Partners in Pain: New Insights into The Role of CGRP Signaling in Cross-Organ Sensitization

Disorders associated with visceral pain represent a major problem in modern healthcare. Abdominal and pelvic pain are some of the most frequent and consequential symptoms that patients present to healthcare providers for. They are also each integral components of the diagnostic criteria for some of the most common urological and digestive disorders, including interstitial cystitis/bladder pain syndrome (IC/BPS) and irritable bowel syndrome (IBS). These conditions, and other similar disorders, account for a significant portion of the cases that primary care providers, gastroenterologists and urologists manage (Anger et al., 2022; Peery et al., 2022). They are also directly responsible for an outsized proportion of healthcare-related costs in these fields as well as a significant detrimental impact on patient quality of life (Anger et al., 2022; Peery et al., 2022). However, in spite of the relative familiarity healthcare providers have with these disorders (and their associated symptoms) remain very challenging to manage for several reasons. First, the primary drivers of chronic visceral pain are still poorly understood. This is due, at least in part, to the realization that conditions such as IBS and IC/BPS are themselves heterogeneous in nature. Thus, the pain(s) that different patients experience (even when carrying the same diagnosis) may be attributable to relatively divergent sources. Second, growing evidence demonstrates that conditions associated with visceral pain, including IBS and IC/BPS, are frequently coincident and may potentiate one another (Chang et al., 2021). Thus, attempts to manage one, without incorporating therapeutic strategies to at least help control the other, may result in suboptimal symptom control. Unfortunately, finding appropriately targeted, safe and efficacious therapies to successfully manage either IC/BPS or IBS, let alone both, has proven to be very challenging. A wide variety of analgesic medications have been used to help manage these disorders. Unfortunately, currently available conventional analgesics (such as acetaminophen, non-steroidal anti-inflammatory drugs and opioids) and even other, more evidence-based pharmacological options (including anti-spasmodics, tricyclic antidepressants and other neuromodulatory therapies) are frequently ineffective and/or associated with significant side effects (Chang et al., 2022; Clemens et al., 2022; Lembo et al., 2022).

There is a massive ongoing and urgent need to improve our overall understanding of the pathophysiology underlying chronic visceral pain disorders, such as BPS/IC and IBS, and to develop new, better-targeted therapies to address the abdominopelvic pain associated with these conditions.

In this issue of The Journal of Pharmacology & Experimental Therapeutics, Noor-Mohammadi et al. describe the findings of a compelling animal (i.e., rat) study which reinforces the importance of calcitonin gene related peptide (CGRP) signaling as a significant driver of visceral pain and, in particular, abdominopelvic pain associated with the bladder and colon (Noor-Mohammadi et al., 2023). They also demonstrate the importance of CGRP in the development of nociceptive cross-sensitization between the bladder and colon, as well as the multi-functional promise of targeting CGRP to simultaneously manage pain associated with both of these organs, offering new hope for the management of many challenging associated disorders, including BPS/IC and IBS.

Cross-sensitization (or cross-organ sensitization) describes a scenario in which pain-related activity and/or signals from a diseased organ (or tissue) influence the perception of pain arising from an otherwise normal adjacent organ (or tissue). This phenomenon has been studied in the context of several organs associated with the abdomen and pelvis, including the bladder and colon. Investigators have identified key anatomic contributors to pain-related cross-sensitization. For example, retrograde labeling studies have
demonstrated that afferent nerve fibers innervating both the bladder and colon at least partially overlap at the level of the primary sensory neurons in dorsal root ganglia neurons as well as second-order neurons of the spinal cord (Christianson et al., 2007; Herrity et al., 2014). In previous studies utilizing rodent colitis models, development of colonic inflammation was associated with increases in the resting firing rates of nociceptive C-fibers associated with the bladder as well as demonstration of mechanical hypersensitivity to normal pressures within the bladder (Ustinova et al., 2006). Similarly, a rodent model of cyclophosphamide-induced cystitis induced mechanical hypersensitivity in muscular afferent nerves as well as an increased proportion of chemosensitive nerve fibers associated with the colon (Bruvonskoy et al., 2009). While the precise molecular mechanisms underlying these relationships has remained unclear, several signaling systems, including CGRP signaling, have also been implicated in this process.

CGRP has been progressively recognized as having a significant influence on pain transmission as well as the development of peripheral and central sensitization. Immunohistochemical and in situ hybridization studies have demonstrated that CGRP and its receptor are widely expressed in the somatosensory and enteric nervous systems, and are increasingly described in components of the central nervous system (Iyengar et al., 2017). Specifically, CGRP and its receptor have been frequently identified in nerves, particularly localized to sensory neurons. CGRP knockout mice have also previously been demonstrated to exhibit diminished somatosensory and visceral pain responses (Salmon et al., 2001). This is particularly relevant, as both peripheral and central sensitization have been hypothesized as primary causes of the pain associated with IC/BPS and IBS (Tillisch et al., 2011; Kaya et al., 2013; Reynolds et al., 2016; Wouters et al., 2016). Notably, Noor-Mohammadi et al. have previously demonstrated that use of a monoclonal antibody against CGRP could reduce central sensitization and visceral hypersensitivity in rat models exposed to early stress or chronic stress in adulthood (Noor-Mohammadi et al., 2021).

In their present study, Noor-Mohammadi et al. used rodent models of cystitis and colitis to carefully evaluate the potential role of CGRP signaling in the development and maintenance of simultaneous bladder and colon-derived pain in a rat model (Noor-Mohammadi et al., 2023). They were able to successfully target CGRP with a monoclonal antibody, and this subsequently led to reduction in both colonic and bladder hypersensitivity in the cystitis and colitis models. This work provided further evidence that targeting CGRP could provide a novel treatment strategy for a variety of conditions associated with abdominopelvic pain (either individually or simultaneously). Notably, CGRP-targeting antibodies are already approved for management of other conditions (e.g., migraine prevention) (Mohanty and Lippmann, 2020), and so this approach could potentially be adopted relatively rapidly. Importantly, they also demonstrated that CGRP was associated with increased permeability in both the colonic mucosa and bladder urothelium in their models, and that this change in epithelial barrier function could be reversed with systemic treatment with an anti-CGRP antibody. This was a novel finding that provided further important insights into the potential mechanisms underlying cross-sensitization between the colon and bladder. It also provides an additional potential therapeutic approach to consider in the management of visceral pain disorders: optimization of epithelial barrier function.

Questions remain regarding the relative impact of CGRP on inflammation in the colitis and cystitis models used, and how that may have influenced measures of nociception. Additionally, although anti-CGRP was given systemically (e.g., intraperitoneally), its effects were peripherally-acting. However, it is still not clear exactly what the differential impact of the monoclonal antibody used in this study was on CGRP-associated central and peripheral mechanisms related to pain perception. Future studies could incorporate CGRP knockout mice to further confirm the contribution of CGRP signaling in colitis and cystitis-induced nociception. The dosing frequency used in this study was also notably higher than has been relied upon in the clinical setting for management of migraines. Thus, it will be important to determine (particularly in future human studies) whether a less frequent dosing regimen exhibits similar efficacy in this context. Determination of anti-CGRP effects on colon and/or urinary bladder function (beyond pain-related measures) would also be valuable in demonstrating functional as well as sensory impacts. In the present study by Noor-Mohammadi et al., urinary bladder sensation was assessed using von Frey filament testing, but given its subjective nature, use of visceromotor response testing in response to bladder distention would further strengthen the present studies. Additionally, incorporation of other models of colitis and cystitis beyond those in the present study, would demonstrate model independence of the promising results. As mentioned above, CGRP-targeting monoclonal antibody therapies are already approved to treat migraines, potentially facilitating rapid adoption for conditions associated with abdominopelvic pain. However, it should be noted that at least a third of migraine patients are unresponsive to these new drugs, and others stop them due to adverse issues (including development of constipation, a condition that could theoretically exacerbate abdominopelvic pain) (Cullum et al., 2022; Vernieri et al., 2022). Considering this fact, future studies focused on this topic may benefit from parallel or separate evaluation of alternative therapeutic strategies that target the CGRP signaling system (e.g., small molecule inhibitors) (Dos Santos and Da Silva, 2022). Thus,
perhaps excitement about the potential of these agents to manage viscerally-based conditions, including IC/BPS and IBS, should be tempered, at least until we gain a more complete understanding of how CGRP signaling influences visceral pain generation. Nonetheless, while the search for additional targets to more safely and effectively target abdominopelvic pain should continue, the insights provided by this study may prove to be important steps in a promising direction toward the future management of visceral pain disorders.

Matthew D. Coates and Margaret A. Vizzard

**References**


