexmedetomidine-induced analgesic activity has been antagonized by naloxone [79]. It is unlikely that this is a result of direct stimulation of opioid receptors by dexmedetomidine, but it does suggest close links between the two systems, at least in the spinal cord. In the locus coeruleus, both \( \mu \) opioid receptors and alpha\(_2\) adrenoceptors regulate the same potassium conductance [46]. Using tail pinch as a method of studying analgesia, evidence has been presented that \( \kappa \) opioid agonists, but not morphine, activate noradrenergic and serotonergic pathways in mice [48]. However, as the authors point out, the method of testing for analgesic activity has a significant influence on the results obtained in this type of experiment.

Histamine, via its H\(_2\) receptor, has been suggested as a mediator of antinociceptive responses [35]. Direct administration of histamine H\(_2\) antagonists into the brain had no effect on baseline nociceptive scores, but inhibited the action of morphine. The maximum inhibition was 70 to 80\%, with larger doses causing less effect (i.e. a U-shaped dose-response relationship) [36]. These findings, which were found using two separate tests of antinociceptive activity, were interpreted as evidence for the involvement of histamine in the antinociceptive activity of morphine.

**Cholecystokinin**

The cholecystokinin (CCK) group of peptides are distributed widely in the brain and periphery. The 33 amino acid form, CCK-33, is secreted from endocrine cells whilst neuronal tissue utilizes the octapeptide CCK-8. The A type cholecystokinin receptor is found in greater concentrations in the periphery than the B type receptor. Rodents have relatively few CCK-A receptors in the brain, but this is not true of primates [38]. There are a number of
suggestions in the literature that cholecystokinin may act as an antagonist system to the endogenous opioids. This appears to be specific for the μ or κ opioid system as analgesia elicited by δ opioid receptors [86] or non-opioid mechanisms are not affected [30]. Acutely, cholecystokinin antagonists and antibodies enhance morphine-induced analgesia, but this effect is lost on chronic treatment [45]. CCK-B receptors are believed to mediate opioid interactions [17], although this may reflect the relative lack of CCK-A receptors in rodent brain. It has been suggested that endogenous opioid systems are engaged when danger is signalled, so that pain can be ignored and the chances of survival are increased. In contrast, safety signals could switch on cholecystokinin systems so that any wounds would be attended to promptly [88]. Using this reasoning, Wiertelak, Maier and Watkins [88] suggested that rapid tolerance to opioids may be expected when given in a familiar non-stressful environment. In contrast, the fear-provoking environment of hospitals may be expected to retard tolerance development.

The cholecystokinin story is complicated by earlier reports in the literature that CCK-8, in the absence of opioid activity, could produce analgesia when injected systemically and centrally [43].

In view of the above discussion, it is perhaps not surprising that the opioid antagonist naloxone should be attended to promptly [88]. Using this reasoning, Wiertelak, Maier and Watkins [88] suggested that endogenous opioid systems depending on the circumstances [8]. The nociceptive state depends on a balance between the activity of all opioid peptide systems interacting with its various receptors, as well as other neurotransmitters acting via opioid and non-opioid systems. As our understanding of the mechanisms of pain and analgesia increase, one may only be thankful that man found opium by serendipity and used it as an analgesic, surprising that the opioid antagonist naloxone should act as an antagonist system to the endogenous opioid system as analgesia elicited by 8 opioid agonist U50,488-sensitive k1 subtypes and a novel κ2 subtype. 

REFERENCES