ADRENAL HORMONES: An Overview

University of PNG
School of Medicine & Health Sciences
Division of Basic Medical Sciences
Discipline of Biochemistry & Molecular Biology
BMLS III & BDS IV

VJ Temple

Adrenal Hormones

- Adrenal gland consist of:
  - Outer Cortex
  - Inner Medulla

- Hormones secreted by Adrenal Cortex are:
  - Glucocorticoid,
  - Mineralocorticoid,
  - Sex Steroids;

What hormones are synthesized in Adrenal Cortex?

- Hormones produced in 3 Zones in Adrenal Cortex:

- Zona Glomerulosa produces: **Mineralocorticoids** (mainly **Aldosterone** in humans) that promotes reabsorption of Na^+ and excretion of K^+ and H^+ ions by kidney tubules;

- Zona Fasciculata and Zona Reticularis produces: **Glucocorticoids** (mainly Cortisol in humans) that promotes Gluconeogenesis;

- Zona Reticularis produces mainly **Sex Steroids**;

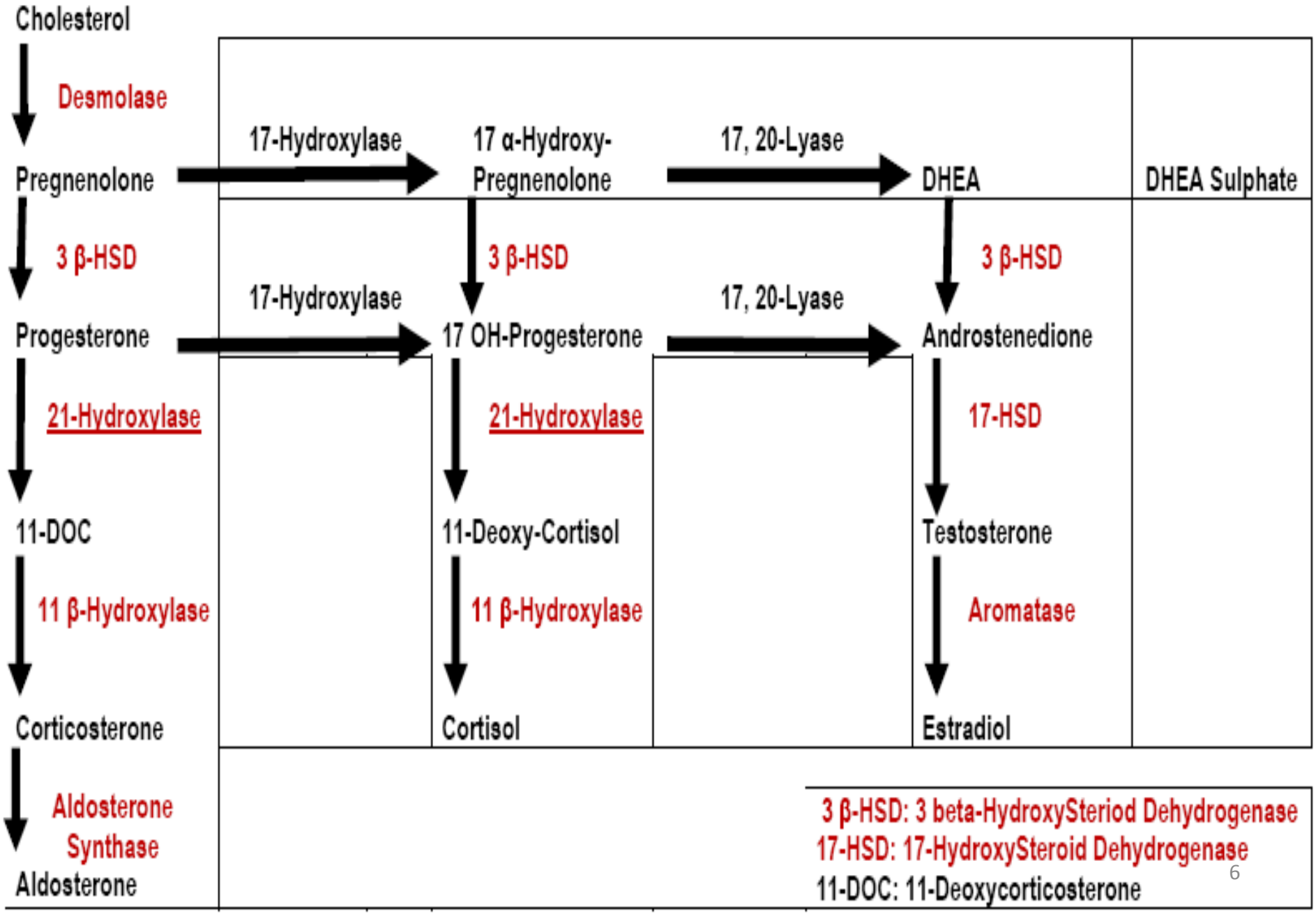
Cortisol and Aldosterone are Steroid Hormones

- Steroidogenesis: Pathway for biosynthesis of steroid hormones is presented as a flow chart,
- Specific steroid hormone synthesized in given tissue depends upon:
  - Complement of Peptide Hormone Receptors on tissue,
  - Tissue response to Peptide Hormone Stimulation,
  - Genetically expressed enzymes in tissue;
- Flow chart does not go to completion in all tissues;
- **Fig. 1**: Schematic diagram of Steroidogenesis (pathway for biosynthesis of different steroid hormones);

CORTISOL (MAIN GLUCOCORTICOID)
How is Cortisol synthesized?

- Glucocorticoids are 21-Carbon steroids,
- Glucocorticoids are natural or synthetic steroids with Cortisol-like effects;
- Cortisol is synthesized from Cholesterol delivered to Adrenal Cortex by Low-Density Lipoprotein (LDL);
  - LDL receptors are increased when Adrenal cortex is stimulated by **AdrenoCorticoTrophic Hormone (ACTH**);
- **Fig. 1**: Steroidogenesis flow chart shows pathway for biosynthesis of Cortisol;

Fig. 1: Flow diagram of pathways for biosynthesis of steroid hormones

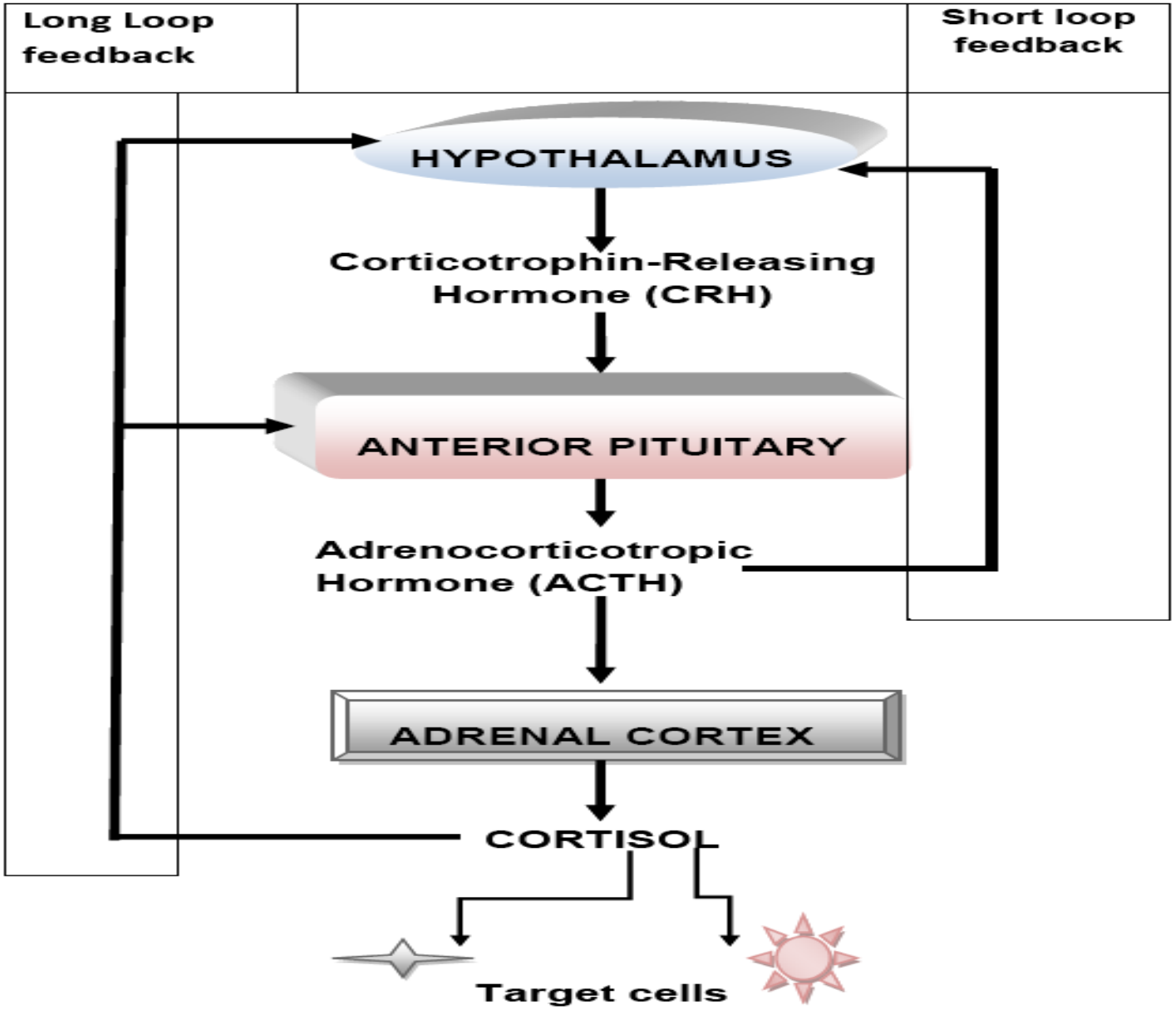


How are biosynthesis & secretion of Cortisol regulated?

- Biosynthesis & secretion of Cortisol is regulated via Hypothalamic-Pituitary-Adrenocortical axis (**HPA- axis**) with classic Negative Feedback Control (**Fig. 2**);
- Corticotrophin-Releasing Hormone (**CRH**) is secreted by Hypothalamus under influence of Cerebral Factors;
- Binding of CRH to Anterior Pituitary induces production of large compound **Pro-opiomelanocortin (POMC)**,
- POMC is cleaved into fragments: **ACTH, Melanocyte-Stimulating Hormones (MSH), Beta-Lipotrophins, and Beta-Endorphins**;

- ACTH acts on Adrenal Cortex stimulating biosynthesis and secretion of Cortisol;
- Hypothalamic secretion of CRH and Pituitary secretion of ACTH are regulated by Cortisol in **Negative Feedback**;
- In humans, only Cortisol exerts Negative Feedback on ACTH release;

Fig. 2: Negative Feedback Control of Cortisol Hypothalamic-Pituitary-Adrenocortical Axis (HPA-Axis)



Briefly describe negative feedback control of Cortisol secretion

- Hypothalamus is stimulated to produce CRH by:
  - Low Plasma Cortisol level,
  - Emotional stress, Fear, Physical stress, Pain or Cold),
- CRH stimulates Anterior Pituitary to produce ACTH,
- ACTH acts on Adrenal Cortex to produce Cortisol, which is released in plasma,
- Excess plasma Cortisol produces Negative Feedback Control on Hypothalamus and Anterior Pituitary (Long-Loop Feedback) (**Fig. 2**)
- Resultant effect is decreased secretion of CRH and ACTH;

IMPORTANT TO NOTE:

- **Only** Cortisol exerts Negative feedback on ACTH release,
- Lack of Cortisol caused by enzyme deficiencies (e.g., **21-Hydroxylase**), leads to failure in Feedback control of ACTH secretion,
  - High and continuous production of ACTH causes Adrenal Hyperplasia, leading to **Congenital Adrenal Hyperplasia,**
- Condition is controlled by Administration of Cortisol:
  - Correcting Cortisol deficiency will reduce ACTH secretion via feedback inhibition of Hypothalamus and Anterior Pituitary

Does daily rhythm affect plasma Cortisol & ACTH levels?

- Daily diurnal rhythm is expressed by ACTH & Cortisol;
- Cortisol levels are:
  - Highest in the morning and shortly after waking-up,
  - Lowest in late afternoon and evening,
- ACTH & Cortisol secretion are Minimal at Midnight,
- Rhythm may be independent of sleep, is abolished by stress and Cushing's syndrome (excessive ACTH production)

How is Cortisol transported in Plasma?

- Cortisol is transported in plasma mainly bound to **Corticosteroid-Binding Globulin (CBG, Transcortin);**
- **Free Fraction** of Cortisol in plasma is **biologically active**,
- Half-life of Cortisol in plasma of about 1.5 to 2.0 hours,
- Plasma level of CBG is affected by several factors:
  - Pregnancy and Estrogen treatment (Oral Contraceptives) increases Plasma CBG level;
  - Hypo-proteinaemic state (e.g., Nephrotic Syndrome) causes decrease in plasma CBG level,
  - Parallel changes occur in plasma levels of total Cortisol,

How is Cortisol excreted from the body? (Metabolism and Urinary Excretion of Cortisol):

- Cortisol metabolism occurs in Liver as conjugated metabolites (Glucuronides) for excretion in urine,
- Small amount of Free Cortisol is excreted in urine,
- In healthy individuals, urinary Cortisol excretion is less than 250nmol/24hour,
- Products of Cortisol metabolism are excreted in urine as **17-Hydroxy-Cortico-Steroids** (**17-OHCS**),

What are some functions of Cortisol?

- Glucocorticoids affect Carbohydrate, Fat and Protein metabolism;
- Cortisol stimulates:
  - Gluconeogenesis,
  - Uptake and Degradation of Amino Acids,
  - Ketogenesis in Liver,
  - Lipolysis in Adipose tissue,
  - Protein degradation in Muscle,
- Cortisol helps to regulate stress response,
- Glucocorticoids are also involved in regulation of Sodium and Water homeostasis,

- Glucocorticoids act as Anti-inflammatory or Immunosuppressive Agents,
- Glucocorticoids are Insulin Counter Regulatory Hormones
  - Increase in blood glucose due to excess Glucocorticoid activity is known as **Adrenal Diabetes,**
- Prolonged excess Glucocorticoids release may damage beta cells in Pancreas causing Diabetes Mellitus,
- Glucocorticoids decrease protein matrix of bone through their protein catabolic effect, causing increased loss of Ca^{2+} from bone, resulting in Osteoporosis;

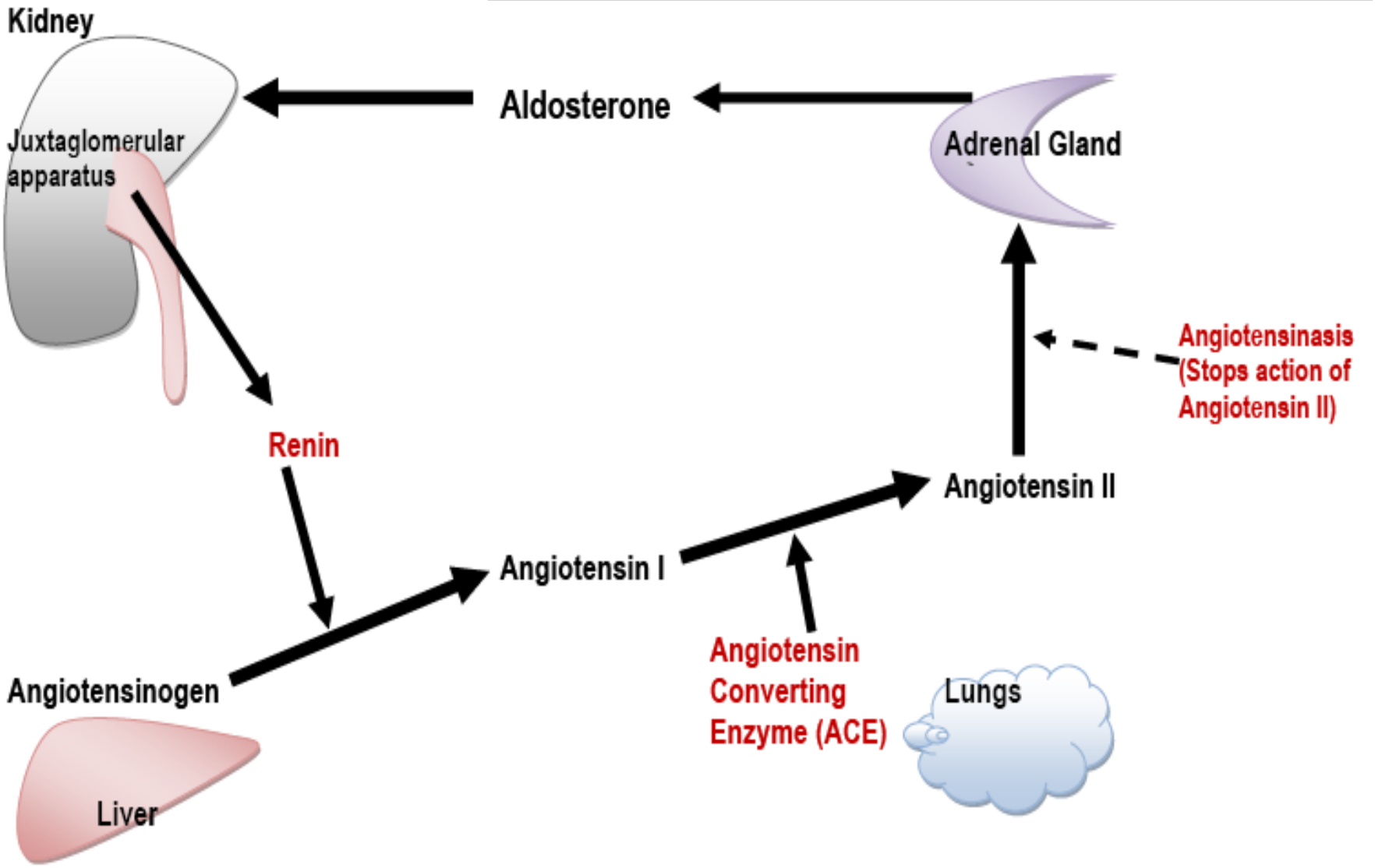
ALDOSTERONE (Main MINERALOCORTICOID)
How is Aldosterone produced?

- Mineralocorticoids are natural or synthetic steroids with Aldosterone-like effects;
- Aldosterone is a 21-Hydroxyl Steroid hormone,
- Aldosterone is produced in the Adrenal Cortex,
- **Fig. 1**: Steroidogenesis flow chart shows the pathway for biosynthesis of Aldosterone;

How are biosynthesis & secretion of Aldosterone regulated?

- Biosynthesis & secretion of Aldosterone regulated via **Renin-Angiotensin- Aldosterone Axis (RAA-axis); Fig. 3**
- Renin is released from Juxtaglomerular cells in kidneys,
- Renin converts Angiotensinogen to Angiotensin-I (AI),
- Angiotensin Converting Enzyme (ACE) from the lungs converts Angiotensin-I to Angiotensin-II (AII),
- Angiotensin-II acts on Adrenal Cortex to synthesize and secretion Aldosterone,
- Angiotensinasis terminates action of Angiotensin-II,
- Aldosterone acts on Renal Tubules to reabsorption Na^+ ions in exchange for secretion of K^+ and H^+ ions;

Fig. 3: Renin-Angiotensin-Aldosterone Axis (RAA axis) for regulation of Aldosterone secretion



What factors affect the release of Renin?

- **Renin:** Enzyme in **Juxtaglomerular Apparatus** in Kidneys is released in circulation in response to certain factors;
- Factors that influence release of Renin include:
- **Stimulators of Renin release**:
  - Dehydration,
  - Decreased blood pressure,
  - Fluid or blood loss,
  - Salt depletion,
  - Change from supine to erect posture,
  - Beta-Adrenergic agents,
  - Prostaglandin,

- **Inhibitors of Renin release**:
  - Increased blood pressure,
  - Change from erect to supine posture,
  - Salt loading,
  - Prostaglandin inhibitors,
  - Beta-Adrenergic antagonists,
  - Potassium,
  - Vasopressin,
  - Angiotensin-II,

How does ACTH affect secretion of Aldosterone?

- High plasma level of ACTH increases biosynthesis of Aldosterone by increasing availability of steroid substrates (e.g., cholesterol) in Adrenal cortex,
- In general ACTH Control mechanism is relatively unimportant, except in stress conditions and in Congenital Adrenal Hyperplasia due to deficiency of 21-Hydroxylase,

How are Aldosterone and other Mineralocorticoids transported in Plasma?

- Aldosterone and other Mineralocorticoids do not have any specific plasma transport protein, they form very weak bonds with albumin,
- Aldosterone is very rapidly cleared from plasma by the Liver,
  - Tetra-hydro-Aldosterone–3–Glucuronide formed in live, is excreted in the urine;

What are some of the functions of Aldosterone?

- Major regulator of Electrolyte balance,
- Primary role is regulation of Na^+ by Distal Tubules,
  - Stimulates re-absorption of Na^+ , secretion of K^+ & H^+ ions,
- Actions of Aldosterone cause Kidneys, Gut, Salivary and Sweat Glands to maintain Electrolyte Balance,
- **Aldosterone deficiency** causes Hyponatraemia, Hyperkalemia and Acidosis;
- **Excess Aldosterone** results in Sodium Retention, Hypokalemia, and Alkalosis,
- Hyperkalemia stimulates Aldosterone release to improve Potassium excretion;
- Aldosterone is first-line defense against Hyperkalemia,

REFERENCES

- Textbook of Biochemistry with Clinical Correlations 4th Edition. Edited by Thomas M. Delvin. Chapter on Steroid Hormone.
- Harper's Illustrated Biochemistry 26th Edition; 2003; Ed. By R. K. Murray et. al.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition.
- Hames BD, Hooper NM, JD Houghton; Instant Notes in Biochemistry, Bios Scientific Pub, Springer; UK.
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.
- G Beckett, S Walker, P Rae, P Ashby, Lecture Notes: Clinical Biochemistry 7th Ed. 2008, Blackwell Publishing, Australia.