MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE- DISTANCE LEARNING CENTRE
DIVISION OF ENDOCRINOLOGY AND METABOLISM

Lecture №4

Adrenal glands

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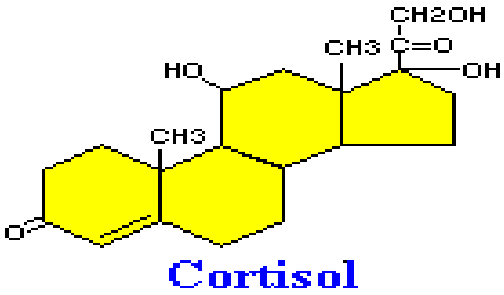
Circadian Release of Cortisol

Cortisol secretion is suppressed by classical negative feedback loops.

When blood concentrations rise above a certain theshold, cortisol inhibits CRH secretion from the hypothalamus, which turns off ACTH secretion, following of turning off of cortisol secretion from the adrenal.

The combination of **positive and negative control on CRH** secretion results in **pulsatile secretion of cortisol**.

Biological effects of cortisol



Cortisol

Effects on Metabolism

In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood.

1. Stimulation of gluconeogenesis, particularly in the liver: This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids.

Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.

2. Mobilization of amino acids from extrahepatic tissues: These serve as substrates for gluconeogenesis.

3. Inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose.

4. Stimulation of fat breakdown in adipose tissue*:* The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

Hyperadrenocorticism or Cushings disease

The most prevalent disorder involving excess of glucocorticoids

Etiology of Cushings disease.

Excessive levels of glucocorticoids are seen in three situations:

Primary adrenal defect: Excessive endogenous production of cortisol, (ACTH-independent, Cushing's Syndrome)

Secondary adrenal defect: Excessive secretion of ACTH, (ACTH-dependent,Cushing's Disease).

Administration of glucocorticoids for theraputic purposes. This is a common side-effect of drugs.

Clinical symptoms

Cushing's disease has widespread effects on metabolism and organ function, which is due to general distribution of glucocorticoid receptors.

Too much cortisol can produce some of the hallmark signs of Cushing's syndrome **— a fatty hump between shoulders, a rounded face, and pink or purple striae**.

Cushing's syndrome can also result in **high blood pressure, bone loss and, diabetes mellitus**.

Common signs and symptoms

1. Progressive obesity:

Weight gain and fatty tissue deposits, particularly around the upper back, in the face (moon face) and between the shoulders (buffalo hump).

2. Skin changes:

Pink or purple striae on the skin of the abdomen, thighs, breasts and arms

Thinning skin that bruises easily

Slow healing of cuts, insect bites and infections, Acne

3. Muscle loss and fatigue,

4. Depression and psychosis

Cushing's syndrome is characterized by insulin resistance and hyperinsulinaemia with glucose intolerance evident in 20% to 30%, and overt diabetes mellitus in 30% to 40% of patients

There is an increase in total cholesterol and triglyceride levels, and variable effect on high-density lipoprotein (HDL).

Diagnosis of Cushing's syndrome

Physical and visual examination, with full family medical history

Blood tests to check the levels of cortisol and ACTH. A combination of these two tests gives great accuracy for diagnosis

Diurnal rhythm of cortisol and **Late night salivary cortisol**

Urine tests for 24 hours cortisol excretion **- Urinary free cortisol**

Dexamethasone suppression test with 2mg, 4mg dexamethazone.

Magnetic resonance imaging (MRI) scans and computed tomography (CT) scans to check for gland size and evidence of tumours.

Treatment for Cushing's syndrome

Tumour of the pituitary gland – the tumour is surgically removed. Other options include radiation therapy and drug therapy to reduce the tumour and stop it from producing hormones.

Tumour of the adrenal gland – the tumour is surgically removed. Replacement hormone therapy may be necessary for a short while.

ACTH-producing tumours – treatment includes surgery to remove the tumour, followed possibly by chemotherapy, immunotherapy and radiation therapy.

MEN1 – radiation therapy and surgery are used to remove the tumours and associated glands. Ongoing hormone replacement therapy is needed after surgery.

Glucocorticoid hormone therapy – induced latrogenic Cushing's syndrome –Treatment should never be stopped suddenly because of the possibility of adrenal suppression.

Addison‘s disease

Hypocorticismus –

Deficiency of glucocorticoids

Adrenal insufficiency

Primary adrenal insufficiency (Addison's disease)
- results from damage to or dysfunction of the adrenal gland itself; it occurs in 1 in 100,000 people, affecting slightly more women than men

Secondary adrenal insufficiency
- results from inadequate pituitary ACTH secretion resulting in low cortisol release

Tertiary adrenal insufficiency
- results from inadequate CRH release from the hypothalamus and the resultant decrease in ACTH release.

Primary Adrenal Insufficiency (Addison's Disease)

Autoimmune diseases (**most common cause - 80%**)
- approximately 50% of patients with autoimmune adrenal insufficiency have one or more other autoimmune endocrine disorders, such as type 1 diabetes mellitus, Hashimoto's autoimmune thyroiditis, or Graves' disease.

The combination of autoimmune adrenal insufficiency with other autoimmune endocrine disorders is referred to as the *polyglandular autoimmune syndromes types I and II*

Secondary and Tertiary Adrenal Insufficiency

Suppression of the adrenals after long-term use of steroids (**most common cause**)
following the cure of Cushing's syndrome

Hypothalamic or pituitary lesion (e.g: tumours, trauma, surgery or radiation)

Acute Primary Adrenal Insufficiency – Adrenal Crisis

Adrenal or **Addisonian crisis** may result from an acute exacerbation of chronic insufficiency, usually precipitated by **serious infection or surgical stress**.

This can occur if a previously diagnosed Addisonian patient does not increase their glucocorticoid replacement during a major illness.

The major symptoms of a patient with acute adrenal primary insufficiency are:

Shock

Anorexia

Nausea , vomiting

Abdominal pain

Lethargy , weakness

Confusion

Hypotension

Hyperpigmentation

Chronic Adrenal Insufficiency

People with Addison's disease develop symptoms as a result of this loss of adrenal hormones. Patients with chronic primary adrenal insufficiency have clinical signs and symptoms of :

glucocorticoid, mineralocorticoid and androgen deficiency.

Patients with secondary or tertiary adrenal insufficiency usually maintain **mineralocorticoid function.**

The clinical features of chronic adrenal insufficiency usually have an insidious, slow onset with many non-specific symptoms.

The most common signs and symptoms of chronic primary adrenal insufficiency

Lethargy, weakness

Nausea, vomiting

Abdominal pain

Anorexia, weight loss

Hypotension

Hyperpigmentation - occurs on the **exposed areas of the body, points of friction or in palmar creases**.

Pigmentation is also seen in **the buccal mucosa** (the lining of the mouth), in scars and in the conjunctivae (the lining of the eye).

It is caused by excessive melanin production in the skin due to the melanocyte-stimulating hormone (MSH) produced in the pituitary.

The clinical features of secondary adrenal insufficiency are similar to those above **except that hyperpigmentation is not present (as ACTH and MSH are not elevated).**

Diagnosis

1. Confirmation of the biochemical diagnosis of hypoadrenalism

Measurement of Basal Cortisol Secretion

A low plasma cortisol level (<140nmol/L) in the morning is evidence of adrenal insufficiency.

NB! Plasma cortisol levels are normally high in the early morning and increase with stress.

Diagnosis

2. Distinguishing between primary, secondary and tertiary adrenal insufficiency

1. In primary adrenal insufficiency, **basal early morning plasma ACTH concentrations are elevated** compared to the low normal levels found in secondary and tertiary disease.

2. Primary adrenal insufficiency can also be distinguished from secondary and tertiary by using a **prolonged ACTH stimulation test**.

Stimulation of the adrenal gland in primary disease will not result in the release of cortisol. In secondary and tertiary insufficiency the atrophic adrenal glands still produce some cortisol when exposed to ACTH.

Treatment

There are different treatment protocols depending on the nature of the insufficiency.

Acute Adrenal Insufficiency: ADRENAL CRISIS

Adrenal Crisis is a life-threatening emergency that requires immediate treatment.

1.The first stage is to treat the hypotension and correct the electrolyte abnormalities and hypoglycemia. Large volumes (2-3 litres) of saline (or dextrose in saline) should be given intravenously.

2. The second stage is to replace the cortisol with **dexametazone, immediately injected intravenously, or,**

Hydrocortisone sodium phosphate - 100 mg. i.v. every 6 hours for 24 hours (converted by the body to cortisol) **or Methylprednisolone- 100mg every 12 h.**

3. After the initial management, the precipitating cause can be treated. Evaluate and correct infection or other precipitating factors.

4. In primary adrenal insufficiency, **mineralocorticoid replacement using fludrocortisone** is also given, when the patient is stable, or **DOKA i.m.**

Patients with primary adrenal insufficiency will then require lifelong glucocorticoid and mineralocorticoid replacement therapy.

Chronic Primary Adrenal Insufficiency

1. Style of life

The patient's own management of the disease is the key to successful treatment, so patient education is vital. At all times a medical alert bracelet should be worn with an emergency medical card indicating the diagnosis and daily medications. The patient can lead a normal active life, but must take precautions against an emergency situation.

2. Medication

The aim of the therapy is to replace the glucocorticoids (with hydrocortisone or dexamethasone) and in some cases mineralocorticoids (with fludrocortisone).

Higher doses of glucocorticoids are given during times of illness or major stress (e.g. surgery) to prevent Addisonian crisis.

Treatment

1. Replacement of adrenal insufficiency

Hydrocortisone 10-15 mg. in 7 h.AM, and 5-10 mg in the afternoon (4-5h)

in Bulgaria: Dehydrocortison (Prednisolon) 5 mg. in 7h AM, and 2.5mg in 4-5h PM.

2. **Mineralcorticoid replacement**

Fludrocortisone 0.05-0.1mg, orally in AM

DOKA(deoxicorticosterone acetate) amp=50 mg im.