



ADRENOCORTICO TROPIC HORMONE

**LEC. 2 PHARMACOLOGY
4TH YEAR STUDENTS**

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ADRENOCORTICOTROPIC HORMONE

Adrenocorticotrophic hormone (ACTH, corticotrophin) is the anterior pituitary secretion that controls the synthesis and release of the glucocorticoids of the adrenal cortex. It is a 39-residue peptide derived from the precursor *pro-opiomelanocortin* (POMC) by sequential proteolytic processing. Failure of ACTH action because of defects in its receptor or intracellular signaling pathways can lead to severe glucocorticoid deficiency.

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) MC3 receptors. 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. The concentration of ACTH in the blood is reduced by glucocorticoids, forming the basis of the **dexamethasone** suppression test.

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 recognized action was to stimulate the production of melanin by specialized skin cells called *melanocytes*. As such, they play an important part in determining hair coloration, skin color and reaction to ultraviolet light.

Melanocyte-stimulating hormone acts on *melanocortin receptors*, of which five (MC1–5) have been cloned. These are G-protein-coupled receptors that activate cAMP synthesis. Melanin formation is under the control of the MC1 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-1 β and tumor 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. MC1 and MC3 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 behavior, 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 MC4 receptor.

Two naturally occurring ligands for melanocortin receptors (*agouti signaling protein* and *agouti-related peptide*, together called the *agouti*) have been discovered in human tissues. These are proteins that competitively antagonize 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 fibers terminate in dilated nerve endings in close association with capillaries in the posterior pituitary gland.

Peptides, synthesized 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) and ADH (also called **vasopressin**). Several similar peptides have been synthesized that vary in their antidiuretic, vasopressor and oxytocic (uterine stimulant) properties.

ANTIDIURETIC HORMONE

Regulation of secretion and physiological role

Antidiuretic hormone released from the posterior pituitary has a 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. The hypothalamic nuclei that control fluid balance lie close to the nuclei that synthesize 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 (hypovolemia) 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: V1, V2 and V3.

V2 receptors stimulate adenylyl cyclase, which mediates its main physiological actions in the kidney, whereas the V1 and V3 receptors are coupled to the phospholipase C/inositol trisphosphate system.

Actions

Renal actions

Antidiuretic hormone binds to V2 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 luminal membrane, thus increasing the permeability of the membrane to water. 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 hyponatremia) 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 V2 receptors are also used for SIADH and in some patients with heart failure.

Other non-renal actions

Antidiuretic hormone causes contraction of smooth muscle, particularly in the cardiovascular system, by acting on V1 receptors. The affinity of these receptors for ADH is lower than that of the V2 receptors, and smooth muscle effects are seen only with doses larger than those affecting the kidney. ADH also stimulates blood platelet aggregation and mobilization 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 V3 receptors.

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 V1 and V2 receptors.

The main substances used are

vasopressin (ADH itself; short duration of action, weak selectivity for V2 receptors, given by subcutaneous or intramuscular injection, or by intravenous infusion),

desmopressin (increased duration of action, V2-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.

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 minimized if the antidiuretic peptides are administered intranasally.

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, and the outer *cortex*, which secretes adrenal steroids. The cortex 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 activity, some sex steroids (mainly androgens) are also secreted by the gland.

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 defense mechanisms. 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 *11 β -hydroxy-steroid dehydrogenase* converts hydrocortisone to the inactive metabolite *cortisone*, thereby protecting the receptor from inappropriate activation. With the exception of *replacement therapy*, glucocorticoids are most commonly employed for their anti-inflammatory and immunosuppressive properties. 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, but it has not been possible to separate the anti-inflammatory from the other actions of the glucocorticoids completely.

| 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 |

^aData obtained in human fetal lung cells.

^bDuration 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.)

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 characterized by muscular weakness, low blood pressure, depression, anorexia, loss of weight and hypoglycemia.

Addison's disease may have an autoimmune etiology, 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*. 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 tumors of the adrenals (*primary hyperaldosteronism*, or *Conn's syndrome*, an uncommon but important cause of hypertension, 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*).

GLUCOCORTICOIDS

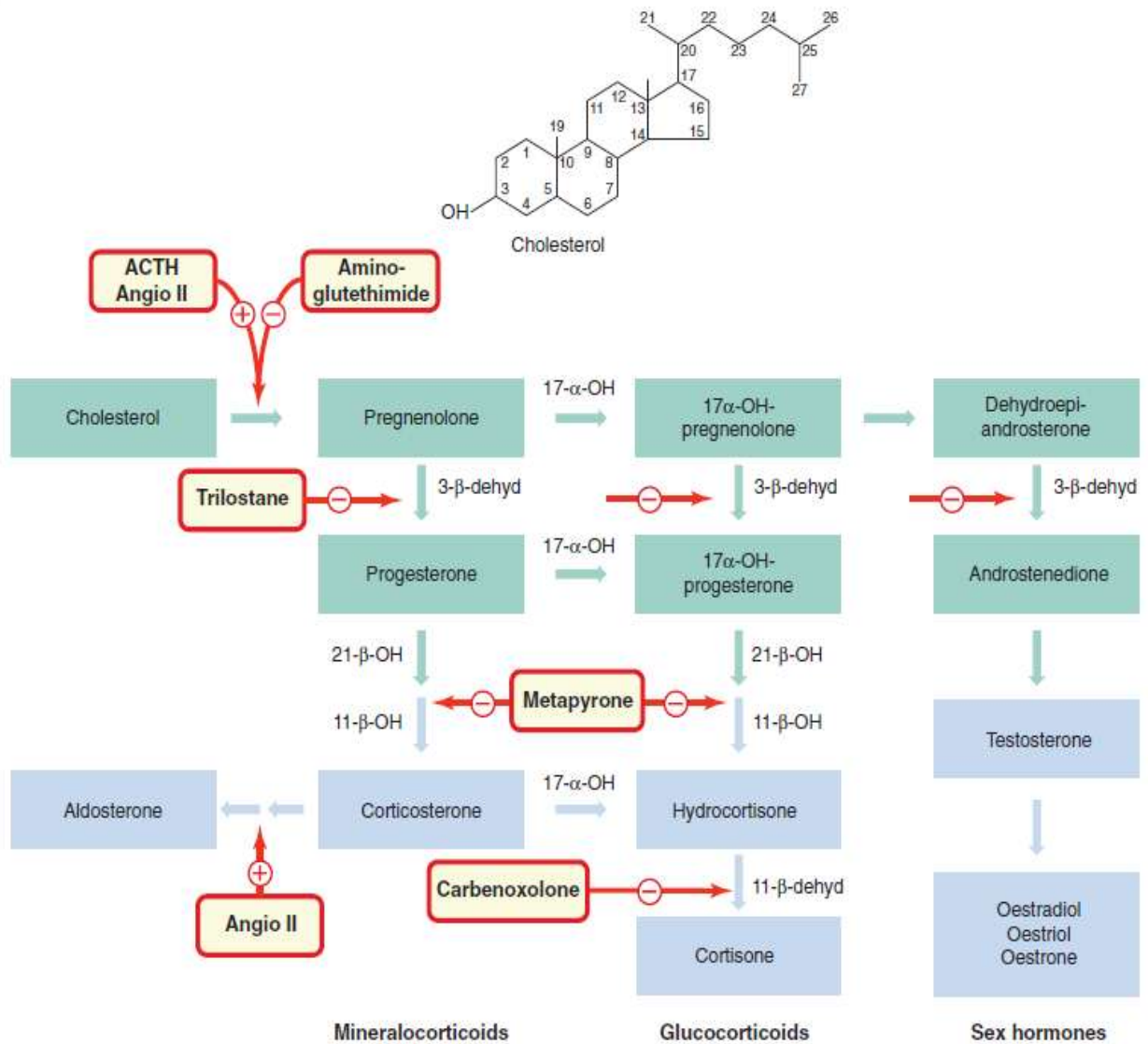
Synthesis and release

Glucocorticoids are not stored in the adrenal. They are synthesized under the influence of circulating ACTH secreted from the anterior pituitary gland 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. 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-deoxycorticosteroid 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 *3 β -dehydrogenase*.

Aminoglutethimide inhibits the initial step in the biosynthetic pathway and has the same overall effect as metyrapone. **Ketoconazole**, an antifungal agent, used in higher doses also inhibits steroidogenesis and may be of value in the specialized 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. This superfamily also includes the receptors for mineralocorticoids, the sex steroids, thyroid hormones, vitamin D3 and retinoic acid.

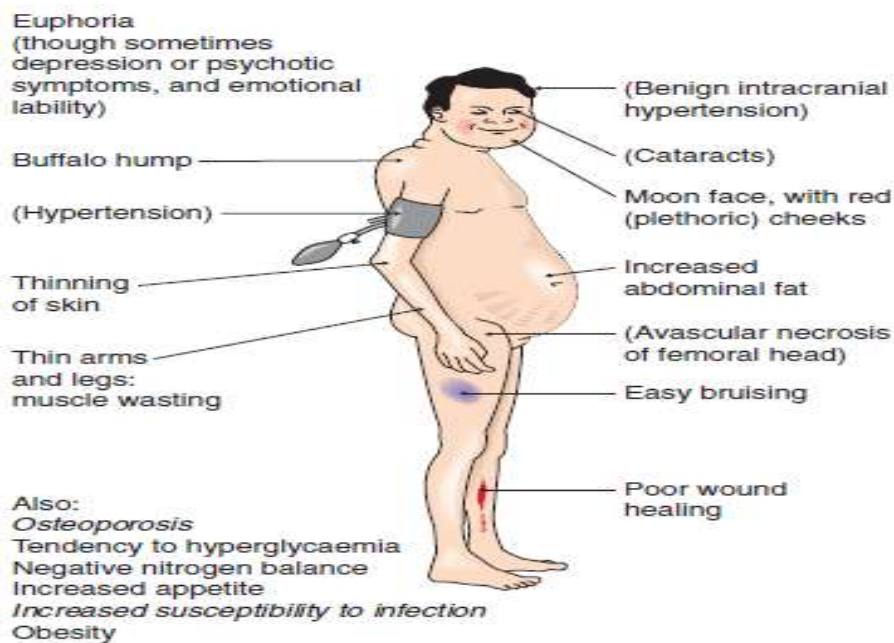
In addition to controlling gene expression, the ligand receptor itself, in either a monomeric or a dimeric form, may trigger important signal transduction events while still in the cytosolic compartment. One of these cytosolic effects, germane to the anti-inflammatory action of these drugs, is the release, 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.

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 utilization of glucose and an increase in gluconeogenesis, resulting in a tendency to hyperglycemia. 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 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. Large doses of glucocorticoids given over a long period result in the redistribution of body fat characteristic of *Cushing's syndrome*.



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. In higher, non-physiological concentrations, the glucocorticoids have some mineralocorticoid actions, causing Na^+ retention and K^+ loss—possibly by swamping the protective 11β -hydroxysteroid 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. 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. 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.

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.
- 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 include:

- decreased production of prostanoids owing to decreased expression of cyclooxygenase-2.
- decreased generation of many cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, tumor 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.

The anti-inflammatory and immunosuppressive actions may play a crucial counter-regulatory role, in that they prevent excessive activation of inflammation and other powerful defense reactions that might, if unchecked, themselves threaten homeostasis. While these drugs are of great value in treating conditions characterized by hypersensitivity and unwanted inflammation, they carry the hazard that they are able

to suppress the same defense reactions that provide protection to infection and promote healing.

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) frequently occurs when glucocorticoids are taken by inhalation, because of suppression of local anti-infective mechanisms.
- ***Cushing's syndrome.***
- ***Osteoporosis.*** 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).
- ***Hyperglycaemia*** produced by exogenous glucocorticoids may develop into actual diabetes.
- ***Muscle wasting*** and proximal muscle weakness.
- In children, ***inhibition of growth*** 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 synthesize corticosteroids. 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

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.

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).

Lec. 5

Insulin and Other Glucose- Lowering Drugs

Pharmacology-4th Year Students

OVERVIEW

The pancreas is both an endocrine gland that produces the peptide hormones *insulin*, glucagon, and somatostatin and an exocrine gland that produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (β cells produce *insulin*, α cells produce glucagon, and δ cells produce somatostatin). These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose. Glucagon increases blood glucose and causes breakdown of fat and protein. It acts on specific G-protein-coupled receptors to stimulate adenylyl cyclase, and its actions are somewhat similar to β -adrenoceptor mediated actions of adrenaline. Unlike adrenaline, however, its metabolic effects are more pronounced than its cardiovascular actions. Glucagon is proportionately more active on liver, while the metabolic actions of adrenaline are more pronounced on muscle and fat. Glucagon stimulates glycogen breakdown and gluconeogenesis, and inhibits glycogen synthesis and glucose oxidation. Its metabolic actions on target tissues are thus the opposite of those of insulin. Glucagon increases the rate and force of contraction of the heart, although less markedly than adrenaline. Somatostatin is secreted by the D cells of the islets. It is also generated in the hypothalamus, where it acts to inhibit the release of growth hormone. In the islet, it inhibits release of insulin and of glucagon.

Hyperinsulinemia (due, for example, to an insulinoma) can cause severe hypoglycemia. A relative or absolute lack of *insulin*, such as in diabetes mellitus, can cause serious hyperglycemia. If this condition is left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of *insulin* preparations or other injectable or oral glucose lowering agents can prevent morbidity and reduce mortality associated with diabetes.

DIABETES MELLITUS

The incidence of diabetes is growing rapidly both in the United States and worldwide. For example, it is estimated that more than 250 million people worldwide are afflicted with diabetes, and the prevalence is expected to exceed 350 million by the year 2030. In the United States, approximately 23.6 million people are estimated to suffer from diabetes, and it is a major cause of morbidity and mortality. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose caused by a relative or absolute deficiency of *insulin*.

The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes:

Type 1 diabetes (formerly, insulin dependent diabetes mellitus),

Type 2 diabetes (formerly, non-insulin dependent diabetes mellitus),

Gestational diabetes, and

Diabetes due to other causes (for example, genetic defects or medications).

Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy.

Pregnancy, for example, is a prominent change of metabolic conditions, under which the mother has to reduce her muscles' insulin sensitivity to spare more glucose for the brains (the mother's brain and the fetal brain). This can be achieved through raising the response threshold (i.e., delay the onset of sensitivity) by secreting placental growth factor to interfere with the interaction between insulin receptor substrate (IRS) and PI3K, which is the essence of the so-called *adjustable threshold hypothesis* of insulin resistance.

It is important to maintain adequate glycemic control during pregnancy, because uncontrolled gestational diabetes can lead to fetal macrosomia (abnormally large body) and shoulder dystocia (difficult delivery), as well as neonatal hypoglycemia. Diet, exercise, and/ or *insulin* administration are effective in this condition. *Glyburide* and *metformin* may be reasonably safe alternatives to *insulin* therapy for gestational diabetes.

A. Type 1 diabetes

Type 1 diabetes most commonly afflicts individuals in puberty or early adulthood, but some latent forms can occur later in life. The disease is characterized by an absolute deficiency of *insulin* caused by massive β -cell necrosis. Loss of β -cell function is usually ascribed to autoimmune-mediated processes directed against the β cell, and it may be triggered by an invasion of viruses or the action of chemical toxins. As a result of the destruction of these cells, the pancreas fails to respond to glucose, and the type 1 diabetic shows classic symptoms of *insulin* deficiency (polydipsia, polyphagia, polyuria, and weight loss). Type 1 diabetics require exogenous *insulin* to avoid the catabolic state that results from and is characterized by hyperglycemia and life-threatening ketoacidosis.

Cause of type 1 diabetes: In a normal post-absorptive period, low basal levels of circulating *insulin* are maintained through constant β -cell secretion. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of *insulin* secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in the levels of circulating glucose and amino acids. This lasts for up to 15 minutes and is followed by the postprandial secretion of *insulin*. However, having virtually no functional β cells, those with type 1 diabetes can neither maintain a basal secretion level of *insulin* nor respond to variations in circulating fuels.

The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or hemoglobin A1c [HbA1c]).

Treatment: A person with type 1 diabetes must rely on exogenous (injected) *insulin* to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c). [*Note: The rate of formation of HbA1c is proportional to the average blood glucose concentration over the previous 3 months. Therefore, HbA1c provides a measure of how well treatment has normalized blood glucose in diabetic patients.*]

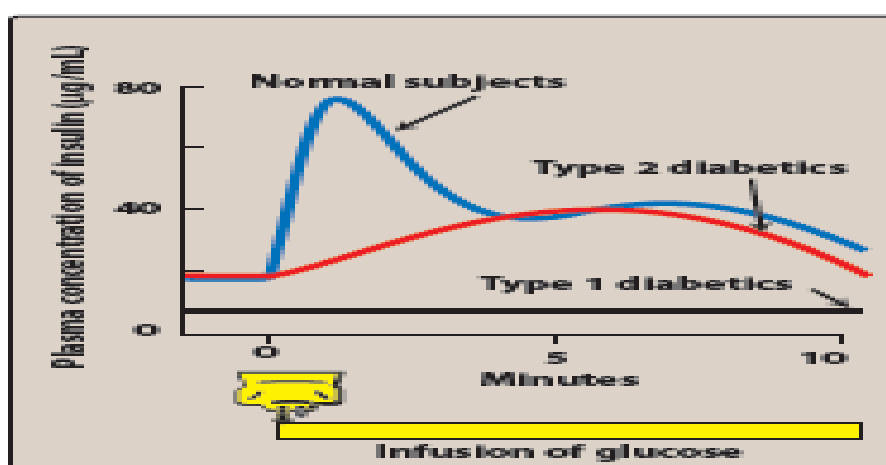
The goal in administering *insulin* to those with type 1 diabetes is to maintain blood glucose concentrations as close to normal as possible and to avoid wide swings in glucose levels that may contribute to long-term complications. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin injections. Continuous subcutaneous *insulin* infusion (also called the *insulin* pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating the multiple daily injections of insulin. The pump is programmed to deliver a basal rate of *insulin* secretion, and it also allows the patient to control delivery of a bolus of insulin to compensate for high blood glucose or in anticipation of postprandial needs. Other methods of insulin delivery, such as transdermal, buccal, and intranasal, are currently under investigation.

Amylin It is cosecreted with insulin from the pancreatic β -cells in the ratio of approximately 100:1. **Amylin** plays a **role** in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing post-prandial elevated in blood glucose levels. **Pramlintide**, a synthetic analog of amylin, may be used as an adjunct to *insulin* therapy.

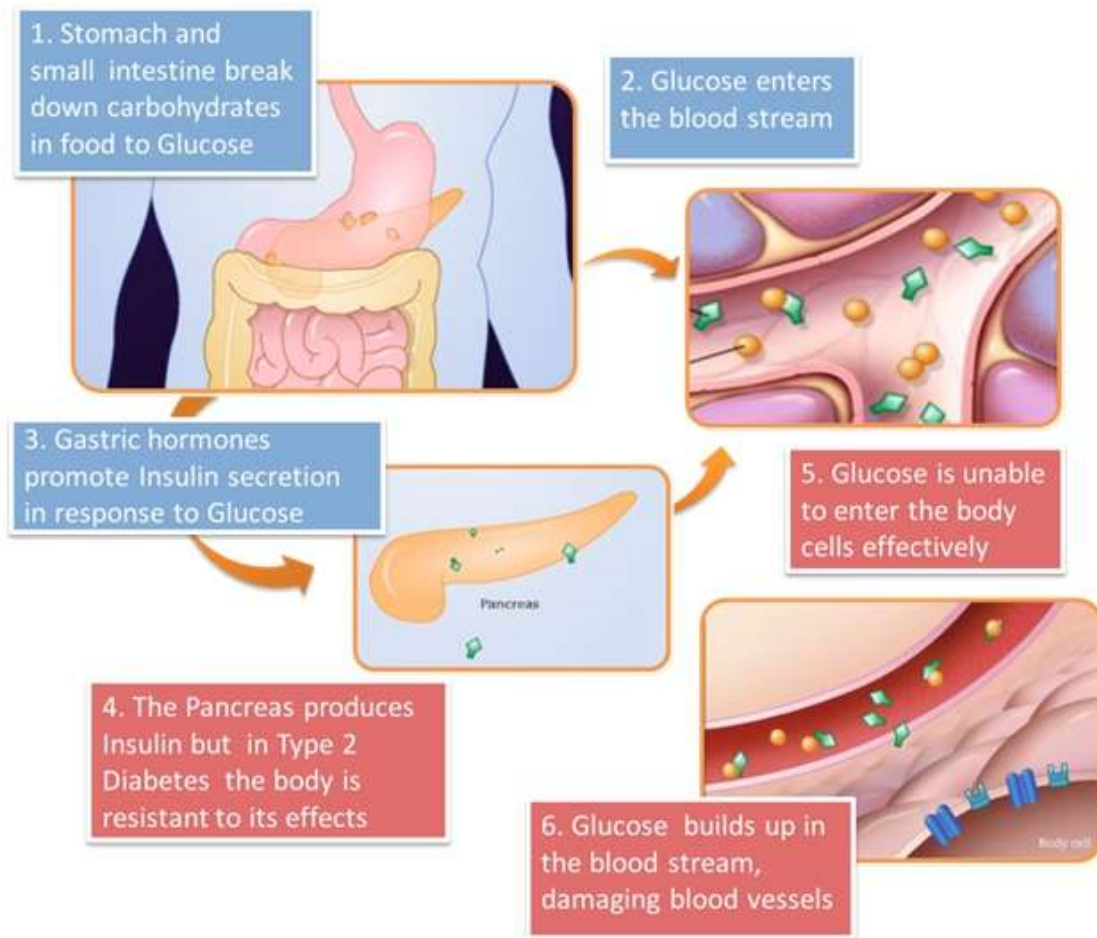
B. Type 2 diabetes

Most diabetic patients have type 2 disease. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral *insulin* resistance, rather than by autoimmune processes or viruses. The metabolic alterations observed are milder than those described for type 1 (for example, type 2 patients typically are not ketotic), but the long-term clinical consequences can be just as devastating (for example, vascular complications and subsequent infection can lead to amputation of the lower limbs).

Causes: In type 2 diabetes, the pancreas retains some β -cell function, but variable *insulin* secretion is insufficient to maintain glucose homeostasis.



The β -cell mass may become gradually reduced in type 2 diabetes. In contrast to patients with type 1, those with type 2 diabetes are often obese. [Note: Not all obese individuals become diabetic.] Type 2 diabetes is frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous *insulin*. This resistance to *insulin* is considered to be a major cause of this type of diabetes.



Treatment: The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Weight reduction, exercise, and dietary modification decrease *insulin* resistance and correct the hyperglycemia of type 2 diabetes in some patients. However, most patients are dependent on pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β -cell function declines and *insulin* therapy is often required to achieve satisfactory serum glucose levels.

INSULIN AND ITS ANALOGS

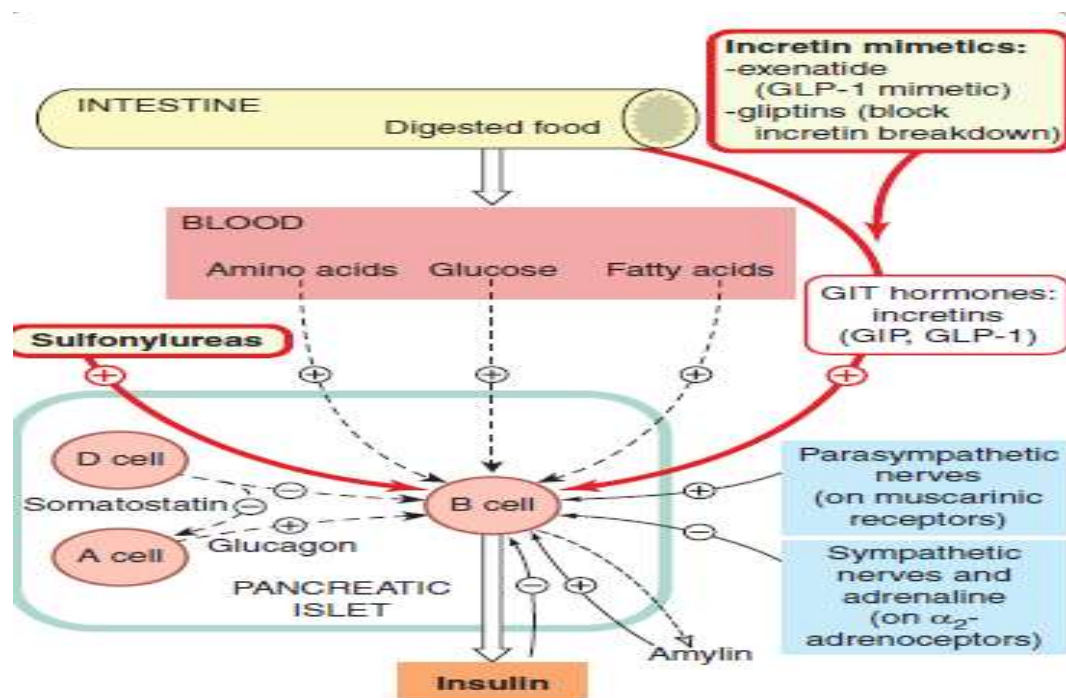
Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form *insulin* and C-peptide, both of which are secreted by the β cells of the pancreas. [Note: Because *insulin* undergoes significant hepatic extraction, circulating plasma *insulin* levels may not accurately reflect *insulin*

production. Thus, measurement of circulating C-peptide provides a better index of insulin levels.]

A. Insulin secretion

Insulin secretion is regulated not only by blood glucose levels but also by certain amino acids, other hormones, and autonomic mediators. Secretion is most commonly triggered by high blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor.

The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a block of K^+ channels, leading to membrane depolarization and an influx of Ca^{2+} . The increase in intracellular Ca^{2+} causes pulsatile *insulin* exocytosis. The sulfonylureas and glinides have their hypoglycemic effect through inhibition of K^+ channels. [Note: *Glucose given by injection has a weaker effect on insulin secretion than does glucose taken orally. When given orally, glucose stimulates production of incretin hormones by the gut, which, in turn, stimulate insulin secretion by the pancreas.*]



Excretin & Incretin

Excretin which stimulates the exocrine pancreas and ‘incretin’, which stimulates insulin release. Incretin action proved to be due to peptide hormones released from the

gut, mainly *glucagon-like insulinotropic peptide* (GIP) and *glucagon-like peptide-1* (GLP-1). These are both members of the glucagon peptide superfamily. Release of GIP and GLP-1 by ingested food provides an early stimulus to insulin secretion before absorbed glucose or other products of digestion reach the islet cells in the portal blood

As well as stimulating insulin secretion, both these hormones inhibit pancreatic glucagon secretion and slow the rate of absorption of digested food by reducing gastric emptying. They are also implicated in control of food intake via appetite and satiety

The actions of GIP and GLP-1 are terminated rapidly by dipeptidyl peptidase-4 (DPP-4).

B. Sources of insulin

Human *insulin* is produced by recombinant DNA technology using special strains of *Escherichia coli* or yeast that have been genetically altered to contain the gene for human *insulin*. Modifications of the amino acid sequence of human *insulin* have produced insulins with different pharmacokinetic properties. For example, three such insulins, ***lispro***, ***aspart***, and ***glulisine***, have a faster onset and shorter duration of action than regular *insulin*, because they do not aggregate or form complexes. On the other hand, ***glargine*** and ***detemir*** are long-acting insulins and show prolonged, flat levels of the hormone following injection.

C. Insulin administration

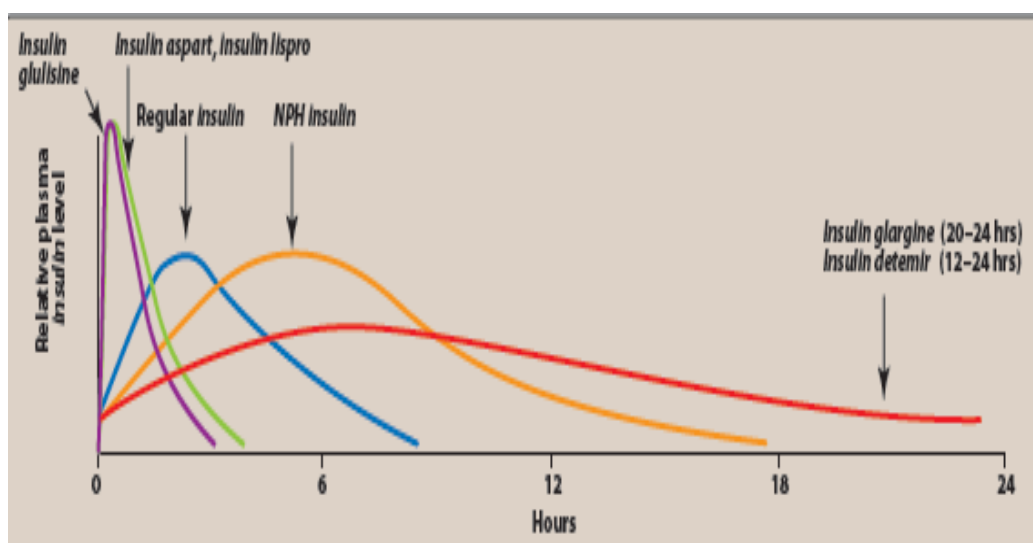
Because *insulin* is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection. Continuous subcutaneous *insulin* infusion (*insulin* pump) has become popular, because it does not require multiple daily injections. *Insulin* preparations vary primarily in their onset of activity and in duration of activity. This is due to differences in the amino acid sequences of the polypeptides. Dose, site of injection, blood supply, temperature, and physical activity can affect the duration of action of the various preparations. *Insulin* is inactivated by insulin-degrading enzyme (also called insulin protease), which is found mainly in the liver and kidney.

D. Adverse reactions to insulin

The symptoms of hypoglycemia are the most serious and common adverse reactions to an excessive dose of *insulin*. Long-term diabetic patients commonly do

not produce adequate amounts of the counter-regulatory hormones (glucagon, epinephrine, cortisol, and growth hormone), which normally provide an effective defense against hypoglycemia. Other adverse reactions include weight gain, lipodystrophy (less common with human *insulin*), allergic reactions, and local injection site reactions. Diabetics with renal insufficiency may require adjustment of the *insulin* dose.

INSULIN PREPARATIONS AND TREATMENT



A. Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: regular *insulin*, *insulin lispro*, *insulin aspart*, and *insulin glulisine*. Regular *insulin* is a short-acting, soluble, crystalline zinc *insulin*. Regular *insulin* is usually given subcutaneously (or IV in emergencies), and it rapidly lowers blood glucose. Regular *insulin*, *insulin lispro*, and *insulin aspart* are pregnancy category B, and *insulin glulisine* is pregnancy category C. Because of their rapid onset and short duration of action, the *lispro*, *aspart*, and *glulisine* forms are classified as rapid acting insulins. These agents offer more flexible treatment regimens and may lower the risk of hypoglycemia. *Insulin lispro* differs from regular *insulin* in that lysine and proline at positions 28 and 29 in the B chain are reversed. This results in more rapid absorption after subcutaneous injection than is seen with regular *insulin*. Consequently, *insulin lispro* acts more rapidly. Peak levels of *insulin lispro* are seen at 30 to 90 minutes after injection, as compared with 50 to 120 minutes for regular *insulin*. *Insulin lispro* also has a shorter duration of activity. *Insulin aspart* and *insulin glulisine* have pharmacokinetic and pharmacodynamics properties similar

to those of *insulin lispro*. They are administered to mimic the prandial (mealtime) release of *insulin*, and they are usually not used alone but with a longer-acting *insulin* to ensure proper glucose control.

Insulin lispro is usually administered 15 minutes prior to a meal or immediately following a meal, whereas *glulisine* can be taken either 15 minutes before a meal or within 20 minutes after starting a meal. *Insulin aspart* should be administered just prior to the meal or up to 15 minutes following the meal. All of the rapid-acting formulations are suitable for IV administration, although regular *insulin* is most commonly used when the IV route is needed. *Insulin lispro*, *insulin aspart*, and *insulin glulisine* may also be used in external *insulin* pumps.

B. Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin is a suspension of crystalline *zinc insulin* combined at neutral pH with the positively charged polypeptide protamine. [Another name for this preparation is *insulin isophane*.] Its duration of action is intermediate because of the delayed absorption from its conjugation with protamine, forming a less-soluble complex. *NPH insulin* should only be given subcutaneously (never IV) and is useful in treating all forms of diabetes except diabetic ketoacidosis and emergency hyperglycemia. It is used for basal control and is usually given along with rapid- or short-acting *insulin* for mealtime control.

C. Long-acting insulin preparations

1. Insulin glargine: The isoelectric point of *insulin glargine* is lower than that of human *insulin*, leading to precipitation at the injection site and extending its action. It is slower in onset than *NPH insulin* and has a flat, prolonged hypoglycemic effect with no peak. Like the other insulins, it must be given subcutaneously.

2. Insulin detemir: *Insulin detemir* has a fatty-acid side chain. This addition enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of *insulin glargine*. Neither *insulin detemir* nor *insulin glargine* should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamics and pharmacokinetic properties.

D. Insulin combinations

Various premixed combinations of human insulins, such as 70-percent *NPH insulin* plus 30-percent regular *insulin*, 50 percent of each of these, and 75-percent *NPH insulin* plus 25-percent *insulin lispro*, are also available.

E. Standard treatment versus intensive treatment

For patients with diabetes mellitus who require *insulin* therapy, standard treatment involves injection of *insulin* twice daily. In contrast, intensive treatment seeks to normalize blood glucose through more frequent injections of *insulin* (three or more times daily in response to monitoring blood glucose levels). The ADA recommends a target mean blood glucose level of 154 mg/dL or less (corresponding to HbA1c of 7 percent or less) for patients with diabetes, and this is more likely to be achieved with intensive treatment. [Note: Normal mean blood glucose is approximately 115 mg/dL or less, with an HbA1c content of 5.7 percent or less.] The frequency of hypoglycemic episodes, coma, and seizures due to excessive *insulin* is higher with intensive treatment regimens. Nonetheless, patients on intensive therapy show a significant reduction in such long-term complications of diabetes as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care. Intensive therapy should generally not be recommended for patients with longstanding diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness. Intensive therapy has not been shown to significantly reduce the macrovascular complications of diabetes.

Glucose lowering drugs

4th Year Students- Pharmacology

Dr. Ahmed Hamed Ataimish

Lec.6

INSULIN SECRETAGOGUES

These agents are useful in the treatment of patients who have type 2 diabetes but who cannot be managed by diet alone. Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are those most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of glucose-lowering drugs with or without *insulin* to control their hyperglycemia. *Insulin* is added because of the progressive decline in β cells that occurs due to the disease or aging. Oral glucose-lowering agents should not be given to patients with type 1 diabetes.

A. Sulfonylureas

These agents are classified as *insulin* secretagogues, because they promote *insulin* release from the β cells of the pancreas. The primary drugs used today are the second-generation drugs *glyburide*, *glipizide*, and *glimepiride*.

1. Mechanism of action: The mechanism of action includes

- 1) Stimulation of *insulin* release from the β cells of the pancreas by blocking the ATP-sensitive K^+ channels, resulting in depolarization and Ca^{2+} influx;
- 2) Reduction in hepatic glucose production; and
- 3) Increase in peripheral insulin sensitivity.

2. Pharmacokinetics and fate: Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted by the liver or kidney. The duration of action ranges from 12 to 24 hours.

3. Adverse effects: Weight gain, hyperinsulinemia, and hypoglycemia.

These drugs should be used with caution in patients with hepatic or renal insufficiency, because delayed excretion of the drug and resulting accumulation may cause hypoglycemia. Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds such as *glyburide*. *Glyburide* has minimal transfer across the placenta and may be a reasonably safe alternative to insulin therapy for diabetes in pregnancy.

B. Glinides

This class of agents includes *repaglinide* and *nateglinide*.

1. Mechanism of action: Like the sulfonylureas, their action is dependent on functioning pancreatic β cells. They bind to a distinct site on the sulfonylurea receptor

of ATP-sensitive potassium channels, thereby initiating a series of reactions ending in the release of *insulin*. However, in contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of *insulin* that occurs after a meal and are categorized as postprandial glucose regulators. Combined therapy of these agents with *metformin* or the glitazones has been shown to be better than monotherapy with either agent in improving glycemic control. Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.

2. Pharmacokinetics and fate: These drugs are well absorbed orally after being taken 1 to 30 minutes before meals. Both glinides are metabolized to inactive products by cytochrome P450 3A4 in the liver and are excreted through the bile.

3. Adverse effects: Although these drugs can cause hypoglycemia, the incidence of this adverse effect appears to be lower than that with the sulfonylureas. [Note: Drugs that inhibit CYP3A4, like *ketoconazole*, *itraconazole*, *fluconazole*, *erythromycin*, and *clarithromycin*, may enhance the glucose-lowering effect of *repaglinide*, whereas drugs that increase levels of this enzyme, such as barbiturates, *carbamazepine*, and *rifampin*, may have the opposite effect.] *Repaglinide* has been reported to cause severe hypoglycemia in patients who are also taking the lipid-lowering drug *gemfibrozil*, and concurrent use is contraindicated. Weight gain is less of a problem with the glinides than with the sulfonylureas. These agents must be used with caution in patients with hepatic impairment.

ORAL AGENTS: INSULIN SENSITIZERS

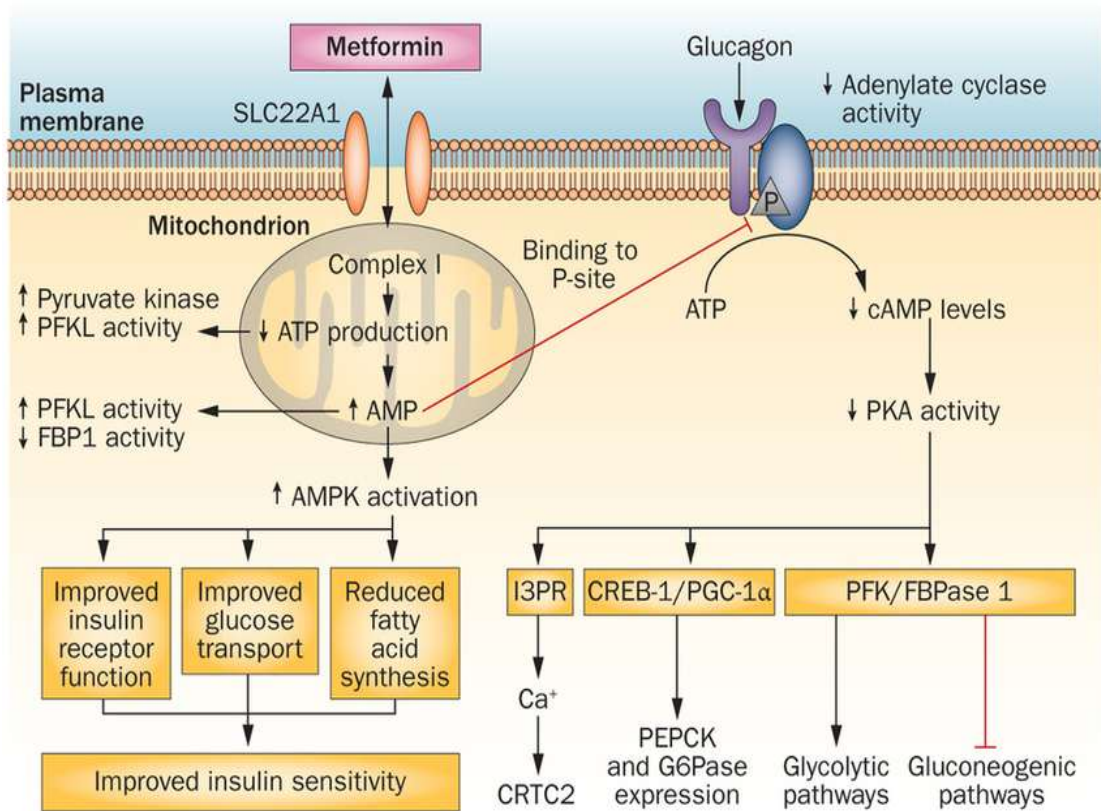
Two classes of oral agents, the biguanides and thiazolidinediones, improve *insulin* action. These agents lower blood sugar by improving target-cell response to *insulin* without increasing pancreatic *insulin* secretion.

A. Biguanides

Metformin, the only currently available biguanide, is classed as an *insulin* sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing *insulin* resistance. *Metformin* differs from the sulfonylureas in that it does not promote *insulin* secretion so hyperinsulinemia is not a problem. Therefore, the risk of

hypoglycemia is far less than that with sulfonylurea agents, and it may only occur if caloric intake is not adequate or exercise is not compensated for calorically.

1. Mechanism of action: The main mechanism of action of *metformin* is reduction of hepatic glucose output, largely by inhibiting hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for the high blood glucose on waking in the morning]. *Metformin* also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. Metformin enters the cell and inhibits mitochondrial complex I. Complex I inhibition results in reduced ATP levels and an accumulation of AMP. AMP binds to the so called 'P-site' at the adenylate cyclase enzyme and inhibits its activity, leading to reduced generation of cAMP upon stimulation of the glucagon receptor. As a result, PKA activation and its downstream pathways are inhibited. Gluconeogenesis is suppressed as a result of reduced activity of enzymes involved in the gluconeogenic flux. Metformin-induced change in energy charge also activates AMPK, which suppresses fat metabolism and possibly also contributes to the reduced gluconeogenic gene expression and induction of phosphorylation of GLUT4 enhancer factor.



An important property of this drug is its ability to modestly reduce hyperlipidemia (low-density lipoprotein [LDL] and very-low-density lipoprotein [VLDL] cholesterol concentrations fall, and high-density lipoprotein [HDL] cholesterol rises). These effects may not be apparent until 4 to 6 weeks of use.

The patient commonly loses weight because of loss of appetite. The ADA treatment algorithm recommends *metformin* as the drug of choice for newly diagnosed type 2 diabetics. *Metformin* may be used alone or in combination with one of the other agents as well as with *insulin*. Hypoglycemia may occur when *metformin* is taken in combination with *insulin*. [Note: If used with *insulin*, the dose of *insulin* may require adjustment because *metformin* decreases the production of glucose by the liver.]

2. Pharmacokinetics and fate: *Metformin* is well absorbed orally, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

3. Adverse effects: These are largely gastrointestinal. *Metformin* is contraindicated in diabetic patients with renal disease and in those with diabetic ketoacidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of congestive heart failure, and severe infection. *Metformin* should be used with caution in patients older than age 80 years and in those with a history of congestive heart failure or alcohol abuse. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may interfere with vitamin B12 absorption.

4. Other uses: In addition to the treatment of type 2 diabetes, *metformin* is effective in the treatment of polycystic ovary disease. Its ability to lower *insulin* resistance in these women can result in ovulation and, therefore, possibly pregnancy.

B. Thiazolidinediones (glitazones)

Another group of agents that are *insulin* sensitizers are the thiazolidinediones (TZDs), also called the glitazones. *Troglitazone* was the first of these to be approved for the treatment of type 2 diabetes but was withdrawn after a number of deaths from hepatotoxicity were reported. The two members of this class currently available are *pioglitazone* and *rosiglitazone*.

1. Mechanism of action: They are known to target the peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear hormone receptor. Ligands for PPAR γ regulate adipocyte production and secretion of fatty acids as well as glucose metabolism, resulting in increased *insulin* sensitivity in adipose tissue, liver, and skeletal muscle. Hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and

elevated HbA1c levels are improved. *Pioglitazone* and *rosiglitazone* can be used as monotherapy or in combination with other glucose-lowering agents or *insulin*. The dose of *insulin* required for adequate glucose control in these circumstances may have to be lowered. *Rosiglitazone* is not recommended due to concerns regarding cardiac adverse effects.

2. Pharmacokinetics and fate: Both *pioglitazone* and *rosiglitazone* are well absorbed after oral administration and are extensively bound to serum albumin. Both undergo extensive metabolism by different CYP450 isozymes. Some metabolites of *pioglitazone* have activity. Renal elimination of *pioglitazone* is negligible, with the majority of the active drug and metabolites excreted in the bile and eliminated in the feces. The metabolites of *rosiglitazone* are primarily excreted in the urine. No dosage adjustment is required in renal impairment. It is recommended that these agents not be used in nursing mothers.

3. Adverse effects: Because there have been deaths from hepatotoxicity in patients take *trogliptazone* it is recommended that liver enzyme levels of patients on these medications be measured initially and periodically thereafter. Very few cases of liver toxicity have been reported with *rosiglitazone* or *pioglitazone*. Weight increase can occur, possibly because TZDs may increase subcutaneous fat or cause fluid retention. [Note: The latter can lead to or worsen heart failure.] TZDs have been associated with osteopenia and increased fracture risk. Several meta-analyses identified a potential increased risk of myocardial infarction and death from cardiovascular causes with *rosiglitazone*. However, the Food and Drug Administration has maintained that *rosiglitazone* should remain on the market with stricter warnings and restrictions on its use. Other adverse effects of the TZDs include headache and anemia.

4. Other uses: As with *metformin*, the relief of *insulin* resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.

α-GLUCOSIDASE INHIBITORS

Acarbose and *miglitol* are orally active drugs used for the treatment of patients with type 2 diabetes.

A. Mechanism of action

These drugs are taken at the beginning of meals. They act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels. Both drugs exert their effects by reversibly inhibiting membrane-bound α -glucosidase in the

intestinal brush border. This enzyme is responsible for the hydrolysis of oligosaccharides to glucose and other sugars. [Note: *Acarbose* also inhibits pancreatic α -amylase, thereby interfering with the breakdown of starch to oligosaccharides.]

Consequently, the postprandial rise of blood glucose is blunted. Unlike other oral glucose-lowering agents, these drugs neither stimulate *insulin* release nor increase *insulin* action in target tissues. Thus, as monotherapy, they do not cause hypoglycemia. However, when used in combination with the sulfonylureas or with *insulin*, hypoglycemia may develop. [Note: It is important that the hypoglycemic patient be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]

B. Pharmacokinetics and fate

Acarbose is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. On the other hand, *miglitol* is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

DIPEPTIDYL PEPTIDASE-IV

INHIBITORS

Sitagliptin and *saxagliptin* are orally active dipeptidyl peptidase-IV (DPP-IV) inhibitors used for the treatment of patients with type 2 diabetes. Other agents in this category are currently in development.

A. Mechanism of action

These drugs inhibit the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1). Prolonging the activity of incretin hormones results in increased *insulin* release in response to meals and a reduction in inappropriate secretion of glucagon. DPP-IV inhibitors may be used as monotherapy or in combination with a sulfonylurea, *metformin*, glitazones, or *insulin*.

B. Pharmacokinetics and adverse effect

Saxagliptin is metabolized via CYP450 3A4/5 to an active metabolite. The primary route of elimination for *saxagliptin* and the metabolite is renal.

Pancreatitis has occurred with use of *sitagliptin*. Strong inhibitors of CYP450 3A4/5, such as *ketoconazole*, and *clarithromycin*, may increase levels of *saxagliptin*. Therefore, reduced doses of *saxagliptin* should be used.

INCRETIN MIMETICS

Exenatide and *liraglutide* are injectable incretin mimetic used for the treatment of patients with type 2 diabetes. These agents may be used as adjunct therapy in patients who have failed to achieve adequate glycemic control on a sulfonylurea, *metformin*, a glitazone, or a combination thereof.

A. Mechanism of action

The incretin mimetic are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists. These agents not only improve glucose- dependent *insulin* secretion but also slow gastric emptying time, decrease food intake, decrease postprandial glucagon secretion, and promote β -cell proliferation. Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.

B. Pharmacokinetics and fate

Being polypeptides, *exenatide* and *liraglutide* must be administered subcutaneously. *Liraglutide* is highly protein bound and has a long half-life, allowing for once-daily dosing without regard to meals. *Exenatide* is eliminated mainly via glomerular filtration and has a much shorter half-life.

Because of its short duration of action, *exenatide* should be injected twice daily within 60 minutes prior to morning and evening meals.

C. Adverse effects

Similar to *pramlintide*, the main adverse effects of the incretin mimetic consist of nausea, vomiting, diarrhea, and constipation. Because of the peptide nature of incretin mimetic, patients may form antibodies to these agents. In most cases the antibodies do not result in reduced efficacy of the drug or increased adverse effects. *Exenatide* and *liraglutide* have been associated with pancreatitis. *Liraglutide* causes thyroid C-cell tumors in rodents. However, it is unknown if it causes these tumors or thyroid carcinoma in humans.

ESTROGENS

Pharmacology-4th Year Students

Lec. 8

Ahmed Hamed Ataimish

Introduction

Estradiol also known as *17 β-estradiol* is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in the premenopausal woman. *Estrone* is a metabolite of *estradiol* that has approximately one third the estrogenic potency of *estradiol*. *Estrone* is the primary circulating estrogen after menopause, and it is generated mainly from conversion of androstenedione in peripheral tissues. *Estriol*, another metabolite of *estradiol*, is significantly less potent than *estradiol*. It is present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta.

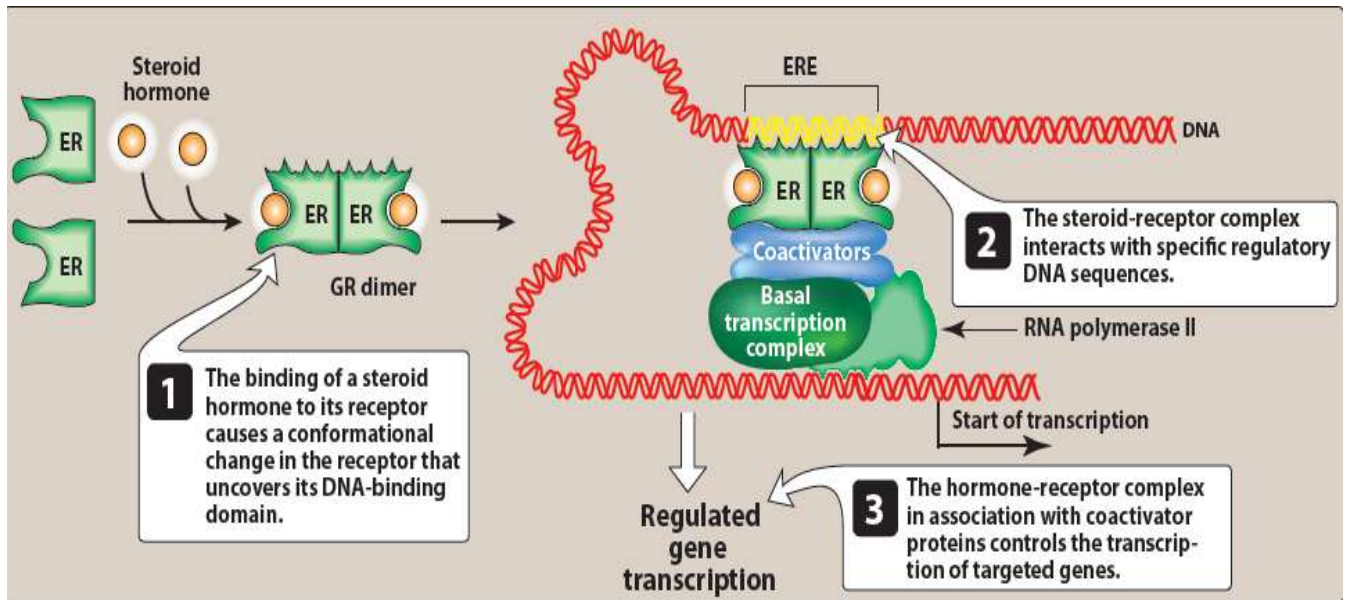
A preparation of conjugated estrogens containing sulfate esters of *estrone* and *equilin* (naturally occurring estrogen obtained from pregnant mares' urine) is an oral preparation used for hormone replacement therapy. Plant-derived conjugated estrogen products are also available. Synthetic estrogens, such as *ethinyl estradiol*, undergo less first-pass metabolism than naturally occurring steroids and, thus, are effective when administered orally at lower doses. Non-steroidal compounds that bind to estrogen receptors and exert either estrogenic or antiestrogenic effects on target tissues are called selective estrogen-receptor modulators. These include *tamoxifen* and *raloxifene*, among others.

A. Mechanism of action

After dissociation from their binding sites on sex hormone-binding globulin or albumin in the plasma, steroid hormones diffuse across the cell membrane and bind with high affinity to specific nuclear-receptor proteins. Two estrogen-receptor subtypes, α and β , mediate the effects of the hormone. The α -receptor may be considered as the classic estrogen receptor, and the β -receptor is highly homologous to the α -receptor. However, the N-terminal portion of the α -receptor contains a region that promotes transcription activation, whereas the β -receptor contains a repressor domain. As a result, the transcriptional properties of the α and β estrogen receptors are different. Affinity for the receptor type varies with the particular estrogen. These receptor isoforms vary in structure, chromosomal location, and tissue distribution. The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions.

Other pathways that require these hormones have been identified that lead to more rapid actions. For example, activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade.

In addition, estrogen-mediated dilation of coronary arteries occurs by the increased formation and release of nitric oxide and prostacyclin in endothelial cells.



B. Therapeutic uses

Estrogens are most frequently used for contraception and postmenopausal hormone therapy (HT). Due to concerns over the risks of HT, the National American Menopause Society recommends that HT be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms. Estrogens were previously widely used for prevention of osteoporosis, but current guidelines recommend use of other therapies such as *alendronate* over estrogen. Estrogen may be used for prevention of osteoporosis if other therapies are inappropriate or not tolerated.

Estrogens are also used extensively for replacement therapy in premenopausal patients who are deficient in this hormone. Such a deficiency can be due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause.

1. Postmenopausal HT: The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, “hot flashes” or “hot flushes”) and vaginal atrophy. For women who have an intact uterus, a progestogen is always

included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen. For women who have undergone a hysterectomy, unopposed estrogen therapy is recommended because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters.

2. Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral or transdermal route.

3. Other uses: Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women (11 to 13 years of age) with primary hypogonadism. Continued treatment is required after growth is completed. Similarly, estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure. Replacement therapy is usually continued until about age 50, the average age of normal menopause.

C. Pharmacokinetics

1. Naturally occurring estrogens: These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized *estradiol* is available and has better bioavailability. Although there is some first-pass metabolism, it is not sufficient to lessen the effectiveness when taken orally.

2. Synthetic estrogen analogs: These compounds, such as *ethinyl estradiol* and *mestranol*, are well absorbed after oral administration. *Mestranol* is quickly demethylated to *ethinyl estradiol*, which is metabolized more slowly than the naturally occurring estrogens by the liver and peripheral tissues. Being fat soluble, they are stored in adipose tissue, from which they are slowly released. Therefore, the synthetic estrogen analogs have a prolonged action and a higher potency compared to those of natural estrogens.

3. Metabolism: Estrogens are transported in the blood bound to serum albumin or sex hormone-binding globulin. As mentioned above, bioavailability of estrogen taken orally is low due to first-pass metabolism in the liver. To reduce first-pass metabolism, the drugs may be administered via the transdermal route (patch, topical gel, topical emulsion, or spray), intravaginally (tablet, cream, or ring), or by injection. They are hydroxylated in the liver to derivatives that are subsequently glucuronidated or sulfated. The parent drugs and their metabolites undergo

excretion into bile and are then reabsorbed through the enterohepatic circulation. Inactive products are excreted in urine. [Note: In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism, causing feminization in males or signs of estrogen excess in females.]

D. Adverse effects

Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. Postmenopausal uterine bleeding can occur. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.]

III. SELECTIVE ESTROGEN-RECEPTOR MODULATORS

Selective estrogen-receptor modulators (SERMs) are a class of estrogen related compounds that interact at estrogen receptors but have different effects depending on the tissues (that is, they display selective agonist or antagonism according to the tissue type).

This category includes *tamoxifen*, *raloxifene*, *toremifene* (orphan drug), and *clomiphene*.

Mechanism of action

Considered to be the first SERM, *tamoxifen* competes with estrogen for binding to the estrogen receptor in breast tissue. *Raloxifene* is a second-generation SERM that is related to *tamoxifen*. Like *tamoxifen*, *raloxifene* also exhibits antagonism of estrogen receptors in the breast tissue. In addition, *raloxifene* decreases bone resorption and overall bone turnover. Bone density is increased, and vertebral fractures are decreased. Unlike estrogen and *tamoxifen*, *raloxifene* apparently has little to no effect on the endometrium and, therefore, may not predispose to uterine cancer. *Raloxifene* lowers total cholesterol and low-density lipoprotein (LDL) in the serum, but it has no effect on high-density lipoprotein (HDL) or triglyceride levels. *Clomiphene* acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect thereby increases the secretion of gonadotropin-releasing hormone and gonadotropins leading to stimulating ovulation.

B. Therapeutic uses

Tamoxifen is currently used in the palliative treatment of metastatic breast cancer in postmenopausal women. It may also be used as adjuvant therapy following mastectomy or radiation in breast cancer and as a prophylactic therapy to reduce the risk of breast cancer in high risk patients. *Raloxifene* is approved for the prophylaxis of breast cancer in high-risk women and also for the prevention and treatment of osteoporosis in postmenopausal women. *Clomiphene* has been used successfully to treat infertility associated with an-ovulatory cycles, but it is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure.

C. Pharmacokinetics

The SERMs are readily absorbed after oral administration. *Tamoxifen* is extensively metabolized by cytochrome P450 (CYP450) enzymes. *Raloxifene* is rapidly converted to glucuronide conjugates through first-pass metabolism. More than 95 percent of *raloxifene* is bound to plasma proteins. All three agents undergo enterohepatic cycling, and the primary route of excretion is through the bile into feces.

D. Adverse effects

The most frequent adverse effects of *tamoxifen* treatment are hot flashes and nausea. Menstrual irregularities and vaginal bleeding can also occur. Due to its estrogenic activity in the endometrium, hyperplasia and malignancies have been reported in women who have been maintained on *tamoxifen*. This has led to recommendations for limiting the length of time on the drug for some indications. Because it is metabolized by various CYP450 isozymes, *tamoxifen* is subject to many drug interactions. Some CYP450 inhibitors may prevent the formation of active metabolites of *tamoxifen* and possibly reduce the efficacy (for example, *amiodarone*, *haloperidol*, *risperidone*). Thus, concurrent drug therapy should be reviewed carefully to screen for potential drug interactions with *tamoxifen*. Similar to *tamoxifen*, hot flashes and leg cramps are common adverse effects with *raloxifene*. In addition, there is an increased risk of deep-vein thrombosis, pulmonary embolism, and retinal-vein thrombosis. Women who have a past or active history of venous thromboembolic events should not take the drug. In addition, *raloxifene* should be avoided in women who are or may become pregnant. Coadministration with *cholestyramine* can reduce the absorption of *raloxifene* by 60 percent. Therefore, these drugs should not be taken together.



PROGESTOGENS & ANDROGENS

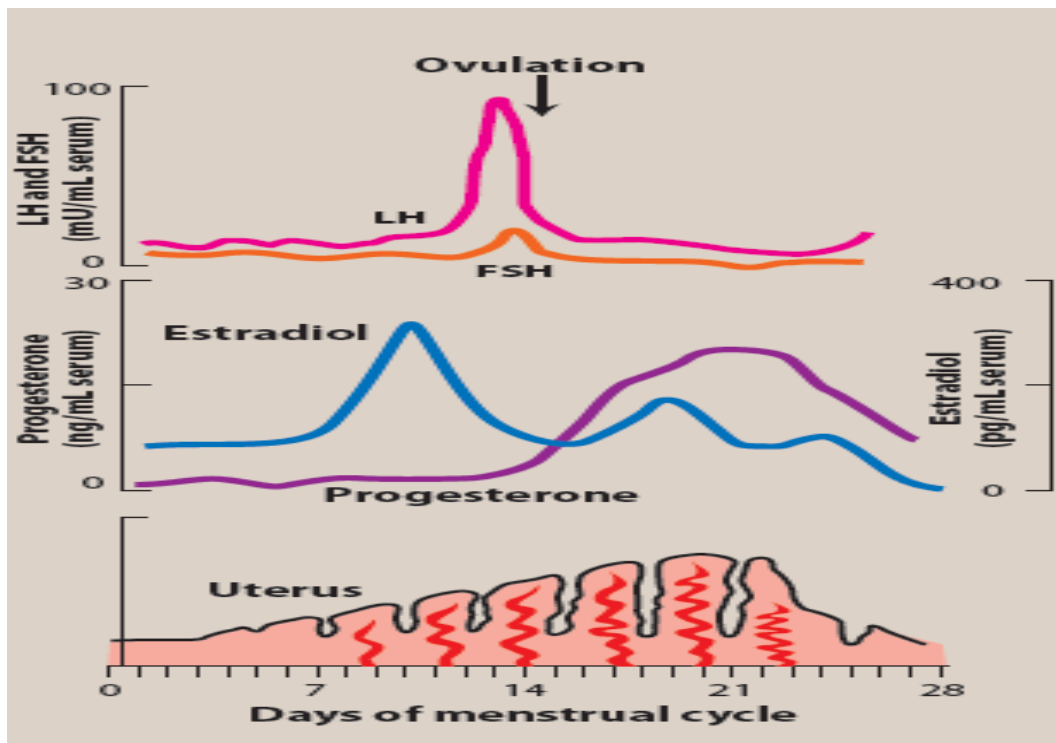
4th Year Students

Lec. 9



PROGESTOGENS

Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes. In females, *progesterone* promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of *progesterone* that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, *progesterone* continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of *progesterone* from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation.



A. Mechanism of action

Progestogens exert their mechanism of action in a manner analogous to that of the other steroid hormones. They cause:

- 1) Increase in hepatic glycogen, probably through an insulin-mediated mechanism;

- 2) Decrease in Na⁺ reabsorption in the kidney due to competition with aldosterone at the mineralocorticoid receptor;
- 3) Increase in body temperature through an unknown mechanism;
- 4) Decrease in some plasma amino acids; and
- 5) Increase in excretion of urinary nitrogen.

B. Therapeutic uses of progestogens

- 1- Hormonal deficiency and
- 2- Contraception. For contraception, they are generally used with estrogens, either in combination or in a sequential manner. *Progesterone* by itself is not used widely as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability.

Synthetic progestogens (that is, progestins) used in contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include *norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*, *desogestrel*, *norgestimat*, and *drospirenone*.

Most synthetic progestins used in oral contraceptives (for example, *norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*) are derived from 19-nortestosterone and possess some androgenic activity because of their structural similarity to *testosterone*. *Medroxyprogesterone acetate* is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT.

- 3- Progestins are also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

C. Pharmacokinetics

A micronized preparation of *progesterone* is rapidly absorbed after oral administration. It has a short half-life in the plasma and is almost completely metabolized by the liver. The glucuronidated metabolite is excreted primarily by the kidney. Synthetic progestins are less rapidly metabolized.

Oral *medroxyprogesterone acetate* has a half-life of 30 days. When injected intramuscularly or subcutaneously it has a half-life of about 40 to 50 days and provides contraceptive activity for approximately 3 months. The other progestins have half-lives of 1 to 3 days, allowing for once-daily dosing.

D. Adverse effects

The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido.

Some progestins, such as the 19-nortestosterone derivatives, have androgenic activity and can increase the ratio of LDL to HDL cholesterol and cause acne and hirsutism. Less androgenic progestins, such as *norgestimate* and *drospirenone*, may be preferred in women with acne. Injectable *medroxyprogesterone acetate* has been associated with an increased risk of osteoporosis, which has led to recommendations for limiting the duration of use to 2 years.

E. Antiprogestin

Mifepristone is a progesterone antagonist with partial agonist activity. [*Mifepristone* also has potent antigluocorticoid activity.] Administration of this drug to females early in pregnancy usually results in abortion of the fetus due to interference with the *progesterone* needed to maintain pregnancy.

Mifepristone is often combined with the prostaglandin analog *misoprostol* (administered orally or intravaginally) to induce uterine contractions.

This combination increases the chance for successful termination of pregnancy. The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion. *Mifepristone* has also been investigated as an oral contraceptive and an emergency contraceptive agent.

CONTRACEPTIVES

Drugs are available that decrease fertility by a number of different mechanisms, such as preventing ovulation, impairing gametogenesis or gamete maturation, and interfering with gestation. Currently, interference with ovulation is the most common pharmacologic intervention for preventing pregnancy.

A. Major classes of contraceptives

1. Combination oral contraceptives: Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives. Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 days. Triphasic oral contraceptive products attempt to mimic the natural female cycle and most contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods.

With either type of combination oral contraceptive, active pills are taken for 21 days followed by 7 days of placebo. Withdrawal bleeding occurs during the hormone-free interval. [The most common estrogen in the combination pills is *ethinyl estradiol*. The most common progestins are *norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*, *desogestrel*, *norgestimate*, and *drospirenone*.] These preparations are highly effective in achieving contraception.

2. Transdermal patch: An alternative to combination oral contraceptive pills is a transdermal contraceptive patch containing *ethinyl estradiol* and the progestin *norelgestromin*. One contraceptive patch is applied each week for 3 weeks to the abdomen. Week 4 is patch free, and withdrawal bleeding occurs. The transdermal patch has efficacy comparable to that of the oral contraceptives, but it has been shown to be less effective in women weighing greater than 90 kilograms. Contraindications and adverse effects for the patch are similar to those of oral contraceptives.

Pharmacokinetic studies have indicated that total estrogen exposure with the transdermal patch is up to 60 percent greater than that seen with a 35- μ g estrogen oral contraceptive. Increased exposure to estrogen may increase the risk of adverse events such as thromboembolism.

3. Progestin-only pills: Products containing a progestin only, usually *norethindrone* (called a “mini-pill”), are taken daily on a continuous schedule. Progestin-only pills deliver a low, continuous dosage of drug. These preparations are less effective than the combination pill, and they may produce irregular menstrual cycles more frequently than the combination product. The progestin-only pill has limited patient acceptance because of anxiety over the increased possibility of pregnancy and the frequent occurrence of menstrual irregularities. The progestin-only pill may be used for patients who are breastfeeding (unlike estrogen, progestins do not have an effect on milk production), are intolerant to estrogen, are smokers, or have other contraindications to estrogen-containing products.

5. Injectable progestin: *Medroxyprogesterone acetate* is an injectable contraceptive that is administered every 3 months. It is available in both intramuscular and subcutaneous injection formulations. Weight gain is a common adverse effect of *medroxyprogesterone acetate*.

Because this product provides high sustained levels of progestin, many women experience amenorrhea with *medroxyprogesterone acetate*. In addition, return to fertility may be delayed for several months after discontinuing use of this agent. *Medroxyprogesterone acetate* may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the

drug should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options.

6. Progestin implants: A subdermal implant containing *etonogestrel* offers long-term contraception. One 4-cm capsule is placed sub-dermally in the upper arm and provides contraception for approximately 3 years. Principal side effects of the implants are irregular menstrual bleeding and headaches.

7. Progestin intrauterine device: A *levonorgestrel*-releasing intrauterine system offers a highly effective method of long-term contraception. This intrauterine device provides contraception for up to 5 years. It is a suitable method of contraception for women who already have at least one child and do not have a history of pelvic inflammatory disease or ectopic pregnancy.

B. Mechanism of action

Combination of estrogen and progestin administered over an approximately 3-week period inhibits ovulation. [The estrogen provides a negative feedback on the release of LH and follicle-stimulating hormone (FSH) by the pituitary gland, thus preventing ovulation. The progestin also inhibits LH release and thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.]

Adverse effects

Most adverse effects are believed to be due to the estrogen component, but cardiovascular effects reflect the action of both estrogen and progestin. The incidence of adverse effects with oral contraceptives is relatively low and is determined by the specific compounds and combinations used.

1. Major adverse effects: The major adverse effects are breast fullness, depression, fluid retention, headache, nausea, and vomiting.

2. Cardiovascular: Although rare, the most serious adverse effect of oral contraceptives is cardiovascular disease, including thromboembolism, thrombophlebitis, hypertension, increased incidence of myocardial infarction, and cerebral and coronary thrombosis. These adverse effects are most common among women who smoke and who are older than age 35 years, although they may affect women of any age.

3. Carcinogenicity: Oral contraceptives have been shown to decrease the incidence of endometrial and ovarian cancer. The incidence of cervical cancer may be increased with oral contraceptives, because women are less likely to use additional barrier methods of contraception

that reduce exposure to human papilloma virus (the primary risk factor for cervical cancer). The ability of oral contraceptives to induce other neoplasms is controversial. The production of benign tumors of the liver that may rupture, and hemorrhage is rare.

4. Metabolic: Abnormal glucose tolerance (similar to the changes seen in pregnancy) is sometimes associated with oral contraceptives.

Weight gain is common in women who are taking the *nortestosterone* derivatives. Weight gain may be less with oral contraceptives containing *drospirenone*.

5. Serum lipids: The combination pill causes a change in the serum lipoprotein profile: Estrogen causes an increase in HDL and a decrease in LDL (a desirable occurrence), whereas progestins may negate some of the beneficial effects of estrogen. Therefore, estrogen- dominant preparations are best for individuals with elevated serum cholesterol.

6. Contraindications: Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy. Combination oral contraceptives should not be used in patients over the age of 35 who are heavy smokers.

ANDROGENS

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosterone*, the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovary of the female and by the adrenal gland in both sexes. Other androgens secreted by the testes are **5 α -dihydrotestosterone (DHT)**, **androstenedione**, and **dehydroepiandrosterone (DHEA)** in small amounts. In adult males, *testosterone* secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. *Testosterone* or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates *testosterone* production. The androgens are required for

- 1) normal maturation in the male,
- 2) sperm production,
- 3) increased synthesis of muscle proteins and hemoglobin, and
- 4) decreased bone resorption.

A. Mechanism of action

Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although *testosterone* itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, *testosterone* is converted by 5 α -reductase to DHT, which binds to the receptor. In the brain, liver, and adipose tissue, *testosterone* is bio-transformed to *estradiol* by CYP450 aromatase. The hormone-receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins.

B. Therapeutic uses

1. Androgenic effects: Androgenic steroids are used for males with inadequate androgen secretion. [Hypogonadism can be caused by testicular dysfunction (primary hypogonadism) or due to failure of the hypothalamus or pituitary (secondary hypogonadism). In each instance, androgen therapy is indicated.]

2. Anabolic effects: Anabolic steroids can be used to treat senile osteoporosis and chronic wasting associated with human immunodeficiency virus (HIV) or cancer. They may also be used as adjunct therapy in severe burns and to speed recovery from surgery or chronic debilitating diseases.

3. Endometriosis: *Danazol*, a mild androgen, is used in the treatment of endometriosis (ectopic growth of the endometrium) and fibrocystic breast disease. [*Danazol* also possess antiestrogenic activity.] It inhibits release of FSH and LH but has no effect on the aromatase. Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects. *Danazol* has been reported occasionally to suppress adrenal function.

4. Unapproved use: Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders. In some popular publications, DHEA (a precursor of *testosterone* and estrogen) has been touted as the anti-aging hormone as well as a “performance enhancer.” With its ready availability in health food stores, the drug has been abused. There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses.

Pharmacokinetics

1. Testosterone: This agent is ineffective orally because of inactivation by first-pass metabolism. As with the other sex steroids, *testosterone* is rapidly absorbed and is metabolized to relatively or completely inactive compounds that are excreted primarily in the urine.

C17-esters of *testosterone* (for example, *testosterone cypionate* or *enanthate*) are administered intramuscularly. [Note: The addition of the esterified lipid makes the hormone more lipid soluble, thereby increasing its duration of action.] Transdermal patches, topical gels, and buccal tablets of *testosterone* are also available.

2. Testosterone derivatives: Alkylation of the 17 α position of *testosterone* allows oral administration of the hormone. Agents such as *fluoxymesterone* have a longer half-life in the body than that of the naturally occurring androgen.

Fluoxymesterone is effective when given orally, and it has a 1:2 androgenic to anabolic ratio. *Oxandrolone* is another orally active testosterone derivative with anabolic activity 3 to 13 times that of *testosterone*. Hepatic adverse effects have been associated with the 17 α -alkylated androgens.

D. Adverse effects

1. In females: Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus.

2. In males: Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia. Cosmetic changes such as those described for females may occur as well. Androgens can also stimulate growth of the prostate.

3. In children: Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

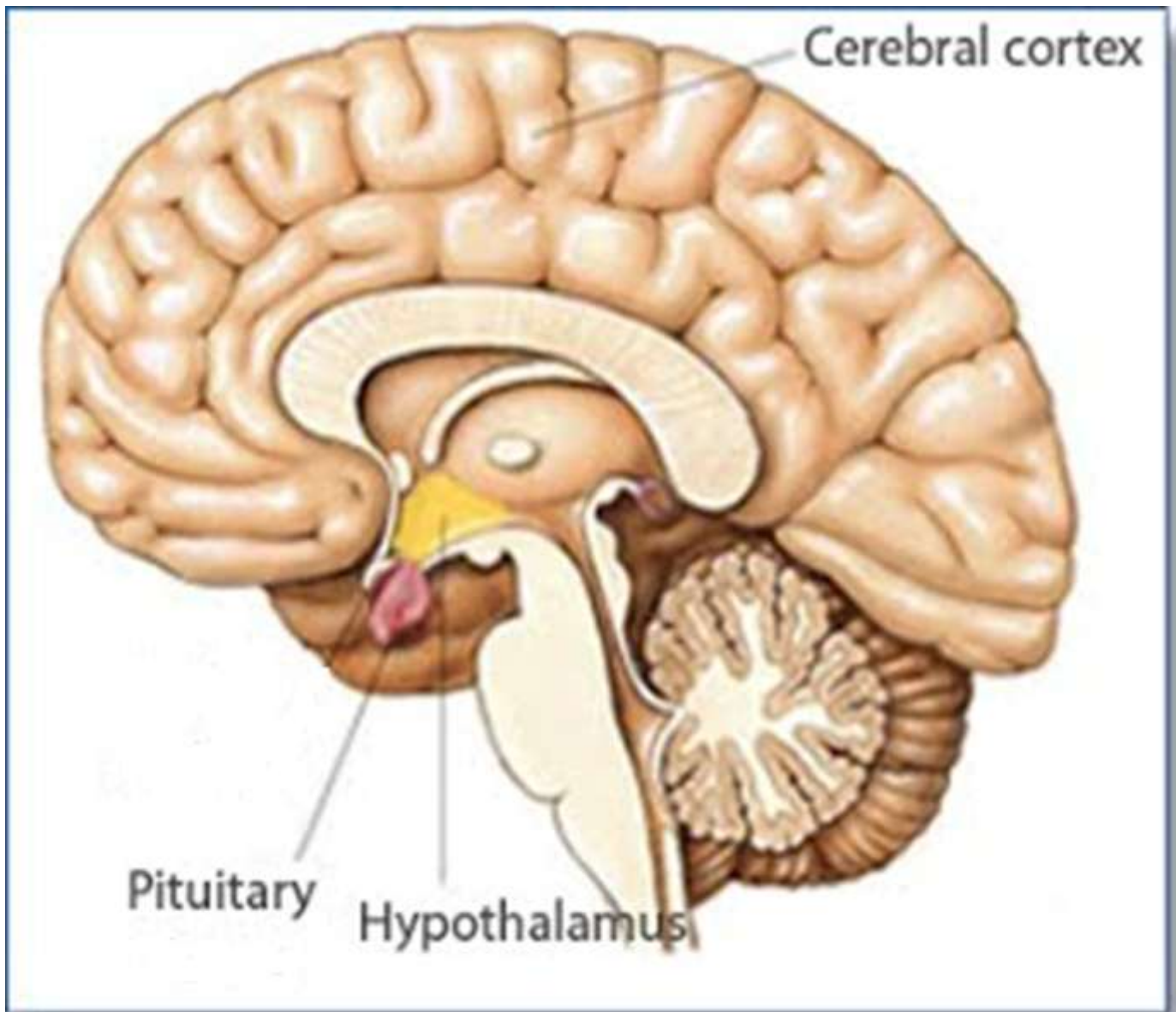
4. General effects: Because androgens increase serum LDL and lower serum HDL levels, they increase the LDL: HDL ratio and potentially increase the risk for premature coronary heart disease. Androgens can also cause fluid retention, leading to edema.

5. In athletes: Use of anabolic steroids, (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities,

increased aggression (“roid rage”), major mood disorders, and other adverse effects described above.

E. Antiandrogens

Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. For example, at high doses, the antifungal drug *ketoconazole* inhibits several of the CYP450 enzymes involved in steroid synthesis. *Finasteride* and *dutasteride*, agents used for the treatment of benign prostatic hypertrophy, inhibit 5 α -reductase. The resulting decrease in formation of dihydrotestosterone in the prostate leads to a reduction in prostate size. Antiandrogens, such as *flutamide*, act as competitive inhibitors of androgens at the target cell. *Flutamide* is used in the treatment of prostatic carcinoma in males. Two other potent antiandrogens, *bicalutamide* and *nilutamide*, are effective orally for the treatment of prostate cancer.



LEC.1 PHARMACOLOGY-4TH YEAR STUDENTS

THE PITUITARY GLAND

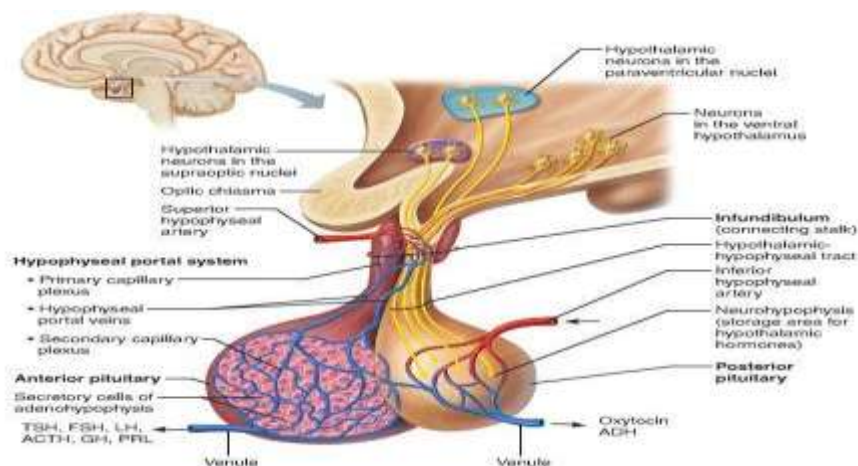
OVERVIEW

The neuroendocrine system, which is controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues. This contrasts with the nervous system which communicates locally by electrical impulses and neurotransmitters directed through neurons to other neurons or to specific target organs, such as muscle or glands. Nerve impulses generally act within milliseconds.

The endocrine system releases hormones into the bloodstream, which carries these chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. The two regulatory systems are closely interrelated. For example the release of hormones is stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses.

HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The hormones secreted by the hypothalamus and the pituitary are all peptides or low-molecular-weight proteins that act by binding to specific receptor sites on their target tissues. The hormones of the anterior pituitary are regulated by neuropeptides that are called either “releasing” or “inhibiting” factors or hormones. These are produced in cell bodies in the hypothalamus, and they reach the cells of the pituitary by the hypophyseal portal system.



The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo post-translational modification to produce hormones which are released into the circulation. [Unlike those of the posterior pituitary, the hormones of the anterior pituitary are not stored in granules prior to release.]

THE ANTERIOR PITUITARY GLAND (ADENOHYPHYSIS)

Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary. The hypothalamic-releasing hormones are primarily used for diagnostic purposes (that is, to determine pituitary insufficiency).

[Note: The hypothalamus also synthesizes the precursor proteins of the hormones vasopressin and oxytocin, which are transported to the posterior pituitary, where they are stored until released.]

Although a number of pituitary hormone preparations are currently used therapeutically for specific hormonal deficiencies, most of these agents have limited therapeutic applications. Hormones of the anterior and posterior pituitary are administered either intramuscularly (IM), subcutaneously, or intranasally, but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

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

| 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) Releases luteinising hormone (LH) or interstitial cell-stimulating hormone (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 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 |

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

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.

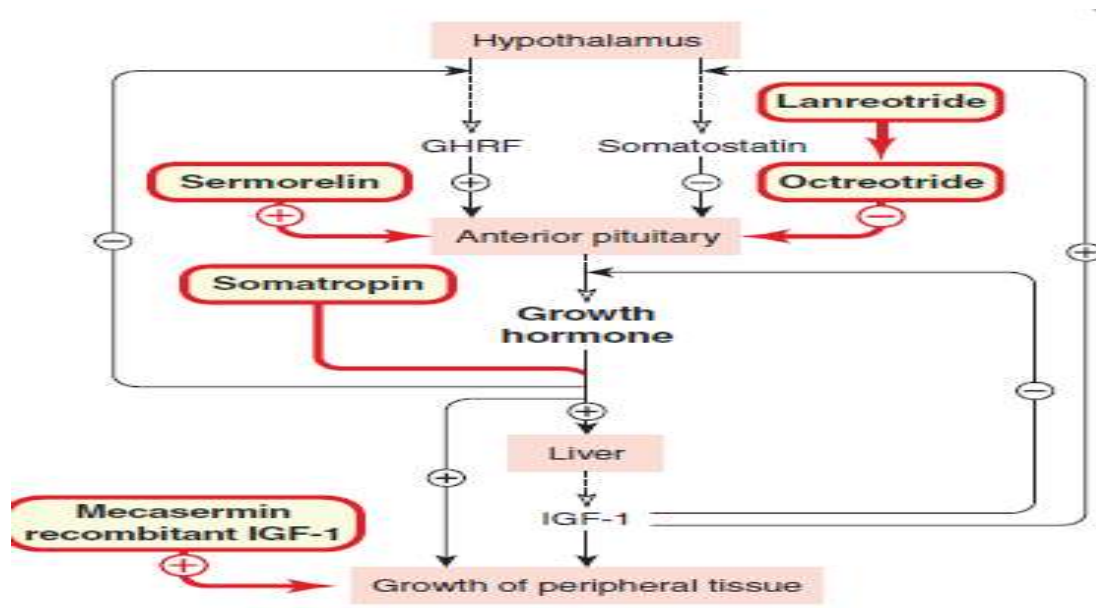
In *long negative feedback* pathways, hormones secreted from the peripheral glands exert regulatory actions on both the hypothalamus and the anterior pituitary. The mediators of the *short negative feedback* pathways are anterior pituitary hormones that act directly on the hypothalamus. The peptidergic neurons in the hypothalamus are themselves influenced by other centers 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) Hypothalamic control of the anterior pituitary is also exerted through the *tuberohypophyseal dopaminergic pathway*. 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. 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.

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, 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. It is used for the treatment of *carcinoid* and other hormone-secreting tumors. It also has a place in the therapy of *acromegaly* (a condition in which there is over secretion of growth hormone in an adult). It also constricts splanchnic blood vessels, and is used to treat bleeding esophageal 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 hyperglycemia 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 tumors.

GONADOTROPHIN-RELEASING HORMONE

Gonadotrophin- (or luteinizing hormone-) releasing hormone is a decapeptide that releases both *follicle stimulating hormone (FSH)* and *luteinizing hormone (LH)* from gonadotrophs.

It is also available as a preparation called **gonadorelin**, used mainly in the treatment of infertility.

GROWTH HORMONE-RELEASING FACTOR (SOMATORELIN)

Growth hormone-releasing factor (GHRF) is a peptide with 40–44 amino acid residues. An analogue, **sermorelin**, may be used as a diagnostic test for growth

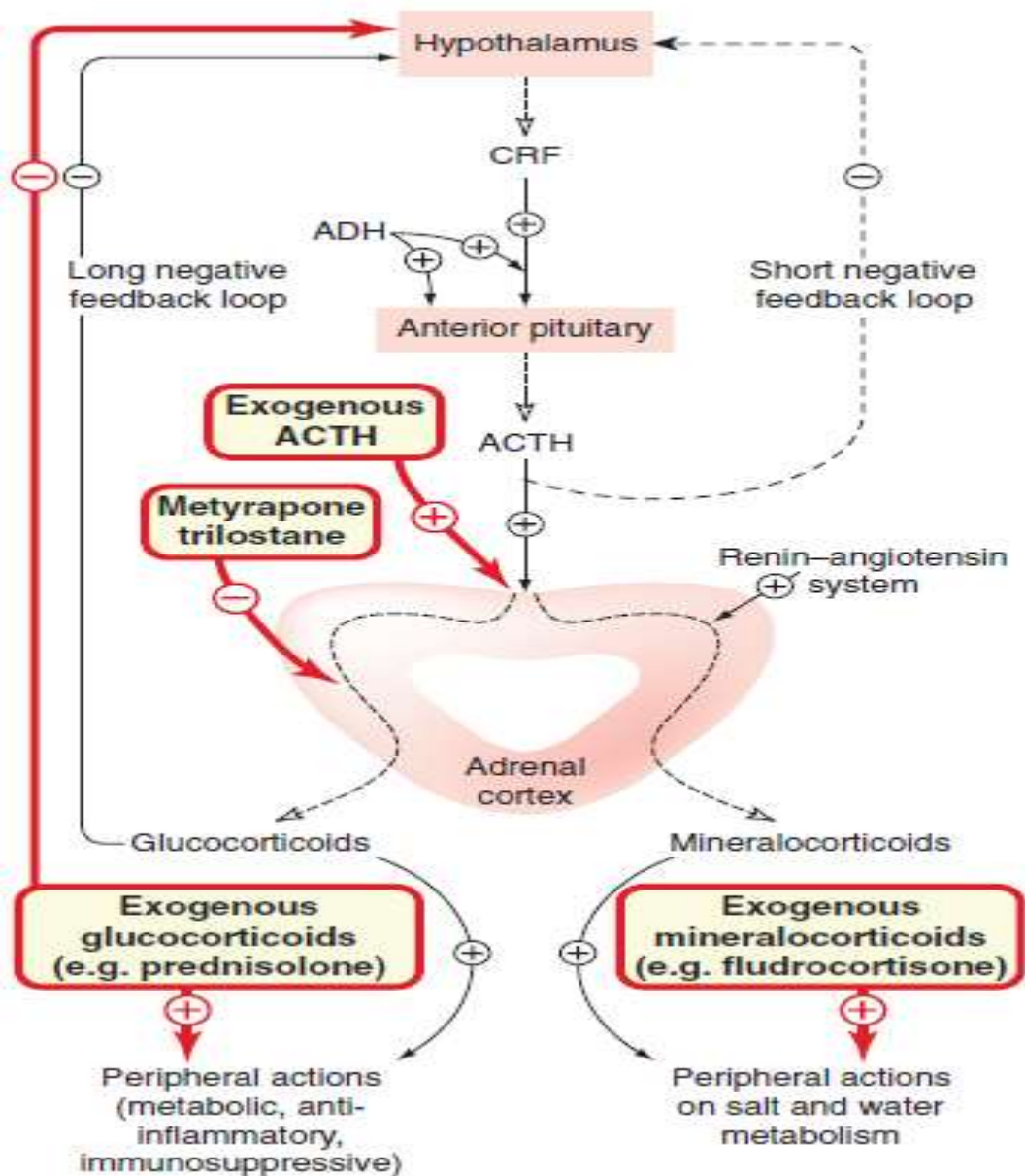
hormone secretion. Given intravenously, subcutaneously or intranasally (generally the former), it causes secretion of growth hormone within minutes and peak concentrations in 1 h. The action is selective for the somatotrophs in the anterior pituitary, and no other pituitary hormones are affected. *Unwanted 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. Given intravenously in normal subjects, it causes an increase in plasma TSH concentration, whereas in patients with *hyperthyroidism* there is a blunted response because the raised blood thyroxine concentration has a negative feedback effect on the anterior pituitary. The opposite occurs with *hypothyroidism*, 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*.



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.

ANTERIOR PITUITARY HORMONES

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.

Regulation of secretion

Secretion of growth hormone is regulated by the action of hypothalamic GHRF and modulated by somatostatin. One of the mediators of growth hormone action, *insulin-like growth factor (IGF)-1*, which is released from the liver, 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*, which may result from lack of GHRF or a failure of IGF generation or action. 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. 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 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*.

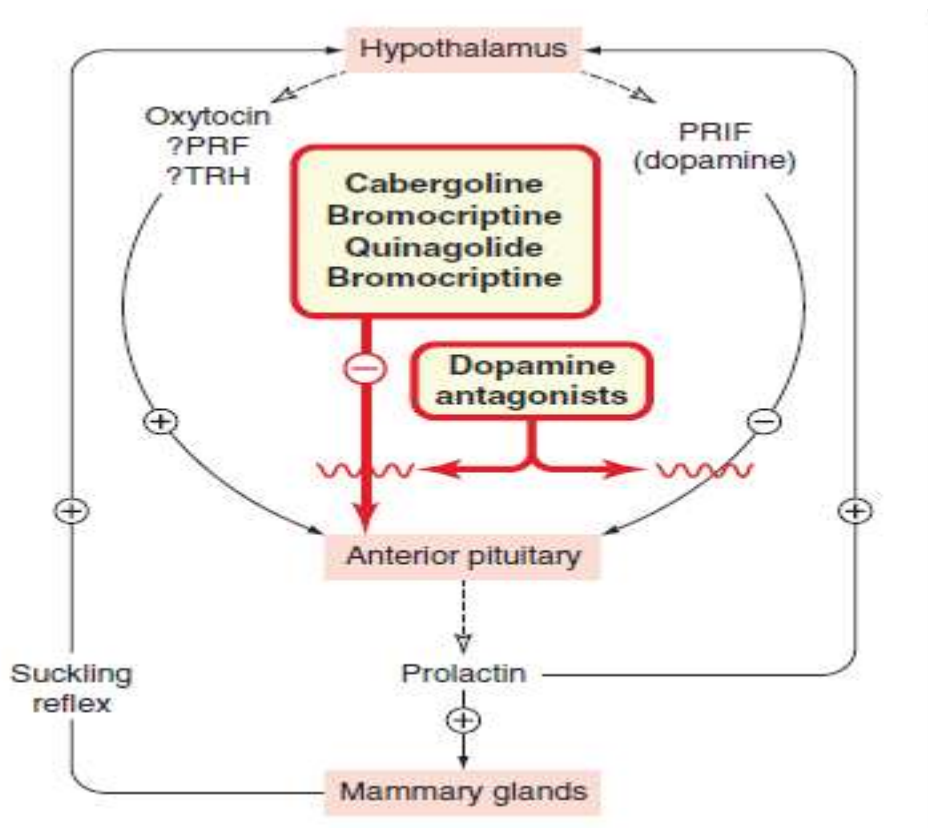
An excessive production in adults, which is usually the result of a benign pituitary tumour, results in *acromegaly*, in which there is enlargement mainly of facial structures and of the hands and feet. The dopamine agonist **bromocriptine** and octreotide may reduce the condition. Another useful agent 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, the inhibitory mediator being dopamine (acting on D2 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 of the neuropeptide *galanin*. Dopamine antagonists (used mainly as antipsychotic drugs) are potent stimulants of prolactin release, whereas agonists such as bromocriptine suppress prolactin release. Bromocriptine is also used in Parkinsonism.

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, 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.

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

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.

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Lec. 3

MINERALOCORTICIDS

Pharmacology 4th Year Students

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Introduced by Dr. Ahmed Hamed Ataimish

MINERALOCORTICOIDS

The main endogenous mineralocorticoid is aldosterone. Its main action is to increase Na^+ reabsorption by the distal tubules in the kidney, with concomitant increased excretion of K^+ and H^+ . An excessive secretion of mineralocorticoids, as in Conn's syndrome, causes marked Na^+ and water retention, with increased extracellular fluid volume, and sometimes hypokalemia, alkalosis and hypertension. Decreased secretion, as in Addison's disease, causes Na^+ loss (desalinization) and a marked decrease in extracellular fluid volume. There is a concomitant decrease in the excretion of K^+ , resulting in hyperkalemia.

Regulation of aldosterone synthesis and release

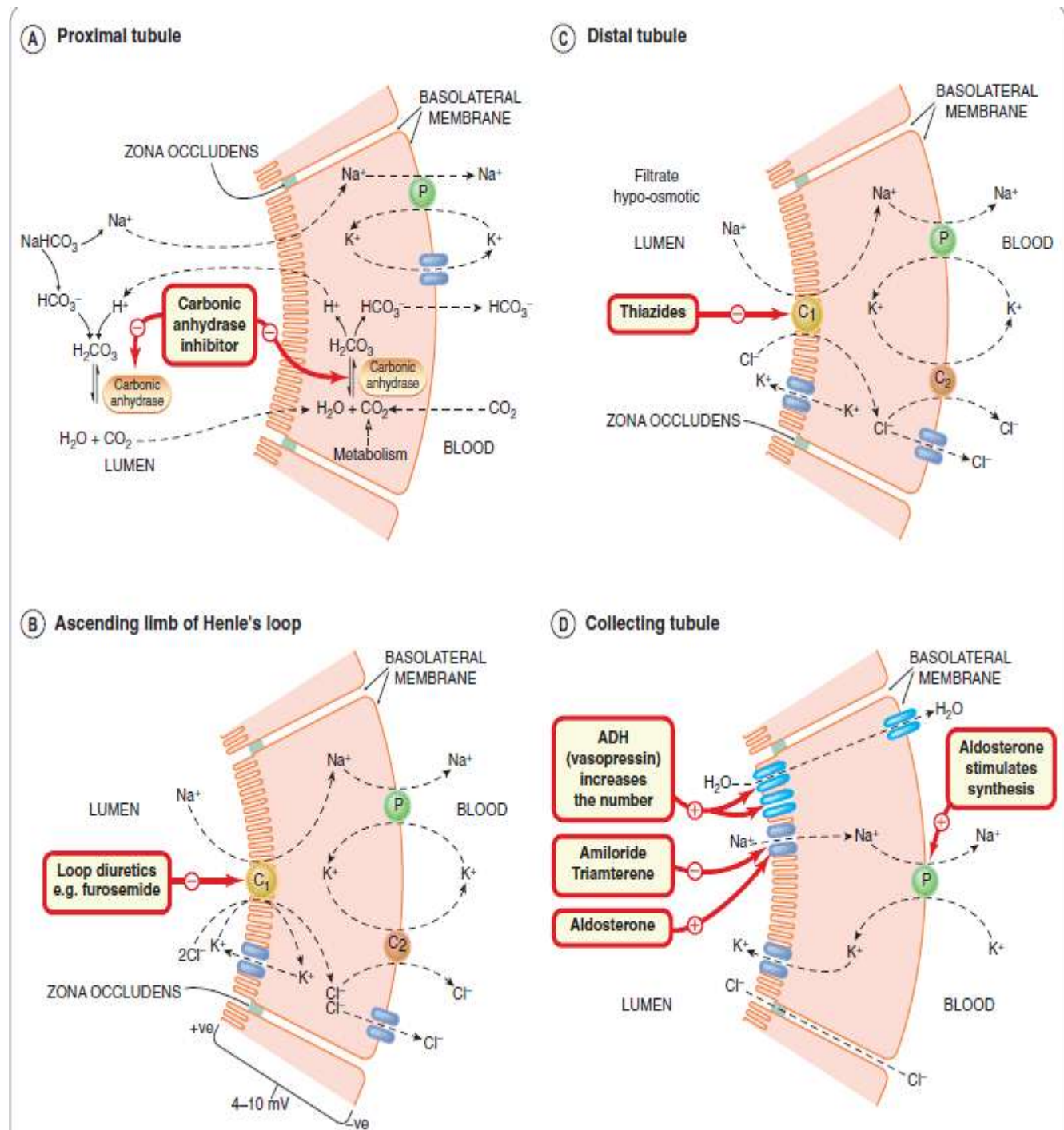
The regulation of the synthesis and release of aldosterone is complex. Control depends mainly on the electrolyte composition of the plasma and on the angiotensin II system. Low plasma Na^+ or high plasma K^+ concentrations affect the zona glomerulosa cells of the adrenal directly, stimulating aldosterone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

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 -hydroxy-steroid dehydrogenase type 2 enzyme, which converts hydrocortisone (cortisol) into inactive cortisone, thus ensuring that the cells are affected only by the mineralocorticoid hormone itself. Interestingly, this enzyme is inhibited by **carbenoxolone** (previously used to treat gastric ulcers through increasing mucus synthesis in human gastric mucosa. This was particularly attributed to an increase in the N-acetylneuraminic acid-containing mucoproteins, and was suggested to be due to stimulation of microsomal glycosyl transferases by carbenoxolone.), 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, causing increased K^+ excretion. 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**, 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. Side effects include gynecomastia

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 and resistant edema. **Eplerenone** has a similar indication and mechanism of action, although fewer side effects.

Spirolactone: This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. *Spirolactone* is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

Eplerenone: *Eplerenone* specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of *spironolactone*. It is approved as an antihypertensive

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 *downregulating* genes (e.g. cytokine genes) that promote the inflammatory response, whereas many of the side effects are caused by *overexpression* 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.

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. 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. 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.

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Lec. 4

The thyroid Gland

Pharmacology-4th Year Students

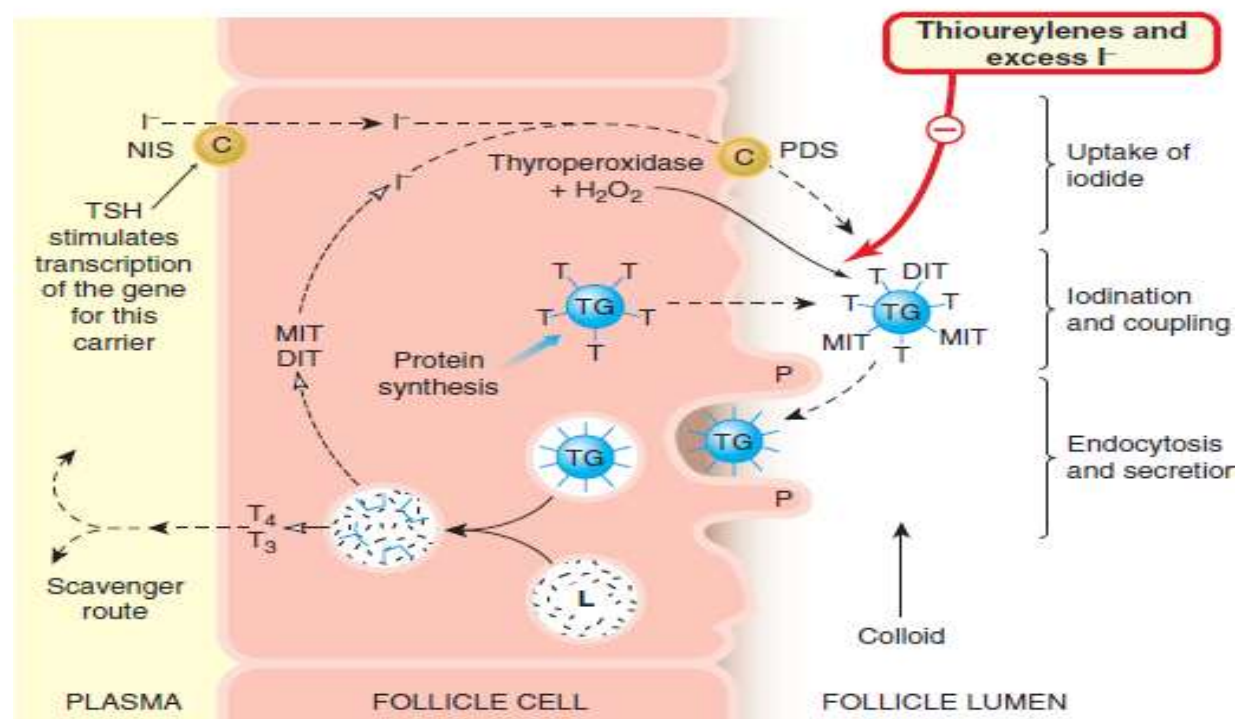
The thyroid Gland

SYNTHESIS, STORAGE AND SECRETION OF THYROID HORMONES

The thyroid gland secretes three main hormones: *thyroxine* (T₄), *tri-iodothyronine* (T₃) and *calcitonin*. T₄ and T₃ are critically important for normal growth and development and for controlling energy metabolism. Calcitonin is involved in the control of plasma [Ca²⁺] and is used to treat osteoporosis and other metabolic bone diseases. 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 synthesized, 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 are:

- Uptake of plasma iodide by the follicle cells
- Oxidation of iodide and iodination of tyrosine residues of thyroglobulin
- Secretion of thyroid hormone.

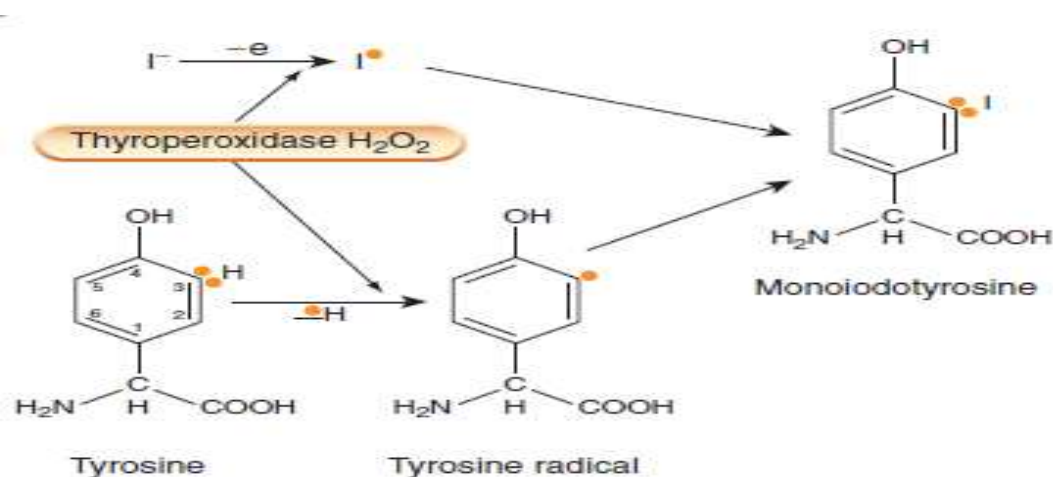


UPTAKE OF PLASMA IODIDE BY THE FOLLICLE CELLS

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* (PDS), an I⁻/Cl⁻ porter in the apical membranes. Uptake is very rapid: labelled iodide (¹²⁵I) is found in the lumen within 40 s of intravenous injection.

OXIDATION OF IODIDE AND IODINATION OF TYROSINE RESIDUES

The oxidation of iodide and its incorporation into thyroglobulin (termed the *organification* of iodide) is catalyzed by *thyroperoxidase*. The reaction requires the presence of hydrogen peroxide (H₂O₂) as an oxidizing agent. Iodination occurs after the tyrosine has been incorporated into thyroglobulin.

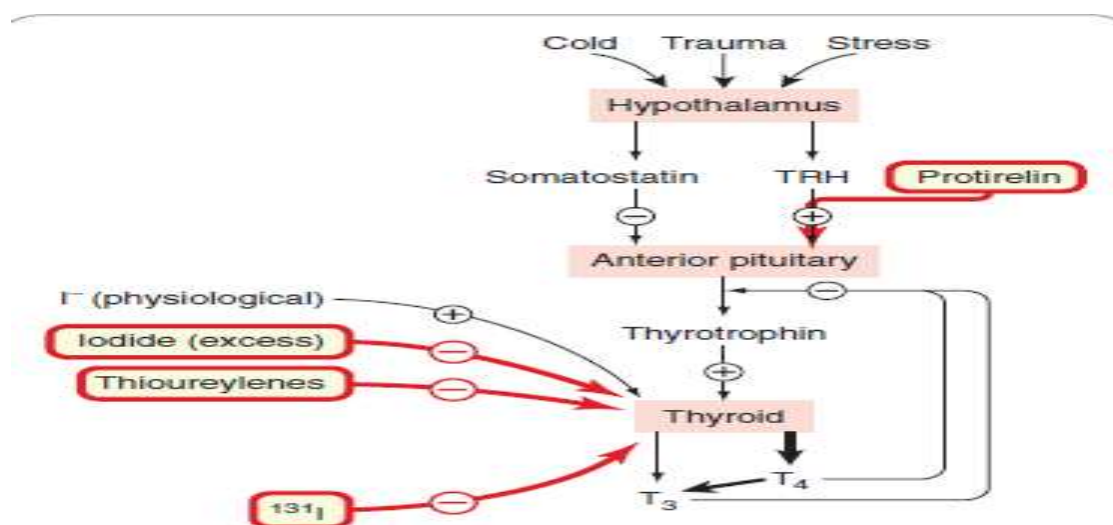


Tyrosine residues are iodinated first at position 3 on the ring, forming *monoiodotyrosine* (MIT) and then, in some molecules, on position 5 as well, forming *di-iodotyrosine* (DIT). While still incorporated into thyroglobulin, these molecules are then coupled in pairs, either MIT with DIT to form T₃, or two DIT molecules to form T₄. 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 synthesized and released as required.

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, as does the synthetic tripeptide **protirelin**, 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 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 T3 and T4
- 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, T3 being more active than T4 in this respect.

The other main factor influencing thyroid function is the plasma iodide concentration. About 100 nmol of T4 is synthesized daily, necessitating uptake by the gland of approximately 500 nmol of iodide each day (equivalent to about 70 μ g 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. 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. 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.

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.

A. 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, T₃ being three to five times more active than T₄ in this respect.

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 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 calorogenic 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.

B. 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.

MECHANISM OF ACTION

Both thyroid hormones are transported in the blood bound mainly to *thyroxine-binding globulin* (TBG). 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 T3 is 20 times faster than that of T4 (plasma half-life about 6 days). The long half-life of T4 is a consequence of its strong binding to TBG.

While there is some evidence for non-genomic actions, these hormones act mainly through a specific nuclear receptor, TR. Two distinct genes, TR α and TR β , code for several receptor isoforms that have distinct functions. T4 may be regarded as a prohormone, because when it enters the cell, it is converted to T3, 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 T3 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.

ABNORMALITIES OF THYROID FUNCTION

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 and increased appetite associated with loss of weight occur. There are several types of hyperthyroidism, but only two are common: *diffuse toxic goiter* (also called *Graves' disease* or *exophthalmic goiter*) and *toxic nodular goiter*.

Diffuse toxic goiter 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 goiter have protrusion of the eyeballs. The pathogenesis of this condition is thought to be caused by the presence of TSH receptor like proteins in orbital tissues.

Toxic nodular goiter is caused by a benign neoplasm or adenoma, and may develop in patients with long-standing simple goiter. This condition does not usually have concomitant exophthalmos.

SIMPLE, NON-TOXIC GOITER

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 goiter. 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 and 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 tumors with **radioiodine** is another cause of hypothyroidism.

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 anti-thyroid 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 . 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 T4. 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. Another use for this drug is the treatment of thyroid cancer.

THIOUREYLENES

The thioureylene group of drugs (thioamides) comprises **carbimazole**, **methimazole** and **propylthiouracil**.

Mechanism of action

Thiourelenes 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 mediated by inhibit the iodination of tyrosyl residues in thyroglobulin. It is thought that they inhibit the thyroperoxidase-catalysed oxidation reactions by acting as substrates for the peroxidase–iodinium complex, thus competitively inhibiting the interaction with tyrosine. Propylthiouracil has the additional effect of reducing the deiodination of T4 to T3 in peripheral tissues.

Pharmacokinetic aspects

Thiourelenes are given orally. Carbimazole is rapidly converted to its active metabolite 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. This is not only because T4 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 T₄ to T₃. 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. 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.

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 H₂O₂ 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**, 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, 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.

Thyroid storm: Thyroid storm presents with extreme symptoms of hyperthyroidism. The therapeutic options for thyroid storm are the same as those for hyperthyroidism, except that the drugs are given in higher doses and more frequently. β -Blockers that lack sympathomimetic activity, such as *propranolol*, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.

Intravenous administration is effective in treating thyroid storm. An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, *diltiazem*. Other agents used in the treatment of thyroid storm include *PTU*, iodides, iodinated contrast media (which rapidly inhibits the conversion of T4 to T3) and glucocorticoids (to protect against shock).

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), 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 $\mu\text{g}/\text{day}$ 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.