The understanding of pain transmission and modulation has improved considerably since the revolutionary gate control theory of Melzack and Wall in 1965. However, current pharmacological options, while effective for most patients, are not without their problems. For example, the cardiovascular and renal toxicity associated with non-steroidal anti-inflammatory drugs recently delivered a huge blow to pain management. In addition, although opioids represent the most effective analgesic choice for most painful conditions, long-term opioid therapy is associated with potential hormonal and immunological consequences. Nonetheless, major advances in the understanding of molecular and cellular mechanisms of pain have uncovered new potential pharmacological targets, although their clinical application is unlikely for several years. Figure 1 illustrates a number of actual and potential targets on a peripheral nociceptor. Several new products are in clinical development and promise to be potentially more effective and safer alternatives.

### Pain mechanisms

Peripheral tissue damage generates pain signals that are usually transmitted via unmyelinated C-fibres (slow) and small myelinated Aδ-fibres (fast) to the dorsal horn of the spinal cord. Signals continue via several tracts in the spinal cord, although the spinothalamic tract is considered the main pathway. This terminates in the thalamus, where the signals are then relayed to other areas of the brain, such as the prefrontal cortex. Pain sensation is not, however, a one-way process descending pathways can inhibit or facilitate pain signals. The degree of pain is not proportional to the amount of physical injury: affective and emotional aspects may influence the degree of suffering through interaction with the descending facilitatory pathway. (See Figure 2.)

### Plasticity

Persistent peripheral input causes changes in membrane channel and receptor (e.g., TRPV1, prostanoid, etc. — see Figure 1) density and distribution which, in turn, lead to reduced activation thresholds and the eventual development of peripheral sensitisation. As a result, nociceptors become more sensitive to peripheral stimulation (e.g., heat, chemical, mechanical), with lower thresholds for subsequent pain signals. Similar changes occur within the spinal cord, causing activity-dependent modification of synaptic transmission of pain signals referred to as plasticity.

Dorsal horn plasticity causes central neurons to become hyperexcitable, producing central sensitisation (also referred to as wind-up). Clinically, these effects will manifest as allodynia (pain caused by a normally non-harmful, non-noxious stimulus) and hyperalgesia (increased sensitivity and lowered threshold to a normally painful stimulus). Such changes may be brief, while others can be long-lasting and irreversible, forming the basis of chronic pain.

### Neurophysiology and pharmacology

A multitude of neurotransmitters, modulators and receptors are involved in the perception of pain.

#### Peripheral pain

Injury within the periphery triggers the release of several neuromodulators, such as adenosine triphosphate (ATP), protons, prostaglandins E2 and I2 (PGE2, PGI2) and leukotriene-B4 (LTB4). ATP enables immediate detection of tissue damage through an excitatory effect at purinergic (P2X) receptors on C and Aδ nociceptive fibres. In contrast, protons slowly accumulate after tissue damage and cause pain (e.g., a burning sensation) some time after the initial injury by activating the TRPV1 ion channel (capsaicin also activates this channel). The arachidonic acid pathway is an important component of the inflammatory response and is involved in the development and maintenance of pain. Arachidonic acid is

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a substrate for both cyclo-oxygenase isoenzymes (COX-1 and COX-2) and the 5-lipoxygenase (5-LOX). COX-1 and COX-2 mediated synthesis of prostaglandins E2 and I2 (PGE2 and PGI2) occurs several hours after the initial injury.

By binding to specific prostanoid receptors on the cell membrane, prostaglandins increase the sensitivity of other receptors and ion channels (eg, TRPV1 and voltage-gated sodium channels). This indirectly increases the excitability of the nociceptor. After sunburn, for example, a warm shower becomes a painful experience because of prostaglandin-mediated increase in sensitivity of TRPV1 ion channels.

5-LOX produces a variety of leukotrienes, which have both pro-inflammatory and gastrotoxic properties. In particular, LTB4 has been associated with a multitude of actions within the inflammatory process that can culminate in hyperalgesia.

Inhibition of PGI2 synthesis is believed to be the major cause of NSAID-induced renal and cardiovascular adverse effects. Rather than blocking prostaglandin synthesis, alternative pharmacological strategies involve the downstream targets of peripheral sensitisation, such as the TRPV1 ion channel and voltage-gated sodium channels.

Alterations in the expression and distribution of voltage-gated sodium channels are also associated with neuropathic pain (pain caused by damage to or changes in the central or peripheral nervous system). Neuropathic pain typically responds poorly to conventional analgesics and adjuvant analgesics are generally required. An increase in voltage-gated sodium channel density occurs as a result of nerve injury, which lowers the nociceptive threshold of a neuron and may result in ectopic discharges.

There are several isoforms of the voltage-gated sodium channel and they are key regulators of neuronal excitability. The accumulation of certain isoforms that occurs as a result of nerve injury is implicated in neuropathic and inflammatory pain. Ectopic discharges produced by the increased density of channels is the probable cause.

Some drugs block sodium channels, and therefore may also interfere with normal nerve function. Fortunately, these isoforms of voltage-gated sodium channels are affected by low drug concentrations, allowing normalisation of activation thresholds — effectively controlling neuronal hyperexcitability — without affecting physiological activity. For example, the low dose delivered by a lidocaine plaster produces local anaesthesia rather than local anaesthesia.

LTB4 has a multitude of actions within the inflammatory process that can culminate in hyperalgesia.

Opioids have traditionally been associated with central analgesia. It is now known, however, that opioid receptors are present on peripheral nociceptors and are activated following local tissue damage. Lymphocytes have been shown to secrete opioid peptides that have analgesic and anti-inflammatory
**Future analgesics**

**Ziconotide** Although already available, ziconotide represents a new therapeutic option for the treatment of pain. It is a synthetic derivative of ω-conotoxin obtained from the venom of a predatory sea snail. Ziconotide is a selective antagonist of the N-type voltage-gated calcium channel. It is administered intrathecally for the management of severe chronic pain in patients who are intolerant of, or refractory to, other treatment. Pre-clinical work is examining the possibility of an oral alternative.

**Analgesics not yet available**

**Bicifadine** Bicifadine is not a new drug, having been described in clinical use nearly 30 years ago. However, with the improving knowledge of pain transmission and modulation, interest has been rekindled. Bicifadine is an azabicyclohepane and is unlike any other analgesic. It is a potent inhibitor of noradrenaline and serotonin reuptake and, to a lesser extent, dopamine reuptake. Bicifadine is also believed to be an NMDA receptor antagonist. In early studies, bicifadine was shown to be an effective analgesic. Nausea, vomiting, drowsiness and dizziness are the commonly reported adverse effects. Phase III clinical trials are currently in progress examining the safety and efficacy of bicifadine in a variety of clinical conditions, such as post-operative pain and chronic back pain.

**Lacosamide** Lacosamide is a novel drug currently in phase III clinical trials for the treatment of both epilepsy and neuropathic pain. It appears to work by selectively blocking voltage-gated sodium channels that accumulate after nerve injury (see main text). It has been shown to be effective in the treatment of diabetic neuropathy and appears to have been reasonably well tolerated, with adverse effects seemingly dose-related. The most common side effects seem to be dizziness, nausea, headache and fatigue.

**Licofelone** Licofelone is an inhibitor of cyclo- oxygenase-1, COX-2 and 5-lipoxygenase. In addition to the effects of prostaglandin inhibition, licofelone also reduces the production of pro-inflammatory and gastrotoxic leukotrienes. Pre-clinical studies have shown that licofelone has the expected analgesic, anti-inflammatory, antipyretic and antiplatelet activities of an NSAID. Clinical studies have shown licofelone to be at least as effective as NSAIDs and COX-2 inhibitors for the symptomatic relief of osteoarthritis.

**Commonly reported side effects included loose stools, dyspepsia, nausea and vomiting, although licofelone was generally better tolerated than NSAIDs and COX-2 inhibitors.**

**Naproxinod** Naproxinod is a Cox-inhibiting nitric oxide donor (CINOD). Essentially, a nitric oxide donator (CINOD). Essentially, a nitric oxide donor is a nitric oxide (NO) releasing agent that acts as a nitric oxide donor. It has been shown to be effective in the treatment of osteoarthritis and diabetic neuropathy. It is a synthetic derivative of the last panacea, the COX-2 inhibitors. There are no active metabolites. The analgesic effect resides in one enantiomer only. Does not affect serotonergic pathways and the analgesic effect resides in one enantiomer only. Tapentadol does not require hepatic activation, it activates the descending inhibitory pathways through the facilitation of the endogenous opioid system and the associated toxicity of NSAIDs. It appears to be less than those experienced by patients using strong opioids.

**Tetrodotoxin** Derived from the puffer fish, tetrodotoxin has been successfully used in phase II trials to treat refractory cancer pain. It is believed to selectively block slow sodium channels. It appears to be well tolerated and can be administered via intramuscular or subcutaneous injection. Phase III trials are currently in progress.

Voltage-gated calcium channels modulate nociceptive transmission in the dorsal horn. Upon depolarisation, there is an influx of calcium ions into neurons and release of neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate, and substance P. Increased activity of voltage-gated calcium channels appears to facilitate the hyperexcitability seen in chronic neuropathic pain states. There are several subtypes of the voltage-gated calcium channel, with the N-type channel seemingly important for pain transmission.

Cannabinoids have been used for centuries to treat pain but it is only recently that specific endocannabinoids and receptors have been identified. Anandamide was the first endocannabinoid described. There are at least two cannabinoid receptors, CB₁ and CB₂. It is believed anandamide is produced by CB₁ receptors. Like opioids, cannabinoids have multiple sites of action throughout the periphery, spinal cord and supraspinal sites.

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Effects so opioid receptors are a target. For example, topical opioid formulations have been used for wounds, producing analgesia via a local effect, rather than a systemic effect.

**Central pain** Changes within the dorsal horn are believed to occur in response to persistent activation. One such change involves increased extracellular levels of the excitatory neurotransmitter glutamate, which binds to NMDA (N-methyl-D-aspartate) receptors. Activation of NMDA receptors amplifies and facilitates the transmission of the pain signal. The NMDA receptor is implicated in persistent nociceptive and neuropathic pain and is a potential pharmacological target.

Opioid receptors located on pre- and post-synaptic neuronal membranes in the dorsal horn are activated by endogenous opioids released by interneurons. These interneurons are, in turn, activated by the descending serotonergic and noradrenergic inhibitory pathways. Activation of the opioid receptor raises the neuronal activation threshold, thereby attenuating nociception. Opioid receptors are also found in supraspinal sites, such as the amygdala, hippocampus and rostral ventromedial medulla. Manipulation of the endogenous opioid system, or descending inhibitory pathway, represent additional pharmacological targets.

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**Future analgesics**

With emerging problems of long-term opioid therapy and the associated toxicity of NSAIDs, new safe and effective analgesics are required. The Panel discusses analgesics that are currently in phase III trials. The future of analgesia is set to change with the development of highly specific targeted therapy and the promise of reduced toxicity. In addition to the treatments described above, many more drugs are in early development. Examples include P2X antagonists, synthetic cannabinoids, cholecystokinin antagonists, enkephalins inhibitors and antagonists of the TRPV1 channel. Whether these drugs will fulfil expectations remains to be seen. The repercussions of the last panacea, the COX-2 inhibitors, are all too evident.

Further reading