Plasticity in Vagal Afferent Neurons: Nutrient and Microbial Drivers

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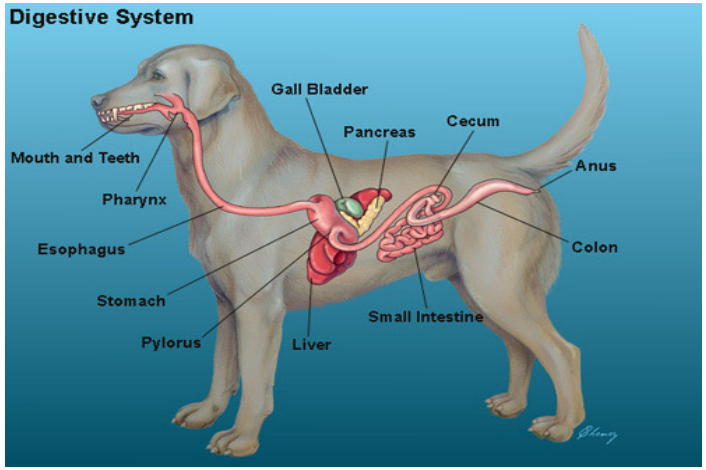
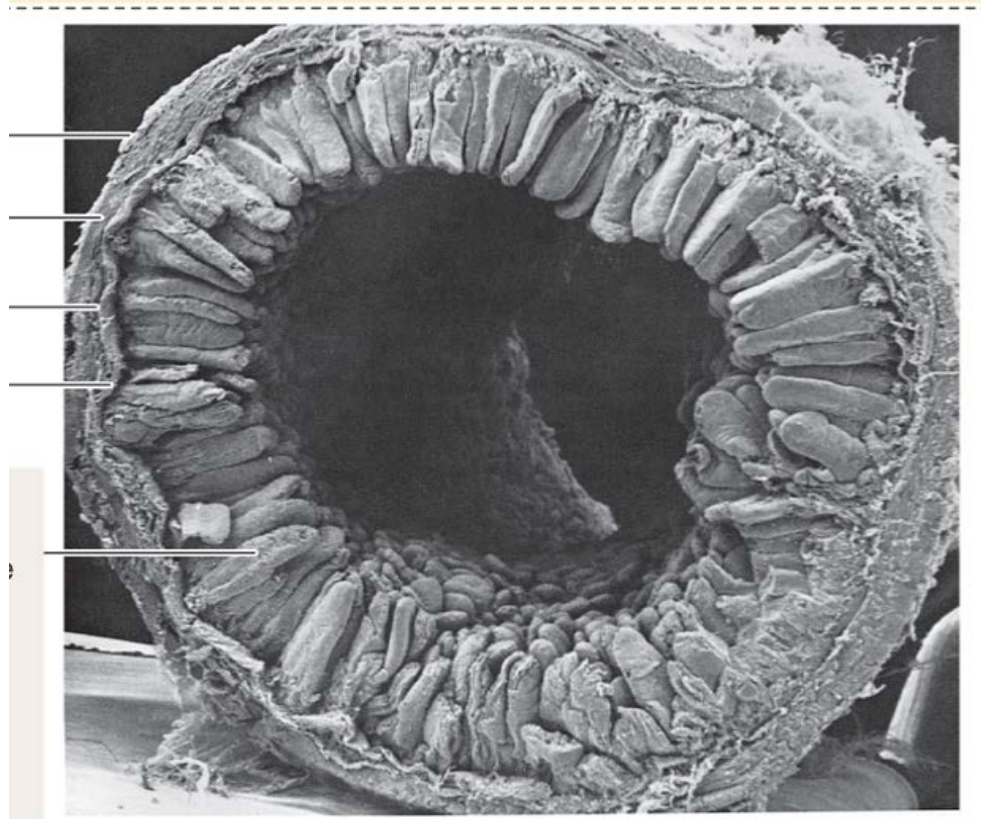


The Gastrointestinal Tract - a sensory organ

- Intake, digestion and absorption of nutrients and water.
- Largest immune and endocrine organ in the body.
- Regulates food intake and glucose homeostasis.
- Largest interface between outside and inside world.

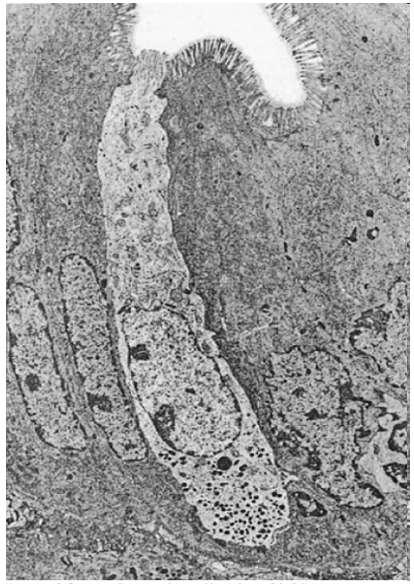


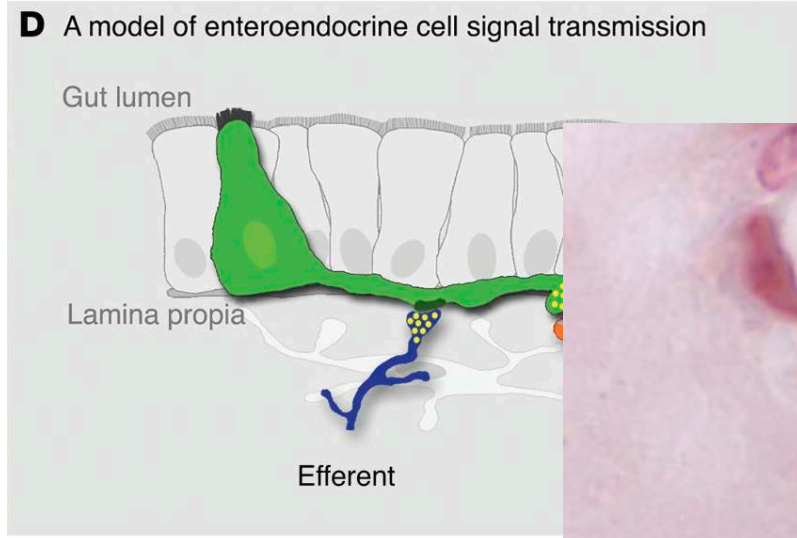
nning electron micrograph from Kessel RG, Kardon RH: Tissues and Organs. New York, WH Freeman, 1979.

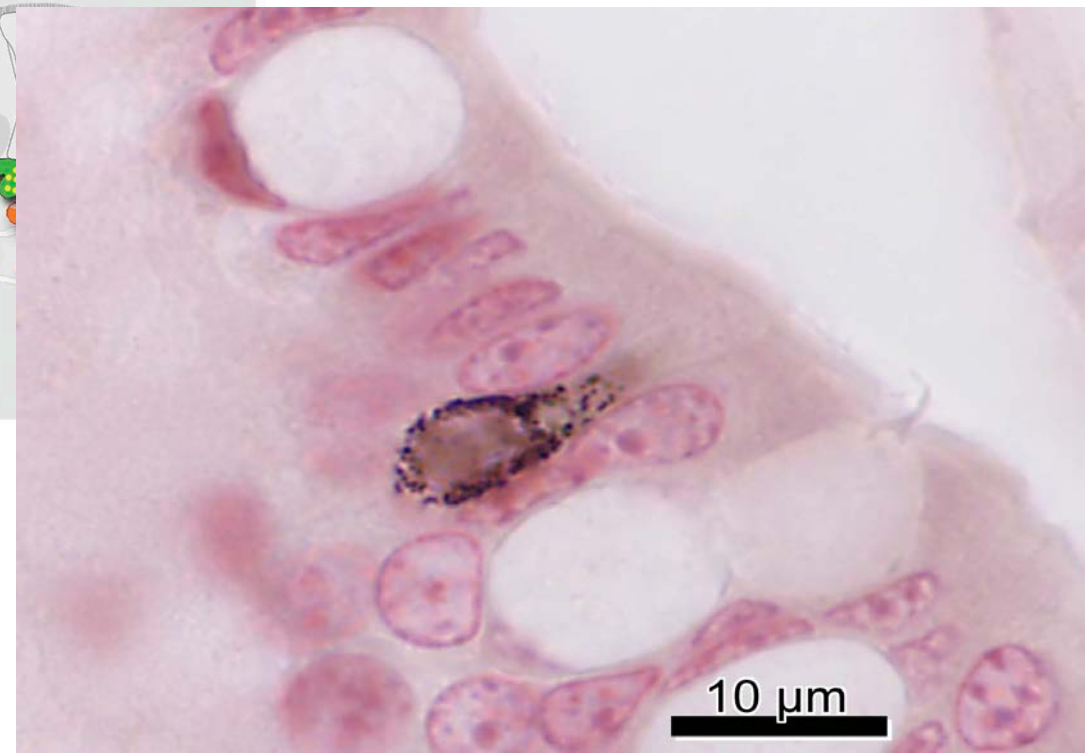
enbaum: Histology and Cell Biology: An Introduction to Pathology 2e - www.studentconsult.com

GI Tract is a Sensory Organ

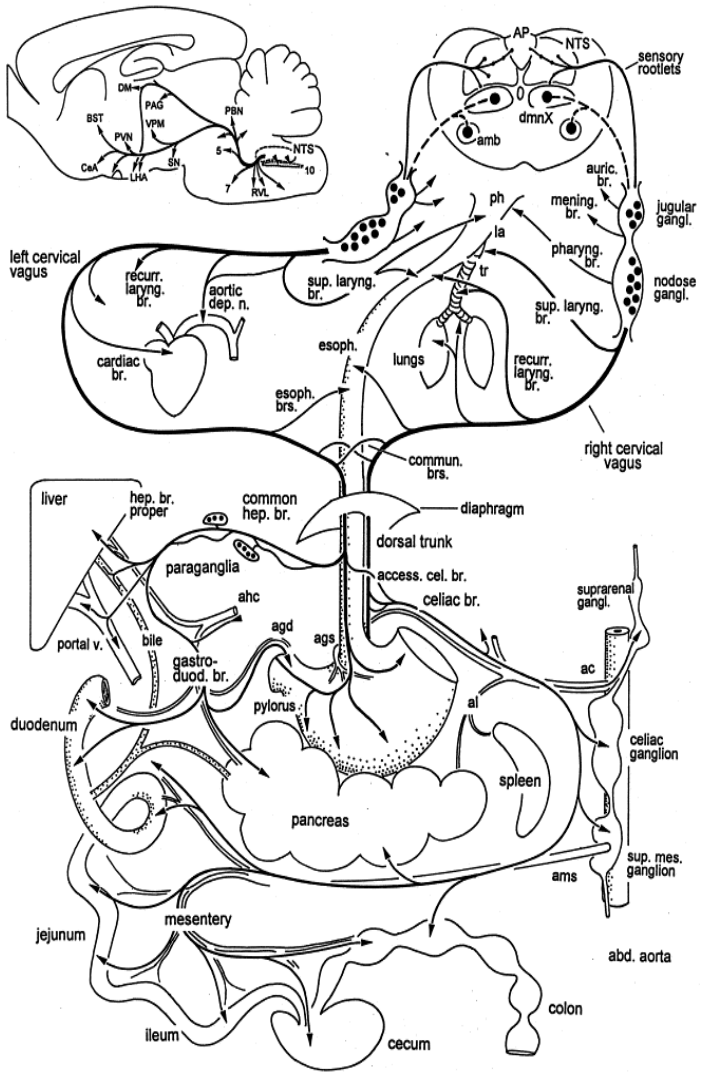
- Epithelium detects luminal signals –most epithelial cells can sense physiological parameters
- Nutrient and non-nutrient chemicals (toxins and bacterial factors)
- Specialized chemosensing cells (enteroendocrine cells, enterochromaffin cells and brush cells)







Schematic representation of the gross anatomical distribution of the vagus nerve

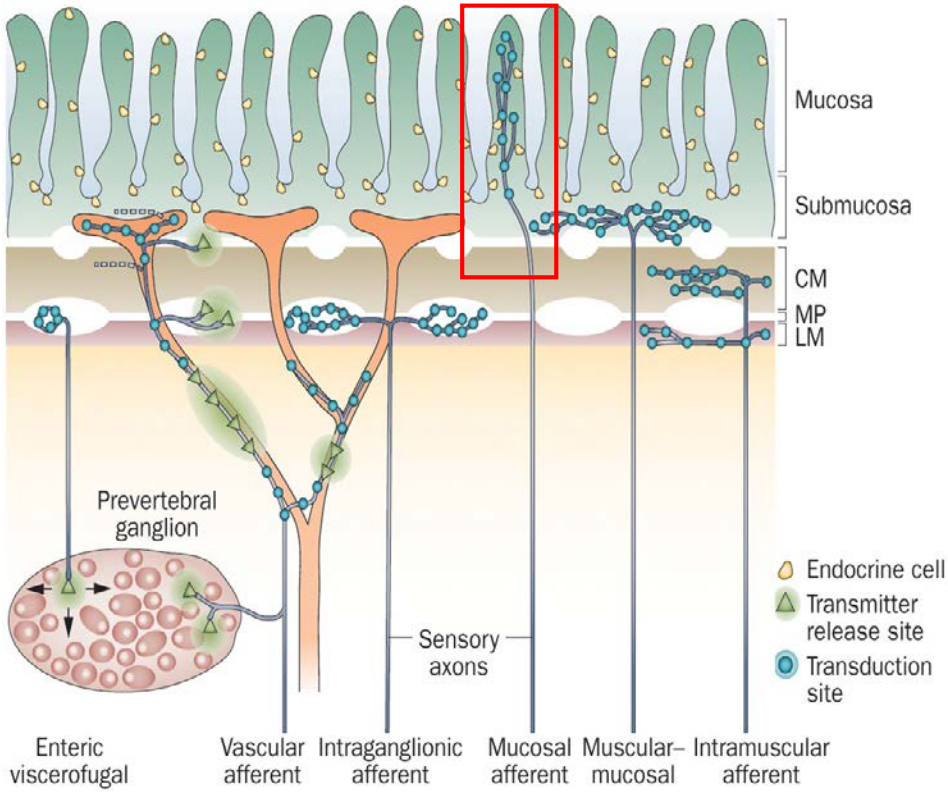


From: Berthoud and Neuhuber, Autonomic Neuroscience, 2000

1. Vagal afferent neurons innervate most of the gut – less dense innervation in the small and large intestine but is present and functionally important.
2. These afferents terminate in all levels of the gut wall.
3. Send information to the brain to regulate gut function via activation of reflexes and information sent to higher brain centers to regulate behavior
4. Adequate stimuli are both chemical and mechanical
5. Afferent activity can lead to conscious sensations (hunger, satiation, nausea) but mostly not perceived (information about digestive state and generation of reflexes)

In general, even conscious sensations are not finely grained – large receptive fields, respond to systemic circulating stimuli

Classification of extrinsic sensory neurons to the gut: morphology and electrophysiology



Mucosal Afferents

Morphology – two types:

- in villus, branching and located underneath the epithelial cell layer (cf Powley)
- surrounding the crypts and do not penetrate the villus

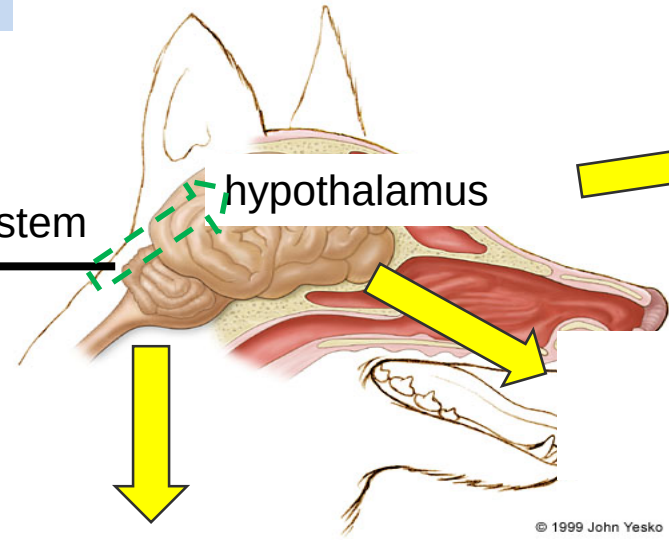
Electrophysiology – one or many:

- Sensitive to light stroking of the mucosa – no activity at rest but activated by inflammatory stimuli.
- Insensitive to contractions and stretch.
- ***Chemosensitive*** – activated by gut hormones and other mediators

Brookes, S. J. H. *et al.* (2013) Extrinsic primary afferent signalling in the gut *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2013.29

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

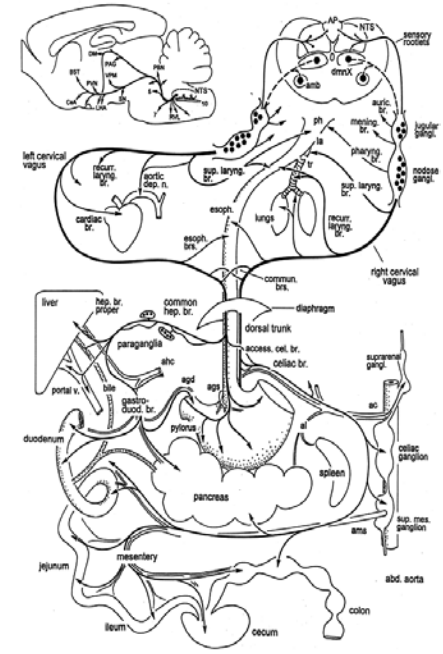
Gut-Brain Axis: Activation of Vagal Afferent Pathway



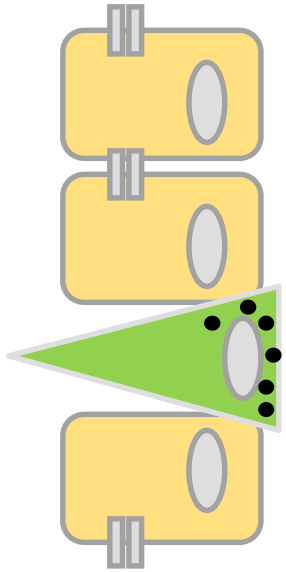
Higher brain function
change in behavior

Vagal afferent neurons
transmission to CNS

Parasympathetic efferent outflow
change in effector function

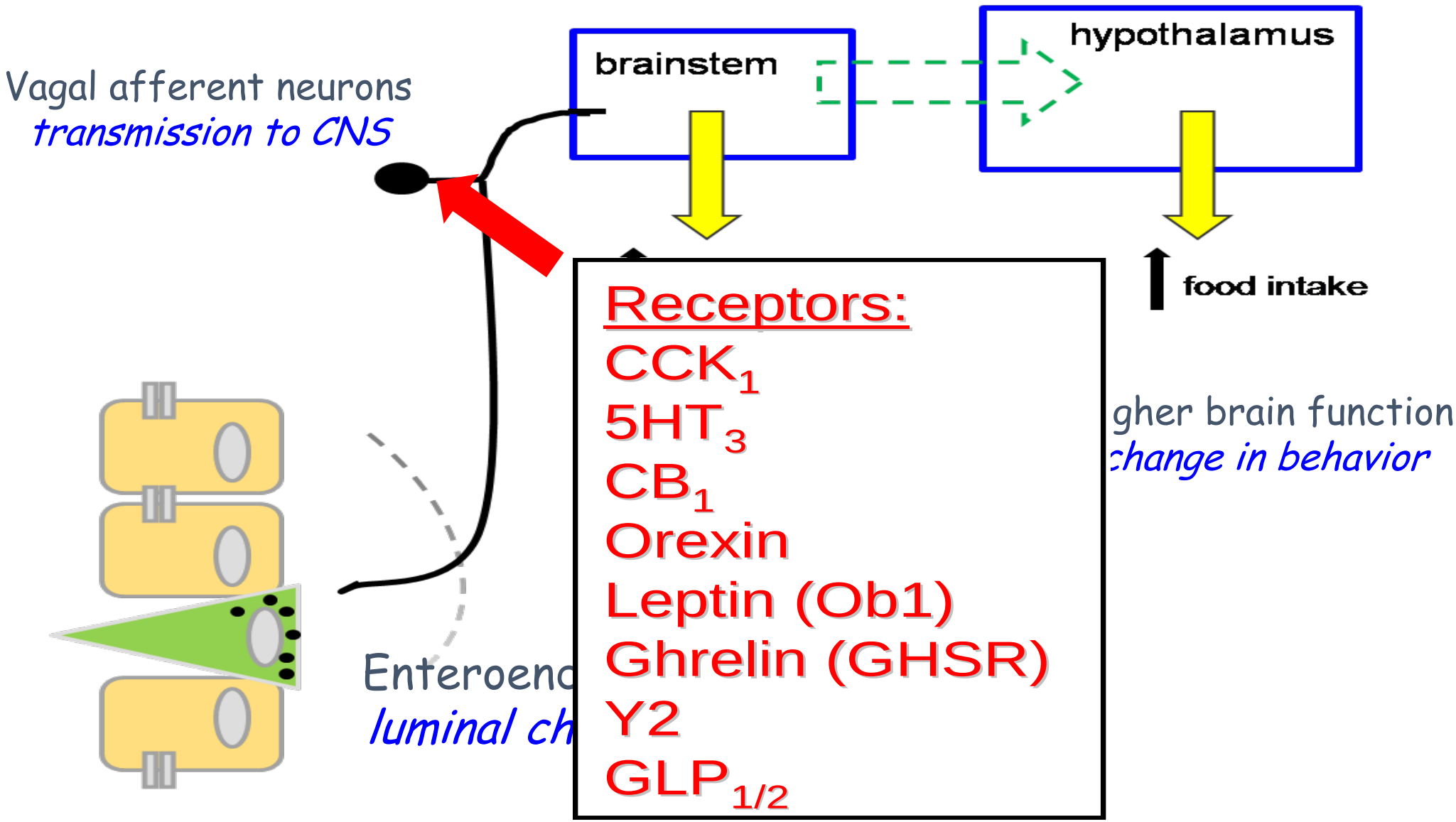


GUT LUMEN



Enteroendocrine cells
luminal chemosensors

Gut-Brain Axis: Regulation of GI Function and Food Intake



Acute Changes in Phenotype

Nutrient availability alters *receptor* expression in vagal afferents

Y2 receptor

MCH1 receptor

CB1 receptor

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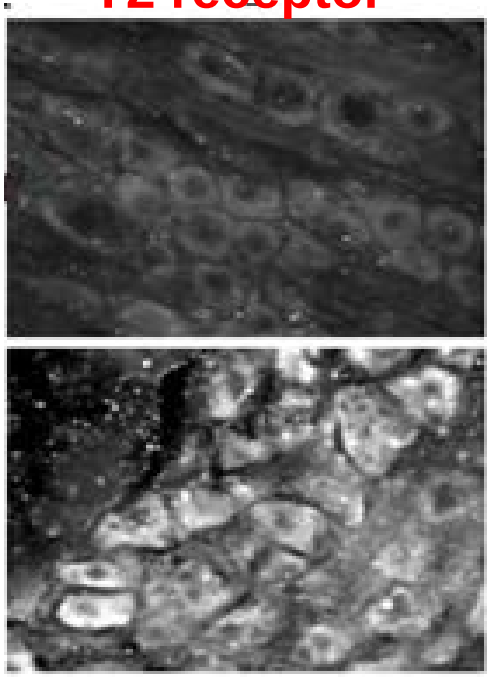
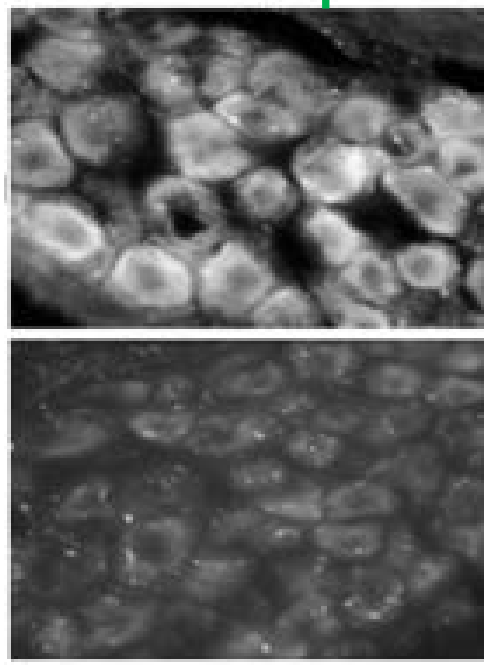
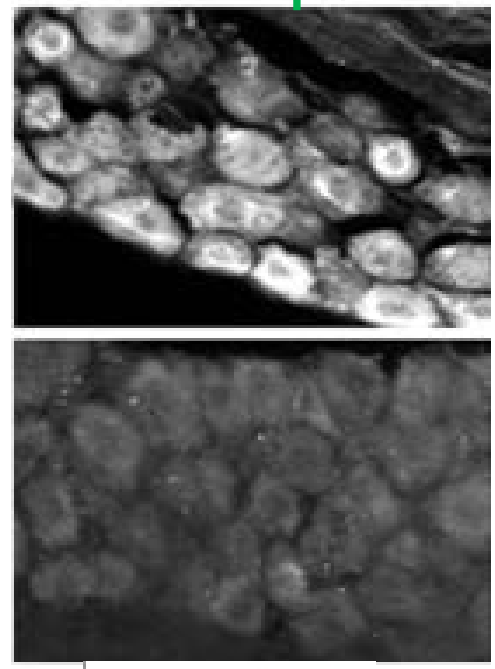
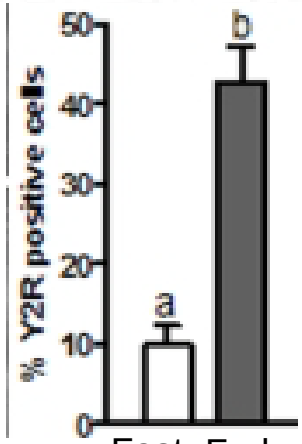
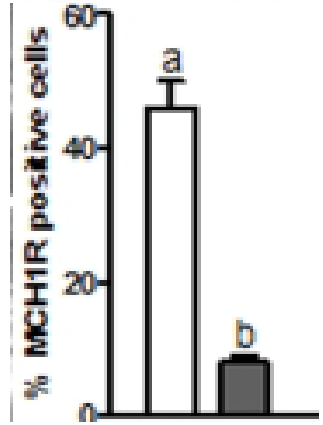
Fed

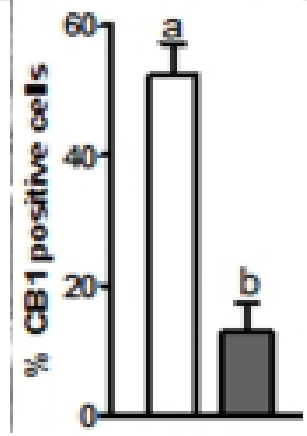












Acute Changes in Phenotype:

Nutrient availability alters *peptide* expression in vagal afferents

CART

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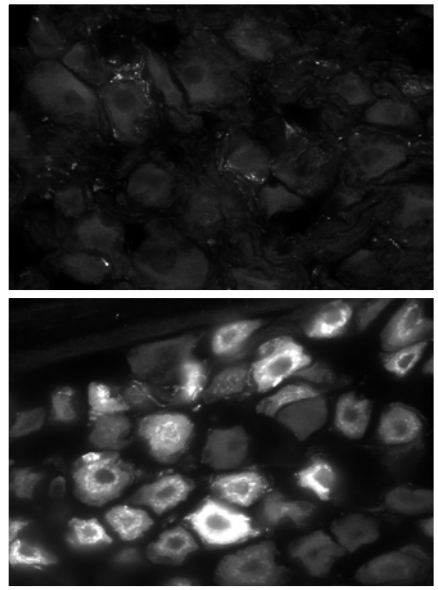

MCH

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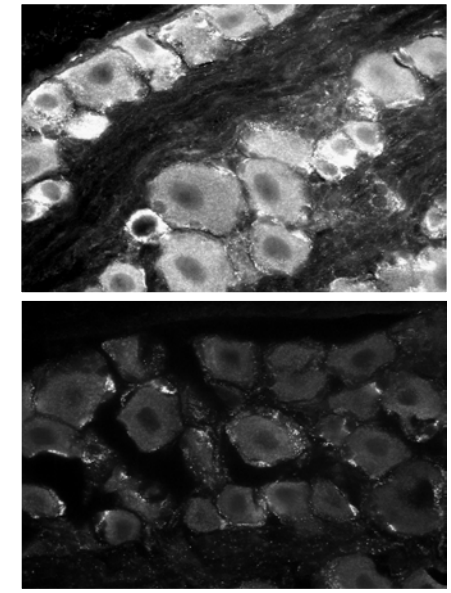
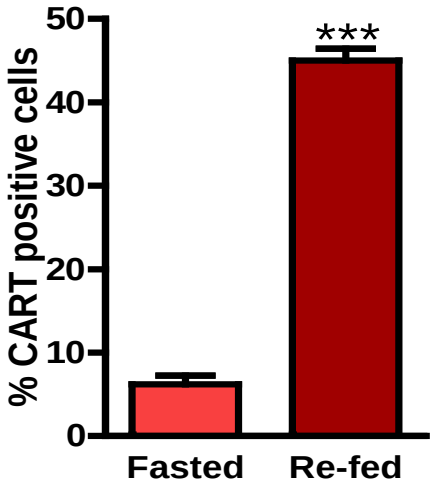
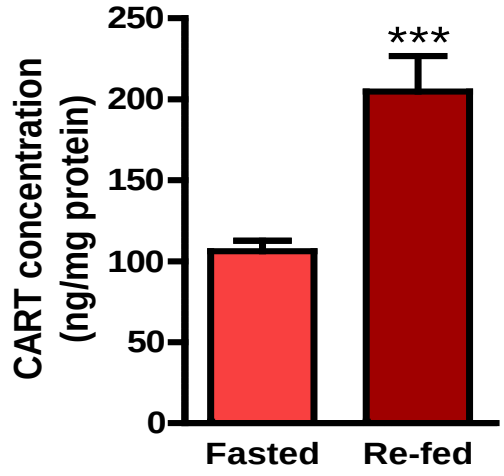
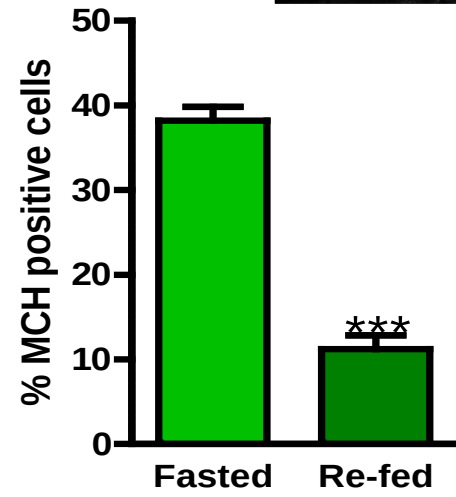
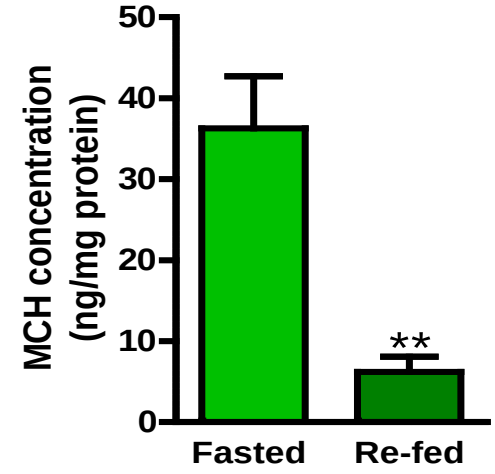
Fed



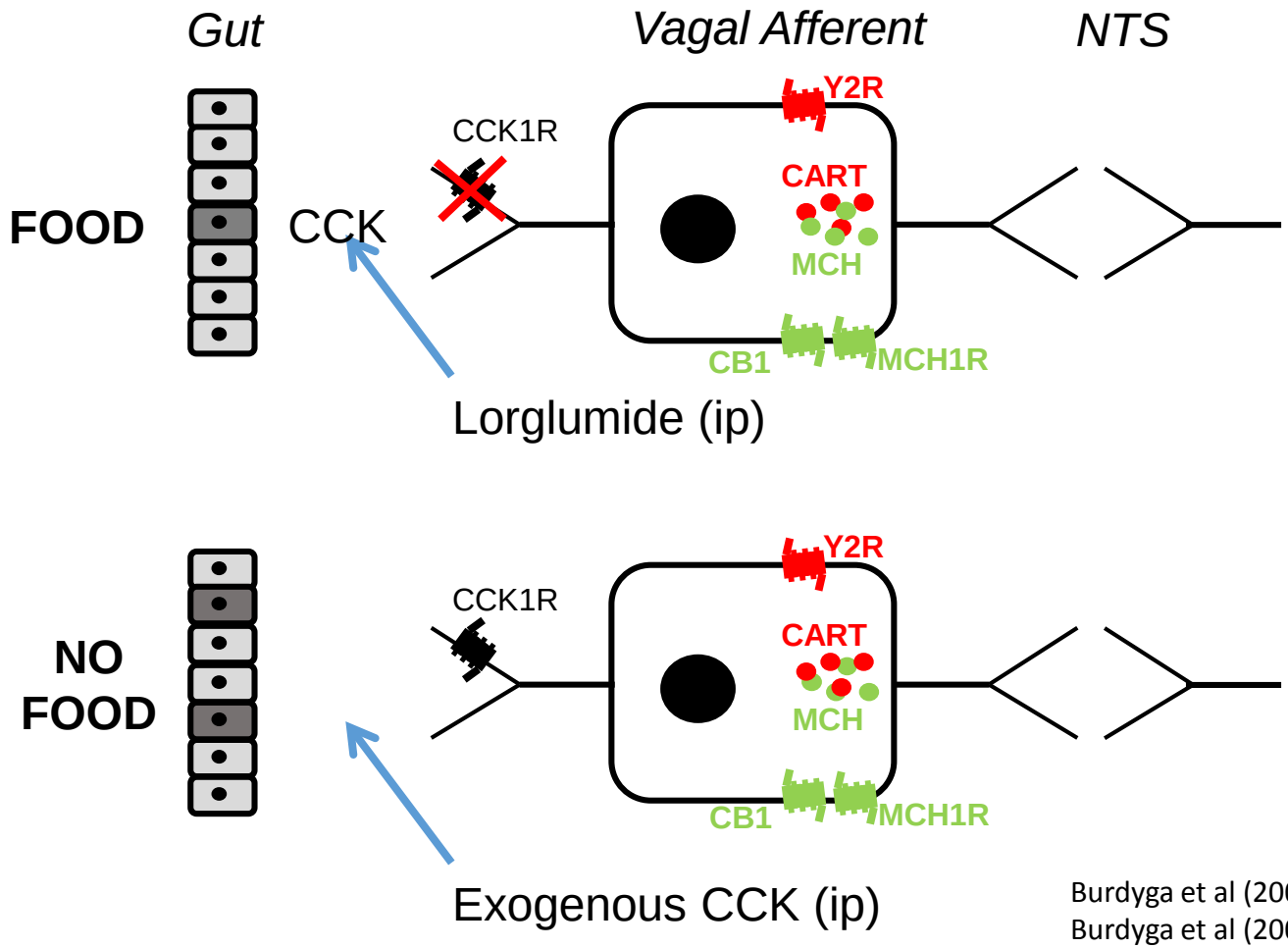








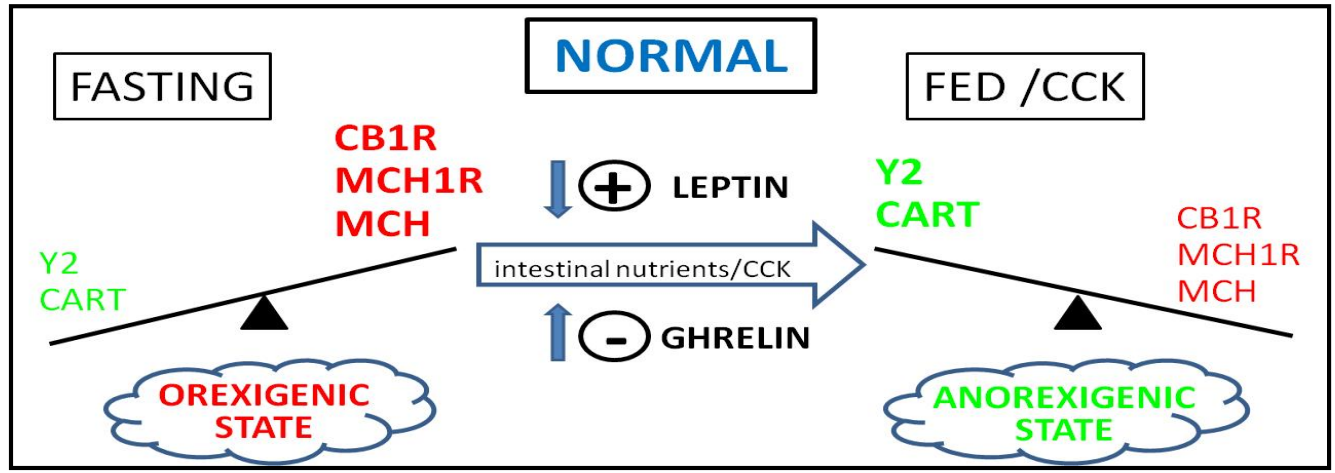
The neurochemical switch of vagal afferent neurons is regulated by cholecystokinin (CCK)



Burdyga et al (2004) *J Neurosci*;
Burdyga et al (2006) *Neuroscience*
Burdyga et al (2006) *AJP Gastrointest Liver Physiol*
Burdyga et al (2008) *J Neurosci*
de Lartigue et al (2007) J Neurosci

Feeding-Induced Phenotypic Change of Vagal Afferent Neurons

- *Dependent on feeding status (CCK)*
- *Potentiated by leptin*
- *Inhibited by ghrelin*



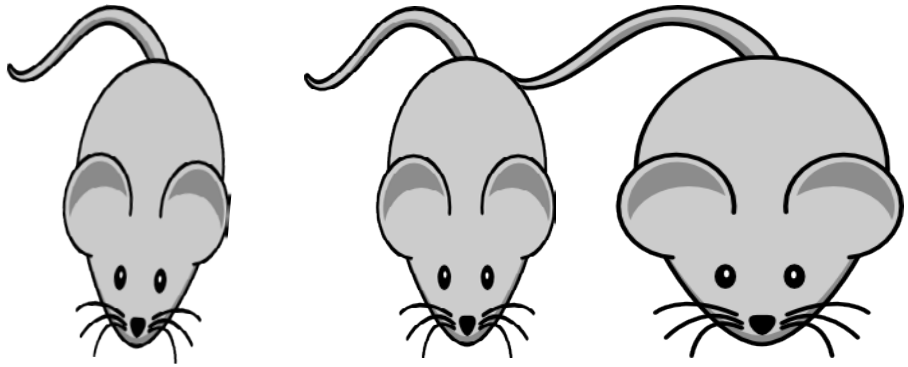
Lack of intestinal satiety signaling leads to increase in meal size and hyperphagia

Has been demonstrated in human studies of obesity (Westerterp-Plantega, Feinle-Bisset)

Diet-Induced Obesity in Sprague-Dawley Rats

Low fat diet

High fat diet

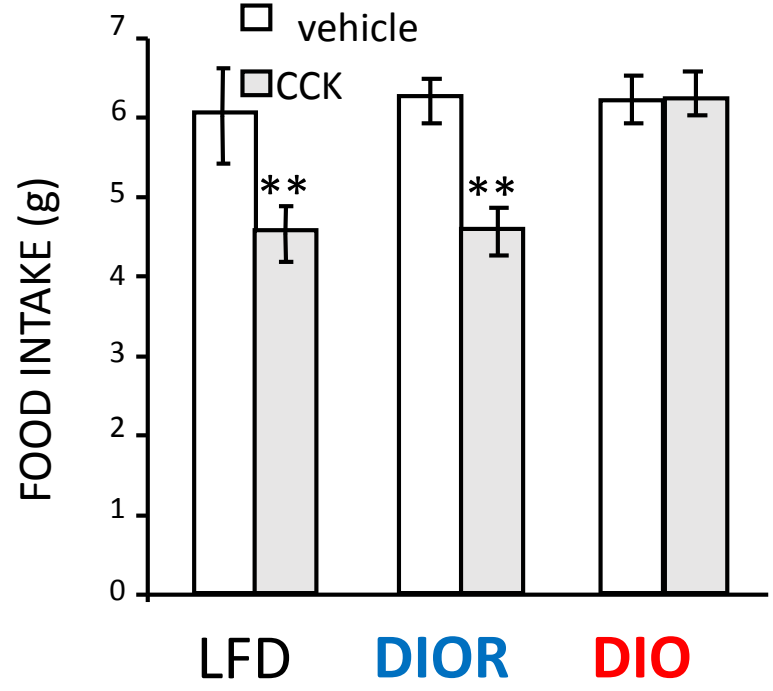


DIO-R DIO-P

SD rats outbred strain:
DIO-resistant and **DIO-prone** on HF diet

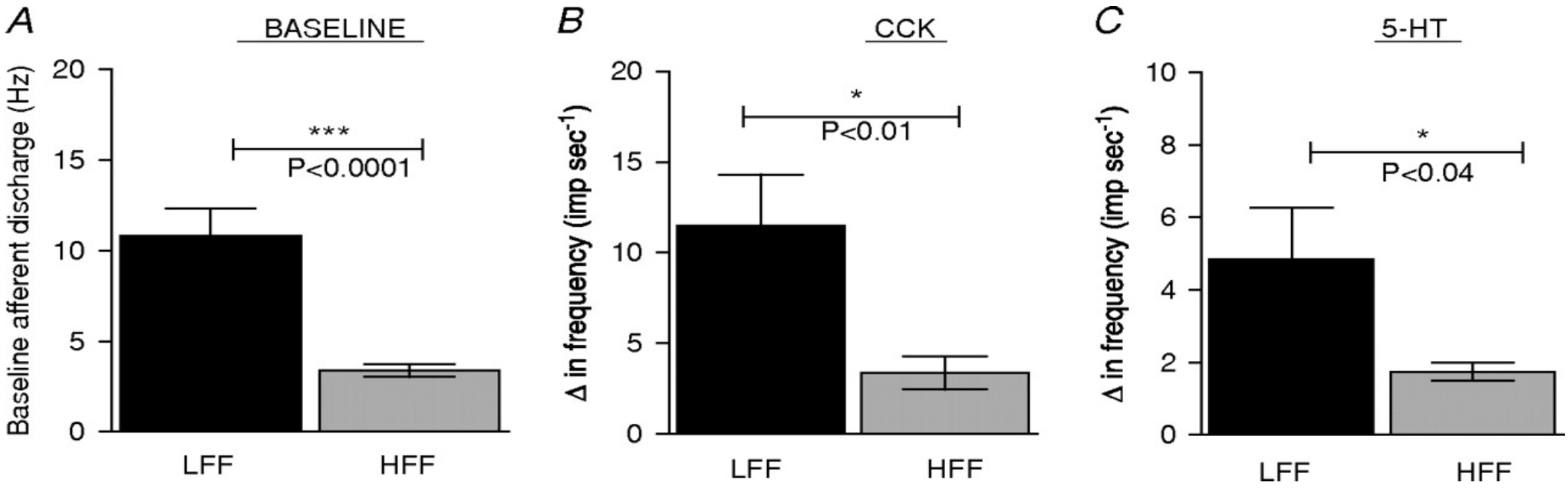
DIO-P vs **DIO-resistant** rats
- increase in body weight gain
- increase in adiposity
- hyperphagic
- increase in plasma leptin

Reduced sensitivity to the satiety effects of CCK DIO rats



de la Serre, AJPGLP 2010

Attenuated intestinal afferent responses to chemical stimulation in high fat diet-induced obese mice

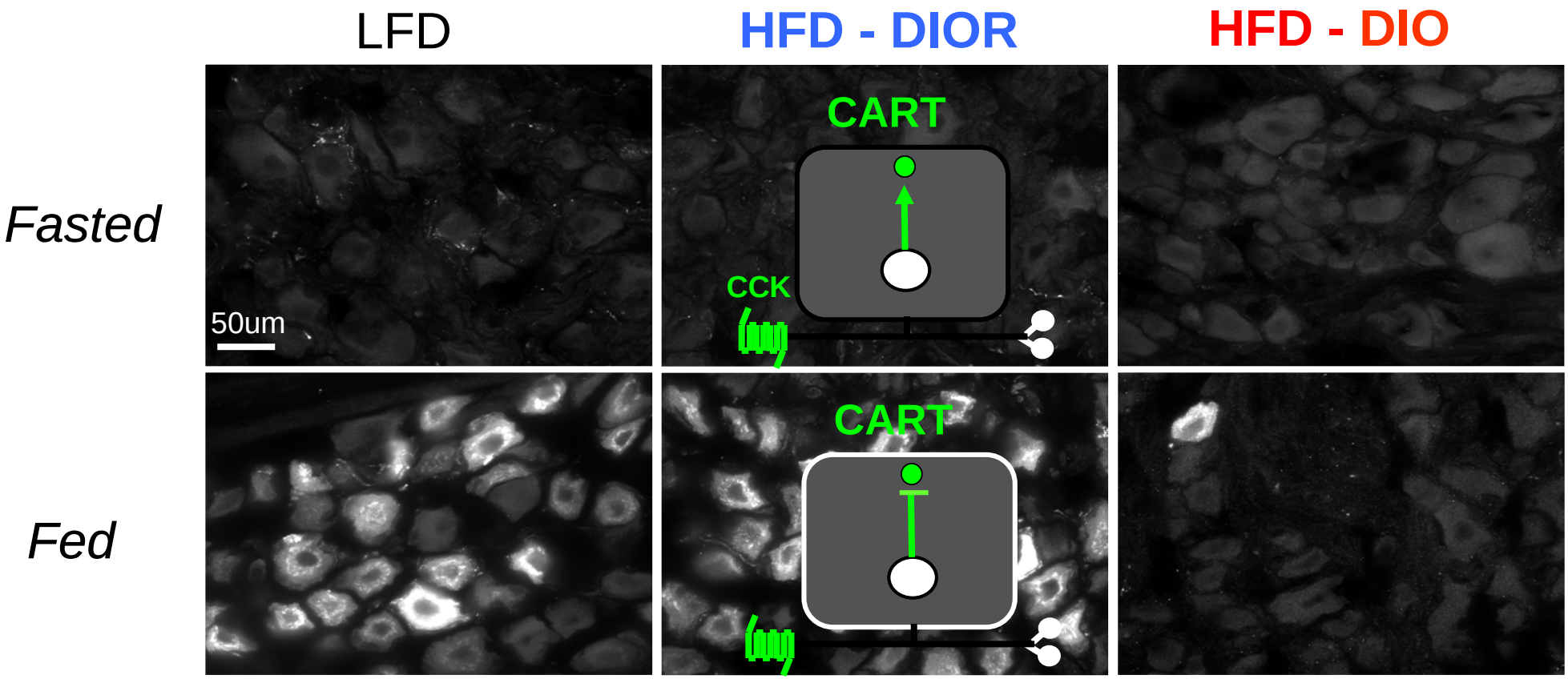


*** a global decrease in the excitability of vagal afferent neurons in HF diet-induced obesity**

Daly D M et al. J Physiol 2011;589:2857-2870

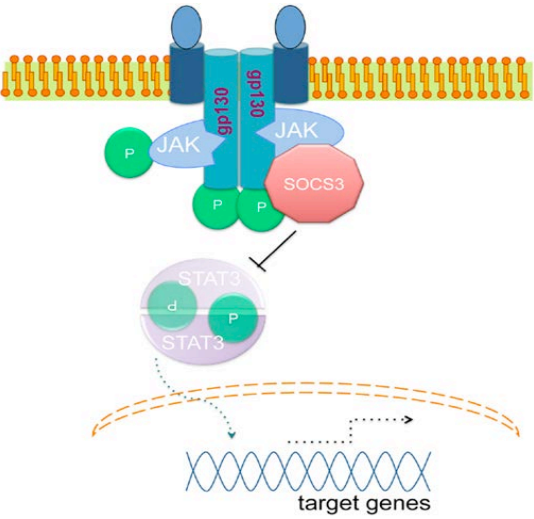
The Journal of Physiology

Vagal Afferent Neurons in Diet-Induced Obese Rats ***do not*** upregulate CART expression to feeding

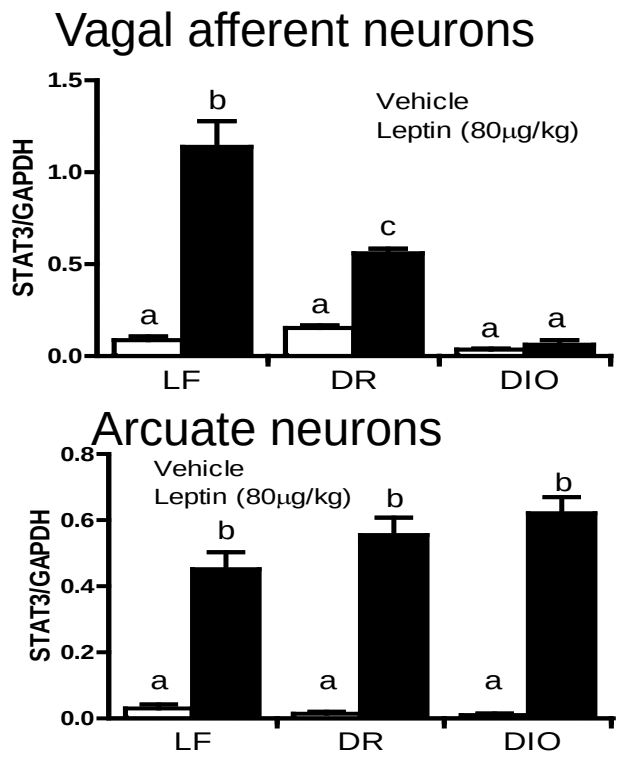


* vagal afferents of DIO rats are unable to signal satiety to the brain in response to food

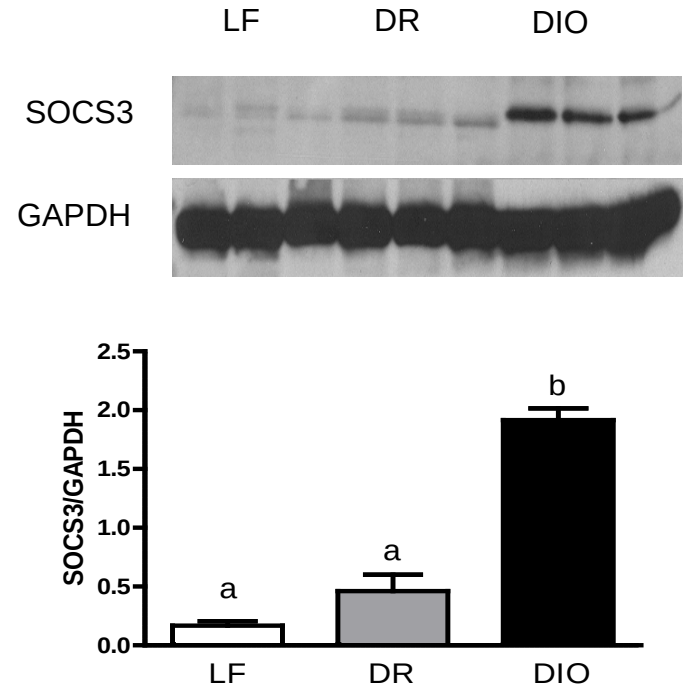
Vagal Afferent Neurons Develop Leptin-Resistance



Leptin resistance in vagal afferents precedes hypothalamic changes



Leptin resistance associated with increase SOCS3

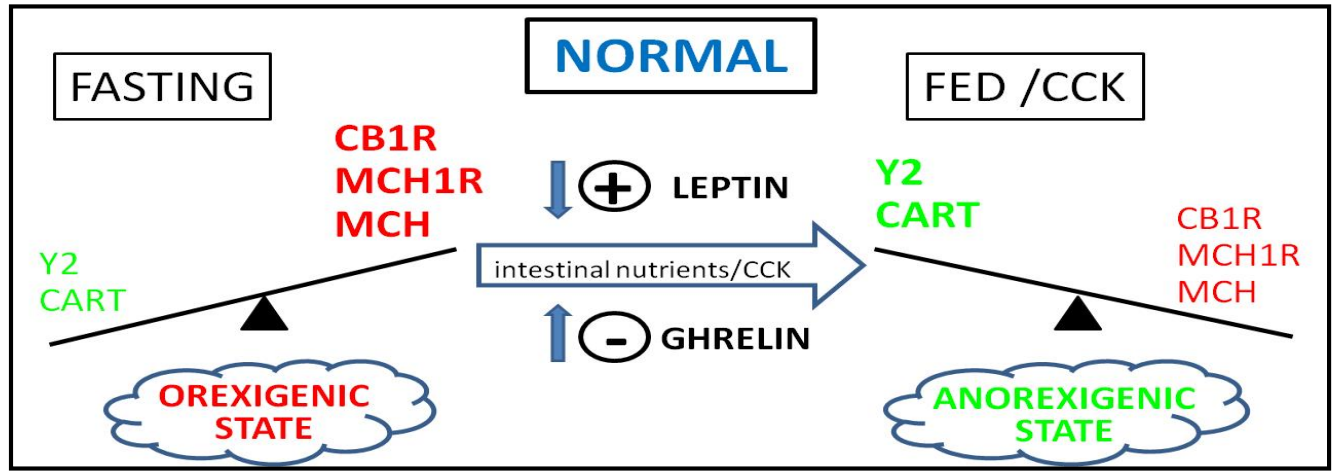


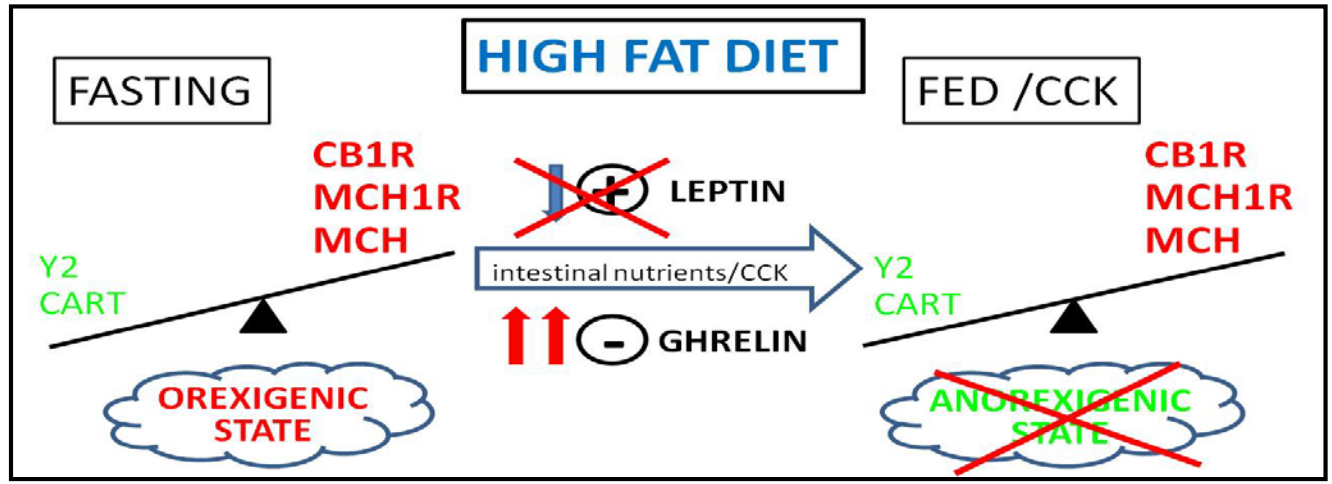
de Lartigue et al 2010, 2011, 2014

Feeding-Induced Phenotypic Change of Vagal Afferent Neurons

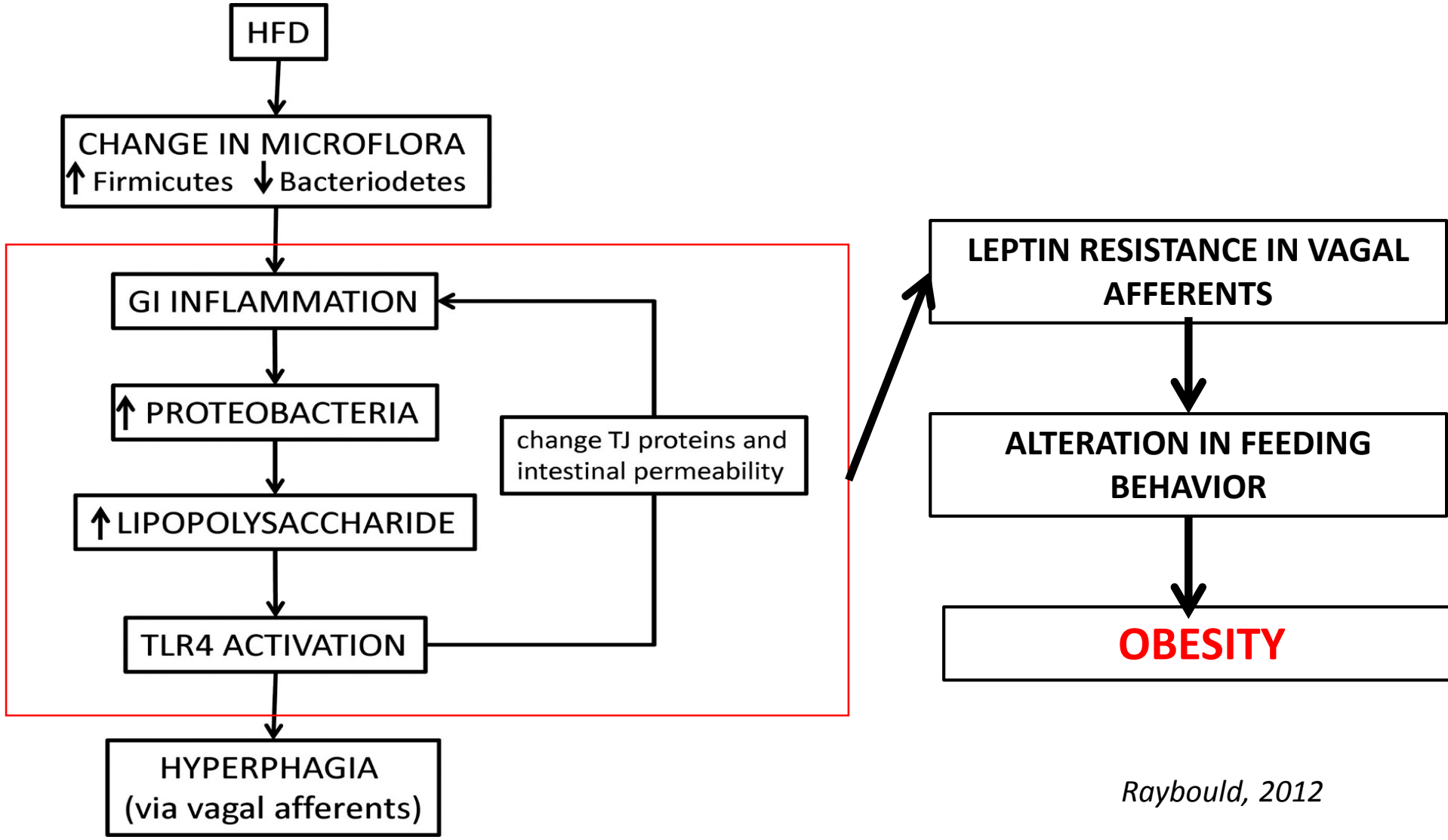
- dependent on feeding status (CCK)

- absent in diet-induced obesity



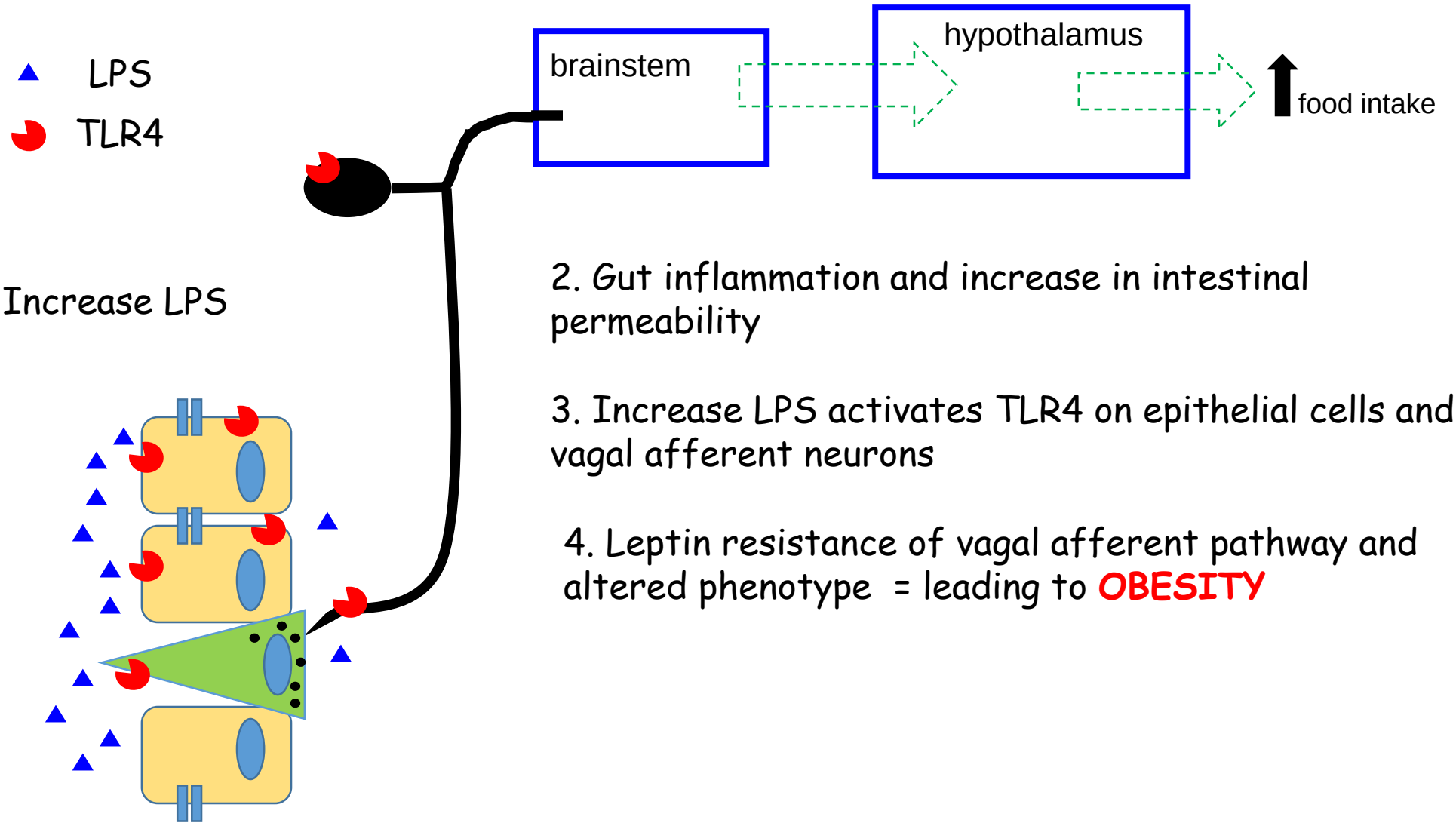


Gut Barrier Function and Gut-Brain Axis



Raybould, 2012

Hypothesis: bacterial LPS drives phenotypic change in VAN



1. Increase LPS

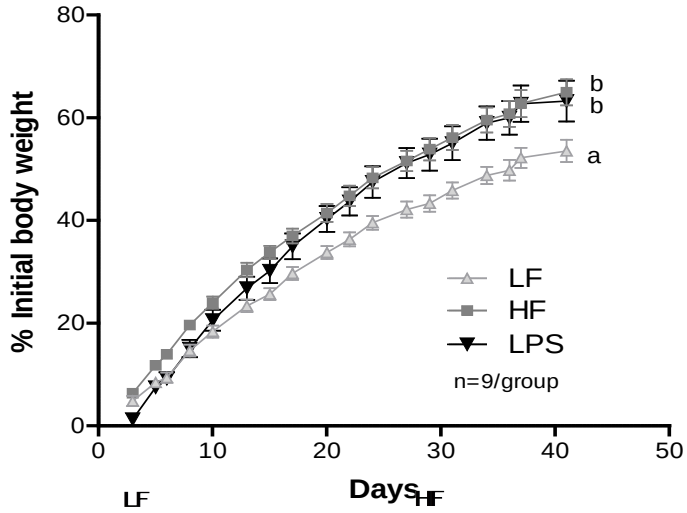
2. Gut inflammation and increase in intestinal permeability

3. Increase LPS activates TLR4 on epithelial cells and vagal afferent neurons

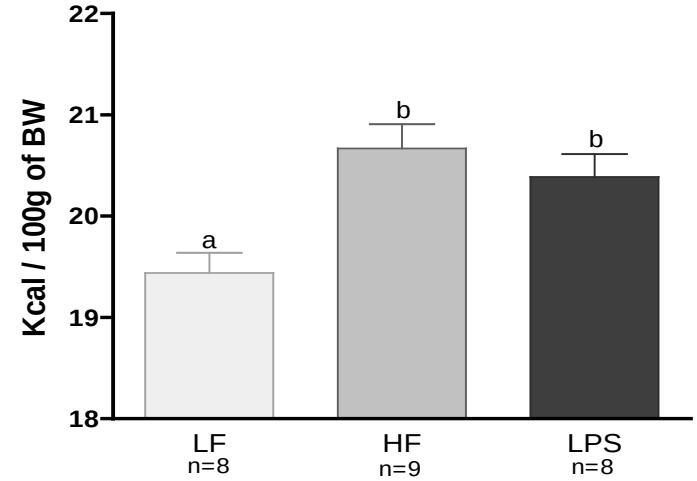
4. Leptin resistance of vagal afferent pathway and altered phenotype = leading to **OBESITY**

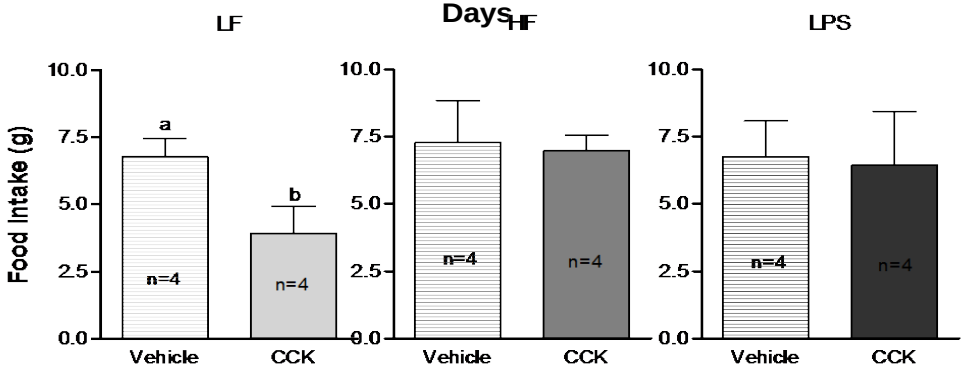
Chronic administration of *low-dose* LPS recapitulates diet-induced obesity

- increases body weight



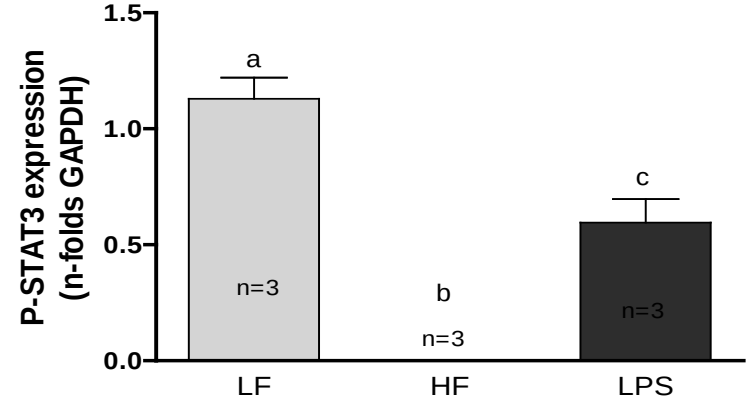
- induces hyperphagia





- inhibits CCK-induced satiety

Decrease leptin-induced pSTAT3



De Lartigue et al, 2014

Challenges

- What is the relationship between the morphological, electrophysiological and neurochemical phenotypes of vagal afferent neurons that innervate the GI tract?
- GLIA!!!!
- Can the changes in phenotype seen in vagal afferent neurons in diet-induced obesity be reversed?
- How well do these changes in vagal afferent neurons in obesity translate to human obesity?

Acknowledgements

- Members of Raybould lab, in particular Will de Lartigue