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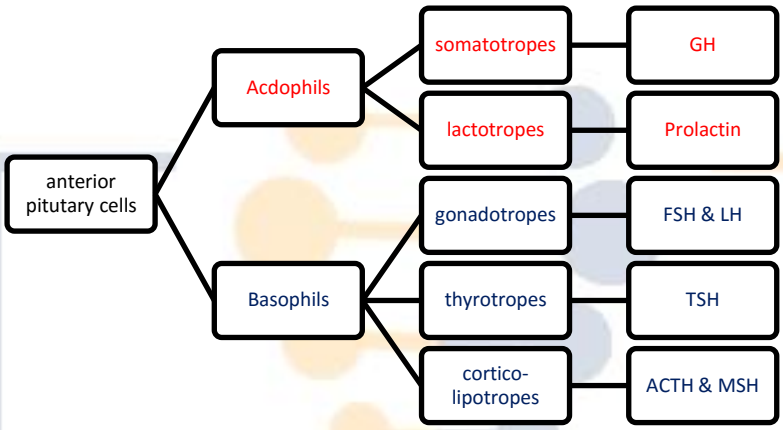
DESTINATION
PHARMAGENS

Anterior pituitary hormones

Anterior pituitary hormones produced by characteristic cells which are characterized by their stainig properties



HORMONE	Amino Acid Count	Mol Wt
GH	Single chain: 191	22000
SOMATOSTATIN	Single chain: 14	-
PL	199	23000
FSH	Chain A: 92 & Chian B: 111	33 kDa
LH	Chain A: 92 & Chian B: 121	30 kDa
TSH	210	30000
ACTH	39	4500

GROWTH HORMONE (GH)

Physiological functions

- Growth promotion of all organs (except brain and eye)
- Increased utilization of fat by muscles and lipolysis by adipose tissue

- Decreased glucose utilization by muscles and increased gluconeogenesis, glycogenolysis
- Increased amino acid uptake and Protein synthesis
- Increase calcium uptake and retention

Somatomedins or Insulin-like growth factors (mainly IGF-1, also IGF-2)

- peptides in nature
- extracellular mediators of GH response like growth promoting, nitrogen retaining and certain metabolic actions of GH

Pathological involvement

	GH produced in excess	GH produced insufficient
Childrens	Gigantism	Pitutary Dwarfism
Adult	Acromegaly	-

Therapeutic uses

Pitutary dwarfism	Renal failure
Turners synydrome	Catabolic states

Adverse effects of GH and similar preparations

Immune reaction, glucose intolerance and insulin like state, lipodystropy

GH Inhibitors: Somatostatin

- inhibits the secretion of GH, prolactin, and TSH by pituitary; insulin and glucagon by pancreas,
- inhibits almost all gastrointestinal secretions including that of gastrin and HCl.
- Somatostatin constricts splanchnic (thus decreases gi blood flow), hepatic and renal blood vessels.
- During Surgical removal of pituitary adenomas these are preferred, but somatostatin analogues are being increasingly used.

Disadvantages of somatostatin

- short duration of action (t½ 2–3 min),
- lack of specificity for inhibiting only GH secretion and GH rebound on discontinuation.
- The g.i. action produces steatorrhoea, diarrhoea, hypochlorhydria, dyspepsia and nausea as side effect

Synthetic analouges of somatostatin

Octreotide	Lanreotied	Pegvisomant
90 min	10-15 days	-

PROLACTIN

Physiological function

- Growth and development of breast during pregnancy.
- induces synthesis of milk proteins and lactose.
- After parturition, prolactin induces milk secretion,
- Continued high level of prolactin during breastfeeding is responsible for
    - lactational amenorrhoea,
    - inhibition of ovulation and
    - infertility for several months postpartum.
- Prolactin suppresses hypothalamo-pituitarygonadal axis by inhibiting GnRH release.
- Prolactin may affect immune response through action on T-lymphocytes.

Regulation of secretion

- Prolactin is under predominant inhibitory control of hypothalamus through **PRIH** which is **dopamine** that acts on pituitary lactotrope **D2 receptor**.
- Dopaminergic agonists decrease plasma prolactin levels
- dopaminergic antagonists and DA depleter cause increase plasma prolactin levels
- Prolactin levels in blood are low in childhood, increase in girls at puberty and are higher in adult females than in males. A progressive increase occurs during pregnancy, peaking at term.

- Subsequently, high prolactin secretion is maintained by suckling: it falls if breast feeding is discontinued.
- Stress, exertion and hypoglycaemia also stimulate prolactin release.

Physio-pathological involvement

Prolactin levels	Male	Female
High (hyperprolactinaemia)	Galactorrhea	Loss of libido
	Ammenorrhea	Infertility

The causes of hyperprolactinaemia are

- Disorders of hypothalamus > removing the inhibitory control over pituitary
- Antidopaminergic and DA depleting drugs
- Prolactin secreting tumours—these may be microprolactinomas or macroprolactinomas.

Prolactin inhibitors: Bromocriptine, Cabergoline

Actions

Decreases prolactin release from pituitary by activating dopaminergic receptors on lactotrope cells: is a strong antigalactopoietic.

Uses

- As antigalactopoietic in Hyperprolactinemia due to microprolactinomas causing galactorrhoea, amenorrhoea and infertility in women;
- Gynaecomastia, impotence and sterility in men.
- Acromegaly due to small pituitary tumours and inoperable cases.

Adverse effects: Hypotension, Behavioral alterations, mental confusion, hallucinations, abnormal movements, livedo reticularis

Gonadotropins: FSH & LH

Actions

	FSH	LH
MALE	• supports spermatogenesis and • trophic influence on seminiferous tubules • testicular atrophy	• stimulates testosterone secretion by the interstitial cells • ICSH
FEMALE	• induces follicular growth, development of ovum • secretion of estrogens • Ovarian atrophy	• It induces preovulatory swelling of the ripe of graafian follicle and triggers ovulation • luteinization of the ruptured follicle and sustains corpus luteum till the next menstrual cycle. • atresia of the remaining follicles. • Progesterone secretion occurs only under the influence of LH.

- Gametogenesis promotion
- Conversion of cholesterol to pregnenolone (RDS in steroidal hormones synthesis)

Receptors of gonadotropins

	Location of FSH receptors	Location of LH receptors
MALE TESTES	Seminiferous tubules (sertoli cells)	Interstitial (leydigs) cells
FEMALE OVERIES	Granulosa cells	Theca cells, Granulosa cells, luteal cells

Secretion regulation

- Decapeptide **Gonadorelin** (GnRH) by hypothalamus stimulates release of FSH and LH
- In men, the levels of FSH and LH remain practically constant (LH > FSH) while in menstruating women they fluctuate cyclically. The Gn secretion increases at puberty and is higher in women than in men.
- Inhibin—a peptide from ovaries and testes, selectively inhibits FSH release, but not LH release.
- Dopamine inhibits only LH release.
- Testosterone is weaker than estrogens in inhibiting Gn secretion, but has effect on both FSH and LH.
- In females estradiol and progesterone inhibit both FSH and LH secretion mainly through hypothalamus, but also by direct action on pituitary.

Pathological involvement

- delayed puberty or precocious puberty both in girls and boys.
- Inadequate Gn secretion results in amenorrhoea and infertility in women;
- Inadequate Gn secretion results in oligozoospermia, infertility in men.
- Excess production of Gn in adult women causes polycystic ovaries.

PREPARATION	CONTENT	SOURCE
Menotropins	FSH+LH	Urine of menopausal women
Urofollitropins/ Menotropins	FSH	-
HCG	HCG	Urine of pregnant women
rFollitropins (Follitropins α , β)	FSH	Recombinant preparation
rLH (leutropin)	LH	Recombinant preparation
rHCG (choriogonadotropins)	HCG	Recombinant preparation

USES

- Amenorrhea & Infertility females
- Hypogonadotropic hypogonadism in males
- Cryptorchidism
- In vitro fertilization

Synthetic gonadorelin (GnRH)

Short acting analogue (4-8 min) metabolized by enzymatic hydrolysis

Uses

- Testing pituitary gonadal axis in males
- Hypogonadism in females

Superactive GnRH agonist : Goserelin, Leuprolide, Nafarelin, Triptorelin,

- longer acting (t½ 2–6 hours) because of high affinity for GnRH receptor and resistance to enzymatic hydrolysis.

MOA

- Because physiological release of GnRH is in pulses, whereas these agonists act continuously; they only initially increase Gn secretion.
- After 1–2 weeks they cause desensitization and down regulation of GnRH receptors > inhibition of FSH and LH secretion > suppression of gonadal function.
- Spermatogenesis or ovulation cease and testosterone or estradiol levels fall to castration levels.
- Recovery occurs within 2 months of stopping treatment.

Uses

precocious puberty, prostatic carcinoma, endometriosis, premenopausal breast cancer, uterine leiomyoma, polycystic ovarian disease

to assist induced ovulation

They also have potential to be used as contraceptive for both males and females.

TSH : THYROTROPIN

thyroid to synthesize and secrete thyroxine (T4) and triiodothyronine (T3).

Its actions are:

• Induces hyperplasia and hypertrophy of thyroid follicles and

increases blood supply to the gland.

• Promotes trapping of iodide into thyroid by increasing Na+: Iodide symporter (NIS).

• Promotes organification of trapped iodine and its incorporation into T3 and T4 by increasing

peroxidase activity.

• Enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin

to release more of T3 and T4.

Regulation of secretion

Synthesis and release of TSH by pituitary is controlled by hypothalamus primarily through TRH, while somatostatin inhibits TSH secretion.

Dopamine also reduces TSH production induced by TRH.

In majority of cases of myxoedema TSH levels are markedly elevated because of deficient feedback inhibition.

Graves' disease is due to an immunoglobulin of the IgG class which attaches to the thyroid cells and stimulates them in the same way as TSH. Consequently, TSH levels are low.

ADRENOCORTICOTROPIC HORMONE (**ACTH, CORTICOTROPIN**)

derived from a larger peptide **pro-opio melanocortin** (MW 30,000) which also gives rise to endorphins, two lipotropins and two MSHs.

Physiological function

ACTH promotes steroidogenesis in adrenal cortex by stimulating cAMP formation in cortical cells (through specific cell surface GPCRs) > rapidly increases the availability of cholesterol for conversion to pregnenolone which is the rate limiting step in the production of gluco, mineralo and weakly androgenic steroids.

Induction of steroidogenic enzymes occurs after a delay resulting in 2nd phase ACTH action. The stores of adrenal steroids are very limited and rate of synthesis primarily governs the rate of release.

ACTH also exerts trophic influence on **adrenal cortex** (again through cAMP): high doses cause hypertrophy and hyperplasia. **Lack of ACTH results in adrenal atrophy**.

However, **zona glomerulosa** is little affected because **angiotensin II** also exerts trophic influence on this layer and sustains aldosterone secretion.

Regulation of secretion

Hypothalamus regulates ACTH release from pituitary through corticotropin-releasing hormone (CRH). The **CRH receptor** on **corticotropes** is also a GPCR which increases ACTH synthesis as well as release by raising cytosolic cAMP.

Secretion of ACTH has a circadian rhythm. Peak plasma levels occur in the early morning, decrease during day and are lowest at midnight.

Corticosteroids exert inhibitory feedback influence on ACTH production by acting directly on the pituitary as well as indirectly through hypothalamus.

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THYROID HORMONE & DRUGS

The thyroid gland secretes 3 hormones—

triiodothyronine (T_3) thyroxine (T_4)	Thyroid hormones	produced by thyroid follicles
Calcitonin	Ca level regulating hormone	produced by interfollicular 'C' cells

The thyroid hormones are synthesized and stored in the **thyroid follicles** as part of ***thyroglobulin*** molecule—which is a **glycoprotein** synthesized by **thyroid cells**

The synthesis, storage and release of T4 and T3 involves the following processes.

1. *Iodide uptake*

Thyroid cells have an active transport process **Na+: iodide symporter (NIS)** to concentrate this anion; is stimulated by TSH

2. *Oxidation and iodination*

Iodide carried across the **apical membrane** by another transporter termed **'*pendrin*'**

oxidized by **thyroid peroxidase enzyme** to **iodinium (I+) ions** or **hypoiodous acid (HOI)** or **enzyme-linked hypoiodate (E-OI)** with the help of **H2O2**.

These **oxidized forms** of iodine combine with **tyrosil residues** of **thyroglobulin** to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)** these residues are remain attached to the thyroglobulin chains.

3. *Coupling*

Pairs of iodinated tyrosil residues couple together to form T3 and T4.

Normally much more T4 than T3 is formed, but during I2 deficiency relatively more MIT is available and a greater proportion of T3 is formed.

Thus, more active hormone is generated with lesser amount of I2.

Coupling is an **oxidative reaction** and is catalysed by the same **thyroid peroxidase**.

Oxidation of iodide and coupling are both stimulated by TSH

4. Storage and release

Thyroglobulin containing **iodinated tyrosil** and **thyronil** residues is transported to the interior of the follicles and remains stored as **thyroid colloid** till it is taken back into the cells by **endocytosis** and broken down by **lysosomal proteases**.

The T4 and T3 so released is secreted into circulation while MIT and DIT residues are deiodinated and the iodide released is reutilized.

5. *Peripheral conversion of T4 to T3*

Peripheral tissues, especially liver and kidney, convert T4 to T3. About 1/3 of T4 secreted by thyroid undergoes this change and most of the T3 in plasma is derived from liver.

Target tissues take up T3 from circulation for their metabolic need, except brain and pituitary which take up T4 and convert it to T3 within their own cells.

Almost equal amounts of 3, 5, 3´ triiodothyronine (normal T3 : active) and 3, 3´, 5´ triiodothyronine (reverse T3 or rT3: inactive) are produced in the periphery.

The T4 to T3 conversion is carried out by the enzyme *iodothyronine deiodinase* which exists in 3 forms (D1, D2, D3). These forms differ in their organ and cellular localization as well as product formed.

Whereas type 2 deiodinase (D2) generates T3 and D3 generates rT3, the D1 form generates both T3 and rT3.

ACTIONS

1. Growth and development

- ✓ T4 and T3 are essential for normal growth and development.
- ✓ The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system.

2. Intermediary metabolism

Lipid

- ✓ enhance lipolysis
- ✓ plasma free fatty acid levels are elevated.
- ✓ cholesterol metabolism are accelerated, but its conversion to bile acids dominates.
- ✓ hypocholesterolemia. LDL levels in blood are reduced.

Carbohydrate

- ✓ Carbohydrate metabolism is also stimulated.
- ✓ utilization of sugar by tissues is increased (mainly secondary to increased BMR),
- ✓ glycogenolysis and gluconeogenesis in liver
- ✓ hyperglycaemia occurs

Protein

- ✓ protein being used as energy source.
- ✓ negative nitrogen balance and tissue wasting.
- ✓ Weight loss is a feature of hyperthyroidism

3. Calorigenesis

- ✓ T3 and T4 increase BMR by stimulation of cellular metabolism and resetting of the energystat.
- ✓ important for maintaining body temperature
- ✓ However, metabolic rate in brain, gonads, uterus, spleen and lymph nodes is not significantly affected.

4. CVS

- ✓ Heart rate, contractility and output are increased
- ✓ Atrial fibrillation and other irregularities are common in hyperthyroidism.

5. Nervous system

- ✓ Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema.
- ✓ Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

6. Skeletal muscle

- ✓ Muscles are flabby and weak in myxoedema
- ✓ thyrotoxicosis produces increased muscle tone, tremor and weakness due to myopathy

7. GIT

- ✓ Propulsive activity of gut is increased by T3/T4.
- ✓ Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism.

8. Kidney

T3 and T4 do not cause diuresis in euthyroid individuals, but the rate of urine flow is often increased when myxoedematous patients are treated with it.

9. Haemopoiesis

- ✓ Hypothyroid patients suffer from some degree of anaemia which is restored only by T4 treatment.
- ✓ Thus, T4 appears to be facilitatory to erythropoiesis.

10. Reproduction

- ✓ Fertility is impaired in hypothyroidism and women suffer from oligomenorrhoea.
- ✓ Normal thyroid function is required for maintenance of pregnancy and lactation.

USES

The most important use of thyroid hormone is for *replacement therapy* in deficiency states:

1. Cretinism

2. Adult hypothyroidism (Myxoedema)

3. Myxoedema coma

4. Nontoxic goiter

5. Thyroid nodule

6. Papillary carcinoma of thyroid

Thyroid inhibitors

ANTITHYROID DRUGS (Thioamides)

Antithyroid drugs bind to the thyroid peroxidase and prevent oxidation of iodide/ iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin

(ii) Inhibit coupling of iodotyrosine residues to form T3 and T4.

As a result thyroid colloid is depleted over time and blood levels of T3/T4 are progressively lowered

Action (ii) has been observed at lower concentration of antithyroid drugs than action (i).

Pharmacokinetics

All are concentrated in thyroid: intrathyroid t½ is longer: effect of a single dose lasts longer than would be expected from the plasma t½.

Carbimazole acts largely by getting converted to methimazole in the body and is longer acting than propythiouracil.

Adverse effects

Hypothyroidism and goiter can occur due to overtreatment, but is reversible on stopping the drug.

Use

Anti-thyroid drugs control thyrotoxicosis in both Graves' disease and toxic nodular goiter.

IODINE AND IODIDES

it is the fastest acting thyroid inhibitor.

Excess iodide inhibits its own transport into thyroid cells by interfering with expression of NIS on the cell membrane.

In addition, it attenuates TSH and cAMP induced thyroid stimulation.

Excess iodide rapidly and briefly interferes with iodination of tyrosil and thyronil residues of thyroglobulin (probably by altering redox potential of thyroid cells) resulting in reduced T3/T4 synthesis (Wolff-Chaikoff effect).

However, within a few days, the gland 'escapes' from this effect and hormone synthesis resumes.

Uses

1. *Preoperative preparation* for thyroidectomy in Graves' disease

2. *Thyroid storm*

3. *Prophylaxis of endemic goiter*

4. *Antiseptic* As tincture iodine, povidone iodine

Adverse effects

1. *Acute reaction*

Manifestations are swelling of lips, eyelids, angioedema of larynx (may be dangerous), fever, joint pain, petechial haemorrhages, thrombocytopenia, lymphadenopathy.

2. *Chronic overdose (iodism)*

Inflammation of mucous membranes, salivation, rhinorrhoea, sneezing, lacrimation, swelling of eyelids, burning sensation in mouth, headache, rashes, g.i. symptoms, etc.

Given to pregnant or nursing mothers, it may be responsible for foetal/infantile goiter and hypothyroidism.

Thyrotoxicosis may be aggravated in multinodular goiter.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I, isotope of medicinal importance is: ^{131}I: physical half-life 8 days.

The chemical behaviour of ^{131}I is similar to the stable isotope.

^{131}I emits X-rays as well as β particles. The former are useful in tracer studies, because they traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells.

131I is concentrated by thyroid, incorporated in colloid—emits radiation from within the follicles.

The β particles penetrate only 0.5–2 mm of tissue.

The thyroid follicular cells are affected from within, undergo **pyknosis** and **necrosis** followed by **fibrosis** when a sufficiently large dose has been administered, without damage to neighbouring tissues.

With carefully selected doses, it is possible to achieve partial ablation of thyroid.

Radioactive iodine is administered as sodium salt of 131I dissolved in water and taken orally.

Therapeutic The most common indication is *hyperthyroidism* due to Graves' disease or toxic nodular goiter.

Advantages

1. Treatment is simple, outpatient basis and inexpensive.

2. No surgical risk, scar or injury

3. Once hyperthyroidism is controlled, cure is permanent.

131I is the treatment of choice after 25 years of age and if CHF, angina or any other contraindication to surgery is present.

Disadvantages

1. Hypothyroidism

2. Long latent period of response.

3. Contraindicated during pregnancy.

4. Not suitable for young patients

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity, *viz.* palpitation, tremor, nervousness, severe myopathy, sweating.

They have little effect on thyroid function and the hypermetabolic state.

They are used in hyperthyroidism in the following situations.

(i) While awaiting response to propylthiouracil/ carbimazole or 131I.

(ii) Along with iodide for preoperative preparation before subtotal thyroidectomy.

(iii) *Thyroid storm (thyrotoxic crisis):* This is an emergency due to decompensated hyperthyroidism.

CORTICOIDS

Biosynthesis (steroidogenesis)

Adrenal steroidogenesis takes place under the influence of ACTH which

Role of ACTH in steroidogenesis

- Makes more cholesterol available for conversion to pregnenolone
- induces steroidogenic enzymes.

In **adrenal cortical cells** only minute quantities of the hormones is stored, **rate of release** is **governed by** the **rate of biosynthesis**.

The **circulating corticosteroids levels** controls

- ACTH release from pituitary
- CRH release from hypothalamus

Thus provide feedback regulation of the **hypothalamo-pituitary- adrenal (HPA) axis**

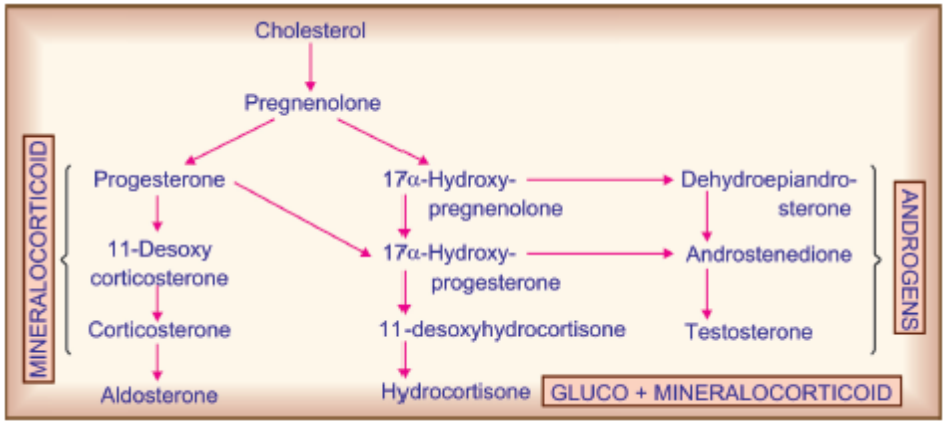


Fig. 20.1: Simplified depiction of the pathways of adrenal steroid hormone biosynthesis

Actions

Corticoids have **direct** and **permissive actions** on the basis of way of producing effect

- By **direct action**- produces effect of own actions

- By **permissive action**- they do not themselves produce an effect, their presence facilitates other hormones to exert that action

Corticoids have **Mineralocorticoidal** and **Glucocorticoidal actions** on the basis of effect they are producing

Mineralocorticoid actions

Target cell > **action** > **consequences**

- Enhancement of Na^+ **reabsorption** in the **distal convoluted tubule** in kidney.
- There is an associated increase in K^+ **and** H^+ **excretion**.

Deficiency mineralocorticoid-**Aldosterone**

- decreased tubular reabsorptive capacity for Na_+; Na_+ deficient state occurs
- kidney is not able to retain Na_+ even in the Na_+ deficient state → Na_+ is progressively lost: kidneys absorb water without the attendant Na_+ (to maintain e.c.f. volume which nevertheless decreases) → dilutional hyponatraemia
- because of dilutional hyponatraemia → excess water enters cells as reflex action of body→ cellular hydration: decreased blood volume and raised haematocrit.
- increase in K^+ and H^+ excretion → Hyperkalaemia and acidosis accompany.

These distortions of fluid and electrolyte balance progress and contribute to the circulatory collapse.

MOA mineralocorticoid-**Aldosterone**

The action of aldosterone is exerted by gene mediated increased transcription of m-RNA in renal tubular cells which promotes synthesis of aldosterone-induced proteins-**AIP** eg: Na^+K^+ ATPase.

The Na^+K^+ ATPase of tubular basolateral membrane responsible for generating gradients for movement of cations in these cells is the major AIP.

Glucocorticoid actions (Glucocorticoids are catabolic)

Carbohydrate metabolism

- **promote glycogen deposition** in **liver** by **inducing hepatic glycogen synthase**
- **promoting gluconeogenesis** (amino acids are utilized)
- inhibit **glucose utilization** by **peripheral tissues**.
- increased **glucose release** from **liver**

These all actions results in **hyperglycaemia + resistance to insulin**

= diabetes-like state

Protein metabolism

- amino acids mobilized into **liver** → used up in **gluconeogenesis**, as a result **excess urea is produced**
- They also cause **protein breakdown** from **peripheral tissues**
- They also increase **uric acid excretion**

negative nitrogen balance

Fat metabolism

- The **lipolytic action** of glucocorticoids is permissive, by promoting lipolysis due to Glucagon, Growth hormone, Adr and Thyroxine.
- **cAMP induced breakdown of triglycerides** is enhanced.
- *Fat depots in different areas of the body respond differently—redistribution of body fat occurs.*

peripheral adipocytes	truncal adipocytes
These adipocytes less sensitive to insulin and more sensitive to corticosteroid	These adipocytes respond mainly to raised insulin levels caused by glucocorticoid induced hyperglycaemia
Subcutaneous tissue loses fat deposited over face, neck and shoulder producing 'moon face', 'fish mouth' and 'buffalo hump'	

Calcium metabolism

- Glucocorticoids **inhibit intestinal absorption** and **enhance renal excretion** of Ca^{2+}.
- **Loss of osteoid** (decreased formation and increased resorption) indirectly results in **loss of Ca^{2+}**

negative Ca^{2+} balance

Water excretion

- The effect on water excretion is independent of action on Na+ transport; hydrocortisone and other glucocorticoids, but not aldosterone, maintain normal g.f.r.
- In adrenal insufficiency, the capacity to excrete a water load is markedly reduced—such patients are prone to water intoxication from i.v. infusions.
- Glucocorticoids also enhance secretory activity of renal tubules.

CVS

They have a **Direct action,** where

Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility.

They have a **Permissive action,**

- for the pressor action of Adr and angiotensin
- Thus in development of hypertension—should be used cautiously in hypertensives

Adrenal insufficiency responsible for **cardiovascular collapse** due to-

low cardiac output, arteriolar dilatation, poor vasoconstrictor response to Adr (repeated doses of Adr cause destructive changes in blood vessels) and increased permeability of capillaries, hypovolemia (due to lack of mineralocorticoid)

Skeletal muscles

Optimum level of corticosteroids is needed for normal muscular activity.

Hypocorticism: diminished work capacity and weakness are primarily due to hypodynamic circulation.

Hypercorticism: excess mineralocorticoid action → hypokalaemia → weakness; Excess glucocorticoid action → muscle wasting and myopathy → weakness.

CNS

- Mild euphoria is quite common with pharmacological doses of glucocorticoids. This is a direct effect on brain.
- Glucocorticoids also maintain the level of sensory perception and normal level of excitability of neurones.

Stomach

Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

Lymphoid tissue and blood cells

- enhance the rate of **destruction of lymphoid cells** (T cells are more sensitive than B cells)
- However, a marked lytic response is shown by malignant lymphatic cells. This is the basis of their use in lymphomas.
- Glucocorticoids **increase** the number of **RBCs, platelets and neutrophils** in circulation.
- They **decrease** **lymphocytes, eosinophils and basophils**. This is not due to destruction of the concerned cells, but due to their sequestration in tissues.
- Blood counts come back to normal after 24 hours.

Inflammatory responses

- Inflammatory response is suppressed. The action is nonspecific and covers all components and stages of inflammation.
- most important overall mechanism appears to be limitation of recruitment of inflammatory cells at the local site and production of proinflammatory mediators like PGs, LTs, PAF through indirect inhibition of phospholipase A_2.

Immunological and allergic responses

The clinical effect appears to be due to suppression of recruitment of leukocytes at the site of contact with antigen and of inflammatory response to the immunological injury.

Glucocorticoids cause greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection. This is the basis of their use in autoimmune diseases and organ transplantation

PHARMACOKINETICS

All natural and synthetic corticoids, **except DOCA** are absorbed and are effective by the oral route.

Oral bioavailability of synthetic corticoids is high.

Hydrocortisone is 90% bound to plasma protein, mostly to a specific cortisol-binding globulin (CBG; transcortin) as well as to albumin. Transcortin concentration is increased during pregnancy and by oral contraceptives—corticoid levels in blood are increased but hypercorticism does not occur, because free cortisol levels are normal.

Metabolic Pathways are—

(i) **Reduction** of 4, 5 double bond and hydroxylation of 3-keto group.
(ii) **Reduction** of 20-keto to 20-hydroxy form.
(iii) **Oxidative cleavage** of 20C side chain (only in case of compounds having a 17-hydroxyl group) to yield 17-ketosteroids.
(iv) These metabolites are further conjugated with **glucuronic acid or sulfate** and are excreted in urine.

Uses based on replacement therapy

Acute adrenal insufficiency

It is an emergency situation where low levels of cortisol can cause weakness, fatigue, Low blood pressure and Loss of consciousness.

DOC- Hydrocortisone or dexamethasone

The amount of fluid infused i.v. is guided by monitoring central venous pressure, because these patients have reduced capacity to excrete water load.

Short-term i.v. infusion of a vasopressor (dopamine) may be needed.

Chronic adrenal insufficiency (Addison's disease)

Hydrocortisone given orally is the most commonly used drug along with adequate salt and water allowance.

Some patients who continue to excrete excess Na^+ need additional mineralocorticoid: fludrocortisone is added.

Congenital adrenal hyperplasia (Adrenogenital syndrome)

It is a familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase. As a result the synthesis of hydrocortisone and aldosterone suffers.

There is compensatory increase in ACTH secretion— adrenals hypertrophy; enzyme deficiency being only partial in most cases, normal amounts of gluco - and mineralocorticoids are produced along with excessive amounts of weak androgens → virilization and/or precocious sexual development.

If the deficiency is severe, salt wasting also occurs.

Uses based on pharmacotherapy

1. **Arthritides:** as adjuvants to NSAIDs, in Rheumatoid arthritis, Osteoarthritis, Rheumatic fever, Gout.
2. **Collagen diseases** (systemic lupus erythematosus, nephrotic syndrome, glomerulonephritis and related diseases)
3. **Severe allergic reactions** (used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness) However, even i.v. injection of a glucocorticoid takes 1–2 hours to act and is not a substitute for Adr (which acts immediately) in anaphylactic shock and angioedema of larynx.
4. **Autoimmune diseases** (Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis) respond to corticoids.
5. **Bronchial asthma** inhaled glucocorticoid therapy is now recommended in most cases needing inhaled β2 agonists almost daily. Systemic corticosteroids are used only for: Status asthmaticus, Actue asthma exacerbation, Severe chronic asthma
6. **Other lung diseases:** Corticosteroids benefit aspiration pneumonia and pulmonary edema from drowning. Given during late pregnancy, corticoids accelerate lung maturation and surfactant production in the foetal lung and prevent respiratory distress syndrome at birth.

7. **Infective diseases** : lepra reaction, certain forms of bacterial meningitis and Pneumocystis carinii pneumonia with hypoxia in AIDS patients.
8. **Eye diseases:** Used in inflammatory ocular diseases, in diseases of the anterior chamber—allergic conjunctivitis, iritis, iridocyclitis, keratitis
9. **Skin diseases**: Used in many eczematous skin diseases, Systemic therapy is needed exfoliative dermatitis, Stevens-Johnson syndrome
10. **Intestinal diseases:** used in Ulcerative colitis, Crohn's disease, coeliac disease are inflammatory bowel diseases with exacerbations and remissions.
11. **Cerebral edema or inflammatory conditions:** due to tumours, tubercular meningitis, DOC Dexa-or betamethasone are preferred because they donot have Na+ retaining activity. In Neurocysticercosis: When albendazole/praziquantel is used to kill cysticerci lodged in the brain, prednisolone given for 2–4 weeks to suppress the reaction to the dying larvae.
12. **Malignancies**
13. Used chemotherapy of acute lymphatic leukaemia, Hodgkin's and other lymphomas (because of their marked lympholytic action in these conditions)
14. Used in hormone responsive breast carcinoma— act probably by causing HPA suppression so as to reduce production of adrenal androgens which are converted to estrogens in the body
15. **Organ transplantation and skin allograft:** High dose corticoids are given along with other immunosuppressants to prevent the rejection reaction.
16. **To test pituitary-adrenal axis function** Dexamethasone used
17. **Thyroid storm and septic shock**

Adverse effects

A. Mineralocorticoid

- Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids.
- Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid

- Cushing's habitus
- Fragile skin, purple striae, Cutaneous atrophy localized to the site occurs with topical application as well.
- Hyperglycaemia, may be glycosuria, precipitation of diabetes.
- Muscular weakness

- Susceptibility to infection
- Delayed healing of wounds and surgical incisions.
- Peptic ulceration
- Osteoporosis
- Posterior subcapsular cataract may develop after several years of use, especially in children.
- Glaucoma
- Growth retardation in children
- Psychiatric disturbances: mild euphoria frequently accompanies high dose steroid treatment.
- Suppression of hypothalamo-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy.

Diabetes mellitus (DM)

metabolic disorder characterized by:

- **Hyperglycaemia _**
- **Glycosuria _**
- **Hyperlipidaemia _**
- **negative nitrogen balance _**
- **ketonaemia _**

A widespread **pathological change** is

- thickening of capillary basement membrane
- increase in vessel wall matrix and
- increase in vascular cellular proliferation

Leads to **vascular complications** → *lumen narrowing, atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy*

- Enhanced nonenzymatic glycosylation of tissue proteins (such as glycosylated haemoglobin HbA1c) due to persistent exposure to high glucose concentrations
- accumulation of sorbitol (*a reduced product of glucose*) in tissues are ***believed to be causative in the pathological changes of diabetes***.

Index of protein glycosylation

- concentration of glycosylated haemoglobin (HbA1c) in blood
- it reflects the state of glycaemia over the preceding 2–3 months

Types of diabetes mellitus

Type I Insulin-dependent diabetes mellitus (IDDM)/juvenile onset diabetes mellitus:

There is β cell destruction in pancreatic islets; majority of cases are

- autoimmune (type 1A) - β cell antibody is found
- idiopathic (type 1B) - no β cell antibody is found
- circulating insulin levels are low or very low
- patients are more prone to ketosis
- low degree of genetic predisposition

Type II Noninsulin-dependent diabetes mellitus (NIDDM)/maturity onset diabetes mellitus

- There no loss or moderate reduction in β cell
- insulin in circulation is low, normal or even high
- no β cell antibody is found
- high degree of genetic predisposition;
- late onset (past middle age)
- Over 90% cases of diabetes are type 2 DM

Causes of *Type II DM* may be:

- impaired insulin secretion due to
  - Abnormality in gluco-receptor of β cells, respond at higher glucose concentration
  - relative β cell deficiency
- Reduced sensitivity of peripheral tissues to insulin: 'down regulation' of insulin receptors.
- Excess of hyperglycaemic hormones (glucagon, etc.)/obesity: cause relative insulin deficiency— the β cells lag behind.

INSULIN

- Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide *Preproinsulin* (110 AA) from which 24 AAs are first removed to produce *Proinsulin*
- The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell.
- The C peptide is secreted in the blood along with insulin.

Assay

Insulin is bioassayed by measuring blood sugar depression in rabbits (1 U reduces blood glucose of a fasting rabbit to 45 mg/dl) or by its potency to induce hypoglycaemic convulsions in mice.

1 mg of the International Standard of insulin = 28 units.

Plasma insulin can be measured by radioimmunoassay or enzyme immunoassay.

Regulation of insulin secretion

Under basal condition ~1U insulin is secreted per hour by human pancreas.

Much larger quantity is secreted after every meal.

Secretion of insulin from β cells is regulated by chemical, hormonal and neural mechanisms.

Chemical

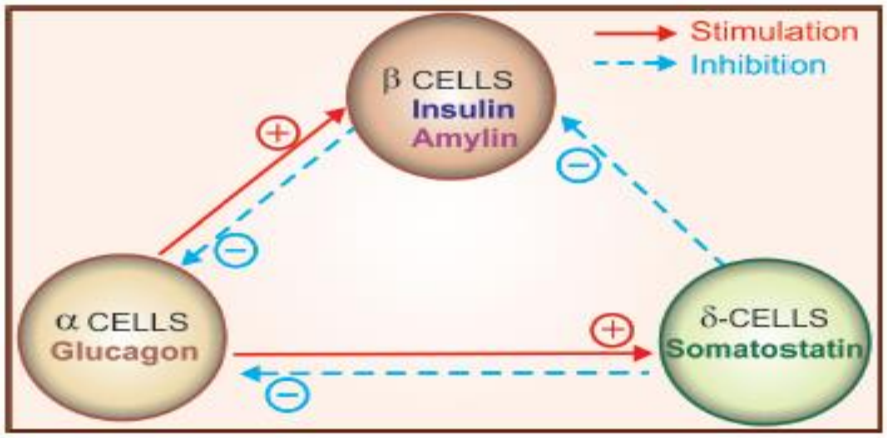
- The β cells have a glucose sensing mechanism dependent on entry of glucose into β cells (by a glucose transporter GLUT1) and its phosphorylation by *glucokinase*.
- Glucose entry and metabolism leads to activation of the **glucosensor** which indirectly inhibits the **ATP-sensitive K^+ channel (K^+ ATP)** resulting in **partial depolarization of the β cells**.
- ly rectifying ATP-sensitive K+ channel (KATP) in the membrane of pancreatic β cells.
- This increases **intracellular Ca2+ availability** (due to increased influx, decreased efflux and release from intracellular stores) → **exocytotic release of insulin** storing granules.

Glucose and insulin release

- glucose is the principal regulator and synthesis stimulator of insulin
- Glucose induces a brief pulse of insulin output within 2 min (*first phase*) followed by a delayed but more sustained *second phase* of insulin release.
- Glucose and other nutrients are more effective in invoking insulin release when given orally than i.v.
- They generate chemical signals ***'incretins'*** from the gut which act on β cells in the pancreas to cause anticipatory release of insulin. The incretins involved are glucagon-like peptide-1 (***GLP- 1***), glucose-dependent insulinotropic polypeptide (***GIP***), vasoactive intestinal peptide (***VIP***), pancreozymin-cholecystokinin

Hormonal

A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose.



Neural

Adrenergic α2 receptor activation	Adrenergic β2 receptor stimulation	Cholinergic—muscarinic activation
decreases insulin release (predominant)	increases insulin release (less prominent)	insulin release

The primary central site of regulation of insulin secretion is in the hypothalamus: stimulation of ventrolateral nuclei evokes insulin release, whereas stimulation of ventromedial nuclei has the opposite effect.

ACTIONS OF INSULIN The overall effects of insulin are to dispose meal derived glucose, amino acids, fatty acids and favour storage of fuel. It is a major anabolic hormone: promotes synthesis of gylcogen, lipids and protein. The actions of insulin and the results of its deficiency can be summarized as:

1. Insulin facilitates **glucose transport** across **cell membrane; skeletal muscle and fat cells** are highly sensitive.

Regulating dynamic equilibrium of **GLUT1 & GLUT 4**, synthesis of GLUT4 is upregulated by insulin.

2. **intracellularly** glucose is utilization by its [1]**phosphorylation** and [2]**increased glycogen synthesis** and [3]**decreased glycogenolysis**

[1]**Phosphorylation of glucose** to form **glucose- 6-phosphate**,promoted by insulin through increased **glucokinase** production.

[2]**glycogen synthesis** from glucose in **liver, muscle and fat** by stimulating the enzyme **glycogen synthase**.

[3]Insulin also **inhibits** glycogen degrading enzyme phosphorylase → **decreased glycogenolysis** in **liver**.

3. Insulin inhibits **gluconeogenesis** (from protein, FFA and glycerol) in **liver** by **gene mediated decreased synthesis of phosphoenol pyruvate carboxykinase**.

In insulin deficiency, proteins and amino acids are funneled from peripheral tissues to liver where these substances are converted to carbohydrate and urea.

Thus, in diabetes there is underutilization and over production of glucose → hyperglycaemia → glycosuria.

4. Insulin inhibits **lipolysis** in **adipose tissue** and favours **triglyceride synthesis**.

In diabetes increased lipolysis due to unchecked action of lipolytic hormones (glucagon, Adr, thyroxine) → increased **FFA and glycerol** in blood → taken up by liver to produce **acetyl-CoA**.

Normally acetyl-CoA is resynthesized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate).

The ketone bodies are released in blood—partly used up by muscle and heart as energy source, but when their capacity is exceeded, **ketonaemia** and **ketonuria** result.

5. Insulin enhances synthesis of vascular endothelial **lipoprotein lipase** and thus increases **clearance of VLDL and chylomicrons**.

6. Insulin facilitates Amino Acids entry and their synthesis into proteins, as well as inhibits protein breakdown in muscle and most other cells.

Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to **pyruvate, glucose and urea**. The excess urea produced is excreted in urine resulting in **negative nitrogen balance**.

Thus, catabolism takes the upper hand over anabolism in the diabetic state.

Mechanism of action

Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich.

The insulin receptor is a **receptor tyrosine kinase (RTK)** which is **heterotetrameric glycoprotein** consisting of **2 extracellular α and 2 transmembrane β subunits** linked together by **disulfide bonds**. It is oriented across the cell membrane as a **heterodimer**

The **α subunits** carry **insulin binding sites**, while the **β subunits** have **tyrosine protein kinase** activity.

Fate of insulin

Insulin is distributed only extracellularly. It is a peptide; gets degraded in the g.i.t. if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. During biotransformation the disulfide bonds are reduced—A and B chains are separated. These are further broken down to the constituent amino acids. The plasma t½ is 5–9 min.

Preparations of insulin

Highly purified insulin preparations In the 1970s improved purification techniques like gel filtration and ion-exchange chromatography were applied to produce 'single peak' and 'monocomponent (MC)' insulins which contain <10 ppm proinsulin. The MC insulins are more stable and cause less insulin resistance or injection site lipodystrophy. The immunogenicity of pork MC insulin is similar to that of recombinant human insulin.

Types of insulin preparations

1. **Regular (soluble) insulin**
   - **buffered neutral pH solution** of **unmodified insulin**
   - stabilized by a small amount of **zinc**.
   - **Self-aggregation** to form **hexamers** around **zinc ions**
   - After s.c. injection, insulin **monomers** are released gradually by dilution, so that absorption occurs slowly.
   - The slow onset of action is not applicable to i.v. injection, because insulin hexamer dissociates rapidly to produce prompt action.
   - longacting 'modified' or 'retard' preparations of insulin developed. Recently,
   - rapidly acting as well as peakless and long-acting insulin analogues have become available.
2. **Lente insulin (Insulin-zinc suspension):**

Two types of **insulin-zinc suspensions** have been produced.

ultralente - **large** particles is **crystalline** and practically insoluble in water & **long-acting**.

semilente - **smaller** particles and is **amorphous** & **shortacting**.

Lente insulin - Their **7**:**3** ratio mixture is called '**Lente insulin**' and is **intermediate-acting**.

3. Isophane (Neutral Protamine Hagedorn or NPH) insulin:

Protamine is added in a quantity just sufficient to complex all insulin molecules; neither of the two is present in free form and pH is neutral.

On s.c. injection, the complex dissociates slowly to yield an intermediate duration of action.

It is mostly combined with regular insulin (70:30 or 50:50) and injected s.c. twice daily before breakfast and before dinner (splitmixed regimen)

1. Highly purified (MC) pork regular insulin

2. Highly purified (MC) pork lente insulin

3. Highly purified (MC) pork isophane (NPH) insulin

4. Mixture of highly purified pork regular insulin (30%) and isophane insulin (70%)

Human insulins In the 1980s, the human insulins (having the same amino acid sequence as human insulin) were produced by recombinant DNA technology in *Escherichia coli*—'proinsulin recombinant bacterial' (prb) and in yeast— 'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin' (emp).

In the USA pork and beef insulins are no longer manufactured, but they are still available in U.K., India and some European countries. In Britain now > 90% diabetics who use insulin are taking human insulins or insulin analogues.

In India also human insulins and analogues are commonly used, except for considerations of cost.

Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin.

It has a slightly more rapid s.c. absorption, earlier and more defined peak and slightly shorter duration of action. Human insulin is also modified similarly to produce isophane (NPH) and lente preparations. Lente human insulin is no longer prepared in the USA.

The allegation that human insulin produces more *hypoglycaemic unawareness* has not been substantiated. However, after prolonged treatment, irrespective of the type of insulin, many diabetics develop relative hypoglycaemic unawareness/change in hypoglycaemic symptoms, because of autonomic neuropathy, changes in perception/attitude and other factors.

Clinical superiority of human insulin over pork MC insulin has not been demonstrated. Though new patients may be started on human insulins, the only indication for transfer from purified pork to human insulin is allergy to pork insulin. It is unwise to transfer stabilized patients from one to another species insulin without good reason.

Insulin analogues

- Using recombinant DNA technology, analogues of insulin have been produced with modified pharmacokinetics on s.c. injection, but similar pharmacodynamic effects.
- Greater stability and consistency are the other advantages.

Insulin analogue	Chemical changes	Pharmacokinetics	Pharmacodynamics
Insulin lispro	reversing proline and lysine at the carboxy terminus B 28 and B 29 positions	✓ dissociate rapidly s.c. on injection ✓ quick and more defined peak ✓ shorter duration of action	✓ better control of meal-time glycaemia ✓ lower incidence of late post-prandial hypoglycaemia ✓ slightly greater reduction in HbA1c
Insulin aspart	proline at B 28 of human insulin is replaced by aspartic acid	This change reduces the tendency for self-aggregation	✓ closely mimics the physiological insulin release pattern after a meal
Insulin glulisine	lysine replacing asparagine at B 23 and glutamic acid replacing lysine at B 29	rapidly acting insulin analogue continuous subcutaneous insulin infusion *(CSII)*	✓ better control of meal-time glycaemia ✓ lower incidence of late post-prandial hypoglycaemia
Insulin glargine	biosynthetic insulin has 2 additional arginine residues at the carboxy terminus of B chain and glycine replaces asparagine at A 21	soluble at pH4 of the formulation, precipitates at neutral pH. Because of acidic pH, it cannot be mixed with any other insulin preparation; must be injected separately. A depot is created from which monomeric insulin dissociates slowly to enter the circulation	✓ smooth 'peakless' effect ✓ once daily injection ✓ Fasting and interdigestive blood glucose levels are effectively lowered irrespective of time ✓ Lower incidence of night-time hypoglycaemic episodes compared to isophane insulin ✓ does not control meal-time glycaemia
Insulin detemir	Myristoyl (a fatty acid) radical is attached to the amino group of lysine at B29 of insulin chain	it binds to albumin after s.c. injection from which the free form becomes available slowly twice daily dosing may be needed	✓ Fasting and interdigestive blood glucose levels controlled ✓ does not control meal-time glycaemia

to control meal-time glycaemia, for which a rapid acting insulin or an oral hypoglycaemic is used concurrently.

REACTIONS TO INSULIN

1. Hypoglycaemia

This is the most frequent and potentially the most serious reaction.

The symptoms can be divided into

counter-regulatory sympathetic stimulation	neuroglucopenic symptoms
sweating, anxiety, palpitation, tremor	behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination
Occur early	Occurs late

Treatment Glucagon, Glucose must be given orally or i.v. (for severe cases)—reverses the symptoms rapidly.

2. Local reactions Swelling, erythema and stinging, ***Lipodystrophy*** of the subcutaneous fat.

3. Allergy (Urticaria, angioedema and anaphylaxis) due to contaminating proteins, and is very rare with human/highly purified insulins.

4. Edema short-lived dependent edema (due to Na+ retention) when insulin therapy is started.

USES OF INSULIN

Diabetes mellitus

The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.)

Insulin is **must for** type **1DM** cases, as well as for **post pancreatectomy diabetes** and **gestational diabetes**.

Many type 2 cases can be controlled by diet, reduction in body weight and appropriate exercise supplemented, if required, by oral hypoglycaemics.

When instituted, insulin therapy has to be tailored according to the requirement and convenience of each patient.

Diabetic ketoacidosis (Diabetic coma)

Ketoacidosis of different grades generally occurs in insulin dependent diabetics. It is infrequent in type 2 DM. The most common precipitating cause is infection; others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.

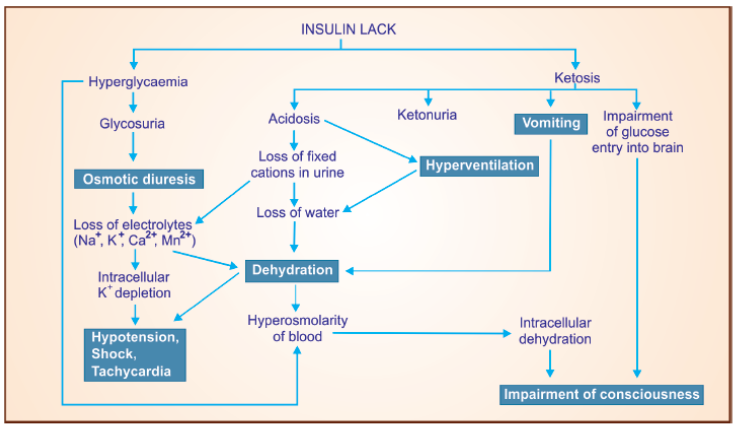


Fig. 19.5: Schematic depiction of the development of diabetic ketoacidosis due to insulin lack. Symptoms produced are shown within boxes

1. *Insulin* Regular insulin is used to rapidly correct the metabolic abnormalities.

Fall in blood glucose level by 10% per hour can be considered adequate response.

2. *Intravenous fluids* It is vital to correct dehydration.

After the blood sugar has reached 300 mg/dl, 5% glucose in ½N saline is the most appropriate fluid because blood glucose falls before ketones are fully cleared from the circulation. Also glucose is needed to restore the depleted hepatic glycogen.

3. *KCl*

Though upto 400 mEq of K+ may be lost in urine during ketoacidosis, serum K+ is usually normal due to exchange with intracellular stores. When insulin therapy is instituted ketosis subsides and K+ is driven back intracellularly— dangerous hypokalemia can occur.

After 4 hours it is appropriate to add 10–20 mEq/hr KCl to the i.v. fluid. Further rate of infusion is guided by serum K+ measurements and ECG.

4. *Sodium bicarbonate*

It is not routinely needed.

Acidosis subsides as ketosis is controlled.

However, if arterial blood pH is < 7.1, acidosis is not corrected spontaneously or hyperventilation is exhausting, 50 mEq of sod. bicarbonate is added to the i.v. fluid.

Bicarbonate infusion is continued slowly till blood pH rises above 7.2.

5. *Phosphate* When serum PO4 is in the lownormal range, 5–10 m mol/hr of sod./pot. phosphate infusion is advocated. However, routine use of PO4 in all cases is still controversial.

6. *Antibiotics* and other supportive measures and treatment of precipitating cause must be instituted simultaneously.

Hyperosmolar (nonketotic hyperglycaemic) coma This usually occurs in elderly type 2 patients. Its cause is obscure, but appears to be precipitated by the same factors as ketoacidosis, especially those resulting in dehydration.

Oral hypoglycemic

Sulfonylureas (K_{ATP} Channel blockers)

MOA

- Sulfonylureas provoke rate & release of insulin from pancreas, at any glucose concentration, even at low-glucose concentration risking production of severe and unpredictable hypoglycaemia.
- In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed and subdued.
- The SUs primarily augment the 2nd phase insulin secretion with little effect on the 1st phase.
- That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action), confirms their indirect action through pancreas.
- Hepatic degradation of insulin is also slowed.
- **Extrapancreatic action** : With down regulation of sulfonylurea receptors (SUR1) on β cells, they sensitize the target tissues (especially liver) to the action of insulin.

Adverse effects

1. **Hypoglycaemia**

✓ more common in elderly, liver and kidney disease patients
✓ Tolbutamide carries lowest risk due to its low potency and short duration of action.

2. Nonspecific side effects

✓ weight gain upto 1–3 kg, as a consequence insulinaemic action.
✓ Nausea, vomiting, flatulence, diarrhoea or constipation

3. Hypersensitivity

Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

Meglitinide / D-phenylalanine analogues (K_{ATP} Channel blockers)

Repaglinide

- normalise mealtime glucose excursions.
- quick and short lasting insulinemic action.
- It is administered before each major meal to control postprandial hyperglycaemia; the dose should be omitted if a meal is missed.
- Because of short lasting action it may have a lower risk of serious hypoglycaemia.
- Side effects are mild headache, dyspepsia, arthralgia and weight gain.

Nateglinide

- D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion
- faster onset and shorter lasting hypoglycaemia than repaglinide.
- Ingested 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia.
- There is little effect on fasting blood glucose level
- Side effects dizziness, nausea, flu like symptoms and joint pain.

Uses of Meglitinide

1. Type 2 DM Patients with pronounced post prandial hyperglyceamia
2. To supplement metformin/long-acting insulin.

Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1 is an important **incretin** released from the gut in response to ingested glucose.

- By GLP-1 action on pancreatic β cells, it causes insulin release only at high glucose concentration, promote β cell health as well.
- inhibits glucagon release from α cells

- slows gastric emptying and suppresses appetite
- Failure of incretins has been implicated in the pathogenesis of β cell dysfunction of type 2 DM, particularly progression of the disease.
- GLP-1 based therapy appears to be the most effective measure for preserving β cell function in type 2 DM.
- not suitable for clinical use because of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4)

Exenatide

- It is a synthetic DPP-4 resistant peptidal analogue which activates GLP-1 receptors.
- Being a peptide, it is inactive orally. Given by s.c.
- Benefits noted are lowering of postprandial as well as fasting lood glucose, HbA1c and body weight.
- The most important side effect is nausea and vomiting occurring in ~ 50% recipients, but tolerance develops later

Liraglutide

- tight binding to plasma proteins extends t½ to > 12 hours and duration of action to > 24 hours.
- Nausea and diarrhoea are the frequent side effects
- Use of liraglutide
    - improved glycaemic control in type 2 diabetics.
    - as an antiobesity drug even for nondiabetics.

Dipeptidyl peptidase-4 (DPP-4) inhibitor

Sitagliptin

- competitive and selective DPP-4 inhibitor
- potentiates the action of GLP-1 and GIP
- boosts post prandial insulin release

- decreases glucagon secretion and
- lowers meal-time as well as fasting blood glucose in type 2 diabetics.
- It is body weight neutral and carries low risk of hypoglycaemia unless combined with SUs or insulin.
- The HbA1c lowering caused by sitagliptin is equivalent to that with metformin.
- t½ averaging 12 hours, dose reduction is needed in renal impairment, but not in liver disease.
- **side effects** are nausea, loose stools, headache, rashes, allergic reactions and edema. Nasopharyngitis and cough

Vildagliptin

- enzyme covalently. The complex dissociates very slowly resulting in persistent DPP-4 inhibition even after the free drug has been cleared from circulation. This explains the longer duration of action (12–24 hours) despite short plasma t½ (2–4 hours).
- Dose reduction is needed in moderately severe liver and kidney disease.
- No significant drug interactions have been reported.
- Vildagliptin is less selective than sitagliptin for DPP-4; causes some inhibition of DPP-8, DPP-9 as well

Saxagliptin

- it binds covalently with DPP-4 and acts for 24 hours despite a plasma t½ of 2–4 hours.
- It is metabolized by CYP3A4 and generates an active metabolite that has a t½ of 3–7 hours.

Biguanide (AMPK activator)

METFORMIN

Mechanism of action

- Biguanides do not cause insulin release, but presence of insulin is essential for their action.
- **activation** of **AMP dependent protein kinase (AMPK)**, consequences are:

- Suppresses hepatic gluconeogenesis and glucose output from liver. This is the major action responsible for lowering of blood glucose in diabetics.
- Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Insulin resistance exhibited by type-2 diabetics is thus overcome. This translates into—
  - Promotion of glycogen storage in skeletal muscle
  - reduced lipogenesis in adipose tissue
  - enhanced fatty acid oxidation

- Interferes with mitochondrial respiratory chain and promotes peripheral glucose utilization through anaerobic glycolysis.

Pharmacokinetics It accumulates in renal failure and increases the risk of lactic acidosis.

Adverse effects Lactic acidosis & Vit B12 deficiency

Uses DOC for all type 2 DM patients

Advantages of metformin are:

- nonhypoglycaemic
- weight loss promoting
- has potential to prevent macrovascular as well as microvascular complications of diabetes
- no acceleration of β cell exhaustion/ failure in type 2 DM
- antihyperglycaemic efficacy (HbA1c reduction by 0.8–1.2%) equivalent to other oral drugs.
- can be combined with any other oral or injectable antidiabetic, if one drug is not adequate.

Thiazolidinedione (PPARγ agonist) Pioglitazone

MOA

- selective agonists for the **nuclear peroxisome proliferator-activated receptor γ (PPAR γ)** which is expressed **mainly in fat cells**, but also **in muscle and some other cells**. **Thus, fatty tissue is a major site of their action.**

- Activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue contributes to the **insulin sensitizing action.** Lipolysis and plasma fatty acid levels are reduced. Adipocyte turnover and differentiation is accelerated by glitazones.
- lowers serum triglyceride level and raises HDL level without much change in LDL level.
- Glitazones tend to reverse **insulin resistance** by enhancing **GLUT4 expression and translocation**. Entry of glucose into muscle and fat is improved.
- Hepatic gluconeogenesis is also suppressed.
- Improved glycaemic control results in lowering of circulating HbA1C and insulin levels in type 2 DM patients.

adverse effects:

plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia.

Contraindications

CHF may be precipitated or worsened. Monitoring of liver function is advised. It is contraindicated in liver disease and in CHF.

Failure of oral contraception may occur during pioglitazone therapy.

Uses

Pioglitazone is indicated in type 2 DM, but not in type 1 DM. It reduces blood glucose and HbA1c (by 0.5–1.2%) without increasing circulating insulin.

About 25% patients may not respond (nonresponders), probably due to low baseline insulin levels. It should be stopped if HbA1c reduction is < 0.5% at 6 months.

α Glucosidase inhibitors

Acarbose , Voglibose

- Interference with digestion and absorption of carbohydrates by reversibly inhibition of **α-glucosidases**
- **GLP-1 release** is promoted
- Postprandial glycaemia is reduced without significant increase in insulin levels.
- Regular use lowers HbA1c modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal.
- Acarbose is a mild antihyperglycaemic and not a hypoglycaemic.
- Flatulence, abdominal discomfort and loose stool are produced in about 50% patients due to fermentation of unabsorbed carbohydrates.

Miglitol

- it is a stronger inhibitor of sucrase. Potency for other α-glucosidases is equivalent to acarbose.

Amylin analogue

Amylin, 'islet amyloid polypeptide' (IAP), is produced by pancreatic β cells & acts in the brain

- to reduce glucagon secretion from α cells,
- delay gastric emptying,
- retard glucose absorption and promote satiety.

Pramlintide

- before meal attenuates postprandial glycaemia and exerts a centrally mediated anorectic action.
- The duration of action is 2–3 hours.
- It has been used as an adjuvant to meal time insulin injection to suppress the glycaemic peak in both type 1 and type 2 diabetics.
- Reduction in body weight is an additional benefit.

Androgens & Related drugs

Natural androgens

Testosterone is secreted by the interstitial (Leydig) cells of the testes

Testes_____> ***testosterone***_____ 5α-reductase _____> ***dihydrotestosterone***

Adrenal cortex _____> ***dehydroepiandrosterone*** and ***androstenedione***

In women ovary produces small quantity of testosterone

Androsterone

It is a metabolite of testosterone which is excreted in urine. It has 1/10 the activity of testosterone. In male, large quantity of equilin is produced which has 1/5 estrogenic potency of estradiol

Regulation of secretion

- **Testosterone** is secreted by the **interstitial (Leydig) cells** of the **testes** under the influence of **LH**.
- high concentration of **testosterone**
  - inhibits LH secretion from pituitary _ feedback mechanism
  - causes atrophy of interstitial cells (diminish in size and may be accompanied by loss of function)
- **FSH** is mainly responsible for promotion of **spermatogenesis** in **seminiferous tubular (Sertoli) cells**.
- **Inhibin**, (**a protein**) produced by **Sertoli cells**, inhibits **FSH** secretion from pituitary _ feedback mechanism
- ***Estrogens*** *are more potent inhibitors of Gn secretion even in males*, small amount of **estradiol** produced by **testes** as well as that resulting from **conversion of testosterone to estradiol in liver** and **fat** plays a role in feedback inhibition.

ACTIONS

1. **Sex organs and secondary sex characters (Androgenic)**

Growth of genitals, Growth of hair, Thickening of skin and increased activity of sebaceous glands, Behavioral changes, intrauterine development of the male phenotype.

2. Testes

High concentration of **testosterone** is attained locally in the seminiferous tubules by diffusion from the neighbouring **Leydig cells** causes **spermatogenesis and maturation of spermatozoa**.

3. Skeleton and skeletal muscles (Anabolic)

There is rapid bone growth, both in thickness as well as in length.

Estradiol produced from testosterone, and not testosterone itself, is responsible for

- fusion of epiphyses in boys *(as well as in girls)*
- bone mineralization.

Testosterone also promotes muscle building, especially if aided by exercise. There is accretion of nitrogen, minerals (Na, K, Ca, P, S) and water—body weight increases rapidly, more protoplasm is built.

Appetite is improved and a sense of well being prevails.

4. Erythropoiesis

- Testosterone accelerates erythropoiesis by
  - **increasing erythropoietin production** and
  - **increasing haeme synthesis**.
- Men have higher hematocrit than women.

PHARMACOKINETICS

- after i.m. injection slowly absorbed esters of testosterone—are hydrolysed to the active free form.
- The major metabolic products of testosterone are **androsterone** and **etiocholanolone** which are excreted in urine, mostly as conjugates with glucuronic acid and sulfate.
- Small quantities of **estradiol** are also produced **from testosterone** by **aromatization of A ring** in **extraglandular tissues** (liver, fat, hypothalamus).

SIDE EFFECTS with Testosterone

Males	Females
Virilization, excess body hair	menstrual irregularities in women
Acne	Acne
painful erections in males	-
Oligozoospermia, Gynaecomastia	-
Precocious puberty (if given in young age)	Precocious puberty (if given in young age)
early closure of epiphysis (if given in young age)	early closure of epiphysis (if given in young age)
Salt retention and edema (elderly)	Salt retention and edema (elderly)
Lowering of HDL and rise in LDL levels	Lowering of HDL and rise in LDL levels

- **Cholestatic jaundice**: occurs with **methyltestosterone** and other **17-alkyl substituted derivatives** (fluoxymesterone and some anabolic steroids like oxymetholone, stanozolol) in a **dose dependent manner**, but not with parenterally used esters of testosterone. For this reason, the latter are preferred. However, jaundice is reversible on discontinuation.
- **Hepatic carcinoma**
- **Gynaecomastia**: may occur, especially in children and in patients with liver disease. This is *due to peripheral conversion of testosterone to estrogens*. **Dihydrotestosterone does not** cause gynaecomastia because it is not converted to estradiol.
- Lowering of HDL and rise in LDL levels, especially with 17α-alkylated analogues.

Androgens are contraindicated in

- carcinoma of prostate and male breast, liver and kidney disease and
- during pregnancy (masculinization of female foetus).
- They should not be given to men aged >65 years
- to those with coronary artery disease or CHF.

USES

1. *Testicular failure*

2. *Hypopituitarism- associated Hypogonadism*

3. *AIDS related muscle wasting*

Testosterone therapy has been shown to improve weakness and muscle wasting in AIDS patients with low testosterone levels.

ANABOLIC STEROIDS

The anabolic : androgenic ratio of testosterone is considered as 1; The anabolic selectivity of these steroids is modest with ratios between 1 to 3 in the rat model, and probably still lower in man.

The anabolic : androgenic activity ratio is determined by injecting the drug in castrated rats and measuring the increase in weight of levator ani muscles to that of ventral prostate.

Side effects

The 17-alkyl substituted compounds oxymetholone, stanozolol, can produce jaundice and worsen lipid profile.

Uses

1. Catabolic states

2. Osteoporosis

3. Suboptimal growth in boys

4. Hypoplastic, haemolytic and malignancy associated anaemia

IMPEDED ANDROGENS / ANTIANDROGENS

Danazol

- weak androgenic, anabolic and progestational activities.
- it binds to the AR and induces some androgen-specific mRNA production
- the **most prominent action** is suppression of Gn secretion from pituitary in both men and women → **inhibition of testicular/ovarian function**.

- In addition, it **suppresses gonadal function** directly by **inhibiting steroidogenic enzymes**.
- In women endometrial atrophy occurs over few a weeks and amenorrhoea may supervene.

Uses are:

- *Endometriosis,* dysmenorrhea*, Menorrhagia, Fibrocystic breast disease* (chronic cystic mastitis)
- *Hereditary angioneurotic edema*

Side effects

- Complete amenorrhoea, Androgenic side effects
- hot flashes in women
- night sweats, muscle cramps, g.i. upset
- elivation of hepatic enzymes

Cyproterone acetate

- AR antagonist is chemically related to progesterone.
- In contrast to flutamide which increases LH release by blocking feedback inhibition,
- cyproterone inhibits LH release by its progestational activity.
- Lowering of serum testosterone (consequent to LH inhibition) supplements the direct antiandrogenic action of cyproterone.
- Its clinical indications are— precocious puberty in boys, inappropriate sexual behaviour in men, acne and hirsutism in women (usually in combination with an estrogen).

Flutamide

Its **active metabolite 2-hydroxyflutamide** competitively blocks **androgen action** on **accessory sex organs as well as on pituitary**.

Thus, it increases **LH secretion by blocking feedback inhibition**.

Plasma testosterone levels increase *in males which partially overcome the direct antiandrogenic action. This* ***limits utility*** *of* ***monotherapy with antiandrogens*** *in* ***carcinoma prostate***. They are now used only when

- in conjunction with a GnRH agonist (to suppress LH and testosterone secretion) or
- after castration to block the residual action of adrenal androgens as ***combined androgen blockade (CAB) therapy*** of metastatic carcinoma prostate.

Reports of liver damage have restricted its use.

Bicalutamide

- This more potent and longer acting (t½ 6 days) congener of flutamide is suitable as a component of CAB therapy.
- Side effects are hot flashes, chills, edema and loose stools
- Elevation of hepatic transaminase above twice normal is a signal for stopping the drug.

5 α-REDUCTASE INHIBITOR

Finasteride

- A relatively selective & competitive inhibitor of 5 α-reductase type 2 isoenzyme which predominates in male urogenital tract.
- Circulating and prostatic DHT concentration are lowered
- Treatment with finasteride has resulted in decreased prostate size and increased peak urinary flow rate in ~50% patients with symptomatic benign hypertrophy of prostate (BHP).
- Finasteride has also been found effective in male pattern baldness, though hair follicles have primarily type 1 enzyme.
- Finasteride is effective orally, extensively metabolized in liver—metabolites are excreted in urine and faeces; plasma t½ 4–8 hours (elderly 6–15 hours).
- It is well tolerated by most patients; side effects are decreased libido, impotence and decreased volume of ejaculate (each in 3–4% patients).

Dutasteride

- inhibits both type 1 and type 2 5α-reductase and reduces DHT levels.
- It is metabolized by CYP3A4 and is very long-acting (t½ is ~ 9 weeks).
- used in BHP and can benefit male pattern baldness.

DRUGS FOR ERECTILE DYSFUNCTION

1. Androgens

Androgens used if Hypogonadism is cause of ED. In such cases testosterone therapy is given.

2. Phosphodiesterase-5 (PDE-5) inhibitors

the first line therapy for ED.

Inhibition of PDE-5, the cGMP degrading isoenzyme in cavernosal and vascular smooth muscle, results in accumulation of cGMP and marked potentiation of NO action.

3. Papaverine/Phentolamine induced penile erection (PIPE) therapy

4. Prostaglandin E1

Alprostadil (PGE1) injected directly into the corpus cavernosum using a fine needle produces erection lasting 1–2 hours to permit intercourse.

Estrogens, Progestins and Contraceptives

Natural estrogens

Estradiol is the major estrogen secreted by the ovary. It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol.

Estradiol is rapidly oxidized in liver to **estrone** which is hydroxylated to form **estriol**.

All three are active and circulate in blood, but **estradiol** is the most potent estrogen.

In male, large quantity of **equilin** is produced which has 1/5 estrogenic potency of estradiol.

Synthetic estrogens

inactive orally and have a short duration of action due to rapid metabolism in liver.

Regulation of secretion

Females	Males
menstruating women varies from 10–100 µg depending on the phase of the cycle	derived primarily by extraglandular aromatization of adrenal androgens
During pregnancy, placenta secretes large quantities of estrogens reaches 30mg/day max	
postmenopausal women, daily production of estrogen has been estimated as 2–10 µg derived primarily by extraglandular aromatization of adrenal androgens	

Estrogens exercise feedback inhibition of FSH (also of LH at higher concentrations) by direct action on pituitary as well as through hypothalamus.

ACTIONS

1. Sex organs

- pubertal changes & Secondary sex characters
- proliferation of endometrium in the preovulatory phase
- In the absence of progesterone (anovulatory cycles) withdrawal of estrogens alone produces menstruation.
- Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.

3. Metabolic effects

- Estrogens are anabolic, similar to but weaker than testosterone.
- Continued action of estrogen promotes fusion of epiphyses both in girls and boys.
- It promotes positive calcium balance

4. **Bone Formation and resorption**

- Estrogen is important in maintaining bone mass primarily by retarding bone resorption.
    - Osteoclast pit formation is inhibited
    - there is increased expression of **bone matrix proteins** such as **osteonectin, osteocalcin, collagen and alkaline phosphatase**.

The major action of estrogens is to reduce maturation and activity of osteoclasts by modifying regulatory cytokine signals from osteoblasts

Estrogens enhance elaboration of **OPG** (**osteoprotegerin**) from osteoblasts which binds RANKL and prevents activation of osteoclast-precursors from fusing and maturing into osteoclasts.

The direct action on osteoclasts is to accelerate their apoptosis.

5. carbohydrate & Lipid metabolism

- higher doses of estrogens impair glucose tolerance.
- Normal blood sugar is not affected but diabetes may be precipitated or its control vitiated.
- However, amounts used for HRT and low dose contraception do not affect carbohydrate metabolism.
- HDL : LDL ratio improved

7. Miscellaneous

- **blood coagulability** is increased due to induction of synthesis of clotting factors (factors II, VII, IX and X).
- **Fibrinolytic activity** in plasma also tends to increase due to lowering of plasminogen-activator inhibitor-1 (PAI-1).
- Estrogens induce nitric oxide synthase and PGI2 production in vascular endothelium. The increased availability of NO and PGI2 could promote vasodilatation.
- They increase lithogenicity of bile by increasing cholesterol secretion and reducing bile salt secretion.

Mechanism of action

Two distinct ERs designated Erα and ERβ

ERα predominates in uterus, vagina, breast, bone, hypothalamus and blood vessels

ERβ predominates in prostate gland of males and ovaries in females.

Estradiol binds to both ERα and ERβ with equal affinity, but certain ligands have differing affinities.

ADVERSE EFFECTS

Most of the adverse effects of estrogens are described with HRT and with oral contraceptives (*see* p. 325). In addition, dose dependent adverse effects noted when use is made for other indications are—

Female	Male
Fusion of epiphyses and reduction of adult stature	Fusion of epiphyses and reduction of adult stature
	Suppression of libido, gynaecomastia and feminization
In postmenopausal women, estrogens can increase the risk of irregular bleeding and endometrial carcinoma, breast cancer, Benign hepatomas	
genital abnormalities in offspring	genital abnormalities in offspring

USES

- *Senile vaginitis*
- *Delayed puberty in girls*
- *Dysmenorrhoea*
- *Acne*
- *Dysfunctional uterine bleeding*
- *Carcinoma prostate*
- *Hormone replacement therapy (HRT)*

Hormone replacement therapy (HRT)

Due to cessation of ovarian function at menopause women suffer a number of physical, psychological and emotional consequences. Medical problems related to menopause are:

- *Vasomotor disturbances*
- *Urogenital atrophy*
- *Osteoporosis*
- *Dermatological changes*
- *Psychological/Cognitive disturbances*
- *Increased risk of cardiovascular diseases*

Benifites of HRT

- Menopausal symptoms and atropic changes are arrested
- Prevention ofosteoporosis and fracture
- Improved cardiac activity and lipid profile

Tibolone It is a 19-norsteroid developed specifically to be used for HRT. It is converted into 3 metabolites which exert estrogenic, progestational and weak androgenic actions in specific tissues.

ANTIESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

ANTIESTROGENS

Clomiphene citrate

- It binds to both ERα and ERβ and acts as a pure estrogen antagonist in all human tissues
- It induces Gn secretion in women by blocking estrogenic feedback inhibition of pituitary. The amount of LH/FSH released at each secretory pulse is increased.
- the ovaries enlarge and ovulation occurs if the ovaries are responsive to Gn.

uses

- To aid in vitro fertilization
- Oligozoospermia

Adverse effects

- Polycystic ovaries, hot flushes, Risk of ovarian tumour may be increased.
- The chief use of clomiphene is for infertility due to failure of ovulation

Fulvestrant

- 'selective estrogen receptor down-regulators' (SERDs) or 'pure estrogen antagonists'
- **MOA:** it inhibits ER dimerization so that ER interaction with DNA is prevented and receptor degradation is enhanced. The ER is thus down regulated resulting in more complete suppression of ER responsive gene function.
- **USES:** for the treatment of metastatic ER positive breast cancer in postmenopausal women which has stopped responding to tamoxifen.

Selective estrogen receptor modulators (SERMs)

Tamoxifen citrate, Toremifene

- acts as potent estrogen antagonist in breast carcinoma cells, blood vessels and at some peripheral sites, but as partial agonist in uterus, bone, liver and pituitary.
- Inhibition of human male breast cancer cells and hot flushes reflect antiestrogenic action, while the weak estrogen agonistic action manifests as stimulation of endometrial proliferation, lowering of Gn and prolactin levels in postmenopausal women as well as improvement in their bone density.
- A decrease in total and LDL cholesterol without any change in HDL and triglyceride level reflects estrogenic action.
- With its use following
    - **risk of endometrial carcinoma**
    - **risk of deep vein thrombosis**
- Used in breast carcinoma, human male breast cancer, Male infertility
- Side effects: Hot flushes, , vaginal bleeding, vaginal discharge, menstrual irregularities

Raloxifene

- This SERM has a different pattern of action than tamoxifen.
- It is an estrogen partial agonist in bone and cardiovascular system, but an antagonist in endometrium and breast.
- It has high affinity for both Erα and ERβ, and has a distinct DNA target the *'raloxifene response element'* (RRE).
- raloxifene prevents bone loss in postmenopausal women; bone mineral density (BMD)
- In postmenopausal women raloxifene reduces LDL cholesterol, probably by upregulating hepatic LDL receptors. In contrast to estrogen HRT there is no increase in HDL and triglyceride levels.

- reduces the risk of breast cancer by 65%, though the protection was confined to ER-positive breast cancer.
- Raloxifene does not stimulate endometrial proliferation and there is no increase in the risk of endometrial carcinoma.
- *Side effects* increase in **risk of deep vein thrombosis** and **pulmonary embolism**.

Use

second line drug for prevention and treatment of osteoporosis

AROMATASE INHIBITORS

Aromatization of 'A' ring of testosterone and androstenedione is the final and key step in the production of estrogens (estradiol/estrone) in the body.

In addition to the circulating hormone, locally produced estrogens appear to play an important role in the development of breast cancer.

Letrozole

- It is an orally active nonsteroidal (type 2) compound that reversibly inhibits aromatization all over the body, including that within the breast cancer cells, resulting in nearly total estrogen deprivation.
- Proliferation of estrogen dependent breast carcinoma cells is suppressed to a greater extent than with tamoxifen.
- Randomized clinical trials have established its utility in:
    - *Early breast cancer:* Letrozole is a first line drug for adjuvant therapy after mastectomy in ER+ive postmenopausal women.
    - *Advanced breast cancer:* Current guidelines recommend letrozole as first line therapy

Anastrozole

- nonsteroidal and reversible (Type 2) AI, more potent, accumulates in the body to produce peak effect after 7–10 days.
- Uses:
    - early as well as advanced breast carcinoma in postmenopausal women
    - adjuvant therapy in early ER+ive breast cancer
    - palliation of advanced cases in postmenopausal women
- Side effect: shot flushes, vaginal dryness & bleeding, Arthralgia and acceleration of osteoporosis

Exemestane:

- This steroidal and irreversible (Type 1) inhibitor of aromatase acts like a suicide substrate by covalent binding to the enzyme.
- As a result >90% suppression of estradiol production is obtained. However, it has weak androgenic activity similar to androstenedione.
- Early breast cancer, advanced breast cancer

PROGESTINS

Natural progestin

It is secreted by the **corpus luteum** (10–20 mg/day) in the later half of menstrual cycle under the influence of LH.

Its production declines a few days before the next menstrual flow.

If the ovum gets fertilized and implants—the **blastocyst** immediately starts producing **chorionic gonadotropin** which is absorbed into maternal circulation and sustains the **corpus luteum** in early pregnancy.

Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term.

Synthetic progestins

Progesterone derivatives (21 C) or 19-nortestosterone

- These are either progesterone derivatives (21 C) or 19-nortestosterone derivatives, also called *'estranes'* (18 C).
- The progesterone derivatives are almost pure progestins, have weaker antiovulatory action
- used primarily as adjuvants to estrogens for HRT in postmenopausal women, threatened abortion, endometriosis, etc. for selective progestational effect.
- additional weak estrogenic, androgenic, anabolic and potent antiovulatory action: are used primarily in combined contraceptive pills.

13-ethyl substitution 'gonanes'

- Estranes with a 13-ethyl substitution are called '*gonanes*',
- Gonanes are more potent (especially the levoisomers, e.g. *levonorgestrel*)
- strong antiovulatory action with little or no androgenic property.

- Desogestrel and *norgestimate* are prodrugs. Therefore, they do not antagonise the beneficial action of estrogens on lipid profile and are preferable in women with hyperandrogenemia.
- High antiovulatory potency allows reduction of ethinylestradiol dose when these are combined in oral contraceptives.

ACTIONS

The main function of progesterone is preparation of the uterus for nidation and maintenance of pregnancy. The latter is due to prevention of endometrial shedding, decreased uterine motility and inhibition of immunological rejection of the foetus: progesterone depresses T-cell function and cell-mediated immunity (CMI).

1. Uterus

preparation of the uterus for nidation and maintenance of pregnancy

- By **secretory changes** in the **estrogen primed endometrium**.
- When pregnancy occurs it brings about **decidual changes in endometrium**.

2. *Breast*

- Progesterone causes proliferation of acini in the mammary glands. Cyclic epithelial proliferation and turnover occurs during luteal phase
- Continuous exposure to progesterone during pregnancy halts mitotic activity and stabilizes mammary cells.
- Acting in concert with estrogens, it prepares breast for lactation.

3. *CNS*

- High circulating concentration of progesterone (during pregnancy) appears to have a sedative effect & affect mood.
- A slight (0.5 °C) rise in body temperature by resetting the hypothalamic thermostat and increasing heat production is induced. This is responsible for the higher body temperature seen during the luteal phase.

4. *Metabolism*

Prolonged use of oral contraceptives **impairs glucose tolerance** in some women. This has been ascribed to the progestational component.

Progestins, especially those with androgenic activity (19-nortestosterone derivatives) **raise LDL and lower HDL cholesterol levels**. This may reduce the beneficial effect of estrogen used

concurrently for HRT or in contraceptives. Such effect not found in Micronized oral progesterone formulation

5. *Pituitary*

- Progesterone is a weak negative feedback inhibitor of Gn secretion from pituitary.
- Administration of progestin during follicular phase inhibits the preovulatory LH secretion and prevents ovulation. This effect is synergestic with estrogen.
- The gonanes are potent suppressor of GnRH and thus potent antiovulatory drugs.

PHARMACOKINETICS

- Progesterone, inactive orally due to high first-pass effect
- Even after an i.m. in oily solution dose it is rapidly cleared from plasma, has a short t½ (ntural 5–7 min & synthetic 8-24 hrs).
- major metabolic product is **pregnanediol** which is excreted in urine as **glucuronide** and **sulfate conjugates**.

ADVERSE EFFECTS

- Breast engorgement, increase in the risk of breast cancer
- rise in body temperature, and mood swings may occur
- Irregular bleeding or amenorrhoea
- lower plasma HDL levels (only with 19-nortestosterone derivatives), Blood sugar may rise and diabetes may be precipitated
- Given in early pregnancy, progestins can cause congenital abnormalities.

USES

- contraceptive
- Hormone replacement therapy (HRT) A progesterone derivative lacking androgenic activity is preferred.
- Dysfunctional uterine bleeding associated with anovular cycles.
- Endometriosis due to presence of endometrium at ectopic sites.
- Premenstrual syndrome/tension ('premenstrual dysphoric disorder')
- Threatened/habitual abortion
- Endometrial carcinoma

ANTIPROGESTIN

- **Mifepristone** It is a 19-norsteroid with potent anti-progestational and significant antiglucocorticoid, antiandrogenic activity. Progestational activity in absence of progestin.
- In **follicular phase**, its antiprogestin action suppresses midcycle Gn surge from pituitary → slowing of **follicular development and delay/failure of ovulation**.
- In **luteal phase**, it prevents secretory changes by blocking progesterone action on the endometrium. Later in the cycle, it **blocks progesterone support to the endometrium**
- Mifepristone also sensitizes the myometrium to PGs and induces menstruation.
- If implantation has occurred, it blocks decidualization, so that **conceptus is dislodged**, **HCG production falls**, secondary **luteolysis** occurs–All these effects lead to **abortion**.
- In the absence of progesterone (during anovulatory cycles or after menopause) it exerts weak progestational activity—induces predecidual changes.
- Mifepristone is a partial agonist and competitive antagonist at both A and B forms of PR.
- Therefore, it is now regarded as 'progesterone receptor modulator' rather than 'pure antagonist.' The weak agonistic action is not manifest in the presence of progesterone.

Uses

- Termination of pregnancy of up to 7 weeks:
- Cervical ripening
- Postcoital contraceptive
- Once-a-month contraceptive
- Induction of labour
- Cushing's syndrome

HORMONAL CONTRACEPTIVES

FEMALE CONTRACEPTION

TYPES OF METHODS

Oral

1. *Combined pill*

It contains an estrogen and a progestin in fixed dose for all the days of a treatment cycle (monophasic).

2. *Phased pill*

The estrogen dose is kept constant (or varied slightly between 30–40 µg), while the amount of progestin is low in the first phase and progressively higher in the second and third phases.

recommended for women < 35 years & for women with no withdrawal bleeding or breakthrough bleeding

3. *Progestin-only pill (Minipill)*

A low-dose progestin-only pill is an alternative for women in whom an estrogen is contraindicated.

4. *Emergency (postcoital) pill*

• Levonorgestrel 0.75 mg two doses 12 hours apart, or 1.5 mg single dose taken as soon as possible, but before 72 hours of unprotected intercourse.

• Ulipristal 30 mg single dose as soon as possible, but within 120 hours of intercourse.

• Mifepristone 600 mg single dose taken within 72 hours of intercourse.

Injectable

(a) Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals. After i.m. injection peak blood levels are reached in 3 weeks and decline with a t½ of ~ 50 days.

(b) Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals. NORISTERAT 200 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle.

MALE CONTRACEPTIVE

Drugs and approaches tried are—

1. Antiandrogens.

2. Estrogens and progestins.

3. Androgens.

4. Superactive Gn RH analogues.

5. Cytotoxic drugs.

6. Gossypol.