Non-opioid analgesics

Christopher Hebbes

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. More recently, the discovery of a fourth opioid-like receptor and eventually its endogenous ligand, nociceptin has highlighted new possibilities in the management of pain. However, nociceptin and its analogues are yet to reach clinical practice.

Whilst used for their analgesic and sedating effects, the common mechanism of action of opioids produces a number of adverse effects, limiting their use and driving research to find analgesics devoid of deleterious sequelae. Aside from common side-effects of nausea, constipation, tolerance and dysphoria, there is increasing evidence of longer term complications such as immunosuppression and risk of cancer recurrence in malignancy surgery.

Non-opioid analgesics, acting independently of opioid receptors may reduce or remove the requirement for narcotics. Providing analgesia is important for humanitarian reasons, but also to reduce the complications associated with pain, such as poor mobility, reduced quality of life, increased inpatient stays and delirium. Therefore, the use of non-opioid drugs is important for analgesia and sedation pre-emptively, perioperatively, and as part of 'enhanced recovery' regimes and on the intensive care unit postoperatively throughout the entire patient journey.

Whilst effective for acute pain, opioid analgesia is of limited effectiveness for chronic and neuropathic pain states. This is partly due to problems with chronic administration and pharmacologic tolerance although also relates to the different mechanisms of acute (e.g. surgical) and chronic pain and involvement of additional neurotransmitters such as substance P, γ-aminobutyric acid (GABA) and glutamate in the latter.

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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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 is outside the scope of this paper; a detailed knowledge of the macro- and molecular processes involved in nociception are critical to the identification of analgesic targets. An overview is given below, in Figure 1 which illustrates sites in the pathway for therapeutic intervention.

Therapeutic strategies include targeting inflammatory pain stimuli, modulating peripheral nociceptors, reducing afferent pain transmission, and reducing central transmission of pain.

1) 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.

2) Modulating the peripheral threshold for stimulus transmission

Peripheral nociceptors depolarize via the transient receptor potential cation channel subfamily V member 1 (TRPV1) ligand-gated ion channel to a variety of noxious stimuli, including the mediators released during inflammation. The resultant depolarization may induce an action potential and proximal transmission, which also renders the nerve refractory to further stimulus until repolarization has occurred. Therefore, continuous stimulation, or blockade of TRPV1 may both produce analgesia. Whilst no antagonists exist in clinical practice, capsaicin gel is effective in this context for the treatment of arthritic inflammatory joint pain.[1] Local anaesthetics block sodium channels in peripheral nerves to increase the threshold for signal transmission, thereby reducing nociception via a similar mechanism.

3) 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'. Primary afferent nociceptive signals arrive in Rexed laminae I and II of the spinal cord, where they 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, which act within the spinal cord where spinal nerves synapse with ascending pathways.

The dorsal horn of the spinal cord has a multitude of receptors on primary afferent and descending nerves and interneurones. Drugs known to promote analgesia through activity at this level include α_2—agonists (clonidine), ketamine N-methyl-D-aspartate (NMDA) and tramadol (5-HT and μ-opioid (MOP)).

4) 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.

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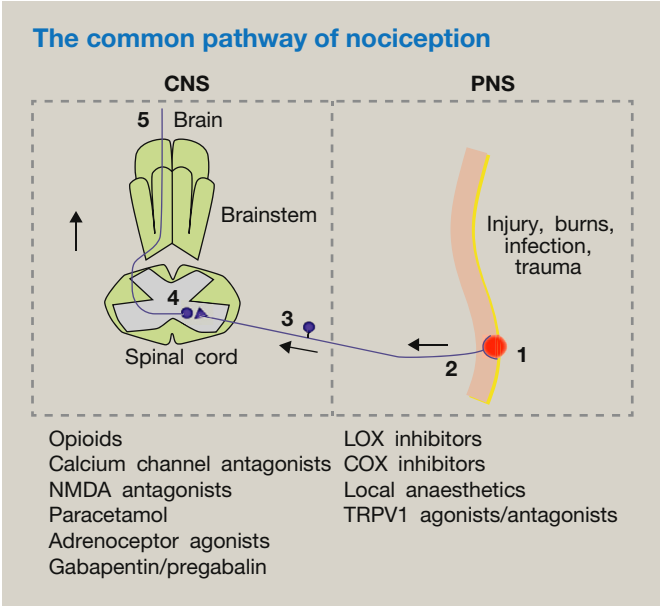

Figure 1 (1) Noxious stimuli cause activation of *peripheral nociceptors*. Noxious inflammatory mediators (or their synthesis) may be blocked directly (e.g. cyclooxygenase (COX) inhibitors), or the nociceptive afferents may be hyperpolarized (Na^+ antagonists, e.g. local anaesthetics). (2) Signals are *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 thence 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, N-methyl-D-aspartate 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 (COX3) and cannabinoids. COX – Cyclooxygenase, HTM – High Threshold Mechanoreceptors, LOX – Lipoxygenase, PMN – Polymodal nociceptors.

Neuronal excitability is determined by membrane potential, the surrounding cellular environment and the influence of local mediators and neurotransmitters, the basis of the action of many non-opioid analgesics (Table 1).

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 (e.g. 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 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, with a high oral bioavailability of greater than 60%. Also available as an intravenous preparation, it is an excellent drug for perioperative analgesia. It distributes rapidly, into a small volume of distribution, is rapidly cleared and is metabolized by hepatic cytochrome P450. Paracetamol is generally safe and efficacious, although has been the subject of safety concerns following iatrogenic overdose and resultant fulminant hepatic failure. Therefore paracetamol requires dose reduction in hepatic failure, and for low body weight.

Despite its common use, the mechanism of action of paracetamol is poorly understood. Paracetamol shares properties with NSAIDs and is thought to antagonize cyclooxygenase (COX). Inhibition of the central isoform COX-3 may be responsible for paracetamol's effects.[3,4] 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 multi-modal 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, anti-pyretic, anti-uricemic, anti-platelet and analgesic properties. They act via inhibition of the 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. Inhibiting these compounds is therefore associated with deranged renal autoregulation, gastric irritation, bleeding and impaired wound healing.

COX-1 is constitutively expressed and responsible for a number of adverse effects, whereas COX-2 is upregulated in inflammation. Avoiding the adverse effects of nonselective blockade by selectively targeting COX-2 led to the development of COX-2 selective inhibitors. These are no-longer recommended due to cardiovascular side effects.

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, those taking anticoagulants or who are taking a prolonged NSAID course are at an increased risk,[5] and proton pump inhibitors are recommended in this group.

Novel receptor targets – TRPV1

TRPV1 is a peripheral ion channel located on afferent c-type fibres which, when activated, promotes depolarization. Following