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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

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 McMaster 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 from³

	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.

Use of peripherally targeted biologics

In recent years, the emerging use of biologics (e.g. functional blocking antibodies against inflammatory mediators), suggests that the activity of individual mediators could be targeted to treat painful conditions. Such treatments are usually proteins which do not cross the blood–brain barrier (BBB); therefore, they must be exerting their beneficial effects in the periphery. Examples of these will be discussed further in the following section.

Known peripheral mediators

The evidence presented in the previous section begs the question of what underlies abnormal nociceptor activity in persistent pain states. In some circumstances, changes intrinsic to the nerve fibre themselves may be responsible. One example would be ectopic impulses that develop in some neuropathic conditions that are likely to be secondary to alterations in the expression of ion channels in these neurones.²⁵ Another putative example, is the sensitization of channels (e.g. TRPV1) that might be sufficient to allow nociceptors to fire at normal body temperature.²⁶ However, in both these cases, something has to initiate the change and that is likely to be a chemical signal initiated from the damaged tissues. Where nociceptors have normal properties but are simply activated, again the reason in nearly all cases will be chemical signals liberated by the affected peripheral tissues. These chemical mediators are prime targets for analgesic drug development because, as reviewed above, blocking the peripheral drive has, when it is possible to do this, proved to be an effective way of relieving pain in some individuals. Several such peripheral pain mediators have already been identified, as we briefly review below.

Prostanoids

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used and are the first line of treatment for many persistent pain states. Their mechanism of action was first described by Vane in 1971 who showed that they inhibit the enzyme cyclooxygenase (COX) and prevent the subsequent production of prostanoids (lipid mediators) which are responsible for the inflammatory and algesic effects.²⁷ A major site of action of NSAIDs is known to be in peripheral tissue,²⁸ although there is additionally good experimental evidence for a central action.²⁹ When NSAIDs are given systemically, it is not certain where their site of action is as they can cross the BBB.³⁰ However, NSAIDs can be applied topically. In this case, plasma concentrations remain far below those achieved after systemic delivery, clearly indicating a local site of drug action.³¹ In addition, much greater tissue concentrations can be achieved compared with systemic delivery³² and, in pre-clinical models, topical application of NSAIDs can attenuate inflammatory hypersensitivity.³³ Pre-clinical work has also demonstrated that pro-inflammatory prostaglandins (e.g. PGE₂) can sensitize nociceptors, produce pain-like behaviour when injected peripherally^{34–37} and are over-expressed in hypersensitive tissue areas after inflammation.³⁸

NSAIDs are used clinically to treat chronic musculoskeletal pain.³⁹ Meta-analysis of 25 randomized, double-blind, placebo-controlled clinical trials in patients suffering from chronic musculoskeletal pain including but not exclusive to OA, found that topical NSAID treatment was significantly effective in reducing pain scores. In addition, in the few trials which compared systemic and topical treatment, albeit with different compounds, no difference was found in the successful reduction of pain in patients.³⁹ This analysis also reveals that the magnitude of analgesia offered by NSAIDs is often limited by dose-limiting side-effects and intrinsic limited efficacy. These findings argue for an important role of other mediators not regulated by COX activity.

Tumour necrosis factor-alpha

The use of function-blocking antibodies highlights the importance that individual peripheral mediators can play in persistent pain states as these are large proteins which do not cross the BBB to a significant degree. Inhibitors of tumour necrosis factor-alpha (TNF α) have been used successfully to treat inflammatory diseases, most prominently RA. This autoimmune disease is commonly associated with persistent pain and it is well known that these biologics help to reduce the symptoms of RA. For example, the assessment of two anti-TNF α agents (Etanercept and Adalimumab) over a 3-month period found that they significantly improved a variety of RA patients assessed in multiple ways; one of the of the most prominent improvements was in the reduction of pain.⁴⁰ This effect is also seen in patients where the disease is well established (mean duration 12.5 yr).⁴¹ It is claimed that some TNF α blockers may be particularly effective in reducing pain scores.⁴² As anti-TNF α drugs are disease modifying, it is difficult to know whether the pain relief is a primary or a secondary event. Some authors have argued that the time course of analgesic onset precedes that of disease modification (suggesting a primary analgesic action)⁴³ but this is not supported by some studies. The analgesic effects of TNF α inhibitors are not limited to RA⁴⁴ but equally these agents are not broadly acting analgesics.

Interleukin 1 β

As with TNF α inhibitors, the analgesic ability of interleukin 1 β (IL1 β) block is well known. Anakinra is a recombinant protein of the naturally occurring IL1 receptor antagonist and binds to IL1 receptors to prevent their activation by IL1 β . In numerous clinical trials, this drug has proved effective in the relief of pain in RA.⁴⁵ In a pilot study, another IL1 β inhibitor (Riloncept) was used to treat patients with chronic gouty arthritis. Two weeks after Riloncept treatment, visual analogue scale (VAS) pain scores were significantly reduced compared with placebo and, after 6 weeks, half of the patients reported a 75% improvement in their pain ratings.⁴⁶ The same caveats apply as to whether the analgesia is a primary or a secondary phenomenon.

Nerve growth factor

A considerable body of pre-clinical data suggests that peripherally produced nerve growth factor (NGF) may be an important pain mediator⁴⁷ (for review see⁴⁸). These data prompted the trial of several anti-NGF antibodies by different pharmaceutical companies. The major focus of these trials has been in OA pain and it appears the different antibodies have similar effects).⁴⁹ Some of the trial data have been published; for example, Figure 1 is taken from a large phase II trial of Tanezumab in OA pain.⁵⁰ The antibody was given twice, 8 weeks apart at different doses. Patients entered the trial with an average VAS rating of 71 (100-point scale). The figure shows the improvement in VAS ratings. It is clear that this drug has unparalleled efficacy in treating OA pain, with the highest doses resulting in an average VAS reduction amounting to ~50%. The Food and Drug Administration stopped these trials in 2010 because of the need for earlier than expected joint replacement in a small number of patients. The ban on trials was lifted last year and it is yet to be seen whether rapidly progressing OA associated with the early trials will limit or even prevent the use of this approach. However, the data demonstrate that targeting a single peripheral mediator can be extremely effective in treating pain, and pain that, in some cases, is very long lasting and associated with numerous co-morbidities. In smaller trials, anti-NGF treatment has also been found to have efficacy in conditions often refractory to other analgesics [e.g. low back pain⁵¹ and bladder pain

syndrome (formally interstitial cystitis)].⁵² These findings are important as it is sometimes said that the 'inflammatory soup' present in many disease states will limit the effectiveness of strategies targeting a single mediator. This is clearly not the case.

Other mediators

There are a large number of other mediators suggested by pre-clinical work, including adenosine triphosphate (acting on P2X receptors expressed on nociceptors), bradykinin, and several chemokines. However, because these have not yet been demonstrated to show efficacy in the clinic they fall outside the scope of this review. The interested reader is directed to a review by McMahon and colleagues.⁵³

Finding novel pain mediators

Most of the research aimed at increasing understanding of pain mechanisms has been undertaken using animal models. That is, the pain state of interest, or a surrogate for it, is created in a laboratory animal, usually rodent. Mechanisms can then be studied at any of a number of levels including behavioural responses, anatomy, electrophysiology and, more recently, measures of gene expression of function. These animal models have some clear advantages, such as the ability to make similar lesions at a given developmental age of genetically similar animals. A wealth of invasive experiments is

A patient's assessment of knee pain while walking

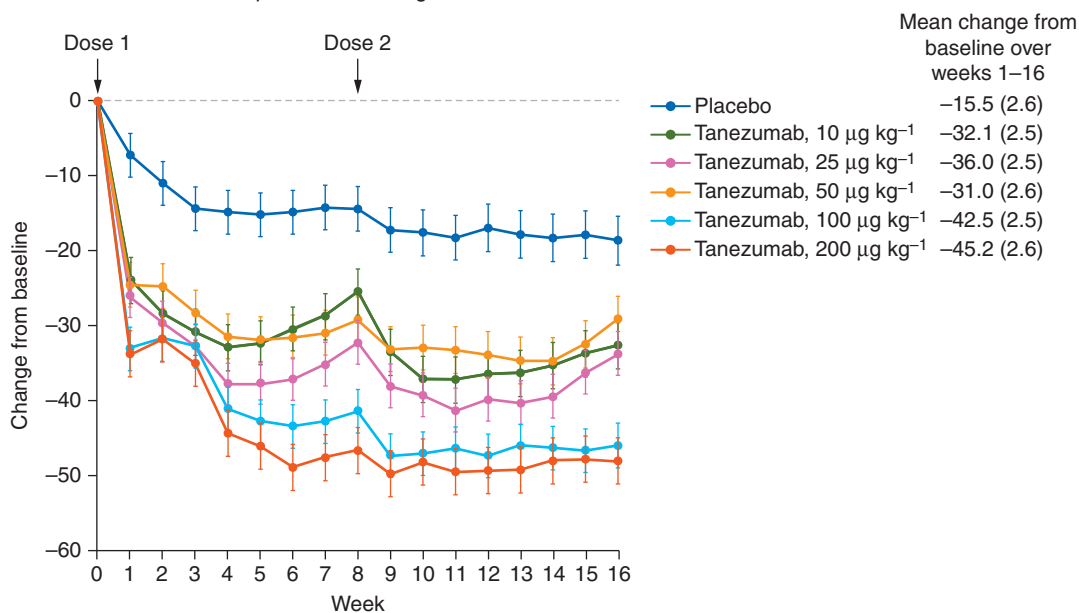


Fig1 Targeting pain individual peripheral mediators can relieve pain. The figure shows data from a phase II trial using Tanezumab to neutralize NGF in patients with painful OA. The pain experienced while walking was assessed on a 100 point VAS scale. Tanezumab (10–200 µg kg⁻¹) or placebo was given at the start of the study and at Week 8, and the change in VAS score from baseline was calculated. A decrease in VAS score is indicative reduced pain. Patients entering the study had an average VAS rating of 71. Data from⁵⁰. Reprinted with permission from Massachusetts Medical Society.

possible. However, there has recently been considerable debate about the usefulness of this approach, driven largely by the very low conversion of mechanisms identified in pre-clinical models to effective new therapies in the clinic. As the same problems of translation have been found, not only in relation to pain, but in nearly all therapeutic areas, it is not clear whether putative failings in animal models are particularly a problem for pain research. However, it has led to renewed efforts to start, not with animal models, but with human disease states. The search for novel peripheral pain mediators is entirely suited to this approach.

Recently, we have started an effort in this direction which aims to collect small biopsy specimens of human tissue and use the power of modern analytical techniques ('omics') to identify putative mediators in these samples. The effects of these candidates and their mechanism of action are then pursued in animal studies. We recently published one test of this approach⁵⁴ using an experimental model of pain induced by UVB irradiation. It is a common experience that sunburn leads to a marked hyperalgesic state and much or all of this is peripherally mediated.⁵⁵ This model was chosen because it can be implemented in both rats and humans. We took 3 mm punch biopsies from normal and UVB skin in both species and measured the levels of mRNA for a wide number of cytokines and chemokines. The most upregulated factor was a chemokine known as CXCL5. This factor, when injected into rodent skin, recapitulates the sensory disturbances of sunburn and blocking antibodies to CXCL5 given to UVB irradiated skin ameliorates the burn-associated sensory changes. We were, thus, able to show that this novel factor contributes to the pain of UVB irradiation.

Conclusion

The evidence we have presented here suggests that targeting peripheral chemical mediators may be a fruitful avenue to pursue in developing analgesic drugs. An important by-product of this approach is the opportunity to avoid or minimize CNS side-effects. What is less clear is how many important mediators there will be. Of course, the maximum benefit to patients is likely to arise if there are relatively few mediators that participate in a wide range of painful conditions. However, the limited data we already have (e.g. the different efficacy of anti-TNF α and anti-NGF treatments) suggests that distinct mediators may drive different pain states. The challenge in this latter case will be to identify those different factors. We believe the research strategy we have outlined will be beneficial in this endeavour.

Declaration of interest

None declared.

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