Chapter objectives

After studying this chapter you should be able to:

1. Understand the role of erythropoietin in preventing anaemia.
2. Understand the role of the pineal gland and melatonin.
3. Appreciate the interactions between paracrine factors and hormones that control blood pressure.
4. Appreciate the complexity of interaction between the immune and endocrine systems, including the nature and roles of cytokines.
5. Appreciate the hormonal changes that occur with ageing.
6. Describe the principal endocrine components in the regulation of appetite.
The previous chapters of this book have dealt with the major endocrine systems of the body and their associated disorders. There are several other hormones that have not been covered and some processes that are controlled by an interaction between different systems. This chapter aims to cover the odds and ends of endocrinology and to consider some integrated systems, such as the regulation of blood pressure and volume, and the hormonal regulation of appetite.

Erythropoietin is classified as a cytokine (see below) and acts through a specific receptor which is a member of the cytokine receptor family, linked to protein phosphorylation through JAK-STAT activation (see Ch. 2).

The major action of erythropoietin is on the bone marrow, where it stimulates the formation of red blood cells by preventing apoptosis of erythrocyte precursor cells. An erythropoietin deficiency results in fewer red cells that contain normal amounts of iron and are a normal shape and size—in other words, a normochromic, normocytic anaemia.

Increasingly, treatment for renal failure includes replacement therapy with recombinant erythropoietin. This is indicated when other causes of anaemia, such as iron, B12 or folate deficiency, have been ruled out.

**Interesting fact**

It has been recognized for many years that athletes can boost their red blood cell count by training at high altitudes, where the oxygen pressure is lower, causing erythropoietin stimulation. With a higher concentration of red blood cells, athletes participating in endurance sports, such as long-distance running or cycling, will be at an advantage. More recently, with the development of recombinant erythropoietin, some athletes bypassed the altitude training and simply injected erythropoietin to boost their red blood cells. In several cases this led to pathological levels of red blood cell production (polycythaemia), resulting in stroke and thrombosis. This is likely to explain the sudden deaths of a number of athletes over recent years.

**Case history**

Mr Singh, a 55-year-old man with a long history of progressive chronic renal failure, is seen in outpatients for routine review. The cause of his kidney disease is chronic glomerulonephritis and the disease process can only be slowed down by good control of blood pressure. His serum creatinine level has risen from 210 mmol/L 2 years ago (estimated glomerular filtration rate (GFR) 32 mL/min) to 268 mmol/L 1 year ago (estimated GFR 28 mL/min) to 303 mmol/L at present (estimated GFR 24 mL/min).

His haemoglobin (Hb) level has fallen during recent months:

- 12 months ago: Hb 12.0 g/dL
- 6 months ago: Hb 13.4 g/dL
- Today: Hb 10.6 g/dL

Other results:

- Ferritin: 243 ng/mL (normal)
- B12 and folate: Normal
- White cell and platelet counts: Normal

What is the most likely cause of Mr Singh’s anaemia? How would you treat it?

**Erythropoietin**

We shall start by looking at a hormone produced by the kidney. We have already seen that the kidney is a target tissue for arginine vasopressin (AVP), aldosterone and parathyroid hormone (PTH), and that it controls the activation of vitamin D. However, the kidney is also an endocrine gland, producing a peptide hormone called erythropoietin (EPO or epo, pronounced ‘E.P.O.’ and ‘eepo’, respectively).

Erythropoietin is a glycosylated peptide hormone secreted by the fibroblasts adjacent to the renal tubules. It is secreted in response to either hypoxia or anaemia, but secretion is impaired in renal failure.

Erythropoietin is likely to be caused by erythropoietin deficiency as a direct consequence of his renal failure. The test results indicate that it is not due to iron, B12 or folate deficiency.

He will be started on treatment with one of the forms of erythropoietin currently available. Treatment begins with a low dose and is varied over several weeks until the target Hb concentration of around 11–13 g/dL is reached. Erythropoietin is a peptide hormone, so must be given by injection. The different forms of erythropoietin have different durations of action, but treatment is typically given one to three times per week. It is also important to ensure that Mr Singh has adequate iron stores or the erythropoietin will not be as effective.
Immune-endocrine interactions: cytokines and eicosanoids

Previous chapters in this book have briefly mentioned some interactions between the immune and endocrine systems, including the effects of glucocorticoids on inflammatory and immune processes and the effects of autoimmune disease on the thyroid and pancreas. These are examples of the more obvious manifestations of the significant and complex interactions between the immune and endocrine systems. In order to look more closely at this we need to consider some of the molecules involved.

Cytokines

Cells of the immune system produce a range of chemical messengers called cytokines. However, it is not just immune cells that secrete cytokines: they are also made in vascular endothelial cells, the liver, adipocytes and many other tissues. The cytokines are families of peptides that include interleukins, erythropoietin, interferons, bone morphogenetic proteins (BMPs) and several families of growth factors, including insulin-like growth factor-1 (IGF-1) which mediates many of the effects of growth hormone, as we saw in Chapter 4. More than 100 cytokines have been identified to date.

These cytokines can act in an endocrine, paracrine or autocrine manner to bring about their effects, mediated by specific receptors, mostly of the single-transmembrane domain class, which act by activation of the Janus kinase (JAK)-STAT pathway (see Ch. 2). The different cytokines have a wide range of effects on the immune system, stimulating activation of lymphocytes and macrophages and promoting differentiation of B cells and eosinophils. Although cytokines were originally identified as messengers within the immune system, they have a somewhat broader range of effects than this, particularly in fetal development and cellular differentiation.

Cytokines also have a role in the regulation of endocrine systems. They have been implicated in the acute regulation of hormone secretion, including the release of hypothalamic stimulating factors, particularly in the response to exercise and stress. Cytokines are also known to regulate the expression of steroid-metabolizing enzymes and to have a major role in ovarian follicle maturation. They also have a longer-term role in the growth and differentiation of every endocrine tissue. It is becoming increasingly clear that cytokines are ubiquitous signalling molecules and have effects on every tissue in the body, including the endocrine system. The possibility of exploiting cytokines therapeutically is very exciting, and they are already used in the treatment of some cancers. We do not yet know how the actions of cytokines may be used in the management of endocrine disorders, and much research will be required to advance this field, but there is clearly a great deal of potential in the clinical application of cytokine research.

Eicosanoids

Some cytokines, such as interleukin-1, have a role in the promotion of inflammation. In this role, they interact with a family of signalling molecules termed eicosanoids. The eicosanoids include prostaglandins, prostacyclins, thromboxanes and leukotrienes, which are all synthesized from membrane phospholipids via arachidonic acid (Fig. 13.1). Prostaglandins were given this name because they were first isolated from semen and found to be secreted by the prostate gland. Prostaglandins are thought to have an immunosuppressive effect on the female reproductive tract, allowing the sperm to reach the uterus without triggering an immune response. It has been suggested that blocking prostaglandin synthesis may be used in the management of endocrine disorders, and much research will be required to advance this field, but there is clearly a great deal of potential in the clinical application of cytokine research.
Age-related changes in hormone secretion

It is well known that women go through the menopause at around the age of 50 years and may experience adverse effects of the associated decrease in oestrogen secretion, but the age-related decrease in other hormones is much less recognized. Men do not go through any process comparable to the menopause, but there is an age-related decline in testosterone secretion, and some men experience hypogonadal symptoms associated with this. Perhaps predictably this has been termed andropause. The growth hormone (GH)–IGF axis also shows a marked decrease with age, a phenomenon termed somatopause, and, to complete the set, the adrenocortical secretion of its major androgen, dehydroepiandrosterone (DHEA), also declines with age—termed adrenopause.

It is not clear why age-related changes to these specific endocrine systems occur. There are no comparable patterns of change in thyroid function, for example, and the adrenopause does not include significant decreases in cortisol or aldosterone secretion.

It has been suggested that the mechanisms of andropause and somatopause might be linked, with an intact GH–IGF axis required for appropriate testicular function and an appropriate level of testosterone required to support GH secretion, but there is little evidence to support this suggestion.

Hormone replacement therapy in ageing

There are plenty of websites offering to sell you anti-ageing hormone treatments. DHEA, testosterone and GH are all readily available. But is there any evidence that they will keep you fit and healthy in old age? For most treatments the answer is ‘no’. Unless somebody has a properly diagnosed hormone deficiency then there is no benefit at all in taking ‘replacement therapy’. Hormone replacement therapy for postmenopausal women is well established, and testosterone replacement therapy for men with hypogonadism of old age is also a routine part of clinical practice. Administration of GH to older people who do not have a defined GH deficiency is associated with a number of adverse effects, including carpal tunnel syndrome. Probably the most popular and potentially least harmful hormonal anti-ageing treatment is DHEA. In the USA, DHEA is available over the counter and appears to be taken by a large number of individuals in a huge uncontrolled and unsupervised experiment. Although there appear to be very few side-effects from taking DHEA, other than greasy skin and acne, it does not appear to have any major beneficial effects either.

Melatonin

Melatonin is a hormone involved in regulating circadian rhythms. It is produced by the pineal gland—a small gland in the brain, named because it is the size and shape of a pine nut. Melatonin was discovered by Lerner in 1958 when he was looking for the hormone that controls

![Diagram of hormone secretion](image-url)
Melatonin is synthesized from tryptophan (Fig. 13.2) and its production is negatively controlled by light, so that light falling on the retina inhibits melatonin secretion. There is not a direct neural pathway from the retina to the pineal gland, but a rather complex reflex involving the cervical ganglion (Fig. 13.3). As a consequence, damage to the spinal column in this area can severely disrupt diurnal rhythms.

In humans there is a circadian rhythm of melatonin secretion, with levels being very low during the daylight hours and increasing from dusk until a peak is reached at around 0300 hours. Subsequently melatonin levels decline until daytime. This secretory pattern is controlled by a number of zeitgebers (time-givers), which include light, posture, social cues and melatonin itself. There is also a marked age dependency of melatonin secretion, with maximal secretion seen in early childhood, at around 3 years, and a gradual diminution of the amplitude of the nocturnal increase in melatonin secretion with advancing years.

The major role of melatonin is in regulating circadian rhythms of the body, including body temperature and the secretion of other hormones. It has been described as the ‘circadian glue’, responsible for holding the other biological rhythms in phase. In other animals, melatonin has a key role in regulating seasonal fertility by controlling the hypothalmo–pituitary–gonadal axis. There is some evidence that melatonin can affect luteinizing hormone and follicle stimulating hormone production in the human, and it has even been suggested that it may play a role in the timing of menarche, but the extent of its role remains unclear. There has been a lot of recent interest in both the antioxidant properties of melatonin and its complex interactions with the immune system. Although these functions are poorly understood, melatonin’s potential as an immune modulator and in cancer treatment is being researched extensively.

Clinically, melatonin has been used in the treatment of sleep disorders in older people and in regulating the body clock of ‘blind free-runners’, a group of profoundly blind people whose body clock does not naturally follow the usual 24-hour cycle.

**Interesting fact**

In the USA melatonin, like DHEA, is classified as a food-stuff and so is freely available and marketed for its supposed health benefits, one of which is the treatment of jetlag. Given at an appropriate time, melatonin may be used to phase-advance or phase-delay the circadian clock (Fig. 13.4), as desired. However, both the dose and the timing of melatonin are critical for it to have an effect.
**Table 13.1** Gastrointestinal hormones

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure (No. of amino acids)</th>
<th>Main sites of production</th>
<th>Major actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secretin family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretin</td>
<td>27</td>
<td>S cells in duodenum and jejunum</td>
<td>↑ Bicarbonate secretion from pancreas</td>
</tr>
<tr>
<td>Glucagon</td>
<td>29</td>
<td>A cells in upper GI tract</td>
<td>↑ Plasma glucose</td>
</tr>
<tr>
<td>VIP</td>
<td>28</td>
<td>Nerves throughout GI tract</td>
<td>↑ Intestinal secretion of electrolytes and water into lumen of gut, relaxation of sphincters</td>
</tr>
<tr>
<td><strong>Gastrin family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCK</td>
<td>39 (variously sized fragments)</td>
<td>I cells in duodenum</td>
<td>↑ Pancreatic enzyme secretion</td>
</tr>
<tr>
<td>Gastrin</td>
<td>34</td>
<td>G cells in antral portion of gastric mucosa</td>
<td>↑ Contraction of gall bladder</td>
</tr>
<tr>
<td>GIP</td>
<td>43</td>
<td>K cells in duodenum and jejunum</td>
<td>↑ Gastric acid and pepsin secretion</td>
</tr>
<tr>
<td><strong>Other hormones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRP</td>
<td>27</td>
<td>Vagal nerve endings on G cells</td>
<td>↑ Gastrin secretion</td>
</tr>
<tr>
<td>Motilin</td>
<td>22</td>
<td>Enterochromaffin cells and motilin-immunopositive cells in stomach, small intestine and colon</td>
<td>↑ Contraction of smooth muscle and promotes GI motility</td>
</tr>
<tr>
<td>Substance P</td>
<td>11</td>
<td>Neurons throughout GI tract</td>
<td>↑ Motility of small intestine</td>
</tr>
<tr>
<td>Guanylin</td>
<td>15</td>
<td>Cells of intestinal mucosa</td>
<td>↑ Cl⁻ secretion into gut lumen</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>28</td>
<td>Stomach</td>
<td>Stimulates appetite</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>13</td>
<td>Neurons in ileum</td>
<td>Inhibits GI motility</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>14</td>
<td>D cells in gastrointestinal mucosa</td>
<td>↑ Ileal blood flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Secretion of gastrin, VIP and GIP</td>
</tr>
</tbody>
</table>

*CCK, cholecystokinin; GI, gastrointestinal; GIP, gastric inhibitory peptide; GRP, gastrin releasing peptide; VIP, vasoactive intestinal polypeptide.*

**Gut hormones**

The first hormone to be discovered, in 1905, was a gut hormone, secretin. Over the past 100 years the study of endocrinology has flourished as we have characterized more hormones, and recognized their effects. That secretin was the first hormone to be discovered is somewhat paradoxical, as it is among the least important of all the hormones recognized today. Indeed, secretin is frequently relegated to a historical footnote in endocrine texts. Although secretin is recognized as an important gut hormone, regulating bicarbonate secretion from the pancreas, there is little pathology associated with this peptide, so it does not excite much interest. We now know that secretin is just one of a large number of polypeptide hormones secreted by cells of the gastrointestinal tract. These hormones, their major sites of production and their main physiological actions are summarized in Table 13.1. These hormones,
and the cells that produce them, are considered to be part of the ‘diffuse endocrine system’. This term describes the myriad hormones secreted by endocrine and neuroendocrine cells that are scattered throughout the body, rather than being assembled into discrete endocrine glands.

Endocrine disorders involving these gastrointestinal hormones are relatively uncommon. Occasionally tumours of the gastrointestinal cells secreting these hormones are detected, but they are rare. The tumour most frequently seen is gastrin secreting, termed a gastrinoma, and causes Zollinger–Ellison syndrome. When a gastrinoma is detected, the patient is investigated for multiple endocrine neoplasia (MEN), a condition that is commonly found in patients presenting with gastrinoma (see below).

Other tumours include glucagonoma, somatostatinoma and VIPoma. The latter is interesting because it presents with high volumes of watery diarrhoea, sometimes exceeding 5L/day. Surgical removal of the tumour is the usual treatment, although the synthetic somatostatin analogue, octreotide, may be used to treat excess vasoactive intestinal peptide (VIP) or gastrin secretion.

**The hormonal control of appetite: fat is an endocrine tissue**

Recently, with the increase in the incidence of obesity and the metabolic syndrome in the general population, there has been a huge interest in the possibility of using hormones to manipulate appetite pharmacologically. It was hoped that an appetite-suppressant drug could be developed that would make dieting easier. As a result of all the research effort, we now have an improved understanding of the hormonal signals that make us hungry and also tell us when we have eaten enough. The hormonal signals regulating appetite are summarized in Figure 13.5. There are hormones produced by the gut, the pancreas and by adipose tissue that tell the appetite centre in the brain that we do not need to eat. Perhaps the most interesting of these hormones is leptin, a peptide hormone produced by fat cells.

In previous chapters we have seen that adipose tissue (fat) has a role in the conversion of testosterone to oestra-diol by the action of the enzyme aromatase, which is expressed in adipose tissue. Adipocytes also secrete peptide hormones, including a range of cytokines, and leptin, a peptide hormone involved in appetite regulation. The circulating concentration of leptin is directly proportional to the absolute mass of fat in the body. Synthesis of leptin is regulated by food intake and rises after a meal. On the other hand, leptin levels decrease with fasting and it is this decrease that signals hunger. One of the actions of leptin is to inhibit secretion of the hypothalamic hormones, orexins, which have a powerful stimulatory effect on appetite (Ch. 3). Several cases of people with a leptin deficiency have been described. These individuals have a raging hunger that is never satisfied, except by injection of leptin. In theory, it should be possible to suppress appetite by administering leptin, but in practice this does not work. In obese individuals, there is already a high level of circulating leptin and injection of more leptin has little effect on appetite.

There have been recent clinical trials on peptide YY that have had promising results. People who had infusions of this peptide ate less than people infused with saline. The problem is that the peptide has to be injected, which is not very practical, and although it reduces the amount eaten at the next meal we do not know whether it will work over a longer period of time.

In endocrinology, having several hormones doing the same job tells you that the job is important, and we can certainly see that with appetite regulation. There is so much redundancy in this system that it is not surprising that we have not found a magic diet pill.

**Interesting fact**

There is growing evidence that there are endocrinological differences between adipose tissues in different parts of the body. In particular, adipocytes (fat cells) in subcutaneous fat (under the skin) appear to metabolize and synthesize steroid hormones differently from adipocytes in omental fat (in the abdominal cavity). It is already known that ‘central obesity’, with a high waist to hip ratio, is a better predictor of cardiovascular risk than total body fat. Research into the endocrinology of fat is an exciting and rapidly developing area.
Multiple organ disorders in endocrinology

Multiple endocrine neoplasia (MEN)

MEN is an inherited condition that affects approximately 1 in 10 000 of the population. There are three distinct forms of MEN, with different characteristics (Table 13.2). MEN1 is also known as Wermer’s syndrome and includes hyperparathyroidism in nearly all cases. In this condition there are often tumours of the gastrointestinal tract or pancreas, most commonly secreting gastrin or insulin. MEN2a, also known as Sipple’s syndrome, nearly always features medullary carcinoma of the thyroid, with phaeochromocytoma seen in around half of the patients. MEN2b, also known as MEN3, is characterized by a high incidence of mucosal neuromas in addition to the medullary thyroid carcinoma characteristic of MEN2a.

Multiple endocrine neoplasia is difficult to treat. As well as the possibilities of multiple disorders simultaneously, the individual disorders are often complicated.

Table 13.2 Multiple endocrine neoplasia

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>Parathyroid tumour</td>
<td>≈80</td>
</tr>
<tr>
<td></td>
<td>Pancreatic tumour</td>
<td>≈75</td>
</tr>
<tr>
<td></td>
<td>Pituitary tumour</td>
<td>≈65</td>
</tr>
<tr>
<td>MEN2a</td>
<td>Medullary thyroid carcinoma</td>
<td>≈100</td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma</td>
<td>≈50</td>
</tr>
<tr>
<td></td>
<td>Parathyroid tumour</td>
<td>≈40</td>
</tr>
<tr>
<td>MEN2b (MEN3)</td>
<td>Mucosal neuroma</td>
<td>≈100</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma</td>
<td>≈100</td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma</td>
<td>≈45</td>
</tr>
<tr>
<td></td>
<td>Parathyroid tumour</td>
<td>Rare</td>
</tr>
</tbody>
</table>

MEN1 is caused by a loss of function mutation of the MENIN tumour-suppressor gene on chromosome 11. MEN2a and 2b are both associated with activating mutations in the RET proto-oncogene on chromosome 10.

Figure 13.6 Hormonal regulation of blood pressure, volume and osmolality. There is a complex interaction between different organs in the body to control blood volume, pressure and osmolality, which are clearly closely related. The major hormones involved are arginine vasopressin (AVP), atrial natriuretic peptide (ANP) and aldosterone. AVP, also known as antidiuretic hormone (ADH), is secreted from the posterior pituitary and increases water resorption from urine. ANP is a hormone secreted by the right cardiac atrium that acts on the kidney to promote diuresis, with the loss of both water and sodium. Aldosterone is a mineralocorticoid secreted by the adrenal gland that increases sodium resorption in the kidney. Adrenaline and angiotensin II maintain blood pressure by acting directly on the blood vessels to produce constriction. BP, blood pressure.
For example, in MEN1 it is more common to find all four parathyroid glands affected than just one.

As the MENs are inherited in an autosomal dominant manner, first-degree relatives of individuals with MEN may undergo genetic screening, with regular medical screening offered to those found to be carrying a MEN gene (Table 13.2). In the families of people with MEN2, specific screening for the RET proto-oncogene is carried out. This gene encodes a version of tyrosine kinase and so mutations are associated with disordered cell signalling and cell growth. Specific mutations in this gene are associated with a particularly aggressive form of medullary thyroid carcinoma at an early age. A thyroidectomy is performed in children found to be carrying the most significant mutations. This can be performed as early as 6 months of age.

Autoimmune polyglandular endocrinopathy

This is a rare group of diseases, characterized by the failure of more than one endocrine organ. The commonest form, type II, is also known as Schmidt’s syndrome. It affects women more frequently than men and is associated with particular HLA genotypes. The glands most frequently affected are the adrenals, thyroid and endocrine pancreas.

**Regulation of blood pressure and volume**

The regulation of blood pressure and volume is achieved through the integration of many different hormonal and paracrine signals. Some of these mechanisms are shown in Figure 13.6. The actions of aldosterone, angiotensin II and adrenaline are covered in detail in Chapters 5 and 6, and arginine vasopressin is considered in Chapter 3. The other hormone involved is atrial natriuretic peptide (ANP), a hormone secreted by the cells of the heart. This peptide acts on the kidney, via single-transmembrane ANP receptors (see Ch. 2), coupled to cyclic guanosine monophosphate (cGMP) signalling, to promote water and sodium loss in the urine. Figure 13.6 shows a simplified scheme of the major mechanisms involved in the systemic regulation of blood pressure.

In addition to the systemic regulation of blood pressure, there are several other factors that act at a local level to maintain local vascular tone (Fig. 13.7). There is evidence that nitric oxide secretion may be impaired in some patients with endocrine hypertension. It has also been suggested that adrenomedullin has a role in the vasodilatation associated with septic shock.

**The next 100 years of endocrinology**

We started this book by observing that endocrinology is a young scientific discipline, with 2005 being recognized as the centenary of its origin. Given the wealth of knowledge that has accumulated over the last 100 years, it is tempting to speculate what an edition of this book might contain in 2105. For the centenary edition of *The Endocrinologist*, the newsletter of The Society for Endocrinology, prominent scientists and clinicians working in the field were asked to predict the status of endocrinology in 100 years’ time. One of the common themes to emerge was that our understanding of the detailed
interaction between different endocrine systems would be considerably greater by 2105. This ‘integrated physiology’, with an understanding of complex functions such as regulation of appetite, sexuality, reproduction, ageing and even body shape, could lead to tailoring of lifestyles by hormonal ‘treatments’. Taken to its extreme, this argument suggests that we may even be able to use hormones to alter social behaviour. If these speculations turn out to be only partly true, it is clear that the next 100 years of hormone research will throw up many moral and ethical questions.