31 Obesity

OVERVIEW

Obesity is a growing health issue around the world and is reaching epidemic proportions in some nations. The problem is not restricted to the inhabitants of the affluent countries, to the adult population or to any one socioeconomic class. Body fat represents stored energy, and obesity occurs when the homeostatic mechanisms controlling energy balance become disordered or overwhelmed. In this chapter, we explore first the endogenous regulation of appetite and body mass, and then consider the main health implications of obesity and its pathophysiology. We conclude with a discussion of the two drugs currently licensed for the treatment of obesity, and glance at the future of pharmacological treatment of this condition.

INTRODUCTION

Survival requires a continuous provision of energy to maintain homeostasis even when the supply of food is intermittent. Evolution has furnished a mechanism for storing any excess energy latent in foodstuffs in adipose tissue as energy-dense triglycerides, such that these can be easily mobilised when food is scarce. This mechanism, controlled by the so-called *thrifty genes*, was an obvious asset to our hunter-gatherer ancestors. However, in many societies a combination of sedentary lifestyle, genetic susceptibility, cultural influences and unrestricted access to an ample supply of calorie-dense foods is leading to a global epidemic of obesity, or 'globesity' as it sometimes called.

DEFINITION OF OBESITY

If the 'ideal weight' of an individual is that which maximises life expectancy, 'obesity' may be defined as an illness where the health (and hence life expectancy) is adversely affected by excess body fat.[1] But at what point does an individual become 'obese'? The generally accepted benchmark is the *body mass index* (BMI). The BMI is expressed as W/h^2, where W = body weight (in kg), h = height (in metres). Although it is not a perfect index (e.g. it does not distinguish between fat and lean mass), the BMI is generally well correlated with other measurements of body fat, and it is widely employed in obesity studies. While there are problems in defining a 'healthy' weight for a particular population, the World Health Organization (WHO) classifies people with a BMI of < 18.5 kg/m^2 as 'underweight', and those with a BMI of 18.5–24.9 kg/m^2 as of 'acceptable' or 'normal' weight. A BMI in the range of 25.0–29.9 kg/m^2 signifies 'grade 1 overweight'. If it is between 30.0 and 39.9 kg/m^2, the patient is deemed to be obese or 'grade 2 overweight', while those with a BMI of > 40 kg/m^2 are said to be 'grade 3 overweight' or *morbidly obese*. Childhood obesity is more difficult to assess.

As the BMI obviously depends on the overall energy balance, another operational definition of obesity would be that it is a multifactorial disorder of energy balance in which calorie intake over the long term exceeds energy output.

[1]'Persons who are naturally very fat are apt to die earlier than those who are slender' observed Hippocrates.

THE HOMEOSTATIC MECHANISMS CONTROLLING ENERGY BALANCE

A common view, and one that is implicitly encouraged by authors of numerous dieting books as well as the enormously lucrative dieting industry in general, is that obesity is simply the result of bad diet or wilful overeating (*hyperphagia*). In truth, however, the situation is more complex and, on its own, dieting does not usually provide a lasting solution. The failure rate of such diets is high (probably 90%), with most dieters eventually returning to their original starting weight. This suggests the operation of some intrinsic homeostatic system that strives to maintain a particular set weight. This mechanism is normally exceptionally precise, and it has been calculated that it is capable of regulating energy balance to 0.17% per decade (Weigle, 1994). An astonishing feat considering the day-to-day variations in food intake.

When exposed to the same dietary choices some individuals will become obese whereas others will not. Studies of obesity in monozygotic and dizygotic twins have established a strong genetic influence on the susceptibility to the disease, and studies of rare mutations in mice (and more recently in humans) have led to the discovery and elucidation of the neuroendocrine pathways that match food intake with energy expenditure, and to the concept that it is, in fact, disorders of this system that are largely responsible for the onset and maintenance of the disease of obesity.

THE ROLE OF GUT AND OTHER HORMONES IN BODY WEIGHT REGULATION

At the beginning of the 20th century, it was observed that patients with damage to the hypothalamus tended to gain weight. In the 1940s, it was also shown that discrete lesions in the hypothalamus of rodents caused them to become obese or exhibit unusual feeding behaviour. As early as 1953, Kennedy proposed, on the basis of experiments on rats, that a hormone released from adipose tissue acted on the hypothalamus to regulate body fat and food intake. These seminal findings set the stage for future discoveries in this area.

It also was observed that mice could become obese as a result of mutations in certain genes. At least five of these have now been characterised, including the *ob* (obesity), *tub* (tubby), *fat* and *db* (diabetes) genes. Mice that are

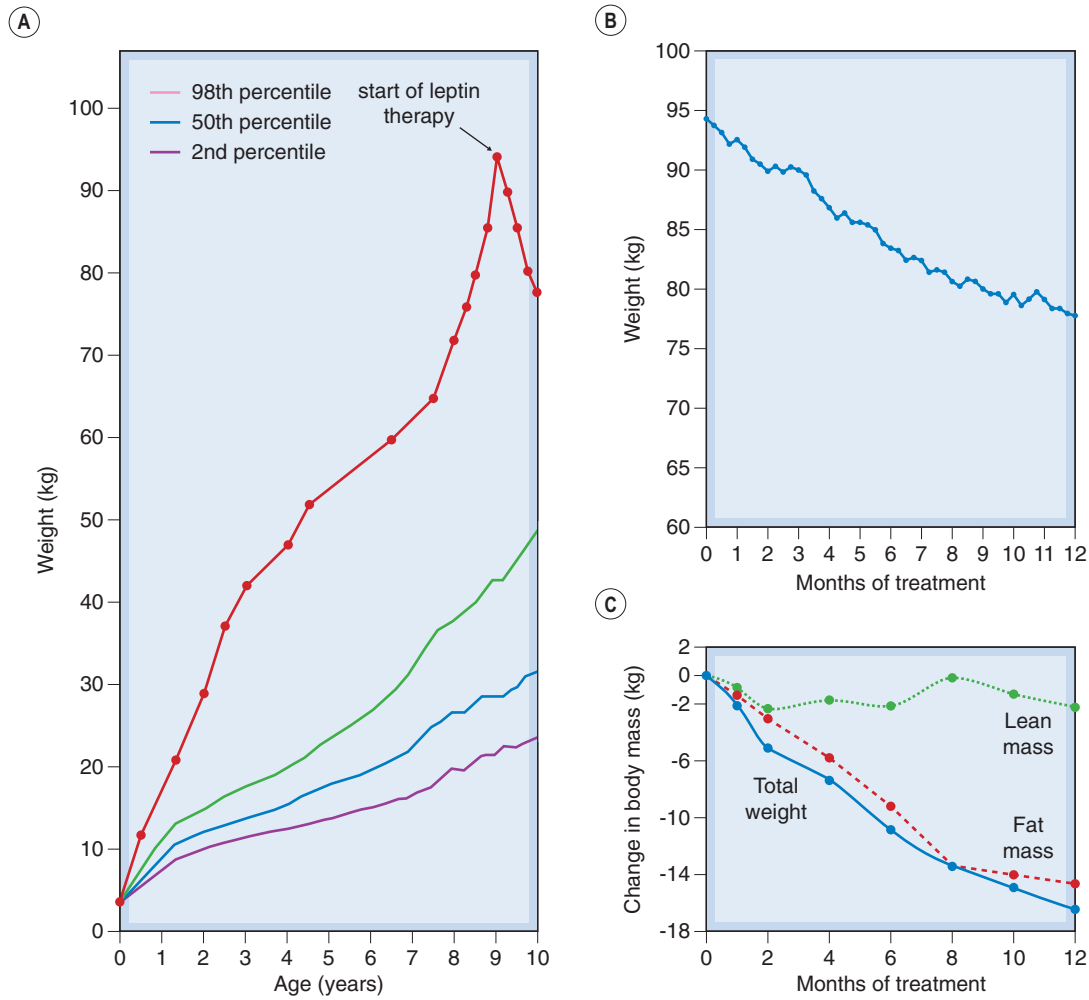

Fig. 31.1 The effect of recombinant leptin on body weight in a 9-year-old severely obese child deficient in endogenous leptin because of a frame shift mutation in the leptin gene. Although of normal birth weight, the child began gaining weight at 4 months and was constantly demanding food. When treatment was initiated, the child weighed 94.4 kg. Weight loss began after 2 weeks' treatment, and her eating pattern returned to normal. She had lost 15.6 kg of body fat after 1 year of treatment. (Data and figure adapted from Farooqi et al. 1999).

homozygous for mutant forms of these genes—*ob/ob* mice and *db/db* mice—eat excessively, have low energy expenditure, become grossly fat and have numerous metabolic and other abnormalities. Weight gain in an *ob/ob* mouse is suppressed if its circulation is linked to that of a normal mouse, implying that the obesity is caused by lack of a blood-borne factor.

An important conceptual breakthrough came in 1994, when Friedman and his colleagues (see Zhang et al., 1994) cloned the *ob* gene and identified its protein product as *leptin*.[2] When recombinant leptin was administered to *ob/ob* mice, it strikingly reduced food intake and body weight. It had a similar effect when injected directly into the lateral or the third ventricle, implying that it acted on the regions of the brain that control food intake and energy balance. Recombinant leptin has similar effects in humans (see Fig. 31.1).

Leptin mRNA is expressed in adipocytes; its synthesis is increased by glucocorticoids, insulin and the oestrogens, and it is reduced by β-adrenoceptor agonists. In humans, the release of leptin is pulsatile and varies according to the fat stores and BMI in normal subjects. Insulin (see Ch. 30) also functions in a similar manner although it is probably less important than leptin.

Today, it is recognised that in addition to leptin and insulin, several other peripheral hormones originating mainly from the gastrointestinal (GI) tract, play a crucial role in determining food intake, meal size and the feeling of satisfaction produced.[3] Peptide hormones secreted by cells in the wall of the small intestine in response to the arrival of food (see Ch. 30) are important in this connection. Table 31.1 and Figure 31.2 summarise the main characteristics of these hormones.

[2]The word is derived from the Greek *leptos*, meaning thin.

[3]The language can be confusing. 'Hunger' obviously refers to the desire to eat; 'satiation' is the feeling that you have eaten enough. 'Satiety' refers to the feeling that one will postpone the next meal.

Table 31.1 Some peripheral hormones that regulate eating behaviour

Hormone	Source	Stimulus to release	Target	Effect
CCK	GI tract	During feeding or just before	Vagus	Limits size of meal
Amylin	Pancreas	During feeding or just before	Vagus	
Insulin				
Glucagon				
$PYY_{3–36}$	Ileum, colon	After feeding	Brain stem, hypothalamus	Postpones next meal
GLP-1	Stomach			
Oxycyntomodulin	Stomach			
Leptin	Adipose tissue	Adiposity 'status'	Brain stem, arcuate nucleus	Longer-term regulation of food intake
Ghrelin	Stomach	Hunger, feeding	Vagus, hypothalamus	Increases food intake by increasing size and number of meals

CCK, cholecystokinin; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; $PYY_{3–36}$, peptide YY.

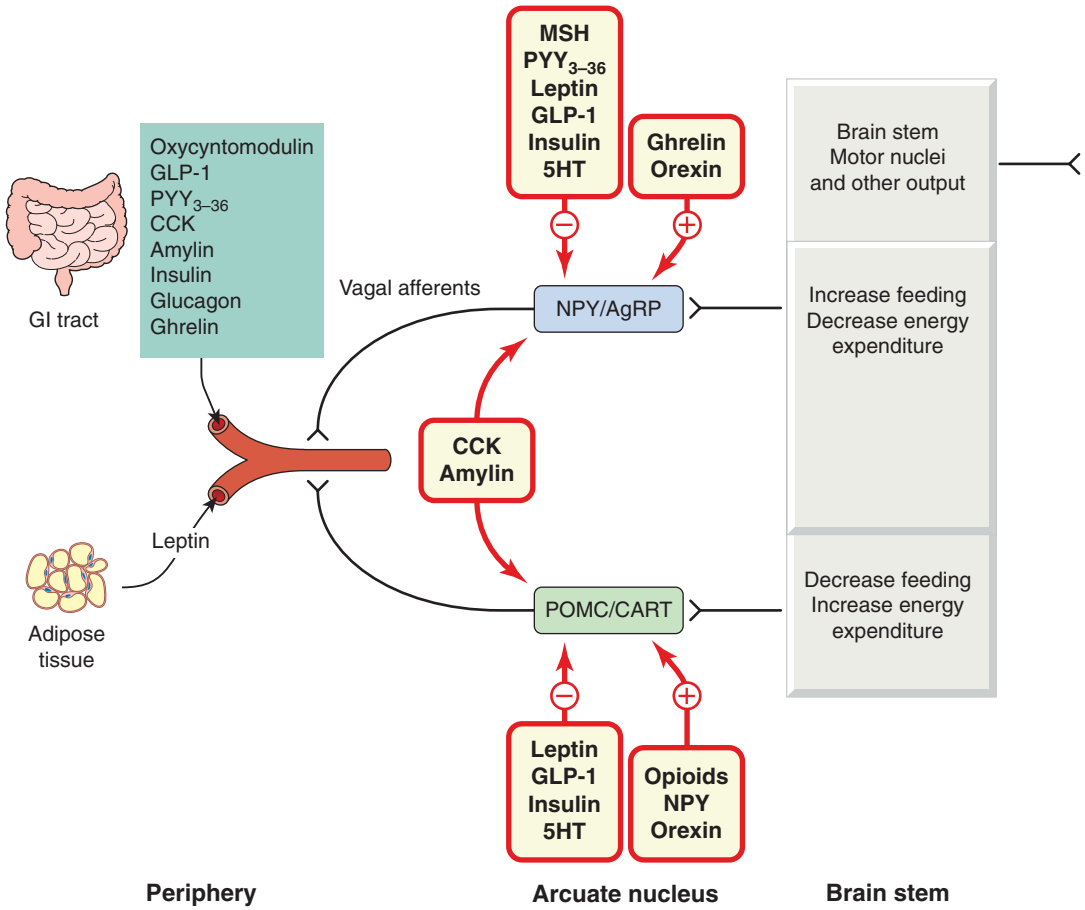

Fig. 31.2 A simplified representation of the role of peripheral hormones and other mediators in the regulation of energy balance and fat stores. The primary level of hypothalamic control is vested in two groups of neurons, with opposing actions, in the arcuate nucleus (ARC). In one group, the peptides neuropeptide Y (NPY) and agouti-related protein (AgRP) are co-localised; the other contains the polypeptides prepro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART), which release α-melanocyte-stimulating hormone (MSH). Blood-borne hormones arising from the gastrointestinal (GI) tract or adipose tissue are sensed by receptors on vagal and other afferents and are relayed through the nucleus tractus solitarius to modify the activity of these neuronal circuits. The influence of hormones on each neuronal group is indicated. Hormones marked in blue (e.g. leptin) arise from the peripheral blood and influence the ARC neurons directly or indirectly through neuronal signals; mediators in green (e.g. 5HT, orexin) originate within the central nervous system itself. Activation of the NPY/AgRP group by, for example, a fall in leptin or an increase in ghrelin levels results in increased food intake and decreased energy expenditure. In the POMC/CART group of neurons, increased leptin or other hormone levels triggered by overfeeding produces a predominately inhibitory effect on feeding behaviour. A number of other hormones such as cholecystokinin (CCK) and amylin also alter the properties of the ARC neurons although the mechanism is not clear. GLP-1, glucagon-like peptide-1. (Modified from Adan et al. 2008.)

The majority of these factors are released either during, or in anticipation of, eating and most are inhibitory in nature producing either satiety or satiation. Two exceptions are the gastric hormone, *ghrelin*, which promotes hunger, and leptin itself, which is controlled by the amount of adipose tissue and is thus more involved with the longer-term energy status of the individual. The main targets for these hormones are receptors on vagal afferent fibres or within the hypothalamus (or elsewhere in the central nervous system [CNS]). Here, they modulate the release of other neurotransmitters that exert a fine regulation over eating behaviour, energy expenditure and body weight. Other actions of these peptide hormones include the release of insulin by the *incretins*, namely *glucagon-like peptide-1* (GLP-1) and *gastric inhibitory peptide* (GIP).

NEUROLOGICAL CIRCUITS THAT CONTROL BODY WEIGHT AND EATING BEHAVIOUR

CONTROL OF FOOD INTAKE

The manner in which all these hormonal signals are processed and integrated with other viscerosensory, gustatory or olfactory information within the CNS is complex. Many sites within the CNS are involved in different aspects of the process and some 50 hormones and neurotransmitters are implicated. The account we present here is therefore necessarily an oversimplification: the Further Reading list should be consulted for a more complete picture.

As early lesioning studies predicted, the hypothalamus is the main brain centre that regulates appetite, feeding behaviour and energy status, although other sites in the brain such as the *nucleus accumbens* (NAc), the *amygdala* and especially the *nucleus tractus solitarius* (NTS) in the medulla, are also crucial. Within the hypothalamus, the *arcuate nucleus* (ARC), situated in the floor of the third ventricle, is a key site. It receives afferent inputs originating from the GI tract and contains receptors for leptin and other significant hormones. It also has extensive reciprocal connections with other parts of the hypothalamus involved in monitoring energy status, in particular the *paraventricular nucleus* and the *ventromedial hypothalamus.* Figure 31.2 summarises some of the complex interactions that occur in the ARC but it must be realised that this is only part of the overall control system and is presented in a simplified fashion.

Within the ARC are two groups of functionally distinct neurons that exert opposite effects on appetite. One group, termed *anorexigenic* (appetite suppressing), secrete *pro-opiomelanocortin* (POMC)-derived peptides (such as *α-melanocyte-stimulating hormone*; *α-MSH*) or *cocaine- and amphetamine-regulated transcript* (*CART*)[4]-derived peptides. The other group, termed *orexigenic* (appetite promoting) neurons, secrete *neuropeptide Y* (NPY) or *agouti-related peptide* (AgRP). As these groups of neurons have opposing actions, energy homeostasis depends, in the first instance, on the balance between these actions whose final effects are realised by the brain stem motor system as changes in feeding behaviour.

Monoamines such as noradrenaline, 5-hydroxytryptamine (5-HT) and dopamine also play a role in the modulation of satiety signals. Noradrenaline is co-localised with NPY in some neurons and greatly potentiates its hyperphagic action. Deficit of dopamine impairs feeding behaviour, as do agonists at the 5-HT_{2C} receptor; antagonists at this receptor have the reverse effect.

Many neural signals arising from the GI tract are integrated, and relayed on to the hypothalamus, by the NTS in the medulla. Some of these signals, including those of gustatory, olfactory, mechanical and viscerosensory signals, arise from vagal and other spinal afferents originating in the GI tract or liver. Endocrine signals have more complex signalling pathways. For example, *cholecystokinin* (CCK) is secreted by the duodenum in response to the process of eating and digestion of (especially fatty) foodstuffs. CCK acts locally on CCK_A receptors in the GI tract to stimulate vagal afferents and may also act on CCK_B receptors in the brain in order to function as a satiety factor. Ghrelin also has complex actions. It stimulates growth hormone release (Ch. 32) and also has a direct action on neurons in the ARC to modify feeding behaviour. Blood ghrelin levels normally fall after eating but not in obese individuals (English et al., 2002). Interestingly, polymorphisms in the ghrelin gene may be important in the pathogenesis of the *Prader–Willi syndrome*, which predisposes to morbid obesity.

Leptin also targets these neurons in the ARC. Falling leptin levels activate the orexigenic neurons, resulting in increased food intake, and synthesis and storage of fat (anabolism), as well as decreased energy expenditure. Conversely, rising leptin levels activate the second group of neurons, producing the opposite anorexigenic and catabolic effect.

Inputs from other parts of the CNS also influence feeding behaviour. Of importance to us is the input from the NAc. This centre seems to regulate those aspects of eating that are driven by pleasure or reward—the so-called 'hedonic' aspects of eating (see also Ch. 48). The endocannabinoid system is important in this response. The hypothalamus contains large amounts of 2-arachidonyl glycerol and anandamide as well as the CB_1 receptor (Ch. 18). Administration of endogenous or exogenous (e.g. Δ^9-THC) cannabinoids provokes a powerful feeding response.[5] This system in turn may be modulated by 'stress' and other factors in the environment.

CONTROL OF ENERGY EXPENDITURE

Balancing food intake is the energy expenditure required to maintain metabolism, physical activity and *thermogenesis* (heat production). The metabolic aspects of energy expenditure include, among other things, cardiorespiratory work and the actions of a multitude of enzymes. Physical activity increases all these, as well as increasing energy expenditure by the skeletal muscles. Exposure to cold or feeding also stimulates thermogenesis, and the reverse is also true. The, often dramatic (20–40% increase), thermogenic effects of feeding may provide a partial protection against developing obesity.

The sympathetic nervous system (sometimes in concert with thyroid hormone) plays a significant part in the regu-

[4]So called because the administration of cocaine or amphetamine stimulates the transcription of this gene. Its expression in the hypothalamus is related to nutritional status implicating it in the control of appetite. Its receptor is unknown but it probably modulates the action of NPY and leptin.

[5]This effect is responsible for the 'munchies', a common side effect of smoking cannabis.

lation of energy expenditure in cardiovascular and skeletal muscle function during physical activity, as well as in the thermogenic response of adipose tissue and the response to cold. Both 'white' and 'brown' (the colour is apparently caused by the high density of mitochondria) fat cells (but especially the latter) have a major role in thermogenesis. Brown fat, which is densely innervated by the sympathetic nervous system, is abundant in rodents and human infants, although in human adults these cells are generally to be found more interspersed with white fat cells. Because of their abundant mitochondria, they are remarkable heat generators, producing more heat and less ATP than white fat cells. The basis for this, as determined in mice, is the presence of *mitochondrial uncoupling proteins* (UCP). Three isoforms, UCP-1, -2 and -3, are known and have different distributions, although all are found in brown fat. These proteins 'uncouple' oxidative phosphorylation, so that mitochondria continue oxidative metabolism but produce much less ATP, thus promoting net energy loss as heat. As one might anticipate, exposure to cold or leptin administration increases both the activity and (after prolonged stimulation) the amount of UCP-1 in brown fat. Noradrenaline, acting on β-adrenoceptors (mainly β_3) in brown fat, increases the activity of the peroxisome proliferator-activated receptor-γ (PPARγ) transcription factor which, in turn, activates the gene for UCP-1. The expression of β_3-adrenoceptors is decreased in genetically obese mice.

OBESITY AS A HEALTH PROBLEM

Obesity is a growing and costly global health problem. According to the WHO (2005 figures), there are already more than 1.6 billion overweight adults, approximately one-quarter of whom are obese according to the criteria outlined above, and this is expected to rise to 2.3 billion overweight and 700 million obese people by 2015. National obesity levels vary enormously, being less than 5% in China, Japan and parts of Africa, to a staggering 75% in parts of Samoa. Obesity levels in the USA, Europe and the UK (among others) have increased three-fold since 1980, with figures of 31% being quoted for the USA and about 25% for many other industrialised nations (Padwal et al., 2003). The disease is not confined to adults: some 22 million children under 5 years old are estimated to be overweight. In the USA, the number of overweight children has doubled and the number of overweight adolescents has trebled since 1980. Ironically, obesity often co-exists with malnutrition in many developing countries. All socioeconomic classes are affected. In the poorest countries, it is the top socioeconomic classes in whom obesity is prevalent, but in the West it is usually the reverse.

Energy balance

Energy balance depends on food intake, energy storage in fat and energy expenditure. In most individuals, the process is tightly regulated by a homeostatic system that integrates inputs from a number of internal sensors and external factors. Important components of the system include the following:

- Hormones that signal the status of fat stores (e.g. leptin). Increasing fat storage promotes leptin release from adipocytes.
- Hormones released from the gut during feeding that convey sensations of hunger (e.g. ghrelin), satiety (e.g. CCK) or satiation (e.g. $PYY_{3–36}$).
- This hormonal information together with neural gustatory, olfactory and viscerosensory input is integrated in the hypothalamus. The arcuate nucleus is a key site.
- Two groups of opposing neurons in the arcuate nucleus sense hormonal and other signals. Those secreting POMC/CART products promote feeding while those secreting NPY/AgRP inhibit feeding. Many other CNS neurotransmitters (e.g. endocannabinoids) are involved.
- The net output from this process is relayed to other sites in the brain stem motor nuclei that control feeding behaviour.

▼ While obesity itself is rarely fatal, it brings with it the risk of increased susceptibility to a host of metabolic and other disorders, the most important of which are type 2 diabetes, metabolic syndrome, hypertension and cardiovascular conditions, cancers (particularly hormone dependent), respiratory (particularly sleep apnoea) and digestive problems, as well as osteoarthritis. One commentator (Kopelman, 2000) has remarked that obesity '*… is beginning to replace under-nutrition and infectious diseases as the most significant contributor to ill health*'. The total costs of obesity-related illness are hard to estimate. Figures in the range of 2–7% of the total healthcare budget are often given but are probably an underestimate. Increasingly, social stigma is suffered by obese individuals, leading to a sense of psychological isolation.

The risk of developing type 2 diabetes (which represents 85% of all cases of the disease) rises sharply with increasing BMI. The WHO reports that 90% of those diagnosed with the disease are obese. In a study of the disease in women, the risk of developing diabetes was closely correlated with BMI, increasing five-fold when the BMI was 25 kg/m^2, to 93-fold when the BMI was 35 kg/m^2 or above (Colditz et al., 1995). Cardiovascular disease is also increased in the obese individual, and the increased thoracic and abdominal adipose tissue reduces lung volume and makes respiration difficult. Obese subjects also have an increased risk of colon, breast, prostate, gall bladder, ovarian and uterine cancer. Numerous other disorders are associated with excess body weight, including osteoarthritis, hyperuricaemia and male hypogonadism. Gross obesity (BMI over 40 kg/m^2) is associated with a 12-fold increase in mortality in the group aged 25–35 years compared with those in this age group with a BMI of 20–25 kg/m^2.

THE PATHOPHYSIOLOGY OF HUMAN OBESITY

In most adult subjects, body fat and body weight remain more or less constant over many years, even decades, in the face of very large variations in food intake and energy expenditure—amounting to about a million calories per year. The steady-state body weight and BMI of an individual is, as has been stressed above, the result of the integration of multiple interacting regulatory pathways. How, then, does obesity occur? Why is it so difficult for the obese to lose weight and maintain the lower weight?

The main determinant is manifestly a disturbance of the homeostatic mechanisms that control energy balance, but genetic endowment underlies this disturbance. Other factors, such as food availability and lack of physical activity, contribute, and there are, of course, social, cultural and psychological aspects. We will deal below with the imbalance of homeostatic mechanisms and genetic endowment in obesity. The role of social, cultural and psychological aspects we will leave (with a profound sigh of relief) to the psychosociologists!

FOOD INTAKE AND OBESITY

As Spiegelman & Flier (1996) point out, '*one need not be a rocket scientist to notice that increased food intake tends to be associated with obesity*'. A typical obese subject will usually have gained 20 kg over a decade or so. This means that there has been a daily excess of energy input over energy requirement of 30–40 kcal initially, increasing gradually to maintain the increased body weight.

The type of food eaten, as well as the quantity, can disturb energy homeostasis. Fat is an energy-dense foodstuff, and it may be that the mechanisms regulating appetite react rapidly to carbohydrate and protein, but too slowly to fat to stop an individual consuming too much before the satiety systems come into play.

However, when obese individuals reduce their calorie intake as part of a diet regime, they shift into negative energy balance. When they lose weight, the resting metabolic rate decreases, and there is a concomitant reduction in energy expenditure. Thus an individual who was previously obese and is now of normal weight generally needs fewer calories to maintain that weight than an individual who has never been obese. The decrease in energy expenditure appears to be largely caused by an alteration in the conversion efficiency of chemical energy to mechanical work in the skeletal muscles. This adaptation to the caloric reduction contributes to the difficulty of maintaining weight loss by diet.

PHYSICAL EXERCISE AND OBESITY

It used to be said that the only exercise effective in combating obesity was pushing one's chair back from the table. It is now recognised that physical activity—i.e. increased energy expenditure—has a much more positive role in reducing fat storage and adjusting energy balance in the obese, particularly if associated with modification of the diet. An inadvertent, natural population study provides an example. Many years ago, a tribe of Pima Indians split into two groups. One group settled in Mexico and continued to live simply at subsistence level, eating frugally and spending most of the week in hard physical labour. They are generally lean and have a low incidence of type 2 diabetes. The other group moved to the USA—an environment with easy access to calorie-rich food and less need for hard physical work. They are, on average, 57 lb (26 kg) heavier than the Mexican group and have a high incidence of early-onset type 2 diabetes.

OBESITY AS A DISORDER OF THE HOMEOSTATIC CONTROL OF ENERGY BALANCE

The long-term regulation of energy balance by adiposity signals such as leptin and insulin must obviously occur against a background of day-to-day variations in meal size, frequency and content.[6] Because the homeostatic control of energy balance is extremely complex, it is not easy to determine exactly what goes wrong in obesity. When the leptin story unfolded, it was thought that alterations in leptin kinetics might provide a simple explanation. There is a considerable interindividual variation in sensitivity to leptin, and some individuals seem to produce insufficient amounts of this hormone. Paradoxically, however, plasma leptin is often higher in obese individuals compared with non-obese subjects, not lower as might be expected. The reason for this is that resistance to leptin rather than insufficient hormone is more prevalent in obesity. Such resistance could be caused by defects in leptin carriage in the circulation, transport into the CNS, in leptin receptors in the hypothalamus (as occurs in *db/db* mice) or in postreceptor signalling.

Mediators other than leptin are certainly implicated in obesity. For example, TNF-α, a cytokine that can relay information from fat tissue to brain, is increased in the adipose tissue of insulin-resistant obese individuals. Another pathophysiological alteration in obesity is a reduced insulin sensitivity of muscle and fat, and decreased β_3-adrenoceptor function in brown adipose tissue (see above) may also occur; alternatively, UCP-2, one of the proteins that uncouple oxidative phosphorylation in adipocytes, may be dysfunctional in obese individuals.

A further suggestion is that alterations in the function of specific nuclear receptors, such as PPARα, β and γ, may play a role in obesity. These receptors regulate gene expression of enzymes associated with lipid and glucose homeostasis, and they also promote the genesis of adipose tissue. PPARγ is expressed preferentially in fat cells and synergises with another transcription factor, C/EBPα, to convert precursor cells to fat cells (see Spiegelman & Flier, 1996). The gene for UCP (see above) in white fat cells also has regulatory sites that respond to PPARα and C/EBPα. The *thiazoladinediones* bind to and activate PPARγ (see Ch. 30). One of these, **pioglitazone**, is licensed in the UK for treatment of type 2 diabetes and both cause weight gain. The pathophysiology of obesity could involve disturbance(s) in any of the multitude of other factors involved in energy balance.

GENETIC FACTORS AND OBESITY

Analyses of large-scale (> 100 000) studies in human monozygotic and dizygotic twin pairs indicate that 50–90% of the variance of BMI can be attributed to genetic factors, and suggest a relatively minor role for environmental factors (Barsh et al., 2000). This conclusion may seem surprising, but feeding studies using laboratory rodents where food intake is held constant have demonstrated the importance of genetic background to body weight regulation, and this is especially true for high-fat diets. The prevailing viewpoint is that susceptibility to obesity is largely determined by genetic factors, while environmental factors determine the expression of the disease.

The discovery that spontaneous mutations arising in single genes (e.g. the *ob/ob* genotype) produced obese phenotypes in mice led to a search for equivalent genes in humans. A review (Pérusse et al., 2005) identified over 170 human obesity cases that could be traced to single gene mutations in 10 different genes. Leptin receptor or POMC mutations are sometimes observed, but melanocortin $(MC)_4$ receptor mutations seem to be more prevalent (3–5%) in obese patients (e.g. see Barsh et al., 2000). In general, however, human obesity should be regarded as a polygenic disorder involving the interaction of many genes. At the time of writing, some 600 genes, markers and chromosomal regions are under investigation for linkage to human obesity (Pérusse et al., 2005).

[6]Even the type of gut flora has come under scrutiny as a potential determining factor in obesity. The notion that this could be supplemented with probiotics to modify the risk is obviously attracting attention. 'Holy shit!' was the title of one magazine article on the subject (*The Economist*, 12 November 2009).

Obesity

- Obesity is a multifactorial disorder of energy balance, in which long-term calorie intake exceeds energy output.
- A subject with a BMI (W/h^2) of 20–25 kg/m^2 is considered as having a healthy body weight, one with a BMI of 25–30 kg/m^2 as overweight, and one with a BMI > 30 kg/m^2 as obese.
- Obesity is a growing problem in most rich nations; the incidence—at present approximately 30% in the USA and 15–20% in Europe—is increasing.
- A BMI > 30 kg/m^2 significantly increases the risk of type 2 diabetes, hypercholesterolaemia, hypertension, ischaemic heart disease, gallstones and some cancers.
- The causes of obesity may include:
  - dietary, exercise, social, financial and cultural factors
  - genetic susceptibility
  - deficiencies in the synthesis or action of leptin or other gut hormone signals
  - defects in the hypothalamic neuronal systems responding to any of these signals
  - defects in the systems controlling energy expenditure (e.g. reduced sympathetic activity), decreased metabolic expenditure of energy or decreased thermogenesis caused by a reduction in β_3-adrenoceptor-mediated tone and/or dysfunction of the proteins that uncouple oxidative phosphorylation.

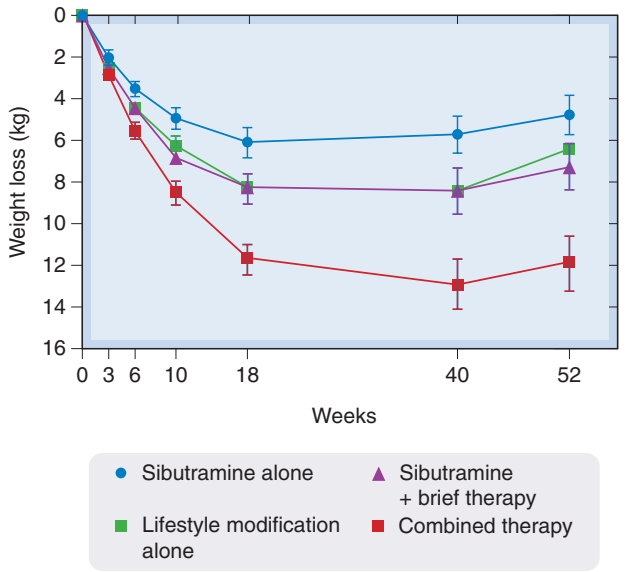

Fig. 31.3 The effect of treatment with sibutramine alone or in combination with lifestyle modification. In this study, 224 obese patient were given sibutramine alone, lifestyle modification counselling alone or sibutramine together with a 'brief' or more extensive programme of lifestyle counselling. The Y-axis shows the weight loss in kg (± SE) over time (X-axis). It is evident that sibutramine is far more effective as a weight-loss therapy when combined with changes in patients' lifestyle. This is a common experience when treating obesity (From Wadden et al. 2005.)

Other genes that appear to be involved include the β_3-adrenoceptor and the glucocorticoid receptor. Decreased function of the β_3-adrenoceptor gene could be associated with impairment of lipolysis in white fat or with thermogenesis in brown fat. A mutation of this gene has been found to be associated with abdominal obesity, insulin resistance and early-onset type 2 diabetes in some subjects and a markedly increased propensity to gain weight in a separate group of morbidly obese subjects. Alterations in the function of the glucocorticoid receptor could be associated with obesity through the permissive effect of glucocorticoids on several aspects of fat metabolism and energy balance. The significance of polymorphisms in the ghrelin gene has already been mentioned.

PHARMACOLOGICAL APPROACHES TO THE PROBLEM OF OBESITY

The first weapons in the fight against obesity are diet and exercise. Unfortunately, these often fail or show only short-term efficacy, leaving only surgical techniques (such as gastric stapling or bypass)[7] or drug therapy as a viable alternative. Surgery is much more effective than currently licensed drugs.

The attempt to control appetite with drugs has had a long and largely undistinguished history. Many types of 'anorectic' (e.g. appetite suppressant) agents have been tested in the past, including the uncoupling agent **dinitrophenol** (DNP), **amphetamines** and **fenfluramine**. However, these are no longer used and the only drug currently (2010) licensed in the UK for the treatment of obesity is **orlistat** (see below). It should not be used without concomitant dietary and other therapy (e.g. exercise). As might be imagined, the quest for further effective antiobesity agents is the subject of a prodigious effort by the pharmaceutical industry.

SIBUTRAMINE

Sibutramine inhibits the reuptake of 5-HT and noradrenaline at the hypothalamic sites that regulate food intake.[8] Its main effects are to reduce food intake and cause dose-dependent weight loss (see Fig. 31.3), the weight loss being associated with a decrease in obesity-related risk factors. Sibutramine enhances satiety and is reported to produce a reduction in waist circumference (i.e. a reduction in visceral fat), a decrease in plasma triglycerides and very-low-density lipoproteins, but an increase in high-density lipoproteins. In addition, beneficial effects on hyperinsulinaemia and the rate of glucose metabolism are said to occur. There is some evidence that the weight loss is associated with higher energy expenditure, possibly through an

[7]Such *bariatric* (weight loss) surgery owes at least part of its efficacy to the changes in blood levels of the hormones that regulate feeding behaviour.

[8]Many antidepressant drugs act by the same mechanism (see Ch. 46), and also cause weight loss by reducing appetite. However, sibutramine does not have antidepressant properties. Furthermore, depressed patients are often obese, and antidepressant drugs are used to treat both conditions (see Appolinario et al., 2004).

increase in thermogenesis mediated by the sympathetic nervous system.

A meta-analysis of three long-term treatment studies comparing sibutramine with placebo (Padwal et al., 2003) concluded that there was a 4.6% loss of weight after 1 year's treatment with the drug, and a 15% increase in the number of patients who lost more than 10% of their body weight. Sibutramine was much more effective when combined with lifestyle modification (Wadden et al., 2005) and it was usually recommended only in conjunction with such measures.

The marketing authorisation for sibutramine was recently suspended by the European Medicines Agency because of concerns that its cardiovascular risks (see below) outweighed its benefits.

PHARMACOKINETIC ASPECTS AND UNWANTED EFFECTS

Sibutramine is given orally; it is well absorbed and undergoes extensive first-pass metabolism. The metabolites are responsible for the pharmacological actions. Steady-state blood levels of the metabolites occur within 4 days. The active metabolites are inactivated in the liver, and 85% of the inactive residues are excreted in the urine and faeces.

Sibutramine increases heart rate and blood pressure and is contraindicated in hypertension, which often co-exists with obesity. Other unwanted effects include dry mouth, constipation, insomnia and drug interactions (e.g. antidepressants, see Ch. 46).

ORLISTAT

In the intestine, **orlistat** reacts with serine residues at the active sites of gastric and pancreatic lipases, irreversibly inhibiting these enzymes and thereby preventing the breakdown of dietary fat to fatty acids and glycerols. It therefore decreases fat absorption and correspondingly increases faecal fat excretion up to some 30% of dietary fat. Given in conjunction with a low-calorie diet in obese individuals, it produces a modest but consistent loss of weight compared with placebo-treated control subjects. In a meta-analysis of 11 long-term placebo-controlled trials encompassing over 6000 patients, orlistat was found to produce a 2.9% greater reduction in body weight than in the control group, and 12% more patients lost 10% or more of their body weight compared with the controls (Padwal et al., 2003).

Orlistat is also reported to be effective in patients suffering from type 2 diabetes and other complications of obesity, to reduce leptin levels and blood pressure, to protect against weight loss-induced changes in biliary secretion, to delay gastric emptying and gastric secretion, to improve several important metabolic parameters and not to interfere with the release or action of thyroid and other important hormones (Curran & Scott, 2004). It does not induce changes in energy expenditure.

PHARMACOKINETIC ASPECTS AND UNWANTED EFFECTS

Virtually all (97%) of orlistat is excreted in the faeces (83% unchanged), with only negligible amounts of the drug or its metabolites being absorbed.

Abdominal cramps, flatus with discharge and faecal incontinence can occur, as can intestinal *borborygmi* (rumbling) and oily spotting. Surprisingly, in view of the possibility of these antisocial effects occurring, the drug is well tolerated. Supplementary therapy with fat-soluble vitamins may be needed. The absorption of contraceptive pills and ciclosporin (see Ch. 26) may be decreased. The former is probably not clinically significant but the latter is more serious. Given its good safety record, orlistat has recently been licensed for inclusion in some over-the-counter medicines for weight loss.

Clinical uses of antiobesity drugs

- The main treatment of obesity is a suitable diet and increased exercise.
- **Orlistat**, which causes fat malabsorption, is considered for severely obese individuals, especially with additional cardiovascular risk factors (e.g. diabetes mellitus, hypertension).
- Many centrally acting appetite suppressants have been withdrawn because of addiction, pulmonary hypertension or other serious adverse effects.

NEW APPROACHES TO OBESITY THERAPY

Rare cases of leptin deficiency in patients have been successfully treated by long-term treatment with the hormone, but this is an unusual intervention and unlikely to be of more than limited use in the future. Many other approaches are being piloted; in fact, a comprehensive review of the area estimated that there were more than 150 novel agents under development (Kaplan, 2005). Some of these aim to exploit the action or production of neuroendocrine satiety signals such as CCK to produce appetite suppression. Many of these GI satiety hormones produce such effects when given systemically to humans or rodents although these are not always useful; for example, CCK reduces meal size but increases meal frequency (West et al., 1984).

Other strategies aim to alter the CNS levels of neurotransmitters such as NPY or melanocortins, which transduce changes in these hormonal signals (Halford, 2006). The tractability of the MC_4 receptor itself as a drug target, coupled with the observation that defects in MC_4 signalling are prevalent in obesity, has attracted much interest from the pharmaceutical industry.

Given the importance of the sympathetic nervous system in the control of energy regulation, one might predict that β_3-adrenoceptor agonists might be useful therapeutics. This field has been extensively researched (see Arch, 2008, for a recent review) but disappointingly has so far failed to produce an acceptable drug. The search continues.

Another novel approach originated from research in the cannabinoid field (see Ch. 18 for further details). As noted above, the endocannabinoid system is involved in the regulation of feeding behaviour and from this observation arose the idea that this could be a useful site of pharmacological intervention. Such a drug was the CB_1 receptor antagonist **rimonabant** that was originally developed for smoking cessation. This drug was introduced into therapy following some encouraging clinical trails (see Fig. 18.5) but was eventually withdrawn in 2008 because of adverse effects on mood seen in some patients.

REFERENCES AND FURTHER READING

Body weight regulation

Adan, R.A., Vanderschuren, L.J., la Fleur, S.E., 2008. Anti-obesity drugs and neural circuits of feeding. Trends Pharmacol. Sci. 29, 208–217. (*Very accessible overview of the area. Recommended*)

Ahima, R.S., Flier, J.S., 2000. Leptin. Annu. Rev. Physiol. 62, 413–437. (*Comprehensive review of leptin: its expression, actions in hypothalamus, role in energy homeostasis and other actions*)

Ahima, R.S., Osei, S., 2001. Molecular regulation of eating behaviour: new insights and prospects for future strategies. Trends Mol. Med. 7, 205–213. (*Praiseworthy short review; excellent figures and useful tables of the mediators involved in stimulation and inhibition of feeding behaviour*)

English, P.J., Ghatei, M.A., Malik, I.A., et al., 2002. Food fails to suppress ghrelin levels in obese humans. J. Clin. Endocrinol. Metab. 87, 2984–2987.

Farooqi, I.S., Jebb, S.A., Langmack, G., et al., 1999. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N. Engl. J. Med. 341, 879–884. (*A classic clinical paper on the role of leptin in the control of feeding behaviour and weight control*)

Frühbeck, G., Gómez-Ambrosi, J., Muruzábal, F.J., Burrell, M.A., 2001. The adipocyte: a model for integration of endocrine and metabolic signalling in energy metabolism regulation. Am. J. Physiol. Endocrinol. Metab. 280, E827–E847. (*Detailed review covering receptors on and the factors secreted by the fat cell, and the role of these factors in energy homeostasis*)

Kennedy, G.C., 1953. The role of depot fat in the hypothalamic control of food intake in the rat. Proc. R. Soc. Lond. B. Biol. Sci. 140, 578–592. (*The paper that put forward the proposal, based on experiments on rats, that there was a hypothalamus-based homeostatic mechanism for controlling body fat*)

Schwartz, M.W., Woods, S.C., Porte, D.J., et al., 2000. Central nervous control of food intake. Nature 404, 661–671. (*Outlines a model that delineates the roles of hormones and neuropeptides in the control of food intake. Outstanding diagrams. Note that there are several other excellent articles in this* Nature Insight *supplement on obesity*)

Spiegelman, B.M., Flier, J.S., 1996. Adipogenesis and obesity: rounding out the big picture. Cell 87, 377–389.

Spiegelman, B.M., Flier, J.S., 2001. Obesity regulation and energy balance. Cell 104, 531–543. (*Excellent review with up-to-date coverage of the CNS control of energy intake/body weight, monogenic obesities, leptin physiology, central neural circuits, the melanocortin pathway, the role of insulin and adaptive thermogenesis*)

Weigle, D.S., 1994. Appetite and the regulation of body composition. FASEB J. 8, 302–310.

Obesity as a disease

Colditz, G.A., Willett, W.C., Rotnitzky, A., Manson, J.E., 1995. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann. Intern. Med. 122, 481–486.

Kopelman, P.G., 2000. Obesity as a medical problem. Nature 404, 635–643.

Obesity genetics

Barsh, G.S., Farooqi, I.S., O'Rahilly, S., 2000. Genetics of body-weight regulation. Nature 404, 644–651.

Loos, R.J., Rankinen, T., 2005. Gene–diet interactions on body weight changes. J. Am. Diet. Assoc. 105 (Suppl. 1), S29–S34. (*Discusses gene–environment studies relating to obesity, drawing on data from monozygotic twins and candidate gene approaches*)

Pérusse, C., Rankinen, T., Zuberi, A., et al., 2005. The human obesity gene map: the 2004 update. Obes. Res. 13, 381–490. (*Detailed review of the genes, markers and chromosomal regions that have been shown to be associated with human obesity*)

Zhang, Y., Proenca, R., Maffei, M., et al., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425–432.

Drugs in obesity

Appolinario, J.C., Bueno, J.R., Coutinho, W., 2004. Psychotropic drugs in the treatment of obesity: what promise? CNS Drugs 18, 629–651.

Chiesi, M., Huppertz, C., Hofbauer, K.G., 2001. Pharmacotherapy of obesity: targets and perspectives. Trends Pharmacol. Sci. 22, 247–254. (*Commendable, succinct review; table of the potential targets, and useful, simple figures of the central and peripheral pathways of energy regulation and of the regulation of thermogenesis*)

Clapham, J.C., Arch, J.R.S., Tadayyon, M., 2001. Anti-obesity drugs: a critical review of current therapies and future opportunities. Pharmacol. Ther. 89, 81–121. (*Comprehensive review covering, under energy intake; biogenic amines, cannabinoids, neuropeptides, leptin, gastrointestinal tract peptides and inhibitors of fat absorption; and under energy expenditure, β_3-adrenoceptor agonists and uncoupling proteins*)

Collins, P., Williams, G., 2001. Drug treatment of obesity: from past failures to future successes? Br. J. Clin. Pharmacol. 51, 13–25. (*Overview – from a clinical perspective – of currently available antiobesity drugs and potential future drugs; well written*)

Crowley, V.E.F., Yeo, G.S.H., O'Rahilly, S., 2002. Obesity therapy: altering the energy intake-and-expenditure balance sheet. Nat. Rev. Drug Discov. 1, 276–286. (*Review stressing that pharmacological approaches to obesity therapy necessitate altering the balance between energy intake and expenditure and/or altering the partitioning of nutrients between lean tissue and fat*)

Curran, M.P., Scott, L.J., 2004. Orlistat: a review of its use in the management of patients with obesity. Drugs 64, 2845–2864.

James, W.P.T., Finer, N., Kopelman, P., et al., 2000. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. Lancet 256, 2119–2125. (*Report of the results of a multicentre, randomised, double-blind clinical trial*)

Padwal, R., Li, S.K., Lau, D.C., 2003. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Int. J. Obes. Relat. Metab. Disord. 27, 1437–1446.

Wadden, T.A., Berkowitz, R.I., Womble, G., et al., 2005. Randomized trial of lifestyle modification and pharmacotherapy for obesity. N. Engl. J. Med. 353, 2111–2120.

Future drug treatments for obesity

Arch, J.R., 2008. The discovery of drugs for obesity, the metabolic effects of leptin and variable receptor pharmacology: perspectives from beta3-adrenoceptor agonists. Naunyn. Schmiedebergs Arch. Pharmacol. 378, 225–240. (*A comprehensive review that focuses on the quest for antiobesity drugs that act through the β_3-adrenoceptor. Useful comments and insights into the field as a whole*)

Di Marzo, V., Matias, I., 2005. Endocannabinoid control of food intake and energy balance. Nat. Neurosci. 8, 585–589. (*A discussion of the putative role of endocannabinoids in this complex physiological mechanism; also considers therapeutic applications arising from this area*)

Fong, T.M., 2008. Development of anti-obesity agents: drugs that target neuropeptide and neurotransmitter systems. Expert Opin. Investig. Drugs 17, 321–325. (*Deals with drugs in late-stage development that target the regulatory neuropeptide pathways discussed in this chapter*)

Halford, J.C., 2006. Obesity drugs in clinical development. Curr. Opin. Investig. Drugs 7, 312–318.

Kaplan, L.M., 2005. Pharmacological therapies for obesity. Gastroenterol. Clin. North Am. 34, 91–104.

Lefebvre, P.J., Scheen, A.J., 2001. Obesity: causes and new treatments. Exp. Clin. Endocrinol. Diabet. 109 (Suppl. 2), S215–S224.

Mertens, I.L., Van Gaal, L.F., 2000. Promising new approaches to the management of obesity. Drugs 60, 1–9.

West, D.B., Fey, D., Woods, S.C., 1984. Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. Am. J. Physiol. 246, R776–R787.

Books

Wilding, J.P.H. (Ed.), 2008. Pharmacotherapy of obesity. In: Parnham, M.J., Bruinvels, J. (Eds.), Milestones in drug therapy. Birkhäuser, Basel. (*This book covers a wide variety of topics connected with obesity and its therapy. The contributors are experts in the field*)

Useful Web resource

http://www.who.int (*This is the World Health Organization Web page that carries data about the prevalence of 'globesity' and its distribution around the world; click on the Health topics link and navigate to Obesity in the alphabetical list of topics for further information*)

32 The pituitary and the adrenal cortex

OVERVIEW

The pituitary and adrenal glands are major sites for the synthesis and release of hormones that profoundly affect the biochemistry and physiology of almost all cells, and which are crucial to the understanding of the actions of many endocrine, anti-inflammatory and other drugs. The pituitary itself is controlled by hormones released from the hypothalamus and, in turn, the hypothalamic–pituitary axis orchestrates the activity of the adrenal (and other endocrine) glands. In the first part of this chapter, we examine the control of pituitary function by hypothalamic hormones and review the physiological roles and clinical uses of both anterior and posterior pituitary hormones. The second part of the chapter concentrates on the actions of adrenal hormones and, in particular, the anti-inflammatory effect of glucocorticoids. This should be read in conjunction with the relevant sections of Chapters 3 and 26.

THE PITUITARY GLAND

The pituitary gland comprises three different structures arising from two different embryological precursors. The *anterior pituitary* and the *intermediate lobe* are derived from the endoderm of the buccal cavity, while the *posterior pituitary* is derived from neural ectoderm. The main parts of the gland, the anterior and posterior lobes, receive independent neuronal input from the hypothalamus, with which they have an intimate functional relationship.

THE ANTERIOR PITUITARY GLAND (ADENOHYPOPHYSIS)

The *adenohypophysis* secretes a number of hormones crucial for normal physiological function. Within this tissue are specialised cells such as *corticotrophs*, *lactotrophs* (*mammotrophs*), *somatotrophs*, *thyrotrophs* and *gonadotrophs*, which secrete hormones that regulate different endocrine organs of the body (Table 32.1). Interspersed among these are other cell types, including the *folliculostellate* cells that exert a nurturing and regulatory influence on the hormone-secreting endocrine cells.

Secretion from the anterior pituitary is largely regulated by the release from the hypothalamus of 'factors'—in effect local hormones—that reach the pituitary through the bloodstream.[1] The blood supply to the hypothalamus divides to form a meshwork of capillaries, the primary plexus (Fig. 32.1), which drains into the hypophyseal *portal vessels*. These pass through the pituitary stalk to feed a secondary plexus of capillaries in the anterior pituitary. Peptidergic neurons in the hypothalamus secrete a variety of releasing or inhibitory hormones directly into the capillaries of the primary capillary plexus (Table 32.1 and Fig. 32.1). Most of these regulate the secretion of hormones from the anterior lobe, although the melanocyte-stimulating hormones (MSHs) are secreted mainly from the intermediate lobe.

Negative feedback pathways between the hormones of the hypothalamus, the anterior pituitary and the peripheral endocrine glands regulate the release of stimulatory hormones and integrate the functions of individual components of the endocrine system into a functional whole. In *long negative feedback* pathways, hormones secreted from the peripheral glands exert regulatory actions on both the hypothalamus and the anterior pituitary. The mediators of the *short negative feedback* pathways are anterior pituitary hormones that act directly on the hypothalamus.

The peptidergic neurons in the hypothalamus are themselves influenced by other centres within the central nervous system (CNS) mediated through pathways that release dopamine, noradrenaline, 5-hydroxytryptamine and the opioid peptides (which are particularly abundant in the hypothalamus, see Ch. 19). Hypothalamic control of the anterior pituitary is also exerted through the *tuberohypophyseal dopaminergic pathway* (see Ch. 38), the neurons of which lie in close apposition to the primary capillary plexus. Dopamine secreted directly into the hypophyseal portal circulation reaches the anterior pituitary in the blood.

HYPOTHALAMIC HORMONES

The secretion of anterior pituitary hormones, then, is primarily regulated by the releasing factors that originate in the hypothalamus. These are listed in Table 32.1 and the most significant are described in more detail below. Somatostatin and gonadotrophin-releasing hormone are used therapeutically, the rest being used for diagnostic tests or as research tools. Many of these factors also function as neurotransmitters or neuromodulators elsewhere in the CNS (Ch. 38).

SOMATOSTATIN

Somatostatin is a peptide of 14 amino acid residues. It inhibits the release of growth hormone and thyroid-stimulating hormone (TSH, thyrotrophin) from the anterior pituitary (Fig. 32.2), and insulin and glucagon from the pancreas; it also decreases the release of most gastrointestinal hormones, and reduces gastric acid and pancreatic secretion.

Octreotide is a long-acting analogue of somatostatin (Ch. 19). It is used for the treatment of *carcinoid* and other hormone-secreting tumours (Ch. 15). It also has a place in the therapy of *acromegaly* (a condition in which there is

[1]The word 'factor' was originally coined at a time when their structure and function were not known. These are blood-borne messengers, and as such are clearly hormones. Nevertheless, the term 'factor', however irrational, lingers on.

Table 32.1 Hormones secreted by the hypothalamus and the anterior pituitary and related drugs

Hypothalamic factor/hormone[a]	Effect on anterior pituitary	Main effects of anterior pituitary hormone
Corticotrophin-releasing factor (CRF)	Releases adrenocorticotrophic hormone (ACTH, corticotrophin) Analogue: tetracosactide	Stimulates secretion of adrenal cortical hormones (mainly glucocorticoids); maintains integrity of adrenal cortex
Thyrotrophin-releasing hormone (TRH) Analogue: protirelin	Releases thyroid-stimulating hormone (TSH; thyrotrophin)	Stimulates synthesis and secretion of thyroid hormones, thyroxine and tri-iodothyronine; maintains integrity of thyroid gland
Growth hormone-releasing factor (GHRF, somatorelin) Analogue: sermorelin	Releases growth hormone (GH; somatotrophin) Analogue: somatropin	Regulates growth, partly directly, partly through evoking the release of somatomedins from the liver and elsewhere; increases protein synthesis, increases blood glucose, stimulates lipolysis
Growth hormone release-inhibiting factor (somatostatin) Analogues: octreotide, lanreotide	Inhibits the release of GH	Prevents effects above as well as TSH release
Gonadotrophin (or luteinising hormone)-releasing hormone (GnRH) Analogue: gonadorelin	Releases follicle-stimulating hormone (FSH; see Ch. 34)	Stimulates the growth of the ovum and the Graafian follicle in the female, and gametogenesis in the male; with LH, stimulates the secretion of oestrogen throughout the menstrual cycle and progesterone in the second half
	Releases luteinising hormone (LH) or interstitial cell-stimulating hormone (see Ch. 34)	Stimulates ovulation and the development of the corpus luteum; with FSH, stimulates secretion of oestrogen and progesterone in the menstrual cycle; in male, regulates testosterone secretion
Prolactin-releasing factor (PRF)	Releases prolactin	Together with other hormones, prolactin promotes development of mammary tissue during pregnancy; stimulates milk production in the postpartum period
Prolactin release-inhibiting factor (probably dopamine)	Inhibits the release of prolactin	Prevents effects above
Melanocyte-stimulating hormone (MSH)-releasing factor	Releases α-, β- and γ-MSH	Promotes formation of melanin, which causes darkening of skin; MSH is anti-inflammatory and helps to regulate feeding
MSH release-inhibiting factor	Inhibits the release of α-, β- and γ-MSH	Prevents effects above

[a]These hormones are often spelled without the 'h' (e.g. corticotropin, thyrotropin, etc) in contemporary texts. We have retained the original nomenclature in this edition.

oversecretion of growth hormone in an adult). It also constricts splanchnic blood vessels, and is used to treat bleeding oesophageal varices. Octreotide is generally given subcutaneously. The peak action is at 2 h, and the suppressant effect lasts for up to 8 h.

Unwanted effects include pain at the injection site and gastrointestinal disturbances. Gallstones and postprandial hyperglycaemia have also been reported, and acute hepatitis or pancreatitis has occurred in a few cases.

Lanreotide has similar effects and is also used in the treatment of thyroid tumours.

GONADOTROPHIN-RELEASING HORMONE

Gonadotrophin- (or luteinising hormone-) releasing hormone is a decapeptide that releases both *follicle-stimulating hormone* and *luteinising hormone* from gonadotrophs. It is also available as a preparation called **gonadorelin**, used mainly in the treatment of infertility (see Ch. 34).

GROWTH HORMONE-RELEASING FACTOR (SOMATORELIN)

Growth hormone-releasing factor (GHRF) is a peptide with 40–44 amino acid residues. The main action of GHRF is summarised in Figure 32.2. An analogue, **sermorelin**, may be used as a diagnostic test for growth hormone secretion. Given intravenously, subcutaneously or intranasally (generally the former), it causes secretion of growth hormone within minutes and peak concentrations in 1 h. The action is selective for the somatotrophs in the anterior pituitary, and no other pituitary hormones are affected. *Unwanted effects* are rare.

THYROTROPHIN-RELEASING HORMONE (PROTIRELIN)

Thyrotrophin-releasing hormone (TRH) from the hypothalamus releases thyroid-stimulating hormone (TSH) from the thyrotrophs. **Protirelin** is a synthetic TRH used for the diagnosis of thyroid disorders (see Ch. 33). Given intrave-

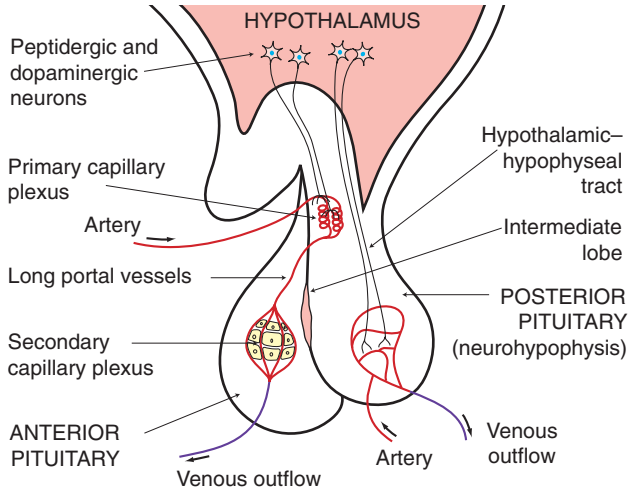

Fig. 32.1 Schematic diagram of vascular and neuronal relationships between the hypothalamus, the posterior pituitary and the anterior pituitary. The main portal vessels to the anterior pituitary lie in the pituitary stalk and arise from the primary plexus in the hypothalamus, but some (the short portal vessels) arise from the vascular bed in the posterior pituitary (not shown).

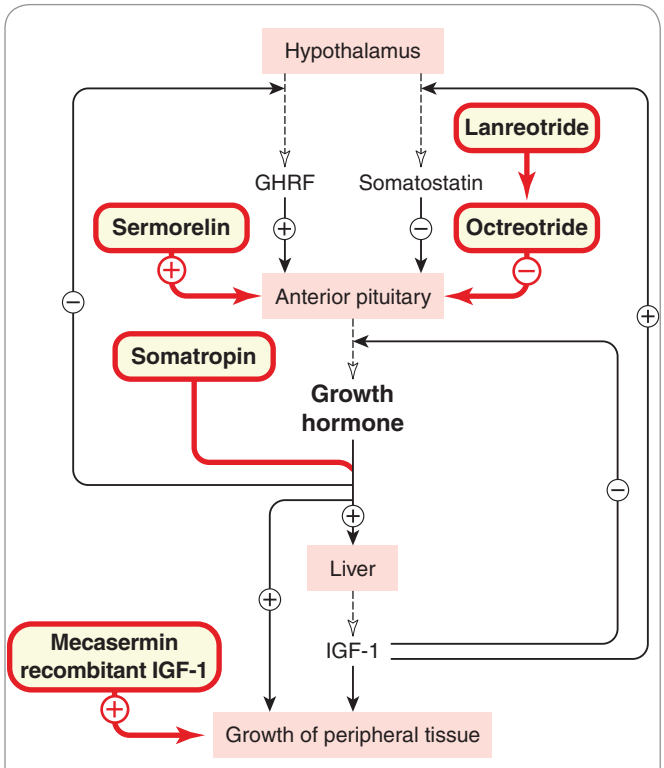

Fig. 32.2 Control of growth hormone secretion and its actions. Drugs are shown in red-bordered boxes. GHRF, growth hormone-releasing factor; IGF-1, insulin-like growth factor-1.

nously in normal subjects, it causes an increase in plasma TSH concentration, whereas in patients with *hyper*thyroidism there is a blunted response because the raised blood thyroxine concentration has a negative feedback effect on the anterior pituitary. The opposite occurs with *hypo*thyroidism, where there is an intrinsic defect in the thyroid itself.

CORTICOTROPHIN-RELEASING FACTOR

Corticotrophin-releasing factor (CRF) is a peptide that releases **adrenocorticotrophic hormone** (ACTH, corticotrophin) and β-endorphin from the corticotrophs. CRF acts synergistically with *antidiuretic hormone* (ADH; arginine-**vasopressin**), and both its action and its release are inhibited by *glucocorticoids* (see Fig. 32.4, below). Synthetic preparations have been used to test the ability of the pituitary to secrete ACTH, and to assess whether ACTH deficiency is caused by a pituitary or a hypothalamic defect. It has also been used to evaluate hypothalamic pituitary function after therapy for Cushing's syndrome (see Fig. 32.7, below).

ANTERIOR PITUITARY HORMONES

The main hormones of the anterior pituitary are listed in Table 32.1. The gonadotrophins are dealt with in Chapter 34 and TSH in Chapter 33. The remainder are dealt with below.

GROWTH HORMONE (SOMATOTROPHIN)

Growth hormone is secreted by the somatotroph cells and is the most abundant pituitary hormone. Secretion is high in the newborn, decreasing at 4 years to an intermediate level, which is then maintained until after puberty, after which there is a further decline. Several recombinant preparations of growth hormone, or **somatropin**, are available for treating growth defects and other developmental problems (see below).

Regulation of secretion

Secretion of growth hormone is regulated by the action of hypothalamic GHRF and modulated by somatostatin, as described above and outlined in Figure 32.2. One of the mediators of growth hormone action, *insulin-like growth factor* (*IGF*)*-1*, which is released from the liver (see below), has an inhibitory effect on growth hormone secretion by stimulating somatostatin release from the hypothalamus.

Growth hormone release, like other anterior pituitary secretions, is pulsatile, and its plasma concentration may fluctuate 10- to 100-fold. These surges occur repeatedly during the day and night, and reflect the dynamics of hypothalamic control. Deep sleep is a potent stimulus to growth hormone secretion, particularly in children.

Actions

The main effect of growth hormone (and its analogues) is to stimulate normal growth and, in doing this, it affects many tissues, acting in conjunction with other hormones secreted from the thyroid, the gonads and the adrenal cortex. It stimulates hepatic production of the IGFs—also termed *somatomedins*—which mediate most of its anabolic actions. Receptors for IGF-1 (the principal mediator) exist on many cell types, including liver cells and fat cells.

Growth hormone stimulates the uptake of amino acids and protein synthesis, especially in skeletal muscle. IGF-1

mediates many of these anabolic effects, acting on skeletal muscle and also on the cartilage at the epiphyses of long bones, thus influencing bone growth.

Disorders of production and clinical use

Deficiency of growth hormone results in *pituitary dwarfism*. In this condition, which may result from lack of GHRF or a failure of IGF generation or action, the normal proportions of the body are maintained. Growth hormone is used therapeutically in patients (often children) with growth hormone deficiency and with the short stature associated with the chromosomal disorder known as *Turner's syndrome*. It may also be used to correct chronic renal insufficiency in children. Satisfactory linear growth can be achieved by giving **somatropin** subcutaneously, six to seven times per week, and therapy is most successful when started early. Humans are insensitive to growth hormone of other species, so human growth hormone (hGH) must be used clinically. This used to be obtained from human cadavers, but this led to the spread of *Creutzfeldt–Jacob disease*, a prion-mediated neurodegenerative disorder (Ch. 39). hGH is now prepared by recombinant DNA technology, which avoids this risk. Human recombinant IGF-1 is also available (**mecasermin**) for the treatment of growth failure in children who lack adequate amounts of this hormone. hGH is also used illicitly by athletes (see Ch. 58) to increase muscle mass. The large doses used have serious side effects, causing abnormal bone growth and cardiomegaly. It has also been tested as a means of combating the bodily changes in senescence; clinical trials have shown increases in body mass, but no functional improvement.

An excessive production of growth hormone in children results in *gigantism*. An excessive production in adults, which is usually the result of a benign pituitary tumour, results in *acromegaly*, in which there is enlargement mainly of facial structures and of the hands and feet. The dopamine agonist **bromocriptine** and octreotide may mitigate the condition. Another useful agent is **pegvisomant**, a modified version of growth hormone prepared by recombinant technology that is a highly selective antagonist of growth hormone actions.

PROLACTIN

Prolactin is secreted from the anterior pituitary by lactotroph (mammotroph) cells. These are abundant in the gland and increase in number during pregnancy, probably under the influence of oestrogen.

Regulation of secretion

Prolactin secretion is under tonic inhibitory control by the hypothalamus (Fig. 32.3 and Table 32.1), the inhibitory mediator being dopamine (acting on D_2 receptors on the lactotrophs). The main stimulus for release is suckling; in rats, both the smell and the sounds of hungry pups are also effective triggers. Neural reflexes from the breast may stimulate the secretion from the hypothalamus of prolactin-releasing factor(s), possible candidates for which include TRH and **oxytocin**. Oestrogens increase both prolactin secretion and the proliferation of lactotrophs through release, from a subset of lactotrophs, of the neuropeptide *galanin*. Dopamine antagonists (used mainly as antipsychotic drugs; see Ch. 45) are potent stimulants of prolactin release, whereas agonists such as bromocriptine (see below and also Chs 38 and 45) suppress prolactin release. Bromocriptine is also used in parkinsonism (Ch. 39).

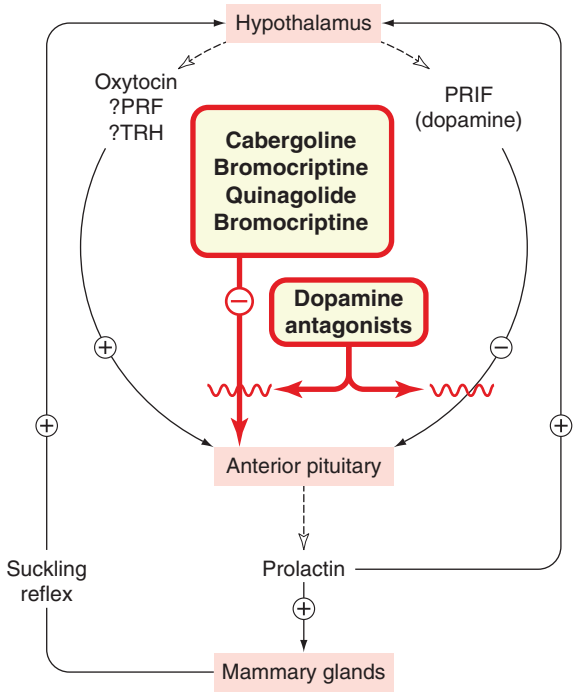

Fig. 32.3 Control of prolactin secretion. Drugs are shown in red-bordered boxes. PRF, prolactin-releasing factor(s); PRIF, prolactin release-inhibiting factor(s); TRH, thyrotrophin-releasing hormone.

Actions

There are at least three specific receptor subtypes that bind prolactin, and these are not only found in the mammary gland but are widely distributed throughout the body, including the brain, ovary, heart and lungs. The main function of prolactin in women is the control of milk production. At parturition, when the blood level of oestrogen falls, the prolactin concentration rises and lactation is initiated. Maintenance of lactation depends on suckling (see above), which causes a 10- to 100-fold increase within 30 min.

Together with other hormones, prolactin is responsible for the proliferation and differentiation of mammary tissue during pregnancy. It inhibits gonadotrophin release and/or the response of the ovaries to these trophic hormones. This is one of the reasons why ovulation does not usually occur during breastfeeding, and it is believed to constitute a natural contraceptive mechanism.

▼ According to one rather appealing hypothesis, the high postpartum concentration of prolactin reflects its biological function as a 'parental' hormone. Certainly, broodiness and nest-building activity can be induced in birds, mice and rabbits by prolactin injections. Prolactin also exerts other, apparently unrelated, actions, including stimulating mitogenesis in lymphocytes. There is some evidence that it may play a part in regulating immune responses.

Modification of prolactin secretion

Prolactin itself is not used clinically. Bromocriptine, a dopamine receptor agonist, is used to decrease excessive prolactin secretion (*hyperprolactinaemia*). It is well absorbed orally, and peak concentrations occur after 2 h. Unwanted reactions include nausea and vomiting. Dizziness, consti-

Clinical uses of bromocriptine

- To prevent lactation.
- To treat galactorrhoea (i.e. non-puerperal lactation in either sex), owing to excessive prolactin secretion.
- To treat prolactin-secreting pituitary tumours (prolactinomas).
- In the treatment of parkinsonism (Ch. 39) and of acromegaly.

pation and postural hypotension may also occur. **Cabergoline** and **quinagolide** are similar.

ADRENOCORTICOTROPHIC HORMONE

Adrenocorticotrophic hormone (ACTH, corticotrophin) is the anterior pituitary secretion that controls the synthesis and release of the glucocorticoids of the adrenal cortex (see Table 32.1). It is a 39-residue peptide derived from the precursor *pro-opiomelanocortin* (POMC; Ch. 19) by sequential proteolytic processing. Failure of ACTH action because of defects in its receptor or intracellular signalling pathways can lead to severe glucocorticoid deficiency (Chan et al., 2008). Details of the regulation of ACTH secretion are shown in Figure 32.4.

▼ This hormone occupies (together with cortisone) an important place in the history of inflammation therapy because of the work of Hench and his colleagues in the 1940s, who first observed that both substances had anti-inflammatory effects in patients with rheumatoid disease. The effect of ACTH was thought to be secondary to stimulation of the adrenal cortex but, interestingly, the hormone also has anti-inflammatory actions in its own right, through activation of macrophage (melanocortin) MC_3 receptors (Getting et al., 2002).

Adrenocorticotrophic hormone itself is not often used in therapy today, because its action is less predictable than that of the corticosteroids and it may provoke antibody formation. **Tetracosactide**, a synthetic polypeptide that consists of the first 24 N-terminal residues of human ACTH, has the same drawbacks but is now widely used in its stead for assessing the competency of the adrenal cortex (see below).

The concentration of ACTH in the blood is reduced by glucocorticoids, forming the basis of the ***dexamethasone suppression test***.

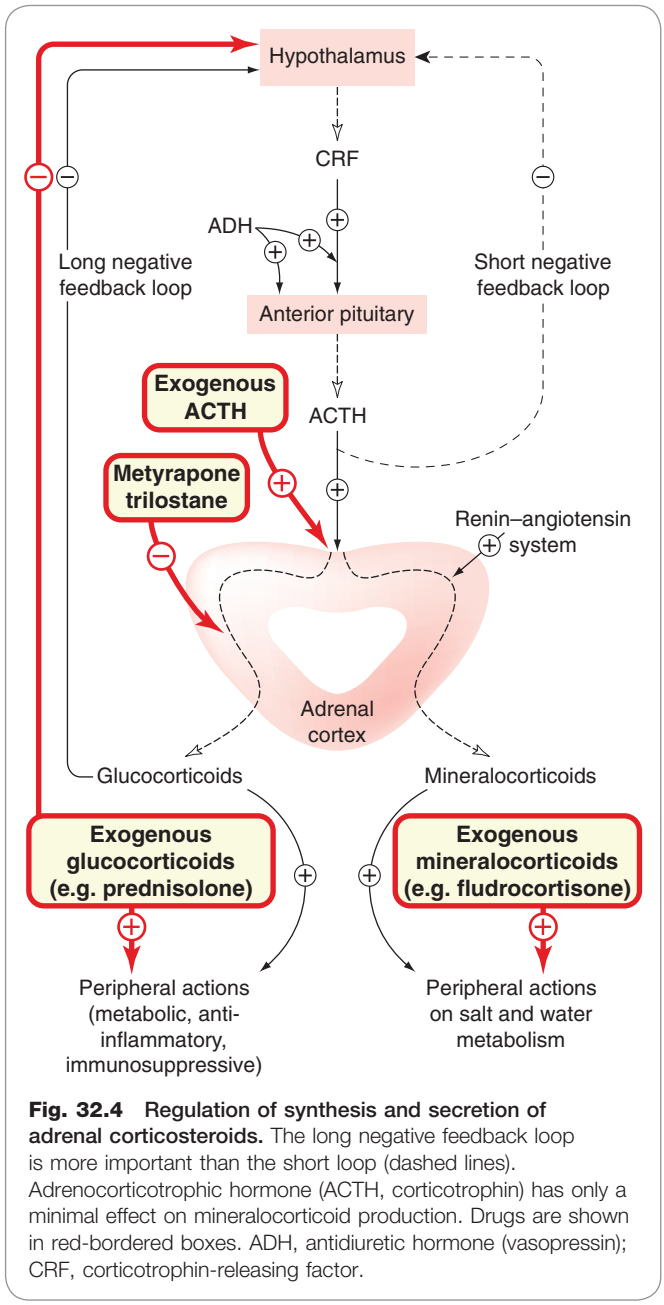

Fig. 32.4 Regulation of synthesis and secretion of adrenal corticosteroids. The long negative feedback loop is more important than the short loop (dashed lines). Adrenocorticotrophic hormone (ACTH, corticotrophin) has only a minimal effect on mineralocorticoid production. Drugs are shown in red-bordered boxes. ADH, antidiuretic hormone (vasopressin); CRF, corticotrophin-releasing factor.

Actions

Tetracosactide and ACTH have two actions on the adrenal cortex:

1. Stimulation of the synthesis and release of glucocorticoids. This action occurs within minutes of injection, and the main biological actions are those of the steroids released.
2. A trophic action on adrenal cortical cells, and regulation of the levels of key mitochondrial steroidogenic enzymes. The loss of this effect accounts for the adrenal atrophy that results from chronic glucocorticoid administration, which suppresses ACTH secretion.

The main use of tetracosactide is in the diagnosis of adrenal cortical insufficiency. The drug is given intramuscularly or intravenously, and the concentration of hydrocortisone in the plasma is measured by radioimmunoassay.

MELANOCYTE-STIMULATING HORMONE (MSH)

α-, β- and γ-MSH are peptide hormones with structural similarity to ACTH and are derived from the same precursor. Together, these peptides are referred to as *melanocortins*, because their first recognised action was to stimulate the production of melanin by specialised skin cells called *melanocytes*. As such, they play an important part in determining hair coloration, skin colour and reaction to ultraviolet light.

Melanocyte-stimulating hormone acts on *melanocortin receptors*, of which five (MC_{1-5}) have been cloned. These are G-protein-coupled receptors that activate cAMP synthesis. Melanin formation is under the control of the MC_1

receptor, and excessive α-MSH production can provoke abnormal proliferation of melanocytes and may predispose to melanoma.

▼ Melanocortins exhibit numerous other biological effects. For example, α-MSH inhibits the release of interleukin IL-1β and tumour necrosis factor (TNF)-α, reduces neutrophil infiltration, and exhibits anti-inflammatory and antipyretic activity. Levels of α-MSH are increased in synovial fluid of patients with rheumatoid arthritis. MC_1 and MC_3 receptors mediate the immunomodulatory effect of MSH. Agonists at these receptors with potential anti-inflammatory activity are being sought. Central injection of α-MSH also causes changes in animal behaviour, such as increased grooming and sexual activity as well as reduced feeding.

γ-MSH increases blood pressure, heart rate and cerebral blood flow following intracerebroventricular or intravenous injection. These effects are likely mediated by the MC_4 receptor.

Two naturally occurring ligands for melanocortin receptors (*agouti-signalling protein* and *agouti-related peptide*, together called the *agouti*) have been discovered in human tissues. These are proteins that competitively antagonise the effect of MSH at melanocortin receptors.

POSTERIOR PITUITARY GLAND (NEUROHYPOPHYSIS)

The neurohypophysis consists largely of the terminals of nerve cells that lie in the *supraoptic* and *paraventricular* nuclei of the hypothalamus. Their axons form the *hypothalamic–hypophyseal tract*, and the fibres terminate in dilated nerve endings in close association with capillaries in the posterior pituitary gland (Fig. 32.1). Peptides, synthesised in the hypothalamic nuclei, pass down these axons into the posterior pituitary, where they are stored and eventually secreted into the bloodstream.

The two main hormones of the posterior pituitary are **oxytocin** (which contracts the smooth muscle of the uterus; for details see Ch. 34) and ADH (also called **vasopressin**; see Chs 22 and 28). Several similar peptides have been synthesised that vary in their antidiuretic, vasopressor and oxytocic (uterine stimulant) properties.

The anterior pituitary gland and hypothalamus

- The anterior pituitary gland secretes hormones that regulate:
  - the release of *glucocorticoids* from the adrenal cortex
  - the release of *thyroid* hormones
  - *ovulation* in the female and *spermatogenesis* in the male, and the *release of sex hormones*
  - *growth*
  - *mammary gland* structure and function.
- Each anterior pituitary hormone is regulated by a specific hypothalamic releasing factor. Feedback mechanisms govern the release of these factors. Substances available for clinical use include:
  - *growth hormone-releasing factor* (sermorelin) and analogues of growth hormone (somatropin)
  - *thyrotrophin-releasing factor* (protirelin) and *thyroid-stimulating hormone* (thyrotrophin; used to test thyroid function)
  - octreotide and lanreotide, analogues of *somatostatin*, which inhibit growth hormone release
  - *corticotrophin-releasing factor*, used in diagnosis
  - *gonadotrophin-releasing factor*.

Adrenocorticotrophic hormone (corticotrophin) and the adrenal steroids

- Adrenocorticotrophic hormone (ACTH) stimulates synthesis and release of glucocorticoids (e.g. hydrocortisone), and also some androgens, from the adrenal cortex.
- Corticotrophin-releasing factor (CRF) from the hypothalamus regulates ACTH release, and is regulated in turn by neural factors and negative feedback effects of plasma glucocorticoids.
- Mineralocorticoid (e.g. aldosterone) release from the adrenal cortex is controlled by the renin–angiotensin system.

ANTIDIURETIC HORMONE

Regulation of secretion and physiological role

Antidiuretic hormone released from the posterior pituitary has a crucial role in the control of the water content of the body through its action on the cells of the distal part of the nephron and the collecting tubules in the kidney (see Ch. 28). The hypothalamic nuclei that control fluid balance lie close to the nuclei that synthesise and secrete ADH.

One of the main stimuli to ADH release is an increase in plasma osmolarity (which produces a sensation of thirst). A decrease in circulating blood volume (hypovolaemia) is another, and here the stimuli arise from stretch receptors in the cardiovascular system or from angiotensin release. *Diabetes insipidus* is a condition in which large volumes of dilute urine are produced because ADH secretion is reduced or absent, or because of a reduced sensitivity of the kidney to the hormone.

Antidiuretic hormone receptors

There are three classes of receptor for ADH: V_1, V_2 and V_3. V_2 receptors stimulate adenylyl cyclase, which mediates its main physiological actions in the kidney, whereas the V_1 and V_3 receptors are coupled to the phospholipase C/inositol trisphosphate system.

Actions

Renal actions

Antidiuretic hormone binds to V_2 receptors in the basolateral membrane of the cells of the distal tubule and collecting ducts of the nephron. Its main effect in the collecting duct is to increase the rate of insertion of water channels (*aquaporins*) into the lumenal membrane, thus increasing the permeability of the membrane to water (see Ch. 28). It also activates urea transporters and transiently increases Na^+ absorption, particularly in the distal tubule.

Several drugs affect the action of ADH. Non-steroidal anti-inflammatory drugs and **carbamazepine** increase, and **lithium**, **colchicine** and **vinca alkaloids** decrease, ADH effects. The effects of the last two agents are secondary to their action on the microtubules required for translocation

of water channels. The antagonist **demeclocycline** counteracts the action of ADH on renal tubules and can be used to treat patients with water retention combined with urinary salt loss (and thus hyponatraemia) caused by excessive secretion of the hormone. This *syndrome of inappropriate ADH secretion* ('SIADH') is seen in some patients with lung or other malignancies or following head injury. More specific antagonists of V_2 receptors are also used for SIADH and in some patients with heart failure (Ch. 22).

Other non-renal actions

Antidiuretic hormone causes contraction of smooth muscle, particularly in the cardiovascular system, by acting on V_1 receptors (see Ch. 22). The affinity of these receptors for ADH is lower than that of the V_2 receptors, and smooth muscle effects are seen only with doses larger than those affecting the kidney. ADH also stimulates blood platelet aggregation and mobilisation of coagulation factors. In the CNS, ADH acts as a neuromodulator and neurotransmitter. When released into the pituitary portal circulation, it promotes the release of ACTH from the anterior pituitary by an action on V_3 receptors (Fig. 32.4).

Pharmacokinetic aspects

ADH, as well as various peptide analogues, is used clinically either for the treatment of diabetes insipidus or as a vasoconstrictor. The analogues have been developed to (a) increase the duration of action and (b) shift the potency between V_1 and V_2 receptors.

The main substances used are vasopressin (ADH itself; short duration of action, weak selectivity for V_2 receptors, given by subcutaneous or intramuscular injection, or by intravenous infusion), **desmopressin** (increased duration of action, V_2-selective and therefore fewer pressor effects, can be given by several routes including nasal spray) and **terlipressin** (increased duration of action, low but protracted vasopressor action and minimal antidiuretic properties). **Felypressin** is a short-acting vasoconstrictor that is injected with local anaesthetics such as **prilocaine** to prolong their action (see Ch. 42).

Vasopressin itself is rapidly eliminated, with a plasma half-life of 10 min and a short duration of action. Metabolism is by tissue peptidases, and 33% is removed by the kidney. Desmopressin is less subject to degradation by peptidases, and its plasma half-life is 75 min.

Unwanted effects

There are few unwanted effects and they are mainly cardiovascular in nature: intravenous vasopressin may cause spasm of the coronary arteries with resultant angina, but this risk can be minimised if the antidiuretic peptides are administered intranasally.

Posterior pituitary

- The posterior pituitary secretes:
  - oxytocin (see Ch. 34)
  - antidiuretic hormone (vasopressin), which acts on V_2 receptors in the distal kidney tubule to increase water reabsorption and, in higher concentrations, on V_1 receptors to cause vasoconstriction. It also stimulates adrenocorticotrophic hormone secretion.
- Substances available for clinical use are vasopressin and the analogues desmopressin, felypressin and terlipressin.

Clinical uses of antidiuretic hormone (vasopressin) and analogues

- Diabetes insipidus: **felypressin**, **desmopressin**.
- Initial treatment of bleeding *oesophageal varices*: **vasopressin**, **terlipressin**, **felypressin**. (Octreotide—a somatostatin analogue—is also used, but direct injection of sclerosant via an endoscope is the main treatment.)
- Prophylaxis against bleeding in *haemophilia* (e.g. before tooth extraction): **vasopressin**, **desmopressin** (by increasing the concentration of factor VIII).
- **Felypressin** is used as a vasoconstrictor with local anaesthetics (see Ch. 42).
- **Desmopressin** is used for persistent *nocturnal enuresis* in older children and adults.

THE ADRENAL CORTEX

The adrenal glands consist of two parts: the inner *medulla*, which secretes catecholamines (see Ch. 14), and the outer *cortex*, which secretes adrenal steroids. The cortex, which concerns us in this section, comprises three concentric zones: the *zona glomerulosa* (the outermost layer) that elaborates mineralocorticoids, the *zona fasciculata* that elaborates glucocorticoids, and the innermost *zona reticularis*. While the principal adrenal steroids are those with glucocorticoid and mineralocorticoid[2] activity, some sex steroids (mainly androgens) are also secreted by the gland but are not considered further in this chapter.

The mineralocorticoids regulate water and electrolyte balance, and the main endogenous hormone is *aldosterone*. The glucocorticoids have widespread actions on intermediate metabolism, affecting carbohydrate and protein metabolism, as well as potent regulatory effects on host defence mechanisms (Ch. 6). The adrenal secretes a mixture of glucocorticoids; the main hormone in humans is *hydrocortisone* (also, confusingly, called *cortisol*), and in rodents, *corticosterone*. The mineralocorticoid and glucocorticoid actions are not completely separated in naturally occurring steroids, some glucocorticoids having quite substantial effects on water and electrolyte balance. In fact, hydrocortisone and aldosterone are equiactive on mineralocorticoid receptors, but, in mineralocorticoid-sensitive tissues such as the kidney, the action of *11β-hydroxysteroid dehydrogenase* converts hydrocortisone to the inactive metabolite *cortisone*,[3]

[2]So named because early experimenters noticed that two crude fractions of adrenal gland extracts caused changes in blood glucose or salt and water retention.

[3]Oddly, it was cortisone that was originally demonstrated to have potent anti-inflammatory activity in the classic studies by Hench and his colleagues in 1949. The reason for this apparent anomaly is that an isoform of 11β-hydroxysteroid dehydrogenase present in some tissues can transform this steroid back into cortisol (i.e. hydrocortisone), thus restoring biological activity.

thereby protecting the receptor from inappropriate activation.

With the exception of *replacement therapy* (see below), glucocorticoids are most commonly employed for their anti-inflammatory and immunosuppressive properties (see Ch. 26). Under these circumstances, all their metabolic and other actions are seen as unwanted side effects. Synthetic steroids have been developed in which it has been possible to separate, to some degree, the glucocorticoid from the mineralocorticoid actions (see Table 32.2), but it has not been possible to separate the anti-inflammatory from the other actions of the glucocorticoids completely.

▼ The adrenal gland is essential to life, and animals deprived of these glands are able to survive only under rigorously controlled conditions. In humans, a deficiency in corticosteroid production, termed *Addison's disease*, is characterised by muscular weakness, low blood pressure, depression, anorexia, loss of weight and hypoglycaemia. Addison's disease may have an autoimmune aetiology, or it may result from destruction of the gland by chronic inflammatory conditions such as tuberculosis.

When corticosteroids are produced in excess, the clinical picture depends on which species predominates. Excessive glucocorticoid activity results in *Cushing's syndrome*, the manifestations of which are outlined in Figure 32.7. This can be caused by hypersecretion from the adrenal glands or by prolonged therapeutic use of glucocorticoids. An excessive production of mineralocorticoids results in disturbances of Na^+ and K^+ balance. This may occur with hyperactivity or tumours of the adrenals (*primary hyperaldosteronism*, or *Conn's syndrome*, an uncommon but important cause of hypertension; see Ch. 22), or with excessive activation of the renin–angiotensin system such as occurs in some forms of kidney disease, cirrhosis of the liver or congestive cardiac failure (*secondary hyperaldosteronism*).

Table 32.2 Comparison of the main corticosteroid agents used for systemic therapy (using hydrocortisone as a standard)

Compound	Relative affinity for receptor[a]	Approximate relative potency in clinical use		Duration of action after oral dose[b]	Comments
		Anti-inflammatory	Sodium retaining		
Hydrocortisone	1	1	1	Short	Drug of choice for replacement therapy (cortisol)
Cortisone	Prodrug	0.8	0.8	Short	Cheap; inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects
Deflazacort	Prodrug	3	?	Short	Must be converted by plasma esterases into active metabolite Similar utility to prednisolone
Prednisolone	2.2	4	0.8	Intermediate	Drug of choice for systemic anti-inflammatory and immunosuppressive effects
Prednisone	Prodrug	4	0.8	Intermediate	Inactive until converted to prednisolone
Methylprednisolone	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others
Dexamethasone	7.1	27	Minimal	Long	Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of adrenocorticotrophic hormone production
Betamethasone	5.4	27	Negligible	Long	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects
Aldosterone	0.38	None	500	–	Endogenous mineralocorticoid

[a] Data obtained in human fetal lung cells.
[b] Duration of action (half-lives in hours): short, 8–12; intermediate, 12–36; long, 36–72.
Some drugs are inactive until converted to active compounds in vivo and therefore have negligible affinity for the glucocorticoid receptor.
(Data for relative affinity obtained from Baxter J D, Rousseau G G (eds) 1979 Glucocorticoid hormone action. Monographs on Endocrinology, vol 12. Springer-Verlag, Berlin.)

GLUCOCORTICOIDS

Synthesis and release

Glucocorticoids are not stored in the adrenal. They are synthesised under the influence of circulating ACTH secreted from the anterior pituitary gland (Fig. 32.4) and released in a pulsatile fashion into the blood. While they are always present, there is a well-defined circadian rhythm in the secretion in healthy humans, with the net blood concentration being highest early in the morning, gradually diminishing throughout the day and reaching a low point in the evening or night. ACTH secretion itself (also pulsatile in nature) is regulated by CRF released from the hypothalamus and vasopressin from the posterior gland. The release of both ACTH and CRF, in turn, is reflexly inhibited by the ensuing rising concentrations of glucocorticoids in the blood. This functional hypothalamic–pituitary–adrenal unit is referred to as the *HPA axis*.

Opioid peptides also exercise a tonic inhibitory control on the secretion of CRF, and psychological factors can affect the release of both vasopressin and CRF, as can stimuli such as excessive heat or cold, injury or infections. This is the principal mechanism whereby the HPA axis is activated in response to a threatening environment.

The precursor of glucocorticoids is cholesterol (Fig. 32.5). The initial conversion of cholesterol to *pregnenolone* is the rate-limiting step and is itself regulated by ACTH. Some of the reactions in the biosynthetic pathway can be inhibited by drugs. **Metyrapone** prevents the β-hydroxylation at C11, and thus the formation of hydrocortisone and corticosterone. Synthesis is blocked at the 11-deoxycorticosteriod stage, and as these substances have no effects on the hypothalamus and pituitary, there is a marked increase in ACTH in the blood. Metyrapone can therefore be used to test ACTH production, and may also be used to treat patients with Cushing's syndrome. **Trilostane** (also of use in Cushing's syndrome and primary hyperaldosteronism) blocks an earlier enzyme in the pathway—the *3β-dehydrogenase*.

Aminoglutethimide inhibits the initial step in the biosynthetic pathway and has the same overall effect as metyrapone. **Ketoconazole**, an antifungal agent (Ch. 52), used in higher doses also inhibits steroidogenesis and may be of value in the specialised treatment of Cushing's syndrome.

Mechanism of action

The glucocorticoid effects relevant to this discussion are initiated by interaction of the drugs with specific intracellular glucocorticoid receptors belonging to the nuclear receptor superfamily (although there may be other binding proteins or sites; see Norman et al., 2004). This superfamily (see Ch. 3) also includes the receptors for mineralocorticoids, the sex steroids, thyroid hormones, vitamin D_3 and retinoic acid. The actual mechanism of transcriptional control is complex with at least four mechanisms operating within the nucleus. These are summarised diagrammatically in Figure 32.6.

In addition to controlling gene expression, the liganded receptor itself, in either a monomeric or a dimeric form, may trigger important signal transduction events while still in the cytosolic compartment (there may even be a subpopulation of receptors that reside there permanently). One of these cytosolic effects, germane to the anti-inflammatory action of these drugs, is the release, following phosphorylation, of the protein *annexin-1*, which has potent inhibitory effects on leukocyte trafficking and other biological actions. The significance of such 'receptor-mediated, non-genomic' actions is that they can happen very rapidly (within seconds), as they do not entail changes in protein synthesis that require a longer time frame.

Glucocorticoids

Common drugs used systemically include hydrocortisone, prednisolone and dexamethasone.

Metabolic actions

- *Carbohydrates*: decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- *Proteins*: increased catabolism, reduced anabolism.
- *Lipids*: a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing's syndrome.

Regulatory actions

- *Hypothalamus* and *anterior pituitary gland*: a negative feedback action resulting in reduced release of endogenous glucocorticoids.
- *Cardiovascular system*: reduced vasodilatation, decreased fluid exudation.
- *Musculoskeletal*: decreasing osteoblast and increasing osteoclast activity.
- *Inflammation* and *immunity*:
  - *acute inflammation*: decreased influx and activity of leukocytes
  - *chronic inflammation*: decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis
  - *lymphoid tissues*: decreased clonal expansion of T and B cells, and decreased action of cytokine-secreting T cells. Switch from Th1 to Th2 response.
- *Mediators*:
  - decreased production and action of cytokines, including interleukins, tumour necrosis factor-α and granulocyte macrophage colony-stimulating factor
  - reduced generation of eicosanoids
  - decreased generation of IgG
  - decrease in complement components in the blood
  - increased release of anti-inflammatory factors such as interleukin-10 and annexin 1.
- *Overall effects*: reduction in the activity of the innate and acquired immune systems, but also decreased healing and diminution in the protective aspects of the inflammatory response.

Actions

General metabolic and systemic effects

The main metabolic effects are on carbohydrate and protein metabolism. The glucocorticoids cause both a decrease in the uptake and utilisation of glucose and an increase in gluconeogenesis, resulting in a tendency to hyperglycaemia (see Ch. 30). There is a concomitant increase in glycogen storage, which may be a result of insulin secretion in response to the increase in blood sugar. Overall, there is

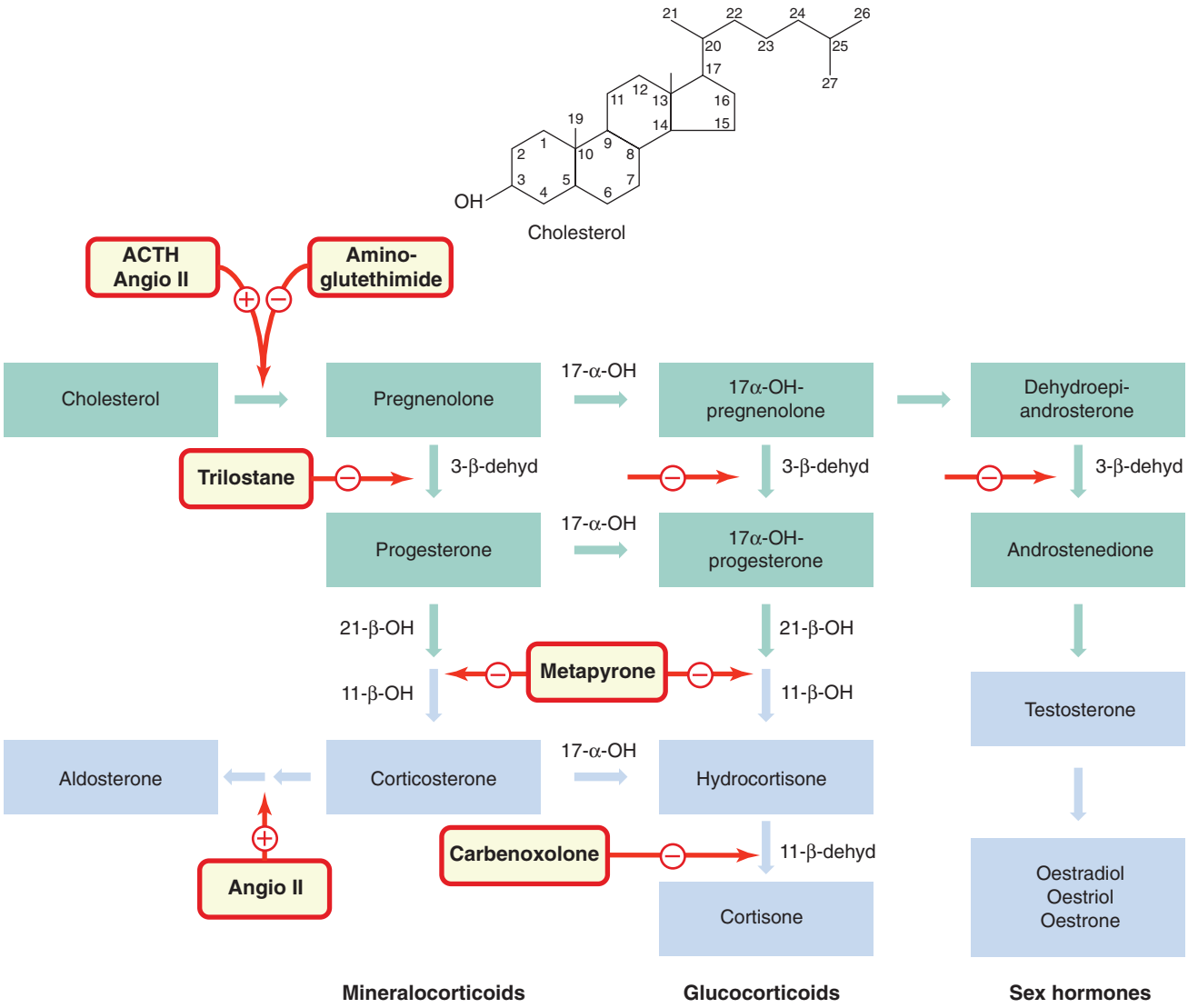

Fig. 32.5 Biosynthesis of corticosteroids, mineralocorticoids and sex hormones. All steroid hormones are synthesised from cholesterol. Successive steps of hydroxylation and dehydrogenation are important in the biosynthetic pathway and are targets for drugs. Intermediates are shown in green boxes; interconversions occur between the pathways. Blue boxes indicate circulating hormones. Drugs are shown in red-bordered boxes adjacent to their sites of action. Glucocorticoids are produced by cells of the zona fasciculata, and their synthesis is stimulated by adrenocorticotrophic hormone (ACTH); aldosterone is produced by cells of the zona glomerulosa, and its synthesis is stimulated by angiotensin II (angio II). Metyrapone inhibits glucocorticoid synthesis, aminoglutethimide and trilostane block synthesis of all three types of adrenal steroid (see text for details). Carbenoxolone inhibits the interconversion of hydrocortisone and cortisone in the kidney. Enzymes: 17-α-OH, 17-α-hydroxylase; 3-β-dehyd, 3-β-dehydrogenase; 21-β-OH, 21-β-hydroxylase; 11-β-OH, 11-β-hydroxylase; 11-β-dehyd, 11-β-hydroxysteroid dehydrogenase.

decreased protein synthesis and increased protein breakdown, particularly in muscle, and this can lead to wasting. Glucocorticoids also have a 'permissive' effect on the cAMP-dependent lipolytic response to catecholamines and other hormones. Such hormones cause lipase activation through a cAMP-dependent kinase, the synthesis of which requires the presence of glucocorticoids (see below). Large doses of glucocorticoids given over a long period result in the redistribution of body fat characteristic of *Cushing's syndrome* (Fig. 32.7).

Glucocorticoids tend to produce a negative calcium balance by decreasing Ca^{2+} absorption in the gastrointestinal tract and increasing its excretion by the kidney. This may contribute to osteoporosis (see below). In higher, non-physiological concentrations, the glucocorticoids have some mineralocorticoid actions (see below), causing Na^+ retention and K^+ loss—possibly by swamping the protective 11β-hydroxysteriod dehydrogenase and acting at mineralocorticoid receptors.

Negative feedback effects on the anterior pituitary and hypothalamus

Both endogenous and exogenous glucocorticoids have a negative feedback effect on the secretion of CRF and ACTH

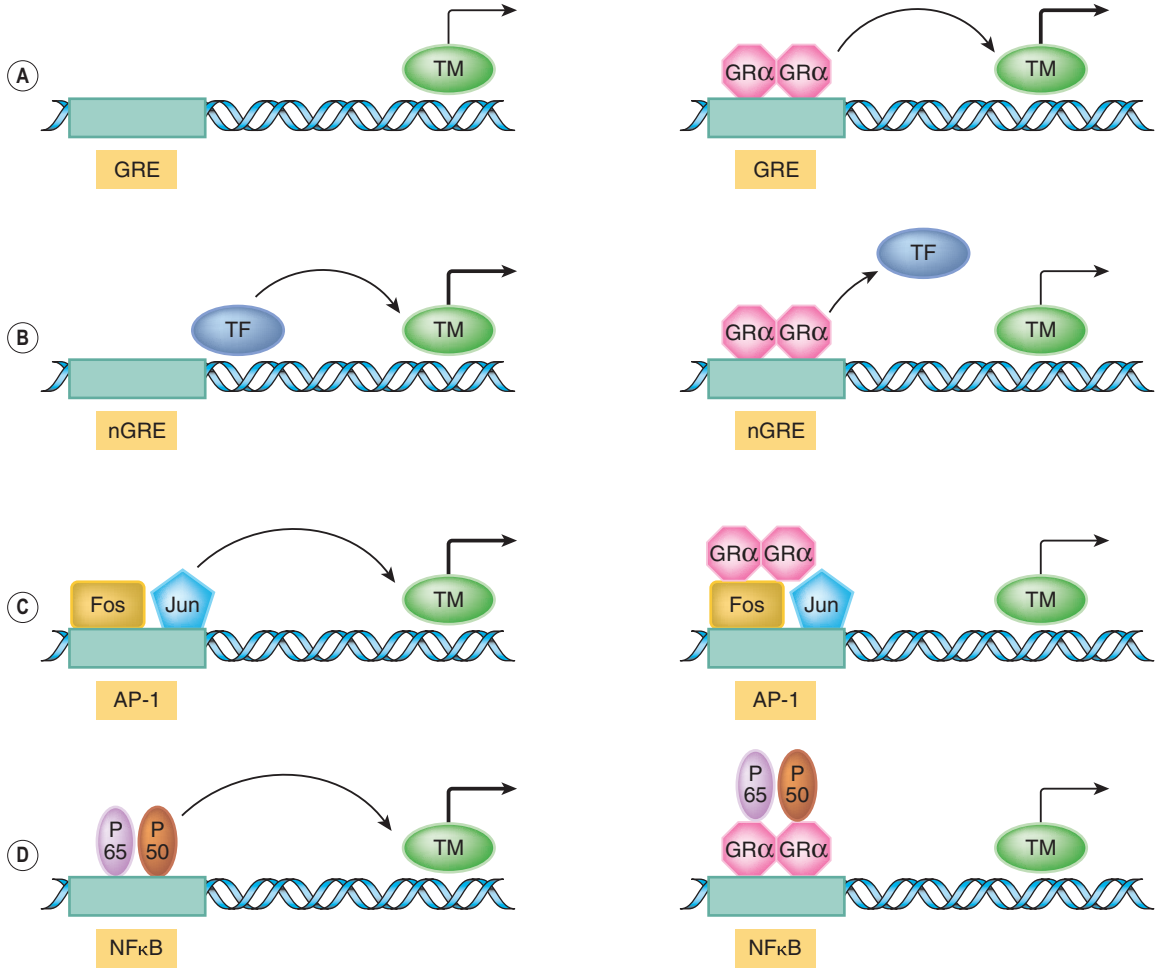

Fig. 32.6 Molecular mechanism of action of glucocorticoids. The schematic figure shows three possible ways by which the liganded glucocorticoid receptor can control gene expression following translocation to the nucleus. [**A**] Basic transactivation mechanism. Here, the transcriptional machinery (TM) is presumed to be operating at a low level. The liganded glucocorticoid receptor (GR) dimer binds to one or more 'positive' glucocorticoid response elements (GREs) within the promoter sequence (shaded zone) and upregulates transcription. [**B**] Basic transrepression mechanism. The transcriptional machinery is constitutively driven by transcription factors (TF). In binding to the 'negative' GRE (nGRE), the receptor complex displaces these factors and expression falls. [**C**] Fos/Jun mechanism. Transcription is driven at a high level by Fos/Jun transcription factors binding to their AP-1 regulatory site. This effect is reduced in the presence of the GR. [**D**] Nuclear factor (NF)κβ mechanism. The transcription factors P65 and P50 bind to the NFκβ site, promoting gene expression. This is prevented by the presence of the GR, which binds the transcription factors, preventing their action (this may occur in the cytoplasm also). (For further details of the structure of the glucocorticoid receptor, see Ch. 3.) (Modified from Oakley R H, Cidlowski J A in Goulding N J, Flower R J (eds) 2001 Glucocorticoids. Birkhauser Verlag.)

(see Fig. 32.4). Administration of exogenous glucocorticoids depresses the secretion of CRF and ACTH, thus inhibiting the secretion of endogenous glucocorticoids and potentially causing atrophy of the adrenal cortex. If therapy is prolonged, it may take many months to return to normal function when the drugs are stopped.

Anti-inflammatory and immunosuppressive effects

That endogenous glucocorticoids maintain a low-level anti-inflammatory tonus can be readily demonstrated by observing the heightened response seen in adrenalectomised animals to even mild inflammatory stimuli. A failure of appropriate secretion in response to injury or infection may underlie certain chronic inflammatory human pathologies.

Exogenous glucocorticoids are the anti-inflammatory drugs *par excellence*, and when given therapeutically inhibit both the early and the late manifestations of inflammation, i.e. not only the initial redness, heat, pain and swelling, but also the later stages of wound healing and repair, and the proliferative reactions seen in chronic inflammation. They reverse virtually all types of inflammatory reaction, whether caused by invading pathogens, by chemical or physical stimuli, or by inappropriately deployed immune responses such as are seen in hypersensitivity or autoimmune disease. When used prophylactically to suppress graft rejection, glucocorticoids suppress the initiation and generation of an immune response mounted against this new 'invader' more efficiently than an established response in which clonal proliferation has already occurred.

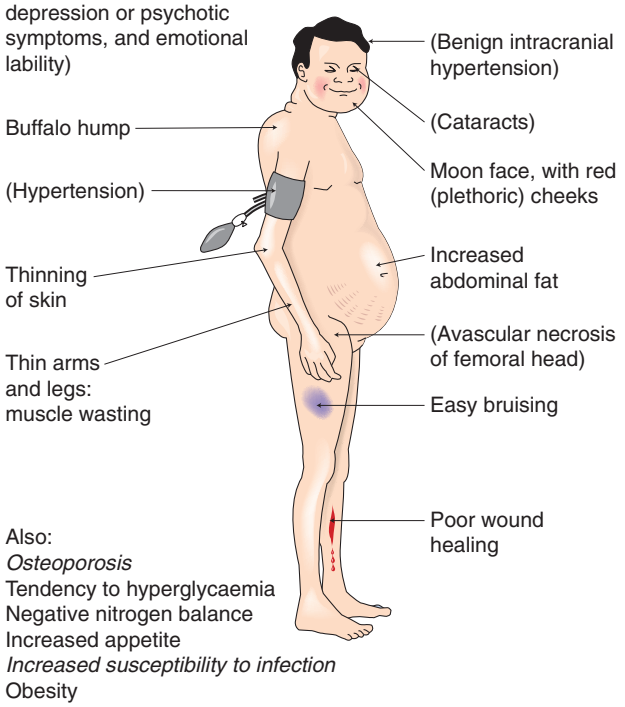

Fig. 32.7 Cushing's syndrome. This is caused by excessive exposure to glucocorticoids, and may be caused by disease (e.g. an adrenocorticotrophic hormone-secreting tumour) or by prolonged administration of glucocorticoid drugs (iatrogenic Cushing's). Italicised effects are particularly common. Less frequent effects, related to dose and duration of therapy, are shown in parentheses. (Adapted from Baxter JD, Rousseau G G (eds) 1979 Glucocorticoid hormone action. Monographs on Endocrinology, vol 12. Springer-Verlag, Berlin.)

Given that the glucocorticoids are able to modify the expression of so many genes, and that the extent and direction of regulation varies between tissues and even at different times during disease, you will not be surprised to learn that their anti-inflammatory effects are fearsomely complex. Some prominent actions may be highlighted, but these should not be considered a complete list.

Actions on *inflammatory cells* include:

- decreased egress of neutrophils from blood vessels and reduced activation of neutrophils, macrophages and mast cells secondary to decreased transcription of the genes for cell adhesion factors and cytokines
- decreased overall activation of T-helper (Th) cells, reduced clonal proliferation of T cells, and a 'switch' from the Th1 to the Th2 immune response (see Ch. 6)
- decreased fibroblast function, less production of collagen and glycosaminoglycans, and thus reduced healing and repair
- reduced activity of osteoblasts but increased activation of osteoclasts and therefore a tendency to develop osteoporosis.

Action on the *mediators* of inflammatory and immune responses (Ch. 17) include:

- decreased production of prostanoids owing to decreased expression of cyclo-oxygenase-2
- decreased generation of many cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, tumour necrosis factor-α, cell adhesion factors and granulocyte macrophage colony-stimulating factor, secondary to inhibition of gene transcription
- reduction in the concentration of complement components in the plasma
- decreased generation of induced nitric oxide
- decreased histamine release from basophils and mast cells
- decreased IgG production
- increased synthesis of anti-inflammatory factors such as IL-10, IL-1-soluble receptor and annexin-1.

Inflammation is an important protective response designed to ensure the survival of an infected or injured host. It therefore strikes many as odd that we should not only have potent anti-inflammatory hormones circulating constantly in the blood, but that these should be dramatically increased during such threatening episodes. A useful explanatory paradigm is that of Munck et al. (1984): according to this idea, the anti-inflammatory and immunosuppressive actions may play a crucial counter-regulatory role, in that they prevent excessive activation of inflammation and other powerful defence reactions that might, if unchecked, themselves threaten homeostasis. Certainly, this view is borne out by experimental work. While these drugs are of great value in treating conditions characterised by hypersensitivity and unwanted inflammation, they carry the hazard that they are able to suppress the same defence reactions that provide protection to infection and promote healing.

Mechanism of action of the glucocorticoids

- Glucocorticoids bind intracellular receptors that then dimerise, migrate to the nucleus and interact with DNA to modify gene transcription, inducing synthesis of some proteins and inhibiting synthesis of others.
- Some rapid non-genomic effects of glucocorticoids have also been observed. These are mediated through signalling systems in the cytosol that are triggered by the liganded glucocorticoid receptor.
- *Metabolic actions*: most mediator proteins are enzymes, for example cAMP-dependent kinase, but not all actions on genes are known.
- *Anti-inflammatory* and *immunosuppressive actions*. Known actions include:
  - inhibition of transcription of the genes for inducible cyclo-oxygenase-2 and inducible nitric oxide synthase, cytokines and interleukins, cell adhesion molecules
  - block of vitamin D_3-mediated induction of the osteocalcin gene in osteoblasts, and modification of transcription of the collagenase genes
  - increased synthesis and release of annexin-1 in cells of the innate immune system. This has potent anti-inflammatory effects on cells and mediator release, and may also mediate negative feedback at the level of the hypothalamus and anterior pituitary gland.

Unwanted effects

Unwanted effects occur with large doses or prolonged administration of glucocorticoids rather than replacement therapy, and are a serious problem. The major effects are as follows:

- *Suppression of the response to infection or injury*: opportunistic infection can be potentially very serious unless quickly treated with antimicrobial agents along with an increase in the dose of steroid. Wound healing is impaired, and peptic ulceration may also occur. Oral thrush (*candidiasis*, a fungal infection; see Ch. 52) frequently occurs when glucocorticoids are taken by inhalation, because of suppression of local anti-infective mechanisms.
- *Cushing's syndrome* (see Fig. 32.7).
- *Osteoporosis*, with the attendant hazard of fractures, is one of the main limitations to long-term glucocorticoid therapy. These drugs influence bone density both by regulation of calcium and phosphate metabolism and through effects on collagen turnover. They reduce osteoblast function (which deposits bone matrix) and increase the activity of osteoclasts (which digest bone matrix). An effect on the blood supply to bone can result in avascular necrosis of the head of the femur (see Ch. 35).
- *Hyperglycaemia* produced by exogenous glucocorticoids may develop into actual diabetes.
- *Muscle wasting* and proximal muscle weakness.
- In children, *inhibition of growth*[4] if treatment is continued for more than 6 months.
- *Central nervous system effects*: euphoria, depression and psychosis.
- *Other effects*: glaucoma (in genetically predisposed persons), raised intracranial pressure and an increased incidence of cataracts.

Sudden withdrawal of the drugs after prolonged therapy may result in acute adrenal insufficiency through suppression of the patient's capacity to synthesise corticosteroids.[5] Careful procedures for phased withdrawal should be followed. Recovery of full adrenal function usually takes about 2 months, although it can take 18 months or more.

Pharmacokinetic aspects

There are many glucocorticoid drugs in therapeutic use. Although **cortisol**, the endogenous hormone, is often used, synthetic derivatives are even more common. These have different physicochemical properties as well as varying potency and have been optimised for administration by different routes. They may be administered orally, systemically or intra-articularly; given by aerosol into the respiratory tract, administered as drops into the eye or the nose, or applied in creams or ointments to the skin. Topical administration diminishes the likelihood of systemic toxic effects unless large quantities are used. When prolonged use of systemic glucocorticoids is necessary, therapy on alternate days may decrease suppression of the HPA axis and other unwanted effects.

As small lipophilic molecules, glucocorticoids probably enter their target cells by simple diffusion. Hydrocortisone has a plasma half-life of 90 min, although its main biological effects have a 2–8 h latency. Biological inactivation, which occurs in liver cells and elsewhere, is initiated by reduction of the C4–C5 double bond. Cortisone and **prednisone** are inactive until converted in vivo to hydrocortisone and **prednisolone**, respectively.

Endogenous glucocorticoids are transported in the plasma bound to *corticosteroid-binding globulin* (CBG) and to albumin. CBG accounts for about 77% of bound hydrocortisone, but many synthetic glucocorticoids are not bound at all. Albumin has a lower affinity for hydrocortisone but binds both natural and synthetic steroids. Both CBG-bound and albumin-bound steroids are biologically inactive.

The clinical use of systemic glucocorticoids is given in the clinical box. **Dexamethasone** has a special use: it can be used to test HPA axis function in the *dexamethasone suppression test*. A relatively low dose, usually given at night, should suppress the hypothalamus and pituitary, and result in reduced ACTH secretion and hydrocortisone output, as measured in the plasma about 9 hours later. Failure of suppression implies hypersecretion of ACTH or of glucocorticoids (Cushing's syndrome).

MINERALOCORTICOIDS

The main endogenous mineralocorticoid is aldosterone. Its chief action is to increase Na^+ reabsorption by the distal tubules in the kidney, with concomitant increased excretion of K^+ and H^+ (see Ch. 28). An excessive secretion

Clinical uses of glucocorticoids

- Replacement therapy for patients with adrenal failure (*Addison's disease*).
- Anti-inflammatory/immunosuppressive therapy (see also Ch. 26):
  - in *asthma* (Ch. 27)
  - topically in various inflammatory conditions of skin, eye, ear or nose (e.g. *eczema*, *allergic conjunctivitis* or *rhinitis*)
  - *hypersensitivity states* (e.g. severe allergic reactions)
  - in miscellaneous diseases with autoimmune and inflammatory components (e.g. *rheumatoid arthritis* and other 'connective tissue' diseases, *inflammatory bowel diseases*, some forms of *haemolytic anaemia*, *idiopathic thrombocytopenic purpura*)
  - to prevent *graft-versus-host disease* following organ or bone marrow transplantation.
- In *neoplastic* disease (Ch. 55):
  - in combination with cytotoxic drugs in treatment of specific malignancies (e.g. *Hodgkin's disease*, *acute lymphocytic leukaemia*)
  - to reduce cerebral oedema in patients with metastatic or primary *brain tumours* (**dexamethasone**).

[4]However, some of the diseases for which glucocorticoids are indicated themselves retard growth. In a classical trial, glucocorticoid treatment *increased* growth in adolescents with inflammatory bowel disease as the disease resolved (Whittington et al., 1977).

[5]Patients on long-term glucocorticoid therapy are advised to carry a card stating, 'I am a patient on STEROID TREATMENT which must not be stopped abruptly'.

Pharmacokinetics and unwanted actions of the glucocorticoids

- Administration can be oral, topical or parenteral. Most naturally occuring glucocorticoids are transported in the blood by corticosteroid-binding globulin or albumen and enter cells by diffusion. They are metabolised in the liver.
- Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually following replacement therapy. The most important are:
  - suppression of response to infection
  - suppression of endogenous glucocorticoid synthesis
  - metabolic actions (see above)
  - osteoporosis
  - iatrogenic Cushing's syndrome (see Fig. 32.7).

Mineralocorticoids

Fludrocortisone is given orally to produce a mineralocorticoid effect. This drug:

- increases Na^+ reabsorption in distal tubules and increases K^+ and H^+ efflux into the tubules
- acts on intracellular receptors that modulate DNA transcription, causing synthesis of protein mediators
- is used together with a glucocorticoid in replacement therapy.

of mineralocorticoids, as in Conn's syndrome, causes marked Na^+ and water retention, with increased extracellular fluid volume, and sometimes hypokalaemia, alkalosis and hypertension. Decreased secretion, as in Addison's disease, causes Na^+ loss (desalinisation) and a marked decrease in extracellular fluid volume. There is a concomitant decrease in the excretion of K^+, resulting in hyperkalaemia.

Regulation of aldosterone synthesis and release

The regulation of the synthesis and release of aldosterone is complex. Control depends mainly on the electrolyte composition of the plasma and on the angiotensin II system (Fig. 32.4; Chs 22 and 28). Low plasma Na^+ or high plasma K^+ concentrations affect the zona glomerulosa cells of the adrenal directly, stimulating aldosterone release. Depletion of body Na^+ also activates the renin–angiotensin system (see Fig. 22.4). One of the effects of angiotensin II is to increase the synthesis and release of aldosterone (see Fig. 28.5).

Mechanism of action

Like other steroid hormones, aldosterone acts through specific intracellular receptors of the nuclear receptor family. Unlike the glucocorticoid receptor, which occurs in most tissues, the *mineralocorticoid receptor* is restricted to a few tissues, such as the kidney and the transporting epithelia of the colon and bladder. Cells containing mineralocorticoid receptors also contain the 11β-hydroxysteroid dehydrogenase type 2 enzyme (see above), which converts hydrocortisone (cortisol) into inactive cortisone. This has a low affinity for the mineralocorticoid receptors, thus ensuring that the cells are appropriately affected only by the mineralocorticoid hormone itself. Interestingly, this enzyme is inhibited by **carbenoxolone** (previously used to treat gastric ulcers; see Ch. 29), a compound derived from liquorice. If this inhibition is marked, it allows corticosterone to act on the mineralocorticoid receptor, producing a syndrome similar to Conn's syndrome (primary hyperaldosteronism) except that the circulating aldosterone concentration is not raised.

As with the glucocorticoids, the interaction of aldosterone with its receptor initiates transcription and translation of specific proteins, resulting in an increase in the number of sodium channels in the apical membrane of the cell, and subsequently an increase in the number of Na^+-K^+-ATPase molecules in the basolateral membrane (see Fig. 28.5), causing increased K^+ excretion (see Ch. 28). In addition to the genomic effects, there is evidence for a rapid non-genomic effect of aldosterone on Na^+ influx, through an action on the Na^+-H^+ exchanger in the apical membrane.

Clinical use of mineralocorticoids and antagonists

The main clinical use of mineralocorticoids is in replacement therapy. The most commonly used drug is **fludrocortisone** (Table 32.2 and Fig. 32.4), which can be taken orally. **Spironolactone** is a competitive antagonist of aldosterone, and it also prevents the mineralocorticoid effects of other adrenal steroids on the renal tubule (Ch. 28). Side effects include gynaecomastia and impotence, because spironolactone also has some blocking action on androgen and progesterone receptors. It is used to treat primary or secondary hyperaldosteronism and, in conjunction with other drugs, in the treatment of resistant hypertension and of heart failure (Ch. 22) and resistant oedema (Ch. 28). **Eplerenone** has a similar indication and mechanism of action, although fewer side effects.

NEW DIRECTIONS IN GLUCOCORTICOID THERAPY

Glucocorticoids are highly effective in controlling inflammation, but severely limited by their unwanted effects. The ideal solution would be a glucocorticoid possessing the anti-inflammatory but not the unwanted metabolic or other effects.

For many years, the pharmaceutical industry pursued this goal using simple strategies based on the development of structural analogues of hydrocortisone. While this yielded many new active and interesting compounds (several of which are in clinical use today), they never achieved 'separation' of the glucocorticoid actions.

Recently, investigators have taken another tack. It has been noted that glucocorticoids suppress inflammation largely by *down*regulating genes (e.g. cytokine genes) that promote the inflammatory response, whereas many of the side effects are caused by *over*expression of metabolic and other genes (causing, for example, diabetes). Because these effects are brought about through different molecular pathways, researchers have sought steroids that may exhibit one set of actions without the other. At the time of writing,

modest successes have been achieved with these 'dissociated' steroids (see Schacke et al., 2002, 2005), but it is too early to tell whether they will really make a difference in the clinic.

A related idea has been to manipulate the *histone deacetylase* enzymes that are responsible for facilitating the transcriptional regulation of genes following nuclear receptor binding to response elements (Hayashi et al., 2004). One current notion is that there may be a specific isoform of this enzyme that deals with gene upregulation, and that if this could be inhibited, it would lessen the possibility of those unwanted effects.

Another approach has been to focus on the actual mechanism of receptor activation. It is clear that not all glucocorticoids bind to the receptor in the same way, and so the dynamics of the resulting liganded complex may vary (Adcock, 2003). This could be exploited to alter the ability of the steroid–receptor complex to initiate transcriptional and other changes in a way that could be beneficial to the profile of the drug.

These (and other) ideas have been reviewed by Song et al., 2005, but despite their ingenuity it is depressing to report that none has yet made a major difference to the tolerability of these most useful drugs.

REFERENCES AND FURTHER READING

The hypothalamus and pituitary

Birnbaumer, M., 2000. Vasopressin receptors. Trends Endocrinol. Metab. 11, 406–410.

Chini, B., Manning, M., Guillon, G., 2008. Affinity and efficacy of selective agonists and antagonists for vasopressin and oxytocin receptors: an 'easy guide' to receptor pharmacology. Prog. Brain Res. 170, 513–517. (*The title is self-explanatory! Also deals with the prospects for new drugs in this area*)

Clark, R.G., Robinson, C.A.F., 1996. Up and down the growth hormone cascade. Cytokine Growth Factor Rev. 1, 65–80. (*A review covering the cascade that controls the primary regulators of growth and metabolism, namely growth hormone and the insulin-like growth factors*)

Drolet, G., Rivest, S., 2001. Corticotropin-releasing hormone and its receptors; an evaluation at the transcription level in vivo. Peptides 22, 761–767.

Freeman, M.E., Kanyicska, B., Lerant, A., Nagy, G., 2000. Prolactin: structure, function and regulation of secretion. Physiol. Res. 80, 1524–1585. (*Comprehensive review of prolactin and its receptors*)

Guillemin, R., 2005. Hypothalamic hormones a.k.a. hypothalamic releasing factors. J. Endocrinol. 184, 11–28. (*This little review focuses on the history of research in this area and covers the discovery and characterisation of the principal releasing factors. Something to read if you are drawn to this area*)

Lamberts, S.W.J., van der Lely, A.-J., de Herder, W.W., Hofland, L.J., 1996. Octreotide. N. Engl. J. Med. 334, 246–254. (*A review covering somatostatin receptors, somatostatin analogues and treatment of tumours expressing somatostatin receptors with octreotide*)

Maybauer, M.O., Maybauer, D.M., Enkhbaatar, P., Traber, D.L., 2008. Physiology of the vasopressin receptors. Best Pract. Res. Clin. Anaesthesiol. 22, 253–263. (*A small review written mainly from a clinical perspective. Discusses future therapeutic uses for receptor agonists*)

Okada, S., Kopchick, J.J., 2001. Biological effects of growth hormone and its antagonist. Trends Mol. Med. 7, 126–132.

Prakash, A., Goa, K.L., 1999. Sermorelin: a review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency. BioDrugs 12, 139–157. (*Mainly a clinical appraisal of sermorelin utility in treating growth deficiency in contrast to growth hormone itself*)

Schneider, F., Tomek, W., Grundker, C., 2006. Gonadotropin-releasing hormone (GnRH) and its natural analogues: a review. Theriogenology 66, 691–709. (*Focuses mainly on the use of such agents in veterinary medicine*)

Thibonnier, M., Coles, P., Thibonnier, A., et al., 2001. The basic and clinical pharmacology of nonpeptide vasopressin receptor antagonists. Annu. Rev. Pharmacol. 41, 175–202. (*Authoritative account of ADH receptors and the search for new antagonists*)

Vance, M.L., 1994. Hypopituitarism. N. Engl. J. Med. 330, 1651–1662. (*Review of causes, clinical features and hormone replacement therapy of hypopituitarism*)

Wikberg, J.E.S., Muceniece, R., Mandrika, I., et al., 2000. New aspects on the melanocortins and their receptors. Pharmacol. Res. 42, 393–420. (*Detailed review of the varied biological roles of melanocortins and their receptors*)

ACTH

Chan, L.F., Clark, A.J., Metherell, L.A., 2008. Familial glucocorticoid deficiency: advances in the molecular understanding of ACTH action. Horm. Res. 69, 75–82. (*This paper and the one below discuss research into the role of the ACTH signalling system in familial glucocorticoid deficiency. An expert piece of scientific detective work. The second paper is more accessible*)

Clark, A.J., Metherell, L.A., Cheetham, M.E., Huebner, A., 2005. Inherited ACTH insensitivity illuminates the mechanisms of ACTH action. Trends Endocrinol. Metab. 16, 451–457.

Mineralocorticoids

Bastl, C., Hayslett, J.P., 1992. The cellular action of aldosterone in target epithelia. Kidney Int. 42, 250–264. (*A detailed review covering the aldosterone receptor and regulation of gene expression, aldosterone action on electrogenic and electroneutral Na^+ transport, and on K^+ and H^+ secretion*)

Glucocorticoids

Mechanism of action

Adcock, I.M., 2003. Glucocorticoids: new mechanisms and future agents. Curr. Allergy Asthma. Rep. 3, 249–257. (*Excellent review of advances in glucocorticoid pharmacology*)

Borski, R.J., 2000. Nongenomic membrane actions of glucocorticoids in vertebrates. Trends Endocrinol. Metab. 11, 427–436. (*A thought-provoking account of the non-genomic effects of glucocorticoids*)

Buckingham, J.C., 1998. Stress and the hypothalamo–pituitary–immune axis. Int. J. Tissue React. 20, 23–34. (*Clear review of the complexities of the effect of stress on HPA axis function*)

D'Acquisto, F., Perretti, M., Flower, R.J., 2008. Annexin-A1: a pivotal regulator of the innate and adaptive immune systems. Br. J. Pharmacol. 155, 152–169. (*Reviews the role of the glucocorticoid-regulated protein annexin-A1 in mediating the anti-inflammatory action of glucocorticoid drugs*)

de Kloet, E.R., 2000. Stress in the brain. Eur. J. Pharmacol. 405, 187–198.

Eberhardt, W., Kilz, T., Akool, el-S., Müller, R., Pfeilschifter, J., 2005. Dissociated glucocorticoids equipotently inhibit cytokine- and cAMP-induced matrix degrading proteases in rat mesangial cells. Biochem. Pharmacol. 70, 433–445. (*A research paper on the action of dissociated glucocorticoids on the expression of proteolytic enzymes during inflammation as an example of their action*)

Falkenstein, E., Tillmann, H.C., Christ, M., et al., 2000. Multiple actions of steroid hormones—a focus on rapid, nongenomic effects. Pharmacol. Rev. 52, 513–556.

Funder, J.W., 1997. Glucocorticoid and mineralocorticoid receptors: biology and clinical relevance. Annu. Rev. Med. 48, 231–240. (*Succinct review of glucocorticoid and mineralocorticoid receptors, differences in glucocorticoid receptor – and mineralocorticoid receptor-mediated transcription and responses, and steroid resistance*)

Getting, S.J., Christian, H.C., Flower, R.J., Perretti, M., 2002. Activation of melanocortin type 3 receptor as a molecular mechanism for adrenocorticotropic hormone efficacy in gouty arthritis. Arthritis Rheum. 46, 2765–2775. (*Original paper that demonstrates that ACTH has intrinsic anti-inflammatory actions that are independent of the adrenals*)

Hayashi, R., Wada, H., Ito, K., Adcock, I.M., 2004. Effects of glucocorticoids on gene transcription. Eur. J. Pharmacol. 500, 51–62. (*Good basic review of glucocorticoid action; easy to read*)

Kirwan, J., Power, L., 2007. Glucocorticoids: action and new therapeutic insights in rheumatoid arthritis. Curr. Opin. Rheumatol. 19, 233–237. (*Written mainly from the viewpoint of a practising rheumatologist, this review offers interesting insights into the use of these drugs to modify severe chronic arthritic disease*)

Lamberts, S.W.J., Bruining, H.A., de Jong, F.S., 1997. Corticosteroid therapy in severe illness. N. Engl. J. Med. 337, 1285–1292. (*Review with succinct coverage of normal response of adrenal to illness, followed by more detail on clinical therapy*)

Munck, A., Guyre, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr. Rev. 5, 25–44. (*Seminal review suggesting that the anti-inflammatory/immunosuppressive actions of the glucocorticoids have a physiological function; required reading if you want to understand glucocorticoid physiology and pharmacology*)

Norman, A.W., Mizwicki, M.T., Norman, D.P., 2004. Steroid-hormone rapid actions, membrane receptors and a conformational ensemble model. Nat. Rev. Drug Discov. 3, 27–41. (*Fairly advanced reading but contains many useful tables and excellent diagrams; well worth the effort if this subject interests you*)

Rhodes, D., Klug, A., 1993. Zinc fingers. Sci. Am. 268, 32–39. (*Clear discussion of the role of zinc fingers, such as those utilised by nuclear receptors, in regulating gene transcription; excellent diagrams, of course*)

Schacke, H., Docke, W.D., Asadullah, K., 2002. Mechanisms involved in the side effects of glucocorticoids. Pharmacol. Ther. 96, 23–43. (*Useful review dealing with side effects and 'dissociated steroids'*)

Schacke, H., Rehwinkel, H., Asadullah, K., 2005. Dissociated glucocorticoid receptor ligands: compounds with an improved therapeutic index. Curr. Opin. Investig. Drugs 6, 503–507. (*More details about the dissociated steroid concept, with several examples*)

Schafer-Korting, M., Kleuser, B., Ahmed, M., et al., 2005. Glucocorticoids for human skin: new aspects of the mechanism of action. Skin Pharmacol. Physiol. 18, 103–114. (*The title is self-explanatory: good discussions of different mechanisms of glucocorticoid action*)

Song, I.H., Gold, R., Straub, R.H., et al., 2005. New glucocorticoids on the horizon: repress, don't activate! J. Rheumatol. 32, 1199–1207. (*Good summary of the various approaches taken to circumvent glucocorticoid side effects*)

Tak, P.P., Firestein, G.S., 2001. NF-kappaB: a key role in inflammatory diseases. J. Clin. Invest. 107, 7–11. (*Succinct and very readable account of the role of nuclear factor (NF)κβ in inflammation*)

Tsai, M.-J., O'Malley, B.W., 1994. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. Annu. Rev. Biochem. 63, 451–486. (*Detailed review, by one of the pioneers of the field, of the molecular biology of these receptors, including gene activation and gene silencing*)

Whittington, P.F., Barnes, H.V., Bayless, T.M., 1977. Medical management of Crohn's disease in adolescence. Gastroenterology 72, 1338–1344.

Wilckens, T., 1995. Glucocorticoids and immune dysfunction: physiological relevance and pathogenic potential of hormonal dysfunction. Trends Pharmacol. Sci. 16, 193–197. (*Covers glucocorticoid interaction with their receptors, heat shock protein 90, AP-1 and nuclear factor NFκβ transcription factors; clear diagrams*)

Books

Buckingham, J.C., Gillies, G.E., Cowell, A.M. (Eds.), 1997. Stress, stress hormones and the immune system. John Wiley, Chichester. (*Another excellent source book for information that covers the concepts of stress, the release of cortisol and its subsequent physiological actions*)

Goulding, N.J., Flower, R.J. (Eds.), 2001. Milestones in drug therapy: glucocorticoids. Birkhäuser Verlag, Basel. (*A useful source of information on all aspects of glucocorticoid biology and pharmacology, containing chapters by some of the leaders in the field*)

33 The thyroid

OVERVIEW

Diseases of the thyroid gland are prevalent, and in this chapter we deal with drug therapy used to mitigate these disorders. We set the scene by briefly outlining the structure, regulation and physiology of the thyroid, and highlight the most common abnormalities of thyroid function. We then go on to consider the drugs that replace the thyroid hormones when these are deficient or cease to function adequately, and the drugs that decrease thyroid function when this is excessive.

SYNTHESIS, STORAGE AND SECRETION OF THYROID HORMONES

The thyroid gland secretes three main hormones: *thyroxine* (T_4), *tri-iodothyronine* (T_3) and *calcitonin*. T_4 and T_3 are critically important for normal growth and development and for controlling energy metabolism. Calcitonin is involved in the control of plasma [Ca^{2+}] and is used to treat osteoporosis and other metabolic bone diseases. It is dealt with in Chapter 35. The term *thyroid hormone* will be used here solely to refer to T_4 and T_3.

The functional unit of the thyroid is the *follicle* or *acinus*. Each follicle consists of a single layer of epithelial cells around a cavity, the follicle lumen, which is filled with a thick colloid containing *thyroglobulin*. Thyroglobulin is a large glycoprotein, each molecule of which contains about 115 tyrosine residues. It is synthesised, glycosylated and then secreted into the lumen of the follicle, where iodination of the tyrosine residues occurs. Surrounding the follicles is a dense capillary network, and the rate of blood flow through the gland is very high in comparison with other tissues. The main steps in the synthesis, storage and secretion of thyroid hormone (Fig. 33.1) are:

- uptake of plasma iodide by the follicle cells
- oxidation of iodide and iodination of tyrosine residues of thyroglobulin
- secretion of thyroid hormone.

UPTAKE OF PLASMA IODIDE BY THE FOLLICLE CELLS

Iodide uptake is an energy-dependent process occurring against a gradient, which is normally about 25:1. Iodide is captured from the blood and moved to the lumen by two transporters: the Na^+/I^- symporter (NIS) located at the basolateral surface of the thyrocytes (the energy being provided by Na^+-K^+-ATPase), and *pendrin*[1] (PDS), an I^-/Cl^- porter in the apical membranes (Nilsson, 2001; Yoshida et al., 2004). Uptake is very rapid: labelled iodide (^{125}I) is found in the lumen within 40 s of intravenous injection. Numerous mutations have been discovered in the *NIS* and *PDS* genes, and these contribute to thyroid disease in some patients.

OXIDATION OF IODIDE AND IODINATION OF TYROSINE RESIDUES

The oxidation of iodide and its incorporation into thyroglobulin (termed the *organification* of iodide) is catalysed by *thyroperoxidase*, an enzyme situated at the inner surface of the cell at the interface with the colloid. The reaction requires the presence of hydrogen peroxide (H_2O_2) as an oxidising agent. Iodination occurs after the tyrosine has been incorporated into thyroglobulin. The process is shown in Figure 33.2.

Tyrosine residues are iodinated first at position 3 on the ring, forming *monoiodotyrosine* (MIT) and then, in some molecules, on position 5 as well, forming *di-iodotyrosine* (DIT). While still incorporated into thyroglobulin, these molecules are then coupled in pairs, either MIT with DIT to form T_3, or two DIT molecules to form T_4. The mechanism for coupling is believed to involve a peroxidase system similar to that involved in iodination. About one-fifth of the tyrosine residues in thyroglobulin are iodinated in this way.

The iodinated thyroglobulin of the thyroid forms a large store of thyroid hormone within the gland, with a relatively slow turnover. This is in contrast to some other endocrine secretions (e.g. the hormones of the adrenal cortex), which are not stored but synthesised and released as required.

SECRETION OF THYROID HORMONE

The thyroglobulin molecule is taken up into the follicle cell by endocytosis (Fig. 33.1). The endocytotic vesicles then fuse with lysosomes, and proteolytic enzymes act on thyroglobulin, releasing T_4 and T_3 to be secreted into the plasma. The surplus MIT and DIT, which are released at the same time, are scavenged by the cell, where the iodide is removed enzymatically and reused.

REGULATION OF THYROID FUNCTION

Thyrotrophin-releasing hormone (TRH), released from the hypothalamus in response to various stimuli, releases *thyroid-stimulating hormone* (TSH; thyrotrophin) from the anterior pituitary (Fig. 33.3), as does the synthetic tripeptide **protirelin** (pyroglutamyl-histidyl-proline amide), which is used in this way for diagnostic purposes. TSH acts on receptors on the membrane of thyroid follicle cells through a mechanism that involves cAMP and phosphatidylinositol 3-kinase. It has a trophic action on thyroid cells

[1]So called because it is implicated in the pathophysiology of Pendred's syndrome, named after the eponymous English physician who first described this form of familial goitre.

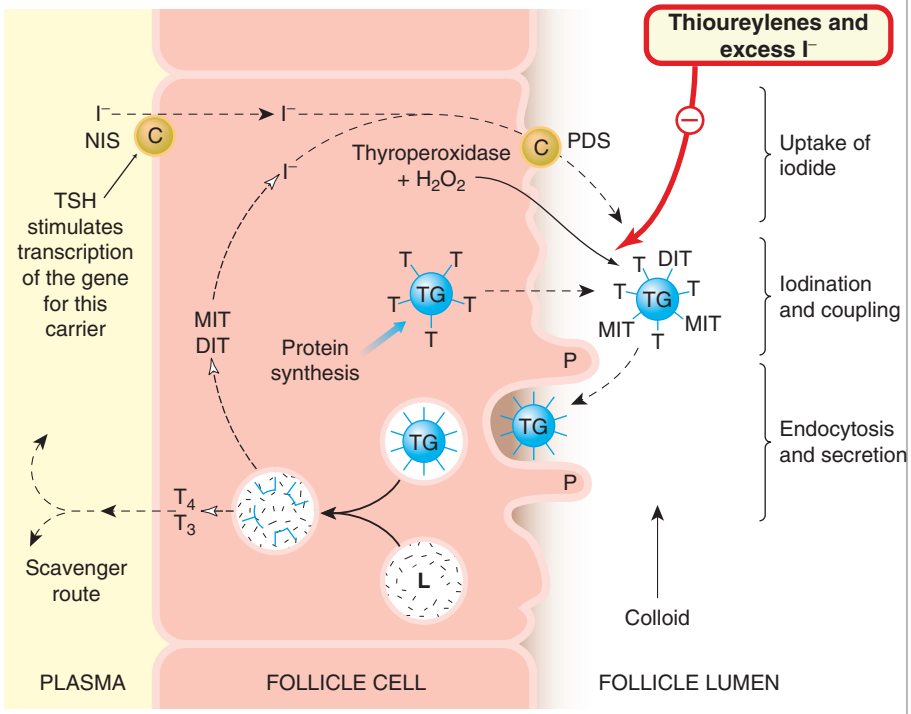

Fig. 33.1 Diagram of thyroid hormone synthesis and secretion, with the sites of action of drugs used in the treatment of thyroid disorders. Iodide in the blood is transported by the carriers NIS and pendrin (PDS) through the follicular cell and into the colloid-rich lumen, where it is incorporated into thyroglobulin under the influence of the thyroperoxidase enzyme (see text for details). The hormones are produced by processing of the endocytosed thyroglobulin and exported into the blood. DIT, di-iodotyrosine; L, lysosome; MIT, monoiodotyrosine; P, pseudopod; T, tyrosine; T_3, tri-iodothyronine; T_4, thyroxine; TG, thyroglobulin; TSH, thyroid-stimulating hormone (thyrotrophin).

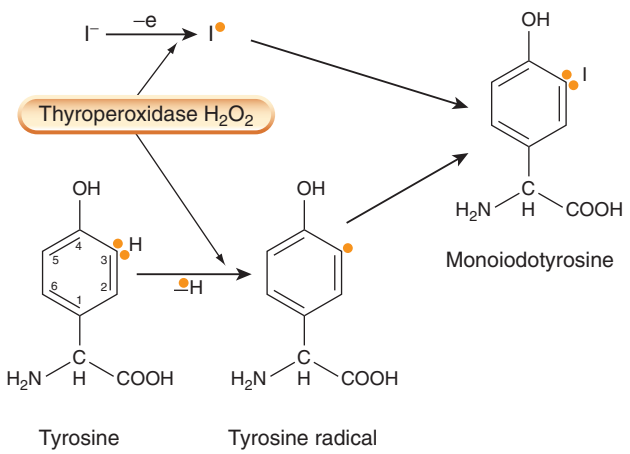

Fig. 33.2 Iodination of tyrosyl residues by the thyroperoxidase–H_2O_2 complex. This probably involves two sites on the enzyme, one of which removes an electron from iodide to give the free radical $I^{\bullet}$; another removes an electron from tyrosine to give the tyrosyl radical (shown by orange dot). Monoiodotyrosine results from the addition of the two radicals.

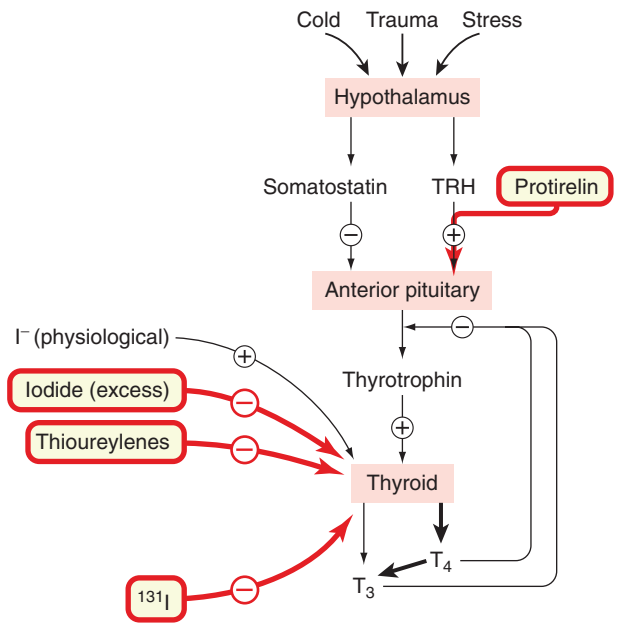

Fig. 33.3 Regulation of thyroid hormone secretion. Iodide (I^-) is essential for thyroid hormone synthesis, but excess of endogenous or exogenous iodide (30 times the daily requirement of iodine) actually inhibits the increased thyroid hormone production, which occurs in thyrotoxicosis. Protirelin as well as recombinant thyrotrophin-releasing hormone (TRH) is sometimes used to stimulate the system for diagnostic purposes, as is the administration of ^{131}I (see text for details). T_3, tri-iodothyronine; T_4, thyroxine.

and controls all aspects of thyroid hormone synthesis, including:

- the *uptake of iodide* by follicle cells, by stimulating transcription of the iodide transporter genes; this is the main mechanism by which it regulates thyroid function
- the *synthesis and secretion of thyroglobulin*
- the *generation of* H_2O_2 and the iodination of tyrosine
- the *endocytosis and proteolysis* of thyroglobulin
- the actual *secretion* of T_3 and T_4
- the *blood flow* through the gland.

The production of TSH is also regulated by a negative feedback effect of thyroid hormones on the anterior pituitary gland, T_3 being more active than T_4 in this respect. The peptide **somatostatin** also reduces basal TSH release. The control of the secretion of TSH thus depends on a balance between the actions of T_3/T_4 and TRH (and probably also somatostatin) on the pituitary, although even high concentrations of thyroid hormone do not totally inhibit TSH secretion.

The other main factor influencing thyroid function is the plasma iodide concentration. About 100 nmol of T_4 is synthesised daily, necessitating uptake by the gland of approximately 500 nmol of iodide each day (equivalent to about 70 µg of iodine). A *reduced* iodine intake, with *reduced* plasma iodide concentration, will result in a decrease of hormone production and an increase in TSH secretion. An *increased* plasma iodide has the opposite effect, although this may be modified by other factors (see below). The overall feedback mechanism responds to changes of iodide slowly over fairly long periods of days or weeks, because there is a large reserve capacity for the binding and uptake of iodide in the thyroid. The size and vascularity of the thyroid are reduced by an increase in plasma iodide and this is exploited therapeutically in preparing hyperthyroid patients for surgery to the gland (see below). Diets deficient in iodine eventually result in a continuous excessive compensatory secretion of TSH, and eventually in an increase in vascularity and (sometimes gross) hypertrophy of the gland.[2]

ACTIONS OF THE THYROID HORMONES

The physiological actions of the thyroid hormones fall into two categories: those affecting metabolism and those affecting growth and development.

EFFECTS ON METABOLISM

The thyroid hormones produce a general increase in the metabolism of carbohydrates, fats and proteins, and regulate these processes in most tissues, T_3 being three to five times more active than T_4 in this respect (Fig. 33.4). Although the thyroid hormones directly control the activity of some of the enzymes of carbohydrate metabolism, most effects are brought about in conjunction with other hormones, such as insulin, glucagon, the glucocorticoids and the catecholamines. There is an increase in oxygen consumption and heat production, which is manifested as an increase in the measured basal metabolic rate. This

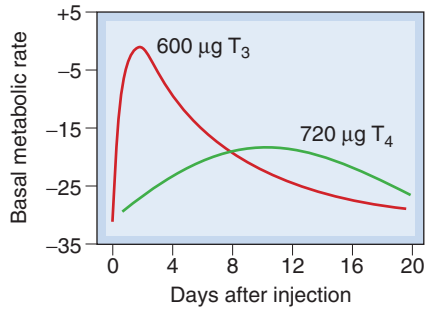

Fig. 33.4 The effect of equimolar doses of triiodothyronine (T_3) and thyroxine (T_4) on basal metabolic rate (BMR) in a hypothyroid subject. Note that this figure is meant only to illustrate overall differences in effect; thyroxine is not given clinically in a single bolus dose as here, but in regular daily doses so that the effect builds up to a plateau. The apparent differences in potency really represent differences in kinetics, reflecting the prehormone role of T_4. (From Blackburn C M et al. 1954 J Clin Invest 33: 819.)

reflects the action of these hormones on tissues such as heart, kidney, liver and muscle, although not on others, such as the gonads, brain or spleen. The calorigenic action is important as part of the response to a cold environment. Administration of thyroid hormone results in augmented cardiac rate and output, and increased tendency to dysrhythmias such as atrial fibrillation.

EFFECTS ON GROWTH AND DEVELOPMENT

The thyroid hormones have a critical effect on growth, partly by a direct action on cells, and also indirectly by influencing *growth hormone* production and potentiating its effects on its target tissues. The hormones are important for a normal response to parathormone and calcitonin as well as for skeletal development; they are also essential for normal growth and maturation of the central nervous system.

MECHANISM OF ACTION

While there is some evidence for non-genomic actions (see Bassett et al., 2003; Lazar, 2003), these hormones act mainly through a specific nuclear receptor, TR (Ch. 3 and Fig. 3.17). Two distinct genes, TRα and TRβ, code for several receptor isoforms that have distinct functions. T_4 may be regarded as a prohormone, because when it enters the cell, it is converted to T_3, which then binds with high affinity to a member of the TR family. This interaction is likely to take place in the nucleus, where TR isoforms generally act as a constitutive repressor of target genes. When T_3 is bound, the receptors change conformation, the co-repressor complex is released and a co-activator complex is recruited, which then activates transcription, resulting in generation of mRNA and protein synthesis.

TRANSPORT AND METABOLISM OF THYROID HORMONES

Both thyroid hormones are transported in the blood bound mainly to *thyroxine-binding globulin* (TBG). Plasma

[2]'Derbyshire neck' was the name given to this condition in a part of the UK where sources of dietary iodine were once scarce.

concentrations of these hormones can be measured by radioimmunoassay, and are approximately 1×10^{-7} mol/l (T_4) and 2×10^{-9} mol/l for T_3. Both are eventually metabolised in their target tissues by deiodination, deamination, decarboxylation and conjugation with glucuronic and sulfuric acids. The liver is a major site of metabolism, and the free and conjugated forms are excreted partly in the bile and partly in the urine. The metabolic clearance of T_3 is 20 times faster than that of T_4 (plasma half-life about 6 days). The long half-life of T_4 is a consequence of its strong binding to TBG. Abnormalities in the metabolism of these hormones may occur naturally or be induced by drugs or heavy metals, and this may give rise to a variety of (uncommon) clinical conditions such as the 'low T_3 syndrome'.

ABNORMALITIES OF THYROID FUNCTION

Thyroid disorders are among the most common endocrine diseases, and subclinical thyroid disease is particularly prevalent in the middle-aged and elderly. They are accompanied by many extrathyroidal symptoms, particularly in the heart and skin. One (rare) cause of organ dysfunction is thyroid cancer. Many other thyroid disorders have an autoimmune basis and like other autoimmune diseases are more common in women than men. The ultimate reason for this is not clear, although it may be linked to polymorphisms in the PDS, tumour necrosis factor (TNF)-α or other genes. Regardless of causation, thyroid dysfunction is often associated with enlargement of the gland, known as *goitre*.

HYPERTHYROIDISM (THYROTOXICOSIS)

In *thyrotoxicosis*, there is excessive activity of the thyroid hormones, resulting in a high metabolic rate, an increase in skin temperature and sweating, and a marked sensitivity to heat. Nervousness, tremor, tachycardia, heat sensitivity and increased appetite associated with loss of weight occur. There are several types of hyperthyroidism, but only two are common: *diffuse toxic goitre* (also called *Graves' disease*[3] or *exophthalmic goitre*) and *toxic nodular goitre*.

Diffuse toxic goitre is an organ-specific autoimmune disease caused by autoantibodies to the TSH receptor which actually stimulate it, increasing thyroxine secretion. Constitutively active mutations of the TRH receptor may also be involved. As is indicated by the name, patients with exophthalmic goitre have protrusion of the eyeballs. The pathogenesis of this condition is not fully understood, but it is thought to be caused by the presence of TSH receptor-like proteins in orbital tissues. There is also an enhanced sensitivity to catecholamines. Toxic nodular goitre is caused by a benign neoplasm or adenoma, and may develop in patients with long-standing simple goitre (see below). This condition does not usually have concomitant exophthalmos. The antidysrhythmic drug **amiodarone** (Ch. 21) is rich in iodine and can cause either hyperthyroidism or hypothyroidism. Some other iodine-containing drugs, such as **iopanoic acid** and its congeners, which are used as imaging agents used to visualise the gall bladder, may also interfere with thyroid function.

[3]After a Dublin physician who connected 'violent and long continued palpitations in females' with enlargement of the thyroid gland. The young ladies' complaints of fluttering hearts and lumps in their throats had previously been attributed to hysteria.

SIMPLE, NON-TOXIC GOITRE

A dietary deficiency of iodine, if prolonged, causes a rise in plasma TRH and eventually an increase in the size of the gland. This condition is known as simple or non-toxic goitre. Another cause is ingestion of *goitrogens* (e.g. from cassava root). The enlarged thyroid usually manages to produce normal amounts of thyroid hormone, although if the iodine deficiency is very severe, hypothyroidism may supervene.

HYPOTHYROIDISM

A decreased activity of the thyroid results in hypothyroidism, and in severe cases *myxoedema*. Once again, this disease is immunological in origin, and the manifestations include low metabolic rate, slow speech, deep hoarse voice, lethargy, bradycardia, sensitivity to cold and mental impairment. Patients also develop a characteristic thickening of the skin (caused by the subcutaneous deposition of glycosaminoglycans), which gives myxoedema its name. *Hashimoto's thyroiditis*, a chronic autoimmune disease in which there is an immune reaction against thyroglobulin or some other component of thyroid tissue, can lead to hypothyroidism and myxoedema. Genetic factors play an important role. Therapy of thyroid tumours with **radioiodine** (see below) is another cause of hypothyroidism.

Thyroid deficiency during development, which is the most prevalent endocrine disorder in the newborn (1 in 3000–4000 births) causes *congenital hypothyroidism*,[4] characterised by gross retardation of growth and mental

The thyroid

- Thyroid hormones, tri-iodothyronine (T_3) and thyroxine (T_4), are synthesised by iodination of tyrosine residues on thyroglobulin within the lumen of the thyroid follicle.
- Hormone synthesis and secretion are regulated by thyroid-stimulating hormone (thyrotrophin) and influenced by plasma iodide.
- There is a large pool of T_4 in the body; it has a low turnover rate and is found mainly in the circulation.
- There is a small pool of T_3 in the body; it has a fast turnover rate and is found mainly intracellularly.
- Within target cells, the T_4 is converted to T_3, which interacts with a nuclear receptor to regulate gene transcription.
- T_3 and T_4 actions:
  - stimulation of metabolism, causing increased oxygen consumption and increased metabolic rate
  - regulation of growth and development.
- Abnormalities of thyroid function include:
  - hyperthyroidism (thyrotoxicosis); either diffuse toxic goitre or toxic nodular goitre
  - hypothyroidism; in adults this causes myxoedema, in infants cretinism
  - simple non-toxic goitre caused by dietary iodine deficiency, usually with normal thyroid function.

[4]An older term for this condition, *cretinism*, has been dropped.

deficiency. *Pendred's syndrome*, an autosomal recessive disorder caused by mutations in the PDS transporter gene, may cause goitre as well as deafness and other symptoms (see Hadj Kacem et al., 2003).

DRUGS USED IN DISEASES OF THE THYROID

HYPERTHYROIDISM

Hyperthyroidism may be treated pharmacologically or surgically. In general, surgery is used only when there are mechanical problems resulting from compression of the trachea, and it is usual to remove only part of the organ. Although the condition of hyperthyroidism can be controlled with antithyroid drugs, these drugs do not alter the underlying autoimmune mechanisms or improve the exophthalmos associated with Graves' disease.

RADIOIODINE

Radioiodine is a first-line treatment for hyperthyroidism (particularly in the USA). The isotope used is ^{131}I (usually as the sodium salt), and the dose generally 5–15 millicuries. Given orally, it is taken up and processed by the thyroid in the same way as the stable form of iodide, eventually becoming incorporated into thyroglobulin. The isotope emits both β and γ radiation. The γ rays pass through the tissue without causing damage, but the β particles have a very short range; they are absorbed by the tissue and exert a powerful cytotoxic action that is restricted to the cells of the thyroid follicles, resulting in significant destruction of the tissue. ^{131}I has a half-life of 8 days, so by 2 months its radioactivity has effectively disappeared. It is given as one single dose, but its cytotoxic effect on the gland is delayed for 1–2 months and does not reach its maximum for a further 2 months.

Hypothyroidism will eventually occur after treatment with radioiodine, particularly in patients with Graves' disease, but is easily managed by replacement therapy with T_4. Radioiodine is best avoided in children and also in pregnant patients because of potential damage to the fetus. There is theoretically an increased risk of thyroid cancer but this has not been seen following the therapeutic treatment.

The uptake of ^{131}I and other isotopes of iodine is also used diagnostically as a test of thyroid function. A tracer dose of the isotope is given orally or intravenously, and the amount accumulated by the thyroid is measured by a γ-scintillation counter placed over the gland. Another use for this drug is the treatment of thyroid cancer.

THIOUREYLENES

The thioureylene group of drugs comprises **carbimazole**, **methimazole** and **propylthiouracil**. Chemically, they are related to thiourea, and the thiocarbamide (S–C–N) group is essential for antithyroid activity.

Mechanism of action

Thioureylenes decrease the output of thyroid hormones from the gland, and cause a gradual reduction in the signs and symptoms of thyrotoxicosis, the basal metabolic rate and pulse rate returning to normal over a period of 3–4 weeks. Their mode of action is not completely understood, but there is evidence that they inhibit the iodination of tyrosyl residues in thyroglobulin (see Figs 33.1 and 33.2). It is thought that they inhibit the thyroperoxidase-catalysed oxidation reactions by acting as substrates for the postulated peroxidase–iodinium complex, thus competitively inhibiting the interaction with tyrosine. Propylthiouracil has the additional effect of reducing the deiodination of T_4 to T_3 in peripheral tissues.

Pharmacokinetic aspects

Thioureylenes are given orally. Carbimazole is rapidly converted to its active metabilite methimazole, which is distributed throughout the body water and has a plasma half-life of 6–15 h. An average dose of carbimazole produces more than 90% inhibition of thyroid incorporation of iodine within 12 h. The clinical response to this and other antithyroid drugs, however, may take several weeks (Fig. 33.5). This is not only because T_4 has a long half-life, but also because the thyroid may have large stores of hormone, which need to be depleted before the drug's action can be fully manifest. Propylthiouracil is thought to act somewhat more rapidly because of its additional effect as an inhibitor of the peripheral conversion of T_4 to T_3.

Both methimazole and propylthiouracil cross the placenta and also appear in the milk, but this effect is less pronounced with propylthiouracil, because it is more strongly bound to plasma protein. After degradation, the metabolites are excreted in the urine, propylthiouracil being excreted more rapidly than methimazole. The thioureylenes may be concentrated in the thyroid.

Unwanted effects

The most dangerous unwanted effect of thioureyline drugs is neutropenia and agranulocytosis (see Ch. 24). This is relatively rare, having an incidence of 0.1–1.2%, and is reversible on cessation of treatment. Patients must be warned to report symptoms (especially sore throat) immediately and have a blood count. Rashes are more common (2–25%), and other symptoms, such as headaches, nausea, jaundice and pain in the joints, can also occur with the thiourelyenes.

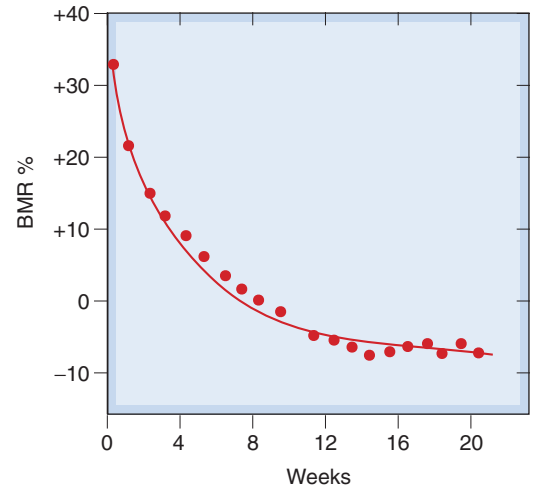

Fig. 33.5 Time course of fall of basal metabolic rate (BMR) during treatment with an antithyroid drug, carbimazole. The curve is exponential, corresponding to a daily decrease in BMR of 3.4%. (From Furth E O et al. 1963 J Clin Endocrinol Metab 23: 1130.)

IODINE/IODIDE

Iodine is converted in vivo to iodide (I^-), which temporarily inhibits the release of thyroid hormones. When high doses of iodine are given to thyrotoxic patients, the symptoms subside within 1–2 days. There is inhibition of the secretion of thyroid hormones and, over a period of 10–14 days, a marked reduction in vascularity of the gland, which becomes smaller and firmer. Iodine is often given orally in a solution with potassium iodide (*'Lugol's iodine'*). With continuous administration, its effect reaches maximum within 10–15 days and then decreases. The mechanism of action is not entirely clear; it may inhibit iodination of thyroglobulin, possibly by reducing the H_2O_2 generation that is necessary for this process.

The main uses of iodine/iodide are for the preparation of hyperthyroid subjects for surgical resection of the gland, and as part of the treatment of severe thyrotoxic crisis (*thyroid storm*). Allergic reactions can occur; these include angio-oedema, rashes and drug fever. Lacrimation, conjunctivitis, pain in the salivary glands and a cold-like syndrome are dose-related adverse effects connected to the concentration of iodide by transport mechanisms in tears and saliva.

OTHER DRUGS USED

The β-adrenoceptor antagonists, for example **propranolol** (Ch. 14), are not antithyroid agents as such, but they are useful for decreasing many of the signs and symptoms of hyperthyroidism—the tachycardia, dysrhythmias, tremor and agitation. They are used during the preparation of thyrotoxic patients for surgery, as well as in most hyperthyroid patients during the initial treatment period while the thioureylenes or radioiodine take effect, or as part of the treatment of acute hyperthyroid crisis. Eye drops containing **guanethidine**, a noradrenergic-blocking agent (Ch. 14), are used to ameliorate the exophthalmos of hyperthyroidism (which is not relieved by antithyroid drugs); it acts by relaxing the sympathetically innervated smooth muscle that causes eyelid retraction. Glucocorticoids (e.g. **prednisolone** or **hydrocortisone**) or surgical decompression may be needed to mitigate severe exophthalmia in Graves' disease. Some other drugs (e.g. cholecystographic agents or antiepileptic drugs) as well as 'endocrine disruptors'[5] may interfere with the normal production of thyroid hormones.

HYPOTHYROIDISM

There are no drugs that specifically augment the synthesis or release of thyroid hormones. The only effective treatment for hypothyroidism, unless it is caused by iodine deficiency (which is treated with iodide; see above), is to administer the thyroid hormones themselves as replacement therapy. **Thyroxine** (official name: **levothyroxine**) and **tri-iodothyronine** (official name: **liothyronine**) are synthetic compounds, identical to the natural hormones, and are given orally. Thyroxine as the sodium salt in doses of 50–100 μg/day is the usual first-line drug of choice. Liothyronine has a faster onset but a shorter duration of action, and is generally reserved for acute emergencies such as the rare condition of myxoedema coma, where these properties are an advantage.

Unwanted effects may occur with overdose, and in addition to the signs and symptoms of hyperthyroidism there is a risk of precipitating angina pectoris, cardiac dysrhythmias or even cardiac failure. The effects of less severe overdose are more insidious; the patient feels well but bone resorption is increased, leading to osteoporosis (Ch. 35).

The use of drugs acting on the thyroid is summarised in the clinical box.

Drugs in thyroid disease

Drugs for hyperthyroidism

- *Radioiodine*, given orally, is selectively taken up by thyroid and damages cells; it emits short-range β radiation, which affects only thyroid follicle cells. Hypothyroidism will eventually occur.
- *Thioureylenes* (e.g. **carbimazole**, **propylthiouracil**) decrease the synthesis of thyroid hormones; the mechanism is through inhibition of thyroperoxidase, thus reducing iodination of thyroglobulin. They are given orally.
- *Iodine*, given orally in high doses, transiently reduces thyroid hormone secretion and decreases vascularity of the gland.

Drugs for hypothyroidism

- **Levothyroxine** has all the actions of endogenous thyroxine; it is given orally.
- **Liothyronine** has all the actions of endogenous tri-iodothyronine; it is given intravenously.

Clinical use of drugs acting on the thyroid

Radioiodine

- Hyperthyroidism (Graves' disease, multinodular toxic goitre).
- Relapse of hyperthyroidism after failed medical or surgical treatment.

Carbimazole or propylthiouracil

- Hyperthyroidism (diffuse toxic goitre); at least 1 year of treatment is needed.
- Preliminary to surgery for toxic goitre.
- Part of the treatment of *thyroid storm* (very severe hyperthyroidism); **propylthiouracil** is preferred. The β-adrenoceptor antagonists (e.g. **propranolol**) are also used.

Thyroid hormones and iodine

- **Levothyroxine** (T_4) is the standard replacement therapy for hypothyroidism.
- **Liothyronine** (T_3) is the treatment of choice for myxoedema coma.
- Iodine dissolved in aqueous potassium iodide (**'Lugol's iodine'**) is used short term to control thyrotoxicosis *preoperatively*. It reduces the vascularity of the gland.

[5]These are man-made chemicals such as pesticides or herbicides (e.g. polychlorinated biphenyls) that linger in the environment and are ingested in foodstuffs. The endocrine system is particularly sensitive to these, especially during development.

REFERENCES AND FURTHER READING

Bassett, J.H.D., Harvey, C.B., Williams, G.R., 2003. Mechanisms of thyroid hormone receptor-specific nuclear and extra nuclear actions. Mol. Cell Endocrinol. 213, 1–11. (*An excellent and comprehensive review dealing with the actions of thyroid hormones through the nuclear receptor mechanism as well as other actions through G-protein-coupled receptors and other pathways*)

Braga, M., Cooper, D.S., 2001. Clinical review 129. Oral cholecystographic agents and the thyroid. J. Clin. Endocrinol. Metab. 86, 1853–1860. (*Discusses the deleterious effect of imaging agents on thyroid function*)

Hadj Kacem, H., Rebai, A., Kaffel, N., et al., 2003. PDS is a new susceptibility gene to autoimmune thyroid diseases: association and linkage study. J. Clin. Endocrinol. Metab. 88, 2274–2280. (*Interesting article on the PDS transporter protein and its contribution to disease susceptibility*)

Kahaly, G.J., Dillmann, W.H., 2005. Thyroid hormone action in the heart. Endocr. Rev. 26, 704–728. (*A very interesting review focusing on the cardiac actions of thyroid hormones; much historical detail*)

Kelly, G.S., 2000. Peripheral metabolism of thyroid hormones: a review. Altern. Med. Rev. 5, 306–333. (*This review focuses on the role of peripheral metabolism in thyroid hormone action*)

Lazar, M.A., 2003. Thyroid hormone action: a binding contract. J. Clin. Invest. 112, 497–499. (*A short and accessible article dealing with the main nuclear receptor-mediated effects of thyroid hormones as well as some other potential mechanisms of action*)

Lazarus, J.H., 1997. Hyperthyroidism. Lancet 349, 339–343. (*A 'seminar' covering aetiology, clinical features, pathophysiology, diagnosis and treatment*)

Lindsay, R.S., 1997. Hypothyroidism. Lancet 349, 413–417. (*A 'seminar' emphasising the management of hypothyroidism*)

Mastorakos, G., Karoutsou, E.I., Mizamtsidi, M., Creatsas, G., 2007. The menace of endocrine disruptors on thyroid hormone physiology and their impact on intrauterine development. Endocrine. 3, 219–237. (*A review of endocrine disrupters and their effects on the thyroid. Not mainstream reading but an interesting topic*)

Nilsson, M., 2001. Iodide handling by the thyroid epithelial cell. Exp. Clin. Endocrinol. Diabetes 109, 13–17. (*Useful and readable review of iodide handling by the thyroid gland*)

Paschke, R., Ludgate, M., 1997. The thyrotropin receptor and its diseases. N. Engl. J. Med. 337, 1675–1679. (*Reviews aspects of TSH biology and disease*)

Roberts, C.G., Ladenson, P.W., 2004. Hypothyroidism. Lancet 363, 793–803. (*Authoritative and accessible review dealing with this thyroid pathology*)

Schmutzler, C., Kohrle, J., 1998. Implications of the molecular characterization of the sodium–iodide symporter (NIS). Exp. Clin. Endocrinol. Diabetes 106, S1–S10. (*Discusses the diagnostic and therapeutic implications of the information now available as a result of the cloning of NIS*)

Surks, M.I., Ortiz, E., Daniels, G.H., et al., 2004. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291, 228–238. (*Discusses and reviews the treatment of subclinical thyroid disease in detail; primarily of interest to clinical students*)

Yen, P.M., 2001. Physiological and molecular basis of thyroid hormone action. Physiol. Rev. 81, 1097–1142. (*Comprehensive review of thyroid hormone–receptor interaction and the effects of thyroid hormone on target tissues*)

Yoshida, A., Hisatome, I., Taniguchi, S., et al., 2004. Mechanism of iodide/chloride exchange by pendrin. Endocrinology 145, 4301–4308. (*An original research article that takes an electrophysiological approach to understanding of the PDS transporter and its relationship to Pendred's syndrome*)

Zhang, J., Lazar, M., 2000. The mechanism of action of thyroid hormones. Annu. Rev. Physiol. 62, 439–466. (*Detailed review of the molecular aspects of thyroid hormone–receptor interaction*)

34 The reproductive system

OVERVIEW

In this chapter, we describe the endocrine control of the female and male reproductive systems as the basis for understanding drug actions in sex hormone replacement, contraception, treatment of infertility, management of labour and treatment of erectile dysfunction.

INTRODUCTION

Drugs that affect reproduction (both by preventing conception and more recently for treating infertility) transformed society in the latter half of the last century. In this chapter, we briefly summarise salient points in reproductive endocrinology as a basis for understanding the numerous important drugs that work on the male and female reproductive systems. Such drugs are used for contraception, to treat infertility, as sex hormone replacement and in obstetric practice to influence labour. The principle of negative feedback is stressed and is central to understanding how hormones interact to control reproduction[1]—many drugs, including agents used to prevent or assist conception, work by influencing negative feedback mechanisms. The chapter concludes with a short section on erectile dysfunction.

ENDOCRINE CONTROL OF REPRODUCTION

Hormonal control of the reproductive systems in men and women involves sex steroids from the gonads, hypothalamic peptides and glycoprotein gonadotrophins from the anterior pituitary.

NEUROHORMONAL CONTROL OF THE FEMALE REPRODUCTIVE SYSTEM

Increased secretion of hypothalamic and anterior pituitary hormones occurs in girls at puberty and stimulates secretion of oestrogen from the ovaries. This causes maturation of the reproductive organs and development of secondary sexual characteristics, and also accelerated growth followed by closure of the epiphyses of the long bones. Sex steroids, *oestrogens* and *progesterone* are thereafter involved in the menstrual cycle, and in pregnancy. A simplified outline is given in Figures 34.1 and 34.2.

The menstrual cycle begins with menstruation, which lasts for 3–6 days, during which the superficial layer of uterine endometrium is shed. The endometrium regenerates during the follicular phase of the cycle after menstrual flow has stopped. A releasing factor, *gonadotrophin-releasing hormone* (GnRH), is secreted from peptidergic neurons in the hypothalamus which discharge in a pulsatile fashion, approximately one burst per hour. GnRH stimulates the anterior pituitary to release gonadotrophic hormones (Fig. 34.1)—*follicle-stimulating hormone* (FSH) and *luteinising hormone* (LH). These act on the ovaries to promote development of small groups of follicles, each of which contains an ovum. One follicle develops faster than the others and forms the Graafian follicle (Figs 34.1 and 34.2E), which secretes oestrogens, and the rest degenerate. The ripening Graafian follicle consists of thecal and granulosa cells surrounding a fluid-filled centre, within which lies an ovum. Oestrogens are responsible for the proliferative phase of endometrial regeneration, which occurs from day 5 or 6 until mid-cycle (Fig. 34.2B,F). During this phase, the endometrium increases in thickness and vascularity, and at the peak of oestrogen secretion there is a prolific cervical secretion of mucus of pH 8–9, rich in protein and carbohydrate, which facilitates entry of spermatozoa. Oestrogen has a negative feedback effect on the anterior pituitary, decreasing gonadotrophin release during chronic administration of oestrogen as oral contraception (see below). In contrast, the high endogenous oestrogen secretion just before mid-cycle sensitises LH-releasing cells of the pituitary to the action of the GnRH and causes the mid-cycle surge of LH secretion (Fig. 34.2C). This, in turn, causes rapid swelling and rupture of the Graafian follicle, resulting in ovulation. If fertilisation occurs, the fertilised ovum passes down the fallopian tubes to the uterus, starting to divide as it goes.

Stimulated by LH, cells of the ruptured follicle proliferate and develop into the *corpus luteum*, which secretes progesterone. Progesterone acts, in turn, on oestrogen-primed endometrium, stimulating the secretory phase of the cycle, which renders the endometrium suitable for the implantation of a fertilised ovum. During this phase, cervical mucus becomes more viscous, less alkaline, less copious and in general less welcoming for sperm. Progesterone exerts negative feedback on the hypothalamus and pituitary, decreasing the release of LH. It also has a thermogenic effect, causing a rise in body temperature of about 0.5°C at ovulation, which is maintained until the end of the cycle.

If implantation of a fertilised ovum does not occur, progesterone secretion stops, triggering menstruation. If implantation does occur, the corpus luteum continues to secrete progesterone, which, by its effect on the hypothalamus and anterior pituitary, prevents further ovulation. The chorion (an antecedent of the placenta) secretes human chorionic gonadotrophin (HCG), which maintains the lining of the uterus during pregnancy. For reasons that are not physiologically obvious, HCG has an additional pharmacological action in stimulating ovulation. As pregnancy proceeds, the placenta develops further hormonal functions and secretes a variety of hormones, including gonadotrophins, progesterone and oestrogens. Progesterone

[1]Recognition that negative feedback is central to endocrine control was a profound insight, made in 1930 by Dorothy Price, a laboratory assistant in the University of Chicago experimenting on effects of testosterone in rats. She referred to it as 'reciprocal influence'.

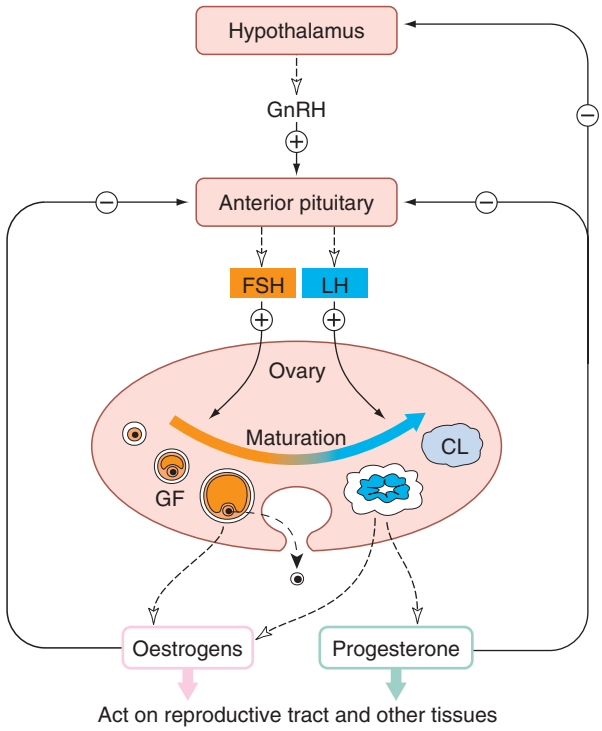

Fig. 34.1 Hormonal control of the female reproductive system. The Graafian follicle (GF) is shown developing on the left, then involuting to form the corpus luteum (CL) on the right, after the ovum (•) has been released. FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone.

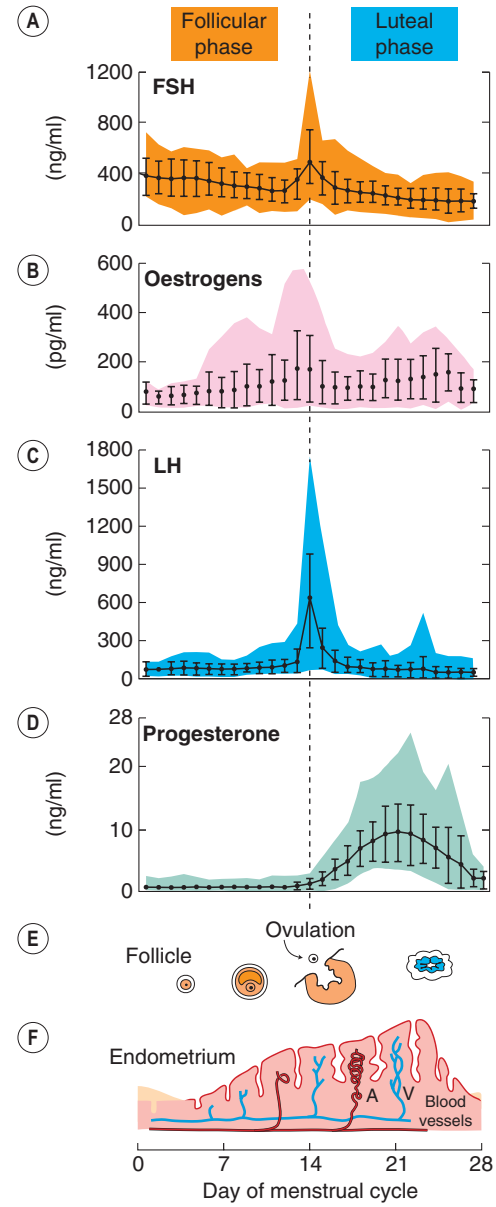

Fig. 34.2 Plasma concentrations of ovarian hormones and gonadotrophins in women during normal menstrual cycles. Values are the mean ± standard deviation of 40 women. The shaded areas indicate the entire range of observations. Day 1 is the onset of menstruation. **E** and **F** show diagrammatically the changes in the ovarian follicle and the endometrium during the cycle. Ovulation on day 14 of the menstrual cycle occurs with the mid-cycle peak of luteinising hormone (LH), represented by the vertical dashed line. A, arterioles; FSH, follicle-stimulating hormone; V, venules. (After van de Wiele R L, Dyrenfurth I 1974 Pharmacol Rev 25: 189–217.)

secreted during pregnancy controls the development of the secretory alveoli in the mammary gland, while oestrogen stimulates the lactiferous ducts. After parturition, oestrogens, along with prolactin (see Ch. 32), are responsible for stimulating and maintaining lactation, whereas high doses of exogenous oestrogen suppress this.

Oestrogens, progestogens (progesterone-like drugs), androgens and the gonadotrophins are described below—see Figure 34.3 for biosynthetic pathways.

NEUROHORMONAL CONTROL OF THE MALE REPRODUCTIVE SYSTEM

As in women, hypothalamic, anterior pituitary and gonadal hormones control the male reproductive system. A simplified outline is given in Figure 34.4. GnRH controls the secretion of gonadotrophins by the anterior pituitary. This secretion is not cyclical as in menstruating women, although it is pulsatile in both sexes (see below). FSH is responsible for the integrity of the seminiferous tubules, and after puberty is important in gametogenesis through an action on Sertoli cells, which nourish and support developing spermatozoa. LH, which in the male is also called *interstitial cell-stimulating hormone* (ICSH), stimulates the interstitial cells (Leydig cells) to secrete androgens—in particular *testosterone*. LH/ICSH secretion begins at puberty, and the consequent secretion of testosterone causes maturation of the reproductive organs and development of secondary sexual characteristics. Thereafter, the primary function of testosterone is the maintenance of spermatogenesis and hence fertility—an action mediated by Sertoli cells. Testosterone is also important in the maturation of spermatozoa as they pass through the epididymis and vas deferens. A further action is a feedback effect on the anterior pituitary, modulating its sensitivity to GnRH and thus influencing secretion of LH/ICSH. Testosterone has marked anabolic

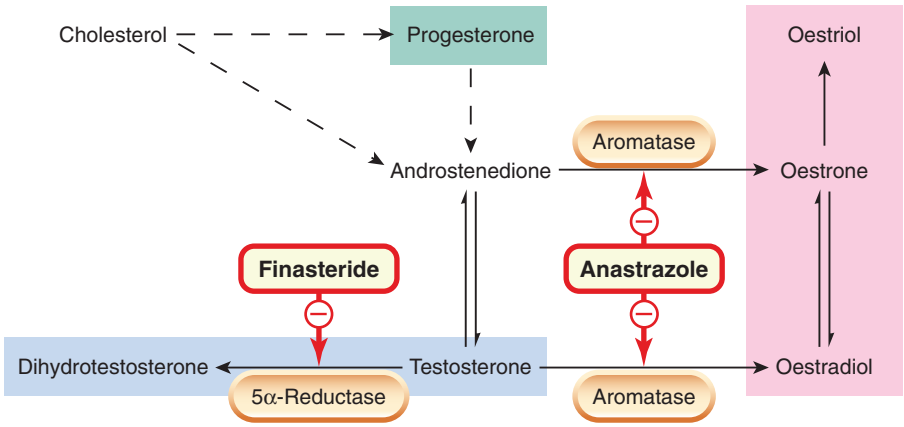

Fig. 34.3 The biosynthetic pathway for the androgens and oestrogens, with sites of drug action. (See also Fig. 32.5.) Finasteride is used in benign prostatic hyperplasia, and anastrazole to treat breast cancer in postmenopausal women.

Hormonal control of the female reproductive system

- The menstrual cycle starts with menstruation.
- Gonadotrophin-releasing hormone, released from the hypothalamus, acts on the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinising hormone (LH).
- FSH and LH stimulate follicle development in the ovary. FSH is the main hormone stimulating oestrogen release. LH stimulates ovulation at mid-cycle and is the main hormone controlling subsequent progesterone secretion from the corpus luteum.
- Oestrogen controls the proliferative phase of the endometrium and has negative feedback effects on the anterior pituitary. Progesterone controls the later secretory phase, and has negative feedback effects on both the hypothalamus and anterior pituitary.
- If a fertilised ovum is implanted, the corpus luteum continues to secrete progesterone.
- After implantation, human chorionic gonadotrophin from the chorion becomes important, and later in pregnancy progesterone and other hormones are secreted by the placenta.

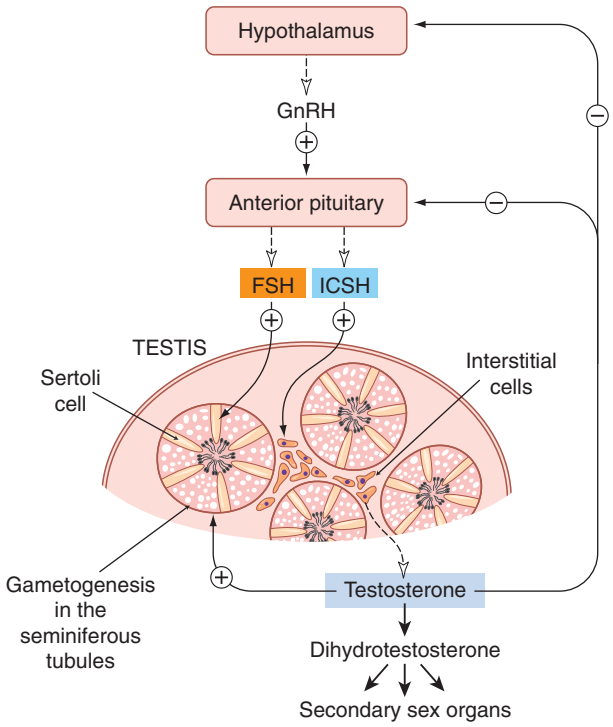

Fig. 34.4 Hormonal control of the male reproductive system. FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; ICSH, interstitial cell-stimulating hormone.

effects, causing development of the musculature and increased bone growth which results in the pubertal growth spurt, followed by closure of the epiphyses of the long bones.

Secretion of testosterone is mainly controlled by LH/ICSH, but FSH also plays a part, possibly by releasing a factor similar to GnRH from the Sertoli cells which are its primary target. The interstitial cells that synthesise testosterone also have receptors for prolactin, which may influence testosterone production by increasing the number of receptors for LH/ICSH.

BEHAVIOURAL EFFECTS OF SEX HORMONES

As well as controlling the menstrual cycle, sex steroids affect sexual behaviour. Two types of control are recognised: *organisational* and *activational*. The former refers to the fact that sexual differentiation of the brain can be permanently altered by the presence or absence of sex steroids at key stages in development.

In rats, administration of androgens to females within a few days of birth results in long-term virilisation of behaviour. Conversely, neonatal castration of male rats causes them to develop behaviourally as females. Brain development in the absence of sex steroids follows female lines, but is switched to the male pattern by exposure of the hypothalamus to androgen at a key stage of development. Similar but less complete behavioural virilisation of female offspring has been demonstrated following androgen

administration in non-human primates, and probably also occurs in humans if pregnant women are exposed to excessive androgen.

The activational effect of sex steroids refers to their ability to modify sexual behaviour after brain development is complete. In general, oestrogens and androgens increase sexual activity in the appropriate sex. Oxytocin, which is important during parturition (see below), also has roles in mating and parenting behaviours, its action in the central nervous system being regulated by oestrogen (see Ch. 32).

DRUGS AFFECTING REPRODUCTIVE FUNCTION

OESTROGENS

Oestrogens are synthesised by the ovary and placenta, and in small amounts by the testis and adrenal cortex. The starting substance for synthesis of oestrogen (and other steroids) is cholesterol. The immediate precursors to the oestrogens are androgenic substances—androstenedione or testosterone (Fig. 34.3). There are three main endogenous oestrogens in humans: *oestradiol*, *oestrone* and *oestriol* (Fig. 34.3). Oestradiol is the most potent and is the principal oestrogen secreted by the ovary. At the beginning of the menstrual cycle, the plasma concentration is 0.2 nmol/l, rising to ~2.2 nmol/l in mid-cycle.

Actions

Oestrogen acts in concert with progesterone, and induces synthesis of progesterone receptors in uterus, vagina, anterior pituitary and hypothalamus. Conversely, progesterone decreases oestrogen receptor expression in the reproductive tract. Prolactin (see Ch. 32) also influences oestrogen action by increasing the numbers of oestrogen receptors in the mammary gland, but has no effect on oestrogen receptor expression in the uterus.

Effects of exogenous oestrogen depend on the state of sexual maturity when the oestrogen is administered:

- In primary hypogonadism: oestrogen stimulates development of secondary sexual characteristics and accelerates growth.
- In adults with primary amenorrhoea: oestrogen, given cyclically with a progestogen, induces an artificial cycle.
- In sexually mature women: oestrogen (with a progestogen) is contraceptive.
- At or after the menopause: oestrogen replacement prevents menopausal symptoms and bone loss.

Oestrogens have several metabolic actions, including mineralocorticoid (retention of salt and water) and mild anabolic actions. They increase plasma concentrations of high-density lipoproteins, a potentially beneficial effect (Ch. 23) that may contribute to the relatively low risk of atheromatous disease in premenopausal women compared with men of the same age. However, oestrogens also increase the coagulability of blood, and increase the risk of thromboembolism. This effect is dose related.

Mechanism of action

As with other steroids, oestrogen binds to type 4 (i.e. nuclear) receptors (Ch. 3). There are at least two types of oestrogen receptor, termed ERα and ERβ. Binding is followed by interaction of the resultant complexes with nuclear sites and subsequent genomic effects. In addition to these 'classic' intracellular receptors, some oestrogen effects, in particular its rapid vascular actions, may be initiated by interaction with membrane receptors (e.g. Chen et al., 1999). Acute vasodilatation caused by 17-β-oestradiol is mediated by nitric oxide, and a plant-derived (phyto-) oestrogen called **genistein** (which is selective for ERβ, as well as having quite distinct effects from inhibition of protein kinase C) is as potent as 17-β-oestradiol in this regard. Oestrogen receptor modulators (receptor-selective oestrogen agonists or antagonists) are mentioned briefly below.

Preparations

Many preparations (oral, transdermal, intramuscular, implantable and topical) of oestrogens are available for a wide range of indications. These preparations include natural (e.g. **estradiol**, **estriol**) and synthetic (e.g. **mestranol**, **ethinylestradiol**, **diethylstilbestrol**) oestrogens. Oestrogens are presented either as single agents or combined with progestogen.

Pharmacokinetic aspects

Natural as well as synthetic oestrogens are well absorbed in the gastrointestinal tract, but after absorption the natural oestrogens are rapidly metabolised in the liver, whereas synthetic oestrogens are degraded less rapidly. There is a variable amount of enterohepatic cycling, which forms the basis for drug interaction, because broad-spectrum antibiotic use alters bowel flora and can thereby render oral contraception ineffective (Ch. 56). Most oestrogens are readily absorbed from skin and mucous membranes. They may be given as intravaginal creams or pessaries for local effect. In the plasma, natural oestrogens are bound to albumin and to a sex steroid-binding globulin. Natural oestrogens are excreted in the urine as glucuronides and sulfates.

Unwanted effects

Unwanted effects of oestrogens include tenderness in the breasts, nausea, vomiting, anorexia, retention of salt and water with resultant oedema, and increased risk of thromboembolism. More details of the unwanted effects of oral contraceptives are given below.

Used intermittently for postmenopausal replacement therapy, oestrogens cause menstruation-like bleeding. Oestrogen causes endometrial hyperplasia unless given cyclically with a progestogen. When administered to males, oestrogens result in feminisation.

Oestrogen administration to pregnant women can cause genital abnormalities in their offspring. Carcinoma of the vagina was more common in young women whose mothers were given diethylstilbestrol in early pregnancy in a misguided attempt to prevent miscarriage (see Ch. 57).

The clinical uses of oestrogens and antioestrogens are summarised in the box. In addition, see the section below on postmenopausal hormone replacement therapy (HRT).

OESTROGEN RECEPTOR MODULATOR

Raloxifene, a 'selective oestrogen receptor modulator' (SERM), has antioestrogenic effects on breast and uterus but oestrogenic effects on bone, lipid metabolism and blood coagulation. It is used for prevention and treatment of postmenopausal osteoporosis (Ch. 35) and also reduces the incidence of oestrogen receptor-positive breast cancer to an extent similar to **tamoxifen** while causing fewer

adverse events (Barret-Connor et al., 2006; Vogel et al., 2006). The US Food and Drug Administration has supported its use to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer. Unlike oestrogen, it does not prevent menopausal flushes.

Tamoxifen has antioestrogenic action on mammary tissue but oestrogenic actions on plasma lipids, endometrium and bone. It produces mild oestrogen-like adverse effects consistent with partial agonist activity. The tamoxifen–oestrogen receptor complex does not readily dissociate, so there is interference with the recycling of receptors.

Tamoxifen upregulates transforming growth factor-β, a cytokine that retards the progression of malignancy, and which also has a role in controlling the balance between bone-producing osteoblasts and bone-resorbing osteoclasts (Ch. 35).

Tamoxifen is discussed further in Chapter 55.

ANTIOESTROGENS

Antioestrogens compete with natural oestrogens for receptors in target organs; in addition to SERMs (raloxifene, tamoxifen) which are partial agonists in some tissues and antagonists in others, there are drugs that are pure oestrogen receptor antagonists.

Clomiphene inhibits oestrogen binding in the anterior pituitary, so preventing the normal modulation by negative feedback and causing increased secretion of GnRH and gonadotrophins. This results in a marked stimulation and enlargement of the ovaries and increased oestrogen secretion. The main effect of its antioestrogen action in the pituitary is to induce ovulation. It is used in treating infertility caused by lack of ovulation. Twins are common, but multiple pregnancy is unusual.

See the box on oestrogens and antioestrogens for a summary of clinical uses.

PROGESTOGENS

The natural progestational hormone (progestogen) is progesterone (see Figs 34.2 and 34.3). This is secreted by the corpus luteum in the second part of the menstrual cycle, and by the placenta during pregnancy. Small amounts are also secreted by the testis and adrenal cortex.

Progestogens act, as do other steroid hormones, on nuclear receptors. The density of progesterone receptors is controlled by oestrogens (see above).

Preparations

There are two main groups of progestogens:

1. The naturally occurring hormone and its derivatives (e.g. **hydroxyprogesterone**, **medroxyprogesterone**, **dydrogesterone**). Progesterone itself is virtually inactive orally, because after absorption it is metabolised in the liver, and hepatic extraction is nearly complete. Other preparations are available for oral administration, intramuscular injection or administration via the vagina or rectum.
2. Testosterone derivatives (e.g. **norethisterone**, **norgestrel** and **ethynodiol**) can be given orally. The first two have some androgenic activity and are metabolised to give oestrogenic products. Newer progestogens used in contraception include **desogestrel** and **gestodene**; they may have fewer adverse effects on lipids than ethynodiol and may be considered for women who experience side effects such as acne, depression or breakthrough bleeding with the older drugs. However, these newer drugs have been associated with higher risks of venous thromboembolic disease (see below).

Actions

The pharmacological actions of the progestogens are in essence the same as the physiological actions of progesterone described above. Specific effects relevant to contraception are detailed below.

Oestrogens and antioestrogens

- The endogenous oestrogens are oestradiol (the most potent), oestrone and oestriol; there are numerous exogenous synthetic forms (e.g. ethinylestradiol).
- Mechanism of action involves interaction with nuclear receptors (termed ERα or ERβ) in target tissues, resulting in modification of gene transcription.
- Their pharmacological effects depend on the sexual maturity of the recipient:
  - before puberty, they stimulate development of secondary sexual characteristics
  - given cyclically in the female adult, they induce an artificial menstrual cycle and are used for contraception
  - given at or after the menopause, they prevent menopausal symptoms and protect against osteoporosis, but increase thromboembolism.
- Antioestrogens are competitive antagonists or partial agonists. **Tamoxifen** is used in oestrogen-dependent breast cancer. **Clomiphene** induces ovulation by inhibiting the negative feedback effects on the hypothalamus and anterior pituitary.
- Selective drugs that are oestrogen agonists in some tissues but antagonists in others are being developed. **Raloxifene** (one such drug) is used to treat and prevent osteoporosis.

Clinical uses of oestrogens and antioestrogens

Oestrogens

- Replacement therapy:
  - primary ovarian failure (e.g. Turner's syndrome)
  - secondary ovarian failure (menopause) for flushing, vaginal dryness and to preserve bone mass.
- Contraception.
- Prostate and breast cancer (these uses have largely been superseded by other hormonal manipulations; see Ch. 55).

Antioestrogens

- To treat oestrogen-sensitive breast cancer (**tamoxifen**).
- To induce ovulation (**clomiphene**) in treating infertility.

Progestogens and antiprogestogens

- The endogenous hormone is progesterone. Examples of synthetic drugs are the progesterone derivative **medroxyprogesterone** and the testosterone derivative **norethisterone**.
- Mechanism of action involves intracellular receptor/altered gene expression, as for other steroid hormones. Oestrogen stimulates synthesis of progesterone receptors, whereas progesterone inhibits synthesis of oestrogen receptors.
- Main therapeutic uses are in oral contraception and oestrogen replacement regimens, and to treat endometriosis.
- The antiprogestogen **mifepristone**, in combination with prostaglandin analogues, is an effective medical alternative to surgical termination of early pregnancy.

Pharmacokinetic aspects

Injected progesterone is bound to albumin, not to the sex steroid-binding globulin. Some is stored in adipose tissue. It is metabolised in the liver, and the products, pregnanolone and pregnanediol, are conjugated with glucuronic acid and excreted in the urine.

Unwanted effects

Unwanted effects of progestogens include weak androgenic actions. Other unwanted effects include acne, fluid retention, weight change, depression, change in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles and breakthrough bleeding. There is an increased incidence of thromboembolism.

Clinical uses of progestogens are summarised in the box.

Clinical uses of progestogens and antiprogestogens

Progestogens

- Contraception:
  - with oestrogen in *combined oral contraceptive pill*
  - as *progesterone-only contraceptive pill*
  - as *injectable* or *implantable* progesterone-only contraception
  - as part of an *intrauterine* contraceptive system.
- Combined with oestrogen for *oestrogen replacement therapy* in women with an intact uterus, to prevent endometrial hyperplasia and carcinoma.
- For *endometriosis*.
- In *endometrial carcinoma*; use in breast and renal cancer has declined.
- Poorly validated uses have included various menstrual disorders.

Antiprogestogens

- Medical termination of pregnancy: **mifepristone** (partial agonist) combined with a prostaglandin (e.g. **gemeprost**).

ANTIPROGESTOGENS

Mifepristone is a partial agonist at progesterone receptors. It sensitises the uterus to the action of prostaglandins. It is given orally and has a plasma half-life of 21 h. Mifepristone is used, in combination with a prostaglandin (e.g. **gemeprost**; see below), as a medical alternative to surgical termination of pregnancy (see clinical box).

POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY

At the menopause, whether natural or surgically induced, ovarian function decreases and oestrogen levels fall. There is a long history of disagreement regarding the pros and cons of hormone replacement therapy (HRT) in this context, with the prevailing wisdom undergoing several revisions over the years (see Davis et al., 2005). HRT normally involves the cyclic or continuous administration of low doses of one or more oestrogens, with or without a progestogen. Short-term HRT has some clear-cut benefits:

- improvement of symptoms caused by reduced oestrogen, for example hot flushes and vaginal dryness
- prevention and treatment of osteoporosis, but other drugs are usually preferable for this (Ch. 35).

Oestrogen replacement does not reduce the risk of coronary heart disease, despite earlier hopes, nor is there evidence that it reduces age-related decline in cognitive function. Drawbacks include:

- cyclical withdrawal bleeding
- adverse effects related to progestogen (see above)
- increased risk of endometrial cancer if oestrogen is given unopposed by progestogen
- increased risk of breast cancer, related to the duration of HRT use and disappearing within 5 years of stopping
- increased risk of venous thromboembolism (risk approximately doubled in women using combined HRT for 5 years).

See Web links in the reference list for a useful table quantifying risks of cancer (breast, endometrium, ovary), venous thromboembolism, stroke and coronary artery disease in relation to age and duration of HRT use.

Oestrogens used in HRT can be given orally (conjugated estrogens, estradiol, estriol), vaginally (estriol), by transdermal patch (estradiol) or by subcutaneous implant (estradiol). **Tibolone** is marketed for the short-term treatment of symptoms of oestrogen deficiency. It has oestrogenic, progestogenic and weak androgenic activity, and can be used continuously without cyclical progesterone (avoiding the inconvenience of withdrawal bleeding).

ANDROGENS

Testosterone is the main natural androgen. It is synthesised mainly by the interstitial cells of the testis, and in smaller amounts by the ovaries and adrenal cortex. Adrenal androgen production is controlled by adrenocorticotrophic hormone (ACTH, corticotrophin). As for other steroid hormones, cholesterol is the starting substance.

Dehydroepiandrosterone and androstenedione are important intermediates. They are released from the gonads and the adrenal cortex, and converted to testosterone in the liver (see Fig. 34.3).

Actions

In general, the effects of exogenous androgens are the same as those of testosterone, and depend on the age and sex of the recipient. If given to prepubertal boys, the individuals concerned do not reach their full predicted height because of premature closure of the epiphyses of the long bones. In boys at the age of puberty, there is rapid development of secondary sexual characteristics (i.e. growth of facial, axillary and pubic hair, deepening of the voice), maturation of the reproductive organs and a marked increase in muscular strength. There is a growth spurt with an acceleration in the usual increase in height that occurs year on year in younger children, followed by cessation of linear growth. In adults, the anabolic effects can be accompanied by retention of salt and water. The skin thickens and may darken, and sebaceous glands become more active which can result in acne. Body weight and muscle mass increase, partly due to water retention. Androgens cause a feeling of well-being and an increase in physical vigour, and may increase libido. Whether they are responsible for sexual behaviour as such is controversial, as is their contribution to aggressive behaviour. Paradoxically, testosterone administration inhibits spermatogenesis, so reducing male fertility.

Administration of 'male' doses to women results in masculinisation, but lower doses (e.g. patches that release 300 μg of testosterone/day) restore plasma testosterone to normal female concentrations and improve sexual dysfunction in women following ovariectomy, without adverse effects (Shifren et al., 2000; Braunstein et al., 2005).

Mechanism of action

In most target cells, testosterone works through an active metabolite, dihydrotestosterone, to which it is converted locally by a 5α-reductase enzyme. In contrast, testosterone itself causes virilisation of the genital tract in the male embryo and regulates LH/ICSH production in anterior pituitary cells. Testosterone and dihydrotestosterone modify gene transcription by interacting with nuclear receptors.

Preparations

Testosterone itself can be given by subcutaneous implantation or by transdermal patches (male replacement dose approximately 2.5 mg/day. Various esters (e.g. enanthate and proprionate) are given by intramuscular depot injection. Testosterone undecanoate and mesterolone can be given orally.

Pharmacokinetic aspects

If given orally, testosterone is rapidly metabolised in the liver. Virtually all testosterone in the circulation is bound to plasma protein—mainly to the sex steroid-binding globulin. The elimination half-life of free testosterone is short (10–20 min). It is inactivated in the liver by conversion to androstenedione (see Fig. 34.3). This has weak androgenic activity in its own right and can be reconverted to testosterone, although approximately 90% of testosterone is eliminated as metabolites rather than the parent compound. Synthetic androgens are less rapidly metabolised, and some are excreted in the urine unchanged.

Androgens and the hormonal control of the male reproductive system

- Gonadotrophin-releasing hormone from the hypothalamus acts on the anterior pituitary to release both follicle-stimulating hormone, which stimulates gametogenesis, and luteinising hormone (also called interstitial cell-stimulating hormone), which stimulates androgen secretion.
- The endogenous hormone is testosterone; intramuscular depot injections of testosterone esters are used for replacement therapy.
- Mechanism of action is via intracellular receptors.
- Effects depend on age/sex, and include development of male secondary sexual characteristics in prepubertal boys and masculinisation in women.

Clinical uses of androgens and antiandrogens

- Androgens (**testosterone** preparations) as hormone replacement in:
  - male hypogonadism due to pituitary or testicular disease (e.g. 2.5 mg/day patches)
  - female hyposexuality following ovariectomy (e.g. 300 μg/day patches).
- Antiandrogens (e.g. **flutamide**, **cyproterone**) are used as part of the treatment of prostatic cancer.
- 5α-Reductase inhibitors (e.g. **finasteride**) are used in benign prostatic hypertrophy.

Unwanted effects

Unwanted effects of androgens include eventual decrease of gonadotrophin release, with resultant infertility, and salt and water retention leading to oedema. Adenocarcinoma of the liver has been reported. Androgens impair growth in children (via premature fusion of epiphyses), cause acne and lead to masculinisation in girls. Adverse effects of testosterone replacement and monitoring for these are reviewed by Rhoden & Morgentaler (2004).

The clinical uses of androgens are given in the clinical box.

ANABOLIC STEROIDS

Androgens can be modified chemically to alter the balance of anabolic and other effects. Such 'anabolic steroids' (e.g. **nandrolone**) increase protein synthesis and muscle development, but clinical use (e.g. in debilitating disease) has been disappointing. They are used in the therapy of aplastic anaemia and (notoriously) abused by some athletes (Ch. 58), as is testosterone itself. Unwanted effects are described above, under Androgens. In addition, cholestatic jaundice, liver tumours and increased risk of coronary heart disease are recognised adverse effects of high-dose anabolic steroids.

ANTIANDROGENS

Both oestrogens and progestogens have antiandrogen activity, oestrogens mainly by inhibiting gonadotrophin secretion and progestogens by competing at androgen receptors in target organs. **Cyproterone** is a derivative of progesterone and has weak progestational activity. It is a partial agonist at androgen receptors, competing with dihydrotestosterone for receptors in androgen-sensitive target tissues. Through its effect in the hypothalamus, it depresses the synthesis of gonadotrophins. It is used as an adjunct in the treatment of prostatic cancer during initiation of GnRH treatment (see below). It is also used in the therapy of precocious puberty in males, and of masculinisation and acne in women. It also has a central nervous system effect, decreasing libido, and has been used to treat hypersexuality in male sexual offenders.[2]

Flutamide is a non-steroidal antiandrogen used with GnRH in the treatment of prostate cancer.

Drugs can have antiandrogen action by inhibiting synthetic enzymes. **Finasteride** inhibits the enzyme (5α-reductase) that converts testosterone to dihydrotestosterone (Fig. 34.3). This which has greater affinity than testosterone for androgen receptors in the prostate gland. Finasteride is well absorbed after oral administration, has a half-life of about 7 h, and is excreted in the urine and faeces. It is used to treat benign prostatic hyperplasia, although α_1-adrenoceptor antagonists, for example **terazosin** or **tamsulosin** (Ch. 14), are more effective (working by the entirely different mechanism of relaxing smooth muscle in the capsule of the prostate gland and opposing α_1-adrenoceptor-mediated prostatic growth). Surgery is the preferred option (especially by surgeons).

GONADOTROPHIN-RELEASING HORMONE: AGONISTS AND ANTAGONISTS

Gonadotrophin-releasing hormone is a decapeptide that controls the secretion of FSH and LH by the anterior pituitary. Secretion of GnRH is controlled by neural input from other parts of the brain, and through negative feedback by the sex steroids (Figs 34.1 and 34.5). Exogenous androgens, oestrogens and progestogens all inhibit GnRH secretion, but only progestogens exert this effect at doses that do not have marked hormonal actions on peripheral tissues, presumably because progesterone receptors in the reproductive tract are sparse unless they have been induced by previous exposure to oestrogen. **Danazol** (see below) is a synthetic steroid that inhibits release of GnRH and, consequently, of gonadotrophins (FSH and LH). **Clomiphene** is an oestrogen antagonist that stimulates gonadotrophin release by inhibiting the negative feedback effects of endogenous oestrogen; it is used to treat infertility (see above and Fig. 34.5).

Synthetic GnRH is termed **gonadorelin**. Numerous analogues of GnRH, both agonists and antagonists, have been synthesised. **Buserelin**, **leuprorelin**, **goserelin** and **nafarelin** are agonists, the last being 200 times more potent than endogenous GnRH.

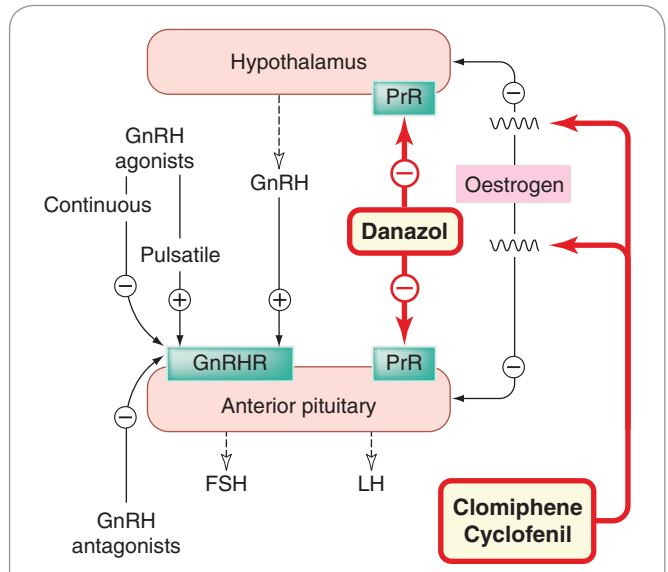

Fig. 34.5 Regulation of gonadotrophin (follicle-stimulating hormone, FSH; luteinising hormone, LH) release from the anterior pituitary. GnRHR, GnRH receptor; PrR, progestogen receptor.

Pharmacokinetics and clinical use

Gonadotrophin-releasing hormone agonists, given by subcutaneous infusion in pulses to mimic physiological secretion of GnRH, stimulate gonadotrophin release (Fig. 34.5) and induce ovulation. They are absorbed intact following nasal administration (Ch. 8). Continuous use, by nasal spray or as depot preparations, stimulates gonadotrophin release transiently, but then paradoxically inhibits gonadotrophin release (Fig. 34.5) because of downregulation (desensitisation) of GnRH receptors in the pituitary. GnRH analogues are given in this fashion to cause gonadal suppression in various sex hormone-dependent conditions, including prostate and breast cancers, endometriosis (endometrial tissue outside the uterine cavity) and large uterine fibroids. Continuous, non-pulsatile administration inhibits spermatogenesis and ovulation, raising the possibility (which is under investigation) that GnRH analogues could be useful as contraceptives. GnRH agonists are used by specialists in infertility treatment, not to stimulate ovulation (which is achieved using gonadotrophin preparations) but to suppress the pituitary before administration of FSH or HCG (see below). It was originally hoped that GnRH antagonists would be useful for contraception, but this has not been realised.

Unwanted effects of GnRH analogues

Unwanted effects of GnRH agonists in women, for example flushing, vaginal dryness and bone loss, result from hypo-oestrogenism. The initial stimulation of gonadotrophin secretion on starting treatment can cause transient worsening of pain from bone metastases in men with prostate cancer, so treatment is started only after the patient has received an androgen receptor antagonist such as **flutamide** (see above and Ch. 55).

[2]Very different doses are used for these different conditions, for example 2 mg/day for acne, 100 mg/day for hypersexuality and 300 mg/day for prostatic cancer.

DANAZOL

Actions and pharmacokinetics

Danazol inhibits gonadotrophin secretion (especially the mid-cycle surge), and consequently reduces oestrogen synthesis in the ovary (Fig. 34.5). In men, it reduces androgen synthesis and spermatogenesis. It has androgenic activity. It is orally active and metabolised in the liver.

Danazol is used in sex hormone-dependent conditions including endometriosis, breast dysplasia and gynaecomastia. An additional special use is to reduce attacks of swelling in hereditary angio-oedema (Ch. 27).

Unwanted effects are common, and include gastrointestinal disturbances, weight gain, fluid retention, dizziness, menopausal symptoms, muscle cramps and headache. Danazol is virilising in women.

GONADOTROPHINS AND ANALOGUES

Gonadotrophins (FSH, LH and HCG) are glycoproteins produced and secreted by the anterior pituitary (see Ch. 32) or chorion and placenta. Large amounts of gonadotrophins are present in the urine of women following the menopause, in whom oestrogen no longer exerts feedback inhibition on the pituitary, which consequently secretes large amounts of FSH and LH.[3] The chorion and placenta secrete HCG.

Preparations

Gonadotrophins are extracted from urine of pregnant (HCG) or postmenopausal women (human menopausal gonadotrophin, which contains a mixture of FSH and LH). Recombinant FSH (**follitropin**) and LH (**lutropin**) are also available.

Pharmacokinetics and clinical use

Gonadotrophin preparations are given by injection. They are used to treat infertility caused by lack of ovulation as a result of hypopituitarism, or following failure of treatment with **clomiphene**; they are also used by specialists to induce ovulation to enable eggs to be collected for in vitro fertilisation. For this use, gonadotrophin is usually administered after secretion of endogenous FSH and LH has been suppressed (see above). Gonadotrophins are also sometimes used in men with infertility caused by a low sperm count as a result of hypogonadotrophic hypogonadism (a disorder that is sometimes accompanied by lifelong anosmia, i.e. lack of sense of smell). (Gonadotrophins do not, of course, work for patients whose low sperm count is the result of primary testicular failure.) HCG has been used to stimulate testosterone synthesis in boys with delayed puberty, but testosterone is usually preferred.

Gonadotrophin-releasing hormone and gonadotrophins

- Gonadotrophin-releasing hormone is a decapeptide; **gonadorelin** is the synthetic form. **Nafarelin** is a potent analogue.
- Given in pulsatile fashion, they stimulate gonadotrophin release; given continuously, they inhibit it.
- The gonadotrophins, follicle-stimulating hormone and luteinising hormone, are glycoproteins.
- Preparations of gonadotrophins (e.g. chorionic gonadotrophin) are used to treat infertility caused by lack of ovulation.
- **Danazol** is a modified progestogen that inhibits gonadotrophin production by an action on the hypothalamus and anterior pituitary.

DRUGS USED FOR CONTRACEPTION

ORAL CONTRACEPTIVES

There are two main types of oral contraceptives:

1. Combinations of an oestrogen with a progestogen (the combined pill).
2. Progestogen alone (the progestogen-only pill).

THE COMBINED PILL

The combined oral contraceptive pill is extremely effective, at least in the absence of intercurrent illness and of treatment with potentially interacting drugs (see below). The oestrogen in most combined preparations (second-generation pills)[4] is **ethinylestradiol**, although a few preparations contain **mestranol** instead. The progestogen may be **norethisterone**, **levonorgestrel**, **ethynodiol**, or—in 'third-generation' pills—**desogestrel** or **gestodene**, which are more potent, have less androgenic action and cause less change in lipoprotein metabolism, but which probably cause a greater risk of thromboembolism than do second-generation preparations. The oestrogen content is generally 20–50 μg of ethinylestradiol or its equivalent, and a preparation is chosen with the lowest oestrogen and progestogen content that is well tolerated and gives good cycle control in the individual woman. This combined pill is taken for 21 consecutive days followed by 7 pill-free days, which causes a withdrawal bleed. Normal cycles of menstruation usually commence fairly soon after discontinuing treatment, and permanent loss of fertility (which may be a result of early menopause rather than a long-term consequence of the contraceptive pill) is rare.

The mode of action is as follows:

- Oestrogen inhibits secretion of FSH via negative feedback on the anterior pituitary, and thus suppresses development of the ovarian follicle.
- Progestogen inhibits secretion of LH and thus prevents ovulation; it also makes the cervical mucus less suitable for the passage of sperm.
- Oestrogen and progestogen act in concert to alter the endometrium in such a way as to discourage implantation.

They may also interfere with the coordinated contractions of the cervix, uterus and fallopian tubes that facilitate fertilisation and implantation.

Hundreds of millions of women worldwide have used this method since the 1960s, and in general the combined

[3]This forms the basis for the standard blood test, estimation of plasma LH/FSH concentrations, to confirm whether a woman is postmenopausal.

[4]The first-generation pills, containing more than 50 μg of oestrogen, were shown in the 1970s to be associated with an increased risk of deep vein thrombosis and pulmonary embolism.

pill constitutes a safe and effective method of contraception. There are distinct health benefits from taking the pill (see below), and serious adverse effects are rare. However, minor unwanted effects constitute drawbacks to its use, and several important questions need to be considered.

Common adverse effects

The common adverse effects are:

- weight gain, owing to fluid retention or an anabolic effect, or both
- mild nausea, flushing, dizziness, depression or irritability
- skin changes (e.g. acne and/or an increase in pigmentation)
- amenorrhoea of variable duration on cessation of taking the pill.

Questions that need to be considered

Is there an increased risk of cardiovascular disease (venous thromboembolism, myocardial infarction, stroke)? With second-generation pills (oestrogen content less than 50 µg), the risk of thromboembolism is small (incidence approximately 15 per 100 000 users per year, compared with 5 per 100 000 non-pregnant non-users per year or 60 episodes of thromboembolism per 100 000 pregnancies). The risk is greatest in subgroups with additional factors, such as smoking (which increases risk substantially) and long-continued use of the pill, especially in women over 35 years of age. For preparations containing the third-generation progestogens **desogestrel** or **gestodene**, the incidence of thromboembolic disease is approximately 25 per 100 000 users per year, which is still a small absolute risk compared with the risk of thromboemolism in an unwanted pregnancy. In general, provided risk factors, e.g. smoking, hypertension and obesity, have been identified, combined oral contraceptives are safe for most women for most of their reproductive lives.

Is cancer risk affected? Ovarian and endometrial cancer risk is *reduced*.

Is blood pressure increased? A marked increase in arterial blood pressure occurs in a small percentage of women shortly after starting the combined oral contraceptive pill. This is associated with increased circulating angiotensinogen, and disappears when treatment is stopped. Blood pressure is therefore monitored carefully when oral contraceptive treatment is started, and an alternative contraceptive substituted if necessary.

Beneficial effects

The combined pill markedly decreases menstrual symptoms such as irregular periods and intermenstrual bleeding. Iron deficiency anaemia and premenstrual tension are reduced, as are benign breast disease, uterine fibroids and functional cysts of the ovaries. Unwanted pregnancy, carrying a maternal mortality ranging from 1 in 10 000 in developed countries to 1 in 150 in Africa, is avoided.

THE PROGESTOGEN-ONLY PILL

The drugs used in progestogen-only pills include **norethisterone**, **levonorgestrel** or **ethynodiol**. The pill is taken daily without interruption. The mode of action is primarily on the cervical mucus, which is made inhospitable to sperm. The progestogen probably also hinders implantation through its effect on the endometrium and on the motility and secretions of the fallopian tubes (see above).

Potential beneficial and unwanted effects

Progestogen-only contraceptives offer a suitable alternative to the combined pill for some women in whom oestrogen is contraindicated, and are suitable for women whose blood pressure increases unacceptably during treatment with oestrogen. However, their contraceptive effect is less reliable than that of the combination pill, and missing a dose may result in conception. Disturbances of menstruation (especially irregular bleeding) are common. Only a small proportion of women use this form of contraception, so long-term safety data are less reliable than for the combined pill.

Pharmacokinetics of oral contraceptives: drug interactions

Combined and progestogen-only oral contraceptives are metabolised by hepatic cytochrome P450 enzymes. Because the minimum effective dose of oestrogen is used (in order to avoid excess risk of thromboembolism), any increase in its clearance may result in contraceptive failure, and indeed enzyme-inducing drugs can have this effect not only for combined but also for progesterone-only pills. Such drugs include (*par excellence*) **rifampicin** and **rifabutin**, as well as **carbamazepine**, **phenytoin** and others. Enterohepatic recycling of oestrogen is mentioned above. Broad-spectrum antibiotics such as **amoxicillin** can disturb this by altering the intestinal flora, and cause failure of the combined pill. This does not occur with progestogen-only pills.

Oral contraceptives

The combined pill

- The combined pill contains an oestrogen and a progestogen. It is taken for 21 consecutive days out of 28.
- Mode of action: the oestrogen inhibits follicle-stimulating hormone release and therefore follicle development; the progestogen inhibits luteinising hormone release and therefore ovulation, and makes cervical mucus inhospitable for sperm; together, they render the endometrium unsuitable for implantation.
- Drawbacks: weight gain, nausea, mood changes and skin pigmentation can occur.
- Serious unwanted effects are rare. A small proportion of women develop reversible hypertension; there is evidence both for and against an increased risk of breast cancer. There is a small increased risk of thromboembolism with third-generation pills.
- There are several beneficial effects, not least the avoidance of unwanted pregnancy, which itself carries risks to health.

The progestogen-only pill

- The progestogen-only pill is taken continuously. It differs from the combined pill in that the contraceptive effect is less reliable and is mainly a result of the alteration of cervical mucus. Irregular bleeding is common.

OTHER DRUG REGIMENS USED FOR CONTRACEPTION

POSTCOITAL (EMERGENCY) CONTRACEPTION

Oral administration of **levonorgestrel**, alone or combined with oestrogen, is effective if taken within 72 h of unprotected intercourse and repeated 12 h later. Nausea and vomiting are common (and the pills may then be lost: replacement tablets can be taken with an antiemetic such as **domperidone**). Insertion of an intrauterine device is more effective than hormonal methods, and works up to 5 days after intercourse.

LONG-ACTING PROGESTOGEN-ONLY CONTRACEPTION

Medroxyprogesterone can be given intramuscularly as a contraceptive. This is effective and safe. However, menstrual irregularities are common, and infertility may persist for many months after cessation of treatment.

Levonorgestrel implanted subcutaneously in non-biodegradable capsules is used by approximately 3 million women worldwide. This route of administration avoids first-pass metabolism. The capsules release their progestogen content slowly over 5 years. Irregular bleeding and headache are common.

A levonorgestrel-impregnated intrauterine device has contraceptive action for 35 years.

THE UTERUS

The physiological and pharmacological responses of the uterus vary at different stages of the menstrual cycle and during pregnancy.

THE MOTILITY OF THE UTERUS

Uterine muscle contracts rhythmically both in vitro and in vivo, contractions originating in the muscle itself. Myometrial cells in the fundus act as pacemakers and give rise to conducted action potentials. The electrophysiological activity of these pacemaker cells is regulated by the sex hormones.

The non-pregnant human uterus contracts spontaneously but weakly during the first part of the cycle, and more strongly during the luteal phase and during menstruation. Uterine movements are depressed in early pregnancy because oestrogen, potentiated by progesterone, hyperpolarises myometrial cells. This suppresses spontaneous contractions. Towards the end of gestation, however, contractions recommence; these increase in force and frequency, and become fully coordinated during parturition. The nerve supply to the uterus includes both excitatory and inhibitory sympathetic components: adrenaline, acting on β_2 adrenoceptors, inhibits uterine contraction, whereas noradrenaline, acting on α-adrenoceptors, stimulates contraction.

DRUGS THAT STIMULATE THE UTERUS

Drugs that stimulate the pregnant uterus and are important in obstetrics include **oxytocin**, **ergometrine** and *prostaglandins*.

OXYTOCIN

As explained in Chapter 32, the neurohypophyseal hormone oxytocin (an octapeptide) regulates myometrial activity. Oxytocin release is stimulated by cervical dilatation, and by suckling, but its role in parturition is incompletely understood.

Oxytocin contracts the uterus. Oestrogen induces oxytocin receptor synthesis and, consequently, the uterus at term is highly sensitive to this hormone. Given by slow intravenous infusion to induce labour, oxytocin causes regular coordinated contractions that travel from fundus to cervix. Both amplitude and frequency of these contractions are related to dose, the uterus relaxing completely between contractions during low-dose infusion. Larger doses further increase the frequency of the contractions, and there is incomplete relaxation between them. Still higher doses cause sustained contractions that interfere with blood flow through the placenta and cause fetal distress or death.

Oxytocin contracts myoepithelial cells in the mammary gland, which causes 'milk let-down'—the expression of milk from the alveoli and ducts. It also has a vasodilator action. A weak antidiuretic action can result in water retention, which can be problematic in patients with cardiac or renal disease, or with pre-eclampsia.[5] Oxytocin and oxytocin receptors are also found in the brain, particularly in the limbic system, and are believed to play a role in mating and parenting behaviour.

The clinical use of synthetic oxytocin is given in the box.

Oxytocin can be given by intravenous injection or intramuscularly, but is most often given by intravenous infusion. It is inactivated in the liver and kidneys, and by circulating placental oxytocinase.

Unwanted effects of oxytocin include dose-related hypotension, due to vasodilatation, with associated reflex tachycardia. Its antidiuretic hormone-like effect on water excretion by the kidney causes water retention and, unless water intake is curtailed, consequent hyponatraemia.

ERGOMETRINE

Ergot (*Claviceps purpurea*) is a fungus that grows on rye and contains a surprising variety of pharmacologically active substances (see Ch. 15). Ergot poisoning, which was once common, was often associated with abortion. In 1935, **ergometrine** was isolated and was recognised as the oxytocic principle in ergot.

Ergometrine contracts the human uterus. This action depends partly on the contractile state of the organ. On a contracted uterus (the normal state following delivery), ergometrine has relatively little effect. However, if the uterus is inappropriately relaxed, ergometrine initiates strong contraction, thus reducing bleeding from the placental bed (the raw surface from which the placenta has detached). Ergometrine also has a moderate vasoconstrictor action.

The mechanism of action of ergometrine on smooth muscle is not understood. It is possible that it acts partly on α-adrenoceptors, like the related alkaloid ergotamine (see Ch. 14), and partly on 5-hydroxytryptamine receptors.

[5]Eclampsia is a pathological condition (involving, among other things, high blood pressure, swelling and seizures) that occurs in pregnant women.

The clinical use of ergometrine is given in the box.

Ergometrine can be given orally, intramuscularly or intravenously. It has a very rapid onset of action and its effect lasts for 3–6 h.

Ergometrine can produce vomiting, probably by an effect on dopamine D_2 receptors in the chemoreceptor trigger zone (see Fig. 29.5). Vasoconstriction with an increase in blood pressure associated with nausea, blurred vision and headache can occur, as can vasospasm of the coronary arteries, resulting in angina.

PROSTAGLANDINS

Prostaglandins are discussed in detail in Chapter 17. The endometrium and myometrium have substantial prostaglandin-synthesising capacity, particularly in the second, proliferative phase of the menstrual cycle. Prostaglandin $(PG)F_{2\alpha}$ is generated in large amounts, and has been implicated in the ischaemic necrosis of the endometrium that precedes menstruation (although it has relatively little vasoconstrictor action on many human blood vessels, in contrast to some other mammalian species). Vasodilator prostaglandins, PGE_2 and PGI_2 (prostacyclin), are also generated by the uterus.

In addition to their vasoactive properties, the E and F prostaglandins contract the non-pregnant as well as the pregnant uterus. The sensitivity of uterine muscle to prostaglandins increases during gestation. Their role in parturition is not fully understood, but as cyclo-oxygenase inhibitors can delay labour (see below), they probably play some part in this.

Prostaglandins also play a part in two of the main disorders of menstruation: dysmenorrhoea (painful menstruation) and menorrhagia (excessive blood loss). Dysmenorrhoea is associated with increased production of PGE_2 and $PGF_{2\alpha}$; non-steroidal anti-inflammatory drugs, which inhibit prostaglandin biosynthesis (see Ch. 26), are used to treat dysmenorrhoea. Menorrhagia, in the absence of uterine pathology, may be caused by a combination of increased vasodilatation and reduced haemostasis. Increased generation by the uterus of PGI_2 (which inhibits platelet aggregation) could impair haemostasis as well as causing vasodilatation. Non-steroidal anti-inflammatory drugs (e.g. **mefenamic acid**) are used to treat menorrhagia as well as dysmenorrhoea.

Prostaglandin preparations

Prostaglandins of the E and F series promote coordinated contractions of the body of the pregnant uterus, while relaxing the cervix. E and F prostaglandins reliably cause abortion in early and middle pregnancy, unlike oxytocin which generally does not cause expulsion of the uterine contents at this stage. The prostaglandins used in obstetrics are **dinoprostone** (PGE_2), **carboprost** (15-methyl $PGF_{2\alpha}$) and **gemeprost** or **misoprostol** (PGE_1 analogues). Dinoprostone can be given intravaginally as a gel or as tablets, or by the extra-amniotic route as a solution. Carboprost is given by deep intramuscular injection. Gemeprost or misoprostol are given intravaginally.

Unwanted effects

Unwanted effects include uterine pain, nausea and vomiting, which occur in about 50% of patients when the drugs are used as abortifacients. Dinoprost may cause cardiovascular collapse if it escapes into the circulation after intra-amniotic injection. Phlebitis can occur at the site of intravenous infusion. When combined with mifepristone, a progestogen antagonist that sensitises the uterus to prostaglandins, lower doses of the prostaglandins (e.g. misoprostol) can be used to terminate pregnancy and side effects are reduced.

See the clinical box for the clinical uses of prostaglandins.

Clinical uses of drugs acting on the uterus

Myometrial stimulants (oxytocics)

- **Oxytocin** is used to *induce or augment labour* when the uterine muscle is not functioning adequately. It can also be used to treat *postpartum haemorrhage*.
- **Ergometrine** can be used to treat *postpartum haemorrhage*. **Carboprost** can be used if patients do not respond to ergometrine.
- A preparation containing both oxytocin and ergometrine is used for the management of the third stage of labour; the two agents together can also be used, prior to surgery, to control bleeding due to incomplete abortion.
- **Dinoprostone** given by the extra-amniotic route is used for late (second trimester) *therapeutic abortion*; given as vaginal gel, it is used for cervical ripening and induction of labour.
- **Gemeprost**, given as vaginal pessary following **mifepristone**, is used as a medical alternative to surgical *termination of pregnancy* (up to 63 days of gestation).

Myometrial relaxants

- The β-adrenoceptor agonists (e.g. **ritodrine**) are used to delay *preterm labour*.
- **Atosiban** (oxytocin antagonist) also delays preterm labour.

DRUGS THAT INHIBIT UTERINE CONTRACTION

Selective β_2-adrenoceptor agonists, such as **ritodrine** or **salbutamol**, inhibit spontaneous or oxytocin-induced contractions of the pregnant uterus. These uterine relaxants are used in selected patients to prevent premature labour occurring between 22 and 33 weeks of gestation in otherwise uncomplicated pregnancies. They can delay delivery by 48 h, time that can be used to administer glucocorticoid therapy to the mother so as to mature the lungs of the baby and reduce neonatal respiratory distress. It has been difficult to demonstrate that any of the drugs used to delay labour improve the outcome for the baby. Risks to the mother, especially pulmonary oedema, increase after 48 h, and myometrial response is reduced, so prolonged treatment is avoided. Cyclo-oxygenase inhibitors (e.g. **indometacin**) inhibit labour, but their use could cause problems in the baby, including renal dysfunction and delayed closure of the ductus arteriosus, both of which are influenced by endogenous prostaglandins.

An oxytocin receptor antagonist, **atosiban**, provides an alternative to a β_2-adrenoceptor agonist. It is given as an intravenous bolus followed by an intravenous infusion for not more than 48 h. Adverse effects include vasodilatation, nausea, vomiting and hyperglycaemia.

Drugs acting on the uterus

- At parturition, **oxytocin** causes regular coordinated uterine contractions, each followed by relaxation; **ergometrine**, an ergot alkaloid, causes uterine contractions with an increase in basal tone. **Atosiban**, an antagonist of oxytocin, delays labour.
- Prostaglandin (PG) analogues, for example **dinoprostone** (PGE_2) and **dinoprost** ($PGF_{2\alpha}$), contract the pregnant uterus but relax the cervix. Cyclo-oxygenase inhibitors inhibit PG synthesis and delay labour. They also alleviate symptoms of dysmenorrhoea and menorrhagia.
- The β_2-adrenoceptor agonists (e.g. **ritodrine**) inhibit spontaneous and oxytocin-induced contractions of the pregnant uterus.

ERECTILE DYSFUNCTION

Erectile function depends on complex interactions between physiological and psychological factors. Erection is caused by vasorelaxation in the arteries and arterioles supplying the erectile tissue. This increases penile blood flow; the consequent increase in sinusoidal filling compresses the venules, occluding venous outflow and causing erection. During sexual intercourse, reflex contraction of the ischiocavernosus muscles compresses the base of the corpora cavernosa, and the intracavernosal pressure can reach several hundred millimetres of mercury during this phase of rigid erection. Innervation of the penis includes autonomic and somatic nerves. Nitric oxide is probably the main mediator of erection and is released both from nitrergic nerves and from endothelium (Ch. 20; Fig. 20.6).

Erectile function is adversely affected by several therapeutic drugs (including many antipsychotic, antidepressant and antihypertensive agents), and psychiatric and vascular disease (especially if this has caused endothelial dysfunction) can themselves cause erectile dysfunction, which is common in middle-aged and older men, even if they have no psychiatric or cardiovascular problems.[6] There are several organic causes, including hypogonadism (see above), hyperprolactinaemia (see Ch. 32), arterial disease and various causes of neuropathy (most commonly diabetes), but often no organic cause is identified.

Over the centuries, there has been a huge trade in parts of various creatures that have the misfortune to bear some fancied resemblance to human genitalia, in the pathetic belief that consuming these will restore virility or act as an aphrodisiac (i.e. a drug that stimulates libido). Alcohol (Ch. 48) 'provokes the desire but takes away the performance', and cannabis (Ch. 18) can also release inhibitions and probably does the same. **Yohimbine** (an α_2 adrenoceptor antagonist; Ch. 14) may have some positive effect in this regard, but trials have proved inconclusive. **Apomorphine** (a dopamine agonist; Ch. 38) causes erections in humans as well as in rodents when injected subcutaneously, but it is a powerful emetic, an effect that is usually regarded as socially unacceptable in this context. Despite this rather obvious disadvantage, a sublingual preparation is licensed for erectile dysfunction.[7] Nausea is said to subside with continued use—but really!

The generally negative picture picked up somewhat when it was found that injecting vasodilator drugs directly into the corpora cavernosa causes penile erection. **Papaverine** (Ch. 22), if necessary with the addition of **phentolamine**, was used in this way. The route of administration is not acceptable to most men, but diabetics in particular are often not needle-shy, and this approach was a real boon to many such patients. **PGE_1** (**alprostadil**) is often combined with other vasodilators when given intracavernosally. It can also be given transurethrally as an alternative (albeit still a somewhat unromantic one) to injection. Adverse effects of all these drugs include priapism, which is no joke. Treatment consists of aspiration of blood (using sterile technique) and, if necessary, cautious intracavernosal administration of a vasoconstrictor such as **phenylephrine**. Intracavernosal and transurethral preparations are still available, but orally active phosphodiesterase inhibitors are now generally the drugs of choice.

PHOSPHODIESTERASE TYPE V INHIBITORS

Sildenafil, the first selective phosphodiesterase type V inhibitor (see also Chs 20 and 22), was found accidentally to influence erectile function.[8] **Tadalafil** and **vardenafil** are also phosphodiesterase type V inhibitors licensed to treat erectile dysfunction. Tadalafil is longer acting than sildenafil. In contrast to intracavernosal vasodilators, phosphodiesterase type V inhibitors do not cause erection independent of sexual desire, but enhance the erectile response to sexual stimulation. They have transformed the treatment of erectile dysfunction.

Mechanism of action

Phosphodiesterase V is the isoform that inactivates cGMP. Nitrergic nerves release nitric oxide (or a related nitrosothiol) which diffuses into smooth muscle cells, where it activates guanylyl cyclase. The resulting increase in cytoplasmic cGMP mediates vasodilatation via activation of protein kinase G (Fig 4.10). Consequently, inhibition of phosphodiesterase V potentiates the effect on penile vascular smooth muscle of endothelium-derived nitric oxide and of nitrergic nerves that are activated by sexual stimulation (Fig. 34.6). Other vascular beds are also affected, suggesting other possible uses, notably in pulmonary hypertension (Ch. 22).

[6]In randomised controlled trials, an appreciable proportion of men who discontinued treatment because of erectile dysfunction had been receiving placebo.

[7]Ironically so, because apomorphine was used as 'aversion therapy' in a misguided attempt to 'cure' homosexuality by conditioning individuals to associate homoerotic stimuli with nausea and vomiting, during the not-so-very-far-off time when homosexuality was classified as a psychiatric disease ('only apomorphine cures'—William Burroughs, *Naked Lunch*. Grove Press, 1966).

[8]Sildenafil was originally intended to treat angina, but volunteers in early phase trials reported an effect on affairs of the heart in a quite different anatomical region from the precordium.

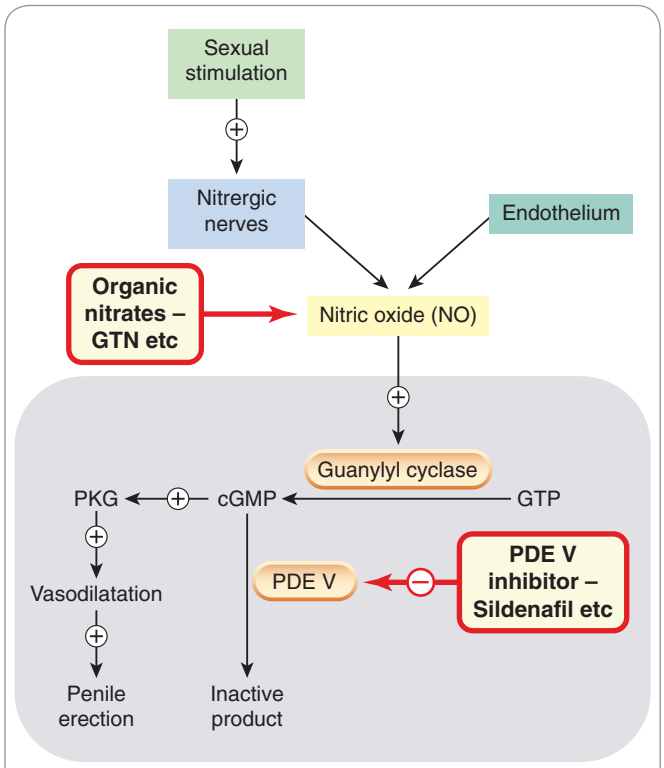

Fig. 34.6 Mechanism of phosphodiesterase V (PDE V) inhibitors on penile erection, and of the interaction of PDE V inhibitors with organic nitrates. The large grey rectangle denotes a vascular smooth muscle cell in the corpora cavernosa. Sexual stimulation releases nitric oxide (NO) from nitrergic nerves and this activates guanylyl cyclase, increasing cGMP production and hence activating protein kinase G (PKG), causing vasodilatation and penile erection. cGMP is inactivated by PDE V, so PDE V inhibitors (e.g. sildenafil) potentiate NO and promote penile erection. NO from organic nitrates such as glyceryl trinitrate (GTN) is also potentiated leading to generalised vasodilatation and hypotension.

Pharmacokinetic aspects and drug interactions

Peak plasma concentrations of sildenafil occur approximately 30–120 min after an oral dose and are delayed by eating, so it is taken an hour or more before sexual activity. It is given as a single dose as needed. It is metabolised by CYP3A4, which is induced by **carbamazepine**, **rifampicin** and **barbiturates**, and inhibited by **cimetidine**, macrolide antibiotics, antifungal imidazolines, some antiviral drugs (such as **ritonavir**) and also by grapefruit juice (Ch. 56). These drugs can potentially interact with sildenafil in consequence. Tadalafil has a longer half-life than sildenafil, so can be taken longer before sexual activity. A clinically important pharmacodynamic interaction of all phosphodiesterase V inhibitors occurs with all organic nitrates,[9] which work through increasing cGMP (Ch. 20) and are therefore markedly potentiated by sildenafil (Fig. 34.6). Consequently, concurrent nitrate use, including use of **nicorandil**, contraindicates the use of any phosphodiesterase type V inhibitor.

Unwanted effects

Many of the unwanted effects of phosphodiesterase type V inhibitors are caused by vasodilatation in other vascular beds; these effects include hypotension, flushing and headache. Visual disturbances have occasionally been reported and are of concern because sildenafil has some action on phosphodiesterase VI, which is present in the retina and important in vision. The manufacturers advise that sildenafil should not be used in patients with hereditary retinal degenerative diseases (such as retinitis pigmentosa) because of the theoretical risk posed by this. Vardenafil is more selective for the type V isozyme than is sildenafil (reviewed by Doggrell, 2005), but is also contraindicated in patients with hereditary retinal disorders.

[9]This is important not only for sufferers from angina who take nitrates such as glyceryl trinitrate or isosorbide mononitrate therapeutically or prophylactically and are at risk of hypotension because of coronary artery disease, but also asymptomatic individuals who take amyl nitrate recreationally ('poppers') because of its effect on pelvic musculature.

REFERENCES AND FURTHER READING

Sex hormones and their control

Barrett-Connor, E., Mosca, L., Collins, P., et al., 2006. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N. Eng. J. Med. 355, 125–137. (*Reduced breast cancer*)

Chen, Z., Yuhanna, I.S., Galcheva-Gargova, Z., et al., 1999. Estrogen receptor-alpha mediates the nongenomic activation of endothelial nitric oxide synthase by estrogen. J. Clin. Invest. 103, 401–406. (*Acute vasodilator action of oestrogen may involve membrane ER rather than the classic intracellular receptor pathway*)

Gruber, C.J., Tschugguel, W., Schneeberger, C., Huber, J.C., 2002. Production and actions of estrogens. N. Engl. J. Med. 346, 340–352. (*Review focusing on the new biochemical aspects of the action of oestrogen – including phyto-oestrogens and selective oestrogen receptor modulators – as well as physiological and clinical aspects*)

Huirne, J.A.F., Lambalk, C.B., 2001. Gonadotrophin-releasing hormone receptor antagonists. Lancet 358, 1793–1803. (*Review discussing their clinical potential*)

Olive, D.L., Pritts, E.A., 2001. Treatment of endometriosis. N. Engl. J. Med. 34, 266–275. (*Critical review of existing evidence – which is thin – forms the basis for sensible recommendations regarding treatment of pelvic pain or infertility from endometriosis using oral contraceptives and GnRH agonist therapy with oestrogen–progestin add-back*)

Rhoden, E.L., Morgentaler, A., 2004. Risks of testosterone-replacement therapy and recommendations for monitoring. N. Engl. J. Med. 350, 482–492. (*Review*)

Vogel, V., Constantino, J., Wickerman, L., et al., 2006. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes. JAMA 295, 2727–2741. (*Raloxifene had similar efficacy as tamoxifen with fewer thrombotic events*)

Contraceptives

Djerassi, C., 2001. This man's pill: reflections on the 50th birthday of the pill. Oxford University Press, New York. (*Scientific and autobiographical memoir by polymath steroid chemist who worked on 'the pill' at its inception under Syntex in Mexico, and has continued thinking about human reproduction in a broad biological and biosocial sense ever since*)

Postmenopausal aspects

Braunstein, G.D., Sundwall, D.A., Katz, M., et al., 2005. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch. Intern. Med. 165, 1582–1589. (*A 300 mg/day testosterone patch increased sexual desire and frequency of satisfying sexual activity and was well tolerated in women who developed hypoactive sexual desire disorder after surgical menopause*)

Davis, S.R., Dinatale, I., Rivera-Woll, L., Davison, S., 2005. Postmenopausal hormone therapy: from monkey glands to transdermal patches. J. Endocrinol. 185, 207–222. (*Reviews the history of knowledge of the menopause and the development of hormonal therapy for climacteric complaints, and summarises current evidence for specific benefits and risks of hormone treatment*)

Hulley, S., Grady, D., Bush, T., et al., 1998. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 280, 605–613. (*A total of 2763 postmenopausal women who had suffered a previous coronary event randomised to active or placebo and observed for a mean of 4.1 years. The incidence of fatal myocardial infarction was similar in the two groups, despite favourable changes in low- and high-density lipoproteins cholesterol in the HRT group. Venous thromboembolism was increased by a factor of 2.89 in the active group*)

Shifren, J.L., Braunstein, G.D., Simon, J.A., et al., 2000. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N. Engl. J. Med. 343, 682–688. (*Transdermal testosterone improves sexual function and psychological well-being in women who have undergone oophorectomy and hysterectomy*)

The uterus

Norwitz, E.R., Robinson, J.N., Challis, J.R., 1999. The control of labor. N. Engl. J. Med. 341, 660–666. (*Review*)

Thornton, S., Vatish, M., Slater, D., 2001. Oxytocin antagonists: clinical and scientific considerations. Exp. Physiol. 86, 297–302. (*Reviews rationale for uterine relaxants in preterm labour; evidence for administering atosiban; and the role of oxytocin, vasopressin and their receptors in the onset of labour*)

Erectile dysfunction

Andersson, K.-E., 2001. Pharmacology of penile erection. Pharmacol. Rev. 53, 417–450. (*Scholarly review covering central and peripheral regulation, and a very wide-ranging coverage of the pharmacology*)

Doggrell, S.A., 2005. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin. Pharmacother. 6, 75–84. (*Vardenafil is similarly effective to sildenafil. Its only advantage is that it does not inhibit phosphodiesterase VI to alter colour perception, a rare side effect that sometimes occurs with sildenafil. Tadalafil has a longer duration of action*)

Useful Web resource

http://www.mhra.gov.uk/mhra/drugsafetyupdate. (*A useful table quantifying risks of cancer [breast, endometrium, ovary], venous thromboembolism, stroke and coronary artery disease in relation to age and duration of HRT use*)

35 Bone metabolism

OVERVIEW

In this chapter, we consider first the cellular and biochemical processes involved in bone remodelling, and the various hormones and other mediators that regulate these processes. We then describe the drugs used to treat disorders of bone and finally deal with the new agents in the pipeline.

INTRODUCTION

The human skeleton undergoes a continuous process of remodelling throughout life—some bone being resorbed and new bone being laid down resulting in the complete skeleton being replaced every 10 years. With advancing age, there is an increasing possibility of structural deterioration and decreased bone mass (osteoporosis). This constitutes a major health problem throughout the world, and there are, in addition, various other conditions that can lead to pathological changes in bone that require therapy. In the past decade, there have been significant advances in the understanding of bone biology, which have already led to new drugs, progress that will no doubt continue.

BONE STRUCTURE AND COMPOSITION

The human skeleton consists of 80% cortical bone and 20% trabecular bone. Cortical bone is the dense, compact outer part, and trabecular bone the inner meshwork. The former predominates in the shafts of long bones, the latter in the vertebrae, the epiphyses of long bones and the iliac crest. Trabecular bone, having a large surface area, is metabolically more active and more affected by factors that lead to bone loss (see below).

The main minerals in bone are calcium and phosphates. More than 99% of the calcium in the body is in the skeleton, mostly as crystalline hydroxyapatite but some as non-crystalline phosphates and carbonates; together, these make up half the bone mass.

The main cells in bone homeostasis are *osteoblasts*, *osteoclasts* and *osteocytes*.

- Osteoblasts are bone-forming cells derived from precursor cells in the bone marrow and the periosteum: they secrete important components of the extracellular matrix—the *osteoid*, particularly the collagen. They also have a role in the activation of osteoclasts (see below).
- Osteoclasts are multinucleated bone-resorbing cells derived from precursor cells of the macrophage/monocyte lineage.
- Osteocytes are derived from the osteoblasts, which, during the formation of new bone, become embedded in the bony matrix and differentiate into osteocytes. These cells form a connected cellular network that, along with the nerve fibres in bone, has a role in the response to mechanical loading in that the cells can sense mechanical strain and cracking, and respond by triggering bone remodelling. To balance this effect they can secrete *sclerostin,* which reduces bone formation (Khosla et al., 2008).
- Other cells of importance are monocytes/macrophages, lymphocytes and vascular endothelial cells; these secrete cytokines and other mediators necessary for bone remodelling.

Osteoid is the organic matrix of bone and its principal component is collagen. But there are also other components such as *proteoglycans*, *osteocalcin* and various phosphoproteins, one of which, *osteonectin*, binds to both calcium and collagen and thus links these two major constituents of bone matrix.

Calcium phosphate crystals in the form of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] are deposited in the osteoid, converting it into hard bone matrix.

In addition to its structural function, bone plays a major role in overall calcium homeostasis in the body.

BONE REMODELLING

There has been substantial progress in our understanding of bone remodelling in recent years (see reviews by Boyce & Xing, 2008; Gallagher, 2008; Deal, 2009; and Wright et al., 2009.)

The process of remodelling involves the following:

- the activity of the two main cell types: osteoblasts and osteoclasts (Fig. 35.1)
- the actions of a variety of cytokines (Figs 35.1 and 35.2)
- the turnover of bone minerals—particularly calcium and phosphate
- the actions of several hormones: parathyroid hormone (PTH), the vitamin D family, oestrogens, growth hormone, steroids, calcitonin and various cytokines.

Diet, drugs and physical factors (exercise, loading) also affect remodelling. Bone loss—of 0.5–1% per year—starts in the 35–40 age group in both sexes. The rate accelerates by as much as 10-fold during the menopause in women or with castration in men, and then gradually settles at 1–3% per year. The loss during the menopause is due to increased osteoclast activity and affects mainly trabecular bone; the later loss in both sexes with increasing age is due to decreased osteoblast numbers and affects mainly cortical bone.

THE ACTION OF CELLS AND CYTOKINES

A cycle of remodelling starts with recruitment of the cells that give rise to osteoclast precursors and the subsequent differentiation of these to mature multinucleated

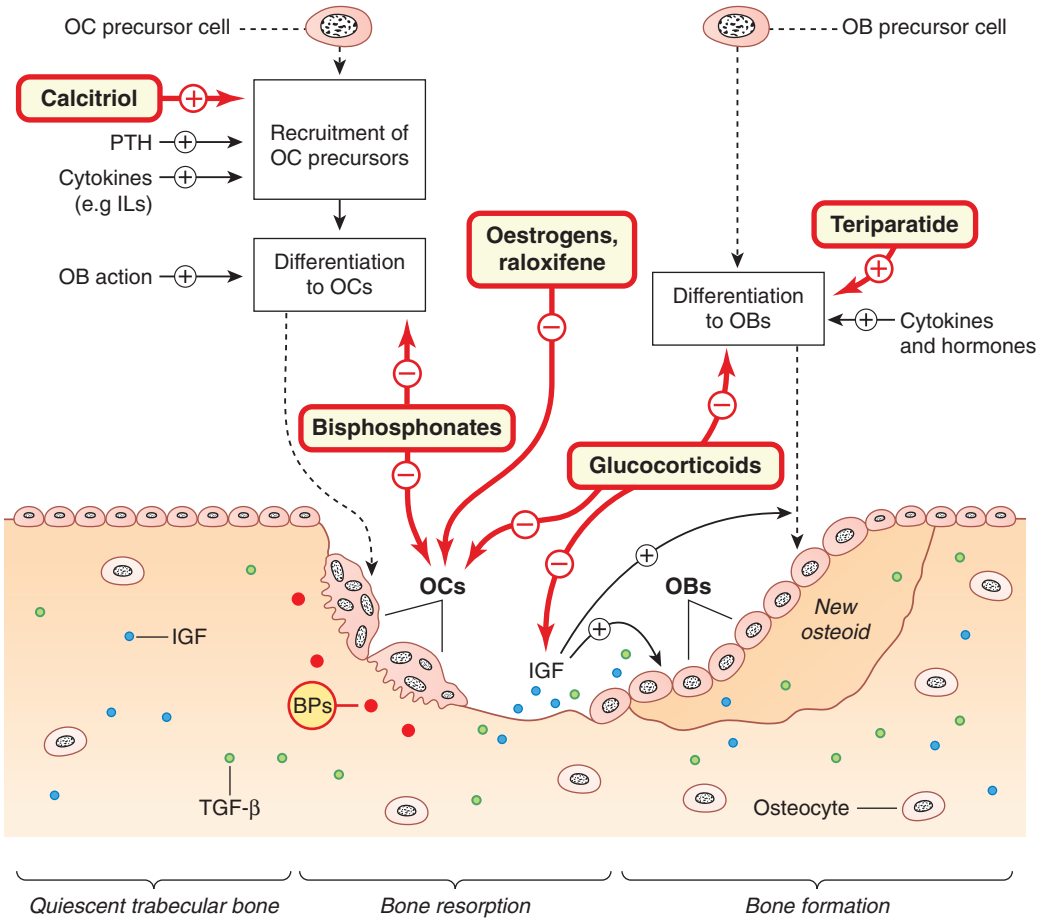

Fig. 35.1 **The bone-remodelling cycle and the action of hormones, cytokines and drugs.** ***Quiescent trabecular bone.*** Cytokines such as insulin-like growth factor (IGF) and transforming growth factor (TGF)-β, shown as dots, are embedded in the bone matrix. ***Bone resorption.*** Osteoclast (OC) precursor cells, recruited by cytokines and hormones, are activated by osteoblasts (OBs) to form mobile multinuclear OCs (see Fig. 35.2) that move along the bone surface, resorbing bone and releasing the embedded cytokines. ***Bone formation.*** The released cytokines recruit OBs, which lay down osteoid and embed cytokines IGF and TGF-β in it. Some OBs also become embedded, forming terminal osteocytes (now known not to be inert). The osteoid then becomes mineralised, and lining cells cover the area (not shown). Oestrogens cause apoptosis (programmed cell death) of OCs. Note that pharmacological concentrations of glucocorticoids have the effects specified above, but physiological concentrations are required for OB differentiation. BPs, embedded bisphosphonates—these are ingested by OCs when bone is resorbed (not shown); IL, interleukin; PTH, parathyroid hormone.

osteoclasts induced by cytokines (Fig. 35.1). The osteoclasts adhere to an area of trabecular bone, developing a ruffled border at the attachment site. They move along the bone, digging a pit by secreting hydrogen ions and proteolytic enzymes, mainly *cathepsin K*. This process gradually liberates cytokines such as insulin-like growth factor (IGF)-1 and transforming growth factor (TGF)-β, which have been embedded in the osteoid (Fig. 35.1); these in turn recruit and activate successive teams of osteoblasts that have been stimulated to develop from precursor cells and are awaiting the call to duty (see Fig. 35.1 and below). The osteoblasts invade the site, synthesising and secreting the organic matrix of bone, the osteoid, and secreting IGF-1 and TGF-β (which become embedded in the osteoid; see above). Some osteoblasts become embedded in the osteoid, forming terminal osteocytes; others interact with and activate osteoclast precursors—and we are back to the beginning of the cycle.

Cytokines involved in bone remodelling other than IGF-1 and TGF-β include other members of the TGF-β family, such as the *bone morphogenic proteins* (BMPs), a range of interleukins, various hormones and members of the tumour necrosis factor (TNF) family. A member of this last family—a ligand for a receptor on the osteoclast precursor cell—is of particular importance. The receptor is termed (wait for it—biological terminology has fallen over its own feet here) *RANK*, which stands for ***r**eceptor **a**ctivator of **n**uclear factor **k**appa B* (NFκB), NFκB being the principal transcription factor involved in osteoclast differentiation and activation. And the ligand is termed, unsurprisingly, RANK ligand (RANKL).

▼ The osteoblast synthesises and releases a molecule termed *osteoprotegerin* (OPG), identical with RANK, which functions as a decoy receptor. In a sibling-undermining process by the two cells (osteoblast and osteoclast precursor), OPG can bind to RANKL[1] (generated by the very cell that OPG itself is generated by) and inhibit RANKL's binding to the functional receptor, RANK, on the osteoclast precursor cell (Fig. 35.2). The ratio of RANKL to OPG is critical in the formation

[1]RANKL is also sometimes confusingly termed OPG ligand.

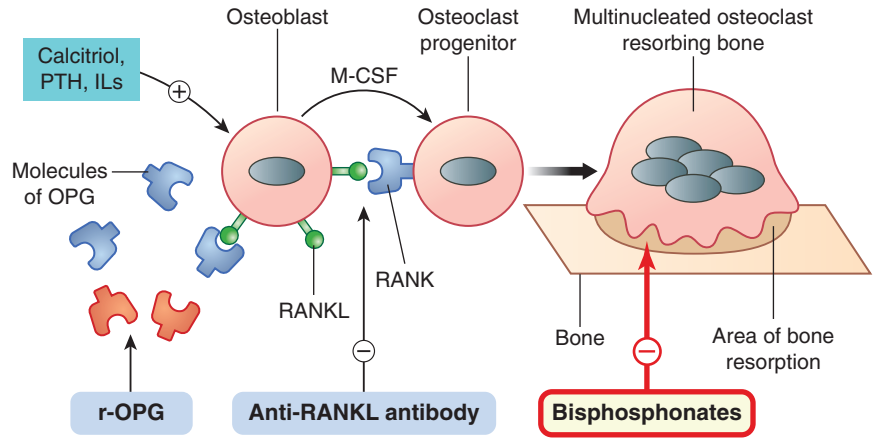

Fig. 35.2 Schematic diagram of the role of the osteoblast and cytokines in the differentiation and activation of the osteoclast and the action of drugs thereon. The osteoblast is stimulated by calcitriol, parathyroid hormone (PTH) and cytokines (not shown) to express a surface ligand, the RANK ligand (RANKL). RANKL expression is increased by various interleukins, PTH, tumour necrosis factor (TNF)-α and glucocorticoids. RANKL interacts with a receptor on the osteoclast—an osteoclast differentiation and activation receptor termed RANK (**r**eceptor **a**ctivator of **n**uclear factor **k**appa B). This, with cytokines (e.g. macrophage colony-stimulating factor, MCSF) released by the osteoblast, causes differentiation and activation of the osteoclast progenitors to form mature osteoclasts (not shown). Fusion of osteoclasts occurs to give giant multinucleated bone-resorbing cells, which are polarised with a ruffled border on the bone-resorbing side (shown). Bisphosphonates inhibit bone resorption by osteoclasts. Anti-RANKL antibodies (e.g. denosumab) bind RANKL and prevent the RANK–RANKL interaction. The osteoblast also releases 'decoy' molecules of osteoprotegerin (OPG), which can bind RANKL and prevent activation of the RANK receptor. Recombinant OPG (r-OPG)—which has this effect—is in clinical trial. Drugs used clinically are in red-bordered boxes, those in development in blue boxes.

and activity of osteoclasts and thus the optimal functioning of the RANK, RANKL, OPG system is fundamental to bone remodelling (reviewed by Boyce & Xing, 2008; Wright et al., 2009).

THE TURNOVER OF BONE MINERALS

The main bone minerals are calcium and phosphates.

CALCIUM METABOLISM

The daily turnover of bone minerals during remodelling involves about 700 mg of calcium. Calcium has numerous roles in physiological functioning. Intracellular Ca^{2+} is part of the signal transduction mechanism of many cells (see Ch. 4), so the concentration of Ca^{2+} in the extracellular fluid and the plasma, normally about 2.5 mmol/l, needs to be controlled with great precision. The plasma Ca^{2+} concentration is regulated by interactions between PTH and various forms of vitamin D (Figs 35.3 and 35.4); calcitonin also plays a part.

Calcium absorption in the intestine involves a Ca^{2+}-binding protein whose synthesis is regulated by calcitriol (see Fig. 35.3). It is probable that the overall calcium content of the body is regulated largely by this absorption mechanism, because urinary Ca^{2+} excretion normally remains more or less constant. However, with high blood Ca^{2+} concentrations urinary excretion increases, and with low blood concentrations urinary excretion can be reduced by PTH and calcitriol, both of which enhance Ca^{2+} reabsorption in the renal tubules (Fig. 35.3).

PHOSPHATE METABOLISM

Phosphates are important constituents of bone, and are also critically important in the structure and function of all the cells of the body. They are constituents of nucleic acids, provide energy in the form of ATP, and control—through phosphorylation—the actitivity of many functional proteins. They also have roles as intracellular buffers and in the excretion of hydrogen ions in the kidney.

Phosphate absorption is an energy-requiring process regulated by *calcitriol*. Phosphate deposition in bone, as hydroxyapatite, depends on the plasma concentration of PTH, which, with calcitriol, mobilises both Ca^{2+} and phosphate from the bone matrix. Phosphate is excreted by the kidney; here PTH inhibits reabsorption and thus increases excretion.

Bone remodelling

- Bone is continuously remodelled throughout life. The events of the remodelling cycle are as follows:
  - osteoclasts, having been activated by osteoblasts, resorb bone by digging pits in trabecular bone. Into these pits the bone-forming osteoblasts secrete osteoid (bone matrix), which consists mainly of collagen but also contains osteocalcin, osteonectin, phosphoproteins and the cytokines insulin growth factor (IGF) and transforming growth factor (TGF)-β
  - the osteoid is then mineralised, i.e. complex calcium phosphate crystals (hydroxyapatites) are deposited.
- Bone metabolism and mineralisation involve the action of parathyroid hormone, the vitamin D family, and various cytokines (e.g. IGF, the TGF-β family and interleukins). Declining physiological levels of oestrogens and therapeutic levels of glucocorticoids can result in bone resorption not balanced by bone formation—leading to osteoporosis.

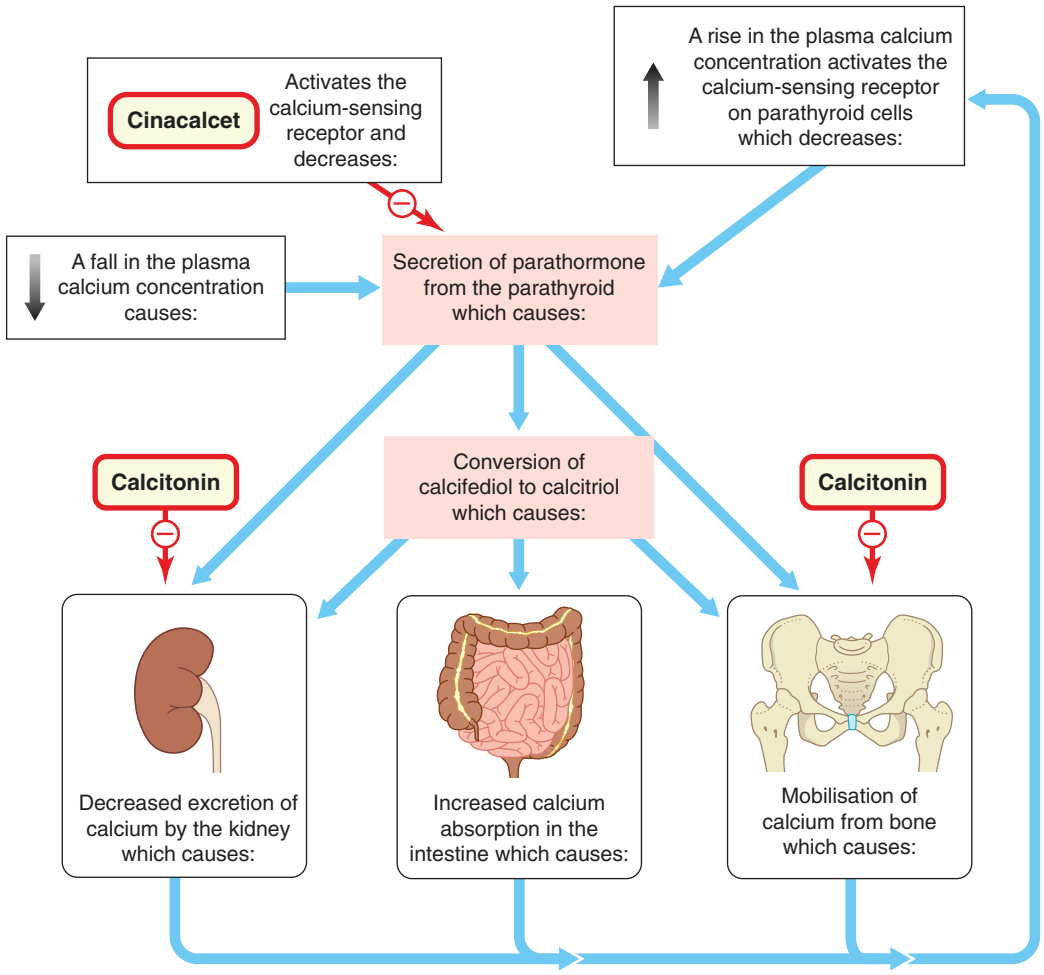

Fig. 35.3 The main factors involved in maintaining the concentration of Ca^{2+} in the plasma and the action of drugs. The calcium receptor on the parathyroid cell is a G-protein-coupled receptor. Calcifediol and calcitriol are metabolites of vitamin D_3 and constitute the 'hormones' 25-hydroxy-vitamin D_3 and 1,25-dihydroxy-vitamin D_3, respectively. Endogenous calcitonin, secreted by the thyroid, inhibits Ca^{2+} mobilisation from bone and decreases its resorption in the kidney, thus reducing blood Ca^{2+}. Calcitonin is also used therapeutically in osteoporosis.

HORMONES INVOLVED IN BONE METABOLISM AND REMODELLING

The main hormones involved in bone metabolism and remodelling are parathyroid hormone (PTH), members of the vitamin D family, oestrogens and calcitonin. Glucocorticoids and thyroid hormone also affect bone.

PARATHYROID HORMONE

Parathyroid hormone, which consists of a single-chain polypeptide of 84 amino acids, is an important physiological regulator of Ca^{2+} metabolism. It acts on PTH receptors in various tissues (bone, kidney, gastrointestinal tract) to maintain the plasma Ca^{2+} concentration. It mobilises Ca^{2+} from bone, promotes its reabsorption by the kidney and stimulates the synthesis of calcitriol, which in turn increases Ca^{2+} absorption from the intestine and synergises with PTH in mobilising bone Ca^{2+} (Figs 35.3 and 35.4). PTH promotes phosphate excretion, and thus its net effect is to increase the concentration of Ca^{2+} in the plasma and lower that of phosphate.

The mobilisation of Ca^{2+} from bone by PTH is mediated, at least in part, by stimulation of the recruitment and activation of osteoclasts. Pathological oversecretion of PTH (hyperparathyroidism) inhibits osteoblast activity (not shown in Fig. 35.1). But given therapeutically in a low intermittent dose, PTH and fragments of PTH paradoxically stimulate osteoblast activity and enhance bone formation.

Parathyroid hormone is synthesised in the cells of the parathyroid glands and stored in vesicles. The principal factor controlling secretion is the concentration of ionised calcium in the plasma, low plasma Ca^{2+} stimulating secretion, high plasma Ca^{2+} decreasing it by binding to and activating a Ca^{2+}-sensing G-protein-coupled surface receptor (see Ch. 3, Figure 35.3). (For reviews, see Stewart, 2004; Deal, 2009.)

VITAMIN D

Vitamin D (calciferol) consists of a group of lipophilic prehormones that are converted in the body into a number of biologically active metabolites that function as true

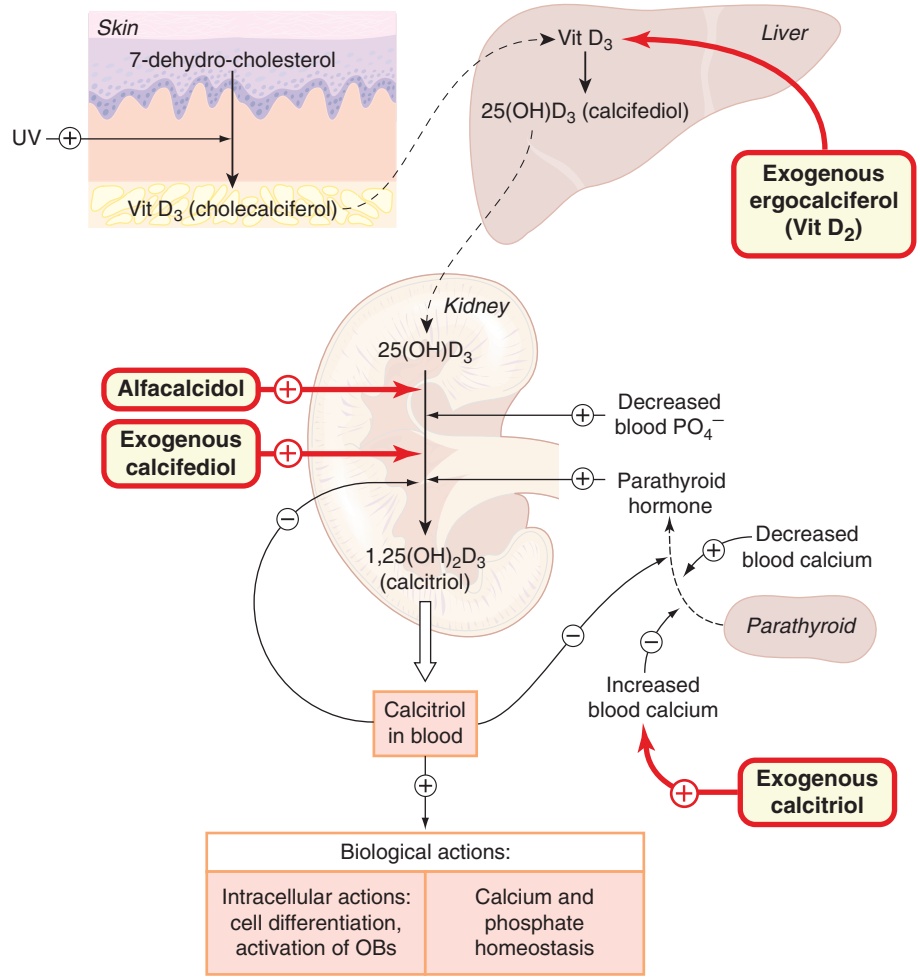

Fig. 35.4 Summary of the actions of the vitamin D endocrine system and the action of drugs. Exogenous ergocalciferol, vitamin (Vit) D_2 (formed in plants by ultraviolet, UV, light), is converted to the corresponding D_2 metabolites in liver and kidney, as is the D_2 analogue dihydrotachysterol (not shown). Alfacalcidol (1α-hydroxycholecalciferol) is 25-hydroxylated to calcitriol in the liver. OB, osteoblast.

hormones, circulating in the blood and regulating the activities of various cell types (see Reichel et al., 1989). Their main action, mediated by nuclear receptors of the steroid receptor superfamily (see Ch. 3), is the maintenance of plasma Ca^{2+} by increasing Ca^{2+} absorption in the intestine, mobilising Ca^{2+} from bone and decreasing its renal excretion (see Fig. 35.3). In humans, there are two sources of vitamin D:

1. Dietary *ergocalciferol* (D_2), derived from ergosterol in plants.
2. *Cholecalciferol* (D_3) generated in the skin from 7-dehydrocholesterol by the action of ultraviolet irradiation, the 7-dehydrocholesterol having been formed from cholesterol in the wall of the intestine.

Cholecalciferol is converted to *calcifediol* (25-hydroxy-vitamin D_3) in the liver, and this is converted to a series of other metabolites of varying activity in the kidney, the most potent of which is *calcitriol* (1,25-dihydroxy-vitamin D_3); see Fig. 35.4).

The synthesis of calcitriol from calcifediol is regulated by PTH, and is also influenced by the phosphate concentration in the plasma and by the calcitriol concentration itself through a negative feedback mechanism (Fig. 35.4). Receptors for calcitriol are ubiquitous, and calcitriol is important in the functioning of many cell types.

The main actions of calcitriol are the stimulation of absorption of Ca^{2+} and phosphate in the intestine, and the mobilisation of Ca^{2+} from bone, but it also increases Ca^{2+} reabsorption in the kidney tubules (Fig. 35.3). Its effect on bone involves promotion of maturation of osteoclasts and indirect stimulation of their activity (Figs 35.1 and 35.3). It decreases collagen synthesis by osteoblasts. However, the effect on bone is complex and not confined to mobilising Ca^{2+}, because in clinical vitamin D deficiency (see below), in which the mineralisation of bone is impaired, administration of vitamin D restores bone formation. One explanation may lie in the fact that calcitriol stimulates synthesis of *osteocalcin*, the Ca^{2+}-binding protein of bone matrix.

OESTROGENS

During reproductive life in the female, oestrogens have an important role in maintenance of bone integrity, acting on both osteoblasts and osteoclasts. They inhibit the cytokines that recruit osteoclasts and oppose the bone-resorbing, Ca^{2+}-mobilising action of PTH. They increase osteoblast proliferation, augment the production of TGF-β and bone morphogenic proteins, and inhibit apoptosis (see Ch. 5). Withdrawal of oestrogen, as happens at the menopause, can (and usually does) lead to osteoporosis.

Parathyroid, vitamin D and bone mineral homeostasis

- The vitamin D family are true hormones; precursors are converted to calcifediol in the liver, then to the main hormone, calcitriol, in the kidney.
- Calcitriol increases plasma Ca^{2+} by mobilising it from bone, increasing its absorption in the intestine and decreasing its excretion by the kidney.
- Parathyroid hormone (PTH) increases blood Ca^{2+} by increasing calcitriol synthesis, mobilising Ca^{2+} from bone and reducing renal Ca^{2+} excretion. (But, paradoxically, small doses of PTH given intermittently increase bone formation.)
- Calcitonin (secreted from the thyroid) reduces Ca^{2+} resorption from bone by inhibiting osteoclast activity.

CALCITONIN

Calcitonin is a peptide hormone secreted by the specialised 'C' cells found in the thyroid follicles (see Ch. 33).

The main action of calcitonin is on bone; it inhibits bone resorption by binding to a specific receptor on osteoclasts, inhibiting their action. In the kidney, it decreases the reabsorption of both Ca^{2+} and phosphate in the proximal tubules. Its overall effect is to decrease the plasma Ca^{2+} concentration (Fig. 35.3).

Secretion is determined mainly by the plasma Ca^{2+} concentration.

OTHER HORMONES

Physiological concentrations of glucocorticoids are required for osteoblast differentiation. Excessive pharmacological concentrations inhibit bone formation by inhibiting osteoblast differentiation and activity, and may stimulate osteoclast action—leading to osteoporosis, which is a feature of Cushing's syndrome (Fig. 32.7) and an important adverse effect of glucocorticoid administration (Ch. 32).

Thyroxine stimulates osteoclast action, reducing bone density and liberating Ca^{2+}. Osteoporosis occurs in association with thyrotoxicosis, and care must be taken not to use excessive thyroxine dosage for treating hypothyroidism (see Ch. 33).

DISORDERS OF BONE

The reduction of bone mass with distortion of the microarchitecture is termed *osteoporosis*; a reduction in the mineral content is termed *osteopenia*. Osteoporotic bone fractures easily after minimal trauma. The commonest causes of osteoporosis are postmenopausal deficiency of oestrogen and age-related deterioration in bone homeostasis. It is calculated that, in England and Wales, one in two women and one in five men over the age of 50 will have a fracture due to osteoporosis (van Staa et al., 2001), while in the USA a 50-year-old woman is estimated to have a 40% lifetime risk of an osteoporotic fracture (Strewler, 2005). Osteoporosis can also occur secondary to conditions such as rheumatoid arthritis, and can result from other factors, such as excessive thyroxine or glucocorticoid administration.

Because life expectancy has increased significantly in the developed world, osteoporosis is now regarded as being of epidemic proportions, and has become an important public health problem, affecting about 75 million people in the USA, Japan and Europe. Drugs that can be used in prevention and treatment are being vigorously sought and substantial progress has been made in recent years.

Other diseases of bone requiring drug therapy are *osteomalacia* and *rickets* (the juvenile form of osteomalacia), in which there are defects in bone mineralisation due to vitamin D deficiency, and *Paget's disease*, in which there is distortion of the processes of bone resorption and remodelling.

DRUGS USED IN BONE DISORDERS

Two types of agent are currently used for treatment of osteoporosis:

1. *Antiresorptive drugs* that decrease bone loss, e.g. bisphosphonates, calcitonin, selective oestrogen receptor modulators (SERMs), calcium.
2. *Anabolic agents* that increase bone formation e.g. PTH, **teriparatide**.

Strontium ranelate has both actions.

Rickets and osteomalacia, nutritionally induced deficiencies in bone mass, result from vitamin D deficiency and are treated with vitamin D preparations.

BISPHOSPHONATES

Bisphosphonates (Fig. 35.5) are enzyme-resistant analogues of pyrophosphate, a normal constituent of tissue fluids that accumulates in bone, and has a role in regulating bone resorption. Bisphosphonates inhibit bone resorption by an action mainly on the osteoclasts. They form tight

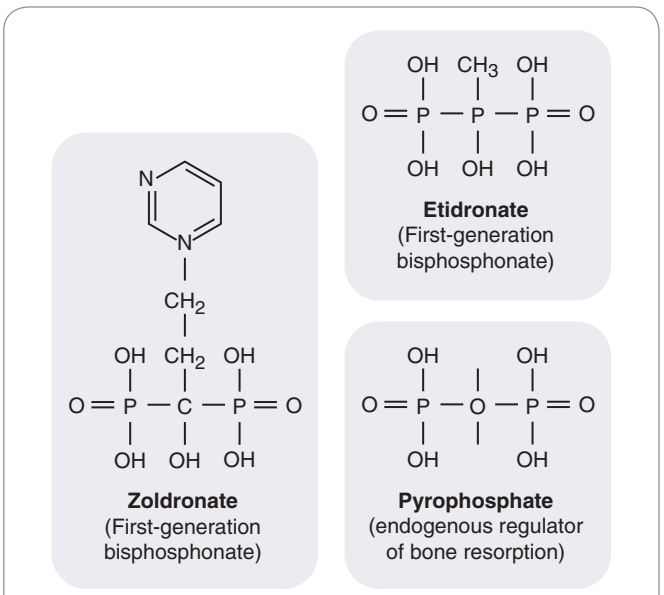

Fig. 35.5 Structure of bisphosphonates. Replacement of the oxygen atom in pyrophosphate renders the compounds enzyme resistant. Addition of an N-containing side chain alters the mechanism of action (see text) and greatly increases potency.

complexes with calcium in the bone matrix, and are released slowly as bone is resorbed by the osteoclasts, which are thus exposed to high concentrations of the drugs.

Mechanism of action

In terms of their molecular mechanism of action, the bisphosphonates can be grouped into two classes:

1. Simple compounds that are very similar to pyrophosphate (e.g. **etidronate**). These are incorporated into ATP analogues that accumulate within the osteoclasts and promote their apoptosis.
2. Potent, nitrogen-containing bisphosphonates (e.g. **alendronate**, **risedronate**, **ibandronate**, **zoledronate**). These prevent bone resorption by interfering with the anchoring of cell surface proteins to the osteoclast membrane by prenylation, which is necessary for their attachment to bone (see Strewler, 2005).

Pharmacokinetic aspects

Bisphosphonates are usually given orally and are poorly absorbed. They may be given intravenously in malignancy. About 50% of a dose accumulates at sites of bone mineralisation, where it remains, potentially for months or years, until the bone is resorbed. The free drug is excreted unchanged by the kidney.

Absorption is impaired by food, particularly milk, so the drugs must be taken on an empty stomach.

Unwanted effects include gastrointestinal disturbances including peptic ulcers and oesophagitis. Bone pain occurs occasionally. Given intravenously, some bisphosphonates (in particular zoledronate) can lead to osteonecrosis of the jaw.

Clinical use

Alendronate and risedronate are given orally for prophylaxis and treatment of osteoporosis. Etidronate is an alternative. **Clodronate** is used in patients with malignant disease involving bone and **pamidronate** is given by intravenous infusion to treat hypercalcaemia of malignancy or for Paget's disease. Ibandronate is given intravenously every 3–4 weeks in patients with breast cancer metastatic to bone or every 3 months to treat postmenopausal osteoporosis. Zoledronate, which is given as an intravenous infusion, is used for advanced malignancy involving bone, for Paget's disease and selected cases of osteoporosis (postmenopausal or in men) when it is administered once a year (see clinical box.)

Bisphosphonates

- Orally active, stable analogues of pyrophosphate, which are incorporated into remodelling bone and remain there for months or years.
- Released when osteoclast-mediated bone resorption occurs, exposing osteoclasts to their toxic effects.
- First-generation compounds (e.g. **etidronate**) act by promoting apoptosis of osteoclasts.
- Second-generation compounds (e.g. **risedronate**) with N-containing sidechains are much more potent, and prevent osteoclast action by inhibiting prenylation reactions required for membrane anchoring of functional proteins.
- Used long term for prevention and treatment of osteoporosis.
- Main unwanted effect is gastrointestinal disturbance

Clinical uses of bisphosphonates

- *Osteoporosis*:
  - 'primary' prevention of fractures in high-risk individuals (e.g. with established osteoporosis, several risk factors for osteoporosis, treated chronically with systemic glucocorticoids)
  - 'secondary' prevention after an osteoporitic fracture
  - **alendronate** by mouth is the bisphosphonate of choice, given daily or once weekly in addition to calcium with vitamin D_3. **Risedronate** or **etidronate** are alternatives; **zoledronate** is given annually by intravenous infusion but is expensive.
- *Malignant disease* involving bone (e.g. metastatic breast cancer, multiple myeloma):
  - to reduce bone damage, pain and hypercalcaemia (e.g. **clodronate**, **ibandronate**, **zoledronate**).
- *Paget's disease* of bone (e.g. **etidronate**, **pamidronate**) administered intermittently and with monitoring of serum phosphate, alkaline phosphatase and urinary hydroxyproline (a marker of collagen turnover).

OESTROGENS AND RELATED COMPOUNDS

The decline in oestrogen levels is a major factor in postmenopausal osteoporosis, and there is evidence that giving oestrogen as hormone replacement therapy (HRT; see Ch. 34) can ameliorate this condition. But HRT has actions on many systems, and newer non-hormonal agents (e.g. **raloxifene**, see Ch. 34) have now been developed that exhibit agonist actions on some tissues and antagonist actions on others. These are termed *selective oestrogen receptor modulators* (SERMs). The most important of these is **raloxifene** (Ch. 34).

RALOXIFENE

Raloxifene is a SERM that has agonist activity on bone, stimulating osteoblasts and inhibiting osteoclasts. It also has agonist actions on the cardiovascular system, and antagonist activity on mammary tissue and the uterus.

It is well absorbed in the gastrointestinal tract, and undergoes extensive first-pass metabolism in the liver to give the glucuronide—resulting in only about 2% bioavailability. **Colestyramine** (Ch. 23), given with it, reduces the enterohepatic cycling of raloxifene by 60%.

Raloxifene is widely distributed in the tissues, and is converted to an active metabolite in liver, lungs, bone, spleen, uterus and kidney. Its half-life averages 32 h. It is excreted mainly in the faeces.

Unwanted effects include hot flushes, leg cramps, flu-like symptoms and peripheral oedema. Less common are thrombophlebitis and thromboembolism. Other rarer adverse effects are thrombocytopenia, gastrointestinal disturbances, rashes, raised blood pressure and arterial

thromboembolism. It is not recommended for primary prevention of osteoporotic fractures, but is one alternative to a bisphosphonate for secondary prevention in postmenopausal women who cannot tolerate a bisphosphonate.

PARATHYROID HORMONE AND TERIPARATIDE

PTH and fragments of PTH given in small doses paradoxically *stimulate* osteoblast activity and *enhance* bone formation, and are used to treat selected patients with osteoporosis. The main compound currently used is **teriparatide**—the peptide fragment (1–34) of recombinant PTH. A new peptide analogue (**ostabolin**—cyclic PTH1–35, which increases bone mass with less effect on plasma calcium concentration than PTH) is in development.

Teriparatide has anabolic effects on bone. It reverses osteoporosis by stimulating new bone formation (Yasothan & Santwana, 2008). It increases bone mass, structural integrity and bone strength by increasing the number of osteoblasts and by activating those osteoblasts already in bone. It also reduces osteoblast apoptosis.

It acts on the G-protein-coupled receptor PTH_1 in the membrane of target cells, and its effects are mediated through adenylyl cyclase, phospholipases A, C and D, and increases in intracellular Ca^{2+} and cyclic AMP (see Brixen et al., 2004; Deal, 2009).

Teriparatide is given subcutaneously once daily. It is well tolerated, and serious adverse effects are few. Nausea, dizziness, headache and arthralgias can occur. Mild hypercalcaemia, transient orthostatic hypotension and leg cramps have been reported.

Teriparatide is used to treat osteoporosis. There is controversy as to whether or not this drug should be given sequentially or in combination with one of the bisphosphonates (Heaney & Recker, 2005); however, a bisphosphonate should be given at the end of a course of teriparatide to prevent bone loss due to teriparatide withdrawal.

STRONTIUM RANELATE

Strontium (given as the ranelate salt) inhibits bone resorption and also stimulates bone formation. In recent trials, it has been shown to be effective in preventing vertebral and non-vertebral fractures in older women (see Fogelman & Blake, 2005). It is approved in the UK and recommended by the National Institute for Health and Clinical Excellence as an alternative to a bisphosphonate in primary or secondary prevention of osteoporotic fractures, when a bisphosphonate is not tolerated, although some authors consider it to be first-line treatment for osteoporosis because of its positive risk–benefit ratio (Reginster et al., 2009).

The precise mechanism of action is not clear. Like calcium it is absorbed from the intestine, incorporated into bone and excreted via the kidney. Strontium atoms are adsorbed onto the hydroxyapatite crystals, but eventually they exchange for calcium in the bone minerals and remain in the bone for many years.

The drug is well tolerated; a low incidence of nausea and diarrhoea is reported.

VITAMIN D PREPARATIONS

Vitamin D preparations are used in the treatment of vitamin D deficiencies, bone problems associated with renal failure and hypoparathyroidism—acute hypoparathyroidism necessitating the use of intravenous calcium and injectable vitamin D preparations.

Clinical uses of vitamin D

- Deficiency states: prevention and treatment of *rickets*, *osteomalacia* and vitamin D deficiency owing to *malabsorption* and *liver disease* (**ergocalciferol**).
- Hypocalcaemia caused by *hypoparathyroidism* (ergocalciferol).
- *Osteodystrophy* of *chronic renal failure*, which is the consequence of decreased calcitriol generation (**calcitriol** or **alphacalcidol**).

Plasma Ca^{2+} levels should be monitored during therapy with vitamin D.

The main vitamin D preparation used clinically is **ergocalciferol**. Other preparations are **alfacalcidol** and **calcitriol**. All can be given orally and are well absorbed from the intestine. Vitamin D preparations are fat soluble, and bile salts are necessary for absorption. Injectable forms are available. A vitamin D analogue with less potential to cause hypercalcaemia is the vitamin D sterol, **paracalcitol** (Salusky, 2005).

Given orally, vitamin D is bound to a specific α-globulin in the blood. The plasma half-life is about 22 h, but vitamin D can be found in the fat for many months. The main route of elimination is in the faeces.

The clinical uses of vitamin D preparations are given in the box.

Excessive intake of vitamin D causes hypercalcaemia. If hypercalcaemia persists, calcium salts are deposited in the kidney and urine, causing renal failure and kidney stones.

CALCITONIN

The main preparation available for clinical use (see the clinical box) is **salcatonin** (synthetic salmon calcitonin). Synthetic human calcitonin is now also available. Calcitonin is given by subcutaneous or intramuscular injection, and there may be a local inflammatory action at the injection site. It can also be given intranasally. Its plasma half-life is 4–12 min, but its action lasts for several hours.

Unwanted effects include nausea and vomiting. Facial flushing may occur, as may a tingling sensation in the hands and an unpleasant taste in the mouth.

CALCIUM SALTS

Calcium salts used therapeutically include **calcium gluconate** and **calcium lactate**, given orally. Calcium gluconate is also used for intravenous injection in emergency

Clinical uses of calcitonin/salcatonin

- *Hypercalcaemia* (e.g. associated with neoplasia).
- *Paget's disease* of bone (to relieve pain and reduce neurological complications).
- Postmenopausal and corticosteroid-induced *osteoporosis* (with other agents).

Clinical uses of calcium salts

- Dietary deficiency.
- Hypocalcaemia caused by *hypoparathyroidism* or *malabsorption* (intravenous for acute tetany).
- Calcium carbonate is an antacid; it is poorly absorbed and binds phosphate in the gut. It is used to treat *hyperphosphataemia* (Ch. 28).
- Prevention and treatment of *osteoporosis* (often with oestrogen, bisphosphonate, vitamin D or calcitonin).
- Cardiac dysrhythmias caused by severe *hyperkalaemia* (intravenous; see Ch. 21).

treatment of hyperkalaemia (Ch. 28); intramuscular injection is not used, because it causes local necrosis.

Calcium carbonate, an antacid, is usually poorly absorbed in the gut, but there is concern about possible systemic absorption with the potential to cause arterial calcification.

Unwanted effects: oral calcium salts can cause gastrointestinal disturbance. Intravenous administration requires care, especially in patients on cardiac glycosides (see Ch. 21).

The clinical uses of the calcium salts are given in the clinical box.

CALCIMIMETIC COMPOUNDS

Calcimimetics enhance the sensitivity of the parathyroid Ca^{2+}-sensing receptor to the concentration of blood Ca^{2+}. The effect is to decrease the secretion of PTH and reduce the serum Ca^{2+} concentration. There are two types of calcimimetics:

1. Type I are agonists, and include various inorganic and organic cations. They are not used clinically.
2. Type II are allosteric activators that activate the receptor indirectly. One such compound is **cinacalcet**, which is used for the treatment of hyperparathyroidism (Fig. 35.3; Peacock et al., 2005).

POTENTIAL NEW THERAPIES

The recent substantial increase in the understanding of bone remodelling (Deal, 2009; Yasothan & Kar, 2008) has opened possible therapeutic approaches that may yield new drugs for clinical use in the foreseeable future. These include:

- RANKL inhibitors (e.g. the monoclonal antibody, **denosumab**)
- cathepsin K inhibitors (e.g. **odanacatib**)
- recombinant human OPG for the treatment of Paget's disease (Deftos, 2005).

Other promising targets are discussed by Deal (2009).

REFERENCES AND FURTHER READING

Bone disorders and bone remodelling

Boyce, B.F., Xing, L., 2008. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch. Biochem. Biophys. 473, 139–146. (*Good review of the role of the RANK/RANKL/OPG in osteoclast formation and the transcription factors involved*)

Compston, J., 2009. Clinical and therapeutic aspects of osteoporosis. Eur. J. Radiol. 71, 388–391. (*Clear brief coverage of epidemiology, clinical aspects, pathogenesis and drugs currently used*)

Deal, C., 2009. Potential new drug targets for osteoporosis. Nat. Clin. Pract. Rheumatol. 5, 174–180. (*Outstanding review; good diagrams*)

Deftos, L.J., 2005. Treatment of Paget's disease—taming the wild osteoclast. N. Engl. J. Med. 353, 872–875. (*Editorial covering the use of OPG and zoledronic acid for Paget's disease; excellent diagram. See also article by Cundy et al. in the same issue, pp. 918–923*)

Gallagher, J.C., 2008. Advances in bone biology and new treatments for bone loss. Maturitas 20, 65–69. (*Article on preventing bone loss by targeting the RANK/RANKL/OPG system with denosumab*)

Heaney, R.P., Recker, R.R., 2005. Combination and sequential therapy for osteoporosis. N. Engl. J. Med. 353, 624–625. (*Editorial*)

Horowitz, M.C., Xi, Y., Wilson, K., Kacena, M.A., 2001. Control of osteoclastogenesis and bone resorption by members of the TNF family of receptors and ligands. Cytokine Growth Factor Rev. 12, 9–18. (*Worthwhile minireview, good diagram*)

Khosla, K., Westendorf, J.J., Oursler, M.J., 2008. Building bone to reverse osteoporosis and repair fractures. J. Clin. Invest. 118, 421–428. (*Good review; covers the role of Wnt signalling and sclerostin secretion*)

Reichel, H., Koeftler, H.P., Norman, A.W., 1989. The role of the vitamin D endocrine system in health and disease. N. Engl. J. Med. 320, 980–991. (*Outstanding comprehensive early review*)

Reid, R., 2008. Anti-resorptive therapies for osteoporosis. Semin. Cell Dev. Biol. 19, 5473–5478. (*Excellent review of the actions of current and novel anti-resorptive drugs*)

Roodman, G.D., 2004. Mechanisms of bone metastasis. N. Engl. J. Med. 350, 1655–1664. (*Has excellent section on bone remodelling, with good diagrams*)

Salusky, I.B., 2005. Are new vitamin D analogues in renal bone disease superior to calcitriol? Pediatr. Nephrol. 20, 393–398.

Stewart, J.F., 2004. Translational implications of the parathyroid calcium receptor. N. Engl. J. Med. 351, 324–326. (*Succinct article with useful diagram*)

Tolar, J., Teitelbaum, S.L., Orchard, P.J., 2004. Osteopetrosis. N. Engl. J. Med. 351, 2839–2849. (*Very good review; has excellent section on the biology of osteoclasts, with very good diagrams*)

van Staa, T.P., Dennison, E.M., Leufkens, H.G., Cooper, C., 2001. Epidemiology of fractures in England and Wales. Bone 29, 517–522.

Wright, H.L., McCarthy, H.S., Middleton, J., Marshall, M.J., 2009. RANK, RANKL and osteoprotegerin in bone biology and disease. Curr. Rev. Musculoskelet. Med. 2, 56–64. (*Synopsis of the structures of RANK, RANKL and OPG, and the intracellular RANK/RANKL signalling pathways with a review of diseases linked to their malfunction*)

Drugs used to treat bone disorders

Brennan, T.C., Rybchyn, M.S., Green, W., et al., 2009. Osteoblasts play key roles in the mechanisms of action of strontium ranelate. Br. J. Pharmacol. 57, 1291–1300. (*A study in human cells showing that strontium ranelate acts at least in part by activating the calcium-sensing receptor*)

Brixen, K.T., Christensen, P.M., Ejersted, C., Langdahl, B.L., 2004. Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. Basic Clin. Pharmacol. Toxicol. 94, 260–270. (*A minireview of the action, mechanism of action, clinical studies and adverse effects*)

Clemett, D., Spenser, C.M., 2000. Raloxifene: a review of its use in postmenopausal osteoporosis. Drugs 60, 379–411. (*Comprehensive review covering the mechanism of action, pharmacology, pharmacokinetic aspects, therapeutic use and adverse effects of raloxifene*)

Cummings, S.R., San Martin, J., McClung, M.R., et al., 2009. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N. Engl. J. Med. 361, 818–820. (*'Freedom Trial' with 239 collaborators. Denosumab was effective in reducing fracture risk in women with osteoporosis*)

Fogelman, I., Blake, G.M., 2005. Strontium ranelate for the treatment of osteoporosis. Br. Med. J. 330, 1400–1401. (*Crisp editorial analysis*)

Khosla, K., 2009. Increasing options for the treatment of osteoporosis. N. Engl. J. Med. 361, 818–820 (*Useful editorial*)

Nemeth, E.F., Heaton, W.H., Miller, M., et al., 2004. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. J. Pharmacol. Exp. Ther. 398, 627–635. (*Detailed study of pharmacokinetic aspects and the pharmacological action of cinacalcet hydrochloride*)

Peacock, M., Bilezikian, J.P., Klassen, P.S., et al., 2005. Cinacalcet hydrochloride maintains long-term normocalcaemia in patients with primary hyperparathyroidism. J. Clin. Endocrinol. Metab. 90, 135–141.

Quattrocchi, E., Kourlas, H., 2004. New drugs. Teriparatide: a review. Clin. Ther. 26, 841–854. (*Excellent review*)

Reginster, J.Y., Deroisy, R., Neuprez, A., et al., 2009. Strontium ranelate: new data on fracture prevention and mechanisms of action. Curr. Osteoporos. Rep. 7, 96–102. (*Stresses that in 5-year studies this drug has proved efficacious in both decreasing bone reabsorption and stimulating bone formation, and has a positive risk–benefit ratio*)

Rogers, M.J., 2003. New insights into the mechanisms of action of the bisphosphonates. Curr. Pharm. Des. 9, 2643–2658. (*Covers the different mechanisms of action of the simple bisphosphonates and the nitrogen-containing bisphosphonates*)

Strewler, G.J., 2005. Decimal point—osteoporosis therapy at the 10-year mark. N. Engl. J. Med. 350, 1172–1174. (*Crisp article concentrating mainly on bisphosphonates; excellent diagram of bisphosphonate action*)

Whyte, M.P., 2006. The long and the short of bone therapy. N. Engl. J. Med. 354, 860–863. (*Succinct article on the present status of and future possibilities for bone therapy. Excellent diagram*)

Yasothan, U., Kar, S., 2008. Osteoporosis: overview and pipeline. Nat. Rev. Drug. Discov. 7, 725–726.

Yasothan, U., Santwana, K., 2008. From the analyst's couch. Osteoporosis: overview and pipeline. Nat. Rev. Drug. Discov. 7, 725–726. (*Crisp outline of current antiosteoporosis drugs with table of new drugs in phase I and phase II development*)