Getting tough on pain

The potential of painkillers that take aim at chronic pain in smart new ways

Philip Hunter

After more than a century since the discovery of nociceptor sensory neurons as the source of pain signals [1], chronic pain remains a major problem for many people and societies at large. It causes poor quality of life for those affected and carries a considerable cost for health services and productivity. Even in developed countries, diagnosis and treatment are largely inconsistent, and many patients suffer from long-term chronic pain without hope of relief. "Of these people, the majority don't get adequate pain relief because medications have limited efficacy and significant side effects, particularly if taken over a long period," explained Steve McMahon, Head of the Physiology Department at King's College London, UK, and a specialist in chronic pain.

McMahon added that the scale of the problem, combined with a lack of new therapies that target chronic pain more specifically, has led to some serious soul searching within the field. For many years, the clinical and social impact of chronic pain had been under-estimated, especially in comparison with cancer, infectious diseases and diabetes, in part because it does not directly kill those it affects. However, our understanding of chronic pain is changing in the light of studies that have revealed the magnitude and devastating effects of this all but invisible problem. Even so, those same studies indicate that this new understanding has yet to be reflected properly in clinical care. For example, although a 2011 survey of 1,309 primary care doctors from across 13 European countries found that 81% of them agree that the impact of chronic pain tends to be under-estimated in primary care [2], 52% of those same physicians failed to use tools to measure their patients' pain. This is in spite of data showing that chronic pain affects one in five adults across Europe.

A similar picture exists in the USA, where a report by the Institute of Medicine concluded that 100 million Americans—more than 30% of the population—suffer from chronic pain at an annual economic cost of at least \$560–635 billion [3]. This estimate combines the incremental cost of health care—\$261–300 billion—with lost productivity attributable to pain—\$299–335 billion. The authors expressed shock at the scale of the problem, which they considered an indictment of the entire US medical care system: "there is a crisis in the impact of and response to pain in America."

However, as McMahon pointed out, chronic pain is a global crisis compounded not only by the lack of clinical understanding, but also by a failure to create new therapeutic solutions. Only two main classes of prescription analgesic drugs are available for treating chronic pain: the non-steroidal anti-inflammatory drugs (NSAIDs) that reduce swelling and fever symptoms causing moderate pain, and the narcotic opioid alkaloids that bind to and stimulate opioid receptors in the brain, decreasing the perception of pain. Steroids such as cortisone are occasionally injected locally to treat chronic pain, but such use is not safe in the long term. Even the NSAIDs and opiates are not ideal for treating chronic pain on a long-term basis, partly because their efficacy diminishes and side-effects accumulate. Of particular concern is gastrointestinal tract damage in the case of NSAIDs, whilst persistent opiate use can cause vomiting and constipation, as well as decreased sensitivity resulting in dose inflation.

On top of this, long-term use of these drugs can exacerbate cognitive impairment, which is itself often caused by chronic pain. David Finn and colleagues at the National

University of Ireland in Galway, for example, have reviewed research on the effect of chronic pain on cognitive function. Overall, they found a lasting general impairment in executive brain operation [4]. "[P]ain utilizes cognitive resources, alters neural plasticity and affects expression and activity of a variety of chemical and cellular neuromediators," Finn explained. "These effects, which are not necessarily mutually exclusive, occur across a complex network of interconnected cognition-related brain regions to produce a net cognitive impairment." He added that the long-term impact of either opiates or NSAIDs can be to accentuate some of these impairment effects.

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It is true that opiates and NSAIDs prove to be effective in many cases, at least for a time. Yet, there are several conditions that remain untreatable, according to John Wood, Head of the Molecular Nociception group at University College London. "There are many cases of pain that do not respond to available medication, and the mechanistic basis of these problems is uncertain," he said, citing as examples thalamic malfunction, which can increase sensitivity to pain in the brain, and the well-documented phenomenon of phantom limb pain in amputees. "Sadly, our range of pain killing drugs does not deal with many complex pain syndromes, hence the need for continuing efforts to define and exploit new analgesic drug targets."

However, significant advances in understanding pain made during the past 5–10 years could eventually change this depressing situation. Research into the mechanisms behind sustained chronic pain has led to several promising therapeutic avenues and a few, partly successful, clinical trials. Most of the new drugs work by blocking pain signalling itself, rather than addressing inflammation or the perception of pain. Whilst some of these emerging therapies are certainly effective, there are still concerns over side-effects. This has been illustrated most pertinently by the story of Tanezumab, a monoclonal antibody raised against nerve growth factor (NGF). NGF promotes the development of the peripheral nervous system in children and has an essential role in transmitting pain signals from the site of damage to the central nervous system. It was first identified as a candidate for drug targeting by McMahon in 1995 [5], and around a decade later, Pfizer developed an antibody that was tested in clinical trials to alleviate chronic pain in osteoarthritis patients. “This demonstrated stunning efficacy and knocked the pants off existing analgesics,” McMahon said (see illustration).

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But Tanezumab’s apparent success was temporarily undermined by an unexpected set-back—some of the patients from the trial developed severe bone degeneration. Although few patients suffered from this apparent side-effect—one in every few thousand—the number was significantly greater than for those taking placebo only, McMahon explained. As a result, the US Food and Drug Administration (FDA) recommended that Pfizer suspend worldwide trials of Tanezumab to treat osteoarthritis in 2010, pending further work to reduce the incidence of side-effects. In response, Pfizer revisited its data and found that most of the patients who had suffered from bone necrosis had also been those selected to take NSAIDs alongside Tanezumab. “They found that’s where the problems lay, and that eliminated 95% of the degenerative cases,” McMahon explained. Most of the rest of

the cases could also be eliminated by not treating patients who already had a progressive form of the disease. In 2011, the FDA lifted the ban and trials resumed, including trials to use Tanezumab to treat patients with lower back pain and patients with diabetic neuropathy—a condition where pain occurs after damage to the nerves caused by poor blood supply [6].

Side-effects have also hampered the progress of a promising treatment to block the sodium channels that transmit signals to neurons and muscle cells. The crucial channel for pain relief is at the endings of the nociceptors and is called Na_v1.7. The channel amplifies the changes in voltage that occur at the nerve endings in response to local damage or inflammation until a threshold level is reached at which the neuron fires.

The idea of targeting the Na_v1.7 channel to treat chronic pain was inspired by studying people who are unable to feel pain as a result of a single point mutation in the *SCN9A* gene, which encodes Na_v1.7 in humans. However, there are two challenges in developing Na_v1.7 antagonists to

block the receptor. One is that any drug to tackle chronic pain should leave the patient still able to feel acute pain, as pain signals are important to warn the body of any damage. The second is that several similar sodium channels have vital functions such as regulating the heart beat, so any drug must be highly specific for $Na_v1.7$ to avoid potentially substantial side-effects. A drug candidate, developed by Convergence Pharmaceuticals in Cambridge, UK, has been undergoing a phase 2 clinical trial for the treatment of pain associated with trigeminal neuralgia, a neuropathic disorder affecting around 1 in 15,000 people and causing episodes of intense facial pain. According to McMahon, it will be crucial for these trials to demonstrate that they leave other vital sodium channels more or less unchanged.

Despite this progress, there is some disagreement over whether therapeutic developments should concentrate only on the signalling pathways involved in pain, or whether they should also investigate possible interventions in the central nervous system. Research suggests that the neural mechanisms underlying pain are interesting not just for understanding and treating pain, but also for predicting and diagnosing it. Some people seem to be more susceptible to chronic pain than others and are sometimes described as having a 'vulnerable brain', which relates to the tendency for an initial injury, disease or other condition that triggers acute pain to develop into chronic pain, rather than just disappear.

The research into the mechanisms behind sustained chronic pain has led to several promising therapeutic avenues and a few, partly successful, clinical trials

A step forwards in the understanding of the transition from acute pain to chronic pain came in 2012, when a team at North Western University in the USA used magnetic resonance imaging to study the changes that had taken place in the brains of patients who had developed chronic pain [7]. "To my knowledge, this is the first brain imaging study designed to elucidate the longitudinal

mechanisms underlying the development of chronic pain after an acute injury," Marwan Baliki, one of the authors of the study commented. The researchers could predict which patients would develop chronic pain with an 85% success rate, which they felt could be further improved by extending the scope of the imaging. "The prediction is based on connectivity between two regions only. Thus, in our case, we are discarding information from the rest of the brain. I think once our knowledge pertaining to the mechanisms underlying such changes are known, we will be able to build better models of prediction," Baliki explained.

The brain regions studied were the medial prefrontal cortex (MPFC) and nucleus accumbens (NAc), and the prediction of which patients would develop chronic pain was based on observations of the communication between these regions. "Most animal research done during the past 30 years or so has focused on spinal cord mechanisms," Baliki said. "It has been thought until recently that brain activity in response to pain is just reflecting spinal cord reorganization. In our paper, we claim that the cortex is playing an active role in governing the transition of pain from an acute to a chronic pain state. In addition, the areas identified in our study—the MPFC–NAc crosstalk—are brain regions that do not directly receive nociceptive input from the classical pain pathways. That also reinforces the novelty of our findings and challenges our understanding of what is chronic pain in general."

Meanwhile, Finn and colleagues at the National University of Ireland have been looking at induced analgesia—the suppression of pain during an emergency to enable greater feats of speed or endurance, often to escape predators. Finn has been focusing on the role of internal cannabinoids, which target the CB1 cannabinoid receptor in response to pain or stress [8]. "Our recent work has demonstrated a key role for the endogenous cannabinoid (endocannabinoid) system in mediating the potent suppression of pain which occurs when animals are in a state of stress or fear," Finn explained. "When the CB1 receptor is blocked, fear-induced analgesia is prevented. Conversely, when we give drugs that inhibit the breakdown of endogenous cannabinoids, fear-induced analgesia is enhanced." Although this work

is still at a relatively early stage involving animal models, Finn believes that it too could lead to some new therapies, not just for the relief of pain, but also to alleviate fear and anxiety-related disorders. In fact, cannabis is already being used to deal with chronic pain as it invokes the same mechanisms that Finn has been analysing.

Thus, after decades of little to no progress, several promising avenues for pain research have opened up that lead in various directions, some of which might yield radical new classes of analgesics for the first time in well over a generation.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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