The metabolic relevance of gastrointestinal physiology

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Introduction

- The gastro-entero-pancreatic system is now regarded as the **largest endocrine organ in the body**, and the range of identified hormones secreted by the gut is extensive.

- **The primary function of the gut** is, of course, the digestion and absorption of nutrients. The gut neuroendocrine system, and at a higher level, the brain–gut axis, functions to optimize this process.

- Many **gut hormones** therefore alter food intake directly and indirectly, the majority acting to reduce food intake and limit meal size.

- **Local effects** such as the inhibition of gastric emptying might contribute to the decrease in energy intake. Activation of **mechano-receptors** as a result of gastric distension may inhibit further food intake via neural reflex arcs.

- Circulating gut hormones have also been shown to act directly on neurons in **hypothalamic and brainstem centres** of appetite control.

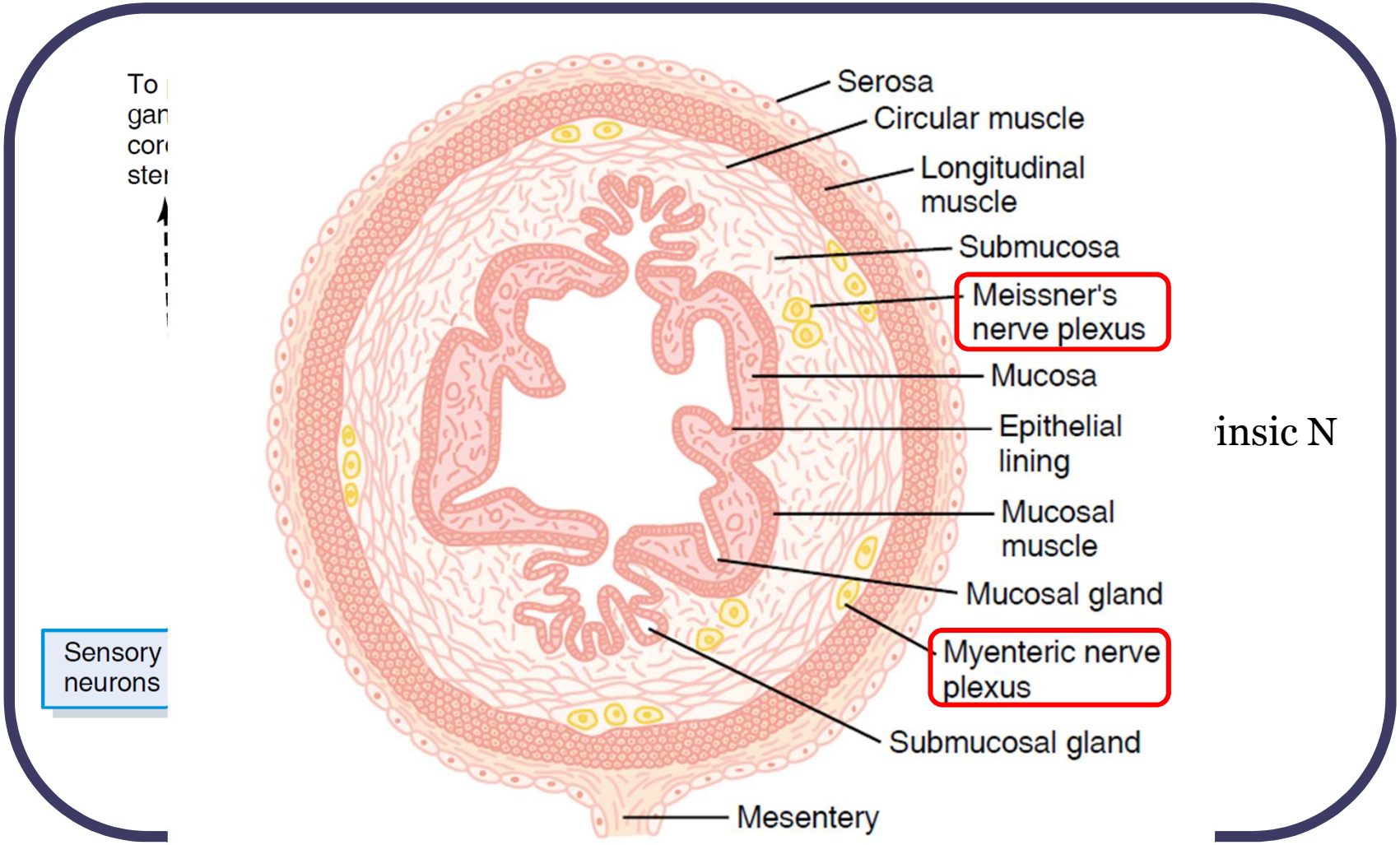
Types of Enteroendocrine cells

Cell type	Highest density	Peptide released
G-cells	Stomach	Gastrin
X-cells	Stomach	Ghrelin
ECL-cells	Stomach	Histamin
Unamed cells	Stomach and duodenum	Gastrin Releasing Peptide (GRP)
S-cells	Duodenum and jejunum	Secretin
I-cells	Duodenum and jejunum	Cholecystokinin (CCK)
K-cells	Duodenum and jejunum	Glucose-dependent insulinotropic polypeptide (GIP)
N-cells	Ileum	Neurotensin
L-cells	Ileum and colon	Glucagon-like peptides (GLP's), Peptide YY (PYY)
D-cells	Entire GI tract	Somatostatin
EC-cells	Entire GI tract	5-hydroxytryptamin (5-HT, Serotonin)

EC-cells, enterochromaffin cells; ECL-cells, enterochromaffin-like-cells; glucagon-like peptides (GLP's) include GLP-1, GLP-2, oxyntomodulin, glicentin.

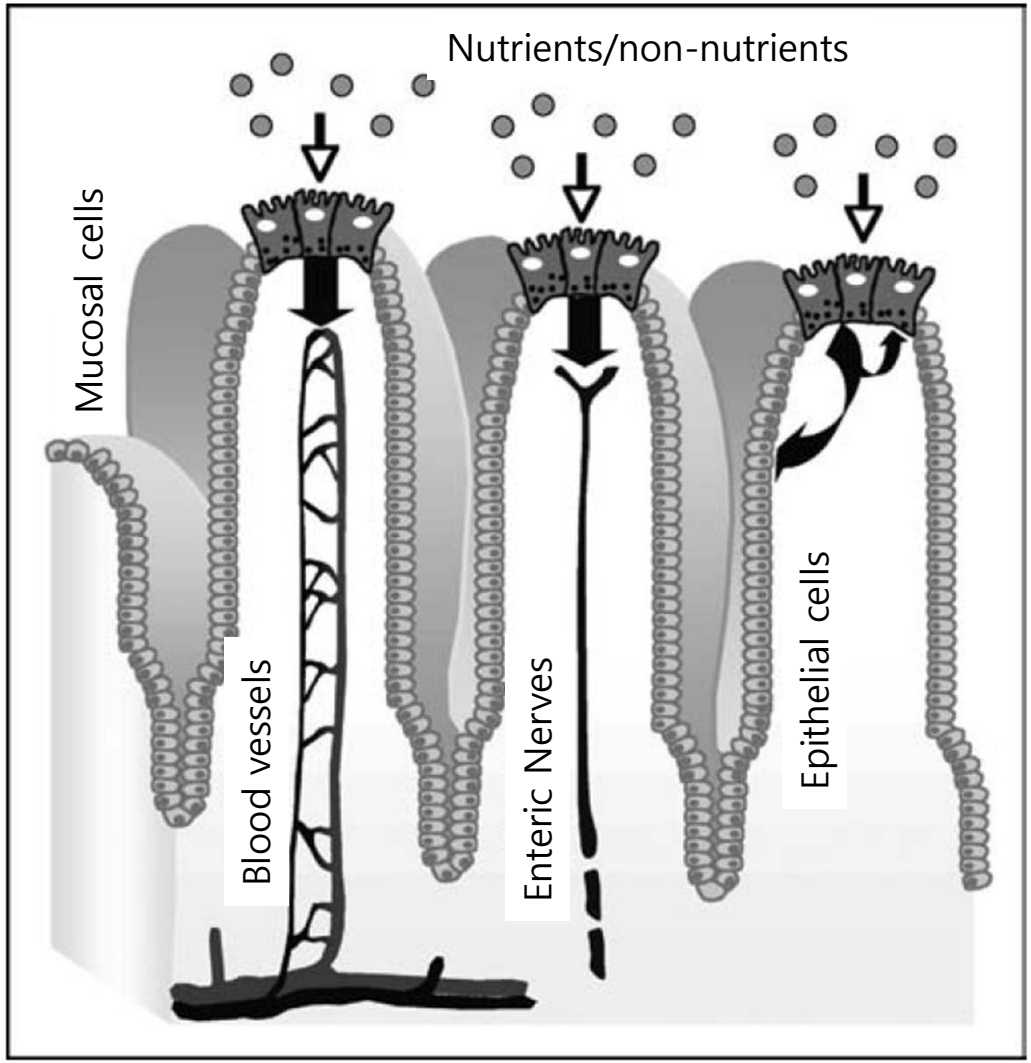
Physiol Behav (2011), doi:10.1016/j.physbeh.2011.02.039

Neurons innervate the GI tract : Mechano-receptors & Chemo-receptors



Guyton. Textbook of medical physiology. 11th ed

Enteroendocrine cells: a site of ‘taste’ in gastrointestinal chemosensing



OPEN cells vs
Closed cells

Current Opinion in Endocrinology, Diabetes & Obesity 2008, 15:73–78

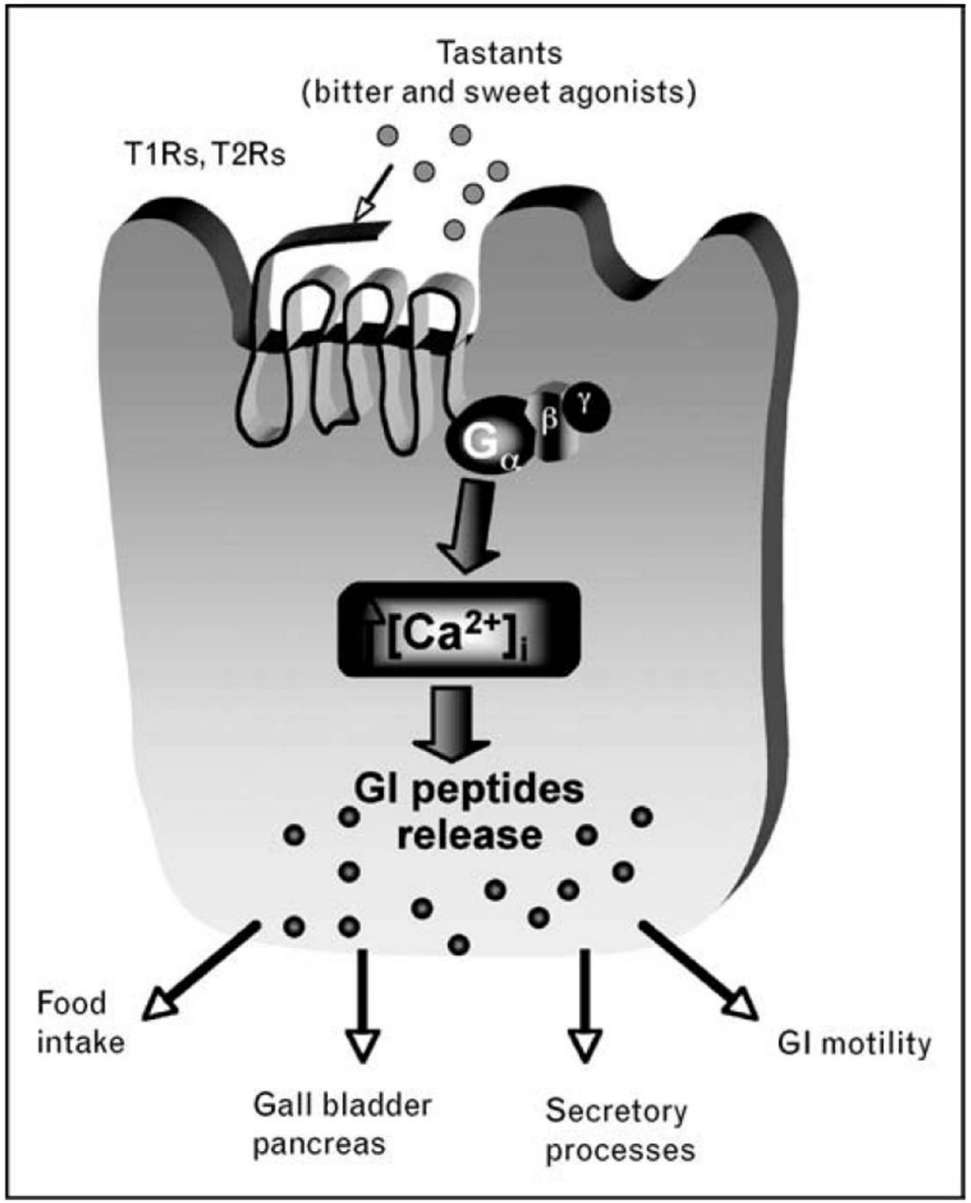
Carbohydrate sensing in EEC

1. Taste receptors
   - GPCRs responsive to bitter, sweet and umami
   - Cells of lingual epithelium
   - T1R family : sweet taste, T1R1, T1R2 and T1R3
   - T2R family : bitter taste, over 30 receptor
   - α-gustducin in L-cell, K-cell, K/L-cell

2. Glucose transporter activity (eg SGLT-1, GLUT-2)
   : GLUTag cells → sugars trigger mb depolarization & GLP-1 secretion via SGLT-1
   : phlorizin (SGLT-1 inhibitor) → glucose absorption block → impaired GLP-1 release
3. KATP channel dependent glucose sensing
   : GLUTag, NCIH716 Cell

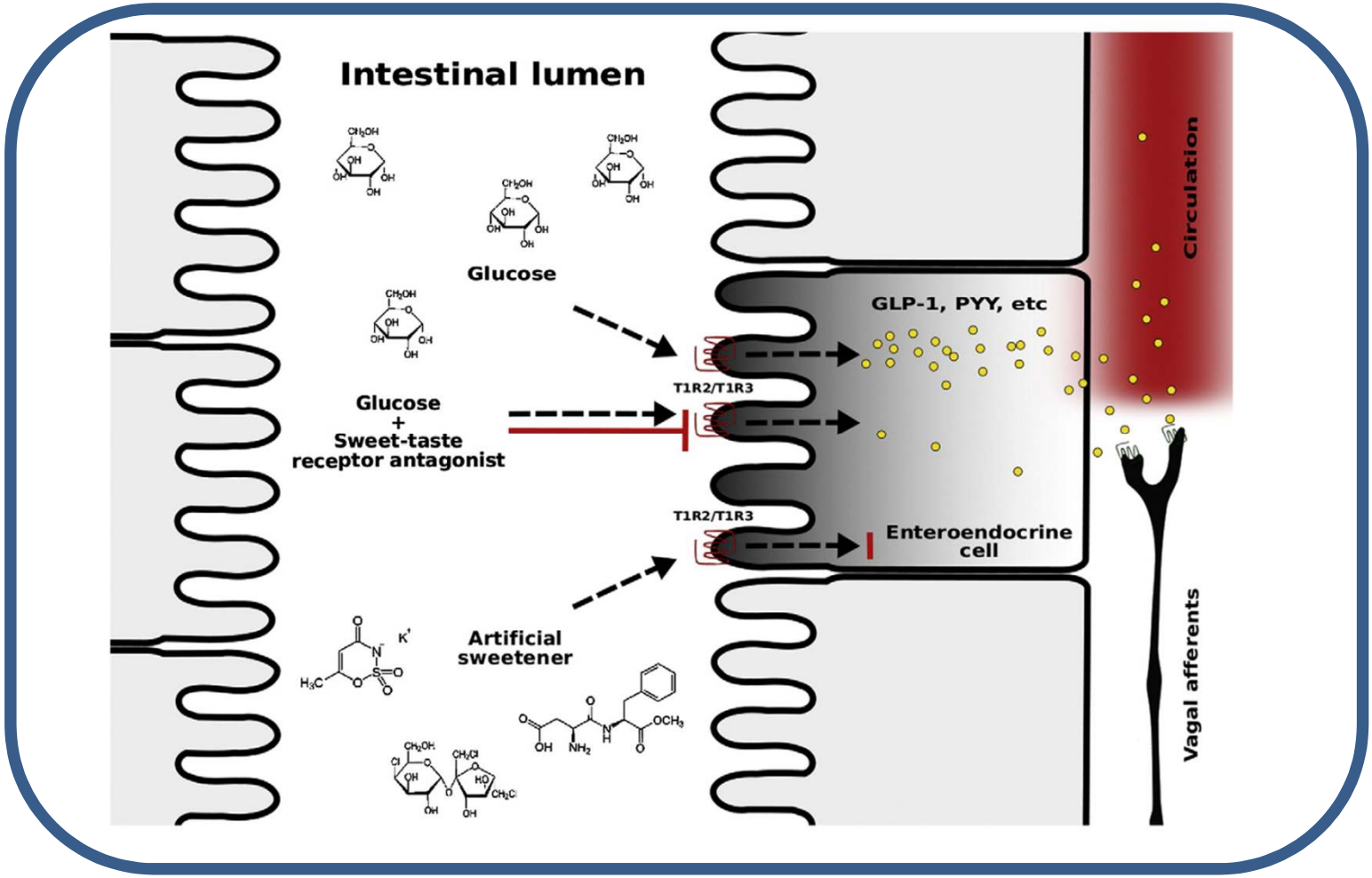
Physiol Behav (2011), doi:10.1016/j.physbeh.2011.02.039

Taste receptors couple to G proteins



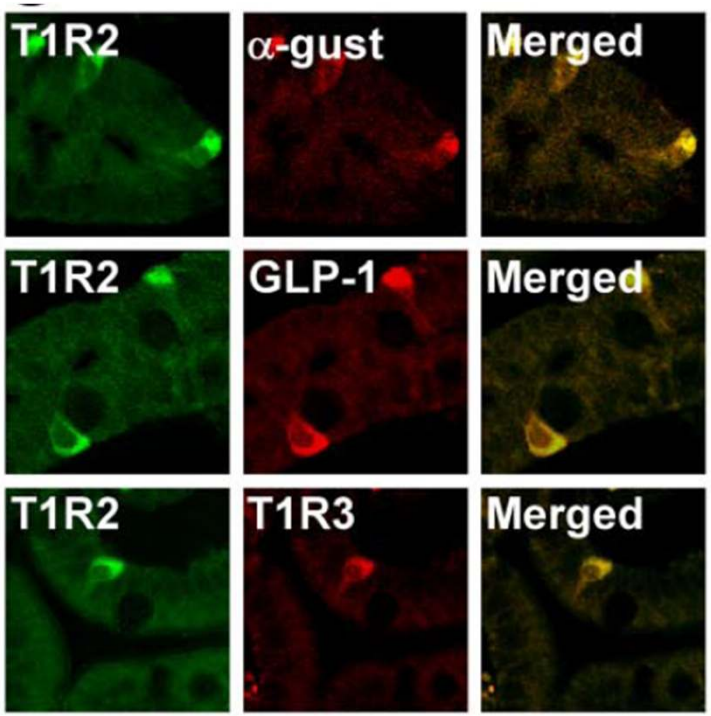
Current Opinion in Endocrinology, Diabetes & Obesity 2008, 15:73–78

sweet-taste receptor sweet-pathway in glucose-stimulated secretion GLP-1 and PYY

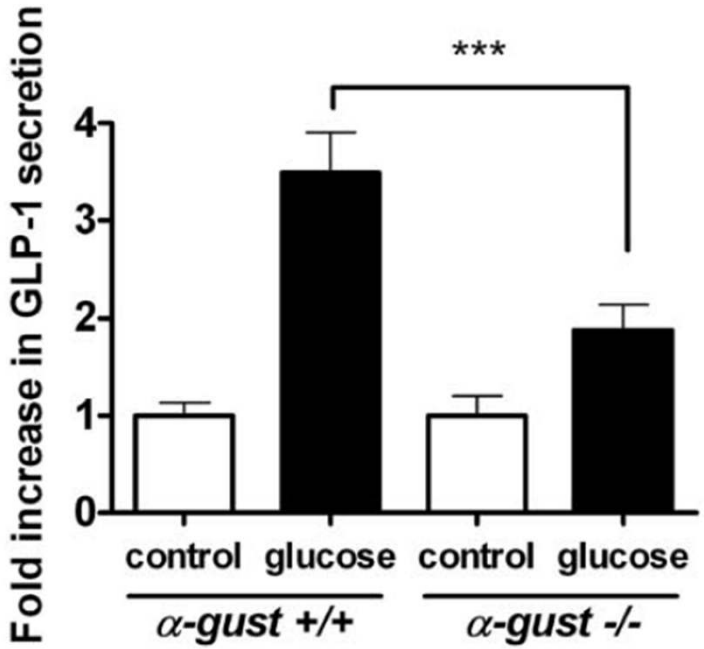


Physiol Behav (2011), doi:10.1016/j.physbeh.2011.02.039

Presence of taste signaling elements in L cells of human small intestine

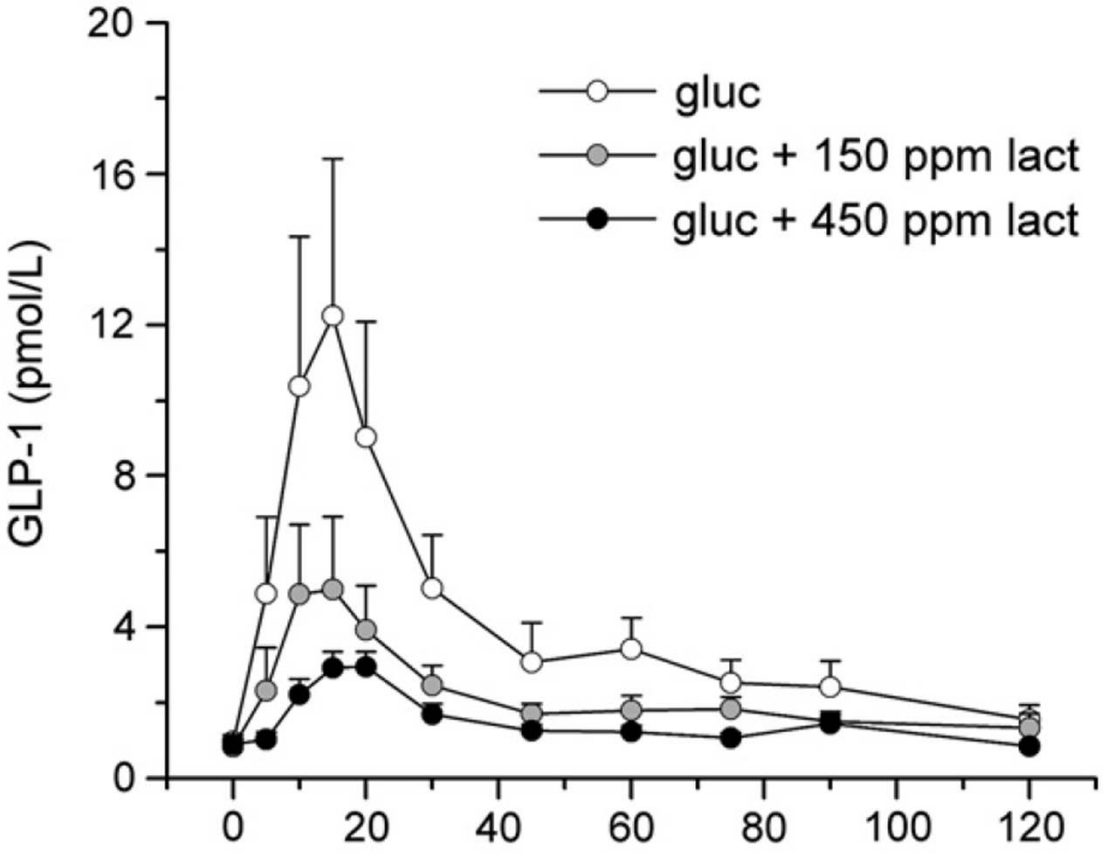


Indirect immunofluorescent imaging showing coexpression of taste signaling elements (*Left*) with GLP-1 (*Center*).



Proc Natl Acad Sci U S A 2007; 104:15069–15074.

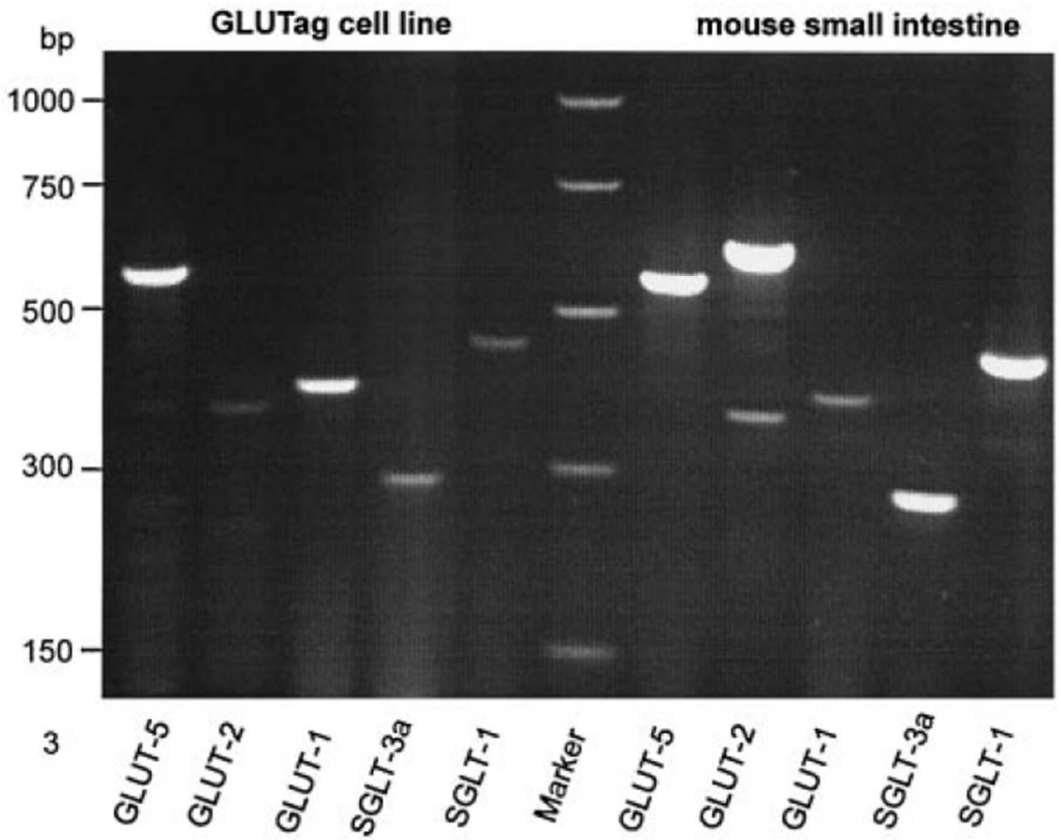
Lactisole induced a dose-dependent reduction in glucose-stimulated secretion of GLP-1

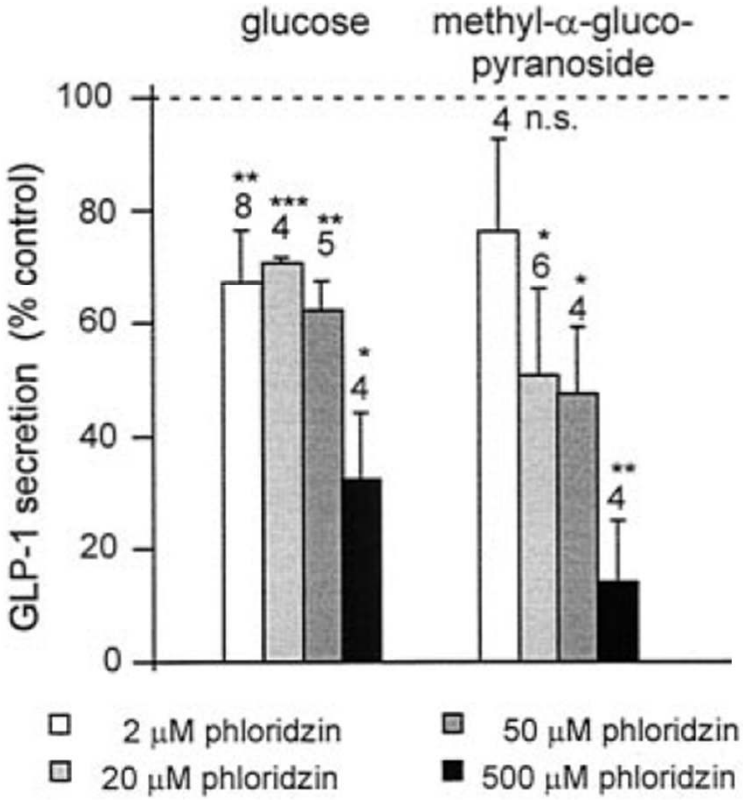


* Lactisole : a sweet-taste receptor antagonist

Physiol Behav (2011), doi:10.1016/j.physbeh.2011.02.039

Glucose transporter expression in the GLUTag cell line





phlorizin, a specific SGLT-1 inhibitor

Diabetes 52:1147–1154, 2003

Lipids sensing in EEC

- Lipids are major stimuli for the secretion of GI peptides but the mechanisms of fat-triggered hormone release remain largely unknown.

- Long-chain FFA(chain length >NC12) potently trigger the release of GLP-1, PYY and CCK. In contrast, C11 or shorter FFA does not, suggesting that a molecular recognition system for FFA resides within the GI tract .

- Specific GPCRs : GPR40, GPR41, GPR43, GPR119, GPR120
  - GPR40 and GPR120 : **medium and long-chain FFA**
  - GPR43 and GPR41 : **short chain FFAs** such as acetate, butyrate

- GPR40 has been identified in EEC in mice where it colocalizes predominantly with GLP-1 and GIP (less with CCK, PYY and ghrelin) suggesting that it mediates FFA stimulated incretin secretion.

- GPR41 and 43 have been identified in rat endocrine cells containing PYY and in mucosal mast cells, which contain 5-hydroxytryptamine (5-HT)

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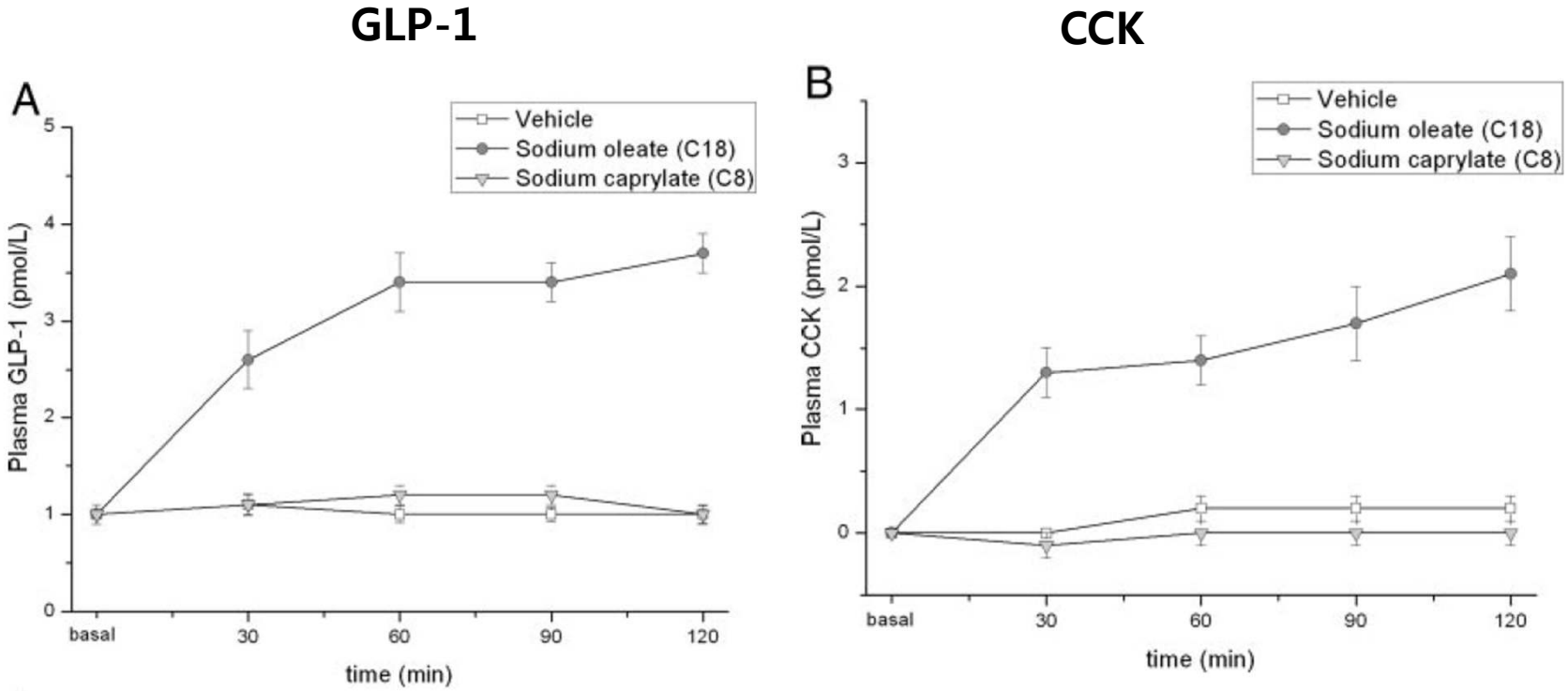
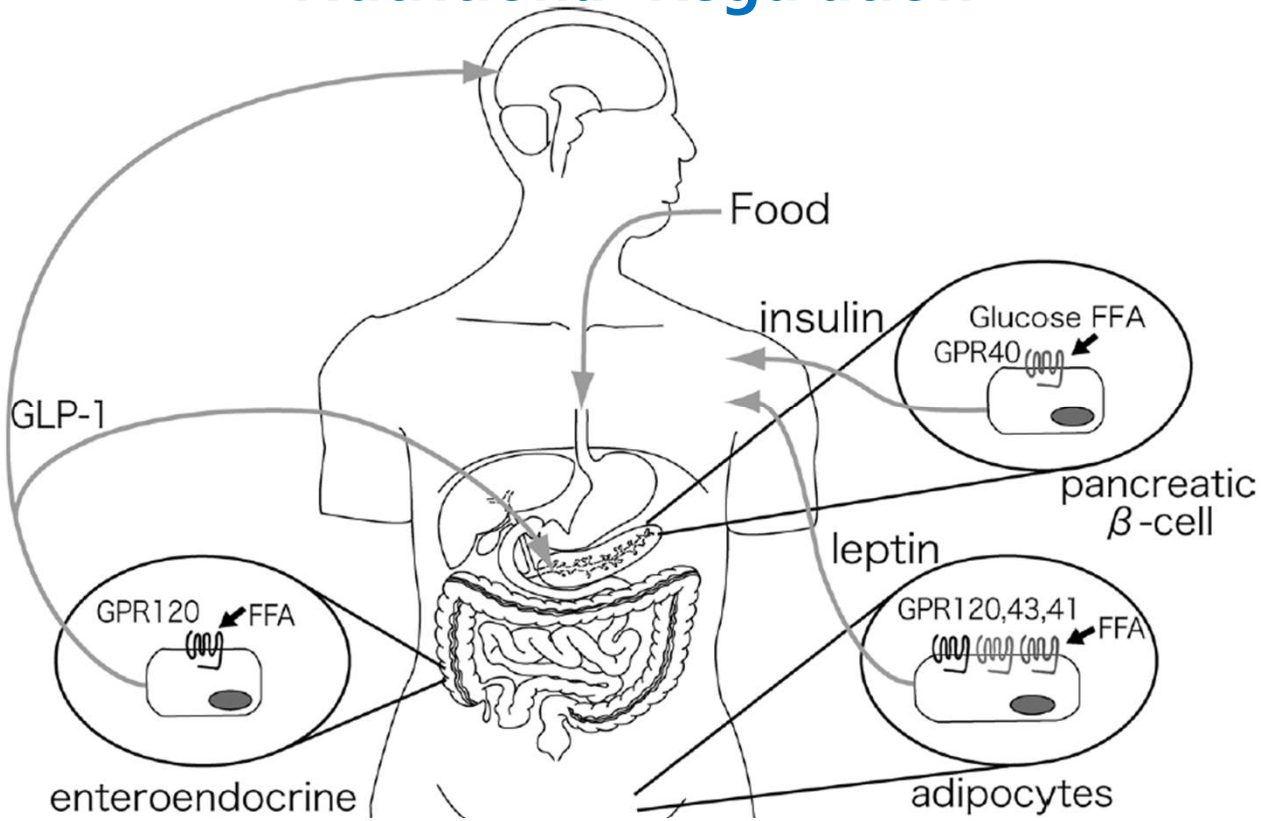
Plasma concentrations of GLP-1 & CCK during intraduodenal infusions of C18 and C8 fatty acids



J. Clin. Endocrinol. Metab. 2010 95:879-886

Free Fatty Acid Receptor Actions in Nutritional Regulation



Nomenclature	GPR41	GPR43	GPR40	GPR120	GPR42 Pseudo gene
Antagonist	—	—	—	—	—
Agonist (FFA) (Other)	Short chain, C3>C4≫C2	Short chain, C3~C4~C2	Medium-long Thiazolidimedione	Medium-long	No activation
G protein coupling	Gi/o	Gq/11, Gi/o	Gq/11	Gq/11	—
Gene/chromosomal	GPR41	GPR43	GPR40	GPR120	GPR42
Localization	19q13.1	19q13.1	19q13.1	10q23.33	19q13.1
Protein (human)	NP_005295, 346 a.a	NP_005297, 330 a.a	NP_005294, 300 a.a	NP_859529, 377 a.a	NP_005296, 346 a.a
Expression	Adipose tissue		Pancreatic β-cell	Colon	
Physiological role	Leptin production		Insulin secretion	GLP-1 secretion	

Biol. Pharm. Bull. **31**(10) 1847—1851 (2008)

Protein sensing in EEC

- products of protein hydrolysis (peptones ,amino acids) also stimulate secretion of GI peptides from EEC, the exact mechanisms by which these molecules are detected remain elusive.

- **GPR93**: increasing the expression of GPR93 in STC-1 cells increased CCK mRNA expression and CCK secretion by protein hydrolysate.

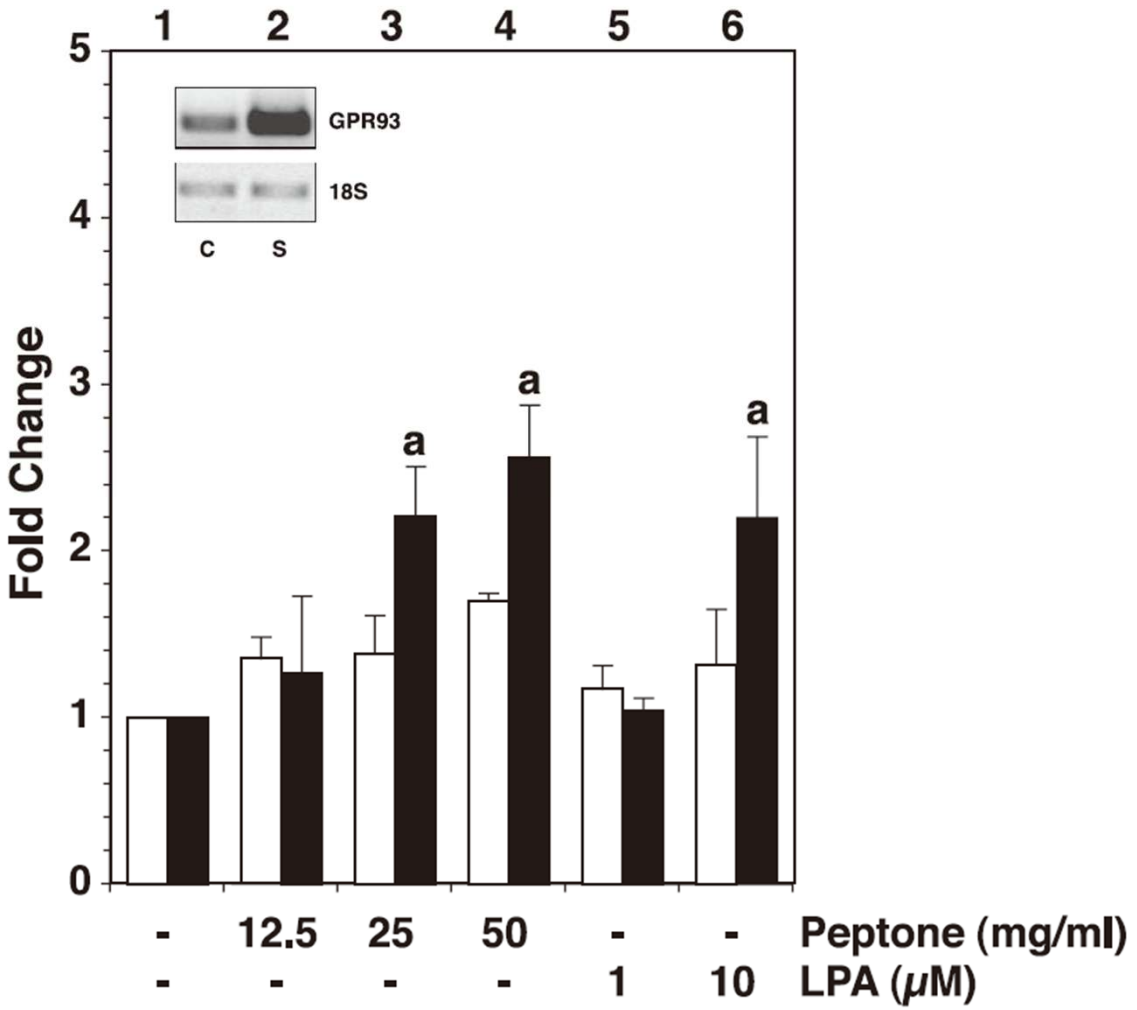
- **Glutamine**, a potent stimulus for GLP-1 release in GLUTag cells, may act in part via the sodium-dependent amino-acid transporter **SLC38A2**

- It is proposed that **oligopeptide transporter** (PEPT1, PEPT2) trigger cell excitability by small inward currents and that this depolarizing effect contributes to peptide release from EEC. Transfection of PEPT1 in STC-1 cells evokes membrane depolarization and di-peptide-stimulated hormone secretion in a pH-dependent manner.

- extracellular **Ca2+ sensing receptor (CaR)** may account for sensing mechanisms in the gut. Several studies show CaR expression along the small and large intestine and suggest potential roles in signaling protein availability.

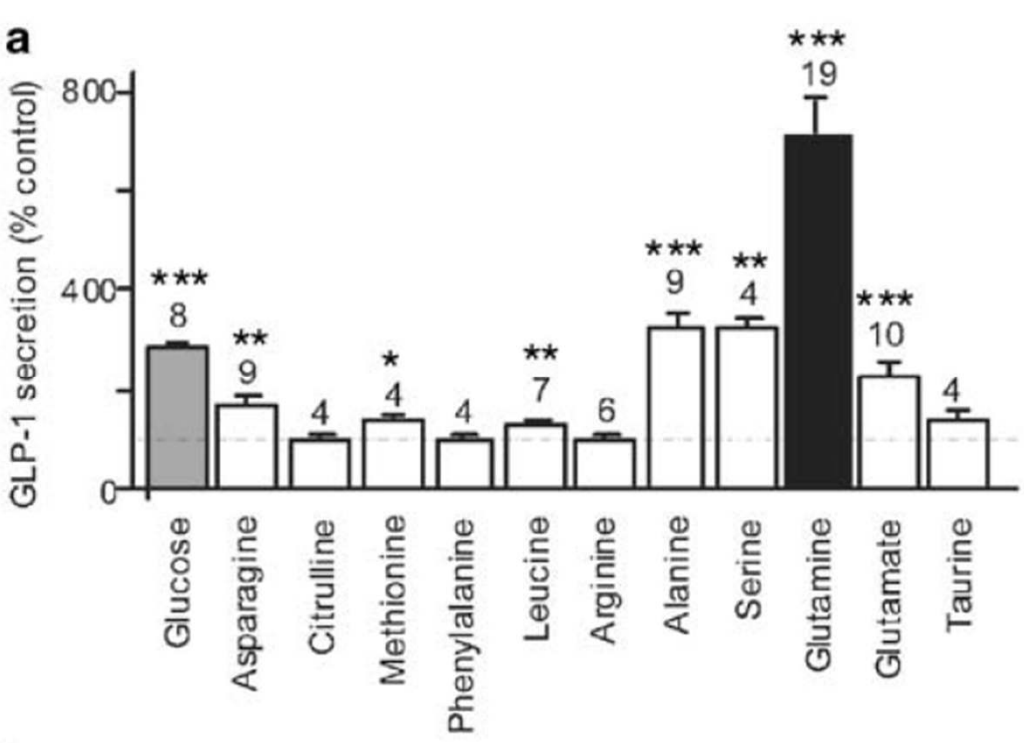
Physiol Behav (2011), doi:10.1016/j.physbeh.2011.02.039

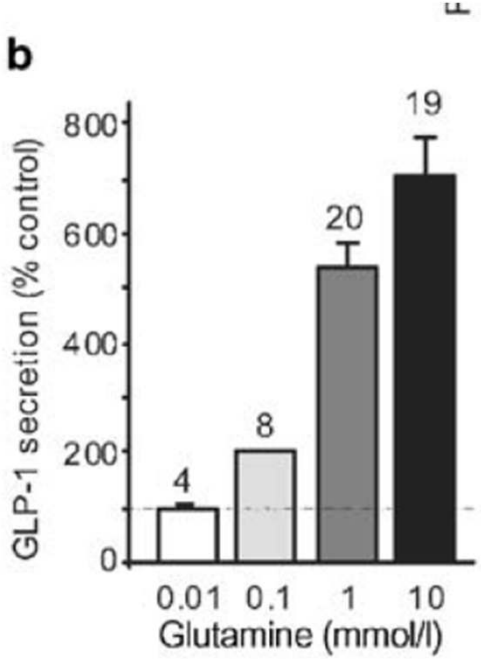
GPR93 activation by protein hydrolysate induces CCK transcription and secretion in STC-1 cells



Am J Physiol Gastrointest Liver Physiol 292: G1366–G1375, 2007

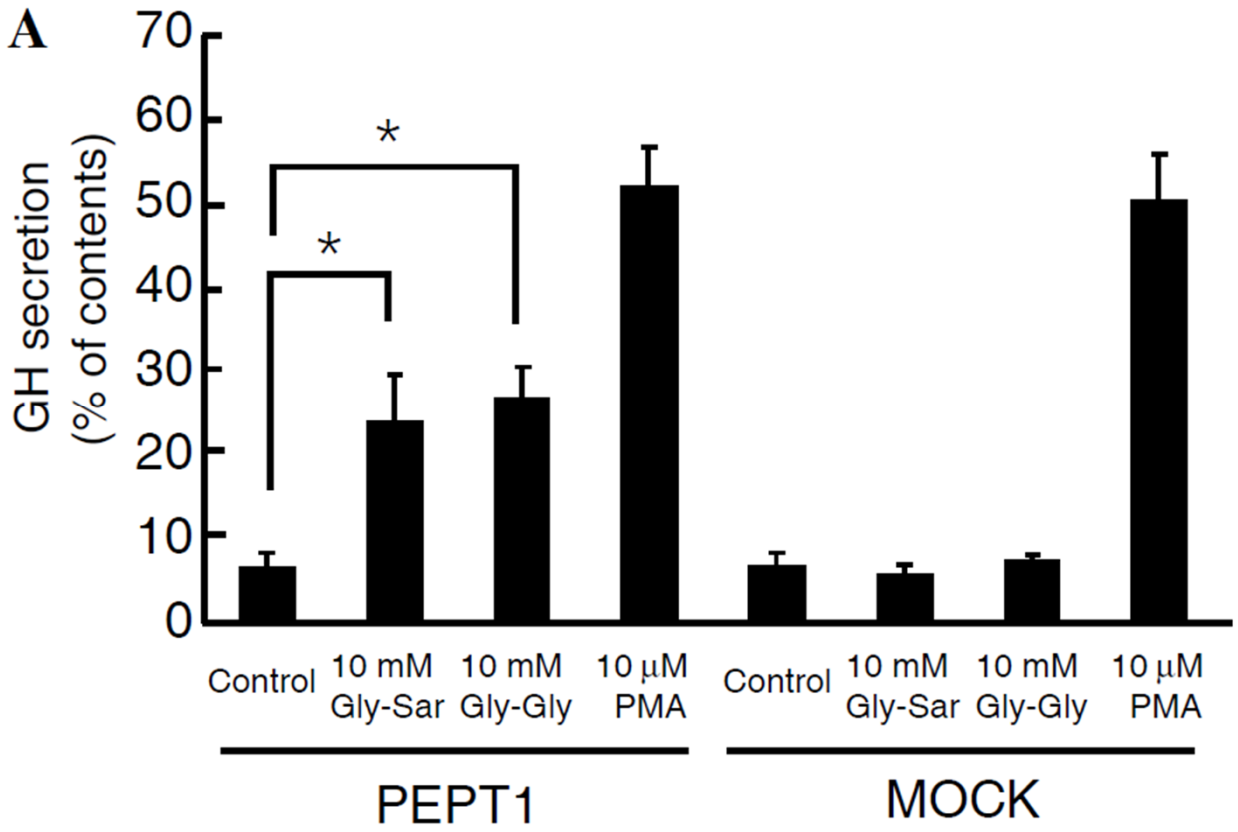
Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells





Diabetologia (2004) 47:1592–1601

Di-peptide induced hormone secretion by PEPT1-transfected STC-1 cells.



Biochemical and Biophysical Research Communications 336 (2005) 1028–1032

Peripheral Signals Conveying Metabolic Information to the Brain

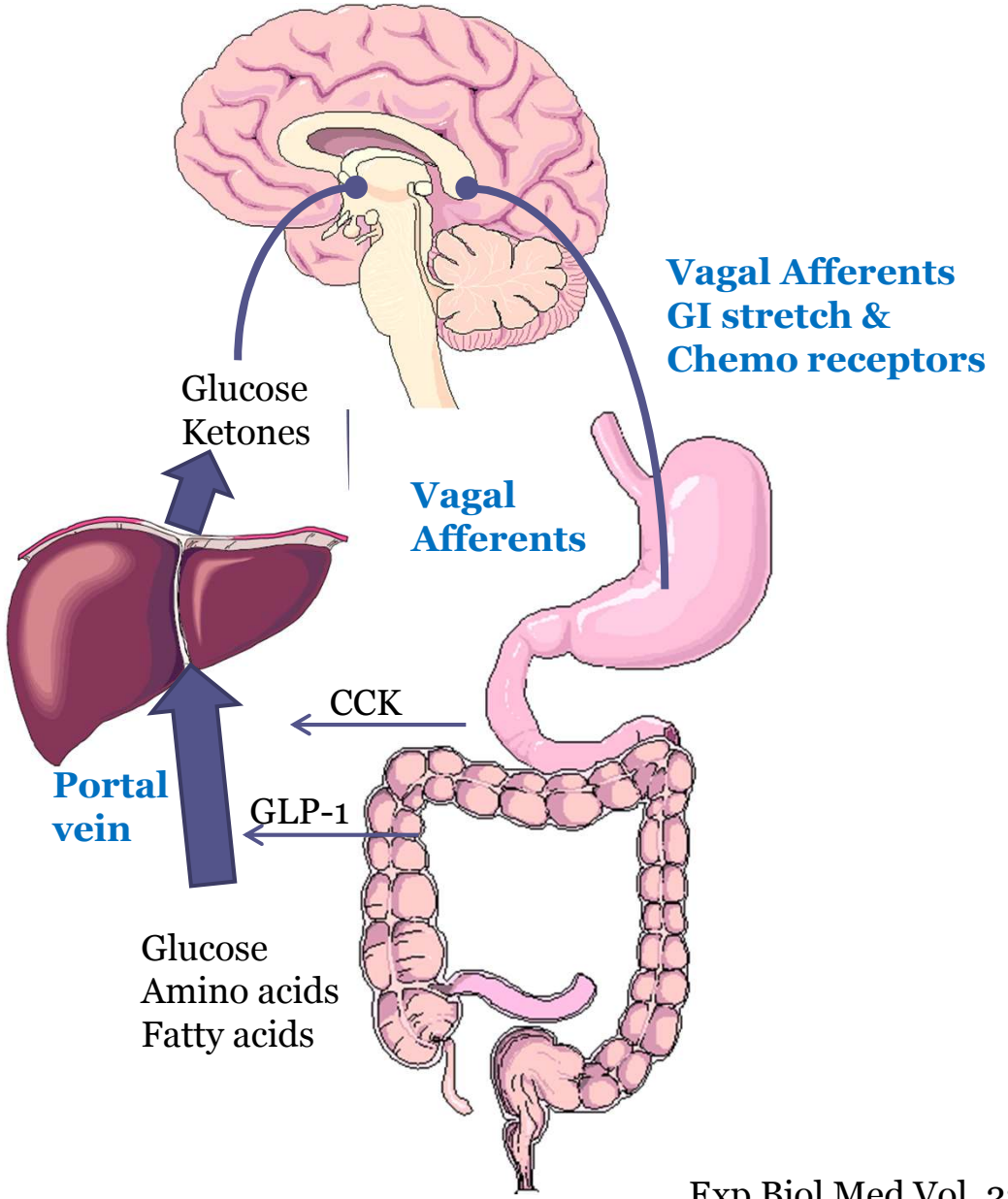
Peripheral signals (short/long-term)
can contribute to feeding behavior
body weight regulation,

1. Short-term signals
- some signals (e.g., nutrients & GI hormones)
- act primarily as determinants of satiety to limit the size of individual meals

2. Long-term signals
- activated in proportion to both body adipose stores to the amount of energy consumed over a more prolonged period of time.
- Insulin and leptin

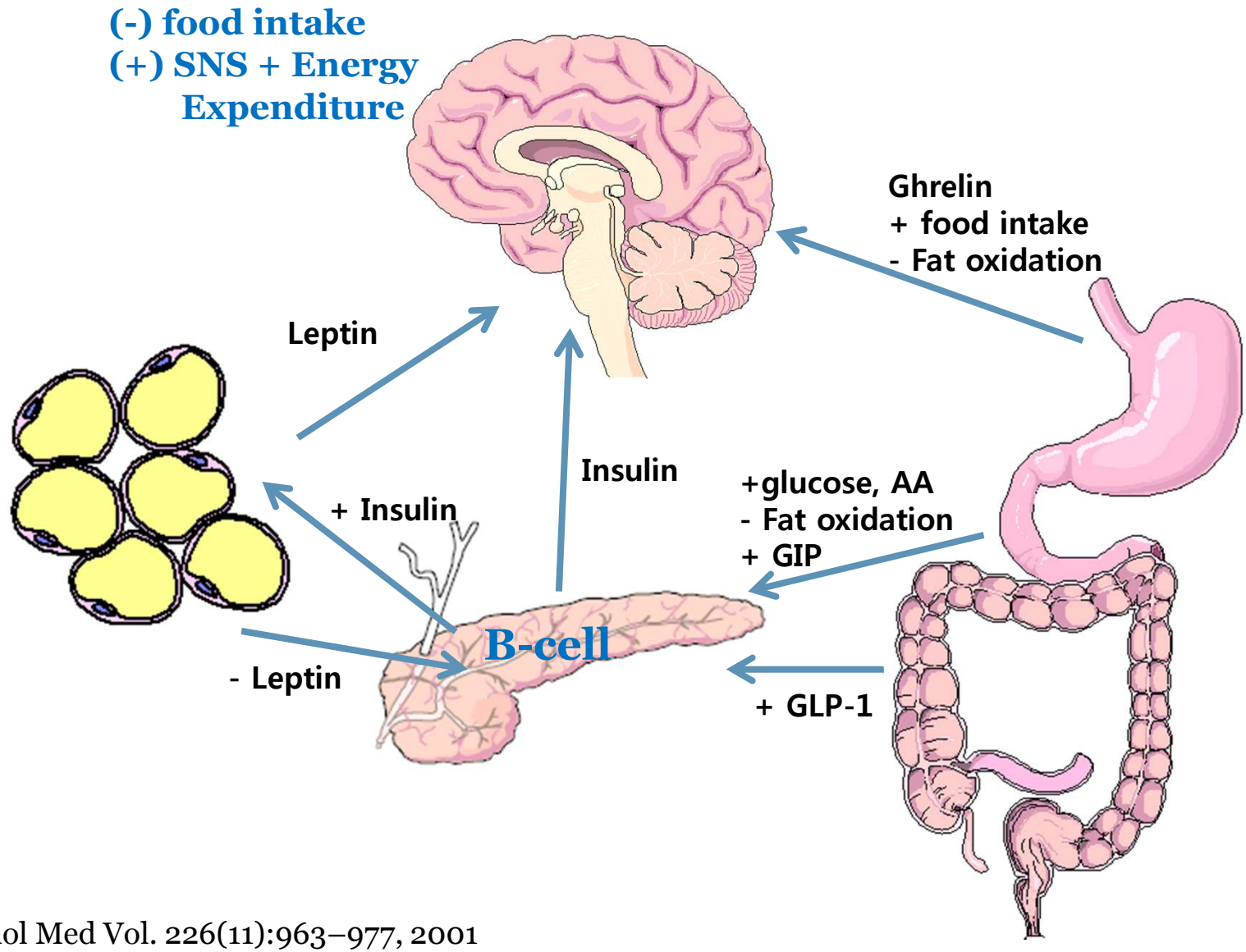
Exp Biol Med Vol. 226(11):963–977, 2001

1. Short-term signals regulating food intake



Exp Biol Med Vol. 226(11):963–977, 2001

2. Long-term signals regulating food intake



Exp Biol Med Vol. 226(11):963–977, 2001

Summary & Conclusion

- The gastrointestinal tract is the largest endocrine organ in the body Gut hormones function to optimize the process of digestion and absorption of nutrients by the gut.

- In recent decades, gut hormones have come to occupy a central place in the complex neuroendocrine interactions that underlie the regulation of energy balance.

- Many gut peptides have been shown to influence energy intake. The most well studied in this regard are cholecystokinin (CCK), pancreatic polypeptide, peptide YY, glucagon-like peptide-1 (GLP-1), oxyntomodulin and ghrelin.

- With the exception of ghrelin, these hormones act to increase satiety and decrease food intake. The mechanisms by which gut hormones modify feeding are the subject of ongoing investigation.

감사합니다