HORMONES AND RELATED DRUGS

Introduction

Hormone (Greek *hormaein*—to stir up) is a substance of intense biological activity that is produced by *specific cells* in the body and is transported *through circulation* to act on its target cells.

Hormones regulate body functions to bring about a programmed pattern of life events (growth, development, metabolism, reproduction, ageing, etc.) and maintain homeostasis in the face of markedly variable external and internal environment.

Body function	Major regulator hormone(s)
1. Availability of fuel	: Insulin, Glucagon, Growth hormone
2. Metabolic rate	: Triiodothyronine, Thyroxine
3. Somatic growth	: Growth hormone, Insulin-like growth factors
4. Sex and reproduction	: Gonadotropins, Androgens, Estrogens, Progestins
5. Circulating volume	: Aldosterone, Antidiuretic hormone
6. Adaptation to stress	: Glucocorticoids, Adrenaline
7. Calcium balance	: Parathormone, Calcitonin, Vitamin D

Hormones are secreted by the *endocrine* or *ductless* glands. These are:

1. *Pituitary*

(a) *Anterior* Growth hormone (GH), Prolactin (Prl),
Adrenocorticotropic hormone (ACTH) or Corticotropin.
Thyroid stimulating hormone (TSH) or Thyrotropin.
Gonadotropins—Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).

(b) *Posterior*—Oxytocin,
Antidiuretic hormone (ADH) or Vasopressin.

2. *Thyroid* Thyroxine (T_4), Triiodothyronine (T_3), Calcitonin.

3. *Parathyroid* Parathyroid hormone (PTH) or Parathormone.

4. *Pancreas* (*Islets of Langerhans*) Insulin, Glucagon.

5. *Adrenals*

(a) *Cortex* Glucocorticoids (hydrocortisone)
Mineralocorticoids (aldosterone)
Sex steroids (dehydroepiandrosterone)

(b) *Medulla* Adrenaline, Noradrenaline

6. *Gonads* Androgens (testosterone)
Estrogens (estradiol)
Progestins (progesterone)

In addition, hypothalamus, which is a part of the CNS and not a gland, produces many releasing and release inhibitory hormones which control the secretion of anterior pituitary hormones. Some important ones of these are given in the box.

Placenta also secretes many hormones:

Chorionic gonadotropin	Prolactin
Estrogens	Progesterone
Placental lactogen	Chorionic thyrotropin

Hypothalamic hormone/factor	Chemical nature
1. Thyrotropin releasing hormone (TRH)	Tripeptide
2. Corticotropin releasing hormone (CRH)	Peptide (41 AAs)
3. Gonadotropin releasing hormone (GnRH, LH-RH/ FSH-RH) or Gonadorelin	Decapeptide
4. Prolactin release inhibitory hormone (PRIH)	Dopamine
5. Growth hormone releasing hormone (GHRH)	Peptide (40, 44 AAs)
6. Somatostatin (Growth hormone release inhibitory hormone)	Peptide (14 AA)

The natural hormones and in many cases their synthetic analogues, which may be more suitable therapeutically, are used as drugs for substitution therapy as well as for pharmacotherapy. In addition, hormone antagonists and synthesis/ release inhibitors are of therapeutic importance.

Sites and mechanisms of hormone action

The hormones act on their specific receptors located on or within their target cells. Receptor activation by the hormones is translated into response in a variety of ways.

1. *At cell membrane receptors*

a. Through alteration of intracellular cAMP concentration → alteration of protein kinase A→ regulation of cell function: Ca^{2+} acting as third messenger in some situations.	Adrenaline, Glucagon, TSH, FSH, LH, PTH, Calcitonin, ACTH, some hypothalamic releasing hormones, Vasopressin (V_2 receptor)
b. Through IP_3/DAG generation: release of intracellular Ca^{2+} and protein kinase C activation.	Vasopressin (V_1 receptor), Oxytocin
c. Direct transmembrane activation of tyrosine protein kinase → phosphorylation cascade → regulation of various enzymes.	Insulin, Growth hormone Prolactin

2. *At cytoplasmic receptors*

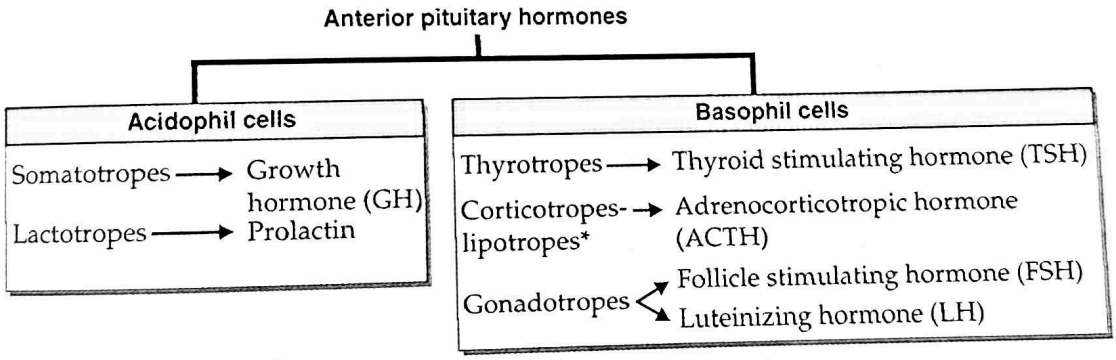
Penetrating cell membrane, hormone combines with a cytoplasmic receptor → exposes its DNA binding domain → migrates to nucleus and binds to specific genes → DNA mediated mRNA synthesis → synthesis of functional proteins.	Steroidal hormones: Glucocorticoids Mineralocorticoid Androgens Estrogens Progestins; Calcitriol

3. *At nuclear receptor*

The hormone penetrates the nucleus → combines with its receptor → alters DNA–RNA mediated protein synthesis.	Thyroid hormones: Thyroxine, Triiodothyronine

Chapter 17 | Anterior Pituitary Hormones

Anterior pituitary (adenohypophysis), the master endocrine gland, elaborates a number of important regulatory hormones. All of these are peptide in nature and act at extracellular receptors located on their target cells. Secretion of pituitary hormones is controlled by the hypothalamus through *releasing* and *release-inhibitory* hormones that are transported *via* hypothalamohypophyseal portal system, and is subjected to feedback inhibition by the hormones of their target glands. Each anterior pituitary hormone is produced by a separate group of cells, which according to their staining characteristic are either acidophilic or basophilic. The pituitary cells and the hormone they secrete are:



*These cells also produce two lipotropins and two melanocyte stimulating hormones (MSHs)

Out of the above hormones only GH and gonadotropins (Gns) are used therapeutically, while TSH and ACTH have only diagnostic application in rare instances. Of greater clinical interest are the drugs which either inhibit or stimulate the secretion of a specific anterior pituitary hormone. These are presented in the chart below.

DRUGS ALTERING ANTERIOR PITUITARY HORMONE SECRETION

Inhibit GH release	Inhibit prolactin release	Enhance prolactin release	Inhibit gonadotropin (Gn) release
Somatostatin Octreotide Lanreotide	Bromocriptine Cabergoline Apomorphine	Chlorpromazine (other neuroleptics) Metoclopramide Reserpine	

Superactive GnRH agonists (Initially enhance Gn release)	GnRH antagonists
Nafarelin Triptorelin Goserelin Leuprolide	Ganirelix Cetrorelix

GROWTH HORMONE (GH)

It is a 191 amino acid, single chain peptide of MW 22000.

Physiological functions During childhood and adolescence GH is required for normal growth and attainment of adult stature. It promotes growth of bones and all other organs by inducing hyperplasia. In general, there is a proportionate increase in the size and mass of all parts, but in the absence of gonadotropins, sexual maturation does not take place. The growth of brain and eye is independent of GH. It promotes retention of nitrogen, calcium and other tissue constituents: more protoplasm is formed. The positive nitrogen balance results from increased uptake of amino acids by tissues and their synthesis into proteins. In addition to protein metabolism, GH affects carbohydrate and fat metabolism throughout life. It promotes utilization of fat and spares carbohydrates. Uptake of glucose by muscles is reduced while its output from liver is enhanced; blood glucose level tends to rise.

GH acts on cell surface JAK-STAT binding protein kinase receptors (*see* p. 59) which are present on practically all types of cells. Binding of one GH molecule to the extracellular domain of a GH-receptor diamer results in the formation of a ternary complex which undergoes a conformational change and activates the intracellular domain to associate with cytoplasmic JAK-STAT tyrosine-protein kinase resulting in metabolic effects as well as regulation of gene expression.

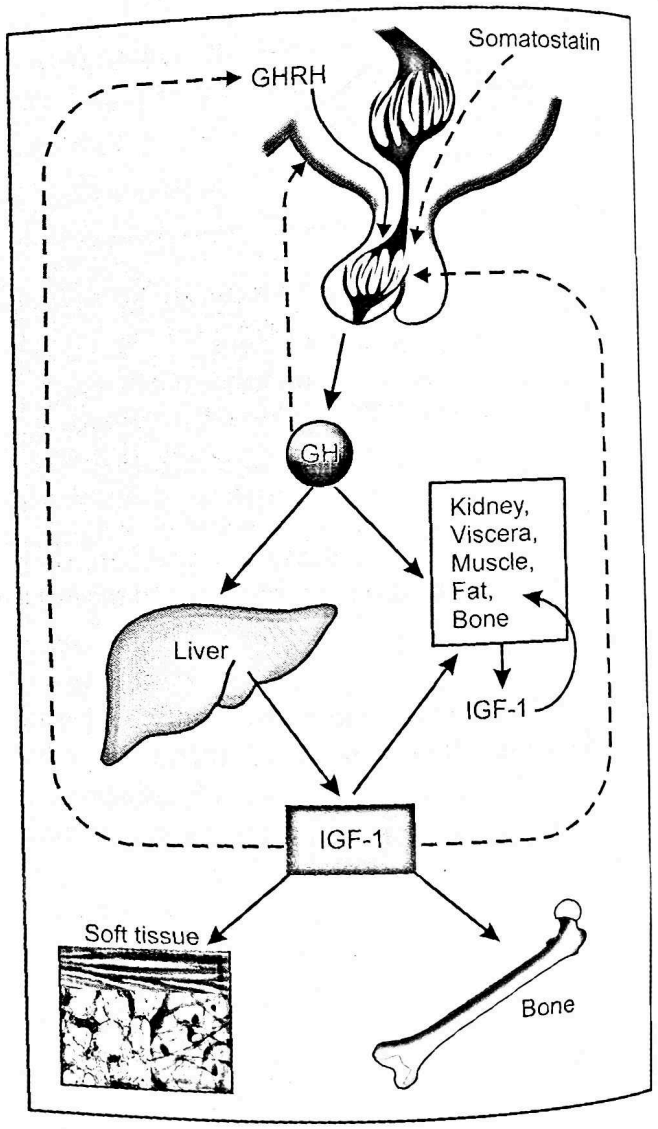


Fig. 17.1: Action of growth hormone (GH) and regulation of its secretion
GHRH—Growth hormone releasing hormone;
IGF-1: Insulin-like growth factor-1;
Stimulation (⟶); Inhibition (- - - -⟶)

The growth promoting, nitrogen retaining and certain metabolic actions of GH are exerted *indirectly* through the elaboration of peptides called *Somatomedins* or *Insulin-like growth factors* (mainly *IGF-1*, also *IGF-2*) which are extracellular mediators of GH response (Fig. 17.1). Liver is the major source of circulating IGF-1, while IGF-1 produced by other target cells acts locally in a paracrine manner. Like insulin, IGF-1 promotes lipogenesis and glucose uptake by muscles. Moreover, the IGF-1 receptor is structurally and functionally analogous to the insulin receptor (*see* p. 284).

GH acts directly as well, but induces lipolysis in adipose tissue, gluconeogenesis and glycogenolysis in liver and decreased glucose utilization by muscles. These effects are opposite to those of IGF-1 and insulin. As such, GH accentuates the metabolic derangement in diabetes.

Regulation of secretion The hypothalamus produces GH releasing (GHRH) as well as release inhibitory (*somatostatin*) hormones. Both are peptides. Receptors for GHRH and somatostatin are G protein coupled receptors (GPCRs) which enhance or inhibit GH secretion by increasing or decreasing cAMP formation respectively in pituitary somatotropes. IGF-1 causes feedback inhibition of GH secretion. Short-loop feedback inhibition of secretion by GH itself has also been described.

Pathological involvements Excess production of GH is responsible for *gigantism* in childhood and *acromegaly* in adults. Hyposecretion of GH in children results in *pituitary dwarfism*. Normal adult height is not attained, muscle mass is low and body fat is increased. Adult GH deficiency is rare, but when it occurs, it results in low muscle and bone mass, lethargy, decreased work capacity, hyperlipidaemia and increased cardiovascular risk.

Uses

Availability of *Somatropin*, the recombinant human GH (rhGH) has considerably widened the clinical application of GH. However, it should be used only by specialists.

1. *Pituitary dwarfism:* It is due to GH deficiency which is noticed in early childhood as subnormal height gain. Daily s.c. injection of somatropin (30–60 μg/kg), preferably in the evening, produces highly gratifying results. Growth is accelerated and near normal adult stature may be attained if therapy is instituted early and continued till the age of 20.
2. *Turner syndrome:* The short stature of girls can be largely corrected by rhGH treatment combined with properly timed androgen and estrogen therapy.
3. *Chronic renal insufficiency* in children causing suboptimal growth: rhGH is approved for restoring growth.
4. *Constitutional (idiopathic) short stature children:* Somatropin treatment has yielded encouraging results, but entails longterm costly medication. Ethical, social and medical objections have been raised.
5. *GH deficiency in adults:* rhGH treatment increases lean body mass, decreases body fat, improves energy and metabolism.
6. *AIDS related wasting:* Somatropin improves physical and mental health of affected patients. It has also been used in other catabolic states like severe burns, bedridden patients, chronic renal failure, etc.[8]

Somatropin is also being promoted for ageing, but benefits are uncertain. Its use by athletes is banned, and it is one of the drugs included in 'dope testing'.

Somatropin: NORDITROPIN, NORDILET 5, 10, 15 mg prefilled pen injector, HUMATROPE 6 mg, 12 mg cartridges, 1.33 and 5.33 mg vials.

Adverse effects Somatropin has low immunogenicity; allergic reactions or resistance to treatment are not a problem. Pain at injection site, lipodystrophy, glucose intolerance, hypothyroidism (due to unmasking of TSH deficiency), salt and water retention, hand stiffness, myalgia, headache are the possible adverse effects. Rise in intracranial tension occurs in few cases.

Mecasermin This is recently produced recombinant human IGF-1 (rhIGF-1), which is useful in children with retardation unresponsive to rhGH and is due to GH receptor/GH signaling pathway abnormality.

GH Inhibitors

Somatostatin

This 14 amino acid peptide inhibits the secretion of GH, prolactin, and TSH by pituitary; insulin and glucagon by pancreas, and of almost all gastrointestinal secretions including that of gastrin and HCl. The g.i. action produces steatorrhoea, diarrhoea, hypochlorhydria, dyspepsia and nausea as side effect. Somatostatin constricts splanchnic, hepatic and renal blood vessels. The decreased g.i. mucosal

blood flow can be utilized for controlling bleeding esophageal varices and bleeding peptic ulcer, but its analogue octreotide is preferred now due to longer duration of action. The antisecretory action of somatostatin is beneficial in pancreatic, biliary or intestinal fistulae; can also be used to reduce complications after pancreatic surgery. It has adjuvant value in diabetic ketoacidosis (by inhibiting glucagon and GH secretion).

Use of somatostatin in acromegaly is limited by its short duration of action (t½ 2–3 min), lack of specificity for inhibiting only GH secretion and GH rebound on discontinuation. Surgical removal of pituitary adenomas is the preferred treatment modality, but somatostatin analogues are being increasingly used.

Dose: (for upper g.i.bleeding) 250 µg slow i.v. injection over 3 min followed by 3 mg i.v. infusion over 12 hours.

STILMEN, SOMATOSAN, SOMASTAT 250 µg and 3 mg amps.

Octreotide This synthetic octapeptide surrogate of somatostatin is 40 times more potent in suppressing GH secretion and longer acting (t½ ~90 min), but only a weak inhibitor of insulin secretion. It is preferred over somatostatin for acromegaly and secretory diarrhoeas associated with carcinoid, AIDS, cancer chemotherapy or diabetes. Control of diarrhoea is due to suppression of hormones which enhance intestinal mucosal secretion.

Dose: Initially 50–100 µg s.c. twice daily, increased upto 200 µg TDS; for acromegaly maintain with 10–30 mg i.m. of microsphere formulation every 4 weeks.

Adverse effects are abdominal pain, nausea, steatorrhoea, diarrhoea, and gall stones (due to biliary stasis). Hyperglycaemia is infrequent.

Octreotide injected i.v. (100 µg followed by 25–50 µg/hr) reduces hepatic blood flow and helps stop esophageal variceal bleeding.

SANDOSTATIN, OCTRIDE 50 µg, 100 µg in 1 ml amps.
SANDOSTATIN LAR (microsphere formulation) 20 mg/5 ml inj.

Lanreotide Another long-acting analogue of somatostatin, very similar in actions and specificity to octreotide, which on i.m. injection acts for 10–15 days. It is indicated for pharmacotherapy of acromegaly.

Pegvisomant This polyethylene glycol complexed mutant GH binds to the GH receptor but does not trigger signal transduction: acts as a GH antagonist. It is approved for treatment of acromegaly due to small pituitary adenomas.

PROLACTIN

It is a 199 amino acid, single chain peptide of MW 23000; quite similar chemically to GH. Prolactin was originally described as the hormone which causes secretion of milk from crop glands of pigeon and later found to be of considerable importance in human beings as well.

Physiological function Prolactin is the primary stimulus which in conjunction with estrogens, progesterone and several other hormones, causes growth and development of breast during pregnancy. It promotes proliferation of ductal as well as acinar cells in the breast and induces synthesis of milk proteins and lactose. After parturition, prolactin induces milk secretion, since the inhibitory influence of high estrogen and progesterone levels is withdrawn.

Prolactin suppresses hypothalamo-pituitary-gonadal axis by inhibiting GnRH release. Continuous high level of prolactin during breastfeeding is responsible for lactational amenorrhoea, inhibition of ovulation and infertility for several months postpartum. Prolactin may affect immune response through action on T-lymphocytes.

A specific prolactin receptor is expressed on the surface of target cells, which is structurally and functionally analogous to GH receptor: action is exerted by transmembrane activation of JAK—cytoplasmic tyrosine protein kinases and STAT.

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 (DA, bromocriptine, cabergoline) decrease plasma prolactin levels, while dopaminergic antagonists (chlorpromazine, haloperidol, metoclopramide) and DA depleter (reserpine) cause hyperprolactinemia.

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.

Physio-pathological involvement Hyperprolactinaemia is responsible for the galactorrhoea–amenorrhoea–infertility syndrome in women. In males it causes loss of libido and depressed

fertility. The most important cause of hyperprolactinaemia is prolactin secreting tumours (micro- or macroprolactinomas). Others are—hypothalamic disorders weakening its inhibitory control over pituitary, antidopaminergic drugs or high TRH levels (due to hypothyroidism) which stimulates prolactin secretion.

Use There are no clinical indications for prolactin.

Prolactin inhibitors

Bromocriptine

This synthetic ergot derivative 2-bromo-α-ergocryptine is a potent dopamine agonist. It has greater action on D2 receptors, while at certain dopamine sites in the brain it acts as a partial agonist or antagonist of D1 receptor. It is also a weak α adrenergic blocker but not an oxytocic. Actions of bromocriptine are:

1. Decreases prolactin release from pituitary and is a strong antigalactopoietic.
2. Increases GH release in normal individuals, but decreases the same from pituitary tumours that cause acromegaly.
3. Has levodopa like actions in CNS—antiparkinsonian and behavioural effects.
4. Produces nausea and vomiting by stimulating dopaminergic receptors in the CTZ.
5. Hypotension—due to central suppression of postural reflexes and weak peripheral a adrenergic blockade.
6. Decreases gastrointestinal motility.

Only 1/3 of an oral dose of bromocriptine is absorbed; bioavailability is further lowered by high first pass metabolism in liver. Metabolites are excreted mainly in bile. Its plasma t½ is 3–6 hours.

PROCTINAL, PARLODEL, SICRIPTIN, 1.25 mg, 2.5 mg tabs.

Uses Bromocriptine is infrequently used now; has been largely superseded by newer D2 agonists. Conditions in which it can be used are:

1. *Hyperprolactinemia* due to microprolactinomas causing galactorrhoea, amenorrhoea and infertility in women; gynaecomastia, impotence and sterility in men but has been replaced by cabergoline.
2. *Acromegaly* Bromocriptine is indicated when acromegaly is due to small pituitary tumours and for inoperable cases; but cabergoline is preferred now.
3. *Parkinsonism* Relatively higher doses are required, which are poorly tolerated. Newer D2 receptor agonists, ropinirole and pramipexole are used now.
4. *Diabetes mellitus (DM)* A new use of bromocriptine based on its dopamine D2 agonistic action in the hypothalamus has been found in type 2 DM, and it has been approved by US-FDA as an adjunctive drug.

Side effects: Side effects are frequent and dose related.

Early: Nausea, vomiting, constipation, nasal blockage. Postural hypotension may be marked at initiation of therapy—syncope may occur if starting dose is high. Hypotension is more likely in patients taking antihypertensives.

Late: Behavioural alterations, mental confusion, hallucinations, psychosis. These side effects are more prominent than with levodopa.
Abnormal movements, livedo reticularis.

Cabergoline

It is a newer D2 agonist; more potent; more selective for pituitary lactotrope D2 receptors, and longer acting (t½ > 60 hours) than bromocriptine. It needs to be given only twice weekly. Incidence of nausea and vomiting is also lower; some patients not tolerating or not responding to bromocriptine have been successfully treated with cabergoline. It is the first choice drug for treatment of hyper-prolactinaemia; serum prolactin levels fall to the normal range in 2–4 weeks, and many women conceive within one year. Cabergoline should be stopped when pregnancy occurs, though no teratogenic effect has been observed. Most micro- and some macroprolactinomas show regression during therapy, and neurological symptoms (visual field defects, etc.) due to pressure on optic chiasma are relieved. Response is generally maintained only till the drug is given, with recurrence on stoppage. Some patients who achieve total regression of prolactinoma and normalization of prolactin levels can stop cabergoline without recurrence.

Cabergoline is also beneficial in acromegaly due to pituitary adenoma, but efficacy is lower. It may be used to supplement surgery/radiation/octreotide.

Dose: Start with 0.25 mg twice weekly; if needed increase after every 4–8 weeks to max. of 1 mg twice weekly. CABERLIN 0.5 mg tab, CAMFORTE 0.5, 1 mg tabs. COLETTE 0.25, 0.5 mg tabs.

GONADOTROPINS (Gns)

The anterior pituitary secretes two Gns *viz.* FSH and LH. Both are glycoproteins containing 23–28% sugar and consist of two peptide chains. The α-chain (92AA) is common between FSH and LH, but their β-chains are different: FSH (111 AA), LH (121 AA). Paradoxically the MW of FSH (~33KD) is greater than that of LH (~30 KD), because of the sugar moieties.

Physiological functions FSH and LH act in concert to promote gametogenesis and secretion of gonadal hormones.

FSH In the female it induces follicular growth, development of ovum and secretion of estrogens. In the male it supports spermatogenesis and has a trophic influence on seminiferous tubules. Ovarian and testicular atrophy occurs in the absence of FSH.

LH It induces preovulatory swelling of the ripe graafian follicle and triggers ovulation followed by luteinization of the ruptured follicle and sustains the corpus luteum till the next menstrual cycle. It is also probably responsible for atresia of the remaining follicles. Progesterone secretion occurs only under the influence of LH. In the male LH stimulates testosterone secretion by the interstitial cells and is designated interstitial cell stimulating hormone (ICSH).

Distinct LH and FSH receptors are expressed on the target cells. Both are G protein coupled receptors which on activation increase cAMP production. This in turn stimulates gametogenesis and conversion of cholesterol to pregnenolone—the first step in progesterone, testosterone and estrogen synthesis.

Regulation of secretion A single releasing factor (decapeptide designated *GnRH*) is produced by the hypothalamus which stimulates synthesis and release of both FSH and LH from pituitary. It is, therefore, also referred to as *FSH/LH-RH* or simply *LHRH* or *gonadorelin*. It has been difficult to explain how hypothalamus achieves a divergent pattern of FSH and LH secretion in menstruating women through a single releasing hormone. Since GnRH is secreted in pulses and the frequency as well as amplitude of the pulses differs during follicular (high frequency, low amplitude) and luteal (lower frequency, higher amplitude) phases, it is considered that frequency and amplitude of GnRH pulses determines whether FSH or LH or both will be secreted, as well as the amount of each. Further, the feedback regulation of FSH and LH may be different. In general, feedback inhibition of LH is more marked than that of FSH. In addition there are other regulatory substances, e.g. *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. GnRH acts on gonadotropes through a G-protein coupled receptor which acts by increasing intracellular Ca^{2+} through PIP_2 hydrolysis.

The Gn secretion increases at puberty and is higher in women than in men. In men, the levels of FSH and LH remain practically constant (LH > FSH) while in menstruating women they fluctuate cyclically. During the follicular phase, moderate levels of FSH and low levels of LH prevail. There is a midcycle surge of both, but more of LH, just before ovulation, followed by progressive fall during the luteal phase. Gn levels are high in menopausal women due to loss of feedback inhibition by sex steroids and inhibin.

Pathological involvement Disturbances of Gn secretion from pituitary may be responsible for delayed puberty or precocious puberty in girls as well as in boys.

Inadequate Gn secretion results in amenorrhoea and sterility in women; oligozoospermia, impotence and infertility in men. Excess production of Gn in adult women causes polycystic ovaries.

Preparations

All earlier gonadotropin preparations were administered by i.m. route. The newer more purified preparations can be given s.c. They are partly metabolized, but mainly excreted unchanged in urine: t½ 2–6 hours.

1. *Menotropins (FSH + LH):* is a preparation obtained from urine of menopausal women:
PREGNORM, PERGONAL, GYNOGEN 75/150; 75 IU FSH + 75 IU LH activity per amp, also 150 IU FSH + 150 IU LH per amp.

2. *Urofollitropin or Menotropin (pure FSH):* METRODIN, FOLGEST, FOLICULIN, PUREGON 75 IU and 150 IU per amp. This preparation has been preferred over the combined FSH + LH preparation for induction of ovulation in women with polycystic ovarian disease. These patients have elevated LH/FSH ratio; use of FSH alone is considered advantageous. This preparation is also claimed to improve chances of obtaining good quality ova for *in vitro* fertilization.

3. *Human chorionic gonadotropin (hCG):* is derived from urine of pregnant women.

CORION, PROFASI, PUBERGEN 1000 IU, 2000 IU, 5000 IU, 10,000 IU, all as dry powder with separate solvent for injection.

The foetal placenta secretes hCG which is absorbed in maternal circulation and maintains corpus luteum of pregnancy. It is a glycoprotein with 33% sugar and 237 amino acids in two chains, MW 38000. It is excreted in urine by the mother from which it is commercially obtained. hCG binds to LH receptor with equal avidity; action of hCG is indistinguishable from that of LH.

Recombinant human FSH (rhFSH or *Follitropin* α and *follitropin* β) and recombinant human LH (rhLH or *Lutropin*) as well as recombinant hCG (rhCG or *Choriogonadotropin* α) have been produced. These are more purified and have virtually replaced the urine derived preparations in the developed countries. They are more expensive. Lutropin (rhLH) has been withdrawn.

Uses

1. *Amenorrhoea and infertility* Exogenous Gns may help when amenorrhoea/infertility is due to deficient production of Gns by pituitary. Gns are generally tried when attempts to induce ovulation with clomiphene have failed or when nonovulation is due to polycystic ovaries. Several protocols for use of Gns have been employed, one of which is to give 1 injection of menotropins (75 IU FSH + 75 IU LH or 75 IU pure FSH)) i.m. daily for 10 days followed the next day by 10,000 IU of hCG. Ovulation occurs within the next 24–48 hours in upto 75% cases and the woman may conceive if inseminated at this time. However, rates of abortion and multiple pregnancy are high, but not of teratogenesis.

To improve the predictability of time of *ovulation (controlled ovarian stimulation)*, it is the standard practice now to concurrently suppress endogenous FSH/LH secretion either by continuous pretreatment with a superactive GnRH agonist or by a GnRH antagonist.

2. *To aid in vitro fertilization* Menotropins (FSH + LH or pure FSH) is used along the GnRH agonist/antagonist (for suppressing endogenous FSH/LH) to induce simultaneous maturation of several ova and to precisely time ovulation so as to facilitate their harvesting for assisted reproductive techniques.

3. *Male hypogonadotropic hypogonadism* It manifests as delayed puberty or defective spermatogenesis producing oligozoospermia and male sterility. Generally, sexual maturation is induced by androgens and therapy with hCG is started when fertility is desired. Start with hCG i.m. 2–3 times a week (to stimulate testosterone secretion), add FSH 75 IU + LH 75 IU after 3–4 months (to stimulate spermatogenesis) and reduce dose of hCG. Treatment is continued for 6–12 months for optimum results, which nevertheless are not always impressive.

4. *Cryptorchidism* A 2–6 weeks course of hCG was used to treat undescended testes in early childhood. However, this is not practiced now due to poor efficacy, risk of precocious puberty and other concerns. Surgical correction is the preferred modality.

Adverse effects and precautions

Ovarian hyperstimulation syndrome is the most serious complication. Polycystic ovary, pain in lower abdomen and even ovarian bleeding and shock can occur in females during ovulation induction.

Multiple pregnancy is another complication.

Precocious puberty is a risk when given to children.

Allergic reactions have occurred and skin tests are advised. Hormone dependent malignancies (prostate, breast) must be excluded.

Other side effects are edema, headache, mood changes.

GONADOTROPIN RELEASING HORMONE (GnRH) (GONADORELIN)

Synthetic human GnRH (gonadorelin) injected i.v. (100 μg) induces prompt release of LH and FSH followed by elevation of gonadal steroid levels. It has a short plasma t½ (4–8 min) due to rapid enzymatic degradation. It has been used for testing pituitary-gonadal axis in male as well as female hypogonadism.

Only pulsatile exposure to GnRH induces FSH/LH secretion, while sustained exposure desensitizes the pituitary gonadotropes resulting in loss of Gn release. Therapy with GnRH is not useful in the treatment of hypogonadism.

Superactive/long-acting GnRH agonists

Many analogues of GnRH, e.g. Goserelin, Leuprolide, Nafarelin, Triptorelin, have been developed which are 15–150 times more potent than natural GnRH and longer acting (t½ 2–6 hours) because of high affinity for GnRH receptor and resistance to enzymatic hydrolysis. Because physiological release of GnRH is in pulses, whereas these agonists act continuously; they only initially trigger Gn secretion. After 1–2 weeks they cause desensitization and down regulation of GnRH receptors causing inhibition of FSH and LH secretion followed by 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.

The superactive GnRH agonists are used as nasal spray or injected s.c/i.m. Long-acting preparations for once a month s.c. injection have been produced (triptorelin, goserelin depot). The resulting reversible pharmacological oophorectomy/orchidectomy is being used in *precocious puberty*, *prostatic carcinoma*, *endometriosis*, *premenopausal breast cancer*, *uterine leiomyoma*, *polycystic ovarian disease* and to *assist induced ovulation*. They also have potential to be used as contraceptive for both males and females.

Menopausal symptoms, *viz.* headache, sweating, hot flashes, mood changes, vaginal dryness amenorrhoea and loss of libido can occur due to suppression of ovarian function. Use of GnRH agonists for more than 6 months carries risk of developing osteoporosis.

Nafarelin This long-acting GnRH agonist is 150 times more potent than native GnRH. It is used as intranasal spray from which bioavailability is only 4–5%.

NASAREL 2 mg/ml soln for nasal spray; 200 µg per actuation.

Down regulation of pituitary GnRH receptors occurs in10 days but peak inhibition of Gn release occurs at one month. It is broken down in the body to shorter peptide segments; plasma t½ is 2–3 hours. Uses are:

Assisted reproduction: Endogenous LH surge needs to be suppressed when controlled ovarian stimulation is attempted by exogenous FSH and LH injection, so that precisely timed mature oocytes can be harvested. This is achieved by 400 µg BD intranasal nafarelin, reduced to 200 µg BD when menstrual bleeding occurs.

Uterine fibroids: Nafarelin 200 µg BD intranasal for 3–6 months can reduce the size of leiomyoma and afford symptomatic relief.

Endometriosis: 200 µg in alternate nostril BD for upto 6 months. It is as effective as danazol, but second course cannot be given due to risk of osteoporosis.

Central precocious puberty: 800 µg BD by nasal spray; breast and genital development is arrested in girls and boys. Treatment is generally carried out till the age of 11 years in girls or 12 years in boys. The effect is reversible; pubertal changes resume when therapy is discontinued.

Adverse effects: Hot flashes, loss of libido, vaginal dryness, osteoporosis, emotional lability.

Goserelin Another long-acting GnRH agonist available as a depot s.c./i.m. injection to be used both for endogenous Gn suppression before ovulation induction, as well as for endometriosis, carcinoma prostate, etc. To achieve pituitary desensitization before ovulation induction with exogenous Gns; 3.6 mg of depot goserelin injection is given once in the anterior abdominal wall 1–3 weeks earlier.

For *endometriosis and carcinoma prostate* 3.6 mg is injected in the same way every 4 weeks or 10.8 mg is injected every 3 months. An androgen antagonist (bicalutamide) is given concurrently for 3–4 weeks when goserelin is used for carcinoma prostate. This is needed to block the effect of androgen secreted under the influence of enhanced Gn production by initial agonistic action of the GnRH agonist on gonadotropes.

ZOLADEX 3.6 mg prefilled syringe, ZOLADEX-LA 10.8 mg vial depot injection.

Triptorelin: This long acting GnRH agonist is formulated as a regular release daily s.c. injection for short term indications, such as female infertility, and as a depot i.m. monthly injection for long-term Gn suppression in the treatment of carcinoma prostate, endometriosis, precocious puberty and uterine leiomyoma. For prostate cancer, it is combined with an androgen antagonist flutamide or bicalutamide to prevent the initial flare up of the tumour that occurs due to increase in Gn secretion for the first 1–2 weeks.

Fibroids, endometriosis, carcinoma prostate: 3.75–7.5 mg i.m. every 4 weeks.

Precocious puberty: 50 µg/kg i.m. of depot inj. every 4 weeks.

Assisted reproduction: 0.1 mg s.c. daily for 10 days from 2nd day of cycle.

DECAPEPTYL DAILY 0.1 mg inj., DECAPEPTYL DEPOT 3.75 mg inj.

Leuprolide This long acting GnRH agonist is injected s.c./i.m. daily or as a depot injection once a month for palliation of carcinoma prostate alongwith an androgen antagonist, as well as for other conditions needing long term Gn suppression. Daily s.c. injections are also used for assisted reproduction.

LUPRIDE 1 mg inj., 3.75 mg depot inj., PROGTASE 1 mg/ml inj.

GnRH antagonists Four analogues of GnRH, *Ganirelix*, *Cetrorelix*, *Degarelix* and *Abarelix* which are more extensively substituted act as GnRH receptor antagonists. They inhibit Gn secretion without causing initial stimulation. *Ganirelix* and *Cetrorelix* are relatively short acting. Administered daily by s.c. injection, they are approved for inhibiting LH surges during controlled ovarian stimulation in women undergoing *in vitro* fertilization. Their advantages over long-acting GnRH agonists include:

- They produce quick Gn suppression by competitive antagonism, and need to be started only from 6th day of attempting ovarian stimulation with Gns.
- They carry a lower risk of ovarian hyperstimulation syndrome.
- They achieve more complete suppression of endogenous Gn secretion.

However, pregnancy rates are similar or may even be lower.

Degarelix and *Abarelix* are long acting GnRH antagonists, approved for androgen withdrawal therapy of advanced carcinoma prostate.

THYROID STIMULATING HORMONE (TSH, THYROTROPIN)

It is a 210 amino acid, two chain glycoprotein (22% sugar), MW 30000.

Physiological function TSH stimulates thyroid to synthesize and secrete thyroxine (T_4) and triiodothyronine (T_3) (*see* Fig. 18.1). 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 T_3 and T_4 by increasing peroxidase activity.
- Enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T_3 and T_4. This action starts within minutes of TSH administration.

The TSH receptor present on thyroid cells is a GPCR which utilizes the adenylyl cyclase-cAMP transducer mechanism (by coupling to Gs protein) to produce its effects. In human thyroid cells high concentration of TSH also induces PIP_2 hydrolysis by the linking of TSH receptor to Gq protein. The resulting increase in cytosolic Ca^{2+} and protein kinase C activation may also mediate TSH action, particularly generation of H_2O_2 needed for oxidation of iodide and iodination of tyrosil residues.

Regulation of secretion Synthesis and release of TSH by pituitary is controlled by hypothalamus primarily through TRH (*see* Fig. 18.3), while somatostatin inhibits TSH secretion. The TRH receptor on pituitary thyrotrope cells is a GPCR which is linked to Gq protein and activates PLC–IP_3/DAG–cytosolic Ca^{2+} pathway to enhance TSH synthesis and release. The negative feedback for inhibiting TSH secretion is provided by the thyroid hormones which act primarily at the level of the pituitary, but also in the hypothalamus.

Pathological involvement Only few cases of hypo- or hyperthyroidism are due to inappropriate TSH secretion. 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.

Use Thyrotropin has no therapeutic use. Thyroxine is the drug of choice even when hypothyroidism is due to TSH deficiency. The diagnostic application is to differentiate myxoedema due to pituitary dysfunction from primary thyroid disease.

ADRENOCORTICOTROPIC HORMONE (ACTH, CORTICOTROPIN)

It is a 39 amino acid single chain peptide, MW 4500, 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). This inturn 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 (*see* Fig. 20.1). 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.

A variety of stressful stimuli, e.g. trauma, surgery, severe pain, anxiety, fear, blood loss, exposure to cold, etc. generate neural impulses which converge on median eminence to cause elaboration of CRH. The feedback inhibition appears to be overpowered during stress—rise in ACTH secretion continues despite high plasma level of cortisol induced by it.

Pathological involvement Excess production of ACTH from basophil pituitary tumours is responsible for some cases of Cushing's syndrome. Hypocorticism occurs in pituitary insufficiency due to low ACTH production. Iatrogenic suppression of ACTH secretion and pituitary adrenal axis is the most common form of abnormality encountered currently due to the use of pharmacological doses of glucocorticoids in nonendocrine diseases.

Use ACTH is used rarely for the diagnosis of disorders of pituitary adrenal axis. Direct assay of plasma ACTH level is now preferred.

For therapeutic purposes, ACTH does not offer any advantage over corticosteroids.