Ghrelin

Ghrelin is secreted by ε-cells of the pancreatic islet and by cells in the body of the stomach. It inhibits GH secretion and is involved in appetite control. No syndrome has been described from its excess or inappropriate action.

Gastrointestinal endocrinology

Intestinal hormone-secreting cells scattered throughout the stomach wall and at the bottom of intestinal crypts are termed ‘enteroendocrine’. They secrete a multitude of hormones that regulate gastrointestinal function and metabolism (see Table). Some of the hormones, such as vasoactive intestinal polypeptide (VIP), are actually released from the enteric nervous system and function as neurotransmitters.

Gastrin

Gastrin is secreted as peptides of three sizes from G-cells in the duodenum, pancreas and antral part of the gastric mucosa following distension of the stomach by food or by the presence of small peptides or amino acids within the stomach (Table 10.1). Anticipation of eating also increases gastrin secretion via the vagus nerve. Gastrin increases stomach acid secretion and blood flow to the gastric mucosa. Gastrin is thought to play a role in gastric motility and peristalsis. Once the pH of the stomach falls below 2.5, negative feedback inhibits further gastrin release. Its secretion is also inhibited by somatostatin, glucagon and VIP.

Vasoactive intestinal polypeptide

VIP is a 28-amino acid peptide neurotransmitter in the gut and central nervous system. At pharmacological doses, VIP increases hepatic glucose release, insulin secretion and pancreatic bicarbonate production, while inhibiting stomach acid production, partly through relaxation of gastric blood vessels and smooth muscle. These actions are similar to those of glucagon, secretin and glucose-dependent insulinotrophic peptide (GIP; also known as gastric inhibitory peptide). GIP and VIP may have evolved from a single gene.

Cholecystokinin, secretin and motilin

Cholecystokinin (CCK), secretin and motilin are all peptide hormones secreted by the small intestine in response to a variety of stimulants and act via cell surface G-protein–coupled receptors (Table 10.1).

- CCK increases gallbladder contraction and stimulates pancreatic exocrine secretion.
- Secretin is released in response to stomach acid entering the duodenum and stimulates the pancreas to secrete bicarbonate-rich fluid that neutralizes the acidity.
- Motilin, synthesized in duodenal and jejunal M-cells, enhances gut peristalsis and pepsin secretion.

Hormone	Amino acids (active form)	Cell type	Location	Major stimulus	Major action	Receptor-signalling (review Chapter 3)
Pancreas						
Insulin	51	β-cell	Islet	High glucose	Lowers serum glucose (see Chapter. 11)	IR-TK
Glucagon	29	α-cell	Islet	Low glucose	Raises serum glucose (see Chapter 11)	GPCR
Somatostatin (SS)	28, 14	δ-cell	Islet		Inhibits secretion of insulin, glucagon, VIP, GIP, secretin, motilin, CCK and GH (SS also in brain – see Chapter 5)	GPCR
Pancreatic polypeptide (PP)	36	PP-cell	Islet	Fasting, hypoglycaemia	Poorly understood; seems to coordinate islet function	GPCR
Ghrelin	28 (+ modification by fatty acid)	ε-cell D1-cell	Islet Stomach	Fasting	Stimulates hunger (see Chapter 15)/stimulates GH (see Chapter 5)	GPCR
Gastrointestinal						
Gastrin	34 (big), 17 (little), 14 (mini)	G-cell	Stomach, duodenum and pancreas	Stomach distension, vagal input, Ca^{2+}, amino acids	Stimulates gastric acid secretion from parietal cells; stimulates pepsinogen secretion	GPCR
Vasoactive intestinal peptide (VIP)	28	Enteric neurones	Nerves in islet and throughout intestine	Cholinergic nerve activity	A range of effects that in combination stimulate intestinal motility	GPCR
Glucagon-like peptide 1 (GLP-1)	37	L-cell	Small intestine, especially the terminal ileum*	High intestinal glucose/ nutrients	Incretin; enhances glucose-sensitive insulin secretion (GSIS) by pancreatic β-cell	GPCR
Glucose-dependent insulinotropic peptide (GIP)	42	K-cell	Duodenum and jejenum	High intestinal glucose/ nutrients	Incretin; enhances GSIS by pancreatic β-cell	GPCR
Cholecystokinin (CCK)	58, 33, 8	I-cell	Duodenum	Fat/protein in duodenum	Stimulates bile and pancreatic secretion to allow fat digestion	GPCR
Secretin	27	S-cell	Duodenum	Low pH	Stimulates pancreatic bicarbonate secretion to buffer stomach acid in small intestine; stimulates bile secretion	GPCR
Motilin	22	M-cell	Duodenum and jejenum	High pH	Stimulates intestinal motility	GPCR
Serotonin	Synthesized from tryptophan	Enteroendocrine cells and enteric neurones	Throughout intestine	Food in intestine causing enteric nerve activity	Regulates intestinal motility	GPCR

*Some GLP-1 is most likely produced by the α-cell in the pancreatic islet and also from the large bowel.
IR, insulin receptor; TK, tyrosine kinase; GH, growth hormone; GPCR, G-protein–coupled receptor.

Hormones that regulate the calcium homeostasis

Vitamin D and parathyroid hormone (PTH) are the two major hormones that regulate Ca^{2+} through a complex interaction. Both hormones increase serum Ca^{2+} levels. Calcitonin and parathyroid hormone-related peptide (PTHrP) can affect $Ca2^{+}$, but they play limited roles in human physiology.

Vitamin D

Vitamin D functions more like a hormone than a vitamin. It is derived from cholesterol and has a similar structure to steroid hormones. There are a number of different forms of vitamin D. At least 10% is acquired from dietary sources like fish and eggs as vitamin D2 (ergocalciferol; Figure 1), which places vegans at increased risk of vitamin D deficiency. Several foodstuffs, including margarine and milk, are fortified with vitamin D2. Vitamin D3 (cholecalciferol) accounts for 90% of total vitamin D and is synthesized in the skin by photoisomerization induced by ultraviolet (UV) light (see below and Figure 1).

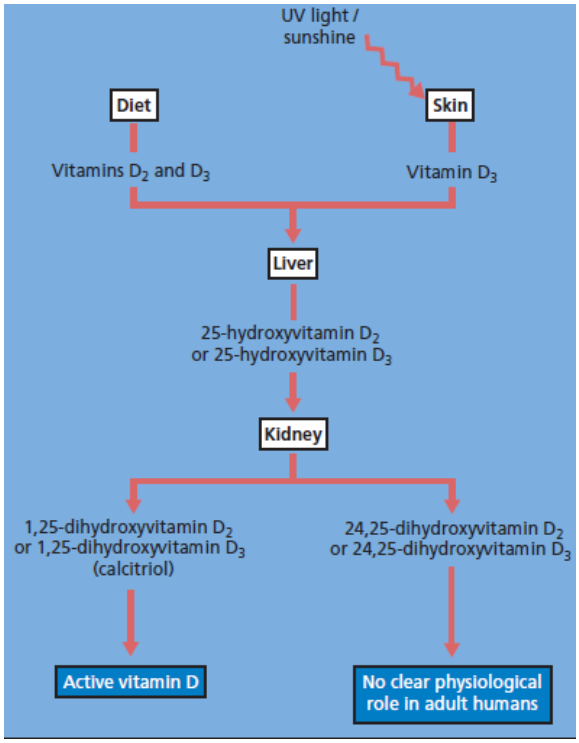

Figure 1: The sources and UV light / metabolism of vitamin D.

Synthesis of active vitamin D

Vitamin D2 and vitamin D3 serve as precursors for active hormone synthesis and are structurally identical except for the double bond in vitamin D2 between carbon (C) 22 and C23 of the side chain. In the inner layers of the sun-exposed epidermis, vitamin D3 is synthesized from 7-dehydrocholesterol. The B ring opens to form pre-vitamin D followed by rotation of the A ring (Figure 2). Activation occurs by two hydroxylation steps. The first occurs predominantly in the liver at C25 to form 25-hydroxyvitamin D, which circulates at quite high concentrations [20–40 nmol/L (8–16 ng/mL)] and is then converted in the kidney to fully active 1,25-dihydroxyvitamin D (calcitriol; Figure 2), the serum concentration of which is very low [48– 110 pmol/L (20–46 pg/mL)]. As for steroid hormones (review Chapter 2), there is a circulating vitamin D-binding protein with high affinity for 25-hydroxyvitamin D but low affinity for calcitriol. This means calcitriol circulates largely free and has a short half-life of ~15 h, compared to 15 days for 25-hydroxyvitamin D. The longer half-life of 25-hydroxyvitamin D makes it a more reliable measure of overall vitamin D status in patients.

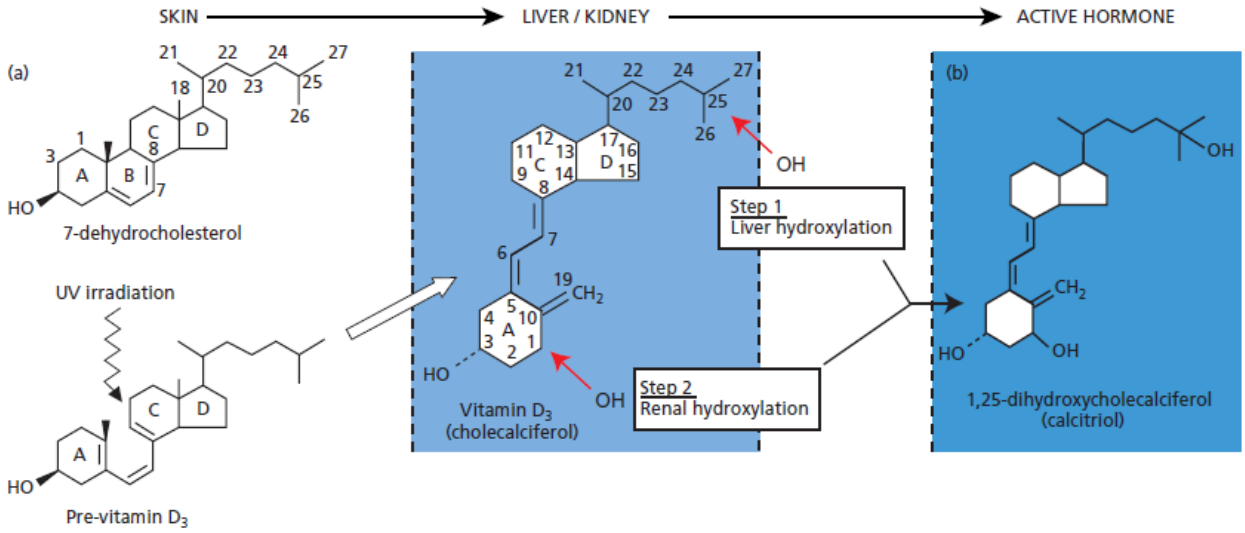

Figure 2: Synthesis of calcitriol. (a) UV irradiation opens the B ring of 7-dehydrocholesterol to give pre-vitamin D3. Rotation of the A ring then gives vitamin D3 (cholecalciferol). (b) Vitamin D3 is hydroxylated in the liver at carbon 25 and then in the kidney at carbon 1 to give 1,25-dihydroxycholecalciferol (calcitriol). The hydroxyl group on carbon 1 is in the α orientation so the enzyme is known as 1α-hydroxylase. Projection of groups is shown relative to the plane of the rings: forwards ; backwards. .

Regulation of vitamin D synthesis

Prevailing Ca2+ levels control production of active or inactive vitamin D by negative feedback. Inactivation of vitamin D occurs in the kidney by 24-hydroxylation to 1,24,25-trihydroxyvitamin D. 24-hydroxlyase also acts on 25-hydroxyvitamin D to form 24,25-dihydroxyvitamin D. This metabolite may play a role in bone development; however, no clear function is apparent in adulthood, other than to limit formation of calcitriol. For instance, high Ca^{2+} increases activity of 24-hydroxylase, thereby restricting levels of active vitamin D in circumstances where it would be detrimental to increase serumCa^{2+} . Conversely, low Ca^{2+} or PO_4^{3-} levels stimulate 1α-hydroxylase to encourage active vitamin D synthesis. The expression of 1α-hydroxylase requires and is increased by PTH. As a consequence, calcitriol rather than cholecalciferol or ergocalciferol needs to be given to treat hypocalcaemia secondary to hypoparathyroidism. 1α-hydroxylase expression is also increased by growth hormone (GH), cortisol, oestrogen and prolactin.

Function of vitamin D

Like steroid and thyroid hormones, calcitriol binds a specific nuclear receptor, the vitamin D receptor (VDR), which functions as a ligand-activated transcription factor in the nucleus by heterodimerizing with the retinoid X receptor (RXR) [RXR also interacts with thyroid hormone receptor. The VDR–RXR heterodimer orchestrates the expression of genes involved in Ca^{2+} absorption and homeostasis, mainly in the intestine, bone and kidney. In the gut, vitamin D increases the absorption of dietary Ca^{2+} and PO_4^{3-} . Vitamin D's effects on bone are complex and in part mediated via complex interactions with PTH. On the whole, if vitamin D is deficient, bones can become demineralized, leading to osteomalacia. However, direct vitamin D action in bone tends to increase the release of Ca^{2+} and PO_4^{3-} by some activation of osteoclast activity. In the kidney, vitamin D increases Ca^{2+} and PO_4^{3-} re-absorption. Vitamin D is implicated outside of Ca^{2+} metabolism in direct effects on the vasculature, insulin secretion and immune function.

Table 9.1 Comparative actions of vitamin D, parathyroid hormone (PTH) and calcitonin

	Vitamin D	PTH	Calcitonin
Bone	↑ Osteoclast activity ↑ Bone resorption (but note that vitamin D deficiency causes demineralization)	↓ Osteoblast activity (if constant) ↑ Bone resorption (if constant) ↑ Osteoblast activity (if intermittent) ↓ Bone resorption (if intermittent)	↓ Osteoclast activity ↓ Bone resorption
Kidney	↑ Calcium re-absorption ↑ Phosphate re-absorption	↑ 1α-hydroxylase synthesis ↑ Calcium re-absorption ↓ Phosphate re-absorption	↓ Calcium re-absorption ↓ Phosphate re-absorption
Gut	↑ Calcium absorption ↑ Phosphate absorption	(Indirect action only) ↑ Calcium absorption ↑ Phosphate absorption	
Blood	↑ Calcium ↑ Phosphate	↑ Calcium ↓ Phosphate	↓ Calcium ↓ Phosphate