



# **Luminal Signaling to Colonic Afferent Nerves**

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Queen's University**



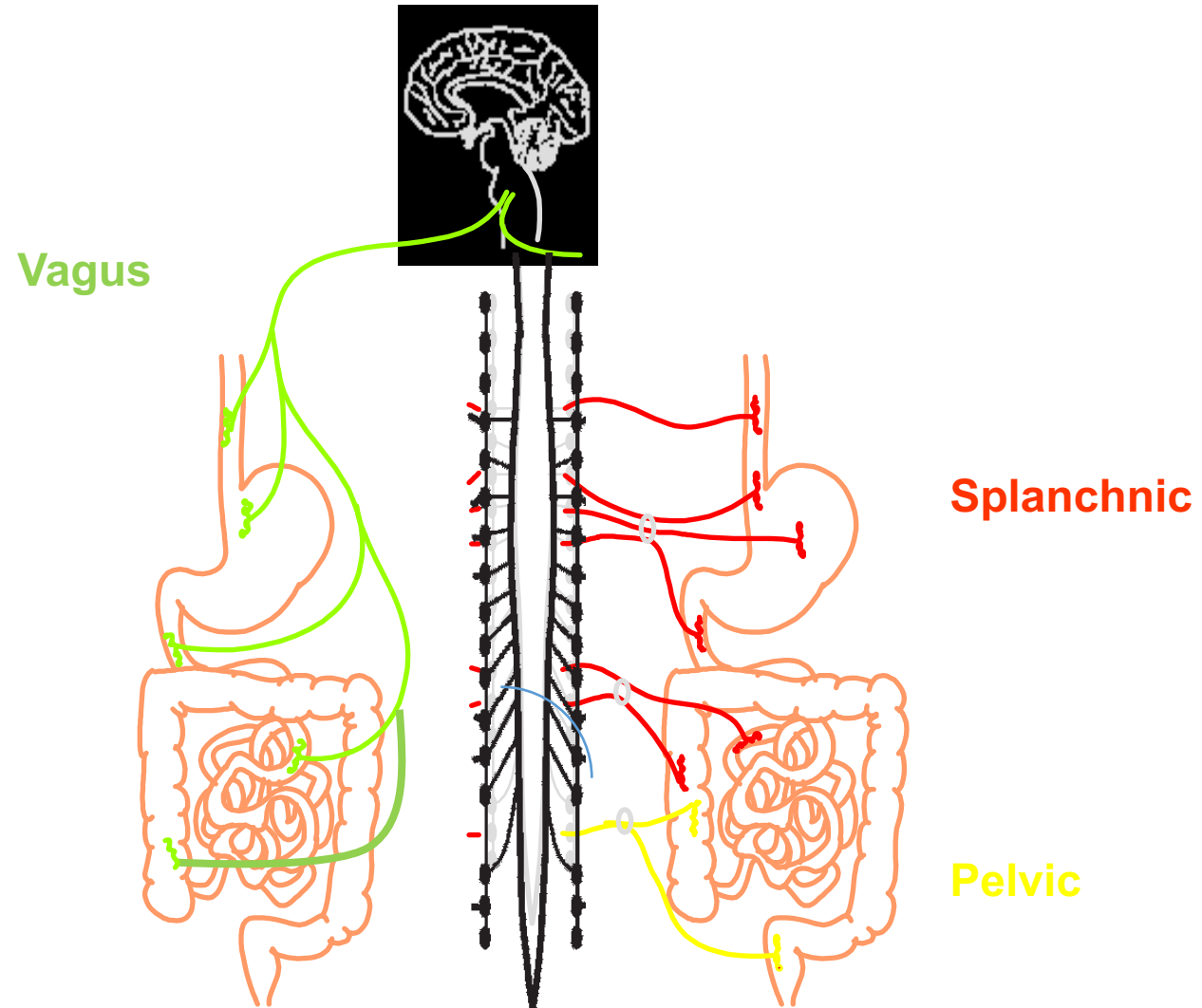
# **DISCLOSURE**

Allergan – honorarium to GIDRU for participation roundtable

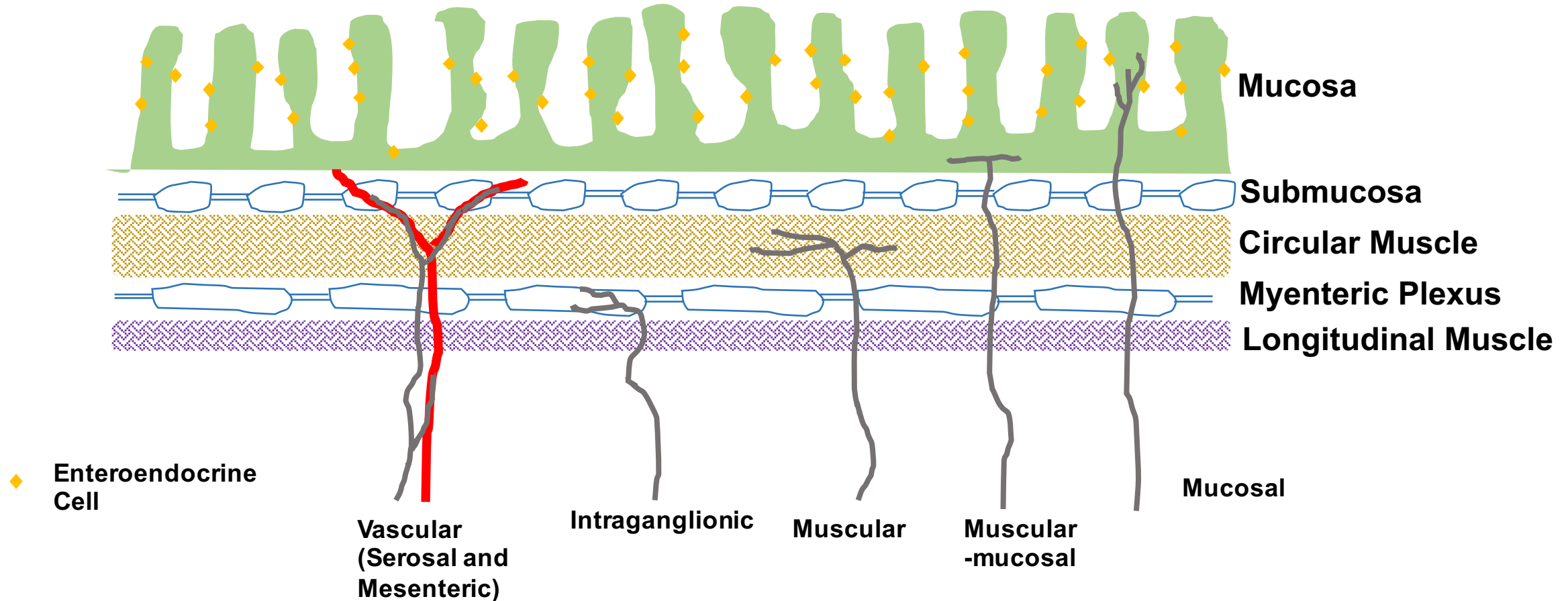
# **OBJECTIVES**

- **Extrinsic innervation of afferent nerves in the colon**
- **Epithelial mediators that can activate extrinsic afferents**
- **Luminal factors that can stimulate release of epithelial mediators to activate afferent nerves**
- **Describe a lumen to nerve inhibitory pathway**

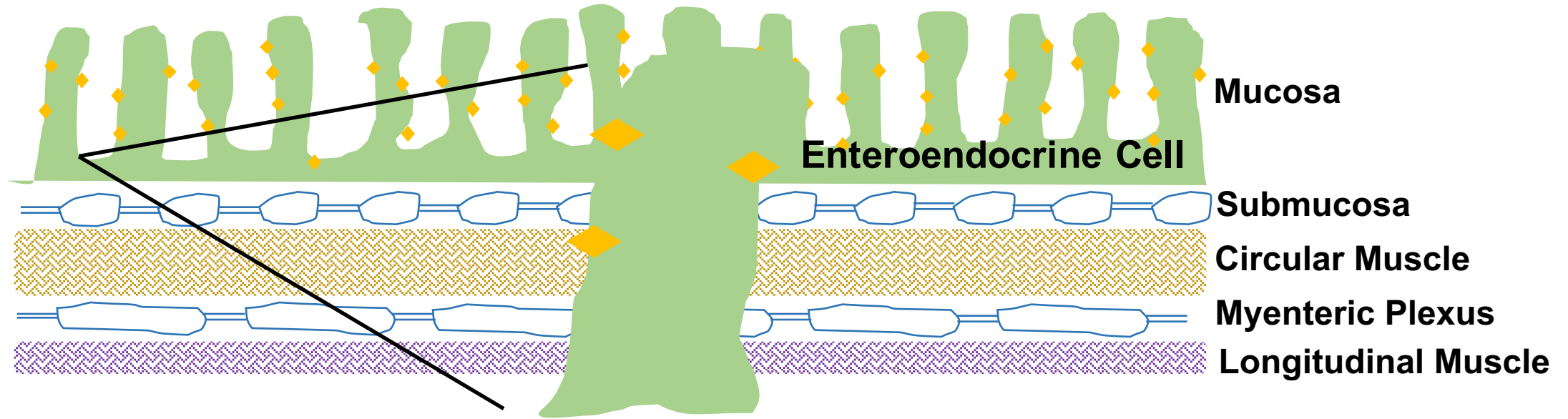
# EXTRINSIC AFFERENTS IN THE COLON



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# COLONIC ENTEROENDOCRINE CELLS

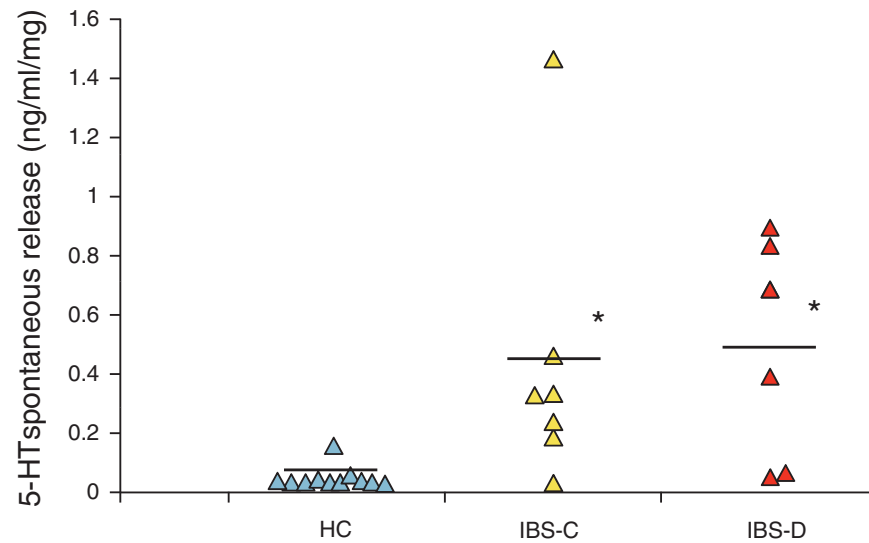


# COLONIC ENTEROENDOCRINE CELLS

- Enteroendocrine cells in the colon contain a number of different mediators
- Predominant mediators include:
  - GLP-1 (*L cells*)
  - Peptide YY (*L cells*)
  - 5-HT (*Enterochromaffin cells*)
- Other mediators
  - Chromogranin A
  - Somatostatin
  - Oxyntomodulin

## 5-HT AND IBS

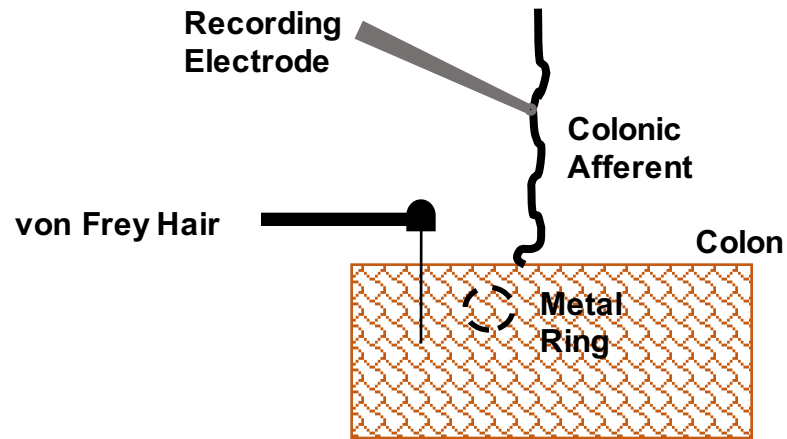
## Mucosal Biopsy



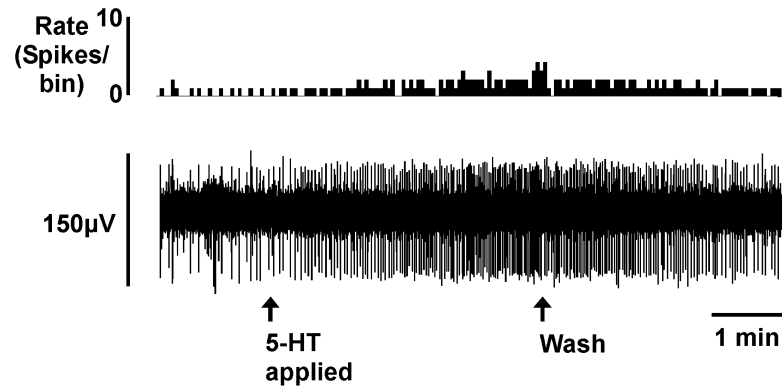
## 5-HT release correlated with abdominal pain severity



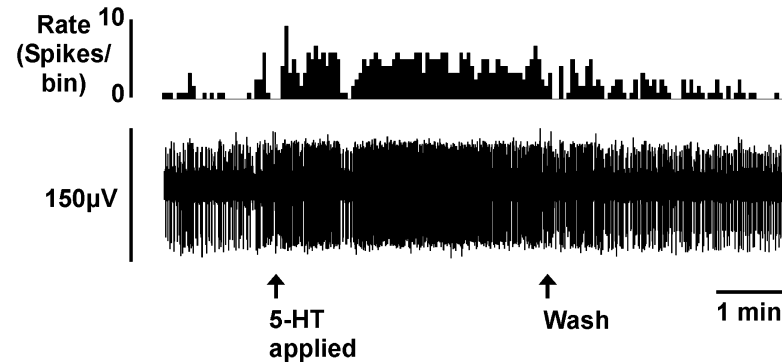
# 5-HT ACTIVATION POST-INFLAMMATION



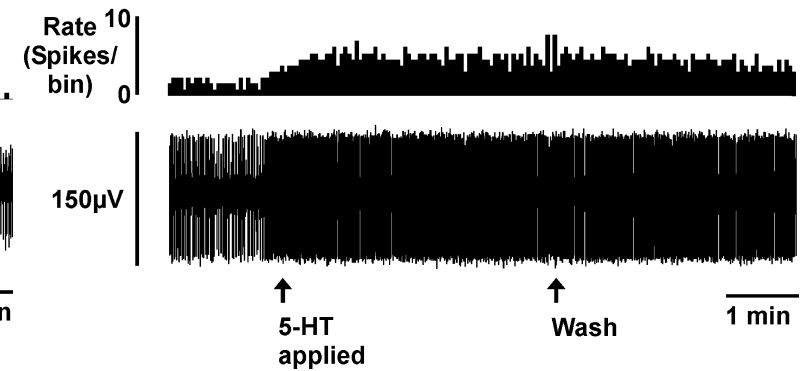
## Control



## Inflammation



## Recovery



# **COLONIC 5-HT RELEASE**

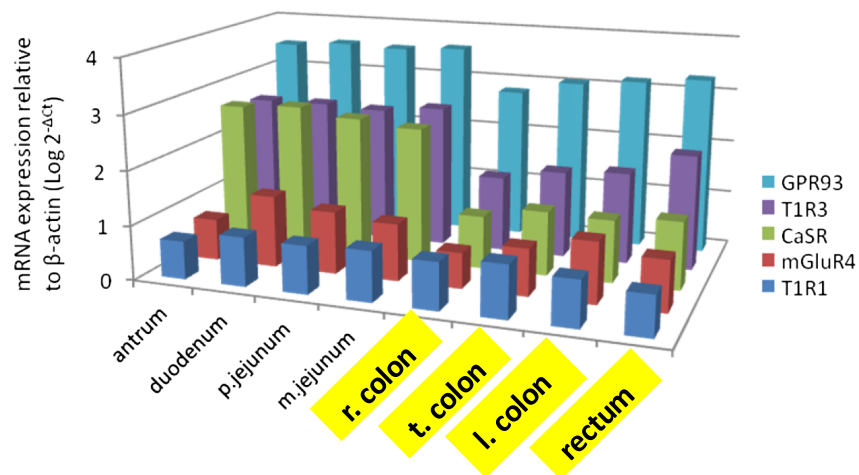
- **5-HT release is increased in IBS patients.**
- **5-HT can activate colonic afferents mainly via 5-HT<sub>3</sub> receptors.**
- **Following recovery from inflammation the response of afferent fibers to 5-HT is increased.**

**What luminal factors could stimulate release of 5-HT from epithelium?**

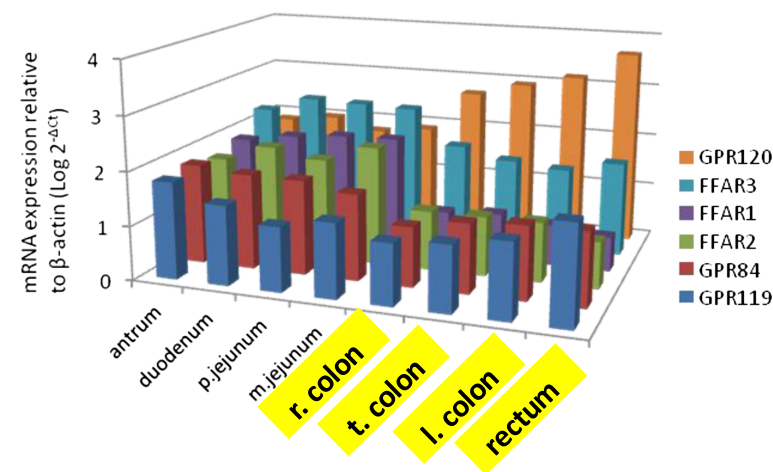
# NUTRIENT SENSING IN THE COLON

- Food is a common trigger for a large proportion of IBS patients
- Recent clinical studies highlight role of diet modification in treating IBS
- Can nutrients signal to colonic afferent nerves?

## Amino Acid Receptors

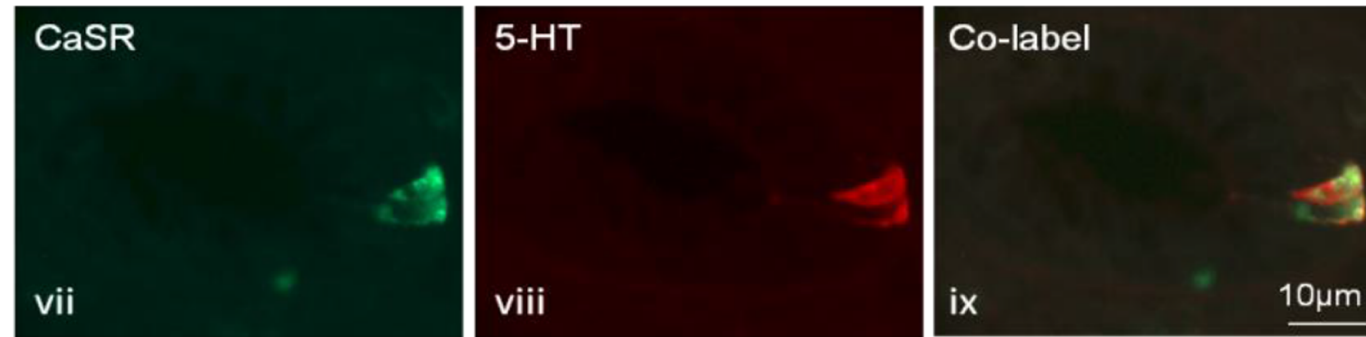


## Fatty Acid Receptors

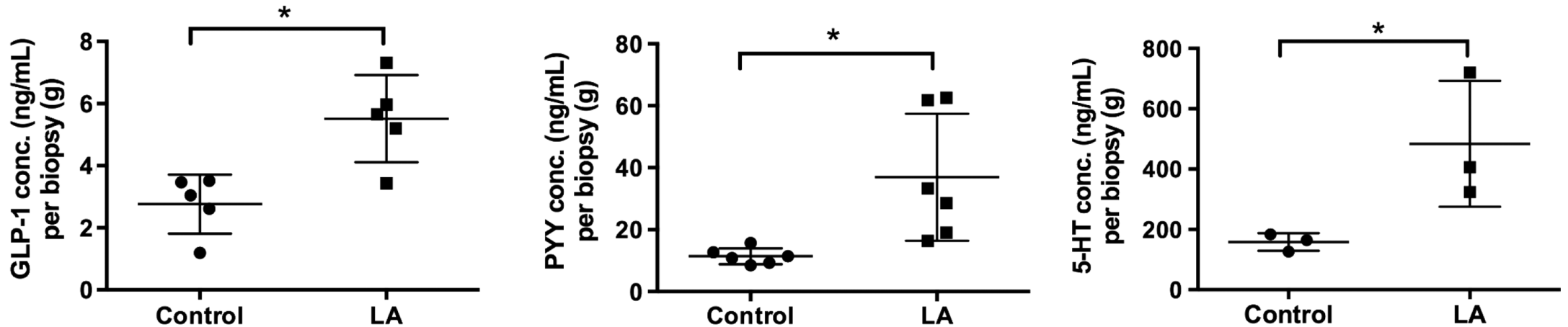


# NUTRIENT SENSING IN THE COLON

**A**

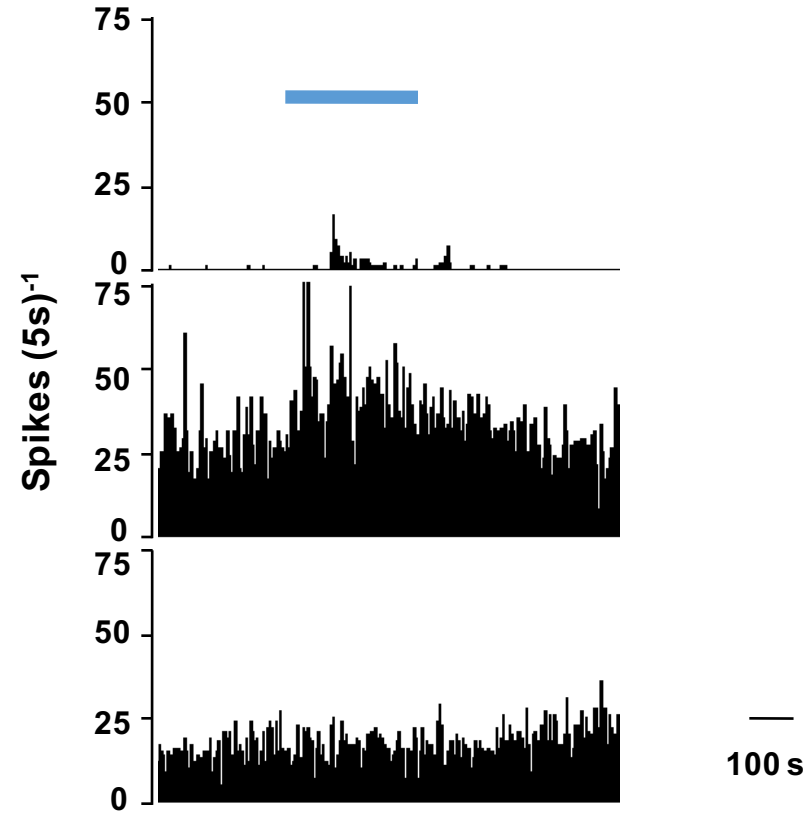
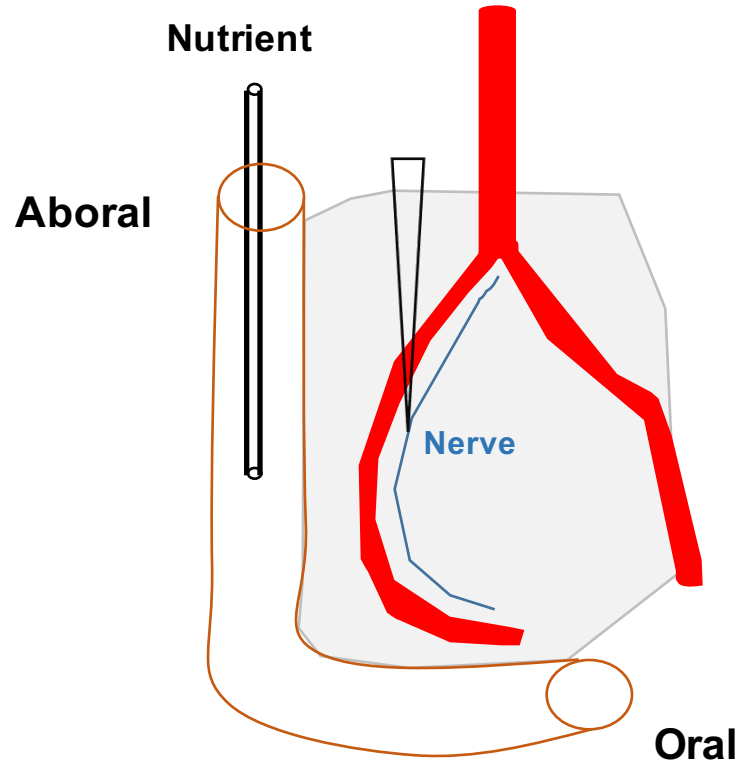


**B**



# NUTRIENT-NEURAL SIGNALING IN THE COLON

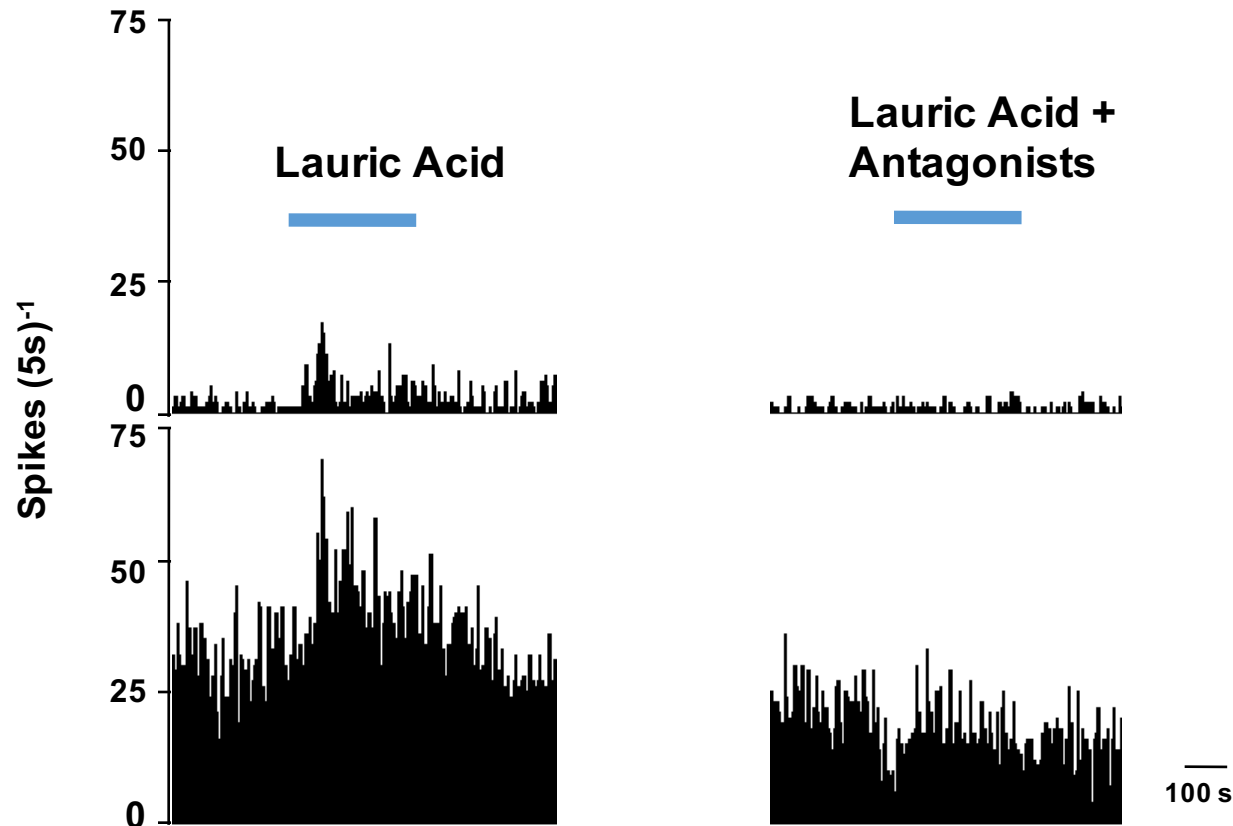
Lauric Acid 25mM



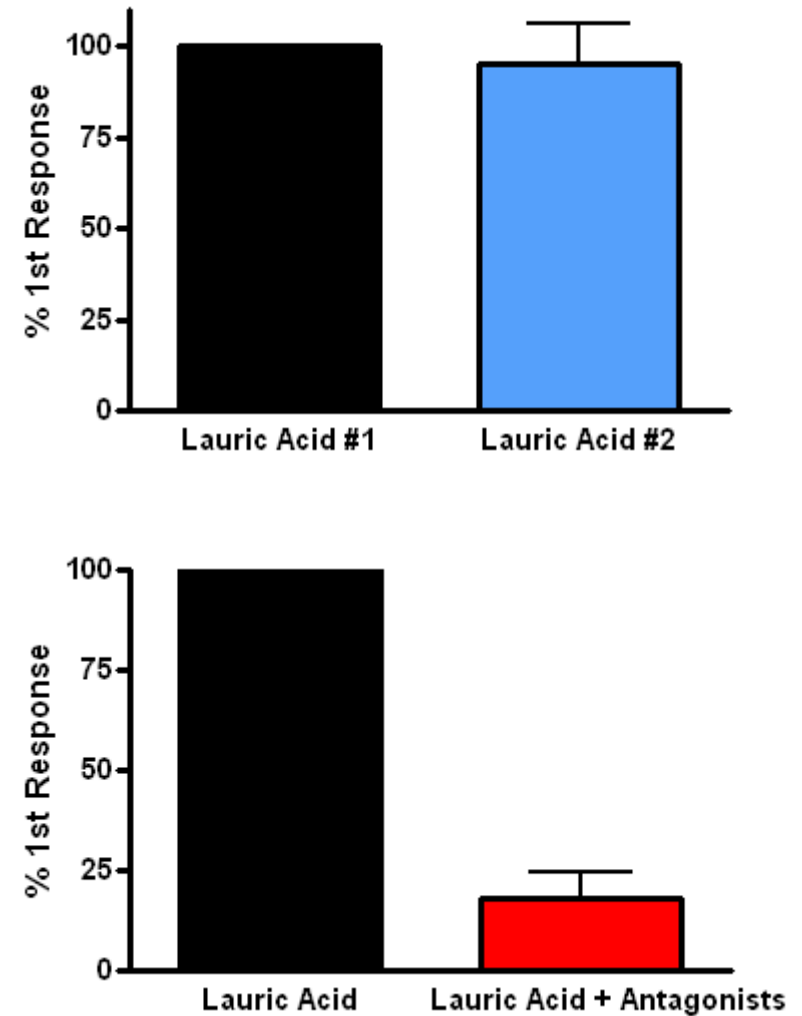
# NUTRIENT-NEURAL SIGNALING IN THE COLON

## Effect of Antagonists to 5-HT3/Y2/GLP-1 Receptors

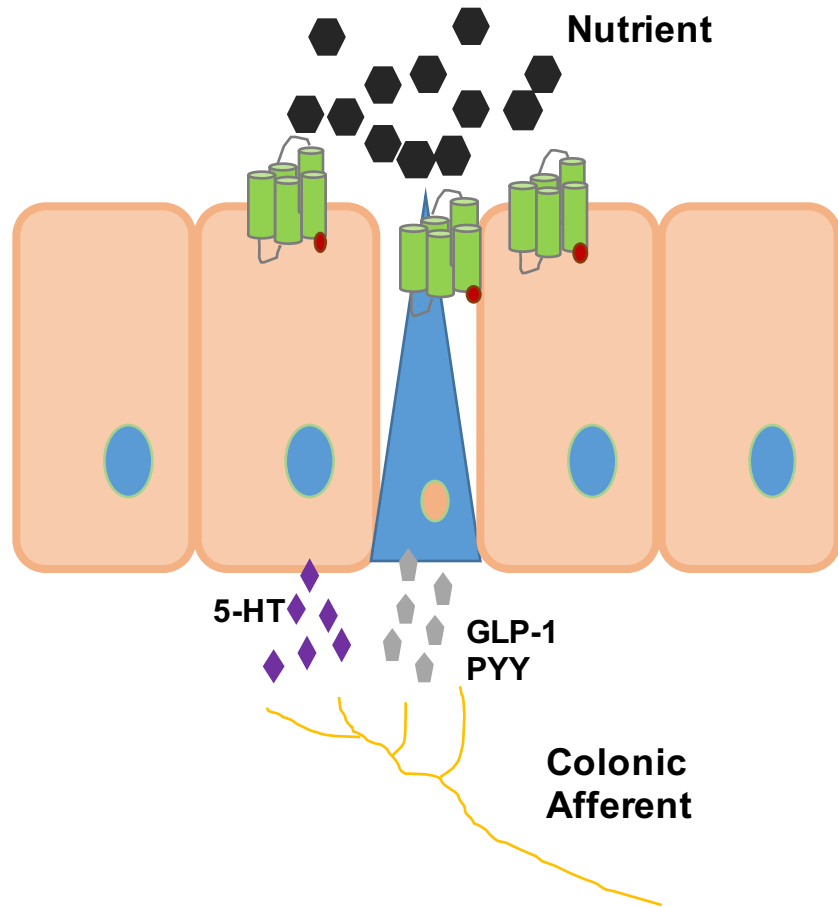
**A**



**B**



# NUTRIENT-NEURAL SIGNALING IN THE COLON



**Is the pathway altered in IBS?**

# **BILE ACID SIGNALING IN THE COLON**

- **~95% of bile acids absorbed in ileum**
- **A subpopulation of IBS patients have increased bile acids in the colon**
  - **Proportion of patients varies depending on method**
- **Most common side effect of bile acid transport inhibitors for constipation is abdominal pain**

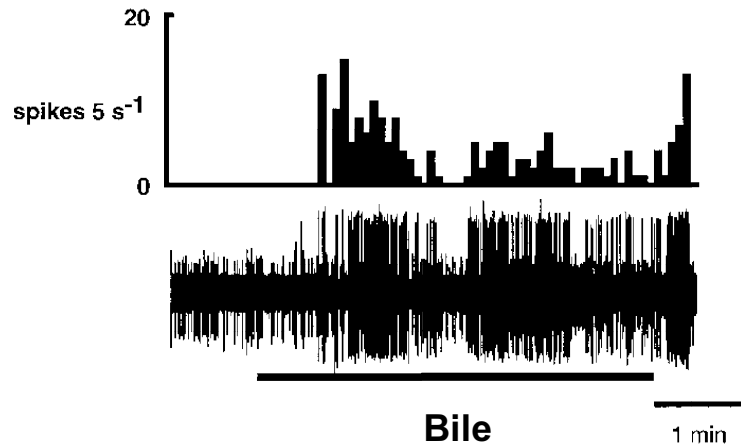
**Do bile acids signal to colonic afferent nerves?**



# BILE ACID SIGNALING IN THE COLON

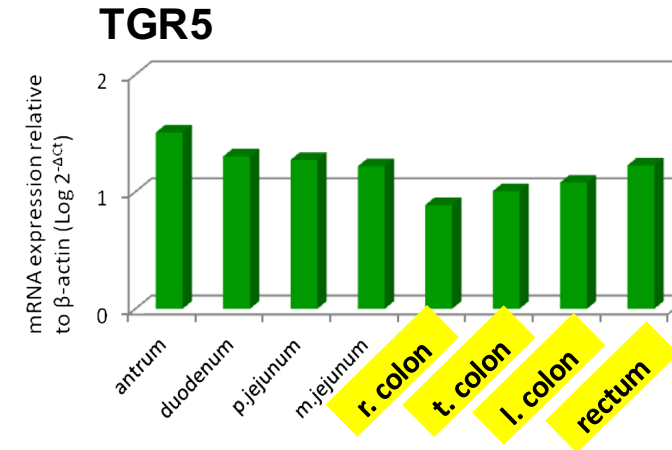
A

## Rat Distal Colon



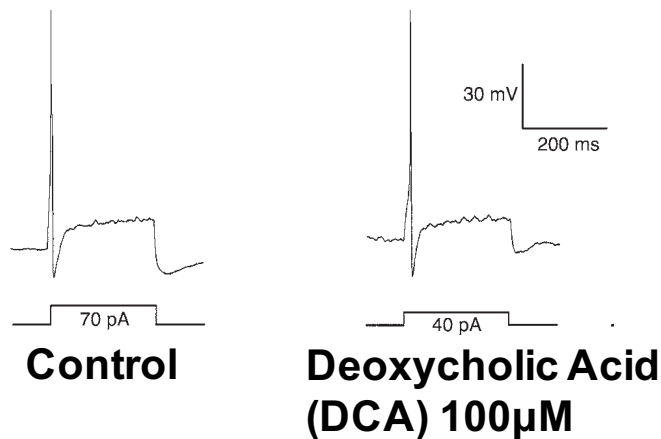
B

## Human Biopsy



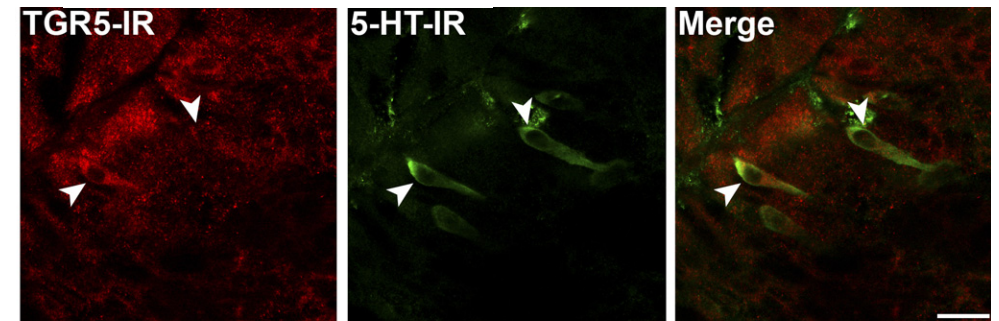
C

## Mouse DRG Neuron



D

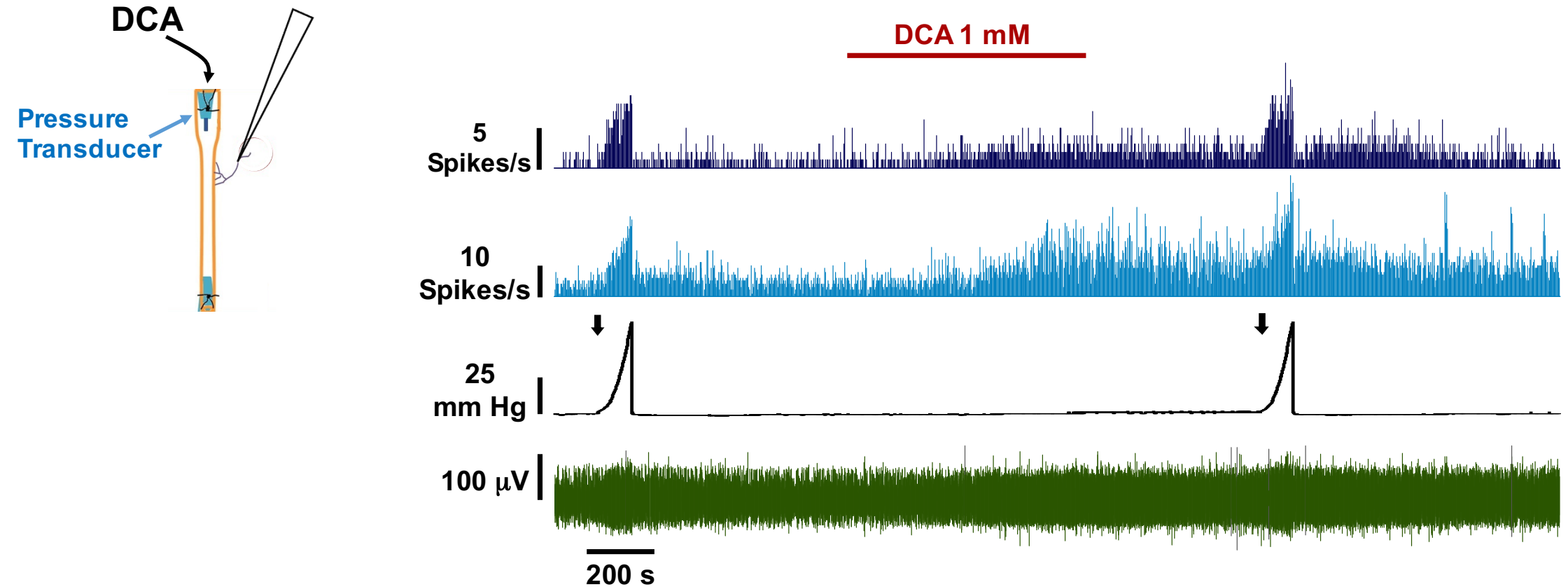
## Mouse Mucosa



Lynn and Blackshaw *J Physiol.* **518**:271-82  
Symonds, Peiris et al *Gut* **64**:618-26  
Alemi et al *J Clin Invest* **123**:1513-30  
Alemi et al *Gastroenterology* **144**:145-54

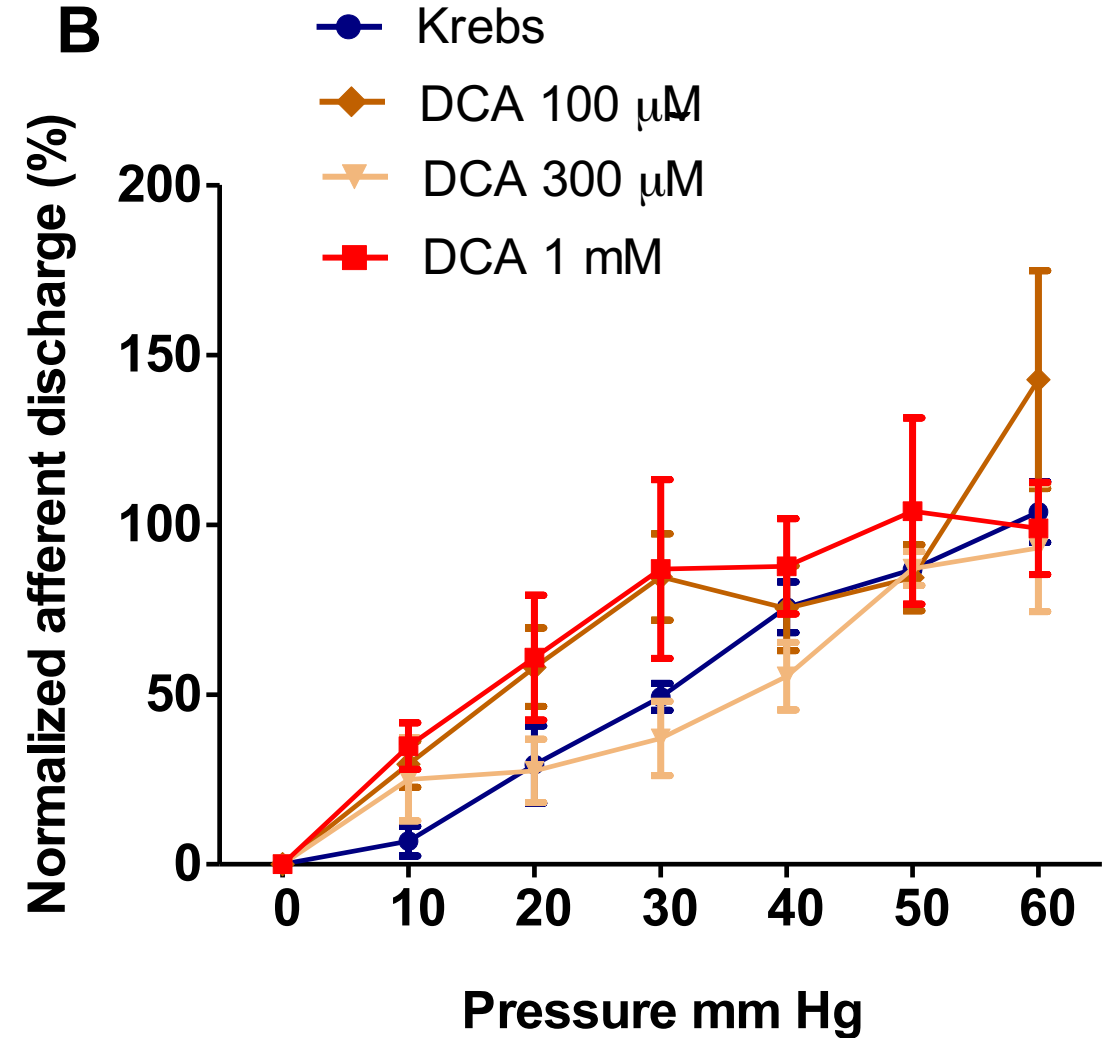
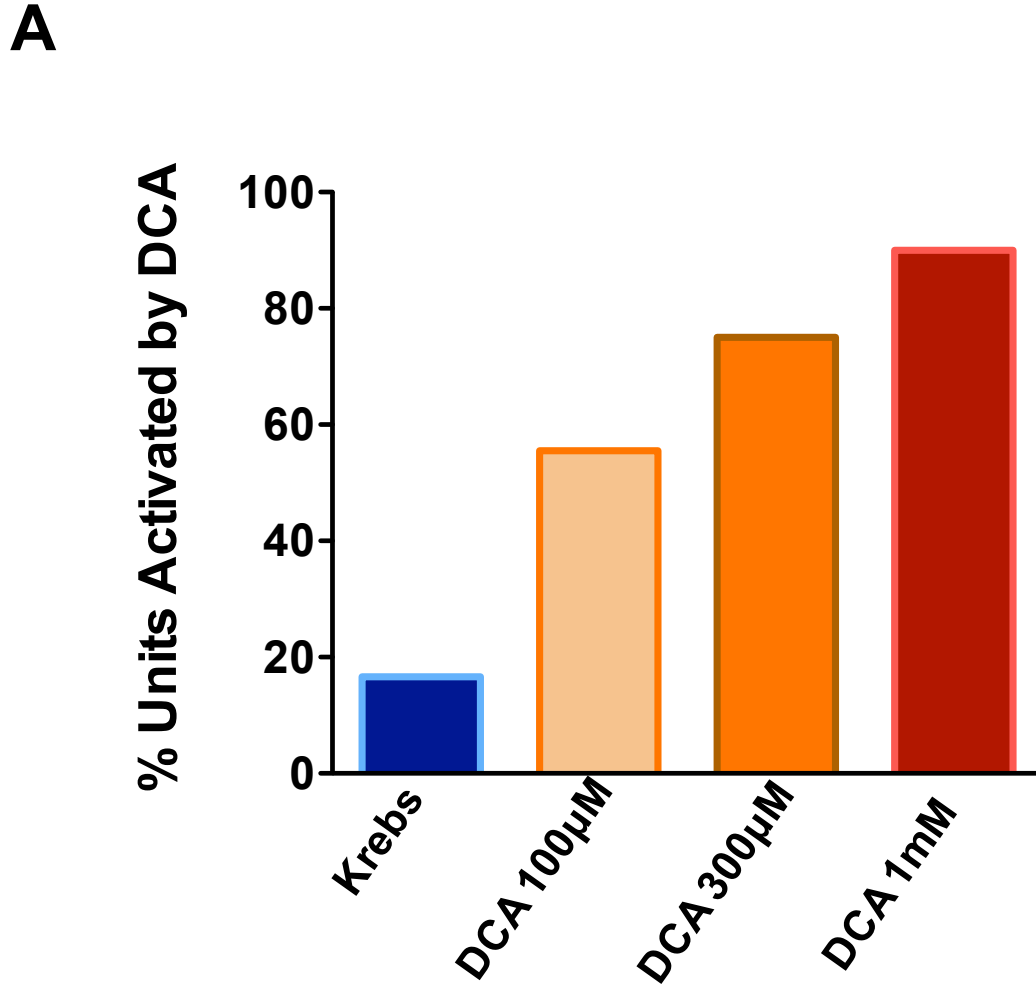
# BILE ACID SIGNALING IN THE COLON

## Deoxycholic Acid (DCA) – TGR5 Agonist



# BILE ACID SIGNALING IN THE COLON

## Deoxycholic Acid (DCA) – TGR5 Agonist



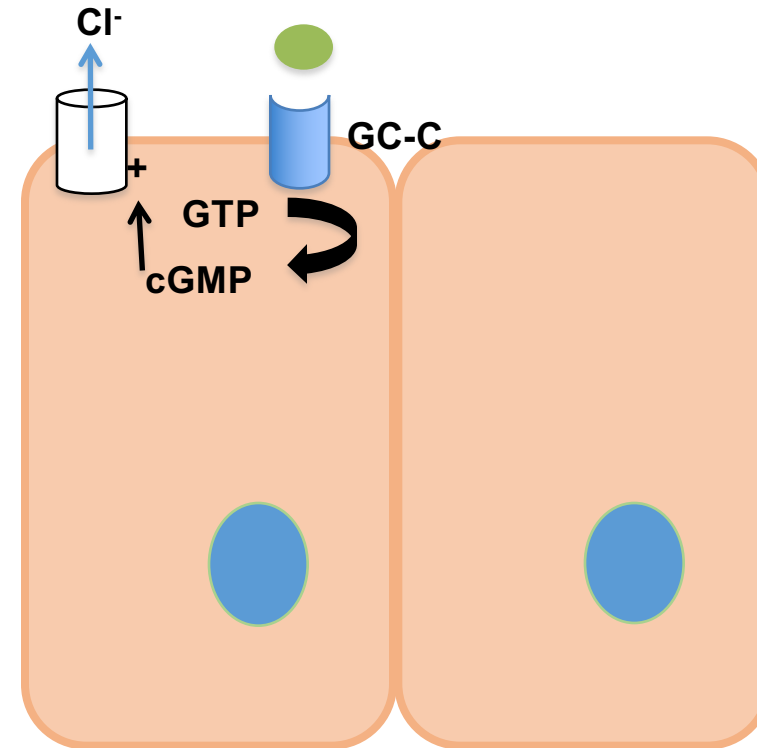
# **BILE ACID SIGNALING IN THE COLON**

- **Bile and bile acids can activate colonic afferents in the proximal and distal colon**
- **Activation may be direct (i.e. activation of nerve terminal) or indirect via release of mediator**
- **Excess bile acids may contribute to abdominal pain in subpopulation of IBS patients**

# LUMINAL INHIBITORY SIGNALING

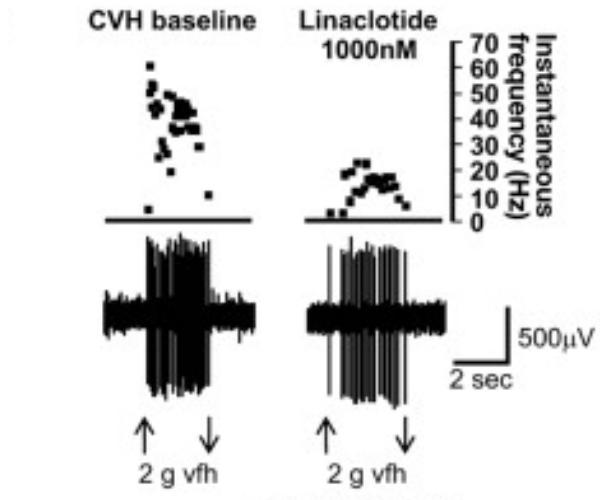
- Activation of guanylate cyclase C (GC-C) on luminal surface increases chloride secretion
- Linaclootide, GC-C agonist, reduces abdominal pain in patients with IBS-C

↓  
Mechanism?

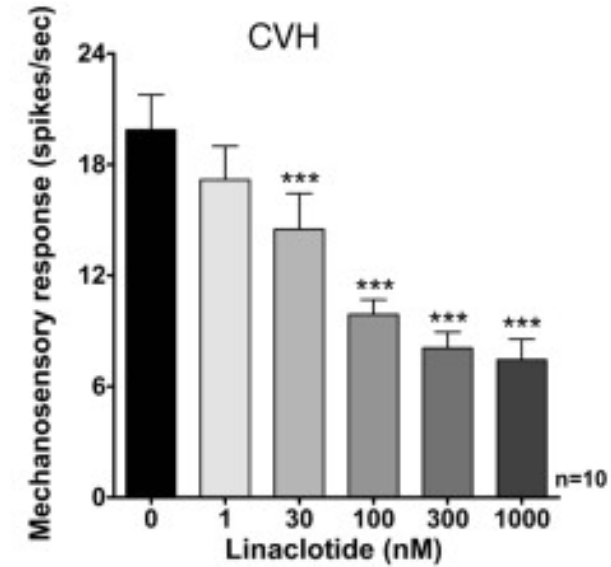


# cGMP INHIBITION OF COLONIC AFFERENTS

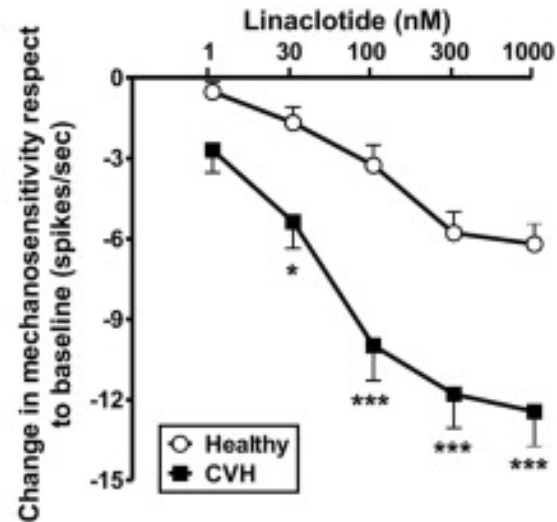
A



B

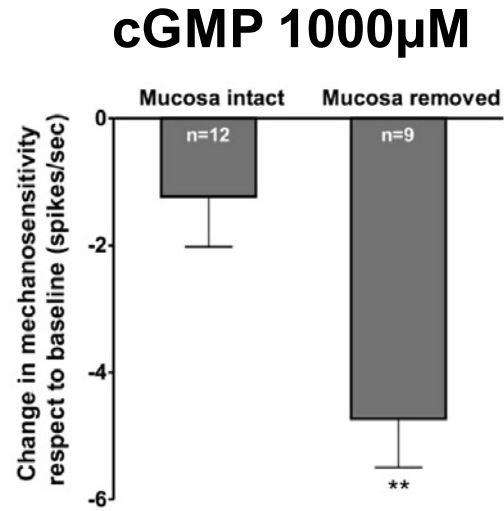


C

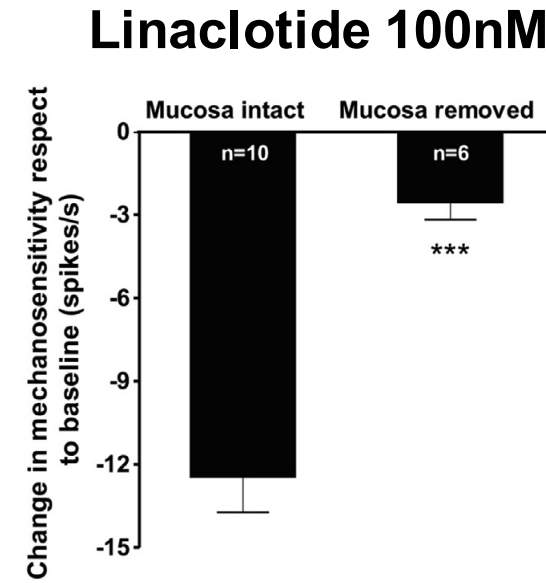


# LINACLOTIDE AND EPITHELIAL cGMP

**A**

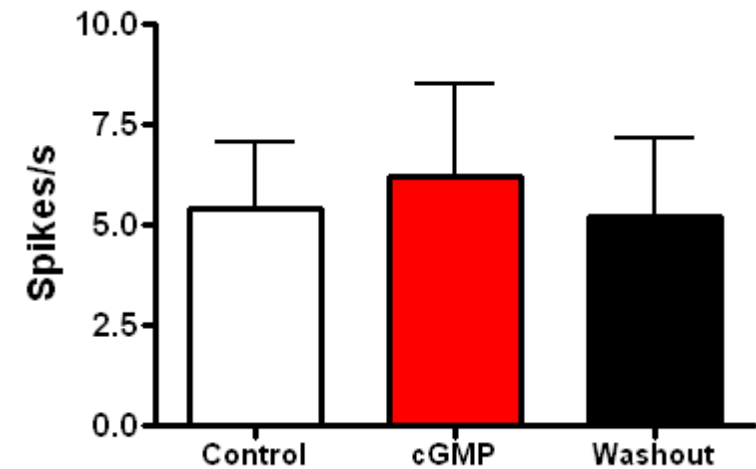
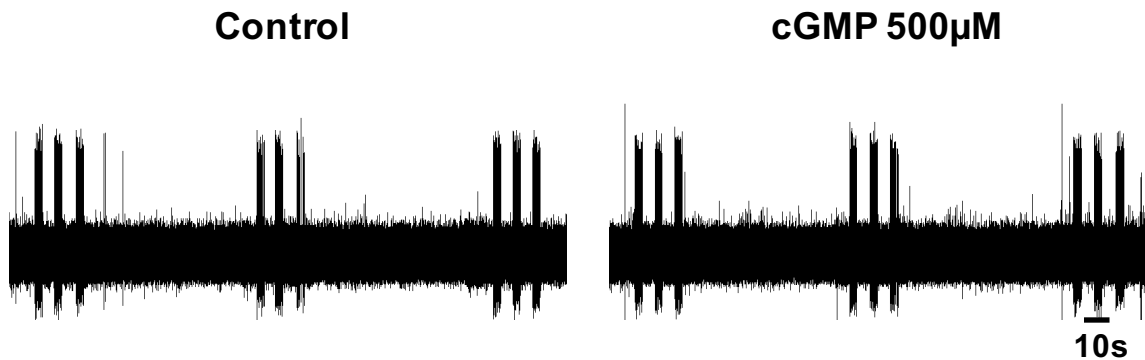
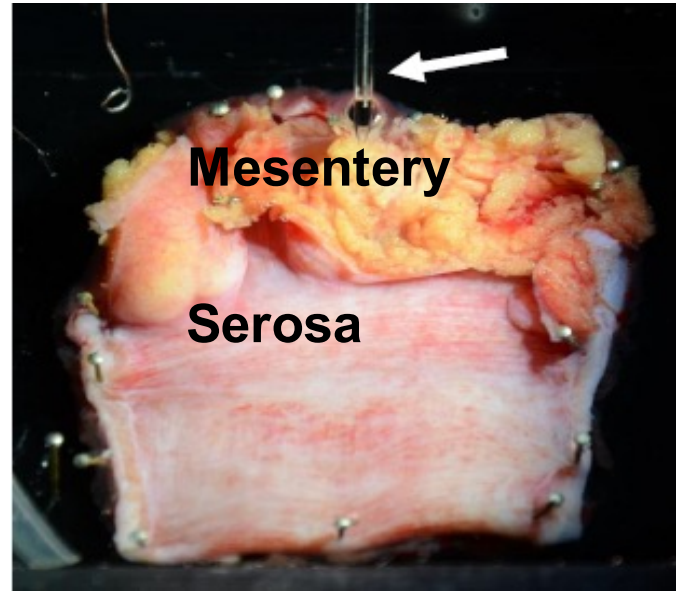


**B**



**Similar mechanism in human afferent nerves?**

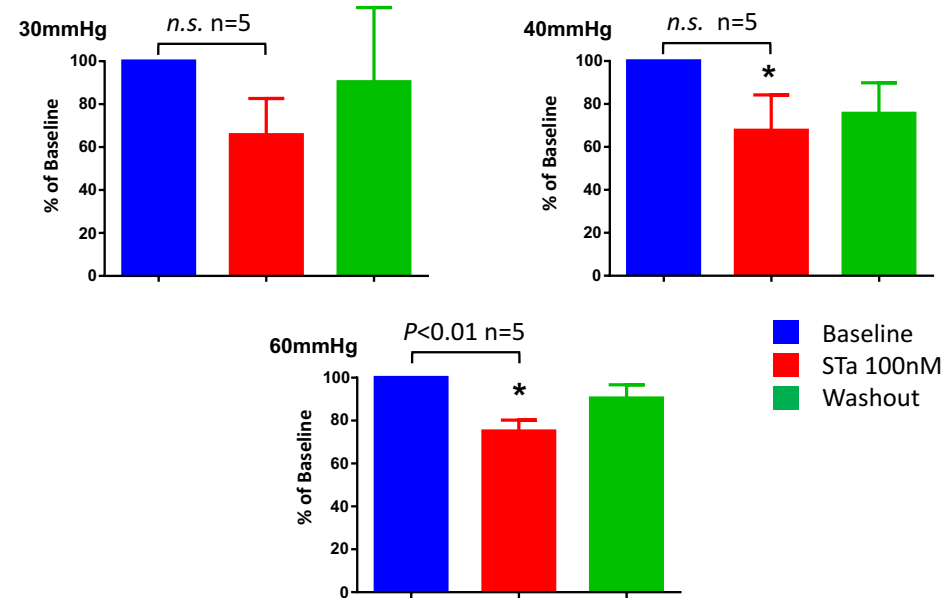
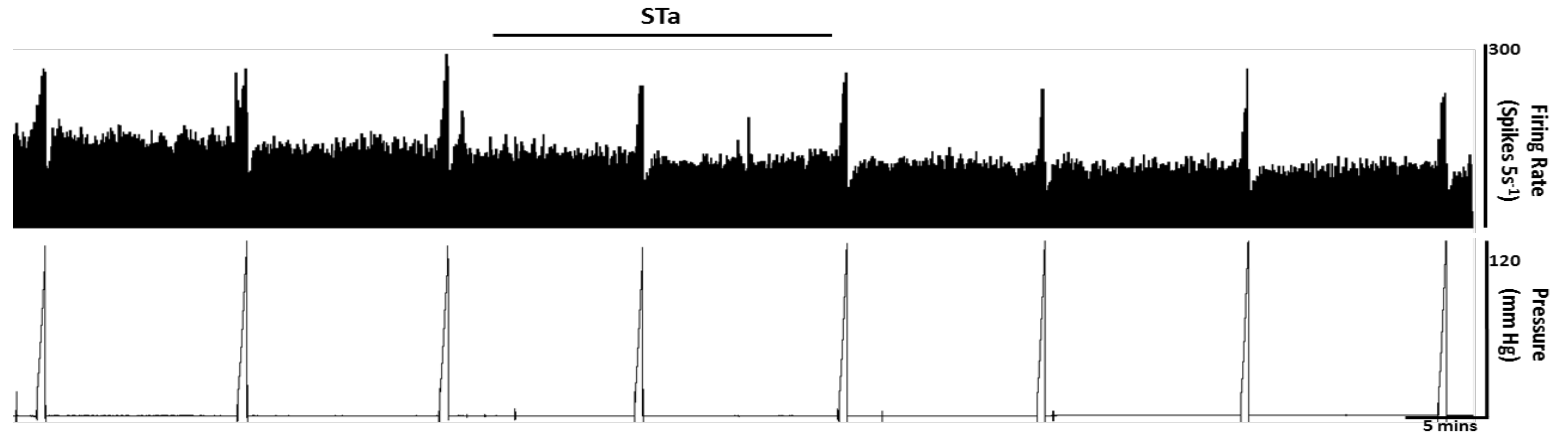
# cGMP INHIBITION OF HUMAN COLONIC AFFERENTS





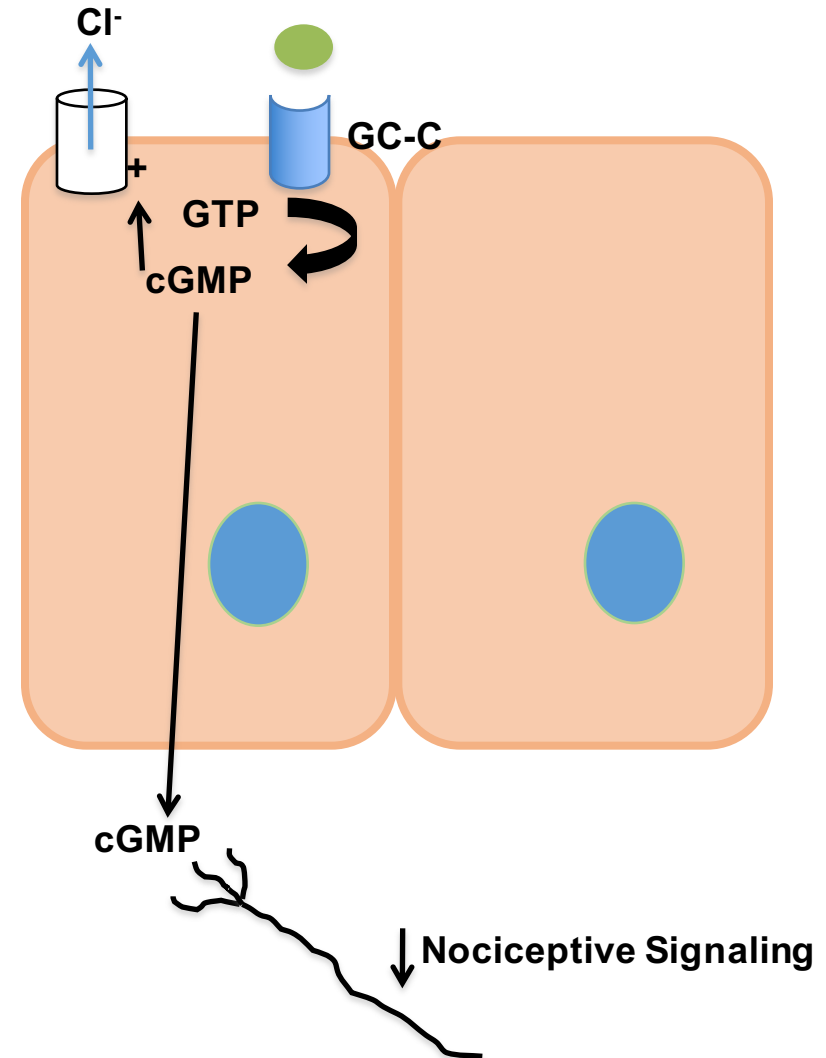
# cGMP INHIBITION OF HUMAN COLONIC AFFERENTS

## Human Appendix



# cGMP INHIBITION OF COLONIC AFFERENTS

- GC-C agonists bind to GC-C to increase cGMP.
- cGMP is released extracellularly to reduce mechanosensitive colonic afferents signaling.
- GC-C agonists cause greater inhibition than exogenous cGMP.



# **SUMMARY**

- **Enteroendocrine cells release mediators (e.g. 5-HT) that can activate extrinsic afferent nerves**
- **Luminal factors (nutrients, bile acids) can activate colonic afferents, in part by release of enteroendocrine mediators**
  - **Meal induced symptoms in IBS**
  - **Increase bile acids in IBS patients**
- **Inhibitory lumen-to-nerve pathway via guanylate cyclase C activation**

# **ACKNOWLEDGEMENTS**

**Ms. Egina Villalobos-Hernandez**

**Dr. Michael Beyak**

**Prof. Ashley Blackshaw**

**Dr. David Bulmer**

**Dr. Cian McGuire**

**Dr. Madusha Peiris**

**Mr. Adam Broadhead**

**CIHR/CAG/CCC Fellowship**