Physical Activity and Health Promotion

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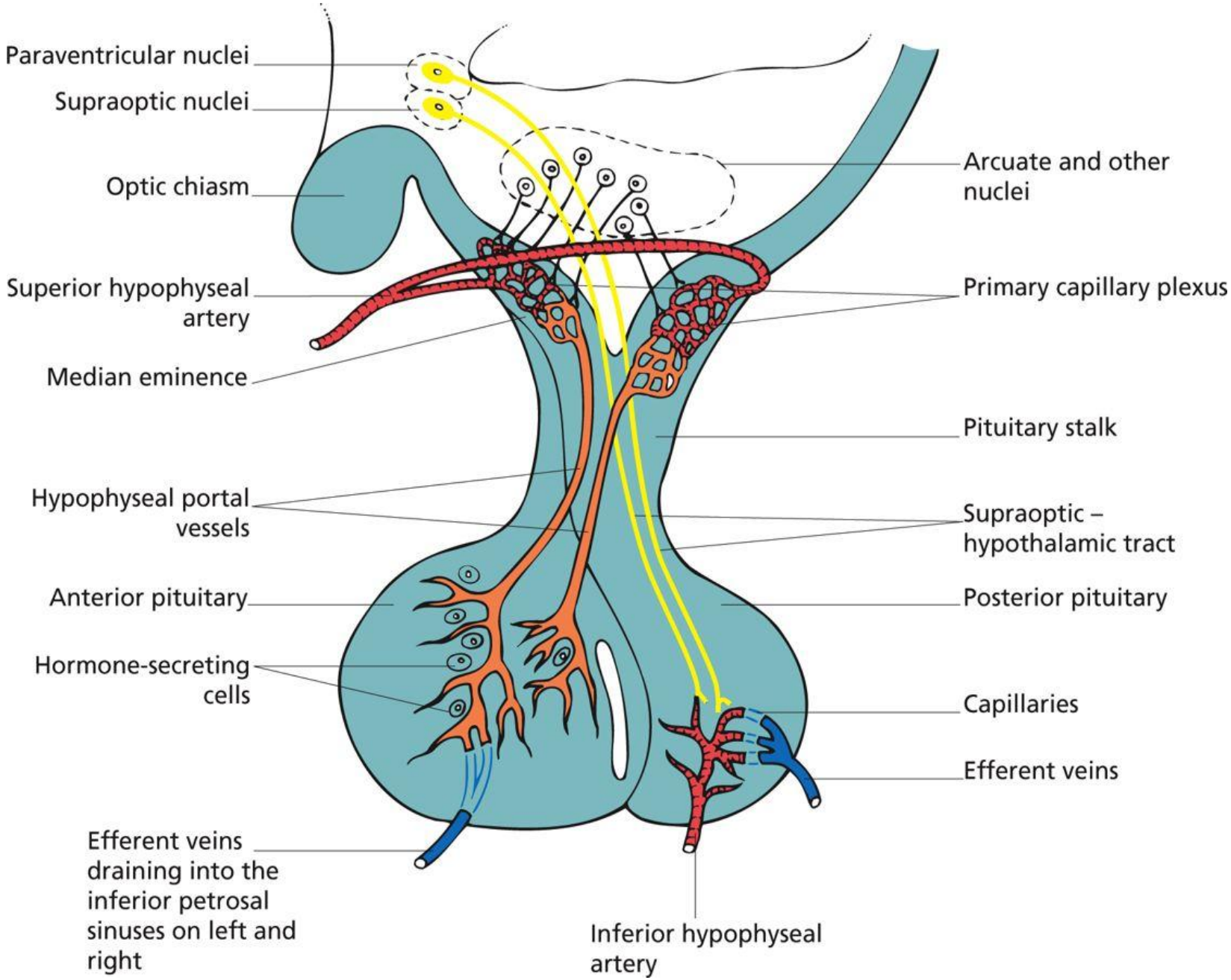
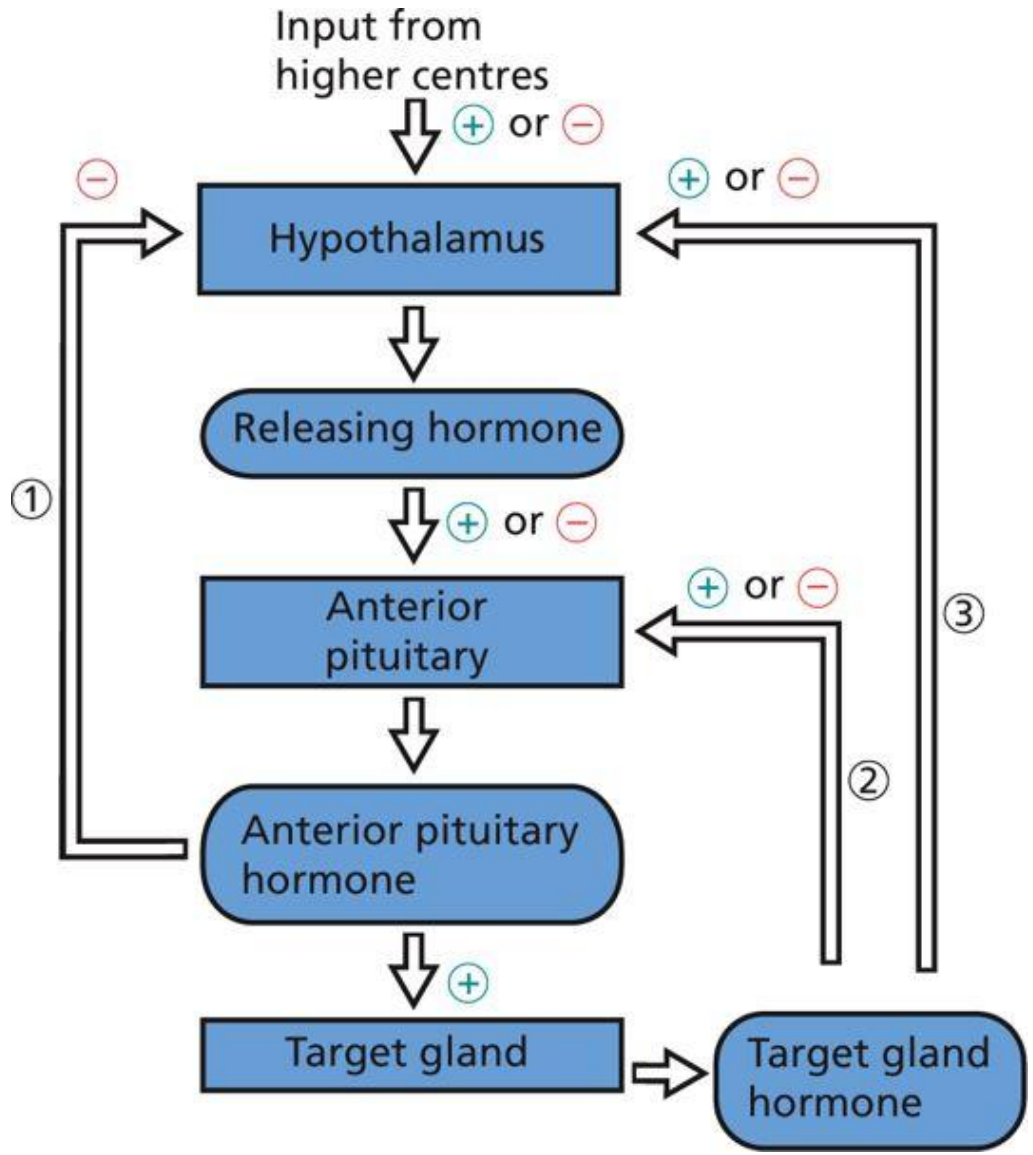
Lesson 3
The adrenal gland

https://www.endocrinologiamoretti.it

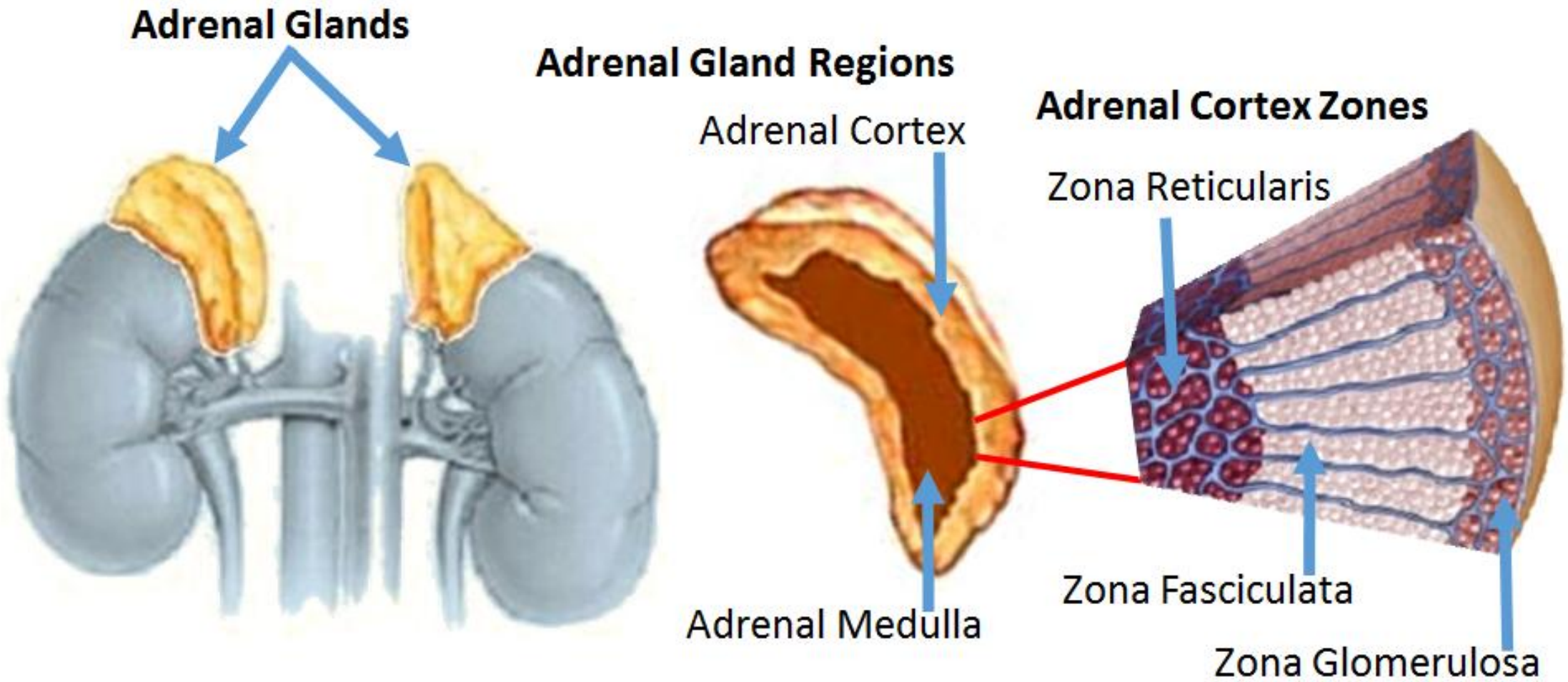

Paraventricular nuclei
Supraoptic nuclei
Optic chiasm
Superior hypophyseal artery
Median eminence
Hypophyseal portal vessels
Anterior pituitary
Hormone-secreting cells
Efferent veins draining into the inferior petrosal sinuses on left and right
Arcuate and other nuclei
Primary capillary plexus
Pituitary stalk
Supraoptic – hypothalamic tract
Posterior pituitary
Capillaries
Efferent veins
Inferior hypophyseal artery

Hormone-secreting cell types of the anterior pituitary

Anterior pituitary cell type	Hormone secreted	Size (number of amino acids)	Target organ	Hypothalamic regulator (+ or – effect)
Somatotroph	Growth hormone (GH)	191	Diverse	GH-releasing hormone (GHRH, +) and Somatostatin (SS, –)
Lactotroph	Prolactin (PRL)	199	Breast	Dopamine (–) and thyrotrophin-releasing hormone (TRH, +)
Corticotroph	Adrenocorticotrophic hormone (ACTH)	39	Adrenal cortex	Corticotrophin-releasing hormone(CRH, +)
Thyrotroph	Thyroid-stimulating hormone (TSH)	204	Thyroid	TRH (+) Somatostatin (SS, -)
Gonadotroph	Follicle-stimulating hormone (FSH) and luteinizing hormone(LH)	Both 204	Ovary or testis	Gonadotrophin-releasing hormone(GnRH, +)


Input from higher centres
+ or −
Hypothalamus
Releasing hormone
+ or −
Anterior pituitary
Anterior pituitary hormone
+
Target gland
Target gland hormone
+ or −
+ or −
+ or −
−
①
②
③

Adrenal Glands

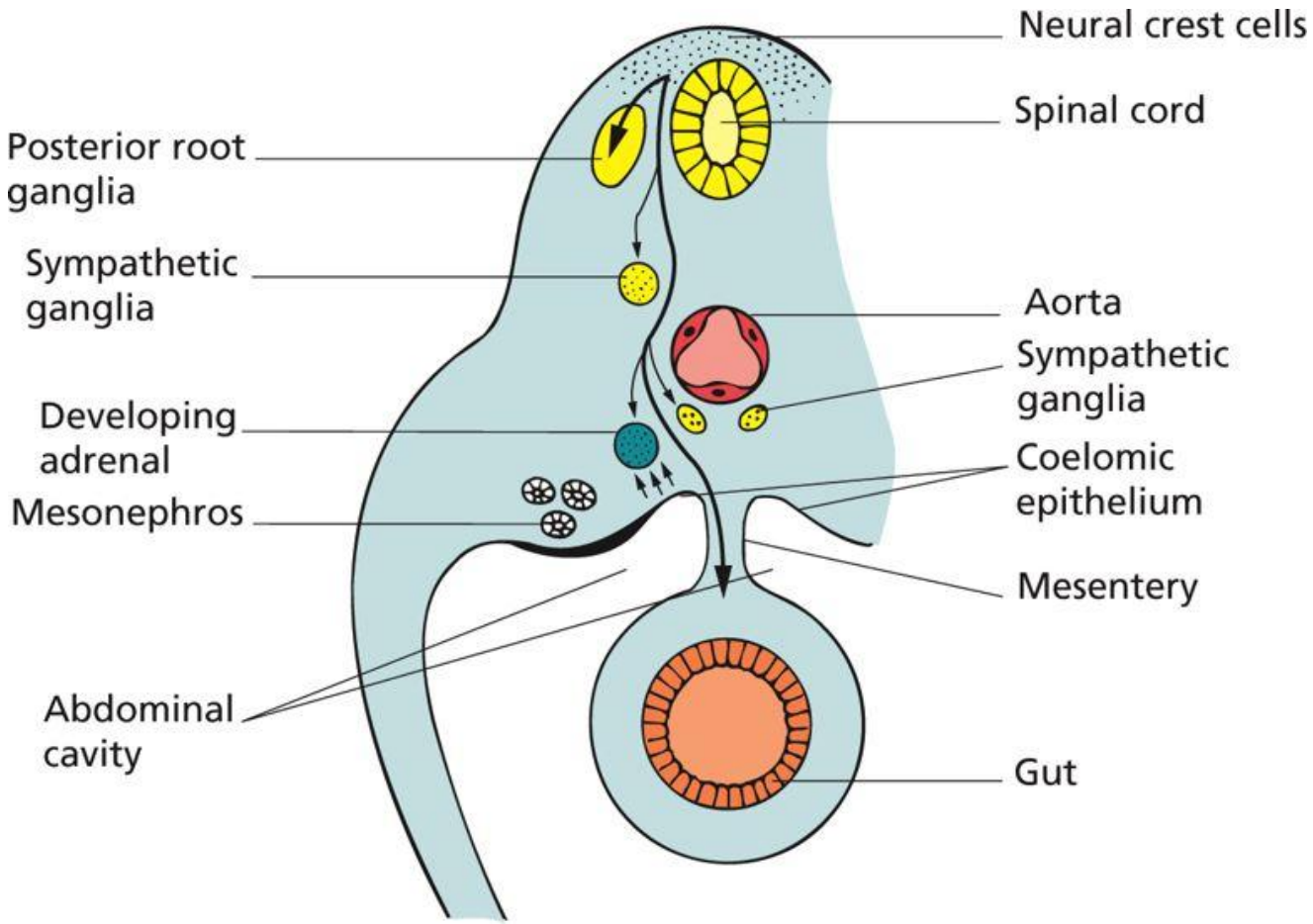


YourHormones.com

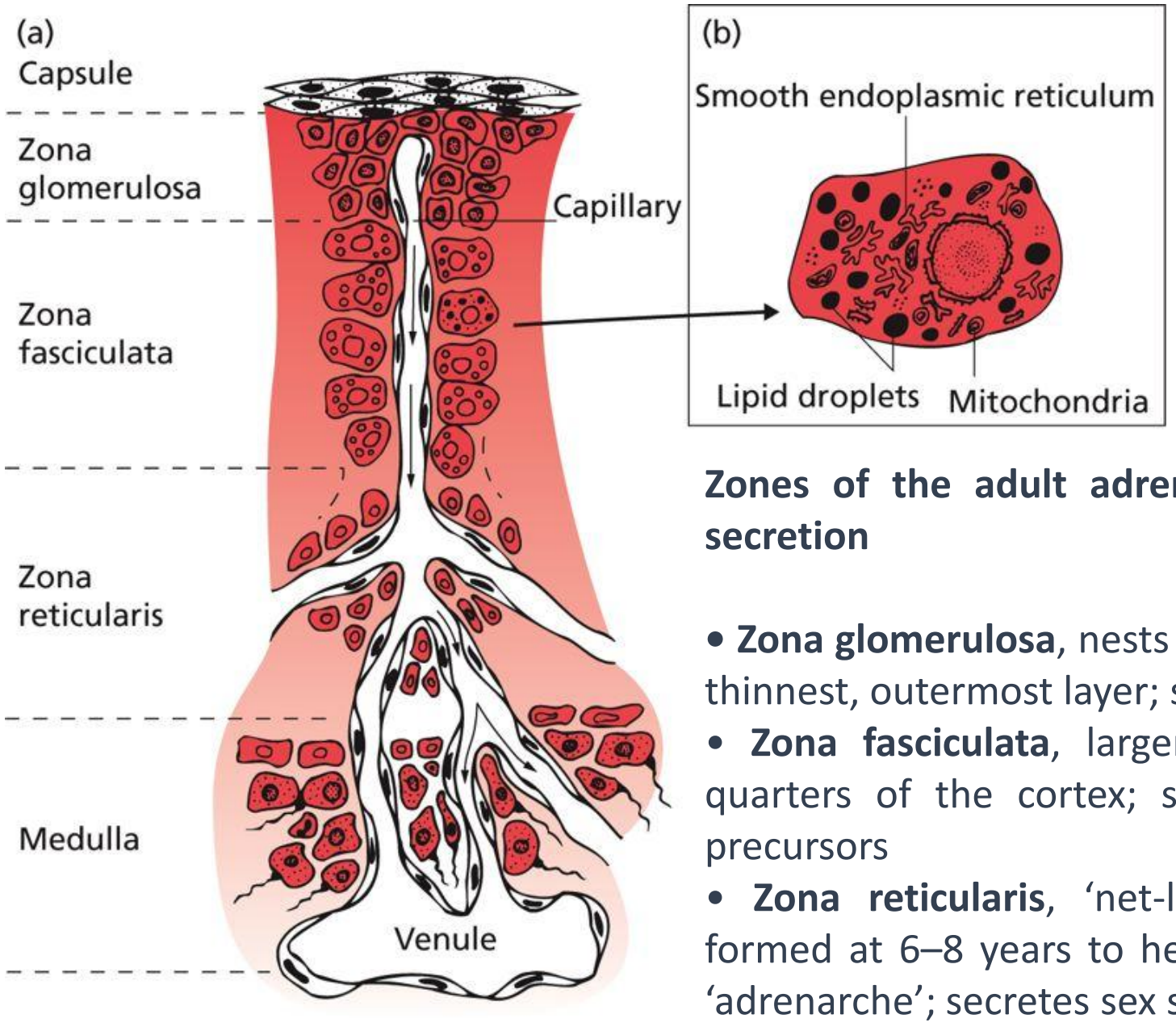
Embryology and anatomy

Clinical consequences of embryology

- The adrenal cortex and medulla develop separately – clinical disorders almost always affect either the cortex or medulla, but not both
- Forming the organ requires cell migration – adrenal disorders can occasionally cause trouble in unexpected places from embryological ‘rests’ of cells
- The cells forming the adrenal cortex also form the steroidogenic cell lineages in the gonad – disorders of steroid production can affect both organs simultaneously

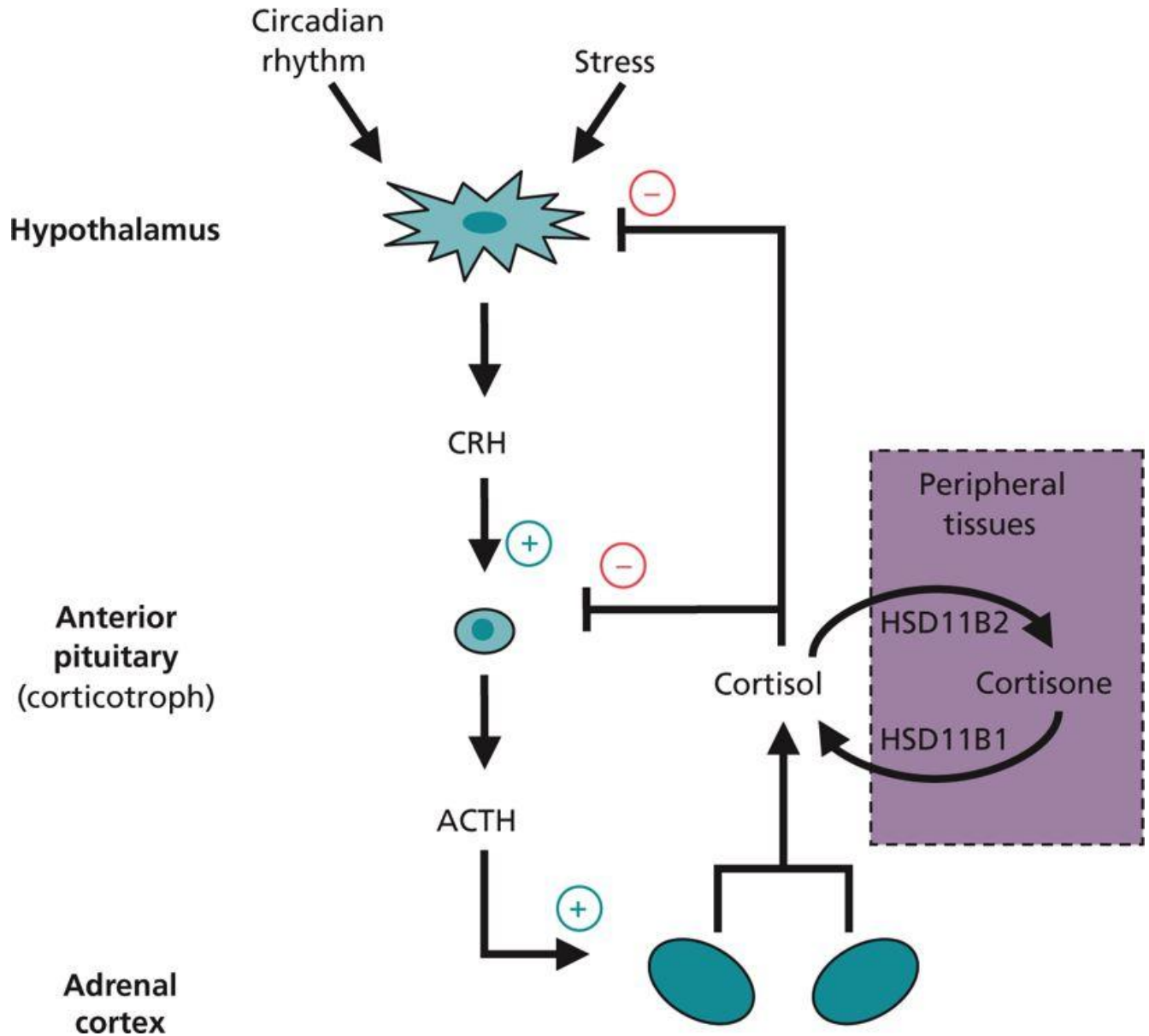


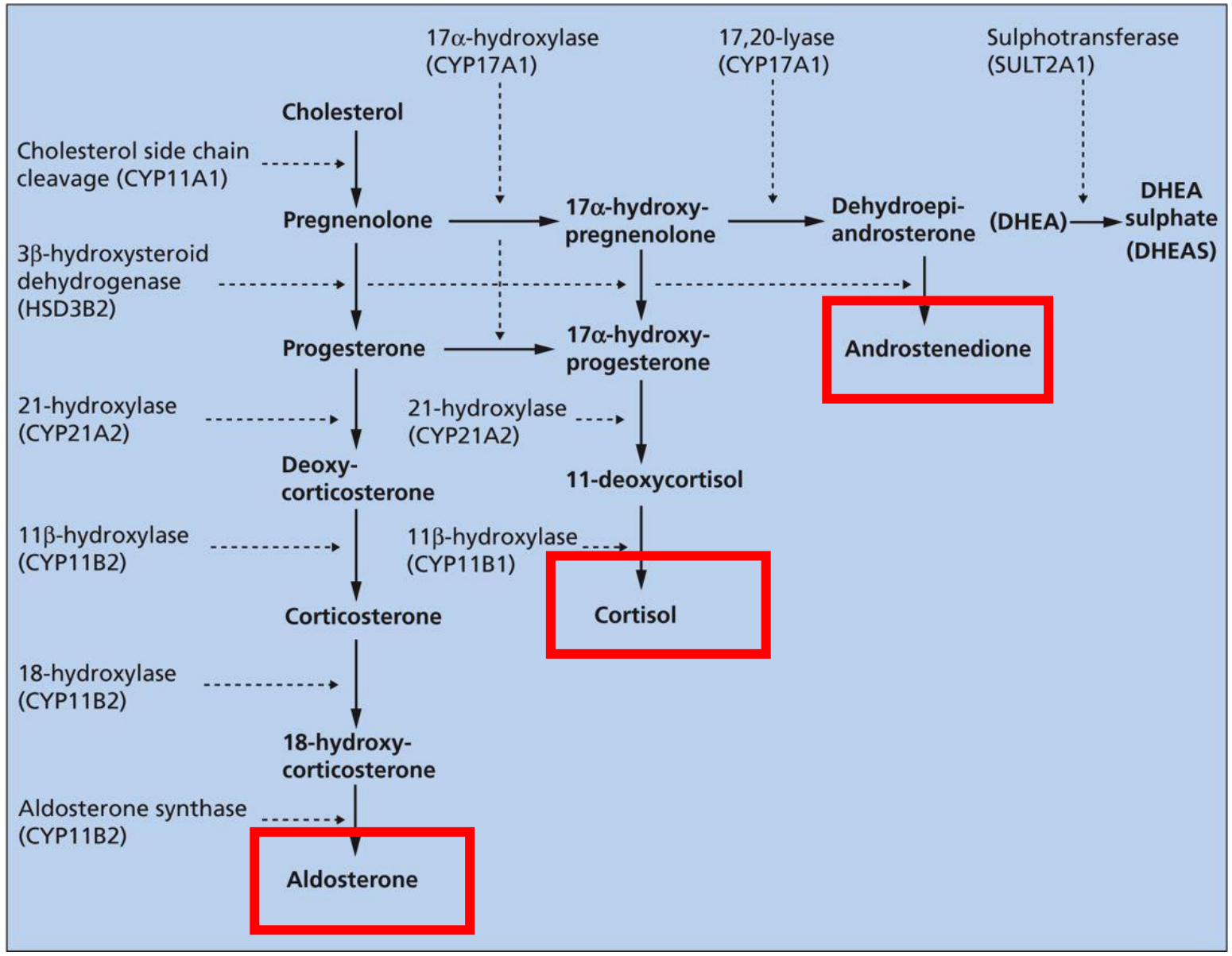
Development of the adrenal gland. The cortex is derived in part from the epithelium lining the abdominal cavity. Neural crest cells migrate from the back of the embryo; some give rise to dorsal root and sympathetic ganglia, while others invade the adrenal cortex to form the medulla. The rim of coelomic epithelium shown in black also gives rise to steroidogenic cells of the gonad.



Zones of the adult adrenal cortex and their steroid hormone secretion

- **Zona glomerulosa**, nests of closely packed small cells creating the thinnest, outermost layer; secretes aldosterone
- **Zona fasciculata**, larger cells in columns making up ~three-quarters of the cortex; secretes cortisol and some sex steroid precursors
- **Zona reticularis**, 'net-like' arrangements of innermost cells, formed at 6–8 years to herald a poorly understood change called 'adrenarche'; secretes sex steroid precursors and some cortisol


Circadian rhythm
Stress
Hypothalamus
CRH
Anterior pituitary (corticotroph)
ACTH
Adrenal cortex
Cortisol
Peripheral tissues
HSD11B2
Cortisone
HSD11B1



Biosynthesis of adrenocortical steroid hormones. HSD3B activity in the adrenal cortex arises from the type 2 isoform. The three steps from deoxycorticosterone to aldosterone are catalyzed by the same enzyme, CYP11B2

Adrenocortical steroidogenesis

• Transport of cholesterol into the mitochondrion by the steroid acute regulatory (**StAR**) protein
• The rate-limiting removal of the cholesterol side chain by **CYP11A1**
• Shuttling intermediaries between mitochondria and endoplasmic reticulum for further enzymatic modification
• Action of two key enzymes at branch points: ◦ **CYP17A1** prevents the biosynthesis of aldosterone and commits a steroid to cortisol or sex steroid precursor. Hence, CYP17A1 is absent from the zona glomerulosa ◦ Early action of HSD3B2 steers steroid precursors away from the sex steroid precursors towards aldosterone or cortisol
• The presence and activity of **CYP11B2** in the zona glomerulosa permitting aldosterone synthesis
• The presence and activity of **CYP11B1** in the fasciculata (and less so the reticularis) zone allowing cortisol production

Cortisol action

1. **Intermediary metabolism**

The net metabolic action of cortisol is to raise circulating free fatty acids and glucose, the latter stimulating glycogen synthesis. Excess cortisol also fosters an unfavourable serum lipid profile: raised total cholesterol and triglyceride with decreased high-density lipoprotein (HDL)–cholesterol. Cortisol has a permissive effect on epinephrine and glucagon, all of which creates a phenotype of ‘insulin resistance’ – the need for greater insulin secretion to maintain a normal blood glucose concentration (euglycaemia) In the long-term, cortisol stimulates adipocyte differentiation, particularly in the viscera, predisposing to centripetal obesity.

Cortisol action

2. Skin, muscle and bone

In skin, glucocorticoids inhibit keratinocyte proliferation and collagen synthesis. In muscle, the catabolic effects reduce protein synthesis, resulting in atrophy. Similar catabolic effects in bone shift the balance of activity from osteoblast (the bone-forming cell type) to osteoclast (the bone-resorbing cell type), predisposing to osteoporosis. Taken together, there is a net flow of amino acids towards the liver.

3. Salt and water homeostasis and blood pressure

Glucocorticoids can potentially increase sodium resorption and potassium loss at the distal tubule through effects, not on the glucocorticoid receptor (GR), but thought to be via the mineralocorticoid receptor (MR). More proximally, cortisol increases glomerular filtration rate (GFR) and inhibits vasopressin to increase free water clearance. Cortisol raises blood pressure by several mechanisms, including increased sensitivity of the vasculature to catecholamines.

4. Growth and development

Cortisol is an important hormone during growth and development of the fetus. It stimulates the differentiation of cell types to their mature phenotype. This is particularly evident in the lung, where it stimulates the production of surfactant, which reduces alveolar surface tension. This is one of the final steps in preparing the fluid-filled fetal airways for post-natal life. Too much glucocorticoid inhibits growth, in keeping with its largely catabolic effects on the musculoskeletal system. Cushing syndrome presents to the paediatric endocrinologist as cessation of linear growth.

Cortisol action

4. Lactation

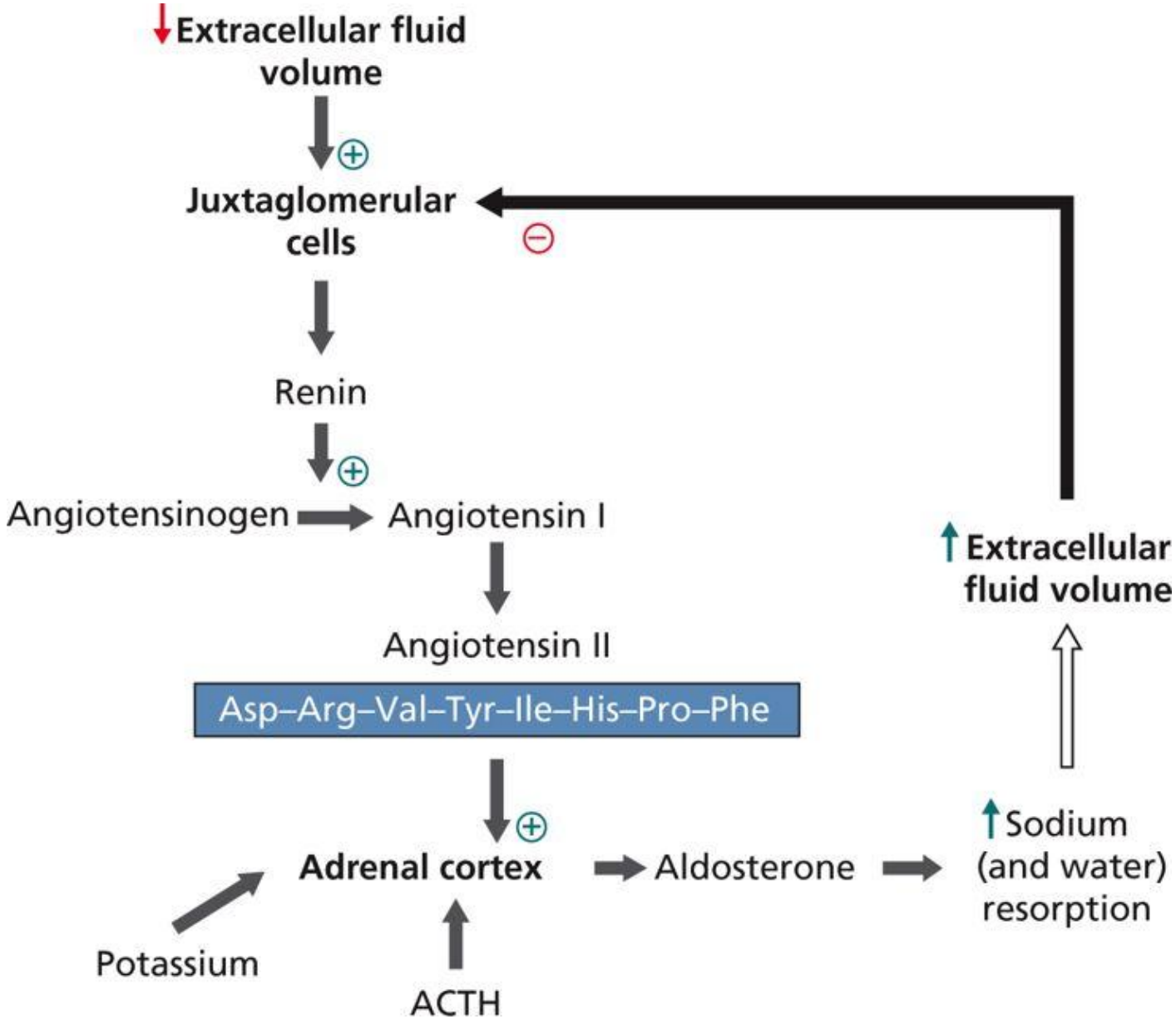
Post-partum, cortisol is required for the initiation of lactation by PRL. Its loss leads to a gradual reduction in milk secretion.

5. Central nervous system and psyche

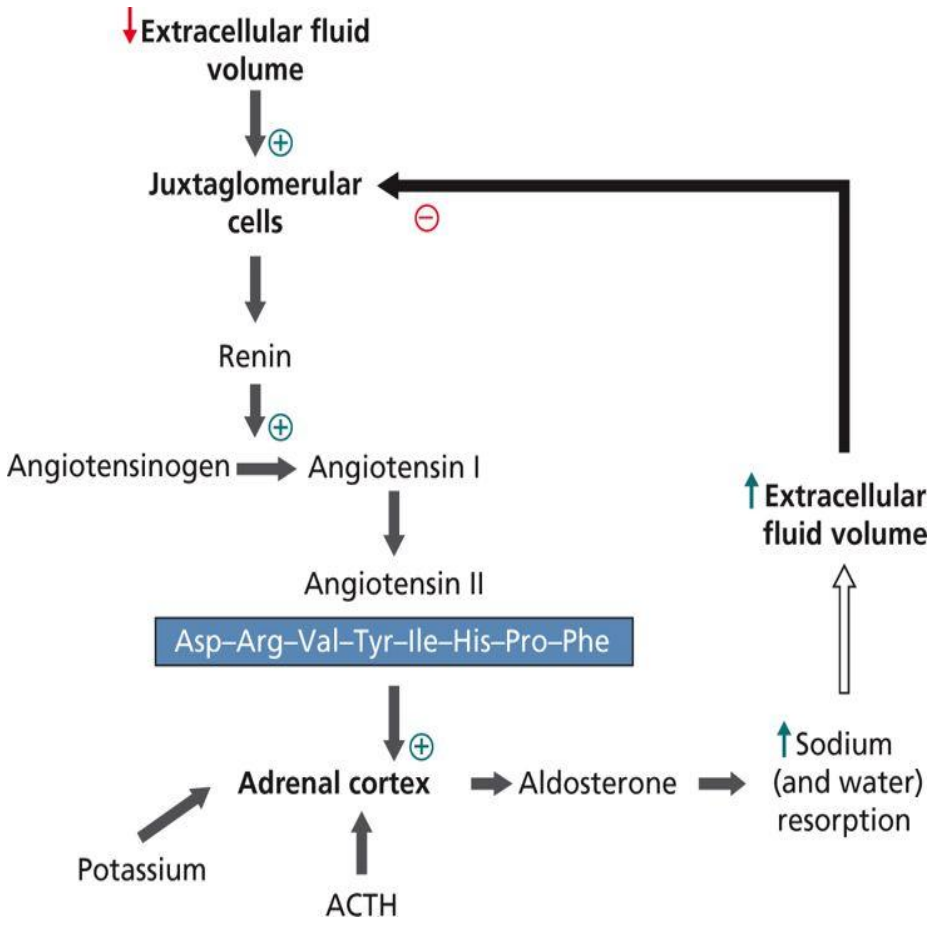
The role of glucocorticoids in the brain is highly complex, matched by their potential to cause a range of emotional symptoms from euphoria to depression.

6. Anti-inflammatory effects

Glucocorticoid actions on inflammation and autoimmunity are among its most important, reflected by the use of potent synthetic steroids to treat a range of disorders. With glucocorticoid treatment, circulating T lymphocytes and eosinophils fall; however, neutrophils rise. This is a catch to remember for the patient with an acute exacerbation of asthma. Raised circulating neutrophil count does not necessarily mean infection; it may simply reflect glucocorticoid treatment. In tissues, for instance, the acutely inflamed joints of a patient with rheumatoid arthritis, glucocorticoids rapidly suppress inflammation by inhibiting cytokine production and antagonizing macrophage action.

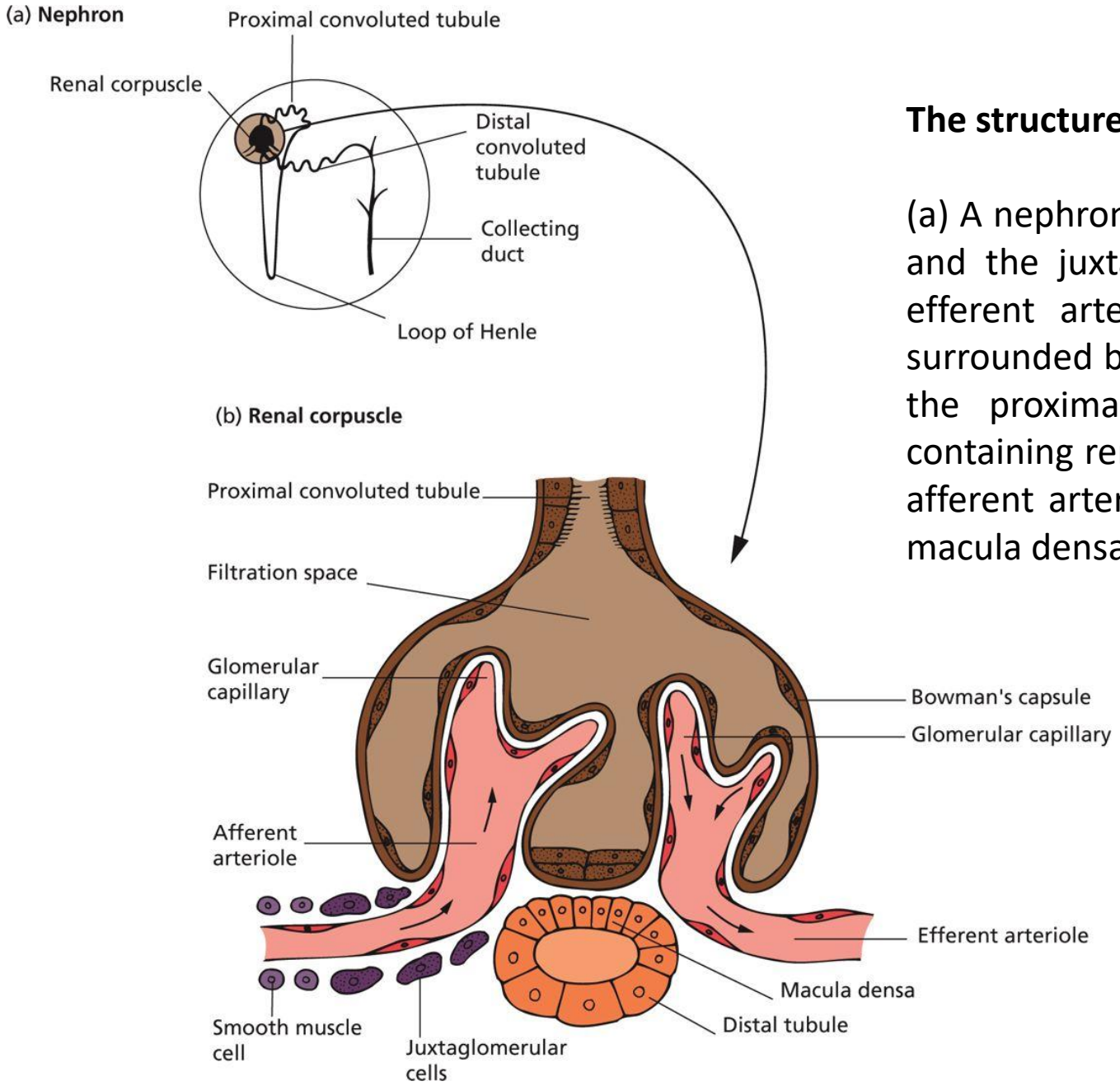

↓Extracellular fluid volume
⊕
Juxtaglomerular cells
⊖
Renin
⊕
Angiotensinogen
Angiotensin I
Angiotensin II
Asp–Arg–Val–Tyr–Ile–His–Pro–Phe
⊕
Adrenal cortex
Aldosterone
Potassium
ACTH
↑Sodium (and water) resorption
↑Extracellular fluid volume

Renin-Angiotensin-Aldosterone axis



The renin–angiotensin–aldosterone axis.

A fall in extracellular fluid (ECF) volume produces increased activity in renal nerves, reduced sodium flux in the macula densa and a fall in transmural pressure. These activate the juxtaglomerular apparatus to increase renin production, which catalyzes the beginning of the cascade that ends with angiotensin II-stimulated aldosterone secretion. This leads to increased sodium resorption with expanding ECF volume providing negative feedback on further renin production. High potassium, and to a lesser extent adrenocorticotrophic hormone (ACTH), also increase aldosterone production.



The structure of a nephron and the juxtaglomerular apparatus.

(a) A nephron. (b) Structure of a renal corpuscle, its blood supply and the juxtaglomerular apparatus. Between the afferent and efferent arterioles lies the glomerular capillaries, which are surrounded by Bowman's capsule. The filtration space drains into the proximal convoluted tubule. The juxtaglomerular cells, containing renin granules, replace the smooth muscle cells of the afferent arteriole and are positioned next to the closely packed macula densa cells of the distal tubule.

Regulation of aldosterone secretion

The enzyme, renin, is synthesized predominantly in the kidney, in specialized cells of the juxtaglomerular apparatus. These cells surround the afferent arteriole before it enters the glomerulus and form a sensing mechanism for intravascular volume whereby decreased volume stimulates renin biosynthesis. Renin acts upon its substrate, circulating angiotensinogen, to generate the decapeptide, angiotensin I, which is subsequently converted into angiotensin II (AII). This latter octapeptide binds to the type 2 angiotensin II receptor in the zona glomerulosa cells to stimulate aldosterone production. In addition, angiotensin II is a very potent ‘pressor’ agent, causing arteriolar vasoconstriction. Renin–angiotensin axes exist to some extent within individual organs, providing an element of paracrine adrenocortical regulation of aldosterone biosynthesis and secretion. High potassium also stimulates aldosterone biosynthesis. ACTH plays a minor role in regulating aldosterone synthesis, although too much or too little ACTH does not impact on circulating aldosterone levels. More importantly, the cellular mass of the zona glomerulosa influences longer term mineralocorticoid production. Thus, ‘westernized’ high salt diets, which expand the intravascular volume and raise blood pressure, suppress the renin–angiotensin system, leading to a shrivelled zona glomerulosa.

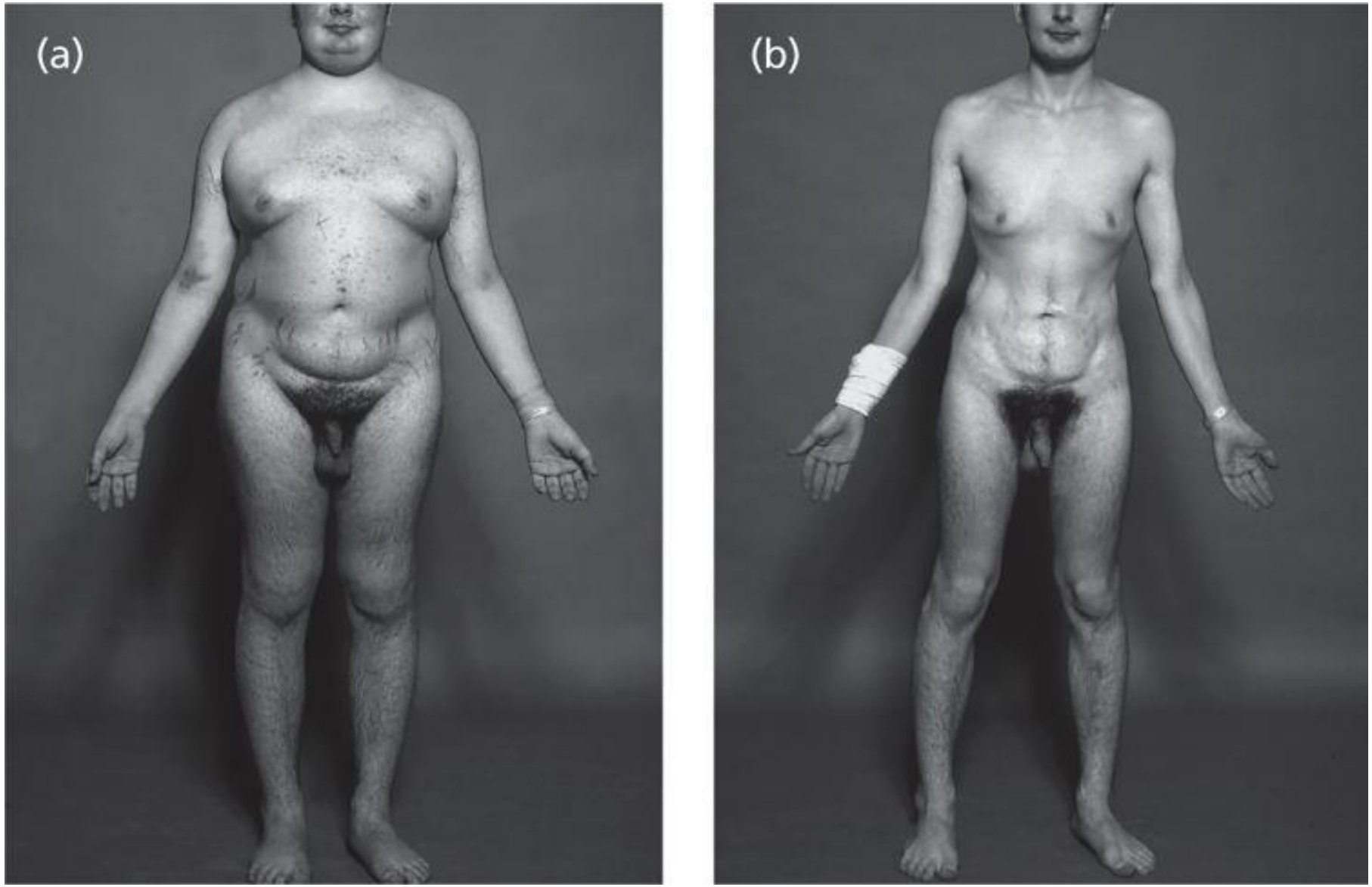
Aldosterone is the body’s major mineralcorticoid

- Promotes sodium resorption from the urine and potassium excretion
- Increases blood pressure

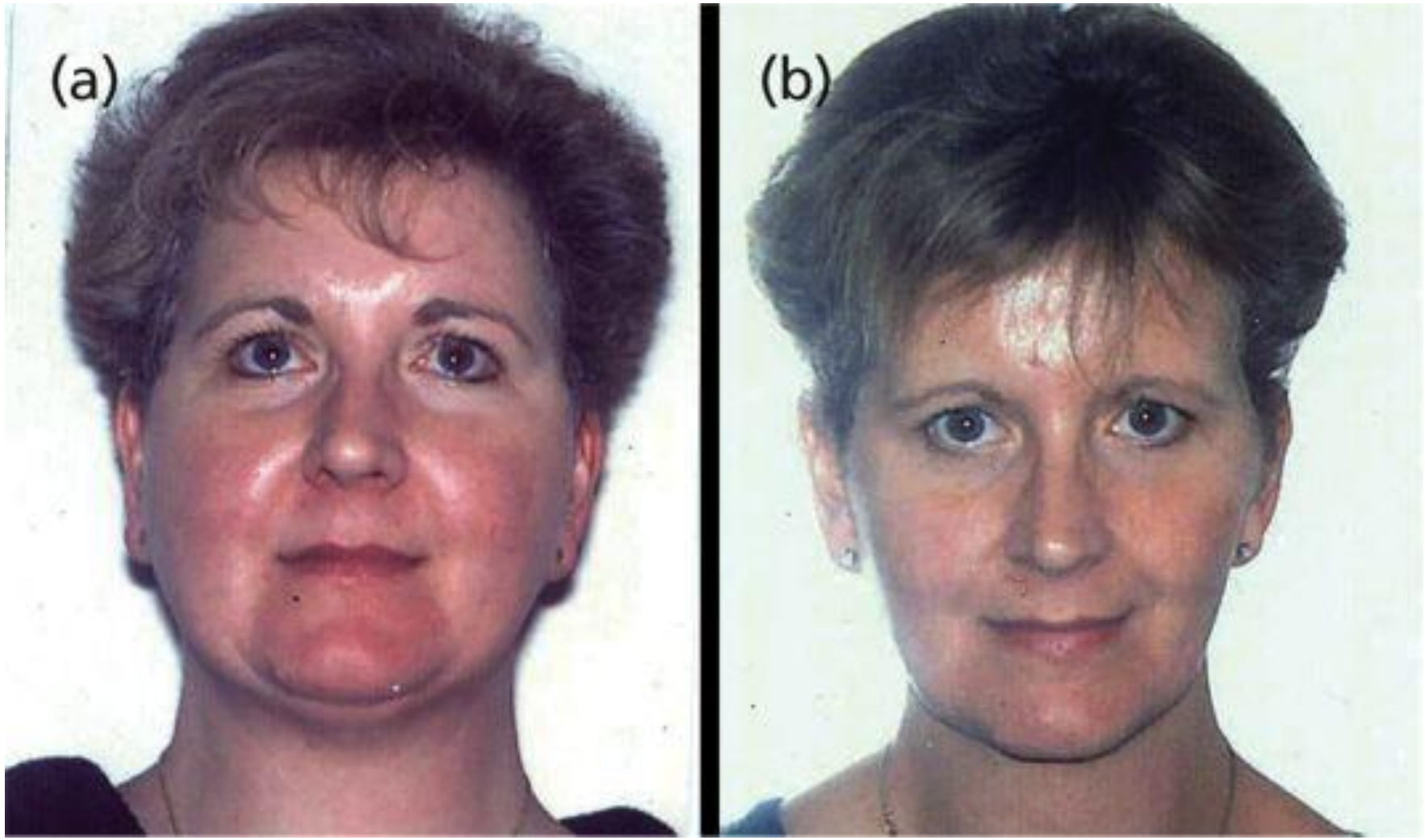
Aldosterone biosynthesis is regulated primarily by:

- Renin–angiotensin system (forming a negative feedback loop)
- Serum potassium concentration

Glucocorticoid excess (Cushing syndrome)



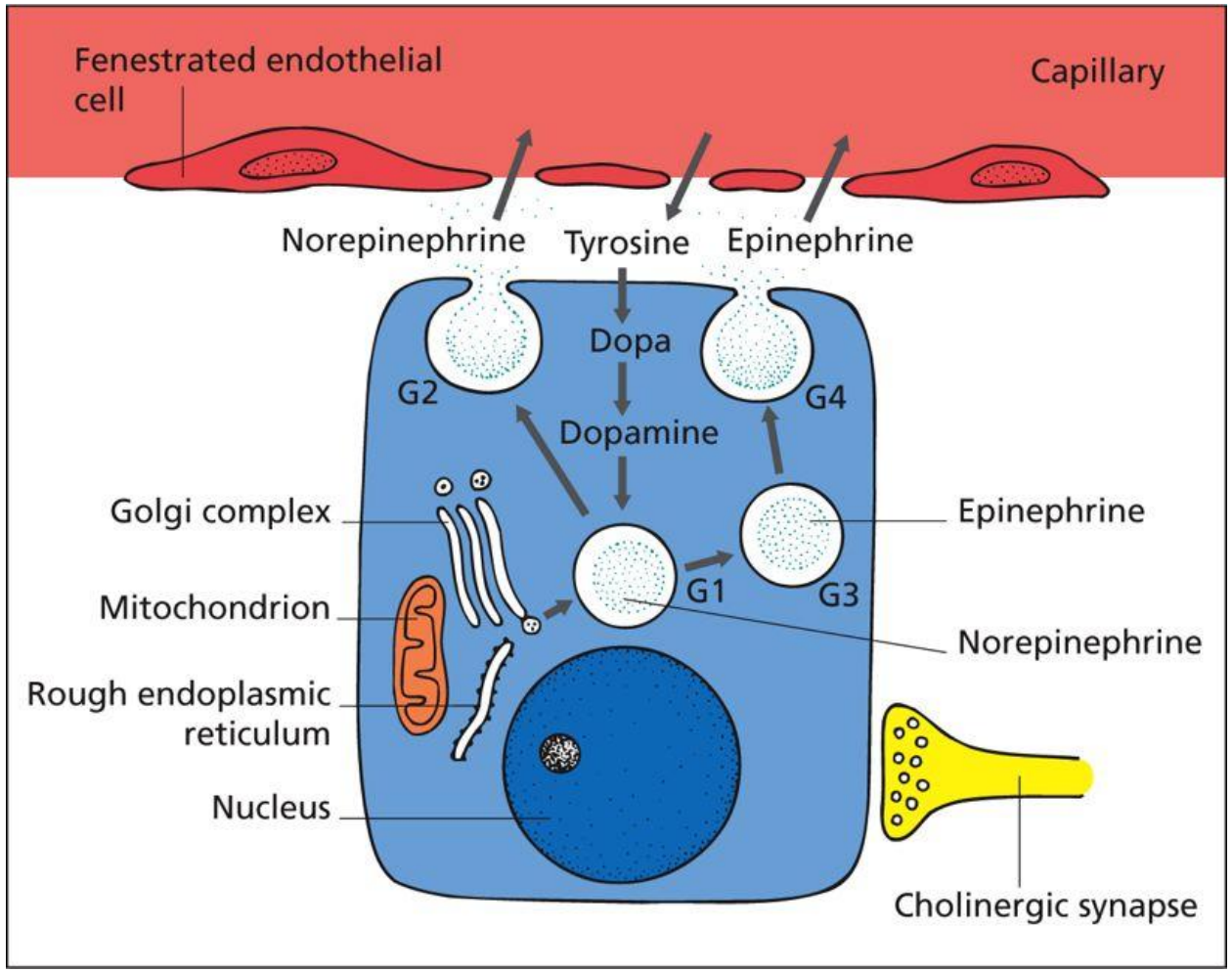
Glucocorticoid excess (Cushing syndrome)



Symptoms and signs of Cushing syndrome

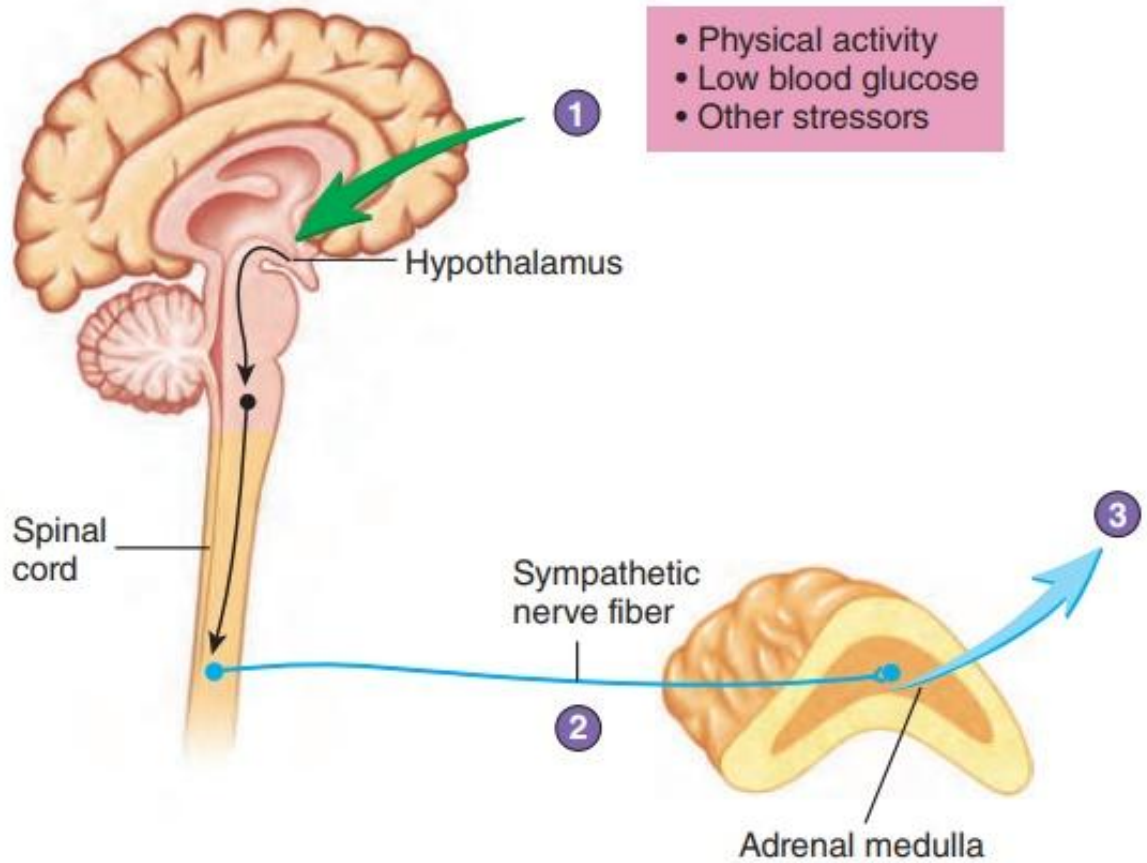
- Muscle wasting, relatively thin limbs
- Easily bruised, thin skin; poor wound healing
- Striae (purple or ‘violaceous’ rather than white)
- Thin (osteoporotic) bones that easily fracture
- Diabetes mellitus
- Central obesity, rounded (‘moon’) face, ‘buffalo hump’
- Susceptibility to infection
- Predisposition to gastric ulcer
- Hypertension
- Disturbance of menstrual cycle; symptoms overlapping with polycystic ovarian syndrome
- Mood disturbance (depression, psychosis)

Adrenal medulla



The adrenal medulla comprises chromaffin cells, which are like post-ganglionic neurones. However, rather than possessing distant nerve terminals, they respond to synaptic activation by releasing preformed catecholamine hormones into the circulation. Norepinephrine (noradrenaline) comprises 20% of circulating catecholamine, with an additional biochemical step generating the remaining 80% as epinephrine (adrenaline). The hormones are stored intracellularly in secretory granules complexed with proteins called chromogranins. The latter serve as clinical biomarkers of endocrine tumours characterized by periodic release of stored hormones into the circulation (sometimes called 'neuroendocrine tumours'), such as phaeo-chromocytoma, paragangliomas, carcinoids and gut endocrine tumors.

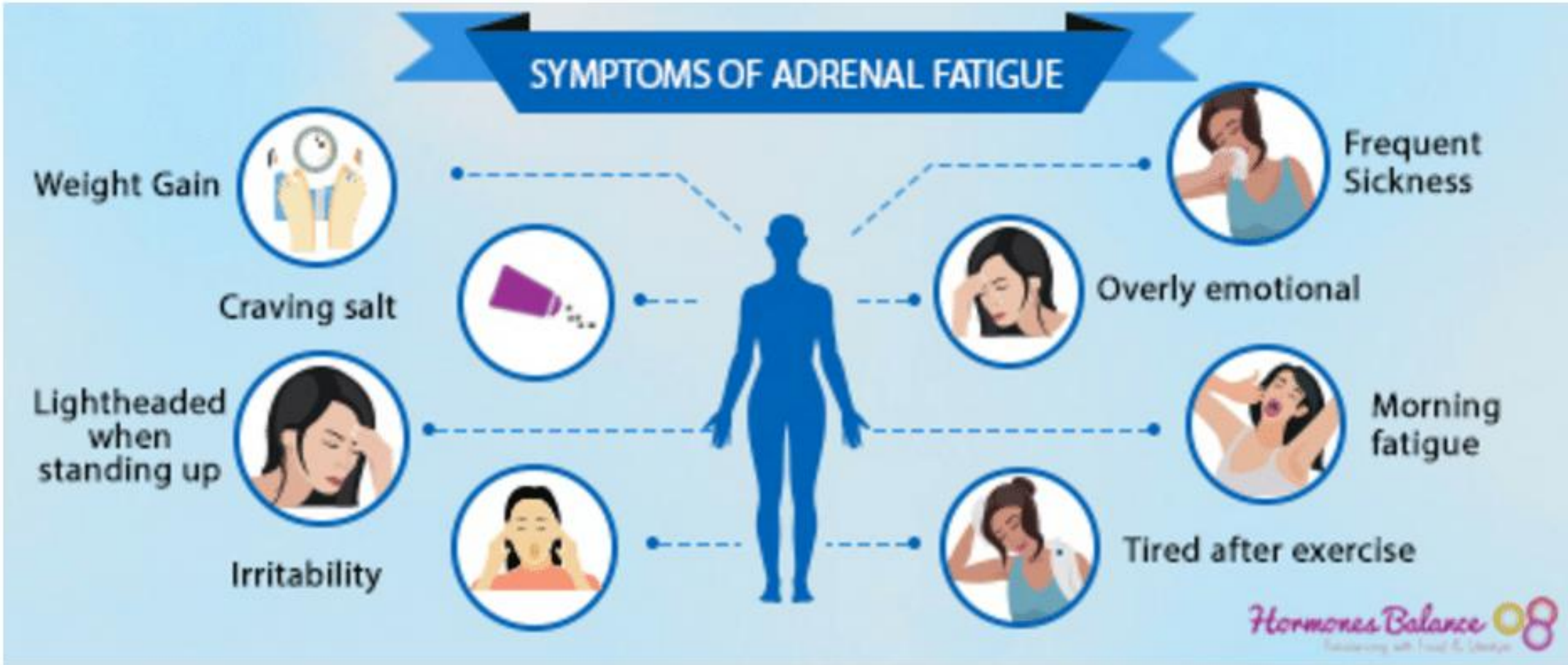
1. Stress, physical activity, and low blood glucose levels act as stimuli to the hypothalamus, resulting in increased sympathetic nervous system activity.
2. An increased frequency of action potentials conducted through the sympathetic division of the autonomic nervous system stimulates the adrenal medulla to secrete epinephrine and some norepinephrine into the circulatory system.
3. Epinephrine and norepinephrine act on their target tissues to produce responses.



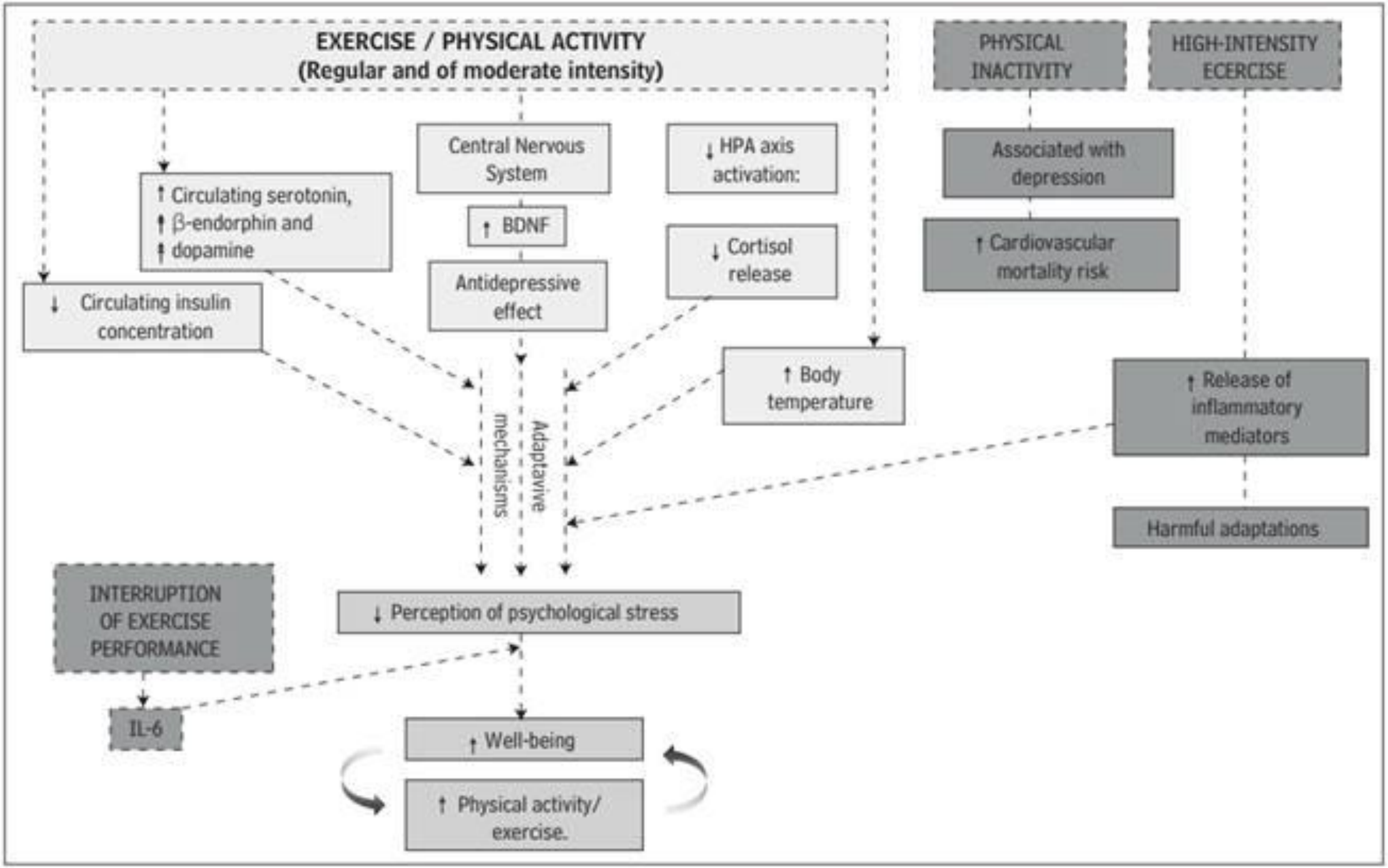
Epinephrine and norepinephrine in the target tissues:
- Increase the release of glucose from the liver into the blood
- Increase the release of fatty acids from adipose tissue into the blood
- Increase heart rate
- Decrease blood flow through blood vessels of most internal organs
- Increase blood flow through blood vessels of skeletal muscle and the heart
- Increase blood pressure
- Decrease the function of visceral organs
- Increase the metabolic rate of skeletal muscles

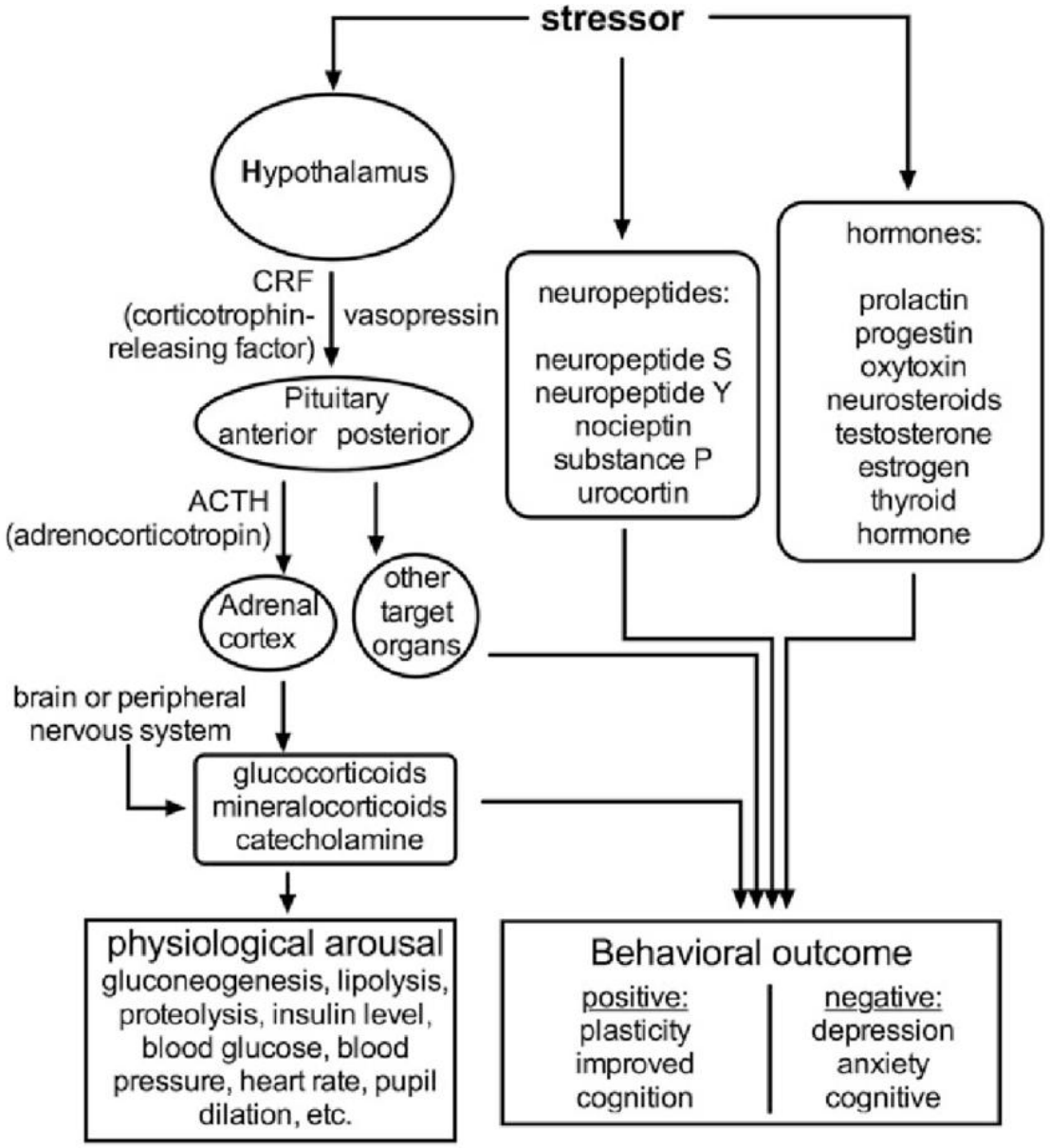
PROCESS Figure 10.19 AP|R Regulation of Adrenal Medullary Secretions

Stimulation of the hypothalamus by stress, physical activity, or low blood glucose levels causes action potentials to travel through the sympathetic nervous system to the adrenal medulla. In response, the adrenal medulla releases epinephrine and smaller amounts of norepinephrine into the general circulation. These hormones have several effects that prepare the body for physical activity.


SYMPTOMS OF ADRENAL FATIGUE
Weight Gain
Craving salt
Lightheaded when standing up
Irritability
Frequent Sickness
Overly emotional
Morning fatigue
Tired after exercise
HormonesBalance

Exercise Reduce Adrenal Fatigue


EXERCISE / PHYSICAL ACTIVITY
(Regular and of moderate intensity)
PHYSICAL INACTIVITY
HIGH-INTENSITY ECERCISE
Central Nervous System
↓ HPA axis activation:
↑ Circulating serotonin, ↑ β-endorphin and ↑ dopamine
↑ BDNF
Associated with depression
↓ Cortisol release
Antidepressive effect
↑ Cardiovascular mortality risk
↓ Circulating insulin concentration
↑ Body temperature
↑ Release of inflammatory mediators
Adaptative mechanisms
Harmful adaptations
INTERRUPTION OF EXERCISE PERFORMANCE
↓ Perception of psychological stress
IL-6
↑ Well-being
↑ Physical activity/ exercise.



Stress alter the sympato-adrenal medullary axis and hypothalamic–anterior pituitary–adrenal axis.

Higher brain function (e.g. circadian rhythm and stress) influences corticotrophin-releasing hormone (CRH) synthesis and release, which acts on the corticotroph of the anterior pituitary to make adrenocorticotrophic hormone (ACTH). Both CRH and ACTH are subject to negative feedback by cortisol, the levels of which are influenced in the periphery and in target cells by the balance of 11β-hydroxysteroid dehydrogenase (HSD11B) activity.

siddha cell salts + flower essences

Stress Pathway Diagram

Sensory Input

Mind

Interpretation

Sympathetic Nervous System

Hypothalamus (Brain)

Pituitary

Adrenal Cortex

Adrenal Medulla

Cortisol

- Decreases Immune Function
- Increases Blood Pressure
- Decreases Bone Formation

Adrenalin/ Epinephrine

- Increases Inflammation
- Enhanced Memory of Traumatic Event
- Increases Blood Sugar
- Increases Blood Lipids
- Fear

Where stress occurs

Flower Essences, Homeopathy, Cell Salts, Acupuncture

- Flower Essences, Homeopathy, Cell Salts and Acupuncture affect stress at its very source of initial interpretation; while Herbs, Nutrients and Rx medicines do not begin to affect stress until it reaches the Sympathetic Nervous System.

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