Non-opioid analgesics

Bharti Seth

Abstract

The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms of such damage'. This definition of the pain experience thus combines both the phenomenon of nociception (the sensory nervous system's response to certain harmful or potentially harmful stimuli) and pain perception (process by which pain is recognized and interpreted by the brain). The *Encyclopaedia Britannica* defines an analgesic as any drug that relieves pains electively without blocking the conduction of nerve impulses, markedly altering sensory perceptions, or affecting consciousness. This selectivity is an important distinction between an anaesthetic and an analgesic drug. Analgesics can thus be broadly classified according to their role primarily on nociception as well as pain perception, both of which are intimately integrated to the pain experience. An understanding of the pain pathway is inherent to a good understanding of how therapeutic targets can act as analgesics. An overview of this is discussed in this article to understand rationale for therapeutic intervention. Opioids are substances that act on opioid receptors to produce morphine-like effects. Opioids have been used as a mainstay for pain management for centuries. As the problem of chronic pain has risen to epidemic proportions, so has the incidence of increase in opioid use as well as misuse and abuse of prescription opioids resulting in increasing morbidity and mortality. While being effective for acute pain and cancer pain management, opioids have not been very effective for the management of chronic pain or neuropathic pain. All other analgesics that do not produce analgesia through a primary effect on opioid receptors can be labelled as non-opioid analgesics (NOA). This article will aim to provide an overview of the pain pathway in relation to the therapeutic targets for providing analgesia, commonly used NAOs and their brief introduction.

Keywords Atypical analgesics; cannabinoids; COX-2 inhibitors; gabapentinoids; non-opioid analgesics; NSAIDs; paracetamol; topical analgesics

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Learning Objectives

After reading this article, you should be able to:

- correlate the pain pathway with the therapeutic targets for analgesia
- state a broad classification for non-opioid analgesics
- describe the concept of multi-modal analgesia

The pain pathway in relation to therapeutic targets

The pain pathway can be considered in terms of transduction, transmission, modulation and perception for purposes of understanding the mechanistic basis of analgesics. The interventional therapies for pain management are aimed towards interrupting or modulating the nociceptive pathways, and the pharmacology of analgesic drugs is geared towards modulating the biochemical processes involved.

Bharti Seth *MD is a Consultant in Anaesthesia and Pain Medicine at The Queen Elizabeth Hospital NHS Foundation Trust, King's Lynn, Norfolk, UK. Conflicts of interest: none declared.*

Transduction

Begins when peripheral terminals of nociceptive C-fibres and A-delta (Aδ) fibres are depolarized by noxious mechanical, thermal or chemical energy. The membranes of these terminals contain proteins and voltage-gated ion channels that convert thermal, mechanical or chemical energy into an action potential (AP). Normally, nociceptor terminals have a high activation threshold. However, nociceptors can be made more sensitive to stimuli. Injury to surrounding tissues (inflammation) or neurons expose neighbouring nociceptors to irritating substances, including neurotransmitters, ATP, prostanoids, bradykinin, serotonin, histamine, hydrogen ions (acid pH), and so on. These substances lower the nociceptor's activation threshold. This is called peripheral sensitization.

Drugs acting at this phase include paracetamol and non-steroidal ant-inflammatory drugs (NSAIDs) by decreasing the inflammatory mediators that cause a decrease in the generation of inflammatory mediators, and drugs acting on the transient receptor potential vanilloid $TRPV_1$ channel such as capsaicin.

Transmission and modulation

Transmission of AP is from the peripheral terminals of the nociceptors to the central terminals of the nociceptive fibres in the dorsal horn of the spinal cord. The dorsal horn is organized into ten different laminae. Nociceptive fibres primarily terminate in laminae I and II. The AP causes the presynaptic terminals of Aδ and C-fibres to release a variety of pro-nociceptive substances into the synaptic cleft, including glutamate which activates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, substance P (SP), which activates postsynaptic NK1 receptors and calcitonin gene-related peptide (CGRP), which activates postsynaptic CGRP receptors. Glutamate can also activate N-methyl-D-aspartic acid (NMDA) receptors that are normally inactive because they are ordinarily blocked by magnesium ions. However, intense or prolonged periods of depolarization can release the magnesium ion from the NMDA-linked channel. Loss of the Mg blockade allows an influx of calcium ions. Increased intracellular calcium ions has two important effects, the first effect leads to a lowered activation threshold and the second effect initiates a cascade that results in the production and release of nitric oxide into the synaptic cleft. Presence of nitric oxide in the synaptic cleft causes an exaggerated release of neurotransmitters from the presynaptic terminal resulting in synaptic hyperexcitability. The NMDA receptor is considered critical for the induction and maintenance of neuropathic pain.

The postsynaptic fibres transmit the pain sensation through second order neurons and interneurons to the central nervous system via the spinothalamic (anterior and lateral) tracts.

The dorsal horn of the spinal cord acts as the interface between the peripheral and central nervous system components of the pain pathway.

Modulation of the action potential (AP) can be peripheral as is seen with:

- inhibiting sensitization of nociceptive terminals as with cyclo-oxygenase inhibitors, e.g. NSAIDs
- inhibiting depolarization and repolarization of the axonal membrane, e.g. local anaesthetics
- inhibiting the inflammatory response to trauma, e.g. steroids.

Central modulation of nociception begins at the dorsal horn of the spinal cord and may be modulated through a multitude of receptors on primary afferent, descending nerves and interneurons. Drugs that produce analgesia through activity at this level include alpha 2-agonists (clonidine), NMDA antagonists (ketamine), opioids and ziconotide. Central modulation also affects through descending pathways from brainstem structures to the dorsal horn. Noradrenergic, serotonergic and opioid systems all have an inhibitory effect.

- Antidepressants enhance the analgesic activity of the descending pathway by increasing the availability of synaptic monoamines. The monoamines serotonin and norepinephrine are the primary neurotransmitters released by descending pathway neuron terminals.
- Stimulation of the nucleus raphe magnus in the brainstem results in antinociception attributed to the release of serotonin (5-HT) within the dorsal horn.
- Stimulation of the locus coeruleus in the medulla results in antinociception attributed to the release of norepinephrine within the dorsal horn. Pre-synaptically noradrenaline increases inhibitory transmitters from interneurons and depresses glutamate release from both Aδ and C afferent terminals.

Perception

Of nociceptive pain is dependent upon neural processing in the spinal cord and several brain regions. Pain becomes more than a pattern of nociceptive action potentials in the cerebral cortex. Action potentials ascending the spinothalamic tract are decoded by the thalamus, sensorimotor cortex, insular cortex and the anterior cingulate to be perceived as an unpleasant sensation that can be localized to a specific region of the body. Action potentials ascending the spinobulbar tract are decoded by the amygdala and hypothalamus to generate a sense of urgency and intensity. It is the integration of sensations, emotions and cognition that result in our perception of pain. This is how hypnosis, biofeedback, CBT and opioids work.

Paracetamol

Paracetamol (acetaminophen) is the most commonly used analgesic and has an impressive place on the WHO analgesic ladder. It is recommended on all three steps of pain treatment intensity. It is a useful first-line drug formula to moderate pain. For more persistent moderate to severe pain, when used in conjunction with other agents including NSAIDs (ibuprofen), caffeine, weak (codeine, tramadol) or strong (morphine) opioids, it improves analgesic efficacy while decreasing the side effects of the adjunct agent. It is the drug of choice in patients in whom NSAIDs are contraindicated.

The mechanism of action of paracetamol is poorly understood. It has been postulated to affect both peripheral (inhibition of cyclo-oxygenase [COX] activity) and central (COX, descending serotonergic pathways, L-arginine/NO pathway, cannabinoid system) antinociceptive processes.

It shares analgesic and antipyretic properties with NSAIDs but does not possess any anti-inflammatory activity. Due to this, it is not considered a member of the NSAIDs family.

It is available in oral, rectal and intravenous formulations. Oral paracetamol is well absorbed from the gut, subject to minimal first pass metabolism with a high though variable bioavailability. Metabolized in the liver by the cytochrome P450 enzyme system, it is generally safe and efficient. However, fulminant hepatic failure has been noted with iatrogenic overdose. Paracetamol dose reduction is advocated in certain patient groups, including the elderly, infants, in starvation or malabsorption, severe renal impairment, or hepatic failure where glutathione stores may be low. Glutathione conjugates with NAPQI (N-acetyl-p-benzo-quinone-imine), a highly toxic metabolite of paracetamol. The use in children requires care and dosage modification according to age as the CYP2E1 enzyme required for the oxidation of paracetamol metabolism reaches adult levels only by 10 years of age.

NSAIDs, cyclo-oxygenase-2 inhibitors

NSAIDs, including non-selective and selective COX-2 inhibitors are widely used for their anti-inflammatory and analgesic effects. They are an essential part of pain management because of the central role of the COX pathway in generation of inflammation and biochemical recognition of pain.

They are effective in a variety of disorders including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, headache disorders, dental pain and dysmenorrhea.

The basic mode of action is inhibition of the pro-inflammatory enzyme COX. The COX enzyme exists in three isoforms: COX-1 and COX-2, COX-3.

COX-1 is expressed constitutively and in quiescent conditions; it performs ongoing regulatory functions including gastro and renal protection, macrophage differentiation, platelet aggregation and mucus production. It has a limited role in inflammatory process.

COX-2 is an inducible enzyme that is unregulated by tissue injury and other stimuli including interleukin-1, tumor necrosis factor alpha (TNFα). It is active at injure sites and in a variety of tissues mediating inflammatory, pain, fever and carcinogenic responses. It also has a regulatory role in reproduction, renal physiology, bone resorption and neurotransmission.

The significance of COX-3 is uncertain. Because of the regulatory effects of these enzymes, their use is associated with significant side effects including gastric irritation and bleeding (15%–30%) in patients taking nonselective NSAIDs, deranged renal autoregulation and impaired wound healing. Selective COX-2 inhibitors while decreasing the gastric side effects are associated with greater incidence of cardiovascular adverse effects and are no longer recommended for long-term use or in patients with risk factors for such effects.

As a group, NSAIDs are excellent analgesics and are more efficient than intramuscular morphine for purposes of acute pain relief. Their use for chronic pain conditions, over long periods of time is not recommended and is associated with significant side effects.

Antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs)

TCAs are considered as first-line analgesics for neuropathic pain. Their analgesic effects starts more rapidly and at lower doses than required for the antidepressant effects. The primary mechanism of action of tricyclic antidepressants (TCAs) is through blockade of noradrenaline (NA) and serotonin (5-HT) at the dorsal horn synapses. TCAs are considered NA and 5-HT re-uptake inhibitors, resulting in increased bioavailability of NA and 5-HT at the synaptic terminals. Both NA and 5-HT modulate the dual descending pain pathways in the body that inhibit pain signals.

One pain pathway originates at midbrain level in the periaqueductal gray and nucleus raphe magnus (5-HT), while the other pain pathway starts at the locus coeruleus in the medulla (NA).

The mechanisms of analgesic effects of TCAs are extensive and the following are postulated:

- monoamine re-uptake inhibition
- interactions with endogenous opioids
- NMDA receptor antagonism
- immune factor expression modulation
- enhancement of gamma-aminobutyric acid beta ($GABA_B$) receptor activity
- blockade of sodium and potassium channels
- histamine inhibition
- adenosine system involvement.

They are also useful in multi-mechanistic chronic pain with a neuropathic component and as adjuvant analgesics in nociceptive and inflammatory pain. Examples of TCAs include amitriptyline, nortriptyline.

Duloxetine (a serotonin–norepinephrine reuptake inhibitor) is effective in treating painful diabetic peripheral neuropathy.

Venlafaxine blocks reuptake of noradrenaline and 5-HT and is relatively free of muscarinic cholinergic, histaminic, and alpha-adrenergic receptor activity. Its analgesic action is postulated to involve the endogenous opioid system. It has been successfully used for management of painful neuropathy and headache control.

In general, TCAs are more effective than selective serotonin reuptake inhibitors because of their nonselective effects. The number needed to treat (NNT) for 50% relief of neuropathic pain is 6.7 for SSRI therapy compared to 2.4 for TCAs. The side effects include drowsiness, sexual dysfunction, weight gain, dry mouth, constipation, blurred vision and prolongation of the QRS interval.

Anticonvulsants

These drugs have been recommended by NICE (National Institute for Health and Care Excellence) for use in neuropathic pain conditions including post herpetic neuralgia, post stroke pain, post amputation pain and persistent pain after hip replacement.

Anticonvulsants decrease ectopic neuronal activity and stabilize neuronal cell membranes through modulation of the voltage-gated sodium or calcium ion channels. These drugs may inhibit sodium channels (phenytoin, lamotrigine and others) or inhibit calcium channels (gabapentinoids, that is, gabapentin and pregabalin). The gabapentinoids have been recommended by NICE for use in neuropathic pain conditions including post amputation pain. Levetiracetam is a novel anticonvulsant agent which appears to exert a synergistic antihyperalgesic effect against inflammatory pain when combined with a non-steroidal anti-inflammatory drug (NSAID) plus caffeine.

Carbamazepine, which acts as a sodium channel blocker is the first line treatment for trigeminal neuralgia as recommended by NICE.

Topiramate, **lamotrigine and valproate** are anticonvulsants that are effective in the treatment of episodic migraine and neuropathic pain. Adverse events associated with anticonvulsant agents are common and may be treatment-limiting. Some of the most frequently reported adverse events include drowsiness, headache, and increased appetite. Teratogenicity is another significant side effect.

Novel topical agents: TRPV1 antagonists, 5% lidocaine patches

Capsaicin: TRPV1 is expressed in all sensory ganglia (dorsal root ganglia, trigeminal ganglia, vagal) and in small sensory C-and Aδ fibres, which may contain various neuropeptides including SP and CGRP. It is activated by capsaicin, noxious heat (>43°C) and low pH. TRPV1 channel activation in nociceptive neurons triggers the release of neuropeptides and transmitters resulting in depolarization. After the depolarization, the afferent nerve is in a refractory state, hence unable to transmit additional signals. Antagonists of $TRPV_1$ provide analgesia by increasing the depolarization threshold required to generate an action potential. Capsaicin is used the management of inflammatory pain. Topical capsaicin in humans is rapidly and well absorbed through the skin and many low concentrations of capsaicin (0.025–0.1%) are available over the counter as creams or patches (8%). It should not be applied to broken skin.

Lidocaine patches (5%) are an option for superficial, localized painful neuropathic conditions such as post herpetic neuralgia. Lidocaine acts through blockade of abnormally functioning (sensitized) Nav 1.7 and Nav 1.8 Na^+ channels in dermal nociceptors, thereby reducing ectopic discharges. It also regulates T-cell activity and inhibits nitric oxide production, thereby reducing inflammatory processes within the deep tissue, such as injured muscle, joints or constricted nerves.

Cannabinoids

Cannabis is a naturally occurring substance with many active compounds including tetra hydro cannabinol (THC), cannabinoid (CBD) and cannabinol (CBL). The CBD receptors CB1 and CB2, located extensively in the brain and peripheral tissues, are G-protein–coupled receptors that are linked to the $G_{i/o}$ system in

the same manner as opioid receptors and result in a reduction in afferent neuronal transmission.

Nabiximols (Sativex) is a sublingual spray containing the combination of THC and CBD in a roughly 1:1 ratio. It is approved for use of multiple sclerosis related spasticity pain. Dronabinol is a synthetic preparation of the transisomer of delta-9-THC dissolved in sesame oil. Along with nabilone, it is used for chemotherapy-related nausea and as an appetite stimulant for HIV wasting syndrome.

Risk of psychological harm, addiction and dependence are present. It is still not available for routine prescription of pain management in the NHS.

The current public opinion is moving toward more widespread acceptance despite the continuing regulatory limbo in which the drug resides. Physicians will increasingly be encountering the use of cannabinoids in their practice whether or not they choose to recommend medicinal cannabis or prescribe cannabis-derived pharmaceuticals.

Muscle relaxants

These are usually prescribed to help treat myalgia and musculoskeletal conditions, including chronic low back pain. This group of drugs are broadly divided into antispastic agents and antispasmodic agents. Antispastics act on the level of spinal cord or skeletal muscles to decrease muscle hypertonicity and relieve involuntary spasms. Antispastic agents (e.g. baclofen) are often prescribed for patients with spinal cord injury, cerebral palsy and multiple sclerosis.

Antispasmodics decrease muscle spasm by affecting conduction through the central nervous system. Muscle relaxants may be helpful in the short-term setting for relieving a flare up of muscle spasms.

Benzodiazepines act by enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor. Non-benzodiazepine antispasmodics act at the level of the brainstem and spinal cord and are frequently prescribed for flare up of chronic painful conditions such as low back pain. These include methocarbamol, carisprodol and cyclobenzaparine. Common side effects include sedation, headaches, visual disturbances, drowsiness, fatigue and dizziness.

Botulinum A toxin (Botox)

Botulinum A toxin is produced by *Clostridium botulinum*. It acts irreversibly at the presynaptic membrane of the neuromuscular junction, preventing release of acetylcholine and triggering chemical denervation by inhibiting subsequent activation of motor nerve endings, through destruction of SNARE (soluble NSF attachment protein receptors) proteins. The effect disappears as collateral form in neuromuscular junction plates on new areas of muscle cells. Botox is recommended by NICE for management of chronic migraine when conservative therapy is not successful. It has not been found to be very effective for myofascial trigger point injection therapy. Common side effects are flu-like symptoms, pain, unintended paralysis of neighbouring muscles and erythema.

Multimodal analgesia

Multimodal analgesia or 'balanced analgesia' combines analgesics from two or more drug classes or analgesic techniques that employ different mechanisms of action, targeting different (peripheral or central) pain pathways, thus achieving a synergistic effect at lower analgesic doses. Non-opioid analgesics form a key component of fast track surgery and enhanced recovery by minimizing side effects associated with traditional opioids used in high doses.

Summary

Analgesic therapy should be based on the patient's pain mechanisms. Non-opioid analgesics play an integral role in providing multimodal analgesia through therapeutic targets along different parts of the pain pathway. They offer safer alternatives to opioid analgesia for inflammatory, postoperative and neuropathic pain. ◆

FURTHER READING

IUPHAR/BPS guide to pharmacology. Jan 2018, http://www.guidetopharmacology.org.

Rang and Dale's pharmacology. 7th edn. Edinburgh: Elsevier Churchill Livingstone, 2011.