Mammalian Physiology

Thyroid Hormone
Adrenal Hormones
Objectives

- Describe the synthesis of thyroid hormone
- Describe the secretion of thyroid hormone
- Describe the actions of thyroid hormone
- Describe the effects of hypo- and hyper-secretion of thyroid hormone
- Describe the structure of the adrenal gland
- Discuss the secretion of adrenal cortical hormones
- Describe the actions of cortisol
- Describe the function of aldosterone
- Discuss the effects of hypo- and hyper-secretion of adrenal cortical hormones
Thyroid Gland

- Early recognition of thyroid dysfunction was possible because of superficial proximity of gland – goiter – or thyroid enlargement occurs when iodine is deficient
- Early treatment was with sheep thyroids or seaweed rich in iodine
- Procedure for surgical removal was developed in 1883, but without replacement therapy, by 4 months post surgery, patients were lethargic, rotund, cold intolerant – signs of hypothyroidism
- Therapy provided with sheep thyroid extracts was successfully tried in 1881
Thyroid Hormone

Largest gland in the body – 20 gms – and most superficial

Only gland requiring an essential trace element – iodine

Product (thyroxine and triiodothyronine) stored extracellularly, not in secretary cells

Thyroid hormones are synthesized in follicular cells and stored in follicles as part of thyroglobulin (30% of thyroid mass) – enough to meet needs for 2-3 months
Thyroid Hormone

Two forms thyroxine (T\textsubscript{4}) and triiodothyronine (T\textsubscript{3} \& rT\textsubscript{3})
Both are bound to thyroglobulin (70-80% as T\textsubscript{4})

Peptide backbone of thyroglobulin molecule
Synthesis and Secretion

Thyrotropin synthesized in follicular cell, is secreted into lumen, where it is iodinated.

Iodinated thyroglobulin is rearranged internally – MIT & DIT conjugate to form $T_4$ and $T_3$.

Thyroglobulin is endocytosed into follicular cell where $T_4$ and $T_3$ are cleaved by hydrolysis in lysosomes for release into plasma.

Iodine taken up into follicular cell by Na/I cotransport.
Synthesis and Secretion

1. Thyroglobulin is synthesized and discharged into the follicle lumen
2a. Trapping (active uptake) of iodide (I⁻)
2b. Oxidation of active form of iodine
3. Iodine enters follicle lumen where it is attached to tyrosine in colloid, forming DIT and MIT
4. Iodinated tyrosines are linked together to form T₃ and T₄
5. Thyroglobulin colloid is endocytosed and combined with a lysosome
6. Lysosomal enzymes cleave T₄ and T₃ from thyroglobulin colloid and hormones diffuse from follicle cell into bloodstream

Capillary

Colloid

Thyroid follicle cell

Iodide (I⁻)

Golgi apparatus

Rough ER

Colloid in lumen of follicle

DIT (T₂) MIT (T₁)

Thyroglobulin colloid

T₄ T₃ T₄ T₃

Lysosome

T₄ T₃

To peripheral tissues
Synthesis and Secretion

\( T_4 \) and \( T_3 \) released into the blood are transported bound to thyroid-binding globulin and transthyretin

\[ T_4 + TBG \leftrightarrow T_4 \cdot TBG \]

90% of thyroid hormone released is \( T_4 \)

Only about 0.03-0.1% \( T_4 \) and 0.3-1% \( T_3 \) circulates as free hormone

Plasma concentration of \( T_4 \) is 50-fold greater than concentration of \( T_3 \)

Because \( T_3 \) is bound more loosely, it is able to diffuse out of the plasma 5 times more quickly than \( T_4 \)

The conversion of \( T_4 \) to \( T_3 \) is critical step in thyroid hormone action – \( rT_3 \) has no calorigenic effect

<table>
<thead>
<tr>
<th>Table 44-1 Average thyroid hormone turnover</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_4 )</td>
</tr>
<tr>
<td>Daily production (( \mu g ))</td>
</tr>
<tr>
<td>From thyroid (%)</td>
</tr>
<tr>
<td>From ( T_4 ) (%)</td>
</tr>
<tr>
<td>Extracellular pool (( \mu g ))</td>
</tr>
<tr>
<td>Plasma concentration</td>
</tr>
<tr>
<td>Total (( \mu g/dl ))</td>
</tr>
<tr>
<td>Free (ng/dl)</td>
</tr>
<tr>
<td>Half-life (days)</td>
</tr>
<tr>
<td>Metabolic clearance (L/day)</td>
</tr>
<tr>
<td>Fractional turnover per day (%)</td>
</tr>
</tbody>
</table>
Regulation of Secretion

TRH from hypothalamus binds to G protein receptor on thyrotrophic cell in pituitary, activating DAG/IP$_3$ pathway → TSH released → binds to G$_s$ receptor on thyroid follicular cell → activating adenyl cyclase and cAMP → initiating thyroid hormone synthesis (TSH stimulates all aspects of thyroid hormone synthesis and release from gland)
Negative feedback exerted on pituitary and hypothalamus by T$_4$ and T$_3$
T₄ Regulation of Secretion

Decrease in radioactivity after injection of ¹³¹I reflects rate of thyroxine secretion. Hypophysectomy & thyroxine treatment are equally effective in decreasing TSH – decreasing hormone release.
Mechanism of Thyroid Action

Free T₃ and T₄ enter cell by diffusion or carrier-mediated transport. T₄ converted to T₃ – both remaining T₄ and T₃ enter nucleus → bind to DNA → initiate transcription/translation.
Peripheral Conversion of $T_4$ to $T_3$

Binding to thyroid hormone to plasma proteins, provides a buffer pool of hormone, prolongs the half-life of $T_3$ and $T_4$. $T_4$ acts as a prohormone for extrathyroid synthesis of $T_3$. $T_3$ is responsible for most of the biologic action of thyroid hormones.

$t_{\frac{1}{2}}$ ↑ with hyperthyroid and ↓ with hypothyroid
Although biological effects of T₄ are predominantly due to its conversion to T₃, T₄ has biological effects of its own -
- Clinical thyroid deficiency with normal T₃ but decreased T₄
- Normal thyroid state with decreased T₃ but normal T₄

In absence of thyroid gland, euthyroid state requires dose of T₃ which produces supranormal T₃ levels in plasma whereas T₄ doses maintaining normal plasma levels are sufficient
Thyroid Action

Accounts for delay (12-48hrs) in effects becoming evident in vivo. Latent period between administration and effect may be due to the fact that hormone must dissociate from protein-carrier before entering cell.

$T_4$ more tightly bound than $T_3$ so longer time for $T_4$ effects to appear.

Prolonged effect on BMR caused by a single large dose of thyroxine.
Thyroid Hormone Action

Thyroid hormone has no specific target organ

Major effects are
Calorogenesis
- increase fuel mobilization
- increase $O_2$ consumption
Growth
- tissue growth
- bone growth
CNS
- first year of life
Thyroid Hormone Effects

Calorigenesis

Heat production = $O_2$ consumption (ml $O_2$/min)

- 150 HypoTh
- 250 Normal
- 400 HyperTH

35-40% decrease in BMR following thyroidectomy – peaks 60-80 days post operative
Thyroid Hormone Effects

Calorogenesis

Change in $O_2$ consumption of whole animal and isolated tissues after large dose of thyroxine in thyroidectomized rats

$\uparrow$ Na/K ATPase activity
$\uparrow$ Futile cycling

Note: certain tissues do not reflect thyroid function or condition of the animal – brain, spleen, testes, uterus
Thyroid Hormone & Cold Exposure

Conversion of $T_4$ to $T_3$ occurs with acute cold exposure.
Catecholamines generate increased muscular activity associated with shivering – Thyroid hormones have permissive effect.

### Components of Daily Energy Expenditure (M)

<table>
<thead>
<tr>
<th>Components</th>
<th>% of Daily M at Thermal Neutrality</th>
<th>% of Daily M in Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting metabolic rate (RMR)</td>
<td>≈70% (1750 kcal)</td>
<td>≈34% (1750 kcal)</td>
</tr>
<tr>
<td>Thermic effect of food (TEF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obligatory M</td>
<td>≈10% (250)</td>
<td>≈ 5% (250)</td>
</tr>
<tr>
<td>Facultative M</td>
<td>≈20% (500)</td>
<td>≈10% (500)</td>
</tr>
<tr>
<td>Exercise-induced M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermoregulatory M</td>
<td>≈0%</td>
<td>≈51% (2625)</td>
</tr>
<tr>
<td>Shivering M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonshivering M</td>
<td>100% (or 2500 kcal)</td>
<td>100% (or 5125 kcal)</td>
</tr>
</tbody>
</table>
Thyroid hormone is a major determinant of growth – growth rate depressed by thyroidectomy – administering either T₃ or T₄ will restore growth rate to normal. BUT growth hormone must also be present.

Thyroxin will not stimulate growth if hypophysectomy was done along with thyroidectomy.

In hypothyroidism, growth hormone depressed, HGH releasing cells are decreased, and stimuli for HGH release are ineffective.
Thyroid Hormone & Growth

Effects of thyroid therapy on growth & development of child with no functional thyroid tissue – daily thyroid treatment began at 4½ years of age – bone age rapidly returned toward normal and rate of growth paralleled normal but mental development remained infantile.

Blood-brain barrier becomes impermeable to thyroid hormone after 1 year of age – early recognition is necessary to prevent irreversible mental retardation.
Thyroid Dysfunction

Hypothyroid – age at which gland becomes non-functional is important

- At birth – Cretinism
  - Short stature
  - Deficits in bone structure
  - Mental retardation
- After 1 yr of age – myxedema
  - Slow-witted
  - Lethargic
  - Cold intolerant
  - Pasty or puffy appearance
  - Weight gain with no change in caloric intake
Hypothyroid Effects

- **CNS**
  - Less than normal growth of brain, especially cerebellum and cerebrum
  - Slower than normal rate of myelination
  - Retardation of major nerve tracts
  - Decreased number and size of neurons
  - Learning impairment

- **Bone**
  - Retardation of ossification centers
  - Lack of epiphyses
  - Lack of linear bone growth (limbs are disproportionally short relative to trunk)

- **Muscle**
  - Stiffness & aches in muscles
  - Decreased tonus
  - Sluggish response to stimulation
  - Prolonged contraction-relaxation time
  - Delayed reflexes
Thyroid Dysfunction

Hyperthyroid – age at which gland becomes non-functional is not important

• Hyperthyroidism – Grave’s Disease
  – Hyperkinetic
  – Intolerance to heat; warm even in cold weather
  – Mild to extreme weight loss - extremely thin
  – Rapid heart rate
  – Excessive sweating
  – Muscle weakness
  – Exophthalmos - wide-eyed stare

• Hyperplasia of thyroid gland
Hyperthyroid Effects

• Bone
  – Hastened bone growth
  – Predominant effect on osteoclasts (bone reabsorption)
  – Hastened bone maturation - osteoporosis
• Muscle
  – Muscle exhaustion
    • Constant tremors
    • Constant bombardment of neural impulses
  – Pronounced creatinurea
  – Fatty infiltration
  – Atrophy of certain muscle groups (muscle wasting)
• Substrates
  – Protein catabolic, negative $N_2$ balance
  – Increased lipolysis – decreased body fat stores \{ amino acids & glycerol for gluconeogenesis \}
Adrenal Gland

80% of adrenal is cortex, 20% medulla

3 cortical zones:
- Glomerulosa - aldosterone
- Fasciculata - cortisol
- Reticularis - androgens
Adrenal Cortex Hormones

- Nature of adrenal glands has been known since mid 1800’s when it was discovered that surgical removal irreversibly resulted in death
- Adrenal gland consists of cortex (mesodermal origin) and medulla (ectodermal origin)
- Removal of medullary portion is not fatal – cortex is responsible for clinical effects of adrenalectomy
- In absence of adrenal cortex, animal is unable to cope with stress
- Adrenal hormones
  - Glucocorticoids – cortisol, corticosterone
  - Mineralcorticoid – aldosterone
  - Androgens – androstenedione, dehydroepiandrosterone (DHEA)
Hypothalamus-Pituitary-Adrenal Axis

Secretion triggered by cerebral cortex in response to stress – physical, emotional, biochemical – stimulating CRH release

CRH released from hypothalamus binds to G-protein receptor activating adenyl cyclase-cAMP-PKA pathway → ↑[Ca^{2+}] → ACTH release

ACTH binds to melanocortin-2 receptors in all zones activating adenyl cyclase-cAMP-PKA pathway initiating cortical hormone synthesis
Adrenal Stress Response

Corticosteroid synthesis and secretion increased 6-fold within 4-20 minutes after fracture of two leg bones.

Stress causes an immediate secretion of ACTH followed within minutes by cortisol secretion.
### Adrenal Stress Response

**Short-term stress response**
1. Increased heart rate
2. Increased blood pressure
3. Liver converts glycogen to glucose and releases glucose to blood
4. Dilation of bronchioles
5. Changes in blood flow patterns leading to increased alertness, decreased digestive system activity, and reduced urine output
6. Increased metabolic rate

**Long-term stress response**
1. Retention of sodium and water by kidneys
2. Increased blood volume and blood pressure
3. Proteins and fats converted to glucose or broken down for energy
4. Increased blood sugar
5. Suppression of immune system

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Mechanism of Action in Target Cells

Hormones diffuse into cell, bind to specific cytosolic receptors, are translocated to nucleus where effects are mediated on translation/transcription → protein synthesis
Cortisol

• Cortisol is most important glucocorticoid
  – Cortisol secretion → 20 mg/day
  – Corticosterone secretion → 2 mg/day
  – Aldosterone secretion → 0.2 mg/day
• Cortisol circulates in plasma bound to specific globulin – transcortin (75-80%) – and albumin (15%) – only 5-10% circulates free
• Only free (unbound) cortisol is biologically active
• Plasma half-life is about 70 minutes
• Secretion is essentially under the control of ACTH
• Cortisol generally exerts permissive effects
  – Amply another hormone on a process it doesn’t affect by itself
  – Act synergistically with another hormone
  – Facilitate a process that is independent of other hormones and which would take place anyway without glucocorticoids
Cortisol Release

Cortisol release is subject to diurnal variations and circadian rhythms – peak just before waking/daylight, lowest just after falling asleep/darkness. When sleep-wake cycle is reversed, separateness of two systems is evident, but cyclical secretion is seen in absence of these stimuli, ie constant light. Secretion is pulsatile, 7-13 pulses throughout the day.
Cortisol Secretion

Pulsatile nature of cortisol secretion shown by individual plasma cortisol profiles obtained by sampling every 20 minutes.
Feedback Regulation of Secretion

Cortisol inhibits action of CRH on pituitary and ACTH release by pituitary
Two major functions of cortisol

1. Gluconeogenesis from amino acids primarily and glycerol
2. Anti-inflammatory and immunosuppressive
Glucocorticoid Response to Decrease in Blood Glucose

Insulin-induced hypoglycemia triggers rapid increase in ACTH which initiates secretion of cortisol

ACTH is reversed as glucose levels are restored
Effect of Cortisol on Fuels

Cortisol is protein catabolic – provides amino acids for gluconeogenesis especially during fasting

- Promote protein catabolism in muscle
- Increase AA trapping in liver
- Stimulate activity of hepatic transaminases
- Augment activity of gluconeogenic enzymes

Promotes ffa mobilization
- Energy supply
- Glycerol – gluconeogenic precursor
- Energy for gluconeogenesis
Cortisol-Induced Proteolysis

Production and plasma BCAA concentrations increase with 8 hr cortisol infusion.

Plasma alanine is less than production because of role as gluconeogenic precursor.
Anti-inflammatory Effect of Cortisol

Glucocorticoids suppress immune system – anti-rejection drugs – and block inflammatory response

Inflammatory response from xylene induced injury to rat’s ear
Anti-inflammatory Effect of Cortisol

- **Inflammation**
  - Release of chemical mediators (histamines, prostaglandins, thromboxane)
  - Increase in local blood flow
  - Leakage of plasma into tissues
  - Infiltration of leukocytes
  - Ingrowth of fibrous connective tissue – collagen matrix for repair

- **Cortisol**
  - Stabilizes lysosomal membranes - ↓ proteolytic enzymes
  - Decreases permeability of capillaries
  - Decreases migration of white blood cells into inflamed area and phagocytosis of damaged cells
  - Suppresses the immune system → decreased lymphocyte production
  - Lowers fever → decreases release of interleukin-1 from white blood cells
Aldosterone

- Major function is to conserve Na\(^+\) and thus to maintain body fluid volume
- Secretion stimulated by ↑ plasma K\(^+\), ↓ Na\(^+\); decreased blood volume/pressure
- Kidney is major site of aldosterone action and source of signal for aldosterone release
- Because Na\(^+\) exchanges with K\(^+\) which cycles with H\(^+\), aldosterone contributes indirectly to acid-base balance
- Aldosterone secretion follows cyclical pattern
  - Peak secretion occurs immediately after rising in morning
  - Lowest point occurs just after retiring at night
- Rhythm obliterated in subjects confined to bed rest
- If sleep wake cycle is reversed, aldosterone secretion pattern is reversed
- 50% of aldosterone is transported loosely bound to transcortin and 50% circulates free
Mechanisms of Aldosterone Secretion

Renin-angiotensin mechanism – kidneys release renin, which is converted into angiotensin II that in turn stimulates aldosterone release

Plasma concentration of sodium and potassium – directly influences the zona glomerulosa cells

ACTH – causes small increases of aldosterone during stress

Atrial natriuretic peptide (ANP) – inhibits activity of the zona glomerulosa
Aldosterone Secretion

Stimulators of aldosterone secretion include angiotensin, ACTH, and K⁺
Macula densa senses change in tubular fluid osmolarity, triggering renin-angiotensin response
Renin-Angiotensin System
Aldosterone promotes Na\(^+\) absorption in the renal tubular epithelial cells by
1. Triggering the insertion of a channel protein in the luminal membrane
2. Stimulating the activity of the Na/K ATPase on the basolateral membrane
3. Increasing the rate of ATP synthesis providing more energy at active site
Adrenal Cortical Dysfunction

- Hypofunction – Addison’s Disease
  - ↓ cortisol
    - Weight loss, fatigue, lethargy
    - Muscle weakness
    - Fasting hypoglycemia
  - ↓ aldosterone
    - Polyuria, dehydration, hypotension
    - ↑K\(^+\), ↓Na\(^+\), acidosis
    - ↑ renin & angiotensin

- Hyperfunction – Cushing’s Syndrome
  - ↑ cortisol
    - Excess fat deposition around face, cheeks – moon face
    - Thoracic and upper abdominal areas – buffalo hump
    - Osteoporosis, vertebral fractures
    - Loss of connective tissue
    - ↑ Protein catabolism – atrophy & weakness of muscles
    - Abnormal carbohydrate catabolism - diabetes
Adrenal Hyperfunction
Cushing’s Syndrome