Endocrine System

Disorders and Drugs

Definitions

- **Endocrine**: secretes into blood
- **Exocrine**: secretes into epithelial surfaces
- **Hormone**: product secreted by endocrine gland
  - **Autocrine**: affects cell that secreted it
  - **Paracrine**: affects nearby cells

Endocrine Organs

- Hypothalamus
- Pituitary
- Pineal
- Thyroid
- Parathyroid
- Thymus
- Adrenals
- Pancreatic Islets
- Ovaries
- Testes
- Other
  - Heart
  - Kidneys
  - Endothelium

Mechanisms of Hormonal Control

- **Rhythms of Release**
  - Diurnal, Pulsatile-cyclical, Substrate level
- **Feedback systems**: +,-
- Act only on cells with appropriate receptors—alter cell action/metabolism
- **Elimination**: kidneys excrete or liver metabolizes
- Under control of nervous system, but in turn influence nervous system

Hormone Structural Classes

- **Water Soluble**
  - Peptides
  - Glycoproteins
  - Polypeptides
  - Amines
- **Lipid soluble**
  - Steroids (cholesterol derivatives)
  - Arachidonic derivatives

Hormone Transport

- **Targets**
  - Autocrine – affect cell that released hormone
  - Paracrine – affect nearby cells
  - Endocrine – affect distant cells
- **Transport**
  - Water soluble travel unbound
  - Lipid soluble are mostly bound to carrier proteins
Hormonal Mechanisms of Action

- Receptors:
  - Location: Surface (membrane), Internal
  - Affinity
- Activation effects
  - Change membrane permeability by affecting existing channel proteins
  - Activate existing proteins via second messenger
  - Stimulate synthesis of new proteins

Thyroid

- Two thyroid hormones
  - T4 (thyroxine), T3
  - Must have iodine to synthesize
- Effects
  - Stimulation of energy use (Na/K pump)
    - ↑O2 use, higher body temp
  - Stimulation of heart
    - ↑HR, ↑contraction
  - Promotion of growth and development
    - Maturation of nervous and muscle tissue

Fate of Thyroid Hormones

- Fate of thyroid hormones
  - More T4 released than T3
  - T4 is converted to T3 by enzymes in peripheral tissues
  - 99.5% of both are bound to plasma proteins
- Hepatic metabolism
- Half-life
  - T3: 1.5 days
  - T4: 7 days

Regulation of Thyroid Hormone

- Hypothalamus – TRH
  - Stimulates:
    - Anterior Pituitary – TSH
    - Stimulates:
      - Thyroid: T3, T4
    - Inhibits:
      - Anterior -TSH

Influence of Iodine

- Not enough iodine
  - Thyroid enlarges: goiter
  - Increases ability to absorb iodine
  - Compensation may be enough to keep T4, T3 at normal levels
- Too much iodine
  - Thyroid decreases iodine uptake
  - Decreased T4, T3 release

Hypothyroidism

- Mild adult: hypothyroidism
- Sever adult: myxedema
- Infancy: cretinism
Adult Hypothyroidism

- **Etiology**
  - Thyroid malfunction
    - Chronic autoimmune thyroiditis (Hashimoto’s dz)
    - Insufficient iodine
    - Surgical removal or radioactive iodine tx
    - Insufficient TSH or TRH
- **Clinical Manifestations**
  - Face: pale, puffy, expressionless
  - Skin: cold and dry
  - Hair Brittle, alopecia
  - ↓ Heart rate, ↓ Body temperature
  - Lethargy, depression, fatigue, cold intolerance

Hypothyroidism

- **Laboratory monitoring**
  - TSH
  - T4
  - T3
- **Treatment**
  - T4 replacement
    - Levothyroxine (T4)
    - Levothyroxine plus liothyronine (T3)

Hypothyroid in Infants

- Mental retardation
- Large protruding tongue, potbelly, dwarfish posture
- Abnormal development of:
  - Nervous system
  - Bones, teeth,
  - Muscles
- Early treatment (2-3 days): normal
- Delayed tx: (2-3 months): physical normal, but mental damage is done

Maternal Hypothyroidism

- Can cause decreased IQ and other neuro problems
- Fetal thyroid gland is fully functional by second trimester
- First trimester is critical
- Screening for all pregnant women

Hyperthyroidism

- **Two forms:**
  - Grave’s Disease: exophthalmos
  - Plummer’s Disease (toxic nodular goiter)
- **Thyrotoxicosis**
  - Heart: Tachy, dysrhythmias, angina
  - Rapid thought, speech
  - Nervousness, insomnia
  - Muscle weakness and/or atrophy
  - Increased appetite, weight loss
Grave's Disease

- 6 times more likely in women; ages 20 – 40
- Thyroid stimulating immunoglobulins
- Treatment
  - Surgical removal of thyroid tissue
  - Destruction of thyroid tissue with radioactive iodine
  - Suppression of thyroid hormone synthesis
  - Adjunct treatment: propanolol and iodine

Hyperthyroid

- Toxic nodular Goiter: thyroid adenoma
  - Same treatment as grave’s Disease
- Thyrotoxic Crisis (Thyroid storm)
  - Manifestations:
    - Hyperthermia
    - Severe tachycardia
    - Profound weakness
    - Unconsciousness, coma, heart failure
  - Etiology: overdose or excess endogenous production

Thyroid Function Tests

- TSH
  - More sensitive
  - Can help to distinguish primary problems from secondary
- T4, Free T4
- T3

Levothyroxine

- Synthroid, Levothroid, Levoxyl
- Pharmacokinetics
  - Absorbed in GI tract
  - Converted to T3 in blood and tissues
  - Half-life
    - Takes four weeks to reach steady state
    - Convenient daily dosing
- Adverse effects
  - Thyrotoxicosis

Levothyroxine Interactions

- Drugs that reduce levothyroxine:
  - Cholestyramine, Colestipol, Calcium, Sucralfate, Aluminum antacids, Iron suppl.
- Drugs that help break down levothyroxine
  - Phenytoin, carbamazepine, rifampin, sertaline, phenobarbital
- Levothyroxine potentiates:
  - Warfarin
  - Catecholamines (epinephrine, et al.)

Levotyroxine

- Almost always PO
- May be given IV if necessary
- Evaluation
  - TSH and T4 levels
  - Symptoms
- Duration of Therapy
  - LIFELONG!!!
Hyperthyroid Medications

- Propylthiouracil (PTU) & Methimazole
  - Inhibits thyroxine production
- Radioactive Iodine-131
  - Taken up by thyroid where it decays and destroys thyroid cells
  - Half-life 8 days
  - Reduction is gradual: effects begin at 2-3 weeks and increase up to 2-3 months
  - 66% of patients cured by one dose

Radioactive Iodine

- Benefits:
  - Cheap
  - No surgery or recovery
  - Death unlikely
  - Only thyroid is affected
- Drawbacks
  - Delayed effects
  - Delayed hypothyroidism (10% in first year)

Pituitary

- Growth Hormone (GH)
  - Too much: gigantism, acromegaly
    - Surgical removal or medical suppression
  - Too little: dwarfism: treat with GH
    - Two forms: somatotropin and somatrem
  - Adverse effects:
    - Hyperglycemia
    - Hypothyroidism
    - Antibody development
    - Are impaired by glucocorticoids

Prolactin Excess:

- Etiology
  - Pituitary adenoma
  - Hypothalamic injury
  - Drugs
  - Idiopathic
- Manifestations
  - Women: amenorrhea, galactorrhea, infertility
  - Men: decreased libido and potency, galactorrhea
  - Delayed puberty

Antiduretic Hormone

- AKA Vasopressin or AVP (arginine vasopressin)
- Actions
  - ↑ water reabsorption in renal collecting ducts
  - Vasoconstriction of vascular smooth muscle and GI tract smooth muscle
- Not enough: Diabetes insipidus
- Too much: SIADH

Adrenal Glands

- Cortex: secretes steroids generally called corticosteroids:
  - Mineralocorticoids
  - Glucocorticoids
  - Androgens (male sex hormones)
- Medulla
  - Nervous tissue
  - Secretes epinephrine and norepinephrine
Glucocorticoids

- Several produced
  - Cortisol is main one (amount and effect)
- Physiologic effects
  - Low levels
- Pharmacologic effects
  - High levels

Glucocorticoids

- Physiological effects
  - Carbohydrate metabolism
    - Gluconeogenesis
    - Reduction of peripheral glucose use
    - Promotion of glycogen formation
  - Protein catabolism
  - Fat catabolism
  - Cardiovascular: membrane permeability, RBC counts, ↑polys, ↓lymphs and monos

Glucocorticoids

- Physiologic effects cont
  - Skeletal muscle – maintain perfusion
  - CNS: affect excitability
    - Too little: depression, lethargy, irritability
    - Too much: excitation, euphoria
  - Stress: in combination with epinephrine, ensure that glucose and blood supply is adequate
  - Respiratory in neonates: stimulates maturation of lung

Glucocorticoids

- Hypothalamus: CRF
- Stimulates Anterior Pituitary: ACTH
- Stimulates Adrenal Cortex: Synthesize and release glucocorticoids
- Glucocorticoids suppress hypothalamus and pituitary release of CRF and ACTH
- Two modes of stimulation
  - Circadian rhythm
  - Stress

Other Cortical Steroids

- Mineralocorticoids
  - Most important is aldosterone
  - Controlled by RAAS
- Adrenal androgens
  - Men: not much effect, testosterone from testes is greater
  - Women: testosterone is metabolized from androgens. Causes axillary & pubic hair and maintains libido

Glucocorticoid Disorders

- Glucocorticoid excess: Cushing’s Syndrome
  - Etiology
    - Excess ACTH (Cushing’s Disease)
    - Hypersecretion by adrenal adenoma or carcinoma
    - Large doses of exogenous glucocorticoids
  - Manifestation
    - Obesity, hyperglycemia, glycosuria, hypertension, F&E imbalances, osteoporosis, muscle weakness, hirsutism, increased infections
    - Weakened skin, striae
    - Fat redistribution: belly, moon face, buffalo hump
Glucocorticoid Disorders

- Glucocorticoid deficit: Addison’s Disease
  - Manifestations
    - Weakness, emaciation, hypoglycemia, hyperpigmentation, F&E imbalances
  - Treatment
    - Glucocorticoid replacement
- Acute adrenal Insufficiency (Adrenal Crisis)
  - Adrenal failure, pituitary failure, sudden d/c of exogenous glucocorticoids
  - Hypotension, dehydration, weakness, lethargy, NVD, shock, death

Glucocorticoid Therapy

- Hydrocortisone: artificial cortisol
  - Has both gluco- and mineralocorticoid properties
  - IV or IM
- Cortisone converts to hydrocortisone in body
  - PO or IM
- Inhibitors of corticosteroid synthesis
  - Ketoconazole
  - Aminoglutethimide

Glucocorticoids used for non-Endocrine purposes

- Pharmacologic Actions
  - Anti-inflammatory and Immune effects
    - Inhibit prostaglandin, leukotriene, and histamine synthesis
    - Suppress infiltration of phagocytes
    - Suppress proliferation of lymphocytes
  - Effects on Metabolism and Electrolytes
    - Glucose levels rise
    - Protein synthesis suppressed
    - Fat deposits mobilized
    - Fewer electrolyte effects, but can inhibit calcium absorption

Therapeutic Uses

- Rheumatoid Arthritis
- SLE
- Inflammatory Bowel Disease (IBD)
- Miscellaneous Inflammatory D/Os
- Allergic conditions (not acute anaphylaxis)
- Asthma
- Dermatologic disorders
- Neoplasms
- Transplant rejection
- Preterm infant

Glucocorticoids Adverse Effects

- Adrenal insufficiency
- Osteoporosis: long term therapy
- Infection
- Glucose intolerance
- Myopathy
- F&E disturbance
- Growth retardation
- Psychological disturbances

Glucocorticoids Adverse Effects

- Cataracts and Glaucoma
- Peptic Ulcer Disease
- Iatrogenic Cushing’s Disease
- Ischemic Necrosis – especially caution with ETOH
### Agents

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<th>Type</th>
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