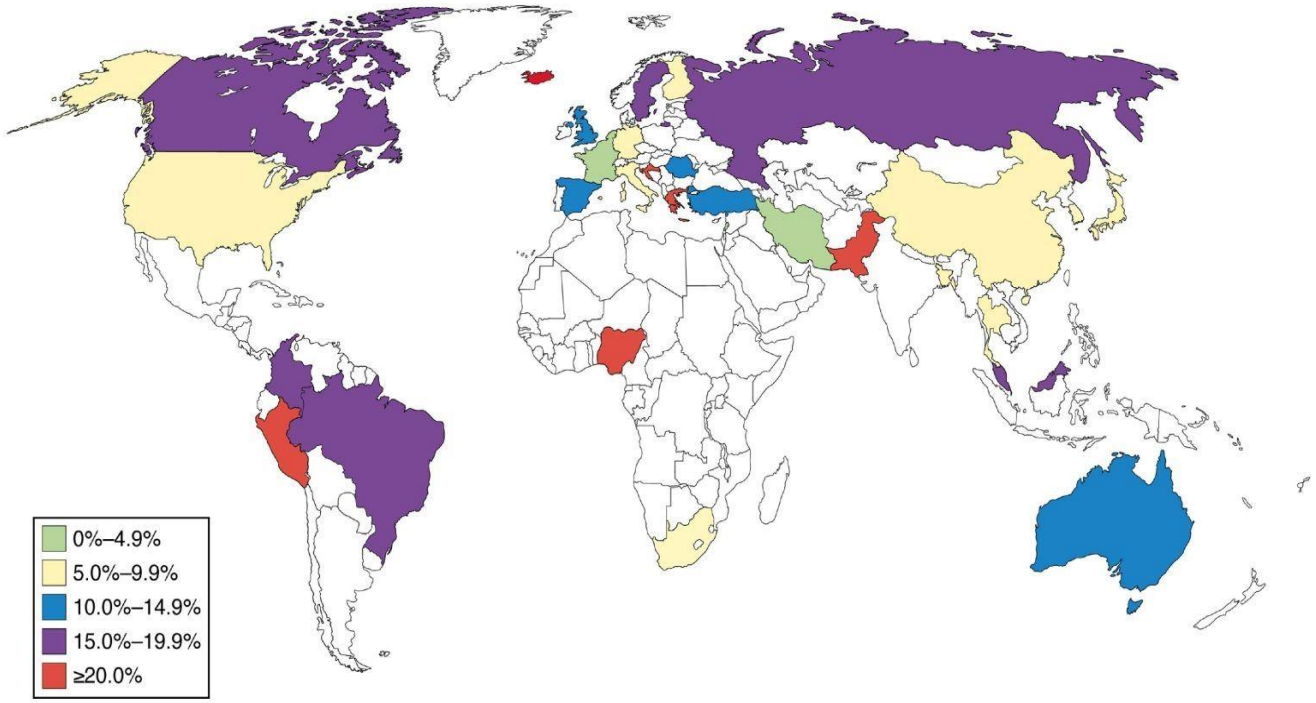
TARGID
Translational Research Center for Gastrointestinal Disorders

Post-infectious IBS

G. Boeckxstaens
KU Leuven, University Hospital Leuven
Leuven, Belgium

Food allergy, food sensitivity, food intolerance and … IBS?

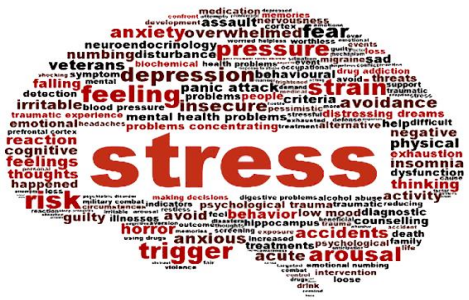
- IBS is a symptom-based diagnosis
- 4-10 % of Western population
- Changes in stool consistency or frequency, discomfort and/or pain
- No detectable abnormalities on endoscopy, radiological imaging or lab tests
- Limited insight in pathophysiology – disappointing treatment
- Heterogenous patient population
- **Common in all patients = abdominal pain**



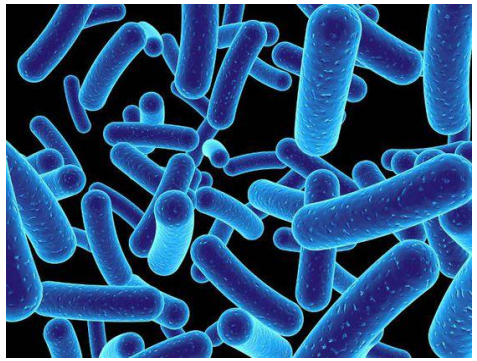
What are the triggers leading to mast cell activation in IBS?

Food

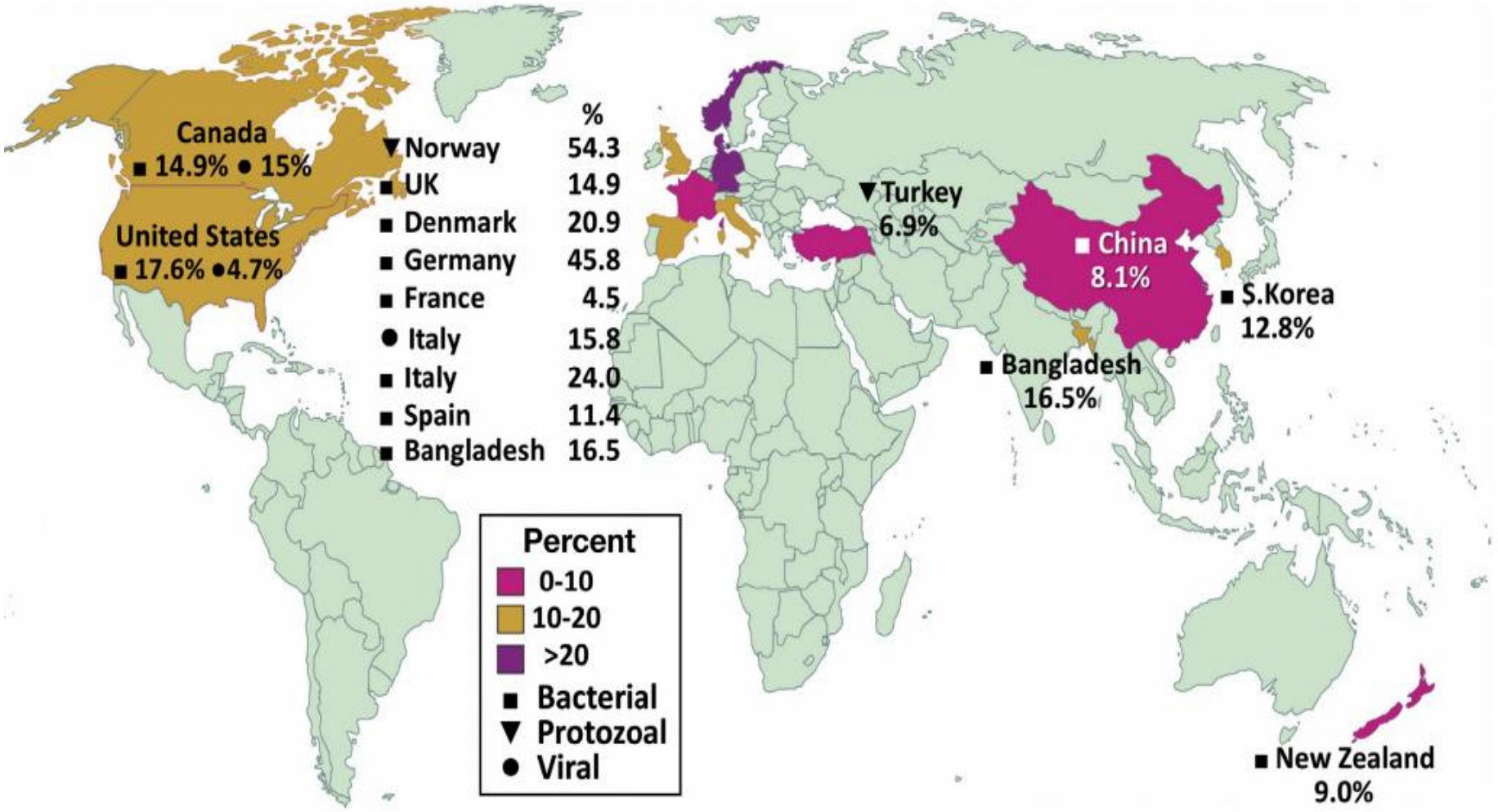
Stress



Infection



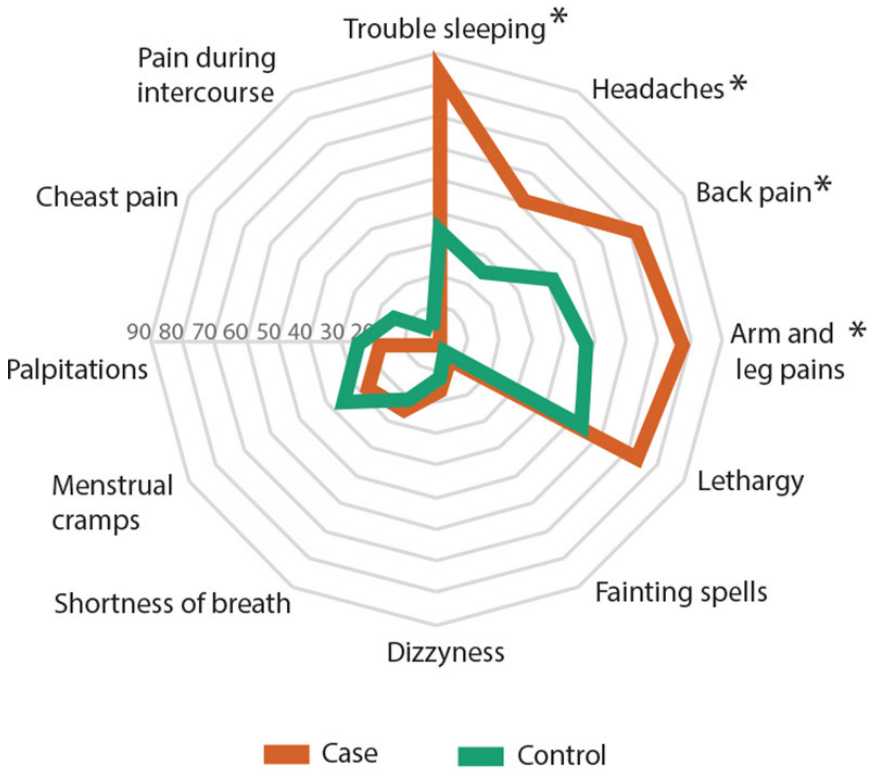
Infectious gastroenteritis as a risk factor to develop IBS

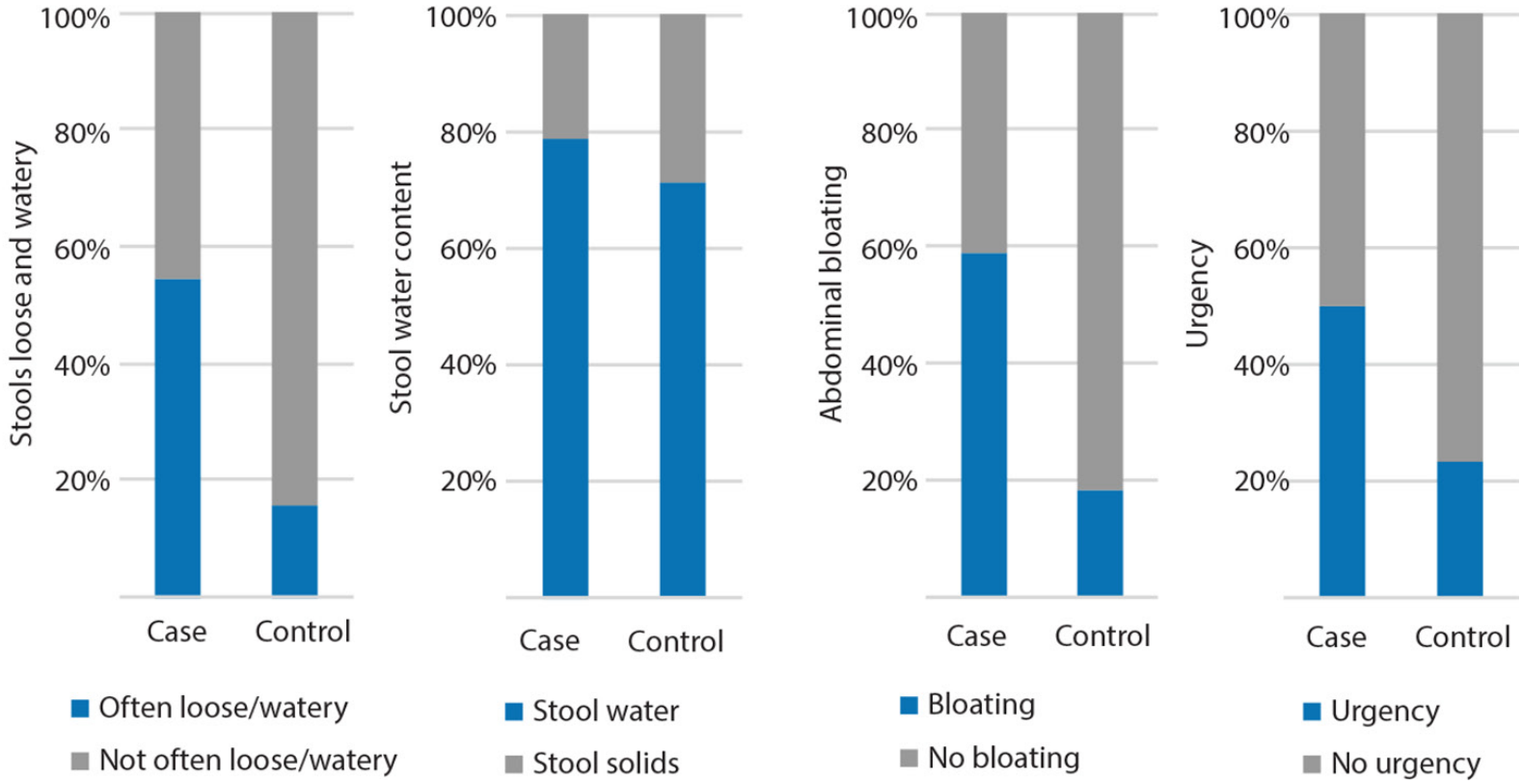


Barbara et al., Gastroenterology 2019

Campylobacter-induced gastrointestinal complaints 3 months following infection

99 subjects infected with Campylobacter jejuni: 22 had persistent GI symptoms after 3 months – 45% fulfilled Rome III criteria for IBS

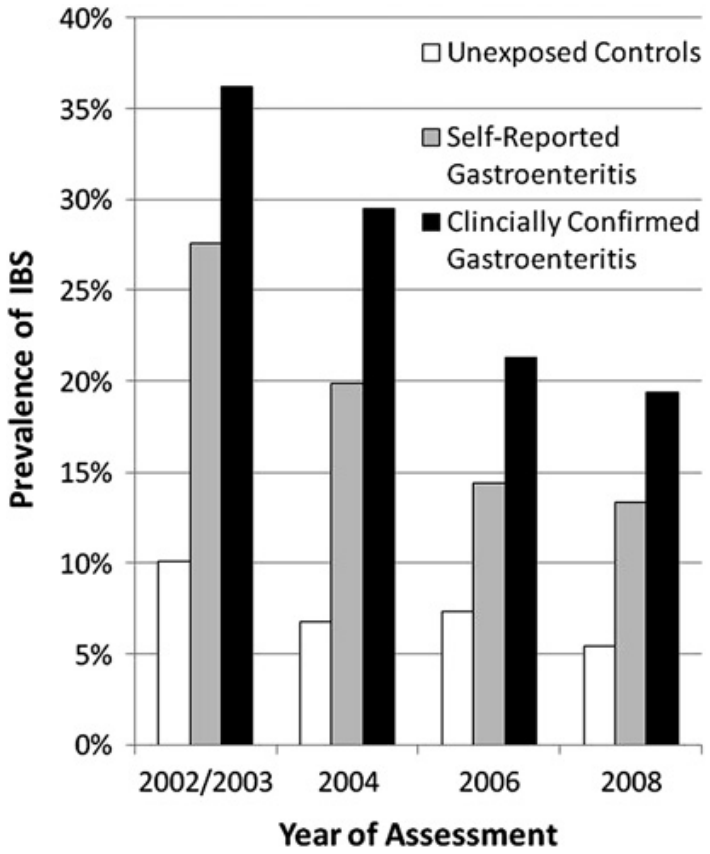


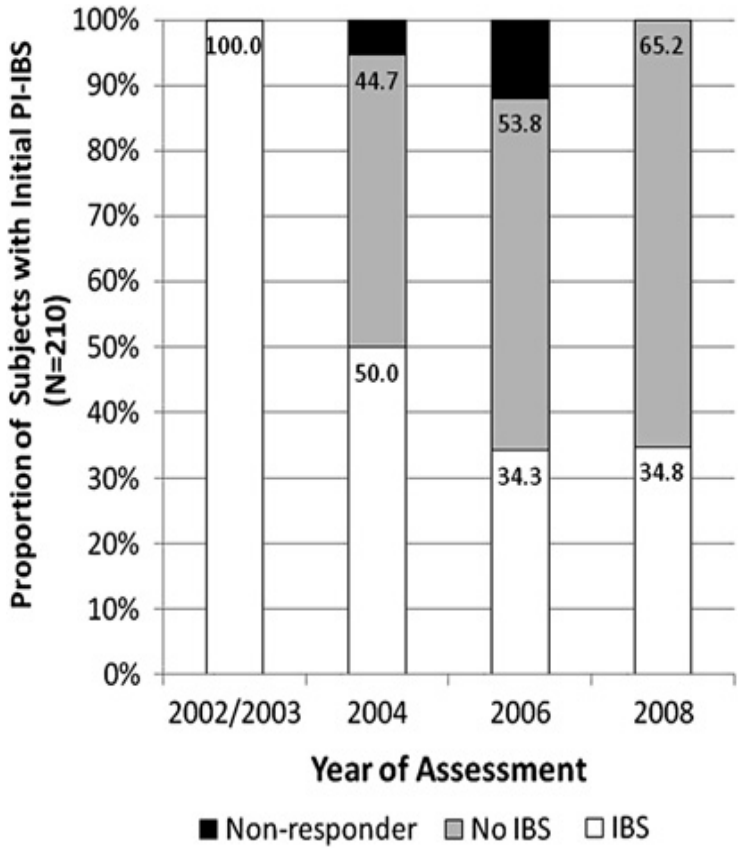


Jalanka et al., Gut 2023

Symptoms of post-infectious IBS can persist for years

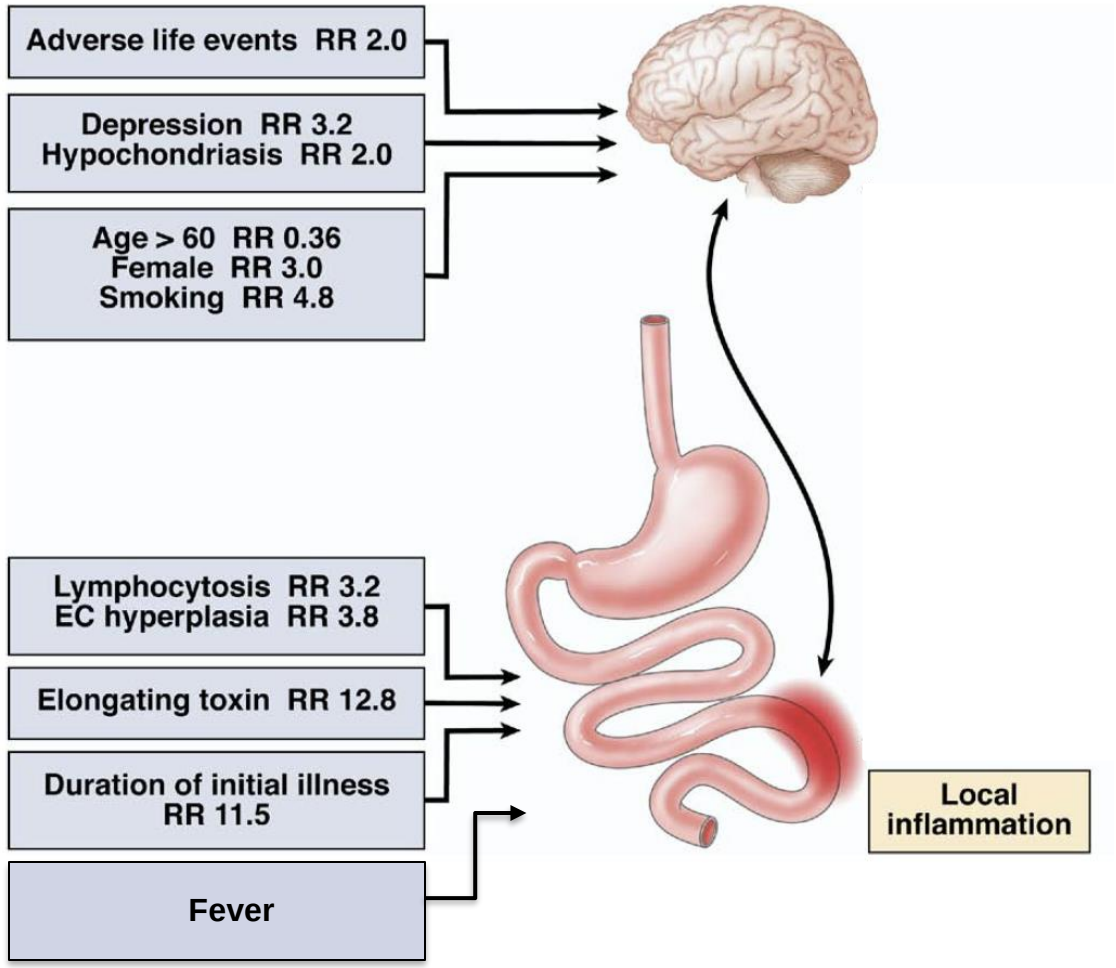
- Walkerton, Ontario, Canada:
- in 2000, heavy rainfall washed livestock fecal resdiue into drinking water supply
- Contamination with E. coli, Campylobacter jejuni and other pathogens affecting at least 2300 locals (6 died)
- Large cohort was followed during 8 years



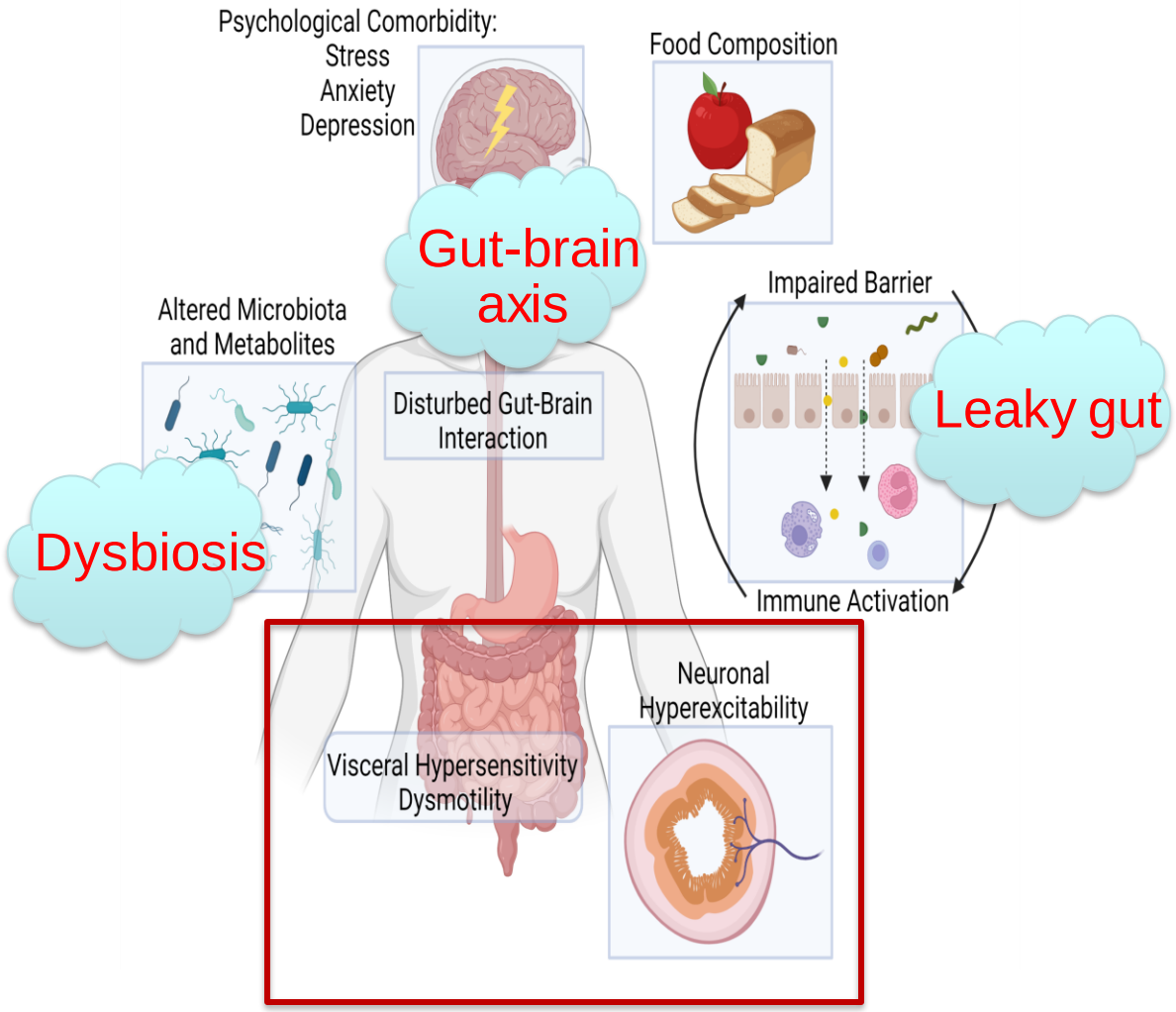


Marshall et al., Gut 2010

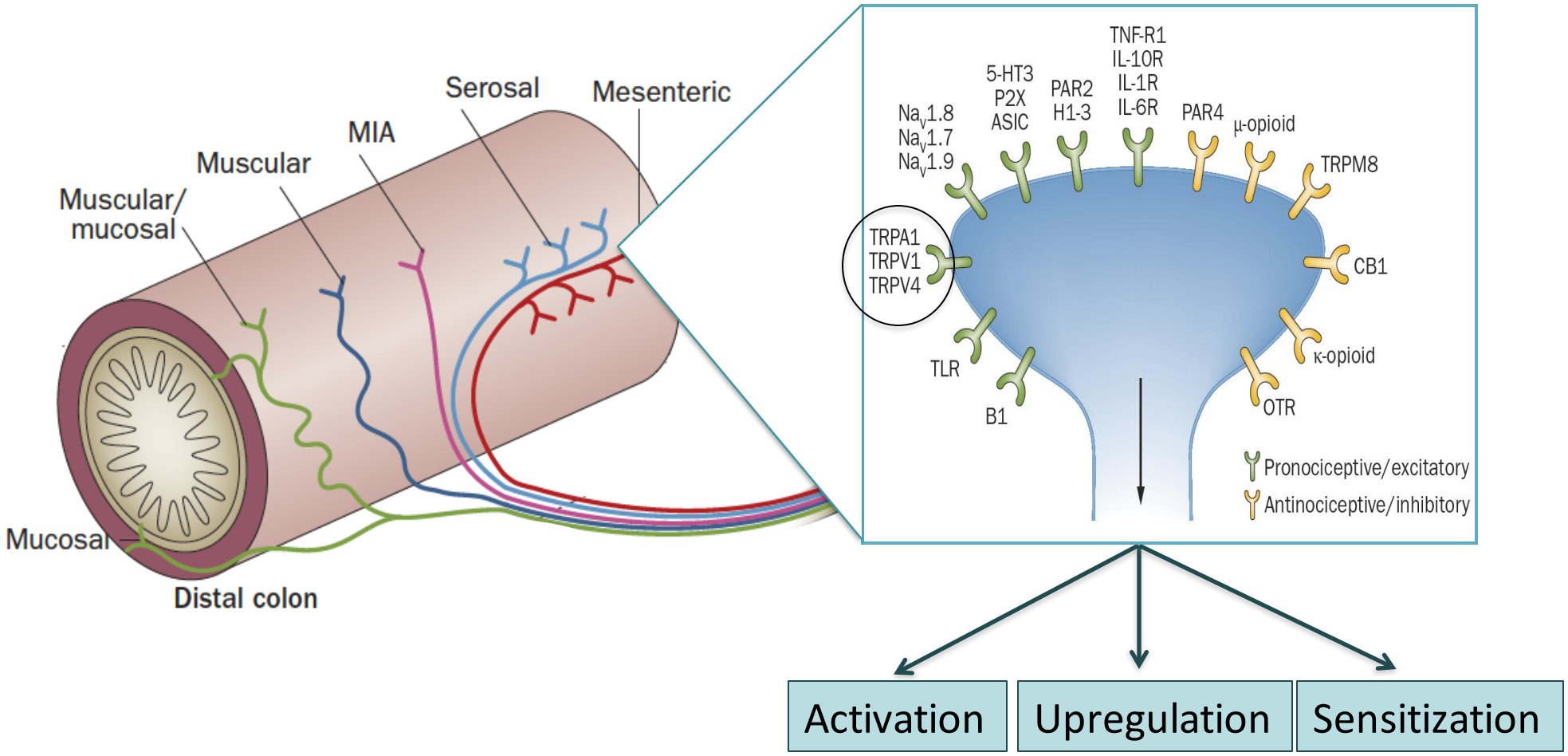
Risks factors of PI-IBS and mechanisms underlying abnormal pain signaling



Spiller Gastroenterology 2009



Abdominal pain is transmitted via extrinsic afferent nerve fibers innervating the intestine

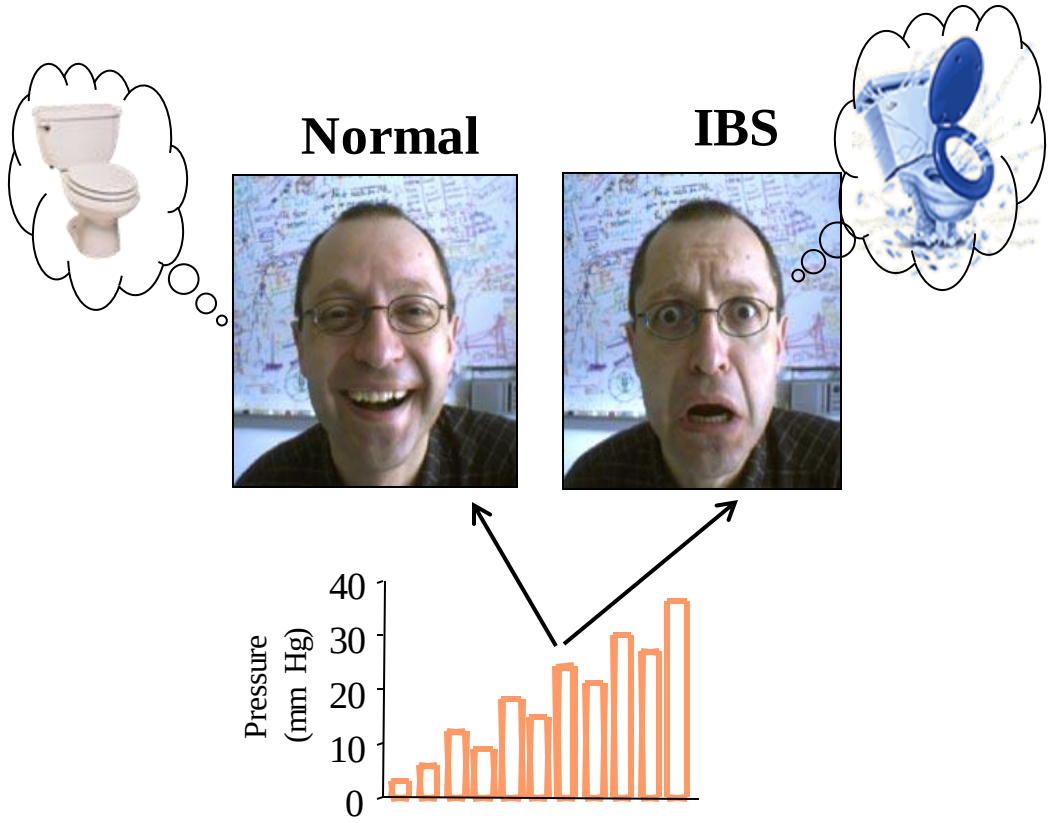


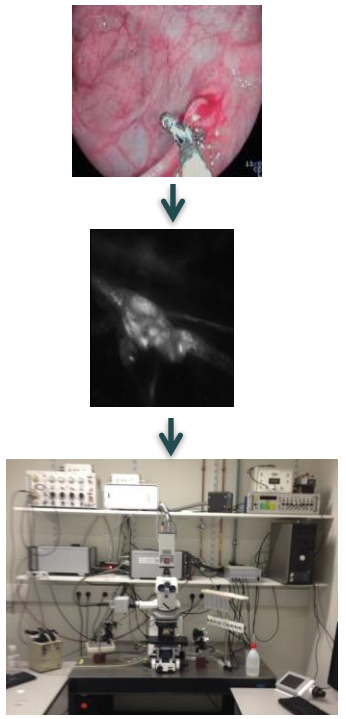
Adapted from: Brierley & Linden, Nat Rev Gastro Hepatol 2014

What do we know about the pathophysiology of IBS?

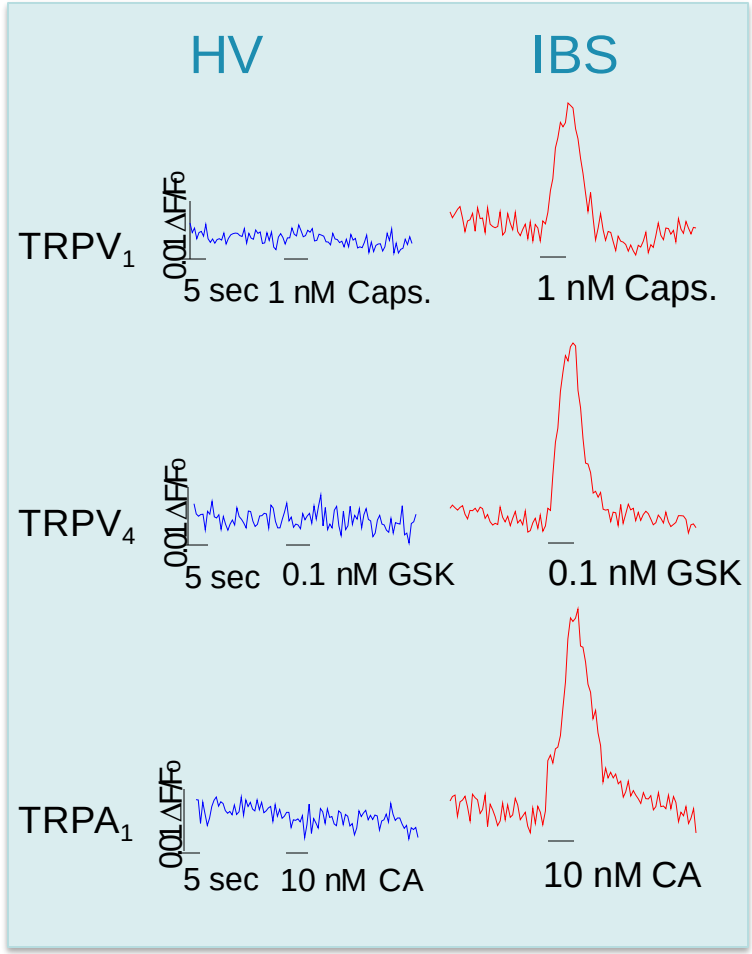
Abnormal pain signaling

Increased sensitivity to colonic distention





Cirillo et al., Gut 2013

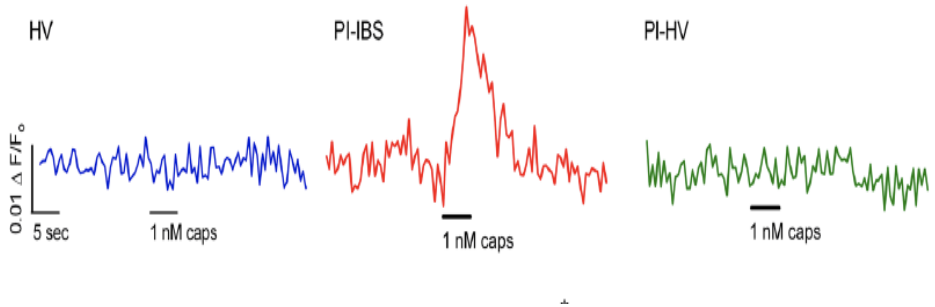


Wouters et al., Gastroenterol 2016; Balemans et al., Am J Physiol 2019

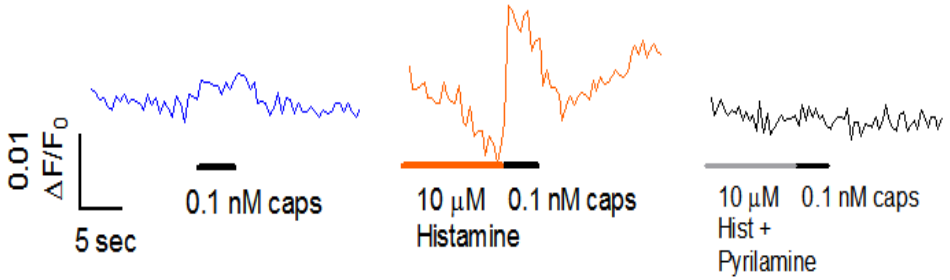
Role of histamine in increased excitability of submucosal neurons and visceral afferents in PI-IBS

Contamination of drinking water in 2 Belgian villages (Hemiksem and Schelle) – rectal biopsies collected after 2 years from controls, infected non-IBS and PI-IBS

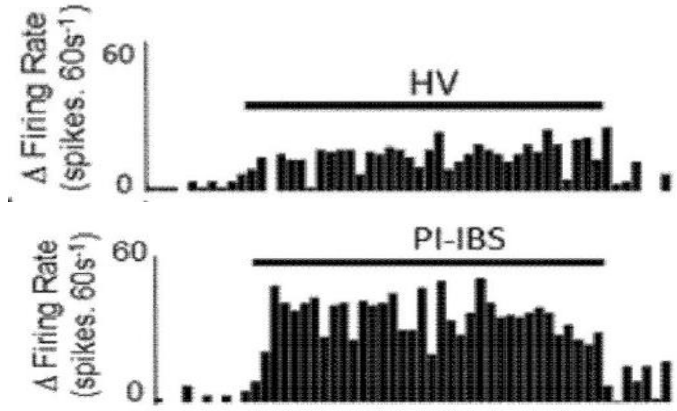
Submucosal neurons

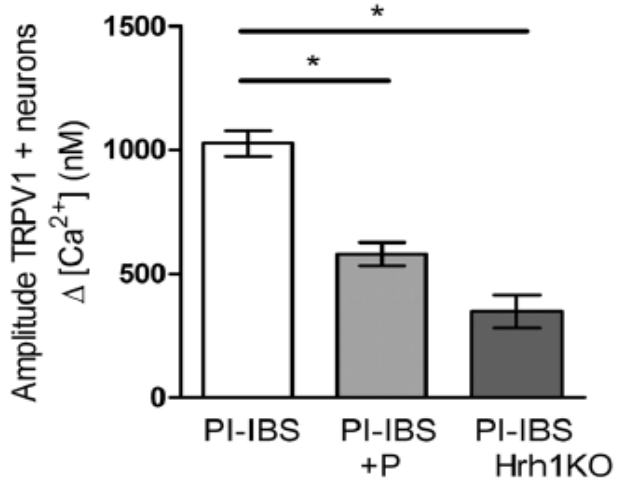


Submucosal neurons (histamine & H1R)



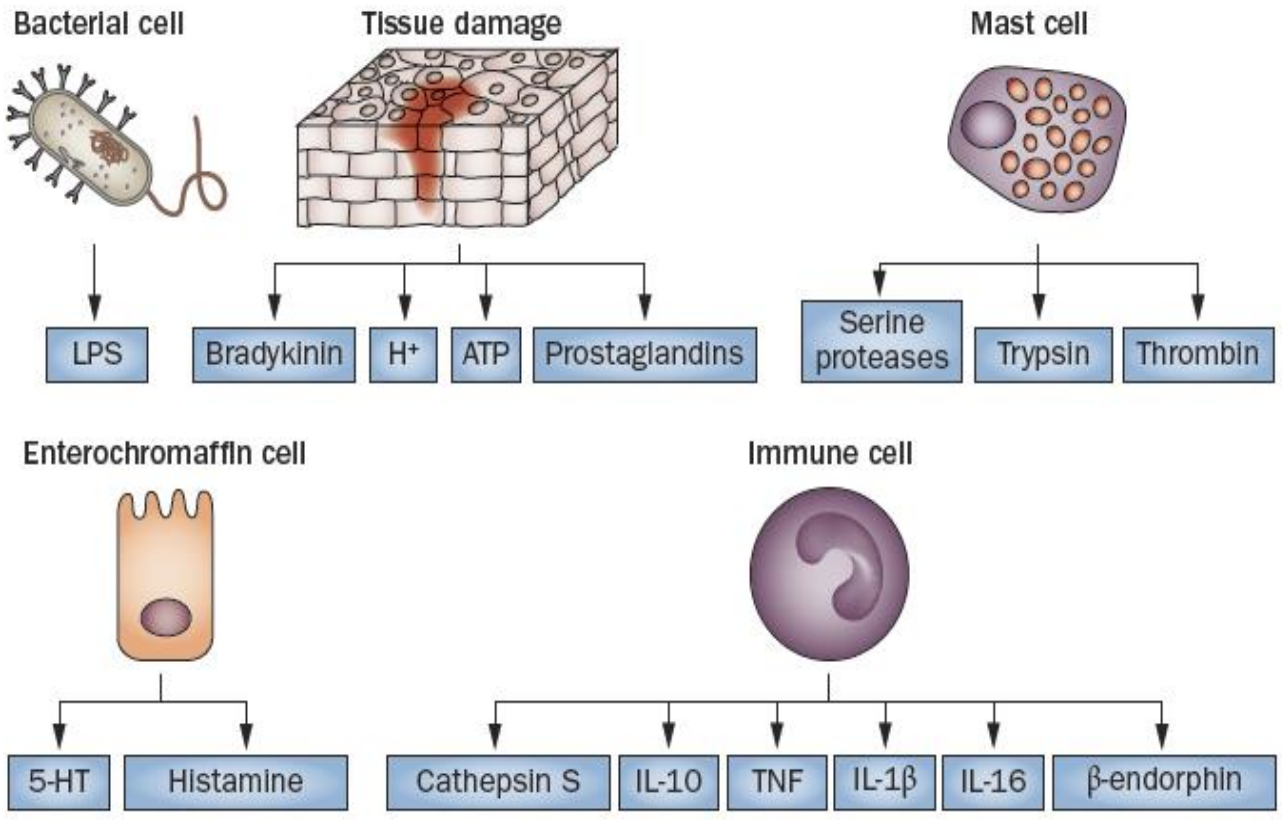
Biopsy supernatant on murine visceral afferents





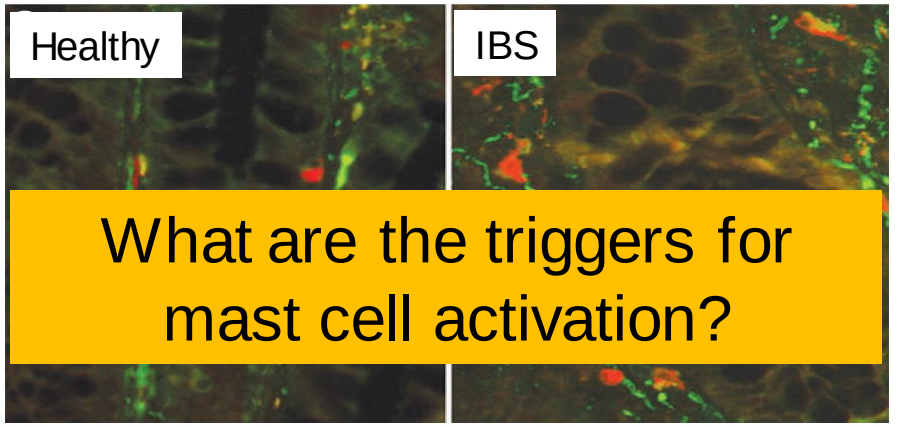
Balemans et al., Sci Reports 2017

Immune cells and mediators potentially interacting with afferent nerves

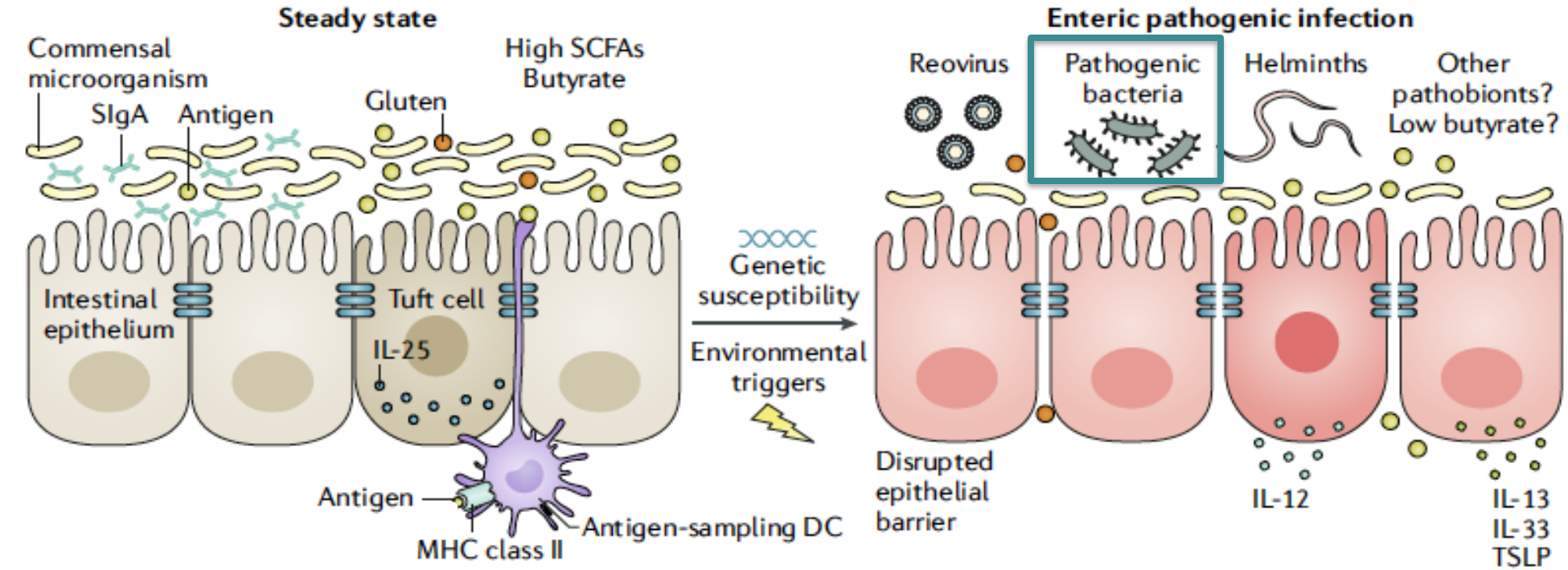


Brierley & Linden, Nat Rev Gastroenterol Hepatol 2014

- Neural activation blocked by antagonist of serotonin, histamine, proteases
- Increased numbers of mast cells in intestinal biopsies
- Increased release of histamine and proteases in supernatant of IBS biopsies



Loss of tolerance to food antigens in IBS?



Oral tolerance to gluten or other dietary antigens

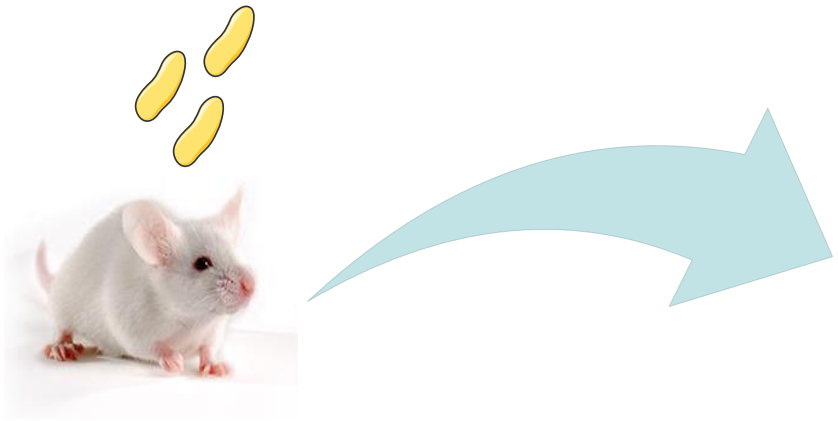
Coeliac disease (Th1)
Food allergy (Th2)

Caminero et al., Nat Rev Gastro Hepatol 2019

Aberrant immune response triggered against food antigens during gastrointestinal infection?

Food antigen re-exposure

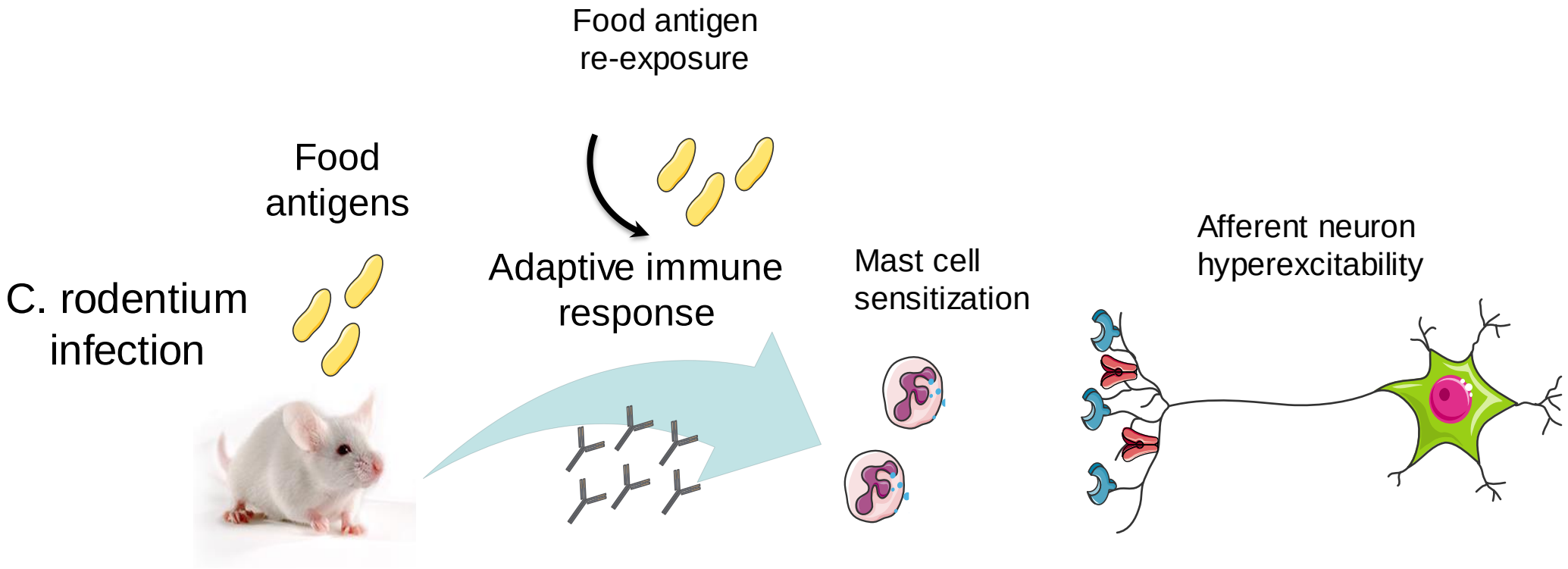
Food antigens



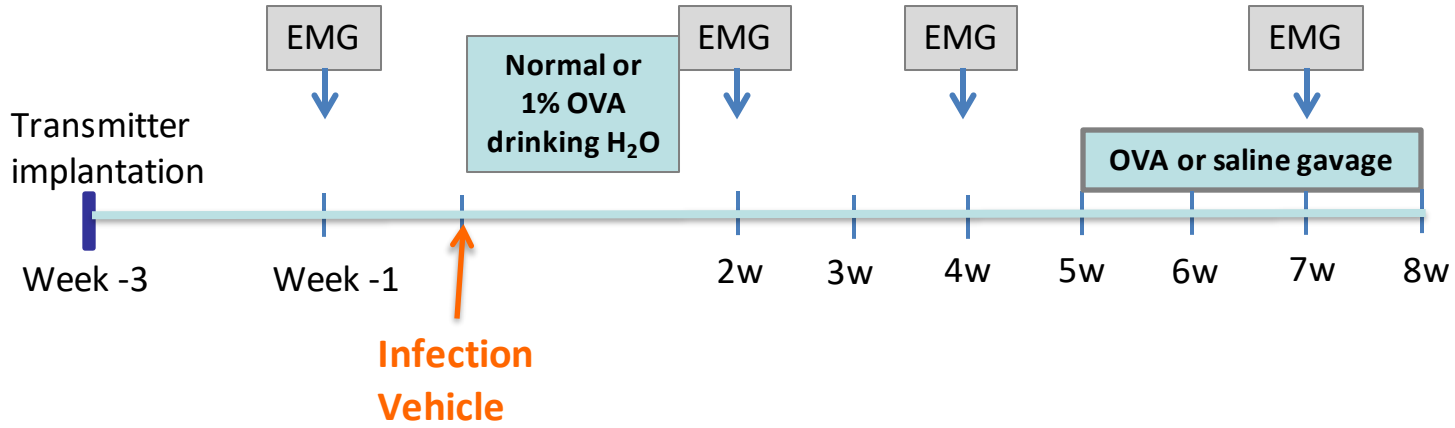
No immune response

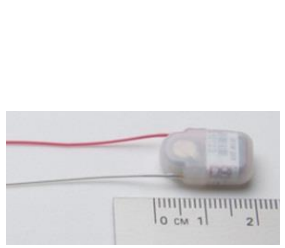
Oral tolerance

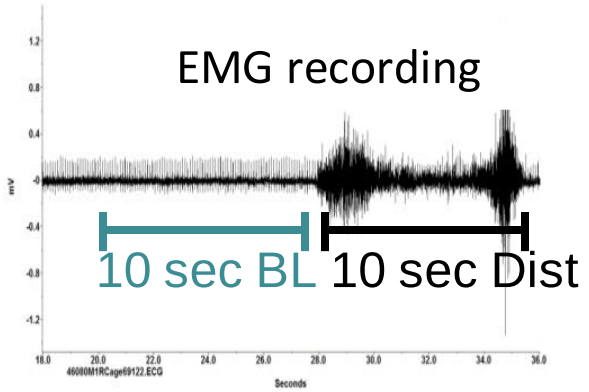
Aberrant immune response triggered against food antigens during gastrointestinal infection?

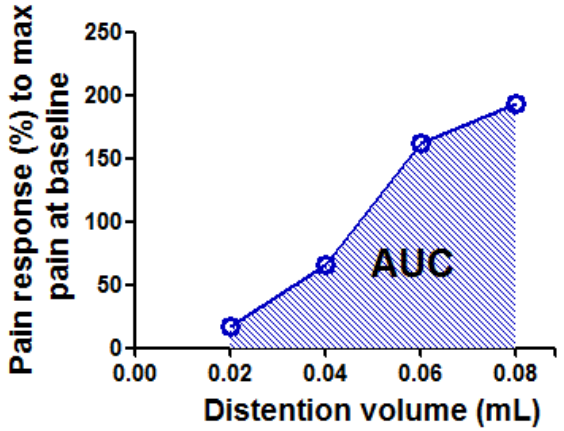


Is loss of oral tolerance to OVA triggering abnormal pain signaling in response to OVA re-exposure?

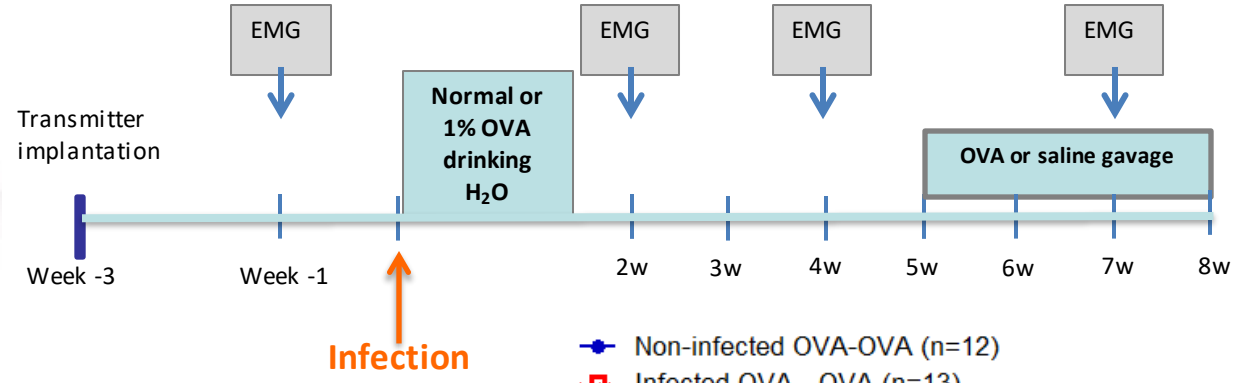


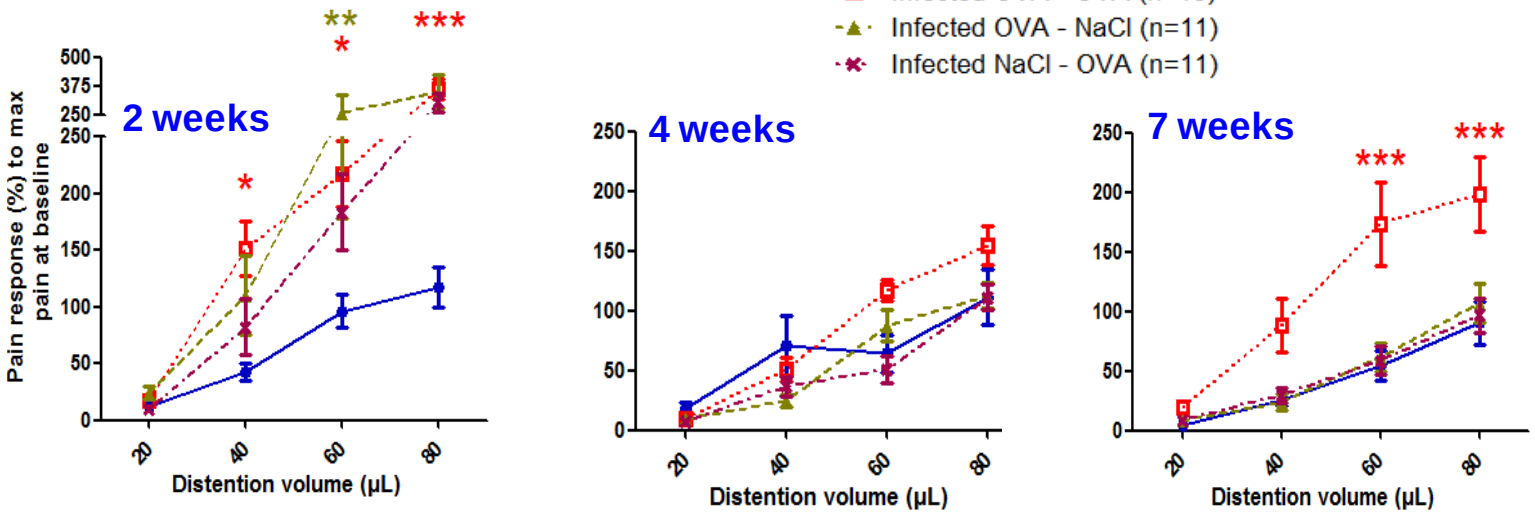


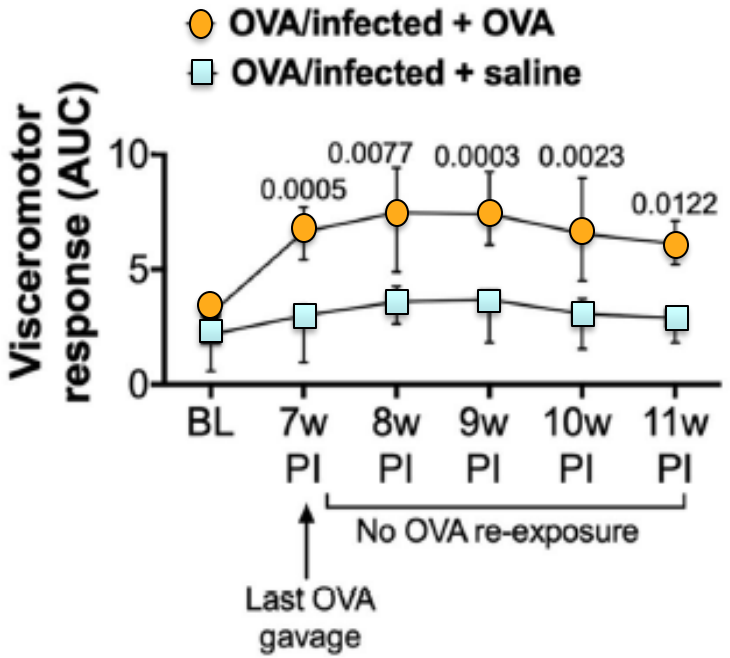




Long-lasting visceral hypersensitivity evoked by re-exposure to OVA following infection with *C. rodentium*

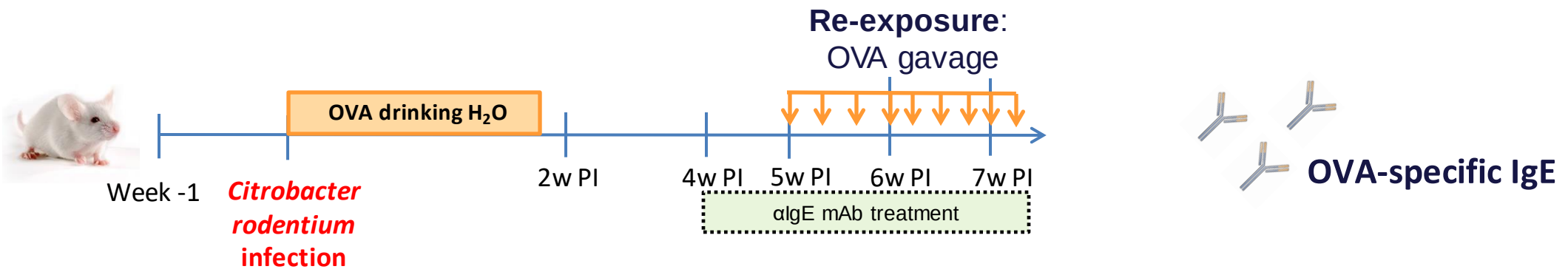


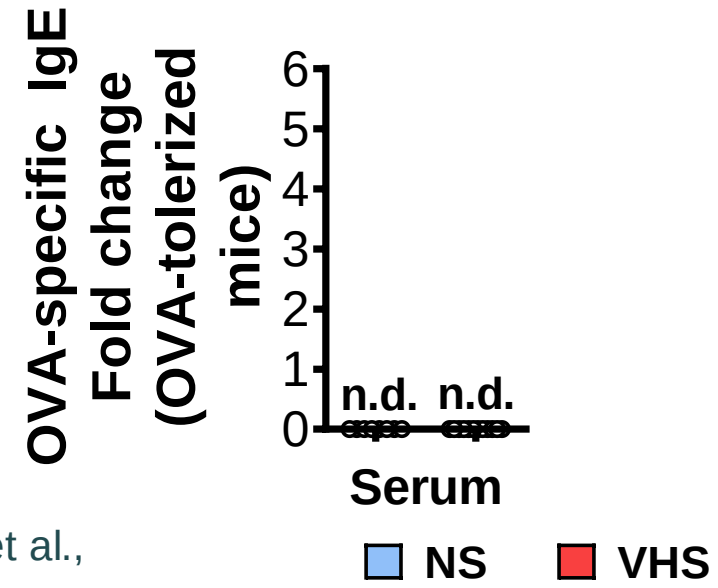


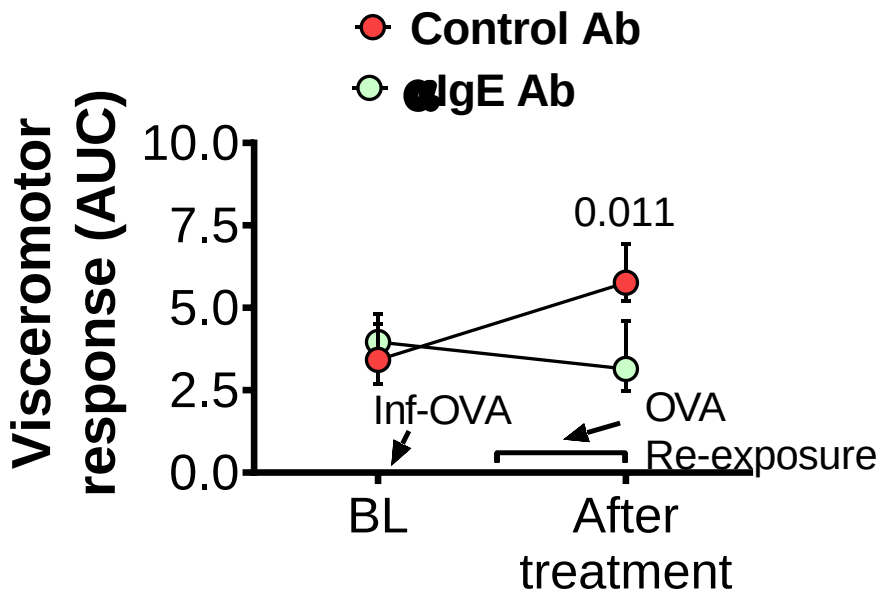


No VHS in mast cell deficient mice

Blockade of OVA-specific IgE with monoclonal IgE antibody prevents visceral hypersensitivity

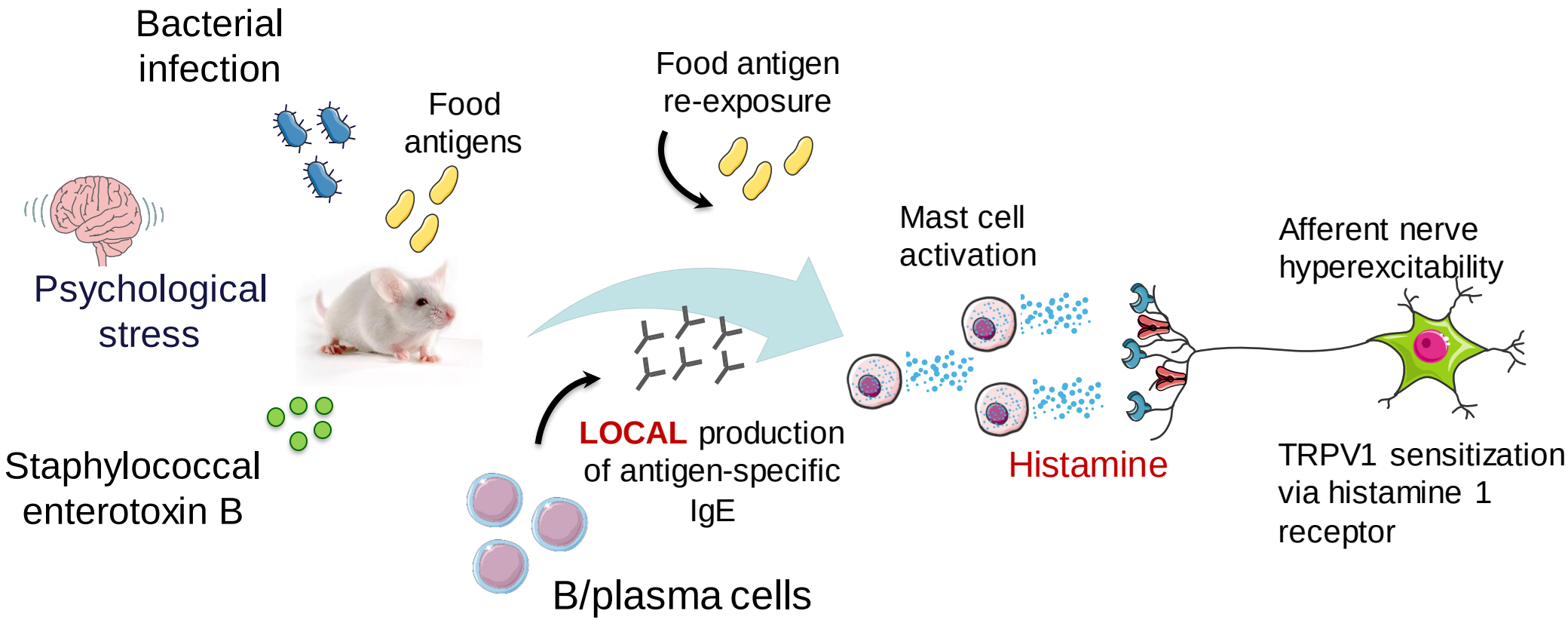






Aguilera-Lizarraga et al., Nature 2021

Food-induced IgE-mediated mast cell activation as underlying mechanism of visceral hypersensitivity (abdominal pain)



Aguilera-Lizarraga et al., Nature 2021

Mucosal reaction to food antigen injection in IBS patients

- IBS patients (neg skin prick test and neg serum IgE levels) vs healthy controls
- Food antigens (wheat, gluten, milk, soy) injected into the mucosa to trigger MC activation
- Development of oedema and visibility of vasculature was scored after 12 minutes

Aguilera-Lizarraga et al., Nature 2021

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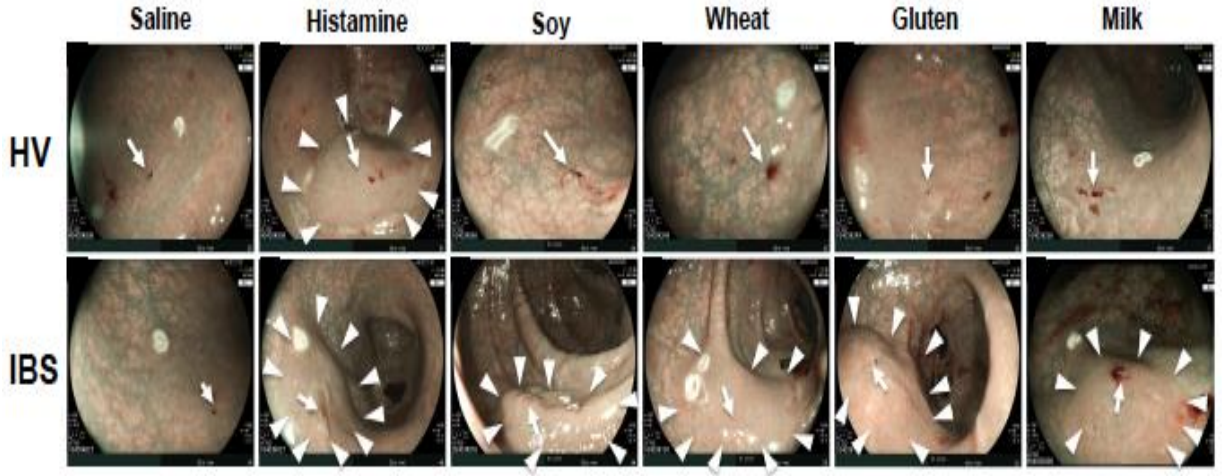
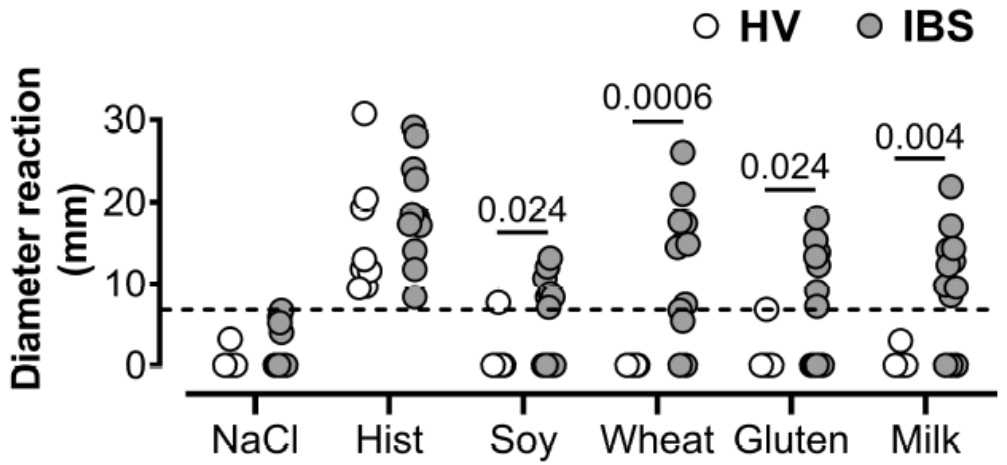
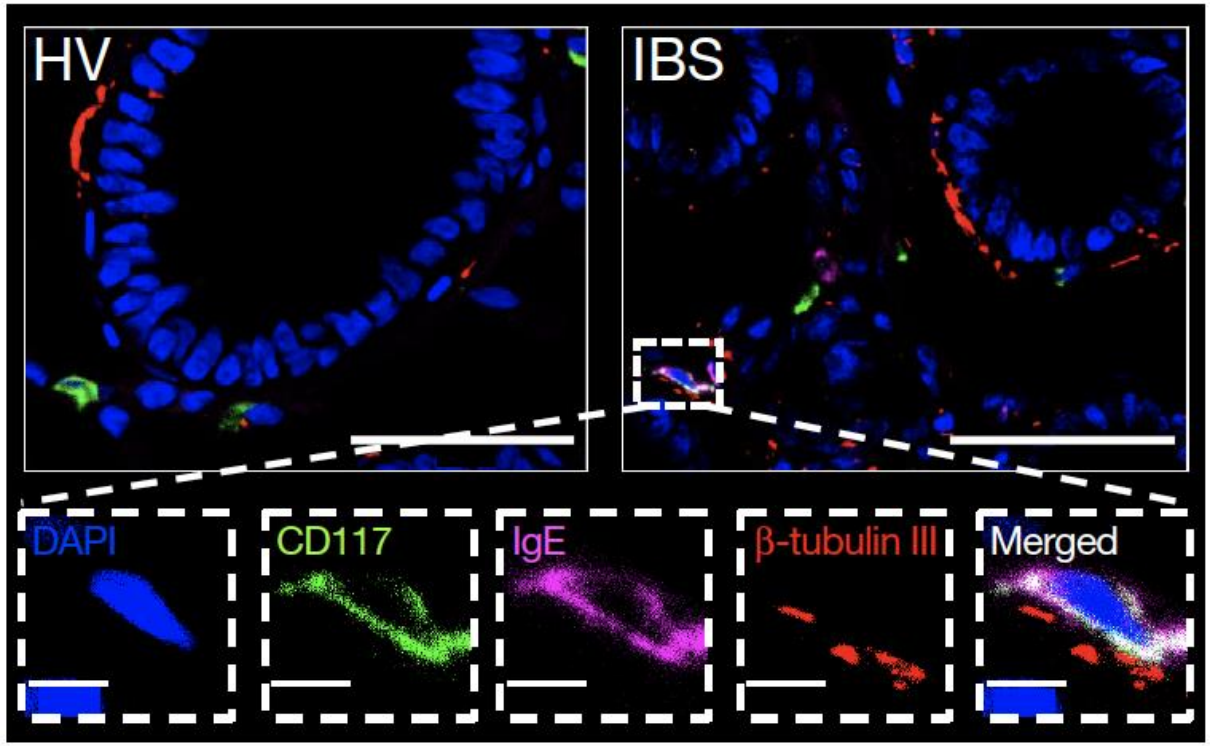
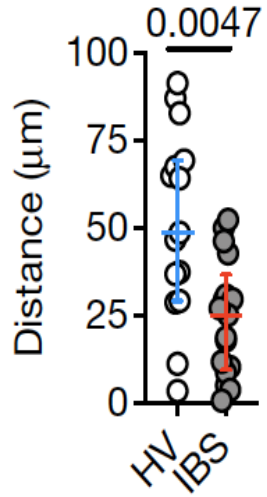


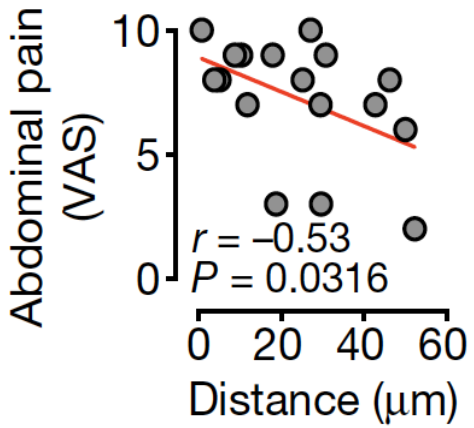


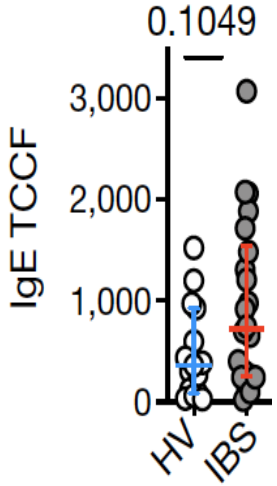
Aguilera-Lizarraga et al., Nature 2021

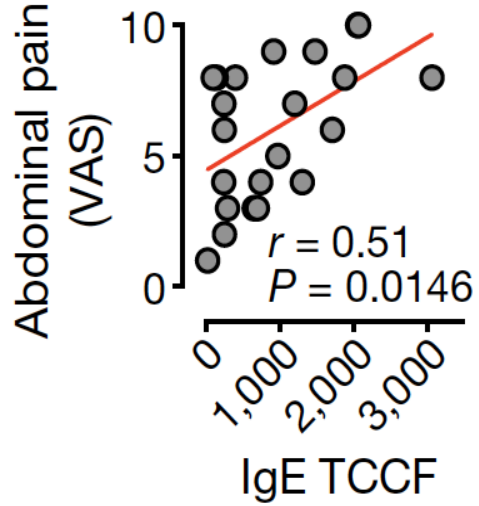
IgE-mediated mast cell activation in IBS patients





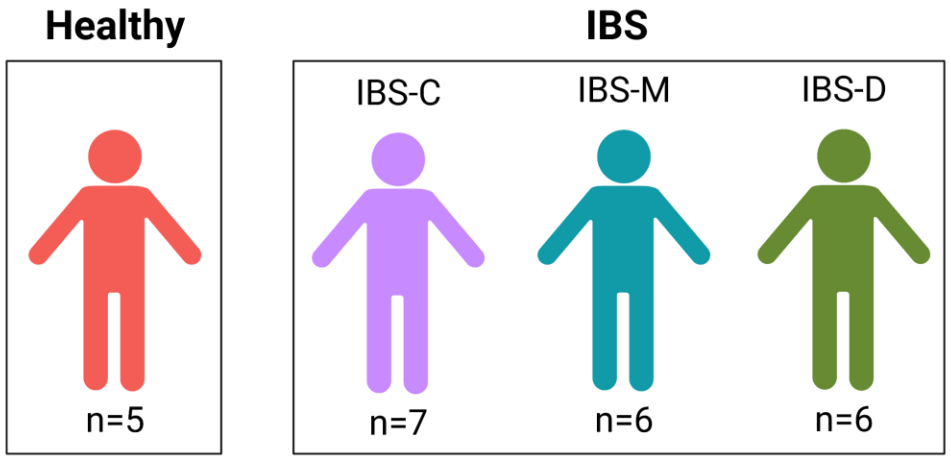


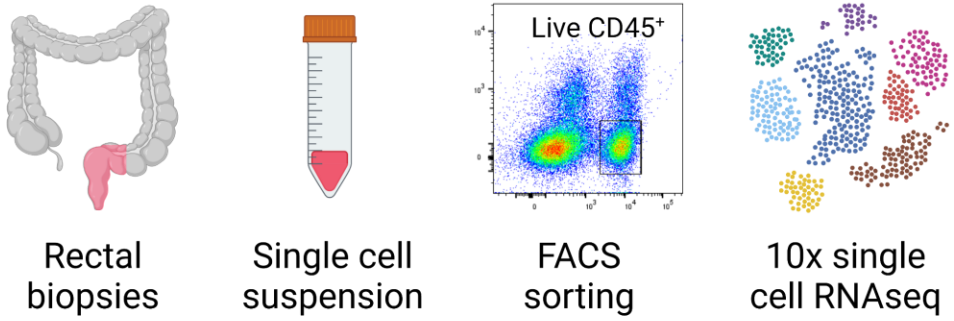




Aguilera-Lizarraga et al., Nature 2021

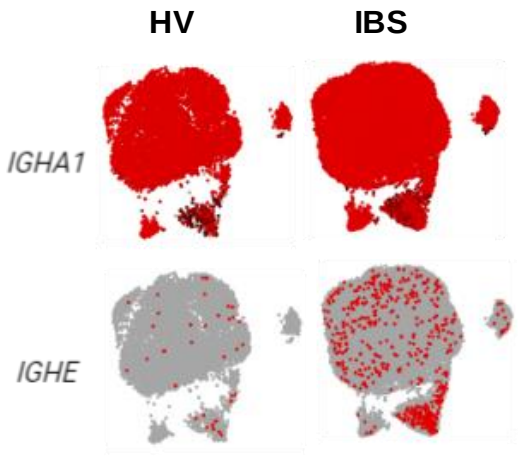
scRNAseq of rectal biopsies collected from healthy volunteers and IBS patients

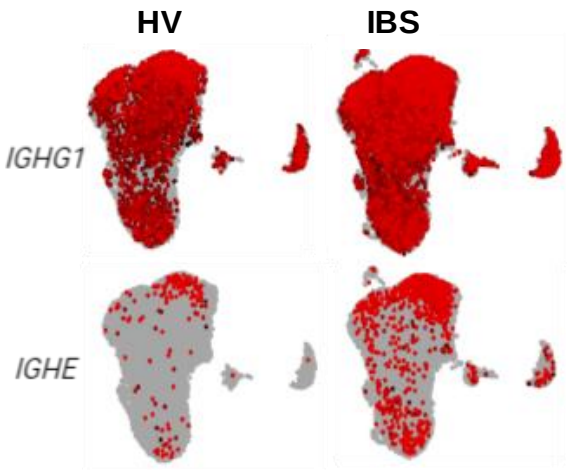




Antibody secreting cells

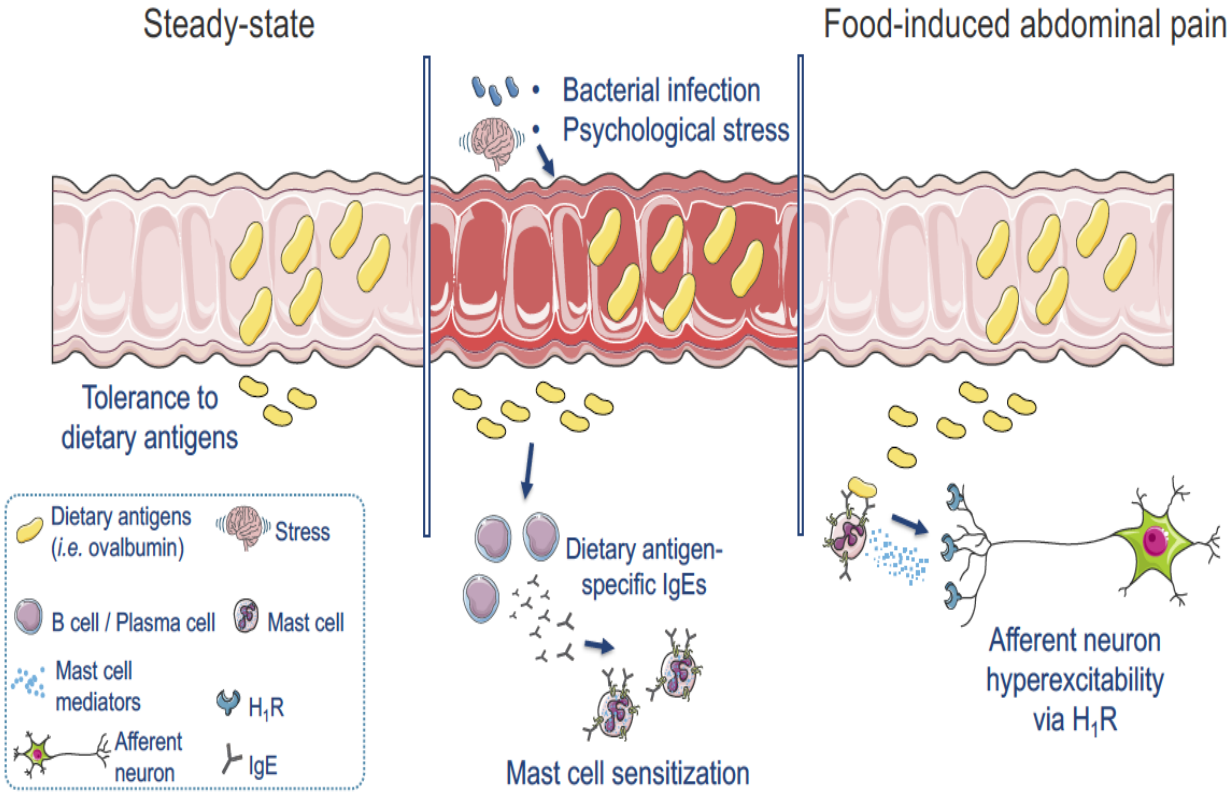
B cells



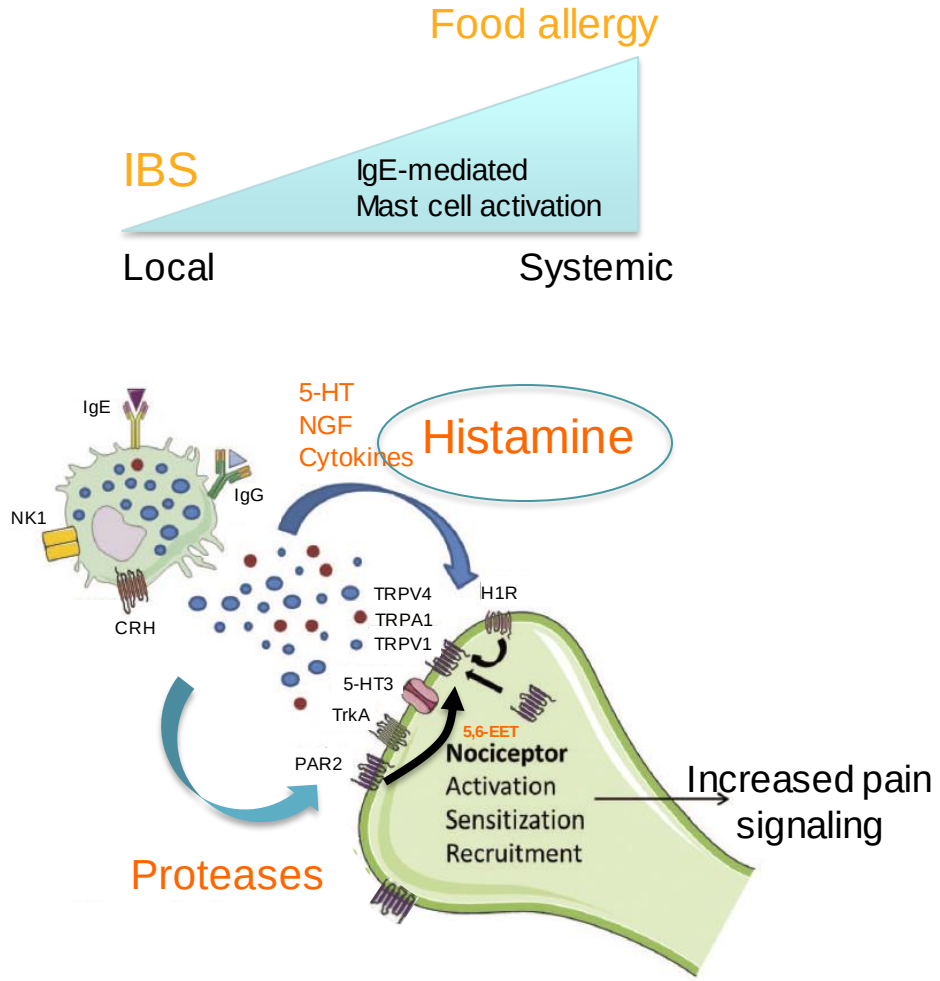


H. Hussein (unpublished)

Mast cells as potential target for treatment of IBS



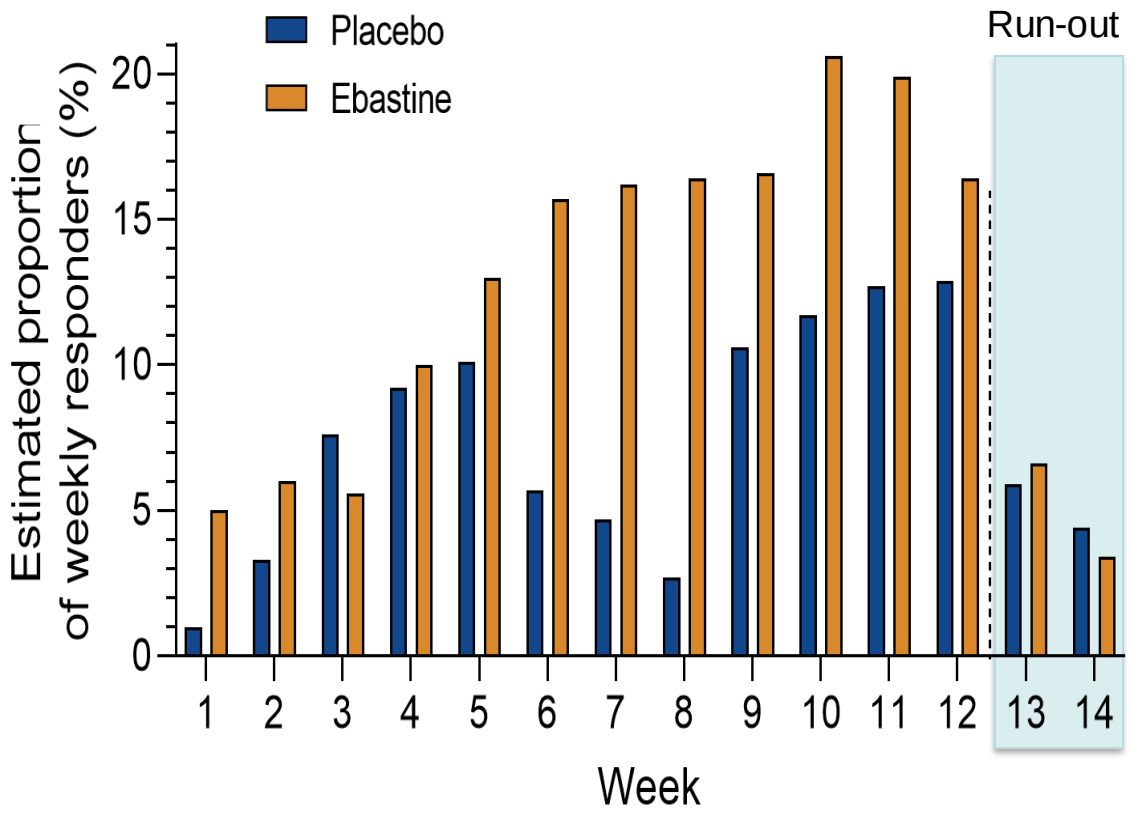
Aguilera-Lizarraga et al., Nature 2021

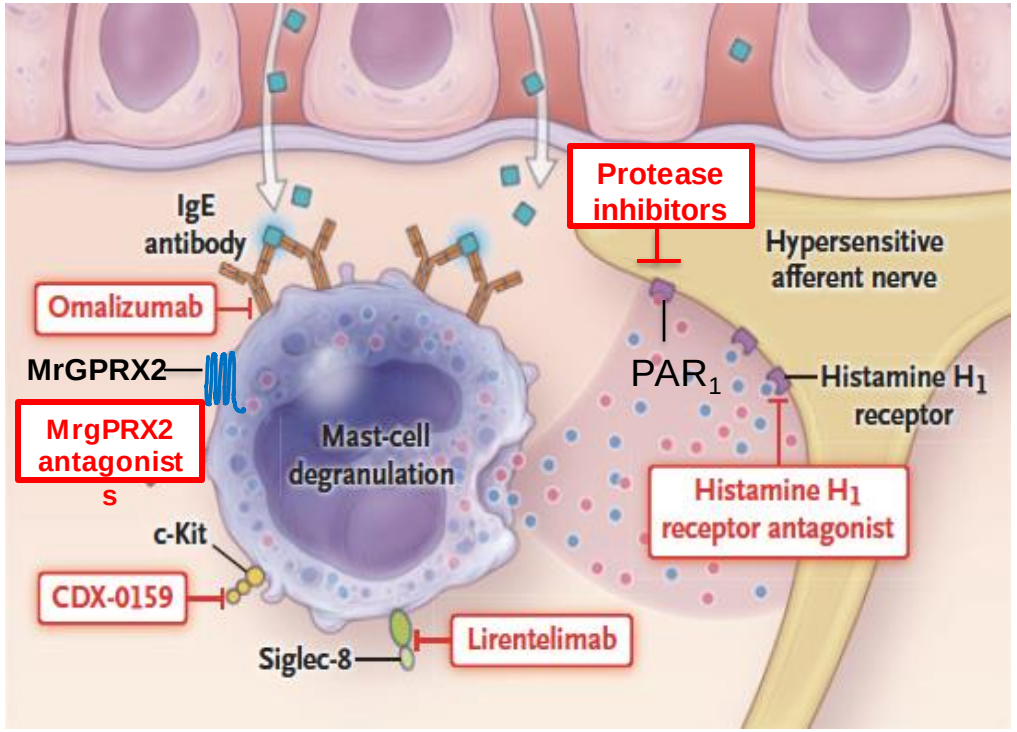


Wouters et al., Gut 2015

Effect of the H_1R antagonist ebastine on weekly global relief and abdominal pain in IBS

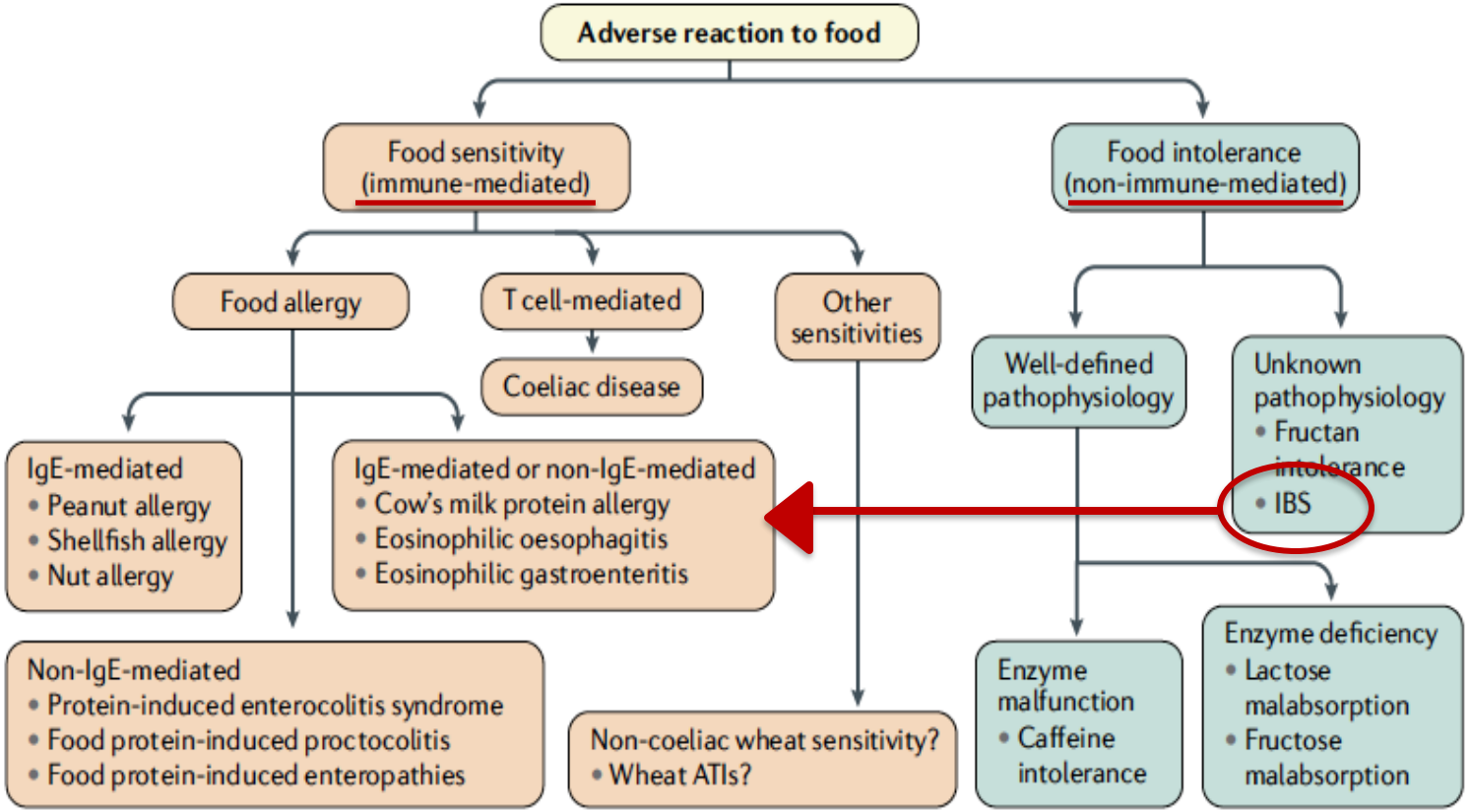
- Placebo-controlled randomized phase 2b trial
- 12 weeks H1R antagonist ebastine vs placebo
- 203 non-constipated IBS patients Rome III

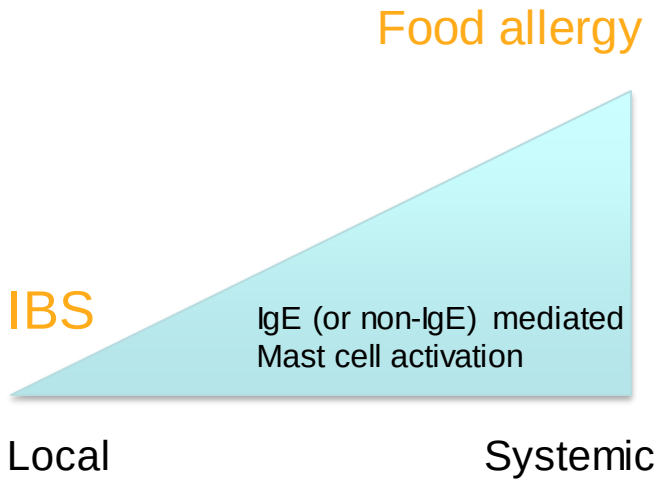




Adapted from Rothenberg, NEJM 2021

Food allergy, food sensitivity, food intolerance and … IBS?





Caminero et al., Nat Rev Gastro Hepatol 2019

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