ADRENAL
HORMONES

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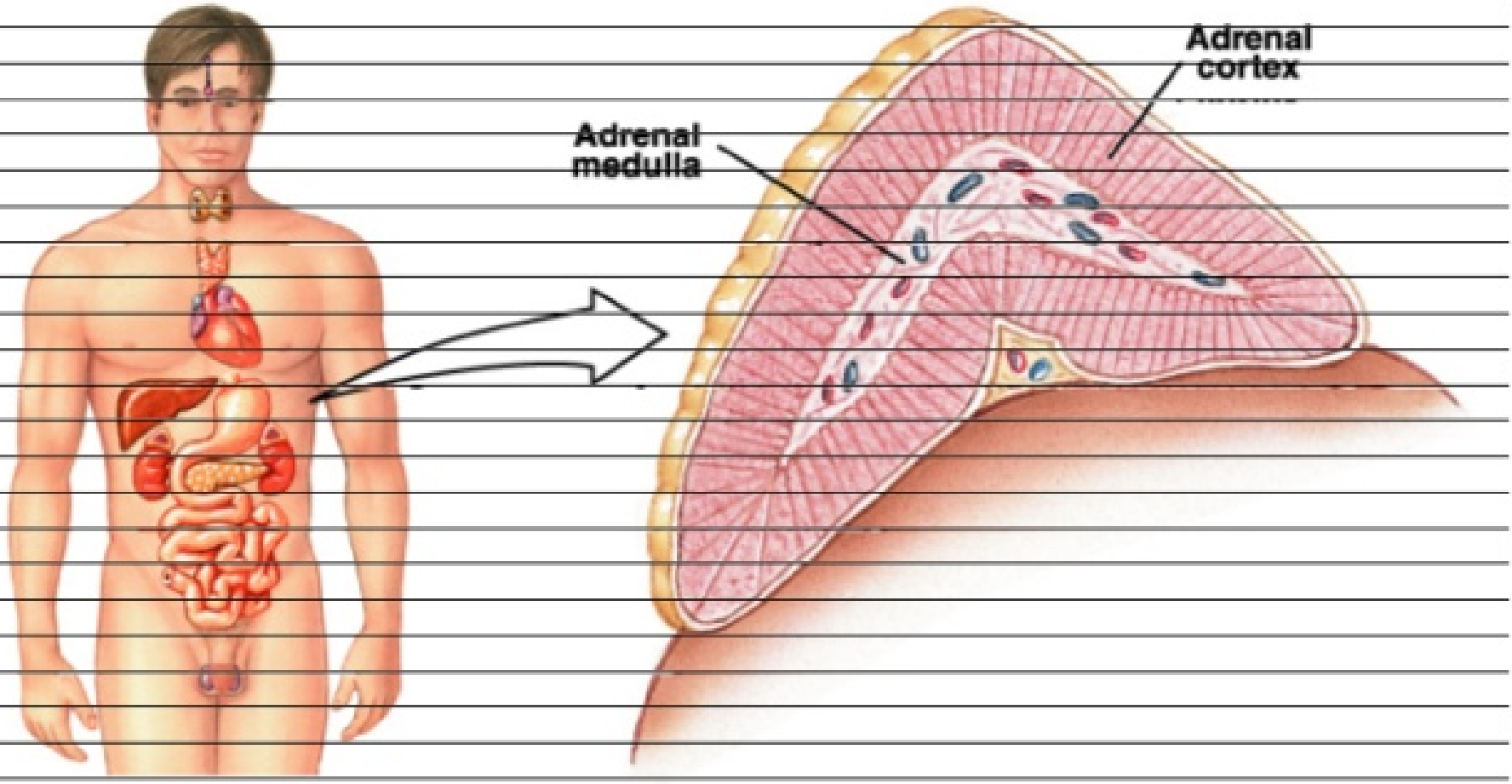
Adrenal glands

- Small, triangular glands loosely attached to the kidneys

- Divided into two morphologically distinct regions

  - adrenal cortex (outer)

  - adrenal medulla (inner)


Adrenal cortex
Adrenal medulla

Steroid Hormones

- Steroid hormones are produced by the gonads and adrenal cortex.

- Steroid hormones are made from cholesterol in the smooth endoplasmic reticulum and mitochondria of endocrine cells.

- Steroid hormones cannot be stored in vesicles in the endocrine cells that produce them. As soon as steroid hormones are produced, they diffuse out of the endocrine cell and enter the bloodstream.
- Steroid hormones are lipid soluble and their receptors are located in the cytoplasm target cell.

Steroid hormone transport

- Lipid soluble hormones require transport proteins
- albumin and transthyretin (prealbumin)
- specific transport molecules (steroid-binding globulin)

- only unbound form can enter the cell

- Steroid and thyroid hormones are 99% attached to special transport proteins

Adrenal Medulla

- an extension of the sympathetic nervous system

- acts as a peripheral amplifier

- activated by same stimuli as the sympathetic nervous system

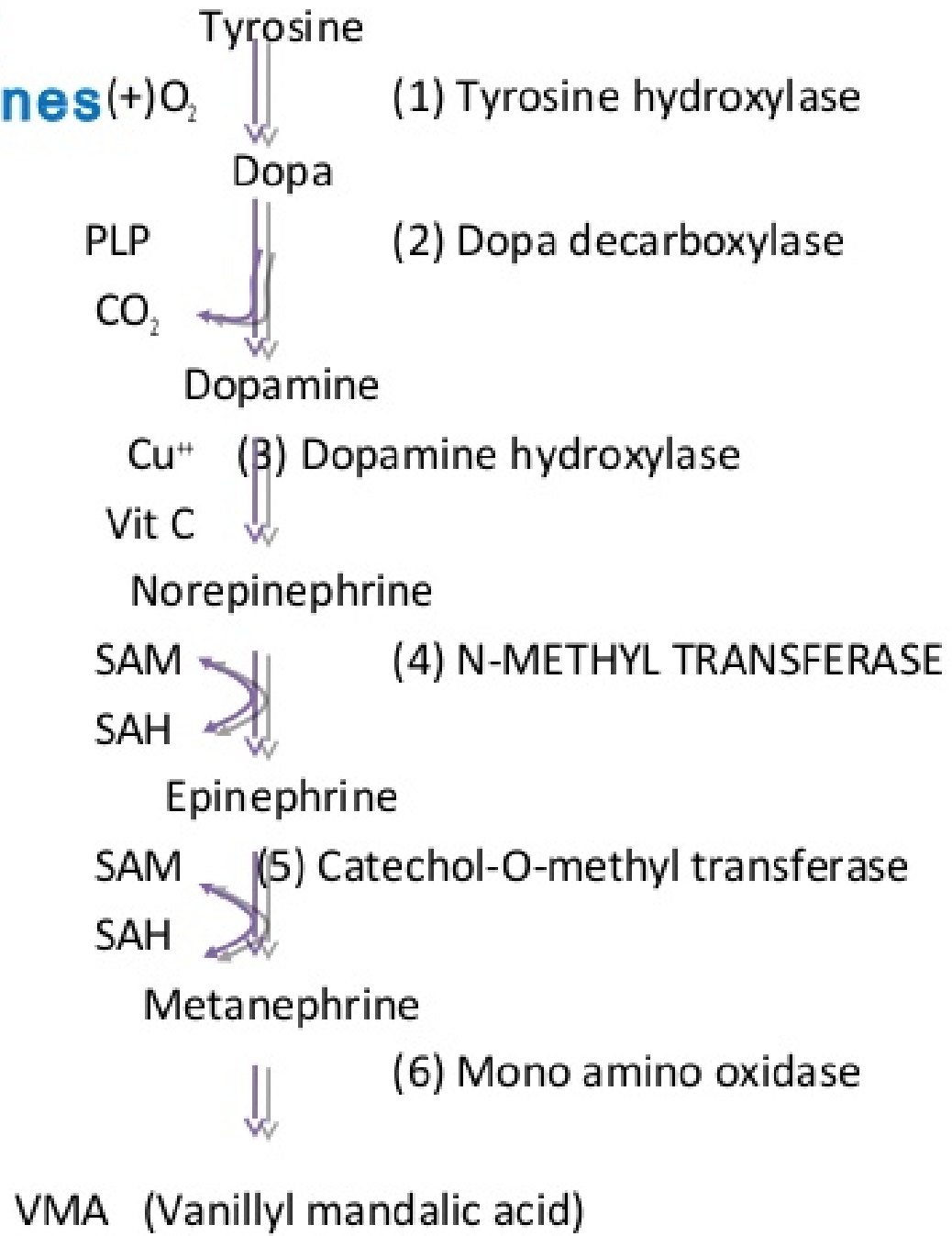
  (examples – exercise, cold, stress, hemorrhage, etc.)

Hormones of the Adrenal Medulla

- Hormones synthesized in adrenal medulla are catacolamines. They are:
- dopamine
- adrenaline/ noradrenaline
  epinephrine/norepinephrine

- 80% of released catecholamine is epinephrine
- Hormones are secreted and stored in the adrenal medulla and released in response to appropriate stimuli

Synthesis of Catecholamines



Mechanism of Action

- receptor mediated – adrenergic receptors

- peripheral effects are dependent upon the type and ratio of receptors in target tissues

Receptor	α	β
Norepinephrine	+++++	++
Epinephrine	++++	++++

Table 24.4. Adrenergic Responses of Selected Tissues

Organ or Tissue	Receptor	Effect
Heart (myocardium)	β_1	Increased force of contraction Increased rate of contraction
Blood vessels	α β_2	Vasoconstriction Vasodilation
Gut	α,β	Decreased motility and increased sphincter tone
Liver	α,β	Increased glycogenolysis
Adipose tissue	β	Increased lipolysis
Skin (apocrine glands on hands, axillae, etc.)	α	Increased sweating
Bronchioles	β_2	Dilation

Differences between Epinephrine and Norepinephrine

Epinephrine >> norepinephrine – in terms of cardiac stimulation leading to greater cardiac output (β stimulation).

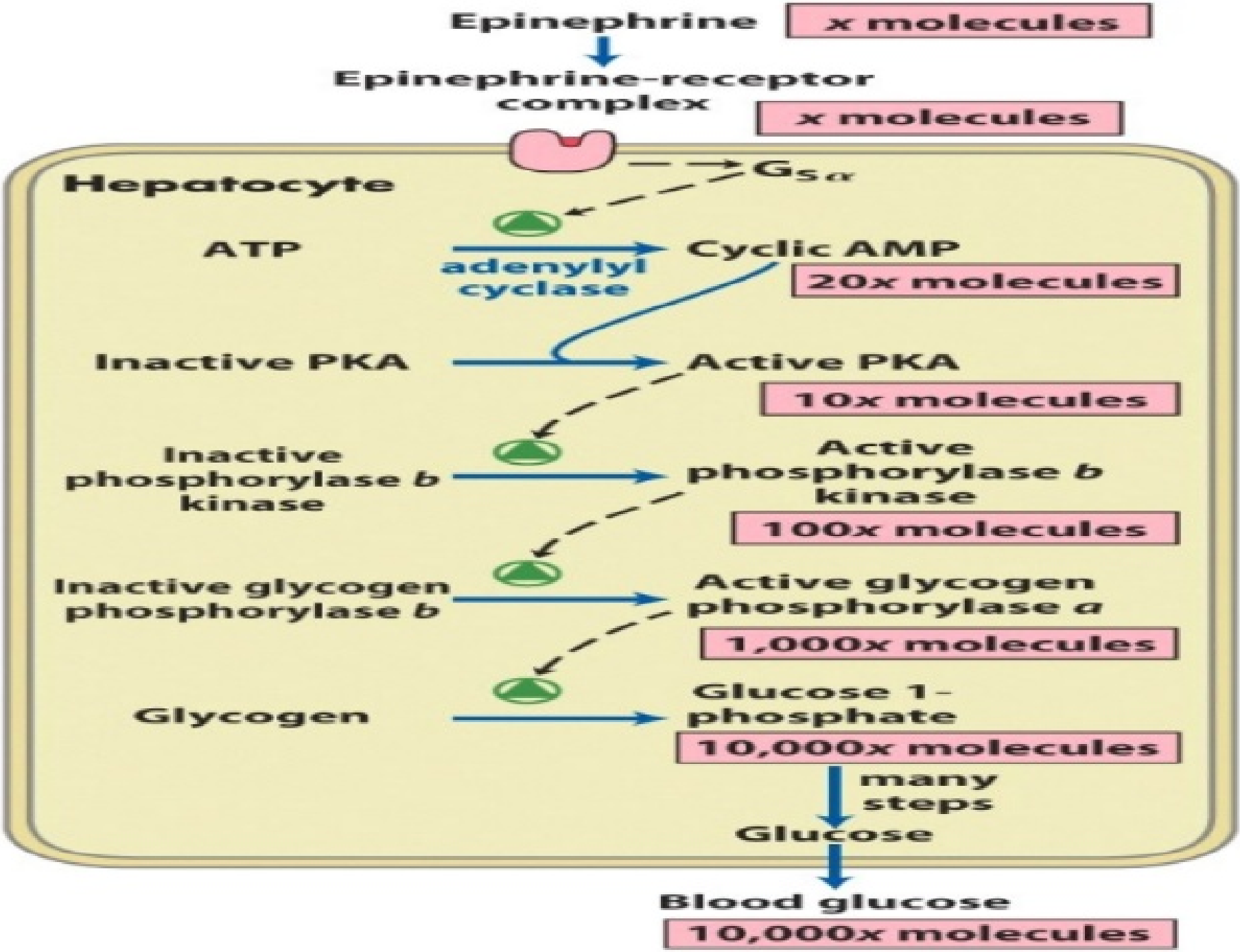
- Epinephrine < norepinephrine – in terms of constriction of blood vessels – leading to increased peripheral resistance – increased arterial pressure.

- Epinephrine >> norepinephrine –in terms of increasing metabolism Epi = 5-10 x Norepinephrine

Effects of Epinephrine

Metabolism:

- glycogenolysis in liver and skeletal muscle
  - can lead to hyperglycemia
- mobilization of free fatty acids
- increased metabolic rate
  - O_2 consumption increases


Epinephrine
x molecules
Epinephrine-receptor complex
x molecules
Hepatocyte
$G_{s\alpha}$
ATP
adenylyl cyclase
Cyclic AMP
20x molecules
Inactive PKA
Active PKA
10x molecules
Inactive phosphorylase b kinase
Active phosphorylase b kinase
100x molecules
Inactive glycogen phosphorylase b
Active glycogen phosphorylase a
1,000x molecules
Glycogen
Glucose 1-phosphate
10,000x molecules
many steps
Glucose
Blood glucose
10,000x molecules

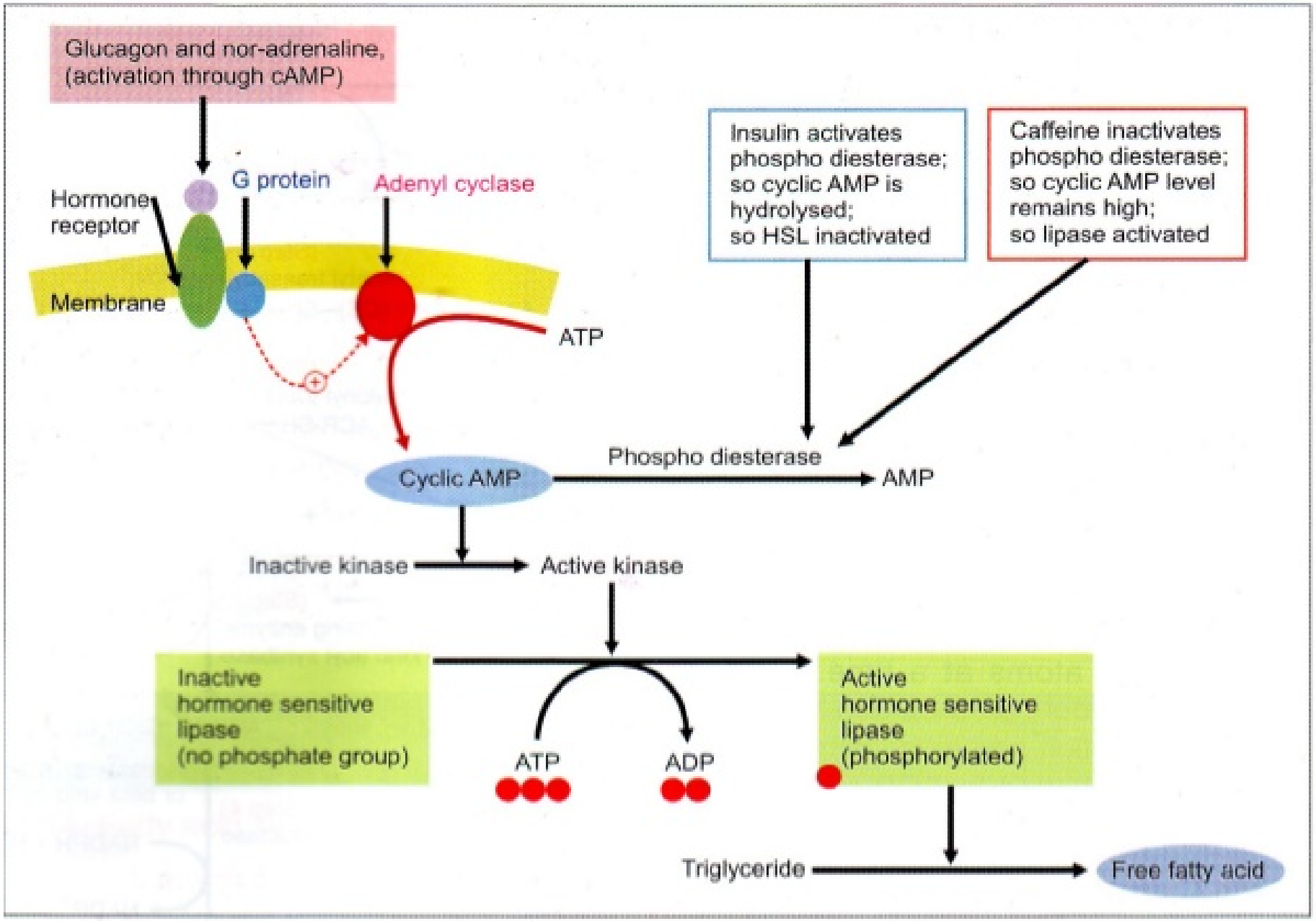


Fig. 11.16. Cascade activation of hormone sensitive lipase

Pheochromocytoma

- a catecholamine-secreting tumour of chromaffin cells of the adrenal medulla

adrenal pheochromocytoma (90%)

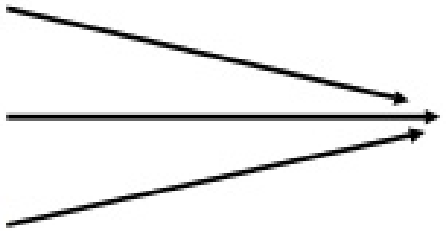
- paraganglioma – a catecholamine secreting tumour of the sympathetic paraganglia

extra-adrenal pheochromocytoma

Signs and Symptoms of Pheochromocytoma

- treatment resistant hypertension (95%)

- headache
- sweating
- palpitations



classic triad

- chest pain
- anxiety
- glucose intolerance
- increased metabolic rate

Diagnosis and Treatment

- diagnosed by high plasma catecholamines and increased metabolites in urine
- no test for adrenal or extra-adrenal
- treatment is surgical resection

Adrenal Cortex

- Hormones produced by the adrenal cortex are referred to as corticosteroids.
- These comprise mineralocorticoids, glucocorticoids and androgens.
- The cortex is divided into three regions:
  - zona glomerulosa
  - zona fasciculata
  - zona reticularis

Zona Glomerulosa

- Outermost zone – just below the adrenal capsule
- Secretes mineralocorticoids.
- Mineralocorticoids are it is termed as they are involved in regulation of electrolytes in ECF.
- The naturally synthesized mineralocorticoid of most importance is **aldosterone.**

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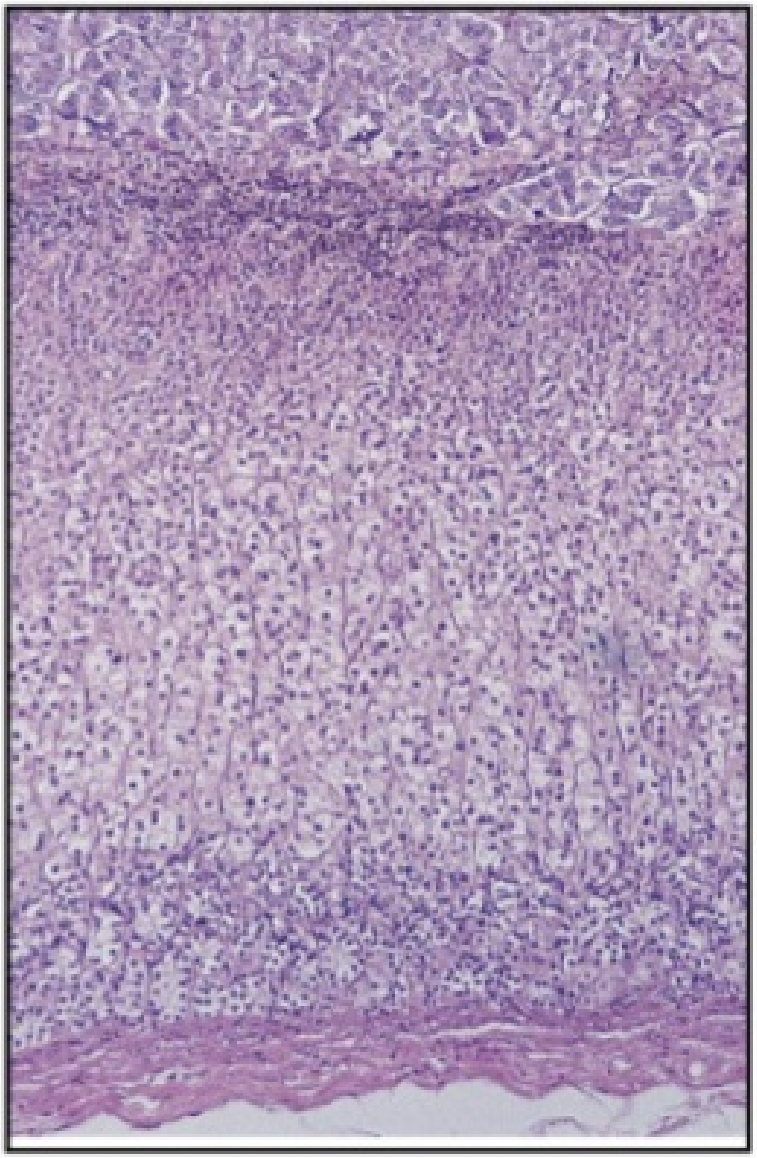
Zona Fasciculata

- Middle zone – between the glomerulosa and reticularis
- Primary secretion is glucocorticoids.
- Glucocorticoids, as the term implies, are involved the increasing of blood glucose levels. However they have additional effects in protein and fat metabolism.
- The naturally synthesized glucocorticoid of most importance is **cortisol.**

Zona Reticularis

- Innermost zone – between the fasciculata and medulla
- Primary secretion is androgens.
- Androgenic hormones exhibit approximately the same effects as the male sex hormone – testosterone.

gion of adrenal gland



Secretes

Adrenal medulla — Catecholamines

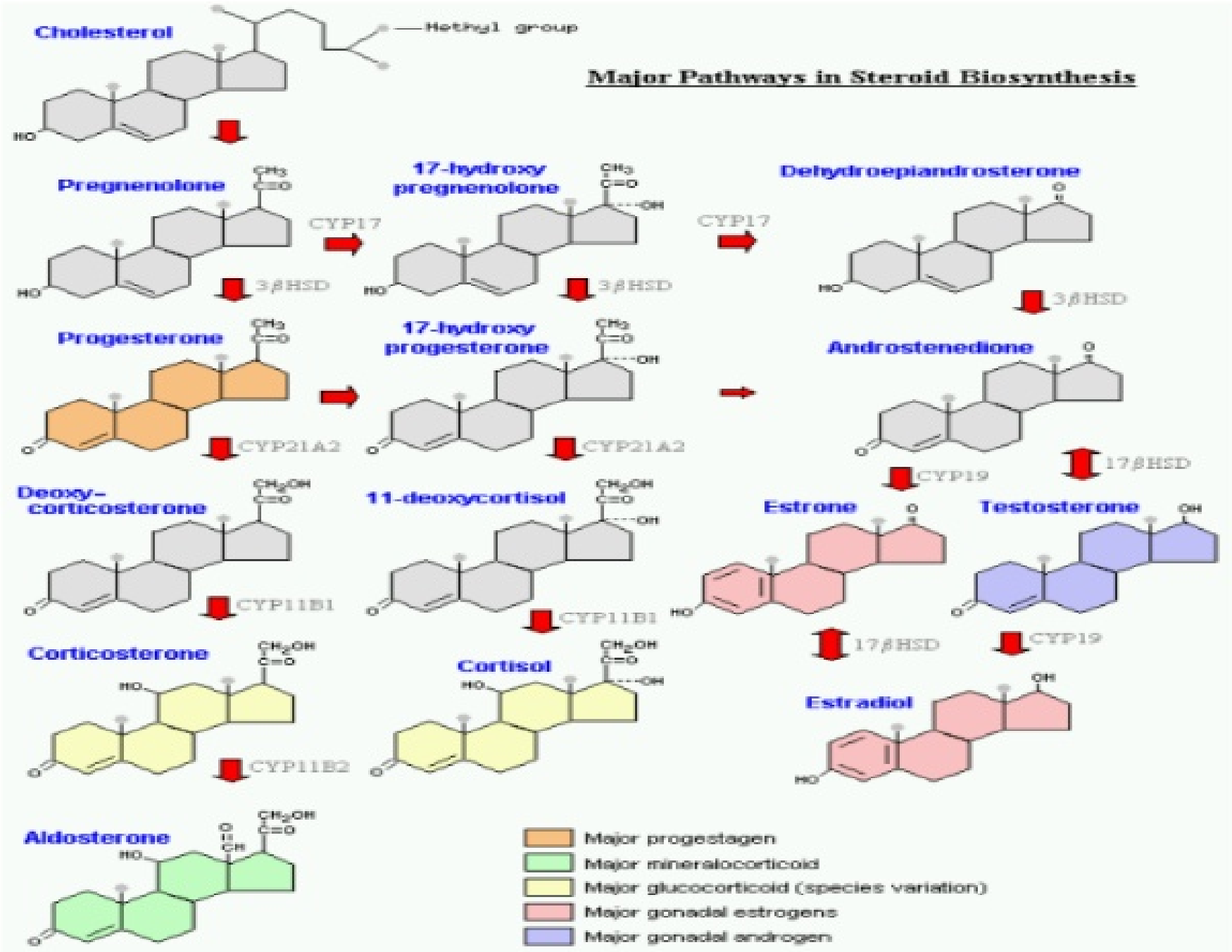
Zona reticularis — Sex hormones

Adrenal cortex

Zona fasciculata — Glucocorticoids

Zona glomerulosa — Aldosterone

Capsule


Major Pathways in Steroid Biosynthesis
Cholesterol
Methyl group
Pregnenolone
CYP17
17-hydroxy pregnenolone
CYP17
Dehydroepiandrosterone
3βHSD
3βHSD
3βHSD
Progesterone
17-hydroxy progesterone
Androstenedione
CYP21A2
CYP21A2
CYP19
17βHSD
Deoxy-corticosterone
11-deoxycortisol
Estrone
Testosterone
CYP11B1
CYP11B1
17βHSD
CYP19
Corticosterone
Cortisol
Estradiol
CYP11B2
Aldosterone
Major progestagen
Major mineralocorticoid
Major glucocorticoid (species variation)
Major gonadal estrogens
Major gonadal androgen

Aldosterone

- a steroid hormone

- essential for life (acute)

- responsible for regulating Na^+ reabsorption in the distal tubule and the cortical collecting duct

- target cells are called “principal (P) cell”

  - stimulates synthesis of more Na/K-ATPase pumps

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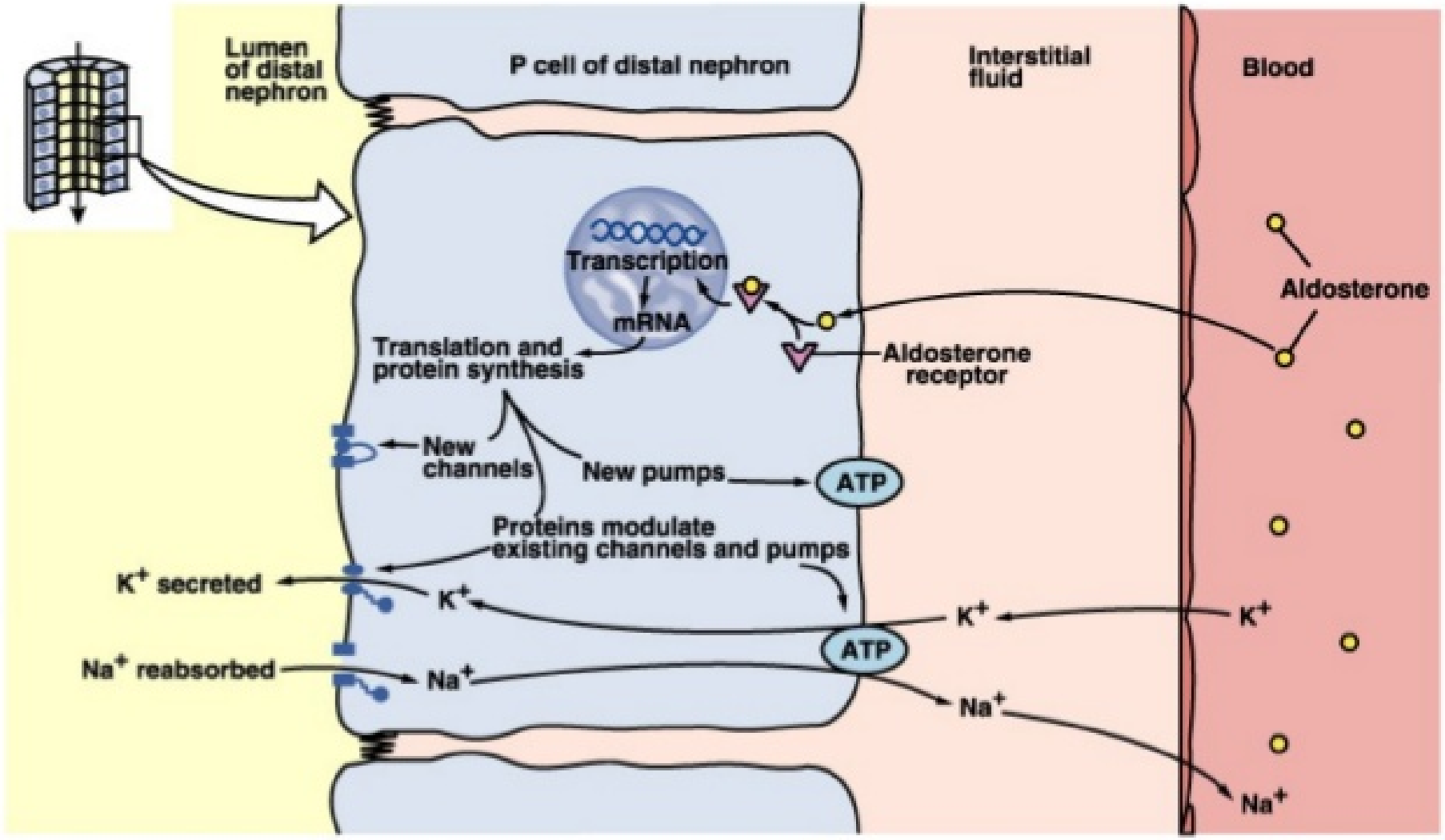

Lumen of distal nephron
P cell of distal nephron
Interstitial fluid
Blood
Transcription
mRNA
Translation and protein synthesis
Aldosterone receptor
Aldosterone
New channels
New pumps
ATP
Proteins modulate existing channels and pumps
K+ secreted
K+
K+
K+
ATP
Na+ reabsorbed
Na+
Na+
Na+

Effects of Aldosterone

- Renal and circulatory effects … covered (ECF volume regulation, sodium and potassium ECF concentrations)
- Promotes reabsorption of sodium from the ducts of sweat and salivary glands during excessive sweat/saliva loss.
- Enhances absorption of sodium from the intestine especial. colon. – absence leads to diarrhea.

Regulation of Aldosterone Release

- direct stimulators of release
  - increased extracellular K^+
  - decreased osmolarity
  - ACTH
- indirect stimulators of release
  - decreased blood pressure
  - decreased macula densa blood flow

Glucocorticoids - **Cortisol**

- a steroid hormone
  - plasma bound to corticosteroid binding globulin (CBG or transcortin)
- essential for life (long term)2hr
- the net effects of cortisol are catabolic
  - prevents against hypoglycemia

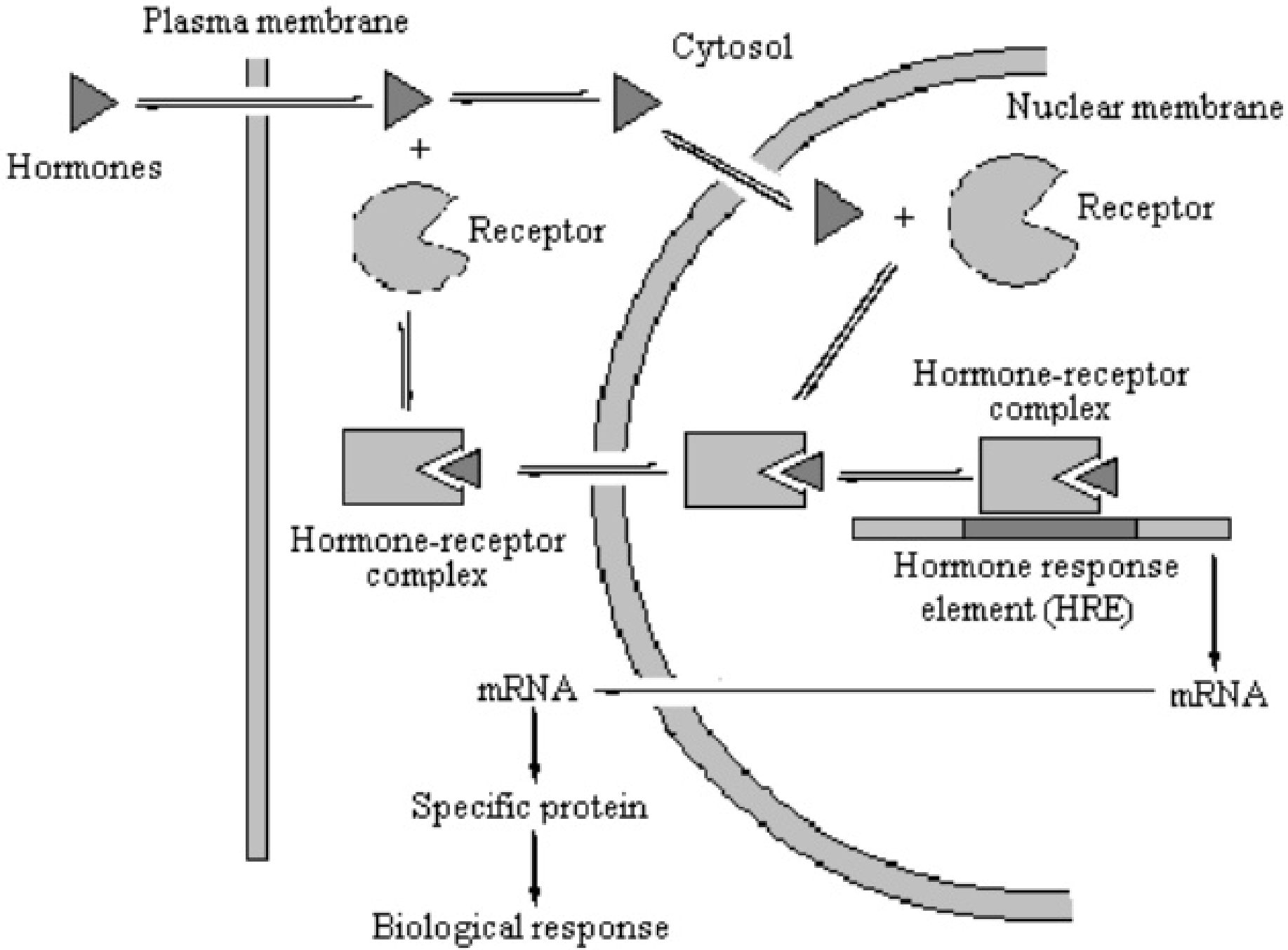

Plasma membrane
Cytosol
Nuclear membrane
Hormones
+
Receptor
+
Receptor
Hormone-receptor
complex
Hormone-receptor
complex
Hormone response
element (HRE)
mRNA
mRNA
Specific protein
Biological response

Table 38.1. Effects of glucocorticoids

System	*Effect*
Carbohydrates	Activity of transaminases and gluconeogenic enzymes (PC, PEPCK, FDP and GP) are stimulated, increasing gluconeogenesis. Glycolytic enzymes (GK, PFK and PK) are suppressed. Decreased glucose uptake by peripheral tissues. All of them lead to hyperglycemia (Diabetogenic).
Lipids	Increase lipid mobilisation; facilitate lipolytic hormones leading to hyperlipidemia.
Proteins and nucleic acids	Catabolism of proteins and nucleic acids increased. Increase urea production.
Fluid and electrolytes	Promote water excretion by increase in GFR and inhibition of ADH secretion.
Bone and calcium	Decrease serum calcium by inhibiting osteoblast function, leading to osteoporosis.
Secretory action	Stimulate secretion of gastric acid and enzyme. Induce acid peptic disease.
Connective tissue	Impaired collagen formation. Poor wound healing.
Immune system	Immunosuppressant. Lysis of lymphocytes. Antiinflammatory and antiallergic.

Physiological Actions of Cortisol

- promotes gluconeogenesis
- promotes breakdown of skeletal muscle protein
- enhances fat breakdown (lipolysis)
- suppresses immune system
- breakdown of bone matrix (high doses)

Anti-inflammatory Effects of Cortisol

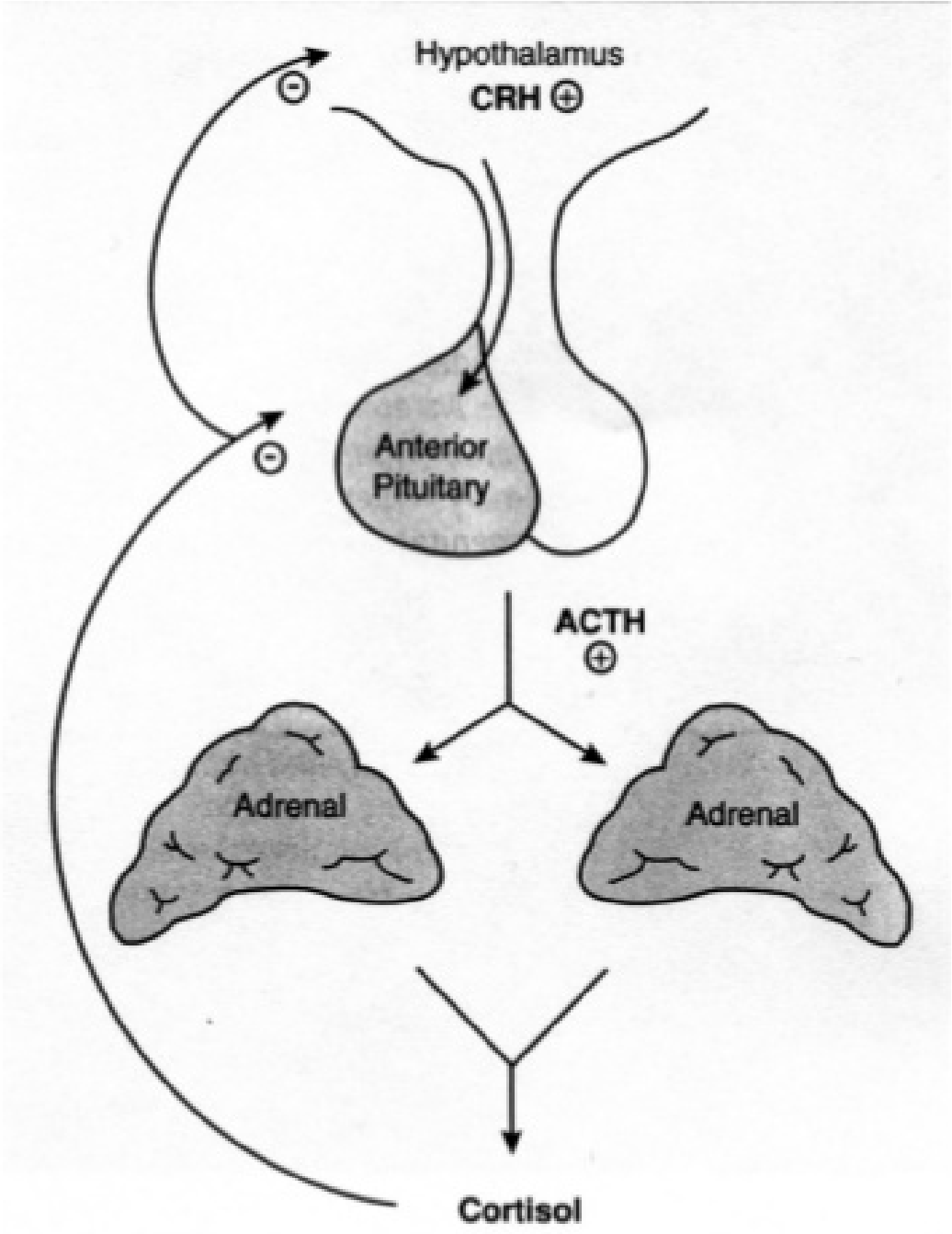
- reduces phagocytic action of white blood cells
- reduces fever
- suppresses allergic reactions
- wide spread therapeutic use

Effect on Blood Cells and Immunity

- Decrease production of eoisinophils and lymphocytes
- Suppresses lymphoid tissue systemically therefore decrease in T cell and antibody production there by 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.

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


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

Regulation of Cortisol Release

Enhanced release can be caused by:

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

Adrenal Cortex Dysfunctions

Hypoadrenalism – Addison's Disease

- adrenal cortex produces inadequate amounts of hormones
- caused by autoimmunity against cortices 80%
- also caused by tuberculosis, drugs, cancer
- plasma sodium decreases and may lead to circulatory collapse

Mineralocorticoid Deficiency

- Lack of aldosterone:
  - Increased sodium, chloride, water loss
  - Decrease ECF volume
  - Hyperkalemia
  - Mild acidosis
  - Increase RBC concentration
  - Decrease cardiac output – shock - death within 4 days to a 2 weeks if not treated

Glucocorticoid Deficiency

- Loss of cortisol
  - Disruption in glucose concentration
  - Reduction in metabolism of fats and proteins
  - Patient is susceptible to different types of stress
  - Sluggishness of energy mobilization result in weak muscle even when glucose and other nutrients are available – cortisol is needed for metabolic function

Melanin Pigmentation

- Characteristic of Addison's disease is uneven distribution of melanin deposition in thin skin eg. Mucous membranes, lips, thin skin of the nipples.
- Feedback and effect on MSH

Treatment

- Total destruction, if untreated, could lead to death with a few days.
- Treatment – small quantities of mineralocorticoids and glucocorticoids daily.

Hyperadrenalism – Cushing's Syndrome

- caused by exogenous glucocorticoids and by tumours (adrenal or pituitary)

- zg tumour increases aldosterone
  - -increased sodium, blood pressure
  - -80% suffer from hypertension
- zr tumour increases cortisol
  - - excess protein catabolism, redistribution of fat

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Characteristics

- 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)

Effects on Carbohydrate Metabolism

- "Adrenal diabetes"
  - Hypersecretion of cortisol results in increase blood glucose levels, up to 2 x normal (200mg/dl)
  - Prolonged oversecretion of insulin "burns out" the beta cells of the pancreas resulting in life long diabetes mellitus

Effects on Protein Metabolism

- Decrease protein content in most parts of the body resulting in muscle weakness
- In lymphoid tissue – decrease protein synthesis results in suppression of the immune system
- Lack of protein deposition in bones can result in osteoporosis
- Collagen fibers in subcutaneous tissue tear forming striae

Adrenogenital syndrome (AG syndrome)

- There is conegenital deficiency of steroid hydroxylases leading to deficient secretion of cortisol.

- Since cortisol, the major feedback effector is not present, ACTH secretion continues leading to congenital adrenal hyperplasia (CAH).

21 –Hydroxylase Deficiency:

- 21 –Hydroxylase Deficiency is the most common type, where the production of cortisol is totally absent.
- The lack of feedback leads to increased androgen synthesis.
- This would result in Virilization of female children who develop ambiguous genitalia. precocious puberty is seen in male children.
- Early diagnosis and supplementation of cortisol is effective in children.

11-Hydroxylase Deficiency:

- In this condition, the symptoms are more serious.

- The hypertensive variety of the AG syndrome manifests and the child may not survive.

Estimation of Glucocorticoids secrtion:

1) Basal level of cortisol: The plasma cortisol level is determined by

- RIA
- ELISA
- CLIA (chemiluminiscent immuno assay)
- The normal range is 5-25 microgram/dl of at 9AM and 2-5 microgram/dl at 10 pm.

2) Estimation of urinary free cortisol:

- The free cortisol in plasma is the biologically active fraction.
- High levels are seen in hyperfunction and low levels in hypoactivity

3) Plasma ACTH:

Suppressed ACTH levels are seen in hyperadrenalism and high ACTH levels in hypoadrenalism as well as in Cushing's disease.

4) Dexamethasone suppression test

- Dexamathasone produce a fall in cortisol secretion due to feedback suppression ofACTH.

5) Urinary steriods

Estimation of 17-ketogenic steriods is indecated only in AG syndrome.

6) Stimulation test

Infusion of synthetic ACTH (synacthen or tetra cosactrin) is given

In the absense of reserve, stimulation tests fail to the any response

7) Metyrapone test :

- metyrapone inhibits the hydrolase enzyme.
- when it is given, cortisol is not formed.
- Then there is no feedback inhibitory effect.
- Hence, alternate pathways of sex steriods are more operative and the urinary excretion of 17-ketosteriods tends to elevate.

8) CRH test:

The test is of importance in establishing the cause of adrenal hyperfunction (primary, secondary or tertiary)

Normal ranges:

- Aldosterone : 6 – 20 ng/ml
- Corticosterone : 130- 820ng/dl
- Cortisol :

  in 9 AM 5-25microgram/dl

  midnight 2-5 microgram/dl
- Progesterone: 12- 30 ng/ml
- Epinephrine 10- 100pg/ml
- nonEpinephrine70-700pg/ml

NORMAL VALUE OF

CORTISOL : plasma

9 AM ----------130 – 600 nmol / L
MIDNIGHT----------30 –- 130 nmol / L

Immunoassay for 17- alpha-hydroxy progesterone

Normal value : urine

female : 5.5 – 22 µmol / d
MALE : 8 – 22 µmol / d

1) VMA (Vanilimandilic acid) :

normal level 2-6mg/day

Estimated by antibody method

2) HVA (Homovanilic acid) in urine: metabolite of dopa and dopamine

VMA /HVA ratio >1 has better prognosis in neuroblastoma

THANK YOU