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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

TRPV1 Sensory Neurons and Enteric Glia in ENS Link Tachykinins to Neuroinflammation and Nociception

Significant interactions may occur between the "immune and nervous systems in the gut"; which include glia, intrinsic and extrinsic neurons, and various immune cells located in close proximity to one another.[1] The complex interactions between these cells and how they are involved in gastrointestinal physiology and disease remain understudied. Among the variety of cell types, enteric glia may represent a "new research frontier in neurogastroenterology" and a novel clinical target in functional gastrointestinal disorders and inflammatory bowel disease (IBD).[2] Findings reported by McClain et al [3] as well as a recent study by Rao et al[4] have indicated that enteric glia are required for normal intestinal motility and that, in the context of inflammation, glia convert to a "reactive glial phenotype" that is associated with neuroinflammation, neurodegeneration, and exaggerated neurogenic contractions and may contribute to IBD, enteric infections, postoperative ileus, motility disorders, and functional gastrointestinal disorders.[2] Reactive enteric glia may be a pivotal player in neuroinflammation, motor disorders, and visceral abdominal pain associated with these disorders, but the precise mechanisms involved are not well understood. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Delvalle et al[5] further probe the role of tachykinins in neuroinflammation in the gut, with a specific focus on how intercellular neuron-glia signaling is linked to neuroinflammation and dysmotility.

Tachykinins are neuropeptides expressed in enteric neurons of the gut and extrinsic nerve fibers from the dorsal root and vagal ganglia. Tachykinins are important excitatory transmitters in gut neural reflexes and they interact with the following tachykinin/neurokinin receptors (NKRs): NK1R, NK2R, and NK3R. Release of substance P, a member of the tachykinin neuropeptide family, is known to contribute to neurogenic inflammation. Although tachykinin activation of NK2Rs on enteric glia via is thought to be involved in enteric nervous system (ENS) dysfunction in irritable bowel syndrome (IBS),[6] the neural–glial mechanisms involved are not well understood. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Delvalle et al[5] defined a previously unrecognized signaling interaction between enteric neurons, extrinsic sensory neurons, and enteric glia that is mediated by NK2R and transient-receptor potential vanilloid-1 (TRPV1). Elegant imaging studies in intact myenteric ganglia of reporter mice expressing a Ca^{2+} sensor to monitor Ca2+ waves provides proof that NK2Rs drive responses in neuronal varicosities that propagate to enteric glia and neurons via a connexin-43–dependent pathway. The study goes on to show that blockade of NK2R signaling can enhance recovery from colitis and alter the development of a reactive glial phenotype. Next-generation RNA sequencing analysis in enteric glia identified the inflammation-induced reactive glial transcriptome signature and showed that NK2R blockade alters the development of this signature.

An important breakthrough reported in this study was that neurokinin A activates TRPV1-positive nociceptors via NK2Rs to drive glial and neural network activity in the ENS. The novel NK2–TRPV1 neural–glial–nociceptive pathway is a potential target for both visceral pain and inflammation in IBD. As highlighted in the article,[5] enteric glia are central to IBD-associated enteric neuroinflammation. The studies showed that enteric glia links neuronal TK_2Rs and TRPV1R. Ultimately, restoring normal enteric glial cell function may provide an effective strategy to combat inflammation, protect the ENS, prevent abnormal motility, and perhaps provide analgesia. The pathway is potentially relevant in IBD, IBS, and motility disorders, and, possibly, in some CD patients in remission who continue to experience pain.

The sensitization of TRPV1 on visceral afferent nociceptive nerve terminals is deemed to be an important mechanism of visceral hypersensitivity. H1-mediated sensitization of TRPV1 was shown to mediate visceral hypersensitivity and symptoms in IBS patients. Ebastine, an H1 antagonist, reduced visceral hypersensitivity, gastrointestinal symptoms, and abdominal pain in IBS patients.[7] In this regard, a key question arising from the study by Delvalle et al[5] is whether neurokinin A can induce NK2-mediated sensitization of the TRPV1 sensory neurons in the neural glial pathway to cause pain?

Tachykinins are implicated in motility disorders and studies have indicated that NK2R antagonists may inhibit the hypermotility associated with intestinal inflammation, infection, or stress, and this may occur without any constipating effect.[8] The study by Delvalle et al[5] suggested that neuron–glia signaling may be the target of NK2R antagonist drugs to restore motility and attenuate colitis by dampening the effects of tachykinins operating in a complex immune regulatory circuit to amplify inflammation in IBD.

More effective drug treatments are needed to treat gastrointestinal disorders, particularly those that cause abdominal pain. With respect to tachykinin drugs in clinical trials, NK1R antagonist drugs did not show significant analgesic activity and failed to get approval for use to treat pain.[9] They also showed variable efficacy as anti-inflammatory drugs. In models of gut inflammation–induced hypersensitivity, NK2R antagonists reduced abdominal pain (cramps) and postoperative ileus,[10] and are promising experimental drugs for IBS.[11,12] In a small phase 2 study, the selective NK2R antagonist ibodutant was shown to improve pain

severity in diarrhea-predominant IBS. A larger phase 2, randomized, double-blind, placebo-controlled trial in 559 patients showed a dose-dependent improvement in gastrointestinal symptoms and abdominal pain in female diarrhea-predominant IBS.[11] In this regard, the study by Delvalle et al[5] has advanced our understanding of the mechanisms underlying the beneficial actions of NK2R antagonists. Future studies in IBS models exploring the neural NK2/TRPV1–glial connexin-43–dependent purinergic signaling pathways at the level of the ENS, sensory nerves, and enteric glia to block abdominal pain and gastrointestinal dysfunction offer exciting possibilities.

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