

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: propranolol 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, sertraline, phenobarbital
- Levothyroxine potentiates:
 - Warfarin
 - Catecholamines (epinephrine, et al.)

Levothyroxine

- 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

Pituitary

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

Antidiuretic 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

Regulation of 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

	Anti-inflammat
• Short Acting	
– Cortisone, Hydrocortisone	1
• Intermediate Acting	
– Prednisone	4
– Prednisolone	4
– Methylprednisolone	5
– Triamcinolone	5
• Long acting	
– Betamethasone	20-30
– Dexamethasone	20-30