Chapter-2
ADRENOCORTICOTROPIC HORMONE (ACTH)

2.1. ACTH human figure

ACTH is secreted in the pituitary gland and travels through the blood stream to the adrenal glands.

ACTH stimulates the adrenal glands to release cortisol.

2.2. Adrenocorticotropic hormone (ACTH)

Adrenocorticotropic hormone (ACTH) is secreted by the pituitary gland to regulate the production of steroid hormones by the adrenal cortex. Control of ACTH secretion from the anterior pituitary involves both a classical negative feedback mechanism and Central Nervous System (CNS)-stress mediated control system. Two hypothalamic peptide hormones modulate this secretion; corticotropin releasing hormone (CRH) simulates ACTH secretion synergistically with vasopressin (AVP). ACTH increase the synthesis and release of all adrenal steroids, aldosterone, cortisol and adrenal androgens [11]. It is the principal modulator of cortisol, the pituitary
glucocorticoid in man. As the effective level of cortisol in the circulation rises, release of ACTH is inhibited directly at a pituitary level. Through this same mechanism, falling cortisol levels lead to elevated ACTH levels.

Like other pituitary hormones, ACTH is secreted in a pulsatile manner. These small pulses are superimposed on a characteristic, diurnal fluctuation of greater amplitude. In normal individuals, ACTH reaches a peak in the early morning (6-8am) and levels become lowest late in the day and near the beginning of the sleep period. Because of this diurnal rhythm, it is customary to draw plasma ACTH sample between 8-10am. However, discrimination of patients with Cushing’s Syndrome from normal individual may be best made on samples obtained in the evening (4-6pm). In Cushing’s and Ectopic ACTH Syndromes the diurnal pattern of ACTH Syndromes the diurnal pattern of ACTH secretion is usually absent.

2.3. ACTH and related diseases

The table below indicates the common patterns of ACTH and cortisol seen with different diseases involving the adrenal and pituitary glands.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cortisol</th>
<th>ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s disease (pituitary tumor making ACTH)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>“Ectopic” ACTH (ACTH made by a tumor outside the pituitary, usually in the lung)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Addison’s disease (adrenal damage)</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
An increased ACTH result can mean that a patient has Cushing’s disease, Addison’s disease, or ectopic ACTH-producing tumors. A decreased ACTH result can be due to an adrenal tumor, Steroid medication, or hypopituitarism. In some cases, the interpretation of the results can be complex. Concentrations of both ACTH and cortisol vary throughout the day. Normally ACTH will be at its highest level in the morning and lowest at night. It will simulate cortisol production, which will follow the same pattern but will rise after ACTH does and fall to its lowest level very late in the evening. Conditions that affect the production of ACTH and cortisol often disrupt this diurnal variation (daily pattern).

2.4. Cushing’s disease

Cushing’s disease is a hormonal disorder caused by prolonged exposure of the body tissues to high levels of the hormone sometimes called hypercortisolism. It is relatively rare and most commonly affects adults age 20 to 50. An estimated 10 every million people are affected each year [138]. There has been a very causative link between mold patients and Cushing’s disease.

2.4.1. Symptoms

Most people have upper body obesity, rounded face, increased fat around the neck and thinning arm and also appear in the skin which becomes fragile and thin. It bruises easy and heals poorly. Purplish pink stretched may appear on the abdomen, thighs, buttocks, arms and breasts [81]. The bones are
weakened, and routine activities such as lifting or rising from a chair may lead to backaches, rib and spinal column fractures. Most people have severe fatigue, weak muscles, high blood pressure and high blood sugar. Irritability, anxiety and depression common.

2.4.2 Causes of cushing’s syndrome

Once hypercortisolism is confirmed, the next step is to determine the cause. Nor pituitary gland produces ACTH (Adrenocorticotropic hormone), which circulates in simulates the adrenal glands to produce cortisol[46]. Right above the pituitary gland the brain, is the hypothalamus. The hypothalamus produces CRH (Corticotropin releasing hormone), which stimulates the pituitary gland to produce ACTH. Therefore hypothalamus can arise from too much CRH, ACTH; or from excessive production of cortisol by adrenal gland. The causes are divided into ACTH dependent and ACTH independent sources. ACTH dependent includes a pituitary tumor producing ACTH and ectopic ACTH production (ACTH produces elsewhere, such as by a carcinoid tumor or lung cancer) [108]. ACTH independent Cushing’s syndrome consists of an adrenal growth, ectopic malignant, producing cortisol. ACTH levels are low, undetectable if there is a source.
2.4.3 Pathophysiology of Cushing's disease

When stimulated by ACTH, the adrenal gland secretes cortisol and other steroid hormones. ACTH is produced by the pituitary gland and released into the petrosal venous sinuses in response to stimulation by corticotrophin-releasing hormone (CRH) from the hypothalamus. ACTH is released in a diurnal pattern that is independent of circulating cortisol levels: peak release occurs just before awakening, and ACTH levels then decline throughout the day. Control of CRH and ACTH release is maintained through negative feedback by cortisol at the hypothalamic and pituitary levels. Neuronal input at the hypothalamic level can also stimulate CRH release[144]. Although the adenomas of Cushing disease secrete excessive amounts of ACTH, they generally retain some negative feedback responsiveness high doses of glucocorticoids. Ectopic sources of ACTH, usually in the form of extracranial neoplasms, are generally not responsive to
negative feedback with high doses of glucocorticoid. Cushing’s syndrome is categorized a ACTH dependent or ACTH independent. This division is convenient for organizing the work-up of patients with suspected hypercortisolism. Depression, alcoholism, medications, eating disorders and other conditions can cause mild clinical and laboratory findings, similar to those in Cushing’s syndrome, termed “pseudo-cushing’s syndrome” laboratory and clinical findings of hypercortisolism disappear if the primary process is successfully treated. Dexamethasone, an exogenous glucocorticoid, is used to test for Cushing’s syndrome[110]. This glucocorticoid does not interfere with cortisol assays but induces similar physiologic responses.

2.5. Ectopic ACTH syndrome

Ectopic ACTH syndrome, which accounts for about 20% of patients with Cushing’s syndrome, occurs two to three times more frequently in male patients. Unlike Cushing’s disease (female preponderance 8:1). Small cell lung carcinoma accounts for about 50-75% of all cases ectopic ACTH secretion. Ectopic CRH syndrome. This is rare and is clinically indistinguishable from Cushing’s disease or ectopic ACTH syndrome associated with comparatively benign tumors. Most cases of ectopic CRH(CH-41) secretion have been associated with bronchial carcinoid tumors.

2.6. Adrenal tumors

An abnormality of the adrenal gland most often an adrenal tumor, causes Cushing’s syndrome, average onset is above 40 years, most of these cases involve non-cancerous tumors of adrenal tissue called adrenal
adenomas, we can find a release excess cortisol into the blood. Adrenocortical carcinomas or adrenal cancers are the least common cause of Cushing's syndrome. Cancer cells secrete levels of several adrenal cortical hormones including cortisol and adrenal and androgens. Adrenocortical carcinomas usually called high hormone levels and rapid development of symptoms.

2.7. Addison's disease

Addison's Disease is an endocrine or hormonal disorder that occurs in all age groups and afflicts men and women equally. The disease is characterized by weight loss, muscle weakness, fatigue, low blood pressure and sometimes darkening of the skin in both exposed and non-exposed part of the body.

Addison's disease occurs when the adrenal gland do not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. The disease is also called adrenal insufficiency or hypocortisolism.

2.7.1. Causes of addison's disease

Failure to produce adequate levels of cortisol can occur for different reasons, the problem may be due to a disorder of the adrenal gland themselves (primary adrenal insufficiency) or to inadequate secretion of ACTH by the pituitary gland (secondary adrenal insufficiency)
2.7.2. **Primary Adrenal insufficiency**

Addison’s disease affects about one in one lakh people. Most cases are caused by the gradual destruction of the adrenal cortex, the outer layer of the adrenal glands by the body’s own immune system. Above seventy percent of reported cases of Addison’s disease are caused by autoimmune disorder in which the immune system makes antibodies that attack the body’s own tissues or organs and slowly destroy them. Adrenal insufficiency occurs when at least ninety percent of the adrenal cortex has been destroyed. As a result, often both glucocorticoid (cortisol) and mineralocorticoid (aldosterone) hormones are lacking. Sometimes only the adrenal gland is affected as an idiopathic adrenal insufficiency. Sometimes other glands are also affected, as in the polyendocrine deficiency syndrome.

2.7.3. **Secondary Adrenal insufficiency**

This form of adrenal insufficiency is much more common than primary adrenal insufficiency and can be traced to a lack of ACTH. Without ACTH to stimulate the adrenals, the adrenal glands production of cortisol drops, but not aldosterone. A temporary form of secondary adrenal insufficiency may occur when a person who has been receiving glucocorticoid hormone such as prednisone for a long time abruptly stops or interrupts taking the medication. Glucocorticoid hormones which are often used to treat inflammatory illnesses like rheumatoid arthritis, asthma, or ulcerative colitis block the release of both CRH and ACTH. Normally CRH instructs the pituitary gland to release ACTH. If CRH levels drop, the pituitary is not stimulated to release ACTH and the adrenals then fail to secrete sufficient levels of cortisol.
2.7.4. Symptoms

The symptoms of adrenal insufficiency usually begin gradually. Characteristics of the disease are

1) Chronic, Worsening fatigue
2) Muscle weakness
3) Loss of appetite
4) Weight Loss

Addison’s disease can cause irritability and depression. Because of salt loss a craving for salty foods also is common. Hypoglycemia or low blood glucose is more severe in children than in the adults. In women menstrual periods may become irregular or stop.
2.8. Stress and ACTH

Fig. 2.3: The HPA axis illustrating negative feedback by cortisol "F" at the hypothalamic and pituitary levels. A short negative feedback loop of ACTH on the secretion of corticotrophin releasing hormone (CRH) also exists.
The physiology secretion of ACTH is mediated through neural influences by means of complex hormones, the most important of which is corticotropin releasing hormone (CRH). **CRH stimulates ACTH in a pulsatile manner.** Diurnal rhythmicity causes a peak before awakening and decline as the day progresses. The diurnal rhythm is a reflection of neural control and provokes concordant diurnal secretion of cortisol from the adrenal cortex [115]. This episodic release of ACTH is independent of circulating cortisol levels that is the magnitude of an ACTH impulse is not related to preceding plasma cortisol levels. An example is the persistence of diagonal rhythm in patients with primary adrenal failure (Addison’s disease). ACTH secretion also increases in response to feeding in both human and animals.

Many stresses stimulates ACTH often superseding the normal diurnal rhythmicity. Physical, emotional and chemical stresses such as pain, trauma, hypoxia, acute hypoglycemia, cold exposure, surgery, depression and pyrogen, vasopressin administration have all been shown to stimulate ACTH and cortisol secretion. The increase in ACTH levels during stress is mediated by vasopressin as well as CRH. Although physiology cortisol levels do not blunt the ACTH response to stress exogenous corticosteroids in high doses suppress it.

Negative feedback of cortisol and synthetic glucocorticoids on ACTH secretion occurs at both the hypothalamic and pituitary levels via two mechanisms: “Fast feedback” is sensitive to the rate of change in cortisol levels while “Slow feedback” is sensitive to the absolute cortisol level. The first mechanism is probably nonnuclear that is this phenomenon occurs too
rapidly to be explained by the influence of the corticosteroids on nuclear transcription of the specific mRNA responsible for ACTH. “Slow feedback” occurring latter may be explained by a nuclear mediated mechanism and a subsequent decrease in synthesis of ACTH. This later form of negative feedback is the type probed by the clinical dexamethasone suppression test. In addition to the negative feedback of the corticoids, ACTH also inhibits its own secretion (short loop feed back).

2.9. ACTH functions

A polypeptide hormone, consisting of 39 amino acids, which is synthesized from POMC (pre-opiomelanocortin) and secreted from corticotrophs in the anterior lobe of the pituitary gland in response to the hormone corticotropin-releasing hormone released by the hypothalamus. Adrenocorticotropic hormone is secreted in short bursts every few hours and is increased by stress. In turn, ACTH controls secretion of corticosteroids, including cortisol (hydrocortisone), aldosterone, and androgens, by the adrenal glands. Most important of these is its stimulation of cortisol production.
ACTH has been used in an effort to induce remission in multiple sclerosis, though its efficacy in this respect is uncertain. ACTH is also used to diagnose disorders of the adrenal glands and, rarely, to treat inflammatory disorders, such as arthritis, ulcerative colitis, and some types of hepatitis.

A tumor of the pituitary gland can cause excessive ACTH production which, in turn, leads to overproduction of cortisol by the adrenal cortex, resulting in Cushing's syndrome. Insufficient ACTH production due, for example, to underactivity of pituitary gland (hypopituitarism), is rare. When it does occur, it causes adrenal failure.
ACTH consists of 39 amino acids, the first 13 of which (counting from the N-terminus) may be cleaved to form \( \alpha \)-melanocyte-stimulating hormone (\( \alpha \)-MSH). (This common structure is hyperpigmentation excessively tanned skin). After a short period of time, ACTH is cleaved into \( \alpha \)-melanocyte-stimulating hormone (\( \alpha \)-MSH) and CLIP, a peptide with unknown activity in humans.

Human ACTH has a molecular weight of 4,540 atomic mass units (Da) and its molecular formula is \( \text{C}_{207}\text{H}_{308}\text{N}_{56}\text{O}_{58} \).

2.10. **ACTH effects on the adrenal cortex**

The delivery of ACTH to the adrenal cortex leads to rapid synthesis and secretion of steroids. Plasma levels of these hormones raise within minutes after ACTH administration. ACTH increases RNA, DNA and protein synthesis. Chronic stimulation leads to adrenocortical hyperplasia and hypertrophy, conversely ACTH deficiency result in decreased steroidogenesis and is accompanied by adrenocorticalatrophy, decreased gland weight, and decreased protein and nucleic acid content[98].

2.11. **ACTH and Steroidogenesis**

ACTH binds to high affinity plasma membrane receptors of adrenocortical cells thereby activating adenylyl cyclase and increasing cAMP which in turn activates intracellular phosphoprotein kinases including steroidogenic acute regulatory protein. This process stimulate the rate limiting step of cholesterol to \( \Delta^5 \)-pregnenolone conversion and initiates steroidogenesis. The exact mechanism of ACTH stimulation of the side chain cleavage enzyme (CYP11A1) are unknown, as is their relative importance.
However, ACTH has a number of effects including increase free cholesterol formation as a consequence of increased cholesterol esterase activity and decreased cholesteryl ester synthetase; increased lipoprotein uptake by the adrenal cortex; increased content of certain phospholipids which may increase cholesterol side-chain cleavage; and increased binding of cholesterol to the cytochrome CYP11A1 enzyme in mitochondria.

---

**Fig. 2.5**: Mechanism of action of ACTH on cortisol secreting cells in the inner two zones of the adrenal cortex. When ACTH binds to its receptors (R), adenyl cyclase (AC) is activated via $G_\delta$. The resulting increase in cAMP activates protein kinase A, and the kinase phosphorylates cholesteryl ester hydrolase (CEH) increasing its activity. Consequently, more free cholesterol is formed and converted to pregnenolone in the mitochondria. Note the subsequent step in steroid biosynthesis, products are shuttled between the mitochondria and the smooth endoplasmic reticulum (SER).
2.12. Neuroendocrine control

Cortisol secretion is closely regulated by ACTH and plasma cortisol levels parallel those of ACTH. There are three mechanisms of neuroendocrine control.

1. Episodic secretion and circadian rhythm of ACTH
2. Stress responsiveness of the HPA axis
3. Feedback inhibition by cortisol of ACTH secretion

Circadian rhythm is superimposed on episodic secretion: it is the result of central nervous system even that regulate both the number and magnitude of CRH and ACTH secretory episodes. Cortisol secretion is low in the late evening and continues to declined in the first several hours of sleep at which time plasma cortisol levels may be undetectable. During the third and fifth hours of sleep there is an increase in secretion but major secretory episodes begin in the sixth to eight hours of sleep and then begin to decline as wakefulness occurs. About half of the total daily cortisol output is secreted during this period. Cortisol secretion then gradually declines during the day with fewer secretory episodes of decreased magnitude; however there is increased cortisol secretion in response to eating and exercise.

Circadian rhythm may be altered by changes in sleep pattern light-dark exposure and feeding times. The rhythm is also changed by

1. Physical stresses such as major illness, surgery, trauma or starvation
2. Psychologic stress, including severe anxiety, endogeneous depression and the manic face of manic depressive psychosis.
3. Central nervous system and pituitary disorders
4. Cushing’s syndrome

5. Liver disease and other conditions that affect cortisol metabolism.

6. Chronic renal failure

7. Alcoholism

Cyproheptadine inhibits the circadian rhythm possibly by its antiserotonergic effects whereas other drugs usually have no effect.

2.13. Plasma ACTH Levels

If adrenal insufficiency is present, plasma ACTH levels are used to differentiate primary and secondary forms. In patients with primary adrenal insufficiency plasma ACTH levels exceed the upper limit of the normal range (>52 pg/ml (11 pmol/L)) and usually exceed 200 pg/ml (44 pmol/L). Plasma ACTH concentration is less than 10 pg/ml (2.2 pmol/L) in patients with secondary adrenal insufficiency[19]. However the basal ACTH levels must always be interpreted in light of the clinical situation, especially because of the episodic nature of ACTH secretion and its short plasma half-life. For example ACTH levels will frequently exceed the normal range during the recovery of the HPA axis from secondary adrenal insufficiency and may be confused with levels seen in primary adrenal insufficiency. Patients with primary adrenal insufficiency consistently have elevated ACTH levels. In fact the ACTH concentration will be elevated early in to course of adrenal insufficiency even before a significant reduction in the basal cortisol level or its response to exogenous ACTH occurs. Therefore plasma ACTH measurements serve as a valuable screening study form primary adrenal insufficiency[45].
2.14. Physiological Effects On ACTH

ACTH is secreted by the light granular basophil cell. It is a polypeptide. M.W is about 20,000. It is resistant to pepsin action but destroyed by trypsin. It is almost inactive by mouth. The most effective route is by slow intravenous infusion.

The physiological effects of ACTH can be divided into

I. Adrenal effects

II. Extra adrenal effects

2.14.1. Adrenal effects

The ACTH of the adenohypophysis is necessary for the maintenance of the bulk of the cells of the adrenal cortex and for regulation of their secretory activity. It stimulates the growth of the adrenal cortex, specifically the proliferation growth of the cells of zona fasciculata and reticularis. It causes increase in the blood flow. It increases the rate of secretion of adrenocortical hormones several fold. Specifically the glucocorticoids secretion is markedly accelerated. It causes depletion of Cholesterol and ascorbic acid content of the cells of adrenal cortex. It increases the rate of O_2 utilization and glucose metabolism of the adrenal cortex.

2.14.2. Extra adrenal effects

ACTH has melonocyte stimulating effect (M.S.H in amphibians-intermedin). ACTH has fat-mobilising activity and ketogenesis activity. The ACTH is very rapidly inactivated in body. It is not excreted in the urine[49].
Increases aminoacid and glucose uptake by muscle. Increases insulin secretion and growth hormone secretion.

2.15. **Effect of physiological stress in ACTH secretion.**

Physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently of cortisol as well, often increasing cortisol secretion as much as 20-fold. It is believed that pain stimuli caused by the stress are first transmitted upward through the brain stem to the perifornical area of the hypothalamus and from here into the paraventricular nucleus of the hypothalamus and eventually to the median eminence, where CRF is secreted into the hypophysial portal system. Within minutes the entire control sequence leads to large quantities of the glucocorticoids in the blood. Inhibitory Effect of Cortisol on the Hypothalamus and the Anterior Pituitary – Decreased ACTH Secretion [123]. Cortisol has direct negative feedback effects on (1) the hypothalamus, decreasing the formation of CRF, and (2) the anterior pituitary gland, decreasing the formation of ACTH. These feedbacks help regulate the plasma concentration of cortisol. That is, whenever the concentration becomes too great, these feedback automatically reduce this concentration back toward a normal control level.

2.16. **Regulation of Cortisol Secretion-Adrenocorticotropic Hormone (ACTH)**

**Control of Cortisol Secretion by ACTH:** Unlike aldosterone secretion by the adrenal cortex, which is controlled mainly by potassium and angiotensin acting directly on the adrenocortical cells themselves, almost no stimuli have direct effect on the adrenal cells to control cortisol secretion.
Instead, secretion of cortisol is controlled almost entirely by adrenocorticotropic hormone (ACTH) secreted by the anterior pituitary gland. This hormone also called corticotropin or adrenocorticotropic, is a large polypeptide chain composed of 39 amino acids. It also enhances the production of adrenal androgens by the adrenal cortex.\[22,112\] Small amounts of ACTH are required for aldosterone secretion, providing a permissive role that allows the other more important factor to exert their more powerful control.

2.17. Control of ACTH secretion

ACTH secretion is under the control of (1) hypothalamus, (2) nervous structures other than the hypothalamus, (3) steroid feedback mechanism, (4) short feedback mechanism, and (5) stress control mechanism.

2.17.1. Hypothalamus: The role of hypothalamus in the secretion of ACTH from the anterior pituitary can be studied under the following conditions. (a) Hypothalamic stimulation - Electrical stimulation of various hypothalamic regions causes increased discharge of ACTH. Sometimes mere presence of electrodes in the median eminence causes discharge of ACTH. Now it is well established that hypothalamic nuclei control the secretion of ACTH through their releasing factor CRF. (b) Hypothalamic lesions - Lesions at certain regions of the hypothalamus cause decreased secretion of ACTH. Weight of the pituitary is decreased after lesions of median eminence. (c) Transplantation of the anterior pituitary - If the anterior pituitary is removed from its normal position and is detached from its normal neurovascular link and then transplanted at a remote side as for instance at the
anterior chamber transplanted at a remote side as for instance at the anterior chamber of the eye or under the kidney capsule, then weight of the adrenal gland is decreased. But if such pituitary is transplanted just beneath the median eminence of the hypophysectomised animals then mostly the normal function of the adrenal gland are retained [54]. This latter effect is due to regeneration of blood vessels creating vascular link in between the hypothalamus and anterior pituitary since misplacement of the transplant a few mm, breaks up the link and the adrenal gland’s weight is decreased.

2.17.2. Nervous structures: other than the hypothalamus. Practically hypothalamus plays as sort of funnel through which all kinds of information collected from the pituitary, are transmitted to the anterior pituitary. The information that are received by the hypothalamus from different parts of the body are the following: (a) Peripheral nerves and spinal cord - It has been observed by Gorden (1950) and Egdahl (1959) that peripheral nerves and spinal cord facilitate the release of ACTH. Role of the spinal cord in the release of ACTH depends upon the nature of stimulation. (b) Midbrain - Midbrain has got both activating and inhibiting (dualistic) effects on the secretion of ACTH from the anterior pituitary. Main function of the midbrain are that of inhibition of ACTH release. Transection or lesion at midbrain level causes increased secretion of ACTH. This inhibition possibly has got some role on the control of circadian rhythm. Stimulation of reticular component of the midbrain, tegmentum and of the peripheral aqueductal region activate ACTH secretion. (c) Limbic system - Different limbic system structures have been observed to participate in the control of secretion of ACTH. Amygdaloid nuclei have got stimulating effects in the secretion of ACTH but forebrain and
rhinencephalic structures have got inhibiting role on the secretion of ACTH. Posterior orbital surface also stimulates the secretion of ACTH.

2.17.3. **Steroid feedback mechanism:** Blood level of steroid hormones plays an essential role in modified the activity of adrenal-pituitary axis. The existence of steroid-ACTH feedback mechanism has been evidenced by the following classical observations: (a) compensatory adrenal hypertrophy and hyper function in unilateral adrenalectomy, (b) prevention of compensatory hypertrophy in the adrenal by adequate doses of cortical hormones, and (c) atrophy of the adrenal glands by increased doses of cortical hormones-corticosterone, cortisol, etc.

Steroid feedback mechanism may operate through the following ways: (a) direct actions on the adrenal cortex, (b) modifications of the responsiveness of the adrenal cortex to ACTH, (c) modifying the synthesis and release of ACTH, taking place in the pituitary, (d) acting directly on the hypothalamus or on the other areas of the brain that control the activity of the hypothalamic pituitary unit, and (e) modification of the responsiveness of the pituitary to its physiologic activators like vasopressin, CRF etc.

2.17.4. **Short feedback or servo mechanism:** Not only the steroid hormones control the secretion of ACTH but also the blood level of ACTH controls the endogenous secretion of ACTH. This is the short, direct or auto feedback mechanism. Increased blood level of ACTH inhibits the endogenous secretion of ACTH.
2.17.5. **Role of stress in the control of secretion of ACTH:**

Different stressful stimuli have got some modifying effects on the secretion of ACTH. Pituitary-adrenal axis is activated by stress. It is suggested that adrenal gland may be activated independently or indirectly through ACTH during stress.

There is no such clear evidence that the same nervous pathways that control ACTH secretion through blood corticosteroid feedback mechanism are also involved in the activation of the pituitary during stress. Non-specific stresses, such as cold, pyrogens, ephinephrine, oestrogen, trauma or psychic reactions may also stimulate the hypothalamus resulting in increased ACTH production and hence protective compensation against stress.

In summary, the hypothalamus is primarily concerned with the synthesis and release of ACTH from the anterior pituitary as because the hypothalamus is the area where the CRF is synthesized and stored and released when necessary for activating the anterior pituitary. Besides this, the hypothalamus is the area where the feedback receptors, sensitive to corticoids and to ACTH are predominantly situated.
2.18. Regulation of synthesis and secretion of adrenocorticosteroids

Hypothalamus → CRF → Anterior pituitary

- ADH

Long negative feedback loop +

Exogenous ACTH

Metyrapone mitotane

ACTH

Renin-angiotensin system

Adrenal Cortex

Glucocorticoids

Mineralocorticoid

Exogenous glucocorticoids (e.g. prednisolone)

Exogenous mineralocorticoids (e.g. fludrocortisone)

Peripheral actions metabolic, anti-inflammatory, immunosuppressive

Peripheral actions on salt and water metabolism

Fig 2.6: The long negative feedback loop is more important than the short one. ACTH has only a minimal effect on mineralocorticoid production.
2.19. Circadian Rhythm of ACTH Secretion

Studies in humans have demonstrated that there is an episodic secretion of ACTH and cortisol, superimposed upon the circadian pattern. The circadian periodically, although influenced by the sleep-wake and light-dark cycle, is endogenous and dependent on the circadian variation in the neural mechanisms involved in regulating CRF. Evidence from patients with localized hypothalamic and limbic-system diseases indicates that the pathways involved in the regulation of circadian CRF-ACTH-cortisol periodicity occupy this central nervous system (CNS) area, roughly similar to that demonstrated in human lesion studies [44]. The circadian periodicity can be altered or abolished by surgical and pharmacological manipulations affecting either 5-HT levels or its action on the CNS and/or serotonergic neural pathways. Therefore, it has been inferred that 5-HT plays a role in mediating circadian periodically. Studies undertaken to investigate the role of neurotransmitters in the regulation of the CRF-ACTH-cortisol circadian periodicity in man are scanty.

Circadian periodicity of plasma cortisol and ACTH concentrations before and during treatment with the 5-HT-antagonist cyproheptadine (CP) in healthy volunteers who conformed to regular sleep-wake and rest-activity schedules. The macroscopic examination of the data shows that circadian periodicity is not abolished by CP, but the magnitude of the secretory peaks of cortisol and ACTH during the early morning hours is significantly lowered [53]. These findings are confirmed by microscopic analysis of plasma cortisol values with the mean cosinor procedure. Before and after CP, the circadian rhythms with similar acrophase values are clearly detected, but mesor and
amplitude values are significantly blunted by CP. This finding is consistent with the report that the increase found in plasma cortisol in the early morning was completely suppressed in subjects given CP (5 mg) infusions from 4.00 to 7.00 a.m. Therefore it appears that CP partially inhibits the diurnal variations of HPA function in man. This suggests that 5-HT plays a role in the nervous pathways mediating circadian periodicity.

![Graph](image)

Fig. 2.7: Circadian pattern of plasma cortisol (means ±1 S.E.M) of six previously synchronized healthy young males in basal conditions (o-o, n=6 and during treatment with cyproheptadine (16 mg/day in four oral doses for 5 days) (---, n=6)
Mathematical analysis of plasma cortisol circadian rhythm with the cosinor procedure. A model consisting of three cosine functions rather than with the use of single one. It gives a more acceptable fit for the plasma cortisol rhythm in both basal conditions and after treatment with CP [84]. Further more this approach to quantitate the cortisol rhythm indicates that the 5-HT antagonist blunts mesor and amplitude values, but does not abolish or modify the cortisol circadian periodicity and the acrophase.
Fig. 2.9: Plasma cortisol circadian pattern in basal conditions (top) and during treatment with cyproheptadine (bottom) solid circles and bars represent experimental data (means ± 1 S.E.M); the curve shown as a dashed line is based on the fit with single cosine function, whereas the solid line results from fitting the data with three cosine functions (240h, 12-h and 8-h components) according to Fourier's analysis.

2.20. Feedback Mechanism and ACTH Secretion

The hypothesis has been proposed that 5-HT mediates the negative feedback action of corticosteroids. The inhibitory effectiveness of corticosteroids is reduced following brain 5-HT depletion and enhanced when
brain 5-HT synthesis is stimulated. Whether CP administration modifies the ACTH-cortisol inhibitory properties of a single dose of dexamethasone in five healthy subjects. The results show that under CP treatment the absolute values of plasma cortisol and ACTH are significantly reduced both before and after dexamethasone administration. When expresses as the percentage inhibition induced by dexamethasone in plasma cortisol and ACTH concentrations, the percent values are significantly higher when dexamethasone is given under CP treatment (Figure 2.9).

Fig. 2.10: Plasma ACTH (left) and cortisol (right) circadian variations (means ±1 S.E.M) in 17 controls and in five hospitalized heroin addicts on methadone maintenance.