INTRODUCTION

System Concept

A. Functional

1. One of 3 overall controlling / regulating systems
    a. Nervous – much overlap with endocrine
    b. Cardiovascular – different context & scope; physical, not functional
2. Accomplished via hormones

B. Structural

1. Endocrine glands – hormone source
2. Lack of relationship
    a. Glands scattered throughout body
    b. Most lack physical interconnection
    c. Exception to all other organ systems
3. Relationships
    a. Glands functionally interrelate
    b. Via dissemination of hormones

Hormones

A. Concept

1. Chemical substances – endocrine glands synthesize & secrete
2. Released in small, variable amounts
3. Transported by blood
4. Produce metabolic changes in distant target cells

B. Chemical Signaling

There are a number of methods involved in cellular chemical communication.

1. Intracrine – this is self-regulation within a cell
2. Autocrine – this occurs with one cell, but the response involves a membrane receptor
3. Juxtacrine – this involves the membranes of two adjacent cells
4. Paracrine – this involves one cell affecting the general immediate surrounding area
5. Neurocrine – this involves a “hormone” from an axon ending, targeting a local area
6. Neuroendocrine – this involves a true hormone in all respects, but from an axon ending and not a typical endocrine organ
7. Endocrine – this involves hormones from the endocrine system

C. Importance

1. Chemical integrator & coordinator of entire body
2. Homeostasis – balance of vital life processes
3. Effects occur in seconds or days – last for hours or years
4. Excesses or deficiencies of severe consequence

D. Structure

1. General – not all in one organic chemical grouping
2. Specific – one of the following, varying in size & complexity
    a. Protein
    b. Polypeptide
    c. Peptide
    d. Amine
    e. Glycoprotein

f. Steroid

E. Secretion

1. Proteins and derivatives as an example
    a. First form – preprohormone
        - Within secretory cell
        - Larger than final form
    b. Second form – prohormone – from cleavage of first form
    c. Final form – hormone
        - Golgi cleaves second form
        - Compacted into secretory vesicles (granules)
2. Storage
    a. Most within secretory cells
    b. Extracellular – within vesicles (thyroid and adrenal medulla)

E. Principles of Action

1. Change reaction rates
2. Catalytic in effect
    a. Enzymatic, but <u>not enzymes</u> *[explained later]*
    b. Disproportionate amount **:** response
3. Specificity
    a. Hormone itself
        - Specific stimulus for release
        - Varies with stimulus amount & nature
    b. Target tissue
        - Specific tissue or same reaction in different tissues

- Specific receptors for each hormone
- Rare exceptions

4. Constantly present – fluctuate with need
5. Continuous inactivation to prevent accumulation, by 2 methods
    a. Disabled
    b. Excreted
6. May influence each other
    a. Stimulation or inhibition
    b. Via influence on synthesis, secretion & / or activity

F. Mechanisms of Action

1. General – recall they are “enzymatic”
    a. Coenzymes
    b. Part of coenzyme structure
    c. Influence coenzyme synthesis
    d. Influence enzyme synthesis
2. Specific examples of effects
    a. Influence rate of cellular reactions – **most overall**; true of all of the following (b-h)
    b. Growth & development – via synthesis of new cell parts
    c. Membrane transport
    d. Osmotic balance
    e. General ionic balances
    f. Acid - base balance
    g. Energy balance – via cellular respiration
    h. Stress responses

3. Membrane receptors

   a. Specific proteins – different kind for each hormone

   b. Hormone is first messenger – usually impermeable

   c. Hormone bonding causes receptor shape change

   d. Two basic mechanisms for changes

      - Enzyme activation (e.g.), which often leads to a cascading series of further reactions

      - Gene expression – via either stimulating or suppressing protein synthesis

   d. Second messenger activated in cytoplasm

      - Examples

        - Cyclic - AMP

        - Cyclic - GMP

        - Ca^{++} -- binds with intracellular calmodulin

        - Membrane phospholipids

          > Split into small substances by phospholipase-c

          > Examples – inositol triphosphate & diacylglycerol

      - Second messenger produces action

      - Not necessary for small, permeable hormones

G. Regulation

1. Negative feedback

   a. Inhibition (negation) of hormonal effects

   b. Feedback loop – simplest, <u>short</u> type

      - An endocrine organ (A) affects a target (B)

      - B inhibits A when sufficient action has occurred

c. Long loop

- Third organ or tissue involved – C
- A affects B, then B affects C
- C feeds back to inhibit A
- Both A & B will be endocrine organs

d. Longer loops possible – e.g. A, B, C, D

Non - Hormonal Chemical Messengers

A. Metabolites

1. Too general – all cells produce them
2. e.g. excessive CO_2 induces metabolic responses

B. Enzymes

1. Too general – all cells produce them
2. Hormones are “enzymatic”, though

C. Pheromones

1. Scents released to affect other individuals
2. Not hormones since action is external

D. Vitamins

1. Indeed have hormone-like effects – from food, not synthesized (termed *essential*
2. Vitamin-D and the retinoids **are** synthesized – actions very much hormone-like

E. Neurotransmitters

1. Substances secreted by nerve cells to affect each other
2. Some goes into blood – negligible amount
3. ***Some nerve cells <u>do</u> secrete true hormones***
    a. These are exceptions
    b. e.g. hypothalamus
4. Some hormones **<u>are</u>** neurotransmitters – e.g. TRH; cRH; CCK

F. Eicosanoids (e.g. Prostaglandins)

1. The most hormone - like messengers
2. Reasons for not being hormones
    a. Produced by almost all cells
    b. Action within producing organ
    c. Responses varied
3. Considered <u>autocrine</u> or <u>paracrine</u> regulators
    a. Modulate hormone action
    b. Co-messenger – works with second messenger
4. All chemically similar – modified fatty acids (mostly arachidonic)
5. Examples of actions
    a. General – regulate hormone release and actions
    b. Inflammatory responses
    c. Anticoagulant
    d. Fat breakdown rate
    e. Blood pressure regulation
    f. Uterine contractions

HYPOPHYSIS (PITUITARY GLAND OR BODY)

Adenohypophysis (Anterior Pituitary)

A. General

1. Most of its hormones termed tropic
2. Target other endocrine organs

B. Adrenocorticotropic Hormone (ACTH)

1. Structure & secretion
   a. Polypeptide – 39 amino acid residues
   b. Secreted by β-basophils of pars distalis
2. Actions
   a. Targets cortex of adrenal glands
   b. Controls secretion of glucocorticoids (mostly), mineralocorticoids (less) and androgens (less) *[all explained later]*
   c. Maintains size & blood flow of entire adrenals

C. Somatotropic (Growth or Human Growth) Hormone (STH, GH or HGH)

1. Structure & secretion
   a. Protein – 191 amino acid residues
   b. Secreted by acidophils of pars distalis
2. Does not affect targets directly, but via mediators from other sources
   a. IGF's (Insulin-like Growth Factors), also termed somatomedins
   b. Polypeptides (70 and 60 amino acid residues)
   c. Similar structure to and action to insulin, but only for cell metabolism
   d. Secreted by liver and many other tissues

e. Have autocrine, paracrine and endocrine functions

f. Both GH and insulin necessary for IGF's to function

3. Actions

a. Directly targets <u>all cells</u> of the body

b. Basically stimulates attainment of adult size

c. After adulthood, maintains body throughout life

d. Accomplishes above via:

- Amino acid intake & use by cells
- Mobilization & respiration of stored fat
- Glycogenolysis – glucose release from glycogen
- Bone calcification & growth

4. Hypersecretion

a. Gigantism

- Before maturity
- Proportionate enlargement of all body parts

b. Acromegaly

- After maturity
- Grossly enlarged jaw, hands & face

5. Hyposecretion

a. Dwarfism

- Before maturity
- Normal mental development (unlike thyroid version)

b. Simmond's disease

- After maturity
- Apathy, muscle atrophy, diminished sexual functions

D. Thyroid-Stimulating Hormone (TSH or thyrotropin)

1. Structure & secretion
    a. Glycoprotein –2 polypeptides + carbohydrate (8%)
    b. Secreted by γ-basophils of pars distalis
2. Actions
    a. Controls synthesis & secretion of thyroid hormones
    b. Maintains size & blood flow of gland
3. Hyper- & hyposecretion
    a. Identical with extremes of the thyroid hormones
    b. *[presented later]*

E. Gonadotropic hormones

1. Follicle-Stimulating Hormone (FSH)
    a. Structure & secretion
        - Glycoprotein – 2 subunits & 10% carbohydrate
        - Secreted by γ-basophils of pars distalis
    b. Actions
        - Female – stimulates ovarian follicle development
        - Male – stimulates sperm formation & maturation
2. Luteinizing (Interstitial Cell-Stimulating) Hormone (LH or ICSH)
    a. Structure & secretion
        - Glycoprotein – almost identical to FSH
        - Secreted by Δ-basophils of pars distalis
    b. Actions
        - Female
            - Follicle maturation

- Ovulation
- Corpus luteum formation
- Secretion of estrogens & progesterone

- Male – secretion of testosterone from testes

3. Luteotropic Hormone (LTH, prolactin, lactogenic hormone or mammotropin)

a. Structure & secretion

- Protein _ 198 amino acid residues
- Secreted by acidophils of pars distalis

b. Actions

- In both sexes, but can only function in females
- Normal mammary gland growth & milk production

F. Melanocyte-Stimulating Hormone (MSH)

1. Structure & secretion

a. Polypeptide – 13 amino acid residues

b. Secreted by pars intermedia

2. Action – in **non-humans**

Stimulation of skin's melanocytes to produce melanin

3. Debated importance

a. Secreted in very small quantities

b. Identical with first part of larger ACTH molecule

c. Often omitted as being a pituitary hormone

G. Hypothalamic control

1. General

a. Controls all hormonal release

b. Via its own set of hormones

- Peptides or polypeptides – 3 to 44 amino acids
- Synthesized by specialized neurons

c. Special vascular connection – hypophyseal portal system

d. Stimulated by sensory input from many sources

2. Releasing hormones

a. Corticotropin-releasing hormone (CRH)

b. Growth hormone-releasing hormone (GHRH or GRH)

c. Thyrotrophin-releasing hormone (TRH)

d. Gonadotrophin-releasing hormone (GnRH)

e. Others

- Prolactin-releasing factors (PRL) – TRH (?); VIP; serotonin
- MSH-releasing hormone debatable

3. Inhibiting hormones

a. Somatostatin (growth hormone-inhibiting hormone – GHIH) – also inhibits TSH and other hormones (insulin; glucagon; gastrin; secretin; VIP)

b. Prolactin-inhibiting factors (PIH or PIF) – dopamine and GABA

c. Others

- Debated presence of any for ACTH, TSH, FSH, LH
- Not necessary in theory
  - GH & LTH have non-endocrine targets
  - Tropic hormones have better feedback loops

Neurohypophysis (Posterior Pituitary)

A. Hypothalamic control

1. Actually synthesizes all hormones from this division
    a. Neurosecretory cells – specialized neurons
    b. Nonapeptides
    c. Bound with carrier proteins for transport & storage
2. Transported through stalk to pars nervosa
3. Pars nervosa stores & releases hormones

B. Antidiuretic Hormone (ADH or arginine vasopressin)

1. Controls rate of water excretion by kidneys *[explained later]*
2. Increases blood pressure
    a. Only in high concentrations – normally very low
    b. Called vasopressin in this situation

C. Oxytocin

1. Stimulates uterine contractions for childbirth
2. Causes milk ejection in mammary glands
    a. Muscle contractions in ducts
    b. Stimulated by suckling

THYROID GLAND

Thyroxine & Triiodothyronine

A. Chemistry

1. Structure
    a. Thyroxine (T_4) – basically 4 iodines + tyrosine

b. Triiodothyronine (T_3) – 3 iodines + tyrosine

2. Formation

a. Synthesized by follicular epithelial cells

b. T_4 & T_3 part of parent molecule – thyroglobulin

c. Thyroglobulin – 2 subunits, each 5,496 amino acid residues

d. Secreted into follicular cavity as colloid

3. Extracellular storage

a. Unusual – most hormones into blood after synthesis

b. Reason – vitally important hormones

c. Approximate one month supply in colloid

4. Release & transport

a. Thyroglobulin back into follicular epithelial cells

b. Hydrolysis within lysosomes – releases T_4 & T_3

c. Much more T_4

d. Secreted into blood

e. Most bound with carrier – thyroid-binding globulin (TBG)

5. Relative effects

a. Free (unbound) hormone acts immediately

b. Bound hormone in reserve – gradually released

b. T_3 more potent, but effects shorter term

B. Actions

1. Protein synthesis

a. Stimulated in all cells

b. Results in more enzymes

c. Basic reason for all other actions

2. Oxidative respiration
    a. Stimulated in most cells
    b. Brain not affected
3. Carbohydrate metabolism (not just respiration)
    a. Stimulated in all cells
    b. Via more absorption, release from storage & utilization
4. Lipid metabolism
    a. Stimulated in all cells
    b. All phases (similar to carbohydrates)
5. Growth & development
    a. Promoted in all cells
    b. Especially affects CNS
    c. Skeletal maturation notable as well

C. Dysfunctions

1. Underlying causes – one of the following
    a. TSH secretion incorrect
    b. Thyroid malfunction
    c. TRH incorrect
    d. Iodine deficiency
2. Goiter
    a. Enlargement of thyroid
    b. From increased activity
    c. Could be fruitless – from iodine deficiency
    d. Could be productive, but harmful, if from hyperthyroidism

3. Hypothyroidism

    a. Before maturity

        Dwarfism with mental retardation

    b. After maturity

        - Myxedema
        - Muscle weakness, lethargy, low body temperature
        - Obesity, but with very small appetite

4. Hyperthyroidism

    a. Graves' disease – before or after maturity

    b. Extreme hyperactivity & mental / emotional instability

    c. Extreme perspiration & feeling hot

    d. Weight loss, but voracious appetite

Thyrocalcitonin (Calcitonin)

A. Chemistry

1. Polypeptide – 32 amino acid residues
2. Synthesized by C-cells (parafollicular cells) between follicles

B. Actions

1. Lowers blood Calcium (Ca^{++}) level

    a. Increases uptake by bone matrix

    b. Decreased resorption (release) – inhibits osteoclasts

2. Regulation

    a. No control from any other organ

    b. C-cells directly monitor blood Calcium level

3. Coordinated with parathyroid *[see below]*

PARATHYROID GLANDS

Hormones

A. Parathyroid hormone or Parathormone (PTH)

1. Polypeptide – 84 amino acid residues
2. Synthesized & secreted by chief (zymogenic) cells

B. Vitamin D (Cholecalciferol)

1. Steroid cholesterol derivative
2. Two sources
   a. Dietary
   b. Synthesized within the skin
      - Ultraviolet radiation necessary for reactions
      - Same potency as dietary form
      - Makes this not a true vitamin
3. Relation to PTH
   a. Final reaction to active form mediated by PTH
   b. In response to need for increased blood calcium

Actions

A. Elevates blood calcium level

1. Bone resorption increased – stimulates osteoclasts
2. Kidney reabsorption increased – less excretion

3. Intestinal absorption increased – vitamin D more active here

B. Overall calcium balance

1. Hypercalcemia – increased blood calcium
    a. Depresses PTH secretion
    b. Less vitamin D synthesis
    c. Stimulation of thyrocalcitonin secretion
    d. Calcium level back down to normal
2. Hypocalcemia – lowered blood calcium
    a. Directly stimulates chief cells – increased PTH
    b. Activates vitamin D
    c. No thyrocalcitonin effect – PTH potent enough
    d. Calcium level back up to normal

Dysfunctions

A. Hypoparathyroidism (Tetany)

1. Severe, uncontrollable hypocalcemia
2. Muscle & nerve cell irritability
3. Muscle spasms – from spontaneous tetanic contractions
4. Sodium is the actual problem
    a. Slight sodium imbalance normally leads to contraction
    b. Insufficient calcium allows massive sodium imbalance

B. Hyperparathyroidism

1. Severe, uncontrollable hypercalcemia
2. Muscle weakness

3. Bone pain from severe decalcification
4. Kidney calculi (stones) – precipitate here, from removal efforts

ADRENAL (SUPRARENAL) GLANDS

Cortex

A. General

1. Hormone Chemistry
    a. All corticosteroids – derived from modified cholesterol
    b. Very similar structures – same basic synthetic pathway

2. Regulation
    a. ACTH directly – CRH indirectly
    b. Controls development & maintenance of entire cortex
    c. More control over glucocorticoids

B. Mineralocorticoids

1. Chemistry
    a. Secreted by zona glomerulosa
    b. Aldosterone – 90% of the total & most potent
    c. Deoxycorticosterone
    d. Glucocorticoids
        - Very slight mineralocorticoid- like activity
        - Greater volume secreted, however

2. Actions

   a. Sodium reabsorption

      - Increased active transport retains sodium
      - Through membranes of epithelial cells
      - Primarily kidneys
      - Other glands – sweat, salivary, intestinal (several)

   b. Potassium excretion

      - Always moves opposite direction from sodium
      - Na^+ / K^+ pump moves both simultaneously

   c. Water reabsorption

      - **This is the reason for sodium reabsorption**
      - Water tends to follow sodium
      - Only if permitted by ADH
      - For fluid volume control *[details later – excretion]*

   d. Other, secondary effects

      - Chloride, bicarbonate & hydrogen ions
      - *[details later – excretion]*

3. Control – in descending importance

   a. Hyperkalemia stimulates secretion

   b. Renin - angiotensin system

      - Kidney hormone / blood enzyme interaction
      - *[explained later – excretion]*

   c. Hyponatremia stimulates secretion

   d. ACTH – very little influence

4. Overall significance

   a. Absence would be fatal – few days to a week or more

   b. Results in cardiac shock

C. Glucocorticoids

1. Chemistry

   a. Secreted by zona fasiculata (mostly) & reticularis

   b. Cortisol (hydrocortisone) --over 90% & more potent

   c. Corticosterone

2. Actions

   a. Glucose – supplies & blood level elevated

      - Gluconeogenesis in liver – from amino acids
      - Decreased transport into all cells
      - Decreased respiration – all cells

   b. Proteins

      - Promotes catabolism – all cells, but mostly muscles
      - Provides amino acids for gluconeogenesis

   c. Fats

      - Hydrolyzed from storage – adipose tissue
      - Respiration stimulated – all cells

[Note: actions a-c related to starvation conditions]

> Maintains blood glucose

> Preserves CNS function

> Maintains cardiovascular function – via CO and BP stimulus

> Depresses reproductive function – via pituitary and gonadal

d. Stress responses
- Stimulated by many stressful situations
- Mobilizes needed nutrients for responses

e. Anti-inflammatory – promotes recovery & healing
- Suppresses immune responses in injured tissues
- Reduces lysosomal self-destruction of cells
- Inhibits mast cells & phagocytes
- Reduces tissue fluid pooling – capillary permeability

3. Control

a. ACTH directly

b. CRH indirectly

c. Stress produces more cortisol in only few minutes

4. Significance

a. Hyposecretion

Not directly nor as rapidly fatal as lack of aldosterone
- Severe metabolic imbalance
- Poor resistance to stress

b. Hypersecretion

Susceptible to minor infections – these could be fatal

C. Sex Hormones

1. Androgens

a. Male hormones – from zona reticularis

b. Dehydroepiandrosterone (DHA) – most important

c. Androstenedione

d. Relation to testosterone from testes

- Less important & potent
- May be converted to testosterone

e. Actions

- Little in men
- Women – influences pubic & axillary hair growth

2. Estrogens & progesterone

a. Female hormones

b. Secreted in very low levels

c. Main source ovaries

D. Dysfunctions

1. Hypoadrenalism

a. Addison's disease – adrenal, ACTH or CRH cause

b. Loss of sodium & water; hyperkalemia

c. Low blood pressure – from mineral imbalance

d. Hypoglycemia

e. Excessive skin pigmentation – low feedback, more ACTH

2. Hyperadrenalism

a. Cushing's syndrome – usually adrenal or pituitary tumor

b. Abnormal fat distribution

c. Weakness from muscle atrophy

d. Hyperglycemia – insulin cannot correct

e. Hypertension – from hypernatremia & water retention

f. Immune & inflammatory suppression

3. Androgenital syndrome
    a. Excessive androgen secretion – usually tumor
    b. Before maturity
        - Males – sexual precocity
        - Females – masculinization of hair, voice & clitoris
    c. After maturity
        - Males – no effects – masked by normal testosterone levels
        - Females – virilism
            - Hirsutism
            - Breasts diminish
            - Male musculature develops
            - Cessation of ovulation & menstruation
    d. Hyposecretion – no effects

Medulla

A. Hormones

1. Essentially identical catecholamines
    a. Epinephrine (adrenaline) – greater amount
    b. Norepinephrine (noradrenaline)
2. Stored within vesicles for later release

B. Actions

1. Mimic nervous system effects ***[review Autonomic System]***
    a. Sympathetic division of autonomic nervous system
    b. Nervous system acts faster, but shorter lived
    c. Concerned with stress responses

2. Glucose *[adrenal only]*
    a. Glycogenolysis – liver & skeletal muscles
    b. Stimulates respiration
3. Fats – hydrolyzed *[adrenal only]*
4. Cardiovascular *[both autonomic and adrenal]*
    a. Heart – increased output
    b. Vasoconstriction
5. Nervous / sensory *[autonomic only]*
    a. Mental stimulation
    b. Pupil dilation

C. Control & Significance

1. Secreted from nervous stimulation by sympathetic division
2. Reinforcement & backup for sympathetic
3. Affects all cells metabolically – sympathetic does not
4. Actions last several minutes

PANCREAS

Insulin

A. Chemistry

1. Protein – 2 subunits (polypeptide chains) – 21 & 30 amino acids
2. Synthesized by beta cells of islets of Langerhans

B. Stimuli

1. For secretion

a. Ingested glucose and some other monosaccharides – glucose most potent stimulus

b. Nervous – vagal (parasympathetic)

2. Amplifiers – if glucose caused

a. Glucagon-like peptide (GLP) – from small intestinal lining

b. Gastric Inhibitory Peptide (GIP)

c. Cholecystokinin (CCK)

d. Secretin

e. Gastrin

3. Inhibitors

a. Sympathetic

b. Somatostatin

B. Actions

1. Glucose

a. Lowers blood glucose – all cells, except brain

b. Mechanisms

- Increased transport into cells
- Increased respiration
- Increased glycogenesis – liver & muscle
- Decreased gluconeogenesis – liver

2. Fats

a. Decreased respiration – via glucose use

b. Fatty acid synthesis – liver

c. Transport to adipose tissue for storage

3. Proteins
    a. Increased amino acid transport into cells
    b. Increased protein synthesis
    c. Decreased gluconeogenesis

C. Dysfunctions

1. Diabetes mellitus
    a. Insufficient insulin (Type I) or defective target cell receptors (Type II)
    b. Insulin-dependent (Type I or juvenile-onset)
        - Daily insulin injections required
        - No other treatments
    c. Non-insulin-dependent (Type II or adult-onset)
        - Insulin need variable
        - Related to obesity
        - Proper diet & exercise may preclude any insulin
    d. Effects
        - Hyperglycemia
        - Abnormal fat metabolism & atherosclerosis
        - Protein loss
2. Potentially fatal
    a. Hyperglycemic coma
        - Excess fatty acid metabolism
        - Acidosis causes blood ph to drop
    b. Hypoglycemic coma
        - Excessive insulin – over-injection or pancreatic tumor
        - Shock from brain glucose deprivation

Glucagon

A. Chemistry

1. Protein – 29 amino acid residues
2. Secreted by alpha cells of islets of Langerhans

B. Actions

1. Elevates blood glucose – insulin antagonist
2. Mechanisms
    a. Stimulates glycogenolysis – liver
    b. Stimulates gluconeogenesis – liver

C. Control

1. Blood glucose – indirect proportion
2. Blood amino acids – direct proportion, since for gluconeogenesis
3. Insulin inhibits alpha cell secretion

D. Other insulin antagonists

1. Growth Hormone – decreases transport into cells
2. Cortisol –stimulates gluconeogenesis
3. Epinephrine – stimulates glycogenolysis

Somatostatin (same substance as hypothalamic GHIH)

A. Chemistry

1. Polypeptide – tetradecapeptide (14 amino acid residues)
2. From delta cells of islets of Langerhans & hypothalamus

B. Actions

1. Depresses insulin & glucagon – also GH and TSH
2. Depresses digestive movements, secretion & absorption
3. Significance debated – may prolong nutrient availability

Pancreatic Polypeptide (PP)

A. 36 amino acid residues

B. Secreted by F-cells of islets

C. Stimulated by ingested proteins, fasting, exercise and hypoglycemia

D. Slows absorption of digested food – possibly to allow more steady protracted absorption