Plasticity in Vagal Afferent Neurons: Nutrient and Microbial Drivers

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- 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.
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

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.

From: Berthoud and Neuhuber, Autonomic Neuroscience, 2000
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

Gut-Brain Axis: Activation of Vagal Afferent Pathway

Vagal afferent neurons

transmission to CNS

Parasympathetic efferent outflow

change in effector function

Enteroendocrine cells

luminal chemosensors

Higher brain function

change in behavior

hypothesis

brainstem

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

Vagal afferent neurons
transmission to CNS

Enteroendocrine cells
luminal chemosensors

brainstem

hypothalamus

Receptors:
- CCK₁
- 5HT₃
- CB₁
- Orexin
- Leptin (Ob₁)
- Ghrelin (GHSR)
- Y₂
- GLP₁/₂

Higher brain function
change in behavior

food intake
Acute Changes in Phenotype

Nutrient availability alters *receptor* expression in vagal afferents

Y2 receptor

MCH1 receptor

CB1 receptor

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<th>Fasted</th>
<th>Fed</th>
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<tr>
<th>% Y2R positive cells</th>
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*Note: Images and graphs depict changes in receptor expression under fasted and fed conditions.*
Acute Changes in Phenotype:
Nutrient availability alters *peptide* expression in vagal afferents

**CART concentration (ng/mg protein)**

- *Fasted*
- *Re-fed*  

**% CART positive cells**

- *Fasted*
- *Re-fed*

**MCH concentration (ng/mg protein)**

- *Fasted*
- *Re-fed*  

**% MCH positive cells**

- *Fasted*
- *Re-fed*
The neurochemical switch of vagal afferent neurons is regulated by cholecystokinin (CCK)

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

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
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

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

HFD

CHANGE IN MICROFLORA
↑ Firmicutes  ↓ Bacteriodetes

GI INFLAMMATION

↑ PROTEOBACTERIA

↑ LIPOPOLYSACCHARIDE

TLR4 ACTIVATION

HYPERPHAGIA (via vagal afferents)

LEPTIN RESISTANCE IN VAGAL AFFERENTS

ALTERATION IN FEEDING BEHAVIOR

OBESITY

Raybould, 2012
Hypothesis: bacterial LPS drives phenotypic change in VAN brainstem hypothalamus food intake

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

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