GASTROINTESTINAL PEPTIDES, VAGAL AFFERENT SYNAPSES, and NEURAL MECHANISMS of SATIATION

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Distribution of Gastrointestinal Peptides in Stomach and Small Intestine

- **S cells**: Secretin
- **G cells**: Gastrin
- **I cells**: CCK
- **L cells**: GLP-1, PYY 3-36, Oxyntomodulin
- **A/X-like cells**: Ghrelin

GI Peptides Coordinate Digestion and Disposition of Nutrients.

Meal-Related Change in Plasma GI Peptide Levels

Human subject data re-plotted from Erlichmann et al., 2008.
GI Peptides Reduce Food Intake by Decreasing Meal Size and Duration

<table>
<thead>
<tr>
<th>Food Intake</th>
<th>Meal Size</th>
<th>Meal Number</th>
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<tbody>
<tr>
<td>CCK</td>
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<td>GLP-1</td>
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<tr>
<td>PYY 3-36</td>
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**VAGAL AFFERENTS MEDIATE RESPONSES TO GI PEPTIDES**

- **Receptor mRNA**
  - CCK
  - GLP-1
  - PYY 3-36
  - Ghrelin

- **Vagal Afferent Activity**
  - CCK-1R
  - GLP-1R
  - Y-2R
  - GHS-1R

- **Food Intake**
  - Intact
  - Vagotomy

- **Modulation**
  - Attenuate

**SUMMARY**

- GI peptide secretion is controlled by food in the GI tract and provides the brain with information related to the food ingested during a meal.
- GI peptides that reduce food intake do so by contributing to the process of satiation – by reducing meal size and duration.
- Vagal afferent neurons participate in reduction of food intake by GI peptides.

**QUESTIONS**

What are the cellular mechanisms by which GI peptides alter vagal afferent function to control food intake?

By what mechanisms is vagal afferent function modulated by non-GI signals that control food intake?

**FOCUS ON MODULATION OF VAGAL AFFERENT SYNAPTIC TRANSMISSION BY CCK**
Vagal Afferent Synaptic Transmission and CCK-Induced Reduction of Food Intake Involve Glutamate

CCK Enhances Efficacy of Vagal Afferent Transmission in the NTS (Appleyard et al., 2005)

CCK-Induced Synapsin Phosphorylation Is Rapid and Transient (Campos et al., 2013)
Inhibition of Protein Phosphatase 2B Enhances CCK-Induced Synapsin Phosphorylation and Reduction of Food Intake

SUMMARY

Reduction of food intake by CCK involves activation of NMDA-type glutamate receptors in the hindbrain.

CCK increases glutamate release from hindbrain vagal afferent endings and enhances vagal afferent synaptic transmission.

CCK triggers an increased glutamate available for synaptic release by triggering phosphorylation of synapsins.

Reduction of food intake by CCK can be prevented by inhibiting synapsin phosphorylation and enhanced by inhibiting dephosphorylation.

Gaps

The possibility that other GI peptides reduce food intake by modulation of glutamatergic transmission in the hindbrain currently is not known.

The possibility that synapsin phosphorylation, or other components of synaptic processes are subject to control via gene induction or release of vagal co-transmitters has not yet been investigated.
How is vagal afferent function modulated by non-GI signals that control food intake?

FOCUS ON MODULATION OF VAGAL AFFERENT SYNAPTIC TRANSMISSION BY MELANOCORTIN RECEPTOR ACTIVATION

Leptin acts directly on peripheral vagus to enhance CCK action.

Leptin reduces food intake by activating melanocortin projections to hindbrain.

Leptin activates hypothalamic melanocortin (POMC) neurons to reduce food intake.

Some evidence of melanocortin involvement in control of food intake by leptin:
- Leptin activates POMC neurons and increases αMSH release.
- αMSH acts at MC4 receptor to reduce meal size.
- Antagonists of MC4 receptor attenuate leptin-induced reduction of food intake.
- Antagonists of MC4 receptor attenuate CCK-induced reduction of food intake.

Leptin reduces food intake by activating melanocortin projections to hindbrain.
Vagal afferent neurons express melanocortin receptors and interact closely with MSH neuronal endings in the hindbrain.

Wan et al., 2008

Postulated Model of Melanocortin Modulation of Vagal Afferent Endings in the NTS

MC4 receptor activation triggers phosphorylation of synapsin 1 in vagal afferent endings in the hindbrain.

Campos, Shiina and Ritter, 2014 submitted

Synapsin Phosphorylation and Synaptic Function
CONCLUSIONS

CCK and other GI peptides control food intake by controlling meal size.

CCK acts on vagal afferents to reduce food intake.

Non-GI signals that reduce meal size also trigger changes in vagal synaptic transmission that enhance vagal synaptic transmission to reduce food intake.

GI peptides and non-GI hormones control food intake by affecting the process of satiation at the first viscerosensory synapse in the hindbrain.