Adrenal Gland Medullary and Cortical Hormones II

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Lecture Objectives:

1. Describe the major physiological effects of glucocorticoids.
2. Describe the regulation of glucocorticoids secretion.
3. Describe defects and consequences of enzymatic deficiency in the pathway of steroid synthesis (BP, blood volume, androgens and blood glucose).

The Glucocorticoids (Cortisol or Hydrocortisone)

- Cortisol (also known as *hydrocortisone*) is the principal glucocorticoid. Almost all cells of the body express glucocorticoid receptors.
- A small but significant amount of glucocorticoid activity is provided by corticosterone.
- Cortisol is essential for life as mineralocorticoids, without it human and animals cannot resist different types of stress, even minor ones such as respiratory tract infections.

Effect on carbohydrate metabolism

- Glucocorticoids stimulate gluconeogenesis by the liver (6-10 fold normal) and mobilization of amino acids from extrahepatic tissues mainly from muscle. As a result, more amino acids become available in the plasma to enter into the gluconeogenesis process of the liver and thereby to promote the formation of glucose
- This increased rate of gluconeogenesis results mainly from:
  1. Direct effects of cortisol on the liver by activating DNA transcription in the liver cell nuclei with formation of mRNAs that in turn lead to the array of enzymes required for gluconeogenesis.
  2. Antagonizing insulin's effects to inhibit gluconeogenesis in the liver.
- As with GH, glucocorticoids reduce cells sensitivity to insulin, especially in skeletal muscle and adipose tissue (interfere with GLUT 4 translocation to the plasma membrane).

Effect on carbohydrate metabolism (cont.)

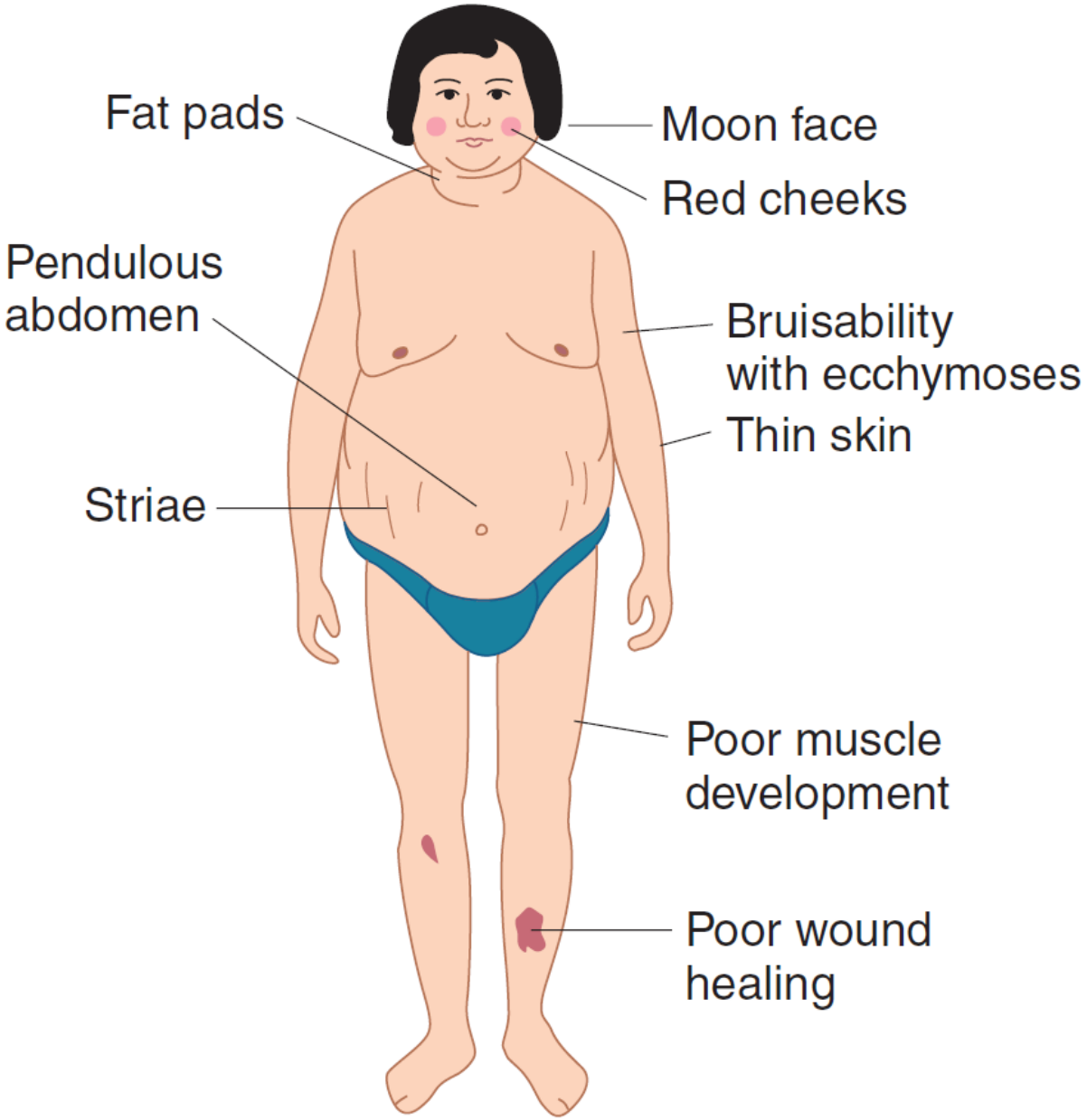
- The increased hepatic gluconeogenesis activity → ↑ glycogen storage in liver.
- Glucocorticoids delay the rate of glucose utilization by most cells in the body (mechanism ?).
- The increased rate of gluconeogenesis + the reduction in glucose utilization → ↑ glucose concentration in blood → stimulation of insulin secretion (adrenal diabetes).
- In bone and cartilage, glucocorticoids decrease insulin-like growth factor 1, insulin-like growth factor-binding protein 1, and growth hormone expression and action, and affect thyroid hormone interactions.
- Therefore, excessive glucocorticoid levels → osteoporosis + ↓ skeletal growth (inhibition of osteoblasts and collagen synthesis)

Effect on protein & lipid metabolism

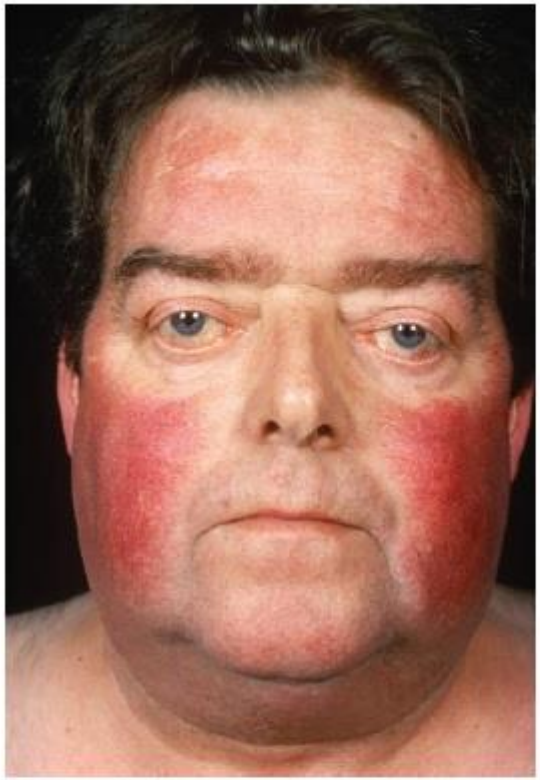
- There is reduction of protein stores in essentially all body cells (proteolysis) except those of the liver (↓ synthesis + ↑ catabolism). This results in weakness of the muscles and decreased immunity functions of the lymphoid tissue (especially T- lymphocytes).
- Cortisol depresses amino acid transport into muscle cells and perhaps into other extrahepatic cells.
- Increased extrahepatic protein catabolism → diffuse of amino acids out of the cells →↑ the plasma amino acid concentration.

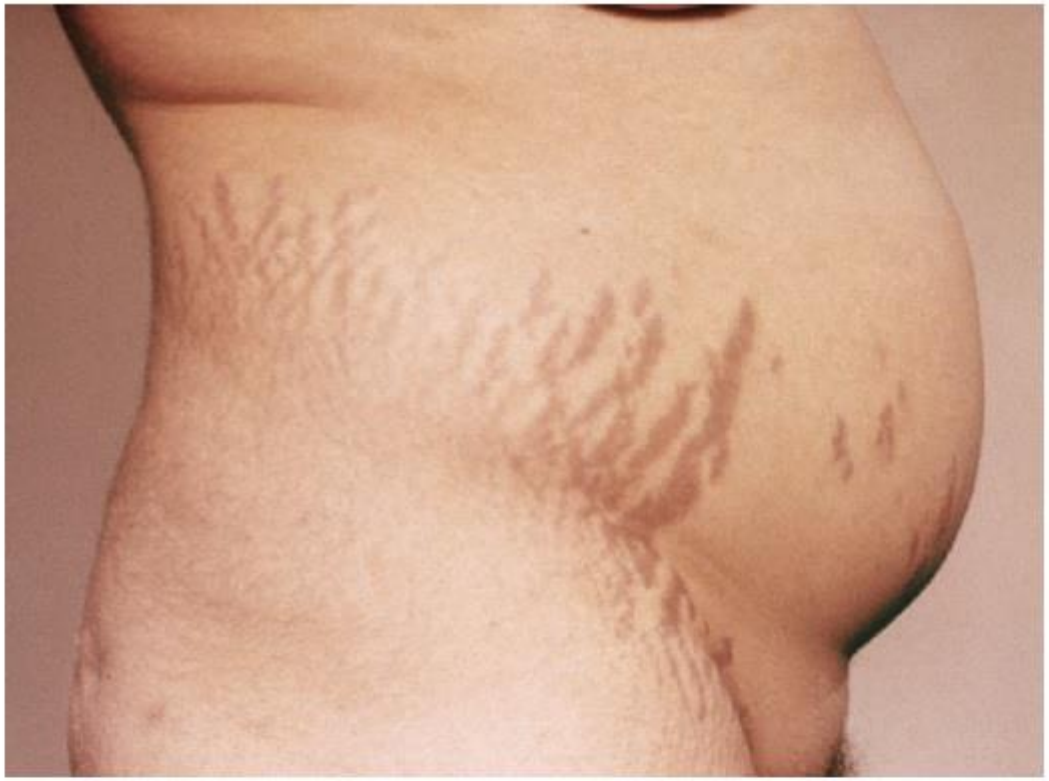
Effect on protein & lipid metabolism (cont.)

- Cortisol does not mobilize the basic contractile proteins and proteins of neurons, until all other proteins have been released.
- Unlike elsewhere in the body, the liver proteins become enhanced as well as plasma proteins that are synthesized by the liver.
- Glucocorticoids promote mobilization of fatty acids from adipose tissue → ↑ fatty acid concentration in plasma → ↑ fatty acid utilization as a source of energy.
- There is deposition of fat in the chest and head regions → buffalo-like torso and a rounded moon face. The cause of this deposition is unknown; it could be due to the increased stimulation of food intake (fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized).



Typical findings in Cushing syndrome





Patient with florid Cushing's syndrome. *Left:* Notice "moon face" and facial plethora (high blood flow leading to redness).
Right: Notice pendulous abdomen (from increased visceral fat) and striae (stretch marks) from thin skin and stretching of the skin due to increased girth.

Role of cortisol in stress resistance:

- Stress (physical or mental) → ↑ ACTH secretion → cortisol secretion.
- The importance of amino acid mobilization in stress is still not well understood.

The anti-inflammatory role of cortisol:

- Block the early stages of the inflammation process, by increasing anti-inflammatory cytokine synthesis and decreasing pro-inflammatory cytokine synthesis.
- If inflammation is going on, glucocorticoids cause rapid resolution of the inflammation and increased rapidity of healing.

Other effects of cortisol

1. Blocks the antigen-antibody allergic reaction.
2. Suppresses immunity (↓ number of eosinophils and lymphocytes, T lymphocytes in particular, in the blood).
3. Cortisol attenuates fever mainly because it reduces release of interleukin-1 from white blood cells.
4. Induces polycythemia. If cortisol is not available, anemia results.
5. In the vasculature, cortisol modulate reactivity to vasoactive substances, like angiotensin II and norepinephrine. If cortisol is deficient, hypotension is manifested with decreased sensitivity to vasoconstrictor administration.
6. In CNS, cortisol modulate perception and emotion and may produce marked changes in behavior.

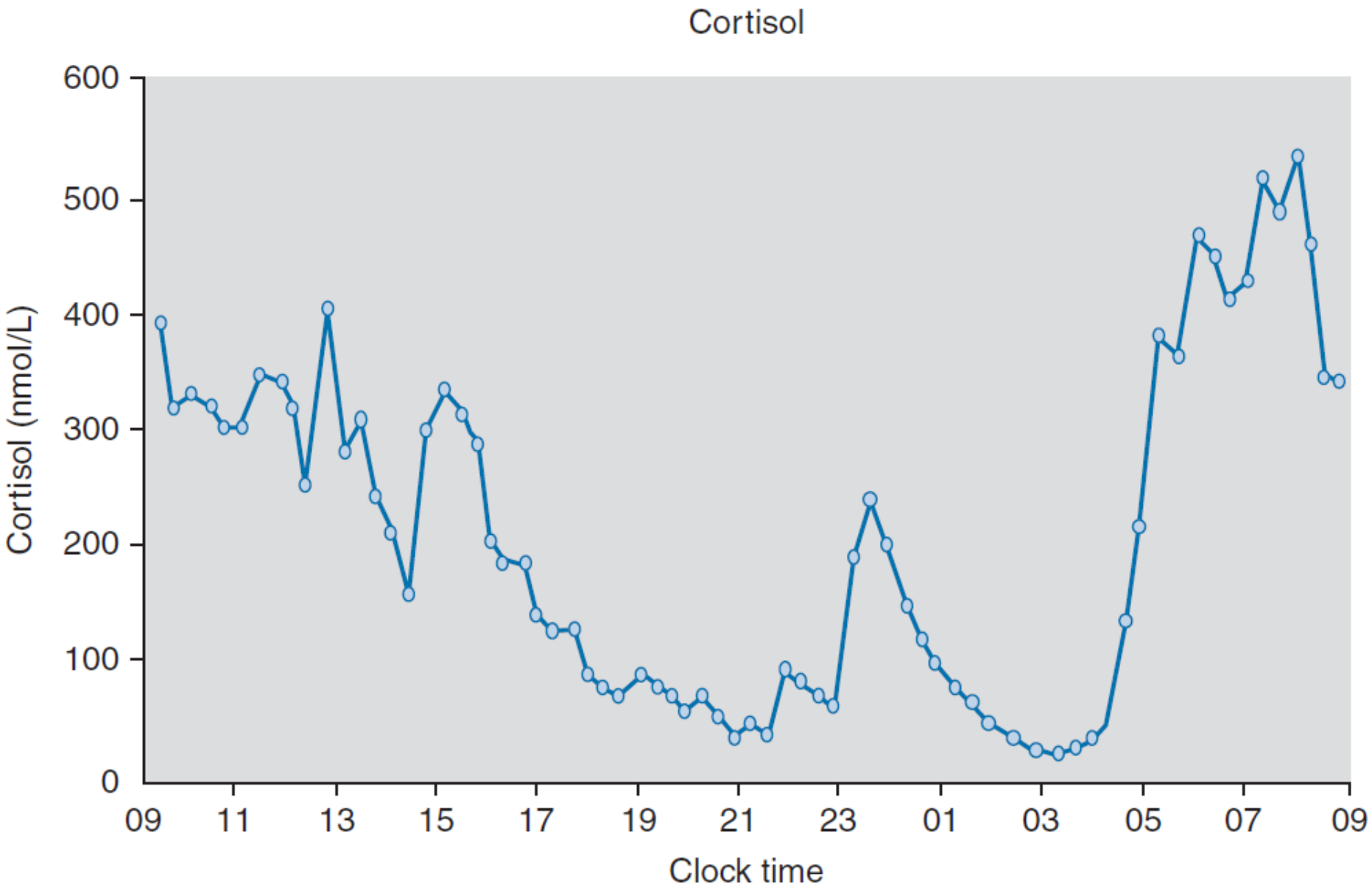
Physiologic effects of glucocorticoids

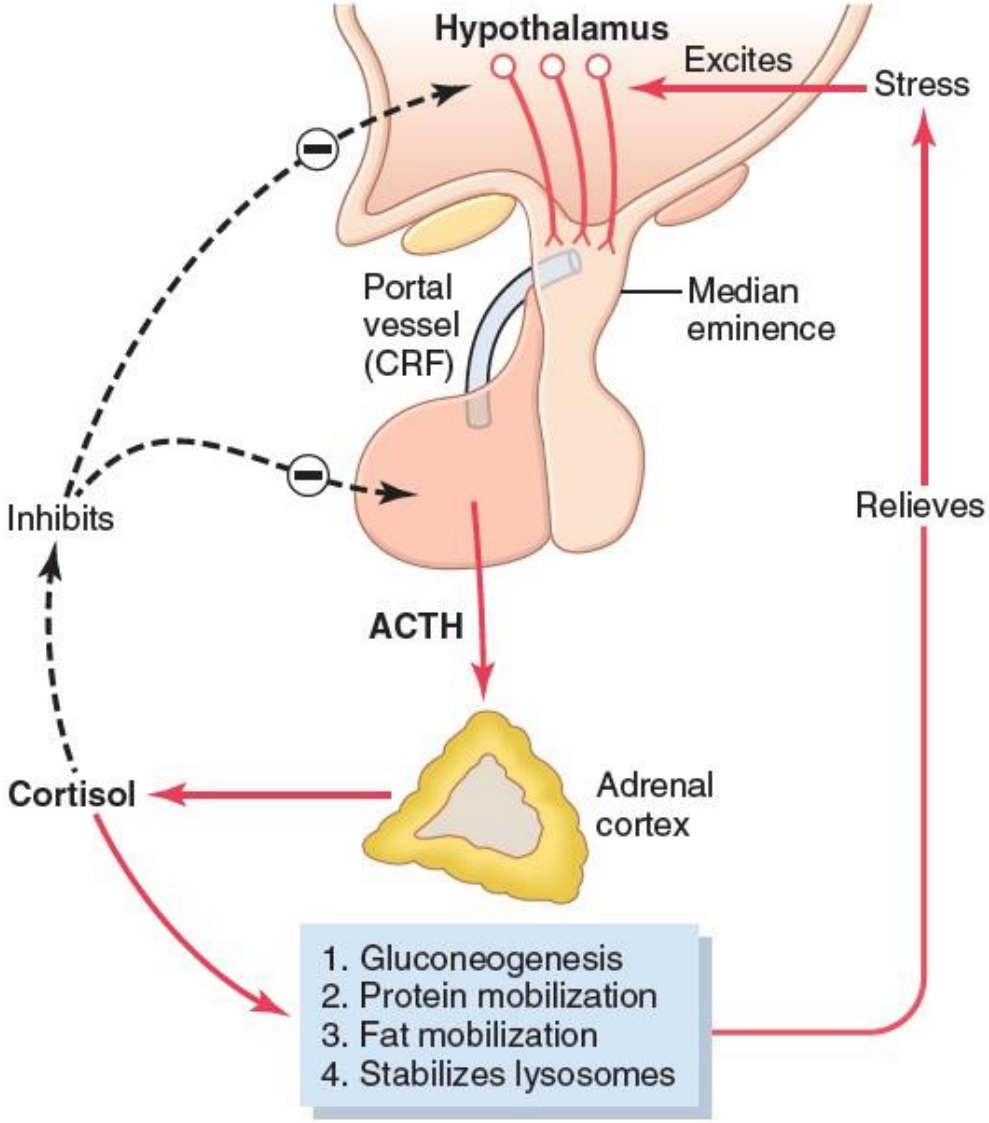
System	Effects
Metabolism	Degrades muscle protein and increases nitrogen excretion Increases gluconeogenesis and plasma glucose levels Increases hepatic glycogen synthesis Decreases glucose utilization (anti-insulin action) Decreases amino acid utilization Increases fat mobilization Redistributes fat Permissive effects on glucagon and catecholamine effects
Hemodynamic	Maintains vascular integrity and reactivity Maintains responsiveness to catecholamine pressor effects Maintains fluid volume
Immune function	Increases antiinflammatory cytokine production Decreases proinflammatory cytokine production Decreases inflammation by inhibiting prostaglandin and leukotriene production Inhibits bradykinin and serotonin inflammatory effects Decreases circulating eosinophil, basophil, and lymphocyte counts (redistribution effect) Impairs cell-mediated immunity Increases neutrophil, platelet, and red blood cell counts
Central nervous system	Modulates perception and emotion Decreases CRH and ACTH release

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Regulation of Cortisol secretion

- The pulsatile secretion of cortisol is ACTH dependent. The release of ACTH is pulsatile with approximately 7-15 episodes per day.
- The stimulation of cortisol release occurs within 15 minutes of the surge in ACTH.
- In addition of being pulsatile in its release, cortisol follows a circadian rhythm that is exquisitely sensitive to environmental and internal factors such as light, sleep, stress, and disease.
- Release of cortisol is greatest during the early waking hours, with levels declining as the afternoon progresses.
- ACTH is released in response to stress. Stress increases the activity of the **limbic system**. Signals will be transmitted to the hypothalamus to release CRH into the hypophyseal portal system → ACTH release by the anterior pituitary.
- Cortisol has a powerful negative feedback effects on (1) the hypothalamus and (2) the anterior pituitary to decrease formation of ACTH.


Cortisol
600
500
400
300
200
100
0
Cortisol (nmol/L)
09
11
13
15
17
19
21
23
01
03
05
07
09
Clock time



Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

Diseases of adrenal cortex

Hormone	**Syndrome**	**Symptoms and Signs**
Glucocorticoid excess	Cushing's syndrome	Moon faces, truncal obesity, buffalo hump, abdominal striae, muscle weakness & wasting, hypertension, diabetes mellitus, hypokalemia and metabolic alkalosis
Mineralocorticoid excess	Conn's syndrome (primary hyperaldosteronism)	K^+ depletion, Na^+ retention, polyuria and hypokalemic alkalosis, ***hypertension***, tetany & m. weakness
Adrenocortical insufficiency (Adrenocortical atrophy due to autoimmune diseases or diseases of the adrenal gland)	Addison's disease	Skin pigmentation, Na^+ depletion, decreased plasma volume, weakness, tiredness and weight loss
Adrenal androgen excess (Androgen secreting tumor, or congenital)	Adrenogenital syndrome Congenital adrenal hyperplasia	*In women:* hirsutism, acne, oligomenorrhea & virilisation. *In male*: precocious puberty

Diseases of adrenal cortex

A. Hypoadrenalism or **Addison's disease**. In 80% of causes, it is due to autoimmunity. Both glucocorticoids and mineralocorticoids are depressed.
B. Hyperadrenalism or **Cushing's syndrome**. Mostly due to increased amount of cortisol. It could be due to:
    1. Adenoma of anterior pituitary that secretes ACTH
    2. More CRH from hypothalamus
    3. Ectopic secretion of ACTH by a tumor
    4. Adenoma of adrenal cortex
    5. Therapeutic causes

Test Question

Q. A 7-year-old boy comes to the pediatric endocrine unit for evaluation of excess body weight. To differentiate between the development of obesity and Cushing syndrome, blood and urine samples are taken. Which of the following would be most diagnostic of Cushing disease?

A. Increased serum ACTH, decreased serum cortisol, and increased urinary free cortisol

B. Decreased serum ACTH, increased serum cortisol, and increased serum insulin

C. Increased serum ACTH, increased serum cortisol, and increased serum insulin

D. Increased serum ACTH, decreased serum cortisol, and decreased serum insulin

E. Increased serum ACTH, decreased serum cortisol, and decreased urinary free cortisol