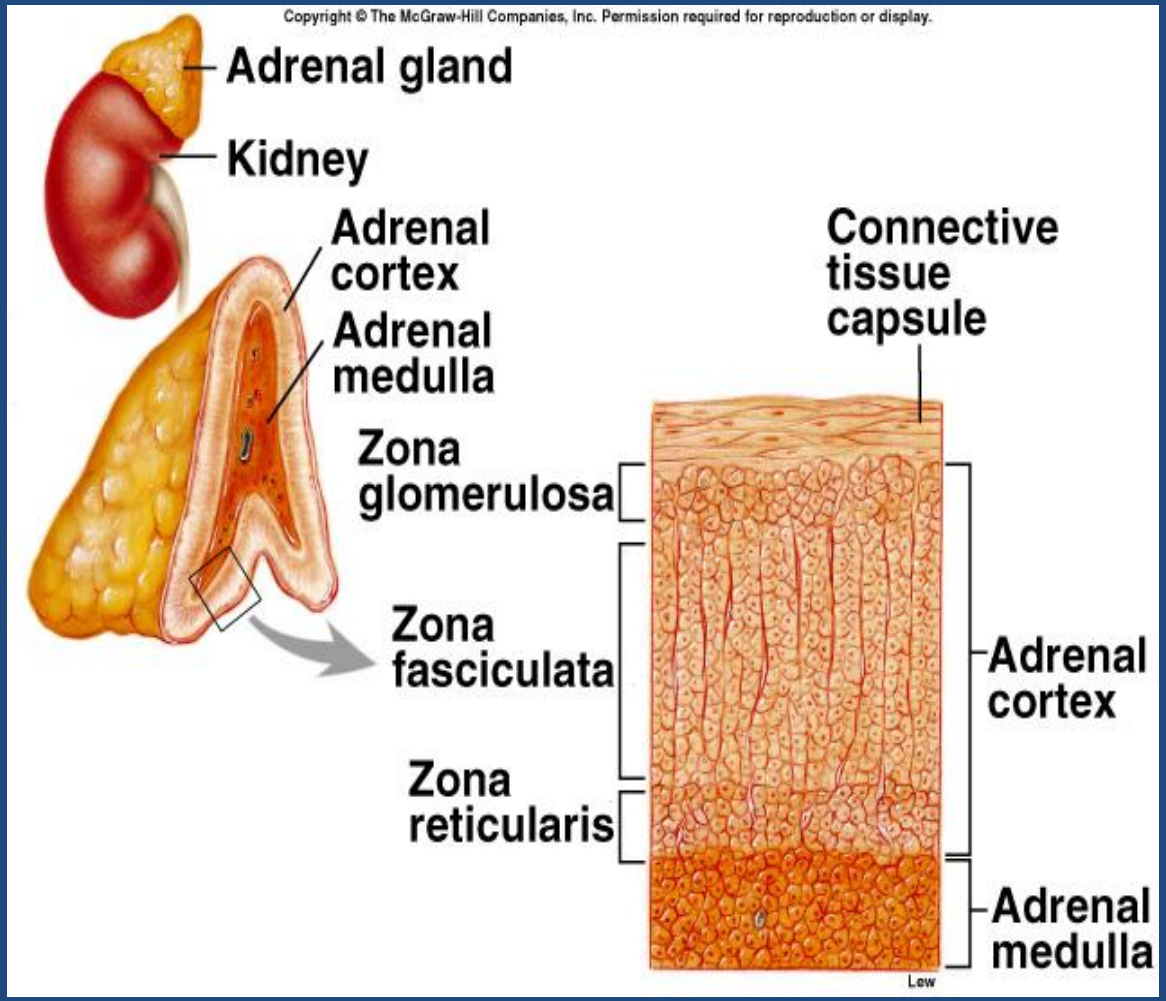
ADRENAL GLANDS

Adrenal Glands

- Paired organs that cap the kidneys.
- Each: outer cortex and inner medulla.



The Adrenal Cortex

Adrenal Cortex: 3 Zones (Glomerulosa, Fasiculata, Reticularis).

1. **Zona Glomerulosa:** aldosterone, deficient in 17 α-hydroxylase
2. **Zona Fasiculata:** cortisol + androgens, ACTH control (acute)
3. **Zona Reticularis:** surrounds medulla, cortisol + androgens, ACTH control (prolonged stimulation)

Steroidogenesis

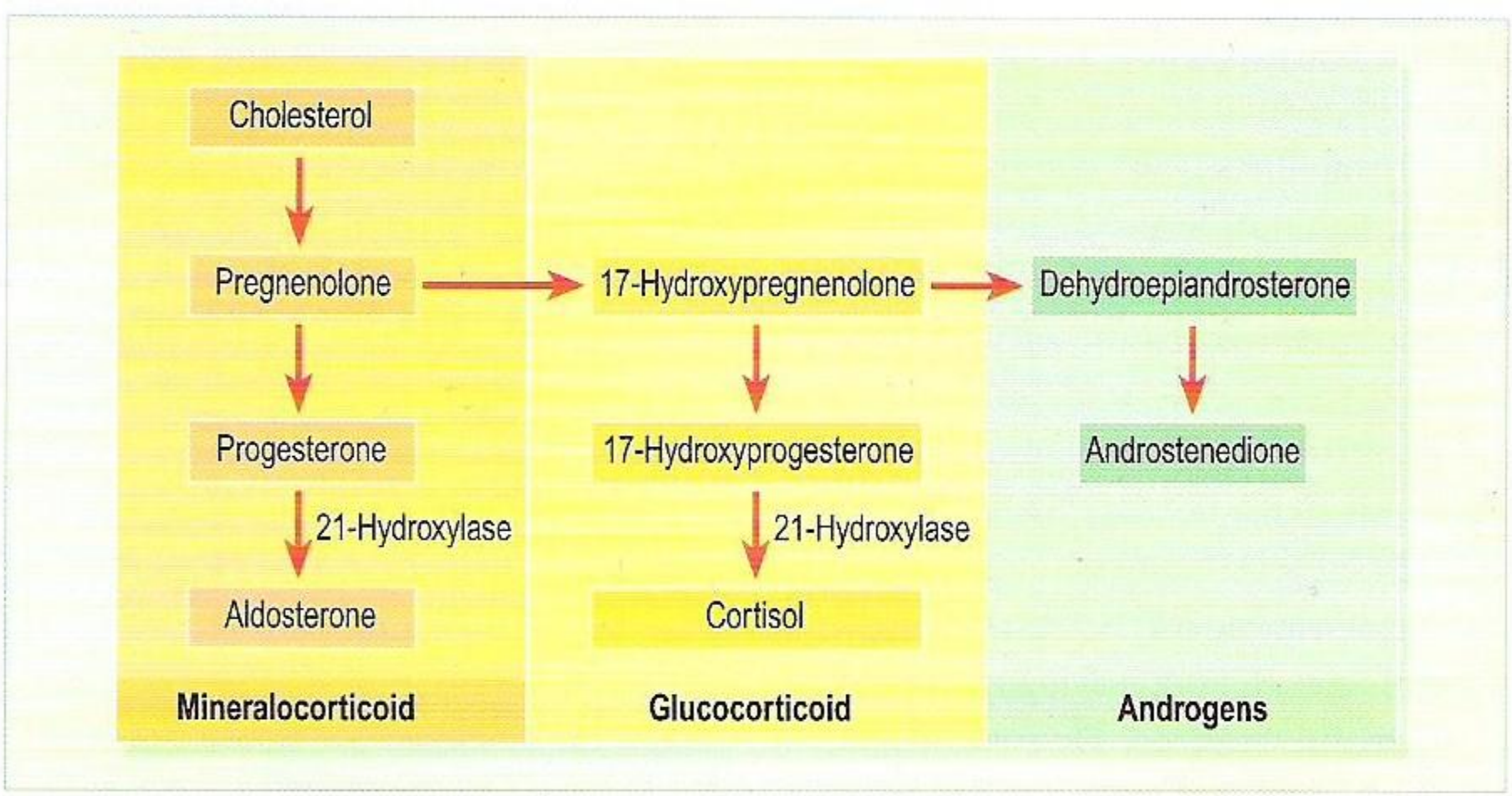


Fig. 2 **The major adrenal steroids and pathways. Note that not all precursors or pathways are shown.**

Synthesis of adrenal hormones

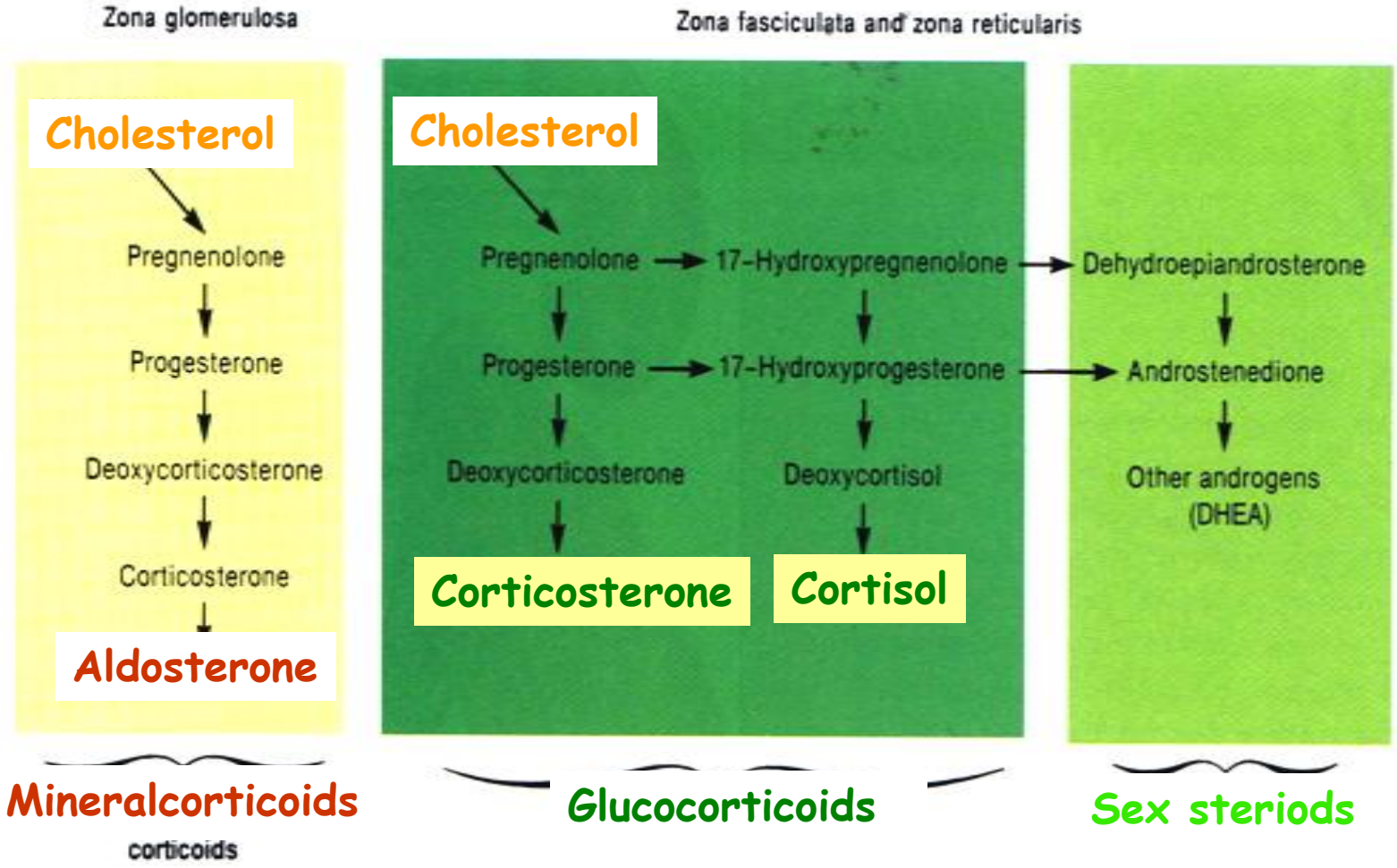
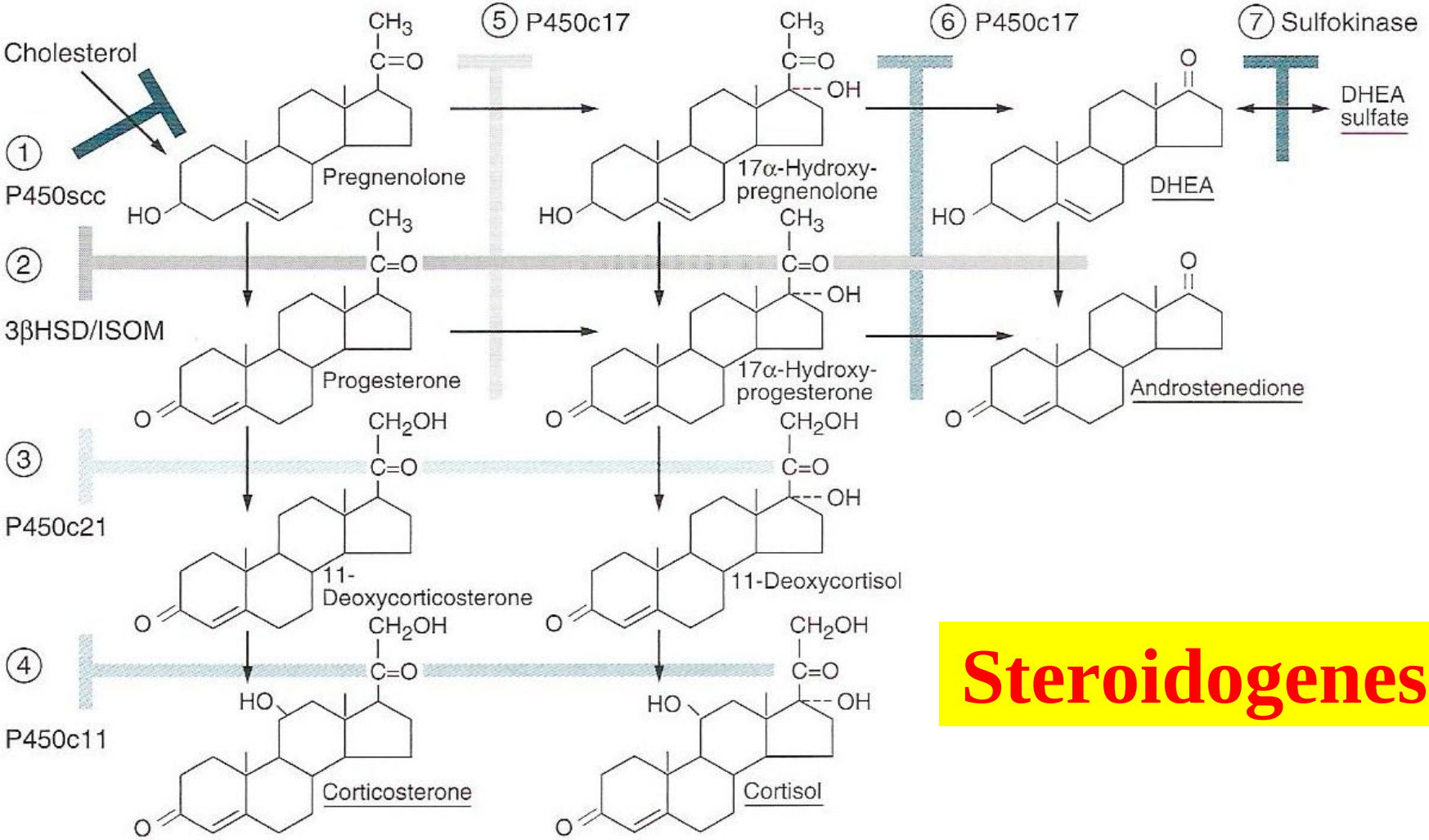


Figure 11.19 Simplified pathways for the synthesis of steroid hormones in the adrenal cortex. The adrenal cortex produces steroids that regulate Na^+ and K^+ balance (mineralocorticoids), steroids that regulate glucose balance (glucocorticoids), and small amounts of sex steroid hormones. (DHEA = dehydroepiandrosterone.)



Steroidogenesis

Figure 9–4. Steroid biosynthesis in the zona fasciculata and zona reticularis of the adrenal cortex. The major secretory products are underlined. The enzymes for the reactions are numbered on the left and at the top of the chart, with the steps catalyzed shown by the shaded bars. ① P450scc, cholesterol 20,22-hydroxylase:20,22 desmolase activity; ② 3βHSD/ISOM, 3-hydroxysteroid dehydrogenase:δ^5-oxosteroid isomerase activity; ③ P450c21, 21α-hydroxylase activity; ④ P450c11 = 11β-hydroxylase activity; ⑤ P450c17, 17α-hydroxylase activity; ⑥ P450c17, 17,20-lyase/desmolase activity; ⑦ sulfokinase. (See also Figures 7–1, 9–2, 10–4, and 11–13.) (Modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 16th ed. McGraw-Hill, 1993.)

Biosynthesis of Cortisol and Adrenal Androgens

Zones

- Adrenal cortex: 2 separate units (glomerulosa + inner 2 zones)
- Aldosterone: regulated by rennin - angiotensin system + K^+

Cholesterol

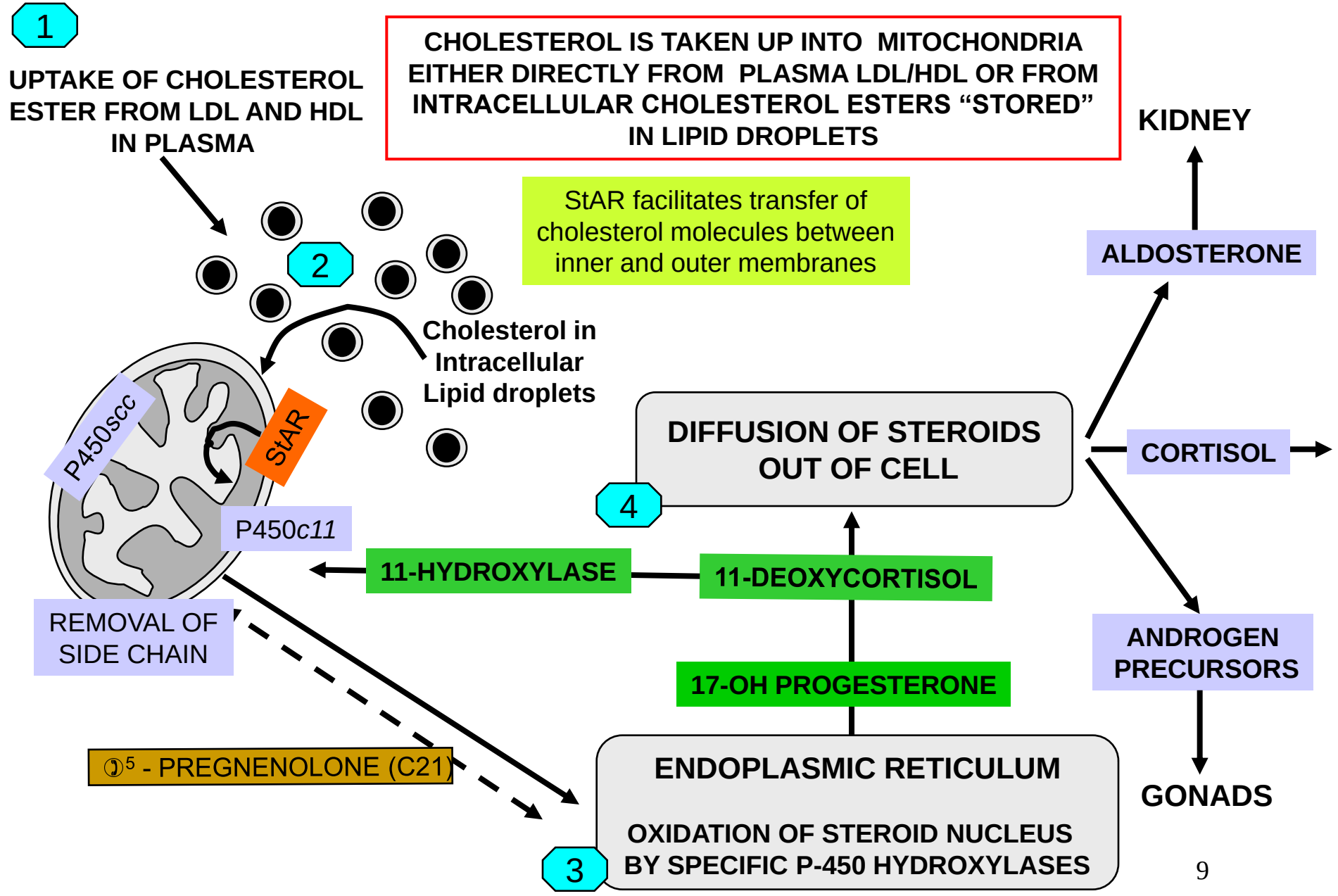
- Precursor of steroid hormones: cholesterol .
- Sources: LDL (80%), free cholesterol (small pool)- cholesterol esters (stored), de novo synthesis.
- StAR (Steroidogenic acute regulatory protein): cholesterol transport from outer to inner mitochondrial membrane.

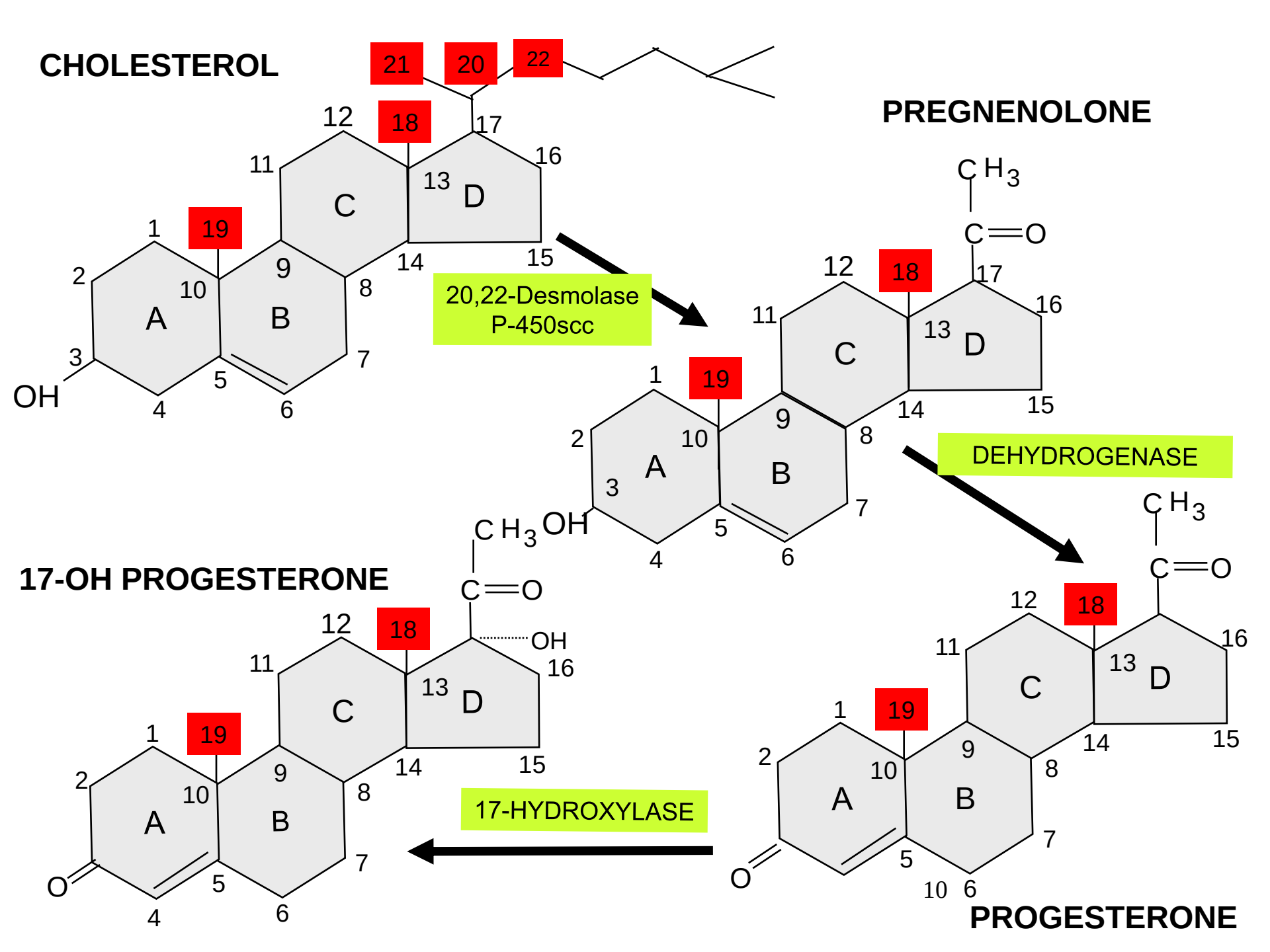
Biosynthesis of Cortisol and Adrenal Androgens

Steroidogenesis

- **Steroidogenic enzymes:**
  - Cytochrome P_{450} Oxygenases
  - Mixed function oxidases (O_2 + NADPH)
- **Mitochondria:**
  - P_{450scc} (cholesterol side chain cleavage)
  - P_{450c11} (11β-hydroxylation: cortisol, corticosterone) in zona fasiculata and reticularis.
- **Endoplasmic reticulum:**
  - P_{450c17} (17α-hydroxylase + 17,20 lyase)
  - P_{450c21} (21-hydroxylation)
  - Non-P_{450} microsomal enzyme: 3β-HDS: $\Delta^{4,5}$-isomerase

SYNTHESIS AND "SECRETION" OF STEROID HORMONES BY ADRENAL CORTEX

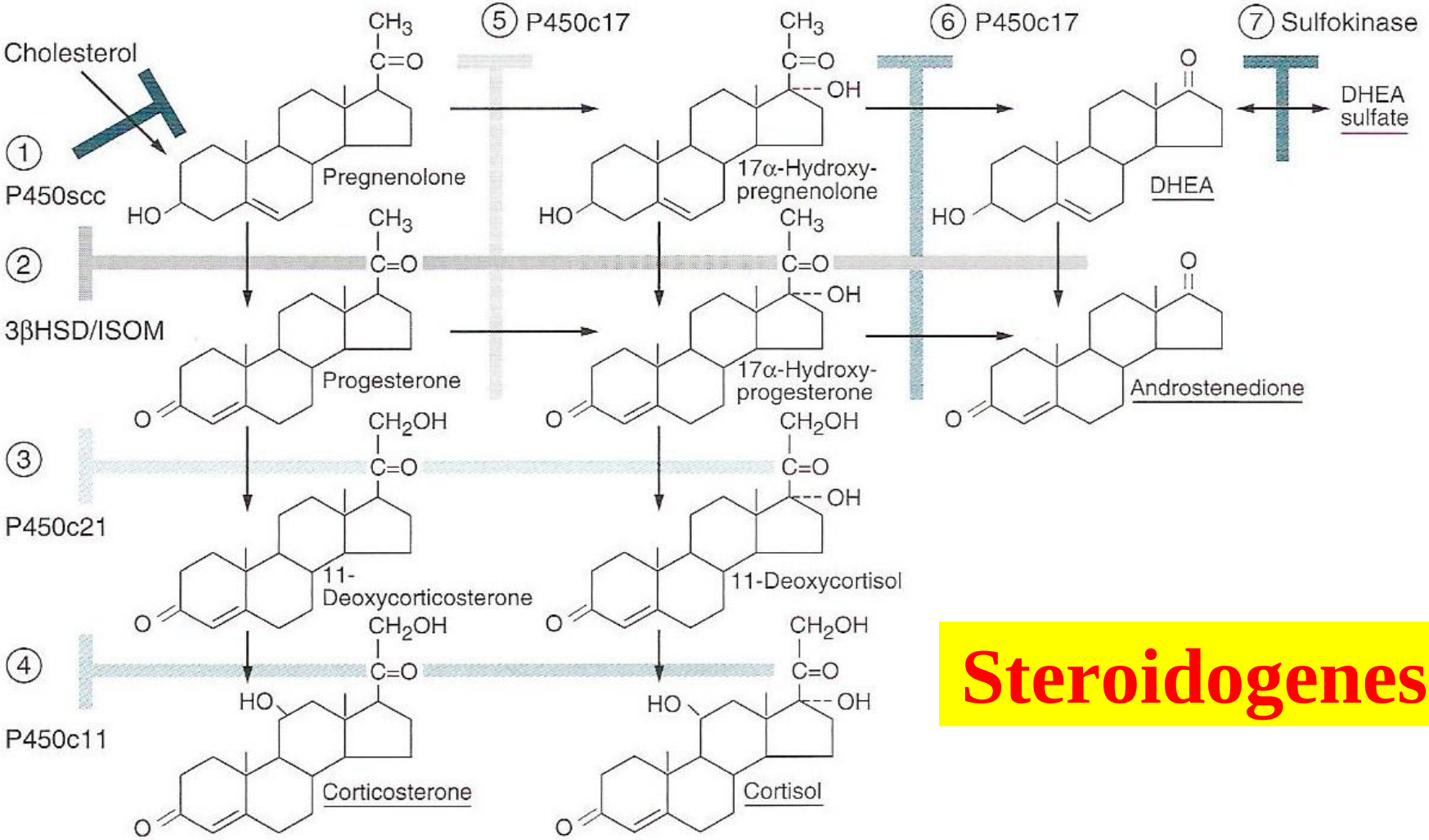



CHOLESTEROL
PREGNENOLONE
20,22-Desmolase
P-450scc
DEHYDROGENASE
17-OH PROGESTERONE
17-HYDROXYLASE
PROGESTERONE

Biosynthesis of Cortisol and Adrenal Androgens

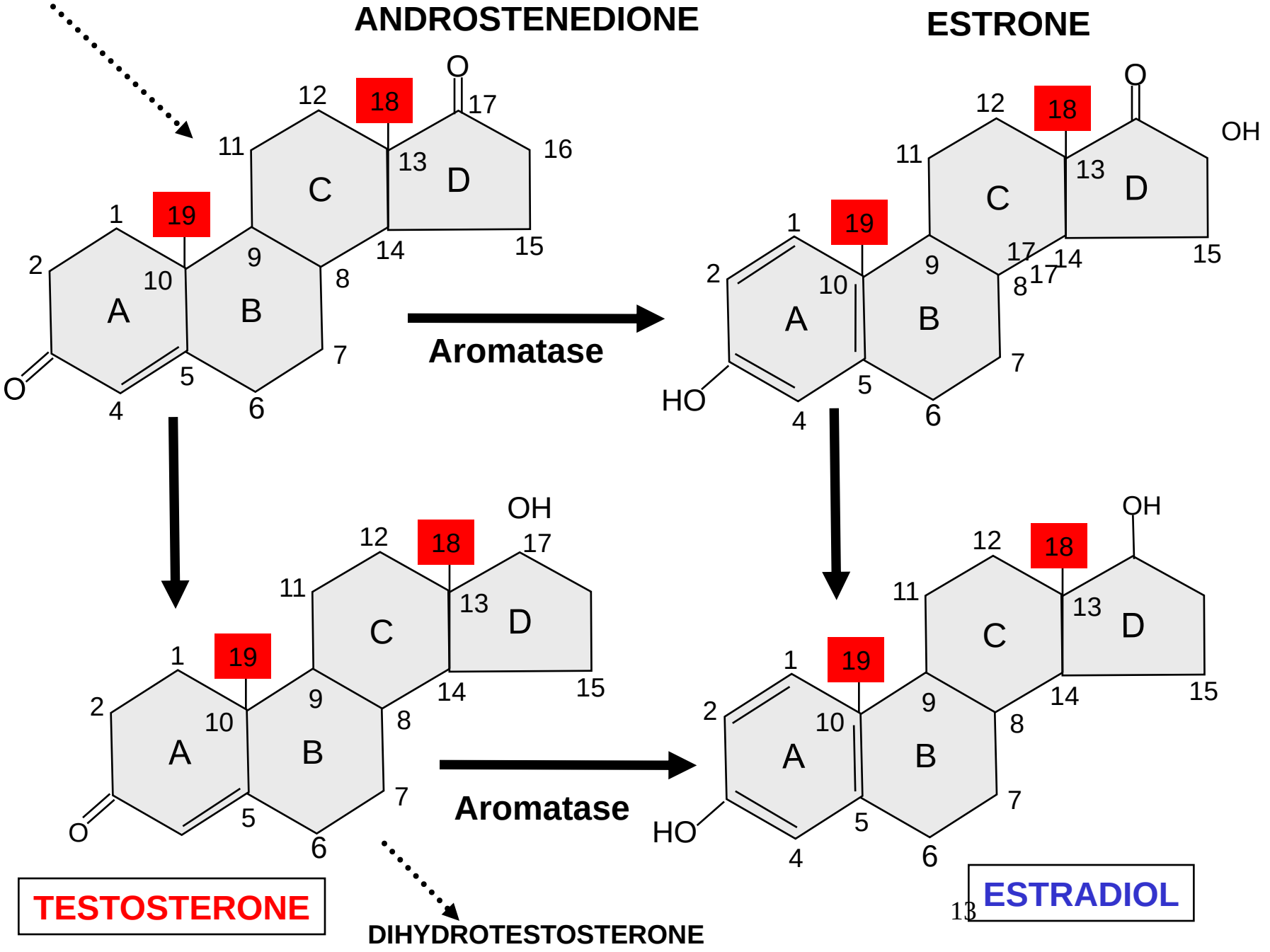
Androgen Synthesis

- Requires 17α-hydroxylation
- 17α-OH pregnenolone →DHEA→ DHEA-sulfate (ER)
- DHEA and 17α-OH progesterone → androstenedione
- Androstenedione → Testosterone (peripheral tissue).



Steroidogenesis

Figure 9–4. Steroid biosynthesis in the zona fasciculata and zona reticularis of the adrenal cortex. The major secretory products are underlined. The enzymes for the reactions are numbered on the left and at the top of the chart, with the steps catalyzed shown by the shaded bars. ① P450scc, cholesterol 20,22-hydroxylase:20,22 desmolase activity; ② 3βHSD/ISOM, 3-hydroxysteroid dehydrogenase:δ^5-oxosteroid isomerase activity; ③ P450c21, 21α-hydroxylase activity; ④ P450c11 = 11β-hydroxylase activity; ⑤ P450c17, 17α-hydroxylase activity; ⑥ P450c17, 17,20-lyase/desmolase activity; ⑦ sulfokinase. (See also Figures 7–1, 9–2, 10–4, and 11–13.) (Modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 16th ed. McGraw-Hill, 1993.)


ANDROSTENEDIONE
ESTRONE
Aromatase
Aromatase
TESTOSTERONE
DIHYDROTESTOSTERONE
ESTRADIOL
A
B
C
D
HO
OH
O

Biosynthesis of Cortisol and Adrenal Androgens

A. Secretion of ACTH and CRH

ACTH: major regulator of cortisol and adrenal androgen.

ACTH: under CRH, AVP.

B. ACTH Effects on the Adrenal Cortex

ACTH: ↑steroid secretion and synthesis.

↑ Adrenal hypertrophy and hyperplasia.

C. ACTH and Steroidogenesis

↑cAMP → activation of phosphoprotein kinases

↑Cholesterol esterase → ↑free cholesterol

↑ LDL uptake

↑ Cholesterol delivery to P_{450scc}

Biosynthesis of Cortisol and Adrenal Androgens …

D. Neuroendocrine Control

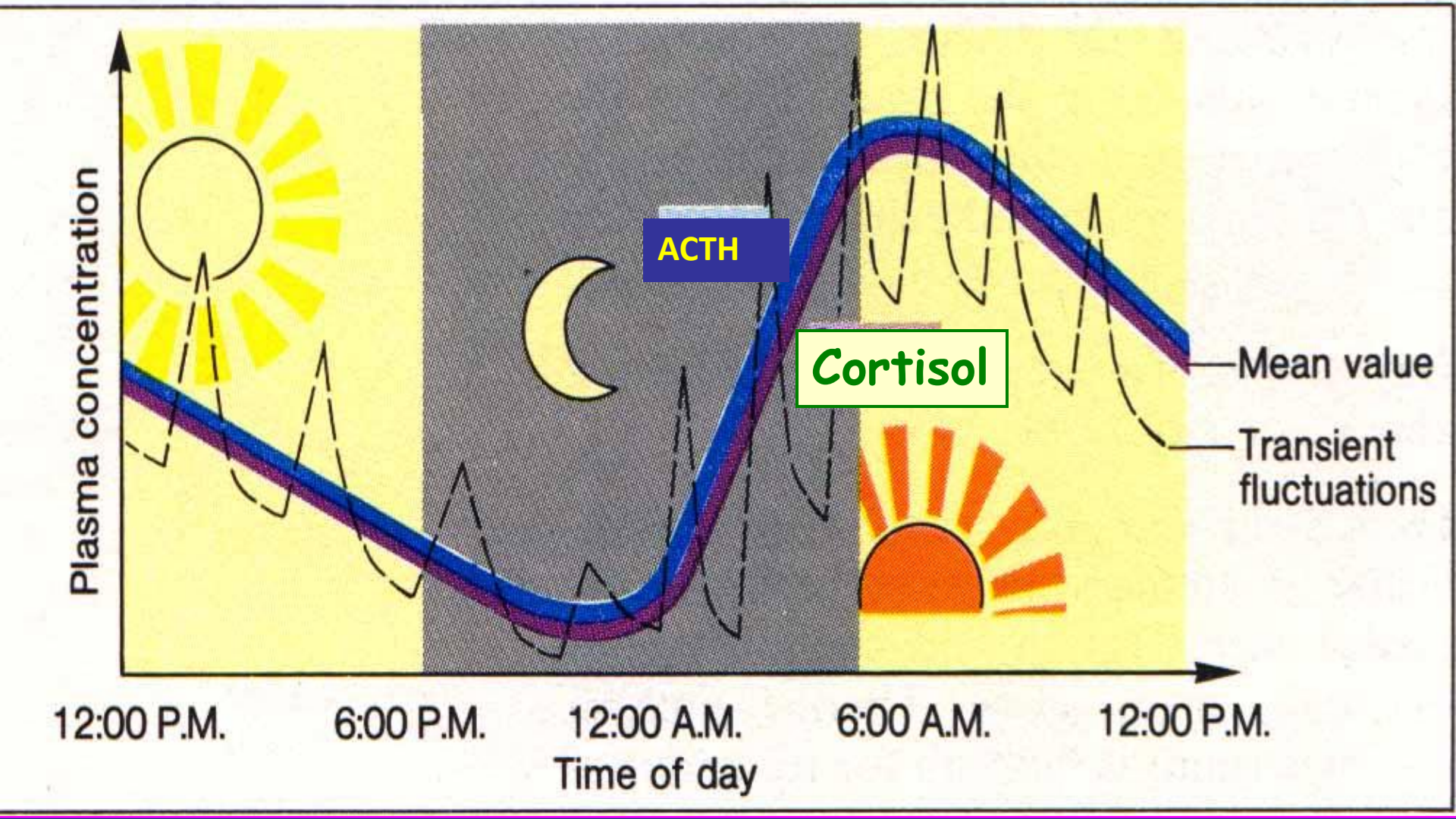
Cortisol levels parallel ACTH.

1. Circadian rhythm: fast, delayed
   - Low cortisol in late evening, high 6-8hr after sleep
   - Altered circadian rhythm by: stress, CNS and pituitary.
2. Stress abolishes circadian rhythm.
3. Feedback inhibition: Glucocorticoids ↓CRH - ACTH

E. ACTH Effects on Androgens:

DHEA, androstenedione, circadian rhythm.

"Diurnal Rhythm"



Circulation of Cortisol and Adrenal Androgens

Plasma Binding Proteins

- **Cortisol**:
  1. 10% free.
  2. 75% bound to Corticosteroid–Binding Globulin (CBG or transcortin).
  3. 15% albumin.
- **Androgens**: mainly to albumin
- **Salivary Cortisol**: free cortisol

Circulation of Cortisol and Adrenal Androgens …

A. Cortisol Binding

1. CBG

- Produced by liver.
- ↑Estrogen (pregnancy, estrogen contraceptives), hyperthyroidism, diabetes →↑CBG.
- Hypothyroidism, familial CBG deficiency, protein deficiency (liver disease, nephritic syndrome) →↓CBG.

2. Albumin

- Greater capacity, lower affinity for cortisol
- Dexamethasone75% to albumin.

B. Androgen Binding

1. Androstenedione , DHEA, DHEA-S: weakly to albumin.
2. Testosterone: to sex hormone–binding globulin (SHBG).

Metabolism of Cortisol and Adrenal Androgens

Steroid metabolism

Inactive, water soluble, conjugation with glucoronide or sulfate → kidney

Cortisol Metabolism

Hepatic Conversion

cortisol → dihydrocortisol → tetrahydrocortisol

→ cortisone

Hepatic conjugation

Cortisol and cortisone metabolites with glucocuronic acid → excreted in urine.

Adrenal Androgen metabolism

Inactivation: glucuronides or sulfates

Activation: Androstenedione → testosterone → DHT

Metabolism of Cortisol and Adrenal Androgens …

Cortisol–Cortisone Shunt

- Cortisol binds to mineralocorticoid receptors in kidney.
- No effect on Na^+ + K^+, cortisol → inactive cortisone by 11β-HSD type 2.
- In liver, skin, placenta, adipose tissue:

  Cortisone → cortisol by 11β-HSD type 1 (effective cortisone cream).

Cushing's syndrome

Pre-receptor conversion of cortisol is overwhelmed in kidney → hypertension, hypokalemia.

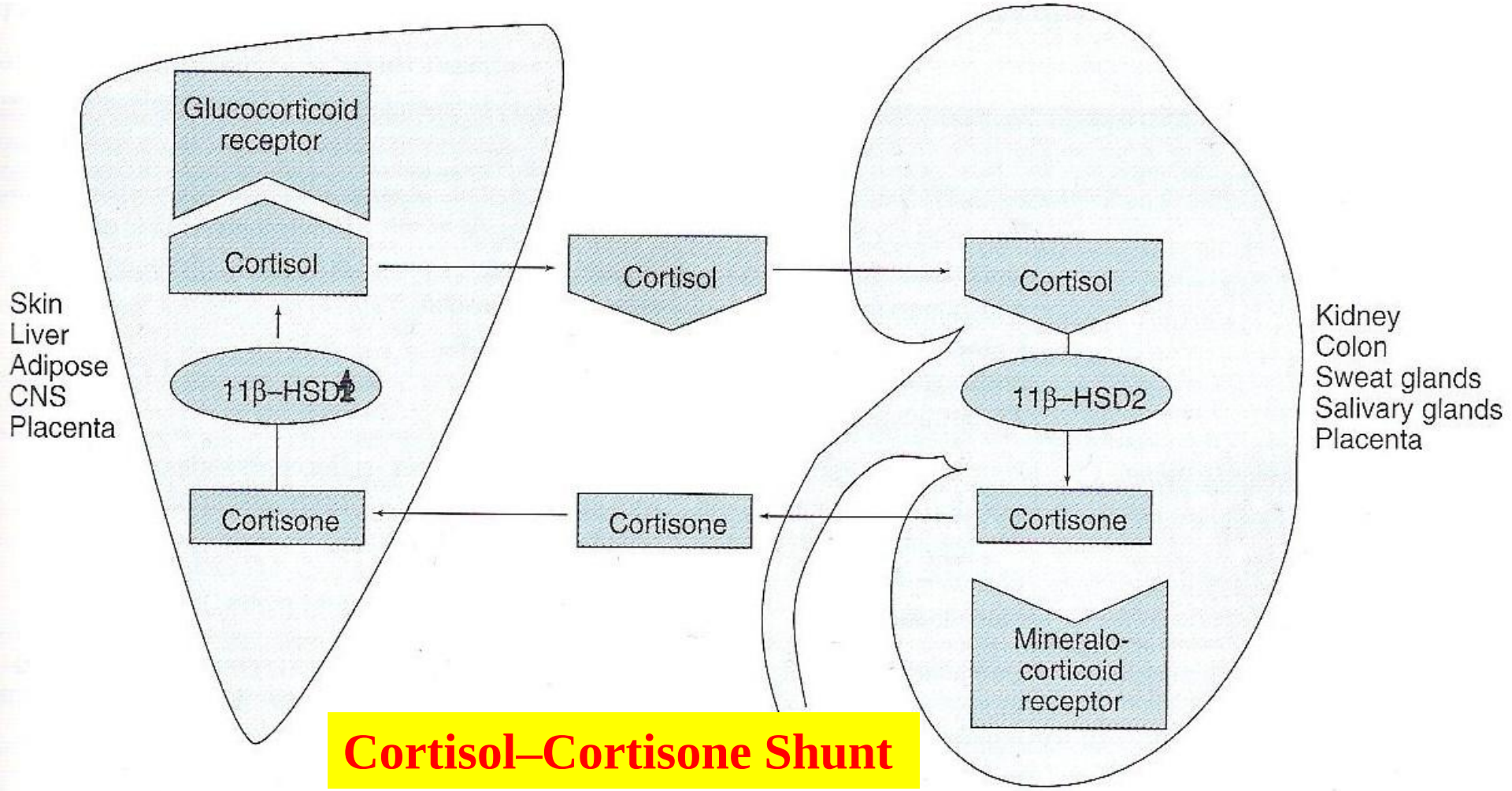


Figure 9–8. Cortisol-cortisone shunt. Contrasting functions of the isozymes of 11β-HSD. 11β-HSD2 is an exclusive 11β-dehydrogenase that acts in classical aldosterone target tissues to exclude cortisol from otherwise nonselective mineralocorticoid receptors. Inactivation of cortisol also occurs in placenta. 11β-HSD1 is a predominant 11β-reductase in vivo that acts in many tissues to increase local intracellular glucocorticoid concentrations and thereby maintain adequate exposure of relatively low affinity glucocorticoid receptors to their ligand. (Modified from Seckl JR, Walker BR: Minireview: 11beta-hydroxysteroid dehydrogenase type 1—a tissue-specific amplifier of glucocorticoid action. Endocrinology 2001;142:1371.)

Biological Effects of Adrenal Steroids

Glucocorticoids

- Cytosolic receptors: include hsp 90
- Synthetic glucocorticoids: e.g. dexamethasone, prednisone (higher activity).
  - higher affinity for glucocorticoid receptors
  - lower plasma clearance.
  - Negligible mineralocorticoid effects.
- Agonists: cortisol, corticosterone and aldosterone.
- Antagonists: progesterone, 17β estradiol, T, DOC.

  RU486 (mifepristone): glucocorticoid antagonist (treatment of Cushing's).

Biological Effects of Adrenal Steroids …

Intermediary Metabolism

- Glucocorticoids ↓DNA synthesis, ↓RNA and protein synthesis (most tissues).
- ↑ Protein catabolism: deleterious effects on muscle, bone, connective tissue, lymphatic tissues.
- ↑ RNA and protein synthesis in **liver**.

Biological Effects of Adrenal Steroids …

Intermediary Metabolism

A. Hepatic Glucose Metabolism

- Glucocorticoids ↑ hepatic gluconeogenesis (↑ PEP-CK, G-6-Pase)
- Permissive effects on glucagon.
- ↓ Peripheral amino acid uptake, protein synthesis, ↑lactate release (muscles), ↑ lipolysis.
- ↑ Glycogen synthetase (insulin - dependent).

B. Peripheral Glucose Metabolism

Glucocorticoids ↓ glucose uptake (muscle and adipose tissue).

C. Effect on Adipose Tissue

- ↑ Lipolysis (release of glycerol + FFA).
- Glucocorticoid excess: ↑ fat deposition (due to ↑appetite, hyperinsulinemia).

Biological Effects of Adrenal Steroids …

1. Fed state: minimal effects of glucocorticoids.

   Fasting: maintenance of plasma glucose (gluconeogenesis) ↑ glycogen deposition.
2. ↑ Hepatic glucose production, RNA, protein synthesis.
3. Catabolic effects on muscle: ↓ glucose uptake,

   ↓ protein synthesis, ↑ release of amino acids.
4. Adipose tissue: ↑ lipolysis.
5. Glucocorticoid deficiency: hypoglycemia.

   Glucocorticoid excess: hyperglycemia, hyperinsulinemia, muscle wasting, weight gain, abdominal fat distribution.

Biological Effects of Adrenal Steroids …

A. Connective Tissue: ↑ glucocorticoids: loss of collagen and connective tissue, inhibit fibroblasts, thinning of the skin, easy bruising, poor wound healing.

B. Bone: ↑glucocorticoids: ↓bone formation (↓cell proliferation, synthesis of RNA, protein, collagen).

↑ Bone-resorbing cells.

↑PTH and 1,25 $(OH)_2$ D_3 activity.

C. Calcium Metabolism

Glucocorticoids ↓ intestinal Ca absorption →↑ PTH

↑ PTH release directly.

Intestinal effect not through vitamin D

↑ cortisol →↑ Ca excretion, ↓tubular reabsorption PO_4

Glucocorticoid excess → osteoporosis.

Biological Effects of Adrenal Steroids …

D. Growth and Development

Fetal tissues: Glucocorticoids ↑ development (mechanism?)

↑ Surfactant production in fetal lungs

↑ Development of hepatic and G.I enzyme systems

Excess glucocorticoids: inhibit growth in children.

E. Blood Cells and Immunologic Function

↓ circulating lymphocytes, monocytes, eosinophils.

↓migration of inflammatory cells to site of injury.

↓ phospholipase A_2→ ↓ PGs, ↓IL-1, ↓Ab.

Glucocorticoids: anti-inflammatory.

Biological Effects of Adrenal Steroids …

F. Cardiovascular Function

Glucocorticoids:

↑ Cardiac output, ↑ peripheral vascular tone.

↑ Catecholamine effect and receptors.

Cause hypertension (renin substrate).

G. Renal Function

Affect H_2O and electrolyte balance through:

- Mineralocorticoid receptors:↑Na^+, ↓K^+, hypertension
- Glucocorticoid receptors: ↑ GFR due to↑ cardiac output, or direct renal effect on salt and H2O retention.

Biological Effects of Adrenal Steroids …

H. Effects on other Hormones

1. Thyroid Function: inhibit TSH synthesis or release, TSH response to TRH.
2. Gonadal Function: inhibit gonadotropin in males.
3. ↓LH response to GnRH in females → inhibition of ovulation, amenorrhea.

I. Miscellaneous Effects

1. Peptic Ulcer: controversial, ↑ risk with non-steroidal anti-inflammatory drugs.
2. Ophthalmologic Effects: Glucocorticoid therapy may cause cataract, intraocular pressure.

Biological Effects of Adrenal Steroids …

Adrenal Androgens

Males

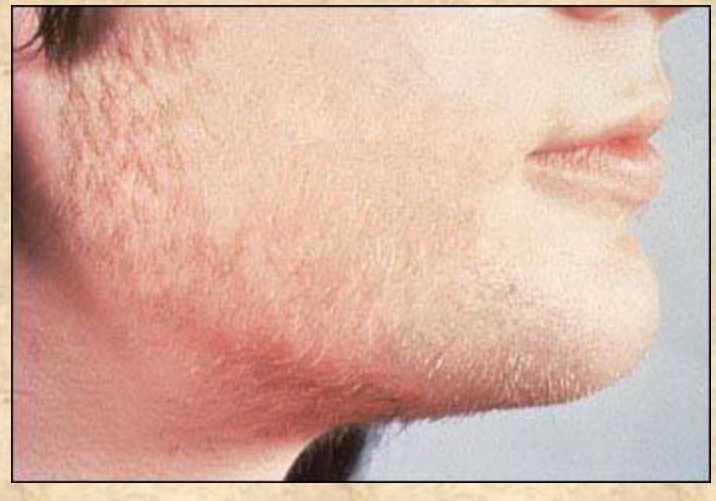
- Androstenedione contribute ~5% of testosterone.
- ↑ Androgens in boys: early development of secondary sexual characteristic.

Females

- Cushing's syndrome, adrenal carcinoma, congenital adrenal hyperplasia causes acne, hirsutism, virilization

Hirsutism

- **Excess hair growth, especially in women.**



Laboratory Evaluation

Plasma ACTH

A. Methods of Measurement

Immunometric Assay (IMA): 9-12 pg/ml

B. Adrenal Insufficiency

Primary adrenal disease: ↑ACTH

Pituitary ACTH deficiency: normal or less than 10 pg/ml

Cushing's syndrome (adrenal tumor: ACTH less than 5 pg/ml)

Cushing's disease (pituitary tumor: ACTH normal or elevated)

Ectopic ACTH syndrome: ACTH markedly elevated

Congenital adrenal hyperplasia: ACTH markedly elevated.

Laboratory Evaluation …

Plasma Cortisol

A. Methods of Measurement

RIA, HPLC, salivary cortisol (Free cortisol), GC-MS

B. Interpretation

1. normal values: 8 am (3-20 μg/dl), 4 pm (½ morning levels) 10 pm -2 am (under 3 μg/dl). Saliva (midnight <0.15 μg/dl).
2. Stress: 40-60 μg/dl
3. High-estrogen states: (pregnancy): 2 - 3 × normal.
4. Other conditions: (severe anxiety, depression, starvation, alcoholism, chronic renal failure: elevated cortisol)

Laboratory Evaluation …

Late-Night Salivary Cortisol

Diagnosis of Cushing's Syndrome:

- > 5.2 μg/dl midnight serum cortisol.
- > 0.1 μg/dl salivary cortisol.

Urinary Corticosteroids

Free Cortisol

Excellent methods for Cushing's syndrome vs. obesity. HPLC 5-50 μg/24h (normal).

Laboratory Evaluation …

Dexamethasone – Suppression Tests

A. Low-Dose Test

1. Dexamethasone suppresses pituitary ACTH 1 mg overnight.
2. Cushing's syndrome excluded if cortisol less than 1.8 μg/dl
3. Cushing's syndrome (probable cause) if cortisol > 10 μg/dl.

Laboratory Evaluation …

Dexamethasone – Suppression Tests …

B. High – Dose Test

Cushing's disease vs. Ectopic ACTH and adrenal tumor

1. Overnight high dose: 8mg at 11.00 pm, measure cortisol at 8.00 am

   Cushing's disease: less than 50% basal

   Ectopic ACTH, adrenal tumor: fail to suppress

2. Two-day high dose: 2 mg every 6 h for 2days

   Cushing's disease: levels < 50% base line

   ↑ 90% decrease in urine free cortisol: 100% Cushing's disease (exclude ACTH ectopic syndrome).

Laboratory Evaluation …

Pituitary – Adrenal Reserve

Assess hypothalamic – pituitary- adrenal axis

A. ACTH stimulation Testing: Synthetic ACTH (1 μg)

1. Inadequate response: adrenal insufficiency

   Primary adrenal insufficiency: destruction of cortical cells → reduced cortisol →↑ ACTH

   Secondary adrenal insufficiency: ACTH deficiency → atrophy of cortical zone.

2. Normal response: exclude both primary and secondary adrenal insufficiency. Does not rule out partial ACTH deficiency: further testing.

Laboratory Evaluation …

Pituitary – Adrenal Reserve …

B. Metyrapone Testing: diagnosis of suspected pituitary ACTH deficiency

- Metyrapone blocks 11 β-hydroxylase: 11 deoxycortisol → cortisol →↑ ACTH (> 100 pg/ml) → 11-deoxycortisol (>7 ng/dl) in normal ACTH secretion and normal adrenal function.
- Subnormal response of adrenal: adrenocortical insufficiency.

Laboratory Evaluation …

Pituitary – Adrenal Reserve …

C. Insulin – induced Hypoglycemia Testing

- Hypoglycemia →↑CRH →↑ ACTH →↑ Cortisol.
- Plasma ACTH response to hypoglycemia >100 pg/ml.
- Normal cortisol response: exclude adrenal insufficiency and decreased pituitary reserve.

D. CRH Testing

- Primary adrenal failure: exaggerated ACTH response.
- Hypopituitarism: absent ACTH response.

Laboratory Evaluation …

Pituitary – Adrenal Reserve …

Androgens

A. **Plasma levels**

DHEA , DHEA-sulfate, androstenedione , T, DHT.

B. **Free Testosterone**

Requires separation bound from free (difficult)

Women: 5 pg/ml free T.

Hirsute women: 16 pg/ml free T.

Disorders of Adrenocortical Insufficiency

Primary Adrenocortical Insufficiency

A. Addison's Disease

Autoimmune Adrenocortical Insufficiency

Two syndromes:

1. Autoimmune polyglandular disease type I (hyperparathyroidism, adrenal failure)
2. Polyglandular autoimmune syndrome type II (Schmidt's)

HLA-related (Diabetes mellitus)

Autoantibodies against 21α-hydroxylase.

Primary Adrenocortical Insufficiency …

B. Adrenal Hemorrhage

Adrenal vein thrombosis.

Primary anti phospholipids antibody syndrome.

C. Infections

Tuberculosis, systemic fungal infections, AIDS.

D. Adrenoleukodystrophy

1. Malfunction of adrenal cortex.
2. Demyelinization in CNS.

↑ Very long chain fatty acids (VLCFAs) in brain, adrenal cortex, testes, liver.

Primary Adrenocortical Insufficiency …

E. Metastatic Adrenal Disease

Lung, G.I., breast and renal neoplasia

Subnormal cortisol response to ACTH

Bilateral adrenal enlargement.

F. Familial Glucocorticoid Deficiency

Hereditary adrenocortical unresponsiveness to ACTH

Mutation in ACTH receptor in adrenal cortex

G. Cortisol Resistance

Abnormalities of glucocorticoid receptor →↑ ACTH →↑ cortisol, mineralocorticoids, adrenal androgens → hypertension, hypokalemia, virilization.

Primary Adrenocortical Insufficiency …

Pathophysiology

- Gradual destruction of adrenal cortex
- Initial phase: decrease adrenal reserve, normal cortisol, no response to stress.

Clinical Features

- Chronic: fatigue, nausea, hypotension, ↓ Na+.
- Hypoglycemia: hyperpigmentation, weakness
- Acute Abdominal, flank and back pain, hypotension, fevers shock, vomiting.

Lab. Findings:

↓ Na^+, ↑ K^+, CT scan: adrenal enlargement

Secondary Adrenocortical Insufficiency

Etiology

1. ACTH deficiency due to exogenous glucocorticoid therapy
2. Pituitary and hypothalamic tumors.

Pathophysiology

1. ↓Cortisol and adrenal androgen (atrophy of fasiculata –reticularis).
2. Normal aldosterone
3. ACTH reserve is impaired.

Secondary Adrenocortical Insufficiency …

Clinical features

1. Dehydration, ↓ Na^+ due to H_2O retention, ↓ GFR due to ↓ cortisol
2. Weakness, nausea, vomiting
3. Pituitary Tumors (hypogonadism and hypothyroidism).
4. Hypersecretion of PRL and GH.

Diagnosis of Adrenocortical Insufficiency

1. Rapid ACTH Stimulation Test

1 mg cosyntropin (synthetic ACTH):

- Subnormal response: adrenocortical insufficiency (primary or secondary) → measure ACTH
- Normal response: excludes primary adrenal failure does not exclude partial secondary adrenocortical insufficiency → metyrapone or insulin – induced hypoglycemia.

2. Plasma ACTH levels

Primary adrenal insufficiency: ACTH > 200 pg/ml

Secondary adrenal insufficiency: ACTH normal or <10pg/ml.

Diagnosis of Adrenocortical Insufficiency

3. Partial ACTH Deficiency

Overnight metyrapone test

Insulin –induced hypoglycemia

- Normal response: excludes secondary adrenal insufficiency
- Subnormal response (normal response to ACTH): secondary adrenal insufficiency.

Cushing's Syndrome

Chronic glucocorticoid excess

Classification

1. ACTH –dependent: ectopic ACTH syndrome and Cushing's disease. Chronic ACTH hypersecretion → Adrenal hyperplasia (fasiculata - reticularis) →↑ cortisol, androgens, DOC.
2. ACTH – independent: primary adrenal tumors ↑ cortisol →↓ ACTH.

Cushing's Syndrome

A. Cushing's disease

most common (70% of cases)

Women: men (8:1).

B. Ectopic ACTH hypersecretion

15-20% of cases, severe hypercortisolism.

Small cell carcinoma of the lung

More common in men.

C. Primary Adrenal Tumors

10% of cases, mostly benign adrenocortical adenomas.

Adrenocortical carcinomas, uncommon.

More common in women.

D. Childhood Cushing's Syndrome

Adrenal carcinomas, most frequent cause

More common in girls (1-8 years)

Cushing's Syndrome …

Clinical Features: Symptoms

1. **Obesity:** most common manifestation, central obesity

   "Moon facies": accumulation of fat in the face.

   "Buffalo hump": accumulation of fat around the neck.

2. **Skin Changes:** Atroply of epidermis "thinning", easy bruisability, striae, acne (from hyperpigmentation) rare in Cushing's disease, common in ectopic ACTH syndrome.

3. **Hirsutism:** due to ↑ adrenal androgens (↑ hair growth in ♀ over abdomin, breasts, chest, upper thighs).

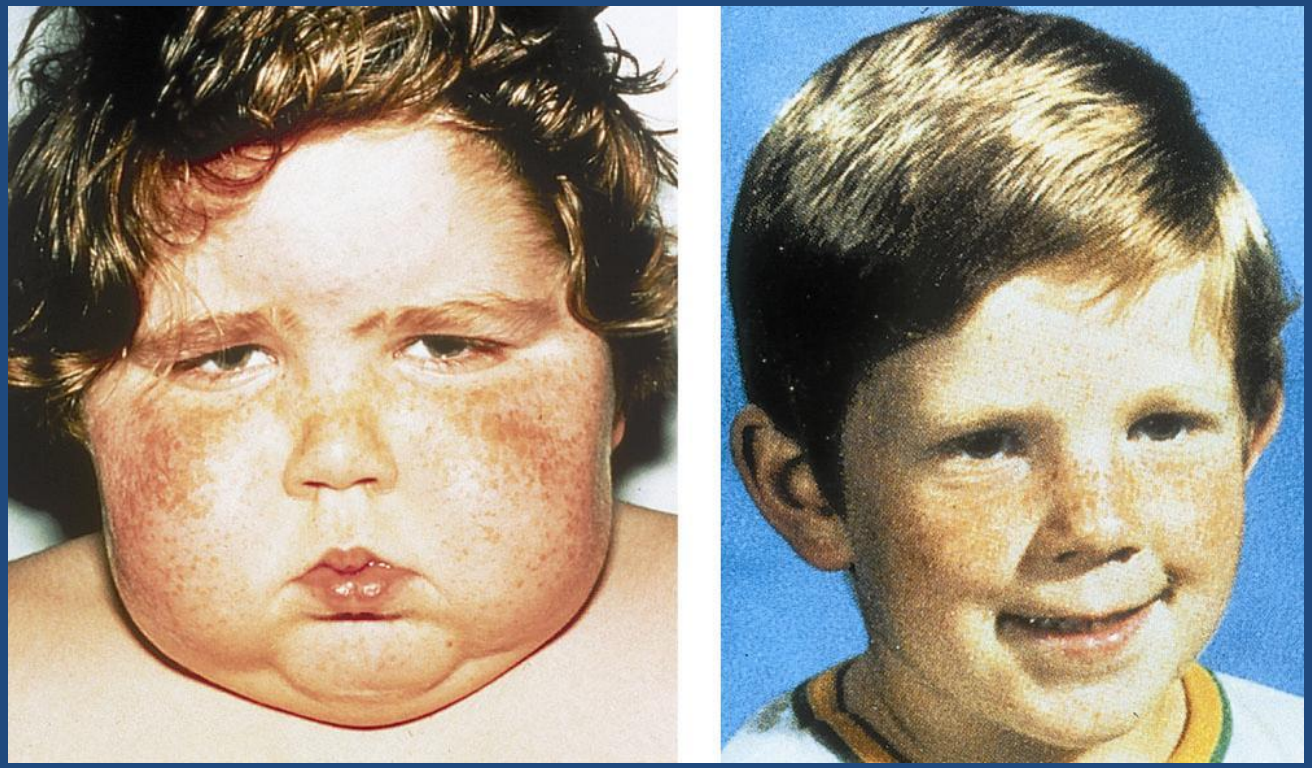
4. **Hypertension**

Cushing's Syndrome …

Clinical Features: Symptoms …

5. **Gonadal Dysfunction:** common in females due to ↑ androgens, in males due to ↑ cortisol. Amenorrhea 75% women
6. **CNS and Psychologic disturbances**
7. **Muscle weakness:** low muscle ass and low total body protein.
8. **Osteoporosis:** osteopenia and osteoporosis.
9. **Renal Calculi:** due to glucocorticoid – induced hypercalciuria.
10. **Thirst ad polyuria:** polyuria due to glucocorticoid inhibition of vasopressin, ↑ GFR.

Cushing's Syndrome

- 

Cushing's Syndrome …

Diagnosis

A. Dexamethasone Suppression Test

Normal subject: cortisol < 1.8µg/dL

B. Urine Free Cortisol

24h urine collection, free cortisol by HPLC, GC-MS

Normal : cortisol < 50µg / 24h.

C. Diurnal Rhythm

Absence of diurnal rhythm: Cushing's syndrome

Serum cortisol > 7µg/dL at midnight: Cushing's syndrome

Salivary cortisol = free cortisol > 0.1µg/dL (Cushing's syndrome).

Cushing's Syndrome …

Differential Diagnosis : Plasma ACTH

1. Measurement of Plasma ACTH by IRMA

   ACTH > 5pg/dL, blunted response to TRH (<10pg/dL)

   = bilateral adrenal cortical hyperplasia.

   ACTH > 10pg/dL (frequently > 52pg/dL)

   = ACTH secreting tumors

   Source of ACTH – secreting tumor (90% pituitary tumor)

2. Plasma ACTH levels are usually higher with ectopic ACTH than pituitary ACTH – dependent Cushing's syndrome.
3. Enhanced ACTH response for CRH; frequently in Cushing's syndrome compared to ectopic – ACTH syndrome (less accurate).

Glucocorticoid Therapy for Nonendocrine Disorders

Principles

Glucocorticoids: anti-inflammatory, immunosuppressive

Rheumatologic disorder: rheumatoid arthritis.

Pulmonary disease: asthma.

Renal disease: glomerulonephritis.

Because of side effects: minimum effective does shortest duration.

Synthetic Glucocorticoids

Prednisone: 3-5 times more glucocorticoid activity.

Dexamethasone: 10-20 times the glucocorticoid activity of cortisol, negligible mineralocorticoid activity.

Side Effects:

Hypothalamic – pituitary – adrenal axis suppression; Cushing's syndrome; Steroid withdrawal.

Mineralocorticoid Hormones

Mineralocorticoid Hormones

Mineralocorticoids:

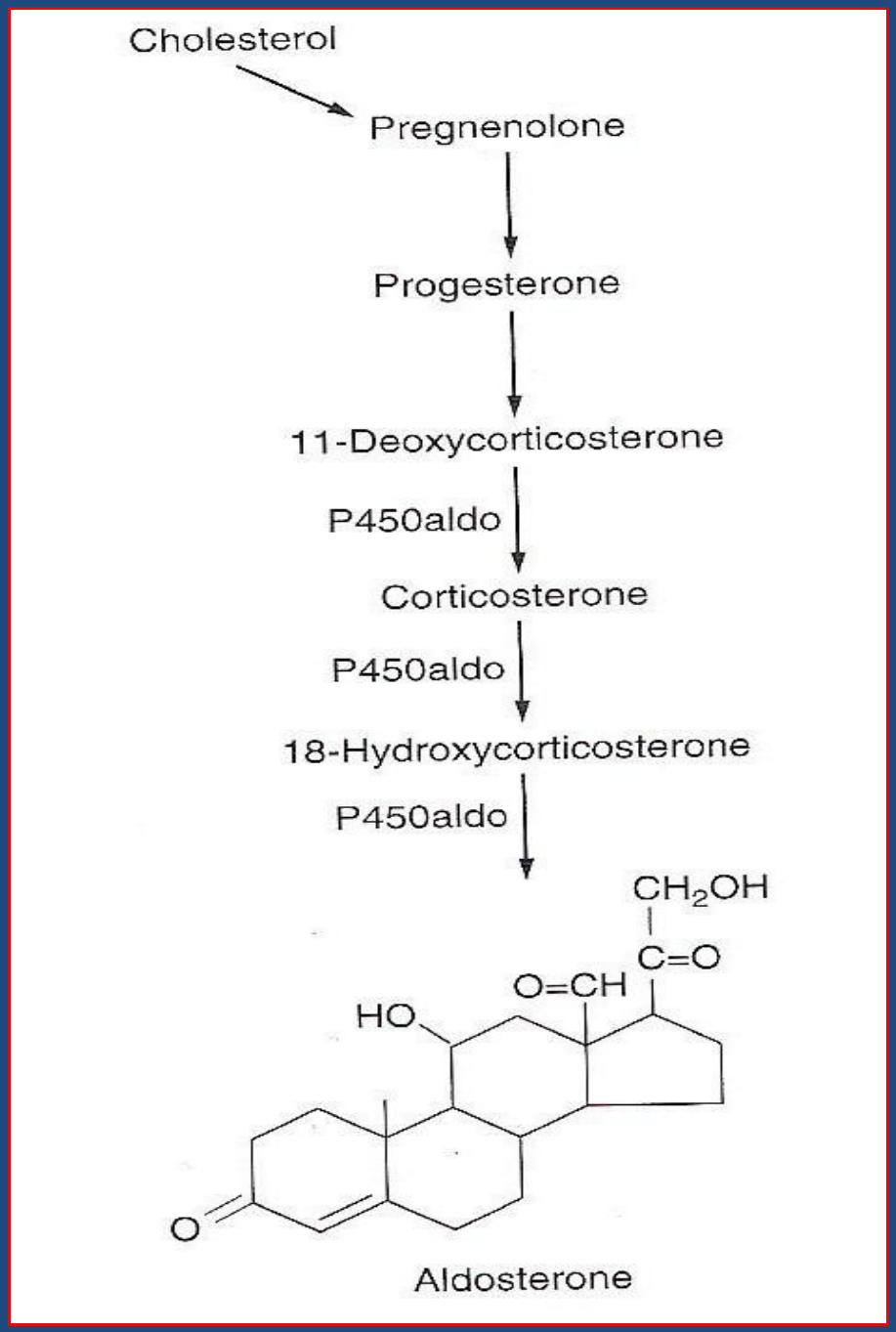
Aldosterone, DOC.

Cortisol: degradation by kidney.

Aldosterone:

- Produced exclusively by zona glomerulosa.
- Controlled by renin-angiotensin system, Na^+ and K^+ levels.

Biosynthesis of aldosterone



Mineralocorticoid Hormones …

- Aldosterone + DOC
- Aldosterone: 30-50% free, binds weakly to CBG, mainly albumin.
- DOC: 5% free, binds mainly to CBG.
- Aldosterone, DOC: same affinity for mineralocorticoid receptor (cytosol), equal concentrations (more free aldosterone).

Mineralocorticoid Hormones …

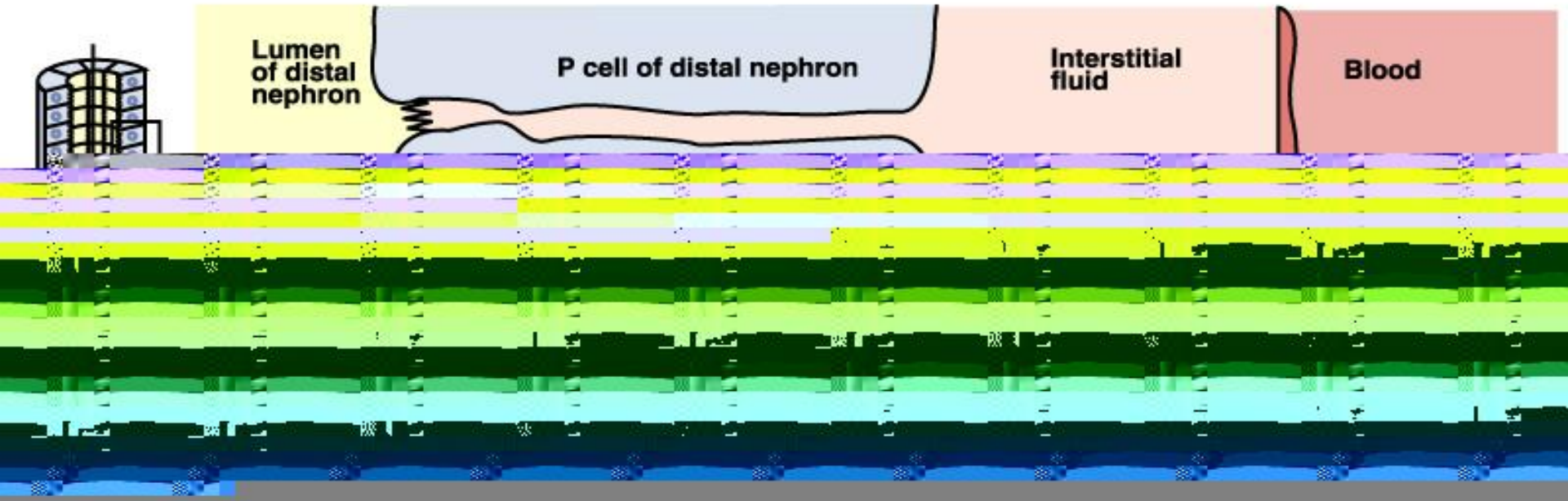
Action

Na^+ channel:

- Increase apical membrane targeting in collecting tubules
- ↑Na^+ movement into cells.
- ↑ aldosterone – regulated kinase (serum glucocorticoid – regulated kinase 56k) →↑ Na^+ channel activity.

↑ K^+, H^+ secretion

Osmoregulation: Aldosterone



Endocrine Hypertension

1. Adrenal Gland: Pheochromocytoma, primary aldosteronism.
2. Pituitary: ACTH producing tumor (Cushing's disease, ectopic ACTH production).
3. Kidney: renin-angiotensin system.

Endocrine Hypertension:
Hypertension of Adrenal Origin

Mineralocorticoid Hypertension

Mineralocorticoids:

- ↑ expansion of plasma + ECF.
- Na^+ and fluid retention →↑ cardiac output.
- Renal K^+ wasting.
- ↑ total peripheral resistance.
- ↑ sensitivity to catecholamine.

Primary Aldosteronism

Zona glomerulosa:

Adenoma or hyperplasia: ↑aldosterone

Aldosterone – Producing adenomas (APA).

Aldosterone, DOC, Corticosterone, 18 (OH) corticosterone.

Lack 17α -hydroxylase = (normal cortisol).

Clinical Features

Symptoms of hypokalemia, hypertension.

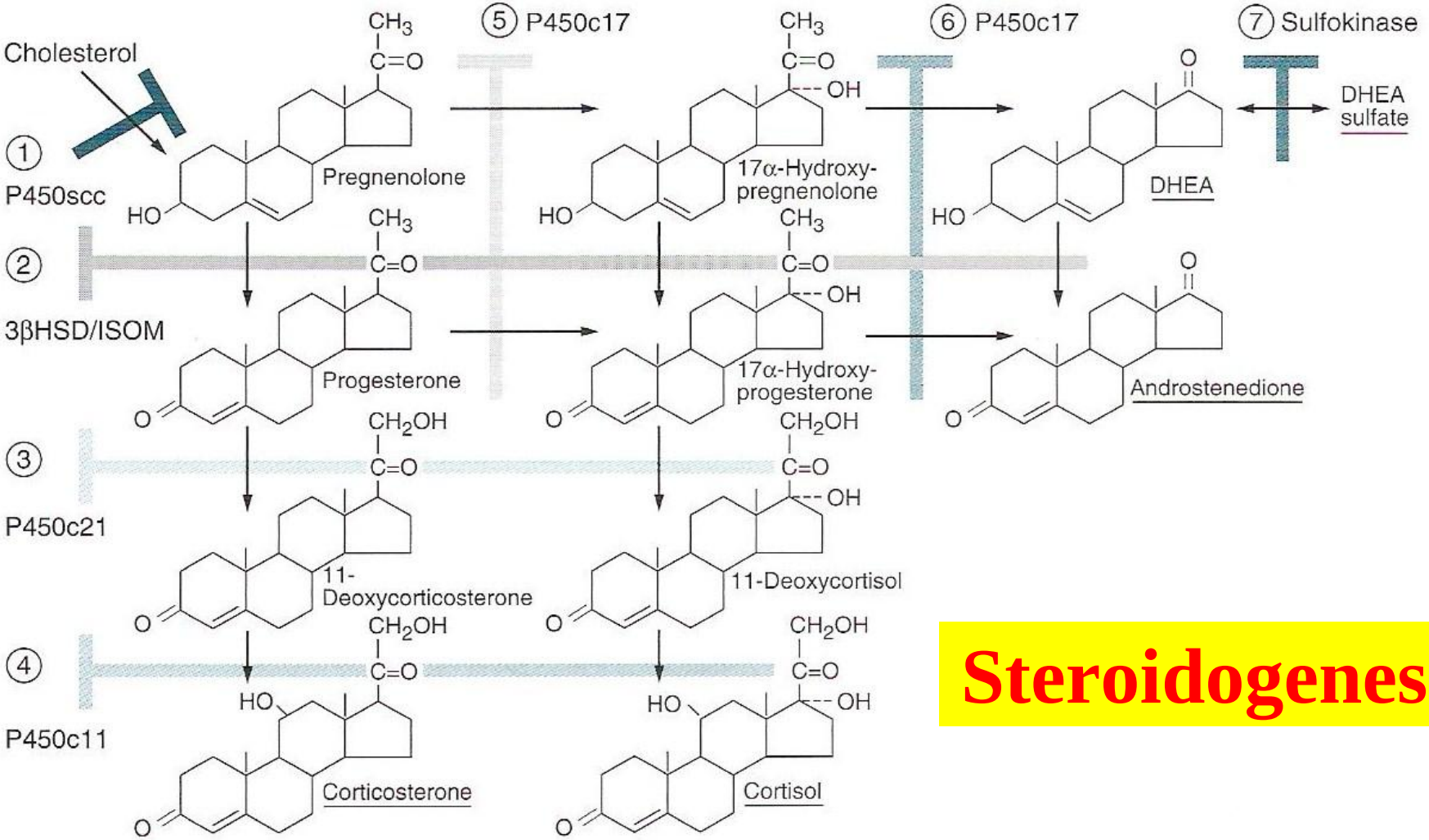
Endocrine Hypertension: Excess DOC

17 α-hydroxylase deficiency:

- Suppression of the renin-angiotensin system.
- High levels of DOC, corticosterone, 18-(OH) corticosterone, 18- (OH) DOC.

11 β –hydroxylase deficiency:

- Virilization (high androgens)
- High levels of DOC, 11-deoxy cortisol, 17 (OH) progesterone.



Steroidogenesis

Figure 9–4. Steroid biosynthesis in the zona fasciculata and zona reticularis of the adrenal cortex. The major secretory products are underlined. The enzymes for the reactions are numbered on the left and at the top of the chart, with the steps catalyzed shown by the shaded bars. ① P450scc, cholesterol 20,22-hydroxylase:20,22 desmolase activity; ② 3βHSD/ISOM, 3-hydroxysteroid dehydrogenase:δ^5-oxosteroid isomerase activity; ③ P450c21, 21α-hydroxylase activity; ④ P450c11 = 11β-hydroxylase activity; ⑤ P450c17, 17α-hydroxylase activity; ⑥ P450c17, 17,20-lyase/desmolase activity; ⑦ sulfokinase. (See also Figures 7–1, 9–2, 10–4, and 11–13.) (Modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 16th ed. McGraw-Hill, 1993.)

Endocrine Hypertension
Cushing's Syndrome …

- Hypertension is common.
- ACTH- dependent hypercortisolism: Cushing's disease, ectopic ACTH production: →↑ DOC, corticosterone, cortisol.

Mechanism of hypertension

Mineralocorticoid- independent mechanisms

↑ angiotensin II (↑ hepatic angiotensinogen)

↑ Vascular reactivity to vasoconstrictors

↓ Catecholamine degradation (↑epinephrine)

↓ vasodilation.

Na^+ shift from ICF → ECF ↑ cardiac output

Hypertension of Renal Origin

The Renin–Angiotensin System

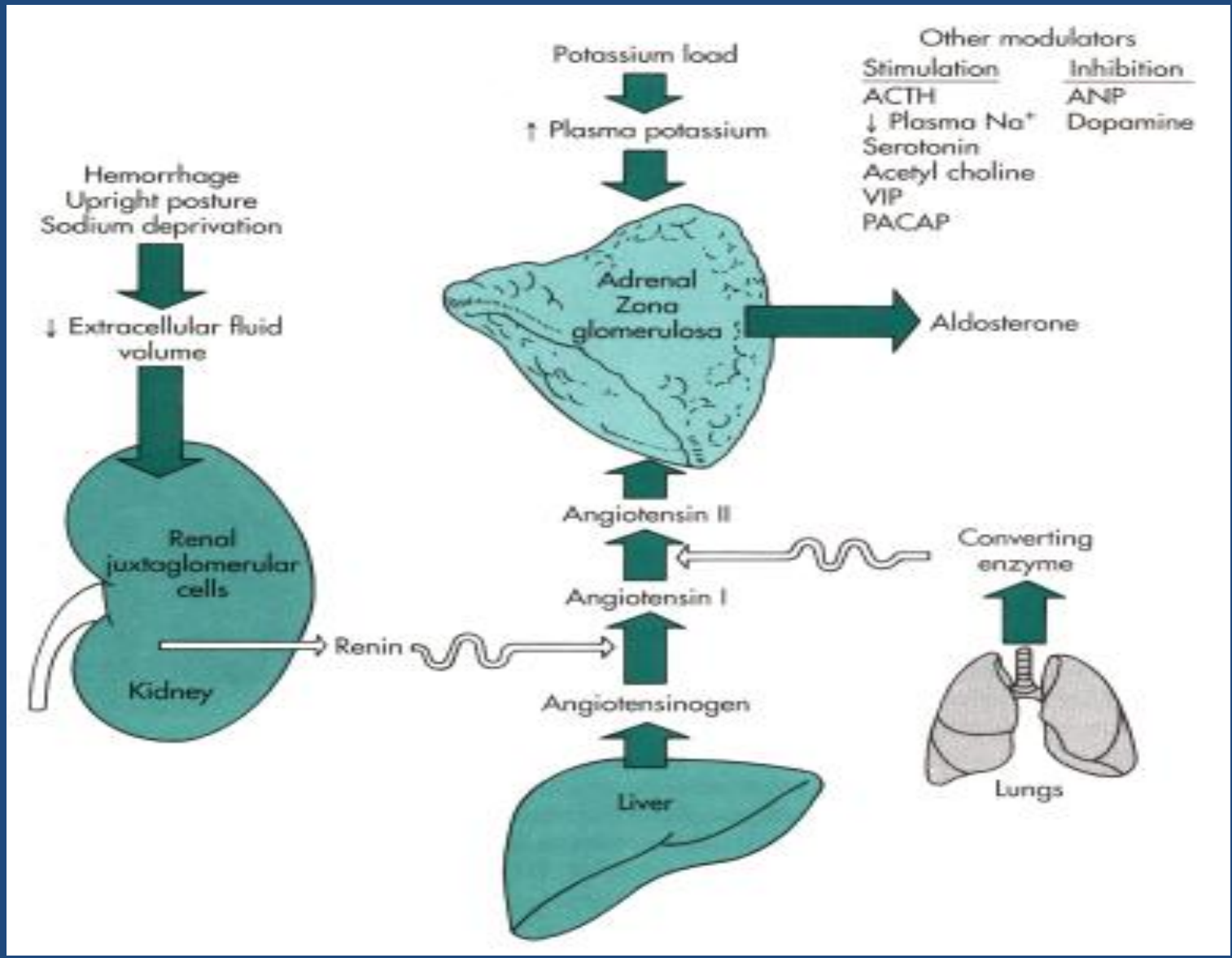
Renin

- Secreted by juxtaglomerular cells (smooth muscle cells of afferent arteriole as it enters the glomerulus).
- A proteolytic enzyme M.W. 40,000
- Secretion: controlled by
  - (1) baroreceptors
  - (2) cardiac and systemic arterial receptors
  - (3) cells of macula densa ($\downarrow Na^+$, Cl^-).
- Catalyzes angiotensin I formation from angiotensinogen
- Angiotensin I is then converted by ACE to angiotensin II.

The Renin–Angiotensin System

Renin-Angiotensin System

Regulation of Aldosterone Secretion



Hypertension of Renal Origin …

The Renin–Angiotensin System

Angiotensinogen

- α2 - Globulin secreted by liver
- M.W. 60,000
- Essential hypertension: linked to variant allele for angiotensinogen gene.
- Glucocorticoid and estrogens (contraceptives) ↑ angiotensinogen

Hypertension of Renal Origin …

The Renin–Angiotensin System

Angiotensin – Converting Enzyme (ACE).

- A dipeptidyl carboxypeptidase, a glycoprotein, M.W. 130,000-160,000
- Substrates: angiotensin I, bradykinin, enkaphlins, substance P.
- Converts angiotensin I to angiotensin II.
- ACE inhibitors: also ↑ nitric oxide (hypotensive) by ↑ kinins → improve insulin sensitivity (↓ glucose) in type 2 diabetes.

Hypertension of Renal Origin …

The Renin–Angiotensin System …

Angiotensin II

- Bind to plasma membrane receptors (AT1 and AT2).
- AT1: mediates cardiovascular, renal, adrenal-stimulatory effects.
- AT2: cell differentiation and growth.
- Vasoconstriction of peripheral arterioles, ↑ aldosterone (Na retention).

Hypertension of Renal Origin …

The Renin–Angiotensin System …
Angiotensin II …

- Chronic volume depletion (↓ Na^+ intake): ↑ angiotensin II → down regulation of AT1 receptors in vasculature (Na reabsorption without ↑ blood pressure.
- Angiotensin II →↑ catecholamines.
- ACE inhibitors + angiotensin receptor blockers (ARBs) ↓ blood pressure.

The Renin–Angiotensin System and Hypertension

Essential Hypertension

- Blood pressure: Cardiac output + peripheral vascular resistance.
- Essential Hypertension: ↑ peripheral vascular resistance (renin-angiotensin system implicated).

Causes of essential hypertension:

- ½ patients: normal or ↑ plasma renin; ¼ low renin.
- Abnormality: local angiotensin II production or AT receptor.
- Genetic linkage between angiotensinogen gene allele and essential hypertension.

The Renin–Angiotensin System and Hypertension …

Essential Hypertension:

Treatment:

- ACE inhibitor (captopril, ↓ angiotensin II → restore adrenal and vascular responsiveness);
- ACE inhibitors: effective by ↑ bradykinins, ↓ local angiotensin II production.
- AT1 antagonist.
- Diuretics, Ca blockers.
- β-Adrenergic antagonists.

The Renin–Angiotensin System and Hypertension …

Renovascular Hypertension

- Renin–dependent hypertension.
- Most common correctable cause of secondary hypertension.
- Due to atherosclerosis or fibromuscular hyperplasia of renal arteries.
- Treatment:

  ACE inhibitor (captopril) or AT1 antagonist.
  Renal stenosis: anatomic correction.

  Ca channel blocker, β-adrenergic antagonist.

Adrenal Medulla

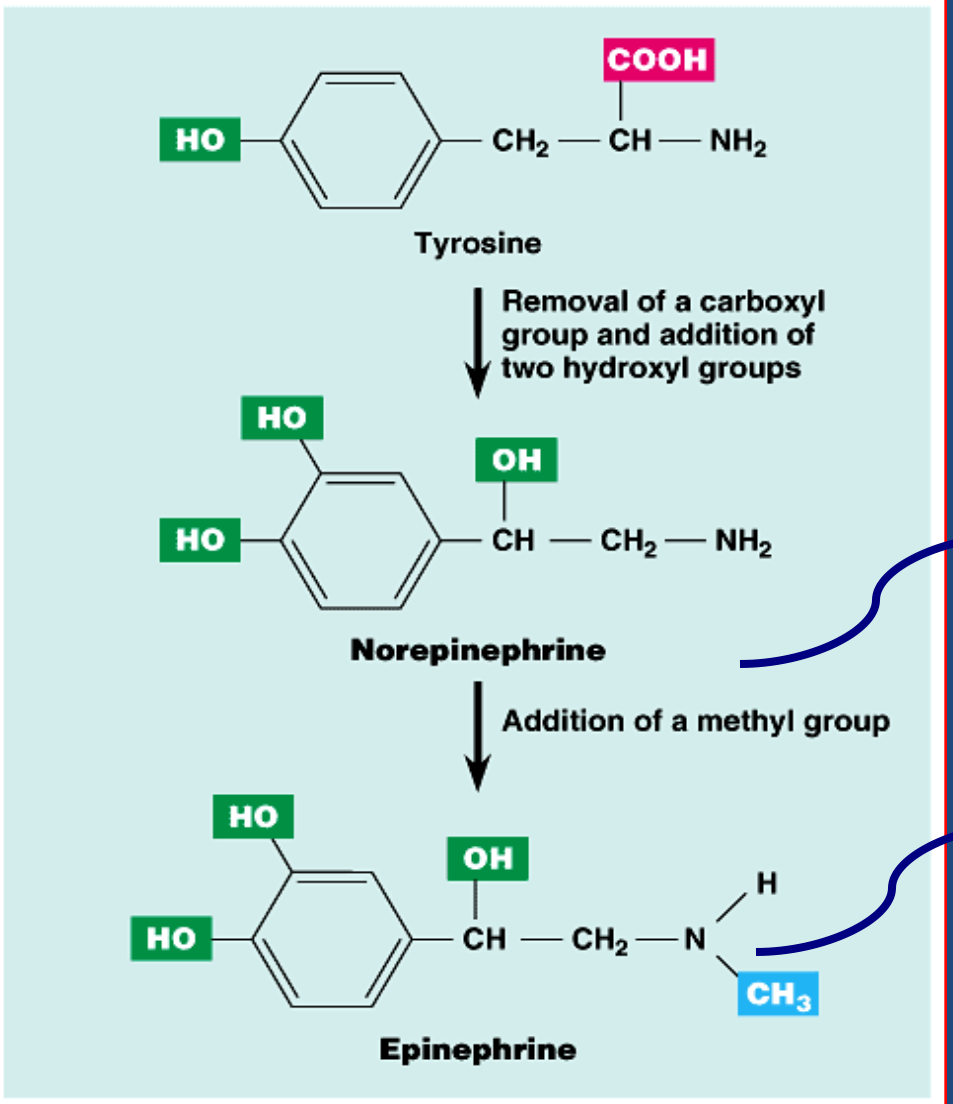
- Is a specialized part of the sympathetic nervous system.
- Secretes catecholamines: epinephrine, nor epinephrine.
- Chromaffin Cells or Pheochromocytes

  80% epinephrine, 20% norepinephrine

Nerve Supply

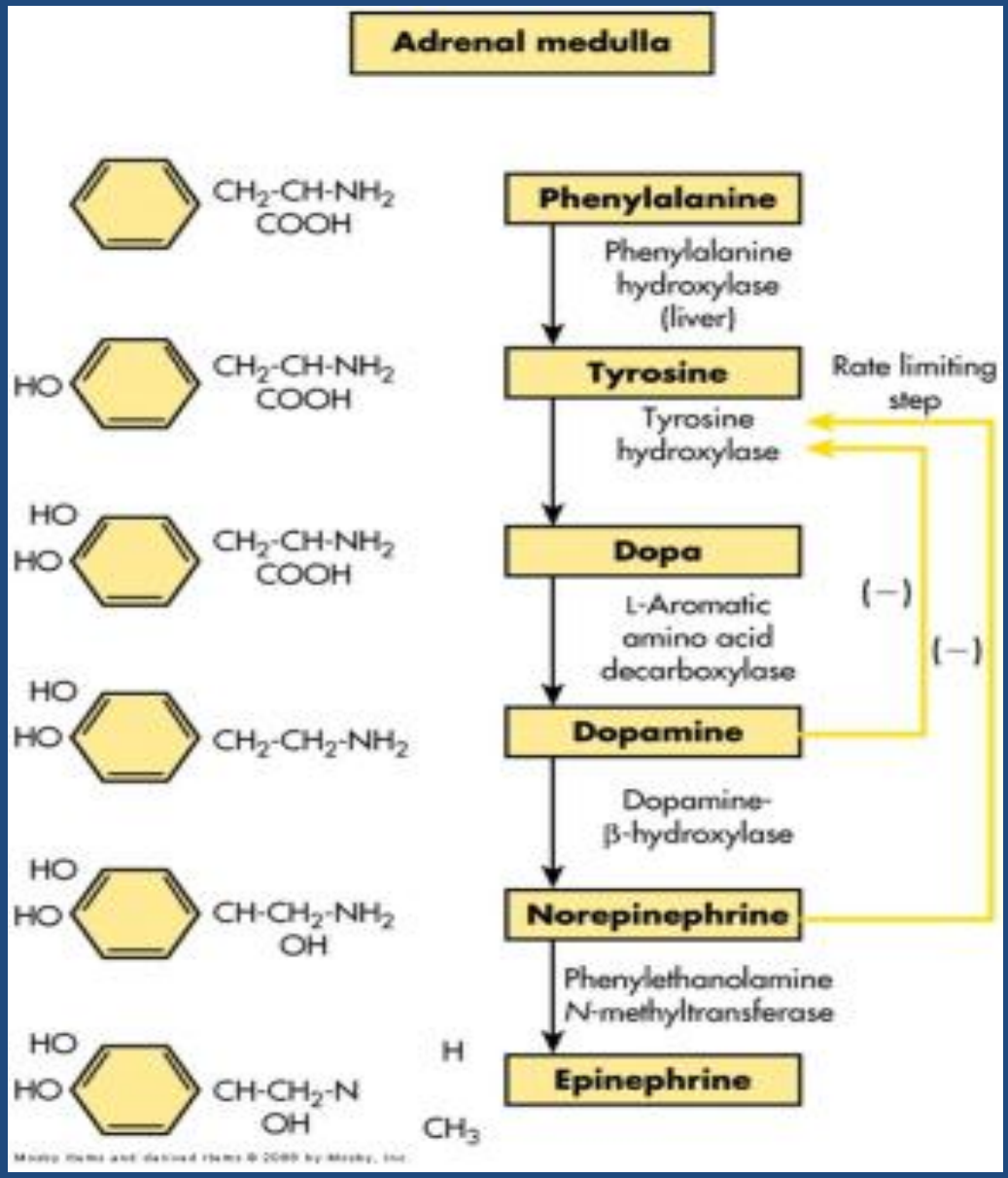
- Innervated by preganglionic fibers: acetylcholine.

Catecholamine hormones - amines that control our response to acute stress



- Cardiac output increases.
- Blood vessels to skeletal muscles dilate.
- Blood vessels to digestive organs constrict
- Liver produces glucose.

Catecholamines: Biosynthesis



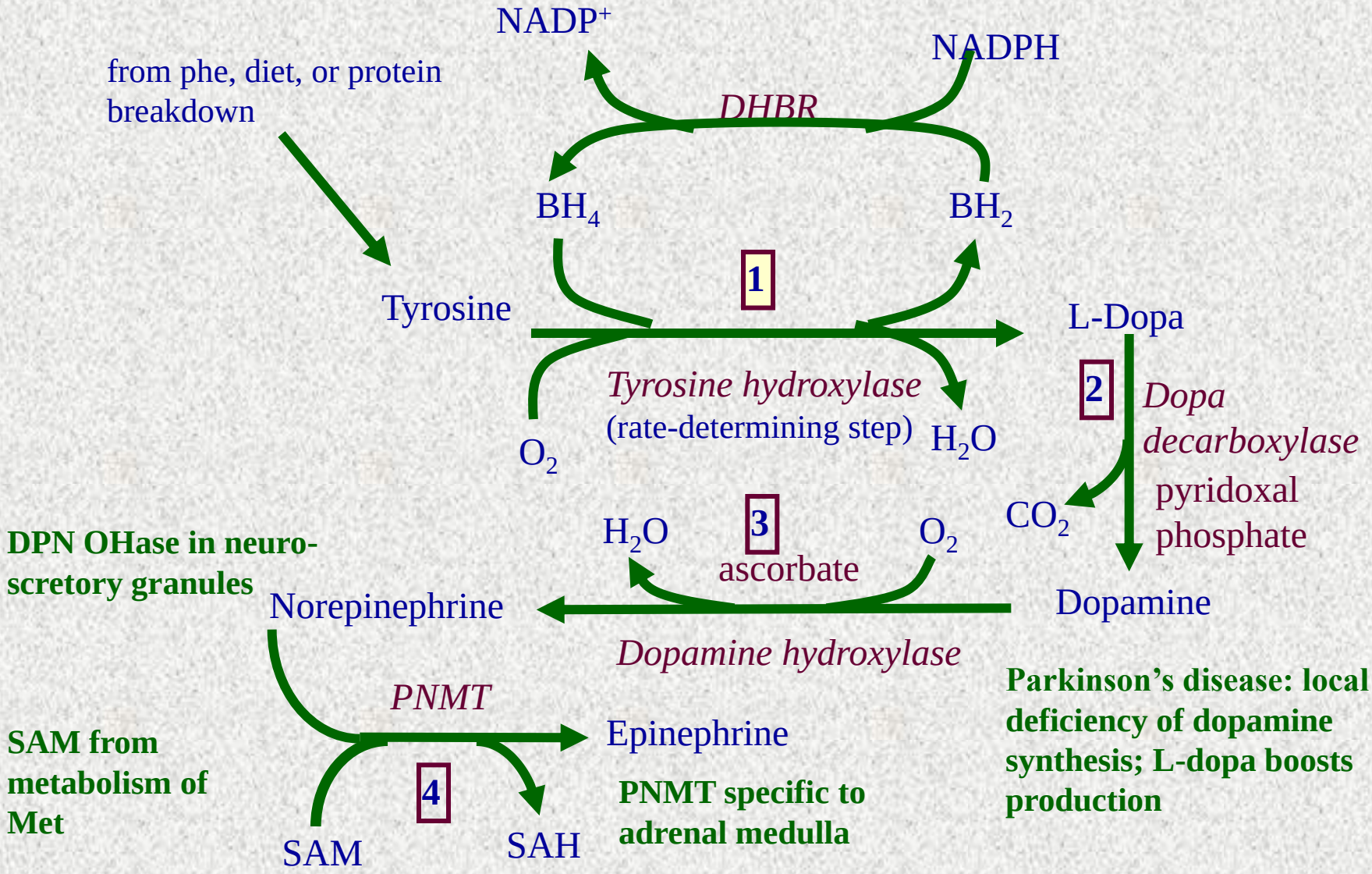
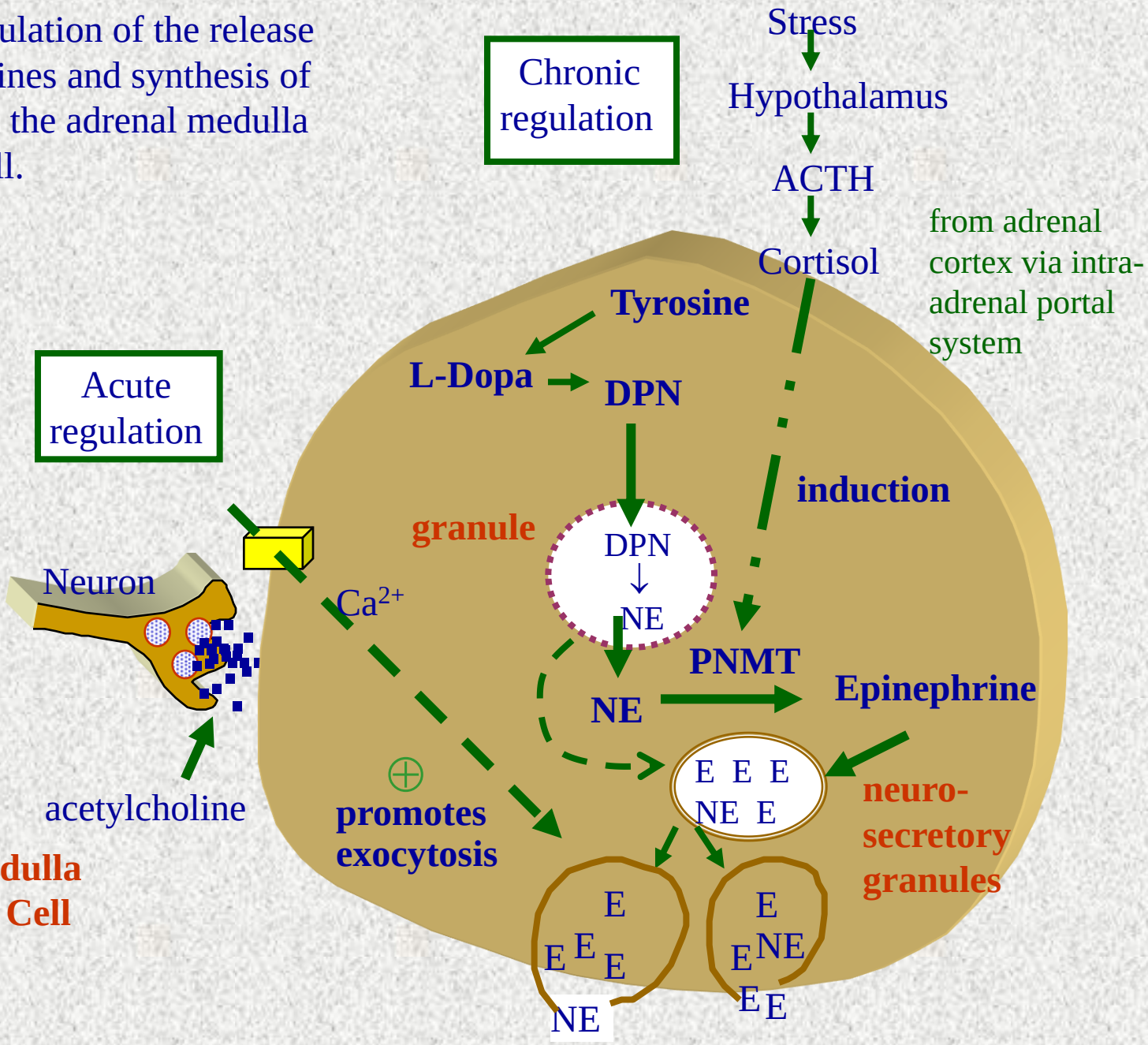


Figure 1. Biosynthesis of catecholamines. BH_2/BH_4, dihydro/tetrahydrobiopterin; DHBR, dihydrobiopterin reductase; PNMT, phenylethanolamine N-CH_3 transferase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine

Figure 2. Regulation of the release of catecholamines and synthesis of epinephrine in the adrenal medulla chromaffin cell.



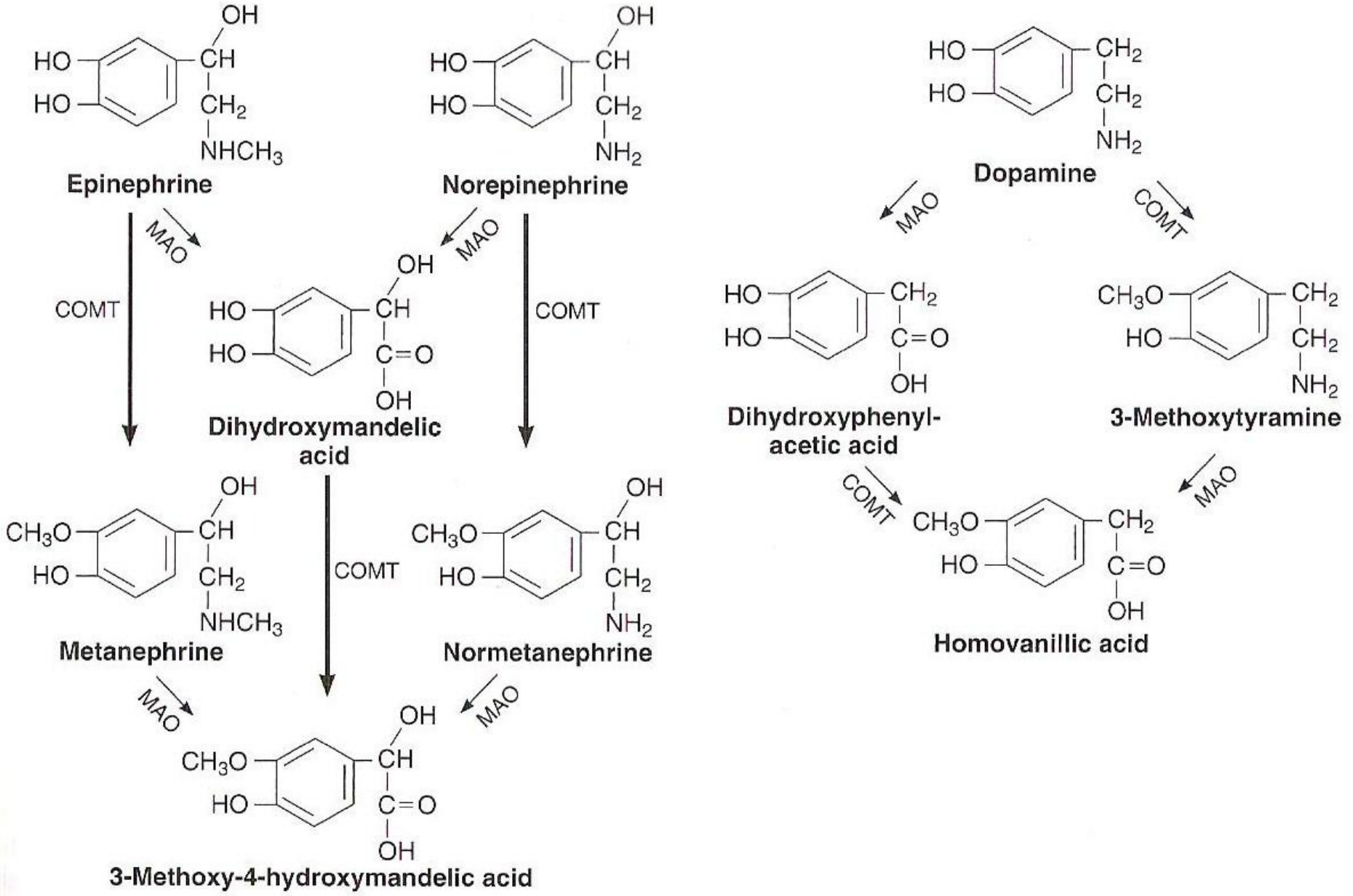


Figure 11–3. Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO).

Table 1. Classification of Adrenergic Hormone Receptors

Receptor	Agonists	Second Messenger	G protein
alpha$_1$ (α_1)	E>NE	IP_3/Ca^{2+}; DAG	G_q
alpha$_2$ (α_2)	NE>E	↓ cyclic AMP	G_i
beta$_1$ (β_1)	E=NE	↑ cyclic AMP	G_s
beta$_2$ (β_2)	E>>NE	↑ cyclic AMP	G_s

E = epinephrine; NE = norepinephrine

Synthetic agonists:

isoproterenol binds to beta receptors

phenylephrine binds to alpha receptors (nose spray action)

Synthetic antagonists:

propranolol binds to beta receptors

phentolamine binds to alpha receptors

Adrenergic Receptors

Transmembrane proteins (7 hydrophobic regions)

A. Alpha – Adrenergic Receptors: smooth muscle contraction

α1 Agonist → G_q

α2 Agonies → G_i

B. Beta – Adrenergic Receptors: Agonist → G_s

β_1 receptors: direct cardiac effects

β_2 receptors: vascular, bronchial, uterine smooth muscle relaxation

β_3 receptors: lipolysis

C. Dopamine Receptors

Five subtypes: D1 to D5.

D1 receptors: ↑ cAMP, postsynaptic in brain

D2 receptors: ↓ cAMP, pituitary open K^+ channel, ↓ Ca^{++} influx.

Catecholamine Actions

1. **Dopamine**

   Important Central neurotransmitter

2. **Norepinephrine**
   - Mainly in sympathetic innervation: heart, kidneys, muscles, salivary glands, vascular smooth muscle, liver; and adrenal medulla.
   - ↑ α1-adrenergic receptors ↑ cardiac contraction, hypertension, dilation of pupils, ↑ sweating.
   - ↑ β3-adrenergic receptors: ↑ lipolysis.
3. **Epinephrine**
   - Stimulates α1- and β1- adrenergic receptors
   - Hypoglycemia ↑ epinephrine →↑ glycogenolysis, lipolysis.
   - ↑ BMR

Physiologic Effects

A. Cardiovascular Effects

↑ Rate and force of contraction (β receptors)

Contraction of vascular smooth muscle (α1 receptors)

B. Effects on Extracellular smooth Muscle

Relaxation and Contraction of uterine myometrium

Relaxation of intestinal and bladder smooth muscle

C. Metabolic Effects

↑ O_2 consumption and heat production

Glucose and fat mobilization (Glycogenolysis and lipolysis)

Disorders of Adrenal Medullary Function

Hypofunction

- No disability: intact sympathetic NS
- Autonomic Insufficiency: orthostatic hypotension

Hyperfunction

- ↑ Blood pressure: ↑ cardiac output, ↑Vasoconstriction, ↑ renin

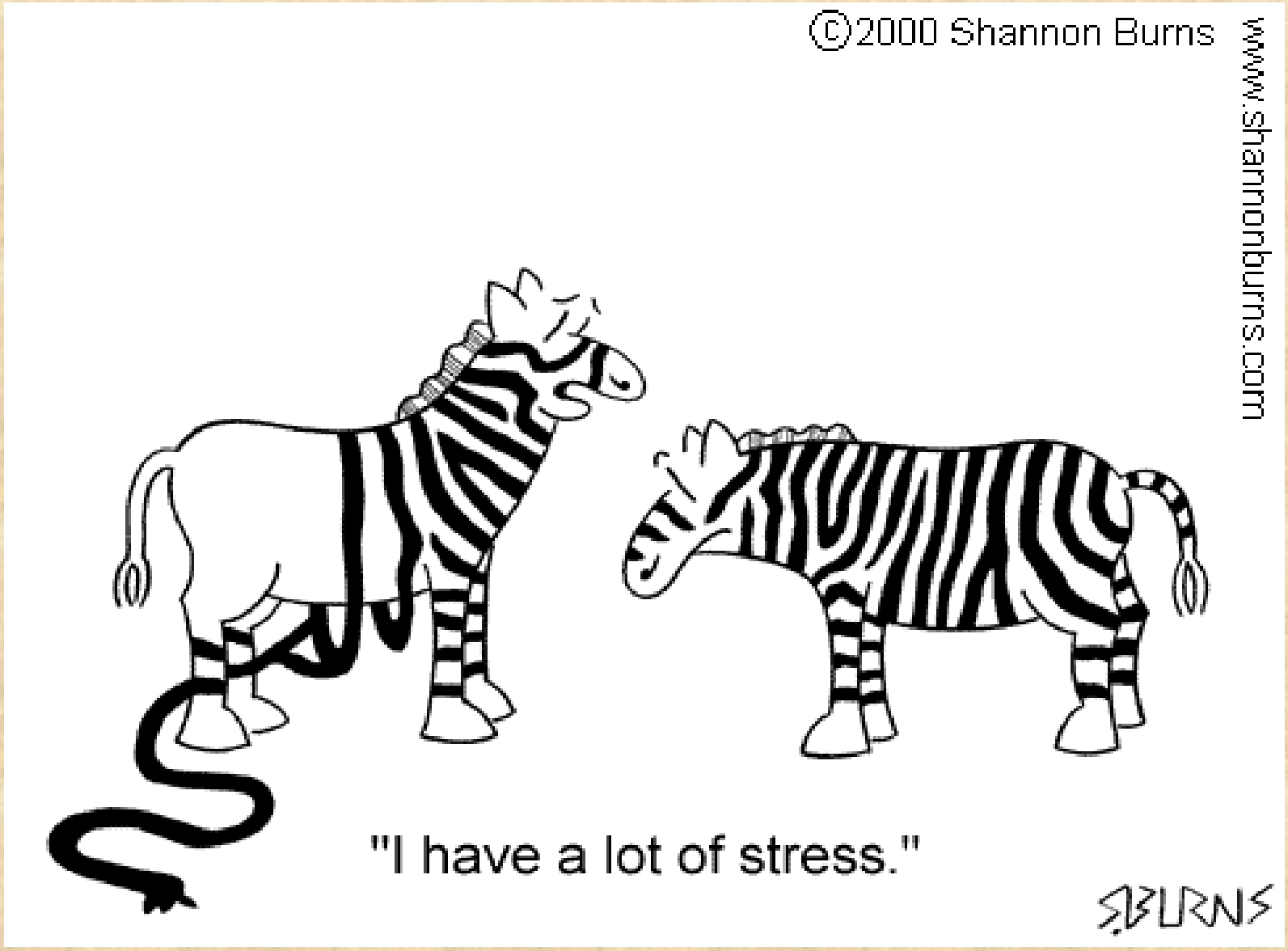
Pheochromocytoma

Pheochromocytomas

- Rare tumors of adrenal medulla (mainly right adrenal)
- Secrete more norepinephrine than epinephrine
- severe hypertensive episodes (spontaneous hemorrhage)

Paragangliomas

- Rarely secrete epinephrine
- Extra-adrenal pheochromocytomas: arise from sympathetic ganglia.
- Metastasize to lungs, lymph nodes, bones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