Non-opioid analgesics

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Abstract

When it was first discovered in the 1500s, opium was heralded as the most potent analgesic. The Latin name for morphine tincture, *laudanum* (to praise), illustrates the high regard in which it was held. The many adverse effects associated with its use (now attributed to non-specific opioid receptor cross-activation between subtypes) necessitate caution in its use. Even today, the adverse effects still remain problematic and are clinically limiting, both in the acute setting and in chronic use, despite ample research into opioid receptor subtype specific agonists, antagonists and bifunctional molecules.

The adverse effects, such as constipation, nausea, dysphoria, respiratory depression and itching, have necessitated the drive to develop non-opioid-related analgesics, both as sole agents and as part of multimodal, opioid-sparing regimens. For example, paracetamol has been shown to reduce patient-controlled analgesia (PCA) morphine doses by 20% when used as an adjunct for acute post-surgical pain. 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-aminobutyric acid and glutamate.

This article will give an overview of the pain pathway relative to therapeutic targets, revisit some common non-opioid analgesic agents and highlight some novel targets and drugs in development.

Keywords Analgesics; NSAID; opioids; pain; paracetamol

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.

The pain pathway, from macroscopic to receptor targets

The pain pathway and pain physiology have already been described in detail elsewhere and are outside the scope of this paper; a detailed knowledge of the macro- and molecular processes involved in nociception are critical to the identification of novel analgesic targets within this system. An overview is given below, (Figure 1) which illustrates points in the pathway where therapeutic targets exist for modulation of nociception.

(1) Stopping the pain before it starts

Inflammatory mediators are potent activators of nociceptors; additionally, they have a role in wind-up and subsequent chronic pain. Anti-inflammatories (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) — see below) have a role in preventing the onset of inflammation and therefore reducing the wind-up and sensitization that is associated with inflammation.

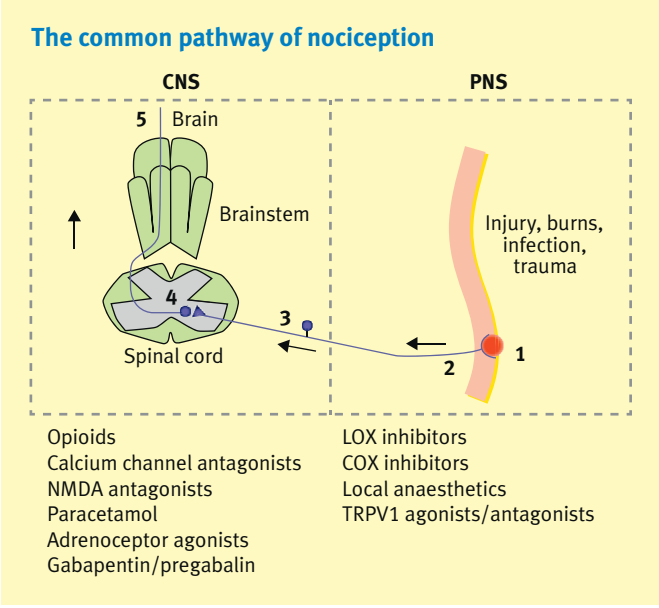

Figure 1 (1) Noxious stimuli cause activation of *peripheral nociceptors*. Noxious inflammatory mediators (or their synthesis) may be blocked directly (e.g. COX inhibitors), or the nociceptive afferents may be hyperpolarized (Na^+ antagonists e.g. local anaesthetics). (2) Signals are *encoded* to reflect 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 interneurones in the nucleus proprius, and hence with the neurones 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 (Ca^{2+} 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; NMDA, *N*-methyl-D-aspartic acid; PNS, peripheral nervous system.

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(2) Modulating the peripheral threshold for stimulus transmission

Nociceptors are activated at the site of the stimulus in response to noxious stimuli, of chemical, mechanical, and thermal means. 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, thereby preventing or significantly reducing afferent transmission. Capsaicin gel is effective in this context for the treatment of arthritic inflammatory joint pain.[1] TRPV1 antagonists are potential novel means of targeting this system to modulate the firing threshold of peripheral nerves.

(3) Modulating afferent transmission in the spinal cord

The substance gelatinosa in the spinal cord is responsible for the processing of afferent stimuli. This is the basis of the 'gate control theory'.[2] Afferent nociceptive signals arriving at the cord are subject to descending and local modulation, which is, in itself subject to higher cerebral control. Descending enkephalinergic pathways are under the control of the periaqueductal grey matter in the medulla and the nucleus raphe magnus. Systemic opioids (in addition to experimental local direct nerve stimulation) affect these pathways. Local modulation occurs via the transmission of non-noxious stimuli through the spinal cord at the given spinal level; the basis of transcutaneous electrical nerve stimulation (TENS).

(4) Modulating central transmission

Central pain pathways are subject to modulation via numerous neurotransmitters. Of current interest is the cannabinoid family of compounds. These act on CB1 and CB2 cannabinoid receptors and are thought to influence pain thresholds.

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 (Table 1).

Paracetamol

Paracetamol (acetaminophen) is a commonly used analgesic, with anti-pyretic and analgesic properties. Discovered accidentially as a metabolite of two experimental compounds, acetanilide and phenacetin in the 1800s, paracetamol remains a ubiquitously used analgesic for mild to moderate pain and as part of opioid-sparing multimodal analgesia.[3] Despite its ubiquity, the mode of action of paracetamol still remains elusive.

Paracetamol has an extremely favourable pharmacologic profile, being well absorbed from the gut and subject to minimal first pass metabolism, it has a high oral bioavailability of >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.

Paracetamol shares properties with NSAIDs although has no effects on the COX-1 or COX-2 variants of the Cyclooxygenase (COX) enzyme system. A third enzyme, COX-3 is inhibited and has been implicated in the mechanism of paracetamol action.[4] The analgesic and anti-pyretic similarities with NSAIDs are appealing and lend weight to this mechanism, although paracetamol does not share anti-inflammatory properties and has significant structural differences which refute this argument. However, this lack of similarity does confer the beneficial property that paracetamol is not associated with gastric erosion or renal damage.

It has been suggested that the central action is due to effects on the *N*-methyl-D-aspartic acid (NMDA) receptor in the spinal cord, which has been implicated in wind-up and central sensitization to peripheral stimuli. Therefore, the administration of pre-procedural paracetamol might be expected to prevent central sensitization under certain circumstances (otherwise known as pre-emptive analgesia). However, pre-emptive analgesia (of any kind) remains an elusive entity and this does not support the implication of NMDA in paracetamol mode of action.

Seretonergic pathways are also known to be affected by paracetamol. These play a role in the central modulation of pain responses in the spinal cord.

It has also been suggested that paracetamol has a role in cannabinoid pathways.

As demonstrated above, the mechanism of paracetamol remains unclear, although there is an increasing basis for a central, multimodal action which, perhaps explains how it still remains effective by targeting multiple points of the pain pathway.

Classes of non-opioid drugs and their mechanisms

Mechanism	Prototypical example
Inhibition of the release of local mediators	Anti-inflammatory drugs (e.g. *Non-steroidal anti-inflammatory drugs, paracetamol*)
Peripheral modulation	*TRPV1*
Spinal modulation	TENS[a] GABA[b] NMDA[c]
Modulation of central transmission	*Cannabinoid ligands* Behavioural therapies

[a] Transcutaneous Electrical Nerve Stimulation.
[b] γ-Aminobutyric acid.
[c] *N*-Methyl D-aspartate.

Table 1

NSAIDs and COX-2 inhibitors

The NSAIDs consist of a group of compounds from a diffuse range of chemical classes, which share anti-inflammatory, anti-pyretic, anti-uricemic and analgesic properties. This mechanism is achieved by inhibition of COX-1 and COX-2, which are responsible for the constitutive and inducible production of thromboxane, prostaglandins and prostacyclins (see Figure 2).

NSAIDs have a multitude of effects within the body (both positive and negative) due to their effects on these substances.

Physiological effects of prostaglandins include the regulation of renal blood flow and gastric mucosal protection and endothelial integrity. They are also critical to the inflammatory response, promoting cellular chemotaxis and the recruitment of immune cells to sites of inflammation (where certain prostaglandins are upregulated in response to the immune system). The non-specific blockade of these compounds is therefore associated

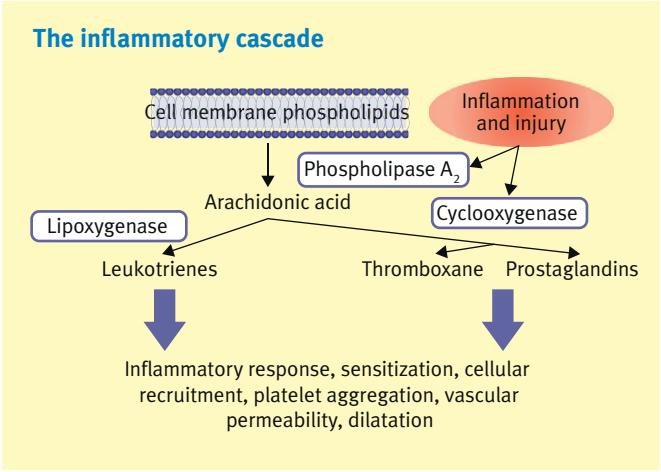

Figure 2 The inflammatory cascade demonstrates the conversion of cell membrane phospholipids into arachidonic acid and subsequently into leukotrienes, thromboxane and prostaglandins. This occurs in response to injury and may be inhibited by direct blockade of the cyclooxygenase enzyme, the mechanism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

with problems with renal autoregulation and blood flow (leading to acute renal failure) and gastric irritation.

The different types of NSAIDs do affect each isozyme to variable degrees and therefore have variable anti-inflammatory and adverse effects; diclofenac has the greatest clinical effect with a number needed to treat (NNT) of 1.8 compared with 2.4 and 2.6 for ibuprofen and ketoralac respectively. For comparison, the NNT of paracetamol is 3.8.[5] Table 2 shows the extent of inhibition of each isozyme.

As the adverse effects are predominantly due to the non-specific effects on constitutively expressed COX, it follows that the incidence of renal impairment and gastric erosion is linked to the activity at COX-1. However, the COX-2 specific antagonists, the coxibs were found to have an unacceptably high rate of cardiovascular complications and have largely been withdrawn, with the exception of parecoxib.

Individual trials show heterogeneity in relative incidence of upper gastrointestinal (GI) haemorrhage in patients taking NSAIDs, although this is likely to be due to differences in the patient populations under study and the presence of confounding factors. Meta-analysis shows the risk of GI haemorrhage to be related to patient and drug-related factors. Irrespective of type of NSAID, smokers, patients with a past history of GI haemorrhage and those taking anticoagulants are at an increased risk.[7] Drug-related factors shown to be significantly related to the risk of haemorrhage are number of concomitant NSAIDs and duration of use, all of which must be taken into consideration when determining the risk-benefit ratio of prescribing or not. The type of NSAID and dose used have a 20-fold and sevenfold effect on the risk of GI haemorrhage respectively.

Adjunctive therapy with proton pump inhibitors or Misoprostol has been used in the past, although these are associated with their own adverse effects.

COX-3 has been recently described as a centrally located enzyme which may have a role in fever and may be the mechanism of action of paracetamol. Discovered by Simmons and colleagues, originally in the dog, COX-3 was shown to be a splice variant of COX-1. The clinical significance of this is uncertain at present.

As Figure 2 shows, the lipoxygenase (LOX) enzyme family is also implicated in the inflammatory response; it has been suggested that a combined LOX/COX inhibitor may be beneficial in treating inflammatory pain. Other combination therapies, such as the COX-inhibiting nitric oxide donors (CINOD) class are in advanced stages of development and the most advanced, naproxcinod is at least as effective as naproxen for the treatment of arthritis, with a 30% reduction in the incidence of gastric ulcer disease.[8]

Novel receptor targets — TRPV1

The transient receptor potential action channel (subfamily V) type 1 (TRPV1) is a peripheral ion channel located on afferent c type fibres which, when activated, promote depolarization. It is multimodal; activated in response to heat, low pH, and chemical stimuli. This coordination of multiple peripheral stimuli may therefore form the basis of a response to pain or the pain threshold.

Agonists at this receptor promote depolarization, thereby rendering the afferent nerves refractory, which subsequently prevents transmission of additional stimuli; there is also depletion of substance P, an inflammatory mediator. Antagonists have also been shown to confer a benefit; raising the threshold stimulus and

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

	Whole blood assay IC50 (μM)				
Drug	**COX-1**	**COX-2**	**Selectivity index**	**OR for gastric disease**	**Group[a]**
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.[6]

Table 2

thereby reducing the afferent transmission of nociceptive signals. Therefore, this is theoretically a promising area of development which has been validated in pre-clinical studies.

Clinically, capsaicin agonists are used in the management of osteoarthritis as an evidence based treatment. Capsaicin confers some useful pharmacological properties. As a synthetic plant alkaloid, it is lipid soluble and may therefore be offered as a transdermal preparation. The 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, postherpetic neuralgia and diabetic retinopathy.[9]

Of equal interest are the TRPV1 antagonists. These drugs are able to globally antagonize this receptor, and also to target specific parts of its response (for example the response to low pH or high temperature). These agents have been limited by their adverse effects — TRPV1 antagonist-mediated hyperthermia.

Novel receptor targets — cannabinoids

Research into cannabinoids, which have for centuries, been used for their analgesic properties, continues. There is evidence for other beneficial effects, in addition to the analgesic effect (such as antiemesis) in post-chemotherapy treatment. After much-publicized abuse as a recreational drug, cannabinoids have found popularity within certain neuropathic pain states (such as multiple sclerosis), although this is limited by their side effect profile. It has been suggested that medicinal cannabinoids may be moderately effective for chronic pain, although these benefits are offset by their adverse effects.

With the rise in medicinal use of cannabinoids, there is increasing interest in the development of receptor-specific forms of these drugs which offer pure agonist/antagonist effects.

The cannabinoid receptors, CB1 and CB2, are G-protein coupled receptors, both of which are 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. This is caused by (a) increased potassium efflux (hence favouring repolarization), and (b) reduced calcium efflux. When located on sensory neurones, it is clear that this may reduce 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 the modulation of pain.

Antiepileptic drugs and other therapies

Pregabalin and gabapentin, both drugs now indicated for use in chronic pain share a degree of structural homology with the neurotransmitter γ-aminobutyric acid (GABA), although recent evidence has shown that this is unrelated to their mechanism[10] which is due to generalized inhibition of the release of a diffuse range of neurotransmitters (substance P, glutamate, aspartate, calcitonin gene-related peptide) linked to voltage-gated calcium channels.

As a result of their action, gabapentin and pregabalin are finding new uses both in the acute perioperative environment (for inflammatory and incisional pain) and in chronic pain (in models of neuropathic pain).[11]

These drugs are known to be effective across a number of chronic pain situations, particularly postherpetic neuralgia and painful diabetic neuropathy with randomized controlled trial evidence showing significant decreases in pain scores for both of these conditions.

Both gabapentin and pregabalin are finding new uses in the management of acute postoperative pain and in the perioperative situation; their analgesic, anxiolytic, antiemetic effects and blunting of the response to intubation give them a favourable profile for these uses. It is thought that the interaction with numerous neurotransmitters acts to reduce the incidence of hypersensitization and 'wind-up' thereby reducing the onset of neuropathic pain post-injury.

Summary

Whilst opioids are the 'gold standard' analgesics, used in severe pain, there are complications associated with their use, both short term and long term. The non-opioid drugs provide an alternative and are in some cases, equally efficacious to these opioid drugs, and may provide some opioid-sparing properties. 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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