Commentary

Descending controls: Insurance against pain?

What protects us against pain is a neglected discussion. The majority of patients with diseases or lesions to the primary afferent branch of the nervous system do not develop chronic pain. Across the different etiologies of neuropathies the percentage varies between 5% and 30%. Furthermore, only a fraction of patients with spontaneous neuropathic pain also develop mechanical hypersensitivity. In a large multi-centre study in Germany punctate mechanical hyperalgesia was present in 9%, 36% and 30% of patients with painful polyneuropathy, postherpetic neuralgia and peripheral nerve injury pain, respectively. Dynamic mechanical allodynia occurred in 12%, 49% and 18% of patients with these different conditions [9].

These clinical observations contrast fundamentally with the situation in animal models. Thus, experimental nerve lesions in rodent strains, which attempt to mimic the clinical phenotype of patients, induce behaviours indicative of pain in the great majority of animals. This scientific paradox has repeatedly been cited by clinicians who treat patients, but was largely neglected by the basic science community, despite the field of pain being a great example of translational research and of the IASP World Congress on Pain and other meetings providing many opportunities for interaction and communication among basic and clinical scientists. Indeed, both forward (moving from basic science to the patient, e.g. assessing novel targets or mechanisms) and backward translation (trying to understand the basis of clinical findings in animal studies) on topics ranging from pain mechanisms, how analgesic therapies work and common areas of brain activation have been very successful in linking the animal to the patient. Despite these advances, the discrepancy in the incidence of pain after nerve damage in animal models and in the clinic has yet to be explained and has been used to question the utility of the animal models. Although strain differences in the development of nerve lesion-induced painful behaviour have been documented for more than 10 years [10], systematic research into the neurobiological mechanisms that underlie these fundamental differences has yet to be performed.

DeFelice et al. [4] very elegantly close this gap with their paper in the current issue of PAIN. This paper, for the first time, systematically addresses the following, clinically very important question: Why do some (the minority) of patients develop a chronic neuropathic pain syndrome while others do not, even though the inciting nerve lesion is identical. Because many more patients are left pain free, the question as to why most patients are protected against pain chronicity may be particularly relevant. DeFelice et al. shed much needed light on this issue. They used two different strains of rats. In one strain, 85% of the rats develop spinal nerve ligation-induced tactile allodynia; in the other the incidence is only 50%. Amongst several very important findings from this paper, the authors convincingly show that changes in several histochemical markers of peripheral nerve injury did not differ in the dorsal root ganglion or spinal cord, suggesting that the behavioural difference between the animal groups lay elsewhere. The key contributor, in fact, is in the brain.

The authors convincingly show that spinaly-projecting inhibitory pathways projecting from the rostroventromedial medulla (RVM) and a descending noradrenergic inhibitory pathway provide protection against spontaneous and mechanically evoked pain. A particularly novel approach (conditioned place preference) was used to gauge stimulus-independent pain after nerve lesion. Of particular interest, blocking RVM in animals with mechanical hypersensitivity reduced pain measures whilst the same tactic in the “non-neuropathic pain” animals triggered “allodynia”. By manipulating via kappa opioids the “off” cells, they demonstrated that excessive facilitation produces pain, as does loss of inhibition. Careful pharmacological studies established that a key component of the latter process is an alpha-2 adrenoceptor-mediated inhibitory control.

The ability of a descending noradrenergic mechanism to protect from pain puts pathways from the brain to the spinal cord once again at the forefront of pain modulation. The ideas of descending inhibitions and facilitations in different pain states has expanded since the seminal studies of Basbaum and Fields [2]. There is now evidence for gain of facilitation and/or loss of inhibition in preclinical pain models [1] and in patients, comparable anatomical regions have been implicated in both descending inhibition (placebo analgesia) [5] and facilitation (patients with high osteoarthritits pain [6]). Indeed, Diffuse Noxious Inhibitory Controls (DNIC), form of endogenous pain modulation involving descending controls has been reported to be deficient in a number of pain states and may also be predictive of subsequent pain problems [11].

Using a very wide range of approaches and monitoring both evoked mechanosensitivity and the level of aversive state, the paper by DeFelice et al. [4] clearly shows that failure to engage descending inhibition or failure to prevent descending facilitation leads to persistent pain.

There are, however, several additional explanations for the authors findings that should be considered and evaluated in future studies. For example, a clear genetic variability of nociception has been reported in mice, including the predisposition to neuropathic pain following neural injury [10]. This observation is in accordance with human data. In fact, a target gene association study in a large cohort of neuropathic pain patients revealed a genetic variant in the TRPV1 channel. The variant is present in about 20% of the general population and is associated with significantly less nerve lesion-induced heat and pinprick hyperalgesia [3]. Unfortunately, DeFelice et al. did not test nerve lesion induced heat hyperalgesia in the different rat strains. An analysis of the function of

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descending control mechanisms, as performed in the present study, in combination with a genetic assessment could shed even more light on the question of predisposition to nerve-injury induced persistent pain.

Furthermore, in patients, several co-morbidities, such as depression and anxiety, have been shown to predict the development of chronic neuropathic pain states [8]. One route by which these factors could influence pain might also involve descending controls. Interestingly, reduced DNIC is seen in patients with irritable bowel syndrome (IBS) and these patients had greater anxiety, depression and catastrophizing compared to controls [7]. Thus, the influence of anxiety on the chronicity of pain and on the descending control pathways should be tested in animal models, using modern techniques such as place preference. Finally, as the authors point out, there are a number of drugs that can act through alpha-2 adrenoceptors. These could be tested for their ability to protect against chronicity in patients. Given that rather large patients cohorts will be required to perform such longitudinal analyses, these will not be easy studies, but they could be extremely valuable.

In summary, this paper provides a wonderful example of “translational pain research”: the preclinical models are clearly relevant to the clinical picture, and will hopefully, influence clinical practice. Basic scientists have listened to their clinical colleagues and have performed studies that model the clinical situation especially well. The results of these analyses could not have been predicted, but they have the potential to unravel many of the complex mechanisms that contribute to the development of persistent pain. This report should encourage interchange between many more basic researchers and clinicians. This interchange is a practice in which the authors of this Commentary are constantly engaged, and one that we find especially enjoyable and informative!

Conflict of interest statement

There is no conflict of interest related to this commentary.

References


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