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Nutrition and Gut hormones – can we apply learning to clinical practice

Gary Frost
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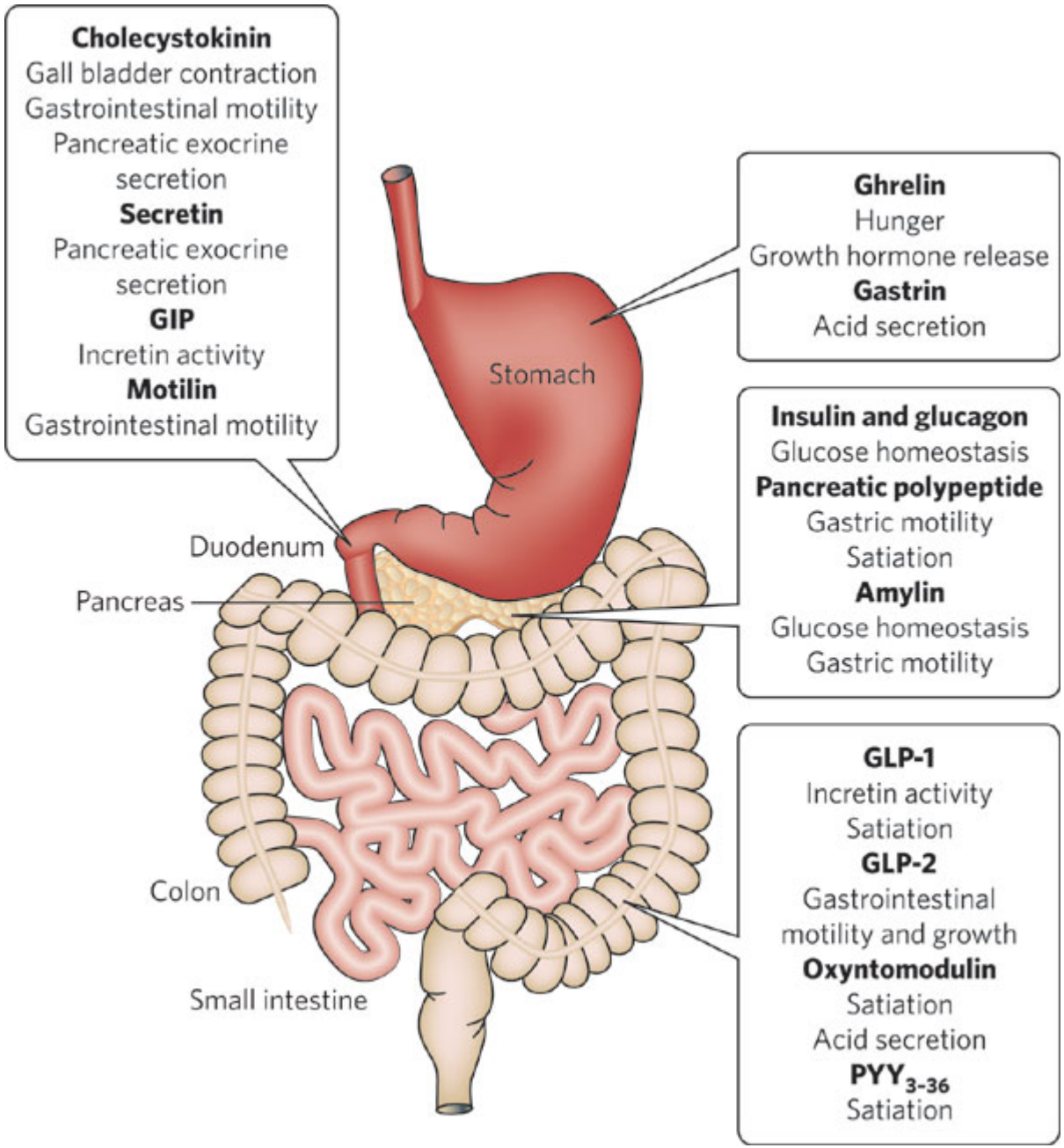
Learning points

1. Gastrointestinal hormones play an important role in appetite regulation, gut motility and gut integrity

1. The relationship between trauma and gut hormones is complicated and we have a lot to learn

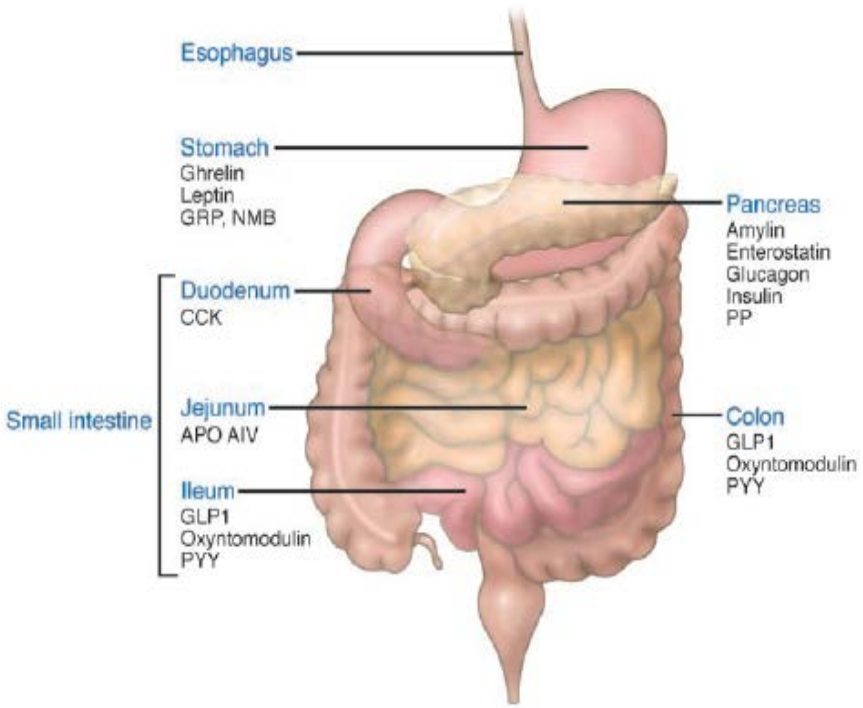
1. To use nutrition as a method to regulate gut hormones in trauma we need to be smart


Cholecystokinin
Gall bladder contraction
Gastrointestinal motility
Pancreatic exocrine secretion
Secretin
Pancreatic exocrine secretion
GIP
Incretin activity
Motilin
Gastrointestinal motility
Ghrelin
Hunger
Growth hormone release
Gastrin
Acid secretion
Stomach
Insulin and glucagon
Glucose homeostasis
Pancreatic polypeptide
Gastric motility
Satiation
Amylin
Glucose homeostasis
Gastric motility
Duodenum
Pancreas
Colon
Small intestine
GLP-1
Incretin activity
Satiation
GLP-2
Gastrointestinal motility and growth
Oxyntomodulin
Satiation
Acid secretion
PYY$_{3-36}$
Satiation

What do they do?

- Appetite
- Glucose homeostasis
- Gut motility
- Acid secretion
- Gall bladder contraction
- One peptide many roles:
  - GLP-1 play a role in glucose homeostasis, appetite, gut motility, lipid handling, liver metabolism

This the enteroendocrine system



Loss of enteroendocrine cells in mice alters lipid absorption and glucose homeostasis and impairs postnatal survival

Georg Mellitzer,[1] Anthony Beucher,[1] Viviane Lobstein,[1] Pascal Michel,[2] Sylvie Robine,[3] Michèle Kedinger,[2] and Gérard Gradwohl[1]

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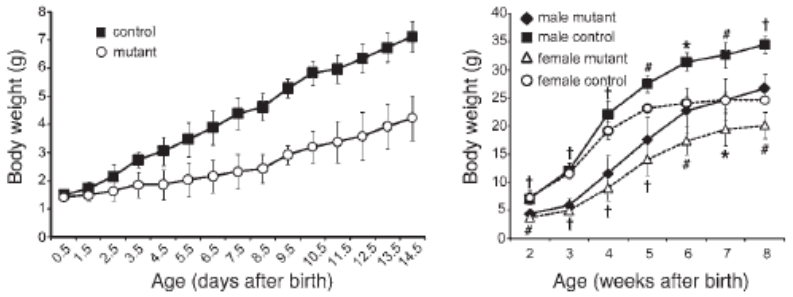
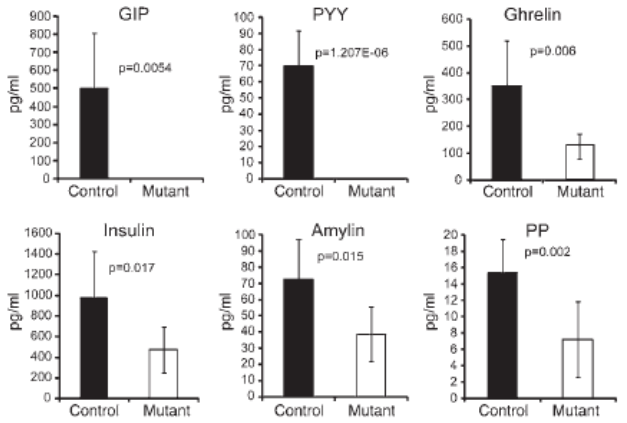
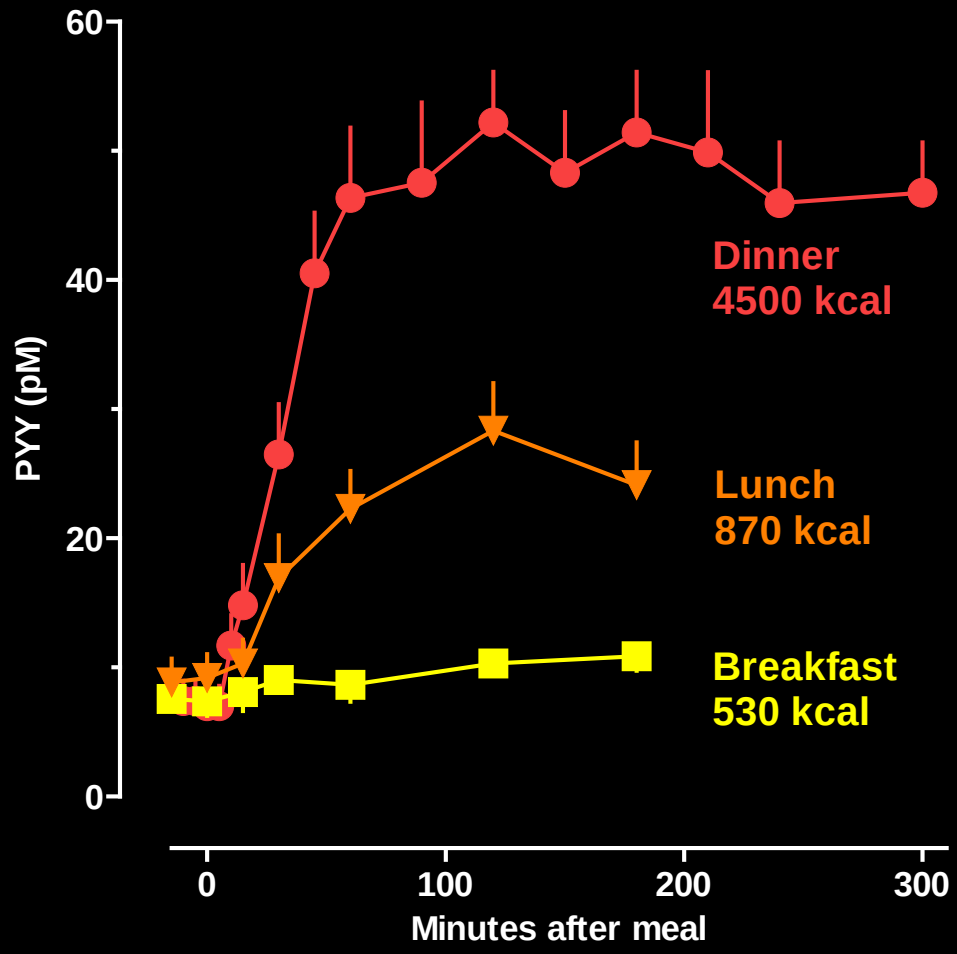




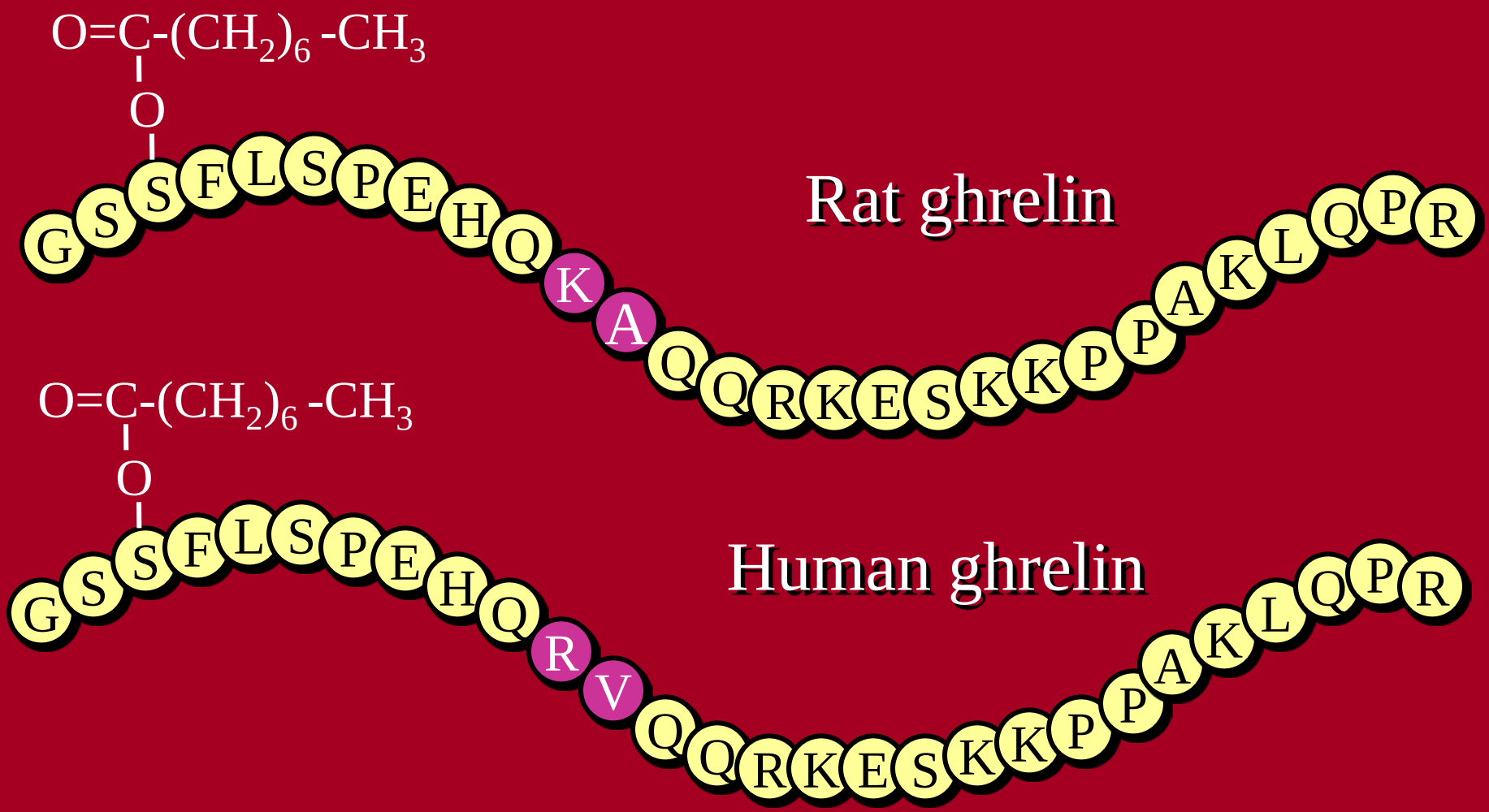
Post-prandial secretion of PYY



Adrian *et al.* (1985), Gastroenterology 89:1070-7

Ghrelin

28aa gastric hormone, high fasting & falls after eating



Damien R. Ashby, Heather E. Ford, Katie J. Wynne, Alison M. Wren, Kevin G. Murphy, Mark Busbridge, Edwina A. Brown, David H. Taube, Mohammad A. Ghatei, Frederick W.K. Tam, Stephen R. Bloom, Peter Choi

Sustained appetite improvement in malnourished dialysis patients by daily ghrelin treatment

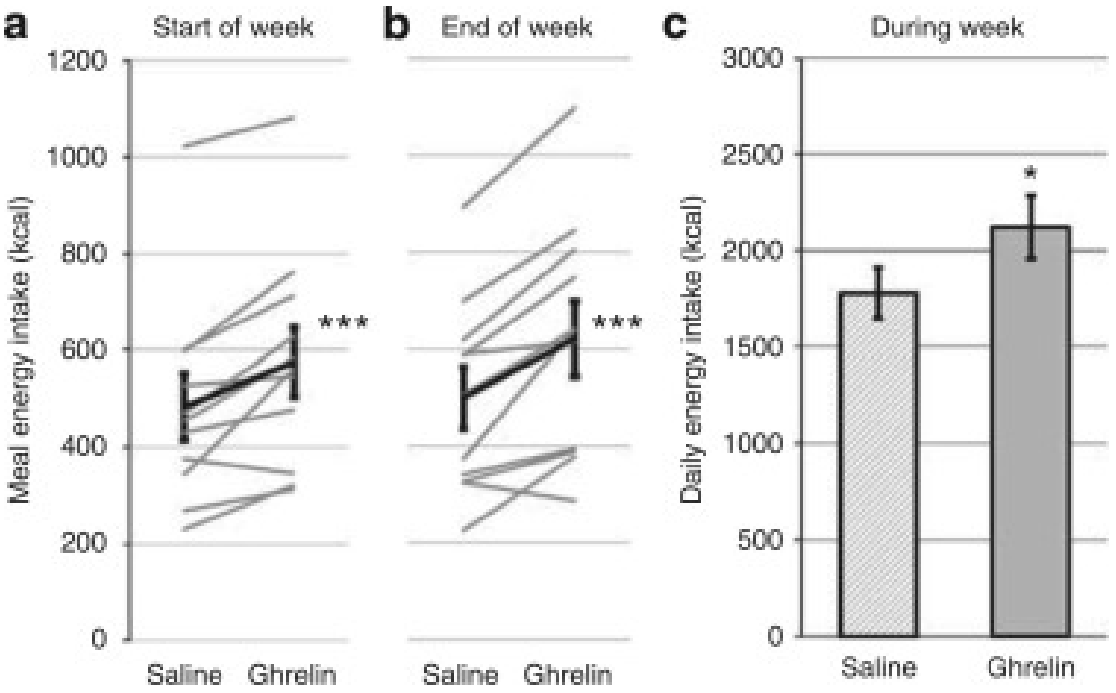


Figure 2. Energy intake with saline compared with ghrelin. (a) Study meals at the start of saline and ghrelin weeks showing an increase in energy intake after the first injection (individual values and mean±s.e., P<0.001); (b) study meals at the end of sali...

Kidney International, Volume 76, Issue 2, 2009, 199–206

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GLP-2

1. Release from the L-cell – same cell as GLP-1 and PYY
2. Promotes highly specific growth and function of the intestinal epithelium
3. Increases intestinal digestive, absorptive and barrier functions
4. GLP-2 receptor (GLP-2R) is almost exclusively restricted to the intestinal tract
5. GLP-2 increases expression of the intestinal stem and transit-amplifying cell markers

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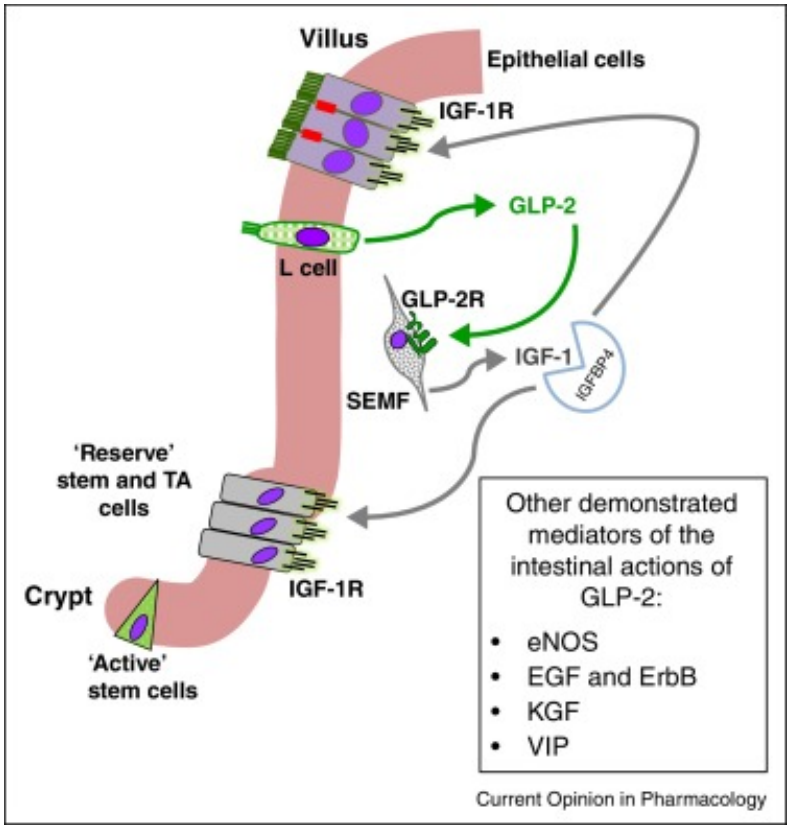
Current and potential therapeutic targets of glucagon-like peptide-2



Kaori Austin, Melanie A Markovic, Patricia L Brubaker *Current Opinion in Pharmacology, Volume 31, 2016, 13–18*

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6. In a number of bowel condition IBF it is Dipeptidyl peptidase-4 activity that is high

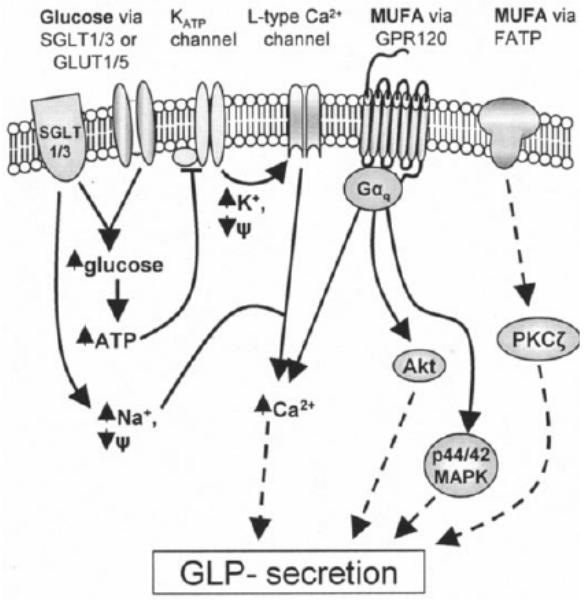
Enteroendocrine cells

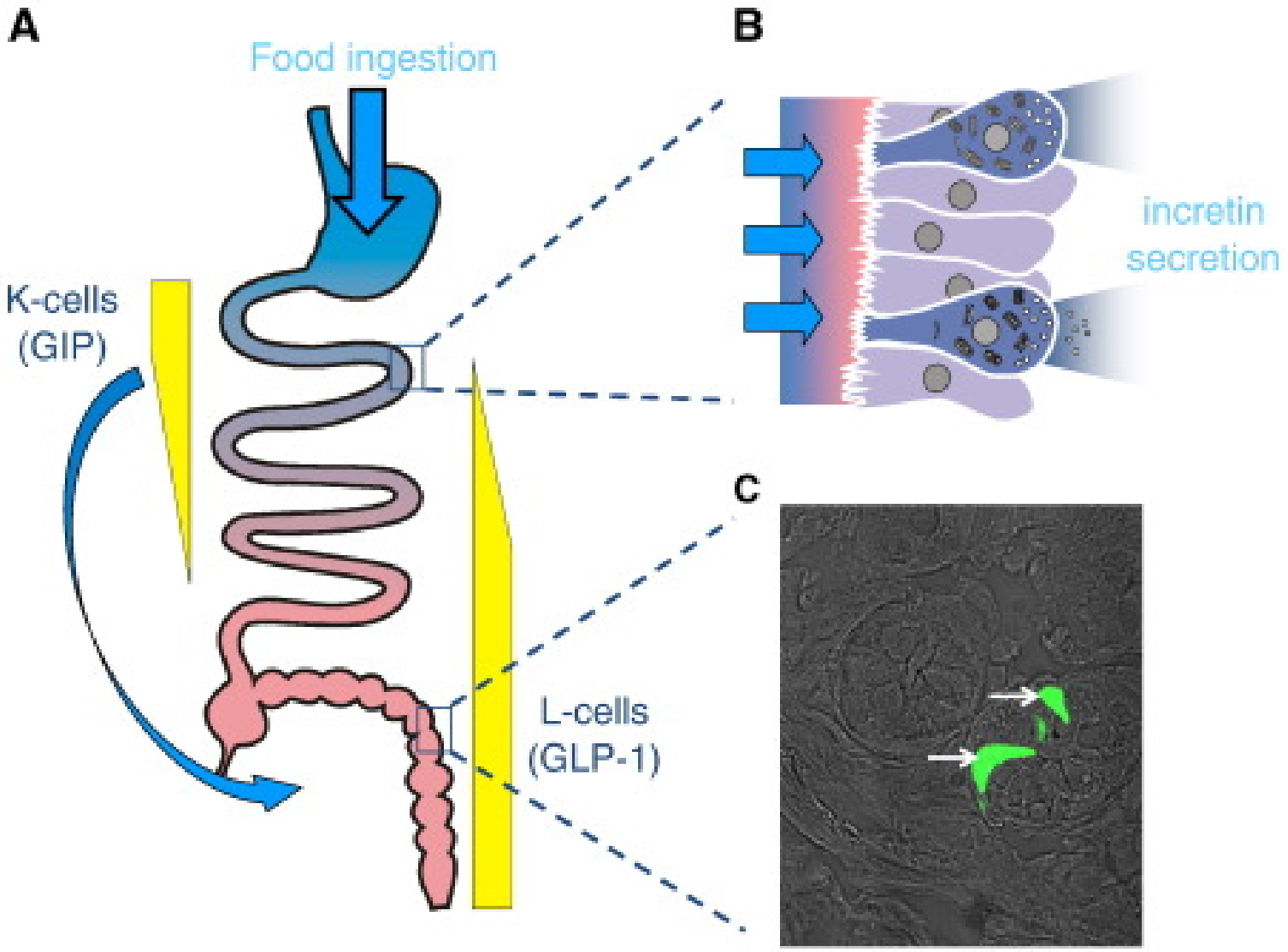
- P/D1 - ghrelin

- G cell – gastrin
- I cells - CCK
- K cells – GIP
- S cells – sectrin
- N cells - neurotensin
- L cell – GLP-1 and PYY

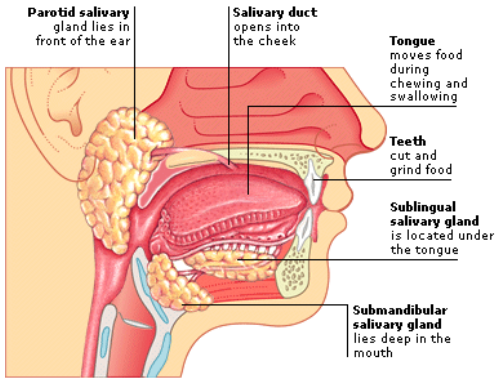
- All variants of one cell population

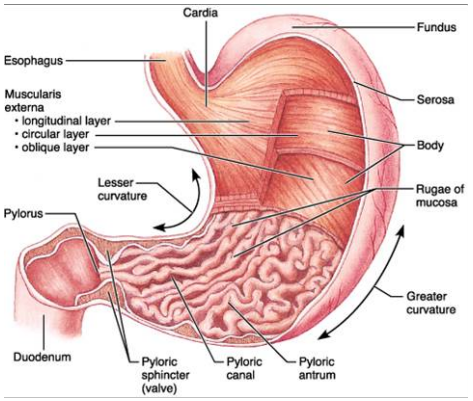
Each cell expresses a large array of G protein coupled receptor nutrient receptors

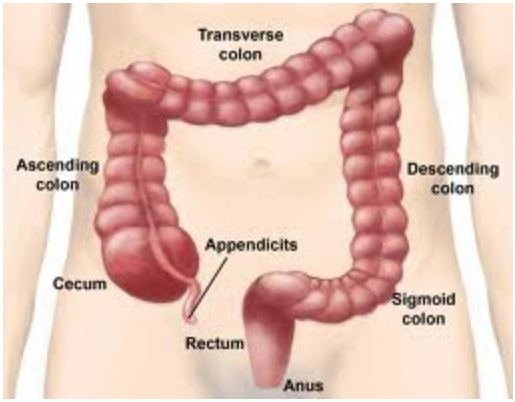


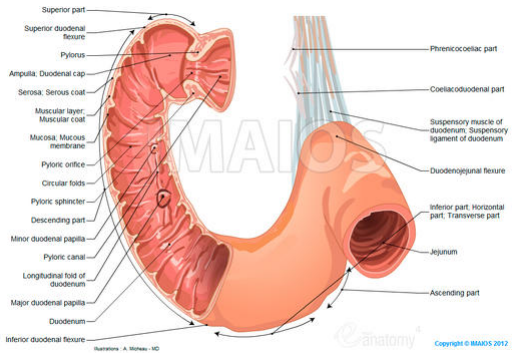

A
Food ingestion
K-cells
(GIP)
L-cells
(GLP-1)
B
incretin
secretion
C

Fragmented science









Working Together

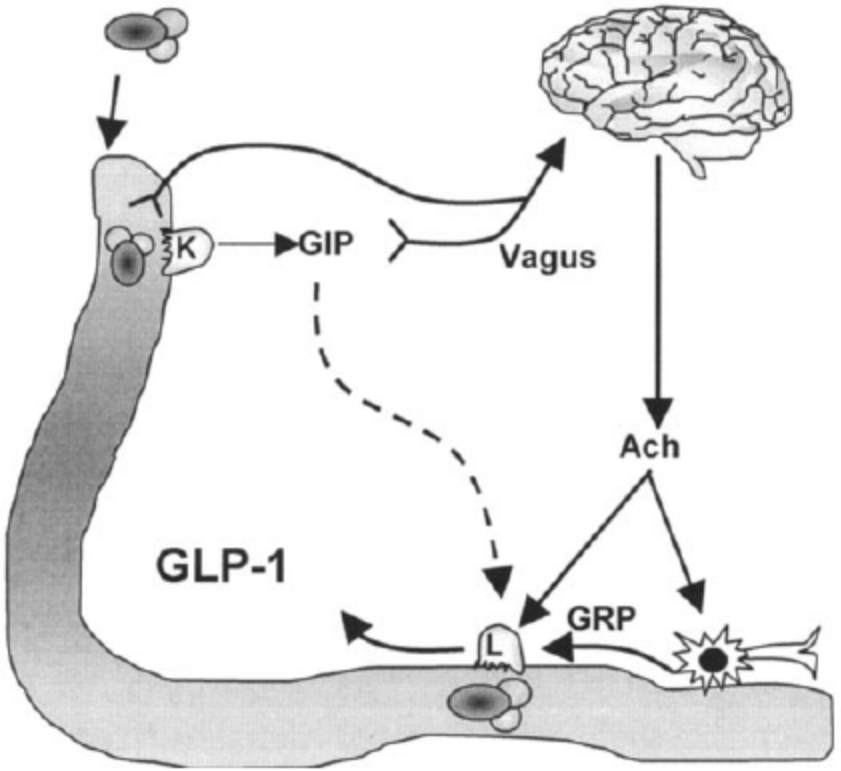
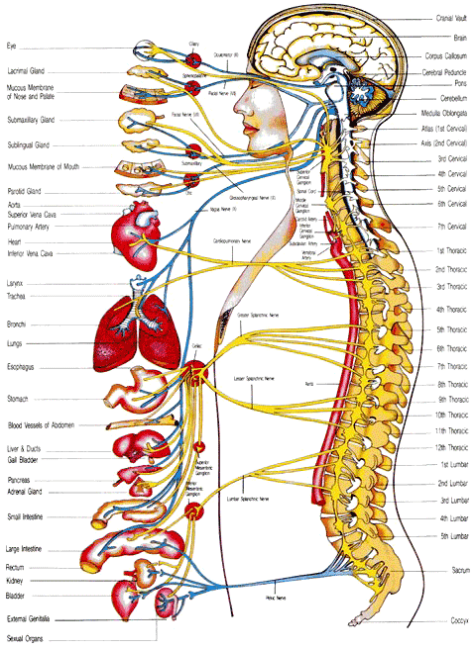
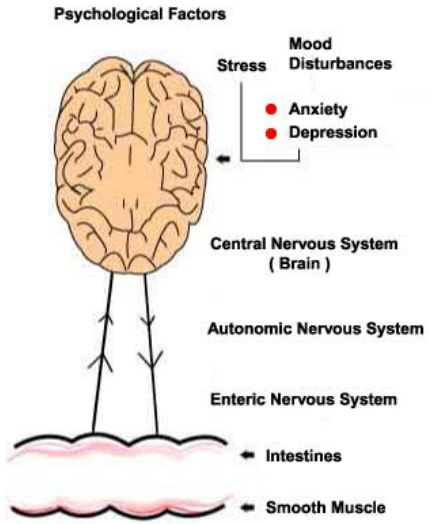


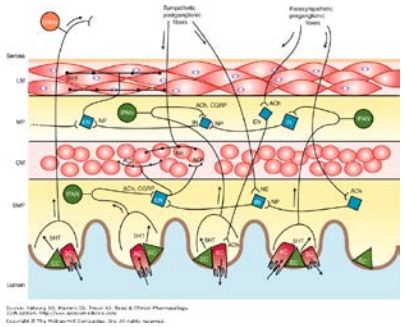
FIG. 2. Regulation of GLP-1 secretion by ingested nutrients. After a meal, nutrients in the duodenum activate a proximal-distal neuroendocrine loop, which stimulates GLP-1 secretion from L-cells in the ileum and colon. In rodents, GIP, released from K-cells, activates vagal afferents, which subsequently causes GLP-1 secretion through vagal efferents and enteric neurons that release acetylcholine (Ach) and GRP. Movement of nutrients toward more distal sections of the intestine leads to the direct interaction of nutrients with L-cells, which also stimulates GLP-1 secretion.

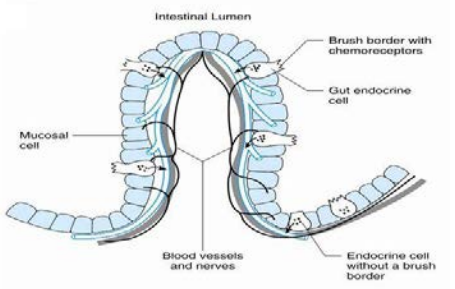
Investigation into short release of GLP-1 possibly reflects indirect release through GIP

Neuronal integration

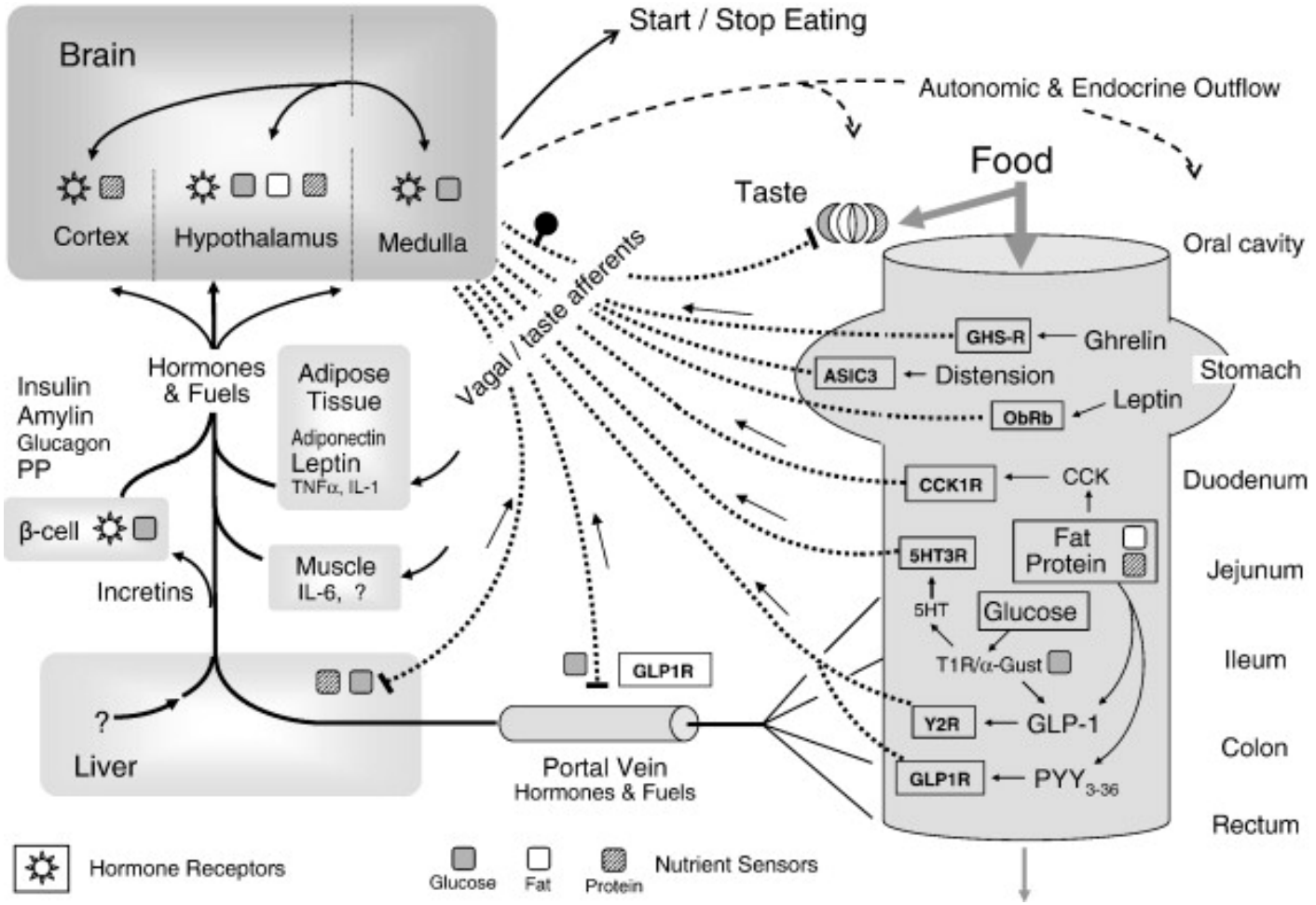








Nutrient signalling is complicated: Old and the new



Research

Open Access

Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study

Mohsen Nematy[1], Jacqui E O'Flynn[2], Liesl Wandrag[2], Audrey E Brynes[3], Stephen J Brett[4], Michael Patterson[5], Mohammad A Ghatei[6], Stephen R Bloom[7] and Gary S Frost[8]

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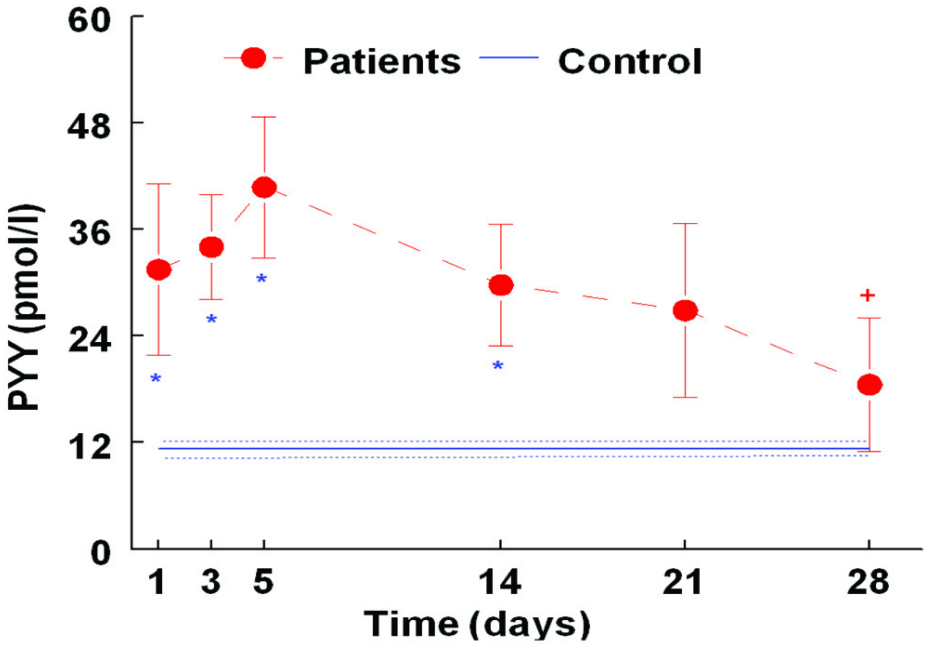
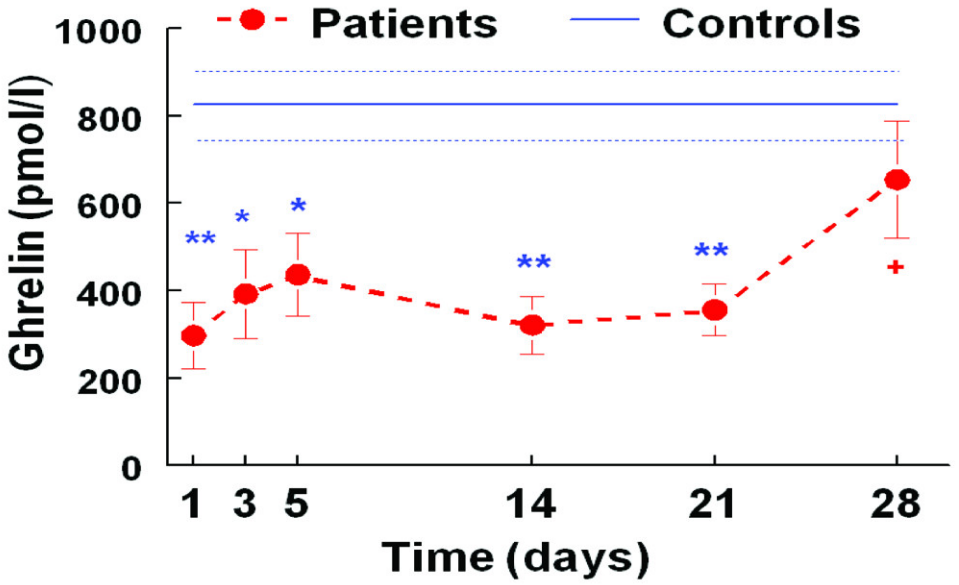

Patients
Control
PYY (pmol/l)
60
48
36
24
12
0
1
3
5
14
21
28
Time (days)


Patients
Controls
Ghrelin (pmol/l)
1000
800
600
400
200
0
1
3
5
14
21
28
Time (days)

Peptide YY (PYY) Is Increased in Elderly Patients With Femoral Neck Fractures: A Prospective Cohort Study

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Michael Pearse, FRCP(orth)†; Michael Patterson, BSc‡; Mohammad A. Ghatei, PhD‡;
Steve R. Bloom, MD, DSc‡; and Gary S. Frost, PhD, SRD§

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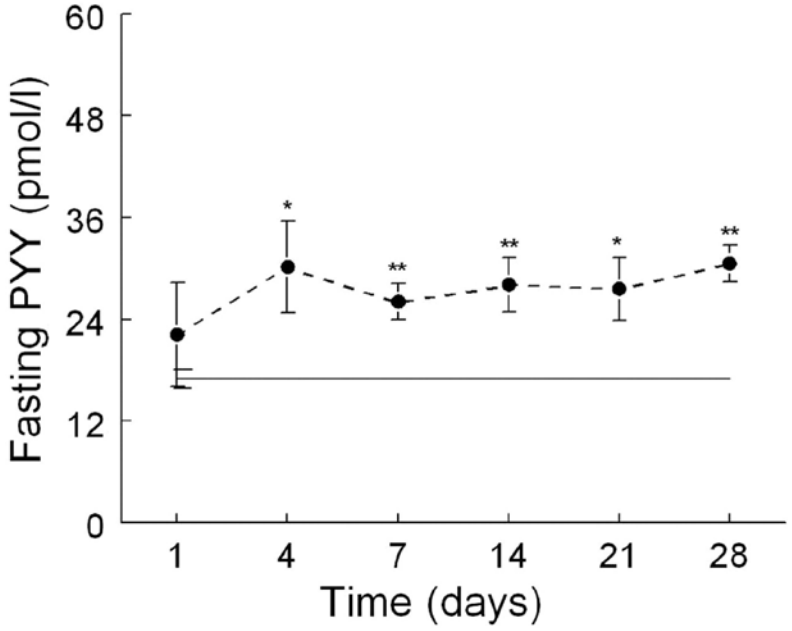
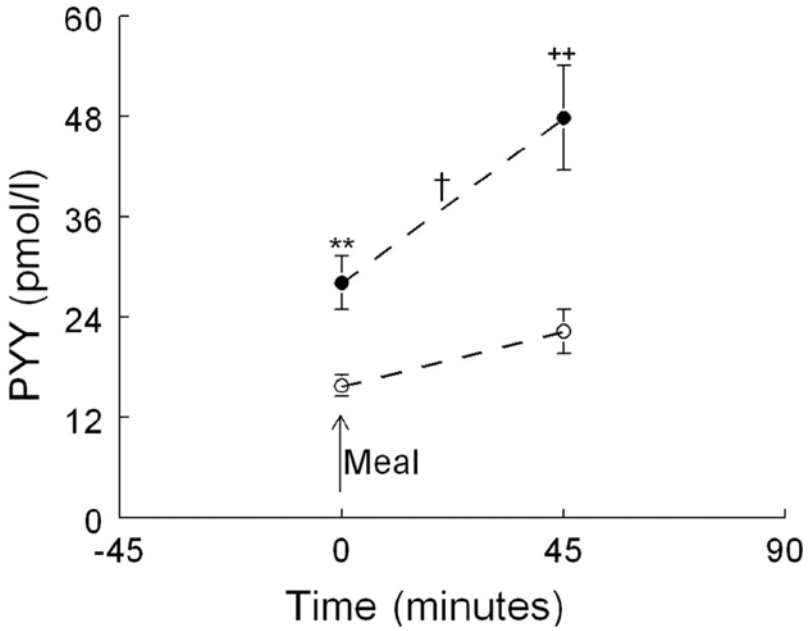




What happens to the gut in trauma

Why does this occur in trauma

- It is complicated
  - Movement of blood flow away from the gut
  - Relative hypoxia at the gut epithelium
  - Loss of tight junction
  - Decrease mucus
  - Change in luminal environment
  - Change in microbiota
  - Result in translocation of PLS and bacteria

Integrated models of gut-origin sepsis

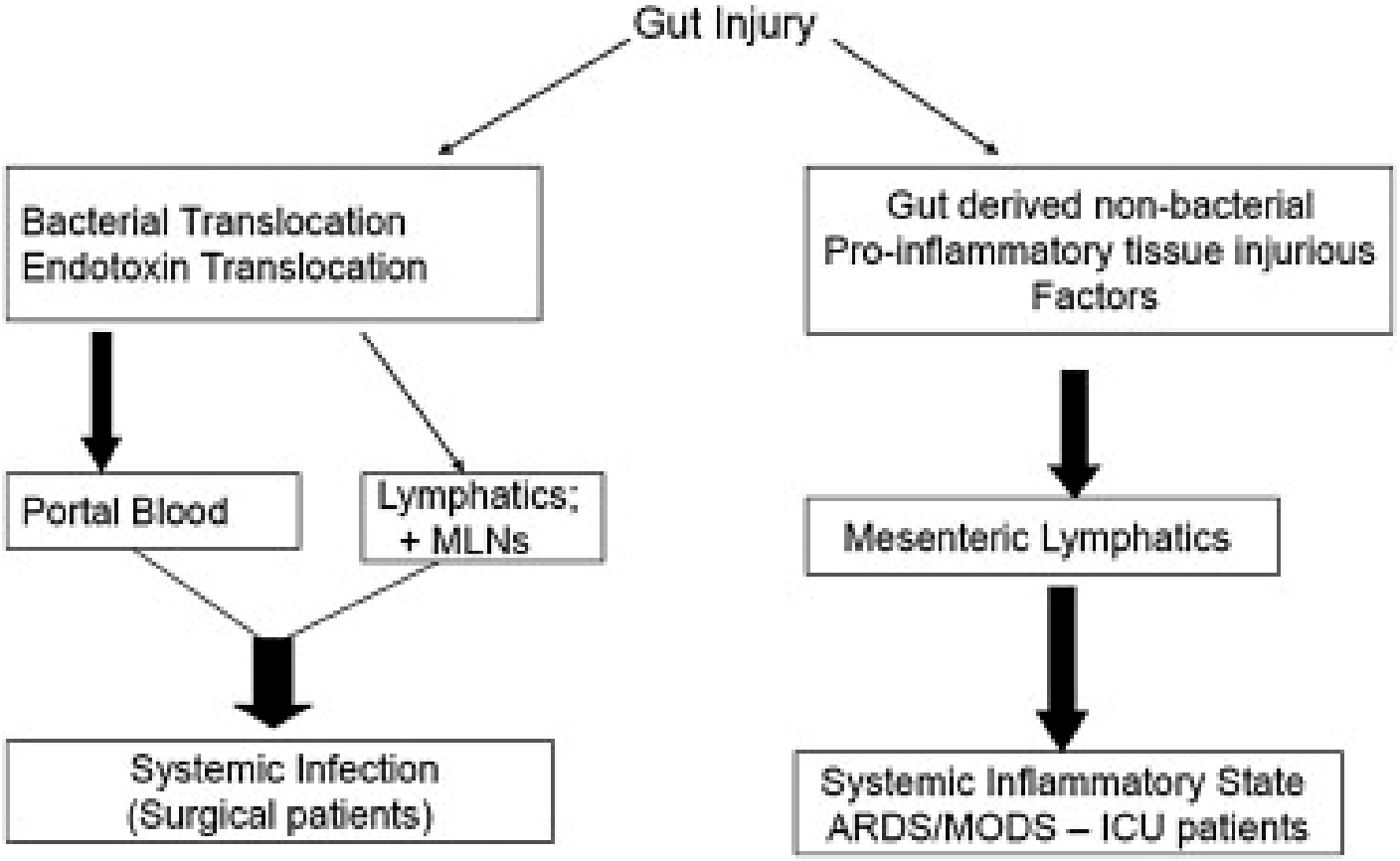
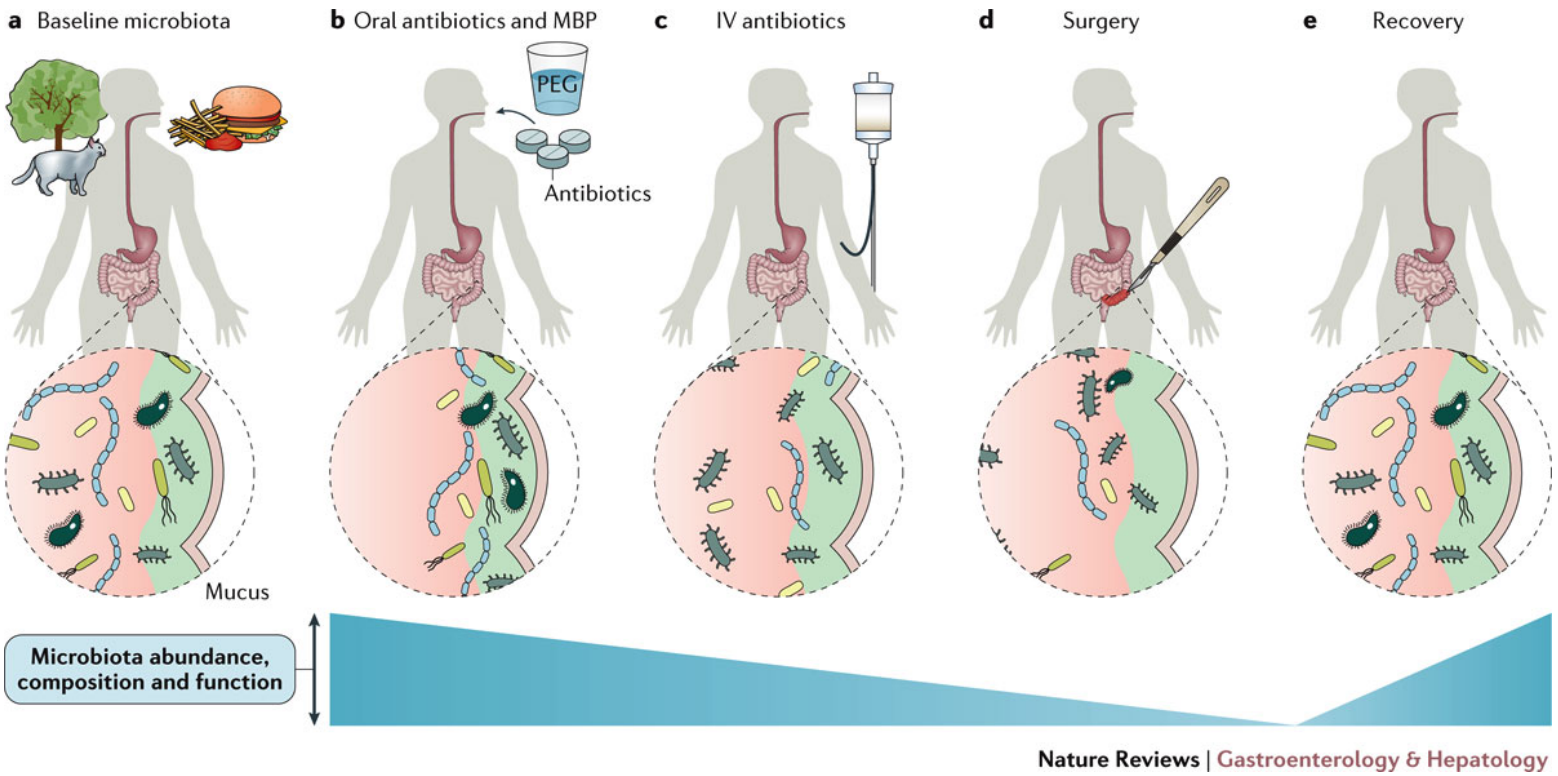
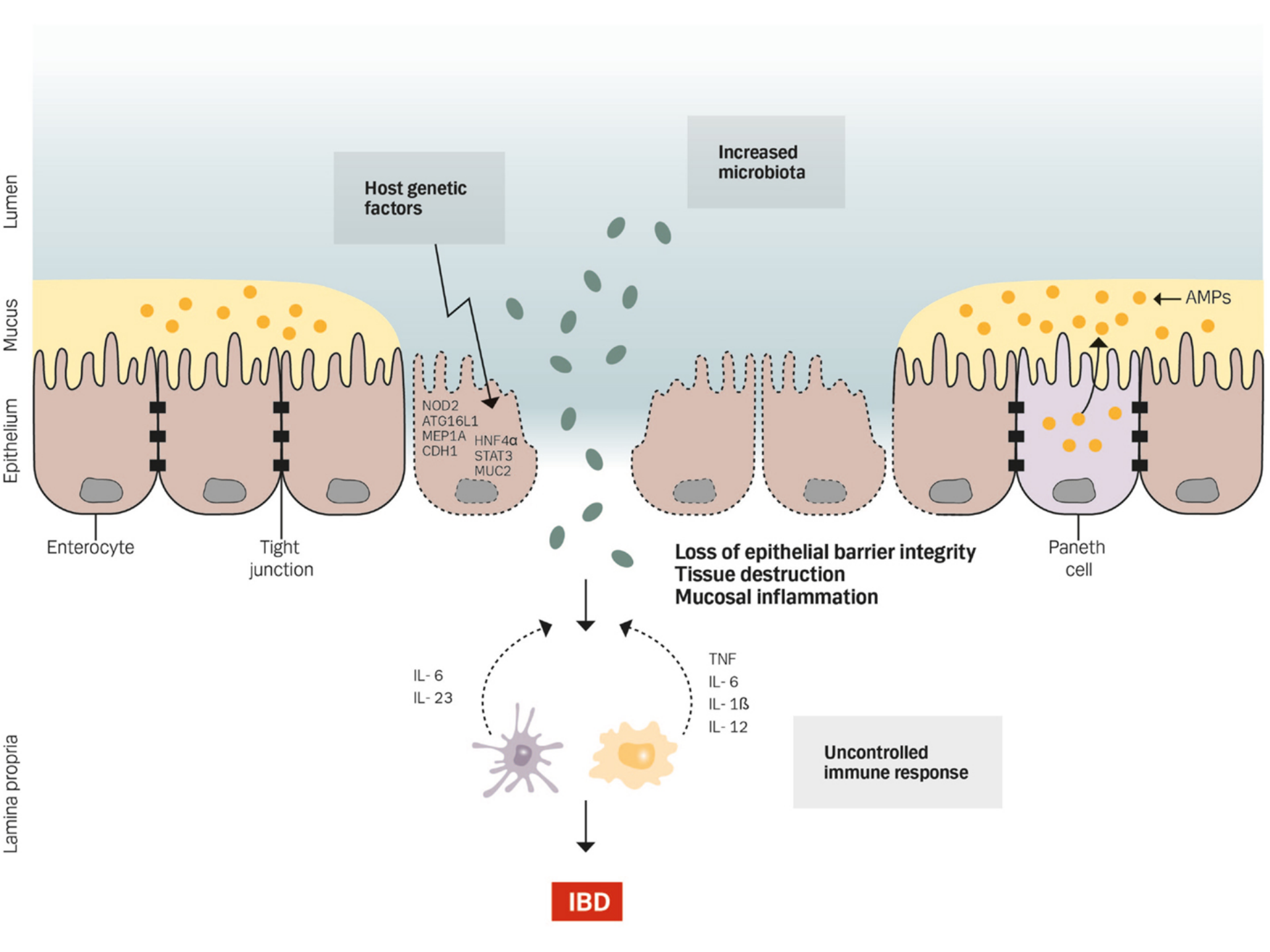


Figure 1 *The effect of perioperative events on the intestinal microbiota*

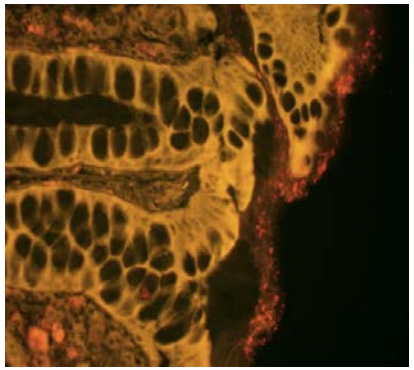


Guyton, K. & Alverdy, J. C. (2016) The gut microbiota and gastrointestinal surgery
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2016.139


Lumen
Mucus
Epithelium
Lamina propria
Host genetic factors
Increased microbiota
NOD2
ATG16L1
MEP1A
CDH1
HNF4α
STAT3
MUC2
AMPs
Enterocyte
Tight junction
Paneth cell
Loss of epithelial barrier integrity
Tissue destruction
Mucosal inflammation
IL-6
IL-23
TNF
IL-6
IL-1ß
IL-12
Uncontrolled immune response
IBD

Loss of gut integrity = abnormal gut hormones

Is the answer short chain fatty acids (SCFA)

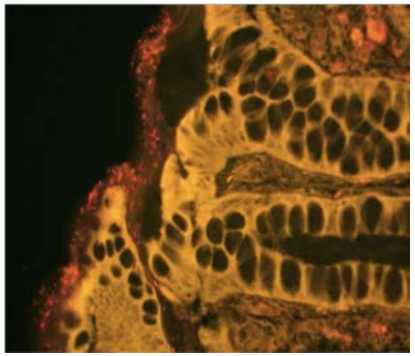


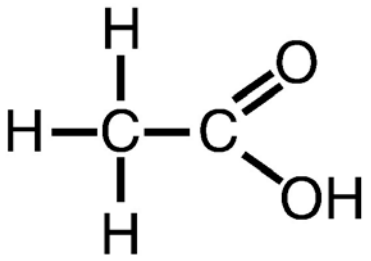
Non-digestible carbohydrates

↓

Colonic bacterial fermentation

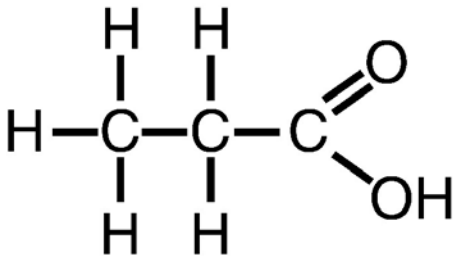
↓





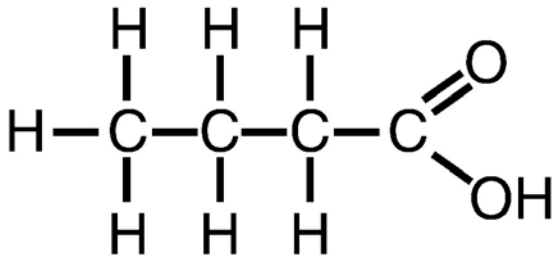
Acetic acid

60 %



Propionic acid

25 %

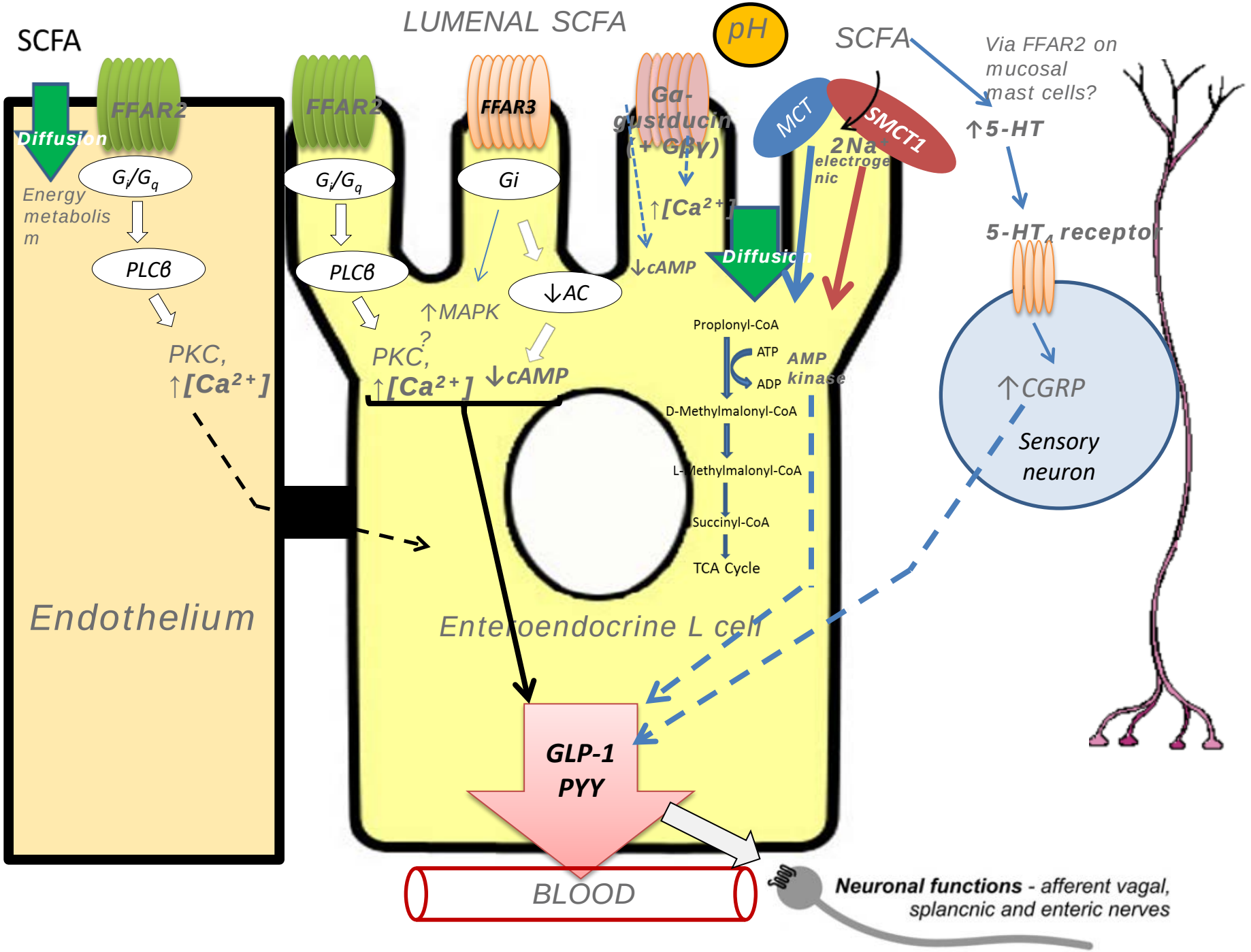


Butyric acid

15 %

SCFA

- Short-chain fatty acids (SCFAs) are an important energy source for the colonic epithelium and a chronic lack of luminal SCFAs may lead to a nutritional deficiency of the colonic epithelium, causing mucosal atrophy
- SCFA stimulate GLP-2
- Colonic concertation of SCFA in trauma fall


SCFA
LUMENAL SCFA
pH
SCFA
Via FFAR2 on mucosal mast cells?
↑5-HT
FFAR2
FFAR2
FFAR3
Gα-gustducin (+ Gβγ)
MCT
SMCT1
2Na+ electrogenic
Diffusion
Diffusion
Energy metabolism
Gi/Gq
Gi/Gq
Gi
PLCβ
PLCβ
↑[Ca2+]
↓cAMP
↓AC
↑MAPK
PKC, ↑[Ca2+]
PKC, ↑[Ca2+]
↓cAMP
Proplonyl-CoA
ATP
ADP
AMP kinase
D-Methylmalonyl-CoA
L-Methylmalonyl-CoA
Succinyl-CoA
TCA Cycle
5-HT4 receptor
↑CGRP
Sensory neuron
Endothelium
Enteroendocrine L cell
GLP-1
PYY
BLOOD
Neuronal functions - afferent vagal, splancnic and enteric nerves

What does this all mean for dietetics

- The gut is important
- We need research in humans with the condition
  - Models of trauma show positive response
- Complicated by antibiotics, change in GI function and food intake

The problem

Nothing seems to work

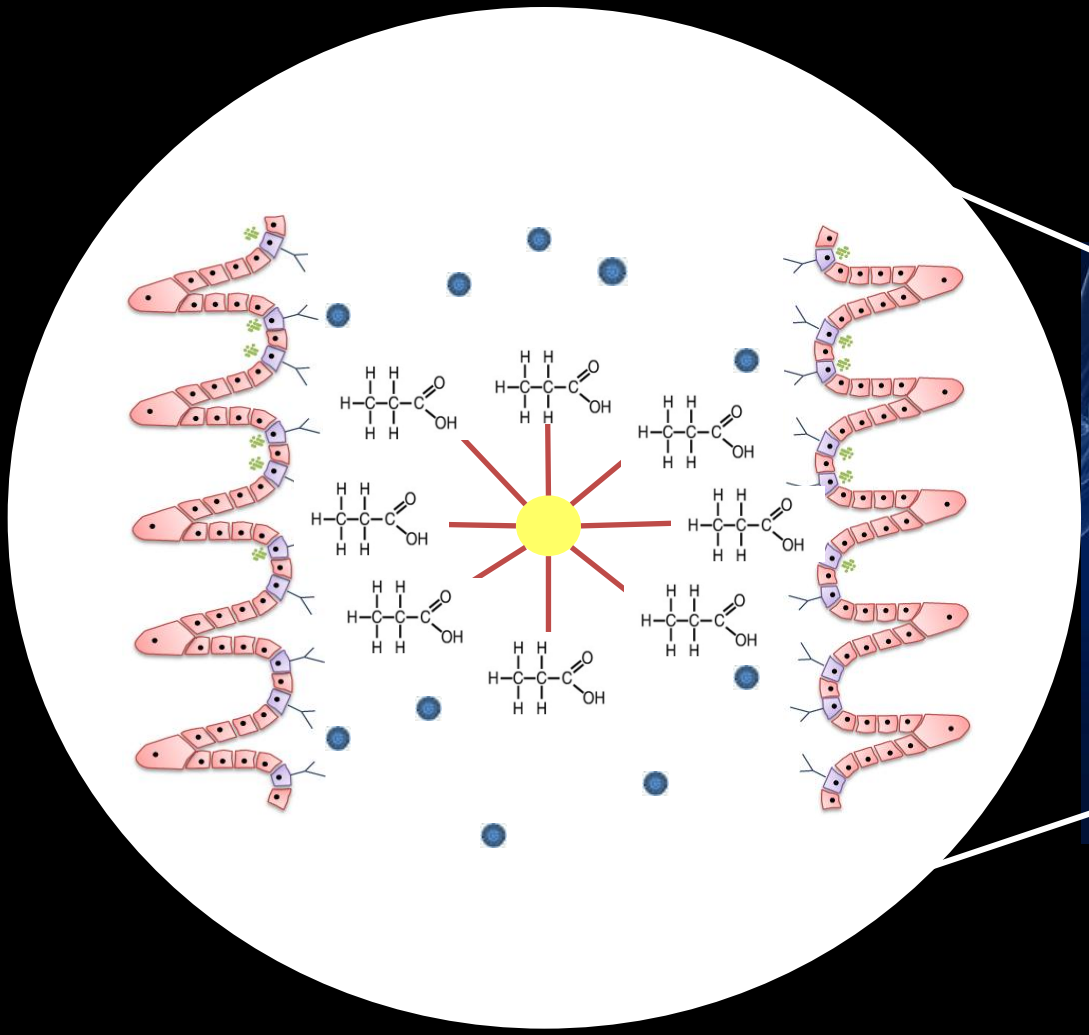
No evidence for dietary fibre in trauma

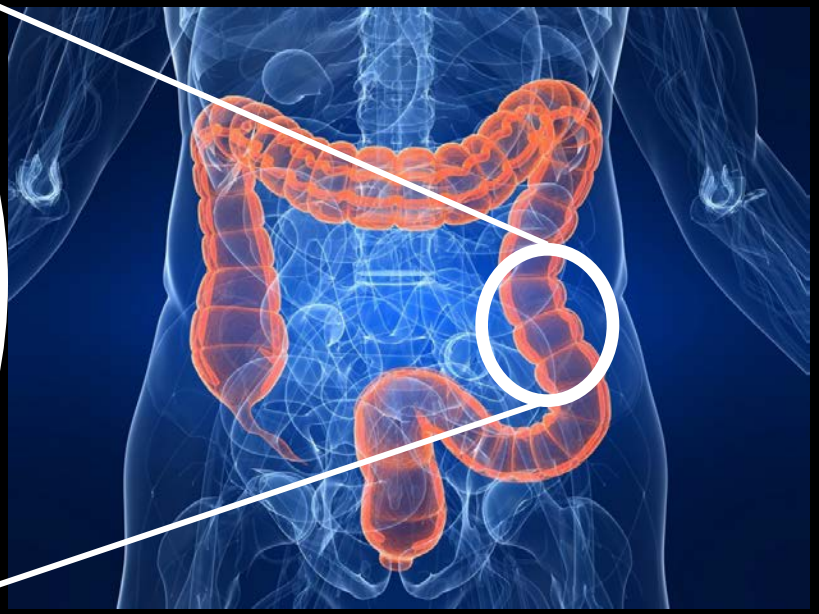
Complicated by cocktail of drugs which effects the gut microbiota

Could colonic delivery of SCFA work

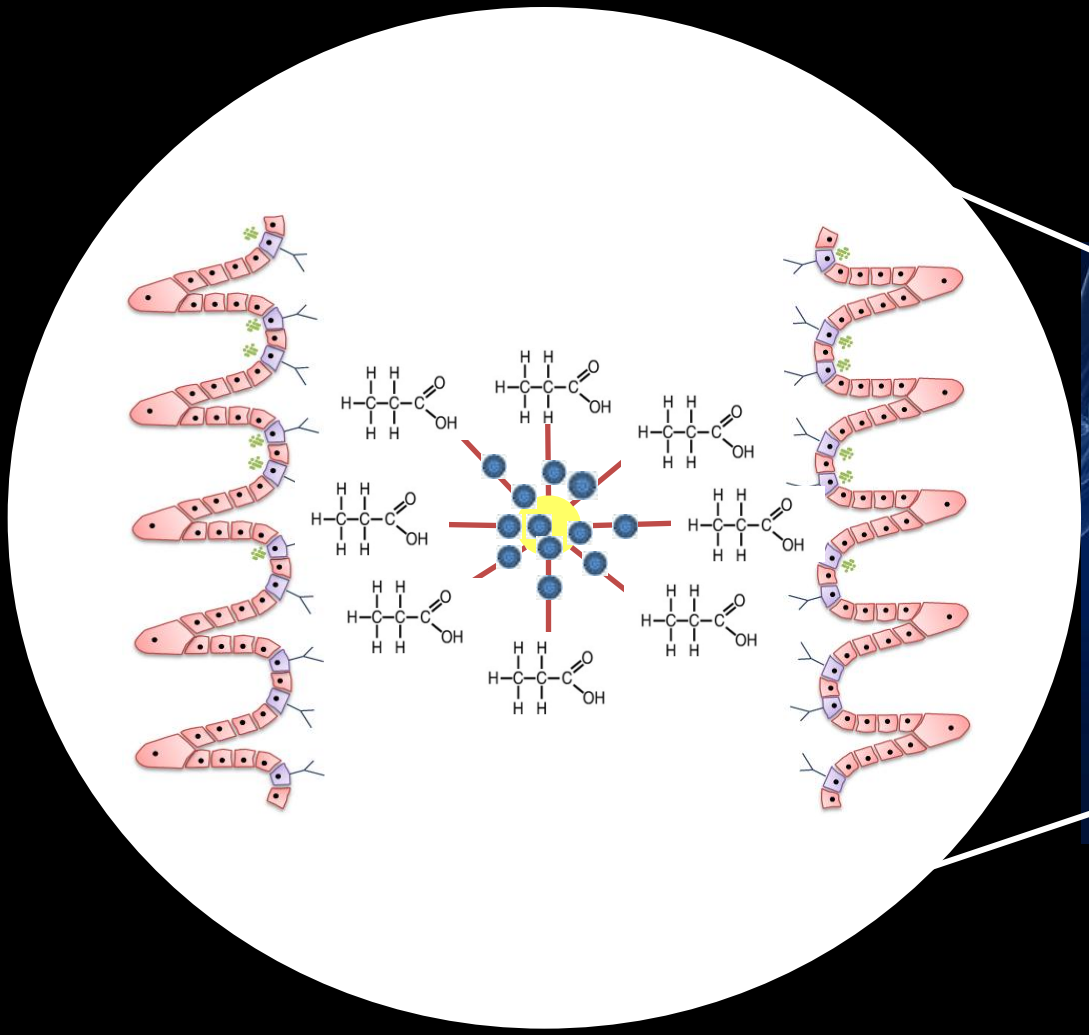
Partnership with Dr Morrison and Prof Preston University of Glasgow

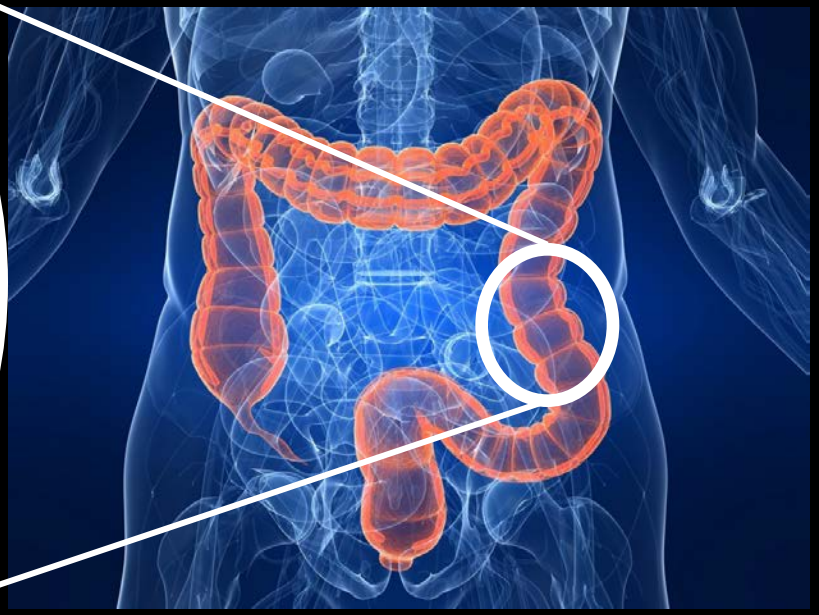
SCFA Ester



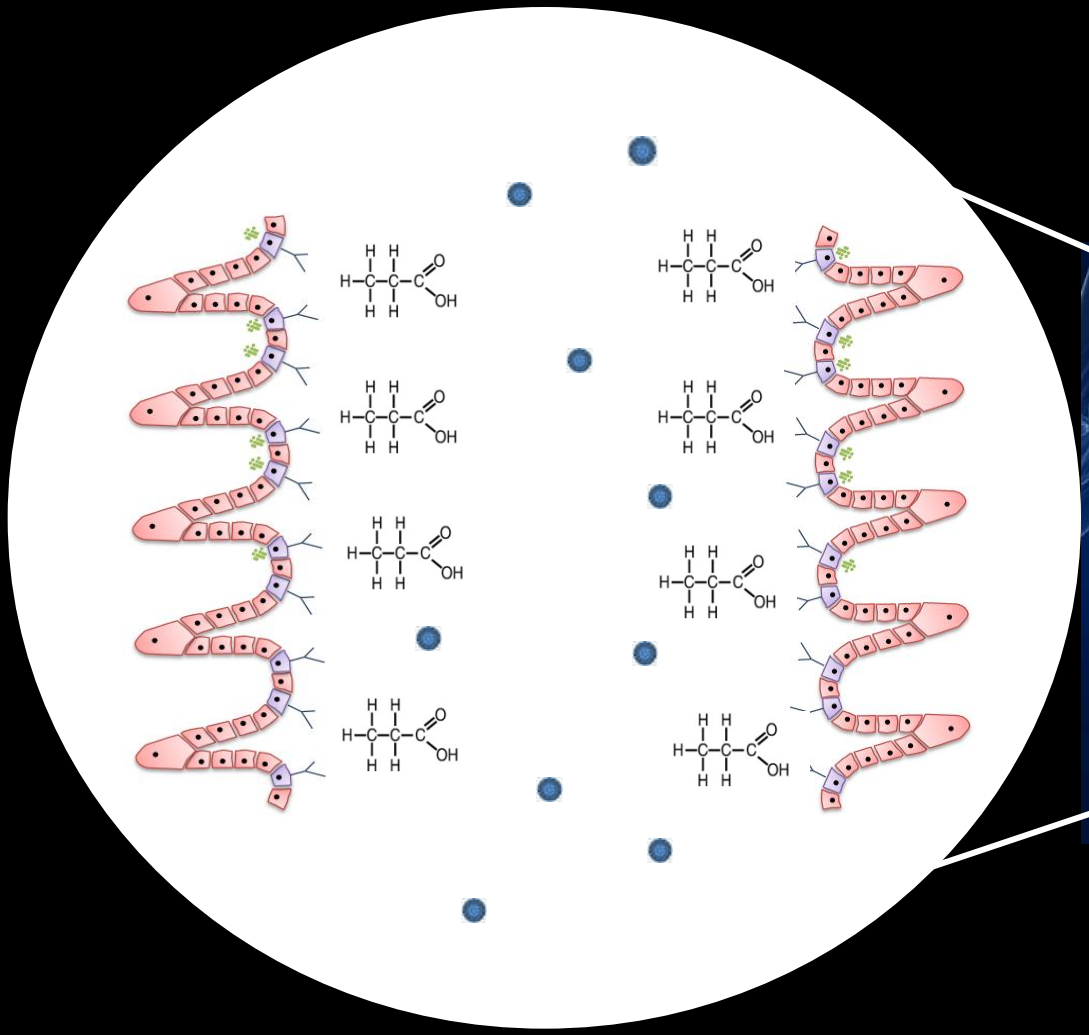


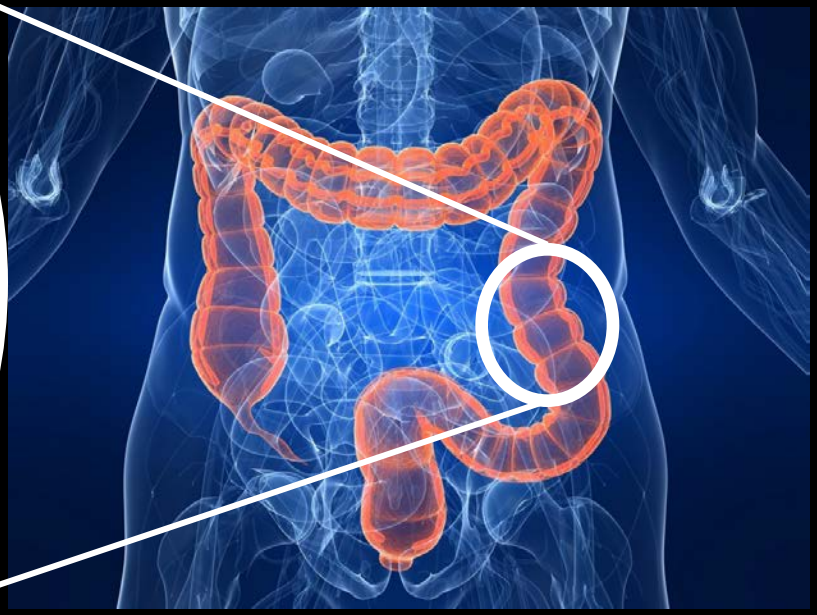
SCFA Ester



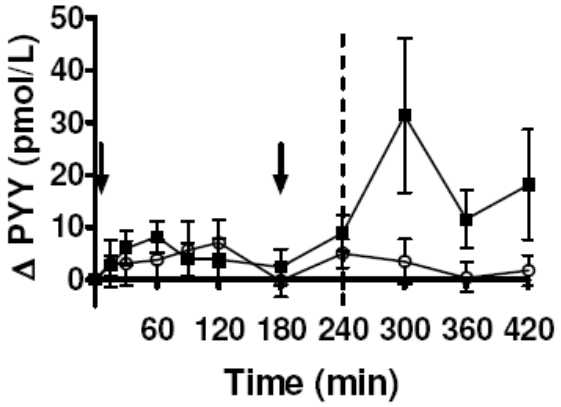


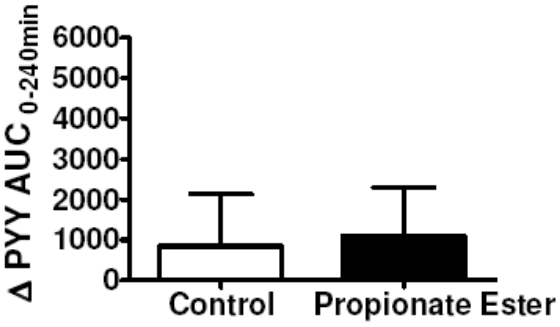
SCFA Ester

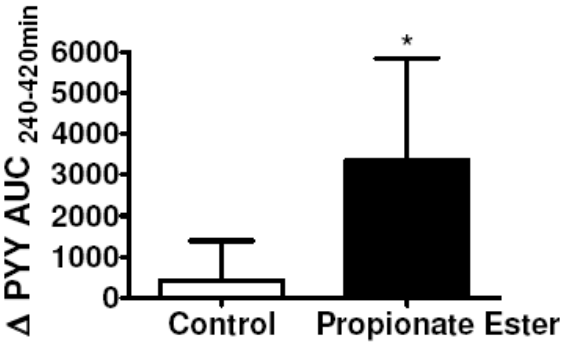


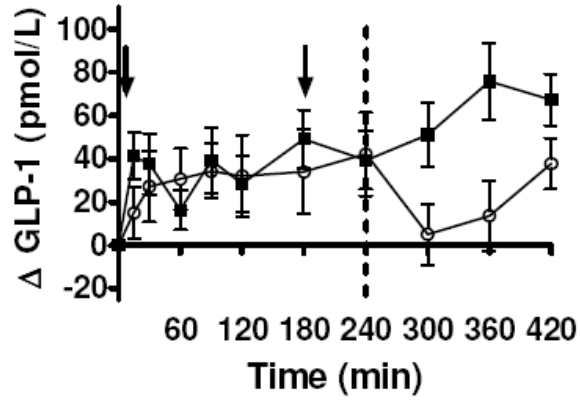


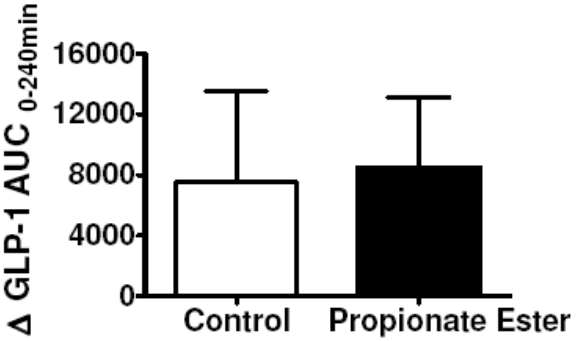
Effect of Ester on gut hormones

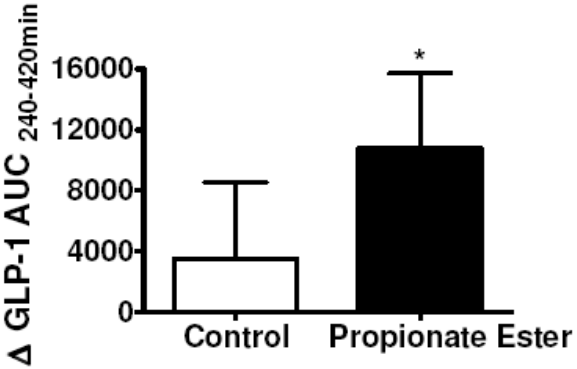












Different SCFA may play different role

- Butyrate
  - energy source of gut endothelium
  - GLP-2 stimulation
  - Gut integrity
- Propionate
  - Stimulation of PYY and GLP-1
- Acetate
  - Energy source

Food for the colon

- Can targeting nutritional support to the colon lead to
  - Improved barrier function
  - Decrease in sepsis
  - Improved appetite regulation

  - Lots of questions to be answers