Gut communication with its environment – Nutrient sensing & uptake

Prof. Barry Campbell

Infection Biology & Microbiomes, IVES

bjcampbl@liv.ac.uk
http://pcwww.liv.ac.uk/~bjcampbl/Nutrient.htm

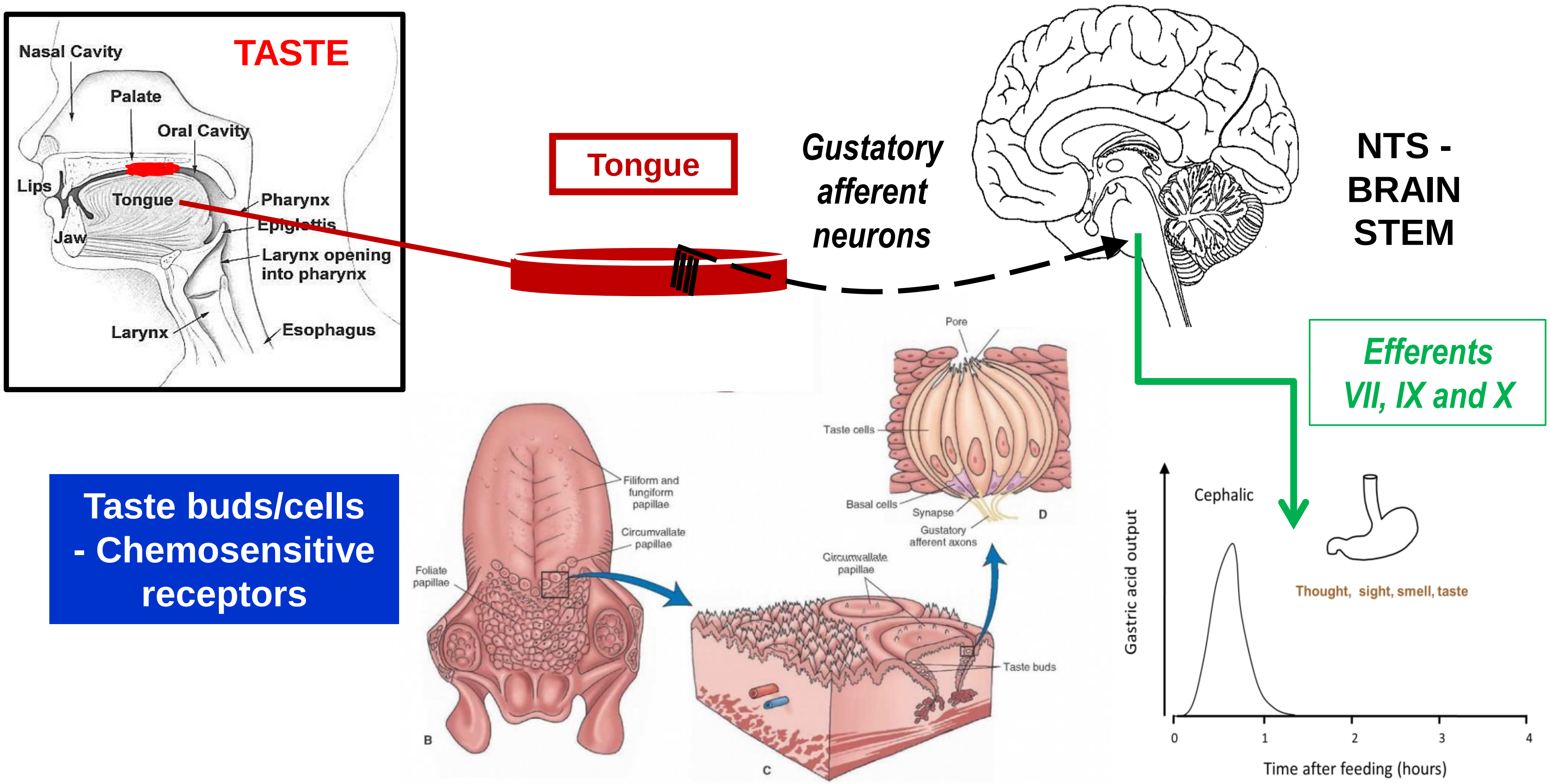
Learning Outcomes:

- **LO1 - Explain nutrient sensing in the GI tract and the "Gustotopic" map of the tongue**
- **LO2 - Describe the taste receptors including the different types and taste modalities**
- **LO3 - Describe the taste receptors in the gut (stomach, gallbladder, small intestine, colon) and define and explain the relevant nutrient transport mechanisms**
- **LO4 - Nutrient sensing and the potential for future medicines**

LO1

The tongue and taste

- **Taste receptors in the tongue send information via VII and IX cranial nerves to reach the nucleus of the solitary tract (NTS) in brain stem.**
- **Initiate visceral reflexes to gut to prepare for incoming meal (Cephalic response)**



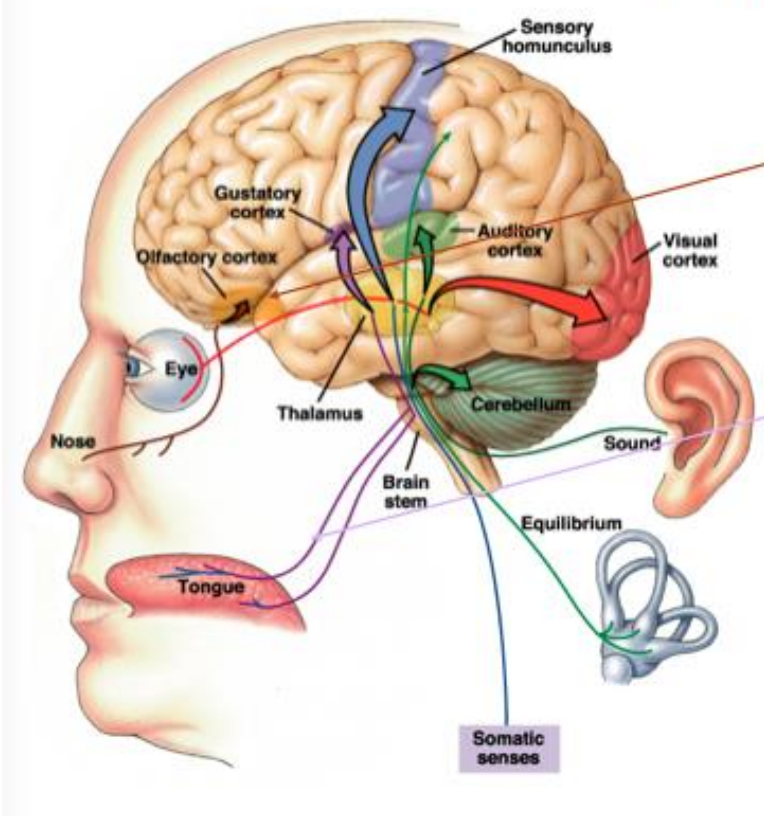
LO1

Taste, olfaction and gustatory responses

- **The nucleus of the solitary tract projects to a specific gustatory nucleus in the thalamus, and from there to the insular cortex.**

- **A great deal of what we call taste is based on olfactory signals. During a nasal infection the olfactory receptors are injured or blocked, we lose ~90% of our ability to appreciate flavours.**

Central pathways



- Olfactory pathways from the nose project directly to the cortex. Bi-directional projections give rise to smell localisation.
- Gustatory pathways pass through the thalamus before they project to their relevant cortical area. Taste afferents from the midbrain are involved in visceral reflexes (eg secretion of gastric juices

Main olfactory pathway

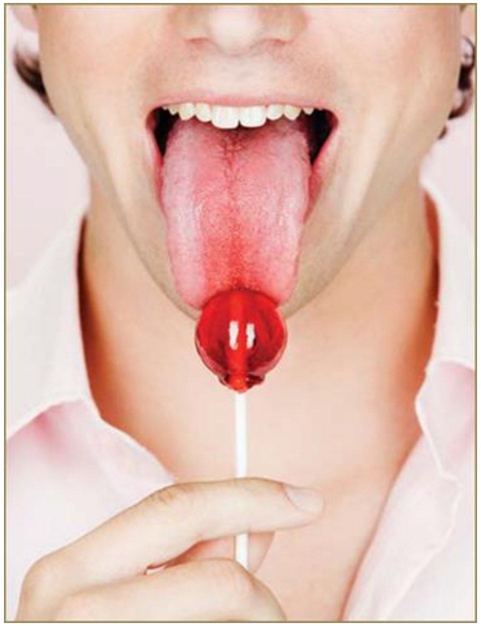
runs from the olfactory bulb to the primary olfactory cortex (piriform cortex) on the underside of the temporal lobe

Visceral responses

- Salivary secretion
- Gastric juice
- Pancreatic secretion
- Gallbladder contraction

Taste in the mouth – the gustotopic map

Old model

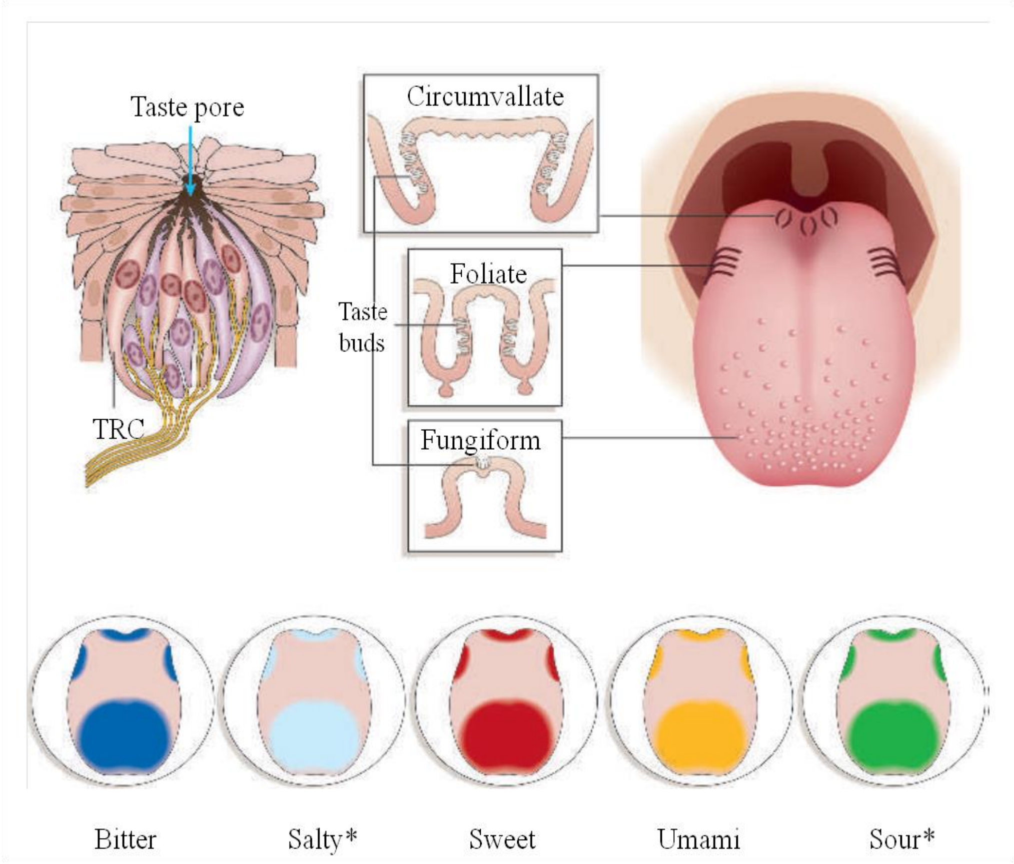


LO1

Taste in the mouth – the gustotopic map

Old model

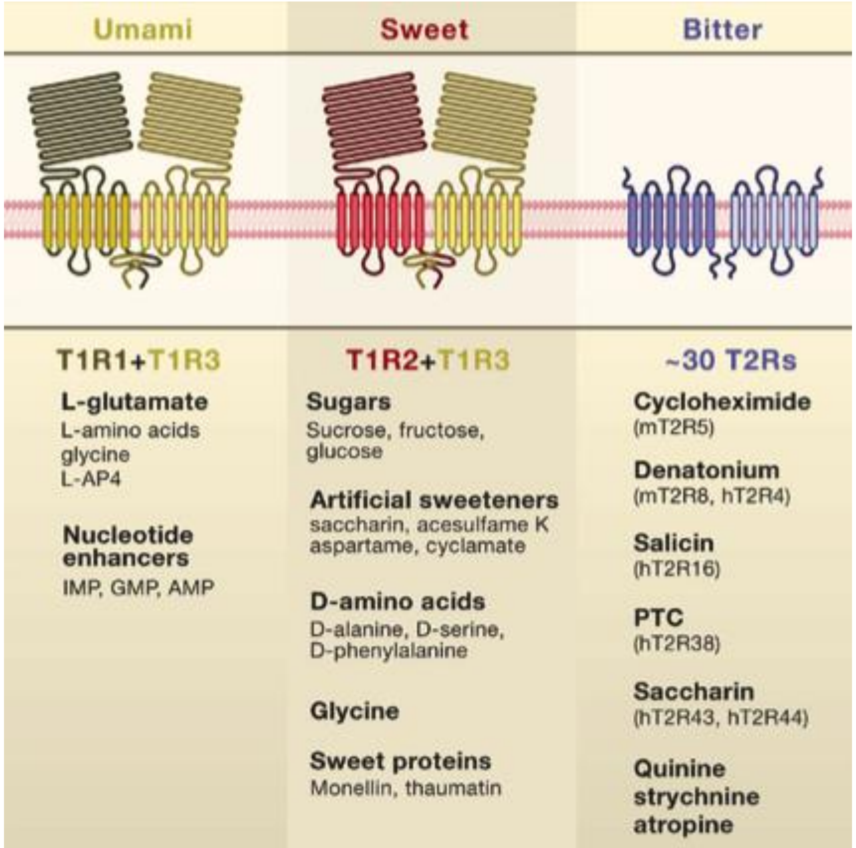
New model



Chandrashekar *et al.* Nature 2006, 444; 288-94

LO2

Lingual Epithelium Taste Receptors



Taste Receptor 1 (T1R) has three members. T1R1, T1R2 and T1R3

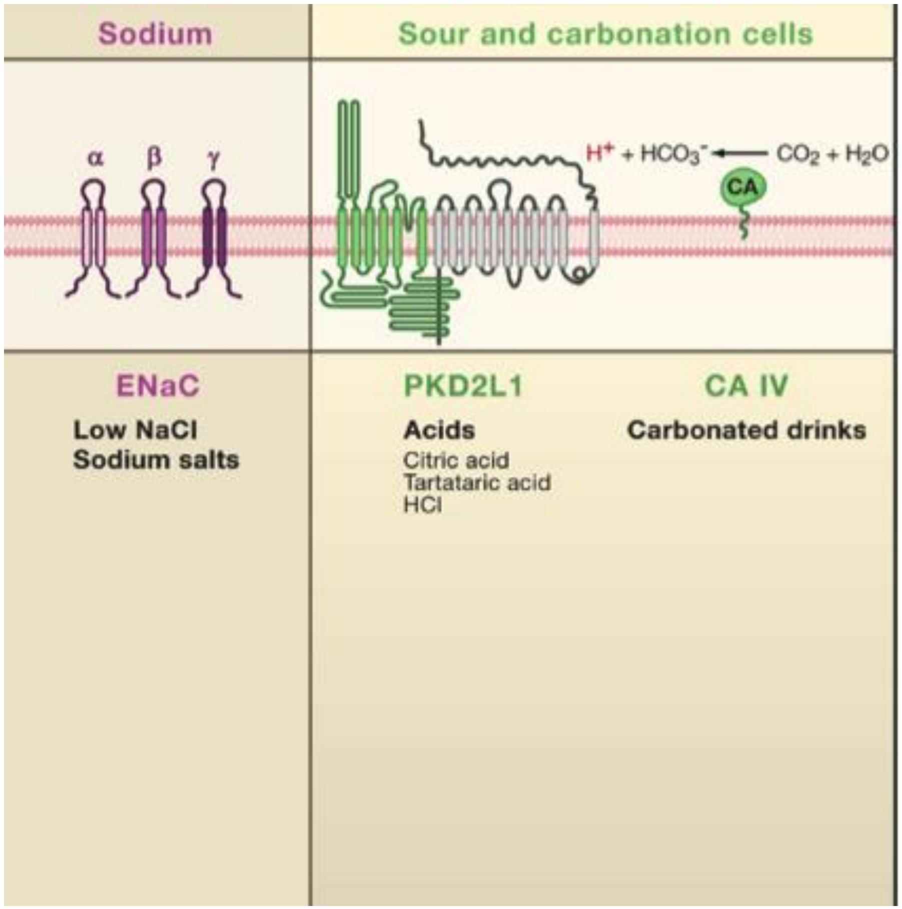
- Combination of T1R1+T1R3 = taste of L-amino acids (umami), taste of monosodium glutamate.
- Combination of T1R2+T1R3 = Sweet taste.

Taste receptor 2 family or T2Rs (~30 separate genes encode members of T2R family) = bitter taste.

- **These receptors are G protein (guanine nucleotide binding protein) coupled receptors (GPCRs).**
- **G-protein that couples to these receptors is called Gustducin, belonging to the Transducin family of GPCRs.**

LO2

Other Lingual Epithelium Taste Receptors



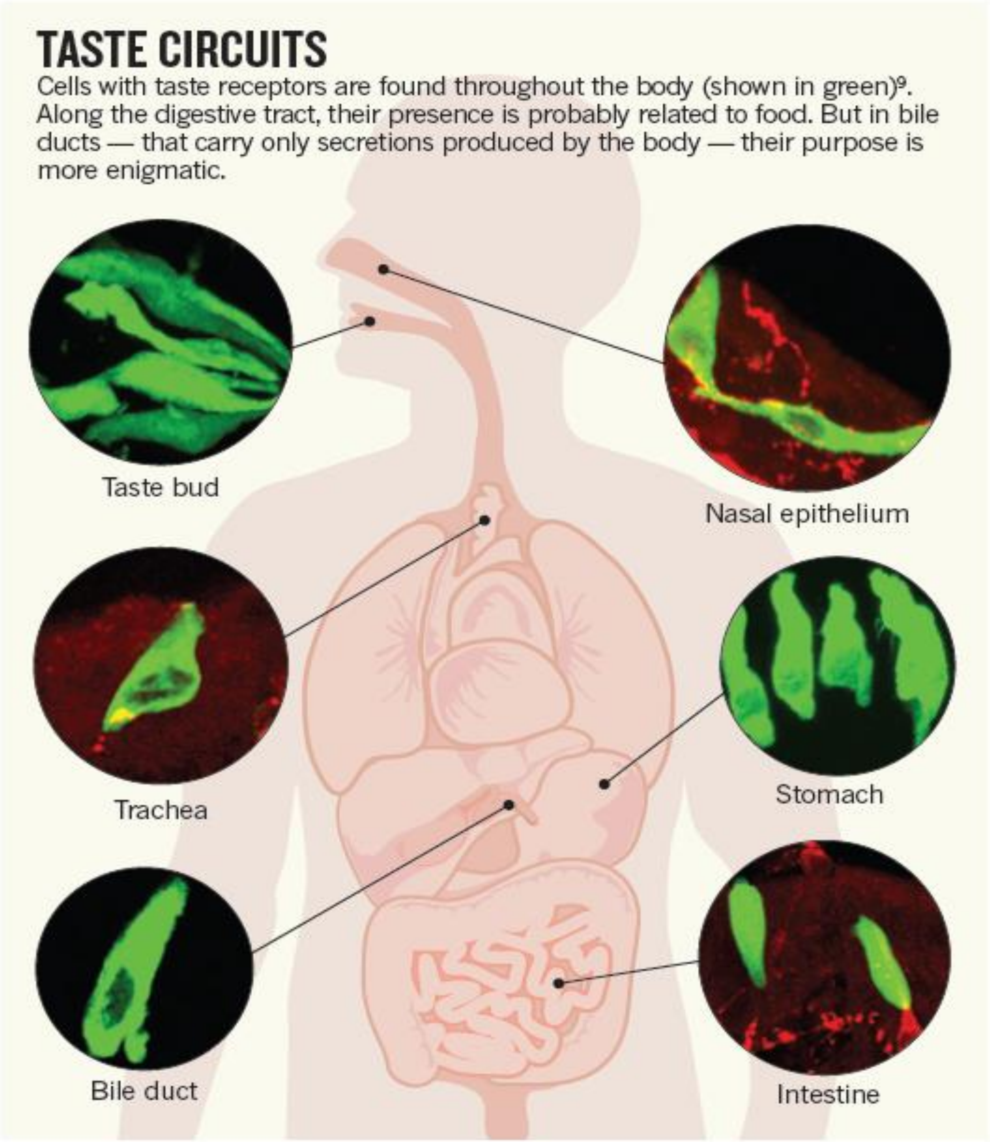
ENaC – epithelial Sodium (Na^+) channel is also found in taste receptors, where it plays an important role in **saltiness perception**.

PKD2L1 - reported to be a candidate receptor for **sour taste** based on molecular biological and functional studies

Roles still being defined

LO3

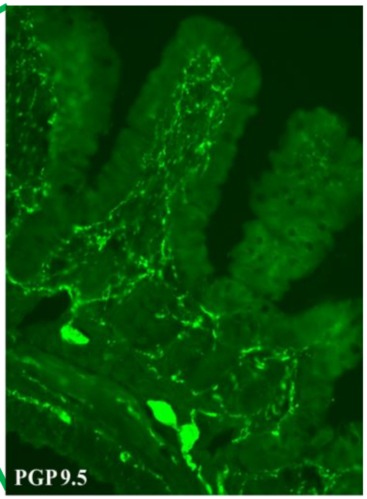
In much the same way as the tongue, the gut also tastes what we eat



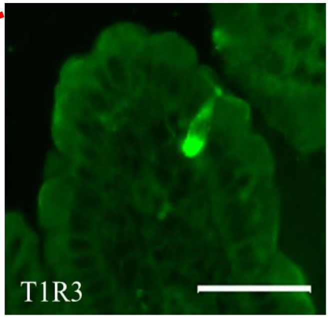
LO3

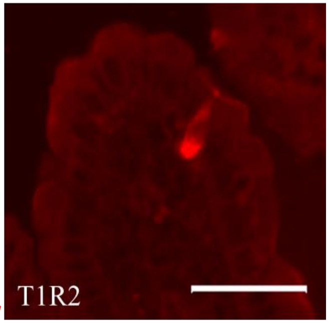
Gut enteroendocrine cells (EECs) - nutrient sensors

Nerve endings that enter the villi do not reach the luminal content. Hence EECs are central to the chemosensing pathway of the intestinal tract.



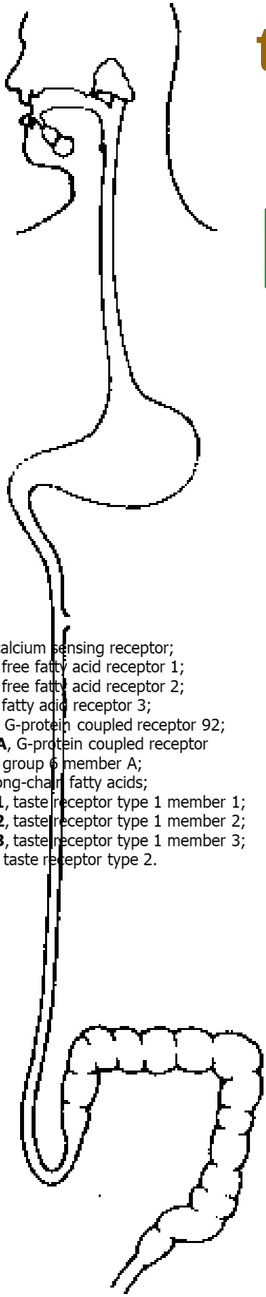
- There are at least 12 different EEC populations of the GI tract producing >20 hormones.
- Nutrient sensing GPCRs are expressed on the luminal membrane of EECs.
- Nutrient sensing through these receptors leads to secretion of key regulatory gut hormones





LO3

Taste receptors on gut endocrine cells control the release of hormones in response to nutrients

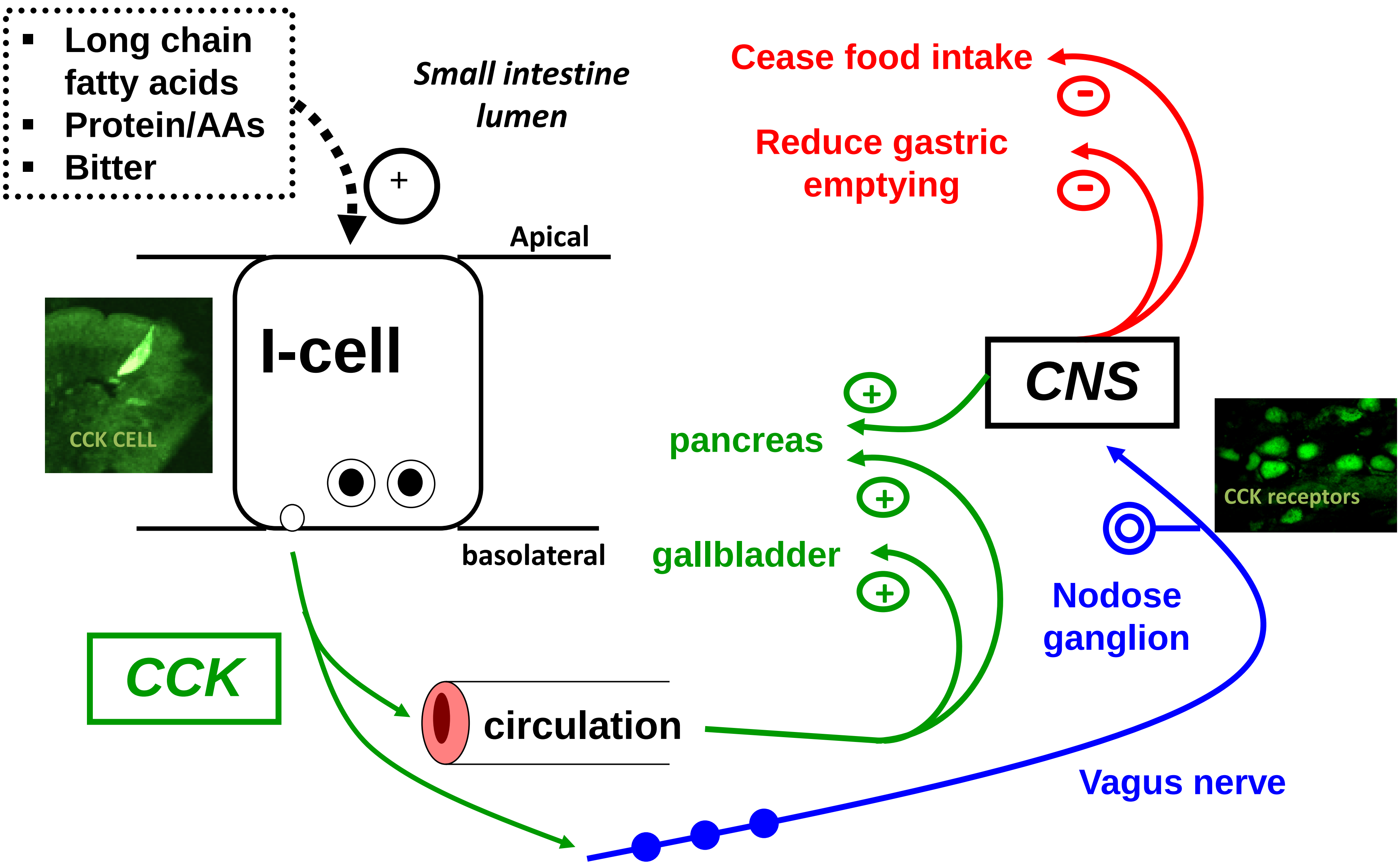


CaSR, calcium sensing receptor;
FFAR1, free fatty acid receptor 1;
FFAR2, free fatty acid receptor 2;
FFAR3, fatty acid receptor 3;
GPR92, G-protein coupled receptor 92;
GPRC6A, G-protein coupled receptor family C group 6 member A;
LCFA, long-chain fatty acids;
TAS1R1, taste receptor type 1 member 1;
TAS1R2, taste receptor type 1 member 2;
TAS1R3, taste receptor type 1 member 3;
TAS2R, taste receptor type 2.

Region	Cell	Hormone/Nutrient/Taste receptors/ Action
Stomach	G cell	gastrin: regulation of acid and pepsinogen secretion peptides: GPR92 AA: CaSR, GPRC6A
	P/D1 cell	ghrelin: control of hunger sugars, AA: TAS1R3 bitter: TAS2R
Duodenum	I cell	CCK: control of satiation and motility LCFA: GPR120, FFAR1 peptides: GPR92 AA: CaSR, TAS1R1-TAS1R3 bitter: TAS2R
Jejunum	Enterocyte	SGLT-1 GLP-1: regulation of glucose levels, s sugars: TAS1R2-TAS1R3
ileum	L cell	GLP-1: regulation of glucose levels, satiation, motility sugars: TAS1R2-TAS1R3 LCFA: GPR120, FFAR1 AA: GPRC6A bitter: TAS2R
Colon	L-cell	PYY, GLP-1: regulation of satiation, ion secetion and motility SCFA: FFAR2, FFAR3

LO3

Nutrient sensing & the cholecystokinin (CCK) I cell

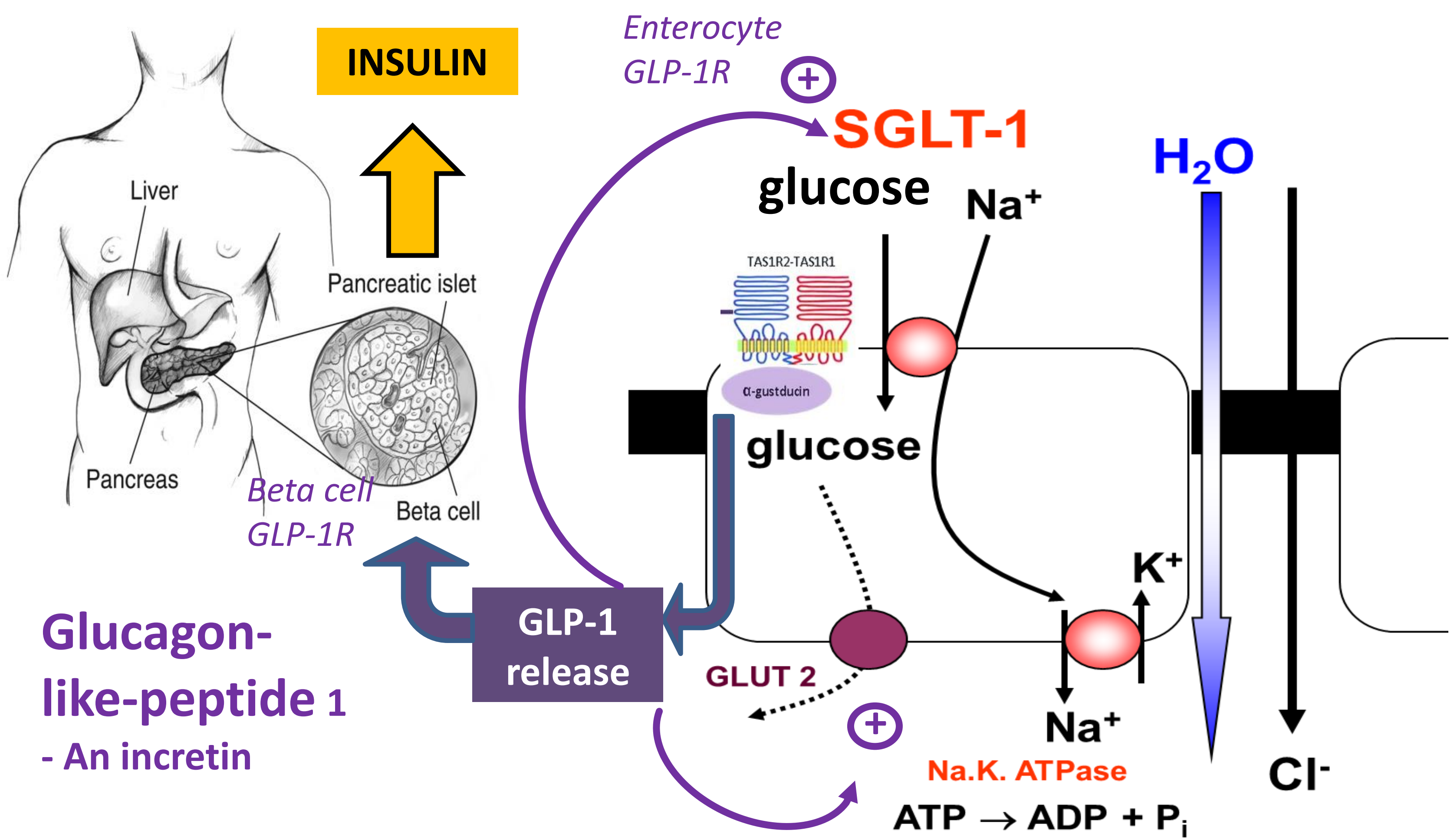


LO3

Sweet sensing & regulation of glucose absorption

SGLT1 - major route for the absorption of dietary sugars from intestinal lumen into enterocytes.

Glucose also stimulates gut hormone secretion (GLP-1) – stimulates pancreas insulin release, increasing glucose uptake to tissues (and enhancing enterocyte glucose uptake via increasing expression of SGLT1 and GLUT2 in enterocytes



Glucagon-like-peptide 1

- An incretin

LO4

Taste receptor targeting to prevent and treat obesity and diabetes

- In disease, disturbances or adaptations in the expression or sensitivity of taste receptors and their signalling pathways may affect digestive behaviour and metabolism

Future clinical potential?

- ➢ Compounds that block activation of the gut's taste receptors might serve as appetite suppressants – e.g. Bitter agonists
- ➢ Selective targeting of taste receptors on cells in the gut to release hormones that signal a feeling of fullness, thereby mimicking the physiological effects of a meal and fooling the body into thinking that it has eaten, could replacement bariatric surgery approaches to cause profound weight loss
- ➢ Diabetes might be treated by activating the taste receptors on gut L cells so that they release GLP-1 to augment insulin release.