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Role of microRNA in chronic visceral nociception

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Chronic pelvic pain is a common functional disorder that leads to substantial morbidity in the United States. Unfortunately, an understanding of the underlying etiologies of chronic visceral pain in the pelvis is incomplete. Animal models that induce a focal irritative or injury to the pelvis may produce a cross-sensitization in functionally comparable afferent pathways of the bowel and bladder. Interestingly, previous work has shown that chronic pelvic pain disorders, such as interstitial cystitis and irritable bowel syndrome, often overlap as a result of neural cross-talk via the convergence of pelvic afferents [5]. Thus, a better understanding of the physiology of primary visceral afferents has led to better understanding of the mechanisms that lead to states of chronic altered sensations from the pelvic viscera such as interstitial cystitis, irritable bowel syndrome, and ureteric colic [4].

MicroRNAs (miRNAs) are a class endogenously expressed RNA's 21–23 nucleotides long, [3]. They are small, non-coding RNA molecules, with a function distinct from but related to that of short interfering RNAs (siRNAs). Mature miRNAs are 19- to 25-nucleotide-long molecules cleaved from 70- to 100-nucleotide hairpin pre-miRNA precursors. Single-stranded miRNAs bind through partial sequence homology to the 3′-untranslated region (UTR) of target mRNAs and cause a block in translation or mRNA degradation [1]. Over the past decade, miRNAs have emerged as regulators involved in gene expression of critical biological processes, including development, differentiation, apoptosis and proliferation. The regulation occurs through imperfect pairing with target mRNAs of protein coding genes [12]. Recent work has shown that miRNAs regulate gene expression by directing sequence-specific degradation of complementary mRNA molecules or by repressing translation [6].

With respect to pain mechanisms, select miRNAs have been implicated in multiple cellular processes, including neuronal plasticity and neurogenesis, nociceptor excitability, pain threshold, and chronic pain conditions [10]. He et al. for example, reported that opioid tolerance is regulated by the let-7 family microRNA, which targets the mu opioid receptor [2]. In their study, they used an LNA-let-7 inhibitor to decrease brain let-7 levels, which they found attenuated opioid antinociception tolerance in mice. Thus, the let-7 family microRNA plays an integral role in opioid tolerance. Recently, Zhou et al. evaluated Irritable Bowel Syndrome patients with chronic abdominal and pelvic pain associated with increased intestinal permeability [13] and found increased miR-29a expression in the colon tissues and blood microvesicles [11]. miR-29a has a complementary site in the 3′-UTRs of the GLUL

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Conflict of interest statement

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gene that leads to decreased glutamine synthetase levels and increased intestinal permeability and chronic visceral pain in Irritable Bowel Syndrome patients. Suppression of miR-29a expression in vitro restored intestinal permeabilty [11]. Therefore, intestinal hyperpermeability is a contributing factor to visceral hypersensitivity and chronic abdominal/pelvic pain in IBS patients [13].

One of the pioneer studies to study miRNA in chronic bladder pain evaluated the role of miRNA in down-regulation of the neurokinin-1 receptor in chronic bladder pain syndrome [7]. This study demonstrated that increased miR-328, miR320, miR-449b and miR-500 expression was directly down regulated NK1R in bladder biopsies from bladder pain patients. Modulation of the NK1 receptor by increased expression of miRNAs may underlie the molecular mechanisms of bladder pain syndrome. In the current issue of PAIN, Sengupta et al. tested the hypothesis that long-term colonic hypersensitivity in neonatally zymosan-induced cystitis is due to miRNA-mediated posttranscriptional suppression of the developing spinal GABAergic system [8]. In their study, cystitis was induced via intravesicular infusion of zymosan during postnatal days 14–16, after which the spinal dorsal horns (L6-S1) were harvested. Evaluation of the spinal cord tissue revealed upregulation of miR-181a in the L6-S1 spinal dorsal horn in the zymosan-treated rats compared to the saline controls. This was true in both re-challenge and unchallenged groups. miR-181a has multiple complementary binding sites for the $GABA_A$ receptor subunit $GABA_{A\alpha\text{-}1}$ gene and increased miR-181a expression results in down regulation of the $GABA_{A\alpha\text{-}1}$ receptor subunit gene. Thus, these findings suggest that miRNA-mediated post-transcriptional deregulation of the GABAergic system plays an integral role in neonatal cystitis-induced chronic pelvic pain.

The current study by Sengupta et al. is very interesting on many levels [8]: (1) The study uses a novel experimental model and provides evidence for cross-sensitization of the lower urinary tract and colon. This cross-sensitization or “neural cross-talk” may be relevant to the significant overlap that has been described in chronic pelvic pain disorders such as irritable bowel syndrome and interstitial cystitis [5]. In the current study, the authors reported that neonatal rats with cystitis exhibited a hypersensitive response to colonic distension indicating the development of overlapping chronic pelvic pain. (2) Another very interesting observation is the presence of $GABA_A$ receptor downregulation in the lumbosacral (LS) segment of the spinal cord in rats that had neonatal cystitis. (3) The findings raise the interesting possibility that an increased of miR-181a in the adult spinal cord following neonatal cystitis underlies a miRNA-mediated transcriptional deregulation of the GABA receptor.

The Sengutpa et al.; study [8] also raises some important questions for future research: (1) What other miRNAs are involved in post-transcriptional regulation of GABA receptors? This is relevant as a single gene can be targeted by multiple miRNAs? For example, Zhao et al. recently reported that both miR-216 and miR-203 = target the $GABA_{A\alpha\text{-}1}$ receptor subunit gene [9]. (2) Although the current study focused on GABAergic neurotransmission in the L6-S1 spinal cord, are there other miRNA changes that occur at the level of the bladder or colonic myenteric plexus that influence this persistent chronic pelvic neuroplasticity and cross-sensitization? Also, are there changes in miRNA levels in the peripheral nervous system or DRG that serve bladder and colon afferents at L6-S1? The

presence of miRNA-mediated changes in bladder or colon tissue or in peripheral nervous system would offer further insight into the relevance of the findings of the current study. Other studies directed at co-localization of the downstream targets of these miRNAs should also be a focus of future studies. (3) Perhaps one of the most important questions raised by this study is whether these findings can be translated to humans with chronic pelvic pain. Clearly, the current study needs to be interpreted with some caution until additional studies are performed, with a focus on other miRNAs that target GABA receptors and in human translational studies.

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