Gastro-intestinal hormones
Coordination of gastro-intestinal function

Other non-endocrine gland sites of hormone production

Functions
G-I hormones, with the enteric & autonomic nervous systems. 
integrate and coordinate mechanisms which
• move 
• digest 
• absorb

They control
• exocrine & endocrine secretion 
• motility, growth, & blood flow 
• appetite

Routes
• endocrine 
• paracrine 
• neurocrine (from nerves of the enteric nervous system)

Difficulty in determining physiologically active concentration of hormone. 
Use of neutralising antibodies to elucidate physiology.
**Gut (entero-) endocrine cells**

Part of G-I tract epithelium
- Originally seen as 'pale cells'
- Derived from endoderm
- Variably positioned in crypts
- Hormone secreted basally
- Most have microvilli on apex open to gut lumen to sense the content of the gut
- Distribution varies between fetus & adult.

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**Gastrin – G cells**

Gastrin (G17) plasma: pmol/l; increased after meal; G17 t½=5 min; (G34 t½=40 min has only 20% potency of G17)

**Release**
- stimulated by:
  - protein digestion products (esp tryptophan, phenylalanine)
  - (also calcium, beer, wine, coffee)
  - vagus, via acetylcholine, GRP
- distension of stomach
- hypercalcaemia – PTH × secretion

**Inhibited by:**
- stomach pH<2.5
  - (alkali short term has little effect; long term causes hyperplasia)
- somatostatin
  - (local negative feedback)
**GASTRIN - EFFECTS**

Gastrin stimulates (via $G_{aq}$ Ca, PKC):
- gastric acid secretion (direct & indirect via histamine H$_2$)
- parietal cell growth
- pepsinogen secretion
- antral motility (churning)
- mucosal blood flow
- trophic to parts of GI tract
- water & electrolyte secretion in liver, pancreas, intestine

High levels:
- stimulate calcitonin,
- food intake,
- insulin & pancreatic enzyme secretion,
- antagonise secretin

*Effects synergise with those of vagal acetylcholine (M3; $G_{aq}$ Ca, PKC)*

**GASTRIN PATHOLOGY**

Gastrinoma (usually in pancreas) causes repeated peptic ulceration due to high acid and pepsin secretion (Zollinger-Ellison syndrome)

*Role in non-gastrinoma duodenal ulceration*

NR Most peptic ulceration now attributed to H. pylori

Duodenal ulcer patients secrete (on average) more acid than controls; but there is overlap of the data

*Duodenal ulcer patients secrete more gastrin in response to a meal*

**HISTAMINE**

- Enterochromaffin-like (ECL) cells of stomach wall.

- **Synthesis:** from histidine by histidine decarboxylase

- **Release:**
  - *vagal stimulation*
  - *gastrin*

- **Actions:**
  - stimulates gastric acid (HCl) secretion via H$_2$ receptors

- **Pharmacology:**
  - use of H$_2$ receptor antagonists for treatment of peptic ulceration (cimetidine, ranitidine)
  - (now superceded by proton pump inhibitors; omeprazole)

**SECRETIN** (first hormone described)

*Distribution:* S cells, from duodenum to distal ileum; in neck region of intestinal glands

-Synthesis: peptide.
- Plasma: pmol/l after meals; $t_{0.5}$=3 min

- **Release:** stimulated by acid in proximal duodenal - lumen pH<4.5; inhibited by somatostatin

- **Actions** (via $G_s$, CFTR, and Cl-HCO$_3$ exchange):
  - stimulates pancreatic secretion of HCO$_3$ & water; this washes pancreatic enzymes into the gut
  - stimulates liver secretion of HCO$_3$ & water into bile

(potentiates CCK)
**CHOLECYSTOKININ (CCK) = Pancreozymin**

*Distribution:* I cells in duodenum, jejunum

*Forms:* CCK33, CCK58, CCK39;
in brain CCK8

*Terminal pentapeptide = terminal of gastrin*

*Release stimulated by:* protein, fat digestion products in duodenum

*Actions:*
- stimulates secretion of pancreatic enzymes
- stimulates contraction of gall bladder
- potentiates action of secretin

(inhibits gastric emptying; increases small bowel transit)

(high levels potentiate secretion of calcitonin)

*CCK acts on vagal afferent terminals to signal satiety* (suppress appetite)

(the feeling that one has had enough to eat)

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**GLUCAGON-LIKE PEPTIDES (GLP-1 & GIP) (facilitation of insulin secretion)**

**GLP-1 Glucagon-Like Peptide**

*Distribution:* L cells in small intestine

*Release:*
- stimulated by meals: especially oral carbohydrate and fat;
- also by GIP

*Actions:*
- powerfully potentiates glucose-stimulated insulin release

**GIP Glucose-dependent Insulinotropic Peptide**

(originally gastric inhibitory peptide: weak action) (peptide of secretin/glucagon family)

*Distribution:* K cells of small intestine

*Release:*
- stimulated by oral glucose, fat, protein

*Actions:*
- potentiates glucose-stimulated insulin release

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**SOMATOSTATIN**

*Local inhibition/negative feedback*

*Distribution:* D cells gastric antrum to colon

*Structure:*
- peptide (14aa; 28aa in brain)
- acts via G_i to inhibit cAMP production

*Release:*
- stimulated by meals: amino acids, glucose, fatty acids, gastrin, secretin

*Actions:*
- suppresses secretion of GI hormones
- suppresses their effects (acid etc)
- retards absorption glucose; protects against post-prandial hyperglycaemia (in liver)

*Pathology:*
- somatostatinoma: - what would it cause?

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**VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)**

*Distribution:*
- in enteric neurons
- in pelvic parasympathetic nerves (NO; erection)
- in brain
- in nerves in pancreas

*Structure:*
- small peptide; secretin/glucagon family
- acts via cAMP (cf choler toxin)

*Release:*
- ? circulating levels don't rise after meal

*Actions:*
- relaxes cardiac sphincter, stomach, anal sphincter; vasodilator
- pancreatic bicarbonate secretion

*Pathology:*
- Tumour - VIPoma (Verner-Morrison syndrome):
  - watery diarrhoea; hypokalaemia; achlorhydria
Motilin
Distribution: endocrine cells antrum to colon
Structure: small peptide
Actions:
- increases the motility of the bowel
- induces migrating myoelectric complexes at antro-duodenal pacemaker

Neurotensin
Distribution: N cells of distal small intestine
Structure: small peptide
Release: intraluminal fat
Actions:
- + pancreatic secretion; - gastric/ small bowel motility; trophic to gut mucosa; protects gastric mucosa

Gut glucagon (enteroglucagon, glicentin)
Distribution: gastric A cells; ileal, colonic L cells
Structure: large glucagon-like; Mₙs 10,000; 4,000
Actions:
- stimulates gastric/intestinal motility
- stimulates intestinal absorption sugars
- systemic glucagon-like effects
- trophic - small bowel (compens. hypertrophy)

Multiple endocrine neoplasia (MEN)
Due to genetic mutations
Tumours are usually multiple

MEN 1: tumours of
- pancreas (gastrinoma, insulinoma, VIPoma);
- anterior pituitary;
- parathyroids (PTH)

MEN 2: tumours of
- thyroid C cells (calcitonin);
- adrenal medulla chromaffin cells (adrenaline)
- parathyroids (PTH)

GUT HORMONES INFLUENCING APPETITE & FEEDING (1)

CCK
- acts on vagal terminals; inhibits feeding

GHRELIN
- Peptide produced in stomach, oxyntic cells before meals and esp. in starvation
- Acts in hypothalamus to stimulate feeding
- When injected into mice increases fat mass
- Increased after dieting weight loss
- Very high in Prader-Willi obesity

GUT HORMONES INFLUENCING APPETITE & FEEDING (2)

PEPTIDE YY (PYY)
- produced in ileum and colon after meals
- has a prolonged effect on Y2 receptors in hypothalamus to decrease appetite and food intake
- has been controversial

Dual X-ray absorption scan showing body fat (white)

Control          Ghrelin analogue

Other sites of hormone production

**Adipose tissue (white fat)**

**Leptin**
- plasma levels reflect total white fat mass;
- inhibits feeding by action in hypothalamus;
- also inhibits insulin secretion

**Adiponectin**
- increases insulin sensitivity in muscle and liver;
- decreased plasma adiponectin is associated with the 'metabolic syndrome' of increased BMI, insulin resistance and plasma lipid disturbance

**Heart**

**Atrial natriuretic peptide (ANP)**
- Production: peptide secreted by atrial myocytes
- Release: atrial dilatation (i.e. increased venous return, right heart failure)
- Actions: stimulates loss of sodium (water) in urine
- inhibits renin-angiotensin-aldosterone system
- reduces BP (- venous return, - cardiac output)

**Kidneys**

**Erythropoietin**
- Production: glycoprotein produced by glomeruli
- Release: reduced $O_2$ saturation of blood;
- androgens, beta-adrenergic
- Actions: + production of RBC (Abuse by athletes)

**Renin-Angiotensin System**

- Renin - protease from afferent arterioles of glomeruli
- Release: stimulated by sodium depletion, hypotension, dehydration, low renal artery blood flow, sympathetic NS.

**Angiotensinogen - angiotensin I → angiotensin II**
- All stimulates aldosterone secretion, thirst, vasoconstriction.
- Pharmacology: ACE inhibitors in treatment of hypertension

**Prostanoids** – prostaglandins, thromboxanes, leukotrienes etc
- produced by most tissues
- have local & endocrine actions – e.g. contraction of uterus; ductus art.

**Gonadal, placental hormones** – see Reproduction lectures

**Cytokines, other Growth Factors** – Pathology (immune) Y2

Year 2 Integrative Physiology – revisit many control systems

**Clinical medicine** – endocrine disturbance, primary or secondary

Hormones are just one class of chemical signals
- Nature/evolution has utilised every possibility
- Distinction hormones, neurotransmitters, local factors is blurred