Adrenal Gland

Glucocorticoids

(Lecture-2)

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Objectives

By the end of this lecture, students should be able to describe:

- Mechanism of action of cortisol
- Effects of cortisol (hydrocortisone):
  - Carbohydrate metabolism
  - Protein metabolism
  - Fat metabolism
  - Anti-inflammatory effects
  - Cortisol and stress
- Regulation of cortisol secretion
- Characterize abnormalities of Adrenocortical Secretion
  - Addison's disease.
  - Cushing's syndrome.

Keywords: glococorticoids, adrenal cortex, adrenocorticotropic hormone (ACTH).

Glucocorticoids

The glucocorticoids have gained their name because they exhibit important effects that increase blood glucose concentration. They have additional effects on both protein and fat metabolism. Glucocorticoids include:

• Cortisol (very potent, accounts for about 95 % of all glucocorticoid activity)

• Corticosterone (provides about 4 % of total glucocorticoid activity, less potent than cortisol)

• Synthetic glucocorticoids are cortisone, prednisone, methylprednisone, dexamethasone.

Transport of cortisol in plasma

90-95 % of the cortisol in the plasma binds to p.proteins, especially a globulin (cortisol-binding globulin or transcortin) and, to a lesser extent, to albumin.

This high degree of binding to p.proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half life of 60 to 90 min.

Cellular Mechanism of Cortisol Action

Because cortisol is lipid soluble, it can easily diffuse through the cell membrane. Once inside the cell, cortisol binds with its protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences to induce or repress gene transcription to alter synthesis of mRNA for the proteins that mediate their multiple physiologic effects.

Functions of the Glucocorticoids

I- Effects of Cortisol on Carbohydrate Metabolism

1- Stimulation of gluconeogenesis by the liver.

This results mainly from two effects of cortisol.

A. Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells.

B. Cortisol causes mobilization of amino acids from the 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.

2- One of the effects of increased gluconeogenesis is a marked increase in glycogen storage in the liver cells. This effect of cortisol allows other glycolytic hormones, such as glucagon, to mobilize glucose in times of need, such as between meals.

3- Decreased glucose utilization by cells by depressing glucose transport into the cell (anti insulin action) such effect leads to hyperglycemia.

4- High levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization. This condition is called adrenal diabetes.

II- Effects of Cortisol on Protein Metabolism

1- Reduction of the protein stores in essentially all body cells except those of the liver. This is caused by both decreased protein synthesis and increased catabolism of protein already in the cells. Both these effects may result from decreased amino acid transport into extrahepatic tissues. In the presence of great excesses of cortisol, the muscles become weak and the immunity functions of the lymphoid tissue decreases.

2- Cortisol Increases Liver and Plasma Proteins.

This results from a possible effect of cortisol to enhance amino acid transport into liver cells and to enhance the liver enzymes required for protein synthesis.

3- Increased Blood Amino Acids, Diminished Transport of Amino Acids into Extrahepatic Cells, and Enhanced Transport into Hepatic Cells to cause such effects:

(1) Increased rate of deamination of amino acids by the liver.

(2) Increased protein synthesis in the liver.

(3) Increased formation of plasma proteins by the liver.

(4) Increased conversion of amino acids to glucose.

III- Effects of Cortisol on Fat Metabolism.

Cortisol promotes mobilization of fatty acids from adipose tissue. This increases the concentration of FFA in the plasma, which also increases their utilization in the cells for energy. This helps shift the metabolic systems of the cells to utilization of fatty acids in times of starvation or other stresses.

IV- Cortisol is Important in Resisting Stress

Physical or neurogenic stress causes an immediate and marked increase in ACTH secretion followed within minutes by greatly increased cortisol secretion. Cortisol causes rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body.

V- Anti-inflammatory Effects of High Levels of Cortisol

Cortisol has two basic anti-inflammatory effects:

(1) It can block the early stages of the inflammation process before inflammation even begins.

(2) If inflammation has already begun, it causes the following:

1. Stabilizes the lysosomal membranes.

2. Decrease the permeability of the capillaries.

3. Decrease both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells. These effects probably result from the fact that cortisol diminishes the formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells.

4. Suppression of the immune system, especially The T lymphocytes.

5. Attenuation of fever mainly because it reduces the release of interleukin-1 from the white blood cells, which is one of the principal excitants to the hypothalamic temperature control system. The decreased temperature in turn reduces the degree of vasodilation.

VI- Effect of Cortisol on blood cells and immunity

- Cortisol increases the No.of RBCs, neutrophils and platelets.
- Cortisol decreases the number of eosinophils, basophils and lymphocytes in the blood.
- Cortisol decreases the size of lymph nodes.

As a result, the level of immunity for almost all foreign invaders of the body is decreased. Therefore cortisol is a useful drug in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

VII- Effect of cortisol on calcium metabolism and bone

Administration of glucocorticoids lowers plasma Ca^{++} level and may cause osteoporosis by decreasing bone formation and increasing bone resorption.

They decrease bone formation by:

a. Inhibiting cellular replication and protein synthesis in bone.
b. Inhibiting osteoblasts.
c. Decrease Ca^{++} and Phosphate absorption from the intestine (anti-vitamib D action).
d. Increase renal excretion of Ca^{++}.

VIII- Permissive action of cortisol

Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by

themselves. This effect is called their permissive action. Permissive effects include the requirement for glucocorticoids to be present for:

- Glucagon and catecholamines to exert their calorigenic effects.
- Catecholamines to exert their lipolytic effects.
- Catecholamines to produce pressor responses and bronchodilation.

IX- Effect of cortisol on skeletal muscle

It is essential for maintenance of muscular activity and even to life itself during severe exercise. Insufficiency causes rapid muscular fatigue.

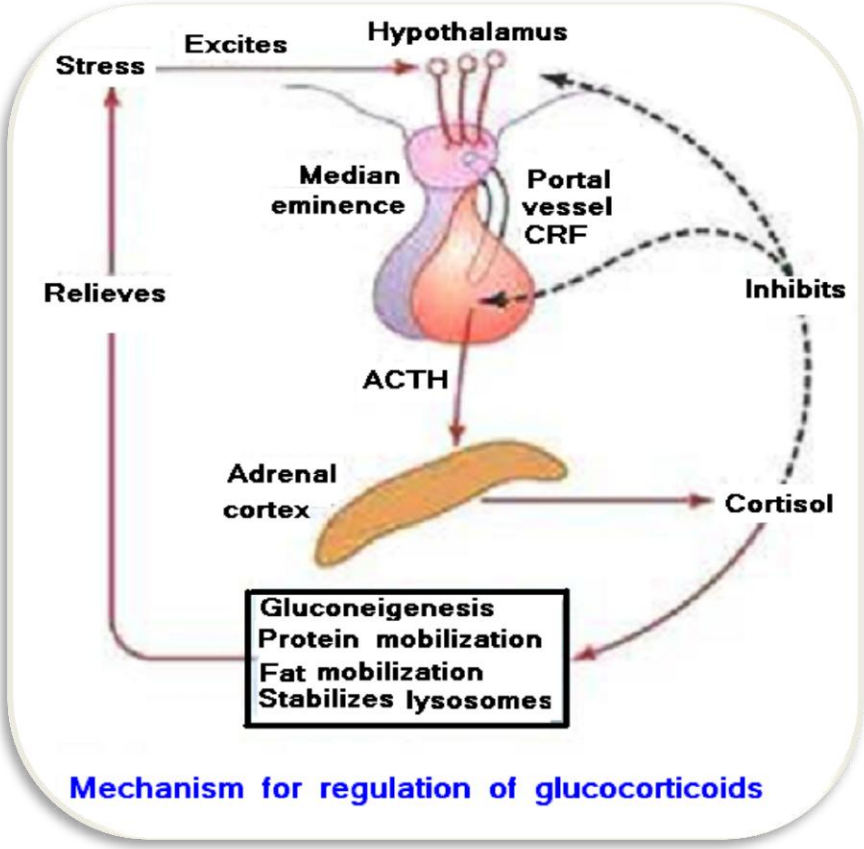
X- Effect of cortisol on nervous system

The brain is highly sensitive to cortisol and variation in its concentration produces changes in certain sensations and higher functions as concentration, memory and intellectual performance.

Regulation of Cortisol Secretion

1- Hpothalamic regulation

Different types of stress, physical or mental stimulates the hypothalamus to release corticotropin-releasing factor (CRF) which acts on anterior pituitary to increase ACTH secretion. ADH is also a potent ACTH secretagogue



Mechanism for regulation of glucocorticoids

2- Pituitary regulation

The anterior pituitary gland secretes ACTH which acts on the adrenocortical cells to

cause formation of the adrenocortical hormones by activation of the enzyme protein kinase A, which causes initial conversion of cholesterol to pregnenolone.

3- Negative feedback mechanism

Cortisol has direct negative feedback effects on (1) the hypothalamus to decrease the formation of CRF and (2) the anterior pituitary gland to decrease the formation of ACTH. Both of these feedbacks help regulate the plasma concentration of cortisol.

4- Circadian Rhythm of Glucocorticoid Secretion.

The secretory rates of CRF,ACTH, and cortisol are high in the early morning but low in the late evening; the plasma cortisol level ranges between a high of about 20 mg/dl an hour before arising in the morning and a low of about 5 mg/dl around midnight. This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.

Abnormalities of Adrenocortical Secretion

Hypoadrenalism-Addison's Disease

Addison's disease results from failure of the adrenal cortices to produce adrenocortical hormones.

Causes of adrenocortical insufficiency:

Primary causes:

- Autoimmunity against the cortices (80 % 0f cases).
- Tuberculous destruction of the adrenal glands.
- Invasion of the adrenal cortices by cancer.

Secondary causes:

Hypopituitarism, suppression by exogenous steroids.

The disturbances in Addison's disease are as follows.

I-Mineralocorticoid Deficiency.

Discussed in the previous lecture

II-Glucocorticoid Deficiency.

1- Inability to maintain normal blood glucose concentration between meals.

2- Reduce mobilization of both proteins and fats from the tissues.

3- Even when excess quantities of glucose and other nutrients are available, the person's muscles are weak, indicating that glucocorticoids are needed to maintain other metabolic functions.

4- Lack of adequate glucocorticoid secretion also makes a person with Addison's disease highly susceptible to the deteriorating effects of different types of stress.

5- Anemia.

6- Melanin pigmentation in the mucous membranes of the lips and the thin skin of the nipples. The cause of the melanin deposition is increased rates of ACTH secretion as well as simultaneous secretion of increased amounts of MSH when cortisol secretion is depressed.

Addisonian Crisis.

In a person with Addison's disease, the output of glucocorticoids does not increase during stress. This critical need for extra glucocorticoids and the associated severe debility in times of stress is called an addisonian crisis.

Hyperadrenalism-Cushing's Syndrome

Causes of hyperadrenalism include:

(1) Adenomas of the anterior pituitary that secrete large amounts of ACTH, which then causes adrenal hyperplasia and excess cortisol secretion.

(2) Abnormal function of the hypothalamus that causes high levels of corticotropin-releasing hormone (CRH), which stimulates excess ACTH release.

(3) Ectopic secretion" of ACTH by a tumor elsewhere in the body, such as an abdominal carcinoma.

(4) Adenomas of the adrenal cortex.

(5) Pharmacological.

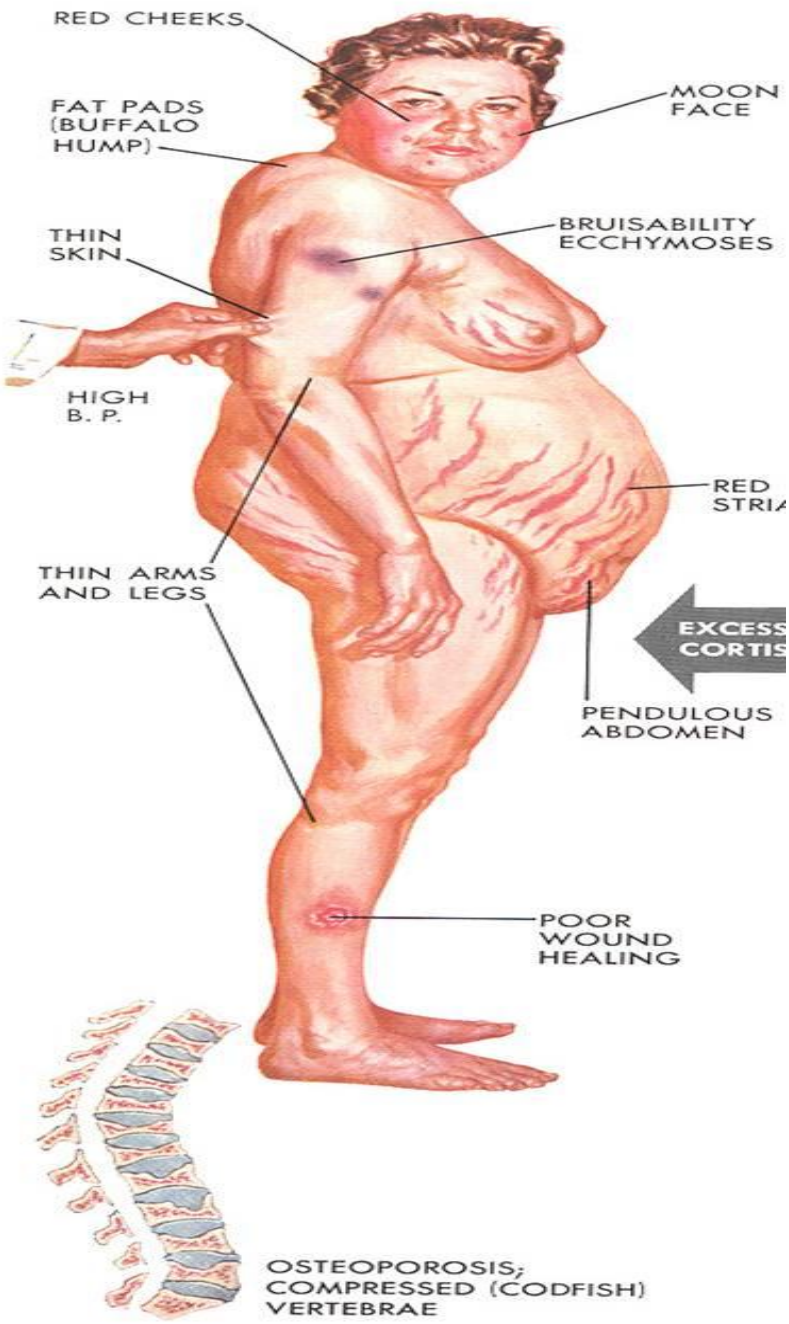
Characteristic of Cushing's syndrome:

1- Mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to a buffalo torso.

2- An edematous appearance of the face "moon face", and the androgenic potency of some of the hormones sometimes causes acne and hirsutism (excess growth of facial hair).

3- About 80 per cent of patients have hypertension, presumably because of the slight mineralocorticoid effects of cortisol.

4- Increase blood glucose concentration, sometimes to values as high as 200 mg/dl after meals-as much as twice normal.



This results mainly from enhanced gluconeogenesis and decreased glucose utilization by the tissues.

5- Decrease tissue proteins almost everywhere in the body with the exception of the liver; the plasma proteins also remain unaffected.

6- The loss of protein from the muscles in particular causes severe weakness.

7- The loss of protein synthesis in the lymphoid tissues leads to a suppressed immune system, so that many of these patients die of infections.

8- Even the protein collagen fibers in the subcutaneous tissue are diminished so that the subcutaneous tissues tear easily, resulting in development of large purplish striae where they have torn apart.

9- Diminished protein deposition in the bones often causes severe osteoporosis with consequent weakness of the bones.