

Non-opioid analgesics

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Abstract

Opium is the natural substance to which modern narcotics owe their existence. First discovered in the 1500s, opium was the most potent analgesic compound in use, held in high regard, hence its Latin name *laudanum* (to praise). Subsequent studies into the effects of opium led to the discovery of the opioid receptors, and then later structure-activity-relationship (SAR) studies led to the development of compounds able to interact with these receptors, and then finally, the synthesis of orphanin FQ, a synthetic ligand manufactured specifically to fit the nociceptin opioid receptor (NOP) G-protein coupled receptor (GPCR). This common ancestry of opioid derivatives brings a common pattern of adverse effects which are problematic and clinically limiting.

These adverse effects have necessitated the development of non-opioid analgesics, both as sole agents and as part of multimodal, opioid sparing regimens. Whilst the mainstays of non-opioid analgesia are accepted practice, as our knowledge of pain pathways increases, this highlights new therapeutic targets which may act synergistically with existing treatments.

Additionally, whilst effective for acute pain, opiate analgesia is of limited effectiveness for chronic and neuropathic pain states, such as phantom limb pain. This is partly due to problems with chronic administration and pharmacologic tolerance although also relates to different mechanisms of acute (e.g. surgical) and chronic pain and involvement of additional neurotransmitters such as substance P, γ -amino butyric acid (GABA) and glutamate.

This article will give an overview of the pain pathway, highlight therapeutic targets and revisit common non-opioid analgesic agents currently in use.

Keywords Analgesics; NSAID; opioids; pain; paracetamol

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The pain pathway, from macroscopic to receptor targets

The pain pathway and pain physiology have already been described in detail elsewhere and is outside the scope of this paper; a detailed knowledge of the macro- and molecular

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Learning objectives

After reading this article you should be able to:

- describe the pain pathway at a macroscopic and molecular level, stating receptor targets for novel analgesics
- state a broad classification system for non-opioid analgesics
- describe the concept of multimodal analgesia and give examples

processes involved in nociception are critical to the identification of novel analgesic targets within this system. An overview is given below, in [Figure 1](#) which illustrates points in the pathway where therapeutic targets exist for modulation of nociception.

Reducing inflammatory pain stimuli

Inflammatory mediators are potent activators of nociceptors; additionally, they have a role in sensitization of the peripheral nervous system and chronic pain. Anti-inflammatory drugs have a role in preventing the onset of inflammation and sensitization.

Modulating the peripheral threshold for stimulus transmission

The sensitivity of nociceptors may be modulated by the surrounding 'sensitising soup' of inflammatory mediators. Transient receptor potential cation channel subfamily V member 1 (TRPV1) is a ligand-gated ion channel which is responsible for modulating the peripheral pain stimulus. Stimulation of TRPV1 produces nerve depolarization such that the nerve remains refractory, significantly reducing nociceptive transmission. Capsaicin gel is effective in this context for the treatment of arthritic inflammatory joint pain.¹

Modulating afferent transmission in the spinal cord

The substance gelatinosa in the spinal cord is responsible for the processing of afferent stimuli, the basis of 'gate control theory'. Nociceptive signals arriving at the cord are subject to descending and local modulation, under the control of the periaqueductal grey matter in the medulla and the nucleus raphe magnus. Systemic opioids activate descending inhibitory pathways. Potentially, preventing the breakdown of endogenous opioids may represent a new mode of analgesia.

The dorsal horn of the spinal cord has a multitude of receptors, the pathways of afferent nociception are complex and not fully understood. Drugs known to promote analgesia through activity at this level include α_2 agonists (clonidine), ketamine (NMDA) and tramadol (serotonin (5-HT) inhibitor and mu opioid peptide (MOP) agonist).

Modulating central transmission

The central pain pathways are complex, with afferent inputs from the spinothalamic tracts in the spinal cord to the thalamus. There are interconnections with diffuse areas including the cortex, hypothalamus, nucleus raphe magnus and periaqueductal grey.

These pathways may be modulated via inhibitory (GABA) or excitatory (glutamate and aspartate) neurotransmitters. The cannabinoid family of compounds acts on CB1 and CB2

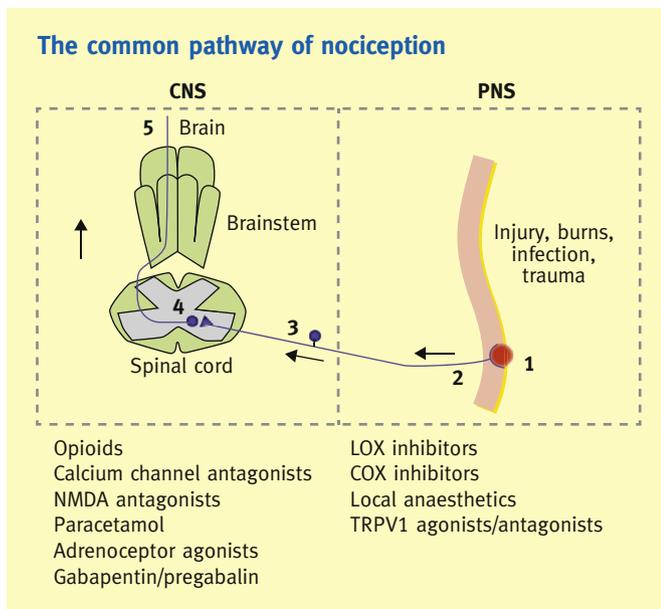


Figure 1 (1) Noxious stimuli cause activation of *peripheral nociceptors*. Noxious inflammatory mediators (or their synthesis) may be blocked directly (e.g. COX inhibitors), or the nociceptive afferents may be hyperpolarized (Na⁺ antagonists e.g. local anaesthetics). (2) Signals are *encoded* to reflect modality, site and intensity. (3) *Transmission* along nociceptive afferents. (4) Afferent signals synapse in the substantia gelatinosa in the dorsal horn of the spinal cord, where they synapse with interneurons in the nucleus proprius, and thence with the neurons of the ascending tracts. The spinal cord is a major site of modulation from downward inhibitory influences and other local influences and hence a major pharmacological target (Ca²⁺ antagonists, opiates, NMDA antagonists). (5) Finally, signals pass to the thalamus, and then on to the cortex where there are numerous synapses with wider brain regions for influences on mood, autonomic nervous system etc. These wider influences are affected by drugs including paracetamol (COX-3) and cannabinoids. CNS, central nervous system; HTM, high-threshold mechanoreceptors; NMDA, N-methyl-D-aspartate; PMN, polymodal nociceptors; PNS, peripheral nervous system; TRPV1, transient receptor potential cation channel subfamily V member 1.

cannabinoid receptors and are thought to influence pain thresholds. A recent mechanism is the modulation of the serotonergic system to influence pain via tramadol and tapentadol.

Clearly, in addition to the use of non-opioid drugs, there are other techniques such as regional anaesthesia, nerve ablations and physical therapies which may be employed in the treatment and management of pain; these are outside the scope of this review. The whole range of non-opioid medications is too expansive to examine in its entirety in this article, although we will discuss examples from each class as shown in [Table 1](#).

Non-opioid drugs may be used in both acute and chronic pain. There are different underlying mechanisms controlling acute and chronic pain, although the complexities of pain perception may lead to crossover (for example, a nerve injury or neuropathic pain originating at the time of surgery, coexisting with acute inflammatory pain).

Paracetamol

Paracetamol (acetaminophen) is a commonly used analgesic, related to non-steroidal anti-inflammatory drugs (NSAIDs), sharing antipyretic and analgesic properties and useful for mild-to-moderate pain and as part of opioid-sparing multimodal analgesia.²

Paracetamol has a favourable pharmacologic profile; being well absorbed from the gut and subject to minimal first pass metabolism, it has a high oral bioavailability of greater than 60%. It distributes rapidly, into a small volume of distribution and is therefore rapidly cleared from the body. Metabolism is by the hepatic cytochrome P450 system, and therefore is reduced in liver failure. Renal clearance is minimal and therefore only affected in severe renal impairment. This profile means that paracetamol is generally safe and efficacious.

Despite being a ubiquitous drug, the mechanism of action of paracetamol is poorly understood. Paracetamol shares properties with NSAIDs and is thought to antagonize COX. A newly discovered centrally located isoform COX-3 is also inhibited and has been implicated in the mechanism of paracetamol action.^{3,4}

Classes of non-opioid drugs and their mechanisms. (Drugs and classes in italics below are covered in this article.)

	Drug	Mechanism	Acute	Chronic
Peripheral modulation	<i>Paracetamol</i>	Multiple	✓	✓
	<i>NSAIDs</i>	Inhibition of the release of local mediators	✓	✓
	<i>COX-2 inhibitors</i>	Inhibition of the release of local mediators	✓	✓
	<i>Capsaicin analogues</i>	Local desensitization		✓
Spinal modulation	<i>Gabapentin</i>	Membrane stabilization		✓
	<i>Ketamine</i>	NMDA	✓	
	<i>Pregabalin</i>	Membrane stabilization		✓
	<i>Clonidine</i>	α-2 adrenoceptor	✓	✓
Central modulation	<i>Carbamazepine</i>	Sodium channels		✓
	<i>Cannabinoids</i>	Modulation of central transmission		✓
	<i>Tapentadol</i>	5-HT and noradrenaline	✓	✓

5-HT, serotonin; NMDA, N-methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 1

The differences in side effect profile with the NSAIDs imply other mechanisms not fully understood. Interactions with the NMDA receptor, serotonergic pathways and cannabinoid receptors have been suggested to be part of the central mechanism of paracetamol. This may be a truly multimodal drug, acting on a multitude of systems which may explain why it is so efficacious without significant side effects.

NSAIDs, COX-2 inhibitors and related drugs

The NSAIDs consist of a group of compounds which share anti-inflammatory, antipyretic, anti-uricaemic and analgesic properties. They act via inhibition of the cyclo-oxygenase (COX) enzyme system, which leads to reduced inflammatory pain, but also deleterious effects through lack of thromboxane, prostaglandins and prostacyclins (Figure 2). There are three numbered enzyme subtypes, with COX-1 and 2 having a role in pain and inflammation. The significance of COX-3 is uncertain.

Prostaglandins regulate renal blood flow and gastric mucosal protection and are critical to the inflammatory response, promoting cellular chemotaxis, the recruitment of immune cells to sites of inflammation. The nonspecific blockade of these compounds is therefore associated with deranged renal autoregulation, gastric irritation, bleeding and impaired wound healing.

COX-1 is constitutively expressed and responsible for the general effects of these compounds, whereas COX-2 is upregulated in inflammation. This was the premise behind the development of COX-2 selective inhibitors. Whilst these are no longer recommended due to cardiovascular side effects (with the exception of parecoxib), nonspecific COX inhibitors have some receptor selectivity (Table 2).

Individual trials show differences in the relative incidence of upper gastrointestinal (GI) haemorrhage in patients taking NSAIDs, due to differences in the population under study. The overall incidence of adverse effects is related to patient- and drug-related factors. Smokers, patients with a past history of GI haemorrhage and those taking anticoagulants are at an increased

risk.⁵ Patients taking NSAIDs for a prolonged duration or who take multiple NSAIDs are also at increased risk. Adjunctive therapy with proton pump inhibitors or misoprostol has been used in the past to reduce this risk, although these drugs are associated with their own adverse effects.

The approach of drug modification and complexing drugs has been used to obliterate these adverse effects, such as the complexing of H₂S or NO with NSAIDs, although no clinical examples of these drugs exist at present. Naproxinod, the first example of the COX-inhibiting nitric oxide donors (CINOD) class has been withdrawn from the USA and UK, despite initially promising trials for use in osteoarthritis.⁶

Novel receptor targets – TRPV1

TRPV1 is a peripheral ion channel located on afferent c type fibres which, when activated by capsaicin, promotes depolarization. Following depolarization, the afferent nerves become refractory and unable to transmit additional signals. Antagonists of TRPV1 may provide analgesia by increasing the stimulus required to generate an action potential.

Clinically, capsaicin is used in the management of inflammatory pain. It is lipid soluble, making it suitable for use as a topical preparation. Adverse effects occur as a result of the hyperstimulation caused by capsaicin; this produces a sensation of paraesthesia when the preparation is first applied. Capsaicin has been demonstrated to be efficacious in the treatment of chronic pain conditions, such as osteoarthritis and postherpetic neuralgia.⁷

Novel receptor targets – cannabinoids

Cannabis is an old analgesic, which has found popularity for the management of chronic painful conditions such as multiple sclerosis, for analgesia, but also for antiemesis and muscle relaxation. Whilst illicit use is widespread, medicinal cannabinoids may be moderately effective for chronic pain and is licensed for some conditions.

The cannabinoid receptors, CB1 and CB2, are G-protein coupled receptors (GPCRs), both located peripherally and centrally. They are linked to the G_{i/o} system in the same manner as opioid receptors, and cause a reduction in afferent transmission.

There is also a suggestion that cannabinoids may be responsible for linkage with the immune system and with reward/tolerance behaviours. The widespread distribution of these receptors is certainly suggestive of a greater role than purely in pain.

Antiepileptic drugs and other therapies

Antiepileptic drugs are commonplace in the pain clinic. Whilst this diffuse class act via a variety of mechanisms, they do share a common central inhibitory, membrane-stabilizing effect, which dampens the sensation of pain. Other mechanisms include inhibition of NMDA, enhanced GABA transmission and membrane stabilization.

Pregabalin and *gabapentin*, named because of their structural similarity with γ -aminobutyric acid (GABA) are both used in the management of chronic pain. Their mechanism is unrelated to this and is thought to involve generalized inhibition of the release of a diffuse range of neurotransmitters (substance P, glutamate,

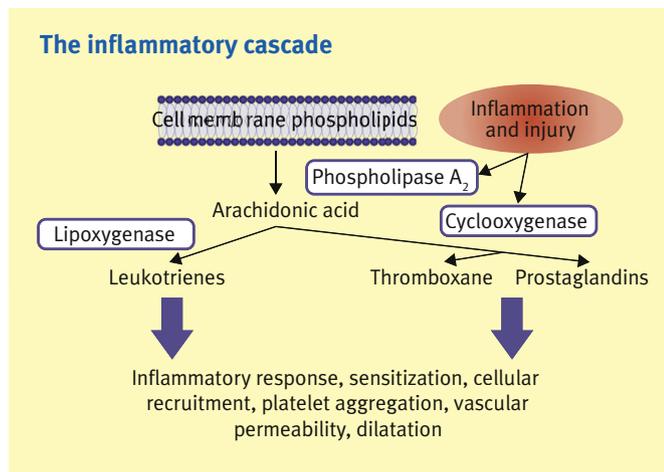


Figure 2 The inflammatory cascade demonstrates the conversion of cell membrane phospholipids into arachidonic acid and subsequently into leukotrienes, thromboxane and prostaglandins. This occurs in response to injury and may be inhibited by direct blockade of the cyclo-oxygenase enzyme, the mechanism of action of NSAIDs.

COX-1/COX-2 specificity correlation with odds ratio (OR) for gastric disease

Drug	Whole blood assay IC ₅₀ (μM)		Selectivity index	OR for gastric disease	Group ^a
	COX-1	COX-2			
Rofecoxib	19	0.53	35.8	—	3
Celecoxib	6.7	0.87	7.7	—	2
Meloxicam	5.7	2.1	2.7	—	2
Paracetamol	>100	49	>2.04	1.2 (1.2–1.5)	—
Diclofenac	0.075	0.038	1.97	4.9 (3.3–7.1)	1
Ibuprofen	7.6	7.2	1.05	1.7 (1.1–2.5)	1
Naproxen	9.3	28	0.33	9.1 (6–13.7)	1
Aspirin	1.7	>100	0.017	—	1
Indomethacin	0.013	1.0	0.013	6 (3.6–10)	1

^a Group 1 – nonselective inhibition of both isoforms, 2 – COX-2 inhibition with 5–50 fold selectivity, 3 – COX-2 inhibition with >50 fold selectivity.⁸

Table 2

aspartate, calcitonin gene-related peptide) linked to voltage-gated calcium channels.⁹

Global central inhibitory effects are utilized in the management of chronic pain conditions such as trigeminal neuralgia (recommended by NICE), neuralgia and painful diabetic neuropathy. More recently, gabapentin is used to prevent spinal cord sensitization post-amputation and after hip replacement.¹⁰ Their additional analgesic, anxiolytic, antiemetic effects and blunting of the response to intubation give these drugs a favourable profile for perioperative use.

Carbamazepine is an anticonvulsant, which provides membrane stabilizing activity by blocking sodium channels. It is recommended as first-line treatment for trigeminal neuralgia by NICE and is supported by systematic reviews.

Fast track surgery and enhanced recovery

Non-opioid analgesic techniques are a key component of modern fast track surgery and enhanced recovery systems. Avoidance of morphine improves mobility, which in turn reduces post-operative complications such as deep vein thrombosis and nosocomial infections.

For example, a fast track protocol for elective hip replacement includes elements which reduce the initial hypersensitization of the spinal cord, supplemented by multimodal intraoperative and postoperative analgesia.¹¹

- Preoperatively
 - Gabapentin premedication
- Anaesthetic
 - Spinal anaesthetic
 - Local anaesthetic nerve block ± wound infusion catheter
- Postoperative
 - Regular paracetamol
 - Regular oxycontin
 - Patient-controlled analgesia for breakthrough pain

Summary

Whilst opioids are the ‘gold standard’ analgesics, used in severe pain, there are complications associated with their use, both in

the short term and long term. The non-opioid drugs provide an alternative and are in some cases, equally efficacious to opioids. The non-opioid analgesics form an interesting and useful class of medications, which is ever expanding with the advent of more targeted therapies with improved efficacy and side effect profiles. ◆

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