Sensing and reacting: micronutrients and beneficient phytochemicals in gut health

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How the gut detects its environment

The gut has (almost) no control over what enters: we decide what we eat and what is fed to animals

The gut must detect the chemical nature of ingested material, the pathogens that accompany food and products of digestion and bacterial actions

It must distinguish the good from the bad components

It must signal this information so that appropriate adjustments of digestive processes are made

To detect and react to its internal environment, the gut has*:*

- ***70-80% of the immune and tissue defence cells in the body***
- ***The most extensive nervous system of all peripheral organs (400 – 600 million neurons in human)***
- ***The largest of the body's endocrine systems, containing 10 major endocrine cell types, that produce around 30 different hormones***

Gut receptors

Nutrient receptors

- Free fatty acids, carbohydrates, monosaccharides, proteins, bitter tastants, amino acids, salts, micronutrients

Bacterial metabolite receptors

- Short chain fatty acids, anions (lactate, succinate etc), triglyceride metabolites, amino acids and their metabolites

Immune receptors

- PAMPs, DAMPs, Toll-like receptors, NOD receptors, antigen recognition sites

Physico-chemical state receptors

- Tension, volume, acidity, sour, tonicity, temperature

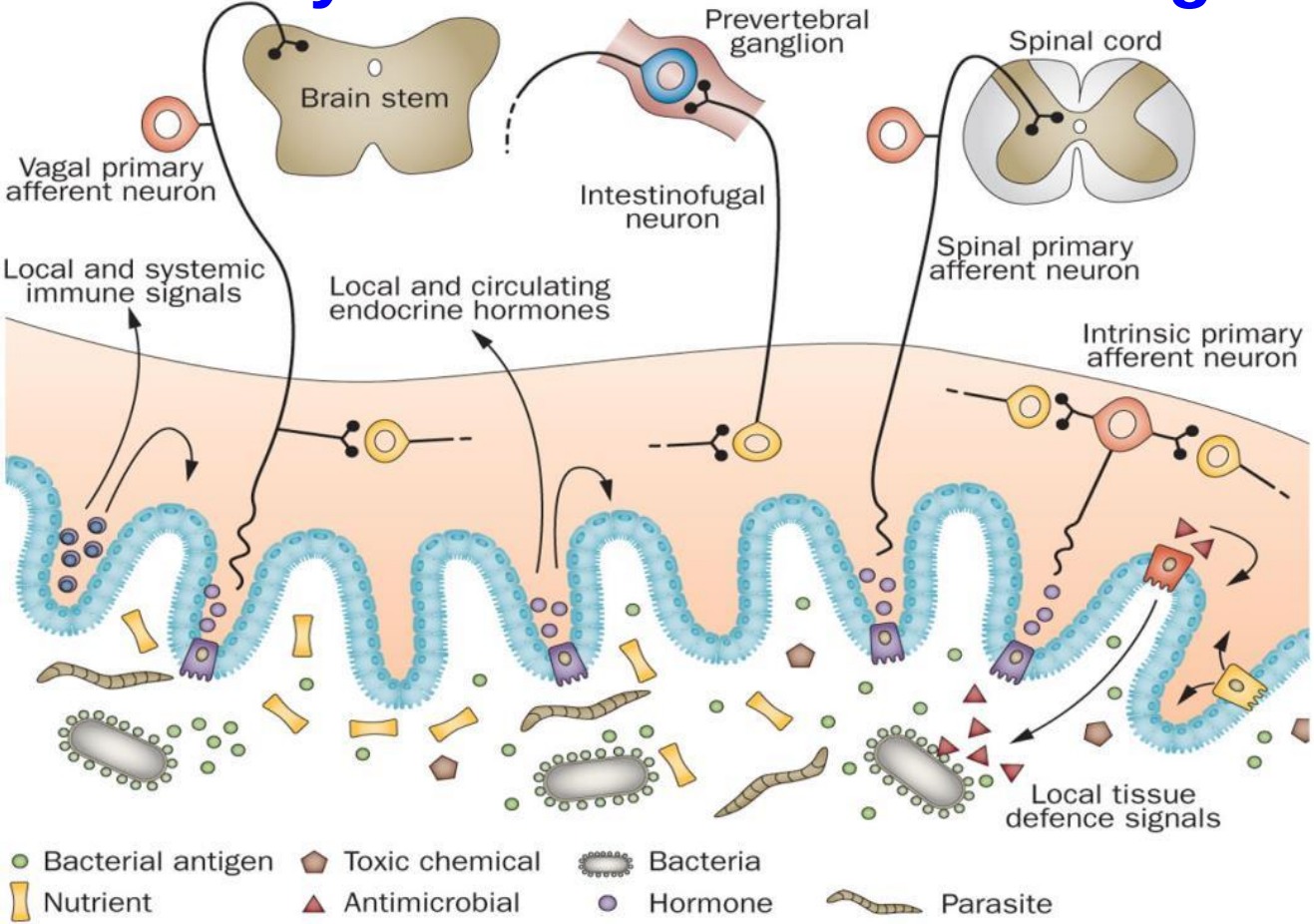
Toxin and foreign chemical receptors

- RAGE receptors, plant alkaloid receptors, receptors for emetogenic toxins

Phytonutrient receptors include

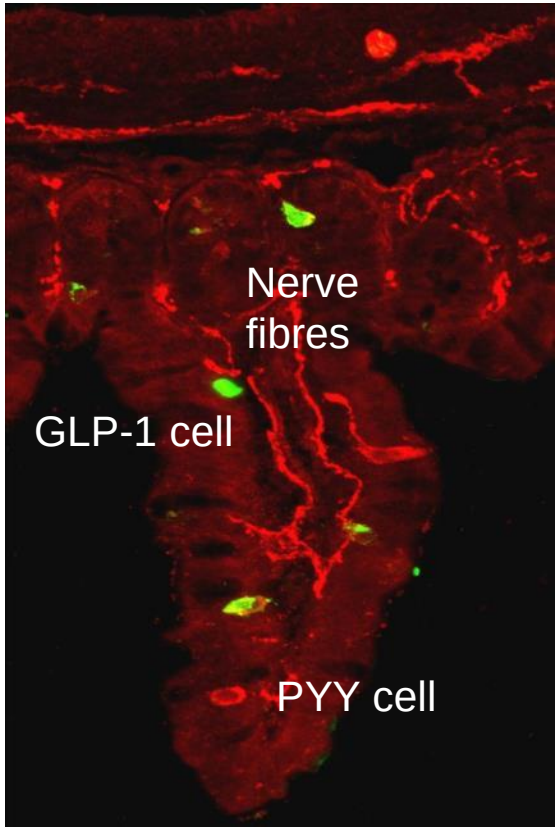
- TRP receptors, bitter receptors

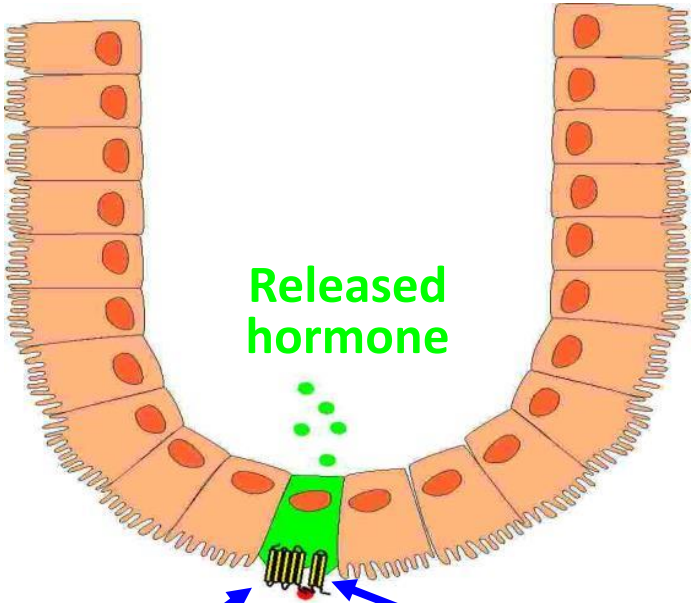
Sensory-linked effectors in the gut



Furness et al 2013

Nutrients and Phytochemicals act on receptors on entero-endocrine cells to release hormonal messengers



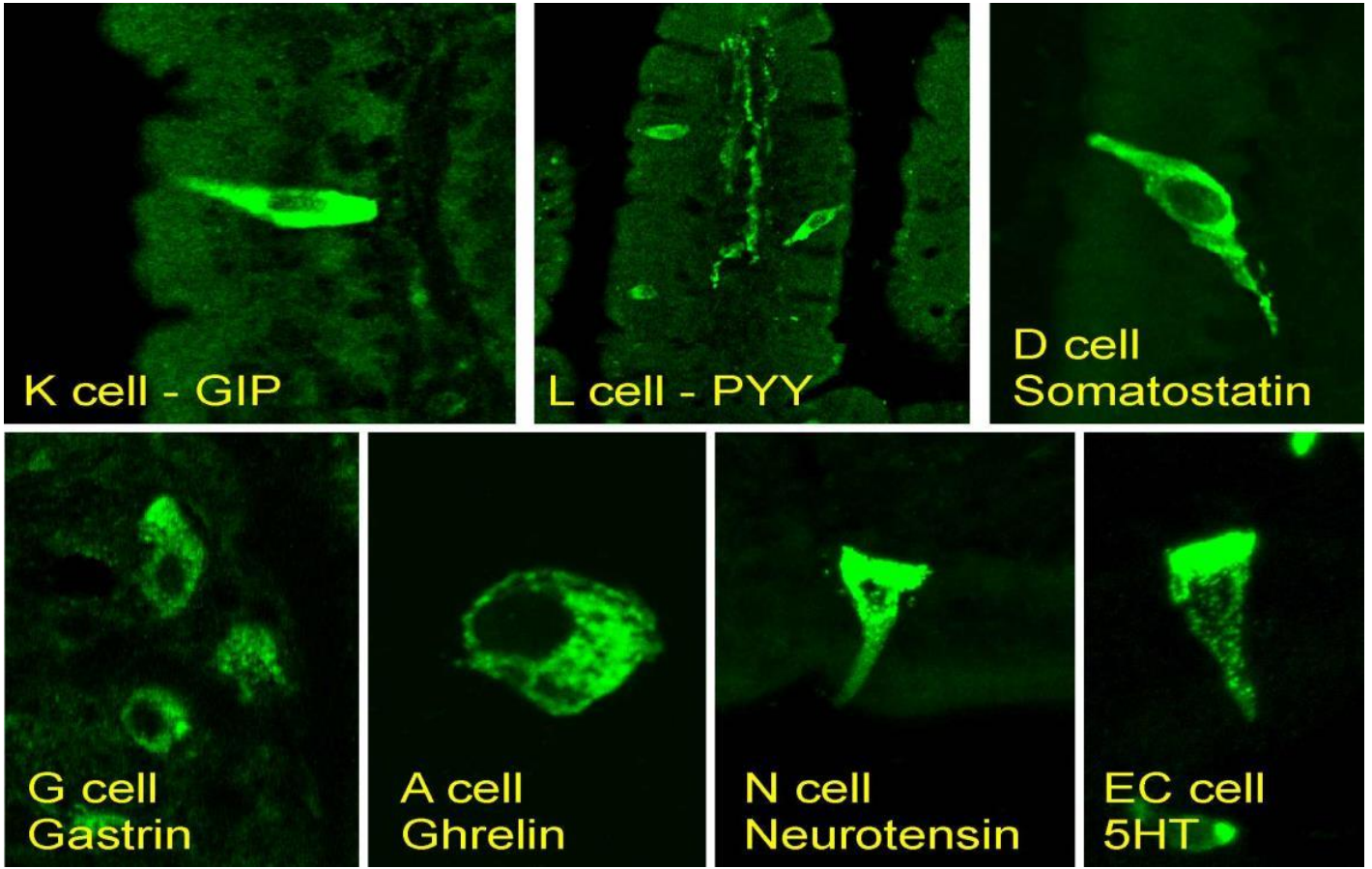


Nutrient receptors
(Free fatty acid receptors, tastant receptors)

Nutrients

Phytochemical receptors
(Many are TRP receptors)

What entero-endocrine cells look like



Our data

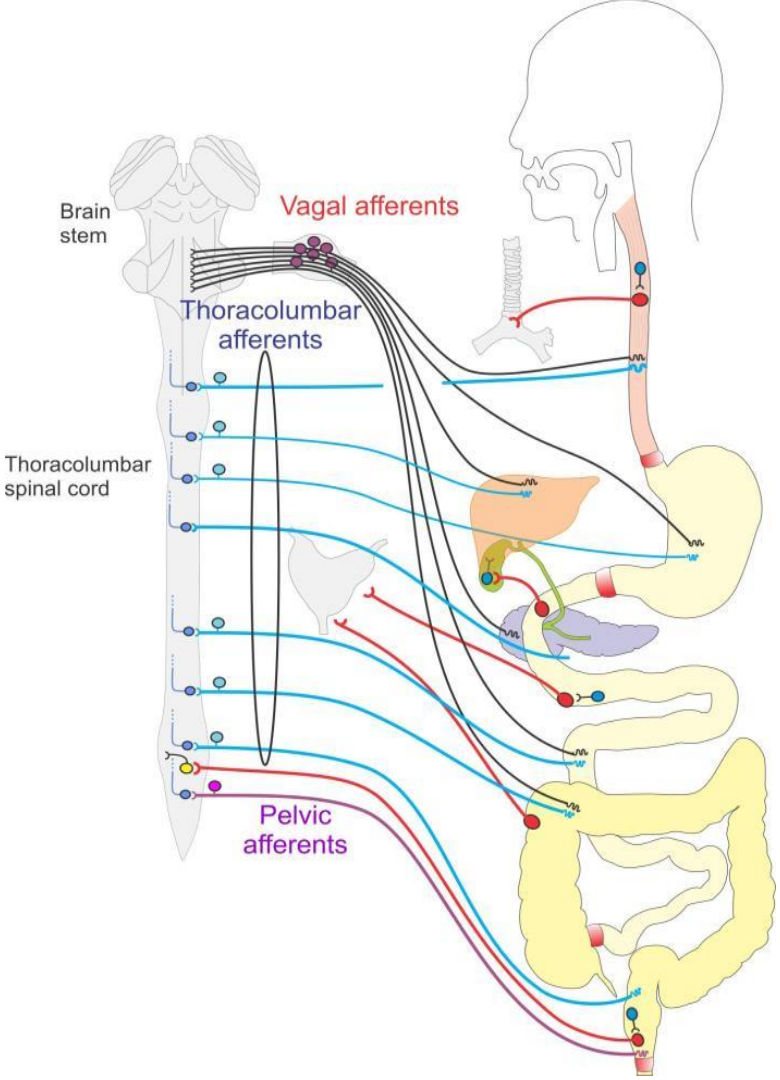
The gut signals to the brain via nerves

The brain,

the gut endocrine system,

the enteric nervous system,

and the immune system intelligently interpret and integrate sensory information to optimise digestive function



From Furness et al 2014

Major Gastrointestinal Hormones

Stomach	
Ghrelin	**Promotes appetite**
Gastrin	Stimulates Acid Secretion
Somatostatin	Inhibits Acid Secretion
Duodenum, Jejunum	
Secretin	Stimulates HCO_3 Production
Cholecystokinin	**Facilitates nutrient metabolism**, Stimulates Gallbladder and Pancreas
GIP	**Promotes insulin secretion**
5-HT (serotonin)	Toxin expulsion
Ileum	
GLP1, GLP2, PYY, Oxyntomodulin, stored together	
GLP1	Increases glucose uptake, Satiety
GLP2	**Stimulates mucosal growth**
Peptide YY	Slows small intestine transit, Inc nutrient uptake
Motilin	Triggers propulsion
Neurotensin	Slows propulsion, stimulates pancreas
5-HT (serotonin)	Stimulates contractile activity and water and electrolyte secretion, influences bone

Beneficient phytochemicals: Plant-derived compounds without direct nutrient value that improve health, particularly gut health and gut immune defence

Not mutually exclusive Properties of various Phytonutrients

- Improved nutrient conversion
- Reduced food spoilage
- Antimicrobial actions
- Improved palatability
- Enhanced gut health
- Growth promotion

Micronutrients: Substances, including vitamins and minerals, required in trace amounts for normal growth and development

Phytochemicals activate TRP receptors

TRPV3

TRPM3

TRPM8

TRPA1

TRPV2

TRPV1

TRPP2

TRPV4

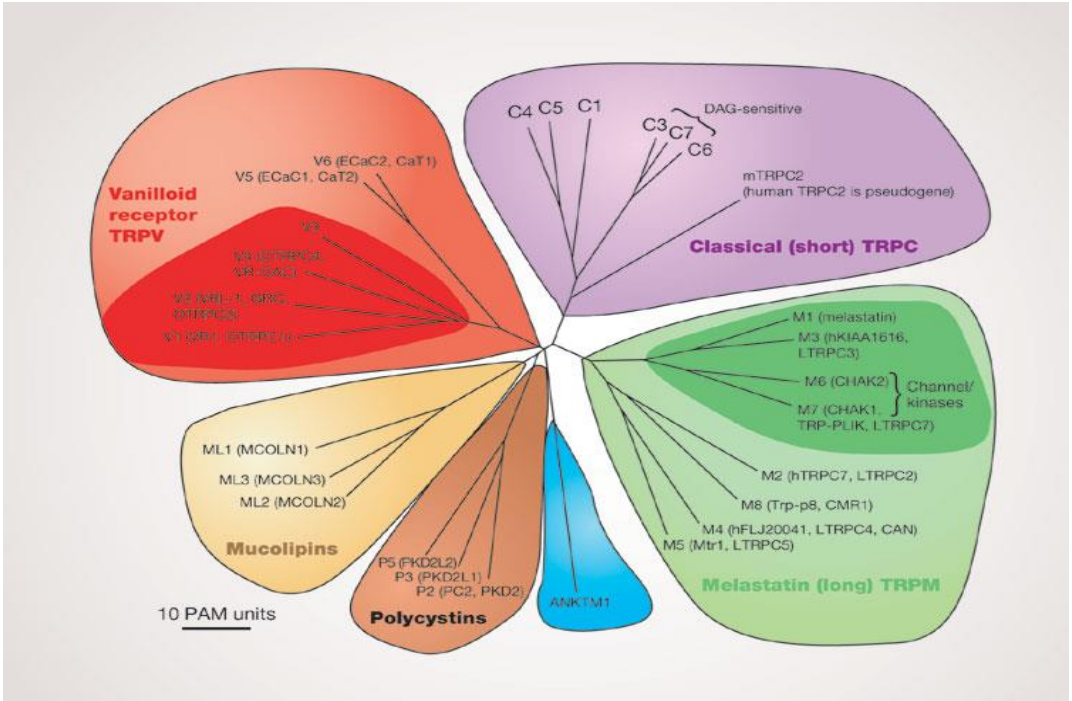
The TRP receptors: Environmental detectors and common targets of Phytochemicals

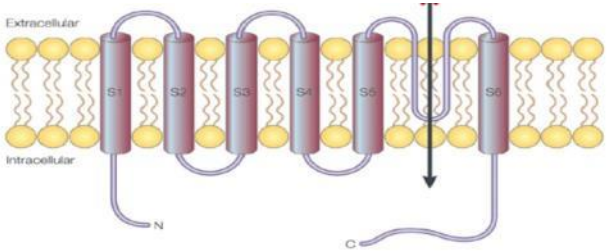
- **TRPV1**: Activators, Capsaicin (hot peppers), Allicin (garlic), Eugenol (cloves et al), Curcumin (geranium)
- **TRPV3**: Activators, Carvacrol (oregano and thyme), Thymol (thyme), Eugenol (cloves)
- **TRPM8**: Activators, Menthol (mint), Eucalyptol (eucalyptus oil), Citral (verbena and citronella)
- **TRPA1**: Activators, Allyl isothiocyanate (mustard and horseradish), Allicin (garlic), Cinnamaldehyde (cinnamon), Linalool (mint, laurel, birch)

Other examples of TRP channels activated by phytochemicals:

- TRPV2: activated by cannabidiol from cannabis (also CB1 receptor)
- TRPV4: activated by phorbols, from croton (croton oil)
- TRPV6: activated by vitamin D from cereals, fish
- TRPM3: activated by plant sphingolipids, inc. arabidopsis
- TRPP2: activated by organic acids

The TRP ligand gated channels: 28 functional channels in 6 families





Opening TRP channels allows calcium and other cations to enter cells

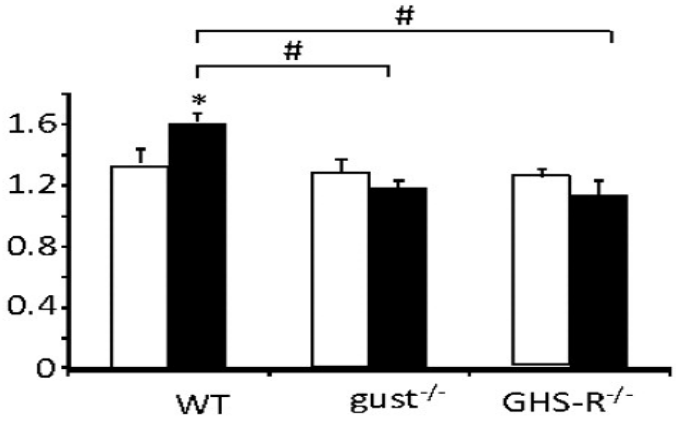
They detect the environment: Heat, cold, touch, painful effects on the body surface, irritants, components of plants that are eaten

Clapham 2003

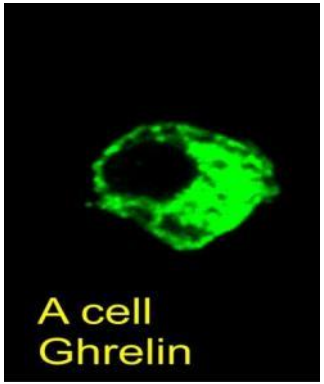
Bitter taste receptor stimulation in stomach

In Wild-type, α-gustucin KO and ghrelin receptor KO

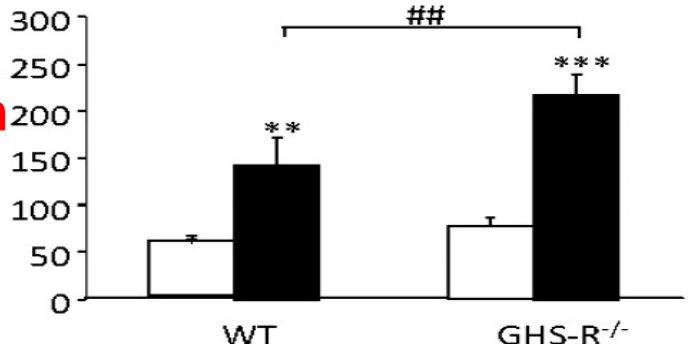
Food Intake g/hr/mouse



Intra-gastric gavage with bitter mix

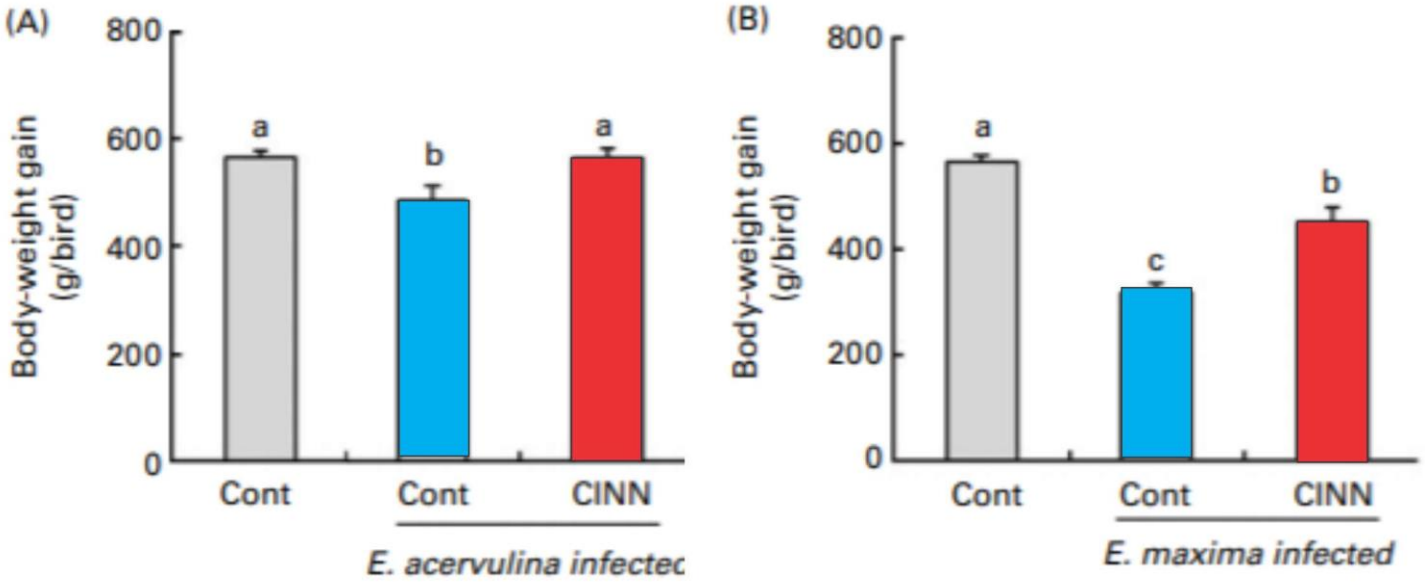


Plasma Ghrelin pg/mL



Janssen 2011

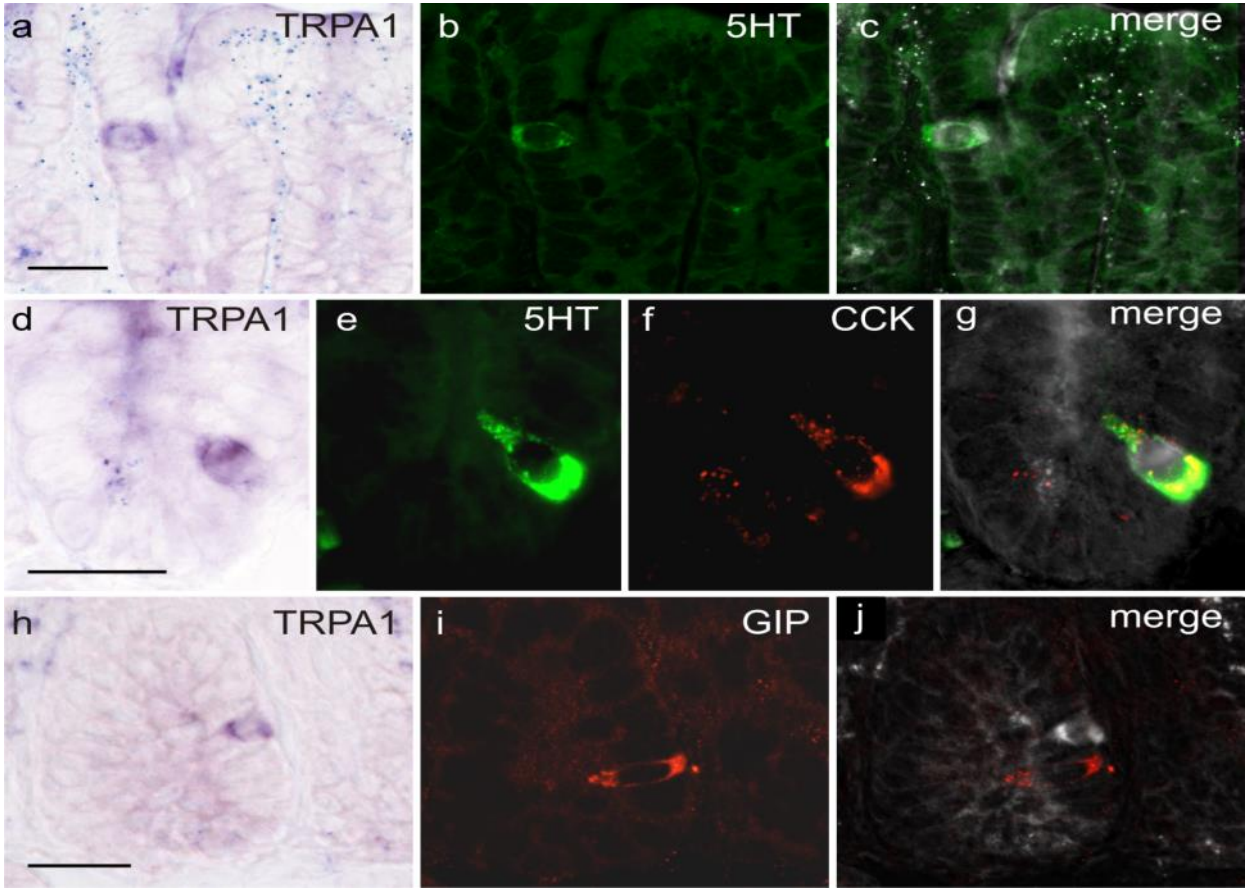
Enhancement of weight gain with Cinnamaldehyde (TRPA1 stimulant) in broilers compromised by coccidiosis



Chicks infected with *Eimeria* at 14 days: fed for further 9 days after coccidiosis induction
Is this a TRPA1 effect?

Lee et al 2011

The TRPA1 receptor is expressed by 5HT & CCK containing EEC in mice, rat, human



Cho et al 2014

Antibacterial effects of Cinnamaldehyde (TRPA1) and Eugenol (TRPV1&V3)

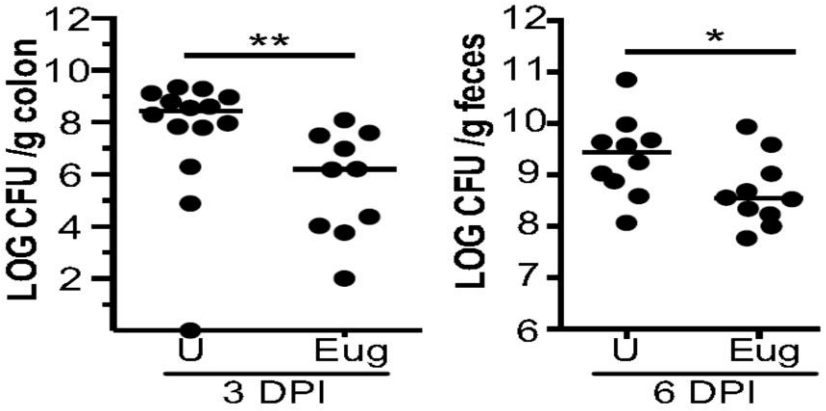
Cinnamaldehyde Minimum inhibitory concentrations (mg/mL)

E.coli	300
Enterobacter	250
*V. cholerae	150
*V. parahaemolyticus	75
*S. Aureus	250

*Antibiotic resistant

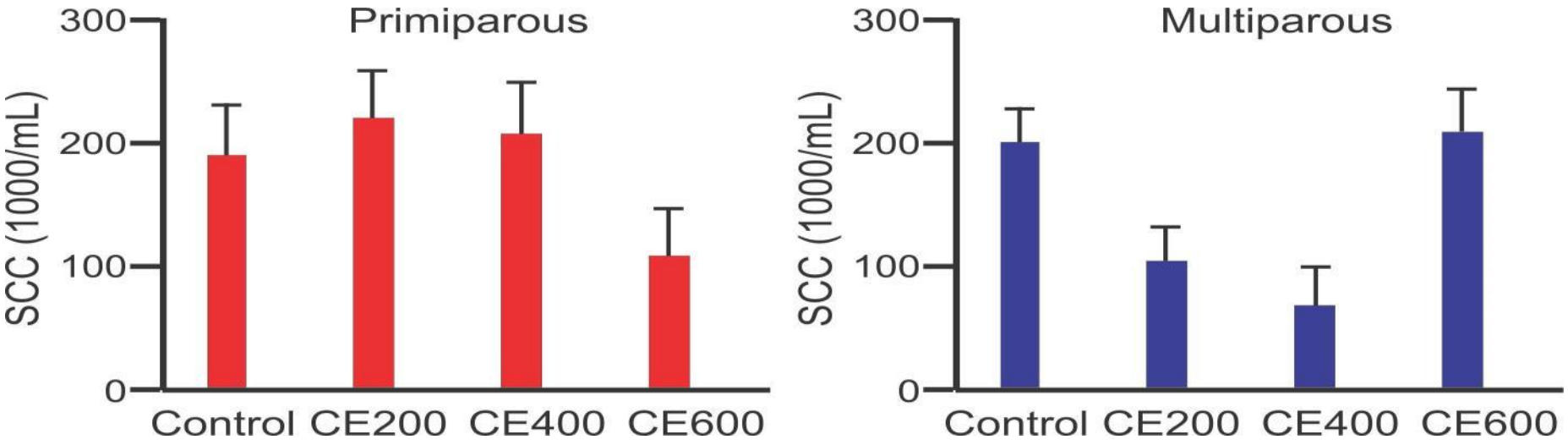
Ooi et al 2002

Reduction of C. rodentium burden with **Eugenol**



Wlodarska et al 2015

Effects of Cinnamaldehyde (TRPA1) plus Eugenol (TRPV1&3) on milk quality in dairy cows differ with parity and dose



Cows treated with cinnamon plus eugenol, 200, 400 or 600 mg/day:
SSC = somatic cell count

Wall et al 2014

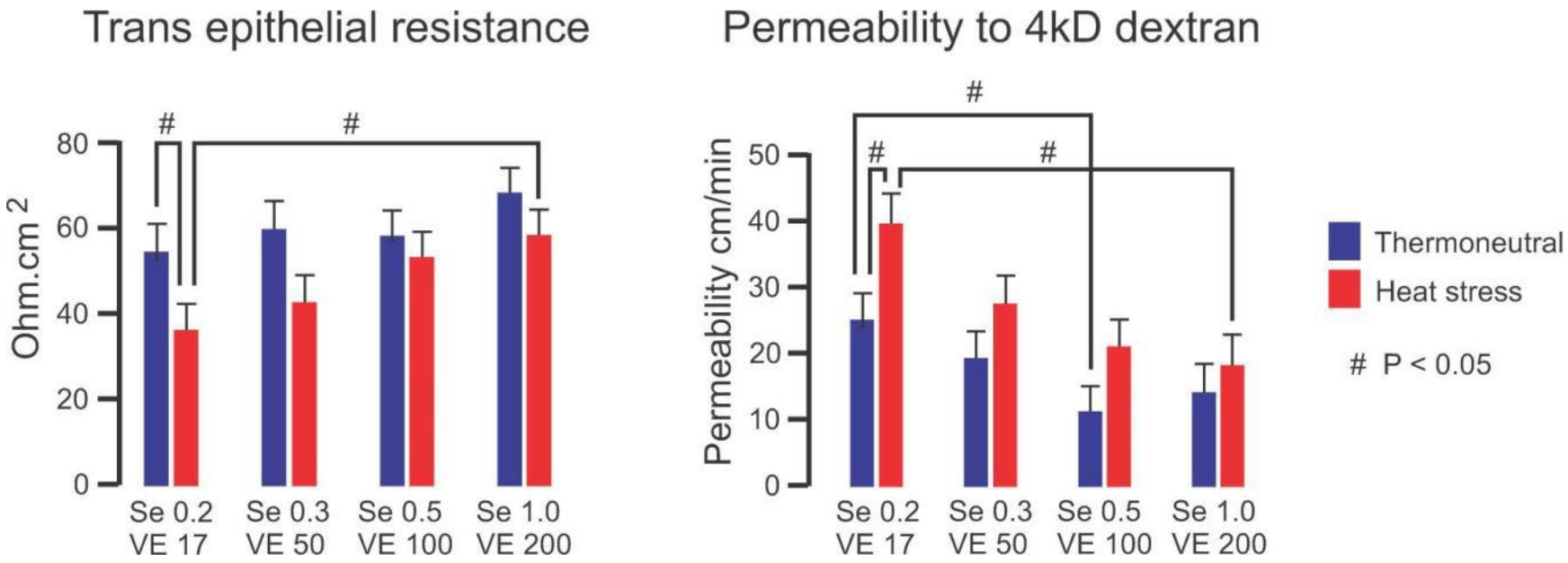
A combination of carvacrol (TRPV3), cinnamaldehyde (TRPA1) and capsicum (TRPV1) improved energy utilization and growth performance of broilers

Item	CON	CON+XT	SEM	*P*-value
Feed Intake	43.9	45.7	1.0	0.222
Weight gain	28.2	32.3	0.9	0.009
Gain/feed	0.644	0.707	0.020	0.055
N retention	0.617	0.628	0.015	0.610
Fat digestibility	0.844	0.862	0.004	0.013
Available energy	14.51	15.03	0.21	0.122
Energy intake	0.638	0.687	0.019	0.098

XT contains 5% carvacrol, 3% cinnamaldehyde, 2% capsicum

Bravo et al 2014

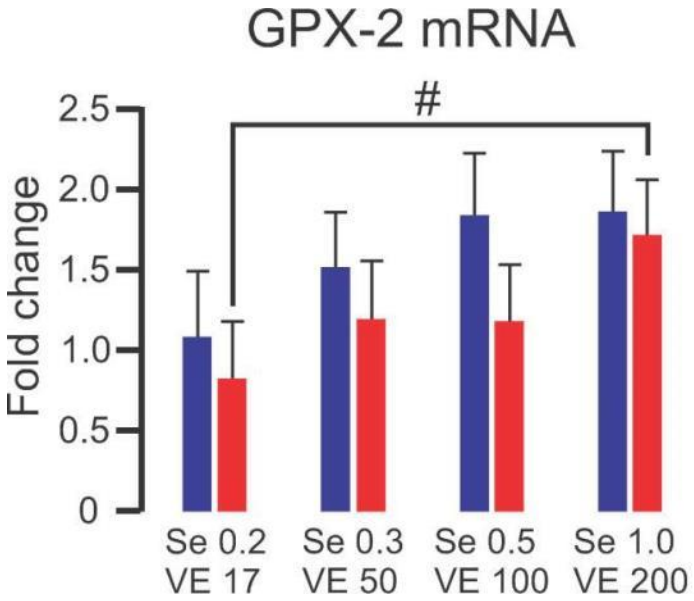
Amelioration of gut leakiness caused by Heat Stress with Micronutrients (Selenium and Vitamin E)

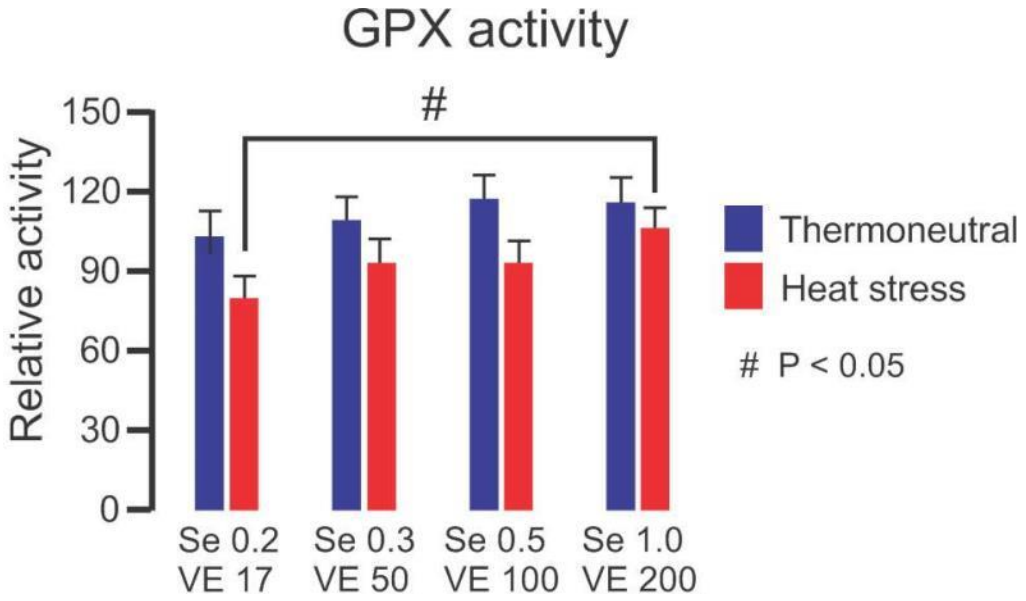


Thermoneutral, 20°C, 35% humid; Heat stress, diurnal, 28-35°C, 35% humid

Liu et al 2016

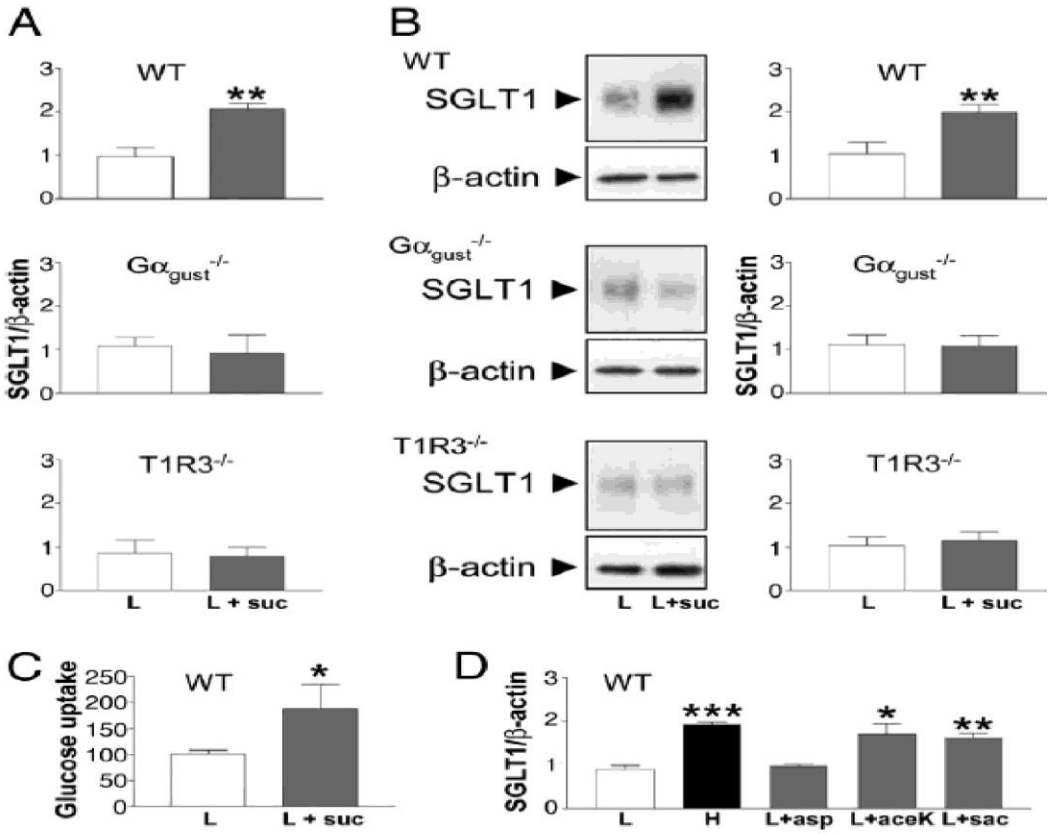
Selenium and Vitamin E increase glutathione peroxidase activity and expression in the small intestine after Heat Stress





Liu et al 2016

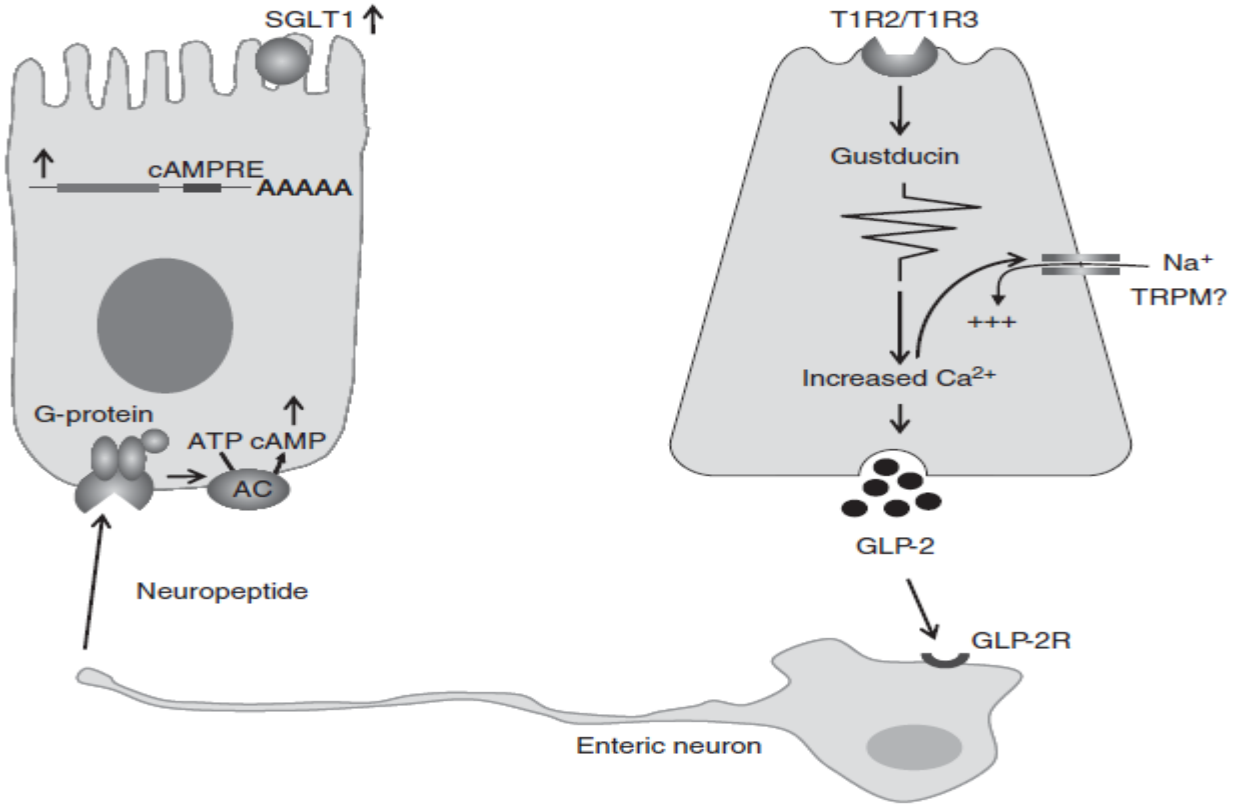
Non-nutrient induction of SGLT1 and glucose uptake by sucralose: a neurally-mediated effect



Acesulfame and saccharine also increase SGLT1 expression and function

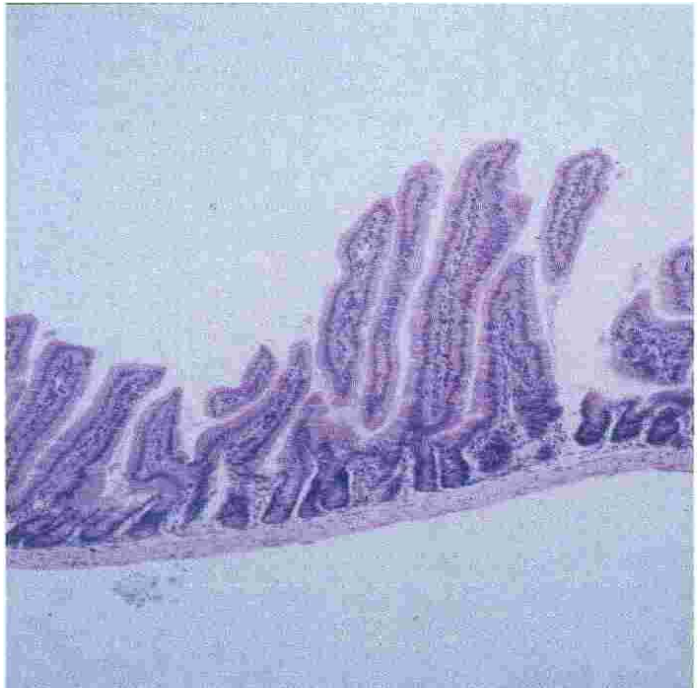
Margolskee, Shirazi-Beechey 2007

Neural site of action of GLP-2

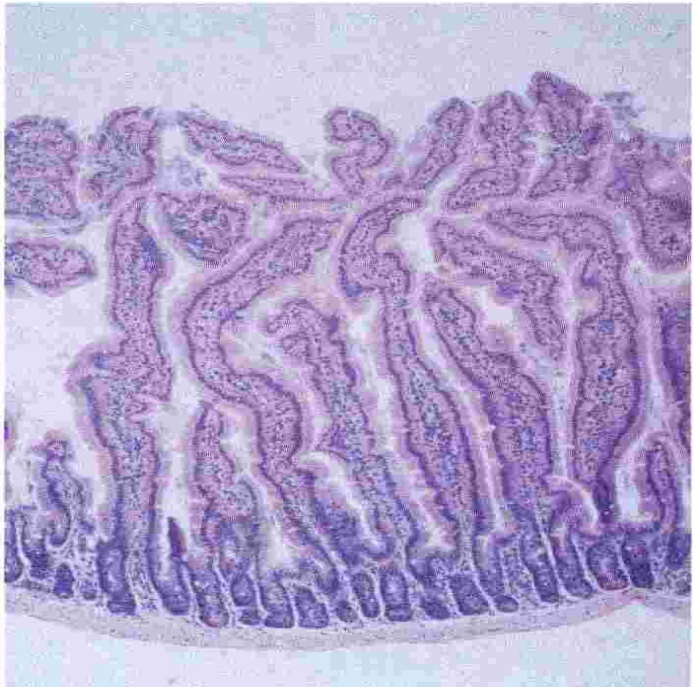


Shirazi-Beechey 2011

Effect of GLP-2 on the mucosa



Control



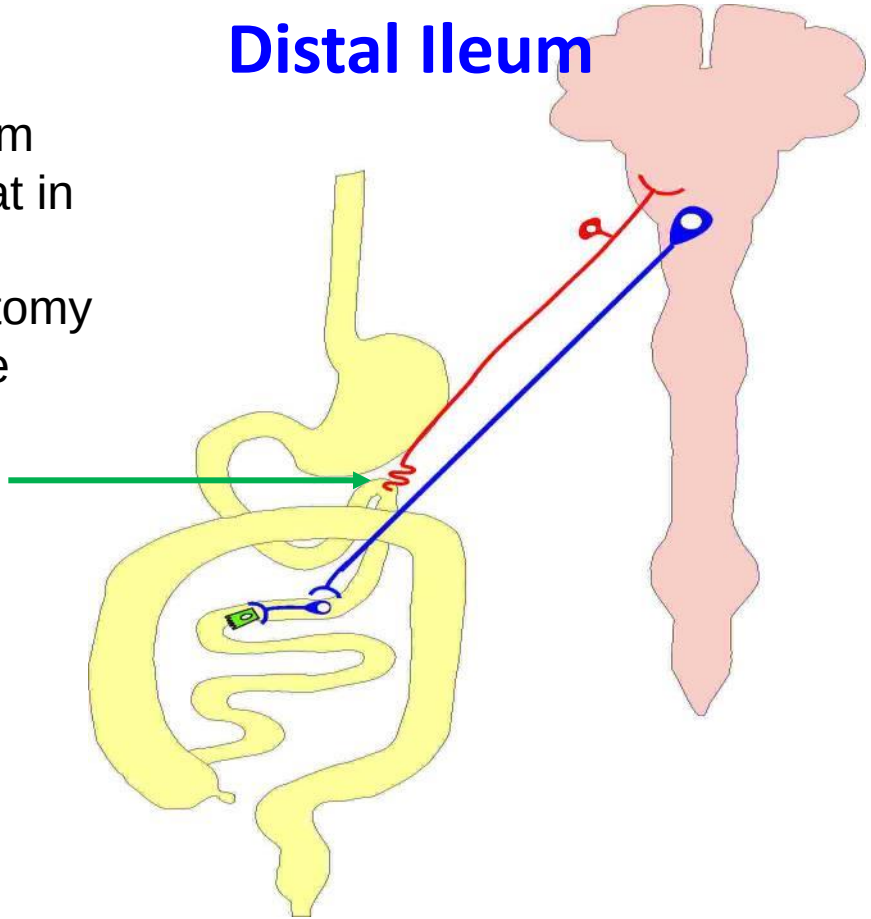
10 days GLP-2, s.c ea 12 hr

Drucker 2006

Neural control of GLP-2 release from Duodenum to Distal Ileum

GLP-2 released from distal intestine by fat in duodenum
Prevented by vagotomy
Blocked by atropine

Mediator
Unknown
?? FFA elicited release of GIP ??



Brubaker 2003

Focus on particular phytochemicals

Phytonutrient	Effects	Receptors
Cinnamaldehyde	Improves nutrient efficiency, flavour, **anti-microbial**, immune enhancement	TRPA1, TRPV3
Allicin and other garlic products	Increased nutrient assimilation	TRPA1, bitter taste
Eugenol	Anti-inflammatory and **anti-oxidant properties**, flavour	TRPV1, TRPV3 + ?
Capsicum	Immune stimulant, **mucosal repair**, improved mucosal blood flow	TRPV1
Curcumin (tumeric)	Immune stimulant, anti-inflammatory, **anti-oxidant,** flavour	ROS, COX-2

But what about the 100s of natural products that have not been adequately investigated?

Discussion

- Several phytochemicals and micronutrients have been shown to improve gut health, but observations are somewhat inconsistent. Results suggest that effects are more prominent if gut health is compromised
- Mechanisms are often not clearly identified
- In particular, the molecular recognition sites (receptors) for phytochemicals are in many cases not known, and when they are known, how actions at these receptors mediate the effects that are observed are not defined
- There are numerous compounds used as food additives, notably herbs and spices, that have been promoted as beneficial in different cultures, whose effects on gut health are under-investigated
- There are pressing needs to investigate the targets, specificity, dose effects and optimal application of phytonutrients AND to explore effects of other phytochemicals and micronutrients