Adrenal cortex (Continue)
(Glucocorticoids)

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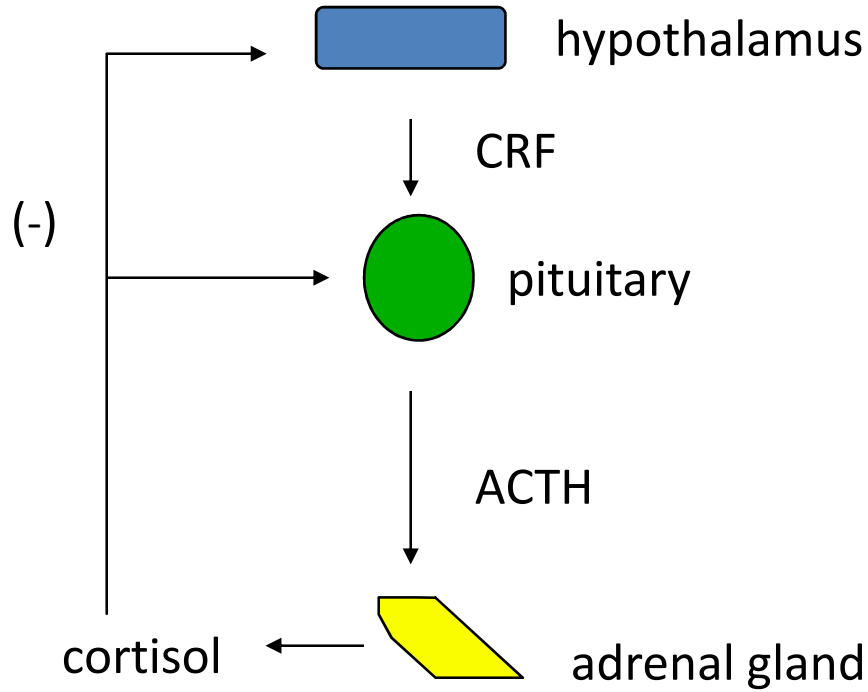
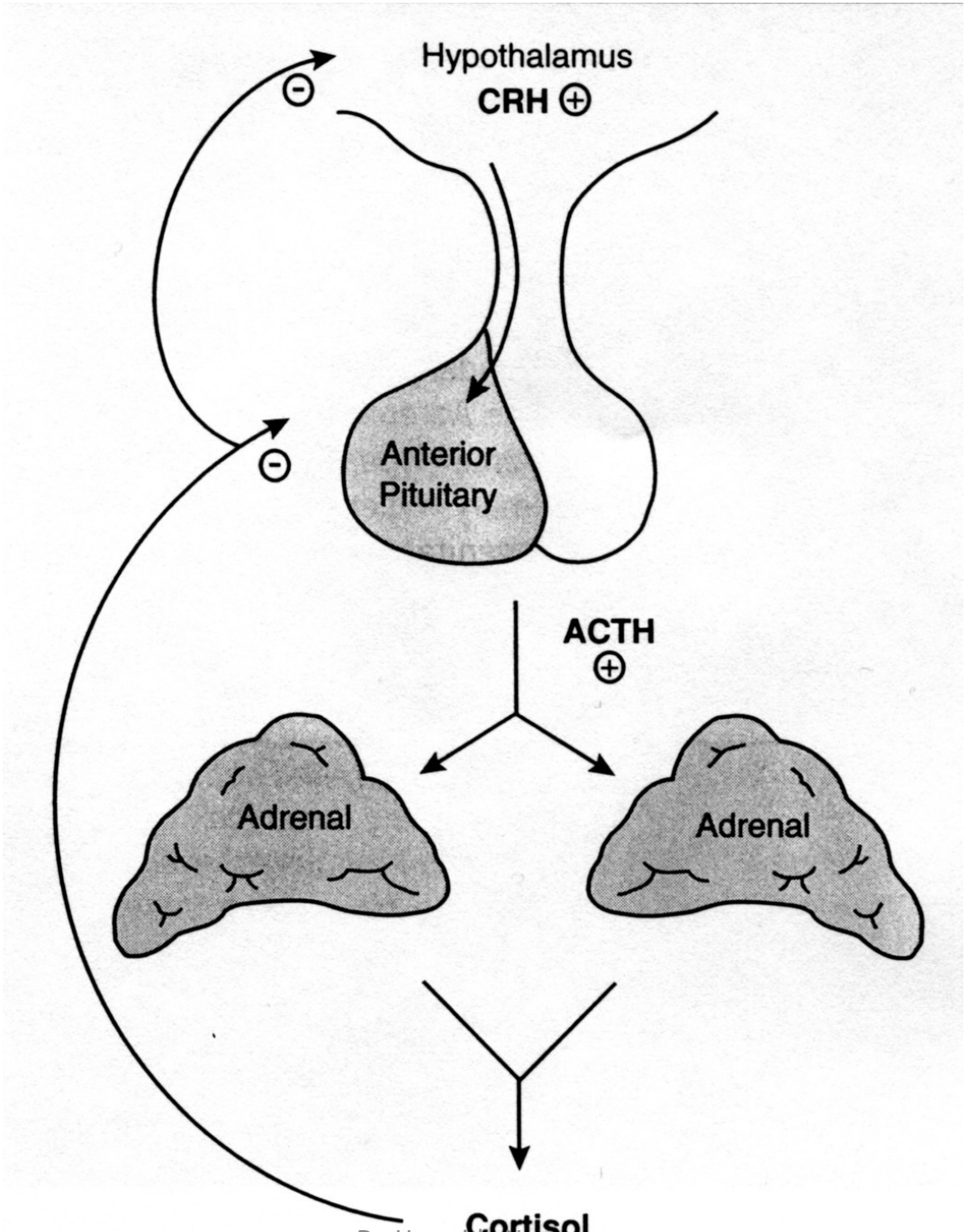
Regulation of Cortisol Release

- cortisol release is regulated by ACTH
- release follows a daily pattern - circadian
- negative feedback by cortisol inhibits the secretion of ACTH and CRH

Regulation of Cortisol Release

- Cortisol release is primarily under neuroendocrine control.




Hypothalamus
CRH ⊕
⊖
⊖
Anterior Pituitary
ACTH ⊕
Adrenal
Adrenal
Cortisol

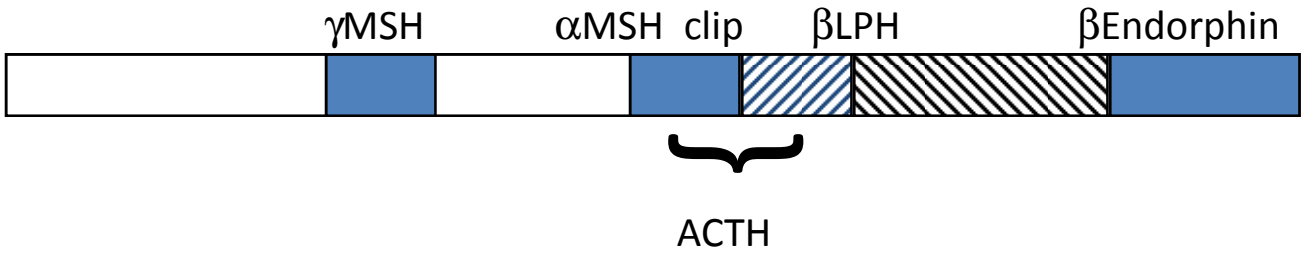
Regulation of Cortisol Release *cont*

Enhanced release can be caused by:

- physical trauma
- infection
- extreme heat and cold
- exercise to the point of exhaustion
- extreme mental anxiety

Some Additional Information:

- CRF acts through a Gs-protein coupled receptor, increasing cAMP levels in pituitary cells.
- ACTH is produced from proopiomelanocortin (POMC):



Action of ACTH on Cortisol Production

- **ACTH** binds to the ACTH receptor (Gs-coupled), resulting in **increased cyclic AMP** and **activation of PKA pathway**.
- **This results in:**

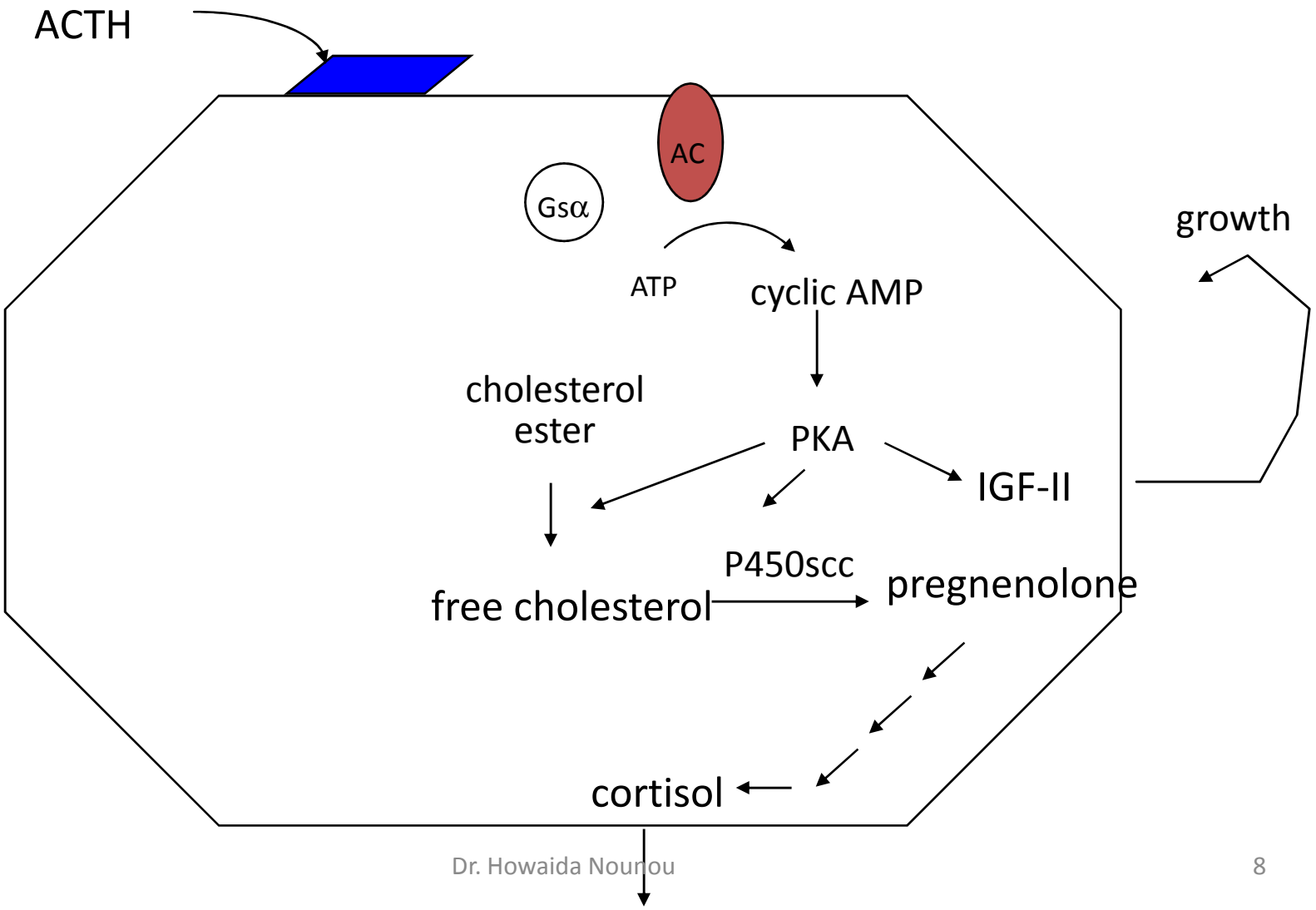
  1- increased conversion of cholesterol esters to free cholesterol

  2- increased expression of steroidogenic acute regulatory protein (STAR) (transfer cholesterol to the P450scc in the mitochondria)

  3- increased expression of P450 side chain cleavage

  4- increased production of IGF-II (stimulation of cell growth)

Action of ACTH on Cortisol Production



Daily Pattern of Cortisol Release

- Changes in cortisol levels occur about 30 minutes after corresponding changes in ACTH.
- Cortisol usually increases a few hours after sleep, then declines (it has a *diurnal rhythm of ACTH*).
- Also an increase shortly after wakening in the morning, and sporadically throughout the day.
- However, Cortisol levels are highest in the morning shortly after awakening, lowest in late afternoon& early evening.

Transport of Cortisol

- The majority of cortisol(90%) is bound to cortisol binding globulin(CBG) (also called transcortin). 4% bound to albumin.
- Only 6% of circulating cortisol is in free form, the biologically active fraction.
- Cortisol bound to CBG is not biologically active.
- CBG is produced by the liver.
- Production of CBG is increased by estradiol.

Metabolism of Cortisol

- Cortisol has a half-life of about 90 minutes.
- Cortisol is metabolized in the liver, where it is conjugated to a glucuronic acid.

  - conjugation increases solubility in water

  - conjugated hormone is excreted via the kidneys

Functions of Cortisol

- Cortisol is the primary glucocorticoid in humans.
- Cortisol is *essential* for life (long term).
- the net effects of cortisol are **catabolic**
- **Roles of cortisol**:

  1- carbohydrate metabolism

  2- permissive effects on body functions and development (epinephrine release, lipid metabolism)

  3- mineralocorticoid activity at the kidney (minor)

  4- anti-inflammatory compound

1. Effect of glucocorticoids: on carbohydrate metabolism

- stimulation of gluconeogenesis by the liver (rate increases 6 to 10 fold) prevents against hypoglycemia.
- enzymes required to convert amino acids into glucose are increased (increases PEPCK activity)

- decreases uptake of circulating glucose by muscle and adipose tissue

- increase in glycogen storage in liver cells

- Decreased glucose utilization by the cells

- **Overall, increases plasma glucose levels.**

Role in Carbohydrate Metabolism

- Cortisol release is inhibited by high blood glucose.

2. Effect of glucocorticoids : on protein metabolism

- * mobilization of amino acids from non-hepatic tissues (increase proteolysis of muscle protein for energy)
- decreased protein synthesis
- decreased amino acids transport into extrahepatic tissues (muscles)

3. Effect of glucocorticoids : on fat metabolism

- mobilization of fatty acids from adipose tissue . for energy (increase lipolysis).

- moderately enhance the oxidation of fatty acids (lower glucose utilization stimulates the cells to utilize energy from fatty acids)

Permissive Actions of Cortisol

- **Cortisol is required for**:

  - synthesis of epinephrine (adrenal medulla)

  - normal vasoconstriction (absence leads to decreased blood pressure)

  - normal glomerular filtration rate at kidney

Effects of Elevated Cortisol on Bone

- **High glucocorticoid levels cause decreased bone mass.** This is due to:
  - antagonizing the effects of vitamin D on calcium uptake
  - inhibiting collagen synthesis
  - synergizing with PTH to break down bone

Mineralocorticoid Activity of Cortisol

- Under normal conditions of blood pressure and sodium levels, cortisol has some mineralocorticoid activity (increasing sodium and water reabsorption at the kidney).
- Cortisol has low affinity for the mineralocorticoid receptor.
- However, much more cortisol than aldosterone is secreted.

Cortisol as an Anti-Inflammatory Agent

- The body responds to bacteria or tissue damage with an inflammatory response:

  1- increased production of chemicals such as **interleukins**

  2- these cause increased vasodilation and blood flow to the area

  3- increased blood flow brings in phagocytes, mast cells, and lymphocytes

  4- these cells trigger lysosomal reactions, histamine release, and collagenase production

- Result: destruction of bacteria; healing and remodeling of tissue.

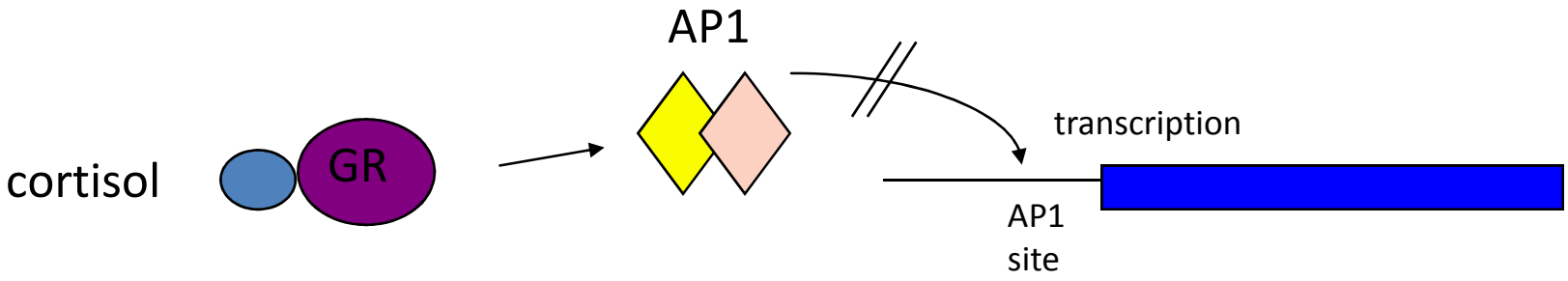
Cortisol and Chronic Stress

Prolonged exposure to high cortisol levels can lead to:

- break down of muscle,
- excessive epinephrine release,
- hyperglycemia,
- weakening of bone,
- destruction of the immune system,
- inhibition of reproductive function, and other complications.

Mechanisms of Cortisol Action

- The actions of cortisol are mediated through the glucocorticoid receptor (intracellular receptor).
- **Stimulates** transcription of target genes by interaction of bound receptor with GRE (glucocorticoid response element).
- **Inhibits** transcription of ***some* genes** by interaction of receptor with AP1 (activated protein 1).



Cushing's Syndrome

- Hypercortisolism
- Can be caused by:
- Primary
  - Adrenal tumors (adenoma, carcinoma)
- Secondary

  1-Pharmacological use of steroids.

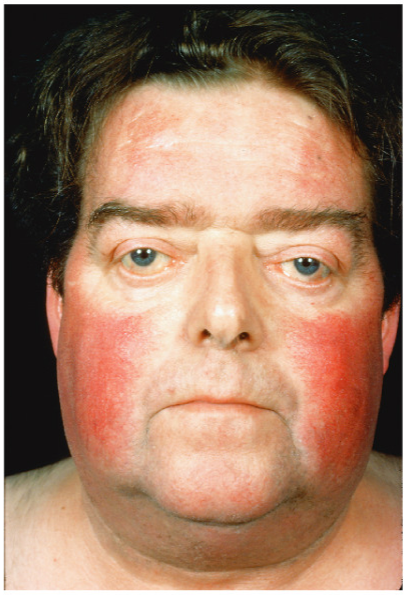
  2- ACTH secreting pituitary adenoma.

Excess of hormones of adrenal cortex

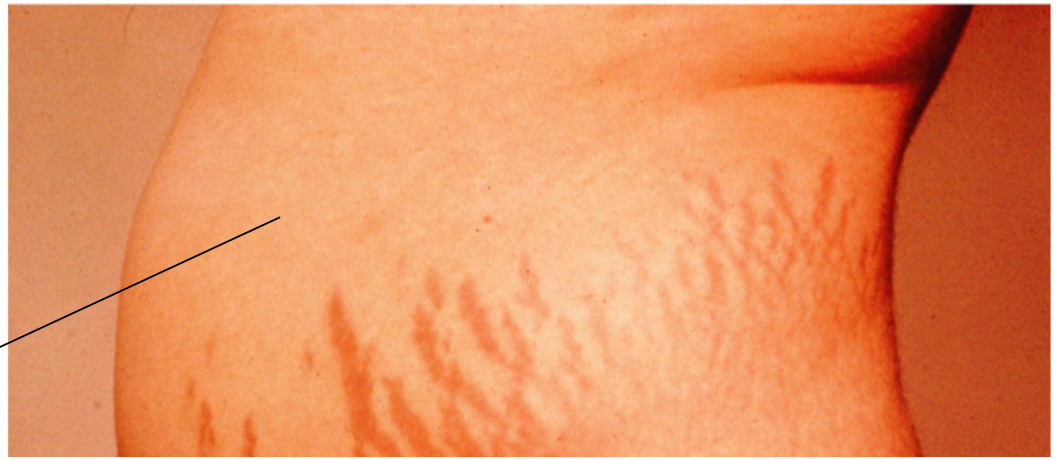
Symptoms include:

- redistribution of body fat – central obesity but thin limbs "buffalo hump", "moon" rounded face
- hypertension (high blood pressure)
- steroid (adrenal) diabetes – increased glucose concentration – „burn-out" of Langherhans's islets of pancreas
- decreased protein synthesis in immune system - infections
- osteoporosis(weak bones).
- fragile skin.
- mood swing.
- Excess protein catabolism cause muscle weakness.
- poor wound healing.

Cushing's Syndrome



"moon face"



striae

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