Congress: United European Gastroenterology Week (UEGW) 2020

Society: United European Gastroenterology

Abstract Type: Abstract

Content: Mandatory subheadings: introduction, aims & methods, results, and conclusions; references allowed (optional and ≤200 words); 1 table per abstract with each row= 50 characters, table title ≤150 characters, including spaces; no figures allowed; define abbreviations at first use in text; only generic drug names; special characters allowed for title + abstract text.

Funding: Supported by Arena Pharmaceuticals, Inc. and NHMRC Australia

COI Information: S. Schmiel and B. Lindstrom are employees of Arena Pharmaceuticals, Inc. S.M. Brierley received research funding from Arena Pharmaceuticals to conduct the study. J. Castro, S. Garcia-Caraballo, J. Maddern, and G. Schober have nothing to declare.

Expression and Localization of Cannabinoid Receptors and the Effect of Olorinab, a Peripherally Acting, Highly Selective, Full Agonist of the Cannabinoid Receptor 2, on Visceral Hypersensitivity in Rodent Models of Irritable Bowel Syndrome and Inflammatory Bowel Disease

Joel Castro,[1] Sonia Garcia-Caraballo,[1] Jessica Maddern,[1] Gudrun Schober,[1] Beatriz Lindstrom,[2] Shirdi Schmiel,[2] Stuart M. Brierley[1]

[1]Visceral Pain Research Group, Flinders University, SAHMRI, Adelaide, SA, Australia; [2]Arena Pharmaceuticals, Inc, San Diego, CA, USA

Introduction: Patients with inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) commonly experience abdominal pain. Treatment options for abdominal pain associated with IBD and IBS are suboptimal, representing a significant unmet need. In preclinical models of gastrointestinal inflammation, increased expression of cannabinoid receptor 2 (CB_2) in the colon has been demonstrated; additionally, CB_2 is upregulated in gut tissue from patients with IBD and IBS. Olorinab—a highly selective, peripherally acting, full agonist of CB_2—has shown antinociceptive activity in animal models of pain and is under investigation for the treatment of chronic visceral pain in patients with IBD and IBS.

Aims and Methods: Here we evaluated the effects of olorinab on visceral hypersensitivity in rodent models of colitis (IBD-like) and chronic visceral hypersensitivity (CVH; IBS-like) and determined potential sites of olorinab activity. Colitis and CVH were induced in male Sprague Dawley rats or C57BL/6 mice by intracolonic enema of 2,4,6-trinitrobenzene sulfonic acid (TNBS) or 2,4-dinitrobenzene sulfonic acid (DNBS), respectively. Colitis was evaluated on Day 4 following induction, while CVH was evaluated on Day 28. In the colitis model, control and colitis rodents were administered vehicle or olorinab (3 or 30 mg/kg twice daily) orally for 5 days starting 1 day before colitis induction. In the CVH model, control and CVH rodents were administered vehicle or olorinab (3, 10, or 30 mg/kg twice daily) orally on Days 24 to 28 following colitis induction. Visceral hypersensitivity was measured through in vivo visceromotor responses (VMR) to colorectal distention (CRD; 0 to 80 mm Hg) on Day 4 (colitis) and Day 28 (CVH). The mRNA expression of CB_1 and CB_2 was determined by quantitative real-time polymerase chain reaction (qRT-PCR) in colonic tissue (mucosa; muscle and enteric nervous system [ENS]) and dorsal root ganglia (DRG) from healthy, colitis, and CVH rodents, and in healthy and IBD human donor DRG. The localization of CB_2 in healthy, colitis, and CVH mice was confirmed through RNA in situ hybridization (ISH).

Results: Vehicle-treated colitis and CVH rodents exhibited pronounced visceral hypersensitivity compared with healthy controls. Treatment with olorinab significantly reduced VMR to CRD in colitis and CVH rodents compared with vehicle-treated counterparts (P <0.05). CB_1 and CB_2 mRNA levels were detected in all tissues analyzed. CB_2 was the predominant transcript in colonic mucosa, while in the colonic muscle + ENS and rodent DRG, CB_1 mRNA was the most abundant. There were no differences in CB_2 expression in colonic mucosa, colonic muscle + ENS, and DRG observed across the healthy, colitis, or CVH states. Additionally, no differences were found in CB_2 mRNA levels in healthy and IBD human donor DRG. The presence of CB_2 in mouse colonic tissues and mouse DRG was verified by ISH.

Conclusion: Olorinab reduced visceral hypersensitivity in colitis and CVH rodents; these results suggest that CB_2 activation causes antinociceptive actions in visceral sensory pathways. The presence of CB_2 in colonic tissue and in primary sensory DRG neurons was validated through qRT-PCR and ISH studies, implying that both sites may contribute to the antinociceptive activity of olorinab. The colocalization of CB_2 receptors in specific cell types are under investigation to identify the mechanisms involved in olorinab-mediated responses. These results support the further investigation of olorinab for the treatment of IBD- and IBS-associated abdominal pain.