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Perspective

Emerging Molecular Approaches to Pain Therapy

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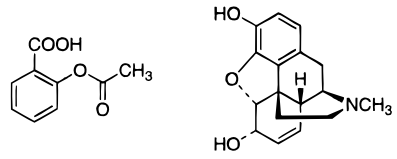
Introduction

The identification of compounds that can more effectively and safely treat both acute and chronic pain states and, additionally, show a reduced tendency to elicit the side effects associated with the use of morphine and its congeners remains a major unmet challenge in biomedical research. The recent identification of the cyclooxygenase 2 (COX-2) inhibitors,[1,2] a novel class of compounds that has the antiinflammatory, analgesic, and antipyretic actions of the traditional nonsteroidal, antiinflammatory drugs (NSAIDs) such as aspirin (**1**) but lacks their limiting gastrointestinal side effects, will probably result in safer compounds for chronic use. However, the current COX-2 inhibitors appear unlikely to result in agents that will have any greater therapeutic efficacy than the NSAIDs.[3]

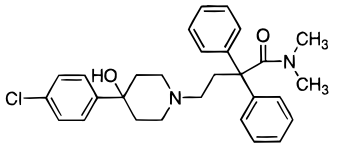
The discovery of the opioid receptor family and the endogenous opioids, the enkephalins and endorphins, in the early 1970s[4] heralded the beginning of the molecular era of pain research. This was a major conceptual advance in identifying the receptors involved in mediating both the analgesic actions of the opioids and their side effects, e.g., addiction, gastric stasis, and respiratory depression. A premise implicit from this seminal research was that it would be relatively straightforward, using the then newly developed techniques of radioligand binding together with traditional medicinal chemistry approaches and molecular modeling, to develop novel ligands that selectively target opioid receptor subtypes. The resultant ligands would be anticipated to be novel analgesics that have the analgesic efficacy of morphine but lack its side effect liabilities.

Despite an intensive research effort over the past two decades involving many innovative approaches in the global academic community and by the pharmaceutical industry, the latter representing an aggregate investment in excess of $2.5 billion, the only new opioid-based pain medications either in clinical development or on the market are alternative dosage forms of the classical opioids, morphine (**2**), loperamide (ADL-2-1294, **3**), and fentanyl (**4**), or compounds such as tramadol (**5**).[5]

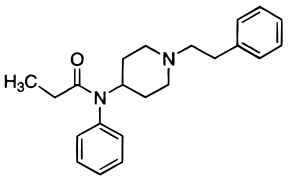


1 (Aspirin)

2 (Morphine)



3 (Loperamide)



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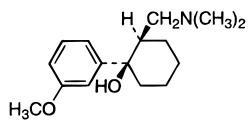

5 (Tramadol)

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Continuing research advances in the understanding of the pharmacology of pain and analgesia that have resulted from the application of molecular biology techniques and the development of selective ligands for the various receptor classes involved in nociceptive transmission have established that pain is an extremely complex and dynamic process involving multiple, interrelated neurotransmitter/neuromodulator systems in the spinal cord, in ascending and descending spinal pathways, and at supraspinal sites. As Dray et al. have noted[6] "not all pain states are created equal".

In this Perspective, the incidence of pain, its types, and its mechanisms are reviewed in the context of the advances in understanding that have occurred in the past 20 years. This is followed by an overview of (i) the current trends in NSAID, opioid, and adjuvant analgesic research and (ii) newly identified molecular targets that are sites at which novel ligands may have analgesic potential and thus represent prototypes that will lead to novel, non-opioid, non-NSAID approaches to pain management early in the first decade of the 21st century.

Pain Prevalence

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage".[7] It is primarily a protective mechanism designed to avoid tissue damage, is very subjective in nature with wide interpatient variability in pain sensitivity,[8] and has been described as "a conscious experience to which the outside observer is not privy". Pain is the most common complaint for which patients seek physician treatment, and it has been estimated that nearly half a billion cases of pain are diagnosed each year and that over 50% of individuals seeking treatment are unsatisfied with their present treatment options[9,10] that involve the use of three main drug classes, the NSAIDs, opioids, and analgesic adjuvants.

Despite the widespread prevalence of pain, it is inadequately managed due to a lack of appropriate formal physician training[11,12] that is coupled with concerns regarding the addictive liabilities of the opioids, a global phenomenon described as "opiophobia".[13] On the other hand, patients may tolerate pain to an extent that can limit effective treatment and result in long-term nerve damage that is frequently irreversible. Self-medication of pain using over the counter (OTC) drugs like aspirin is also extremely common. A recent demographic study[14] of over 13 000 nursing home patients with cancer found that 25−40% of these patients experienced pain on a daily basis. Of these, 25% received no analgesic treatment, 16% received OTC analgesics, 32% received weak opioids, and 26% received morphine or related opioids. Pain was most often untreated in those over 85 years of age, in minorities, in patients with impaired cognitive function, or in those receiving concurrent medications. The authors noted that due to cognitive and sensory impairment, as well as depression, pain was underreported in the elderly. Similarly, in the broader population there is frequently a fatalistic attitude that pain is inevitable despite the potential for it to lead to suppression of the immune system, increased metabolic stress responses, impaired pulmonary and gastrointestinal effects, and the development of chronic pain states. Pain is associated with fear, anxiety, sleep deprivation, depression, suicidal ideation, and an inability to effectively perform daily activities. Pain can also be present as a symptom of psychological stress.[15] In both its acute and chronic forms, pain has a major impact on many quality-of-life measures. Cleeland has noted[12] that "The best pain management requires an informed patient who is willing to report pain and to voice complaints if pain is not controlled....Patients who expect pain relief and know how to request it....are more likely to have better pain control."

In concert with these changes at the patient level, a paradigm shift has occurred in the past decade in understanding the physiology and pathophysiology of nociception.[8,16−20] The various peripheral and central pathways involved in nociception are no longer considered as "hard wired" entities but rather are viewed as being dynamic in nature, undergoing complex and irreversible phenotypic changes in response to tissue trauma and prolonged episodes of pain. Thus, in addition to being symptomatic of the underlying cause, pain is considered a condition in its own right and furthermore, is no longer viewed as a phenomenon analogous to that of turning on and off a flow of water using analgesic agents as the faucet, but rather as a complex and sophisticated set of hierarchical molecular responses that, if inadequately controlled, lead to serious consequences.

With this evolving knowledge of nociceptive physiology, there is a growing trend to use analgesics not only to treat pain once it has occurred but also to prevent it. One example of this is pre-emptive analgesia. Patients undergoing elective surgery receive analgesics and/or anesthetics before the operation to aid in attenuating the pain that occurs as a result of the surgery.[21] Administration of an analgesic before surgery results in effective plasma levels of the drug that lessen the impact of the nerve cell barrage associated with the surgical procedure and results in a reduced level of postoperative pain. Some of the newer mechanistic approaches to analgesia such as the use of purines[20] and α-adrenoceptor agonists[23] can also reduce the need for volatile anesthetics thus providing a better control of the state of consciousness and cardiovascular parameters during surgery with a resultant speedier recovery.

Some 10−15 neurotransmitters/neuromodulators have now been identified as being involved to varying degrees in the various aspects of nociceptive pathway activity in both the spinal cord and in the ascending and descending central nervous system (CNS) pain-processing pathways. These have the potential to provide multiple opportunities for the development of novel analgesics distinct from the traditional NSAIDs and opioids.

Pain Types and Mechanisms

Physiological or nociceptive pain is a normal response to a brief noxious stimulus that elicits negligible tissue injury and for which medical attention is normally not required.[14,24] This type of pain serves as a warning to protect the individual from potential injury and can be illustrated by the "ouch" type of response that is caused by briefly touching a hot surface or by a pin prick, resulting in the activation of C- and Aδ-fibers in primary

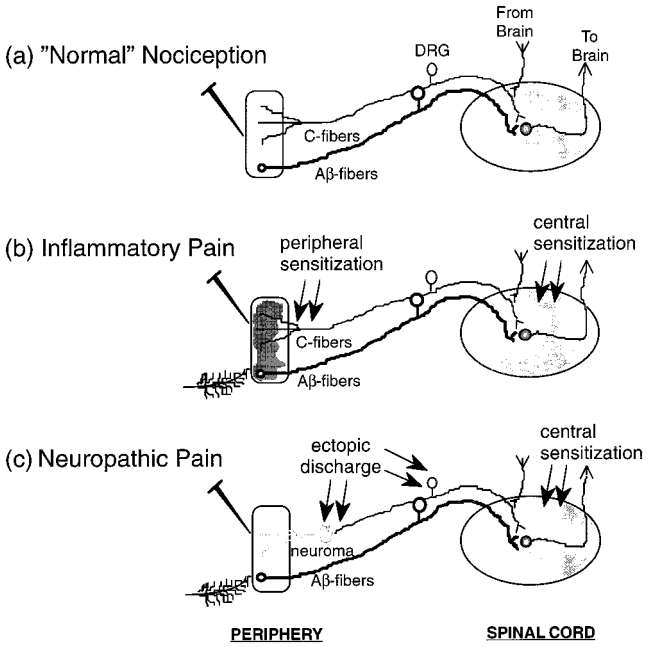


Figure 1. (a) Sensory processing in the "normal" or physiological state when noninjurious stimuli are applied to healthy tissue. A low-intensity stimulus, e.g., touch, activates low-threshold (Aβ) afferents and produces an innocuous sensation. A high-intensity noxious stimulus, like heat, activates high-threshold (C and Aδ) afferents to produce pain (after ref 16). (b) Sensory processing following peripheral tissue injury or inflammation is characterized by an abnormal response to noxious and non-noxious stimuli. Peripheral sensitization results in low-intensity stimuli, like touch, gaining the capacity to activate sensitized high-threshold (C and Aδ) afferents, producing exaggerated pain at the site of injury (primary hyperalgesia). Central sensitization of the dorsal horn of the spinal cord results in low-threshold (Aβ) afferents, gaining the capacity to evoke pain (allodynia). It also results in exaggerated responses of high-threshold (C and Aδ) afferents to normally mildly painful high-intensity stimuli and to an expansion of their receptive fields so that pain is felt beyond the immediate site of injury (secondary hyperalgesia) (after ref 16). (c) Sensory processing following peripheral nerve injury is characterized by an abnormal response to noxious and non-noxious stimuli. Central sensitization (of the dorsal horn of the spinal cord) results in low-threshold (Aβ) afferents, gaining the capacity to evoke pain in response to normally non-noxious stimuli (allodynia), while high-threshold (C and Aδ) afferents respond in an exaggerated manner to normally mildly painful high-intensity stimuli (hyperalgesia) (after ref 16).

afferent nociceptive pathways (Figure 1a). Input from these pathways is then integrated in the dorsal horn of the spinal cord and relayed to the brain. Descending pathways from the CNS can modulate the afferent nociceptive input at the level of the dorsal horn acting via monoaminergic, primarily norepinephrine (NE), mechanisms involving α2-adrenoceptor activation, although serotonin (5HT) systems may also be involved via a tonic descending inhibitory pathway originating in the raphe nucleus. The utility of compounds acting solely via serotoninergic mechanisms as antinociceptive agents is, however, unclear.[25] Aβ-Fibers carry low-intensity stimuli, e.g., touch, that are not perceived as painful in the absence of tissue injury.

In developing novel approaches to analgesia, it is imperative that normal tactile responses are not compromised as this would negate the normal protective responses that are essential to survival. For this reason, local anesthetics are not useful analgesics due to their intrinsic membrane-stabilizing properties that block normal proprioceptive responses.

The clinical diagnosis of pain is often imprecise, reflecting (i) the pain state per se, which varies from individual to individual in terms of intrinsic pain threshold and also shows a demonstrated gender bias,[26,27] (ii) the disease state associated with the pain, and (iii) a learned emotional component.[7,15] Qualitatively, pain is definable in terms of its severity (mild, moderate, and severe), temporality (acute and chronic), and etiology. The latter reflects the association of the algesic (pain) state with acute injury, acute postoperative situations, cancer, musculoskeletal trauma, osteoarthritis (OA), rheumatoid arthritis (RA), etc.

Mechanistically, pain can be delineated in terms of *hyperalgesia*, an exaggerated response to a normally mildly painful stimulus, spontaneous pain that occurs in the absence of external stimuli, and *allodynia*, pain that occurs in response to a normally non-noxious stimulus.[16]

Inflammatory pain[28] (Figure 1b) involves various painful responses resulting from peripheral tissue injury and/or inflammation produced by trauma, infection, surgery, burns, or diseases with an inflammatory component, e.g., arthritis. Inflammatory pain involves the release of a number of pro-algesic mediators at the site of tissue injury that include 5HT, ATP, various monoamines, cytokines, kinins, chemokines, prostaglandins, and growth factors. These mediators activate and sensitize local nociceptive mechanisms via a variety of intracellular signal transduction mechanisms. For example, prostaglandin E_2 (PGE_2) can activate an EP prostanoid receptor, in turn activating protein kinase A (PKA) to phosphorylate a tetrodotoxin (TTX)-resistant sodium channel (TTXr-Na^+, SNS (sensory neuron-specific), PN3) that is uniquely expressed in primary afferent nociceptors.[29] Inflammatory responses also alter the local tissue pH leading to changes in nociceptor function, especially that of a recently cloned dorsal root ganglion (DRG) neuron-specific proton-gated Na^+ channel that is a member of the acid-sensing ion channel family and has been designated dorsal root acid-sensing (DRASIC).[30] Vanilloid[31] and P2X[32] receptor-mediated responses are also pH-sensitive. The resultant increase in peripheral nerve terminal excitability increases spontaneous activity and leads to an exaggerated response to mild noxious stimuli. The resulting *peripheral sensitization* accounts for primary hyperalgesia, the increased pain and tenderness at the injury site (Figure 1b). The consequent increase in C-fiber impulse flow from the sensitized nociceptors leads to spinal cord hyperexcitability and *central sensitization* (Figure 1b). As a result, activation of low-threshold Aβ-fiber touch afferents elicits pain, contributing to a state of allodynia. In addition, the receptive fields of spinal dorsal horn neurons are expanded, so that pain is felt beyond the immediate site of tissue injury, a phenomenon known as *secondary hyperalgesia* or *referred pain*. Transient noxious stimuli may also undergo temporal alterations to evoke a prolonged painful sensation.

Neuropathic pain (Figure 1c) is elicited by injury to the peripheral or central nervous system, due, for example, to tissue trauma, infection, autoimmune dis-

eases such as diabetes and arthritis, and various drug regimens. Following injury, the damaged nerve begins to discharge at atypical (ectopic) locations, including neuromas and demyelinated nerve zones at the site of injury and the associated DRG (Figure 1c). These ectopic discharges result in spontaneous burning pain in the immediate area, while the increased barrage of impulses reaching the spinal cord leads to hyperexcitability and central sensitization of dorsal horn neurons, resulting in hyperalgesia and allodynia.

Peripheral and central sensitization processes are now known to be the result of a neurochemical and phenotypic reorganization of the peripheral nerves and spinal cord. Depending on the pain state,[8] glutamate acting via *N*-methyl-D-aspartate (NMDA) receptors, ATP, the peptide neuromodulators substance P, calcitonin gene-related peptide (CGRP), and neuropeptide Y (NPY), and the trophic factor nerve growth factor (NGF) plays key roles in the molecular events leading to sensitization. The events implicated in central sensitization include an NK-1-mediated activation of PKC that phosphorylates the NMDA receptor, partially removing the Mg^{2+} block that normally stabilizes ion flow through the receptor and increasing the gain of the cell at the resting potential when the NMDA receptor is normally quiescent. Following phosphorylation, NK-1 receptor blockade cannot reverse NMDA receptor−mediated sensitization. Furthermore, BDNF activates a *src* tyrosine kinase on the NMDA receptor that increases open channel time, synergizing with the effects of NK-1. Following chronic pain, Aβ-fiber touch primary sensory afferents can acquire the phenotype of C-fibers by producing substance P.[33]

The changes leading to sensitization occur within hours so that even with acute pain, many temporal alterations in neuronal plasticity occur. As pain persists, glutamate-evoked excitotoxicity can lead to cell loss and atypical rearrangements and reinnervation of afferent pathways in the dorsal horn, changes in neuronal neurotransmitter phenotypes[33] resulting in a loss of inhibitory mechanisms, reinforcing the multifaceted cascade leading to chronic pain. Repetitive stimulation of nociceptive C-fibers at constant intensity induces a progressive enhancement leading to a sudden increase, up to 10-fold, in dorsal horn nociceptive responses. This phenomenon, which is frequency dependent, is known as *wind-up*[34,35] and is a critical event in the development of central hypersensitivity in response to noxious stimuli. Wind-up in animals and in humans can be blocked by NMDA receptor antagonists.[35]

Different types of pain can coexist. For instance, a cancer patient can experience pain from tumor encroachment, inflammatory pain due to tissue damage, and neuropathic pain resulting from radiation or chemotherapy−induced neuropathies.

Pain Categories

Acute Pain. Mild to moderately severe pain represents the largest segment of the acute pain area and is managed by the NSAIDs and acetaminophen. However, as already noted, the side effects associated with the NSAIDs account for over 20% of all adverse drug reactions related to GI, renal, and liver toxicity, and these are accentuated by long-term use. The availability of the selective COX-2 inhibitors[1,2] is anticipated to improve treatment modalities in the mild to moderate arena.

For the treatment of moderate to severe acute pain in the young and elderly populations, there is considerable unmet medical need despite the effectiveness of the opioids. Opioid addiction is an issue in the young, while in the elderly, opioids produce cognitive impairment and constipation.

Chronic Pain. Chronic pain is pain of greater than 6 months duration and associated, for example, with cancer, OA and other arthropathies, AIDS, peripheral nerve disorders, and diabetes.

Cancer Pain. Cancer pain can be acute or chronic in nature depending on the disease stage. The pain source can be the tumor itself, tumor metastases, chemotherapy, radiotherapy, and/or cytotoxic/cytostatic pharmacological approaches to disease therapy and neural ablation following surgical intervention. While tumor-related pain is often associated with late-stage cancer, early stage pain is seen in up to 50% of patients diagnosed with breast, ovarian, prostate, and colon cancer. In the next decade, the total cancer population is projected to grow to greater than 5 million, half of whom will require treatment for moderate to severe pain. Cancer pain is widely under-recognized and under or inappropriately treated.[13,14]

Arthropathy Pain. OA and other arthropathies occur in approximately 20% of the U.S. population. OA and RA account for the majority of arthropathies. By 2008, it has been estimated that over 50 million individuals globally will suffer from OA and RA. Another 15 million individuals are affected by other arthropathies including gout, infectious and psoriatic arthritis, and systemic lupus erythematosus (SLE). First-line therapy for OA includes acetaminophen, NSAIDs, and corticosteroids, pain rather than inflammation being the primary target for palliative treatment. RA is treated with NSAIDs, corticosteroids, and a group of disease-modifying antirheumatic drugs/immunomodulatory drugs (DMARDs) that include sulfasalazine, methotrexate, penicilliamine, various gold salts, and hydroxychloroquine.[36] DMARDs may require weeks to months to provide therapeutic benefit, if it is ever achieved, and have frequent and significant side effects.

AIDS Pain. Pain occurs in 30−80% of AIDS patients with the prevalence increasing with disease progression and is comparable in intensity to the pain associated with cancer.[37] AIDS-related pain may be due directly to the consequences of the viral infection, e.g., HIV-induced neuropathy or myleopathy, Kaposi's sarcoma, organomegaly, secondary infections, etc., or drug therapy.[38] Somatic and visceral pain is the most commonly observed in AIDS, but neuropathic pain also occurs. There are major concerns related to the undertreatment of AIDS-associated pain states, and a more aggressive approach, including the application of cancer pain guidelines, has been advocated.[11]

Visceral Pain. Visceral pain[39,40] including chronic abdominal pain and/or discomfort are the most common symptoms associated with gastrointestinal disease. For the majority of visceral stimuli, there is no conscious perception of physiological events such as distention or

contraction except for behaviorally relevant situations such as satiety, nausea, and the need to defecate. However, processes that lead to peripheral and central sensitization of visceral nociceptive processes can evoke visceral pain. Organic inflammatory conditions such as gastroesophageal reflux, peptic ulcer, infectious gastritis, inflammatory bowel disorder, and colon cancer, or functional bowel disorders such as irritable bowel syndrome (IBS), can lead to sensitization without the detection of organic disease.[39] Pharmacological approaches to these mechanisms are only recently being addressed in controlled clinical studies.[40]

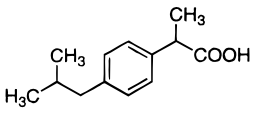
Neuropathic Pain. This pain results from the nerve injury associated with trauma, surgery, limb crush or amputation, radiation damage, drug regimens (e.g., chemotherapeutic or anti-HIV agents, e.g., ddI, vincristine, or cisplatin), and diseases such as herpes zoster, AIDS, multiple sclerosis, arthritis, and diabetes. Postherpetic neuralgia (PHN) and diabetic neuropathic pain are two of the most common neuropathic pain syndromes. Others are carpal tunnel syndrome, trigeminal neuralgia, and rotator cuff bursitis. The pain sensation in these disorders is characterized as 'burning', 'stabbing', 'shooting', 'electric-like', or 'throbbing'. It has been anticipated that the prevalence of all types of neuropathic pain will exceed 75 million worldwide in the next decade.

Diabetic Neuropathy. Two types of neuropathy are associated with diabetes: (1) diffuse symmetric neuropathies that include the hyperglycemic neuropathy that occurs in newly diagnosed type I diabetics or in diabetic patients with poor metabolic control and insulin neuritis and are readily reversible with the establishment of normoglycemia and (2) focal/multifocal neuropathies that occur in older diabetic patients that have maintained normoglycemia. Diabetic neuropathy is manifested as pain or abnormal sensation in the lower extremities.[41] Painful feet and/or legs occurs in 12% of insulin-dependent (type I) diabetics and 32% of non-insulin-dependent (NIDDM, type II) diabetics. The worldwide prevalence of diabetic neuropathy in the next decade is anticipated to approach 12 million.

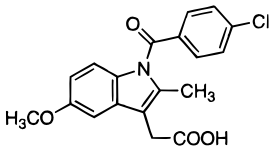
In neuropathic pain there are no uniform guidelines for the treatment of the different types of neuropathic pain, and there is also a lack of controlled clinical trials demonstrating efficacy. Thus many of the studies used to support efficacy are open label and lack an active and, sometimes, a placebo control. Treatment of neuropathic pain is also confounded by the already mentioned deficit in clinician education, especially at the primary care, general practitioner level that limits the delivery of existing albeit less than ideal therapies.

Current Analgesic Therapy

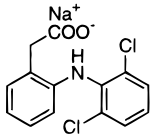
Three major groups of drugs are currently used for the treatment of pain: NSAIDs, which include the COX inhibitors, aspirin, ibuprofen (**6**), indomethacin (**7**), diclofenac (**8**), and ketorolac (**9**), and acetaminophen (**10**), the mechanism of which is unknown; the classical opioids, which include morphine and its congeners; and the analgesic adjuvants, a class of compounds that include antidepressants and local anesthetics that are used empirically to treat chronic pain states that have not responded to other treatments.



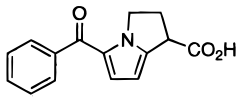
6 (Ibuprofen)



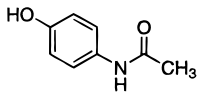
7 (Indomethacin)



8 (Diclofenac Sodium)



9 (Ketorolac)



10 (Acetaminophen)

NSAIDs. NSAIDs are used in the treatment of mild to moderate pain and as an adjunct to opioids in the management of moderate to severe pain.[20] NSAIDs act by inhibiting the prostaglandin biosynthetic enzyme cyclooxygenase that is also known as COX or PGHS (prostaglandin H_2 synthase) and is involved in the conversion of arachidonic acid to prostaglandins F, D, and E, prostacylin, and thromboxane.[2] The liberation of these arachidonic acid pathway products following local tissue injury contributes to peripheral sensitization and hyperalgesia. NSAIDs block prostaglandin production and thus attenuate the peripheral sensitization process. The classical NSAIDs are very effective COX inhibitors, with analgesic, antiinflammatory, and antipyretic activity, and are routinely used to relieve the pain associated with headache, tooth extraction, musculoskeletal trauma, RA, and OA. Their use has also been expanded to cancer pain, postoperative pain, and other indications.

NSAIDs have a ceiling effect in terms of their analgesic efficacy such that complete pain relief cannot be achieved even with dose escalation. This is a result of their mechanism of action that only addresses inhibition of the production of the products of the arachidonic acid pathway and thus limits their utility to treat severe pain. NSAIDs thus do not block the activation of C-fibers and have no direct effect on acute nociceptive pain. However, aspirin may have properties in addition to its effects of COX inhibition that involve inhibition of neutrophil activation via actions on the cell surface adhesion molecules (CD11b/CD18) and may be responsible for some aspects of the analgesic and antipyretic actions of NSAIDs.[36] In addition, COX inhibitors can inhibit the activity of the intracellular signaling molecule NFκB.[42]

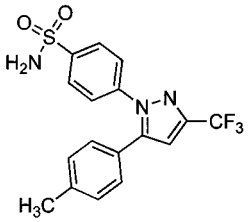
The side effects associated with the classical NSAIDs include gastrointestinal bleeding, ulceration, and perforation, inhibition of platelet aggregation, nephrotoxicity, and, in 10% of those experiencing such side effects, death.[2] These side effects limit their use, and NSAIDs such as ketorolac have labeling for limited duration of use. The identification of two COX isoforms, a consti-

tuitively active enzyme (COX-1) that is involved in the production of those prostaglandins required for normal cellular function and an inducible (COX-2) isoform that mediates the inflammatory effects of prostaglandins,[1,2] suggests that these side effects may be surmountable.

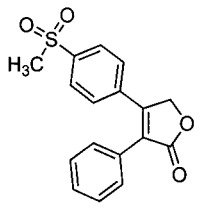
The two COX isoforms show 60% amino acid sequence homology and have almost identical catalytic properties.[43] COX-2 is induced by proinflammatory mediators including IL-1 and TNFα, endothelin,[44] synaptic transmission,[45,46] and injury.[47] Transient focal ischemia and repetitive spreading depression in rat brain induce COX-2 but not COX-1 mRNA and protein levels in cortical layers 2 and 3.[48] COX-2 induction was blocked by the noncompetitive NMDA antagonist MK-801 and by dexamethasone and quinacrine, compounds that inhibit phospholipase A_2 indicating a role for NMDA receptor activation acting via PLA_2. Interestingly, indomethacin, diclofenac, and the NO synthesis (NOS) inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) enhanced COX-2 mRNA expression. In contrast, the antiinflammatory cytokines (IL-4, IL-10, and IL-13) and corticosteroids blocked COX-2 induction. COX-2 inhibitors may thus have potential utility in the treatment of brain ischemia.

An inverse relationship has been reported between aspirin use and cancer risk.[49] Elevated COX-2 levels are found in colorectal cancer,[50] and it has been shown that COX-2 inhibition markedly reduces colorectal polyps in a transgenic mouse model of familial adenomatous polyposis (FAP).[51,52] Human breast tumors also express higher than usual levels of COX-2.[53]

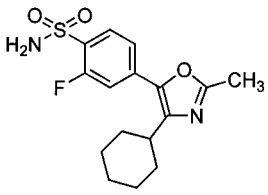
Considerable effort has been focused on developing potent and selective COX-2 inhibitors that would have the analgesic efficacy of traditional NSAIDs without their side effect liabilities and has resulted in the selective and reversible COX-2 inhibitors celecoxib (**11**), MK-966 (**12**), and JTE-522 (**13**). These compounds vary



11 (Celecoxib)



12 (MK-966)

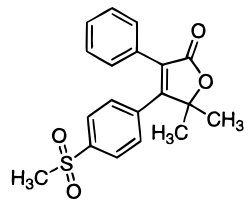


13 (JTE-522)

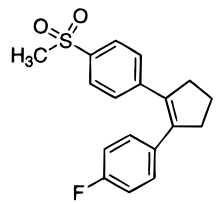
in their COX-2 versus COX-1 selectivity from 375-fold (celecoxib) to greater than 8000-fold (MK-966). It is currently unknown what degree of selectivity is required in a COX-2 inhibitor to differentiate it from a nonselective NSAID in terms of side effect liability and efficacy. MK-966 (50 mg) has equivalent efficacy to 400 mg of ibuprofen in treating the pain associated with third molar extraction[3] Unlike traditional NSAIDs, neither celecoxib nor MK-966 have effects on platelet aggregation and at analgesic doses are no different from placebo in producing GI irritation in short-term trials.[3]

While it was anticipated that the diminished side effects seen with COX-2 inhibitors would provide an opportunity for increased efficacy, this has not been seen in clinical trials to date.[3] COX-2 is also expressed constituitively in the CNS, but the consequences of its inhibition remain to be determined. In the kidney where COX-2 is also expressed constituitively, renal limitations have been described for MK-966.[3] There is also evidence for a role of COX-2 in the febrile response, in nerve transmission, and in central mechanisms of hyperalgesia.[2]

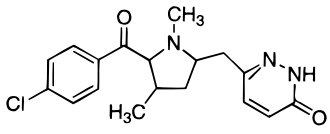
L-783003 (**14**), SC 57666 (**15**), and RS-57067 (**16**) are other selective COX-2 inhibitors. Celecoxib has been approved for marketing in the United States although the labeling regarding GI liabilities is similar to that of nonselective NSAIDs. Additional trials are ongoing to demonstrate the efficacy of celecoxib in the treatment of colorectal cancer and Alzheimer's disease (AD), the latter based on the inverse correlation between NSAID use and the incidence of AD[54−56] and the demonstrated efficacy of indomethacin in attenuating disease progression.[55] A series of selective COX-2 acetylating agents that include APHS (**17**) are irreversible in their effects and may potentially be more effective than reversible/competitive COX-2 inhibitors.[57]



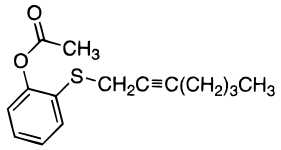
14 (L-783003)



15 (SC 57666)



16 (RS 57067)



17 (APHS)

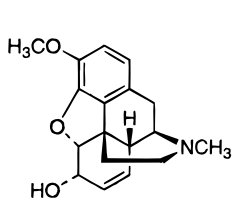
Acetaminophen has analgesic and antipyretic activities but lacks antiinflammatory activity. Its mechanism of action is unknown but appears to involve CNS actions.[58] The compound lacks GI toxicity and does not affect platelet function, but it is hepatotoxic and is a leading cause of the fatal liver damage that follows deliberate overdose.

Opioids. Opioids such as morphine and codeine (**18**) are used as monotherapy in the treatment of moderate to severe pain and are often added when pain is inadequately controlled by NSAIDs. Opioids produce their effects by activating receptors in the brain and

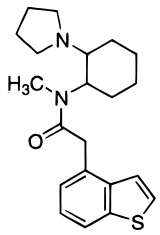
spinal cord. The opioid receptor family is a G-protein-coupled receptor (GPCR) superfamily, characterized by a heptahelical structural motif. Opioid receptors were designated as μ, δ, and κ subtypes[59] based on the synthetic ligands originally used to classify them but have been controversially renamed OP3, OP1, and OP2 by the IUPHAR Nomenclature Committee based on pharmacological criteria.[60] An 'orphan' member of the opioid receptor family, ORL1 has also been identified[61] that is structurally similar to other members of the opioid family but is relatively insensitive to opioid agonists. The heptadecapeptide nociceptin is an endogenous ligand for the ORL1 receptor and produces hyperalgesia, prevents opioid analgesia, and produces analgesia or has no effect in rodent hot plate models.[62] This peptide impairs spatial learning and has been implicated in anxiogenic responses. It does not interact potently with μ, δ, and κ receptors.

Opioid receptors are present on C-fiber terminals in the dorsal horn of the spinal cord, on descending inhibitory pathways projecting from the brain to the spinal cord, in brain regions involved in nociceptive processing,[59] and on cells of the immune system,[63,64] the latter providing a rationale for the well-established immunosuppressant role of opioids.[65] Tissue injury results in the release of a variety of inflammatory mediators that result in inflammation, recruitment of cytokine-producing immune cells and facilitation of nociceptive responses.[66] More recently, however, it has been shown[67] that immunocytes capable of producing the opioid β-endorphin can be recruited to sites of inflammation via a selectin-dependent extravasation mechanism. β-Endorphin release in inflamed tissues is stimulated by corticotrophin-releasing factor (CRF)[68] and produces local analgesia by interacting with opioid receptors present on sensory nerves. The beneficial analgesic effect of immune cell recruitment contrasts with the exacerbation of the immune response generally associated with the presence of immune cells at the sites of tissue trauma and suggests that compounds limiting the inflammatory response may also have the potential to promote nociception. Similarly, the κ-opioid agonist PD-117302 (**19**) can inhibit the adjuvant arthritis-induced upregulation of the intracellular adhesion molecule ICAM-1,[69] indicating that κ agonists can inhibit the effect of inflammatory cytokines. Peripheral modulation of the immune response has been termed "autocoid local inflammatory antagonism" (ALIA)[70,71] and also involves the release of endogenous agonists for the cannabinoid CB2 receptor, the palmitoylethanolamides, from mast cells.[71]

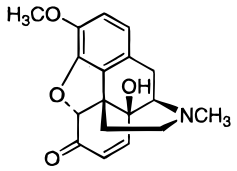
Among the side effects associated with the clinical use of opioids are constipation due to inhibition of gut motility, a significant side effect that is often underestimated and, in many instances, leads the patient to choose pain over the GI side effects of opioids; respiratory depression due to activation of opioid receptors in the respiratory centers of the brain stem; addiction; and tolerance. The social and legal issues related to use, diversion, and regulatory constraints contribute to an underutilization of opioids, particularly for the management of chronic nonmalignant pain.[12,72] However, some physicians are willing to accept what they consider a minor risk in order to achieve a level of pain control



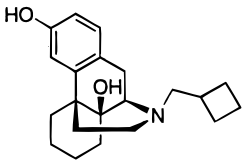
18 (Codeine)



19 (PD 117302)



20 (Oxycodone)



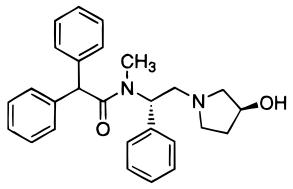
21 (Butorphanol)

that is not achievable by other means. In 25 000 cancer patients taking narcotics, only 7 became addicted,[10] a fact attributed to alternative dosage forms of morphine that avoided the "rush" that leads to addiction. It has also been noted that patients in severe pain do not experience the "high" associated with opioid use in normal subjects.

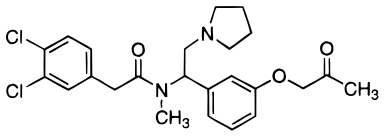
The majority of opioids are available in both oral and parenteral fomulations and can also be administered rectally, intrathecally, epidurally, and by subcutaneous infusion using a self-controlled pump.[73] Advances in opioid therapy have, however, been limited primarily to new dosage forms or combinations to reduce side effects and/or maintain more consistent plasma levels, avoiding the peaks and troughs associated with oral medications or, using pumps, providing pain medication on an as-needed basis. Controlled-release morphine and oxycodone (**20**), transdermal and oral transmucosal fentanyl, and intranasal butorphanol (**21**) represent examples of this approach. Tramadol was introduced in the United States in 1996 after 15 years of use in Europe. It is a weak (2 μM) μ opioid receptor agonist with monamine (NE, 5HT) uptake-blocking activity in the 0.8−1 μM range.[5] The compound has a broad indication for moderate to moderately severe pain. Unlike the majority of opioids, it is not scheduled, a factor that has contributed to its rapid acceptance into clinical use. Tramadol can, however, reinitiate physical dependence in previously opioid-dependent patients.

Despite the major effort undertaken over the past 20 years, the identification of receptor subtype-selective opioid receptor ligands free of the dependence, tolerance, respiratory depression, and constipation associated with the traditional opioids such as morphine has been far from successful. Nonetheless, efforts are continuing to identify such compounds. ADL-2-1294 (**3**) is a topically active formulation of the μ receptor agonist loperamide targeted for use in burns and abrasions; EMD 61753 (asimadiline, **22**)[74] and ICI-204449 (**23**) are peripherally active κ receptor agonists. EMD 61753 has potential utility in treating RA.[75] RP 60180 (apadoline, **24**), SB-205588 (**25**), SNC-80 (**26**), DuP 747 (**27**), and dynorphin A (**28**) are other opioid ligands in development. BW373-

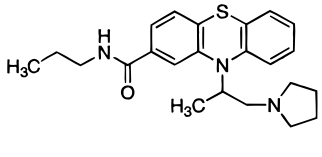
U86 (**29**), is a novel δ-opioid receptor agonist. TRK-820 (**30**) is a κ agonist with μ antagonist activity, and SB-235863 (**31**) is a novel pyrrolomorphinan that is a potent (K_i = 4.8 nM) and selective δ opioid receptor agonist.[76] While this compound was 3-fold weaker than morphine as an antihyperalgesic agent and was inactive in the tail-flick test, SB-235863 did not cause tolerance or withdrawal, motor impairment, GI motility, or respiratory depression as compared to morphine.



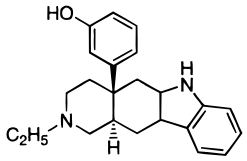
22 (Asimadiline)



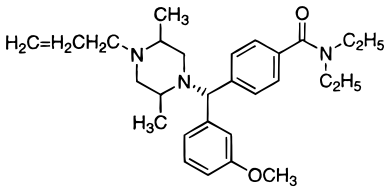
23 (ICI-204448)



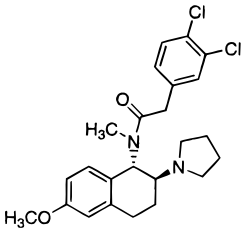
24 (RP 60180)



25 (SB-205588)



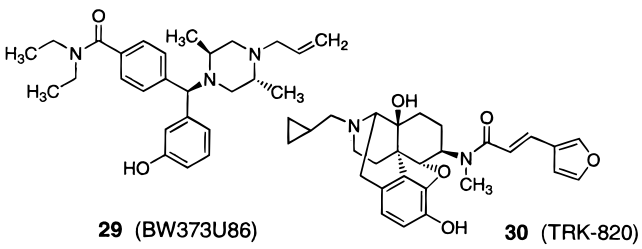
26 (SNC-80)



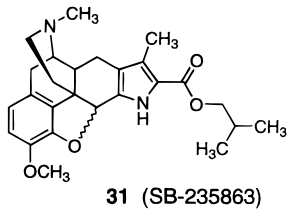
27 (DuP 747)

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Glr

28 (Dynorphin A)



29 (BW373U86) **30** (TRK-820)

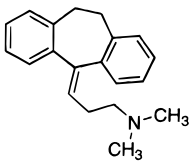


31 (SB-235863)

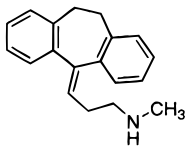
Transplants of opioid-producing cells, e.g., CereCRIB, have shown some promise in clinical situations of intractable neuropathic pain. The utility of this approach in terms of its safety and cost-effectiveness in a managed health care environment remains to be proven.

Analgesic Adjuvants. Analgesic adjuvants include a number of compounds that have primary therapeutic indications other than pain control but which have been found in some instances, in the clinical setting, to be effective in pain control, especially that involving neuropathic pain.[77] Since pain has both physical and psychological components,[15] it is possible that some types of pain that are treated with antidepressants have their etiology in the "affective motivational" component of depression.[78]

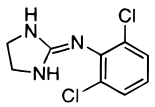
Tricyclic antidepressants (TCAs) like amitryptiline (**32**) and nortryptiline (**33**) are often used when NSAID and opioid therapy have failed to provide pain relief and as first-line treatment for patients experiencing continuous, burning-type pain. Side effects associated with TCA therapy include orthostatic hypotension, sedation, dry mouth, constipation, urinary retention, glaucoma, and cognitive impairment. As a result, therapy is initiated at low doses and titrated over several weeks to an effective dose, often delaying the achievement of adequate pain relief. With the time taken to evaluate NSAIDs and opioids, patients who finally achieve pain relief using TCAs can go from 5 to 9 months or longer before adequate treatment is received. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine are generally considered ineffective as analgesic adjuvants. Another SSRI, sertraline, has modest effects on pain threshold that are confounded by placebo responses.[79] These findings would indicate that the classical TCAs produce their analgesic actions by facilitating descending inhibitory monoaminergic pathways in the dorsal horn of the spinal cord, specifically NE as opposed to 5HT pathways.[25] Given systemically, the α2-adrenoceptor agonist, clonidine (**34**), can modulate neuropathic pain.[80]



32 (Amitryptiline)



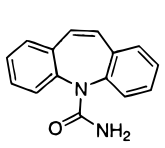
33 (Nortryptiline)



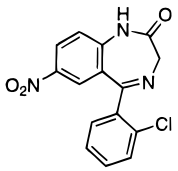
34 (Clonidine)

The anticonvulsants, carbamazepine (**35**), clonazepam (**36**), phenytoin (**37**), and gabapentin (**38**), are used as initial approaches to the treatment of sharp, shooting, "electric-like" (lancinating) neuropathic pain like that of trigeminal neuralgia.[81] The mechanistic basis for their effects is unknown but may involve ion channel modulation, reducing the neuronal excitability that occurs in neuropathic pain states when both Aβ- and C-fibers undergo spontaneous discharge. These characteristics have led to neuropathic pain being likened to an "epilepsy of the spinal cord". Gabapentin is increasingly used for the treatment of neuropathic pain by a ratio of 2:1 over its use as an antiepileptic agent due its extremely benign side effect profile.[81] The compound, a structural analogue of GABA, was initially thought to act via a GABA receptor-mediated mechanism. However, while it can increase GABA levels, it does not

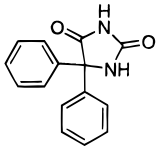
interact with GABA receptors but is a potent modulator of the α2δ calcium channel subunit.[82] While a structure−activity relationship has been established[83] for this "gabapentinoid" site in terms of anticonvulsant activity, there is still some question as to the precise mechanism of action of these compounds in neuropathic pain.[84] An analogue, pregabalin (**39**), is in clinical trials for neuropathic pain. Tiagabine (**40**), an antiepileptic that acts by blocking GABA uptake, has analgesic activity in animal models.[85]



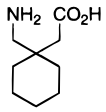
35 (Carbamazepine)



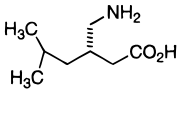
36 (Clonazepam)



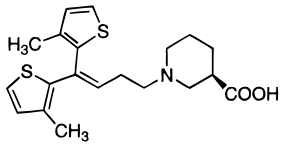
37 (Phenytoin)



38 (Gabapentin)



39 (Pregabalin)



40 (Tiagabine)

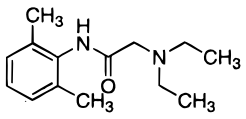
The use of anesthetics as analgesic agents is complicated by their ability to eventually block all sensory processing[81] which impacts the physiological role of tactile input and pain in protecting the individual from injury. However low doses of lidocaine (**41**) and the (*S*)-(−)-isomer of an analogue, mexiletine (**42**), can ameliorate tactile allodynia.[81,86]

The corticosteroids prednisolone (**43**) and its methyl analogue are used in the treatment of pain associated with bone metastases, arthritis, or neuropathic pain associated with tumor compression. These compounds are immunosuppressants, and their use can further complicate the diseases they are being used to treat. The neurosteroid[87] ganaxolone (**44**) recently failed clinical trials for the treatment of acute migraine.

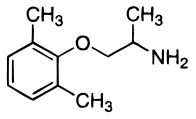
Therapeutic peptides/proteins with antiinflammatory activity and cell transplants are also being used to relieve chronic pain. Enbrel is a TNFR (p75)−IgG fusion protein that inhibits TNFα production[88] and has been approved for the treatment of rheumatoid arthritis. Lenercept is a TNFR (p55)−IgG fusion protein. CDP 751 and CenTNF are TNF antibodies. Keliximab and IgG4 anti-CD4 are CD4 monoclonals under evaluation as novel antiinflammatory agents.

New Mechanistic Approaches to Analgesia

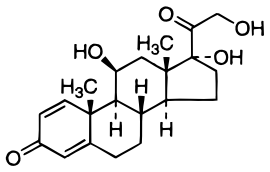
Any novel analgesic agent should be orally active with efficacy similar to, or greater than, that of morphine and be effective in mild, moderate, and severe, acute and chronic pain. Such a compound should be well-tolerated, be nonscheduled, and not develop the tolerance seen



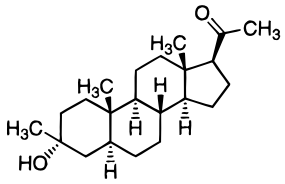
41 (Lidocaine)



42 (Mexiletine)



43 (Prednisolone)



44 (Ganaxolone)

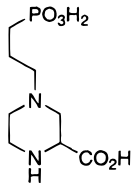
with opioids during prolonged treatment. The side effect profile should be benign and free of the gastrointestinal effects seen with both NSAIDs (bleeding, ulceration) and opioids (constipation) and the respiratory depression associated with opioid use. Antiinflammatory or disease-modifying activity may be an added benefit in certain pain states.

Approximately 300 compounds are currently in development with claims for use as analgesics. Of these, approximately 70 are in the clinic with a primary target of pain. Of these, one-fifth are directed toward novel, non-opioid, non-NSAID molecular targets and include glutamate receptor antagonists, GABA receptor agonists, various neurokinin receptor antagonists, muscarinic and nicotinic acetylcholine receptor agonists, adenosine kinase inhibitors, modulators of various ion channels, α2-adrenoceptor agonists, and bradykinin antagonists. Alternative formulations, delivery technologies, or combinations of marketed analgesics account for another half of the analgesic compounds in development. The remaining compounds are opioids and COX-2 inhibitors. A number of other novel mechanisms are under clinical investigation, including cannabinoid receptor agonists, vanilloid receptor antagonists, P2X receptor antagonists, sodium channel blockers, and growth factors.

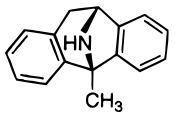
The relative importance and clinical utility of these targets will be dependent on the identification of potent, bioavailable, molecular target-selective ligands that are free of side effects that would compromise long-term use in chronic pain states.

Glutamate Receptor Modulators. The excitatory amino acid glutamate**,** acting via *N*-methyl-D-aspartate (NMDA) receptors, is a key effector in processes related to chronic pain and pain−associated neurotoxicity.[35] NMDA receptor antagonists such as CPP (**45**), MK-801 (**46**), ketamine (**47**), memantine (**48**), and dextromethorphan (**49**) have antinociceptive activity in animal models. In chronic and intractable pain, the phenomenon of "wind-up", the augmented response in C-fibers following an initial burst of repetitive stimulation,[34] can be abolished with CPP.[89] The major limitation with NMDA antagonists, like their potential use in the amelioration of the hypoxic damage associated with stroke,[90] is that their psychotomimetic actions (including dysphoria and cognitive impairment) provide unacceptable risk−benefit profiles even with a disorder like stroke for which there is considerable unmet medical

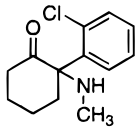
need. MK-801, the competitive NMDA antagonist, CGS 19755 (selfotel, **50**), and the noncompetitive NMDA antagonist, aptiganel (**51**), all reached late-stage clinical trials for stroke but were discontinued because of unacceptable CNS side effect liabilities.[90]



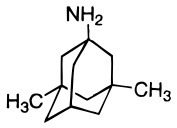
45 (CPP)



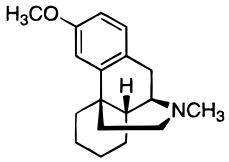
46 (MK-801)



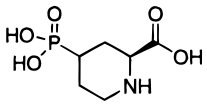
47 (Ketamine)



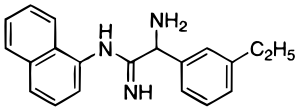
48 (Memantine)



49 (Dextromethorphan)



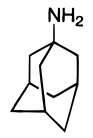
50 (CGS 19755)



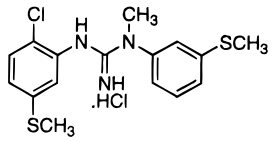
51 (Aptiganel)

Memantine, like MK-801, is an NMDA channel blocker. However, unlike the latter, it is relative weak (K_i = 700 nM) and may have a lesser incidence of psychotomimetic side effects. Memantine is in clinical use in Germany for the treatment of Parkinson's disease and is effective in the treatment of chronic pain.[91] The memantine analogue, amantidine (**52**), which is generally used as an antiviral agent, is also an NMDA receptor antagonist[92] that has shown remarkable efficacy in neuropathic pain in humans when given acutely.[93,94] CNS 5161 (**53**) is another noncompetitive NMDA antagonist that has shown analgesic activity and is being advanced in the clinic for neuropathic pain and migraine indications.[96] The strychnine-insensitive glycine site on the NMDA receptor complex is an alternative approach to directly antagonizing NMDA receptor-mediated responses. MRZ 2/576 (**54**) and GV 196771A (**55**) are novel glycine site modulators that are active in animal models of nociception. The kainic acid receptor antagonist, LY 293558 (**56**), has antinoceptive activity in a capsaicin model of allodynia/hyperalgesia. The glutamate GluR5 receptor antagonist **57** also has analgesic activity.[96]

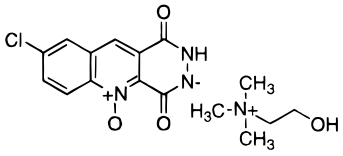
GABA Receptor Agonists. The inhibitory neurotransmitter GABA has effects opposite to that of glutamate. Thus a GABA receptor agonist may be considered functionally equivalent to a NMDA receptor antagonist. Drugs that enhance the actions of GABA in the nervous system include the inhalation anesthetic isoflurane, the barbiturate anesthetic pentobarbital, and the benzodiazepines (e.g., diazepam, clonazepam) that have anticonvulsant, anxiolytic, and hypnotic activities. The anticonvulsant gabapentin can increase brain GABA levels. The prototypic $GABA_A$ agonist, THIP (**58**),



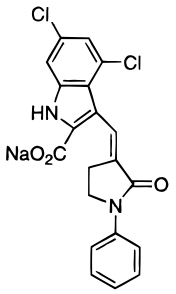
52 (Amantadine)



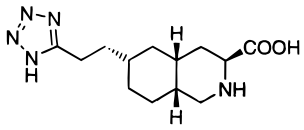
53 (CNS 5161)



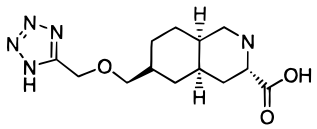
54 (MRZ 2/576)



55 (GV 196771A)

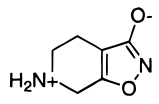


56 (LY 293558)

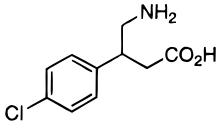


57 (WO9845270-A)

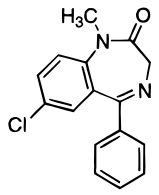
and the $GABA_B$ receptor agonist, baclofen (**59**), have analgesic activity.[97,98] However, the therapeutic index for both GABA agonists limits their therapeutic utility. In a phase II trial in chronic malignant pain, THIP given intramuscularly reduced pain but also produced sedation, dizziness, and blurred vision.[99] The $GABA_A$ receptor modulators, diazepam (**60**) and midazolam (**61**), that allosterically potentiate the actions of GABA are also antinociceptive, while $GABA_A$ antagonists produce analgesia and allodynia.[100]



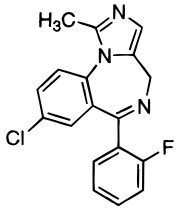
58 (THIP)



59 (Baclofen)



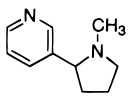
60 (Diazepam)



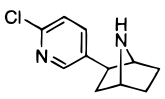
61 (Midazolam)

Acetylcholine Receptor Agonists. Nicotine (**62**) has been known to have weak analgesic activity for more than 60 years. It produces its effects via activation of neuronal nicotinic acetylcholine receptors (nAChRs), a major family of pentameric ligand−gated ion channels.[101,102] The discovery of the analgesic alkaloid epi-

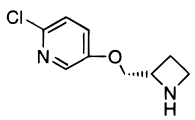
batidine (**63**) by Daly[103] provided a potent neuronal nAChR ligand (K_i = 35−100 pM) to more precisely characterize the role of nicotinic mechanisms in nociception. Epibatidine is 100−200 times more potent than morphine as an analgesic,[103] and these effects are not antagonized by opioid receptor antagonists such as naloxone, but by nAChR antagonists. The alkaloid is, however, nonselective with regard to its actions at neuronal ($\alpha 4\beta 2$), ganglionic ($\alpha 3\beta x$), and neuromuscular ($\alpha 1\beta 1\gamma\delta\epsilon$) nAChR subtypes leading to a very narrow therapeutic window. ABT-594 (**64**) is an azetidine bioisostere of nicotine that retains the analgesic actions of epibatidine with reduced side effects.[104] It is approximately 100 times more potent than morphine in a variety of acute and chronic nociceptive animal models and, unlike morphine, shows no evidence of tolerance or opioid-like dependence liability, nor does it have effects on respiration, GI motility, or cognition. DBO-83 (**65**)[105] and AG-4 (**66**)[106] are other novel nicotinic agonists with analgesic activity in animal models.



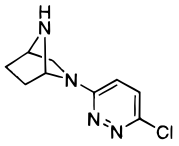
62 (Nicotine)



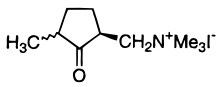
63 (Epibatidine)



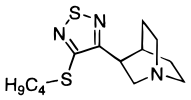
64 (ABT-594)



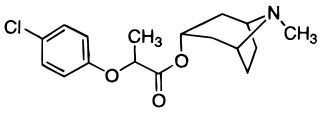
65 (DBO-83)



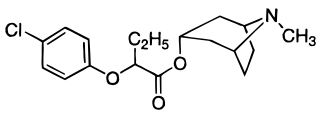
66 (AG-4)



67 (NNC 11-1053/LY297802)



68 (ET 142)

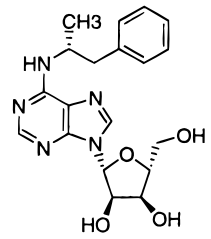


69 (SM21/FID-72021)

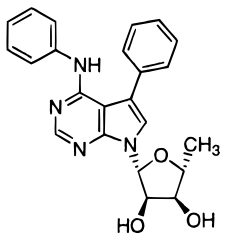
Muscarinic receptor agonists also have potent analgesic activity although this is nearly always confounded by typical muscarinic side effects that include pronounced effects on GI motility. NNC 11−1053/LY297802 (**67**)[107,108] was the most advanced of these agents but has been discontinued for unknown reasons. ET 142 (**68**)[109] and SM21/FID-72021 (**69**)[110] are other muscarinic agonist analgesics at the preclinical stage.

Purinergic Modulators. Ligands active at both P1 (adenosine) and P2 (ATP/UTP) receptors modulate nociceptive processes.[111−113] Adenosine agonists given systemically or spinally have both nociceptive and antinociceptive effects in a range of animal models of acute and chronic pain.[113,114] Adenosine as an inhibitory neuromodulator affects nociceptive transmission by peripheral, spinal, and supraspinal actions, actions that are mediated via A_1 receptor activation.[113,115] Adenosine appears to be more potent in animal models of neuropathic pain than in nociceptive models.[113] Spinal administration of the A_1 agonist, (*R*)-phenylisopropyladenosine (*R*-PIA, **70**), to a patient with a 10-year history of intractable pain relieved allodynia without affecting normal sensory perception.[116] Similarly, infusion of adenosine at doses (75 mg) that lack overt cardiovascular effects improved pain symptoms in several clinical pain models and was superior to placebo in reducing spontaneous pain, ongoing hyperalgesia, and allodynia in patients with neuropathic pain.[117] *R*-PIA also prevents central sensitization evoked by mustard oil.[118] In contrast, A_3 receptor activation can indirectly elicit pain via its ability to induce the release of histamine and 5HT from mast cells.[119] Similarly, activation of A_1 receptors in the rat knee joint can excite nociceptive afferents causing pain.[120] The paradoxical antinociceptive and pain-producing effects of adenosine appear to be dependent on dose, route, and site of administration and, to some degree, the receptor subtype that is activated.

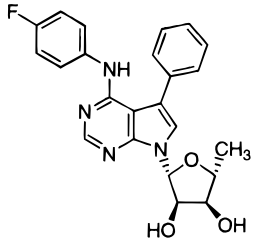
Low-dose perioperative adenosine during surgery can also reduce the requirement for volatile anesthetic and for postoperative analgesia.[22,121] Similar effects have been observed in dogs using the adenosine kinase (AK) inhibitor, GP683 (**71**).[122]



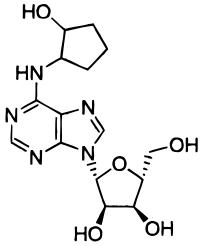
70 (*R*-Phenylisopropyladenosine)



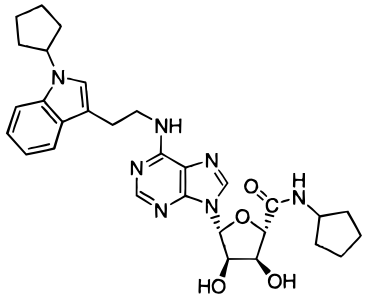
71 (GP 683)



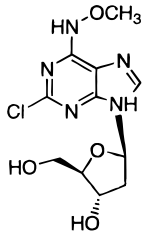
72 (GP 3269)



73 (GR 79236)



74 (UP 202-32)



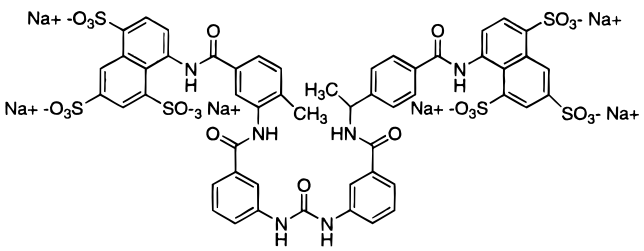
75 (NNC 53-0017)

AK is a key enzyme regulating intra- and extracellular adenosine levels.[123] Inhibition of this enzyme augments the concentrations and actions of adenosine

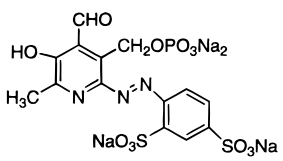
locally at sites of tissue injury. By enhancing the availability of endogenous adenosine in the extracellular space in a localized manner, this "site- and event-specific" approach can potentially avoid the known actions of adenosine on other tissue systems. Adenosine also has antiinflammatory actions that involve A_1, A_{2A}, A_{2B}, and A_3 receptor-mediated mechanisms.[124,125] Adenosine and its analogues also decrease neutrophil free radical production (A_{2A}), inhibit neutrophil rolling and adhesion to vascular endothelium, an effect potentially mediated by selectin blockade (A_{2A}), reduce bradykinin- and histamine-induced vascular leakage via actions on endothelial permeability (A_1 and A_{2A}), decrease macrophage production of the proinflammatory cytokine TNFα, and inhibit expression of the matrix metalloprotease, collagenase (MMP-1), on synoviocytes (A_{2B}). This latter effect resembles that of methotrexate, a widely used second-line (after NSAIDs) treatment for RA, the effects of which can be mediated, in part, via production of endogenous adenosine.[36,125] A mouse knockout of the A_{2A} receptor was hypoalgesic, demonstrating slower response to acute noxious stimuli, and had high blood pressure as well as showed increased aggressive behavior.[126]

Compounds of current interest that act via P1 receptors are the AK inhibitor, GP-3269 (**72**), which has antinociceptive activity and the adenosine agonists, GR-79236 (**73**) and UP 202-32 (**74**). NNC 53-0017 (**75**) is an *N*,9-disubstituted adenine derivative derived from a series of A_3 receptor agonists that inhibits TNFα production but does not interact with the A_3 receptor.[127]

ATP application to sensory afferents results in hyperexcitability and the perception of intense pain. Thus ATP and adenosine can have opposing effects on nociception. The nucleotide can also induce nociceptive responses at local sites of administration and can facilitate nociceptive responses to other noxious stimuli. P2 receptor antagonists such as suramin (**76**) and PPADS (**77**) reduce nociceptive responses in animal models of acute and persistent pain.[128] ATP elicits pain when applied intradermally[129,130] and functions as a fast



76 (Suramin)

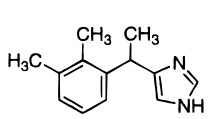


77 (PPADS)

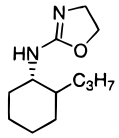
neurotransmitter via P2X receptors in dorsal horn.[131] The recently identified $P2X_3$ receptor[132,133] shows a discrete localization to the dorsal root, nodose, and trigeminal sensory ganglia[134] and is increased in a chronic pain model in rodents.[135] Activation of presynaptic P2X receptors in a DRG−dorsal horn coculture system elicits glutamate release from sensory neurons,[136] consistent with a role in nociceptive signaling involving a multiplicity of signaling molecules. Glutamate activation of NMDA receptors can elicit the release of adenosine from hippocampal interneurons, which in turn inhibits glutamate release.[137] Nociceptive neurons innervating the tooth pulp contain $P2X_3$ receptor mRNA, immunoreactivity, and function, while adjacent nonnociceptive stretch sensory neurons do not, further implicating $P2X_3$ receptor activation in nociception.[138] Since adenosine is a product of the breakdown of ATP via extracellular ectonucleotidase activity, it is likely, as in a number of other instances involving ATP as a fast excitatory neurotransmitter, that adenosine can act to attenuate the effects of ATP.[139]

α2-Adrenoceptor Agonists. The dorsal horn of the spinal cord is the major site at which α2-adrenoceptor agonists such as clonidine modulate nociception.[25,80,140] Clondine and dexmedetomidine (**78**) produce analgesia in the postoperative setting,[141] but their efficacy is limited by the route of administration.[140] When given iv, α2-adrenoceptor agonists are weak analgesics with mechanism-related sedative and hypotensive side effects. Given epidurally, however, clonidine is effective in the treatment of neuropathic and visceral pain, both on its own and in combination with other anesthetics/analgesics including bupivacaine, fentanyl,[80] and morphine.[140]

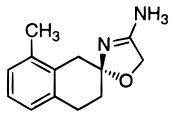
α2A-Adrenoceptors predominate in the spinal cord with α2-selective agonists such as oxymetazoline being antinociceptive.[25] In a mouse expressing a mutated form (D79N) of the α2A-adrenoceptor, the α2-agonist dexmedetomidine was unable to produce anesthetic sparing or analgesic actions further supporting the role of this receptor in the analgesic actions of α2-adrenoceptor agonists.[142] AGN 190837 (**79**) and S-18616 (**80**) are newer α2-adrenoceptor agonists.



78 (Dexmedetomidine)



79 (AGN 190837)

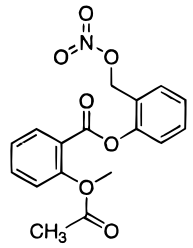


80 (S-18616)

Nitric Oxide. While nitric oxide (NO) can elicit pain in humans,[143] animal studies suggest that endogenously produced NO is involved in analgesic responses.[144] Peripheral nerve damage causes an upregulation of nitric oxide synthase (NOS) activity in the DRG.[145] Both NO donors and inhibitors of NOS have been suggested as novel analgesics.[146] NCX-4016 (**81**) is an NSAID (termed a nitro-aspirin) with NO donor properties.[147]

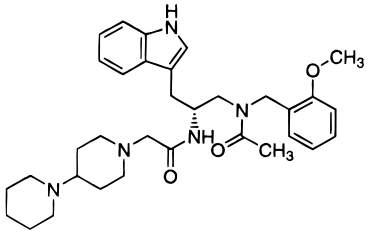
Peptide Receptor Antagonists. Sensory nerves release a number of neuropeptides in response to noxious stimuli which have proinflammatory effects that are collectively termed neurogenic inflammation.[149]

The tachykinin substance P (SP) plays a key role in pain processing as a nociceptive transmitter,[150] promoting central hyperexcitability,[33] and is also involved in the plasma extravasation process[149] that is a key factor in migraine-related pain. SP interacts with the NK-1 receptor, a member of the tachykinin receptor family.

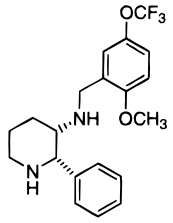


81 (NCX-4016)

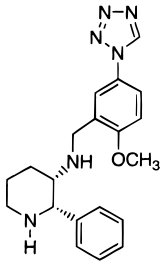
SP is a proinflammatory mediator, and its synthesis is increased in the DRG and spinal cord following inflammatory hyperalgesia.[150] A number of NK-1 antagonists have been developed including: lanepitant (**82**), CP 122,721 (**83**), GR-203040 (**84**), RPR 100893 (**85**), and SDZ NKT 343 (**86**).[151] Nearly all of these compounds are highly effective in animal models of SP-induced and other pain and have excellent human pharmacokinetics but have failed to show efficacy in phase II clinical trials in either pain or migraine. For instance, a selective NK-1 antagonist, MK-869 (**87**) was ineffective in a series of trials for pain that included third molar extraction, postsurgical pain, and neuropathic pain.[152] MK-869 was subsequently evaluated as an antidepressant based on the involvement of stress effects in NK-1-related analgesia[153] and was shown to have equivalent antidepressant efficacy to the SSRIs in one series of clinical trials.[152]



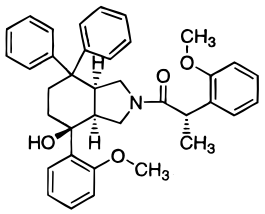
82 (Lanepitant)



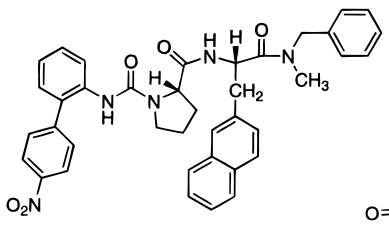
83 (CP 122,721)



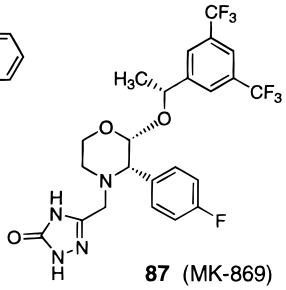
84 (GR-203040)



85 (RPR 100893)



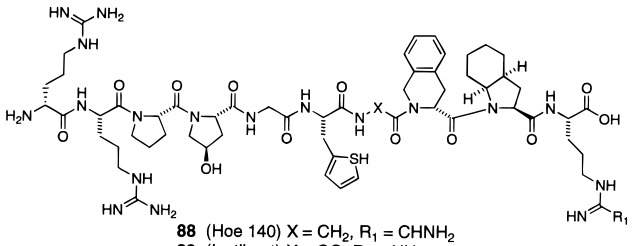
86 (SDZ NKT 343)



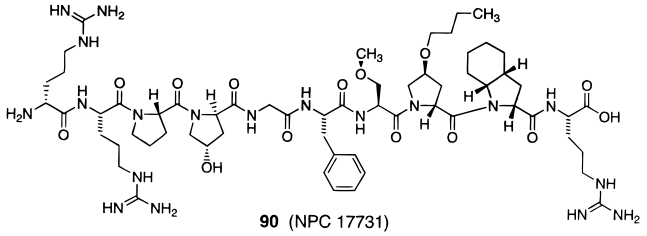
87 (MK-869)

The reason for the lack of human analgesic efficacy for NK-1 receptor antagonists remains unclear and may be due to internalization of the NK-1 receptor after activation by SP[154] or to the complexity of the nociceptive cascade where SP activates a tyrosine kinase to phosphorylate the NMDA receptor secondarily evoking neuronal hypersensitivity via a process that is irreversible. A mouse SP (NK-1) receptor knockout[152] could respond to acute pain and showed signs of hyperalgesia but lacked a wind-up response to repetitive C-fiber stimulation, did not show a full development of stress-induced analgesia, and was less aggressive than control animals.

Bradykinin (BK) is both proinflammatory and algogenic.[155] BK receptor antagonists such as the peptide Hoe 140 (**88**) attenuate BK-induced pain.[156] Icatibant (**89**) and NPC 17731 (**90**) are BK antagonists targeted as analgesics.

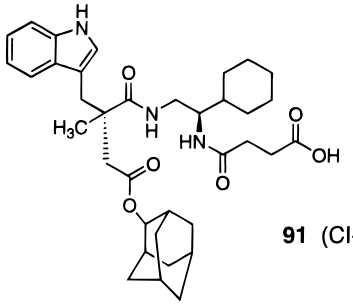


88 (Hoe 140) X = CH_2, R_1 = $CHNH_2$
89 (Icatibant) X = CO, R_1 = NH_2



90 (NPC 17731)

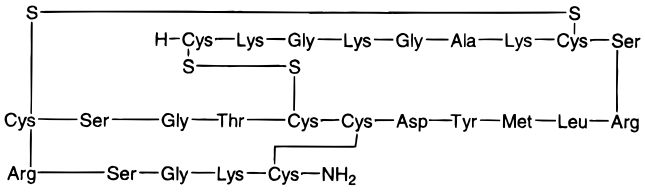
Cholecystokinin (CCK) is present in DRG and dorsal horn of the spinal cord and is upregulated after sciatic nerve section.[157] CCK-8 can attenuate opioid analgesia[59,146] via interactions with the CCK_B (CCK_2) receptors that are present in dorsal horn. CCK is not by itself hyperalgesic, and it does not interact directly with opioid receptors but appears to inhibit enkephalin release.[59] CCK_2 receptor antagonists such as CI-988 (**91**) can enhance opioid analgesia via a naloxone-sensitive mechanism without affecting the actions of morphine on respiratory depression.



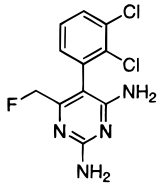
91 (CI-988)

Galanin is a 29-amino acid peptide found in the DRG and dorsal horn and is increased in the latter following peripheral axotomy. Galanin has antinociceptive activity via postsynaptic blockade of the effects of SP and calcitonin gene-related peptide (CGRP),[146] which is another neuropeptide mediator of neurogenic inflammation.

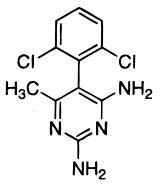
Ion Channel Modulators. In addition to the nAChRs, NMDA receptors, and the $P2X_3$ receptor, N-type calcium channels, TTX-resistant sodium channels (TTXr-Na^+, SNS (sensory neuron-specific)/PN3), proton-gated (acid-sensing) ion channels (ASICs), and voltage-sensitive Na^+ channels are other ion channels also involved in pain processing.[30,158,159] SNX 111 (ziconitide, **92**), a 25-amino acid ω-conotoxin peptide, is an N-type calcium channel antagonist that is currently in late-stage clinical trials for severe cancer pain via the intrathecal route. It may also have potential as an epidural anaglesic where its limiting effects on cardiovascular function are minimized. As already noted, the gabapentinoids, gabapentin and pregabalin, are thought to act via an $\alpha 2\delta$ site on voltage-sensitive calcium channels.[60,61] BW 4030W92 (**93**) is a nonselective Na^+ channel antagonist[160] in phase II clinical trials. GW 273227 (**94**) is a follow-on compound.[161]



92 (Ziconitide/SNX 111)



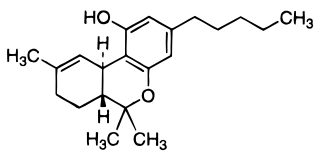
93 (BW 4030W92)



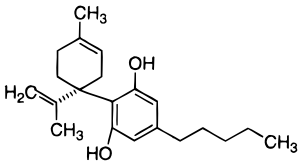
94 (GW 273227)

Cannabinoids. While tetrahydrocannabinol (THC, **95**) elicits the euphoria associated with marijuana use, cannabidiol (CBD, **96**) is a powerful peripheral analgesic acting via CB-1 and CB-2 receptors.[162] An endogenous cannabinoid, anandamide (**97**) acts at cutaneous, spinal, and supraspinal sites to regulate pain initiation.[163,164] Anandamide, WIN-55212−2 (**98**), CP-55,940 (**99**), HU-210 (**100**) and O-823 (**101**) produce their analgesic actions via CB-1 receptor activation.[162] Palmitylethanolamide (PEA, **102**) is coreleased with anandamide and also has analgesic effects acting via CB-2 receptors.[163] PEA is an autocoid that limits local inflammatory responses.[70,71]

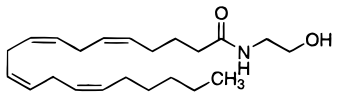
Growth Factors. Growth factors like nerve growth factor (NGF) are important for the survival and function of a variety of neurons that include Aδ- and C-fibers. NGF is algogenic[165,166] causing thermal hyperalgesia of several hours duration and is involved in the processes of peripheral and central sensitization.[165] The low-affinity NGF receptor p75 is upregulated in inflammation[167] and appears to be a critical mediator of sensory changes associated with inflammatory responses.[165] Mice lacking the p75 receptor are insensitive to heat-related pain.[167] The high-affinity NGF receptor *trk* A is involved in the development of tactile allodynia.[168−170] NGF promotes neurogenic extravasation of plasma



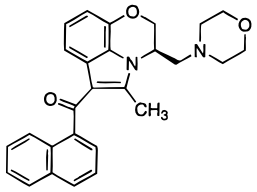
95 (Tetrahydrocannabinol)



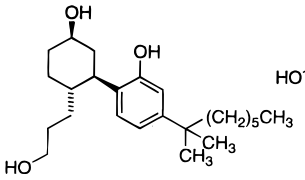
96 (Cannabidiol)



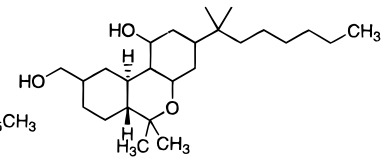
97 (Anandamide)



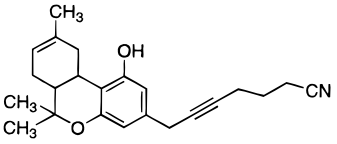
98 (WIN-55212-2)



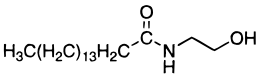
99 CP-55,940



100 (HU-210)

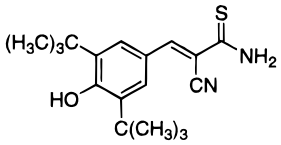


101 (O-823)



102 (PEA)

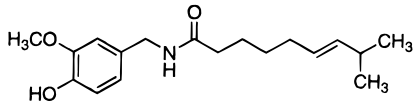
proteins into the area in which it is administered[165] and increases levels of SP and CGRP in sensory neurons,[171] in addition to upregulating vanilloid receptors, sodium channels, and ASICs.[172] Neuropathic pain may result from decreased levels of NGF.[164] AG-879 (**103**) is a recently described NGF antagonist.



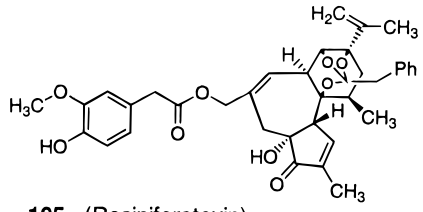
103 (AG-879)

Vanilloids. The polypeptide capsaicin (**104**), isolated from chili peppers, elicits an intense burning sensation via activation of the sensory neurons involved in thermal nociception.[173] Capsaicin cream is used to treat neuropathic pain states, desensitizing nociceptive pathways by hyperexcitation.[174] Capsaicin produces its effects via a specific vanilloid receptor which has recently been cloned as the VR-1 receptor.[31] This is a nonselective cation channel related to the *Drosophilia* retinal protein TRP that is involved in regulating calcium entry into cells depleted of calcium. Cells transfected with VR-1 show an increase in calcium levels in response to elevated (45 °C) temperatures. The VR-1 receptor is activated by the vanilloids, capsaicin, and the naturally occurring analogue resiniferatoxin (RFX, **105**). pH

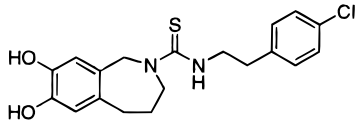
changes that had previously been implicated in capsaicin receptor activation potentiate capsaicin-evoked changes in calcium current flow.[31] Capsazepine (**106**) is a capsaicin receptor antagonist that lacks analgesic activity suggesting that agonism is an absolute requirement for receptor inactivation.[175] NE−21610 (nuvanil, **107**) is a stable analogue of capsaicin that has antinociceptive activity at high doses but has little agonist activity as compared to capsaicin.[176] The compound also has marked hypothermic side effects.[174] SDZ-249482 (**108**) is an orally and topically effective capsaicin agonist that is more potent than either the opioids or NSAIDs in animal models of pain.[177]



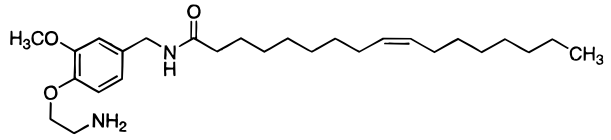
104 (Capsaicin)



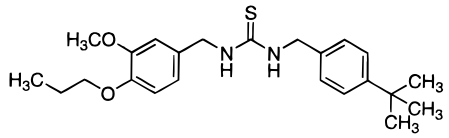
105 (Resiniferatoxin)



106 (Capsazepine)



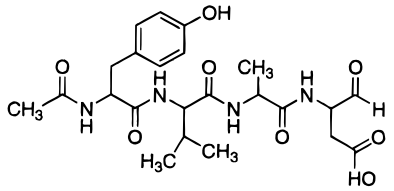
107 (Nuvanil)



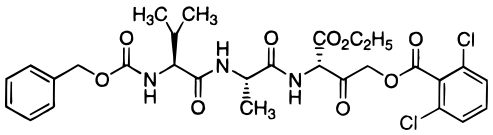
108 SDZ-249482

Cytokines. A number of cytokines released from immune cells including TNFα, IL-1β, IL-6, and IL-8 are proinflammatory and hyperalgesic[178] via effects on prostanoid release and NGF production. One approach to limiting these cytokine effects is inhibition of IL-1β-converting enzyme (ICE).[179] The cytokine convertase inhibitors, L 709049 (**109**) and VE 13045 (**110**), block IL-1 production. An alternative molecular approach to inhibiting ICE is by blocking the effects of ATP on $P2X_7$ receptor-mediated IL-1β maturation processes.[180]

Other Approaches. A number of miscellaneous antiinflammatory agents unrelated to the NSAIDs in terms of mechanism are also under investigation.[177,181]



109 (L 709049)



110 (VE 13045)

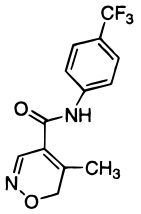
Leflunomide (**111**), a pyrimidine synthesis inhibitor that blocks the enzyme dihydroorotate dehyrogenase in immune cells thus preventing DNA synthesis, was recently approved for use in RA; thalidomide (**112**), the controversial sedative introduced in the 1950s as a racemate but withdrawn due to teratogenicity issues, is a potent inhibitor of TNFα production; ISIS 2302 is an antisense oligonucleotide inhibitor of ICAM-1 synthesis; and several matrix metalloprotease (MMP) inhibitors including marimastat (**113**) have an unusual side effect involving "freezing" of the musculature that requires discontinuation/drug holidays that may represent a limiting side effect for this compound class.[182] The p38 MAP kinase inhibitor, SB 203580 (**114**), has antiarthritic and disease-modifying activity in animal models.[181] Signal transduction pathways involving AP-1 and NFκB are also potential targets in pain control.[183] MG341 (**115**) inhibits the 26S proteasome that degrades IκB (K_i = 0.6 nM) and also inhibits iNOS expression. In vivo, the compound attenuates arthritis, cartilage, and bone erosion and at therapeutic doses given for 3 months has shown no signs of toxicity.[184]

Genetically Modified Models of Nociception. Several knockout mouse models have been recently described that show a pivotal role of the protein products of their respective gene deletions in various aspects of nociception. These include COX-2,[2] adenosine A_{2A},[126] α2-adrenoceptor,[142] and NK-1 knockouts.[153] Mice deficient in the μ opioid receptor are insensitive to morphine.[185,186] Prostacyclin receptor knockout mice showed changes in both pain perception and inflammatory responses,[187] while knockout mice lacking protein kinase C-γ[188] showed normal responses to acute pain but delayed responses in models of neuropathic pain.

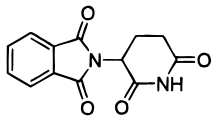
Future Directions

A vast amount of new information on the complexity and hierarchical nature of nociceptive processing at the molecular level coupled with continuing unmet medical need, especially in the treatment of neuropathic pain, has resulted in a renewed interest in developing novel, safe analgesics with efficacy equivalent to that of the classical opioids.

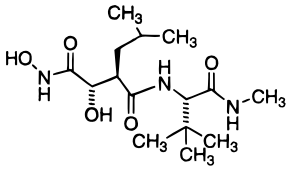
A number of compounds resulting from these new approaches to analgesia are currently in clinical trials and have been reviewed above. However, the path from demonstrating analgesia in animals to a marketed



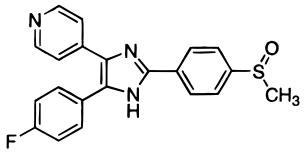
111 (Leflunomide)



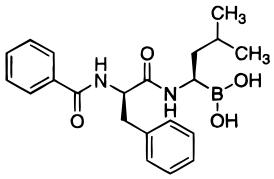
112 (Thalidomide)



113 (Marimastat)



114 (SB 203580)



115 (MG 341)

therapeutic entity is less obvious than might be anticipated given the good predictivity of animal pain models.[189] The lack of efficacy of NK-1 receptor antagonists in the clinic in trials for pain and migraine despite robust preclinical data indicating their analgesic potential has been a cause for concern.[151] While receptor internalization is one explanation,[154] this would suggest major differences in mechanisms for attenuating the algogenic properties of SP in humans versus experimental animals. It also begs the questions as to how compounds such as MK-869 have antidepressant activity via interactions with the NK-1 receptor yet do not have analgesic activity.[152] In transitioning from animals to humans, similar problems have occurred with novel opioid analgesics. Many promising compounds selective for the various opioid receptor subtypes were clearly shown to lack addiction, euphoric liabilities, and respiratory depression activity in sophisticated animal models yet in the clinic evidenced these activities.

Despite the progress made to date, there are still a number of perplexing issues that continue to confound the efforts to discover new analgesics. A number of compounds, e.g., adenosine[113,114] and NO donors,[148] have robust analgesic activity but are also nociceptive in certain situations. Similarly, antagonists for the VR-1 receptor through which capsaicin elicits pain are not analgesic.[175] These findings reinforce the dynamic nature of nociceptive processing and suggest that current research approaches may be overly reductionistic, viewing the molecular targets as static entities. As the majority of pain sensations are polymodal in nature, the overall impact of a given noxious stimulus on the organism reflects the degree, if any, of peripheral and central sensitization resulting from recent pain experience, the psychological (stress) state of the patient, and the nature of the stimulus.

It is well-known that the body has the capacity to produce endogenous analgesics such as the enkephalins and endorphins[59] as well as less-recognized analgesics such as adenosine,[113,114] monoamines,[25,140] and cannabinoids.[162] In addition, nociceptive mechanisms can be potentially self-limiting. Thus, SP interactions with the NK-1 receptors result in receptor internalization,[153] while the nociceptive effects of ATP (which may involve glutamate release) may be self-limiting via the production of adenosine.[137]

Several novel approaches, e.g., NMDA receptor antagonists[36] and GABA agonists,[100] have demonstrated robust analgesic efficacy but have side effect liabilities, which while very distinct from those of the opioids represent new problems that are unacceptable in the clinic, especially in the context of chronic disease states such as neuropathic pain.

In assessing the likelihood of clinical success with the various ligands producing analgesia via novel mechanisms, it is difficult to prioritize these since as much as is known regarding the molecular substrates of pain, there is still more to be learned especially at the integrative level. Since animals can only respond in gross terms to pain produced by external manipulations, the objective evaluation of these newer agents in human clinical trials to key go/no go decision points involving multiple pain states will add considerably to our knowledge regarding the dynamics of analgesic efficacy. In turn, this will allow the various mechanisms to prioritize themselves in the ultimate pain state, that of the patient. To attempt to predict clinical success given the apparent obviousness of the role of NK-1 receptor antagonists based on animal data followed with the multiple clinical failures would, at this time, be premature.

Biographies

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