

The Endocannabinoid System's Intriguing Role in Gut Health

by Chris D. Meletis, ND, and Kimberly Wilkes

References

1. DiPatrizio NV. Endocannabinoids in the Gut. *Cannabis Cannabinoid Res.* 2016 Feb;1(1):67-77.
2. Sharkey KA, Wiley JW. The Role of the Endocannabinoid System in the Brain-Gut Axis. *Gastroenterology.* 2016 Aug;151(2):252-66.
3. Hasenoehrl C, Taschler U, Storr M, et al. The gastrointestinal tract - a central organ of cannabinoid signaling in health and disease. *Neurogastroenterol Motil.* 2016 Dec;28(12):1765-80.
4. Hornby PJ, Prouty SM. Involvement of cannabinoid receptors in gut motility and visceral perception. *Br J Pharmacol.* 2004 Apr;141(8):1335-45.
5. Furness JB, Kunze WAA, Clerc N. Nutrient tasting and signaling mechanisms in the gut II. The intestine as a sensory organ: Neural, endocrine, and immune responses. *Am J Physiol Gastrointest Liver Physiol.* 1999 Nov;277(5 Pt 1):G922-8.
6. Trautmann SM, Sharkey KA. The Endocannabinoid System and Its Role in Regulating the Intrinsic Neural Circuitry of the Gastrointestinal Tract. *Int Rev Neurobiol.* 2015;125:85-126.
7. Wright K, Rooney N, Feeney M, et al. Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. *Gastroenterology.* 2005 Aug;129(2):437-53.
8. Aviello G, Romano B, Borrelli F, et al. Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. *J Mol Med (Berl).* 2012 Aug;90(8):925-34.
9. Romano B, Borrelli F, Pagano E, et al. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. *Phytomedicine.* 2014 Apr 15;21(5):631-9.
10. Izzo AA, Piscitelli F, Capasso R, et al. Peripheral endocannabinoid dysregulation in obesity: relation to intestinal motility and energy processing induced by food deprivation and re-feeding. *Br J Pharmacol.* 2009 Sep;158(2):451-61.
11. Márquez L, Abanades S, Andreu M. [Endocannabinoid system and bowel inflammation]. [Article in Spanish]. *Med Clin (Barc).* 2008 Oct 18;131(13):513-7.
12. Krowicki ZK, Moerschbaecher JM, Winsauer PJ, et al. Delta9-tetrahydrocannabinol inhibits gastric motility in the rat through cannabinoid CB1 receptors. *Eur J Pharmacol.* 1999 Apr 29;371(2-3):187-96.
13. de Filippis D, Iuvone T, d'amico A, et al. Effect of cannabidiol on sepsis-induced motility disturbances in mice: involvement of CB receptors and fatty acid amide hydrolase. *Neurogastroenterol Motil.* 2008 Aug;20(8):919-27.
14. Bashashati M, Nasser Y, Keenan CM, et al. Inhibiting endocannabinoid biosynthesis: a novel approach to the treatment of constipation. *Br J Pharmacol.* 2015 Jun;172(12):3099-111.
15. Cluny NL, Reimer RA, Sharkey KA. Cannabinoid signalling regulates inflammation and energy balance: the importance of the brain-gut axis. *Brain Behav Immun.* 2012 Jul;26(5):691-8.
16. DiPatrizio NV, Piomelli D. The thrifty lipids: endocannabinoids and the neural control of energy conservation. *Trends Neurosci.* 2012 Jul;35(7):403-11.
17. Berthoud HR. The vagus nerve, food intake and obesity. *Regul Pept.* 2008 Aug 7;149(1-3):15-25.
18. DiPatrizio NV, Igarashi M, Narayanaswami V, et al. Fasting stimulates 2-AG biosynthesis in the small intestine: role of cholinergic pathways. *Am J Physiol Regul Integr Comp Physiol.* 2015 Oct 15;309(8):R805-13.
19. Monteleone P, Piscitelli F, Scognamiglio P, et al. Hedonic eating is associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoylglycerol in healthy humans: a pilot study. *J Clin Endocrinol Metab.* 2012 Jun;97(6):E917-24.
20. Rigamonti AE, Piscitelli F, Aveta T, et al. Anticipatory and consummatory effects of (hedonic) chocolate intake are associated with increased circulating levels of the orexigenic peptide ghrelin and endocannabinoids in obese adults. *Food Nutr Res.* 2015 Nov 4;59:29678.
21. Mennella I, Ferracane R, Zucco F, et al. Food Liking Enhances the Plasma Response of 2-Arachidonoylglycerol and of Pancreatic Polypeptide upon Modified Sham Feeding in Humans. *J Nutr.* 2015 Sep;145(9):2169-75.
22. Alhouayek M, Lambert DM, Delzenne NM, et al. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. *FASEB J.* 2011 Aug;25(8):2711-21.
23. Schicho R, Bashashati M, Bawa M, et al. The atypical cannabinoid O-1602 protects against experimental colitis and inhibits neutrophil recruitment. *Inflamm Bowel Dis.* 2011 Aug;17(8):1651-64.
24. Borrelli F, Aviello G, Romano B, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. *J Mol Med (Berl).* 2009 Nov;87(11):1111-21.
25. De Filippis D, Esposito G, Cirillo C, et al. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. *PLoS One.* 2011;6(12):e28159.
26. Wright K, Rooney N, Feeney M, et al. Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. *Gastroenterology.* 2005 Aug;129(2):437-53.
27. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther.* 2010 Apr;126(1):21-38.
28. Massa F, Marsicano G, Hermann H, et al. The endogenous cannabinoid system protects against colonic inflammation. *J Clin Invest.* 2004

Apr;113(8):1202-9.

29. Storr MA, Keenan CM, Emmerdinger D, et al. Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. *J Mol Med (Berl)*. 2008 Aug;86(8):925-36.
30. Sasso O, Migliore M, Habrant D, et al. Multitarget fatty acid amide hydrolase/cyclooxygenase blockade suppresses intestinal inflammation and protects against nonsteroidal anti-inflammatory drug-dependent gastrointestinal damage. *FASEB J*. 2015 Jun;29(6):2616-27.
31. Darmani NA, Izzo AA, Degenhardt B, et al. Involvement of the cannabimimetic compound, N-palmitoyl-ethanolamine, in inflammatory and neuropathic conditions: review of the available pre-clinical data, and first human studies. *Neuropharmacology*. 2005 Jun;48(8):1154-63.
32. Borrelli F, Romano B, Petrosino S, et al. Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. *Br J Pharmacol*. 2015 Jan;172(1):142-58.
33. Jamontt JM, Molleman A, Pertwee RG, et al. The effects of Delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. *Br J Pharmacol*. 2010 Jun;160(3):712-23.
34. Borrelli F, Fasolino I, Romano B, et al. Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochem Pharmacol*. 2013 May 1;85(9):1306-16.
35. Sharkey KA, Wiley JW. The Role of the Endocannabinoid System in the Brain-Gut Axis. *Gastroenterology*. 2016 Aug;151(2):252-66.
36. Camilleri M, Kolar GJ, Vazquez-Roque MI, et al. Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits. *Am J Physiol Gastrointest Liver Physiol*. 2013 Mar 1;304(5):G553-60.
37. Park JM, Choi MG, Cho YK, et al. Cannabinoid receptor 1 gene polymorphism and irritable bowel syndrome in the Korean population: a hypothesis-generating study. *J Clin Gastroenterol*. 2011 Jan;45(1):45-9.
38. Fichna J, Wood JT, Papanastasiou M, et al. Endocannabinoid and cannabinoid-like fatty acid amide levels correlate with pain-related symptoms in patients with IBS-D and IBS-C: a pilot study. *PLoS One*. 2013 Dec 27;8(12):e85073.
39. Camilleri M, Carlson P, McKinzie S, et al. Genetic variation in endocannabinoid metabolism, gastrointestinal motility, and sensation. *Am J Physiol Gastrointest Liver Physiol*. 2008 Jan;294(1):G13-9.
40. Camilleri M, Kolar GJ, Vazquez-Roque MI, et al. Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits. *Am J Physiol Gastrointest Liver Physiol*. 2013 Mar 1;304(5):G553-60.
41. Jiang Y, Nie Y, Li Y, et al. Association of cannabinoid type 1 receptor and fatty acid amide hydrolase genetic polymorphisms in Chinese patients with irritable bowel syndrome. *J Gastroenterol Hepatol*. 2014 Jun;29(6):1186-91.
42. Irving PM, Iqbal T, Nwokolo C, et al. A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis. *Inflamm Bowel Dis*. 2018 Mar 10. [Epub ahead of print.]
43. Storr MA, Sharkey KA. The endocannabinoid system and gut-brain signalling. *Curr Opin Pharmacol*. 2007 Dec;7(6):575-82.
44. Marco EM, Echeverry-Alzate V, López-Moreno JA, et al. Consequences of early life stress on the expression of endocannabinoid-related genes in the rat brain. *Behav Pharmacol*. 2014 Sep;25(5-6):547-56.
45. Morena M, Patel S, Bains JS, et al. Neurobiological Interactions Between Stress and the Endocannabinoid System. *Neuropsychopharmacology*. 2016 Jan;41(1):80-102.
46. Hong S, Zheng G, Wiley JW. Epigenetic regulation of genes that modulate chronic stress-induced visceral pain in the peripheral nervous system. *Gastroenterology*. 2015 Jan;148(1):148-57.e7.
47. Muccioli GG, Naslain D, Bäckhed F, et al. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol*. 2010 Jul;6:392.
48. Everard A, Belzer C, Geurts L, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*. 2013 May 28;110(22):9066-71.
49. Rastelli M, Knauf C, Cani PD. Gut Microbes and Health: A Focus on the Mechanisms Linking Microbes, Obesity, and Related Disorders. *Obesity (Silver Spring)*. 2018 May;26(5):792-800.
50. Rousseaux C, Thuru X, Gelot A, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med*. 2007 Jan;13(1):35-7.
51. Guida F, Turco F, Iannotta M, et al. Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, hippocampal neuroglial reorganization and depression in mice. *Brain Behav Immun*. 2017 Sep 7. Epub ahead of print.]
52. Ringel-Kulka T, Goldsmith JR, Carroll IM, et al. Lactobacillus acidophilus NCFM affects colonic mucosal opioid receptor expression in patients with functional abdominal pain - a randomised clinical study. *Aliment Pharmacol Ther*. 2014 Jul;40(2):200-7.