



Published in final edited form as:

*Pain*. 2018 September ; 159(9): 1679–1680. doi:10.1097/j.pain.0000000000001283.

## Chronic pain and opioid receptor availability: disentangling the molecular contributions and the “chicken or the egg” dilemma

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Starting with the 1973 discovery of opioid receptor sites in the brain [16], substantial evidence from both preclinical and clinical studies has established the endogenous opioid system as a key player in the experience and regulation of pain, both in physiological and pathological conditions [4]. An important source of this evidence has undoubtedly been in vivo molecular imaging, especially positron emission tomography (PET). For instance, through the use of [<sup>11</sup>C]-carfentanil (a selective  $\mu$ -opioid receptor agonist) or [<sup>11</sup>C]- or [<sup>18</sup>F]-diprenorphine (a non-selective, weak partial agonist of the  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors), PET scientists have demonstrated that opioidergic neurotransmission is activated in healthy volunteers during acute pain stimulation [20; 23] or during expectation of pain relief [22]. Importantly, by showing changes in opioid receptor availability in humans with different pain disorders (including central and peripheral neuropathic pain, complex regional pain syndrome, fibromyalgia and arthritis pain [5; 8–10; 12; 14; 21]), molecular imaging studies have provided experimental evidence in support of a role for alterations in the opioid system as likely contributors to several clinical manifestations associated with chronic pain, including the high prevalence of psychiatric comorbidities and the large interindividual variability in the efficacy of opioid therapy.

While results from human PET studies have undeniably advanced our understanding of the opioid system’s contributions to chronic pain, their interpretation can sometimes present challenges. Some of these are to be attributed to the cross-sectional nature of many of these studies, which cannot resolve the question of causality. Are the observed alterations in opioid PET signal caused by the pain condition itself, or are they predated (and perhaps predisposing to) its development? Are these changes induced by the treatment, or even by lifestyle changes (e.g. in the amount of physical exercise, or in the engagement in social and other pleasurable activities) that commonly accompany a chronic pain disorder? Could they just be an epiphenomenon? In addition to the difficulty in solving the “chicken or the egg” question, inferring the exact neurobiological underpinnings of the observed PET signal changes can sometimes present some uncertainties. For instance, the reduction in opioid receptor availability that has been reported in several pain disorders has been alternatively

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**Conflict of interest statement**

The author has no conflict of interest to declare.

interpreted in terms of the loss or inactivation of opioid receptors [10], a reactive increase in opioidergic neurotransmission, competing with the exogenously administered radioligand [21], or a combination of both [14]. Of course, having a better understanding of the biological correlates of our imaging metrics would dramatically enhance our interpretation of the results arising from the PET literature.

By adopting an elegant combination of behavioral testing, in-vivo and ex-vivo imaging (using PET and immunohistochemistry), within a well-controlled longitudinal preclinical design, the study by Thompson et al. [19] is able to generate insights that significantly advance our understanding of the relationship between neuropathic pain and alterations in the opioid system. This well-conceived study overcomes several of the limitations that typically accompany cross-sectional human studies and ultimately aids with the interpretation of their results.

First, due to the longitudinal design of their study, the authors are able to show that the reduction in opioid receptor availability can be a *consequence* of nerve injury itself. The brains of Sprague-Dawley rats were scanned using PET imaging and [<sup>18</sup>F]FDPN (a fluorinated analog of diprenorphine) three months after spared nerve injury (SNI), or sham surgery. The SNI rats, who had clearly developed nocifensive behaviors compatible with neuropathic pain, demonstrated reduction in [<sup>18</sup>F]FDPN PET signal (that is, in opioid receptor availability) in the striatum, as well as motor and insular cortices. While a pre-surgical scan was not performed, it is very reasonable to conclude that the post-surgical differences in PET signal must have been induced by the injury and/or the ensuing persistent pain, because all animals were exposed to a well-controlled environment and randomly assigned to the SNI or sham conditions. Thus, the results from this study suggest that the reduction in opioid receptor availability often observed in humans with chronic pain [5; 9; 10; 12; 14; 21] might be, at least in part, caused by the painful condition itself, and therefore cannot be completely explained by other factors, whether pre-dating (e.g., genetics), or co-occurring with the disorder (e.g., treatment).

The merits of the study by Thompson and colleagues extend further. By performing immunohistochemical analyses of the brain regions previously identified in the PET analyses, the authors were able to show that, at least for the striatum and the anterior insula, a reduction in the expression of the mu-opioid receptor MOR1 was driving the imaging findings, rather than changes in density of opioidergic neurons or increased levels of endogenously-released enkephalin. While a down-regulation of mu-opioid receptors in the central nervous system in preclinical pain models has been previously reported (e.g., [11; 18]), this is the first study directly linking these alterations to changes in opioid PET signal. As such, this work is not only able to address the issue of causality, but also to provide strong hints as to the molecular basis for the opioid PET signal changes observed in chronic pain patients. It should be pointed out, however, that at least one study demonstrated increases in mu-opioid receptor availability, rather than decreases, in patients with a chronic pain condition (nonspecific chronic low back [15]). Thus, the direction of change in opioid receptor availability, and/or its association with the underlying neurobiological mechanism of change, e.g. protein expression or endogenous ligand tone, may vary across conditions.

Finally, Thompson and colleagues were able to show that both opioid receptor availability and expression in the striatum of the SNI rats were positively correlated with the score on the sucrose preference test: the lower the PET signal or MOR1-immunoreactivity, the lower the score. This test is used to measure anhedonia (i.e., the loss of interest in normally rewarding stimuli), which represents one of the clinical hallmarks of depression [7]. Depression and other psychiatric conditions are highly comorbid with chronic pain, likely reflecting a bidirectional association (with pain causing/worsening depression, and depression being a predictor of persistent pain [1; 6]). Further, patients with chronic pain demonstrate anatomic-functional alterations in the reward neurocircuitry (e.g., [2; 3; 13; 17]). While our understanding of the neurobiological mechanisms underlying psychiatric conditions is becoming more and more sophisticated, it still remains very limited. By demonstrating a clear link between the reduction in opioid receptor availability/expression and anhedonia, the authors provide a plausible mechanism linking pain to depression in humans.

In sum, the study by Thompson and colleagues provides an exciting example of how adopting an integrative approach to pain research, which makes clever and synergistic use of multiple techniques (in-vivo imaging to localize a signal, ex-vivo imaging to dissect its molecular sources, behavioral testing to investigate the clinical significance of the observed imaging alterations), can enrich the investigation of neuroscientific questions. It is also important to note that the relevance and significance of this study lies in the fact that the authors chose to focus on a target (opioid receptors) that has already proven to be involved in human pain disorders. At a time in which the clinical translatability of many preclinical studies is questioned, the use of this “reverse-translational” approach (in which a target identified as being relevant for humans is explored more in detail in animal models), seems a promising avenue to further our understanding of the functions of the opioid system in particular, and the neurobiology of pain more broadly.

## Acknowledgments

The author would like to thank Dr. Daniel Albrecht for helpful comments. This work was supported by the following grants from the National Institute of Neurological Disorders and Stroke: 1R01NS094306-01A1 and 1R01NS095937-01A1.

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