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CLIN MED 2

TEST 7

Endocrinology
Endocrine Basics:

Cell bodies empty products into bloodstream
Regulated by nervous system, which in turn are mediated by hormones: Slower response, long duration

Link b/w endo & neuro:

Neurohormones: produced by specialized neurons which move along axons as secretory granales
Stored in "bulb-like" terminals & released into capillaries where they travel to their target organ
Link of environmental cues (visual, tactile, olfactory, auditory, thermal) to effect adjustments in endocrine system

How system works:
Majority by (→) FB system except:
Explosive events: estrogen w/follicular phase causing ovulation
Parturition: oxytocin increases uterine contractions

Positive Feedback Examples

Patient w/high levels of ADH: Normovolemic pt w/Postm -200 and a hypovolemic pt w/a GI bleed
- Posterior pituitary gland: Neural tissue (contains axon terminals), stores neurohormones produced in hypothalamus - ADH, oxytocin
  - Releases hormones upon neural stimulation from hypothalamus
- Oxytocin + Feedback
  - Stimulated by: suckling, vaginal distention, cervical dilation in labor
  - Actions: Milk ejection from breasts (facilitates nursing of infants), stimulates uterine contraction in labor
- Antidiuretic hormone (ADH) (vasopressin)
  - Stimulated by:
    - Increased plasma osmolality
    - Hypovolemia
    - Other nonosmotic stimuli (SIADH)
  - Actions: Conserves water (causes water retention by kidney)
  - Raises blood pressure (constricts arterioles)
- Anterior pituitary gland: endocrine gland which produces hormones; connected to hypothalamus by portal vessels
  - Regulated by releasing and inhibiting hormones from the hypothalamus
  - Growth hormone (GH): promotes growth of bone & muscle mass, protein syn.; ↑ blood glucose (opposes insulin)
  - Adrenocorticotropic hormone (ACTH): stimulates adrenal glands to produce cortisol
  - Thyroid stimulating hormone (TSH): stimulates thyroid gland to produce thyroxine (T4) and T3
  - Proctalin: Stimulates lactation, reproductive functions
  - FSH & LH: Stimulate ovaries to produce estrogen, progesterone; testes produce testosterone; Promote 2º sex characteristics (breast development, pubic hair pattern)

Hormones which affect linear growth & glucose metabolism: GH & thyroxine

Regulation of GH
Stimulated by ↓ [BG], fasting or starvation, ↓ [FFA], hormones of puberty (estro & T), exercise, stress

unfed
Inhibited by: hyperglycemia, obesity, ↑[FFA], somatostatin, somatomedins (inhibitors), senescence: ↑in biology of organism as it ages

Actions of GH:

- **Diabetogenic:** ↑blood glucose; causes insulin resistance in liver, muscle & adipose tissue
- Both of these mediated by IGF-1 (somatomedin)
- **Anabolic:** ↑muscle mass & organ size, stimulates syn of DNA & RNA, ↑protein synthesis
  - Bone growth: increases **linear growth**; stimulates bone & cartilage synthesis
  - Stimulation by TRH from hypothalamus
  - Stimulates TH production & secretion by thyroid gland
  - Stimulates growth of thyroid gland - goiter in pathologic states
  - T₄ - prohormone; major product of thyroid gland
  - T₃ - biologically active; mostly formed in peripheral tissues by conversion from T₄
  - Reverse T₃ (rT₃) - biologically inactive
  - Thyroid hormones circulate mostly bound:
    - Thyroxine-binding globulin (TBG)
    - T₃-binding prealbumin (transthyretin)
    - Albumin
  - **ONLY FREE FRACTIONS OF CIRCULATING T₄ & T₃ ARE BIOLOGICALLY ACTIVE**
  - Alterations of binding protein levels affect total T₄ & T₃, but not free T₄ and T₃

- **Iodine needed for T₃ synthesis**
- Antibodies to Thyroglobulin & thyroid peroxidase occur with autoimmune dz.

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**Regulation of prolactin secretion:**
- Stimulated by:
  - Pregnancy (estrogen); Breast-feeding: increase markedly due to TRH pathway
  - Sleep, Stress
  - Thyrotropin-releasing hormone (TRH), Dopamine antagonists
- Inhibited by:
  - Dopamine (prolactin inhibiting factor; PIF): tonically inhibited
  - Dopamine agonists (bromocriptine, cabergoline)
  - Somatostatin
  - Prolactin

**Used to treat:** Pituitary Tumor

**Parkinson's Hyperprolactinemia**
Actions of prolactin:
- Puberty: stimulates breast development along with estrogen and progesterone
- Pregnancy: stimulates growth and development of mammary alveoli (which make milk) w/estrogen & progesterone
- Lactation: stimulates milk production and secretion in response to suckling; induces synthesis of lactose, casein, and lipids
- Inhibits ovulation: inhibits synthesis & release of GnRH; accounts for decreased fertility during breast-feeding; prevents & during lactation

Least likely to affect aldosterone secretion - ACTH: Renin & K+ more likely
- Stimulated by corticotropin-releasing hormone (CRH) produced in the hypothalamus
- Secreted in a pulsatile and diurnal pattern: night peak
- Stimulates & secretion of adrenal cortical hormones: cortisol, androgens, aldosterone (tonic effect; major control is RAAS & K)
- Stim secret of adrenal glands (produces bilateral hyperplasia in pathologic states)

Actions of glucocorticoids:
- Catabolic and diabetogenic effects
  - Oppose insulin: → proteolysis (catabolic), gluconeogenesis, lipolysis
- Antiinflammatory & immunosuppressive effects
  - Inhibit mediators of inflammation: leukotrienes and interleukins, histamine from mast cells
  - Inhibit mediators of immune system: Ab production by B lymphocytes, proliferation of T lymphocytes
- General Actions:
  - Alter distribution of fat: Truncal obesity, moon face, buffalo hump = Cushing’s D2
  - Maintain normal BP: Enhance vascular responsiveness to catecholamines
  - Inhibit bone formation: ↓ synthesis of bone matrix (collagen), osteoblast production, intestinal calcium absorption
  - Hematologic effects: Stimulation of neutrophil release, involution of lymphoid tissue
  - Effects on electrolytes and renal function: ↑ GFR due to afferent arteriolar dilation
  - Mild mineralocorticoid effect: Na retention, +/− edema, hypokalemia, metabolic alkalosis
  - Effects on gastric secretion: increased HCl and pepsin secretion → ULCER
  - Effects on brain function: ↓ REM sleep, increased wake time, may cause euphoria, irritability, mania, depression

Regulation of Aldo secretion by K⁺:
- Hyperkalemia → ↑ Aldo secretion
- Hypokalemia → ↓ Aldo secretion
- ↑ Renal K⁺ secretion & excretion → ↑ Aldo secretion
- ↓ Renal K⁺ secretion & excretion → ↓ Aldo secretion
- ↑ Plasma K⁺ level → ↑ Aldo secretion
- ↓ Plasma K⁺ level → ↓ Aldo secretion

Actions of Aldosterone & other mineralocorticoids:
- Retention of sodium by the kidney - extracellular fluid volume expansion, HTN, Hypernatremia
- Enhanced excretion of potassium by the kidney - Hypokalemia
- Enhanced excretion of hydrogen ion by the kidney - Metabolic alkalosis

↑ serum Na⁺/H₂O
↓ serum K⁺/H⁺ → alkalosis

Similiar to PTH (the Phosphate-Trapping Hormone)
PTH acts on PDX tubule

Occurs in Distal Tubule
Conundrum: Cortisol and aldosterone have equal affinity for the mineralocorticoid receptors in the kidney. Circulating cortisol levels are much higher than circulating levels of aldosterone. Why then wouldn't cortisol overwhelm and dominate the mineralocorticoid receptors? Why does cortisol have only weak mineralocorticoid activity despite its high levels and high affinity for mineralocorticoid receptors?

Cortisol is inactivated in the renal collecting duct cell.

Actions of Adrenal Androgens:
- **Females:** stimulate growth of pubic and axillary hair and stimulate libido
- **Male** (minor effect cf. testicular testosterone): differentiation of male genital tract in utero
  - Pubertal changes: increase in muscle mass, growth spurt, and closure of epiphysical plates, growth of penis and seminal vesicles, male hair pattern, deepening of voice, spermatogenesis, libido

Parathyroid & vit D BOTH increase bone resorption!!
Parathyroid hormone raises serum calcium & lowers serum phosphorus; not vit D
Vit D raises BOTH serum Ca & serum phosphorus

Regulators of PTH secretion:
- Stimulated by: low serum calcium, high serum phosphorus (lowers serum calcium & inhibits production of 1,25(OH)2D)
- Inhibited by: high serum calcium & 1,25(OH)2D

Effects of PTH:
- **Bone:** Major, chronic effect: Bone resorption
  - Transient, initial effect: Bone formation: seen at low and intermittent concentration
    - Kidney: decreases Ca++ excretion, decreases ammonium (NH4) and hydrogen (H) ion excretion
    - ↑ phosphorus excretion, production of 1,25(OH)2D, bicarbonate excretion
- GI tract: indirectly increases Ca++ and phosphorus absorption by increasing 1,25(OH)2D
- **Net effect:** ↑ serum Ca++, ↓ serum phosphorus

Effects of Vit D (1,25(OH)2D, calcitriol):
- Major effects
  - GI tract: ↑ Ca++ and phosphorus absorption
  - Bone: works w/PTH to ↑ mobilization of Ca++ & P from bone, promotes mineralization of osteoid in growing children
- Other effects:
  - Kidney: ↓ Ca++ and phosphorus excretion
  - Parathyroid glands: ↓ production of PTH
- **Net effect:** ↑ serum Ca++ and phosphorus

Which of the following is NOT produced in the pancreas: Insulin, Amylin, Somatostatin, Incretins. Glucagon
Which of the following would stimulate insulin secretion: Hypokalemia, exercise, somatostatin, HYPERKALEMIA

Regulation of Insulin Secretion:

**Stimulatory Factors**
- Increased concentrations of: glucose, AA, FFA, ketoacids
- Glucagon
- Potassium - Treat deeply Hyperkalemia w/ insulin
- Incretins (GLP-1; GIP)

**Inhibitory Factors**
- Decreased blood [glucose]
- Fasting
- Exercise
- Somatostatin

**Action of Insulin**
- Increases glycogen formation
- Decreases glycogenolysis
- ↑ glucose uptake into cells
- Decreases gluconeogenesis
- Increases protein synthesis (anabolic)
- Increases fat deposition
- Decreases lipolysis
- Increases K+ uptake into cells

**Effect on Blood Level**
- Decrease blood [glucose]
- "
- "
- "
- Decrease blood [amino acid]
- Decrease blood [fatty acid]
- Decrease blood [K+]

Foro is a PTH analog that is used to treat osteoporosis by this mechanism.
Glucagon: hormone of "starvation"—promotes mobilization & utilization of metabolic fuels
Secretion ↑ by fasting & low blood glucose
Secretion inhibited by insulin, somatostatin, ↑ fatty acid & ketoadic concentrations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Effect of Glucagon on Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Increased</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Increased</td>
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<tr>
<td>Ketoadics</td>
<td>Increased</td>
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Somatostatin:
- Pancreatic: secreted in response to a meal. Inhibits secretion of insulin & glucagon; modulates response of these to food
- Hypothalamic: Somatostatin. Inhibits release of growth hormone from pituitary
- Intestinal Somatostatin: Inhibits GI hormones and intestinal motility

Incretins: Peptides secreted by small intestine in response to food
- GLP-1 (glucagon-like peptide 1)
- GIP (glucose-dependent insulinotropic peptide)

**Actions**
- Increases insulin secretion
- Decreases glucagon secretion
- Delays gastric emptying (slows rise of blood glucose)
- Decreases food intake → weight loss
- Increases pancreatic beta cell mass (in animals)

Amylin: peptide produced by pancreatic beta cells
- Secreted in response to meals
- Decreased in insulin-dependent diabetics
- Precursor of islet amyloid in type 2 diabetes

**Decreases postprandial blood glucose and gastric emptying**
- Causes slowly leave stomach, allowing absorption over time rather than all at once.

Adrenal Gland Disorders:
In states of cortisol excess from an overactive adrenal gland, ACTH levels will be low
In adrenal insufficiency, levels of CRH will be high

Hypovolemia → Hypotension → Renin Release → Angiotensinogen → Angiotensin I → Angiotensin II → Aldosterone Release → Peripheral Vasoconstriction

Sodium and Water Retention → Noradrenaline Release

Actions of Adrenal androgens (DHEA & Androstenedione)
- Males: minimal role; most T produced in testes; excess causes suppression of gonadal function
- Females: development of pubic hair & axillary hair; libido, excess causes suppression of gonadal function

Disorders of Adrenal Cortex:
- **HYPERFUNCTION:** Hyperadrenalism
  - Cushing's Syndrome (increased cortisol)