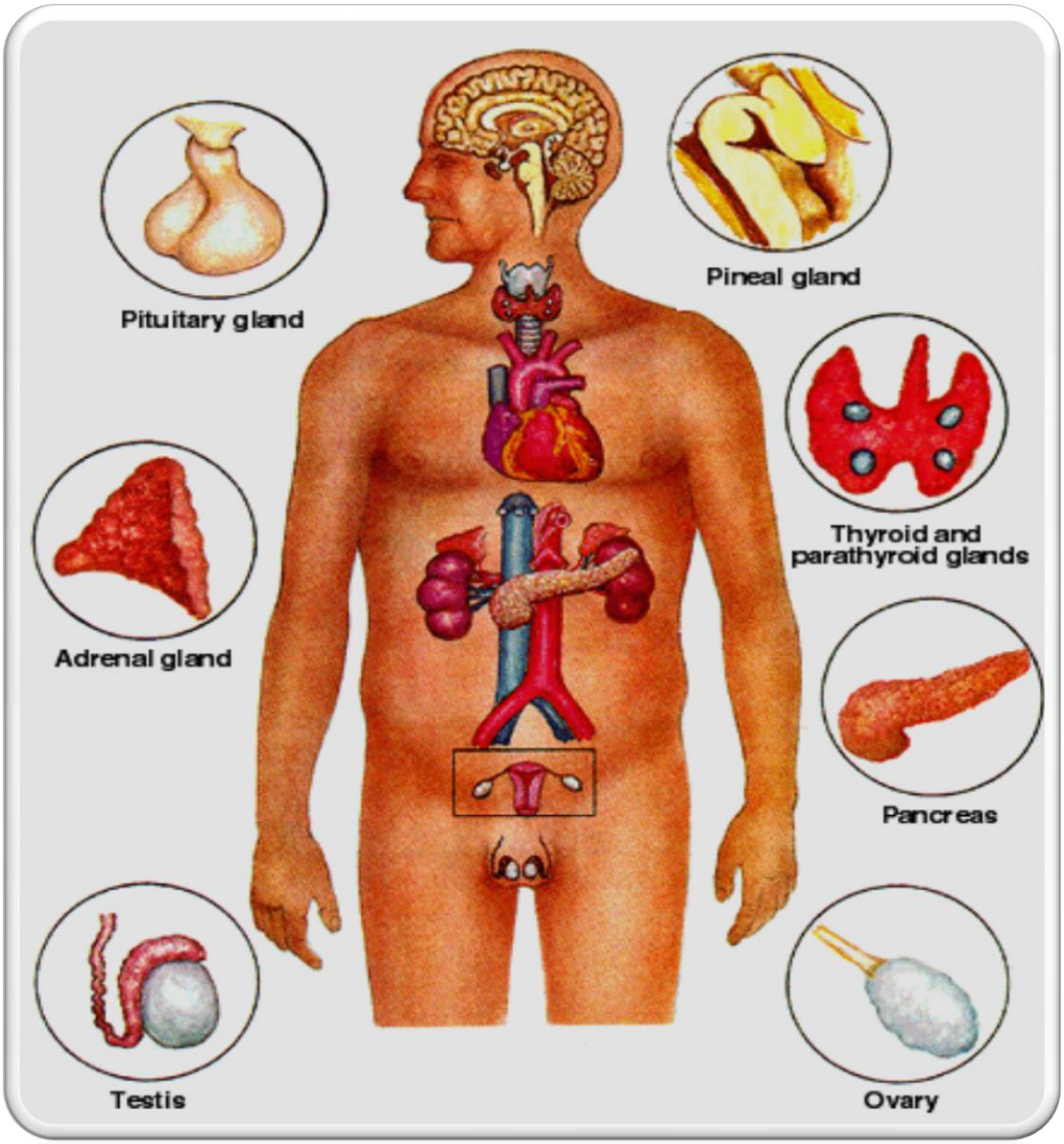
ENDOCRINE BLOCK

PHYSIOLOGY TEAM 431



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Green : team notes
Red : important

Glucocorticoids :

- Produced by the fasciculata and reticularis layers of the adrenal cortex (Mainly from the **ZONA FASCICULATA**)
- Main glucocorticoids in humans:
  - ✓ **Cortisol.**
  - ✓ **Corticosterone.**

- Cortisol:corticosterone produced in humans in a ratio of 10:1

- 90-95% **bound to plasma protein**.

- Under control primarily by **ACTH**.

* Glucocorticoids (cortisol): recognized early to increase plasma glucose levels:
  - Mobilization of amino acids from proteins
  - Enhance liver gluconeogenesis
* Target tissues: most body tissues
- * CRH (and ACTH) are secreted in pulses.

*ACTH is part of bigger protein POMC (**Pro-opiomelanocortin)**

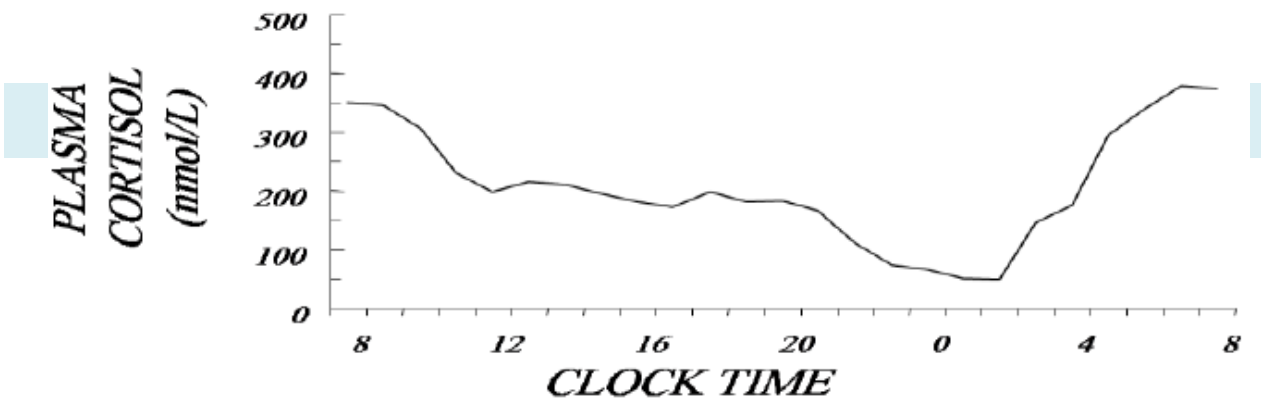
*** Different variants of POMC : (Melanotropin "MSH", β-Endorphin**

*** ↑ ACTH will cause hyperpigmentation because of MSH itself and ACTH has some MSH's action**

Natural episodic Secretion Rhythm ;

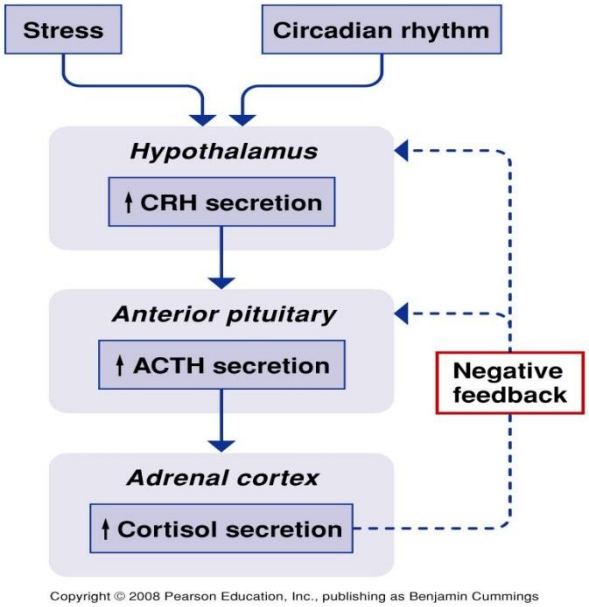
- After ACTH has been produced, cortisol will be evident 15 to 30 minutes later.
- There are usually 7-15 episodes per day
- The greatest ACTH secretory activity occurs in the early morning hours (4-8) (23 µg\dl) and diminish late in the afternoon (lowest level around midnight 5 µg\dl).

- **CRH** from hypothalamus is the major regulator of ACTH secretion.(ADH is also a potent ACTH secretagogue).



Regulation of Cortisol Secretion :

- *Increased* release with **coffee consumption**. (By activating the stress axis, elevating glucocorticoid and catecholamine).
- *Increases* with increased **exercise time & intensity, physical trauma, mental anxiety, infection extreme heat and cold, exercise to the point of exhaustion…**
- ↑ **cortisol** ➔ ↓**testosterone**. (the doctor said; this happened in cases of **chronic stress** –mental or physical- and the presenting symptoms of decreased testosterone in male are more obvious than female, but in case of Cushing's Syndrome the testosterone increase with cortisol, and the presenting symptoms of increased testosterone in female more obvious than male.)



*CRH & ACTH receptors are G-protein coupled receptor. They act through second messenger cAMP.

* If there is a tumor in pituitary gland: ↑ACTH ↑ Glucocorticoid ↓CRH

* There are Ectopic tumors may produce ACTH. (pulmonary small-cell carcinoma)

Steroid Hormone Transport :

- Steroid hormones when released from adrenal cortex into blood stream they bind to protein carriers:
  - ✓ Cortisol binding globulin (**CBG**) (transcortin).
  - ✓ Albumin.
- **Only unbound steroid hormones are <u>biologically active</u> (~2%)**
- To cross the target tissue membrane, the hormone must dissociate from its carrier protein.

Most of hormones that have cytoplasmic or nuclear receptors requires a carrier protein.

Cortisol Metabolism :

- **Free cortisol** ➔ is excreted into urine.
- Metabolized in **liver** by reductases & conjugated to glucuronides and excreted via kidney.

Physiological Effects of Cortisol :

1. Carbohydrate Metabolism:

Increases blood glucose levels by:

- **(+) gluconeogenesis** in the liver via stimulating the enzymes involved in **gluconeogenesis**.
- Decreasing utilization of glucose by cells via direct **inhibition of glucose transport into cells**.
- gluconeogenesis action is Against the action of insulin

2. Protein Metabolism:

Reduces protein formation EXCEPT liver.

- Extrahepatic protein stores reduced **(catabolic).**
- amino acids not transported into muscle cells **↓ protein synthesis & ↑ amino acid blood levels.**
- These high blood amino acid levels are transported more rapidly to hepatic cells **for gluconeogenesis** and protein synthesis in liver.

3. Fat Metabolism:

LIPOLYTIC & increase appetite.

- **Mobilizes fatty acids & glycerol from adipose tissue lead to ↑ their blood concentrations** makes more glycerol available for **gluconeogenesis**.
- Fat broken down & less formed due to less glucose transported to fat cells.
- Redistribution of body fat:

Insulin inhibit gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase & glucose-6-phosphatase

↑ formation of fat in trunk areas & face.

↓ fat (& muscle) from extremities.

4. Anti-inflammatory effects:

Suppresses immune system ;

- Stabilizes lysosomal membrane.
- Reduces degree of vasodilatation.
- Decreases permeability of capillaries.
- Decreases migration of white blood cells.
- Alleviate inflammation by inhibiting the production of prostaglandins and leukotrines (mediate inflammation) via stimulation of an inhibitor of phospholipase A2, which is needed for PG synthesis.

5. Effects on Blood Cells and immunity:

- *Decrease production of eoisinophils and lymphocytes*
- **Suppresses lymphoid tissue** systemically therefore decrease in T cell and antibody production thereby decreasing immunity
- Decrease immunity could be fatal in diseases such as tuberculosis
- Decrease immunity effect of cortisol is **useful during transplant operations in reducing organ rejection.**

6. Effects on the Circulation:

Maintains body fluid volumes & vascular integrity

- Cortisol levels vary with water intake
- Cortisol has mineralcorticoid effect, Not as potent as aldosterone.
- BP regulation & cardiovascular function:

  Sensitizes arterioles to action of noradrenaline (Permissive effect**).**
- **Decreased** capillary permeability.
- **Maintins normal renal function.**

7. CNS:

- **Negative feedback** control on release of ACTH.
- Modulates perception & emotion.

8. Mineral Metabolism:

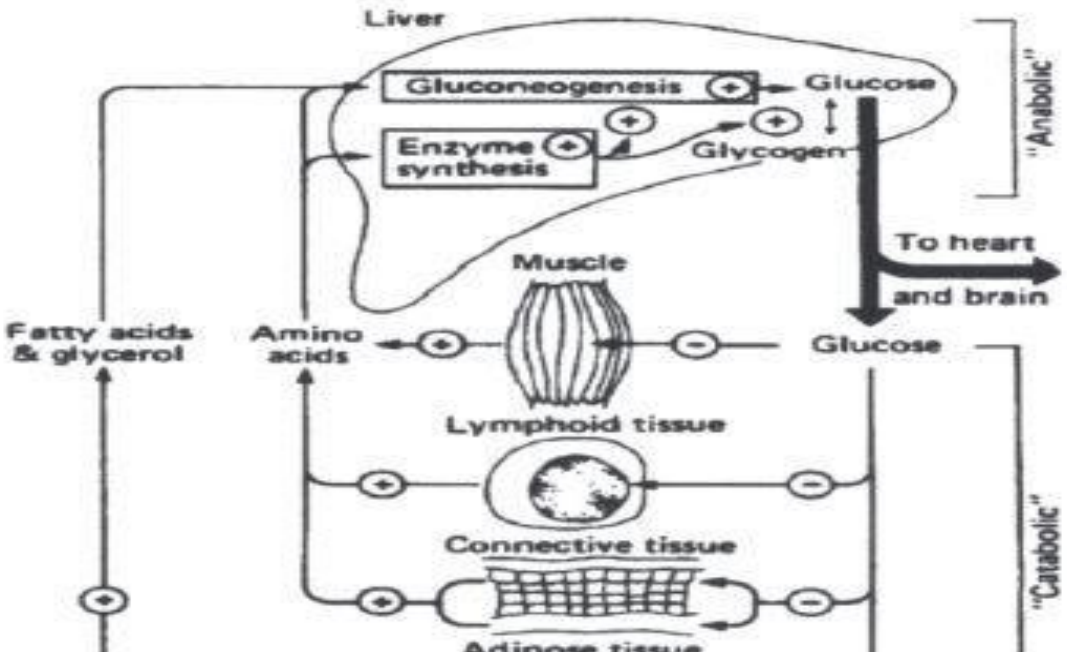
- Anti-vitamin D effect. (In cases of a high cortisol level ➔ Osteoporosis)

9. GIT:

- Increases **HCl** secretion. (In cases of a high cortisol level ➔ Peptic Ulcer)

10. Developmental Functions:

- Permissive regulation of fetal **organ maturation**
- **Surfactant synthesis** (phospholipid that maintains alveolar surface tension).
- **Inhibition of linear growth in children** due to direct effects on bone & connective tissue



Cortisol is ;
- Hyperglycemic
- Lipolytic
- Catabolic on Proteins

Disorders of Cortisol Secretion :

Cushing's Syndrome ;

Cushing's syndrome results from continued high glucocorticoid levels.
3rd - 6th decade, 4 to1 (females)

- **Causes:**
  - **pharmacologic**
  - **pituitary adenoma 75-90%**
  - **adrenal adenoma, carcinoma**
  - **ectopic ACTH**

- **Exogenous:**

✓ Most cortisol excess is induced by steroid therapy.
✓ (prednisone) to manage disease.
✓ Asthma, rheumatoid arthritis, lupus, & other inflammatory diseases.
✓ Immunosuppression after transplantation.

- **Endogenous ;**

Due to excessive production of cortisol:

✓ **ACTH- independent**:
Primary adrenal defect (adenoma).

✓ **ACTH-dependent:**
Overproduction of ACTH by pituitary.
Overproduction of ACTH by ectopic ACTH-producing tumor.

❖ **Both exogenous & endogenous hyperfunction show manifestations of Cushing's disease.**

Signs and Symptoms of excess cortisol ;

- **Carbohydrate metabolism :**

  ↑ blood glucose levels.

  ↓ sensitivity to insulin, **"Adrenal diabetes"**

- **Protein metabolism :**

- ↑ protein loss
- Muscle atrophy
- Thin skin
- ↓ collagen deposition in the skin **(STRIEA)**
- bone matrix & mass losses; bone formation ↓ less Ca2 + absorbed & more excreted in urine
- **osteoporosis.**

- **Fat metabolism :**

- redistribution of body fat:
- **↑ trunk & face fat deposition** & **↓ extremities fat deposition.**

- **Buffalo torso :**

- **Redistribution of fat from lower parts of the body to the thoracic and upper abdominal areas.**

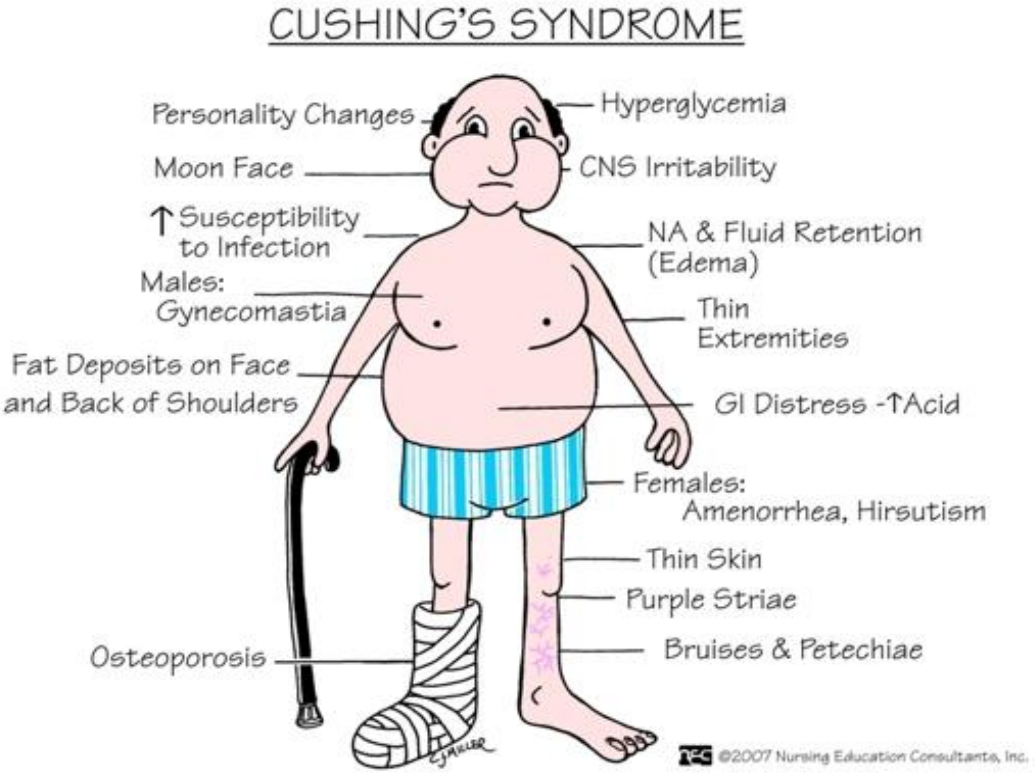
- **Moon Face :**

- **Edematous appearance of face.**
- **Acne & hirsutism** (excess growth of facial hair).

- **Circulation :**

- **Hypertension** due to Na retention & K excretion.
- **Hypervolemia**
- **Hypernatremia** due to increased Na absorption.
- **Hypokalemia** due to increased K excretion.

- **Immunity & Inflammation :**
  - **Decreases** inflammatory response
  - **Increased** infection susceptibility
  - Ab synthesis suppressed & normal immune responses to infecting pathogens suppressed
  - Decrease in fibrous tissue formation & **impaired wound healing.**



Treatment:

- ✓ **Removal of adrenal tumor** if this is the cause
- ✓ **Microsurgical removal of hypertrophied pituitary** elements to reduce ACTH secretion.

Adrenal Insufficiency :

Causes:

Primary: **Failure of adrenal glands (Addison's disease)**

Secondary: Failure of HPA axis:

- **Usually due to chronic exogenous glucocorticoid administration.**
- **Pituitary Failure.**

Tertiary: Hypothalamic dysfunction

Addison's Disease ;

- **Loss of all three types of adrenal steroids** (insufficiency is always nonspecific so all of the adrenal cortex hormones are affected)
- 90% of (both) glands must be destroyed to manifest clinically
- **Progressive neurological symptoms from demyelination.**

Causes:

1. **Autoimmune** (most of cases)
2. Thrombosis/Hemorrhage
3. Sepsis, DIC, Antiphospholipid Syndrome
4. Infiltrative Diseases
5. Bilateral Cancer Metastasis

Chronic Insufficiency ;

(Either the cause Primary, Secondary or Tertiary)

Clinical Presentation: (mostly it is not specific)

Are due to deficiency of glucocorticoids and aldosterone

- Nonspecific: Fatigue, anorexia, weight loss, loss of libido
- Neurological: Headaches, visual changes, diabetes insipidus
- Gastrointestinal: Pain, nausea, vomiting, diarrhea

- Muscle and joint pain
- **Skin pigmentation** (The cause of the melanin deposition is increased rates of ACTH secretion as well as simultaneous secretion of increased amounts of MSH (melanocyte stimulating hormone) when cortisol secretion is depressed).

Others: **Hypotension/Orthostatic**, Cachexia, Thin axillary and pubic hair in women, **Hypoglycemia**, Normocytic anemia, **Hyponatremia, Hyperkalemia, and mild acidosis.**

Adrenal Crisis (Adisonian Crisis) ;

(The crisis most commonly happens in the immediate withdrawal of prolonged cortisol treatment. Also, 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).

Clinical Presentation: (Life-threatening emergency)

- **Hypotension:**
  Typically resistant to catecholamine and IVF resuscitation
  Cause ➔ Abrupt adrenal failure: usually from gland hemorrhage, thrombosis or infection.
- Sudden penetrating pain in the legs, lower back or abdomen
- Sever vomiting and diarrhea, resulting in dehydration
- Loss of consciousness
- **Hypoglycemia**
- Sever lethargy
- **Hyponatremia**
- **Hyperkalemia**
- Convulsions
- Fever

Treatment:

- **Use glucocorticoids only (no mineralocorticoids) (I.V Hydrocortisone)**
- **Correct volume and sugar deficits**

QUESTIONS

1-How are free cortisol excreted mainly?

a- stool

b-urine

c-saliva

d-sweat

2- At what time the greatest ACTH secretory occurs ?

a- early morning (4-8)
b- afternoon (1-4)
c- Night (6-9)
d- Midnight

3- which of the following is a sign of Cushing's Syndrome:

a- fatigability
b- weight loss
c- Moon face
d- Anorexia

Answers : 1) b 2)a 3) c