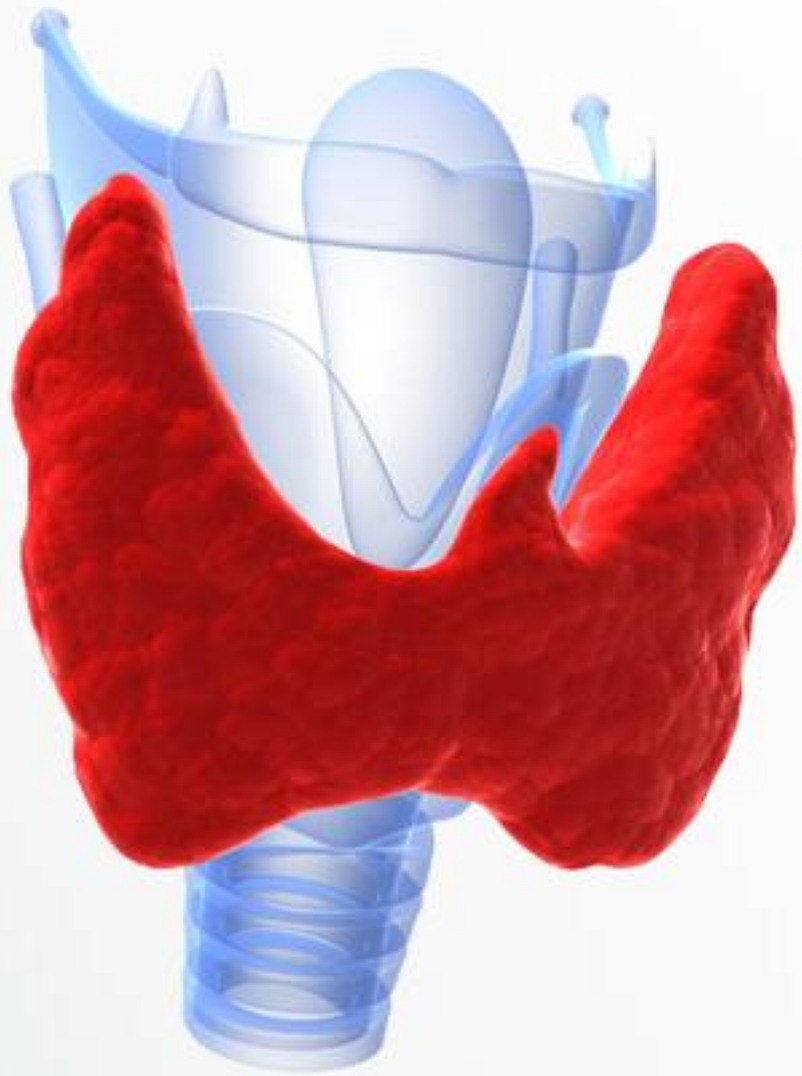
Physiology team

11 Glucocorticoides



Sources:

Female slides (mainly)

Male slides

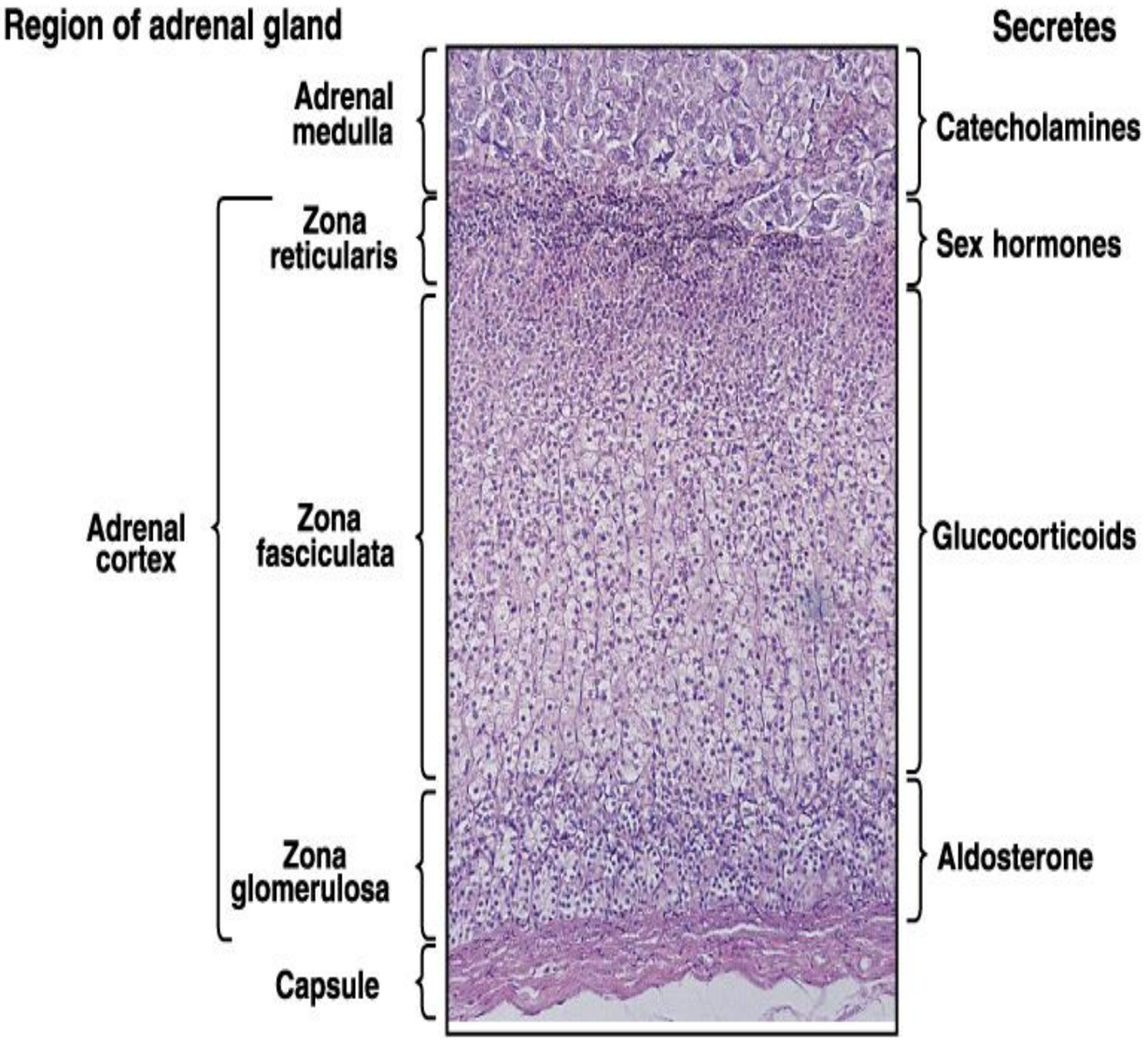
Guyton

Adrenal gland

- Small triangular glands loosely attached to the kidneys.
- Divided into 2 morphologically and distinct regions:

A. Adrenal cortex:
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis

B. Adrenal medulla

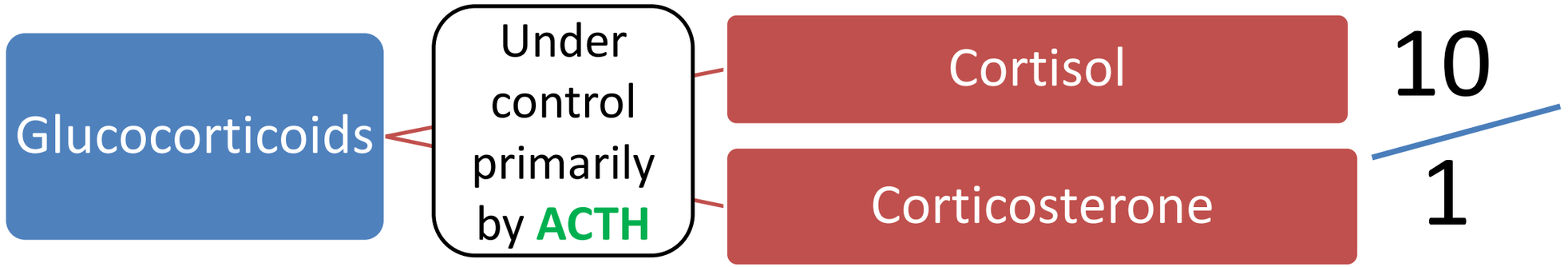


Hormones of Adrenal gland:

- Cortex (Secretes steroid hormones):
  - Glucocorticoids. (Called glucocorticoid, because first action recognized is increase the levels of glucose.)
  - Mineralocorticoids.
  - Androgens.
- Medulla (Amino acid secretions):
  Catecholamines (E & NE)

Glucocorticoids

At least 95% of the glucocorticoids activity of the adrenocortical secretions results from the secretion of cortisol.



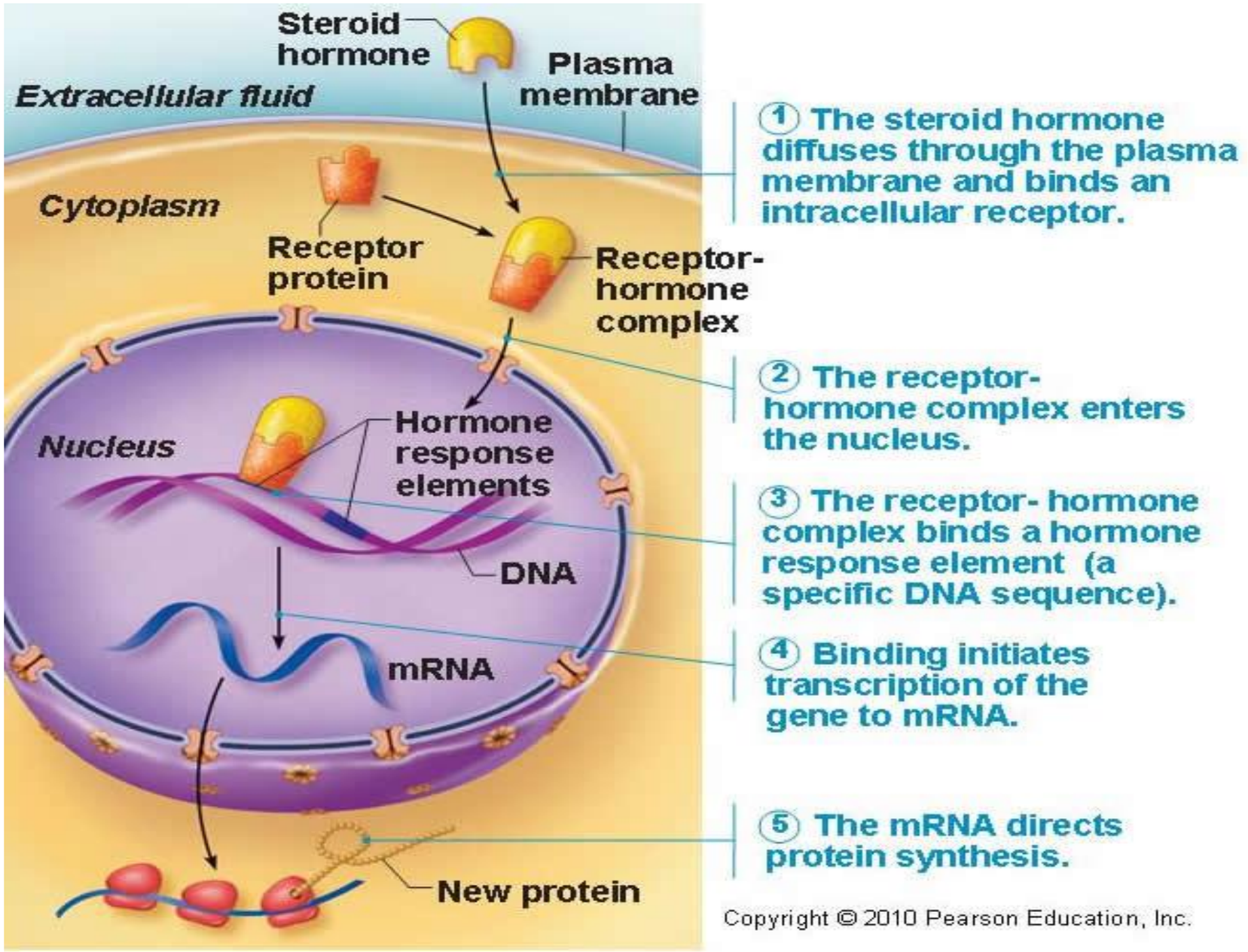
Steroid Hormones Transport

-Steroid hormones when released from adrenal cortex into blood stream they bind to protein carriers:

1. Cortisol binding globulin (CBG) (transcortin).
2. Albumin.
3. Unbound steroid hormones are the only biologically active (~2%)

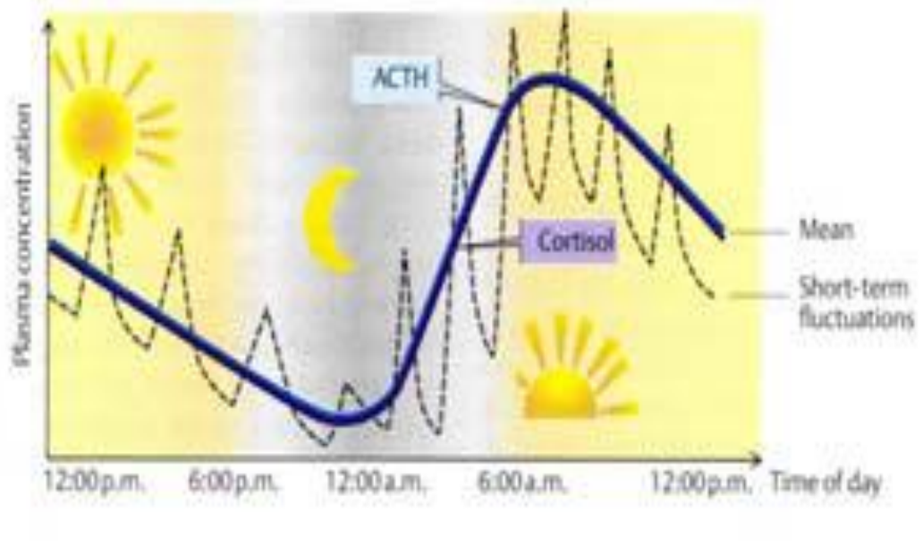
- To cross the target tissue membrane, the hormone must dissociate from its carrier protein.
(The steroids are lipophilic so they diffuse through the cell membrane)
- The importance of Binding to plasma proteins is to act as a reservoirs and ensure a uniform distribution to all tissues.
- Cortisol have long have life (longer than Aldosterone).

Mechanism of action of steroid hormones



Natural episodic secretion rhythms

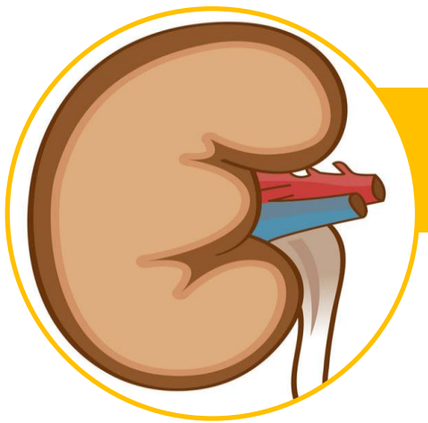
- Controlled by hypothalamus CRH. Also ACTH exhibits the same diurnal pattern.
- After ACTH has been produced, cortisol will be evident 15 to 30 minutes later.
- There are usually 7-15 episodes per day
- There is a major burst in the early morning before awakening.



Pattern of cortisol secretion

- Increased release with coffee consumption.
- Increases proportionately with exercise time & intensity.

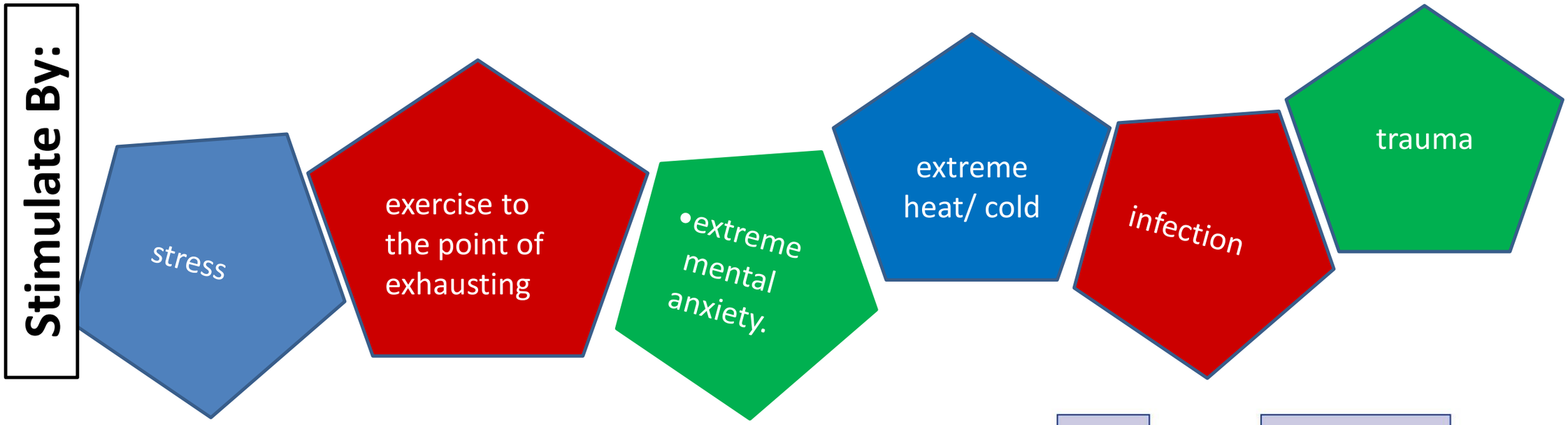
Cortisol metabolism



Free cortisol is excreted into urine.

Metabolized in liver by reductases & conjugated to glucuronides

Regulation of cortisol release



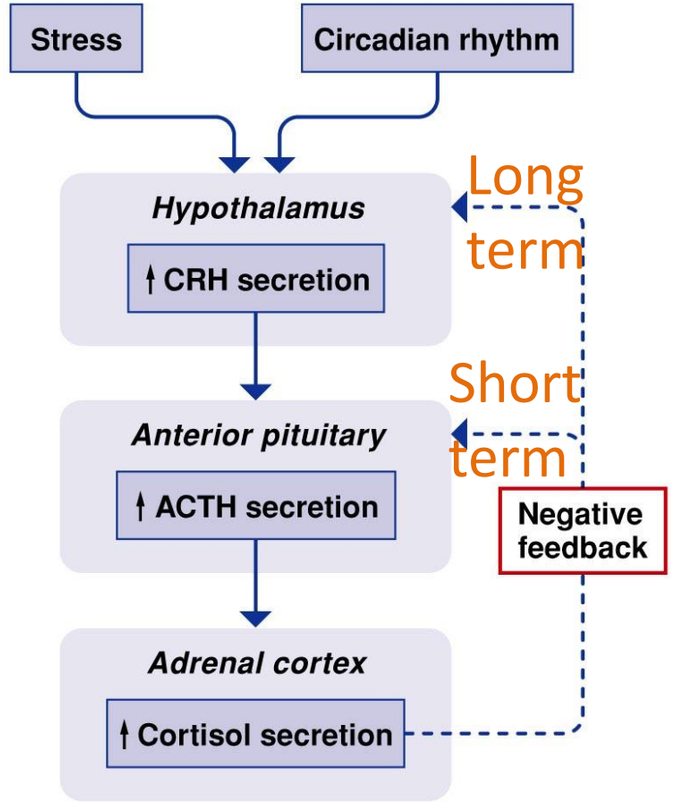
* Negative feedback: (when cortisol level become high)

•Long term:

1. Directly: inhibit CRH secretion from the hypothalamus.
2. Indirect : inhibit CRH secretion by the effect on hippocampal neurons, which synapse on the hypothalamus. (paraventricular nuclei which secret CRH)

• Short term:

Inhibit ACTH secretion from the Anterior pituitary gland.



* From Linda

Physiological effects of cortisol

Carbohydrate metabolism

The overall effect is hyperglaycemia

- Decrease glucose uptake by the cells via direct inhibition of glucose transport into cells.
- Gluconeogenesis in the liver (This process needs amino acids, it will take it from all over the body mainly from the muscles but not the liver.)

Adrenal diabetes:

The increase in blood glucose concentration is occasionally great enough (>50%) that the condition is called adrenal diabetes

Protein metabolism

The overall effect is catabolic

-Reduces protein formation in all tissues 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.

Fat metabolism

The overall effect is lipolysis

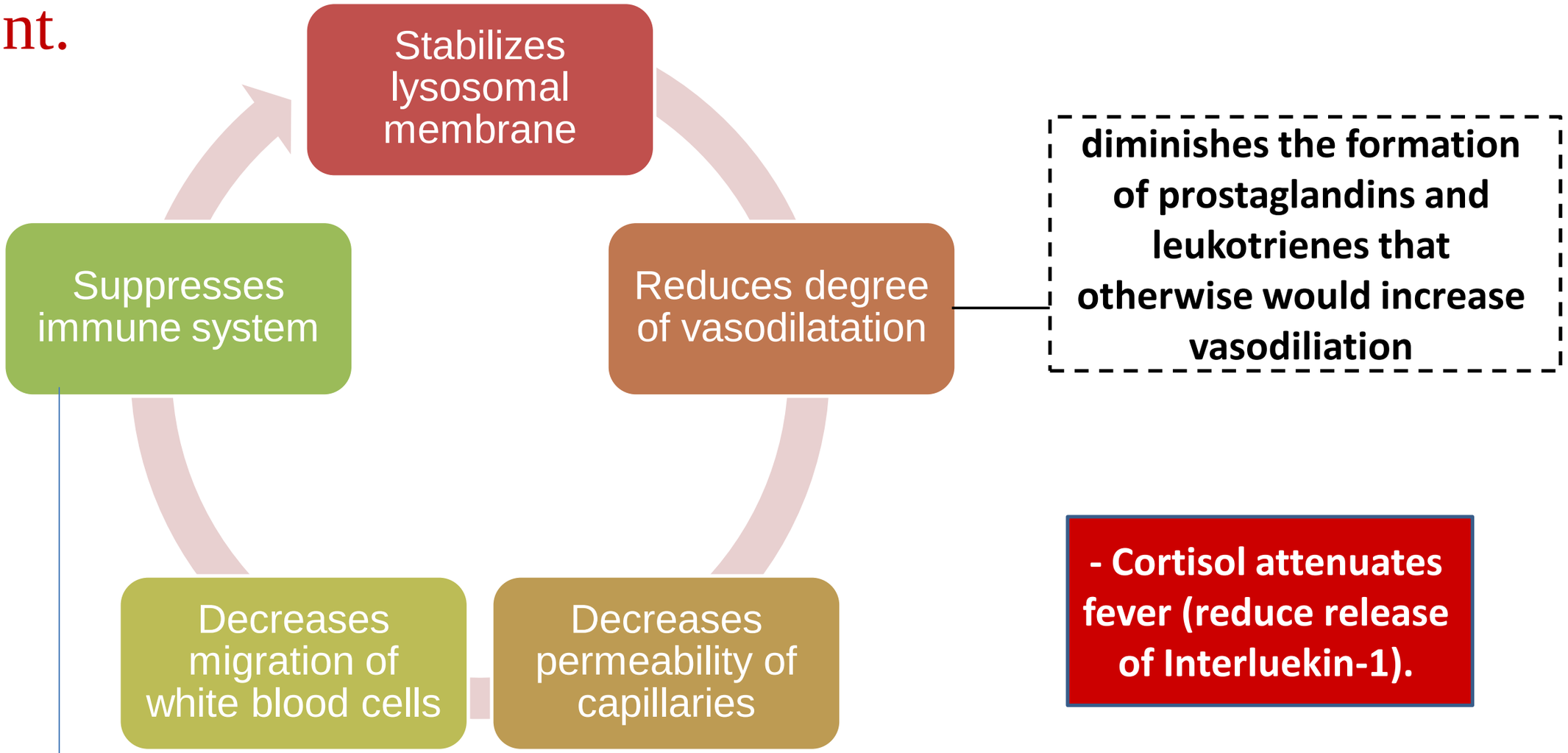
- Mobilizes fatty acids & glycerol from adipose tissue lead to↑ their blood concentrations , so more glycerol available for gluconeogenesis.

- Fat broken down & less formed due to less glucose transported into fat cells.

- Redistribution of body fat:
↑ face & trunk areas (truncal obesity)
↓ fat (& muscle) from extremities

- Increases appetite

Cont.



diminishes the formation of prostaglandins and leukotrienes that otherwise would increase vasodiliation

- Cortisol attenuates fever (reduce release of Interluekin-1).

- **Decrease production of eosinophils and lymphocytes**
- **Suppresses lymphoid tissue systemically therefore decrease T-cell and antibody production decreasing immunity**

• Glucocorticoids are used to alleviate تخفيف inflammation .
• Inhibit production of prostaglandins and leukotrines (mediate inflammation) This occurs via inhibiting phospholipase A2, which is needed for PG synthesis.
• Decrease the inflammation reaction by decreasing permeability of capillary membranes, reducing swelling.
• They also reduce the effects of histamine.

Circulation	Maintenance of vascular integrity and body fluid volume: - Cortisol is necessary for maintenance of normal BP and plays a permissive role in arterioles by up-regulation of α_1-adrenergic receptors, so cortisol is required for the vasoconstrictive response of the arterioles to catecholamine. - Cortisol has a mineralocorticoid effect, but not as potent as aldosterone. - Decrease capillary permeability. - Maintains normal renal function. (By causing vasodilation of afferent arterioles → increasing renal blood flow → increases glomerular filtration rate)
CNS responses:	- Negative feedback control on release of ACTH. - Modulates perception and emotion. (Because glucocorticoid receptors are found in the brain , particularly in the limbic system)
Mineral metabolism	- Anti-vitamin D effect. (decrease calcium absorption → which may lead to osteoporosis)
GIT	- Increases HCl secretion. (it may cause ulcer if it was in excessive amount)

Developmental Functions	Developmental functions: - Permissive regulation of fetal organ maturation. For example, maturation of the lung and production of surfactant. (phospholipid that maintains alveolar surface tension) → given to mothers in case of prematurely delivery to protect the babies from getting respiratory stress syndrome due to surfactant deficiency. - Inhibition of linear growth in children, why? Due to its direct effect on bone and connective tissue by: • Stimulating osteoclastogenesis which will increase bone resorption. • Decreasing calcium absorption due to is anti-vitamin D effect. • Decreasing synthesis of collagen type 1 which considered the major component of bone matrix.

Abnormal amount of cortisol will cause:

- In adults : osteoporosis.
- In children : dwarfism.

Cortisol excess :

Exogenous	Endogenous	
Most cause of exogenous cortisol excess is steroid therapy (prednisone) of diseases like: • Asthma. • Rheumatoid arthritis. • Lupus. (الذئبة) • Immunosuppression after transplantation.	ACTH - dependent	ACTH – independent
	• Overproduction of ACTH by pituitary gland. • Overproduction of ACTH by ectopic ACTH-producing tumor.	Primary adrenal gland defect (adenoma).

Both exogenous & endogenous hyperfunction show manifestation of:

- Cushing’s syndrome: over production of cortisol by adrenal gland.
- Cushing’s diseases: over production of ACTH by pituitary gland.

Cortisol excess :

Intermediary metabolism :

Carbohydrate metabolism:	**- Increase glucose levels.** **- Decrease sensitivity to insulin.**
Protein metabolism:	**- Increase protein loss.** (catabolism) **- Muscle atrophy.** (due to protein loss) **- Thin skin.**
Bone:	**- Loss of bone matrix and mass.** **- Decrease bone formation.** → **less calcium is absorbed and more is excreted in urine → lead to osteoporosis**
Fat metabolism:	**Fat redistribution:** **- Increase fat deposition in the trunk and face.** (moon face) **- Decrease fat deposition in extremities.** (الاطراف)
Inflammation and immunity:	**- Decreases inflammatory response.** **- Increases infection susceptibility.** **- Ab** (antibodies) **synthesis suppressed and normal immune response to infecting pathogens is also suppressed.** **- Decrease in fibrous tissue formation.**
CNS:	**- Initially euphoria but replaced with depression.**
Circulation:	**- Hypertension due to Na and water retention and K excretion.** **- Hypervolemia.** **- Hypernatremia due to increased Na absorption.** **- Hypokalemia due to increased K excretion.**

Effect on carbohydrate metabolism :

Adrenal diabetes due to :

- Hypersecretion of cortisol results in increase blood glucose levels, up to 2x normal (200mg /dl).
- High glucose levels will lead to prolonged oversecretion of insulin → burns out beta cells in of the pancreas → resulting in life long diabetes mellitus.

Effect on protein metabolism :

Muscles:	**muscle weakness due to decrease protein content.** (cortisol increases protein catabolism)
Bones:	**Osteoporosis due to lack protein deposition.**
Skin:	**Striae due to lack of collagen formation.** (cortisol inhibit collagen synthesis)
Lymphoid tissue:	**Suppression of immune system.**

Characteristics of excess cortisol (cushing's) :

- syndrome
- disease

Buffalo torso:

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

Moon face:

- Edematous appearance of the face.
- Acne and hirsutism. (excess growth of facial hair.)

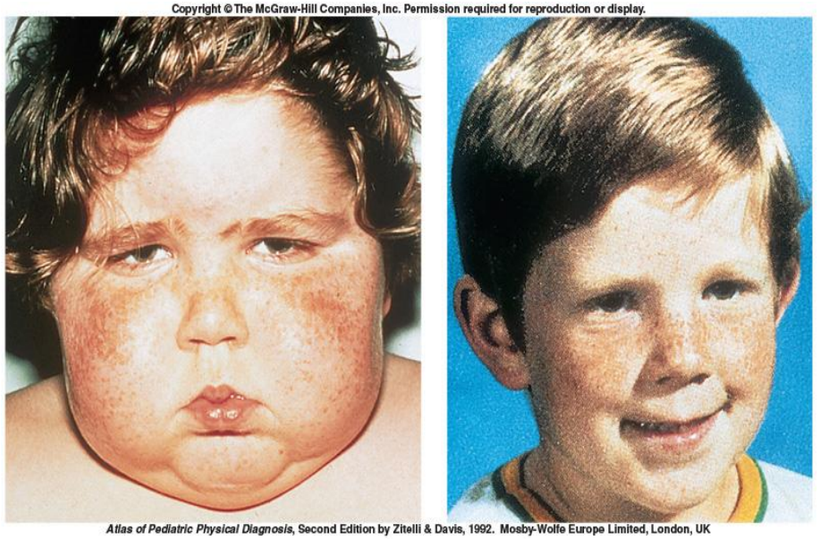
Weight gain:

In the trunk of the body not arms and legs (due to fat mobilization)

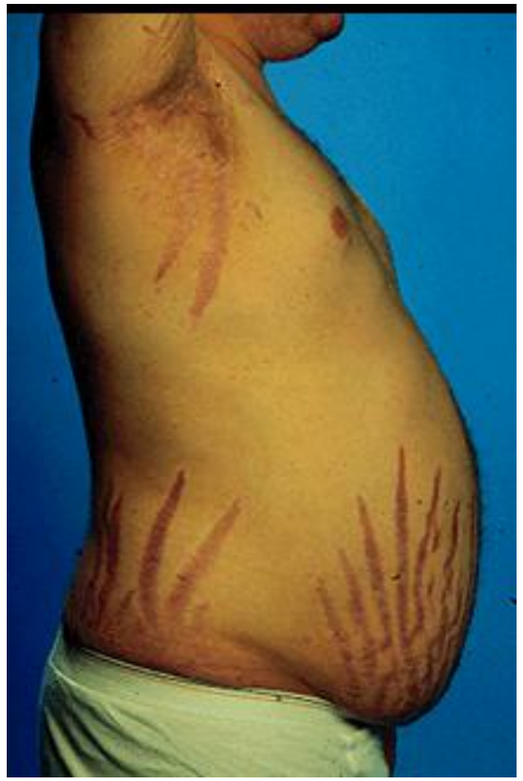
Skin striae

Also it will causes :

- Proximal muscle wasting & weakness. (due to protein catabolism)
- Osteoporosis.
- Glucose intolerance.
- HTN, hypokalemia.
- Thromboembolism. (due to excessive production of RBCs)
- Depression, psychosis.
- Infection.
- Glaucoma.



Atlas of Pediatric Physical Diagnosis, Second Edition by Zitelli & Davis, 1992. Mosby-Wolfe Europe Limited, London, UK



Treatment :

- Removal of adrenal tumor if this is the cause.
- Microsurgical removal of hypertrophied pituitary elements to reduce ACTH secretion.
- Partial or total adrenalectomy followed by administration of adrenal steroids to compensate insufficiencies that develop.

Summery

Regulation of secretion of adrenocortical hormones

a. Glucocorticoid secretion (Figure 7-12)

- oscillates with a 24-hour periodicity, or **circadian rhythm.**
- For those who sleep at night, **cortisol levels are highest just before waking** (≈8 A.M.) and **lowest in the evening** (≈12 midnight).

(1) *Hypothalamic control—corticotropin-releasing hormone (CRH)*

- CRH-containing neurons are located in the **paraventricular nuclei** of the hypothalamus.
- When these neurons are stimulated, CRH is released into hypothalamic–hypophysial portal blood and delivered to the anterior pituitary.
- CRH binds to receptors on corticotrophs of the anterior pituitary and directs them to **synthesize POMC** (the precursor to ACTH) and **secrete ACTH.**
- The second messenger for CRH is **cAMP.**

(2) *Anterior lobe of the pituitary—ACTH*

- **ACTH increases steroid hormone synthesis** in all zones of the adrenal cortex by stimulating **cholesterol desmolase** and increasing the conversion of cholesterol to pregnenolone.
- ACTH also **up-regulates its own receptor** so that the sensitivity of the adrenal cortex to ACTH is increased.
- Chronically increased levels of ACTH cause hypertrophy of the adrenal cortex.
- The second messenger for ACTH is **cAMP.**

(3) *Negative feedback control—cortisol*

- **Cortisol inhibits the secretion of CRH** from the hypothalamus and the **secretion of ACTH** from the anterior pituitary.
- When cortisol (glucocorticoid) levels are chronically elevated, the secretion of CRH and ACTH is inhibited by negative feedback.
- The **dexamethasone suppression test** is based on the ability of dexamethasone (a synthetic glucocorticoid) to inhibit ACTH secretion. In normal persons, low-dose dexamethasone inhibits or "suppresses" ACTH secretion and, consequently, cortisol secretion. In persons with **ACTH-secreting tumors,** low-dose dexamethasone does not inhibit cortisol secretion, but high-dose dexamethasone does. In persons with **adrenal cortical tumors,** neither low- nor high-dose dexamethasone inhibits cortisol secretion.

Actions of glucocorticoids (cortisol)

- Overall, glucocorticoids are essential for the **response to stress.**

a. Stimulation of gluconeogenesis

- Glucocorticoids increase gluconeogenesis by the following mechanisms:

(1) They **increase protein catabolism** in muscle and decrease protein synthesis, thereby providing more amino acids to the liver for gluconeogenesis.
(2) They **decrease glucose utilization** and insulin sensitivity of adipose tissue.
(3) They **increase lipolysis,** which provides more glycerol to the liver for gluconeogenesis.

b. Anti-inflammatory effects

(1) Glucocorticoids **induce the synthesis of lipocortin,** an **inhibitor of phospholipase A_2.** (Phospholipase A_2 is the enzyme that liberates arachidonate from membrane phospholipids, providing the precursor for prostaglandin and leukotriene synthesis.) Because prostaglandins and leukotrienes are involved in the inflammatory response, glucocorticoids have anti-inflammatory properties by inhibiting the formation of the precursor (arachidonate).
(2) **Glucocorticoids inhibit the production of interleukin-2** (IL-2) and inhibit the proliferation of T lymphocytes.
(3) Glucocorticoids **inhibit the release of histamine and serotonin** from mast cells and platelets.

c. Suppression of the immune response

- Glucocorticoids **inhibit the production of IL-2** and T lymphocytes, both of which are critical for cellular immunity. In pharmacologic doses, glucocorticoids are used to **prevent rejection of transplanted organs.**

d. Maintenance of vascular responsiveness to catecholamines

- Cortisol **up-regulates α_1 receptors** on arterioles, increasing their sensitivity to the vasoconstrictor effect of norepinephrine. Thus, with cortisol excess, arterial pressure increases; with cortisol deficiency, arterial pressure decreases.

Summery

a. Adrenocortical insufficiency

(1) *Primary adrenocortical insufficiency—Addison's disease*

- is most commonly caused by autoimmune **destruction of the adrenal cortex** and causes acute **adrenal crisis.**
- is characterized by the following:

(a) ↓ **adrenal glucocorticoid, androgen, and mineralocorticoid**
(b) ↑ **ACTH** (Low cortisol levels stimulate ACTH secretion by negative feedback.)
(c) **Hypoglycemia** (caused by cortisol deficiency)
(d) Weight loss, weakness, nausea, and vomiting
(e) **Hyperpigmentation** (Low cortisol levels stimulate ACTH secretion; ACTH contains the MSH fragment.)
(f) ↓ pubic and axillary hair in women (caused by the deficiency of adrenal androgens)
(g) **ECF volume contraction, hypotension, hyperkalemia,** and **metabolic acidosis** (caused by aldosterone deficiency)

(2) *Secondary adrenocortical insufficiency*

- is caused by primary **deficiency of ACTH.**
- **does not exhibit hyperpigmentation** (because there is a deficiency of ACTH).
- **does not exhibit volume contraction, hyperkalemia,** or **metabolic acidosis** (because aldosterone levels are normal).
- Symptoms are otherwise similar to those of Addison's disease.

Addison's disease (e.g., primary adrenocortical insufficiency)	Hypoglycemia Anorexia, weight loss, nausea, vomiting Weakness Hypotension Hyperkalemia Metabolic acidosis Decreased pubic and axillary hair in women Hyperpigmentation	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids and mineralocorticoids

Adrenocortical excess—Cushing's syndrome

- is most commonly caused by the administration of **pharmacologic doses of glucocorticoids.**
- is also caused by primary **hyperplasia of the adrenal glands.**
- is called **Cushing's disease** when it is caused by overproduction of ACTH.
- is characterized by the following:

(1) ↑ **cortisol and androgen levels**
(2) ↓ ACTH (if caused by primary adrenal hyperplasia or pharmacologic doses of glucocorticosteroids); ↑ ACTH (if caused by overproduction of ACTH, as in Cushing's disease)
(3) **Hyperglycemia** (caused by elevated cortisol levels)
(4) ↑ protein catabolism and muscle wasting
(5) Central obesity (round face, supraclavicular fat, buffalo hump)
(6) Poor wound healing
(7) **Virilization of women** (caused by elevated levels of adrenal androgens)
(8) **Hypertension** (caused by elevated levels of cortisol and aldosterone)
(9) Osteoporosis (elevated cortisol levels cause increased bone resorption)
(10) Striae

- **Ketoconazole,** an inhibitor of steroid hormone synthesis, can be used to treat Cushing's disease.

Cushing's syndrome (e.g., primary adrenal hyperplasia)	Hyperglycemia Muscle wasting Central obesity Round face, supraclavicular fat, buffalo hump Osteoporosis Striae Virilization and menstrual disorders in women Hypertension	Decreased (negative feedback effect of increased cortisol)	Ketoconazole Metyrapone

MCQs

1- What is the most abundant Glucocorticoid that found in the body :

A-Cortisol
B-Corticosterone
C-Aldosterone
D-Prednisone

2- The release of Glucocorticoids is controlled by :

A-TSH
B-ADH
C-ACTH
D-GH

3- Which of the following affect the release of Glucocorticoids :

A-circadian rhythm
B-coffee consumption
C-exercise
D-all of above

4- Which of the following is an effect of cortisol :

A-Increase utilization of glucose
B-Increase gluconeogenesis
C-decrease appetite
D-decrease oxidation of fatty acids

5- Cortisol attenuates fever by :

A-reduce release of Interluekin-1
B-Increase release of TNF
C-Increase release IL-6
D-B&C

6- Cortisol effect in Mineral metabolism is :

A-anti vit-K
B-anti vit-B
C-anti vit-C
D-anti vit-D

7-Which of the following is an ACTH-independent :

A-Cushing's disease
B-Excess Cortisol due nonpituitary tumors
C-Iatrogenic Cushing's syndrome
D-non of above

8-cortisol metabolism in liver by reductases & conjugated to

A- Albumin
B- phosphate
C- Glucuronides

9-when a person had extreme mental anxiety will lead to

A- inhibition releasing cortisol
B- stimuli releasing cortisol
D- A&B

1- A 2- C 3- D 4- B 5- A 6- D 7- C 8-C 9-B

MCQs

physiological effects of cortisol :-

10- Increase blood glucose levels by :

A- gleconeogenesis

B- Increase utilization of glucose

C- A&B

11- redaction protein in all tissue except :

A- liver

B- lungs

C- brain

12- glyconeogenesis combine with cortisol release due to :

A- high blood amino acid levels are transported to hepatic cells

B- high glycerol concentration in the blood

C- A&B

cortisol excess :

13- in Carbohydrate metabolism ..

A- Increase blood glucose level

B- Increase sensitivity to insulin

C- decrease blood glucose level

14- in protien metabolism ..

A- increase protien loss & muscle atrophy

B- thin skin & boon matrix loss

C- A&B

15- patient come to the hospital he have Moon face , buffalo torso , HTN & stariae in his skin .. Which disease dose he have ?

A- Gigantism

B- Acromegally

C- cushing disease

10-A 11-A 12-C 13-A 14-C 15-C

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Endocrine Block