fatty acids which cross endothelium and enter adipocyte or muscle cells are either oxidized to give energy or esterified and stored as triglyceride. Its size is reduced, content of triglyceride is diminished, but its cholesterol ester remain intact called chylomicron remnant, which is cleared by receptor mediated endocytosis in the liver cells, where the chylomicron remnant is digested, and the free cholesterol performs the functions of:

- Synthesis of cell membrane
- Excreted *via* bile
- Stored in liver.

Liver under stimulation of high calorie intake or carbohydrate intake secretes triglyceride and cholesterol in plasma in VLDL (very low density lipoprotein). The lipoprotein lipase of capillary endothelium acts on VLDL and fatty acids pass into adipose tissue. The remnant is called IDL (intermediate density lipoprotein) which contains more cholesterol esters than triglyceride. Half of IDL is taken by LDL receptors in liver and the rest becomes low density lipoprotein containing only cholesterol esters (losing triglycerides). LDL remains in plasma for long time and is the major reservoir of cholesterol in human plasma. Rate of LDL uptake is regulated by LDL receptor synthesis. When liver or extrahepatic tissues require cholesterol for synthesis of steroid hormone, new cell membranes or bile acids synthesize LDL receptors. Thyroxine and estrogen enhances LDL receptor gene expression and has got LDL lowering effects.

When the cells of the body die, the cell membrane undergoes turnover, the free cholesterol is continuously replaced in plasma and high density lipoprotein (HDL) immediately takes it up, esterifies it with the help of enzyme of plasma called lecithin cholesterol acetyl transferase (LCAT) and transfer it back to LDL, IDL, chylomicron for completing cycle with the help of cholesterol ester transfer protein.

Lipoproteins are also disposed off by less specific pathways operating in macrophages and scavenger cells.

VLDL, IDL and LDL are atherogenic, while HDL is protective.

Table 77.1: Functions and sources of lipoproteins

	Source	*Functions*
Chylomicron	Diet	Dietary TG transport
Chylomicron remnants	Chylomicron	Dietary cholesterol transport
VLDL	Liver	Endogenous TG transport
IDL	VLDL	Transport of cholesterol ester and triglyceride to liver; source of LDL
LDL	IDL	Transport of cholesterol to tissue and liver
HDL	Tissue and cell membrane	Removal of cholesterol from tissues

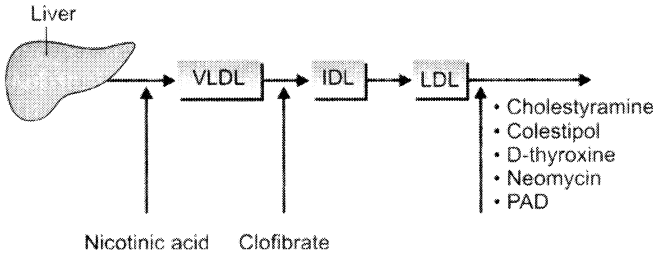

Fig. 77.2: Site of action of hypolipidemic drugs

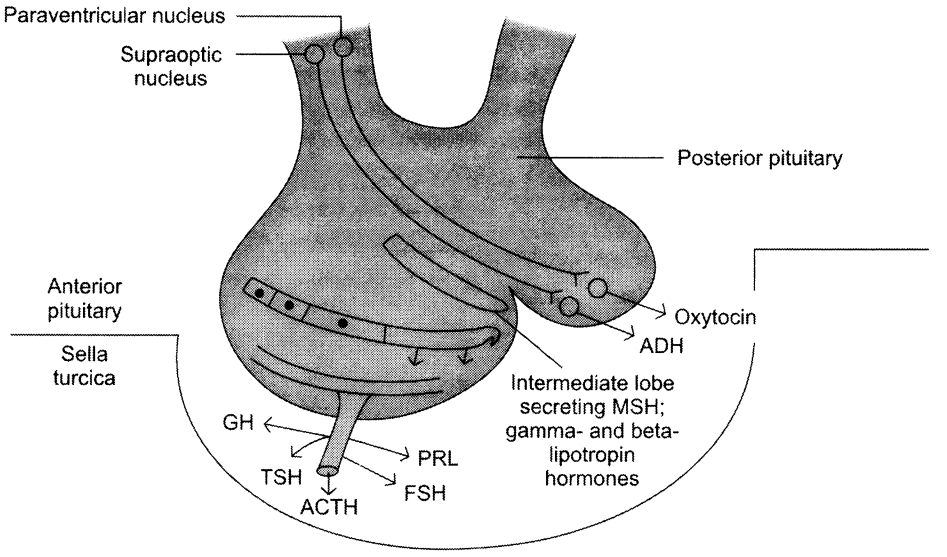

Fig. 78.3: Parts of pituitary and different hormones liberated by it

through releasing and inhibiting hormones. Histologically, anterior pituitary is either acidophilic or basophilic according to staining character and releases separate hormones.

HORMONES SECRETED BY PITUITARY

Anterior pituitary

- Growth hormone (GH) released by acidophil somatotroph.
- Adrenocorticotropic hormone (ACTH) released by corticotroph.*
- Thyroid stimulating hormone (TSH) released by thyrotroph.*
- Gonadotropins: FSH and LH released by gonadotroph.*
- Prolactin released by acidophilic lactotroph
- Melanocyte stimulating hormone (MSH) by intermediate lobe.

All are relased by basophils

Mechanisms of action of hormones

With cell surface receptors

i. With cAMP as second messenger: ACTH, FSH, LH, MSH, PTH, glucagon, catecholamine, ADH, HSG, CRH, TSH and calcitonin
ii. With cGMP as second messenger: Atrial natriuretic factor (ANF)
iii. With Ca or phosphatidyl as second messenger: TRH, GnRH, catecholamine, gastrin, vasopressin, oxytocin, acetylcholine
iv. Mediated by tyrosine kinase: Insulin.
v. Cell surface receptor with unknown intracellular messenger: Growth hormone, prolactin and erythropoietin

Intracellular receptors

- Glucocorticoids
- Mineralocorticoids
- Estrogen
- Progesterone
- Androgen
- Calcitriol
- Thyroxine

*released by basophils

hyperglycemia with insulin resistance in hyperthyroidism.

- **Protein:** In physiological doses, increases protein synthesis and promotes growth and anabolic effect, but in hyperthyroidism it has catabolic effect. Prolonged action results in negative nitrogen balance and tissue wasting.
- **Calorigenesis:** Increases BMR, due to uncoupling of oxidative phosphorylation. Metabolic rates of brain, gonad, uterus, spleen, lymph node are not significantly affected.
- **CVS:** Thyroid hormones stimulate rate and force of contraction in myocardium probably by upregulation of β-adrenergic receptors. May precipitate CCF, angina and systolic hypertension, atrial fibrillation. Myocardial oxygen consumption is increased.
- **CNS:** Hyperthyroid patients are anxious, nervous with tremors and hyperreflexia. Hypothyroidism produces mental retardation.
- **Skeletal muscles** are flabby and weak in myxoedema, but in hyperthyroidism there is tremor; increased muscle tone and weakness due to myopathy.
- **GIT:** Peristalsis increases with T_3 and T_4 producing diarrhea.
- **Hemopoiesis:** T_4 helps in erythropoiesis.
- **Skin:** Thyroid deficiency causes deposition of complex mucopolysaccharides in connective tissue responsible for rough skin in myxoedema.
- **Reproduction:** Oligomenorrhea occurs and fertility is impaired in hypothyroidism. Normal thyroid function is essential for pregnancy and lactation.
- **Miscellaneous**
  i. Excess thyroxine impairs conversion of creatine to creatinine and phosphocreatinine leading to creatinuria.
  ii. Conversion of carotene to vitamin A is defective in hypothyroidism. Requirement of fat- and water-soluble vitamins increases with thyrotoxicosis.

Mechanism of Action of Thyroid

T_4 and T_3 is dissociated from thyroid-binding proteins, enters the cell by active transport. Inside the cell T_4 is converted to T_3 by 5'-deiodinase, the T_3 enters the cell to bind to specific T_3 receptor protein. This protein is a member of c-erbB oncogenic family. The other family members include steroid hormone receptor and receptor for vitamins A and D. T_3 receptor exists in α and β forms and their concentration varies in different tissues which are responsible for variation of effect of T_3 in different tissues. The activation of nuclear receptor causes increased RNA formation and prtoein synthesis, *viz.* Na^+/K^+-ATPase.

In inactive phase, the T_3 receptor bound to thyroid hormone response element (TRE) along with corepressor which suppresses the gene expression.

In active phase, T_4 and T_3 bound to globulin are released and free T_4 and T_3 enter to cells by active transport system, T_4 is converted to T_3 by 5'-deiodinase, T_3 goes towards nucleus and binds to ligand binding domain of thyroid receptor, promoting heterodimerization with retinoid X receptor (RXR) on thyroid hormone response element (TRE) displaces the corepressor and binds to coactivator. This thyroid receptor (TR) coactivator complex activates gene expression and protein synthesis (Fig. 79.2).

Difference between T_3 and T_4

- Thyroid secretes more T_4 than T_3.
- T_3 is five times potent to T_4 and T_3 is avidly bound to nuclear receptor. It has quicker onset of action.
- T_4 is convertable into T_3 in peripheral tissues, therefore, it may be said that T_4 is a prohormone of T_3.

Preparations: L-thyroxine Na (eltroxin, Thyrox 100 μg tab), triiodothyronine (liothyronine) 5, 25 μg tabs (used for myxoedema coma for quick response).

Pharmacokinetics: Absorption of L-thyroxine is incomplete for clinical purposes. L-thyroxine

(erratic steroid doses or withdrawal may lead to pseudorheumatism).

5. **In tuberculosis:** Indicated in:
   - Pleural effusion
   - Pericardial effusion
   - Peritoneal effusion
   - Meningeal or Military tuberculosis
   - Allergic drug reaction with ATD drug
6. **Chronic inhibition of pituitary ACTH** in idiopathic hirsutism.
7. **Alternate days steroid therapy**
   - Bronchial asthma
   - Ulcerative colitis
   - Subacute hepatic necrosis
   - Chronic active hepatitis
   - Hemolytic anemia
   - Acute lymphatic leukemia
   - Hodgkin's disease
   - Sarcoidosis
   - Subacute thyroiditis.

Mineralocorticoids (Aldosterone)

It has main effect on Na retention and K excretion. Increases BP. Preparation available as DOCA, fluodocortisone is used therapeutically in Addison's disease. Other uses are salt losing congenital adrenal hyperplasia, hyporeninemic hypoaldosteronism, severe postural hypotension from autonomic neuropathy of any etiology.

Contraindications of corticosteroids

- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Pregnancy (risk of fetal defect)
- Tuberculosis and varicella infection
- Osteoporosis
- Herpes simplex keratitis
- Psychosis, epilepsy
- CCF
- Renal failure

Antagonist of Adrenocortical Agents

Synthesis inhibitor or antagonist of glucocorticoids:

Glucocorticoid antagonist (antiprogestin mifepristone) is evaluated for the treatment of Cushing's syndrome. It blocks glucocorticoid receptor in high doses by stabilizing hsp glucocorticoid receptor complex and alters its interaction with other coregulators.

Aminoglutethimide, **metyrapone**, **trilostane** and high dose of **antifungal ketoconazole** inhibit steroidogenic enzymes at livers, tried for Cushing's syndrome.

Metyrapone is used to test adrenal function. **Mitotane** has adrenolytic property in dog and to a some extent in human used for adrenal tumor (dose 12 gm/day). Diarrhea, nausea, vomiting, depression, somnolence, skin rash may occur. This prodrug used orally, studied for refractory cancer of prostate patient. It inhibits steroid.

Abiraterone: This prodrug used orally, studied for refractory cancer prostate patient. It inhibits steroid synthesis with compensatory increase in ACTH and aldosterone syntheses but this effect can be prevented by concomittent use of dexamethasone.

Etomidate used as inducing general anesthesia inhibits adrenal steroidogenesis.

Mifepristone: It is antagonist of steroid receptor used to treat ectopic ACTH or cushing patient. It is mainly used for post coital contraception.

Mineralocorticoid Antagonist

These steroid drugs csompete with aldosterone and decrease its action peripherally, *viz.*

a. **Spironolactone** (a potassium sparing diuretic) used in primary aldosteronism in the dose of 50–100 mg/day. It is slow acting and effect lasts for 2–3 days after its discontinuation.

b. **Eplerenone** is used in hypertension (dose 50–100 mg/day) with no reported action on androgen receptor. It is an aldosterone receptor antagonist. It may cause hyperkalemia.

c. **Drospirenone:** This oral contraceptive (progestin) also antagonizes aldosterone effect.