Endocrinology Introductory Lectures
What do You Want to Become?

- Crazy
  - Attention span?
    - Significant
      - Psychiatry
    - Non-existent
      - Emergency medicine
- Medical student
- Sane
  - Hardworking?
    - Very
      - Attitude?
        - Nice
          - Hates adults
            - Paediatrics
          - Hates children
            - Medicine
        - Doesn't matter
          - Patient asleep
            - Anaesthesia
          - Patient dead
            - Pathology
        - Mean
          - Surgery
    - Not so much
      - Afraid of the light
        - Afraid of the dark
          - Afraid of the dark
            - Think big
              - Radiology
            - Think small
              - Dermatology
              - Ophthalmology

Veysman, B. BMJ 2005;331:1529
Definitions

- **Endocrine Gland**: secretes a hormone into the circulation

- **Hormone**: Chemical substance produced by a ductless endocrine gland and secreted into the blood, which carries it to a specific target organ to produce an effect

- **Endocrine**: TSH example

- **Paracrine**: Acting on the contiguous cells (somatostatin example)

- **Autocrine**: Acting on the same cells (IGF, EGF, TGF-B)

- **Endocrinology = Communication**
Gland/Products/Class

- Anterior Pituitary (Adenohypophysis):
  - Luteinising Hormone (LH)
  - Follicle Stimulating Hormone (FSH)
  - Growth Hormone (GH, somatotropin)
  - Prolactin
  - Thyroid Stimulating Hormone (TSH, thyrotropin)
  - Adrenocorticotropic Hormone (ACTH, corticotropin)
  - Peptide/Protein
• Posterior Pituitary (Neurohypophysis)
  • Antidiuretic Hormone (ADH)
  • Peptide
Gland/Product/Class

• Hypothalamus
  • Gonadotropin Releasing Hormone (GnRH)
  • Growth Hormone Releasing Hormone (GHRH)
  • Thyrotropin Releasing Hormone (TRH)
  • Corticotropin Releasing Hormone (CRH)
  • Somatostatin
  • Prolactin Inhibiting Factor (Dopamine)
  • Peptide/Protein
Gland/Product/Class

• Thyroid
  • Thyroxine (T4) Amine
  • Triiodothyronine (T3)
  • Calcitonin Protein

T4

T3
Gland/Product/Class

• Parathyroid
  • Parathyroid Hormone (PTH) Protein
Gland/Product/Class

- Pancreas
  - Insulin
  - Glucagon
  - Somatostatin

Peptide/Protein
Gland/Product/Class

- Adrenal Cortex
  - Cortisol Steroid
  - Aldosterone
  - Adrenal “androgens” - DHEA
Gland/Product/Class

- Adrenal Medulla
  - Epinephrine
  - Norepinephrine
  - Dopamine

Amine
Gland/Product/Class

• Gonads
  • Oestrogens (E2) Steroid
  • Progesterone
  • Testosterone

• Placenta
  • Chorionic Gonadotropin (βhCG) (Protein)
Function of Hormones

- Reproduction
  - Gonadal steroids
  - Gonadotropins (LH/FSH)
  - Prolactin
Function of Hormones

• Growth and development
  • GH
  • Thyroid hormones
  • Adrenal steroids
  • Gonadal steroids
  • Others
Function of Hormones

- Maintenance of internal environment (homeostasis)
  - Thyroid hormones
  - Glucocorticoids
  - Mineralocorticoids
  - Gonadal steroids
  - Catecholamines
Function of Hormones

- Energy production, utilisation and storage
  - Insulin
  - Glucagon
Function of Hormones

- One hormone may have multiple actions:
  - Testosterone: Hair growth (both + & -)
    - Spermatogenesis
    - Prostatic enlargement/growth
    - Libido
    - Increased hemoglobin
    - Increased muscle mass
    - Increased activity of oil glands in skin
Function of Hormones

- One function may be regulated by multiple hormones:
  - Lactation:
    - Oestrogen (LH/FSH)
    - Progesterone (indirectly)
    - Prolactin
    - Thyroxine
    - Cortisol
Chemical Nature of Hormones

• **Polypeptides:**
  - LH/FSH, TSH, hCG, ACTH, PTH, Insulin, Glucagon, Somatostatin, TRH, GnRH, IGF I & II, and others

• **Amino acid derivatives:**
  - Thyroxine, Triiodothyronine, Catecholamines (Epinephrine, Norepinephrine, Dopamine), Serotonin, Histamine
Chemical Nature of Hormones

- Steroids
  - Glucocorticoids
  - Mineralocorticoids
  - Androgens
  - Oestrogens
  - Progestins
  - Vitamin D and metabolites
Common Characteristics of All Hormones

• Present in circulation in small concentration-ranging from pM to uM for steroids and thyroid hormones to fM \(10^{-15} \text{ M}\) for peptide hormones

• Must be directed to site of action very specifically-targeting
Hormone Biosynthesis

- Peptide/Proteins
  - Generally are initially larger peptides (prohormones) synthesised on ribosomes via mRNA translation, that are modified by cleavage, glycosylation, and chemical modification (mostly in the Golgi apparatus and cytosol)
Hormone Biosynthesis

- Steroids: Products of enzymatic modification of cholesterol precursor
- Synthesis depends on availability of synthetic enzymes that are very restricted in their distribution (adrenals and gonads)
Storage

- Most hormones are stored and some, especially the protein hormones, in large quantities in membrane bound vesicles.

- Steroid hormones are stored only in very limited quantities.

- Still others are stored as precursors - i.e. thyroxine as thyroglobulin and 1,25 (OH)2 D as Vitamin D.
Storage

- Thyroglobulin as the store of thyroxine
Secretion

- Proteins/peptides: Active secretion by exocytosis of secretory granules. Secretion not tightly linked to synthesis (although loosely linked)

- Steroids: Passive diffusion down concentration gradient (lipid soluble)

- Secretion tightly linked to synthesis
Transport

- Proteins/peptides: water soluble thus transported by plasma in soluble form without carrier (some exceptions- IGF binding proteins, GH binding proteins)

- Steroids/thyroid hormones: Limited H₂O solubility thus carrier required to keep in solution. Carriers are proteins that may be specific for the hormone (thyroxine binding globulin, sex steroid binding globulin, and cortisol binding globulin) or nonspecific (serum albumin binds thyroxine)
Metabolism

- Clearance from plasma, renal, hepatic, peripheral tissues
- Chemical modification-Cleavage (proteases), glucuronidation, sulfation, oxidation, deiodination (thyroid hormones)
- Influenced markedly by binding proteins
- T 1/2 varies from seconds/minutes (peptides and proteins) to hours/days (steroids/thyroid hormones)
- Some may be receptor mediated
Hormone Targeting

- Specific, high affinity receptors with limited distribution
- Limited circulatory delivery-hypothalamo-hypophyseal portal system (hypothalamic releasing hormone) and hepatic portal circulation (insulin and glucagon)
- Direct diffusion to adjacent sites-testosterone effects on Sertoli/tubular cells and pancreatic islet somatostatin on $\alpha$ and $\beta$ cells
Hormone Targeting

- Local formation of active species from inactive precursor - dehydrotestosterone from testosterone, T4 from T3

- Local inactivation of non-targeted hormones - 11-b-hydroxysteroid dehydrogenase enzyme is part of mineralocorticoid receptor complex and metabolizes cortisol (potent mineralocorticoid) to cortisone (inactive) thus limiting mineralocorticoid effects of endogenous cortisol
Hormone Receptors

- Receptor: A cellular substance (protein) or group of substances that interact (bind) with a hormone in a highly specific manner and elicit a specific cellular response.
- Peptide/Protein hormones - Membrane receptor
- Steroid/Thyroid hormones - Nuclear receptor
Hormone Receptors

- Membrane Receptors:
  - G-protein coupled
  - Non G-protein coupled

- Nuclear Receptors:
  - Steroid hormone receptor “superfamily”
G-protein Coupled
G-Protein Linked Membrane Receptors

Plasma Membrane

Intracellular

GDP GTP

GTP GDP

ATP-Mg

cAMP

PDE

5’AMP

Protein Kinase

Phosphorylated Proteins

Physiologic Effect(s)

AC  Adenylate Cyclase
Rs  Stimulatory Receptor
Ri  Inhibitory Receptor
Hs  Stimulatory Receptor
Hi  Inhibitory Hormone
PDE  Phosphodiesterase
Nuclear Receptors

DNA

Steroid

Acceptor Site

mRNA

Translation

Proteins

Metabolized Steroid

Transcription and Processing
Receptor Concentrations

• Numbers of receptors present in a target tissue may be, in part, regulated by hormone concentrations.

• If hormone concentrations fall, receptor numbers increase—termed “up regulation”

• This serves to maximise the effect of the reduced hormone levels on the tissue.
  • Example: Increased GH receptors in GH deficiency
  • Increased sensitivity to thyroid hormone effects in hypothyroid patients
Receptor Concentrations

• “Down regulation” may occur when hormone levels are chronically high
  • Examples: Pituitary insensitivity to GnRH after continuous infusion or long acting analogs
  • Insulin resistance in chronic hyperglycaemia of Type 2 DM
Second Messengers

- Peptide hormone receptors
- cAMP/adenylate cyclase system
- Inositol triphosphate (IP3)/diacylglycerol (DAG) system
- Intracellular calcium
- Tyrosine kinase
Intracellular Calcium Signaling System

**Inositol phospholipids**

- **R1**
- **R2**
- **P-Inositol (P2)**

**1,2-Diacyl-glycerol**

- **ATP**
- **ADP**
- **Pi**
- **OH**

**Phospholipase C**

**CMP**

**Inositol**

**P - Inositol-(P2)**

**CTP**

**PPi**

**PP - Cytidine**

**CDP - DiacylGlycerol**

**Phosphatidic acid**
Regulation of Hormone Secretion

• All hormones are under some type of feedback control

• Secretary rate may be controlled by levels of various type substances:
  • Cations-Ca++ and K+ control of PTH and aldosterone
  • Metabolites-Glucose control of insulin and glucagon
  • Other hormones-T4 and cortisol control of TSH and ACTH
  • Physiologic parameters-osmolality and ECF volume control of ADH, renin, and aldosterone
Regulation of Hormone Secretion

- All of the following must be present and functional for normal feedback mechanisms to operate:
  - Detection of substance of importance in homeostatic control
  - Coupling of detection to secretory apparatus
  - Secretory apparatus
  - Hormone
  - End organ capable of responding to hormone
  - Detector of response
  - Mechanism of removing hormone from target cell or limiting response
  - Synthesis of new hormone to replenish stores
Measurement of Hormones

- Factors that influence circulating hormone levels:
  - Hormone secretory rate
  - Plasma binding proteins
  - Clearance mechanism
  - Hormone structure, glycosylation, etc.
  - Drugs
  - Circadian rhythms
  - Pulsatility
Dynamic Testing of Endocrine Activity

- Basal measurement of hormone levels may not accurately reflect glandular activity
  - Cushing’s disease - dexamethasone suppression of cortisol production
  - Acromegaly - Glucose suppression of GH
  - Central Hypoadrenalism - Stimulation of ACTH/cortisol by insulin induced hypoglycaemia
  - Insulinoma - Hypoglycaemic suppression of insulin/C-peptide
Measurement of Hormones

- Blood or urine levels of hormones must be interpreted in view of the clinical setting of the individual and the conditions under which the sample was obtained.
Mechanisms of Endocrine Disease

- **HYPERSECRETION:**
  - Tumors (most commonly benign)
    - Multiple tumor types-one syndrome (Cushing’s syndrome)
    - One tumor type-multiple syndromes (pituitary adenomas)
    - One tumor type-one syndrome (choriocarcinomas)
  - Hyperplasia
    - Sporadic, Familial (MEN), Immunogenic
  - Inflammatory
    - Infectious, Immunogenic
Mechanisms of Endocrine Disease

• HYPOSECRETION:
  • Absence of malformation of gland
  • Defective synthetic mechanism
    • Substrate deficiency
    • Enzymatic defect
  • Glandular Destruction
    • Immunogenic, Infectious, Traumatic/XRT, Malignant, Vascular, Surgical
Mechanisms of Endocrine Disease

- Abnormal hormones - rare
- Alterations of Hormone Action (resistance)
  - Abnormal (Mutated) receptor
    - Familial hormone resistance
  - G-protein defect
  - Receptor antibodies
  - Receptor “down regulation”
  - Intracellular defects
  - Deficient hormone inactivation
Any More Questions?