

66th
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ANNUAL MEETING



INNOVATION IN LIVESTOCK PRODUCTION: FROM IDEAS TO PRACTICE

31 AUGUST - 4 SEPTEMBER 2015
WARSAW, POLAND



Brain-gut axis in nutrient sensing

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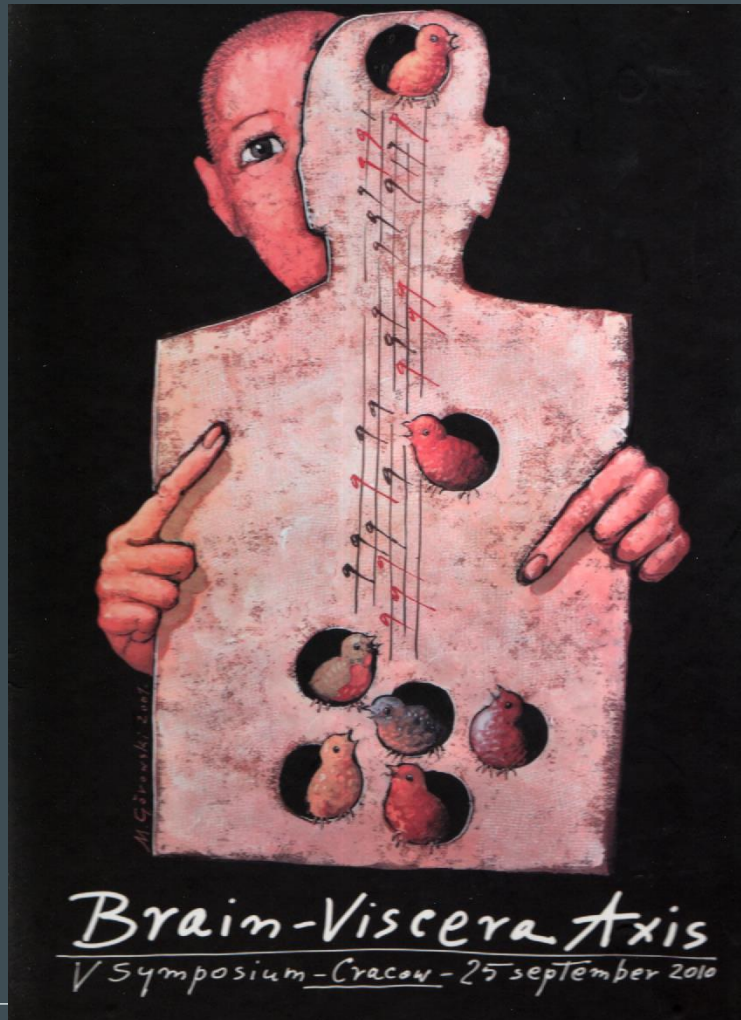


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What is brain-gut axis?

a bidirectional communication system between the central nervous system and the gastrointestinal tract



What is brain-gut axis?

Brain

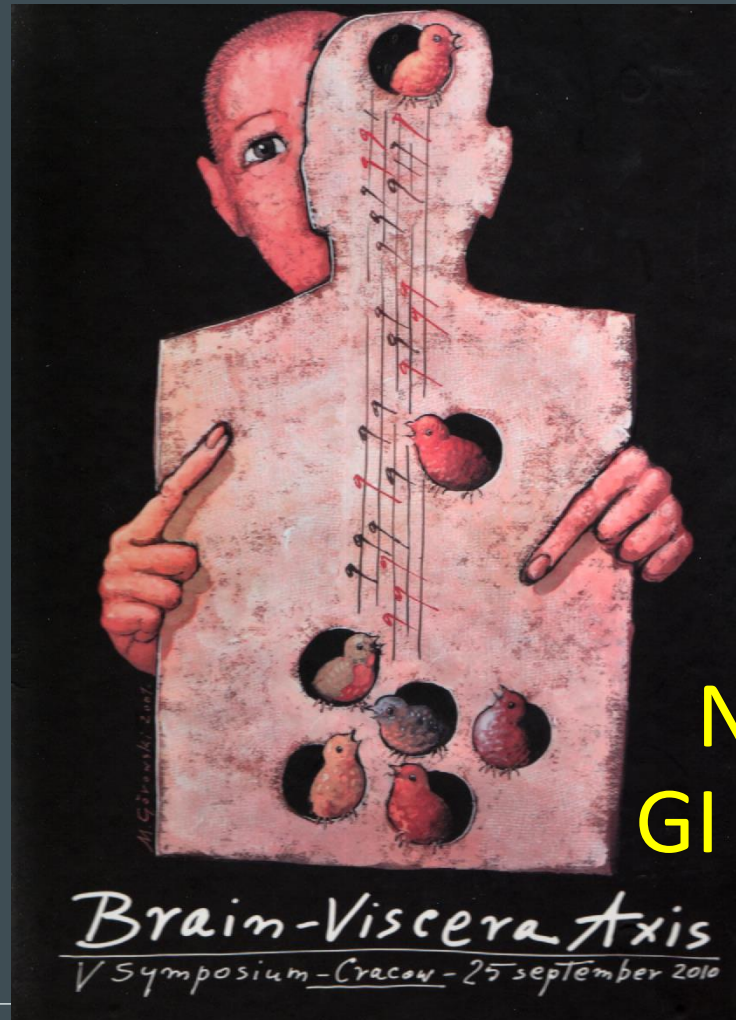


Vagal nerves
GI hormones

ENS
DNES
GALT



Nutrients
GI microbiota



Brain-gut axis function

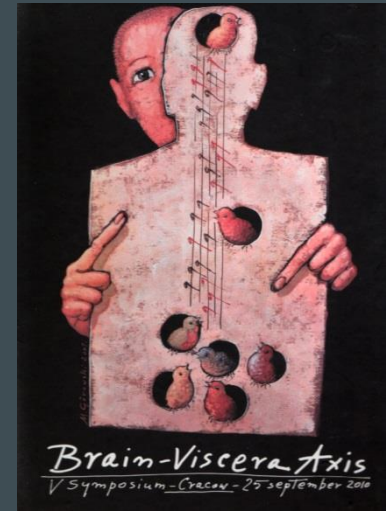
- Sensory info to brain (vagal afferens and GI hormones via bloodstream):
 - volume, content, physical/chemical composition
 - hunger/satiety/hedonic signals
 - pain
- Regulatory info to viscera (vagal efferens):
 - GI motility, secretion, absorption, cytoprotection
- Vagal afferent:efferent fibers ratio **9:1**



Brain-gut axis

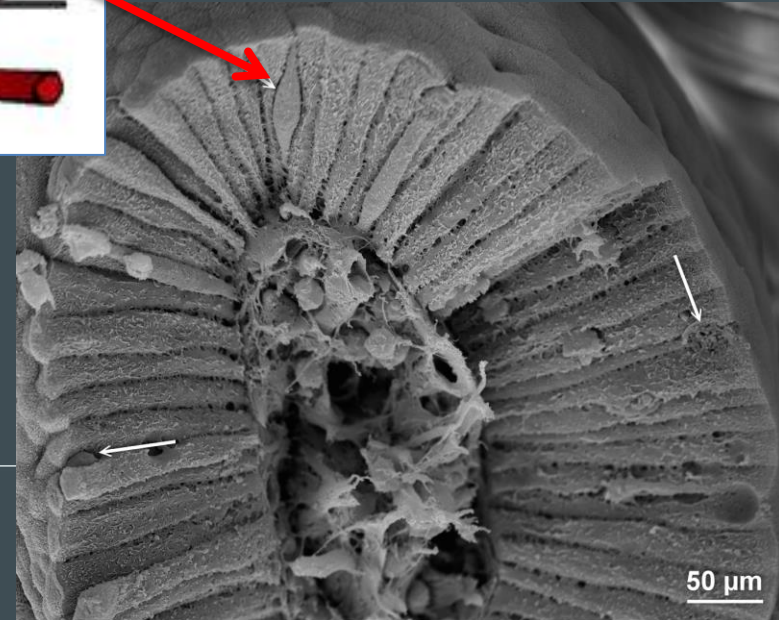
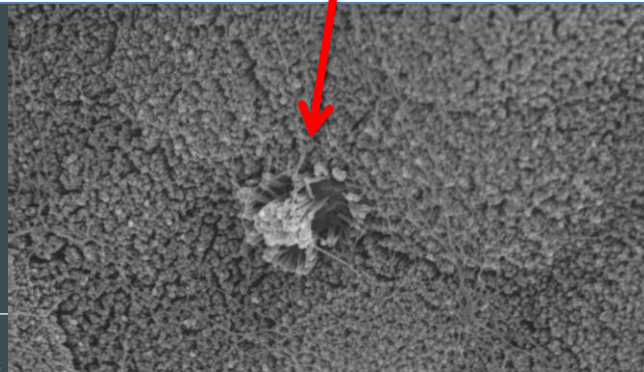
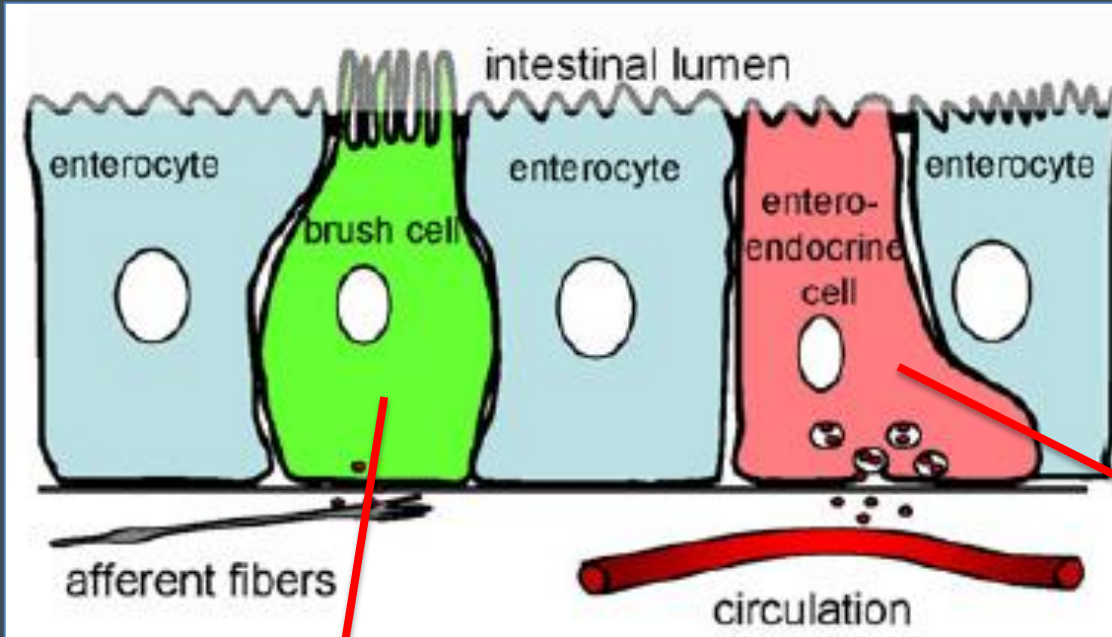
Epithelial cells

- receptors/transporters
- intracellular messengers
- GI peptides
- Bloodstream vs neural pathways
- Brain
- Microbiota and brain-gut axis

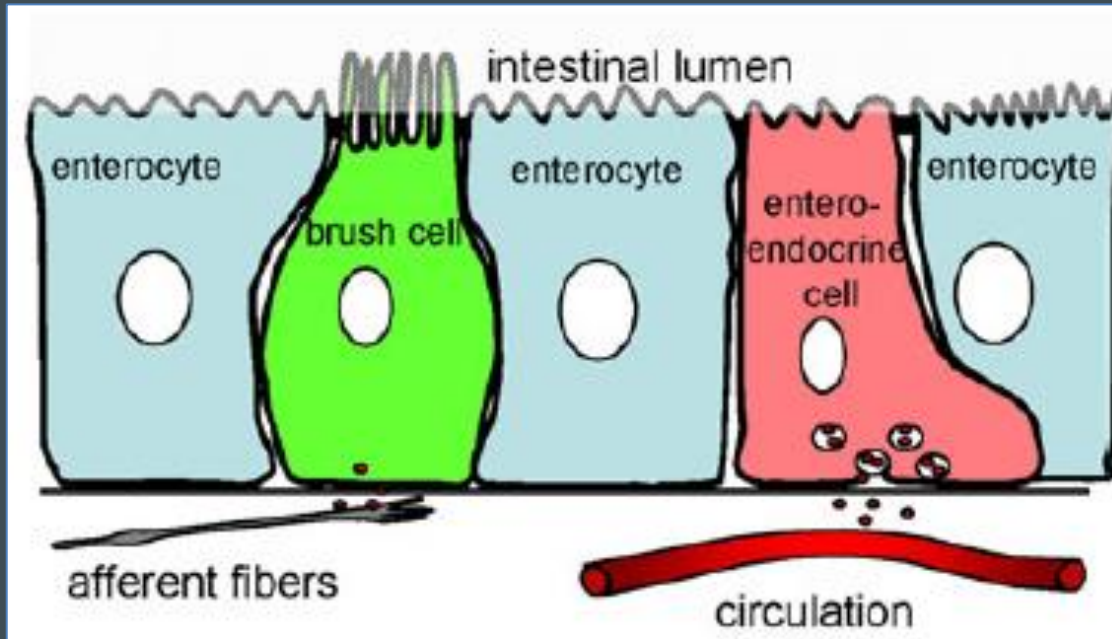


A key to nutrient sensing - intestinal sensor cells

(Breer et al., 2012)



A key to nutrient sensing - intestinal sensor cells

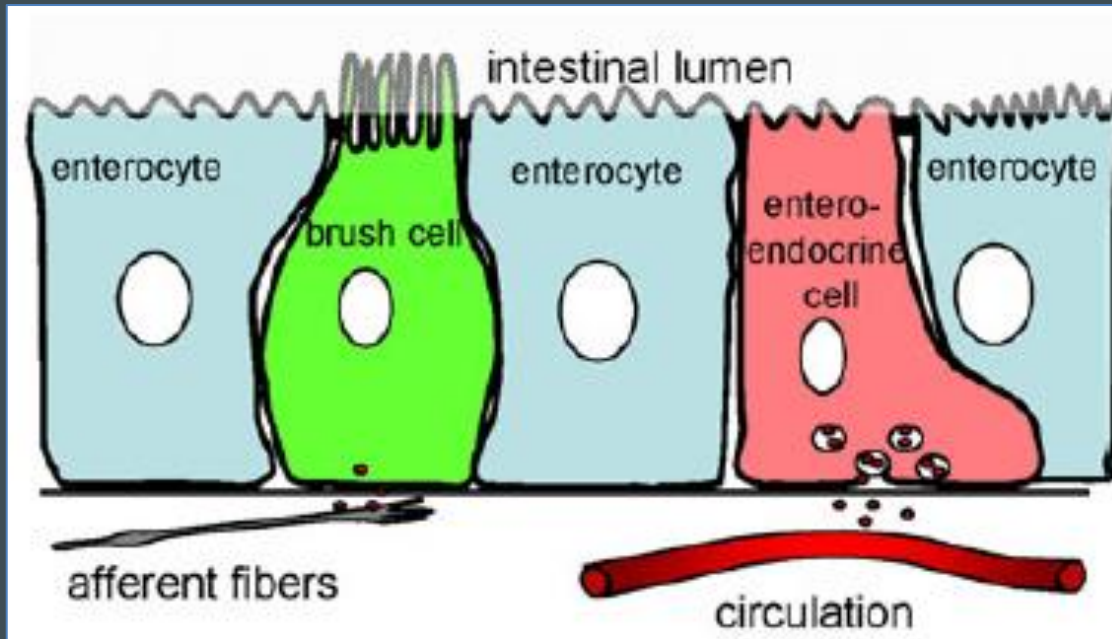


Enterocytes (absorptive cells):

- transfer metabolites (glucose, AA) and charged molecules by ion-coupled transporters and exchangers;
- may release chemical mediators (oleoylethanolamide – OEA, NO) which can activate afferent nerve fibres.



A key to nutrient sensing - intestinal sensor cells

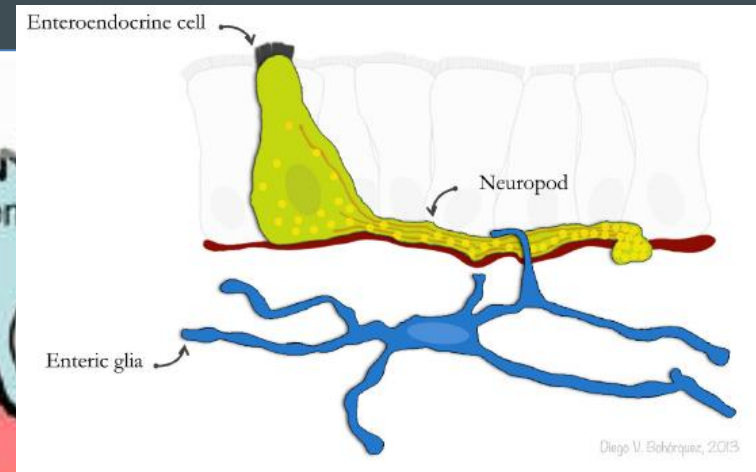
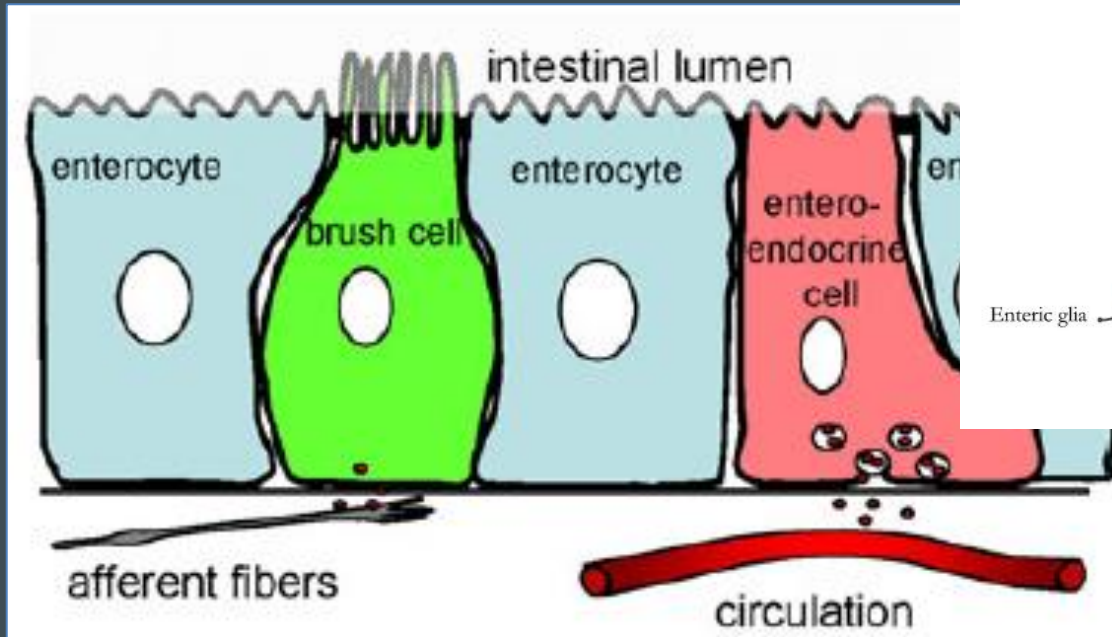


Brush cells (<1% epithelial cells, long microvilli, cell marker - cytokeratin 18):

- structure homology with gustatory sensory cells in the lingual taste buds;
- express gustatory G-protein (α -gustducin) and other messengers and receptors important for gustduction (e.g., T1R1, T1R3, TRPM5);
- elicit paracrine signals (NO?, prostaglandins?), cholinergic (?) which can activate afferent nerve fibres, do not produce GI peptides.



A key to nutrient sensing - intestinal sensor cells



Enteroendocrine cells (<1% epithelial cells):

- produce and release >20 GI peptides that act locally, peripherally and centrally;
- control motility, secretion, absorption, cytoprotection and food intake;
- act on local afferent nerve fibers or nearby target cells or via the blood stream.

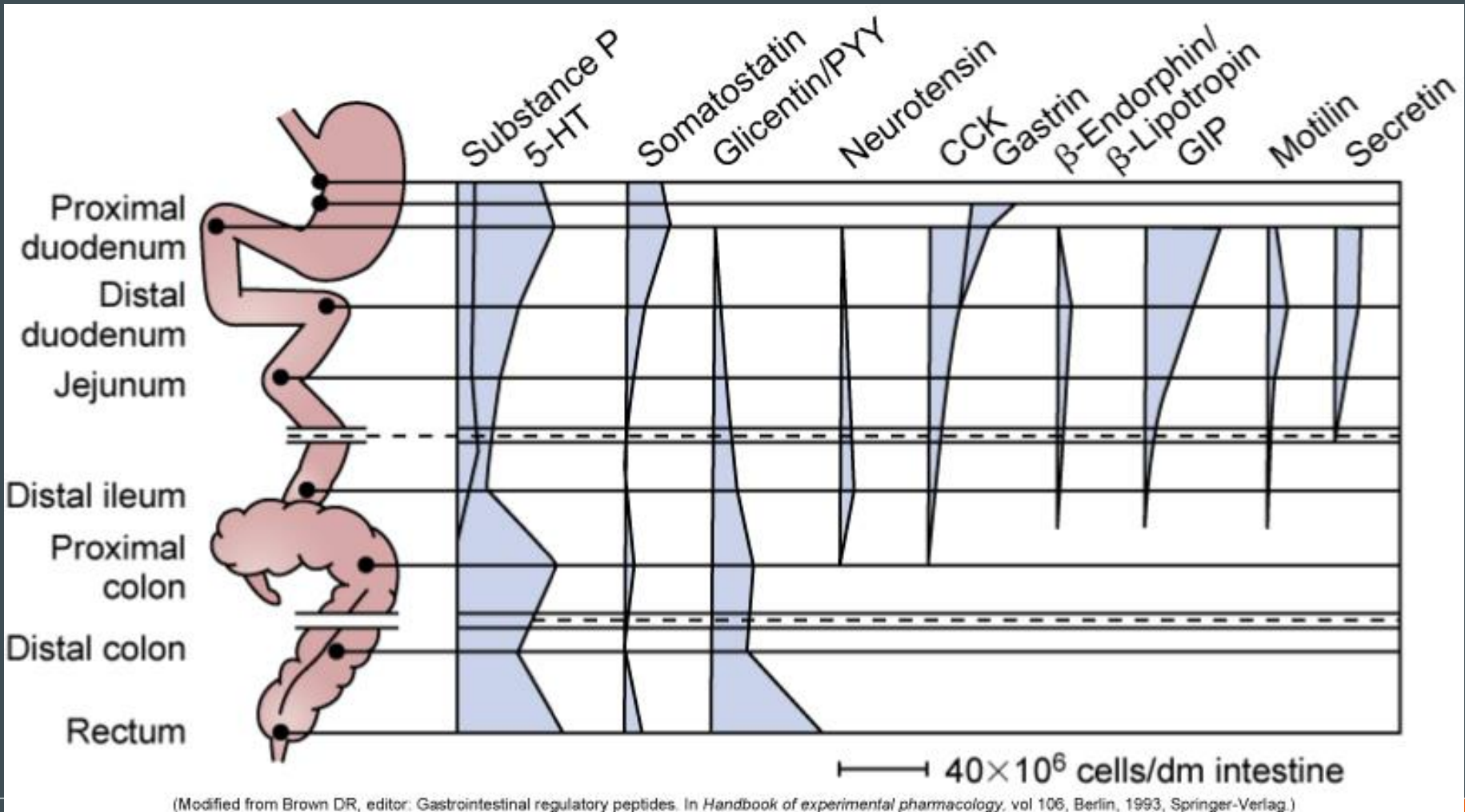


Enteroendocrine cells in the GI mucosa

Cell	GI peptide	Physiological function
G-cell	Gastrin	Control of gastric acid secretion
D-cell	Somatostatin	Inhibition of GI peptide release
X/A like cells	Ghrelin	Stimulation of food intake
S-cell	Secretin	Inhibition of gastric acid secretion, stimulation of pancreatic bicarbonate secretion
K-cell	GIP	Enhancement of insulin secretion
I-cell	CCK	Stimulation of pancreatic enzyme secretion and gallbladder contraction, inhibition of food intake
M-cell	Motilin	Enhancement of gut motility
L-cell	GLP-1, PYY	Enhancement of insulin secretion, inhibition of food intake, secretion and motility



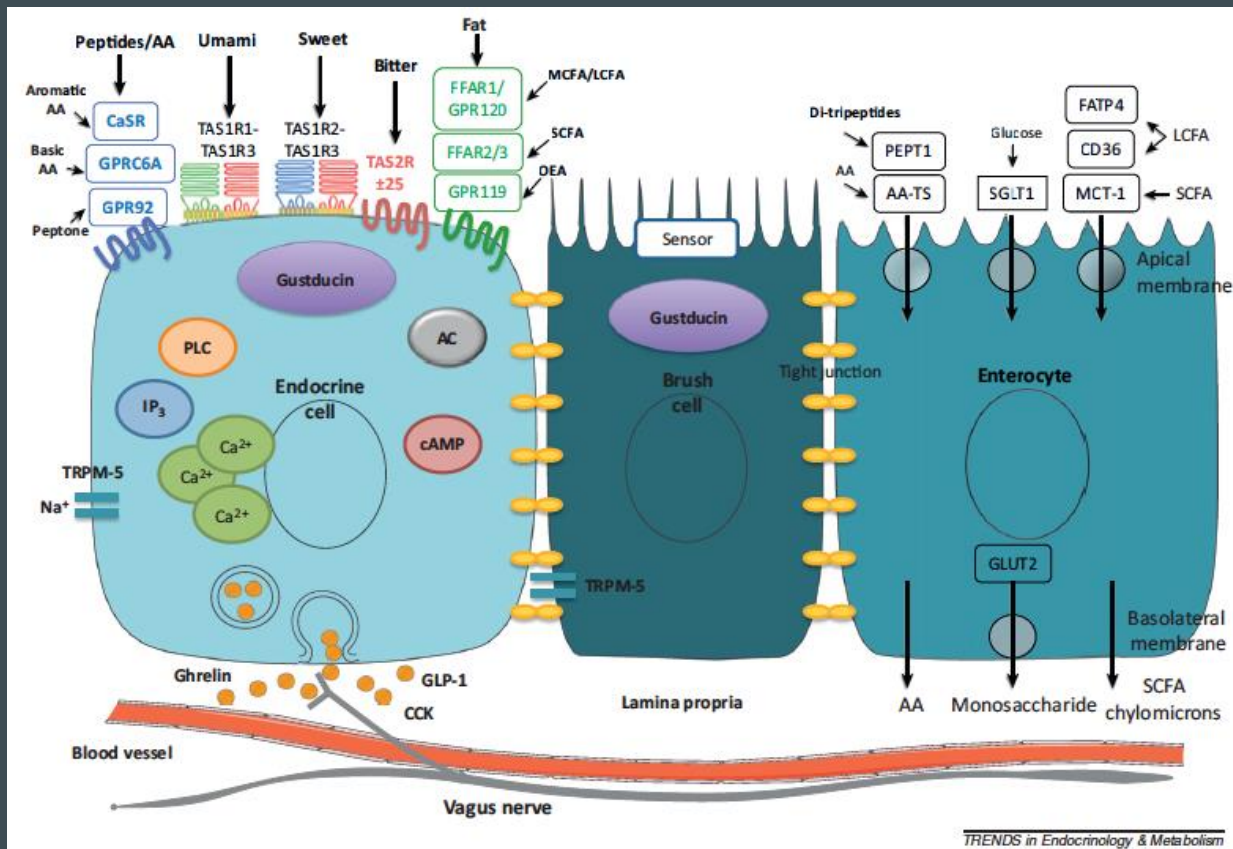
Abundance of endocrine cells in the GI tract



(Modified from Brown DR, editor: Gastrointestinal regulatory peptides. In *Handbook of experimental pharmacology*, vol 106, Berlin, 1993, Springer-Verlag.)



Pathways involved in chemosensory signaling in GI mucosa (Janssen & Depoortere, 2013)



Nutrients are sensed by different GPCR and transporters located on endocrine cells, brush cells, and enterocytes.

GPCRs induce release of second messengers that lead to the release of GI peptides or transmitters...

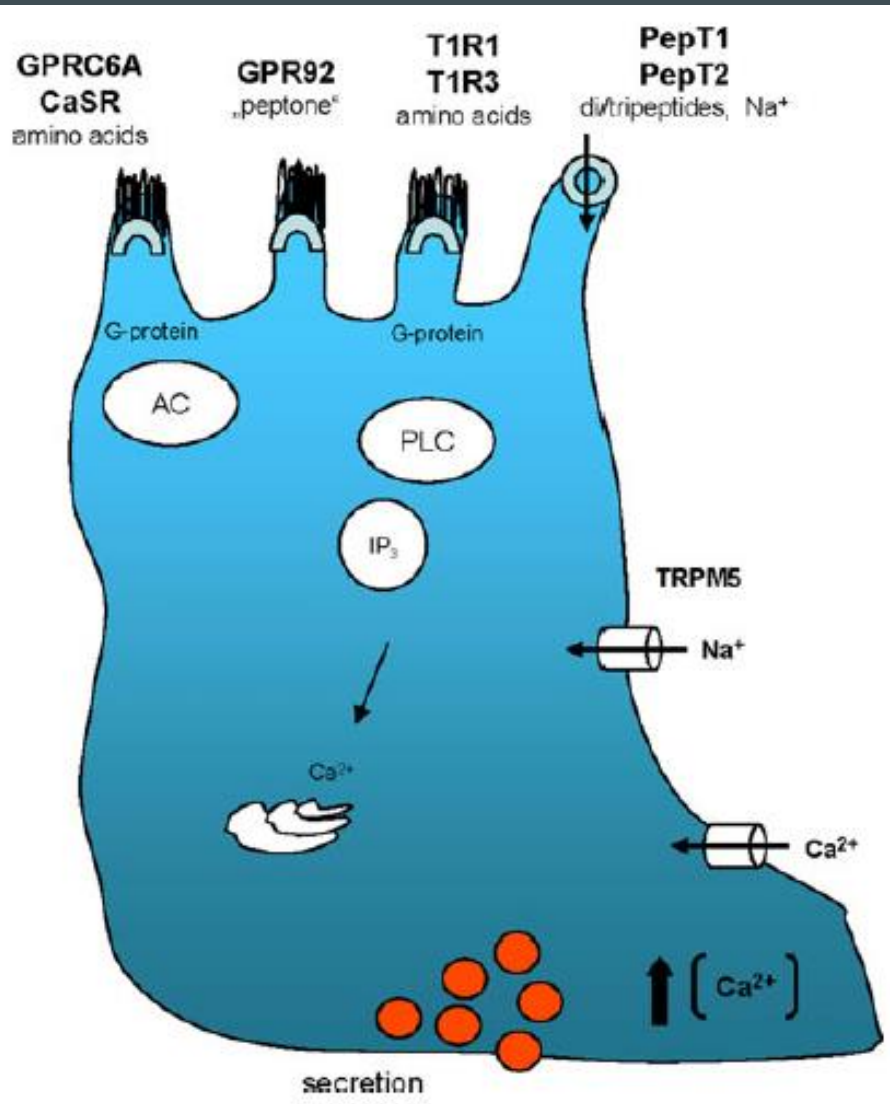
... which can communicate with the brain:

- directly (bloodstream)
- indirectly (vagal nerve).

GPCR - G-protein coupled receptor



Sensing of protein degradation products and AA (Breer et al. 2012)



G-protein coupled receptors:

- GPR92 – protein degradation products taste receptor
- GPRC6A – basic AA taste receptor
- CaSR – aromatic AA taste receptor
- T1R1, T1R3 – AA umami taste receptors

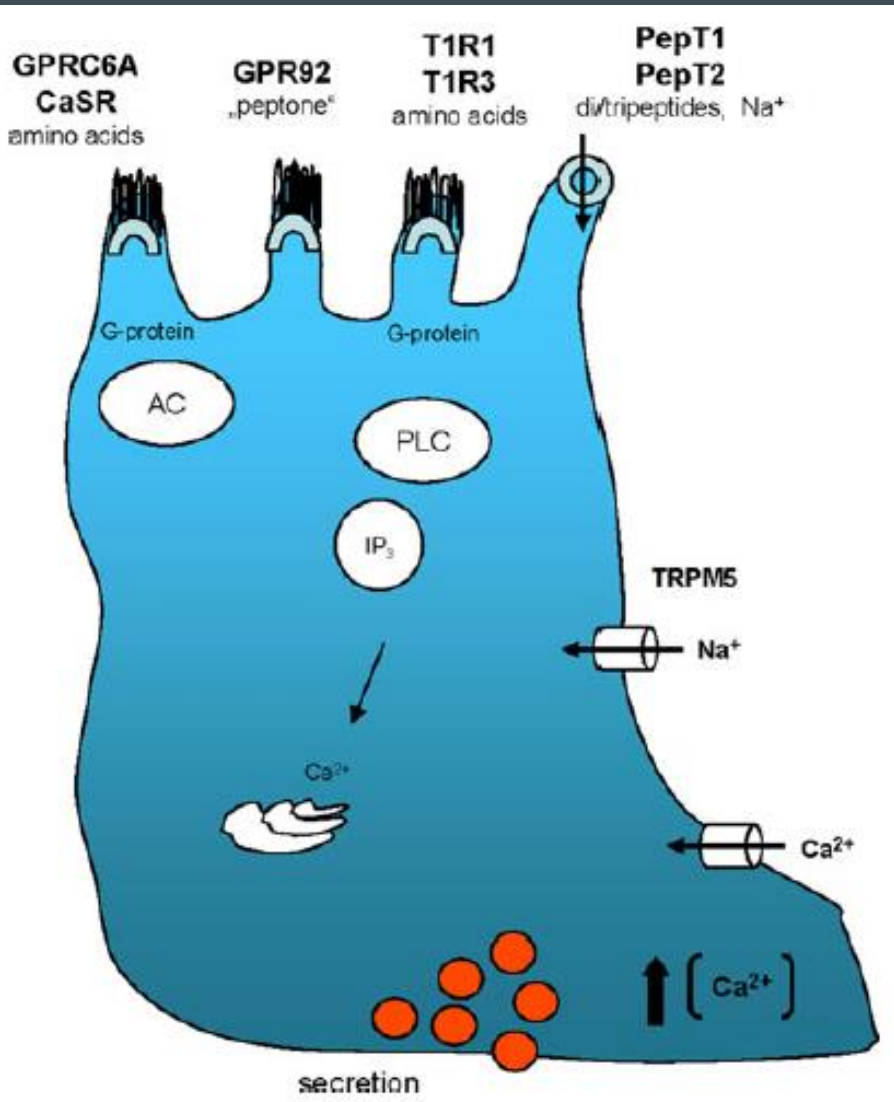
Nutrient transporters:

- PepT1, PepT2 – di- tripeptides transporters

GI peptides released: gastrin, secretin, CCK, somatostatin, GLP-1

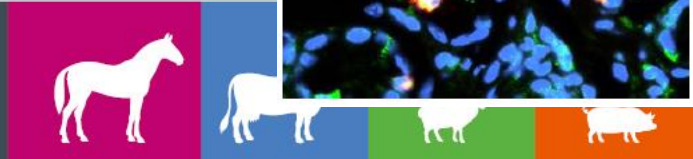
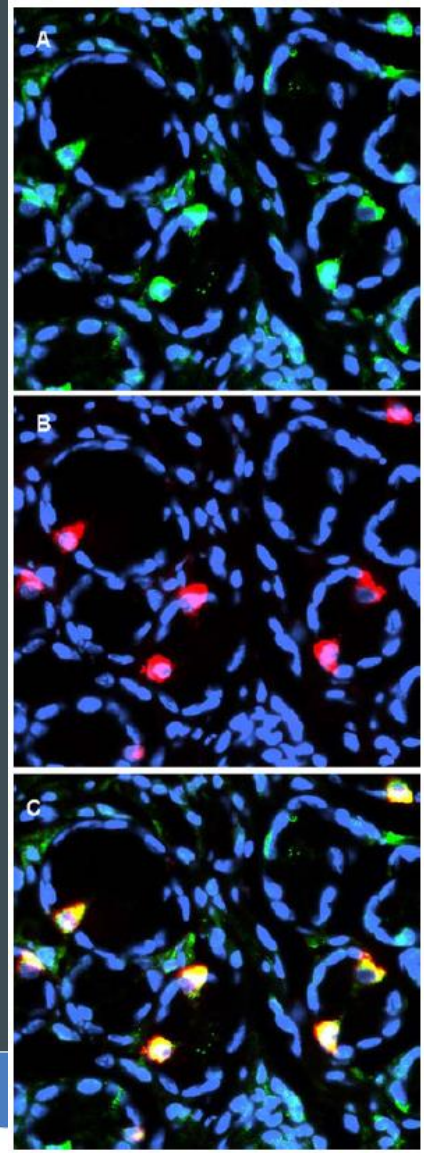


Sensing of protein degradation products and AA (Breer et al. 2012)

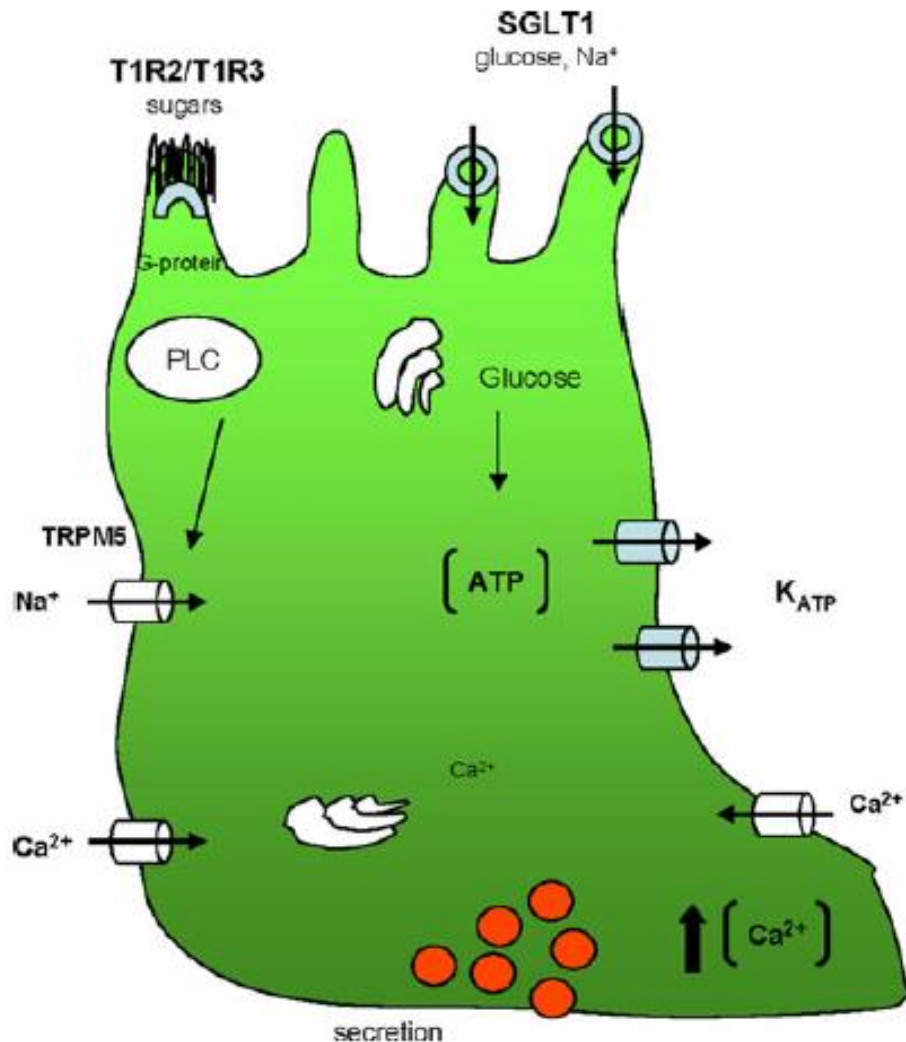


Stomach antrum: GPR92 and gastrin staining.

All gastrin cells express GPR92 suggesting that gastrin can be specific taste signal to protein degradation products.



Sugar sensing of intestinal epithelial cells (Breer et al. 2012)



G-protein coupled receptors:

- T1R2/T1R3 – sweet taste receptor

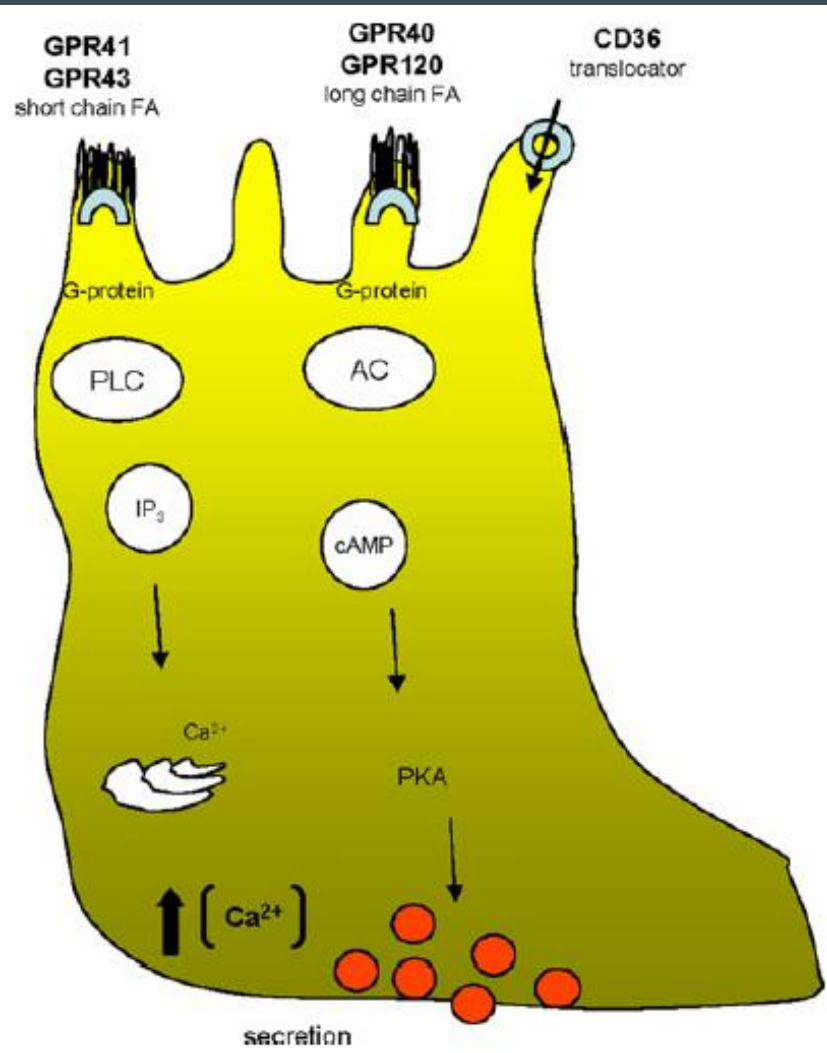
Nutrient transporters:

- SGLT1 – glucose transporter with taste receptor function

GI peptides released: GLP-1, GIP, ghrelin



Lipid sensing of intestinal epithelial cells (Breer et al. 2012)



G-protein coupled receptors:

- GPR40, GPR120 – LCFA, MCFA receptors
- GPR41, GPR43 – SCFA receptors

CD36 - LCFA translocator, can also contribute to lipid sensing

GI peptides released:

GPR120 - GLP-1, CCK

GPR40 - CCK

GPR41, GPR43 (large intestine) - PYY



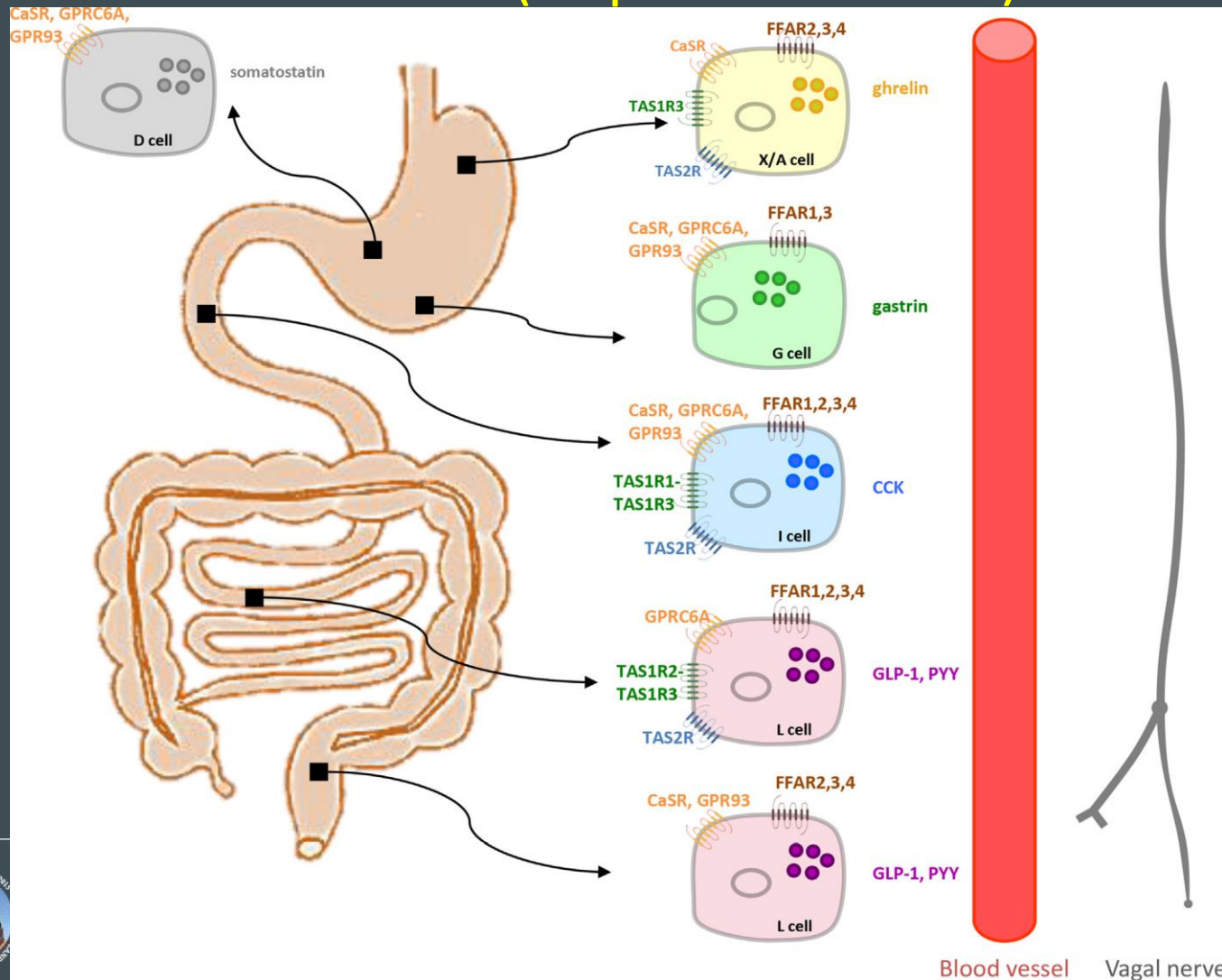
Sensing of non-nutrients by gut epithelial cells

(Breer et al. 2012)

- T2Rs – family of bitter taste receptors (endocrine cells which release CCK, GLP-1, and PYY):
 - second line of quality assesment;
 - initiate protective reactions (vomiting, delayed gastric emptying, reduced absorption, enhanced anion secretion in the colon).
- T2Rs – stimulate ghrelin release (bitter herbs)
- OR – odorant receptors (?) volatile components in the colon (serotonin ?)



Distribution of taste receptors on endocrine cells that control the release of gut peptides in response to nutrients (Depoortere 2015)



Intestinal sensor cells - summary

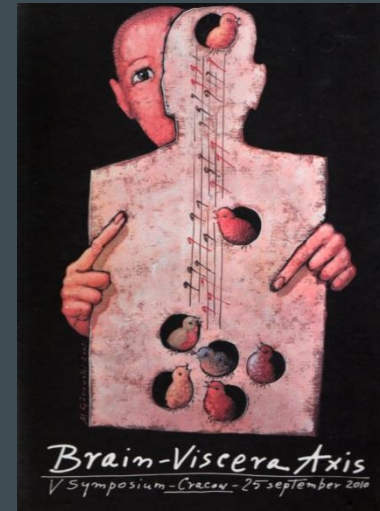
- Gut contains specific sensory mechanisms that may „see” individual nutrients in the diet.
- Nutrient sensors share signaling pathways activating common GI regulatory peptides.
- Differential responses of GI peptides to nutrients are warranted by the site and intensity of GI peptide release.



How the brain is informed?

- hormonal via bloodstream pathway
- neural via vagal nerves
(glutamate, glucose, Na⁺)
- neurohormonal pathway

- metabolic pathway (e.g., glucose, lipids)
 - independent on brain-gut axis
 - brain itself can detect and respond to fluctuations in circulating nutrients
 - hypothalamus and brainstem nuclei are exposed to areas that lack blood-brain barrier and can therefore sense circulating substances

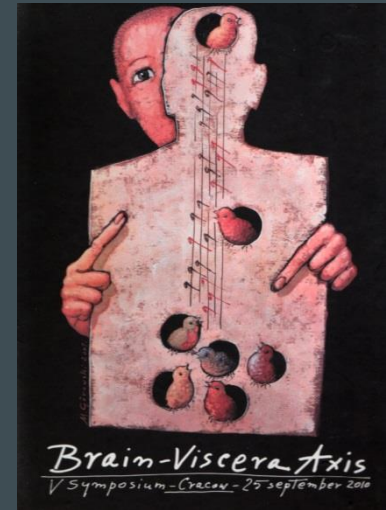


Brain-gut axis

- Epithelial cells
 - receptors/transporters
 - intracellular messengers
 - GI peptides

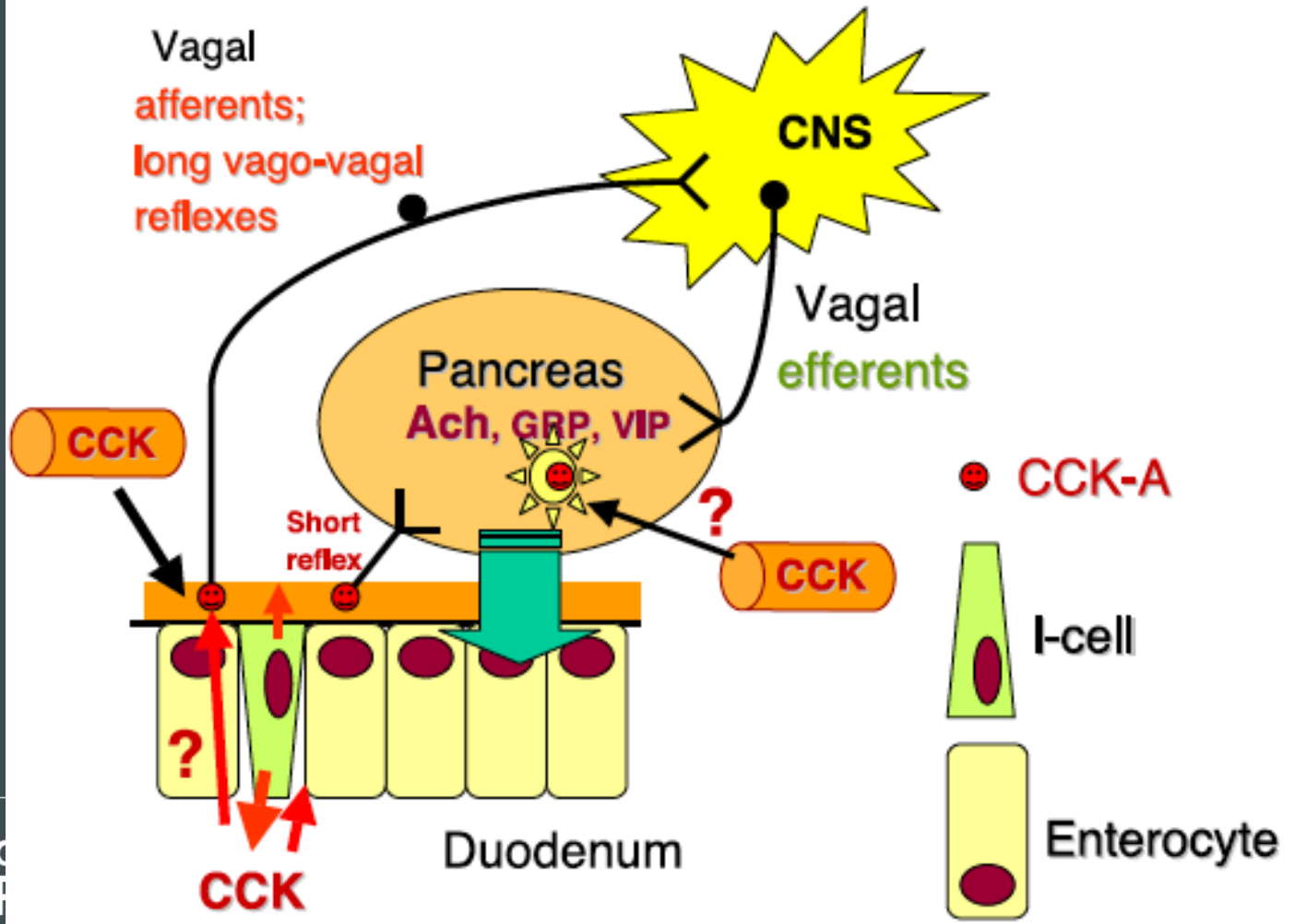
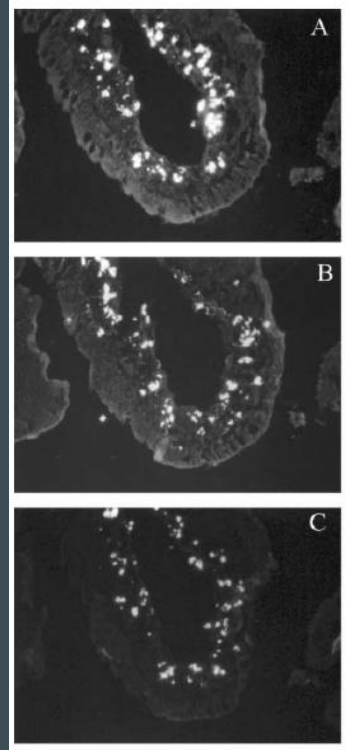
Bloodstream vs neural pathways

- Brain
- Microbiota and brain-gut axis

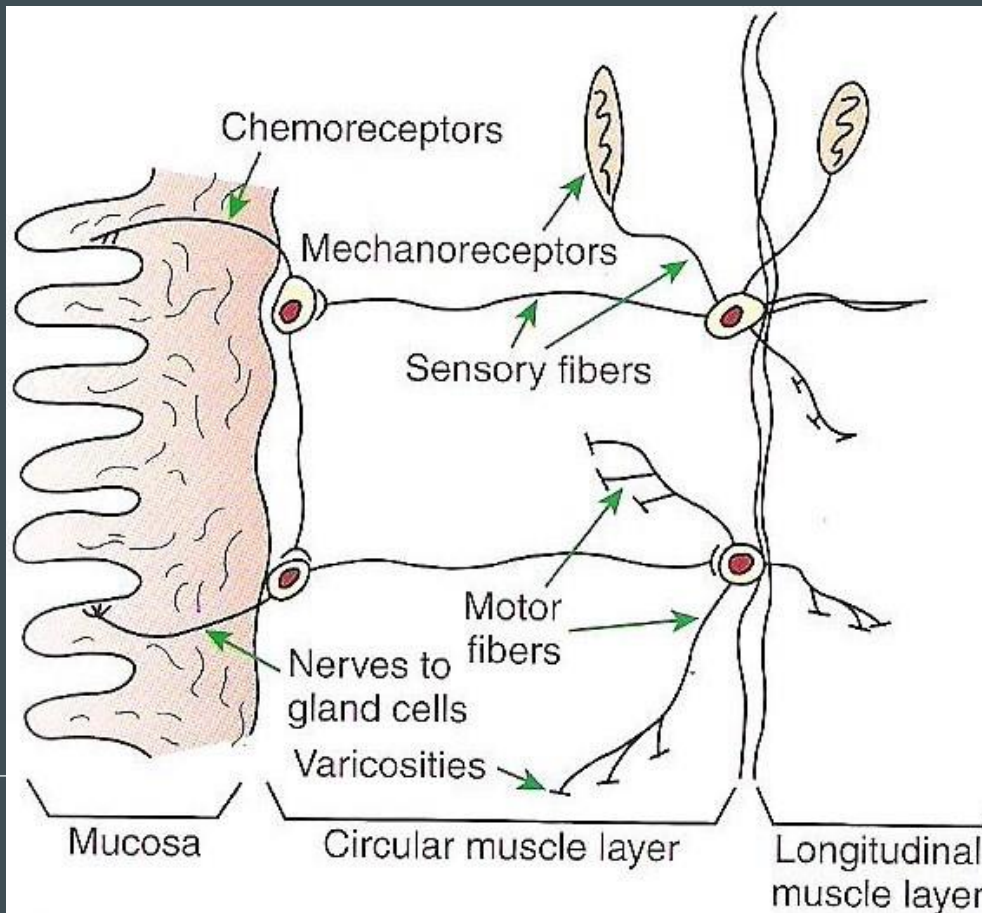


Neurohormonal control of the exocrine pancreas via CCK and vagal nerves

S.J. Konturek et al. / European Journal of Pharmacology 481 (2003) 1-14



How the chemosensory signals get to the afferent nerves?



Afferent nerve fibers have no direct contact to the gut lumen, however, **may penetrate lamina propria!**

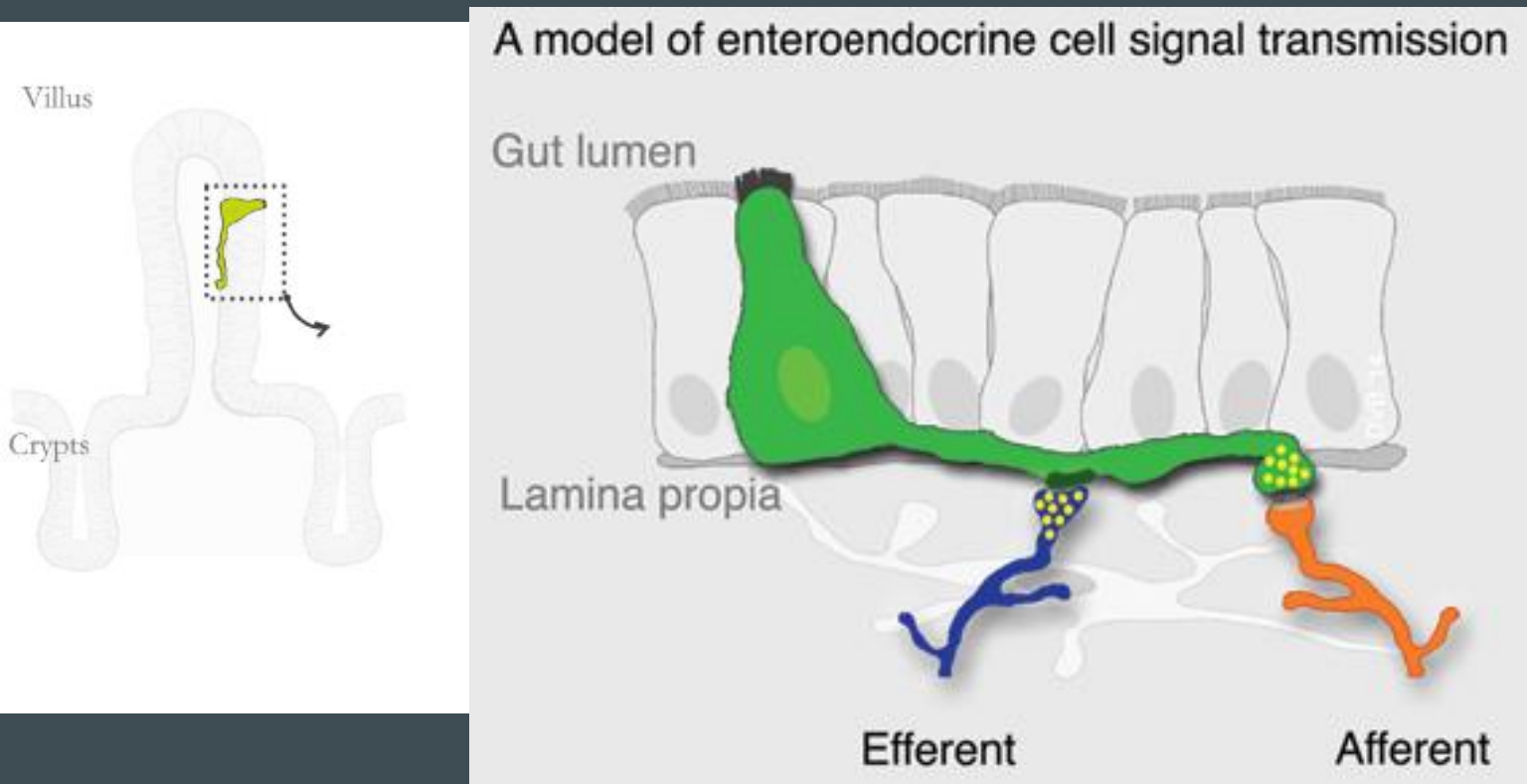
Primary afferent fibers are either vagal or ENS.

Intestinal sensor cells:

- operate as an interface between the gut lumen and the afferent nerve fibers (neuropodes)
- integrate signals from the gut lumen



Endocrine cell-enteric neuron connection



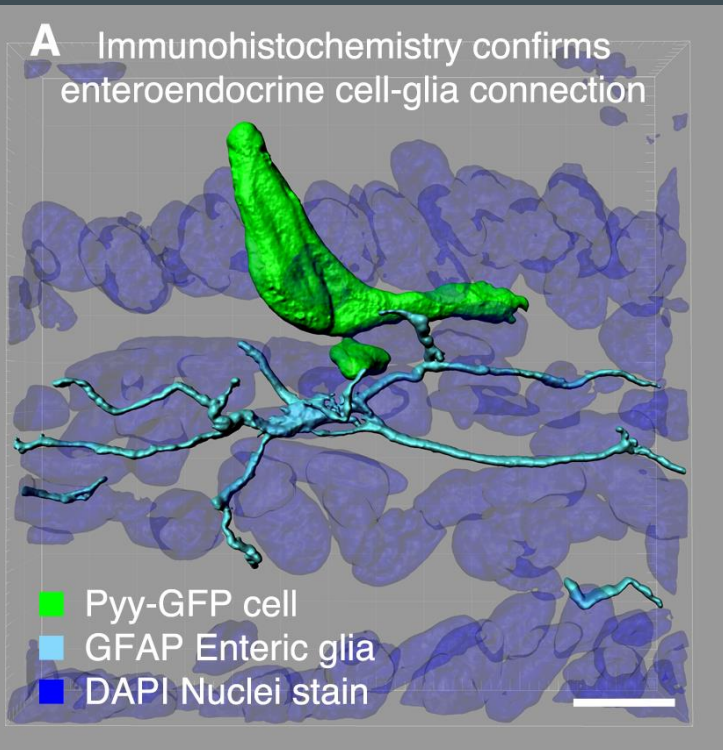
Bohórquez et al. An enteroendocrine cell-enteric glia connection revealed by 3D electron microscopy. PLoS One. 2014 Feb 26;9(2):e89881.

Bohórquez et al. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J Clin Invest. 2015 Feb;125(2):782-6.



Endocrine cell-enteric neuron connection

3D SEM technique – serial block scanning electron microscopy (SBEM) bridged with confocal microscopy (CM) was used to reveal specific synaptic connections of neuronal circuits and the endocrine cells (Bohórquez et al. 2014, 2015).



Neuropods (ca. 70 μm long) have axon-like characteristics:

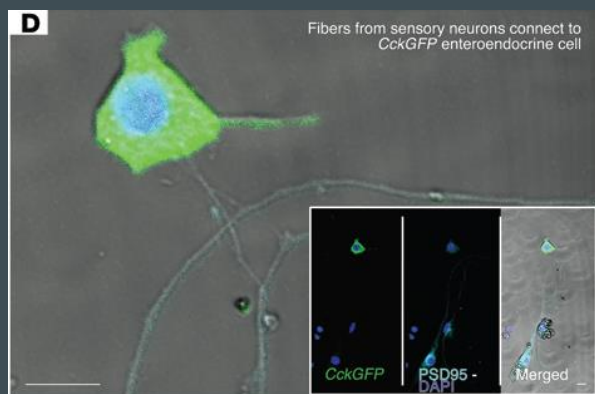
- contain abundant mitochondria, dense core vesicles with GI peptides and filaments;
- physical connections with enteric glia.

Length and number of neuropods depend on the presence of glial-derived neurotrophic factors.

Neuropods and enteric glia protrusions may pass through the lamina propria.



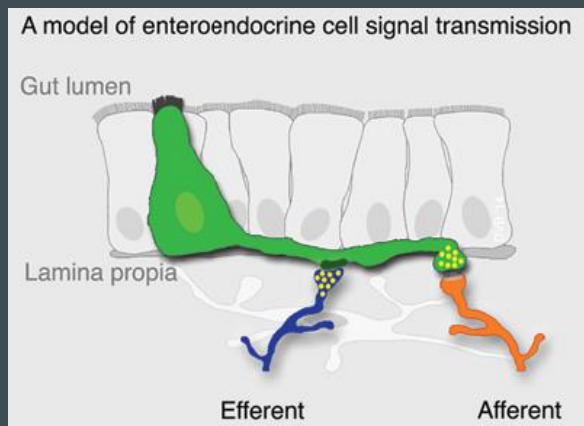
Endocrine cell-enteric neuron connection



Endocrine cell (EC) life-span is >60 days

EC do not come into close contact with blood vessels.

Neural endings penetrate the lamina propria and come into a close contact (<50 nm) with EC neuropods.




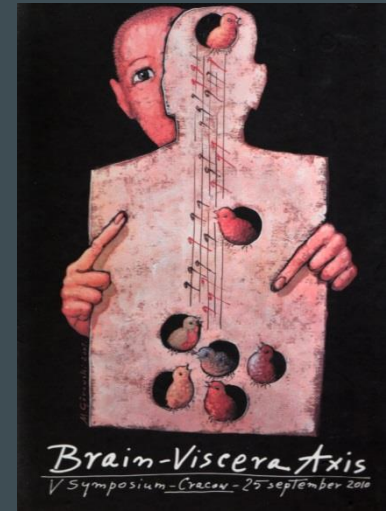
In the ileum and colon, 50-60% PYY-producing cells make synapse-like connections with neural sensory fibers. Both, efferent and afferent transmission is possible.

Efferent neurotransmission can modulate responsiveness of EC to nutrients and bacterial by-products in the gut.

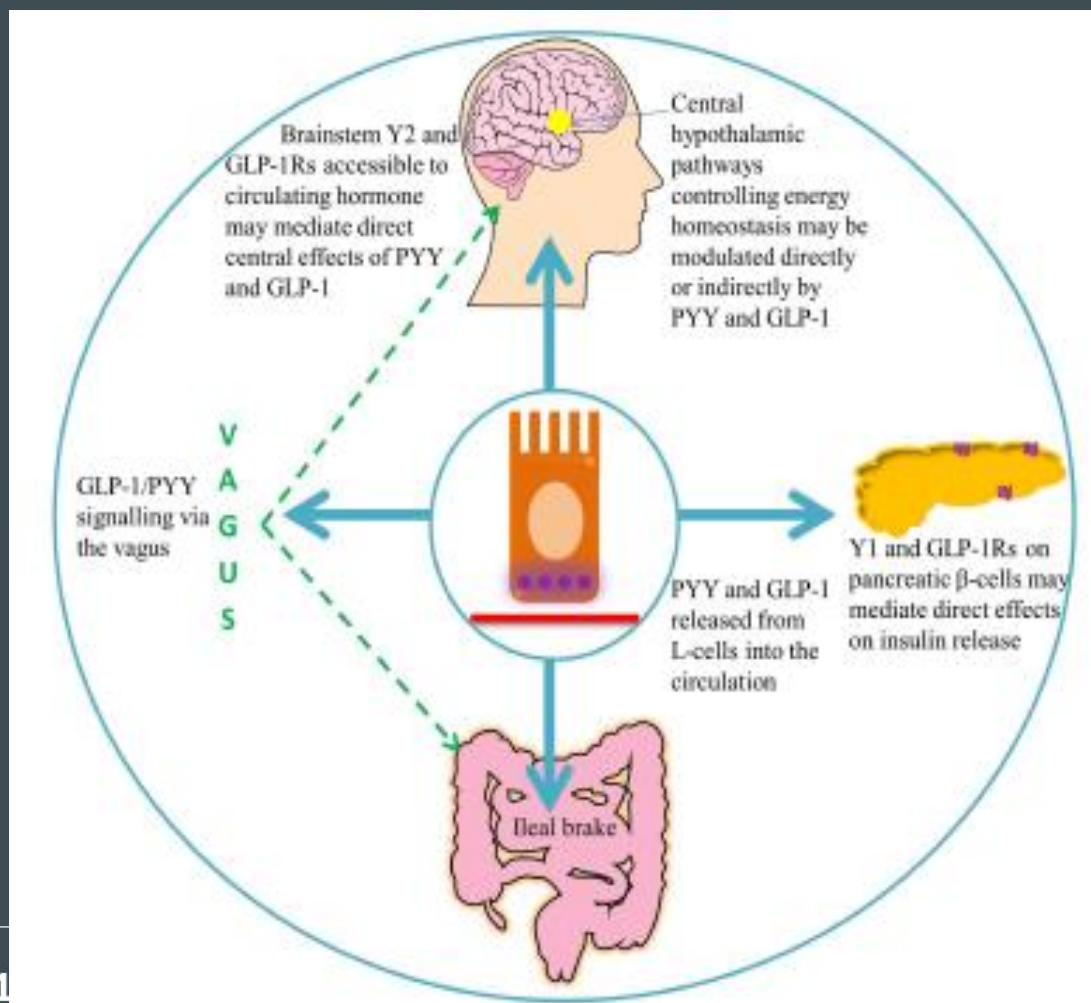


Brain-gut axis

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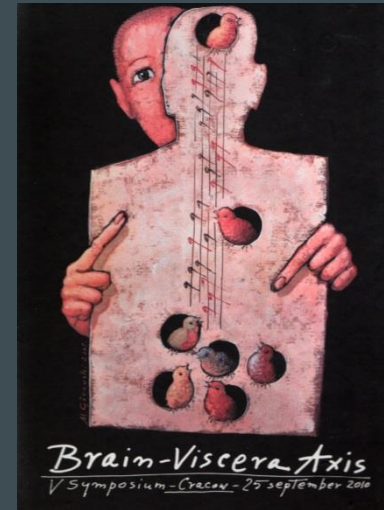
Multiple functions of PYY and GLP-1 released by L-cells in response to nutrient stimulation



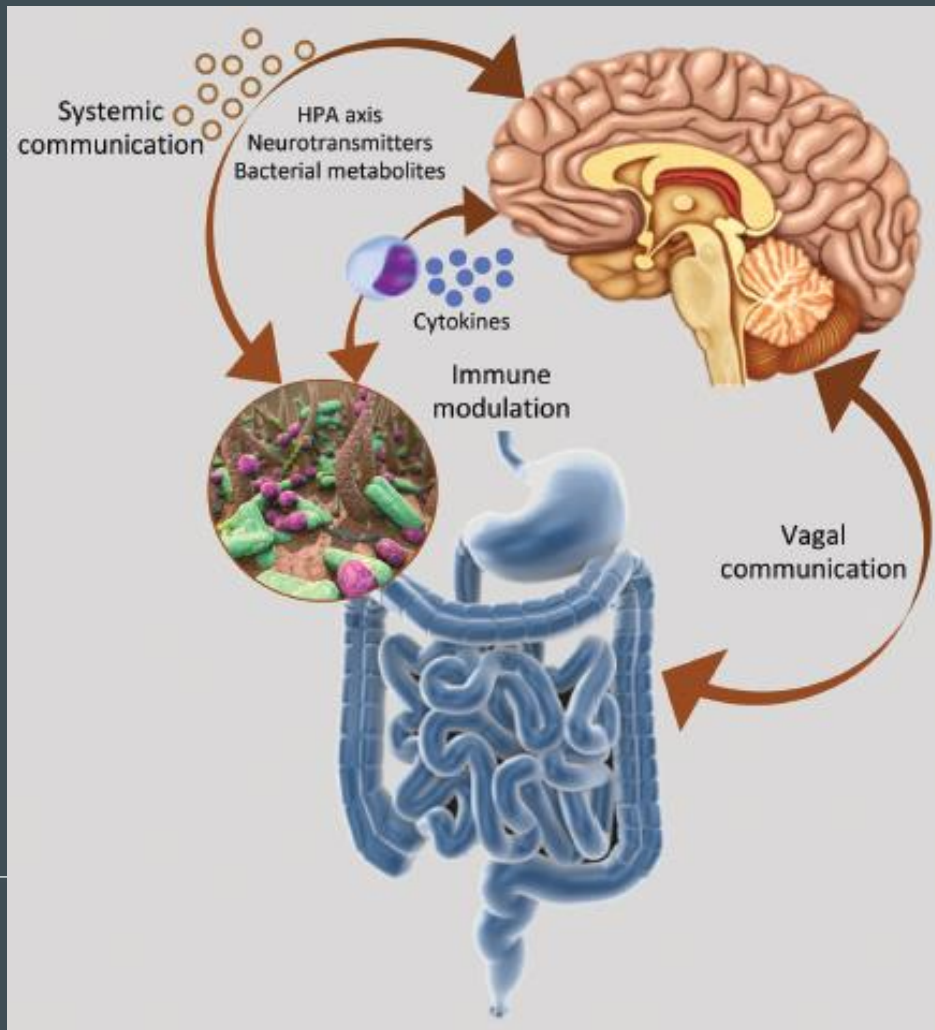
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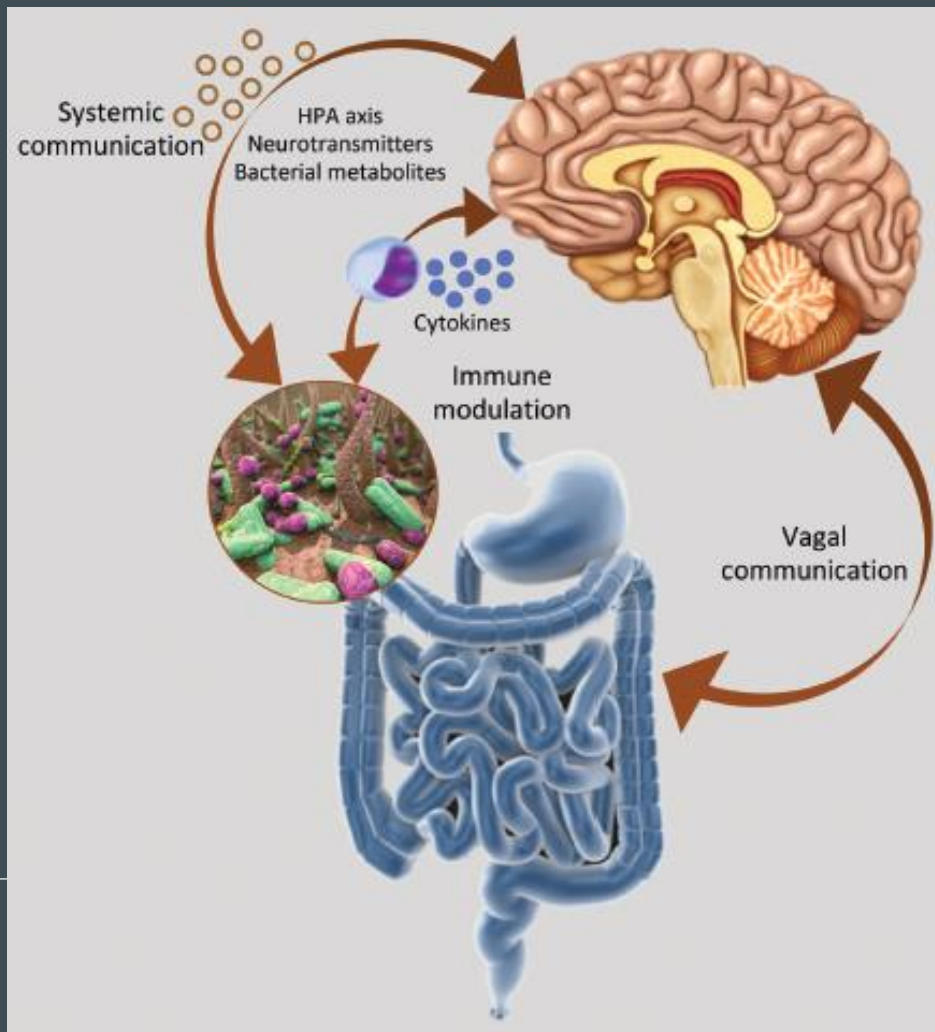
Routes of communication between microbiota and the brain



- Vagal afferent fibers (brain-gut axis)
- Immune pathway
 - Hypothalamic-pituitary-adrenal axis
- Production of active metabolic substances which can induce sense signals like the nutrients (e.g., SCFA, protein degradation products, AA)



Routes of communication between microbiota and the brain



Vagal afferent fibers mediate effects of:

- *Campylobacter jejuni*
- *Lactobacillus rhamnosus*

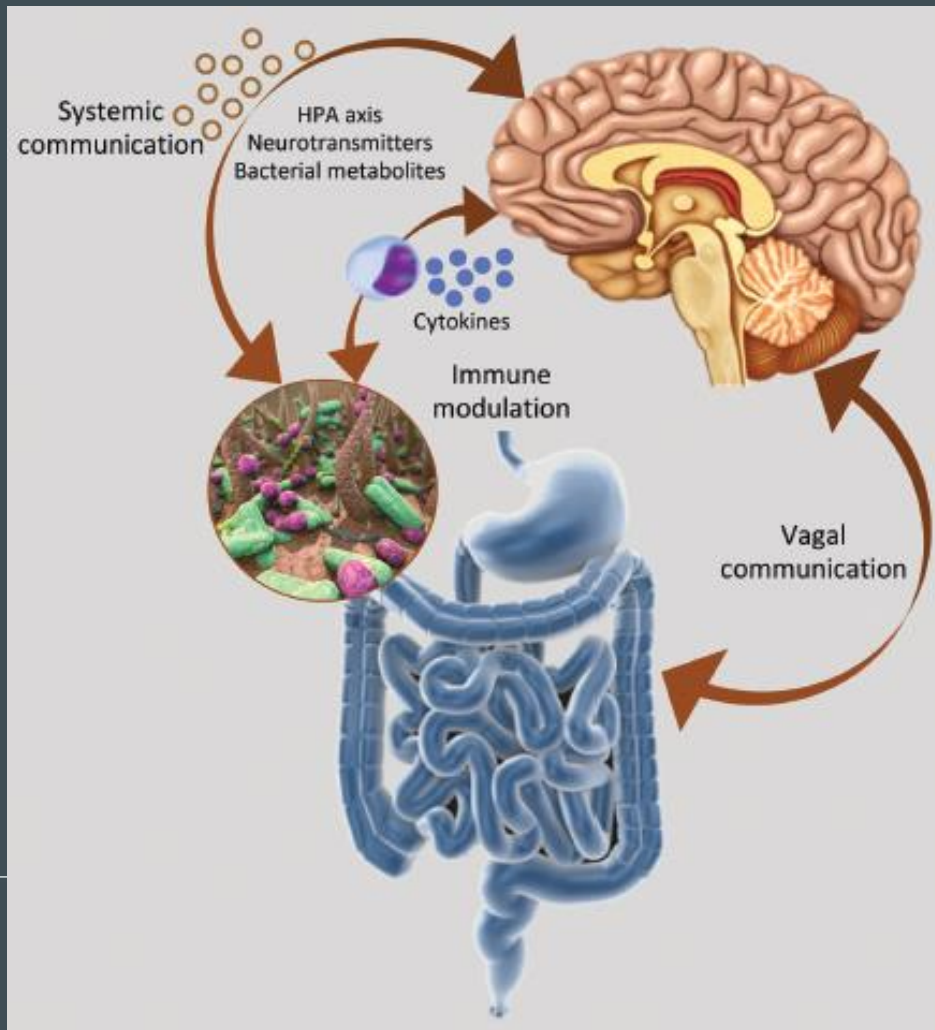
Central effects:

- behavioural (anxiety, depression), respectively, ↗ and ↘

These effects do not appear in vagotomized animals



Routes of communication between microbiota and the brain



GI immune system mediates CSN activity via circulating cytokines causing:

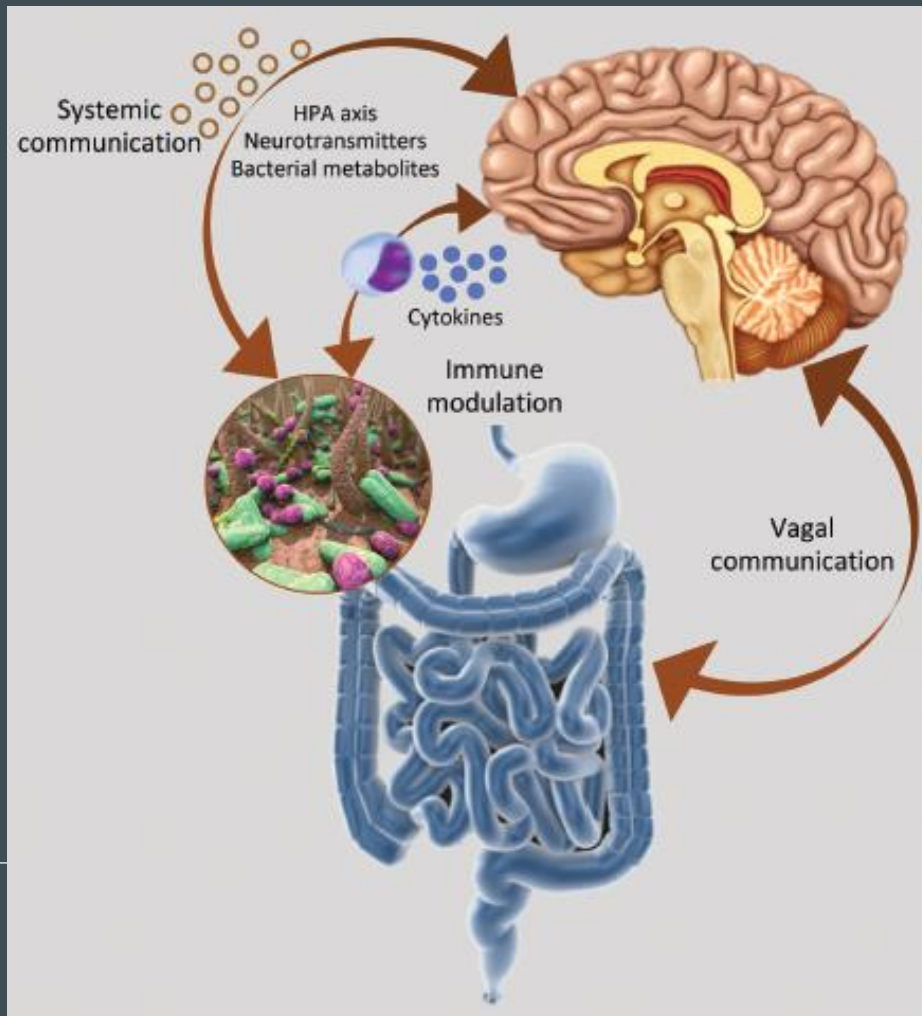
- anorexia,
- anhedonia,
- lower pain threshold,
- slowed psychomotor function

Often local immune activation is associated with:

- altered gut barrier function,
- ENS activation,
- changed sensory-motor function



Routes of communication between microbiota and the brain



Microbials can produce and secrete neurotransmitters:

- GABA,
- serotonin,
- catecholamines,
- histamine

which can affect brain functions via enterochromaffin cells and/or ENS/vagal nerves

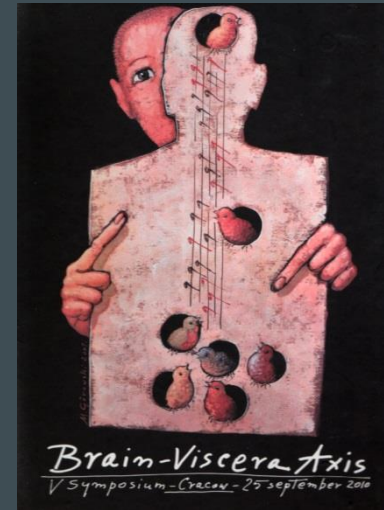
Microbials can produce and secrete:

- SCFA (satiety signals)
- Tryptophan (improved mood)



Summary

- The brain-gut axis via the vagal nerve is the autonomic neurohormonal pathway which integrates brain and gastrointestinal functions in response to nutrients in the gut.
- The mechanisms involved are complex due to abundance of input data.
- Novel findings support close neurohormonal relationship.
- Gut microbiota can modulate brain function via brain-gut axis.



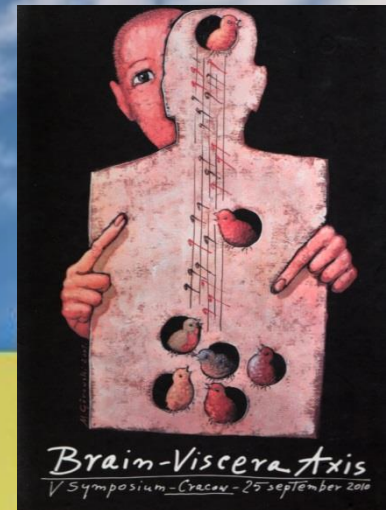
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Thank you
for your attention



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