Title
A piece of the puzzle is revealed for delta opioid receptor-mediated analgesia

Journal
Pain, 152(6)

ISSN
0304-3959

Authors
Cahill, Catherine M
Taylor, Anna

Publication Date
2011-06-01

DOI
10.1016/j.pain.2011.02.006

PAIN® 152 (2011) 1217–1218

PAIN®

www.elsevier.com/locate/pain

Commentary

A piece of the puzzle is revealed for delta opioid receptor-mediated analgesia

Chronic pain is a major public health problem that continues to escalate and affects as many as one in three North Americans, making it one of the most common forms of chronic illness under the age of 60 years [10]. Opioid analgesics remain one of the most commonly prescribed medications for treating a diversity of chronic painful conditions. Nevertheless, the extent of efficacy in long-term treatment, abuse potential, and incidence of a significant number of side effects makes the use of opioids in the treatment of chronic noncancer pain controversial [7]. As a result there continues to be a profound interest in investigating the neural basis of chronic pain, with the ultimate goal of developing novel and more effective treatments.

Numerous preclinical studies provide evidence that delta opioid receptor (DOR) function is enhanced in chronic pain [3]. Indeed, local, systemic, and central administration of selective DOR agonists attenuates pain hypersensitivity in animal models of neuropathic and inflammatory pain (see Gaveriaux-Ruff et al. [6] for a summary of these data). Moreover, mice with global knockout of DOR, but not μ or κ opioid receptors, exhibit enhanced pain behaviors in chronic inflammatory and neuropathic pain models [4,5,9], suggesting that DOR activity elicits an analgesic tone following the genesis of chronic pain.

In this issue of PAIN®, Gaveriaux-Ruff et al. [6] have created a genetically modified animal to selectively ablate DORs from a subset of primary afferent neurons involved in nociceptive transmission. Their objective was to understand better the contribution of these receptors in modulating formalin, complete Freund's adjuvant-induced inflammatory and neuropathic pain. The authors used an approach similar to that of Agarwal et al. [1], who reported that cannabinoids primarily mediate their analgesic effects via peripheral cannabinoid type-1 receptors in the subset of nociceptive primary afferent neurons that express Nav1.8 sodium channels. Gaveriaux-Ruff et al. [6] created a mouse line with engineered floxed sites within the DOR gene, such that when bred with mice expressing Cre recombinase in Nav1.8+ neurons, DOR was specifically deleted from these cells (Nav1.8-Oprd1$^{-/-}$). It is important to appreciate that in the Nav1.8-Oprd1$^{-/-}$ mice, DOR protein continues to be expressed in many regions of the brain, spinal cord, and other sensory neurons, including those involved in nociception, ie, in neurons that do not express the Nav1.8 sodium channel. This is evidenced by normal brain GTPγs activity, DOR binding, PCR products, and DOR-induced hyperlocomotion (a centrally mediated effect).

The seminal finding in this article is that systemic administration of a selective DOR agonist (SNC80) attenuates mechanical and thermal (heat) pain hypersensitivities in models of chronic pain, but that the DOR-mediated regulation is lost in the Nav1.8-Oprd1$^{-/-}$ mice. This result implies that DOR agonists act solely at peripheral targets and in a subset of nociceptive neurons to attenuate evoked pain thresholds (allodynia and hyperalgesia). It is noteworthy that peripheral DORs in Nav1.8-expressing neurons are not the only DORs able to modulate pain behaviors. The authors report that DOR-induced suppression of formalin-evoked nocifensive behaviors (persistent inflammatory pain model) is not altered in the Nav1.8-Oprd1$^{-/-}$ mice. This result suggests that DORs expressed at other anatomical sites are critical in suppressing spontaneous pain behaviors (licking and flinching). Another important result is that Nav1.8-Oprd1$^{-/-}$ mice with either chronic inflammatory or neuropathic pain exhibit exaggerated pain hypersensitivities compared to control animals; this result is similar to that reported in global DOR knockout animals [4,5,9]. Thus, DOR in Nav1.8+ expressing neurons must play a significant role in producing a tonic inhibitory tone on evoked pain.

It is worth reflecting on the role of DOR in various pain modalities when discussing peripheral DOR-mediated effects. A recent published article reported that in chronic pain models, intrathecal administration of DOR agonists are able to modulate *only* mechanical pain, leaving thermal pain modalities unaltered [12]. However, from the present study it is clear that DOR agonists are able to reverse heat hyperalgesia in both inflammatory and neuropathic models, and this effect is absent in the Nav1.8-Oprd1$^{-/-}$ mice, illustrating that DORs on peripheral nociceptors are important modulators for both modalities [6]. The discrepancy in DOR involvement in modulating heat hyperalgesia is intriguing. One plausible explanation for the discrepancy is due to the site of action for DOR-mediated effects. DORs synthesized in dorsal root ganglion neurons can be trafficked to both central sites within afferent terminals in the spinal cord as well as to peripheral sites. The positive effects reported by Gaveriaux-Ruff et al. [6] are produced by systemic administration of the DOR agonist and therefore, could act at DORs within the Nav1.8+ neurons that are present at the site of injury, whereas this effect would be missed by the spinal administration presented by Scherrer et al. [12]. Regardless, contrary to the major message put forth that peripheral DOR cannot modulate thermal pain [12], clearly this study [6] provides further validation for the development of peripherally acting DOR agonists to treat thermal as well as mechanical hypersensitivities.

Gaveriaux-Ruff et al. [6] present an important study elucidating the function of peripheral DORs in chronic pain states, but their report also highlights the value of assessing evoked mechanical and thermal pain thresholds. One could argue that the harmonious results demonstrating that peripheral DOR [6] and cannabinoid type-1 receptors [1] are necessary targets to alleviate allodynia and hyperalgesia provide further validation for the development of topical or peripherally restricted drugs. Indeed, topical administration of various agents, including capsaicin, lidocaine and even antidepressants alleviate allodynia in chronic pain patients [11]. However, a more provocative viewpoint has been argued, namely

doi:10.1016/j.pain.2011.02.006

that evoked threshold nociceptive measures are not valid tools for predicting effectiveness in a clinical pain population [8]. In the last couple of years, both clinical and basic researchers have questioned the validity of commonly used animal neuropathic pain models and behavioral outcome measures. The construct validity of threshold measures has been questioned by the argument that these indices are not measurements of pain, but of reflexes (sometimes hyperactive) that accompany pain. Indeed, ongoing, spontaneous pain, which occurs independent of any stimulus, is of greater prevalence than evoked pain [2], suggesting that capturing such phenomena will improve construct validity of animal models. In fact, clinical trials use validated questionnaires or analogue scales to measure total pain but do not often define an evoked pain (allodynia and hyperalgesia) component in this total pain score. If, indeed, evoked pain can be diminished by targeting peripheral receptors, then perhaps we should advocate that clinical trials include questions that capture evoked pain in addition to total pain, with the hope that better outcomes for pain treatment will be forthcoming.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

References

[1] Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, Rubino T, Michalski CW, Marsicano G, Monory K, Mackie K, Marian C, Batkai S, Parolaro D, Fischer MJ, Reeh P, Kunos G, Kress M, Lutz B, Woolf CJ, Kuner R. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 2007;10:870–9.
[2] Backonja MM, Stacey B. Neuropathic pain symptoms relative to overall pain rating. J Pain 2004;5:491–7.
[3] Cahill CM, Holdridge SV, Morinville A. Trafficking of delta-opioid receptors and other G-protein-coupled receptors: implications for pain and analgesia. Trends Pharmacol Sci 2007;28:23–31.
[4] Filliol D, Ghozland S, Chluba J, Martin M, Matthes HW, Simonin F, Befort K, Gaveriaux-Ruff C, Dierich A, LeMeur M, Valverde O, Maldonado R, Kieffer BL. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat Genet 2000;25:195–200.
[5] Graveriaux-Ruff C, Karchewski LA, Hever X, Matifas A, Kieffer BL. Inflammatory pain is enhanced in delta opioid receptor-knockout mice. Eur J Neurosci 2008;27:2558–67.
[6] Gaveriaux-Ruff C, Nozaki C, Nadal X, Hever XC, Weibel R, Matifas A, Reiss D, Filliol D, Nassar MA, Wood JN, Maldonado R, Kieffer BL. Genetic ablation of delta opioid receptors in nociceptive sensory neurons increases chronic pain and abolishes opioid analgesia. Pain 2011;152:1238–48.
[7] Manchikanti L, Benyamin RM. Long-term opioid therapy. Pain Pract 2009;9:164 [author reply 164].
[8] Mogil JS. Animal models of pain: progress and challenges. Nat Rev Neurosci 2009;10:283–94.
[9] Nadal X, Baños JE, Kieffer BL, Maldonado R. Neuropathic pain is enhanced in delta-opioid receptor knockout mice. Eur J Neurosci 2006;23:830–4.
[10] Rapoport J, Jacobs P, Bell NR, Klarenbach S. Refining the measurement of the economic burden of chronic diseases in Canada. Chronic Dis Can 2004;25:13–21.
[11] Sawynok J. Antidepressants as analgesics: an introduction. J Psychiatry Neurosci 2001;26:20.
[12] Scherrer G, Imamachi N, Cao YQ, Contet C, Mennicken F, O'Donnell D, Kieffer BL, Basbaum AI. Dissociation of the opioid receptor mechanisms that control mechanical and heat pain. Cell 2009;137:1148–59.

Catherine M. Cahill
Department of Pharmacology & Toxicology, Department of Anesthesiology and Perioperative Medicine, Centre for Neuroscience Studies, Queen's University, Botterell Hall, Room 516, Stuart Street, Kingston, Ontario, Canada
Tel.: +1 613 533 6162; fax: +1 613 533 6412.
E-mail address: cathy.cahill@queensu.ca

Anna Taylor
Department of Pharmacology & Toxicology, Queen's University, Kingston, Ontario, Canada