Pain Pathways from the Basic to Translational Science Perspective

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Conflicts of Interest

None

Objectives

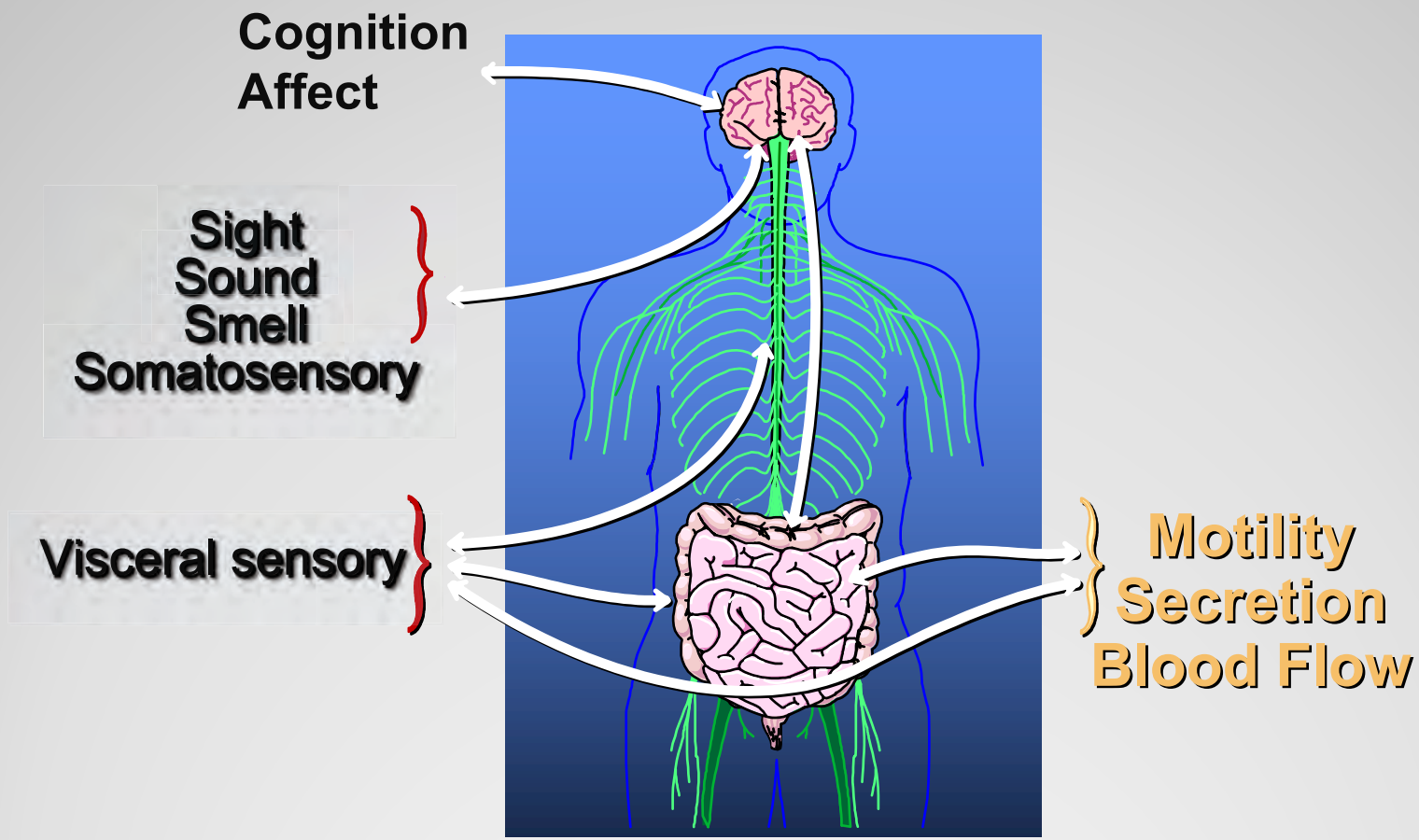
- Discuss the gut-brain-microbiota axis in the context of pain in IBD
- Explore the pain pathways involved in IBD

Pain in IBD – something of a paradox

- 50-70% of patients with IBD experience chronic abdominal pain[1]. Pain can persist even in the relative absence of inflammation or in patients in endoscopic remission.
- 20-30% report no pain, despite having IBD[1].
- Women experience more pain than men.

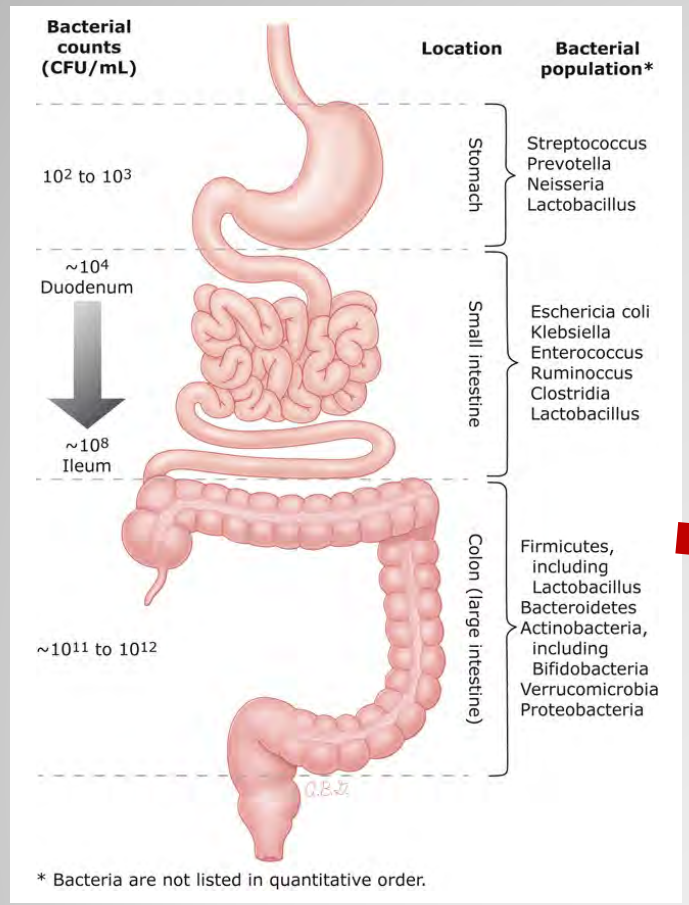
[1]Zeitz et al. PLoS ONE 2016;11:e0156666

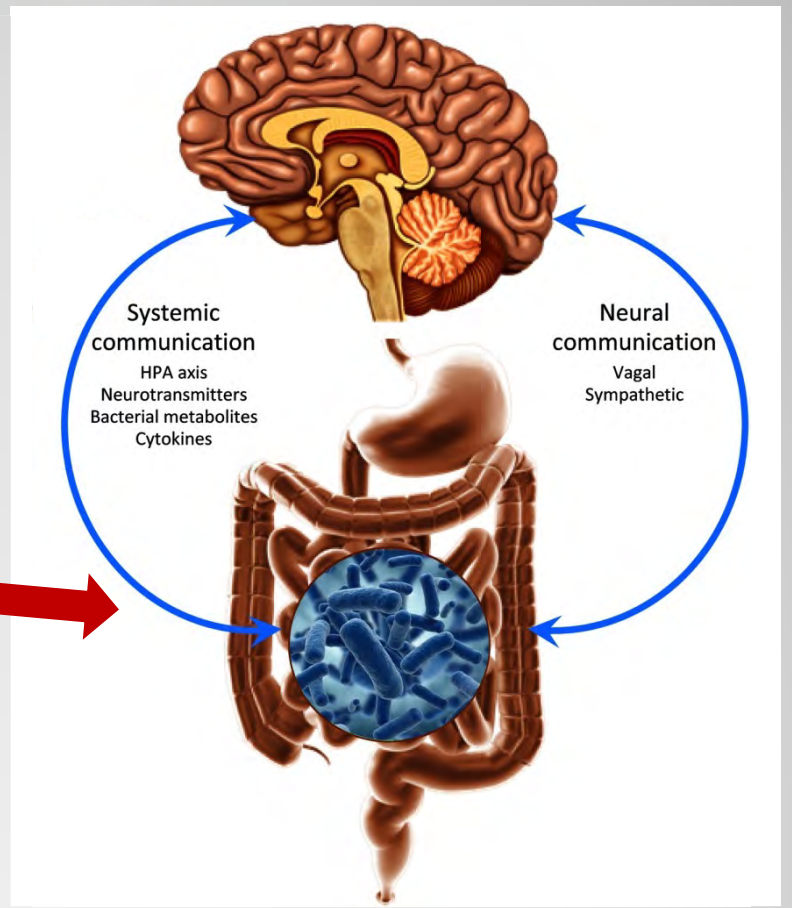
The gut-brain axis



Mayer and Raybould. Gastroenterology 1990;99:1688-1704

The gut-brain axis is now – gut-brain-microbiota axis

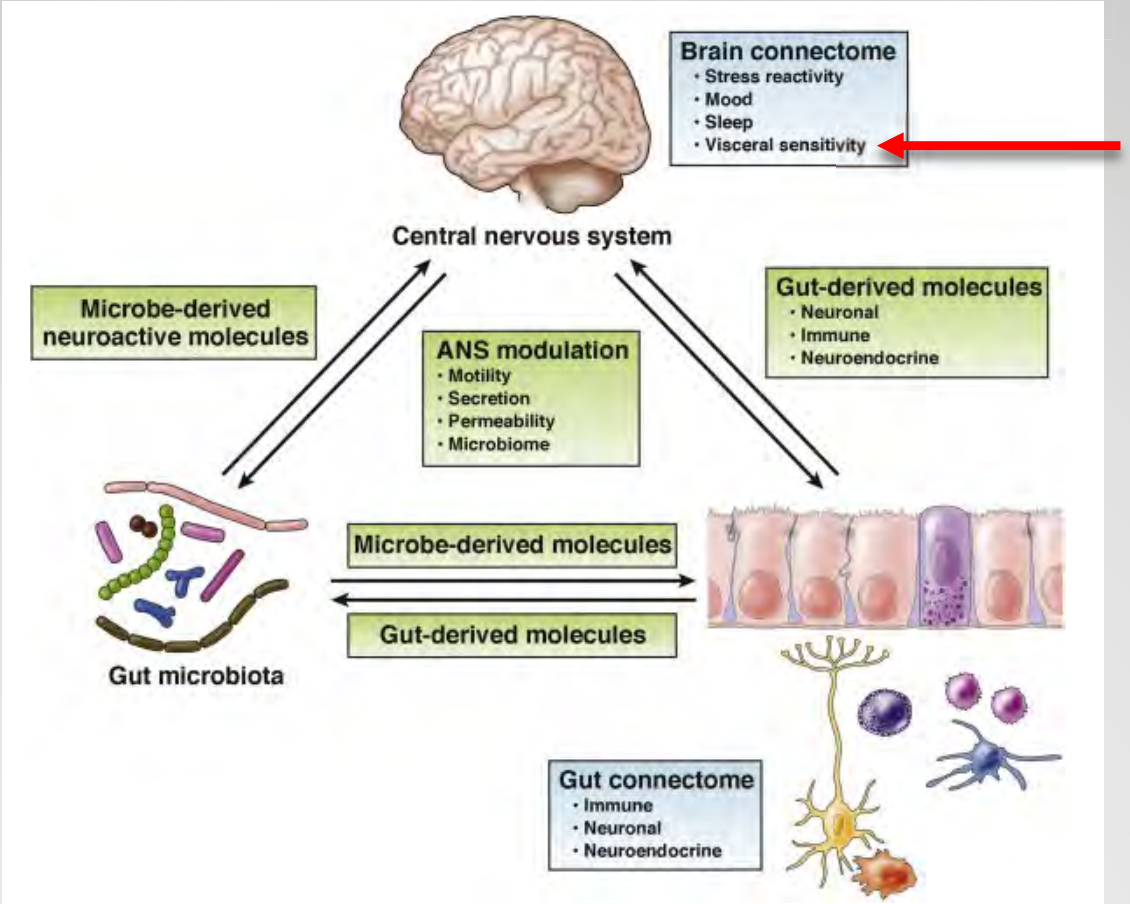




Vanderhoof and Pauley-Hunter 2015

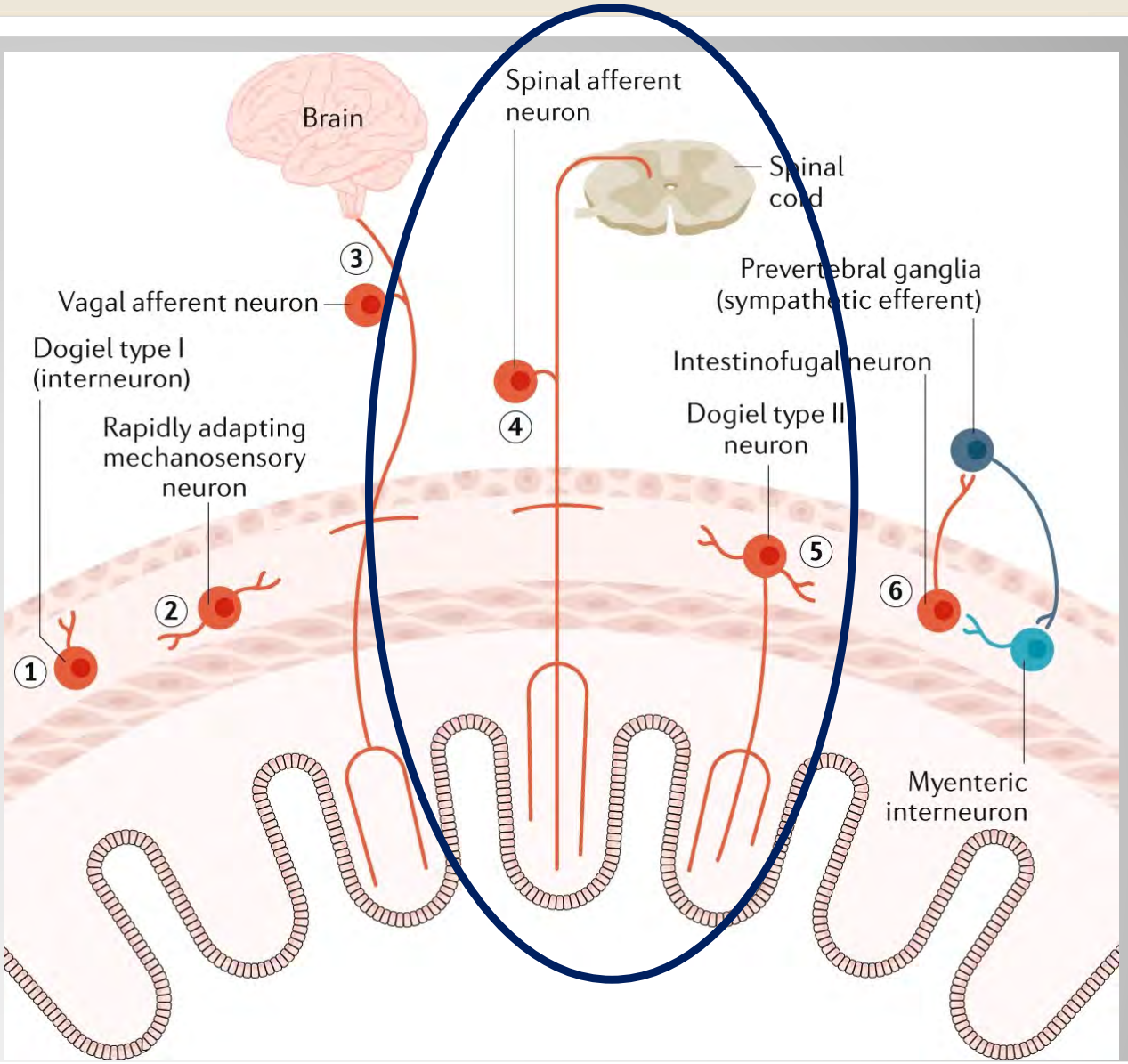
Mayer et al. J Neuroscience 2014;34:15490-15496

The gut-brain-microbiota axis regulates visceral sensation



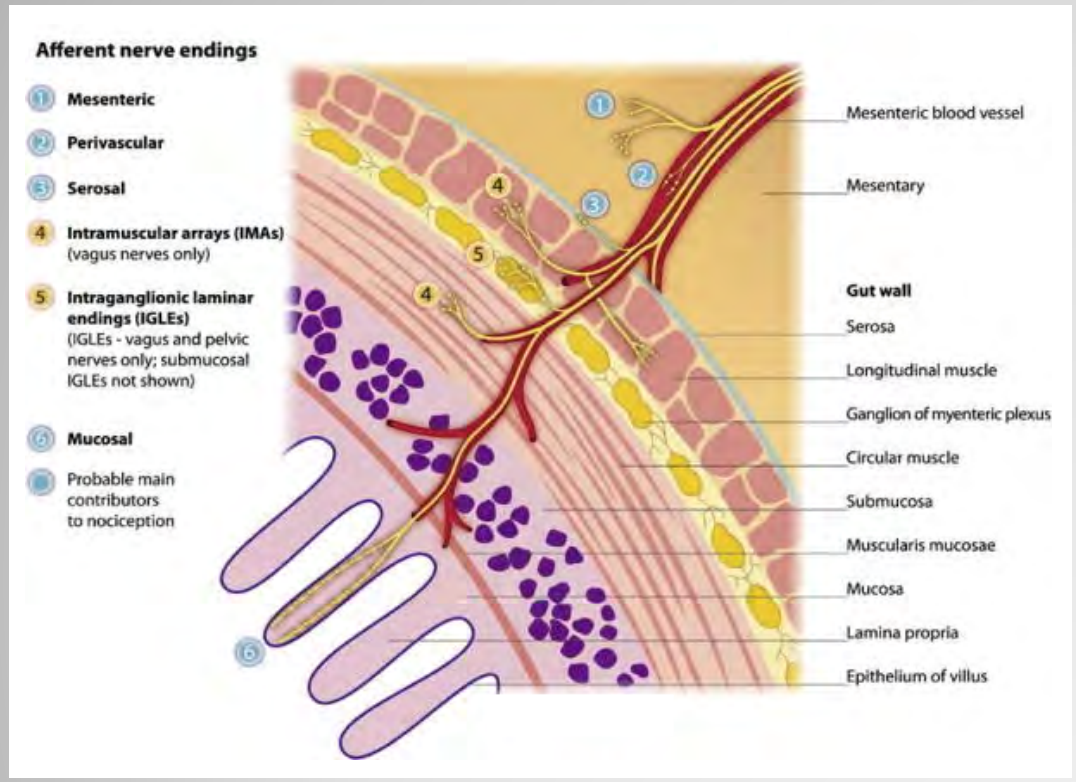
Martin et al. Cell Mol Gastroenterol Hepatol 2018;6:133-148

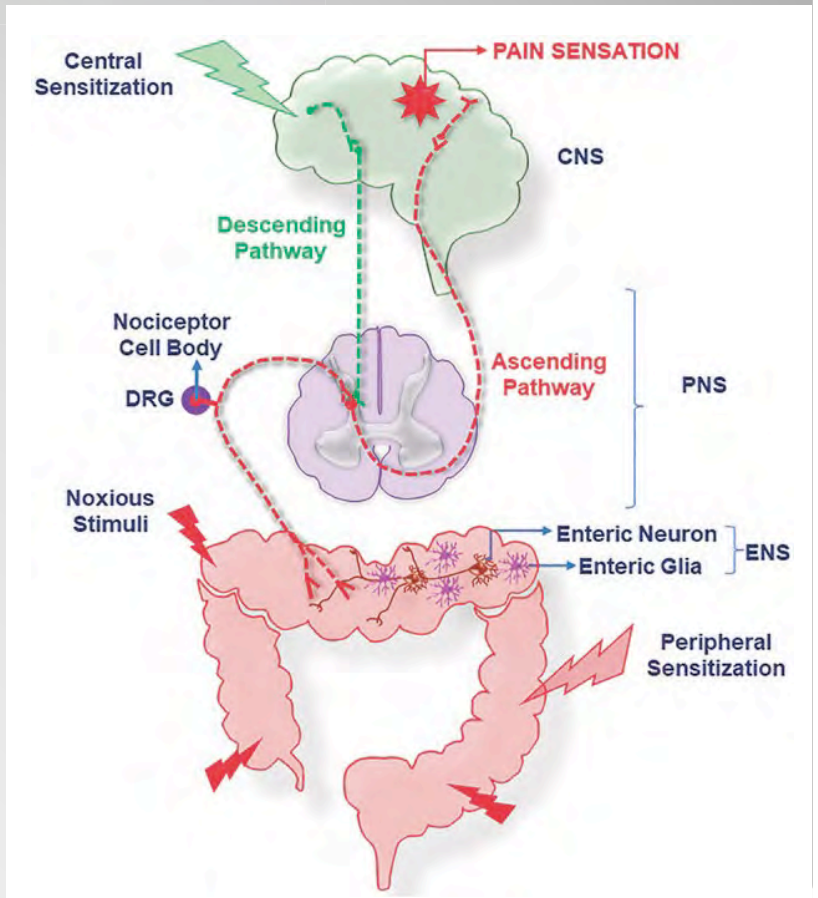
The gut is innervated by intrinsic and extrinsic primary afferent nerves



Spencer NJ and Hu H. Nature Reviews Gastroenterol Hepatol 2020;17:338-351

Chronic visceral pain occurs via activation of peripheral nerve endings

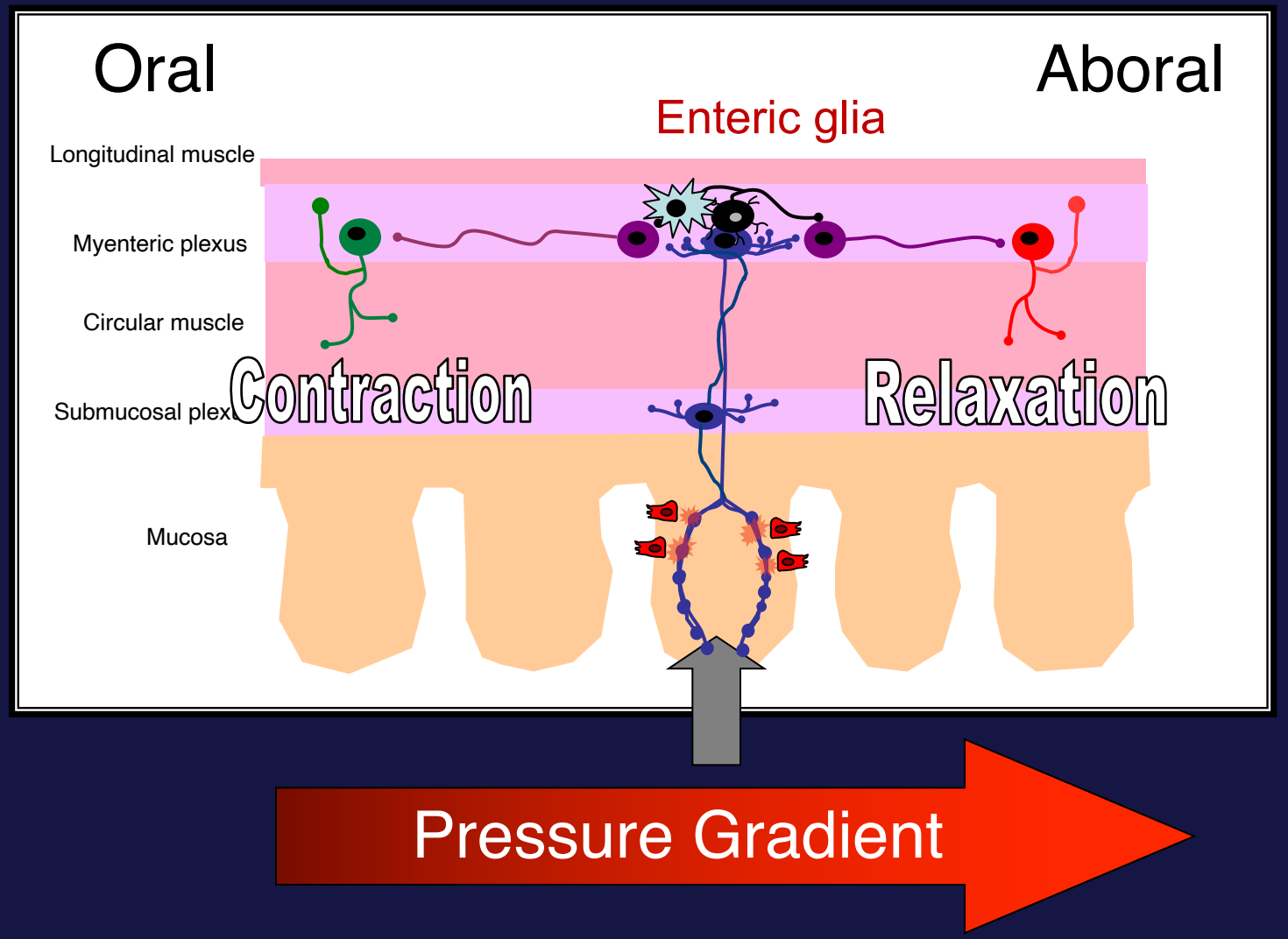




Knowles and Aziz. Pain 2009;141:191–209

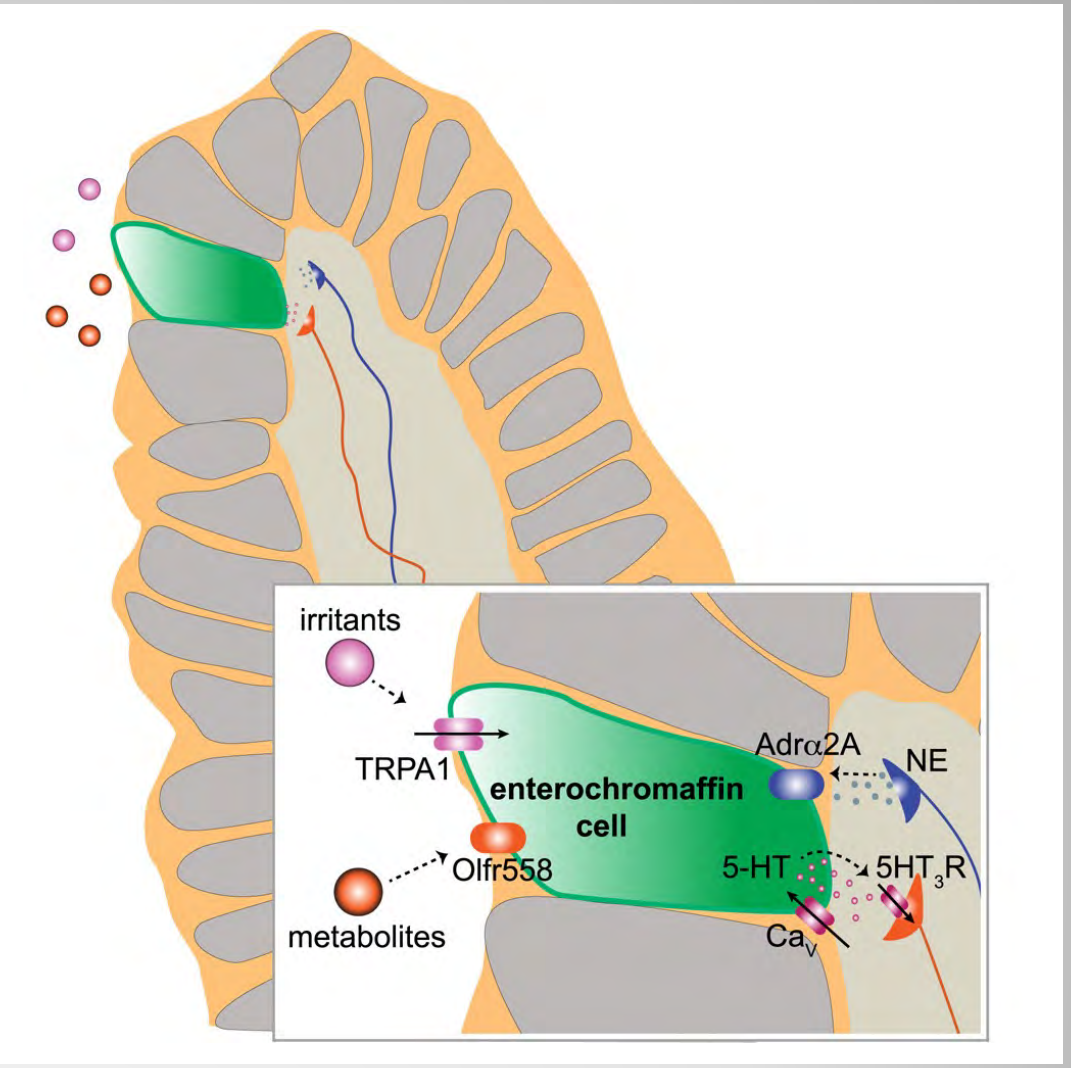
Hurtado-Lorenzo et al. Crohn's & Colitis 360 2021;3:1-10

Intrinsic reflex circuits that control motility involve enteroendocrine, neural and glial signaling



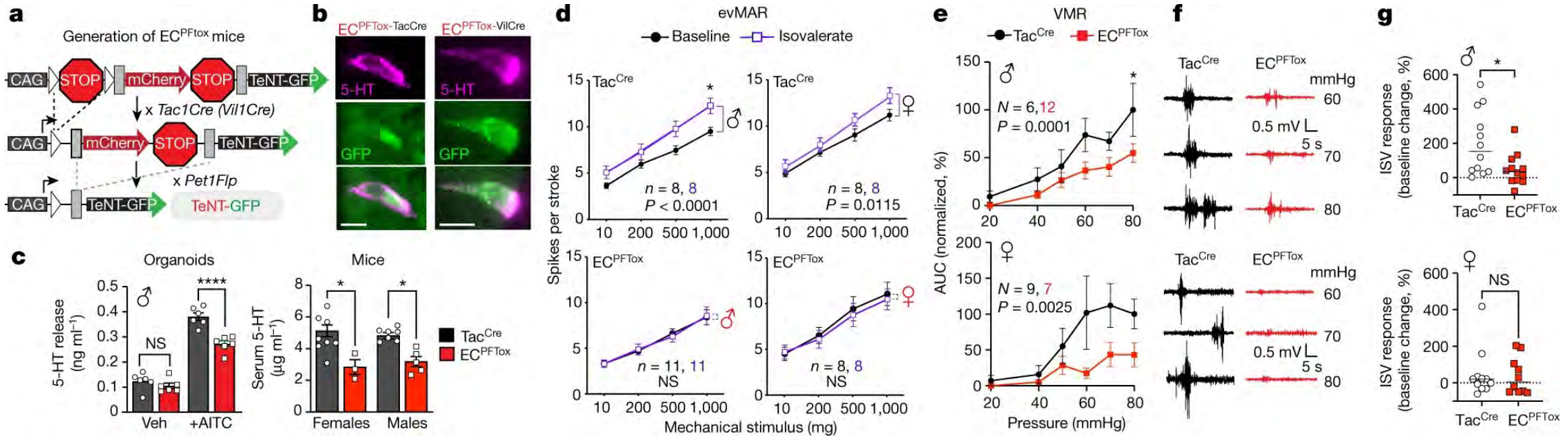
Mawe and Sharkey

Enterochromaffin cells are gut mechano- and chemosensors that couple to sensory neural pathways



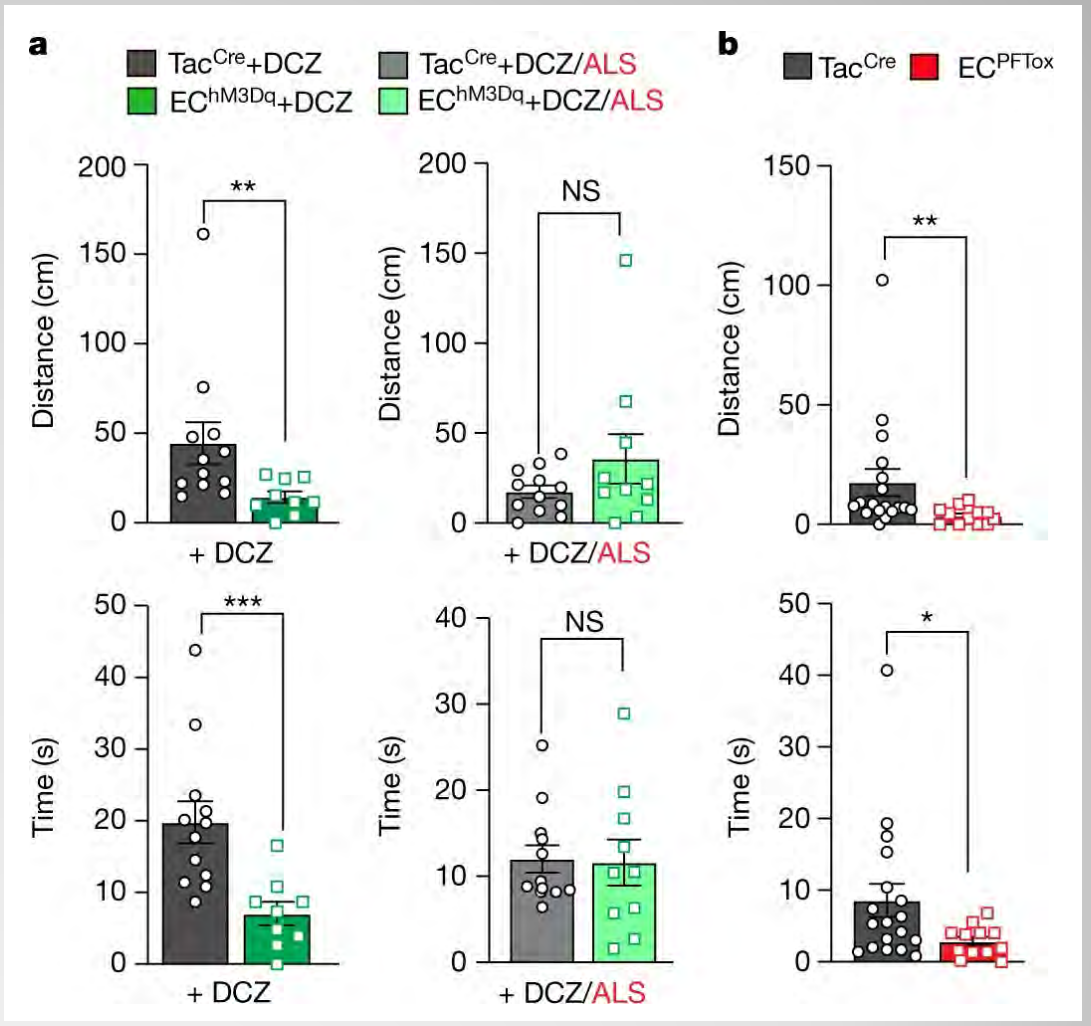
Bellono et al. Cell 2017;170:185-198

Gut enterochromaffin cells drive visceral pain



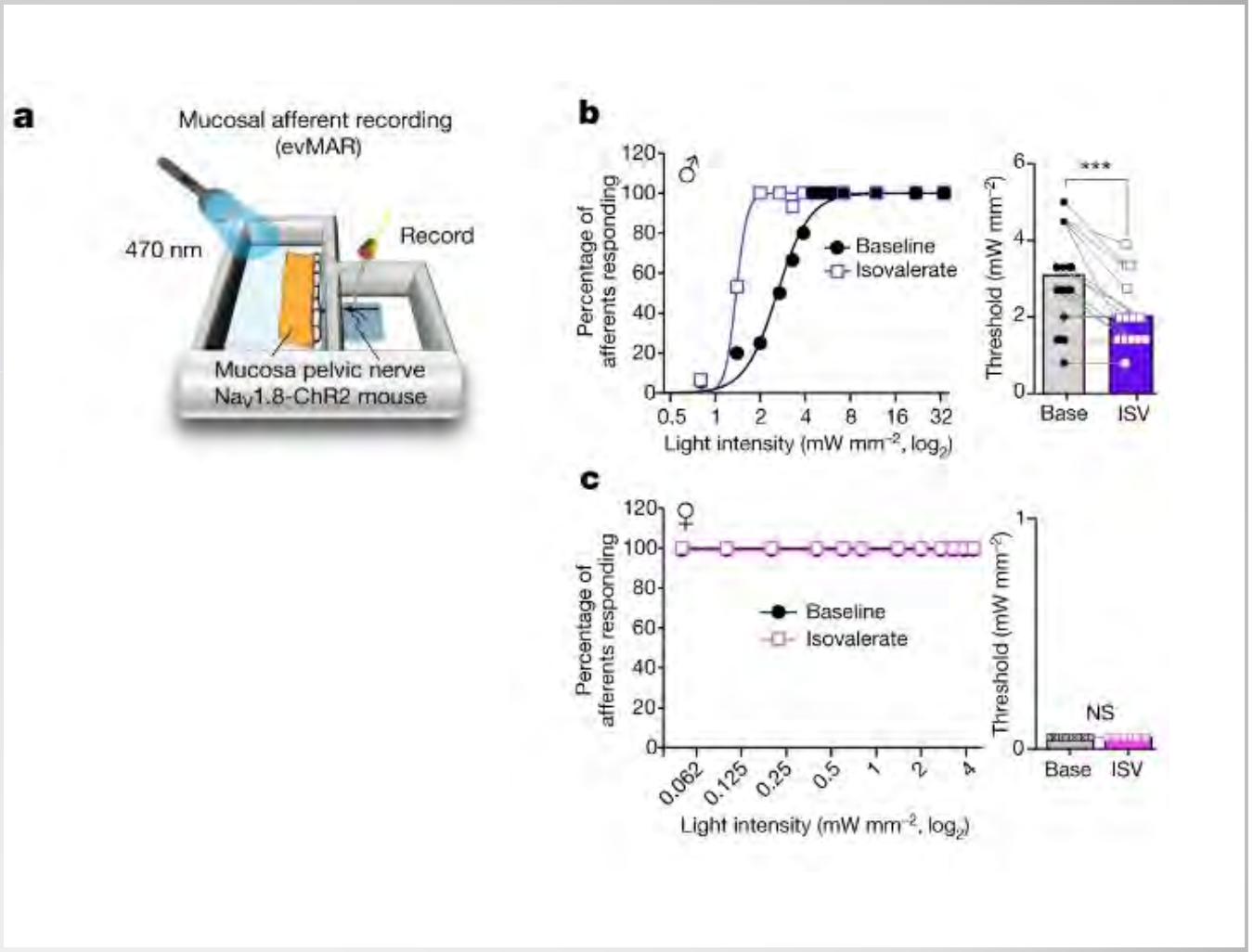
Bayrer et al. Nature 2023;616:137-142

Gut enterochromaffin cells drive visceral pain and anxiety



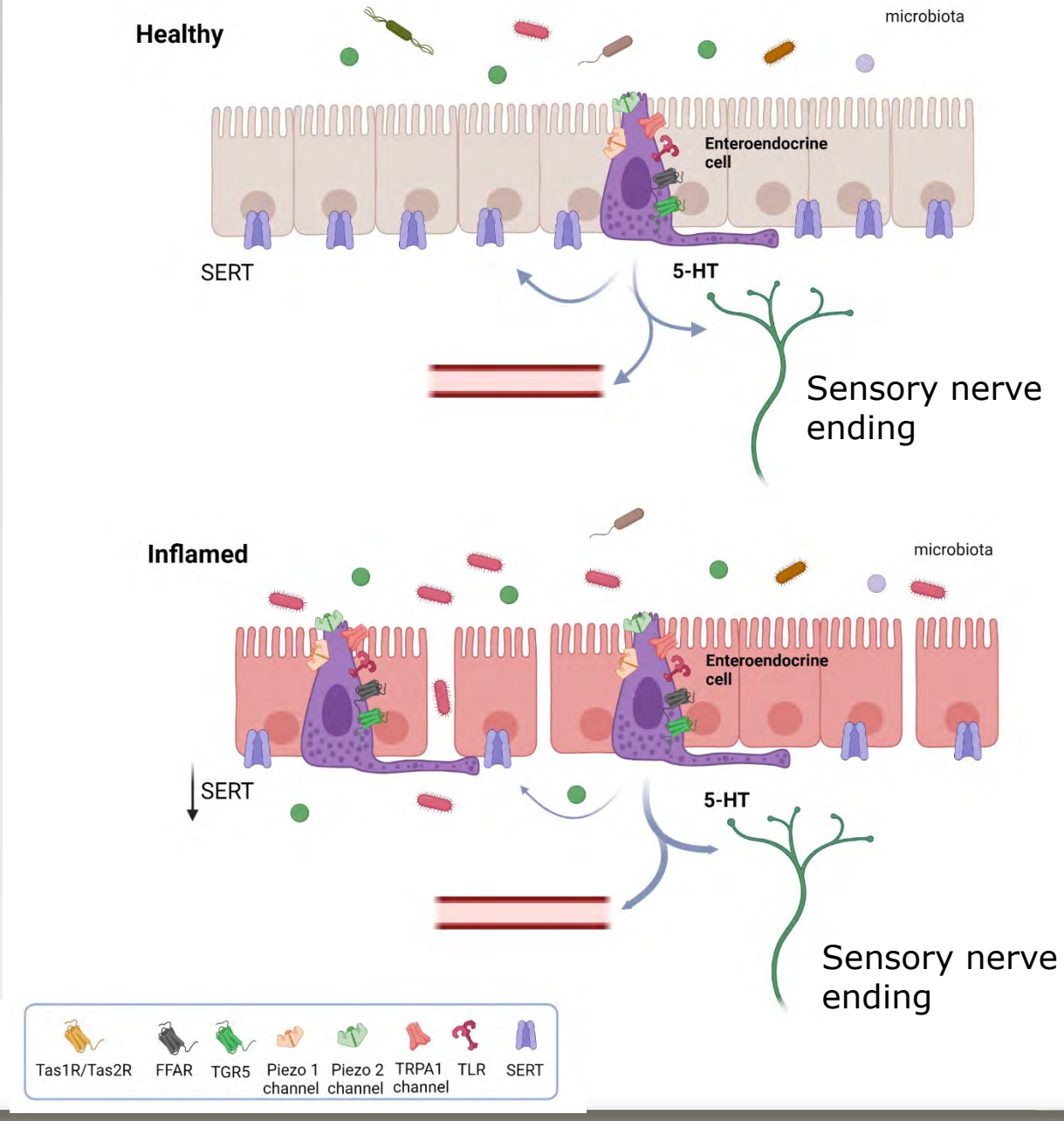
Bayrer et al. Nature 2023;616:137-142

Visceral afferent nerves in females are driven maximally by EC cell stimulation



Bayrer et al. Nature 2023;616:137-142

5-HT cell signaling is significantly increased in intestinal inflammation



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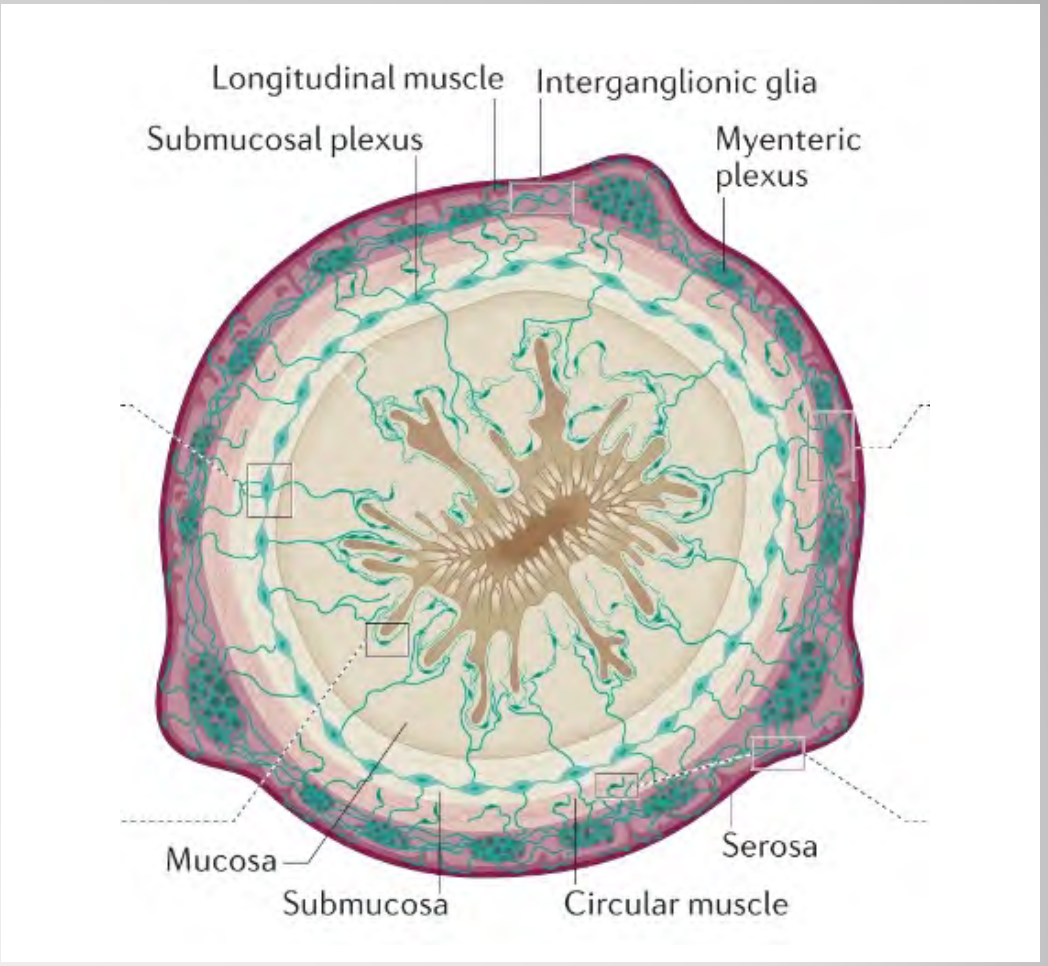
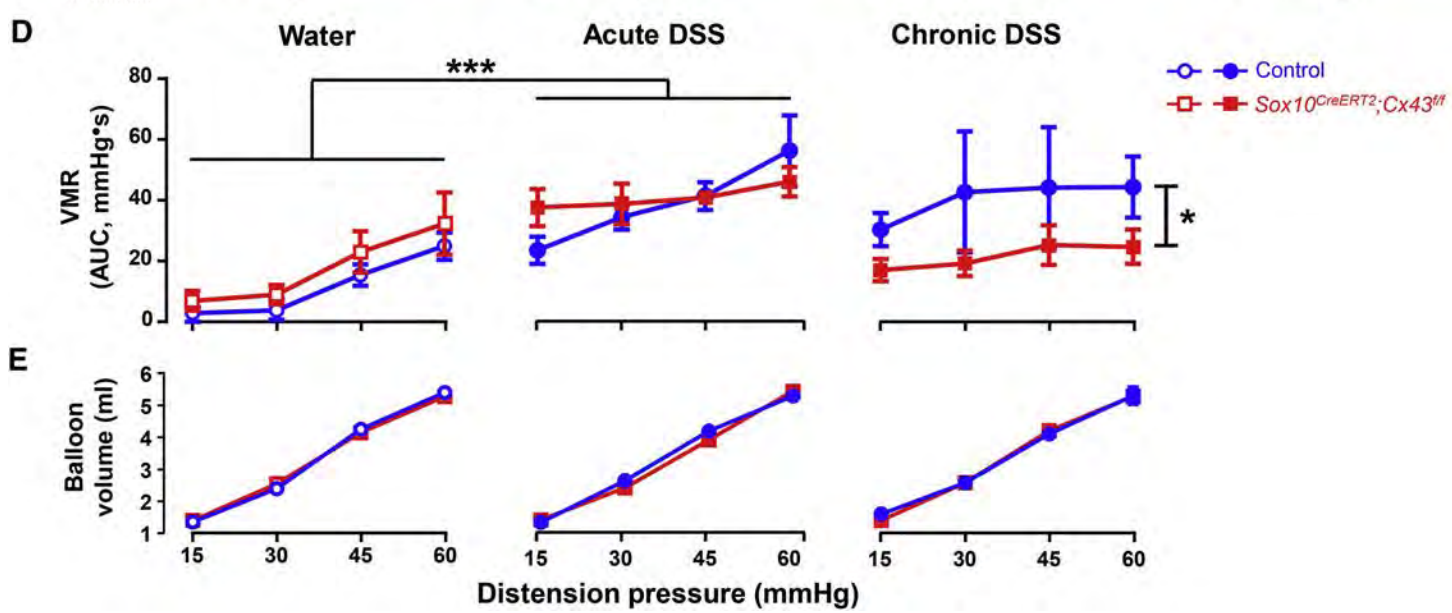
Enteric glia – regulators of intestinal homeostasis



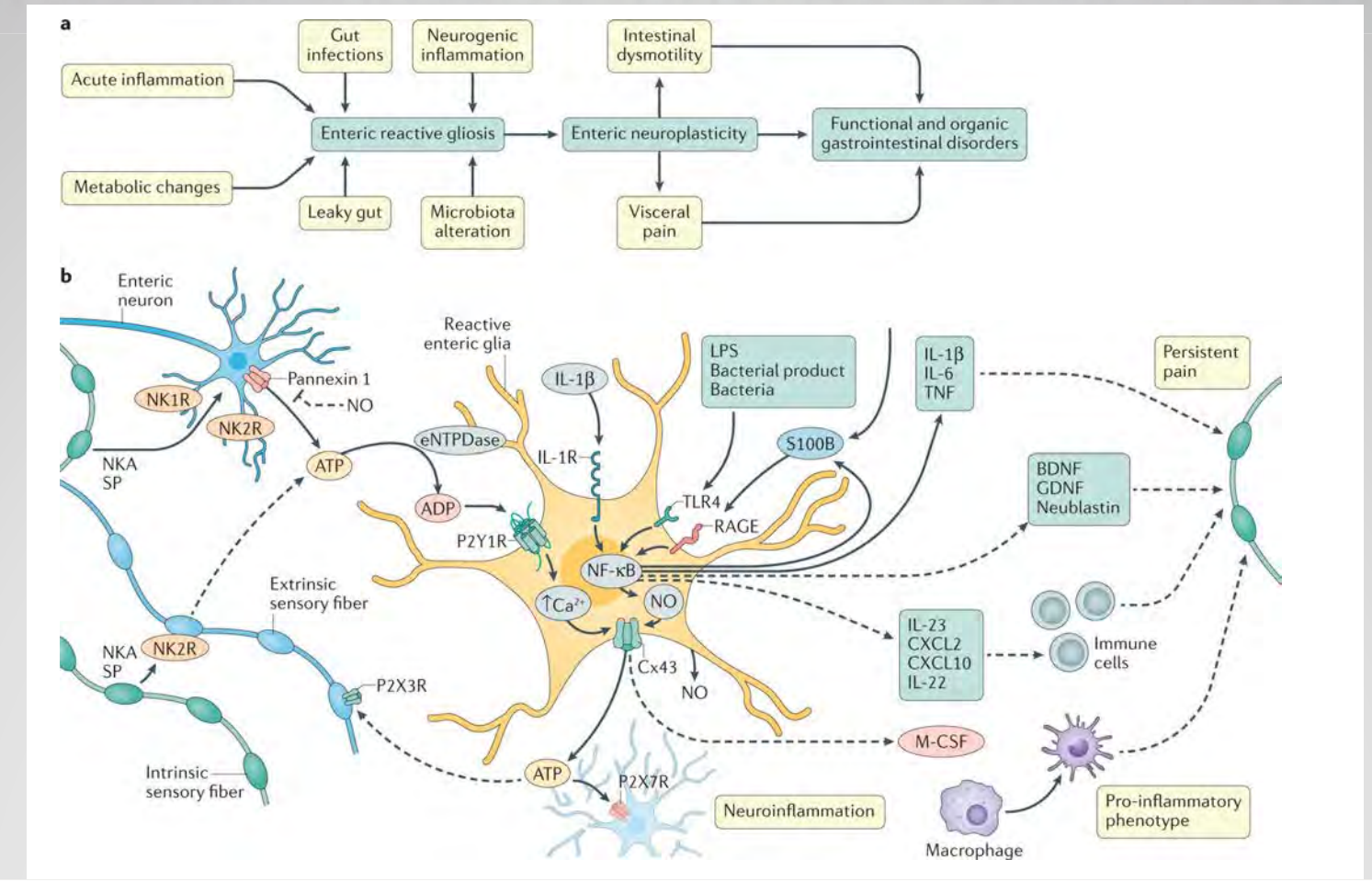
Seguella and Gulbransen. Nature Rev Gastroenterol Hepatol 2021;18:571-587

Enteric glia are required for the sensitization of nociceptors in experimental colitis



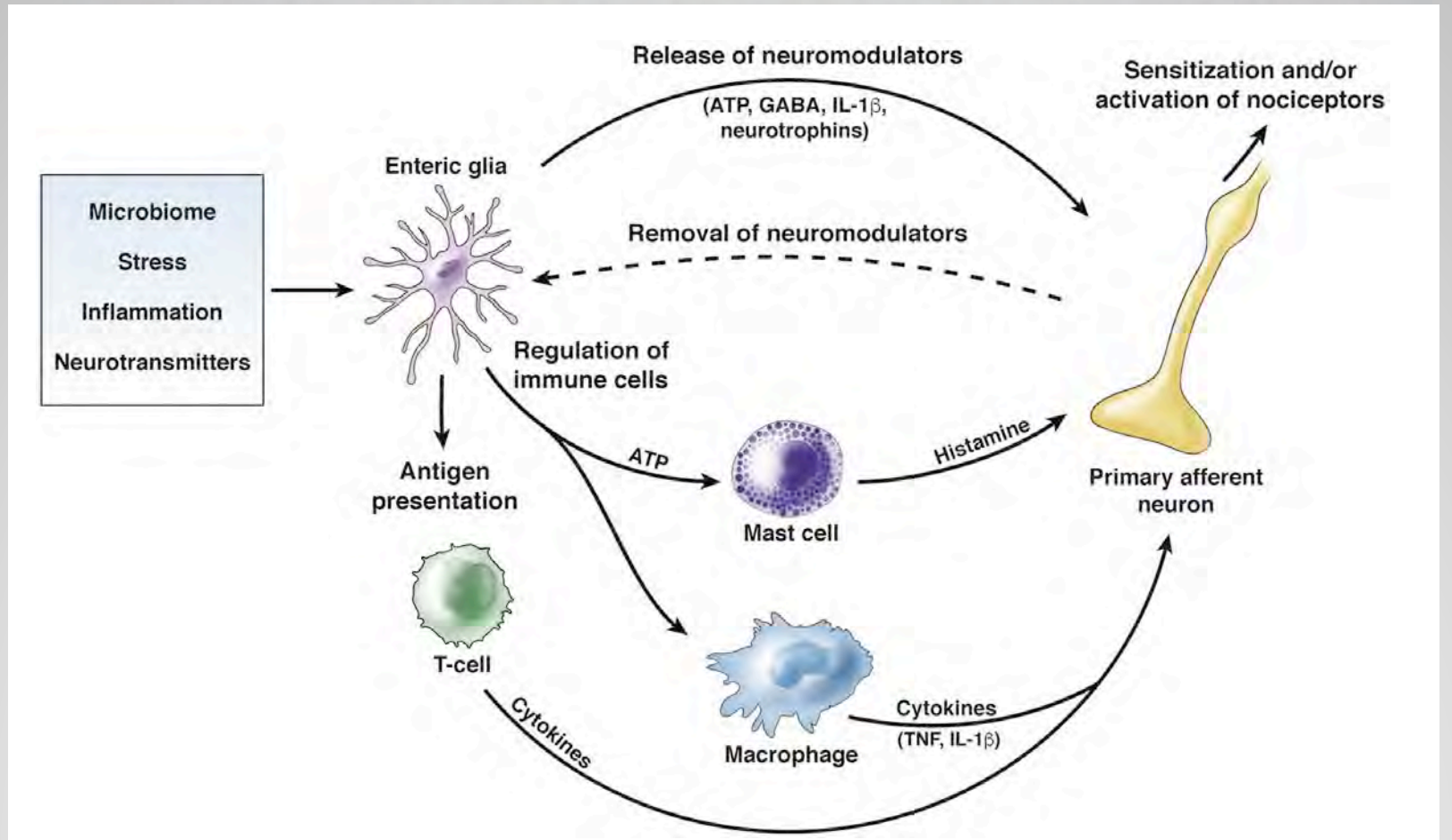
Grubišić et al. Cell Rep 2020;32:108100

Enteric glia respond to microbial and immune signals and release mediators that sensitize nociceptors



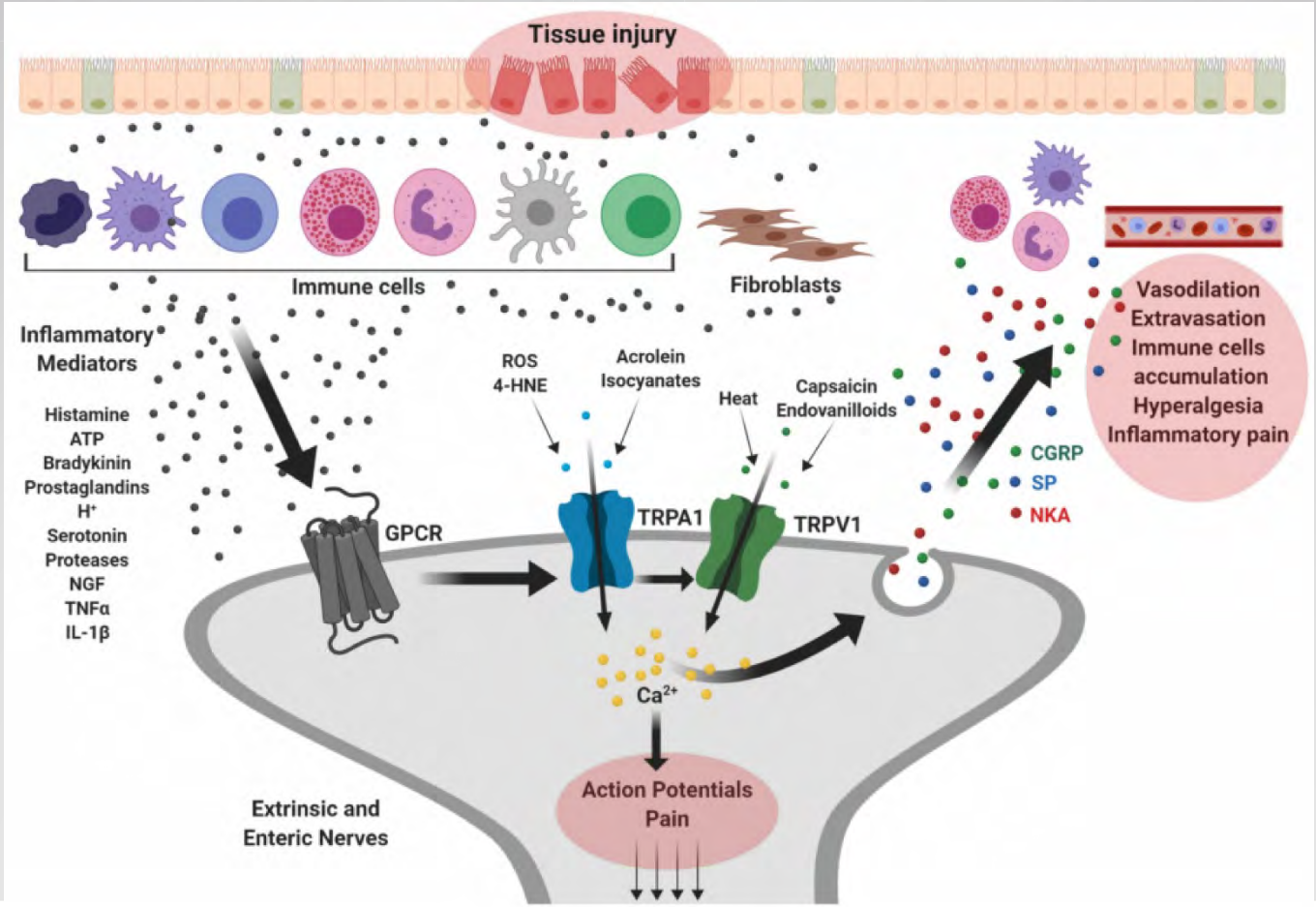
Seguella & Gulbransen. Nature Rev Gastroenterol Hepatol 2021;18:571-587

Enteric glia interact with immune cells to contribute to the sensitization of nociceptors



Morales-Soto & Gulbransen. Cell Molec Gastroenterol Hepatol 2019;7:433-445

Nociceptor sensitization of visceral afferents is mediated by Trp ion channels

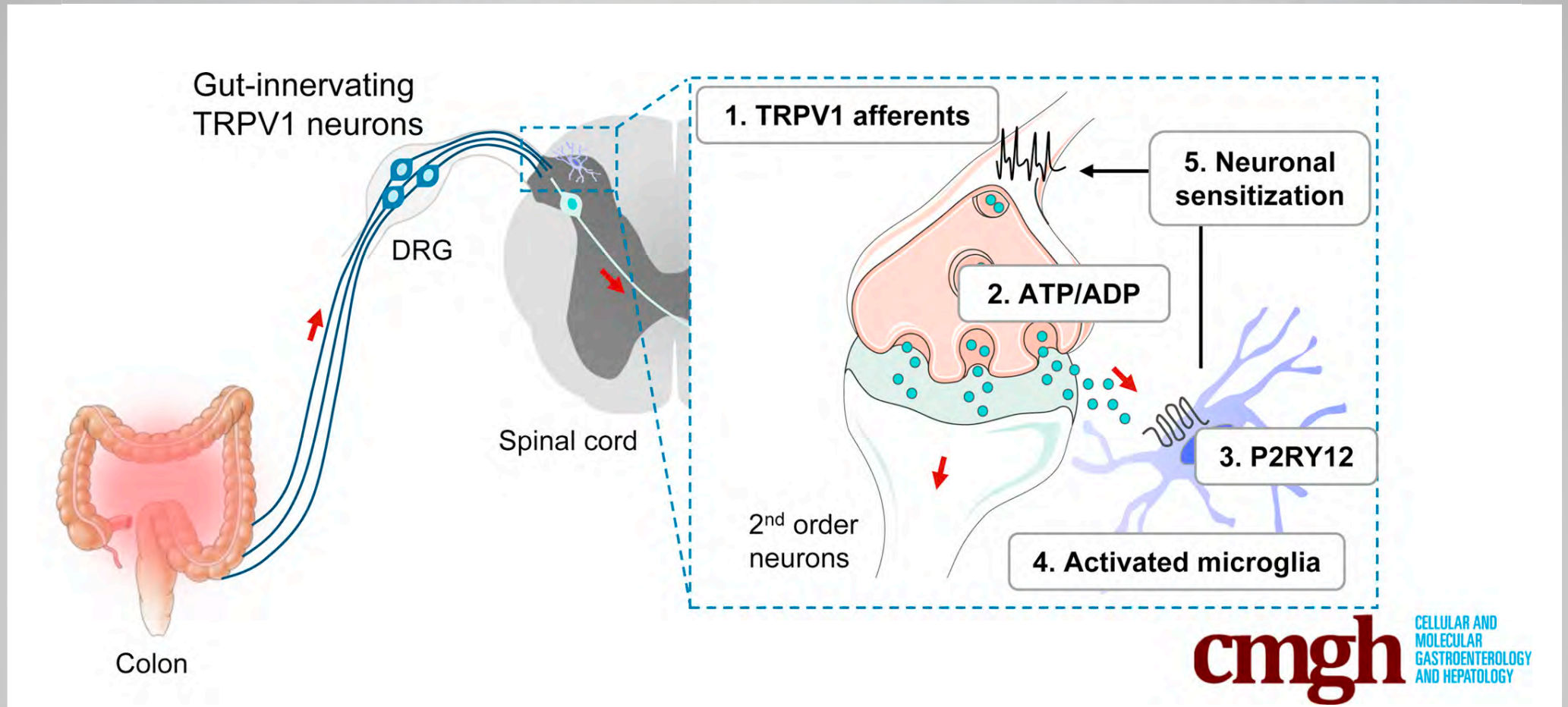


Alaimo & Rubert. Int J Mol Sci 2019;20:5277

TRP channels and chronic pain in IBD

- Increased TRPA1 and TRPV1 is found in IBD and experimental models of colitis.
- IBD patients with chronic pain display increased TRPV1 expression and decreased pain thresholds.

Gut-innervating TRPV1 Neurons Drive Chronic Visceral Pain via Microglial P2Y12 Receptor

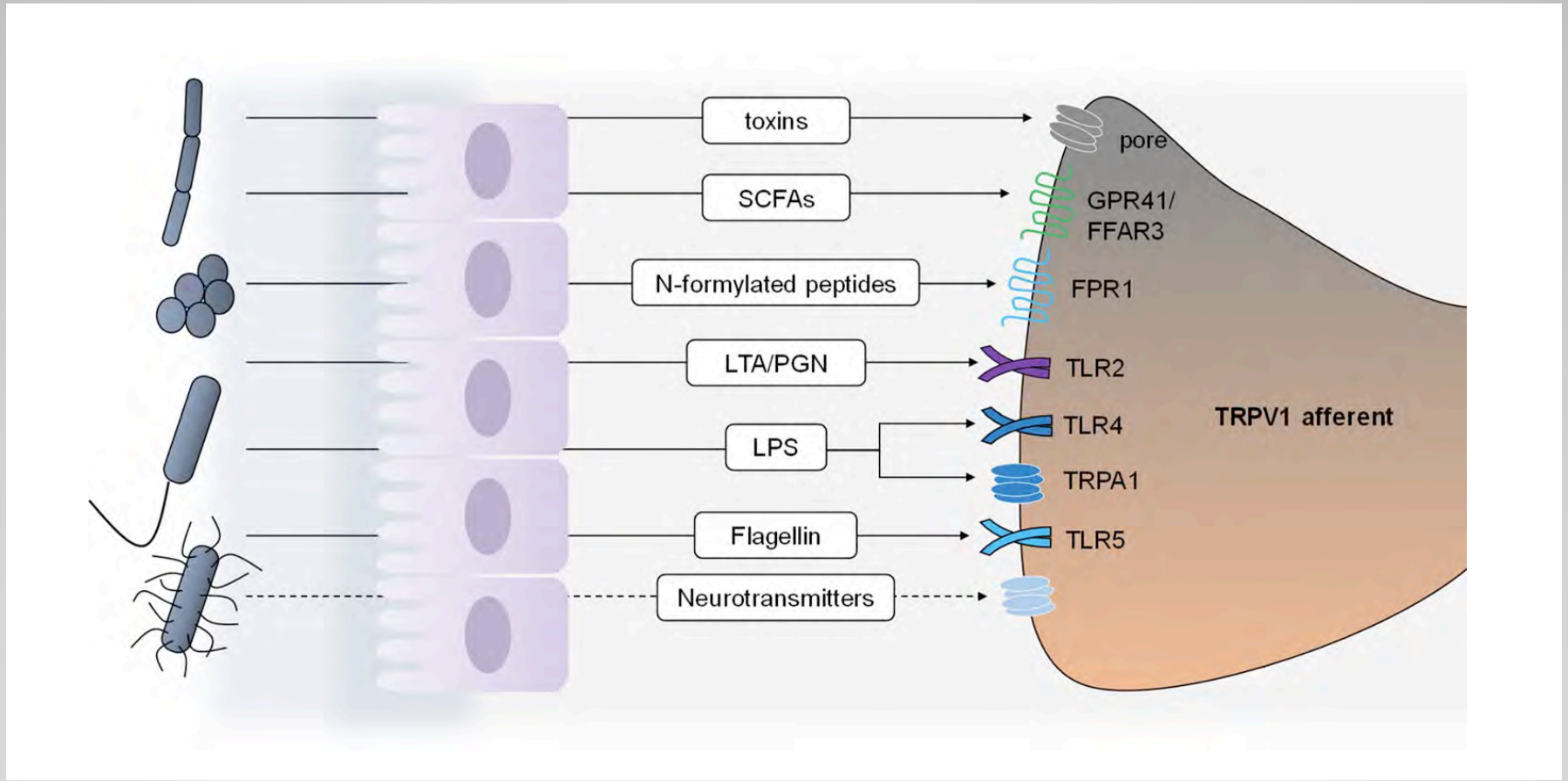


Defaye et al. Cell Molec Gastroenterol Hepatol 2022;13: 977-999

Summary - 1

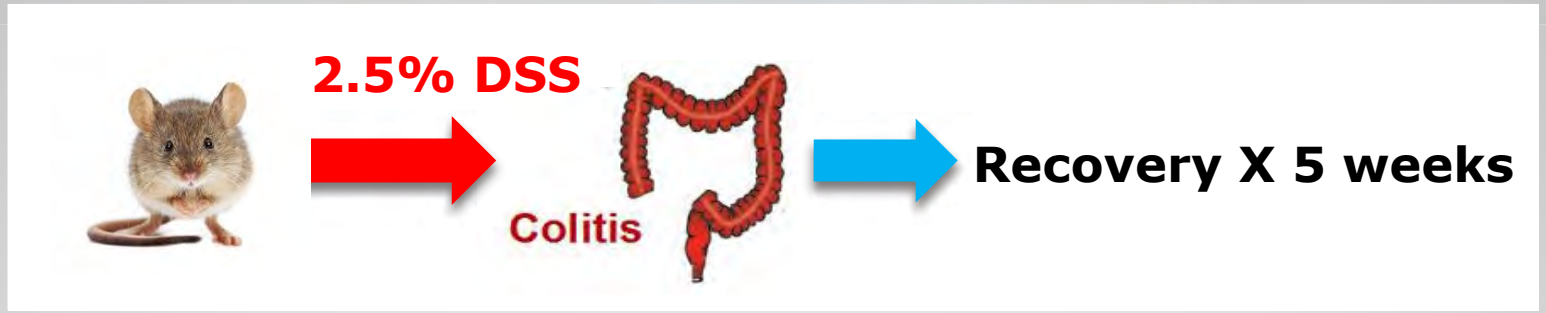
- Enterochromaffin cells and enteric glia regulate visceral sensitivity in colitis.
- Enterochromaffin cell activation also regulates anxiety.
- Sensitized nociceptive primary afferents activate microglia in the spinal cord to further amplify and sustain visceral pain.

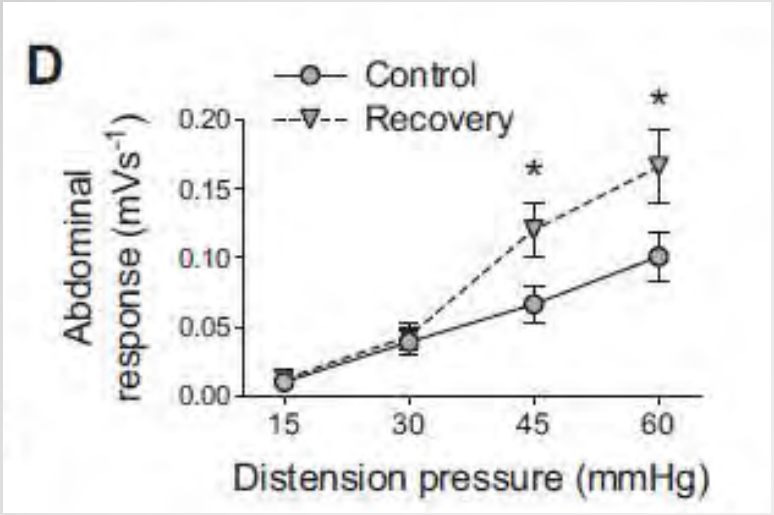
TRPV1 neurons are activated by microbial mediators

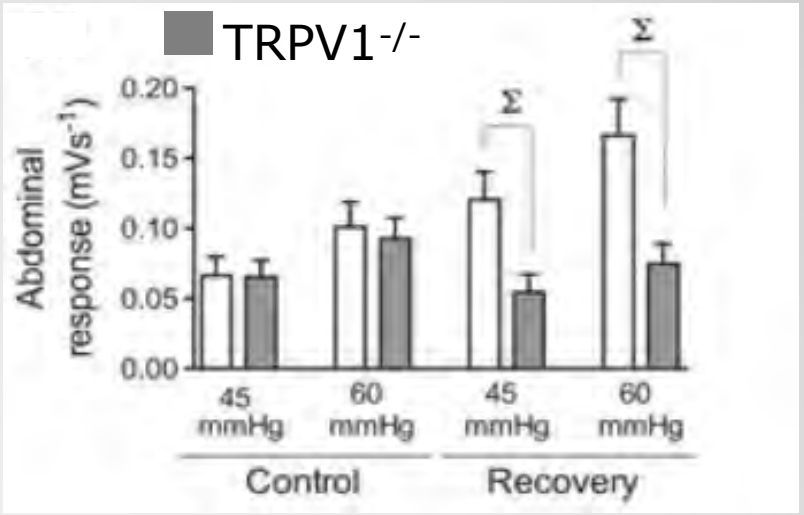


Abdullah et al. Am J Physiol GI & Liver 2020;319:G718-G732

Mice "in remission" from DSS colitis demonstrate post-inflammatory visceral pain

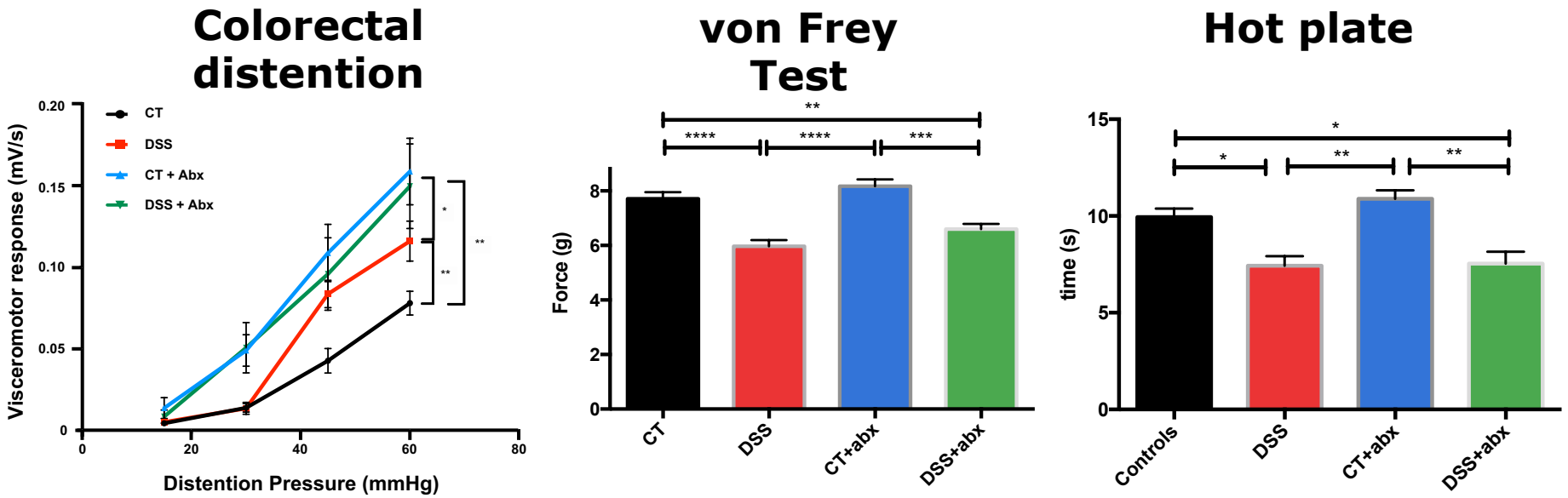






Lapointe et al., Am J Physiol GI & Liver 2017;148:148-157.e7

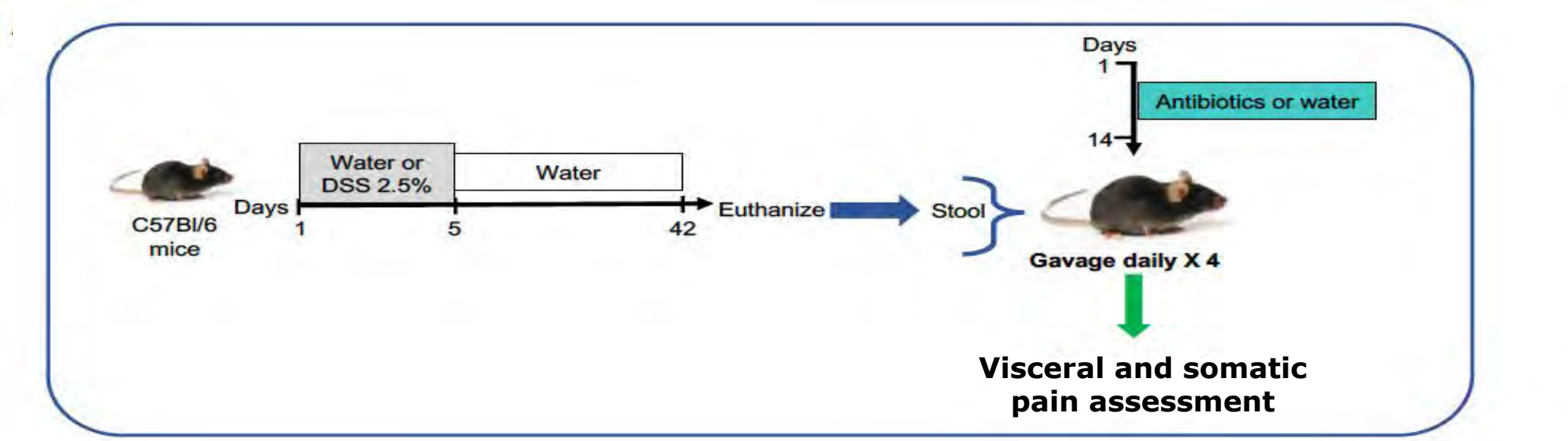
Mice "in remission" from DSS colitis demonstrate post-inflammatory visceral and somatic pain



Controls (CT): n= 15, DSS: n= 15, CT + Abx: n=13 and DSS + Abx: n =15.

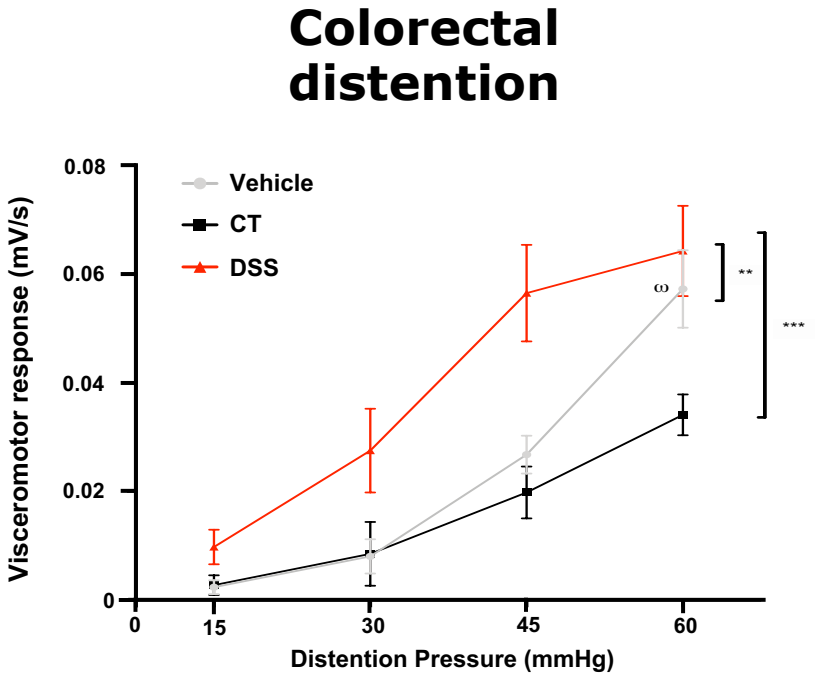
Esquerre et al., Cell Mol Gastroenterol Hepatol 2020;10:225-244

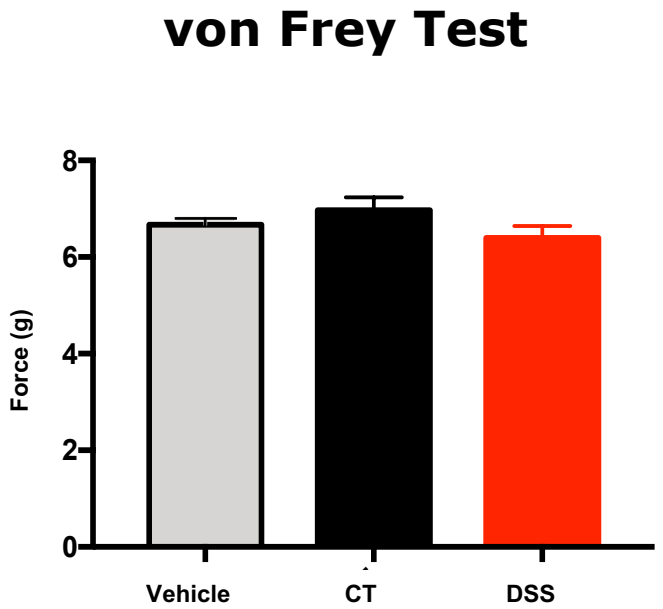
Fecal microbial transplantation of post-inflammatory DSS microbiota



Esquerre et al., Cell Mol Gastroenterol Hepatol 2020;10:225-244

Fecal microbial transplantation of post-inflammatory DSS microbiota transfers visceral but not somatic pain

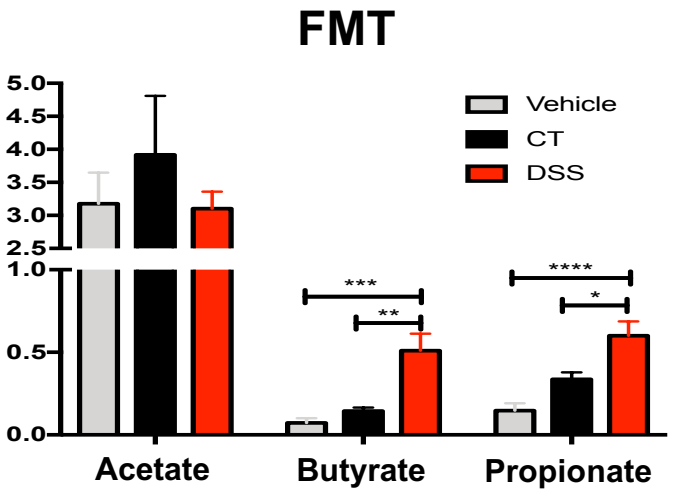




Control (CT): n=7, DSS: n=11, Vehicle: n=10

Esquerre et al., Cell Mol Gastroenterol Hepatol 2020;10:225-244

Butyrate and propionate significantly enhance TRPV1-stimulated calcium fluorescence in DRGs



Veh: n = 12, CT: n = 7, DSS: n = 11

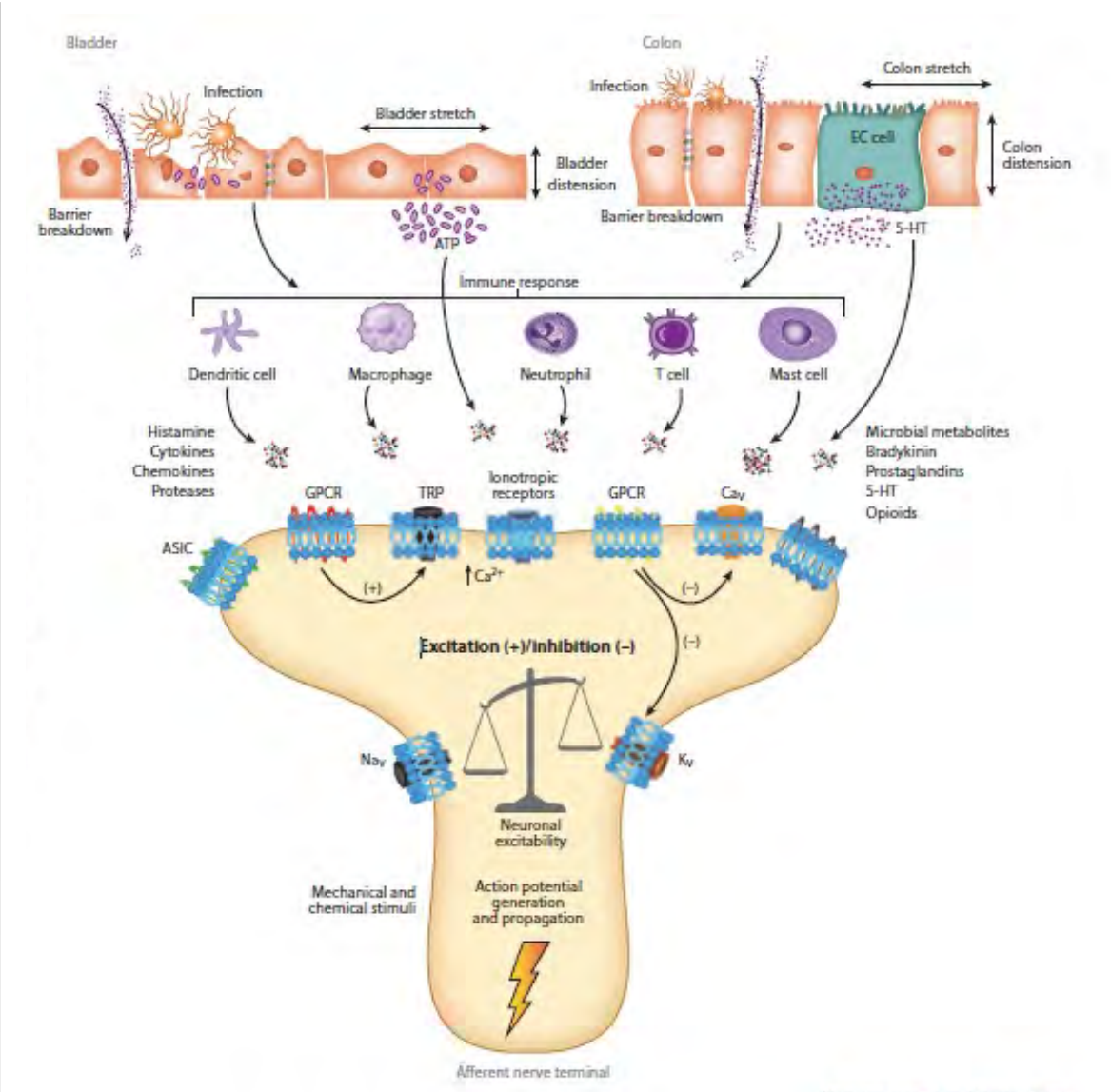
Esquerre et al., Cell Mol Gastroenterol Hepatol 2020;10:225-244

Summary - 2

- Enteric microbiota from animals after a single episode of acute colitis are sufficient to transfer visceral but not somatic pain.
- Microbial derived soluble products, short chain fatty acids, are able to sensitize TRPV1 nociceptive primary afferent neurons leading to increased visceral sensitivity.

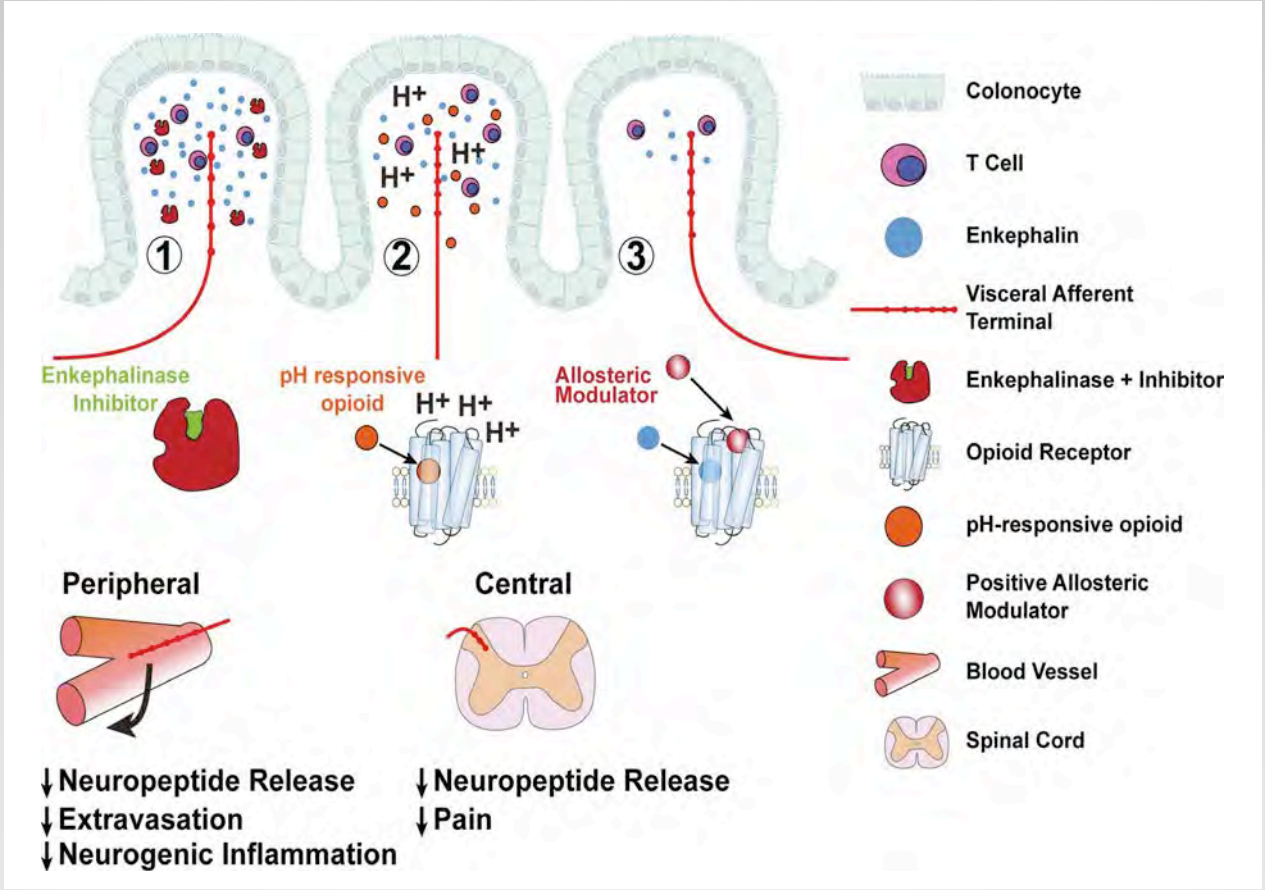
Excitability of visceral afferent nerves is balanced by endogenous inhibitory substances

Endogenous opioids



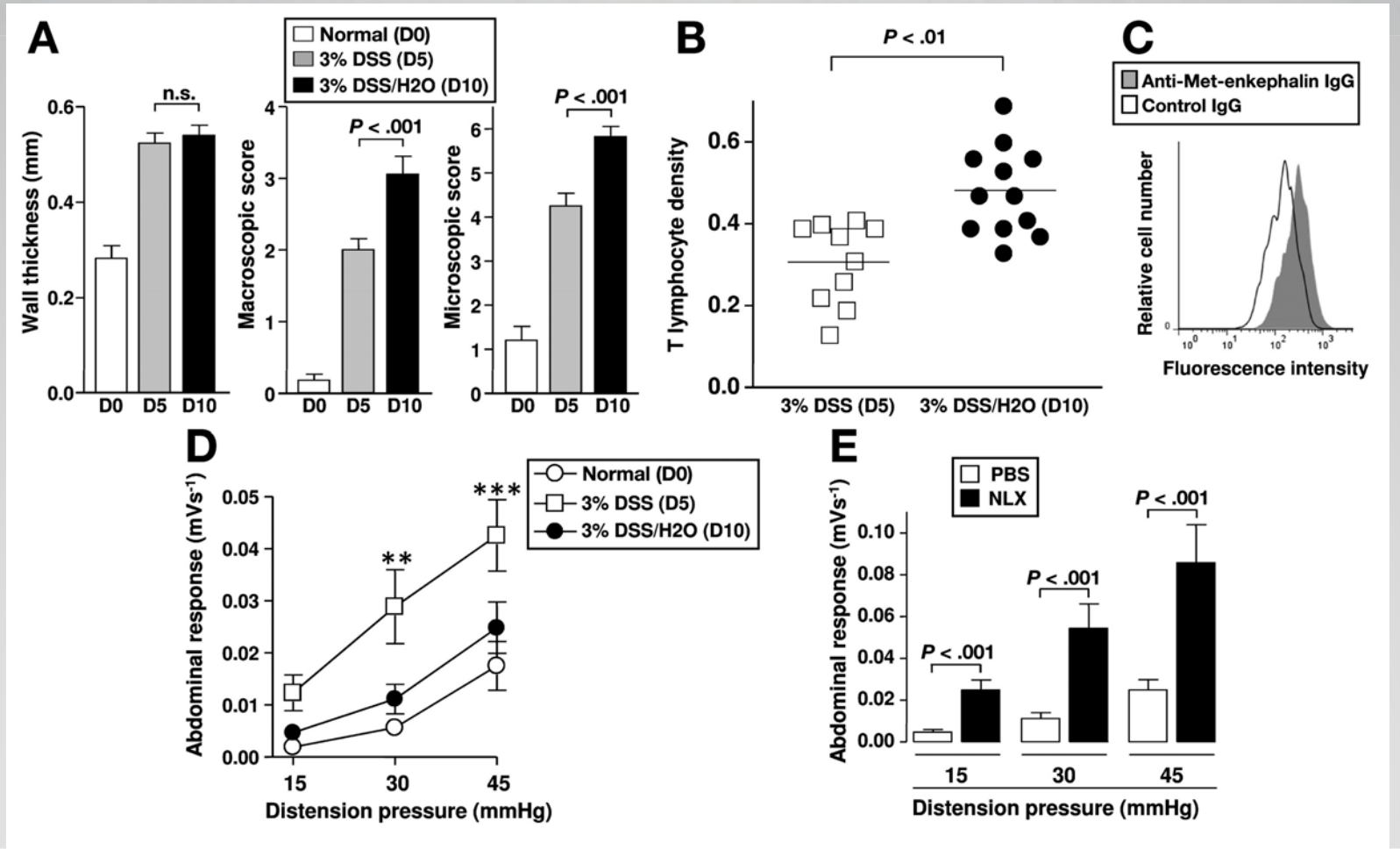
Grundy et al. Ann Rev Physiol 2019;81:261-284

Endogenous opioids are made by T cells in the intestinal mucosa



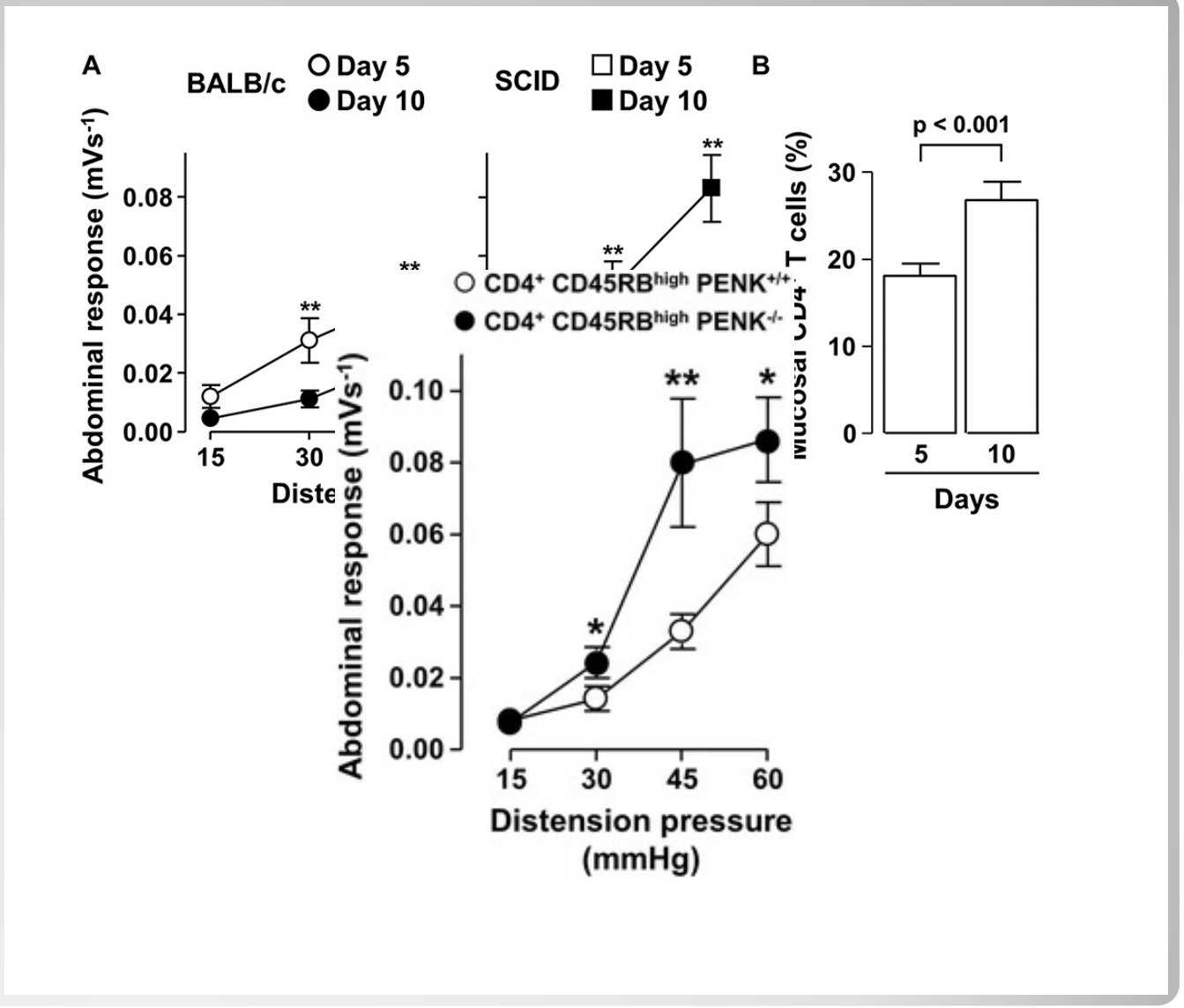
Carbone & Poole. Neurogastroenterol Motil 2020;32:e13787

T cell-derived endogenous opioids reduce visceral pain in the presence of inflammation in animal models of colitis



Boué et al. Gastroenterology 2014;146:166-175

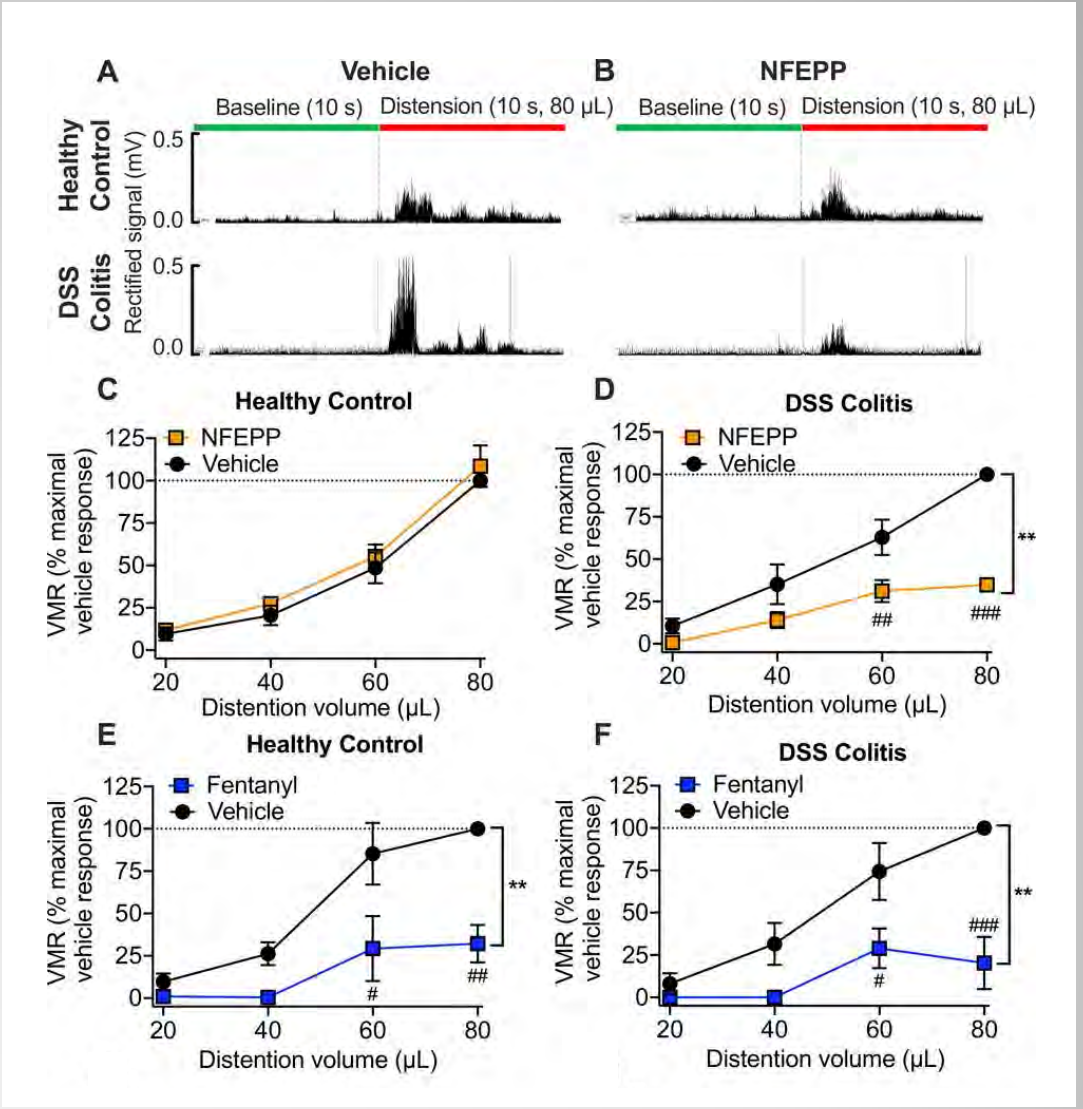
T cell-derived endogenous opioids regulate visceral pain in animal models of colitis



Basso et al. J Gastroenterology 2018; 53:215-226

Locally activating opioid receptors in the inflamed gut can attenuate visceral pain

– with limited side effects



Jiménez-Vargas et al. Gut 2022;71:695-704

Summary - 3

- Endogenous opioids from T cells regulate nociceptive neurons whose activity is dampened even in the face of ongoing colitis.
- Peripherally acting exogenous opioids can reduce visceral pain in animal models of colitis.

Conclusions

- The gut-brain-microbiota axis regulates visceral sensitivity in the context of IBD at the level of the gut, spinal cord and brain.
- Peripheral signaling from enterochromaffin cells, enteric glia and immune cells regulates the excitability of visceral afferent nerves.
- The mechanisms of pain signaling that have recently been discovered provide an explanation for the clinical observations in IBD.
- These mechanisms are being explored as novel therapeutics for the treatment of pain in IBD.

Acknowledgements

Past and present members of the Sharkey lab

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Christophe Altier, University of Calgary

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CIHR IRSC

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Canadian Association of Gastroenterology
L'Association Canadienne de Gastroentérologie

Alberta Enterprise and Advanced Education

Canada Foundation for Innovation
Fondation canadienne pour l'innovation