ADRENAL HORMONES: An Overview

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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

- **Cholesterol**
  - Desmolase
  - Pregnenolone
    - 3 β-HSD
    - 17-Hydroxylase
  - Progesterone
    - 21-Hydroxylase
    - 11-DOC
      - 11 β-Hydroxylase
      - Corticosterone
        - Aldosterone Synthase
        - Aldosterone
  - 17-Hydroxylase
  - 17 α-Hydroxy-Pregnenolone
    - 17, 20-Lyase
    - DHEA
      - DHEA Sulphate
    - 3 β-HSD
    - 17-Hydroxylase
    - 17-OH-Progesterone
    - 17, 20-Lyase
    - Androstenedione
      - 3 β-HSD
      - 17-Hydroxylase
      - 17, 20-Lyase
      - Testosterone
        - 17-HSD
        - Estradiol
          - Aromatase

**Enzymes**: 3 β-HSD: 3 β-HydroxySteroid Dehydrogenase, 17-HSD: 17-HydroxySteroid Dehydrogenase, 11-DOC: 11-Deoxycorticosterone
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,
• Angiotensinisasis 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,
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