Adrenal Gland. Stress.

Adrenal gland

- Adrenal cortex
  - steroid hormones
    - Glucocorticoids (metabolism of carbohydrates and proteins)
    - Mineralocorticoids (maintenance of Na^+ balance, ECF volume)
    - Sex hormones
    - Controlled primarily by adrenocorticotropic hormone (ACTH)
    - Mineralocorticoids – control also via circulating factors (angiotensin II)
- Adrenal medulla
  - epinephrine, norepinephrine, and dopamine
  - Stimulation by the preganglionic nerve fibers
  - To prepare body for emergencies – „FIGHT OR FLIGHT“

Adrenal medulla

- 28 % of the mass
- Interlacing cords of densely innervated granule-containing cells that abut on venous sinuses
- Epinephrine-secreting cells
  - 90 %
  - Larger, less dense granules
  - Opioid peptides – precursor preproenkephalin
- Norepinephrine-secreting cells
  - 10 %
  - Smaller, very dense granules
- Cells secreted dopamine?
- Paraganglia
- Regulation
  - Emergency function of the sympathoadrenal system
  - It prepares the individual for flight or fight
  - Norepinephrine (not epinephrine) secretion is increased by emotional stresses

Adrenal cortex

- Zona glomerulosa – 15 %
- Zona fasciculata – 50 %
- Zona reticularis – approx. 7 %

- All three zones secrete corticosterone
- Zona glomerulosa
  - enzymatic mechanism for aldosterone biosynthesis
  - Production of new cortical cells when ZF/ZR are removed
- Zona fasciculata and zona reticularis – enzymatic mechanisms for cortisol and sex hormones biosynthesis
- Note – hypophysektomy – ZF and ZR = atrophy, ZG = unchanged, action of angiotensin II
- Fetal life
  - Large, under pituitary control
  - Three zones represent only 20 %
  - 80 % = fetal adrenal cortex – rapid degeneration at the time of birth
    - Synthesis and secretion of sulphate conjugates and androgens that are converted in placenta to estrogens

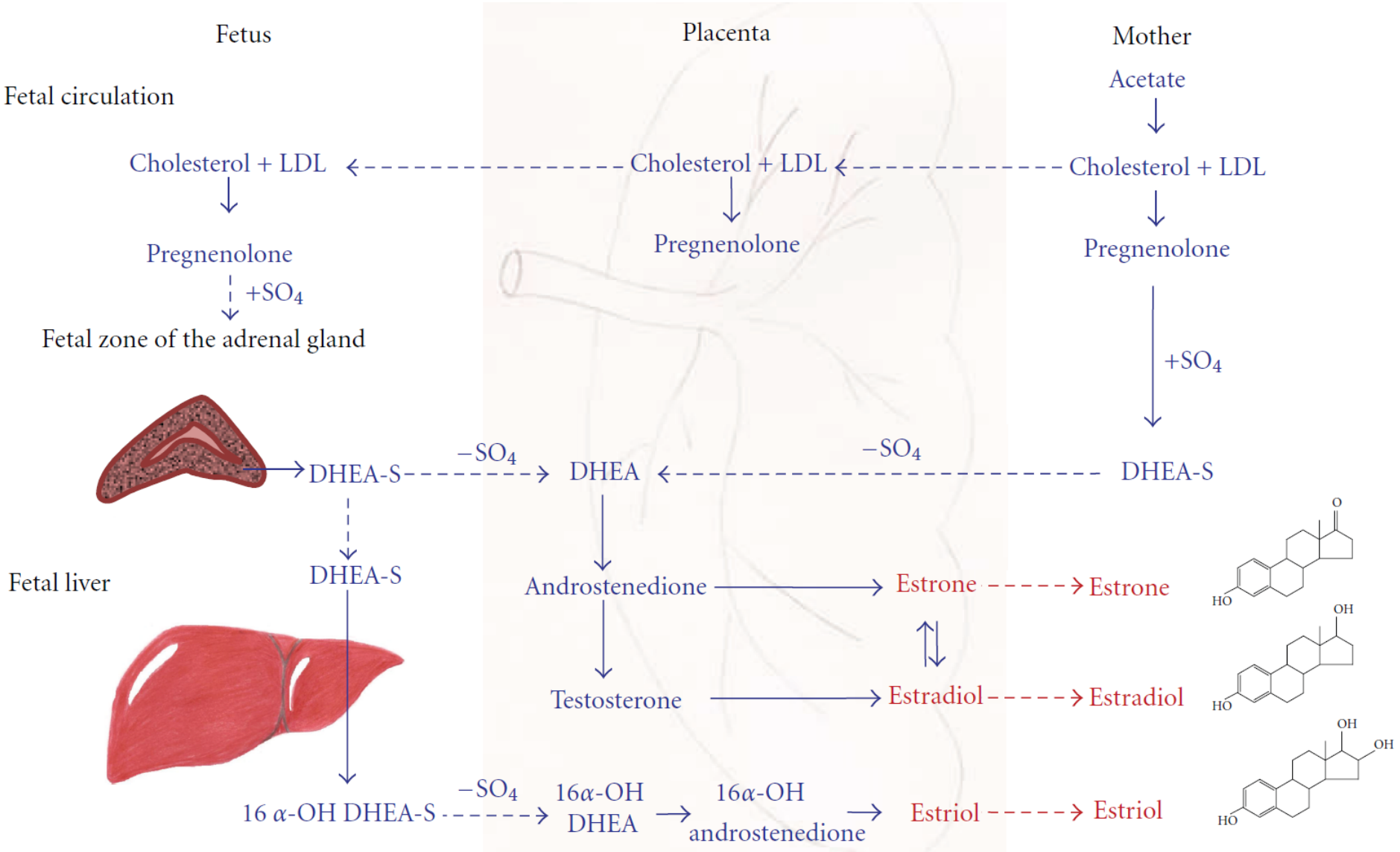


FIGURE 1: The role of maternal, placental, and fetal units in the biosynthesis of estrone, estradiol, and estriol. (LDL: low-density lipoproteins; DHEA-S: dehydroepiandrosterone sulfate; OH: hydroxyl). This figure has been modified from [8, 14].

Kaludjerovic J, Ward WE: **The Interplay between Estrogen and Fetal Adrenal Cortex.** ***Journal of Nutrition and Metabolism 2012. doi:10.1155/2012/837901***

Adrenal medulla - catecholamines

- Norepinephrine, epinephrine, dopamine
- Half-life about 2 min (methoxylation, oxidation)
- Urine – free or conjugated metabolites
- Biosynthesis
  - PNMT – brain, adrenal medulla, induced by glucocorticoids
  - High concentration of glucocorticoids in the blood draining from the cortex to the medulla
  - Changes in the concentration of glucocorticoids (hypophysectomy)
  - Glucocorticoids necessary for normal development of adrenal medulla
- Conjugation to sulphate
  - 95% of dopamine
  - 70% of epinephrine and norepinephrine
  - Inactive!
  - Very low levels at normal state
  - Levels of free catecholamines:
    - Norepinephrine 1.8 $nmol.L^{-1}$
    - Epinephrine 0.16 $nmol.L^{-1}$
    - Dopamine 0.23 $nmol.L^{-1}$
- Note
  - Intrinsic cardiac adrenergic cells (epinephrine)
  - Sympathetic ganglia/autonomic nervous systém (dopamine)

Chromogranin A

- Norepinephrine and epinephrine in granules with ATP and chromogranin A
- Secretion is initiated by acetylcholine released from preganglionic neurons that innervate secretory cells
- Acidic glycoprotein
- Exclusively expressed in the secretory dense core granules of most normal and neoplastic neuroendocrine cell types
- Elevated circulating CgA levels - various hormone-secreting or non-hormone secreting neuroendocrine tumors
- Predictor of bad prognosis in both midgut and pancreatic NETs

Adrenomedullin

- 52 AAS, slight homology with CGRP
- *ADM* gene
- Receptors
  - Calcitonin receptor-like (CALCRL)+RAMP2 (AM1)
  - Calcitonin receptor-like (CALCRL)+RAMP3 (dual CGRP/AM receptor AM2)
- potent vasodilator peptide
- Originally isolated from human pheochromocytoma
- in the human brain in high concentrations
- human adrenal, pheochromocytoma, ganglioneuroblastoma, and neuroblastoma
- neurotransmitter, neuromodulator or neurohormone?
- regulating angiogenesis and increasing the tolerance of cells to oxidative stress and hypoxic injury
- positive influence in diseases such as hypertension, myocardial infarction, chronic obstructive pulmonary disease and other cardiovascular diseases

Effects of epinephrine and norepinephrine

- Adrenergic receptors
  - α_{1-2}- and β_{1-3}-adrenergic receptors
  - 3 subtypes of α_1 and 3 subtypes of $\alpha_2$receptor

- Metabolic effects:
  - Glycogenolysis in skeletal muscle and liver via β-adrenergic receptors (cAMP) and via α-adrenergic receptors (intracellular Ca^{2+})
  - Mobilization of FFA
  - Increased plasma lactate
  - Stimulation of the metabolic rate
    - Due to cutaneous vasoconstriction and heat loss?/increased muscular activity
  - Stimulation (β) or inhibition (α) of secretion of insulin and glucagon
- Increase in alertness (anxiety, fear)
- Note – pheochromocytomas, pulse/continual secretion of E and NE, and hypertension

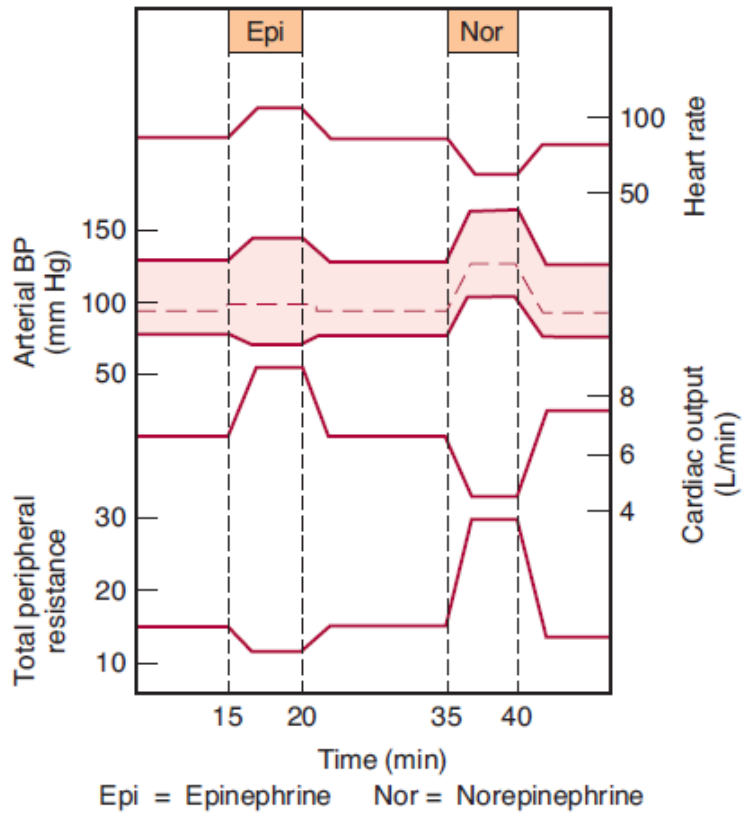


FIGURE 22–5 **Circulatory changes produced in humans by the slow intravenous infusion of epinephrine and norepinephrine.**

Barret, K.E., Boitano, S., Barman, S.M., Brooks, H.L. Ganong´s Review of Medical Physiology. 23rd Ed. McGraw-Hill Companies 2010

Alpha Receptors		Beta Receptors	
1. Vasoconstriction of a. Coronary arteries b. Veins 2. ↓motility of GIT smooth muscle cells			
α1 (postsynaptic)	**α2 (presynaptic)**	**β1 (postsynaptic)**	**β2 (postsynaptic)**
Gq protein coupled Activates **Phospholipase C** **PIP2 → IP3 + DAG**	**Gi protein** coupled Inhitbits **Adenyl Cyclase** **ATP → X → cAMP**	**Gs protein** coupled Activates **Adenyl Cyclase** **ATP → cAMP**	
1. Vasoconstriction of blood vessels of a. Skin b. GIT c. Kidney d. Brain 2. Contraction of smooth muscles of a. Ureter b. Vas deferens c. Urethral spinchter d. Uterus e. Cilliary body (mydiarisis) 3. Glucose metabolism a. Gluconeogenesis b. Glucolysis	1. Glucose metabolism a. Inhibits insulin release b. Stimulates glucagon release 2. Contraction of anal spinchter 3. Inhibits release of Norepinephrine	1. The heart a. ↑heart rate (+ chronotropic) b. ↑impulse conduction (+dromotropic) c. ↑contraction (+ inotropic) d. ↑ejection fraction 2. ↑renin release by Juxtaglomerular cells 3. ↑hunger a. ↑ghrelin release by stomach	1. Smooth muscle relaxation of a. Bronchus b. Bronchioles c. Detrusor muscle d. Uterine muscle 2. Contraction of urethral spinchter 3. ↑renin release by Juxtaglomerular cells 4. Glucose metabolism a. Inhibits insulin release b. Stimulate i. Gluconeogenesis ii. Glucolysis 5. Lipolysis 6. Thickened salivary secretion

Adrenergic receptors and cardiovascular system

- β_1(epinephrin, norepinephrin):
  - Increased force and rate on isolated heart
  - Increased myocardial excitability
- β_2(epinephrin):
  - Dilatation of blood vessels is skeletal muscle
- α_1(norepinephrin):
  - Vasoconstriction in almost all organs

Effect of dopamine

- Unknown physiologic function
  - Probably is involved in the regulation of fluid and electrolyte balance and systemic blood pressure
  - Lack of any of the five dopamine receptor subtypes (D1R, D2R, D3R, D4R, and D5R) results in hypertension
  - D1R, D2R, and D5R have been reported to be important in the maintenance of a normal redox balance
- Renal vasodilatation after i.v. application
- Vasodilatation in the mesentery
- Positively inotropic effect on the heart (β1 AR), increase in systolic pressure with no change in diastolic pressure
- Treatment of traumatic and cardiogenic shock

Adrenal cortex

- Hormones of AC = derivatives of cholesterol
  - C21 steroids, which have a two-carbon side chain at position 17
    - Mineralocorticoids (effects on Na+ and K+ excretion predominates)
    - Glucocorticoids (effects on glucose and protein metabolism predominates)
    - All have both activities!
  - C19 steroids, which have a keto or hydroxyl group at position 17
    - Androgenic activity
  - C18 steroids, which, in addition to a 17-keto or hydroxyl group, have no angular methyl group attached to position 10
- Hormones:
  - Aldosterone, deoxycorticosterone (mineralocorticoids)
  - Cortisol, corticosterone (glucocorticoids)
  - dehydroepiandrosterone (DHEA), androstenedione (androgenes)
- Differences between species!

Barret, K.E., Boitano, S., Barman, S.M., Brooks, H.L. Ganong´s Review of Medical Physiology. 23rd Ed. McGraw-Hill Companies 2010

Enzyme deficiencies

- Congenital adrenal hyperplasia (CAH)
  - Autosomal recessive diseases
  - Congenital deficits in enzymes
  - Deficient cortisol biosynthesis and secretion
  - Due to increased ACTH secretion
  - Ambiguous genitalia (exposure to high concentrations of androgenes in utero)
  - Most common
    - Deficiency in 21β-hydroxylase
    - 11β-Hydroxylase deficient CAH
    - 3β-Hydroxysteroid dehydrogenase II deficient CAH
    - 17α-hydroxylase deficiency CAH
- Congenital lipoid adrenal hyperplasia
  - Defect in the conversion of cholesterol to pregnenolone
- Adrenogenital syndrome

Transport and metabolism of glucocorticoids

- α globulin called transcortin or corticosteroid-binding globulin (CBG)
- Albumin (minor degree of binding)
- Half-life for cortisol 60 – 90 min
- Half-life for corticosterone 50 min
- Binding sites on CBG become saturated when the total plasma cortisol exceeds 200 $\mu g.L^{-1}$ = increase in unbound fraction!
- Estrogenes stimulate CBG synthesis
- CBG levels increased during pregnancy
- CBG levels depressed in cirrhosis, nephrosis, and multiple myeloma
- Increased level of CBD = new equilibrium!

- Metabolisation in liver
- Reduction of cortisol to dihydrocortisol and then to etrahydrocortisol, which is conjugated to glucuronic acid
- 11β hydroxysteroid dehydrogenase in some tissues
  - Type 1 - conversion of cortisol to cortisone and the reverse reaction
  - Type 2 - almost exclusively the one-way conversion of cortisol to cortisone
- About 10% of the secreted cortisol is converted in the liver to the 17-ketosteroid derivatives of cortisol and cortisone
  - Ketosteroids conjugated with sulphate
  - Excreted in urine

Transport and metabolism of aldosterone

- bound to protein to only a slight extent
- Short half-life (20 min)
- total plasma aldosterone level in humans about 0.06 $\mu g.L^{-1}$
- Conversion in liver to tetrahydroglucuronide derivative (40 %) and in liver and kidneys to an 18-glucuronide (acid-labile conjugate, 5 %)
- 1 % in urine in the free form

Transport and metabolism of 17-ketosteroids

- Major adrenal androgen - 17-ketosteroid dehydroepiandrosterone
- Androstenedione si minor.
- (“etiocholanolone fever”)

Physiologic effects of glucocorticoids

- Glucocorticoid receptor (GR, GCR, NR3C1)
  - Almost in all tissues
  - In the absence of hormone – complexes with Hsp70/90 + FKBP52
  - Neuroendocrine integration?
- Complexes = transcription factors
- DNA sequences = glucocorticoid response elements

Physiologic effects of glucocorticoids

- Intermediary metabolism
  - increased protein catabolism
    - reduction of the protein stores in essentially all body cells except those of the liver due to decreased protein synthesis and increased catabolism of proteins
    - decreased amino acid transport into extrahepatic tissues
    - Enhanced level of liver and plasma proteins (mobilization from extrahepatic tissues)
    - Depressed amino acid transport into muscle cells
    - Enhanced utilization of amino acids by liver
  - 6- 10-fold increase in gluconeogenesis
    - formation of carbohydrate from proteins and some other substances by liver
    - Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells
    - Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle.

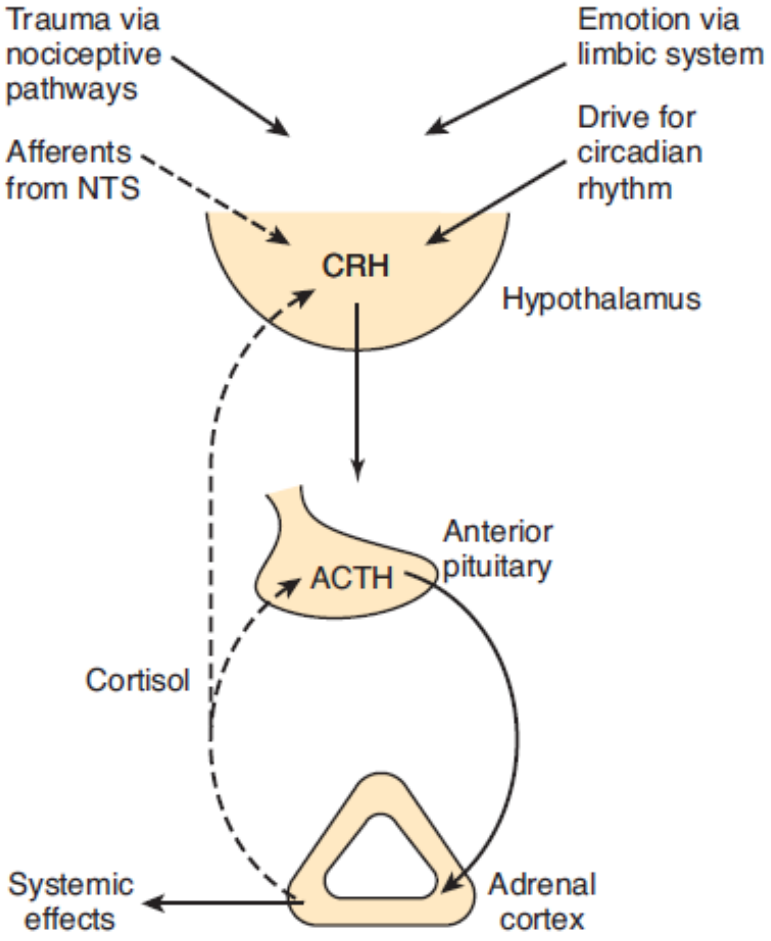
- an anti-insulin action in peripheral tissues
  - Decreased utilization of glucose by cells
  - Cortisol delays the rate of glucose utilization
  - Cortisol depress the oxidation of nicotinamide-adenine dinucleotide (NADH) to form NAD^+.
  - Elevated blood glucose concentration and “Adrenal Diabetes” = blood glucose concentrations rise
  - high levels of glucocorticoid reduce the sensitivity of many tissues (skeletal muscle and adipose tissue) to the stimulatory effects of insulin on glucose uptake and utilization
  - Impairment of high levels of FFA?
- Mobilization of FFA
  - Absence of α-glycerophosphate = increased mobilization of FFA?
  - Obesity? – excess stimulation of food intake

Physiologic effects of glucocorticoids

- Permissive action
  - = small amounts of glucocorticoids must be present for a number of metabolic reactions to occur
  - requirement for glucocorticoids to be present for glucagon and catecholamines to exert their calorigenic effects for catecholamines to exert their lipolytic effects, and for catecholamines to produce pressor responses and bronchodilation
- Glucocorticoids inhibit ACTH secretion
- Glucocorticoids restore vascular reactivity
- Glucocorticoids raise the glomerular filtration
- Resisting stress and inflammation (trauma, infection, intense cold/heat, surgery…)
  - Rapid mobilization of amino acids and fats = substrates for synthesis of new proteins and a source of energy
  - Synthesis of purines, pyrimidines, and creatine phosphate
  - Antiinflammatory effect of high levels of cortisol
    - Blocking the early stages of the inflammation process before inflammation even begins
    - Rapid resolution of the inflammation and increased rapidity of healing
    - Cortisol stabilizes the lysosomal membranes = most important anti-inflammatory effect
    - Cortisol decreases the permeability of the capillaries
    - Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells
    - Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly
    - Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells

Regulation of glucocorticoid secretion

- ACTH
  - Large polypeptide, 39 amino acids
  - A digested product (24 amino acids) with full activity
  - Under control of corticotropine-releasing factor (paraventricular nucleus of hypothalamus, 41 amino acids)
  - ACTH Activates Adrenocortical Cells to Produce Steroids by Increasing Cyclic Adenosine Monophosphate (cAMP)
    - Maximal effect in 3 minutes
    - Activation of protein kinase C = initial conversion of cholesterol to pregnenolone
- ACTH also enhances the production of adrenal androgens
- Physiologic stress increases production of ACTH and adrenocorticoid secretion
  - cortisol secretion is increased often as much as 20-fold
- Inhibitory effect of corticol on ACTH synthesis and secretion
- Note – circadian rhytm of glucocorticoid secretion
- Note - When ACTH is secreted by the anterior pituitary gland, several other hormones that have similar chemical structures are secreted simultaneously – Why?
  - = POMC



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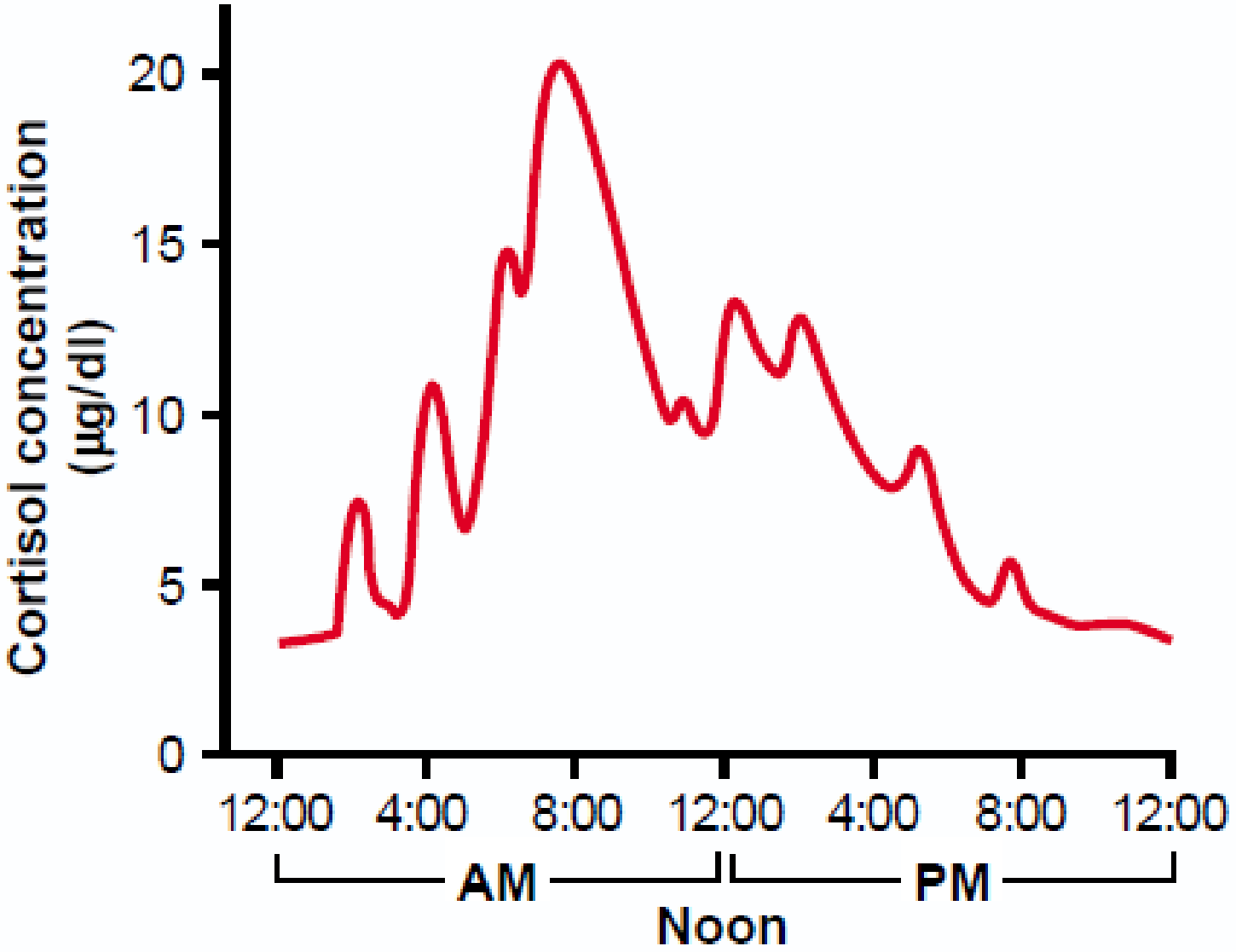

Guyton and Hall Textbook of Medical Physiology. 12th Ed. Elsevier 2006

Effect of mineralocorticoids

- Cytoplasmic receptor (=mineralocorticoid receptor or MR, MLR, MCR)
- equal affinity for mineralocorticoids and glucocorticoids
- expressed in many tissues, such as the kidney, colon, heart, central nervous system (hippocampus), brown adipose tissue
- its activation = expression of proteins regulating ionic and water transports (mainly the epithelial sodium channel or ENaC, Na^+/K^+ pump, serum and glucocorticoid induced kinase or SGK1, a serine-threonine protein kinase)
- SGK1 increases ENaC aktivity
- Nongenomic action?
  - Increased activity of membrane Na^+–K^+ exchangers
  - 10 – 30 min
- Receptor is activated by both mineralocorticoids a glucocorticoids

Effect of mineralocorticoids (MC)

- Aldosterone
- increase the reabsorption of Na+ from the urine, sweat, saliva, and the contents of the colon = retention of Na^+ in the ECF
  - This expands ECF volume (simultaneous osmotic absorption of almost equivalent amounts of water) = final change in sodium concentration is very small
  - ! Na^+ are exchanged for K^+ and H^+ in the renal tubules, producing a K^+ diuresis and an increase in urine acidity
  - Aldosterone stimulates transport of potassium from the extracellular fluid into most cells of the body
    - decrease in the plasma potassium concentration
    - alteration of the electrical excitability of the nerve and muscle fiber membranes
    - deficient aldosterone = cardiac toxicity, including weakness of heart contraction and development of arrhythmia
- MC act primarily on the principal cells (P cells) of the collecting ducts

Apparent mineralocorticoid excess syndrome

- autosomal recessive disorder causing hypertension (high blood pressure) and hypokalemia
- Inhibition or absence of 11β-hydroxysteroid dehydrogenase type 2
  - Cortisol with marked mineralocorticoid effect
  - Clinical picture of hyperaldosteronism
  - Plasma aldosterone level as well as their plasma renin activity is low
  - Licorice!!!! - glycyrrhetinic acid as an inhibitor of 11β-hydroxysteroid dehydrogenase type 2

Regulation of aldosterone secretion

- Effect of ACTH
  - necessary for aldosterone secretion but has little effect in controlling the rate of secretion
- Increased potassium ion concentration in the extracellular fluid greatly increases aldosterone secretion
- Increased activity of the renin-angiotensin system (increased levels of angiotensin II) greatly increases aldosterone secretion
- Increased sodium ion concentration in the extracellular fluid very slightly decreases aldosterone secretion

Adrenocortical hyper- and hypofunctions in human

- Adrenogenital syndrome - excess androgen secretion
- Cushing syndrome - excess glucocorticoid secretion
  - a moon-faced, plethoric appearance, with trunk obesity, purple abdominal striae, hypertension, osteoporosis, protein depletion, mental abnormalities, and, frequently, diabetes mellitus
- Hyperaldosteronism - excess mineralocorticoid secretion
  - K^+ depletion and Na^+ retention, usually without edema but with weakness, hypertension, tetany, polyuria, and hypokalemic alkalosis
  - primary hyperaldosteronism; Conn syndrome - adenoma of the zona glomerulosa, unilateral or bilateral adrenal hyperplasia, adrenal carcinoma
  - Secondary hyperaldosteronism with high plasma renin - cirrhosis, heart failure, and nephrosis
- Addison disease - primary adrenal insufficiency
- Secondary adrenal insufficiency - pituitary diseases that decrease ACTH secretion
- Tertiary adrenal insufficiency - hypothalamic disorders disrupting CRH secretion
- Hyporeninemic hypoaldosteronism - patients with renal disease and a low circulating renin level
- Pseudohypoaldosteronism - resistance to the action of aldosterone