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Targeting novel peripheral mediators for the treatment of chronic pain

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Editor's key points

- Translating findings from pre-clinical models to effective clinical therapy has had limited success.
- Studying peripheral mechanisms directly in human pain states may avoid these problems.
- Evidence from clinical studies emphasizes the importance of peripheral drive in maintaining chronic pain.
- A number of peripheral mediators, including monoclonal antibodies, may have potential as novel analgesics.

Summary. Research efforts over the past two decades have helped us better understand the biological mechanisms that lead to chronic pain. Despite this, there has been limited progress in developing novel analgesics to treat sufferers of persistent pain conditions, who may account for as many as one-fifth of the population. A re-evaluation of the strategies used to discover pain-relieving drugs is needed to meet this widespread clinical need. Here, we discuss the merits of pursuing peripherally acting pain mediators. We review the significant clinical evidence that neuronal activity from the periphery is a major contributor to painful symptom production and that peripheral mediators play a substantial role in this aberrant nociceptor activity. We discuss the clinical benefits of blocking individual known mediators and describe our own approach to identify novel mediators.

Keywords: analgesia; chronic pain; nociception

As several articles in this special edition point out, there is an urgent need to develop new treatments for pain. The reason, of course, is that chronic pain affects large numbers of people—most estimates put the figure at close to 20%—and a considerable proportion of these do not get adequate pain relief from existing therapies.[1 2] It is not that these therapies do not show efficacy. They do, although this efficacy may be limited in scope and have significant and dose-limiting side-effects.

In response, the research community has not been idle. The last two decades has seen a tremendous jump in understanding of the pathophysiological mechanisms in play in persistent pain states. Several technical advances have driven this process, ranging from the now ubiquitous use of transgenic mouse technologies to study the role of particular genes expressed in particular cells, through to the increasingly sophisticated analysis of higher and higher resolution brain imaging studies and, more recently, the ability to undertake genome wide sequencing in studies of transcriptional expression and genetic variants.

These research efforts have identified a myriad of potentially important targets for developing novel therapies using cognitive, surgical (e.g. spinal cord stimulators) and pharmacological strategies. The latter (in common with drug development across a number of disease areas) have not been greatly successful with almost no new registrations for analgesic drugs in the last decade. This article will explore the idea that one of the most fruitful areas for drug development lies in identifying novel peripheral pain mediators. The thrust of the argument is that most persistent pain states are driven or maintained by abnormal activity in peripheral nociceptors and that targeting single mediators can, in appropriate circumstances, offer considerable analgesic efficacy, without complications of central side-effects.

Most chronic pain depends on a peripheral drive

Much effort has been concentrated in recent years on elucidating the underlying mechanisms contributing to persistent pain states. Some conditions (e.g. fibromyalgia) may be the result of plastic changes within the central nervous system. To add further complication, the exact origins of persistent pain can be difficult to identify in situations where pain is referred, e.g. conditions of visceral hypersensitivity. However, for the majority of chronic pain conditions, there is now a large body of evidence which strongly suggests that activity from the periphery is essential, not only to initiate but also to maintain, painful symptoms. Multiple lines of evidence from clinical studies, where block of peripheral nociceptive input has been shown to effectively relieve chronic pain, are considered here.

Joint replacement

Some of the most compelling evidence confirming the necessity for peripheral drive comes from clinical observations following the replacement of persistently painful joints or removal of diseased tissue in the case of osteoarthritis (OA). It has been reported that a large number of patients (up to

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73%; Table 1) who have undergone joint replacement surgery show complete resolution of painful symptoms in the following 2–7 yr.[3 4] Of the patients who still experience pain, 70–80% reported significantly reduced pain scores compared with pre-operative ratings. The persistence of pain in some patients after the removal of the affected joint may be suggestive of an ongoing central component, although it is possible that some are in fact experiencing moderate to severe persistent post-surgical pain, a phenomenon that occurs in a significant number of surgical operations.[5]

Pain is a defining feature of OA, with the majority of sufferers experiencing their most severe symptoms during ambulatory movements with lesser pain at rest.[4] The levels and the duration of the noxious input during movement in these patients suggests that central sensitization could be responsible for the chronic nature of their pain. However, abnormal pain sensation is lost in the majority of OA patients when the diseased peripheral tissue is removed, even taking into account post-surgical complications. This suggests that the pain is either peripherally driven, most likely because of aberrant afferent input as a result of elevated pro-inflammatory mediators, or that spinal cord plasticity requires continued peripheral pathology in order to be maintained.

Local steroids

Glucocorticoids are potent anti-inflammatory and immunosuppressive agents which exert their actions via glucocorticoid receptors on immune cells.[6] They are often administered to patients with arthritis locally (e.g. intra-articularly) to limit the large side-effect profiles of these drugs when given systemically. Interestingly, the most beneficial effect of such local delivery is the reduction of pain associated with the disease. Pain relief from glucocorticoid treatment has been reported to last for up to 3 weeks in OA and 2 months in rheumatoid arthritis (RA).[7] Although the immunosuppressive nature of these agents prevent their long-term use, the efficacy of local glucocorticoids provides robust evidence for a strong peripheral component in chronic pain states associated with inflammation, most likely by inhibiting pro-inflammatory mediator release.

Table 1 Evidence that chronic joint pain is largely driven from the periphery. The majority of patients who undergo total knee or hip replacement report total resolution of their painful symptoms, assessed using the Western Ontario and McMasters Universities Arthritis Index score, after surgery. The failure to eliminate pain in the remainder of patients may be because of the development of post-surgical pain, which can be a result of damage to peripheral nerves during surgery. Data sourced from[3]

	Total knee replacement (*n*-632)	Total hip replacement (*n*-662)
No pain	56%	73%
Mild pain	12%	9%
Moderate pain	17%	11%

Lidocaine patch/regional anaesthesia

During the transmission of normal pain signals, action potentials are generated in nociceptors via the voltage gated sodium channels (VGSCs) whose action can be blocked using local anaesthetics (e.g. lidocaine).[8] Following peripheral nerve injury, such channels accumulate at the site of injury where they are thought to be responsible for the generation of ectopic nociceptor activity and subsequent sensations of spontaneous pain.[9] These ectopic discharges can also be prevented using lidocaine.[10] In addition, the activity of VGSCs can be modulated by inflammatory mediators known to cause nociceptor sensitization [e.g. prostaglandin E2 (PGE2)].[11] Systemic administration of lidocaine has provided analgesia to patients with peripheral neuropathy in clinical trials,[12] although this could be because of central actions.[13] Post-herpetic neuralgia is a painful neuropathic condition whereby the efficacy of locally applied lidocaine can be readily assessed because of the localization of pain to the area of original pathology (shingles). Here, the topical application of 5% lidocaine (as a gel or patch) has been demonstrated to significantly relieve pain and reduce pain intensity with a fast onset (within 30 min) and lasting for the duration of drug application.[14 15] Furthermore, lidocaine has proved more efficacious at relieving pain in post-herpetic neuralgia when compared with treatment with pregabalin, a centrally acting analgesic.[16] Additionally, studies have also shown that lidocaine patches provide highly effective pain relief in patients with various painful neuropathies.[17] Even in persistent pain states where symptoms are largely thought to be a consequence of central sensitization (e.g. complex regional pain syndrome), the use of peripheral lidocaine to block peripheral input into the spinal cord can cause central processing to revert to normal, abolishing the symptoms for the duration of the block.[18] Such observations suggest that peripheral drive could be crucial in the maintenance of chronic pain in some patients.

Capsaicin patch

Capsaicin is a potent agonist for transient receptor potential vanilloid (TRPV1) channels, which are expressed at the peripheral terminals of C-fibre nociceptors. The application of capsaicin to the skin causes burning pain and hyperalgesia;[19 20] although, conversely, high concentrations desensitize TRPV1 and can cause selective C-fibre terminal degeneration leading to increased heat and mechanical pain thresholds.[21 22] Administration of daily topical capsaicin for up to 8 weeks can significantly reduce pain in neuropathic pain patients.[23] Additionally, single applications of high-dose capsaicin patches have provided significant analgesia in post-herpetic neuralgia and neuropathy associated with human immunodeficiency virus 1 (HIV-1).[24] Of course, one problem with these trials is the difficulty in blinding patients to treatment. Nonetheless, because all the actions of capsaicin appear to be mediated via a direct action on nociceptors, these data demonstrate the importance of peripheral drive.

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