Kirk-Othmer Encyclopedia of Chemical Technology.

ANALGESICS, ANTIPYRETICS, AND ANTIINFLAMMATORY AGENTS

Pain, pyresis, and inflammation are distinct physiological responses which can occur independently; they are often associated as the body mounts a response to an injury or insult. Each is an important signal from injured tissue and the signal's continued presence can guide a physician in diagnosing and treating the condition which led to the occurrence. Literature and folklore are replete with remedies which claim to alleviate aches and pains of all kinds. Whereas many treatments are baseless, some, especially those based on herbal medicines, serve as the basis for the rational discovery of the drugs that are used in Western medicine for treating pain and inflammation.

The twentieth century has seen considerable progress in the understanding of pain and inflammation and the relationship of one to the other. It is increasingly apparent that the central and peripheral nervous systems are capable of causing the production of mediators which can attract and activate inflammatory cells thereby initiating or amplifying an inflammatory response. At the same time, inflammatory cells are also capable of releasing substances which not only respond to the original insult, but also stimulate the nervous systems.

A number of interdependent physiological mechanisms, each providing new targets for therapeutic intervention, and allowing for the development of new treatments for pain, pyresis, and inflammation, have been discovered. At least eight distinct types of opioid receptors have been identified and the corresponding individual functions are beginning to be understood. Moreover, a great deal has been learned about the role of lipid mediators in the inflammatory response and how antiinflammatory agents control their production.

1. Endogenous Receptors and Ligands

In 1973 evidence was provided for the existence of receptors which recognize opioid molecules (1). As many as eight opioid receptors are known to exist, but only four, designated as μ (mu), κ (kappa), ς (sigma), and δ (delta), are believed to be important to the central nervous system (CNS). Several portions of the brain, including the hypothalamus and amygdala, the spinal cord, and nuclei concerned with vagal reflexes contain varying concentrations of the different types of opioid receptors.

The development of selective agonists and antagonists has aided in formulating a profile of pharmacological effects for each receptor type (2). The best understood is the μ receptor which plays a role in euphoria, respiratory depression, tolerance, and physical dependence as well as analgesic effects. Studies using highly selective agonists and antagonists imply that there may be μ receptor subtypes (3) suggesting that not all of the ascribed effects result from the same receptor. Antinociceptive activities and possible modulation of selected μ receptor activities can be identified. In addition to analgesia, the κ receptor effects include diuresis, sedation, and physical dependence (4). The effects of the δ receptor are less well understood as there is a lack of highly selective δ receptor ligands.

Shortly following the discovery of the opioid receptors, peptidic substances having opioid activity were detected in the pituitary gland (5). There are three known groups of endogenous opioid peptides: endorphins (6), enkephalins, and dynorphins (see Opiods, endogenous). Examples are given in Table 1. Every member of

Table 1. Opioid Peptides

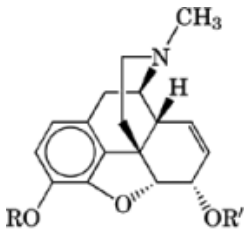
Compound	CAS Registry Number	Structural formula
β-endorphin	[60617-12-1]	H-TyrGlyGlyPheMetThrSerGluLysSerGlnThrProLeu-ValThrLeuPheLysAsnAlaIleValLysAsnAlaHisLysLysGlyGln-OH
leu-enkephalin	[58822-25-6]	H-TryGlyGlyPheLeu-OH
met-enkephalin	[58569-55-4]	H-TyrGlyGlyPheMet-OH
dynorphin A(1–17)	[80448-90-4]	H-TyrGlyGlyPheLeuArgArgIleArgProLysLeuLysTrp-AspAsnGln-OH

the three families is the progeny of a distinct polypeptide precursor. The endorphins are fragments of proopiomelanocortin [66796-54-1] (POMC), a polypeptide also containing β-lipotropic hormone, adrenocorticotropic hormone (ACTH), and melanocyte stimulatory hormone (α-MSH) (8). β-Endorphin, the largest endogenous opioid peptide, is principally synthesized, stored, and ultimately released from cells in the pituitary gland as well as from neurons in the CNS. Although β-endorphin contains the sequence for met-enkephalin, $C_{27}H_{35}N_5O_7S$, the endorphin is not processed to this enkephalin. Instead met-enkephalin is derived from proenkephalin, a polypeptide containing 6 met-enkephalins and 1 leu-enkephalin, $C_{28}H_{37}N_5O_7$ (9). These highly conserved, five amino acid peptides are located in the adrenal medulla, the CNS, and the peripheral nervous systems. Another polypeptide, prodynorphin also contains a leu-enkephalin fragment, as well as other peptidic opioids, including α- and β-neoendorphin and dynorphin A(1–17), $C_{99}H_{155}N_{31}O_{23}$. The latter is further cleaved to dynorphin A(1–8) and dynorphin B(1–3).

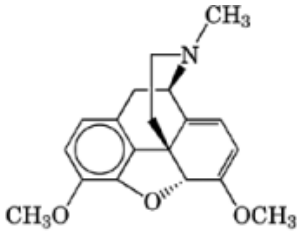
When released, endogenous opioids act upon specific receptors, displaying effects like the quintessential opioid, morphine [57-27-2], $C_{17}H_{19}NO_3$. These endogenous peptides appear to induce analgesia and depress respiratory function, gastrointestinal transit, and several other physiological functions. Leu-enkephalin binds with relatively high selectivity to the δ receptor, dynorphin A(1–17) to the κ receptor. Like morphine, β-endorphin, and met-enkephalin are μ agonists. When administered intravenously, β-endorphin was three times more potent than morphine on a molar basis even though the large size and charged nature of β-endorphin should preclude its passage across the blood-brain barrier. The smaller enkephalins and dynorphins are potential substrates for peptidase degradation when administered systemically. Synthetic enkephalin analogues, designed to resist degradation, demonstrated analgesia in humans. Unfortunately, like morphine, these compounds do not cause analgesia without tolerance and physical dependence.

2. Opioid Agonists

Opium is the dried, powdered sap of the unripe seed pod of *Papaver somniferum*; a poppy plant indigenous to Asia minor. Theophrastus described its medical properties in the third century BC, but the Sumerians, ca BC 4000, probably perceived its utility. Arab physicians knew of the drug, and Arab traders carried it to the Orient where it was used as a treatment for dysentery. Paracelsus is credited with repopularizing the drug in western Europe in the early sixteenth century by formulating opium into "laudanum", which is still in use. More than 20 different alkaloids (qv) of two different classes comprise 25% of the weight of dry opium. The benzylisoquinolines, characterized by papaverine [58-74-2] (1.0%), a smooth muscle relaxant, and noscapine [128-62-1] (6.0%), an antitussive agent, do not have any analgesic effects. The phenanthrenes, the second group, are the more common and include 10% morphine (**1**, R′ = R = H), 0.5% codeine [76-57-3], $C_{18}H_{21}NO_3$, (**1**, R′ = H, R = CH_3), and 0.2 thebaine [115-37-7], $C_{19}H_{21}NO_3$, (**2**).



(**1**)



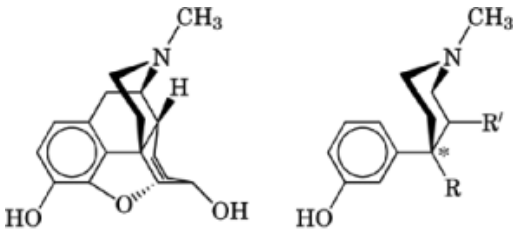
(**2**)

The correct structure of morphine, named after Morpheus, the Greek god of sleep, was first proposed in 1925 (10) and was confirmed in 1955 via total synthesis (11). Substitution at one or both of the two hydroxyl groups, one phenolic and the other allylic, give codeine, methyl morphine, where the substitution is on the phenolic hydroxyl, and heroin [561-27-3], $C_{21}H_{23}NO_5$, (**1**, R′ = R = $COCH_3$) also known as 3,6-diacetoxy morphine, which serves as a prodrug and converts to morphine *in vivo*. Methylating both hydroxyl groups and introducing an additional double bond into the allylic ring leads to thebaine which has little analgesic action.

Morphine, mol wt 285.3, effectively relieves pain and increases an individual's ability to tolerate a painful experience. It also produces a remarkably broad range of other effects including drowsiness, and mood changes, respiratory depression, nausea, decreased gastrointestinal motility, and vomiting. Morphine behaves as a receptor agonist, acting preferentially at the μ receptor, but also exhibiting appreciable affinity for other opioid receptors. A standard therapeutic dose is 10–15 mg, usually administered subcutaneously. Analgesia peaks in about one hour and lasts for four to five hours. Morphine can also be administered orally, but it is only one sixth as potent. When delivered intravenously, morphine-induced respiratory depression is observed at below analgesic dose levels, as early as seven minutes after administration and for as long as 4–5 hours. An important feature of morphine and related drugs is the development of physical dependence on, and tolerance to, some of the effects. Increasingly large doses of drug must be administered to maintain the analgesic effects and the possibility of psychological dependence is a primary limitation to clinical use. However there are studies which suggest that when patients take morphine to combat pain, it is rare to see addiction, and thus morphine usage may be reasonable for the treatment of chronic pain (12). The cessation of drug uptake does produce withdrawal symptoms, such as diarrhea, vomiting, chills, fever, abdominal cramps, and abdominal pain, which are different from those observed during withdrawal from other CNS depressants. The onset and duration of symptoms depend upon the pharmokinetic profile of the drug.

Codeine, mol wt 299.3, is a significantly less potent analgesic than morphine, requiring 60 mg (0.20 mmol) to equal the effectiveness of 10 mg (0.04 mmol) of morphine. However, codeine is orally effective, and it is less addictive and associated with less nausea than morphine. Codeine is used as an antitussive agent, although newer, nonaddictive agents are preferred (see Expectorants, antitussives, and related agents).

Introduced in 1898, heroin was heralded as a nonaddictive alternative to morphine. Subsequent clinical experience showed it to be highly addictive and preferred by addicts over morphine (13). Heroin is approximately



(1) (7)

Fig. 1. Conformational representation of the piperidine ring of morphine (**1**) and analogues meperidine (**7**, R′= H, R= $COOC_2H_5$) and alphaprodine (**7**, R′= CH_3, R= OCC_2H_5). The chiral center of interest in structure (**7**) is starred (see text).

ten times more potent than morphine, with quicker onset and shorter duration of action. It is orally inactive, but is effective when administered intravenously. Although heroin has not been available in the United States for therapeutic use since 1906, it is still used clinically in other countries for its analgesic properties.

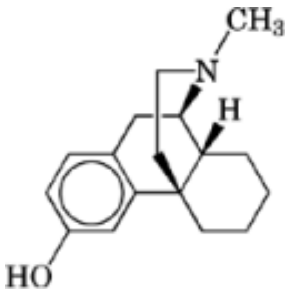
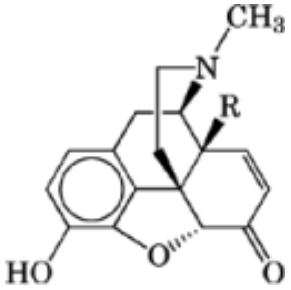
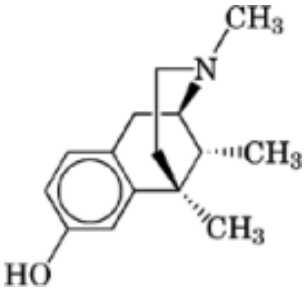
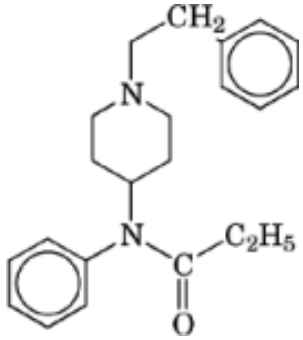
3. Synthetic and Semisynthetic Agonists

In attempts to discover drugs demonstrating fewer undesirable side effects than morphine, many synthetic analogues have been prepared. Some of these are shown in Table 2. The orally effective levorphanol (**3**) retains the complete morphine carbon skeleton, is more potent than morphine, and produces a correspondingly greater degree of respiratory depression (14). Oxymorphone (**4**, R = OH) and hydromorphone (**4**, R = H), both of which contain a C-6 carbonyl group, are more potent than morphine, but also produce greater side effects. Removal of one ring led to phenazocine (**5**), which is more potent than morphine and has the same duration of action, but is equally addictive.

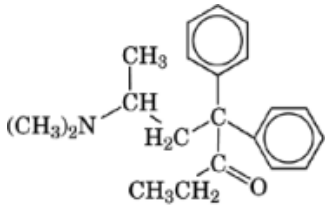
Several common structural features necessary for opioid, analgesic activity have been identified from the action of the analogues. Systematic simplification demonstrated that much of the morphine ring structure could be modified or even eliminated. The piperidine ring, in a chair conformation, (Fig. 1) and in particular the nitrogen atom of that ring, appears essential to pharmacological activity. The nitrogen is believed to attach to an anionic center in the receptor. Also crucial is the presence of the phenyl ring which, through van der Waals forces, binds to the hydrophobic portion of the receptor. As in any receptor-ligand interaction, the sterochemistry of the chiral center shown in Figure 1 must be maintained.

In the late 1930s, meperidine [57-42-1], $C_{15}H_{21}NO_2$, (Fig. 1) was identified as a potent μ receptor agonist (15). The later analogues, fentanyl (**6**) (Table 2) and alphaprodine [77-20-3], $C_{16}H_{23}NO_2$, (Fig. 1), also retain the key 4-phenyl piperidine ring structure. These agents appear to interact more strongly with the κ receptor than morphine, although they are still strong μ agonists. Fentanyl is more potent than morphine, has a much shorter duration of action, and is used to aid the induction and maintenance of inhaled anesthesia. Meperidine and alphaprodine are less potent than morphine, requiring 75 (0.30 mmol) and 40 (0.15 mmol) mg, respectively, to equal the effectiveness of 10 mg (0.04 mmol) of morphine. However, they are more effective orally than morphine, without producing constipating or antitussive effects. Meperidine causes the same degree of respiratory depression as morphine at equivalent doses and is definitely addictive (16).

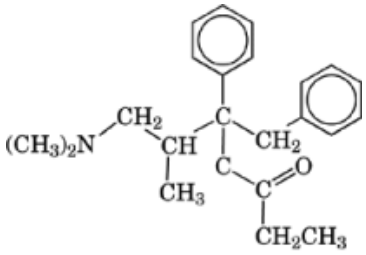
Table 2. Synthetic Morphine Analogues

Name	CAS Registry Number	Molecular formula	Structure number	Structure
levorphanol	[77-07-6]	$C_{17}H_{23}NO$	(**3**)	
hydromorphoneoxymorphone	[466-99-9][76-41-5]	$C_{17}H_{19}NO_3C_{17}H_{19}NO_4$	(**4**, R = OH)(**4**, R = OH)	
phenazocine	[127-35-5]	$C_{22}H_{27}NO$	(**5**)	
fentanyl	[437-38-7]	$C_{22}H_{29}NO_2$	(**6**)	

Phenylpropylamines are another structural class of receptor agonist. The two most important members are methadone [76-99-3], $C_{21}H_{27}NO$, (**8**) (17), discovered in Germany during World War II, and propoxyphene [469-62-5], $C_{22}H_{29}NO_2$, (**9**).

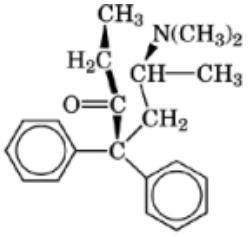


(**8**)



(**9**)

These compounds can adopt a conformation that mimics a disubstituted pseudopiperidine ring.

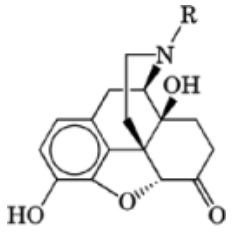


(**8**)

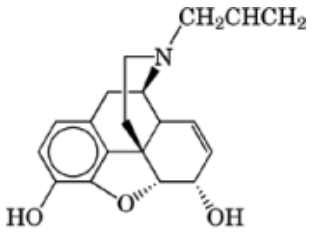
Methadone is orally active, having analgesic potency as great as morphine and longer duration of action. Although as potentially addictive as morphine, methadone causes less severe but more prolonged withdrawal symptoms and is therefore primarily used for the treatment of compulsive heroin users (18). In contrast, propoxyphene is a weak analgesic, only about half as potent as codeine and is often formulated with aspirin or acetaminophen, resulting in combinations which are more effective than either agent alone. Although propoxyphene has less potential for abuse than codeine, the actual incidence of abuse is equivalent, and hundreds of people die each year in the United States from overdoses.

4. Opioid Antagonists and Partial Agonists

The replacement of the *N*-methyl group on the nitrogen atom of the piperidine ring of morphine and analogues by allyl, isopropyl, or methyl cyclopropyl, an isopropyl isostere, results in compounds which antagonize opioid responses, especially respiratory depression. Naloxone [465-65-6], $C_{19}H_{21}NO_4$ (**10** R = CH_2CHCH_2), and naltrexone [16590-41-3], $C_{20}H_{23}NO_4$ (**10**, R = CH_2—cyclopropyl), are both derived from oxymorphone (Table 2) and exhibit agonist activity only at doses that are of little clinical significance (19). In the absence of opioid drugs, naloxone does not cause analgesia, respiratory depression, or sedation. However, when administered with an opioid analgesic, the effects produced by the opioid agonist are promptly reversed. The ability to antagonize opioids at all of the different opioid receptors makes naloxone useful for the treatment of opioid overdose. As is typical for opioid antagonists, naloxone induces withdrawal symptoms in patients addicted to opiatelike drugs. Dosage is generally 0.4 mg (0.001 mmol) given intravenously in several doses because of the drug's short half life. Naltrexone has a similar profile, but it is orally active and has a significantly longer half life.



(**10**)

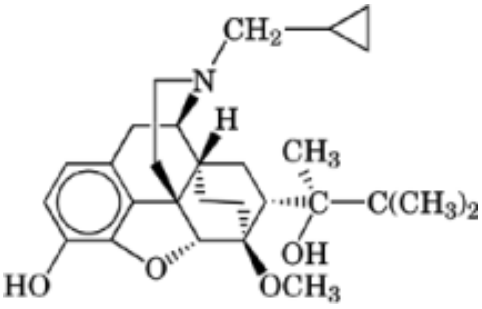
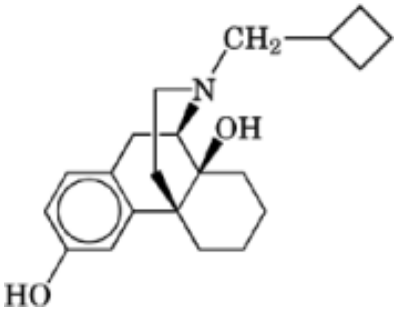
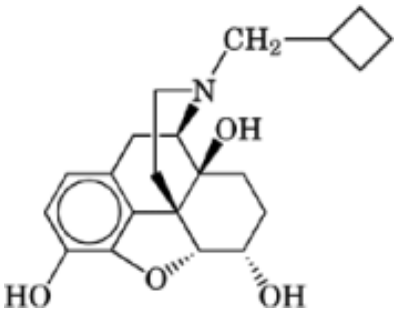
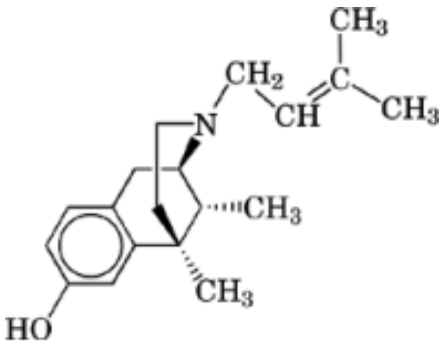


(**11**)

Before the introduction of naloxone, nalorphine [62-67-9], $C_{19}H_{21}NO_3$ (**11**) was the drug most often used for opioid overdose (20). Originally developed in the early 1940s, nalorphine is a morphine derivative and displays both agonist and antagonist properties. By itself, nalorphine causes typical agonist effects, analgesia and respiratory depression (21), but after administration of an opioid, such as morphine, it acts as an antagonist and negates the opioid's agonist effects (22). Its usefulness as an agonist is limited by the dysphoria it causes, and its use as an antagonist has been supplanted by the more effective naloxone.

The quest for compounds that combined the analgesic properties of morphine, were nonaddictive, and lacked the side effects of nalorphine, led to the development of the drugs shown in Table 3. These compounds have both agonist and antagonist activities. Nalbuphine (**14**) (23) and buprenorphine (**12**) (24) are semisynthetic materials derived from oxymorphone (**4**, R = OH) and thebaine (**2**) respectively, whereas pentazocine (**15**) (25) and butorphanol (**13**) (26) are benzomorphan and morphan derivatives. Although structurally similar, they display different receptor affinities: pentazocine is a weak μ-antagonist, but a strong agonist of the κ-receptor; nalbuphine is a competitive antagonist for the μ-receptor, blocking the effects of the morphinelike drugs, but is a partial agonist for the κ and ς receptors; and buprenorphine is a partial agonist for the μ-receptor.

Table 3. Drugs Exhibiting Both Opioid Agonist and Antagonist Activities

Compound name	CAS Registry Number	Molecular formula	Structure number	Structure
buprenorphine	[52485-79-7]	$C_{29}H_{41}NO_4$	(**12**)	
butorphanol	[42408-82-2]	$C_{21}H_{29}NO_2$	(**13**)	
nalbuphine	[20594-83-6]	$C_{21}H_{27}NO_4$	(**14**)	
pentazocine	[359-83-11]	$C_{19}H_{27}NO$	(**15**)	

Pharmacologically, the effects of the drugs in Table 3 resemble those of opioid agonists. All four have analgesic potency equal to or greater than morphine and like morphine, they cause respiratory depression. A ceiling effect is reached, however, above which increased doses do not increase respiratory depression or do not produce proportionally greater depression. Buprenorphine causes a slow onset of the depression, and once the effects have begun, naloxone does not readily reverse the symptoms, suggesting that buprenorphine dissociates very slowly from opioid receptors. In all of these drugs except buprenorphine, high doses induce withdrawal symptoms in opioid dependent patients.

5. Other Analgesic Agents

Most analgesic agents rely on agonism of the μ receptor for their activity, however the ability of the κ and δ receptors to induce analgesia is also well documented (27). For example, the known μ receptor antagonist nalorphine is a κ agonist and still retains analgesic properties. Some nonmorphine analgesics which may preferentially bind to κ and δ receptors are found in Table 4. Spiradoline (**19**, X = H, Y = Cl), a κ agonist identified in preclinical studies, has good analgesic activity and little respiratory or gastrointestinal side effects (28, 29). However spiradoline also produced sedative and psychomimetic effects in humans (30) preventing its development. No κ agonist has undergone rigorous clinical investigation, and the concept of a κ agonist analgesic as an alternative to morphine is not yet clinically validated.

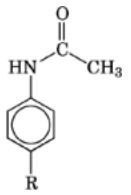
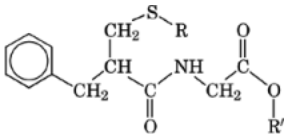
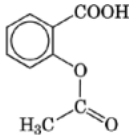
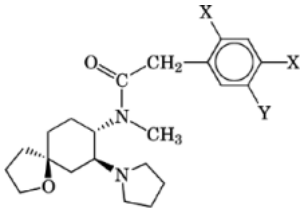
Unselective and μ selective antagonists are well known, but there are few known selective κ receptor antagonists. The first of these, norbinaltorphimine [105618-26-6], (nor BNI), $C_{40}H_{43}N_3O_6$ has 400-fold selectivity for κ over μ receptors and 250-fold for κ over δ (31). Two derivatives of spiradoline (**19**, X = H, Y = Cl) which lack the saturated furan ring, [125132-66-3], $C_{20}H_{27}N_3OS$, where X = NCS, Y = H, and [122407-13-0], $C_{20}H_{25}Cl_2N_3OS$, where X = NCS, Y = Cl, are site-directed, irreversible inhibitors of κ receptors, designed through modification of the spiradoline class of compounds (32). Although these drugs inhibit binding to κ receptors by 90%, they fail to bind all of the previously identified κ receptors, which suggests heterogeneity of the κ receptors.

It has also been suggested that the δ-receptor mediates analgesia. A synthetic peptide, D-Pen (2), D-Pen (5) enkephalin (DPDPE), a specific δ agonist (33), has produced analgesia in test animals, implying that agents of this type could be useful (34). Further studies demonstrated that mice deficient in μ, but not δ, receptors still perceive analgesia when given morphine or DPDPE thus confirming δ mediated analgesia (35). Administration of a δ selective enkephalin to morphine tolerant patients produced clinically significant pain relief, demonstrating that problems of tolerance may be avoided by using drugs of different pharmacological specificity (36). Although active *in vivo,* these drugs are rarely used systematically, because of very poor penetration of the blood brain barrier. The ability of an exogenous δ-receptor agonist to elecit meaningful analgesia in humans has not been demonstrated.

An alternative to the administration of exogenous analgesic agents is to encourage the stability of the endogenous agonists. The endogenous ligand, enkephalin, is enzymatically inactivated by enkephalinases (37) and a strategy to inhibit this event may increase its concentration and duration of action (see Enzymes, inhibitors and antagonists). When administered intravenously, acetorphan, (**17**, R = $COCH_3$, R′ = $CH_2C_6H_5$), a prodrug of thiorphan (**17**, R = R′ = H), the first reported enkephalinase inhibitor, produced analgesia in post-myelography headache pain, but not in shock-induced pain (38). There was no tolerance or dependence observed.

Numerous neuropeptides are believed to be involved with the transmission or inhibition of pain, and the hope is to utilize this approach as a strategy to induce analgesia. Substance P is reported to be a transmitter of nociceptive impulses (39), and therefore antagonists should be analgesic. Capsaicin [404-86-4], $C_{18}H_{27}NO_3$, is known to deplete substance P and cause analgesia (40), but its side effects are intolerable. Antagonists

Table 4. Nonmorphine Analgesics

Name	CAS Registry Number	Molecular formula	Structure number	Structure
acetaminophenacetanilide phenacetin	[103-90-2][103-84-4][62-44-2]	$C_8H_9NO_2$ C_8H_9NO $C_{10}H_{13}NO_2$	(**16**, R = OH)(**16**, R = H)(**16**, R = OC_2H_5)	
acetorphanthiorphan	[81110-73-8][76721-89-6]	$C_{21}H_{23}NO_4S$ $C_{12}H_{15}NO_3S$	(**17**, R = $COCH_3$, R′ = $CH_2C_6H_5$)(**17**, R = H, R′ = H)	
aspirin	[50-78-2]	$C_9H_8O_4$	(**18**)	
spiradoline	[87173-97-5][a]	$C_{22}H_{30}Cl_2N_2O_2$	(**19**, X = H, Y = Cl)	

[a] The Registry Number is for the monomethanesulfonate, CH_3SO_3H, salt.

to bradykinin [58-82-2], $C_{50}H_{73}N_{15}O_{11}$, a substance known to induce pain (41), have shown some success in preclinical trials.

6. Antiinflammatories and Antipyretics

Most of the time, the powerful analgesia supplied by morphine and the other opioid analgesics is not needed. Rather, a mild analgesic, such as aspirin, the most commonly employed analgesic agent, can be used for the treatment of simple pain associated with headaches, minor muscle pain, mild trauma, arthritis, cold and flu symptoms, and fever.

Aspirin, the oldest of the nonsteroidal antiinflammatory drugs (NSAIDs), is a member of the salicylate group. Salicyclic acid, isolated in 1838 from willow bark, was commonly used throughout the Middle Ages for the treatment of headaches. Its therapeutic benefits were well known even to Hippocrates. Many derivatives have

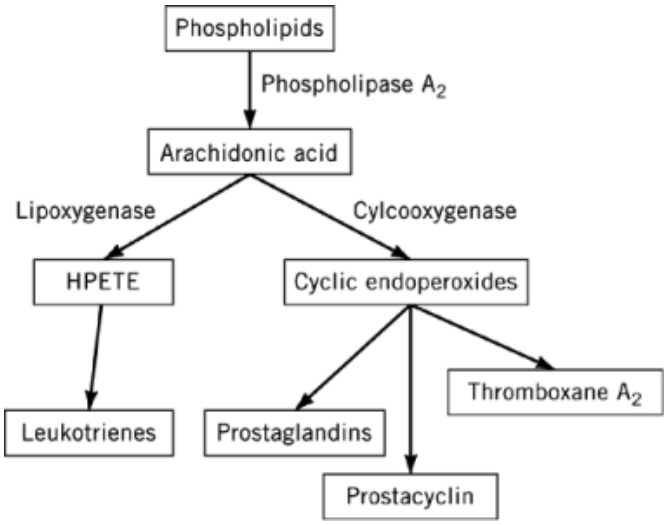


Fig. 2. Arachidonic acid cascade, HPETE=hydroperoxyeicosa−tetraenoic acids.

been prepared to reduce the irritation associated with the pure acid. The most common form is acetylsalicyclic acid [50-78-2] (**18**). Aspirin is an effective treatment for pain, fever, and for symptoms of acute inflammation. It is often the first treatment for the pain and swelling associated with rheumatoid arthritis. Because of its frequent usage, there are over 10,000 cases of serious salicylate intoxication in the United States every year. Many of these cases involve children, and some are fatal. High doses or chronic use of aspirin may aggravate peptic ulcer symptoms, generate gastric ulceration and bleeding, and produce acid-base and electrolyte imbalance.

Aspirin's pain relief results, not through direct action on the central nervous system, but rather through peripheral action. It has been proposed (42) that aspirin and aspirin-like drugs inhibit the enzymatic production of prostaglandins, a group of endogenous agents which are well known to cause erythema, edema, pain, and fever (43). Aspirin does not act as a prostaglandin receptor antagonist, rather it blocks the cyclooxygenase enzyme catalyzed conversion of arachidonic acid [506-32-1], $C_{20}H_{32}O_2$ to cyclic endoperoxides, a prostaglandin precursor as shown in Figure 2. Aspirin controls the synthesis and ultimately the release of prostaglandins from mammalian cells, producing an analgesic effect by decreasing the availability of prostaglandins which typically potentiate the effect of bradykinin on receptors which mediate pain.

The action of endogenous pyrogens on the hypothalmus produces fever, because of a readjustment in the central set point controlling the body's internal temperature. Salicylates and other NSAIDs achieve their antipyretic effect by controlling the prostaglandin-induced release of pyrogens (44). However, hyperthermia induced by exercise, heat stroke, heat exhaustion, or drugs is not affected (45). In these cases the increased temperature is a result of insufficient heat loss. Salicylates block the synthesis of thromboxane A_2, which, in concert with prostacyclin [35121-78-9], controls platelet aggregation (46). The result is a decrease in the clotting rate, a condition which lasts long after the analgesic effects of aspirin and other NSAIDs have worn off and which can have serious consequences for those about to undergo surgery, but may be beneficial for those with a tendency towards thrombosis.

A second class of NSAIDs, the so-called coal tar analgesics, are derived from acetanilide (**16**, R = H). Although it is no longer used therapeutically, its analogues, phenacetin (**16**, R = OC_2H_5) and the active metabolite, acetaminophen (**16**, R = OH) are effective alternatives to aspirin (47). They have analgesic and antipyretic effects that do not differ significantly from aspirin, but they do not cause the gastric irritation, erosion, and bleeding that may occur after salicylate treatment. In contrast to aspirin, however, they are not

cyclooxygenase inhibitors and have no antiinflammatory properties. Clinically acetaminophen is preferred over phenacetin, because it has less overall toxicity.

A more recently introduced, nonprescription analgesic is the aryl propionic acid, ibuprofen (**20**) (48), shown in Table 5, which offers significant advantages over aspirin. Ibuprofen, a cyclooxygenase inhibitor, displays good antiinflammatory activity. It is more potent than aspirin and has a lower incidence of gastrointestinal irritation, although at high doses or chronic exposure, gastric irritation, as well as some renal toxicity, has been observed. Ibuprofen is more effective than propoxyphene (**9**) in relieving episiotomy pain, pain following dental extractions, and menstrual pain.

Table 5. Nonsteroidal Antiinflammatory Drugs

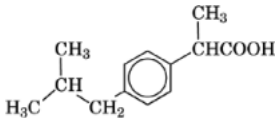
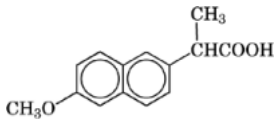
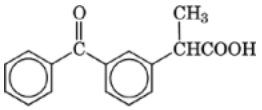
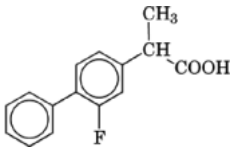
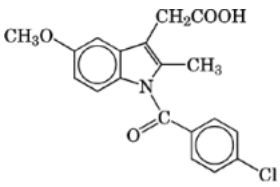
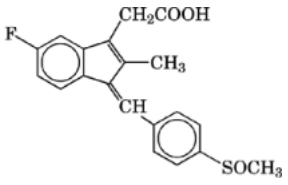
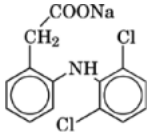
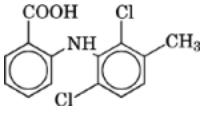
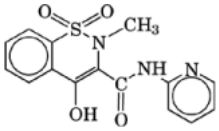
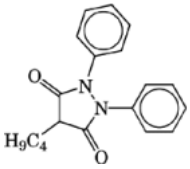
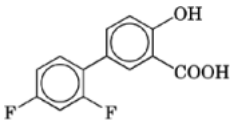
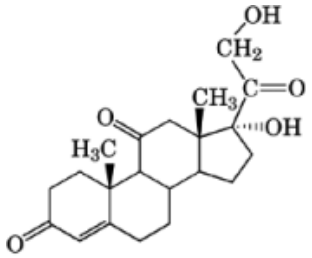
Name	CAS Registry Number	Molecular formula	Structure number	Reference	Structure
			Aryl propionic acids		
ibuprofen	[15687-27-1]	$C_{13}H_{18}O_2$	(**20**)		
naproxen	[22204-53-1]	$C_{14}H_{14}O_3$	(**21**)	50	
ketoprofen	[22071-15-4]	$C_{16}H_{14}O_3$	(**22**)	51	
flurbiprofen	[5104-49-4]	$C_{15}H_{13}FO_2$	(**23**)	52	
			Indoles		
indomethacin	[53-86-1]	$C_{19}H_{16}ClNO_4$	(**24**)	53	

Table 5. ***Continued***

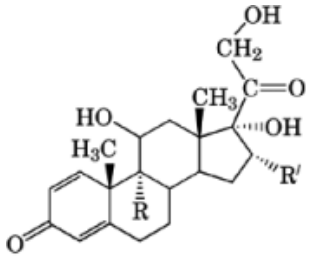
Name	CAS Registry Number	Molecular formula	Structure number	Reference	Structure
sulindac	[38194-50-2]	$C_{20}H_{17}FO_2S$	(**25**)	53	
			Fenamates		
diclofenac	[15307-79-6]	$C_{14}H_{11}Cl_{12}NO_2Na$	(**26**)	54	
meclofenamate	[644-62-2]	$C_{14}H_{11}Cl_2NO_2$	(**27**)	55	
			Others		
piroxicam	[36322-90-4]	$C_{15}H_{13}N_3O_4S$	(**28**)	56	
phenylbutazone	[50-33-9]	$C_{16}H_{20}N_2O_2$	(**29**)		
diflunisal	[22494-42-4]	$C_{13}H_8F_2O_3$	(**30**)	57	

Ibuprofen only recently emerged from an ever growing collection of prescription NSAIDs (49) many of which are shown in Table 5. All of these drugs act by inhibiting the cyclooxygenase enzyme (Fig. 2) and there is little to distinguish in terms of analgesic effectiveness. When prescribed for the treatment of arthritis, patients require large doses for extended periods, exacerbating the side effects. Differences among drugs are found in dose levels, duration of action, and the incidence of gastric ulceration.

The adrenal cortex produces steroidal hormones that are associated with carbohydrate, fat, and protein metabolism, electrolyte balance, and gonadal functions (58). One of these, cortisone [53-06-5], $C_{21}H_{28}O_5$ (**31**), demonstrated a remarkable ability to relieve the symptoms of inflammatory conditions (59). Other glucocorticoid steroids, such as dexamethasone [50-02-2], $C_{22}H_{29}FO_5$ (**32**, R = F, R′ = CH_3), and prednisolone [53-03-2], $C_{21}H_{28}O_5$ (**32**, R = R′ = H), also have antiinflammatory properties.



(31)



(32)

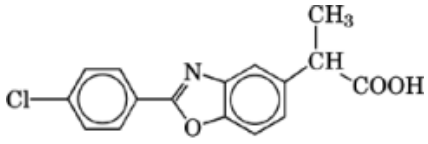
These steroids are capable of preventing or suppressing the development of the swelling, redness, local heat, and tenderness which characterize inflammation. They inhibit not only the acute symptoms of the inflammatory process, such as edema, fibrin deposition, and capillary dilatation, but also the chronic manifestations. There is evidence that glucocorticoids induce the synthesis of a protein that inhibits phospholipase A_2 (60), diminishing the release of arachidonic acid from phospholipids (Fig. 2), thereby reducing chemotaxis and inflammation.

Unfortunately steroids merely suppress the inflammation while the underlying cause of the disease remains. Another serious concern about steroids is that of toxicity. The abrupt withdrawal of glucocorticoid steroids results in acute adrenal insufficiency. Long term use may induce osteoporosis, peptidic ulcers, the retention of fluid, or an increased susceptibility to infections. Because of these problems, steroids are rarely the first line of treatment for any inflammatory condition, and their use in rheumatoid arthritis begins after more conservative therapies have failed.

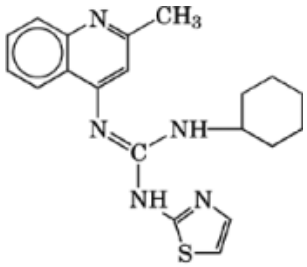
Analgesic antiinflammatory drugs having alternative mechanisms of action are under study. Whereas conventional therapies inhibit prostaglandin synthesis, other products of arachidonic acid metabolism (Fig. 2), such as the leukotrienes (LTs), have yet to be investigated. The 5-lipoxygenase enzyme begins a cascade

of events which converts arachidonic acid to LTB4, LTC4, LTD4, and LTE4 (61). In particular LTB4 plays a significant role in the recruitment of cells to the inflammatory site and is a potent mediator of immune responses. An antagonist of such a mediator might be efficacious in the treatment of inflammation.

The inhibition of both the lipoxygenase and cyclooxygenase pathways of arachidonic acid metabolism could offer improved therapy over conventional NSAIDs. Benoxaproten [51234-28-7], $C_{16}H_{12}ClNO_3$ (**33**), a potent cyclooxygenase and lipoxygenase inhibitor, was introduced in 1982 (62). In clinical trials benoxaprofen showed good analgesic and antiinflammatory activity, but it was removed from the market within months of its release because of unacceptable levels of renal toxicity. The toxicity may not, however, have been related to the mechanism of action (63). Timegadine [71079-19-1], $C_{20}H_{23}N_5S$ (**34**), a drug having a similar mechanistic profile, is undergoing clinical trials (64).



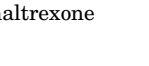
(**33**)



(**34**)

Advances in the isolation and purification of lymphokine and monokine growth and differentiation factors offer the opportunity to interfer with the inflammatory process at the cellular level (65). The best understood factors are the interleukins (1–9), tumor necrosis factor, and the interferons. Produced by activated macrophages, and other cells, interleukin 1 (IL-1) is a local and hormonal mediator, which induces acute phase responses, local inflammation, and pyrogenicity. It is linked to rheumatoid arthritis, psoriasis, gingivitis, gout, islet destruction in diabetes, and wound healing (66). One of the principal functions of IL-1 is to induce the synthesis and release of interleukin 2 (IL-2) (67). IL-2 is a T-cell growth factor, which stimulates the proliferation of T-cells and the release of numerous T-cell cytokines (68), thus amplifying the immune response. Interleukin 4 is produced by T-cells, but acts principally on B-cells and enhances the B-cell's ability to present antigen to T-cells (69). Interleukin 6 (IL-6) is produced by various cell lines upon stimulation with IL-1 or tumor necrosis factor. It acts as a B-cell growth and differentiation factor and acts in concert with interleukin 3 to induce proliferation of pre B-cells in culture (70).

Table 6. Trade Names and Procedures of Analgesics, Antipyretics, and Antiinflammatory Drugs

Compound name	Structure number	Trade name	Producer
levorphanol	(**3**)	Dromoran	Hoffman-LaRoche
phenazocine	(**5**)	Prinadol	Smith Kline & Beecham
meperidine	(1, R′ = H, R = $COOC_2H_5$)	Demerol	Winthrop
propoxyphene	(**9**)	Darvon	Eli Lilly
naloxone	(**10**, R = CH_2CHCH_2)	Narcan	Du Pont
naltrexone	(**10**, R = )	Trexan	Du Pont
nalbuphine	(**14**)	Nubain	Du Pont
buprenorphine	(**12**)	Buprenex	Norwich Eaton
pentazocine	(**15**)	Talwin	Winthrop
butorphanol	(**13**)	Stadol	Bristol
acetaminophen	(**16**, R = OH)	Tylenol	McNeil
ibuprofen	(**20**)	Motrin	Upjohn
naproxen	(**21**)	Naprosyn	Syntex
ketoprofen	(**22**)	Orudis	Wyeth
flurbiprofen	(**23**)	Ansaid	Upjohn
indomethacin	(**24**)	Indocin	Merck Sharpe & Dohme
sulindac	(**25**)	Clinoril	Merck Sharpe & Dohme
diclofenac	(**26**)	Voltaren	CIBA-GEIGY
meclofenamate	(**27**)	Meclomen	Parke-Davis
piroxicam	(**28**)	Feldene	Pfizer
diflunisal	(**30**)	Dolobid	Merck Sharpe & Dohme
benoxaprofen	(**33**)	Oraflex	Eli Lilly

7. Economic Aspects

Analgesics and antiarthritics represent significant worldwide pharmaceutical markets. Table 6 lists trade names and producers of some of the more commercially important agents. The 1989 analgesic market was estimated at approximately $4.0 billion. Of that figure, $792 million is represented by opioid analgesics, whereas much of the nonnarcotic portion of the market is represented by NSAIDs. The 1989 antiarthritic market approached $5 billion. Sales of prescription and nonprescription NSAIDs within this market were approximately $4.5 billion. This figure includes both antiinflammatory and analgesic uses of these agents. The antiarthritic market is expected to continue to grow at a significant rate as the worldwide population ages.

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